Unit-IV **BP502T.(IndustrialPharmacy-I)**

Syllabus

ParenteralProducts:

1. Definition, types, advantages and limitations. Preformulation factors and essential requirements,vehicles, additives, importance of isotonicity.
2. Productionprocedure,productionfacilitiesandcontrols,asepticprocessing
3. Formulationofinjections,sterilepowders,largevolumeparenteralsandlyophilizedproducts.
4. Containersandclosuresselection,fillingandsealingofampoules,vialsandinfusionfluids. Quality control tests of parenteral products

OphthalmicPreparations:

Introduction, formulationconsiderations;formulationof eyedrops,eye ointmentsandeye lotions; methods of preparation; labeling, containers; evaluation of ophthalmic preparations.

Abbreviations:-

LVP: Large volume Parenteral

SVP: Small volume Parenteral

P: Partition coefficient

HEPA: High- efficiency Particulate Air

LAL Test: Limulus Amebocytes Lysate test

BET: Bacterial Endotoxin Test

IPC: In-Process Control

WFI: Waterfor Injection

RH: Relative Humidity

FTM:FluidThioglycolateMedium

SCM:Soyabean-caseindigestMedium

1. Definition:

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 directlyinto the body tissues through skin and mucous membranes**.**

Parenteral products are sterile preparations containing one or more active ingredientsintended for administrationby injection, infusion or implantation into thebody. They are packagedin either single-dose or multi dose containers.

TypesParenteralProducts:

ThetypesofParenteralproductsarebasedonVolumeandthestateofproductaccording toUSP.

BasedonVolume:

- SVP–Aninjectionthatispackedincontainerslabeledascontaining100mlorless.
- LVP – These are parenterals designed to provide fluid, calories and electrolytes to the bodyand the volume is more than 100ml.

Based onStatesofproducts:

- Injection: Injections contain sterile solutions and are prepared by dissolving the active ingredientandother substancesinWaterforInjectionorothersuitablenon-aqueousbase or a mixture of both. The solution to be injected may show sediments which can be dispersed easily by shaking the container. The suspension should remain stable in order to deliver a homogenous dose whenever withdrawal is made from the container.
- Infusions**:**Theseparenteralpreparationsarecomposedofsterileaqueoussolutionwith water as its continuous phase. The preparations are free from bacterial endotoxins orpyrogens and are made isotonic with blood. They do not contain any antimicrobial preservatives.
- Powder for Injection: These are sterile solid compounds that are distributed in their final volume when the vial or container is shaken to form a clear particle-free solution.
- Concentrated Solutions for Injections**:** The concentrated solutions are diluted with water for injection before they are administered through injection or through intravenous infusion.
- Implants: These solid sterile preparations are implanted in the tissue in order to release the active ingredient for long periods. They are stored in sterile containers individually.
- InjectableEmulsion:Theseare liquidpreparationsinwhichthedrugsubstancesare dissolved or dispersed in a suitable emulsion medium. These products provide essential fatty acid and vitamins.
- OilyInjection:Theseareusedtoprepareparenteralcontrolledreleasedosageforms.

AdvantagesofParenteral:

a) Parenteral products can By passes pre systemic or first pass metabolism and theOnset of action is quick

b) Thedrugs,whichcannotbeadministeredorally,canbeadministeredby thisroute.
c) The patients who are vomiting or unconscious cannot take drug by oral route. In such cases, the drug can be administered by this route.
d) Thedrugactioncanbeprolongedbymodifyingtheformulation.
e) Thisroute candeliver transfusion fluids containing nutritiveslikeglucose andelectrolytes such as sodium chloride.

Limitations:

a) Injectioncausespainatthesiteofinjection.
b) Thetrainedpersonsarerequiredtoadministerthedrug.
c) Theadministrationofdrugthroughwrongrouteofinjectionmayprovetobefatal.
d) Itisdifficulttosavea patientwhenoverdoseisgiven.
e) Therearechancesofsensitivity reactionorallergicreactionofadrug byanindividual.These reactions are sometimes fatal and lead to death.

Preformulationfactorsandessentialrequirements:

Preformulation involves the study about physical & chemical properties of drug substance prior formulation. These studies are performed under stressed conditions of temperature, humidity; light and oxygen so that the reactions are accelerated and potential reaction are detected. A few physicochemical properties that affect a drug substance are discussed below.

- **Melting point:** It is the Temperature at which the solid and liquid phases are in equilibrium. Its determination is a primary indication of purity.
- **Solubility**: This property is essential for developing solution to be injected either intraveneouslyorintramuscularly.Itisafunctionofchemicalstructure:saltsofacidor bases are the drugs that can achieve the desired degree of water solubility.
- **Molecularstructureandweight**:Thesearethebasiccharacteristicsofthedrugfrom which the potential properties and reactivities of functional groups can be determined.
- **ParticleSizeandShape**:Study of particle size give information aboutSolubility, dissolution rate and absorption etc.These charcterstics are determined by Scanning electron microscope or an optical microscope with polarizing attachments.
- **Ionisation constant**: This property is used to determine the P^H-dependent solubility of a compound.Potentiometric PH titration or PH-solubility analysis is used for determining the P^{Ka}value.Ionisation constant of a compound also helps in determining the degree of ionization of an acid or base. Degree of ionization depends upon the P^H.
  ForacidicdrugsP^{Ka}rangesfrom3-7.5andforbasicdrugsP^{Ka}rangesfrom7-11.
- **Partition Coefficient (P);** It is a ratio of equilibrium concentration of drug in aqueous and oily phases in contact with each other at a constant temperature. Partition coefficient can be expressed as :P= [C_{oil}/ C_{water}],where, C_{oil}=organic phaseconcentration and C_{water}= aqueous phase concentration.

- **Hygroscopicity:**Thetendencyofasolidtotakeupwaterfromatmosphere,asitis subjected to a controlled RH programe under isothermal condition. A high degree of hygroscopicitycanadverselyaffectthephysicalandchemicalpropertiesofadrug substance.

Essential requirements for Formulation: The formulations of parenteral preparations need careful planning, thorough knowledge of medicaments and additives to be used. The excess use of additives in parenteral products should be avoided as some of these may interfere with the drug. In the preparation of parental products, the following substances are added to make a stable preparation.

1. Vehicles
2. Additives

a) Solubilizing agents b) Stabilizers c)Buffering agents d) Antibacterial agents e) Chelating agents f)Suspending ,emulsifying and wetting agents g)Tonicity factors

1. **Vehicles:**

Therearetwotypesofvehicles,whicharecommonlyusedforthepreparationofinjections

A) Aqueousvehicle- water isused as vehicle for majority of injections becausewater is tolerated well by the body and is safest to administer .The aqueous vehicle used are ;-

1) Waterforinjections.
2) WaterforinjectionfreefromCO2(carbondioxide)
3) Water for injection free from dissolved air, water for injection is sterile water, which is free from volatile, non- volatile impurities and from pyrogens.

Pyrogens are by-product of bacterial metabolism. pyrogens are Lyposaccharide, thermostable,soluble in water ,unaffected by bactericide and can pass through bacterial proof filters. pyrogens can be removed from water by simple distillation process using an efficient trap which prevents the pyrogen to enter into the condenser .immediately after the preparation of water for injection ,it is filled in to the final container, sealed and sterilized by autoclaving .

Waterforinjection,contaminatedwithpyrogensmaycauseriseinbodytemperatureifinjected .Hence,testforpyrogenisdonetoensurethatwaterforinjectionisfreefrompyrogens.

B) Non-aqueousvehicles:-Thecommonlyusednon-aqueousvehiclesareoilsandalcohols.

Fixed oil, such as arachis oil,cottonseed oil ,almond oil and sesame oil are used as vehicle .the oily vehicles are generally used when a depot effect of drug is required or the medicaments are insoluble or slightly soluble in water or the drug is soluble in oil example dimercaprol injection by usingarachis oil as vehicle.

Ethyl alcohol is used in the preparation of hydrocortisone injection .hydrocortisone is insoluble in water, hence the solution is made in 50% alcohol .Alcohol causes pain and tissue damage at the siteof injection. Therefore, it is not used commonly.

Propyleneglycolisusedasavehicleinthepreparationofdigoxininjection.itis relatively non- toxic but it causes pain on S/C or I/M injection.

Sometime polyethylene glycol and glycerine usually diluted with sterile water are used to prepare solutions for injections .they are used as solvent as well as to increase the stability of certain preparations.

2. Additives:

Thesesubstancesareaddedtoincreasethestabilityorqualityoftheproduct.These additives should be used only when it is necessary to use them. While selecting the additives, care mustbetakenthatthey shouldbe compatiblebothphysicalandchemicalwiththeentire formulation, .They should be added in minimum possible quantity .The following additives are commonly used in preparing stable parental preparations.

a) Solubilising agents:- These are used to increase the solubility of drugs which are slightly soluble inwater.thesolubilityofdrugisincreasedbyusingsurfaceactiveagentliketweensand polysorbate or by using co solvents.

b) Stabilizers:- The drugs in the form of solution are more liable to deteriorate due to oxidation and hydrolysis .The stabilizers are added in the formulation to prevent this .the oxidation can bepreventedbyaddingasuitableantioxidantsuchas,thiourea,ascorbicacid,sodiummetabisulphite ,ortheproductissealedinanatmosphereofNitrogenorCarbondioxide.hydrolysiscanbe prevented by using a non-aqueous vehicle or by adjusting the pH of the preparation.

Antioxidants:

Watersoluble: Sulfurousacidsalts,Ascorbicacidisomers,Thiolderivatives

Oilsoluble; Propylgallate,Butylatedhydroxyanisole,Ascorbylpalmitate,alphaTocopherol

c) Buffering agents: -The degradation of the preparation, which is due to change in pH, can be prevented by adding a suitable buffer to maintain the desired P^H.

pH	Buffersystem	Concentration(%)
3.5-5.7	Aceticacid-acetate	1-2
2.5-6.0	Citricacid-citrate	1-5
6.0-8.2	Phosphoricacid-phosphate	0.8-2
8.2-10.2	Glutamicacid-glutamate	1-2

d) Antibacterial agents:- These substance are added in adequate quantity to prevent the growth of microorganismduringstorage.sothesesubstancesactaspreservatives.antibacterialagents are added in single dose containers, where parenteral products are sterilized by filtrationmethod and in multi dose containers to prevent microbial contamination .

Sometypicalpreservativeusedinparenteralsuspensionsandtheircommonlyused concentrations are as follows.-

Benzylalcohol(0.9%to1.5%)

Methylparaben(0.18%to0.2%)

Propylparaben(0.02%)

Benzalkoniumchloride(0.01%to0.02%)

Thiomersal(0.001%to0.01%)

f) **Chelating agent: -** Chelating agents such as EDTA (Ethylene diamine Tetra acetic acid) and its salts, sodium or pottasium salts of citric acid are added in the formulation,to chelate the metallic ions present in the formulation. They form a Complex which gets dissolved in the solvent.

S.No.	Additives	Concentrationrange(%)
1	EDTAdisodium	0.00368-0.05
2	EDTAcalciumdisodium	0.04
3	EDTAtetrasodium	0.01

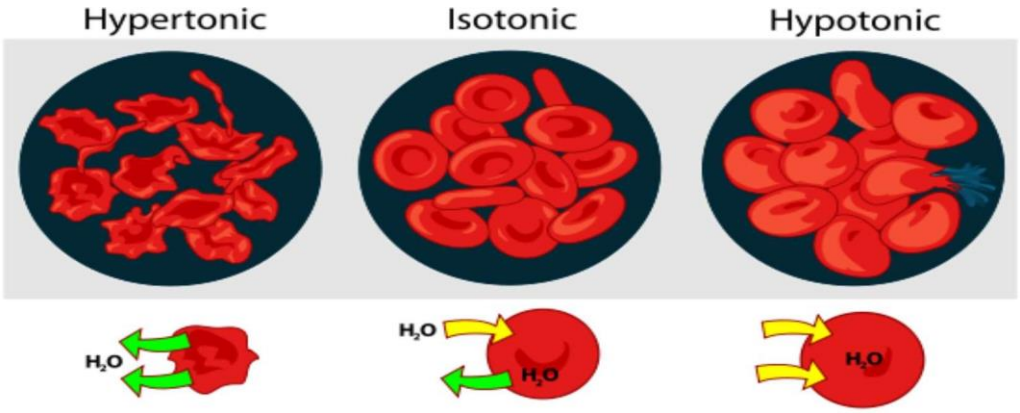
g) **Suspending, emulsifying and wetting agents:-** The suspending agents are used to improve the viscosity and to suspend the particles for a long time. Methyl cellulose, carboxy-methylcellulose, gelatin and acacia are commonly used as suspending agents .Emulsifying agents are usedinsterileemulsions.forthispurposelecithinisgenerallyused.Thewettingagentsare used to reduce the interfacial tension between the solid particles and the liquid, so as to prevent the formulation of lumps. They also act as antifoaming agents to subside the foam produced during shaking of the preparation.

Additives	**Concentrationrange(%)**
Polyethyleneglycol300	0.01-50.0
Polysorbate20	0.01
Polysorbate40	0.05
Polysorbate80	0.04-4.0
Povidone	0.2-1.0
Propyleneglycol	0.2-50.0
Sorbitanmonopalminate	0.05
Dimethylacetamide	0.01
Lecithin	0.5-2.3

h) **Tonicity factors:** - Parenteral preparation should be isotonic with blood plasma or other body fluids.Theisotonicity ofthesolutionmay beadjustedbyaddingsodiumchloride,dextrose and boric acid etc. in suitable quantities. These substances should be compatible with other ingredients of the formulation. Examples of Tonicity adjuster/modifier are Glycerin, lactose, mannitol, dextrose, NaCl, sodium sulfate and sorbitol

ImportanceofIsotonicity:

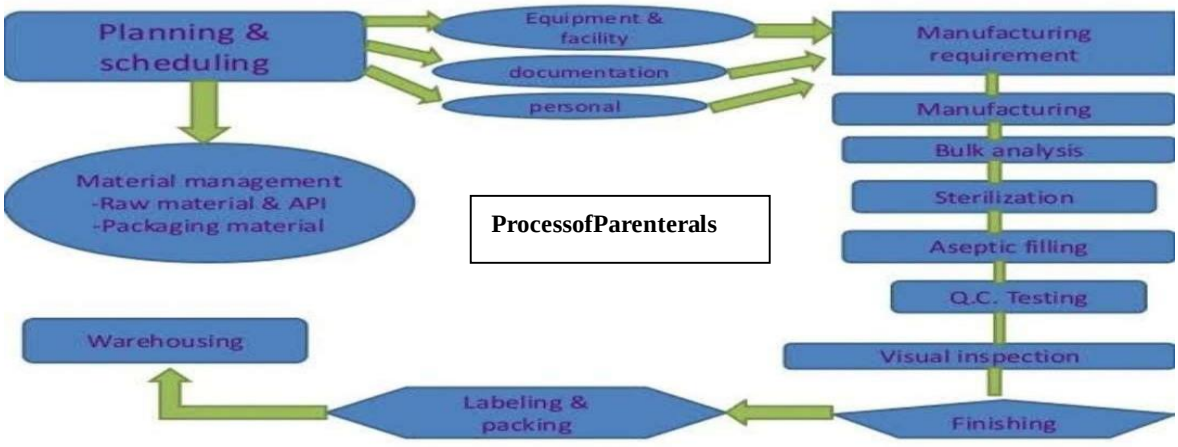
An isotonic solution is one that exhibits the same effective osmotic pressure as blood serum.Isotonicity is important for parenteral preparation because if the solution is isotonic withblood, the possibility of product penetrating the RBC and causing haemolysis is reduced. For hypertonic solution crenation and for hypotonic solution haemolysis will occur.



Crenation **Hemolysis**

2. 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.



ProcessofParenterals

Themanufacturingofparenteralsinvolvesthefollowingsteps;

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

1. **Cleaningofcontainersand 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. **Preparation of 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. **Evaluation of 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

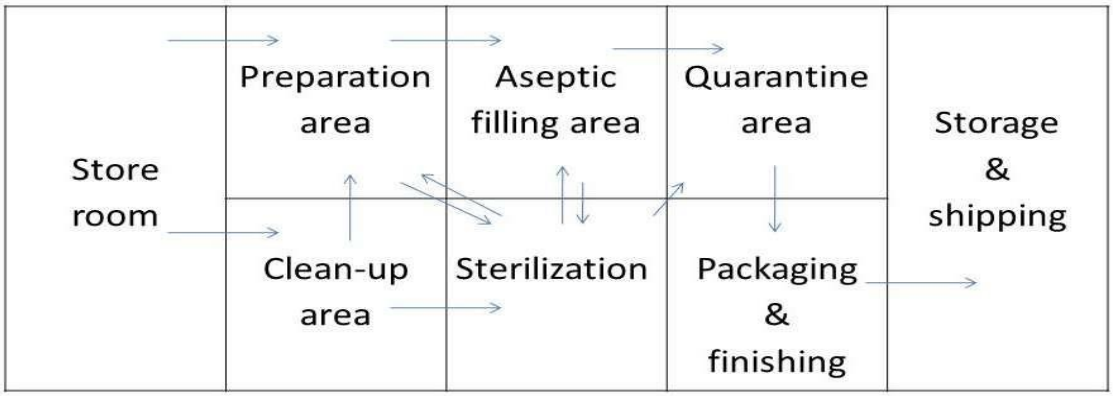
Productionfacilitiesandcontrols:

The production area where the parenteral preparations are manufactured can be divided into thefollowing five sections.

1) Clean-uparea
2) Preparationarea
3) Asepticarea
4) Quarantinearea
5) Finishing&packagingarea

1. **Clean-uparea:**
   - Itisnotasepticarea.
   - Alltheparenteralproductsmustbefree fromforeignparticles&microorganism.
   - Clean-upareashouldbewithstandmoisture,dust&detergent.
   - Thisareashouldbekeptcleansothatcontaminantsmaynotbecarriedoutinto aseptic area.

2. **Preparationarea:**
   - In this area the ingredients of the parenteral preparation are mixed & preparation is made for filling operation.
   - Itisnotessentiallyasepticareabutstrictprecautionsarerequiredtopreventany contamination from outside.



3. **Asepticarea:**
   - Theparenteralpreparationsarefiltered,filledintofinalcontainer&sealedinasepticarea.
   - Theentryofpersonnelintoasepticareashouldbelimited& throughanairlock.
   - Ceiling,wall&floorofthat areashouldbesealed&painted.
   - Theairinthe asepticareashouldbefreefromfibers,dustandmicroorganism.
   - TheHighefficiency particulateairfilters(HEPA)isusedforair.
   - UVlampsarefittedinordertomaintainsterility.

4. **Quarantinearea:**
   - Afterfilling,sealing&sterilizationtheparenteralproductareheldupinquarantinearea.
   - Randomlysampleswerekeptforevaluation.
   - Thebatchorproductpasstheevaluationtestsaretransferintofinishingorpackagingarea.

5. **Finishing&packagingarea:**
   - Parenteralproductsareproperlylabelledandpacked.
   - Properly packingisessentialtoprovideprotectionagainstphysicaldamage.
   - Thelabelledcontainershouldbepackedincardboardorplasticcontainer.
   - Ampoulesshouldbepackedinpartitionedboxes

Controlledenvironmentrequiredforparenteralpreparation:

Clean Room Classified Areas: Due to the extremely high standards of cleanliness and purity that must be met by parenteral products, it has become standard practice to prescribe specificationsfor the environments (clean rooms) in which these products are manufactured. The Critical and General area of clean room: The clean room divides into

1. CriticalArea
2. GeneralArea.

The critical area is the area around the point of the production where contamination can gain direct access to the process. This area often protected by localized laminar flow clean benches and workstations.TheGeneralareaistherestofthecleanroomwherecontaminationwillnotgain direct entry intothe product but should be keptclean because of the transfer of contamination intothe critical area. It is necessary that the critical area be cleaned most often with the best cleaning ability without introducing contamination.

ClassificationofCleanRooms:-

Theclassisdirectlyrelatedtothenumberofparticlespercubicfootofairequaltoor greater than 0.5 micron.

1. Class100,000:Particlecountnottoexceedatotalof100,000particlespercubicfootofasize 0.5µ and larger or 700 particles per foot of size 5.0µ and larger.
2. Class 10,000: Particle count not to exceed a total or 10,000 particles per cubic foot of a size 0.5µ and larger or 65-70 particles per cubic foot of a size 5.0µ and larger.
3. Class1,000:Particlescountnottoexceedatotalof1000particlespercubicfootofasize0.5µ and larger or 10 particles per cubic foot of a size 5.0µ and larger.
4. Class 100: Particles count not to exceed a total of 100 particles per cubic foot of a size 0.5µ and larger.

Class1:Theparticlecountshallnotexceed3000particles/m3ofasize0.5µ.

Class 2: The particle count shall not exceed a total of 3000 particles/m3of a size of 0.5µ or greater; 2000 particles/m3of size 0.5µ or greater; 30 particles of a size 10µ.

Class 3: The particle count shall not exceed a total of 1,000,000 particles of a size of 1µ or greater; 20,000particles/m3ofsize5µorgreater;4000particles/m3ofasize10µorgreater;300particlesof a size of 25µ or greater.

Class 4: The particle count shall not exceed a total of 200,000 particles of a size of 5µ or greater.

For the manufacture of sterile medicinal products normally 4 grades can be distinguished:

GRADE — 'A': The local zone for high risk operations. eg. filling zone, stopper bowls, openampules and vials. GRADE — 'B': In case of aseptic preparation and filling, the back ground environment for grade — 'A' zone. GRADE — 'C' & 'D': Clean areas for carrying out less critical stages in the manufacture of sterile products.

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 sterilizationandtransfer procedures, themaximumholdingperiodoftheproductbeforefillingintothefinalcontainerandthe sterilizing filter. Certain solutions and liquids that cannot be sterilized in the final container can be filteredthroughasterilefilterofnominalporesize0.22micron(orless),orwithatleast 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.

3. 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.

Antimicrobialpreservatives inhibitthegrowthofany microbesthatareaccidentally introduced whiledosesarebeingwithdrawnfrommultiple-dosebottlesandactasadjunctsinaseptic 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.

- Cakingofinjectablesuspensionsisminimizedthroughtheproductionofflocculated systems, comprising clusters of particles (flocs) held together in a loose open structure.
- Excipientsininjectablesuspensionsincludeantimicrobialpreservatives,surfactants, dispersing or suspending agents, and buffers.
- Surfactantswetthesuspendedpowdersandprovideacceptablesyringeabilitywhilesuspending 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. **Sterile Re-crystallization**: The drug is dissolved in a solvent and the obtained solution issterilized 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:

   ThismethodisFlexibleandeconomic.

   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:

   Thismethodinvolvesremovalofwateratlowtemperatures.

   Disadvantage:

   i) Inthismethod,thebiologicalmoleculesaredamagedbythestress associated with freezing, and drying.
   ii) Thismethodisexpensiveandtimeconsuming

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) ThismethodisSimple,Economical,scalableandfaster.
ii) ThismethodinvolvesCoatingofparticlesduringdryingprolongedrelease.

Disadvantage:

i) Inthismethod,thehighprocessingtemperaturesandhighshearforcescaneasilydamage drugs.
ii) Inthismethod,higherlevelsofdrugsarelostincomparisontofreeze-drying.
iii) Thismethodhasalimitedsolventchoiceforagivendrug.
iv) Inthismethod,productcannotbepreparеddirectly invialsorplates.

Formulationoflargevolumeparenterals:-

Large volume injections are intended to be administered by IV Infusion Fluids & are included in the group of sterile products & are known as large volumeParenterals.Theseconsist of single dose injecting a volume of 100 ml or more than 100 ml sometimes additional drugs are added to them by either injecting svp to the administration sets or by piggyback method(small volume infusion of an additional drug is added to the intravenous delivery system).large volume parenteral products include:

1) Infusionfluid(Basicnutrition-Dextroseinj,Fluidreplacementtherapy-Normalsaline)
2) TotalparenteralNutritionsolution(TPN)
3) Intravenousantibiotics
4) Dialysisfluid
5) Irrigationsolutions

Large volume parenterals should be terminally heat sterilized. Apart from water for injection as the main component, other ingredients that should be included are carbohydrates (e.g. dextrose, sucrose and dextran), aminoacids,lipidemulsion,electrolytes (Nacl)andglycerol, sorbitol and mannitol.TheLVParemostlyclearsolutions,exceptfortheoil-in–wateremulsions.The emulsions for infusion are produced by highly specialized method as they are destabilized by heat. This result in many difficulties during production, thus the size of oil droplets should be controlled during heat sterilization.

ProductionofLVP:

i) Themanufacturingandfilling ofLVPfluidsintocontainersarecarriedoutinaahigh standard clean room environment. High standards are required to prevent these products from getting contaminated with organisms, pyrogens and particulate matter.
ii) The fluids from a bulk container are filled into the product container using high speed filling machine. Before filling the fluid into the container, it is passed through an in-line membrane filter to remove the particulate matter.
iii) After filling, the neck of each glass bottle is immediately sealed with a tight fitting rubber closure held in place with a crimped aluminum cap.
iv) In case plastic bags are used, the pre-formed plastic bags are aseptically filled and heat-sealed immediately.
v) Blow –fill-seal system are adopted to minimizes the problems with product handling, cleaning and particulate contamination.

vi) TheLVPproducts,includingirrigationsolutionanddialysisfluidsshouldbemoistheatsterilized immediately after the containers are filled.

Lyophilizationorfreeze-drying:-

Lyophilizationorfreezedryingisaprocessinwhichwaterisremovedfromaproductafter it isfrozen and placed under a vacuum,allowing the ice to change directly from solid to vaporwithout passing through a liquid phase. The process consists of three separate, unique, and interdependent processes like;Freezing, Primary drying (sublimation), and Secondary drying (desorption).

AdvantagesofLyophilization

- Easeofprocessingaliquid,whichsimplifiesaseptichandling.
- Enhancedstabilityofadrypowder.
- Removalofwaterwithoutexcessiveheating oftheproduct.
- Enhancedproductstabilityinadrystate.
- Rapid and easy dissolution of reconstituted product

Disadvantages

- Increasedhandlingandprocessingtime.
- Needforsterilediluentuponreconstitution.
- Costandcomplexity ofequipment

StepsinvolvedinformulationofLyophilizedproducts:-

- Dissolving the drug and excipients in a suitable solvent, generally water for injection (WFI).
- Sterilizing the bulk solution by passing it through a 0.22-micron bacteria-retentive filter.
- Filling into individual sterile containers and partially stoppering the containers under aseptic conditions.
- Transporting the partially stoppered containers to the lyophilizer and loading into the chamber under aseptic conditions.
- Freezing the solution by placing the partially stoppered containers on cooled shelvesin a freeze-drying chamber or pre-freezing in another chamber.
- Applying a vacuum to the chamber and heating the shelves in order to evaporate the water from the frozen state.
- Complete stoppering of the vials usually by hydraulic or screw rod stoppering mechanisms installed in the lyophilizers. There are many new parenteral products, including anti-infectives, biotechnology derived products, and in-vitro diagnostics which are manufactured as lyophilized products.

- Additionally,inspectionshavedisclosedpotency,sterilityandstabilityproblems associated with the manufacture and control of lyophilized products

4. Selectionofcontainersandclosures:

Selection of Containers & Closures should be such that it should ensure that the productsmust remain its purity, potency & quality during intimate contact with the container throughout its shelf life.

Glass:-

Glass is employed as the container material of choice for most SVIs. It is composed, principally, of silicon dioxide, with varying amounts of other oxides, such as sodium, potassium, calcium, magnesium, aluminum, boron, and iron. Glass is preferred for clarity reasons

Types:-

TheUSPprovidesaclassificationofglass:

- TypeI,aborosilicateglass;
- TypeII,a soda-limetreatedglass;
- TypeIII,asoda-limeglass;and
- NP,asoda-limeglassnotsuitableforcontainersforparenteral.

Type I glass will be suitable for all products, although sulfur dioxide treatment is sometimes used for even greater resistance to glass leach-ables. Because cost must be considered, one ofthe other, less expensive types may be acceptable.

Type II glass may be suitable, for example, for a solution that is buffered, has a pH below 7, or is not reactive with the glass.

TypeIIIglassisusuallysuitableforanhydrousliquidsordry substances.

Types II and III glass compounds are composed of relatively high proportions of sodium oxide (~14%) and calcium oxide (~8%). This makestheglasschemically lessresistant. Both types meltata lower temperature, are easier to mold into various shapes.

Type II glass has a lower concentration of the migratory oxides than TypeIII. In addition, Type IIhas been treated under controlled temperature and humidity conditions, with sulfur dioxide or otherde alkalizers to neutralize the interior surface of the container.

Theglasstypesaredeterminedfromtheresultsoftwo USPtests:

ThePowdered Glass Test

The Water Attack Test.

ThePowderedGlassTestchallengestheleachingpotentialoftheinteriorstructureoftheglass, whereas the Water Attack Test challenges only the intact surface of the container.

Selecting the appropriate glass composition is a critical facet of determining the overall specifications for each parenteral formulation. Glass can be the source / cause of leach-ables / extractable, particulates (glass deamination or glass lamellae formation), adsorption of formulation components, especially proteins, and cracks / scratches.

Plastic:-

Plastic packaging has always been important for ophthalmic drug dosage forms and is gaininginpopularityforinjectabledosageforms.Plasticbottlesforlargevolume injectable (LVIs) have been used for many years. Plastic vials for SVIs may be a wave ofthe futureplastic packing offerssuch advantages ofcost savings elimination of the problems caused by breakage of glass and increase convenience of use.Plastics are light weight, less fragile & easy to handle but not clear as that of glass.

Rubber:-

Rubberformulationsareusedasrubberclosures,rubberplungersandotherapplications. The most common rubber polymers used in SVIs closures are natural and butyl rubber. Silicone and neoprene also are used but less frequently in sterile products. Butyl rubber has great advantages over natural rubber in that butyl rubber requires fewer additives, has low water vapor permeation properties and has good characteristics with respect to gaseous permeation reactivity with the active ingredient.

Rubber permits the entry of hypodermic needle into injection vials & also provide resealingof the vial after needle is withdrawn.

FillingandSealingofAmpoules:-

Ampoulesarethin-walledglasscontainers,whichafterfilling,aresealedbyeithertip sealing or pull sealing. The contents are withdrawn after rupture of the glass, or a single occasion only. These are great packaging for a variety of drugs. The filed – in product is in contact with glass only and the packaging is 100% tamper proof. The break system OPC(one –point cut) or the color breakringofferconsistentbreakingforce.Therearewidevarietyofampouletypesfrom0.5to 50ml volume.

- Here,themeasuredamountsofliquiddeliverfromthesmallorificeintotheampoulebyfilling machine.
- The size of the delivery tube is governed by opening in the container to be used, the viscosity anddensity of the liquid and the speed of delivery desired.
- The tube must free enter the neck of the container and deliver the liquid deep enough to permit airto escape without sweeping the entering liquid into the neck or out of the container.
- Filling machine parts should be constructed of non-reactive materials such as borosilicate glass or stainless steel.
- Thesolutionsareusuallyfilledinthebottlebygravity,pressureorvacuumfillingdevice.
- Emulsionandsuspensionrequiredspeciallydesignedfillingequipmentbecauseoftheirhigh viscosity.
- Powders such as antibiotics, are more difficult to subdivide accurately and precisely into Individual dose containers than are liquid.
- Containershouldbesealedintheasepticareainimmediatelyadjacenttothefillingmachine.
- Itisobviousthata sterilecontainer thathasbeenopenedcannolongerbeconsideredto

besterile.Therefore,temperatureproofsealingisessential.

- Ampoulesmay be closedby melting a portionoftheglassof neck toeither form tip-sealsorpull seals.
- **Tip-seals** are made by melting sufficient glass at the tip of the ampoule neck to form a bead of glass and close the opening. This is performed in a high temperature gas oxygen flame.
- **Pull-seals** are made by heating the neck of a rotating ampoule below the tip, then pulling the tip away to form a small, twisted capillary just prior to being melted closed. Pull sealing process is slower one, but the sealing done by this is more secure than that of tip sealing.
- Excessive heating of air and gasses in the neck causes expansion against the soft glass with the formation of fragile bubbles at the point of seal.

FillingandSealingofVialsandInfusionbottle:-

The solutions, which sterilized through filtration, are to be filled under the aseptic conditions. During the filling of product to the containers, should be for the prevention of contamination, especially the product is sterilized by the filtration and will not be sterilized in to the final container. The second one is called as aseptic fill. A liquid is more easily exposed uniformlyintothe container having the narrow mouth than isused for solid. Liquids which are mobile are easier to transfer and subdivide than viscous or sticky fluids, since these require heavy-duty machinery for the rapid production filling. The filling of liquids into containers with high accuracy involves the following methods

i) Volumetricfilling

ii) Time/pressurefilling

Volumetric filling machines have pistons or peristaltic pumps. These are most common used method. Time-pressure filling is used for filling of sterile liquids. A filling system is connected by a production tank that equipped with a pressure sensor. The sensor is used for the measurement of pressure and transmits values PLC system that controls the product flow from the tank to the filling manifold. The product is driven by using pressure mainly uses nitrogen with no pump mechanism.

By closing the opening using the rubber closure (stopper) the glass or the plastic vials are sealed properly. This should be done by after filling with care, to prevent the contamination of the contents inside.Increasedchancesforcontaminationarethelargeopeninginthevialsthantheampoules. The open containers must be protected from contamination, especially with the blanket of HEPA filtered laminar airflow. By using the aluminum caps the rubber stoppers are held in appropriate place. Rubber closures that uses for the intravenous administration have a permanent hole throughthe closure. A 500ml of infusion bottle is considered suitable for preparation of parenteral solutions.Itisassumedthatthebottlehasbeenstoredwithadoublecapprotectingthemouth.Theoutercap 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.

QualityControlTestsofParenteralProducts:-

Thefollowingaretheevaluationtestfortheparenteral.Theyareasfollows.

1. Sterilitytest
2. Claritytest
3. Leakerstest
4. Pyrogentest

1. Sterility test: It is a method carried out to detect confirm absence of any viable form of microbes in product. The method used for sterility tests are

a. Directtransfermethod

b. Membranefiltrationmethod.

a. Direct transfer method:Open each sample container and with draw the require amount of the sample. Inject one-half of sample in a test tube containing fluid Thioglycolate Medium (FTM). Inject another half in the test tube containing Soyabean-casein digest Medium(SCM). Volume of the medium must be sufficient to promote and expedite microbial growth. Adequate mixing between the sample inoculums and the culture medium must take place to maximize interaction andfacilitatemicrobialgrowth.If the product tobe tested containsany anti-microbial agent, using suitable reagent it should be neutralized before the test.

b. Membranefiltrationmethod(MF): Thismethodisemployedinthefollowingcases:

1. Oil&oily preparations
2. Alcoholicpreparations
3. Forpreparationsmiscible with orsolubleinaqueousoroily solvents.

ThestepsinvolvedinMFsterilitytestmethodare

i).Thefilterunitmustbeproperlyassembledandsterilizedpriortouse.

Ii). Thecontentsaretransferredtothefilterassembly understrictasepticconditions.

iii) Themembraneisremovedaseptically.

iv). Membrane iscutinhalf.

iv) One halfisplaceinsuitablevolumeofFTMandanotherinanequalvolumeofSCM.

Interpretationofresults:

i). Ifthereisnovisibleevidenceofmicrobialgrowth,itmaybeinterpretedthatthesampleis without intrinsic contamination and the product complies the test for sterility.

ii). If microbial growth is found, the product does not complies the test for sterility and the sterility test may be repeated.

2. Claritytest(particulatematterevaluation):-

Particulate matter in parenteral solutions has been recognized as an acceptable. Since the user could be expected to conclude that the presence of visible dirtwould suggestthat, the product isof inferior quality.

a). ***In visual method***, the entire product should be inspected by human inspectors under good light baffled against reflection into the eye and against black and white background. Dark background detects light particles and light background detects dark particles. Any container with visible particle if seen is discarded.

b). ***In Coulter counter method***; the principle is based on that there will be an increase in the resistance as a particle approaches and passes through the orifice (2 electrodes).

c). This method require destruction of the product unit since an electrolyte is added to thepreparation before its evaluation.

d). SomeothermethodsofclarityTestingcanbelistedasFiltrationmethod,Lightscattering method, Light absorption, Light blockage methods, etc...

e). Once the particles are detected, then they are identified by various methods like microscopy,X-ray powder diffraction, mass microscopy, micro-chemical tests, polarized light microscopy and scanning electron microscopy.

3. Leakerstest:-

Leaker test for ampoules is intended to detect incompletely sealed ampoules so that they can be discarded in order to maintain sterile condition of the medicines.Open capillaries or cracksat the point of seal result in LEAKERS.

- The leaker testis performed by immersing the ampoules in a dye solution, suchas 1%methylene blue, and applying at least 25 inches of vaccum for a minimum of 15 mins.
- Detection of leaker is prominent when ampoules are immersed in a bath of dye during autoclaving as this has advantage of acomplishing both leaker detection and sterilization in one operation.
- Another means of testing for leakers is a high frequency spark test system, which detectpresence of pinholes in ampoules.
- Bottles and vials are not subjected to such a vaccum test because of the flexibility of the rubber closure.

4. Pyrogentest:-

Pyrogensarethemetabolicproductsofmicrobes.Mostbacteria,mouldsandviruses producePyrogen.Mostpotentpyrogenicsubstancecalledendotoxinsareproducedbygram negative bacteria .Pyrogens when injected into a human, shows marked rise in the temperature ,chills, body aches, cutaneous vasoconstriction and increased arterial blood pressure. The most likely source of pyrogens are water, contaminated solutes and containers.

- ThetestinvolvesmeasurementoftheriseinbodytemperatureofrabbitsfollowingtheIV injection of a sterile solution into ear vein of rabbit.
- Dose not exceeding 10 ml per kg injected intravenously within a period of not more than 10 mins.
- Selectionofanimals-healthy,adult,notlessthan1.5kg.
- Equipmentandmaterialusedintest-glassware,syringes,needles.
- Retaining boxes-comfortableforrabbitsaspossible.
- Thermometers-standardizedpositioninrectum,precisionof0.1°C.

PreliminaryTest(ShamTest):

Ifanimalsareusedforthefirsttimeinapyrogentestorhavenotbeenusedduringthe2 previousweeks,conditionthem1to3daysbeforetestingthesubstancebyinjectingIV10mlperkg

pyrogen free saline solution warmed to about 38.5°c. Record the temperature of the animals, beginning at least 90 mins before injection and continuing for 3 hours after injection. Any animal showing a temperature variation of 0.6° or more must not be used in main test.

MainTest:

Themaintestiscarriedoutbyusingagroupof3Rabbits.Dissolvethesubstancein,or dilutewith,pyrogenfreesalinesolution.Warmtheliquidtoapproximately38.5°before injection.Injectthesolutionunderexaminationslowlyintothemarginalveinsoftheearofeach rabbitoveraperiodnotexceeding4mins.Recordthetemperatureofeachanimalathalfhourly intervalsfor3hoursafterinjection.Thedifferencebetweentheinitialtemperatureandthe maximum temperature which is the highest temperature recorded for a rabbit is taken to be its response.

InterpretationofResult:

a). Thetestiscarriedoutonthefirstgroupof3rabbits;ifnecessary onfurthergroupsof3rabbits to a total of 4 groups, depending on the results obtained.

b). Intervalsofpassingorfailingofproductsareonthebasisofsummedtemperatureresponse. If thedifferenceisnegative,theresultiscountedaszeroresponse.

No.ofRabbits	**Individual Temp. Rise(°C)**	**Temp.Rise in group (°C)**	**Test**
3Rabbits	0.6	1.4	Passes
(Ifabovenot Passes)-: 3+5=8Rabbits	0.6	3.7	Passes
IfaboveTestnotpasses,thesampleissaidtoPyrogenic.			

BacterialEndotoxinTest(BET)orLimulusAmoebocyteLysateTest(LALTest):-

The bacterial endotoxin test (BET) is a test to detect or quantify endotoxins from gram negative bacteria using Amoebocyte lysate from the horse shoe crab (Limulus polyphemus or Tachypleustridentatus) .

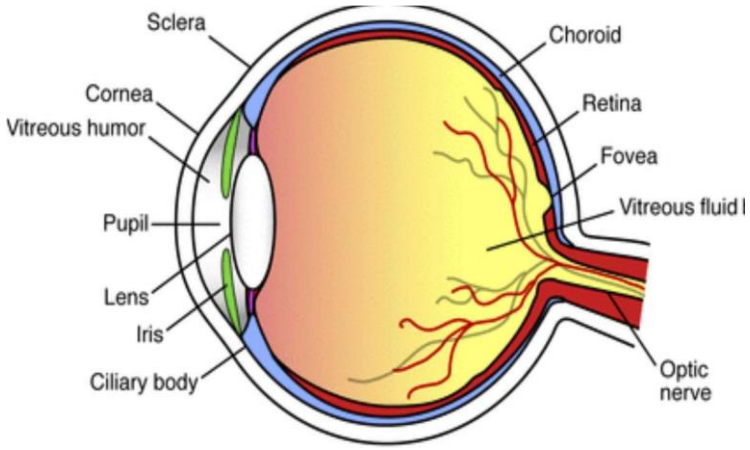
The endotoxins of gram-negative bacteria forms a firm gelwithin 60 mins in the presence of lysateof amebocytes of limulus polyphemus of horseshoe crab, when incubated at 37◦c. Hence, the test is only effective with gram-negative bacteria, which constitute the majority and the most potent of the pyrogens. The addition of a solution containing endotoxins to a solution of a lysate producesturbidity, precipitation or gelation of the mixture.

OphthalmicPreparations:-

Introduction;

Ophthalmic preparations (eye preparations) are sterile, liquid, semisolid, or solidpreparations that may contain one or more active pharmaceutical ingredient(s) intended for application to the conjunctiva, the conjunctival sac or the eyelids. The choice of base and any excipients used for the preparation of ophthalmic preparations must be proven through product development studies not to affect adversely either the stability of the final product or the availability of the active ingredients at the site of action. The most commonly employed ophthalmic dosageforms are solutions, suspensions, and ointments.But these preparations when instilled into the eye are rapidly drained away from the ocular cavity due to tear flow and lachrymal nasal drainage.

Eye is the most easily accessible site for topical administration of a medication. Ideal ophthalmic drugdeliverymustbeabletosustainthedrugreleaseandtoremaininthevicinityoffrontofthe eyefor prolongperiod.The newestdosage formsforophthalmic drug delivery are:gels,gel- forming solutions, ocular inserts, intravitreal injections and implants**.**



Anatomyofthehumaneye.

Formulationconsiderations:-

a) **Tonicity and Tonicity-Adjusting Agents:** The tonicity of aopthalmic solution should be adjust correctly(urge a osmotic pressure equal to that of tear fluids, generaly agreed to be equal to 0.9% NaCl) a range of 0.5-2.0% NaCl equvivalency does not cause a marked pain and range of about 0.2-0.7% sholud be acceptable for most persons. Common tonicity adjusting ingridient are:NaCl, Kcl, Buffer salt, dextrose, glycerine, propylene glycol and mannitol.

b) **pHAdjustmentandBuffers:**pHadjustmentisveryimportantaspHaffects:

- Torendertheformulationmorestable
- Thecomfort,safetyandactivityoftheproduct.Eyeirritation→increaseintearfluid secretion→Rapid loss of medication
- Toenhanceaqueoussolubilityofthedrug.

- Toenhancethedrugbioavailability
- To maximize preservative efficacy Ideally every product buffered to a pH of 7.4(The normal physiological pHof tear fluid) If buffersare required, theircapacity is controlledto be as low as possible.
- ToenablethetearstobringthepHoftheeyebacktothephysiologicalrange
- To avoid effect of buffers on tonicity. Examples of buffer vehicles used:-Boric acid vehicle: pH ofslightly below 5-Isotonic phosphate vehicle: pH ranges from 5.9 -8.

c) **Viscosity-ImpartingAgents:**

Polyvinyl alcohol, methylcellulose, hydroxyl propyl methylcellulose, hydroxylethylcellulose and carbomers are generally used in parentral preparation as viscosity imparting agent. They increase the ocular contact time thereby they decrease the drainage rate, increase the mucoadhessiveness and increase drugbioavilability.

d) **Stabilizers&Antioxidants:**

Stabilizers are the ingredients, which makes the preparation to decrease the rate of decomposition of active ingredient. Antioxidants are principle stabilizers added to some opthalmic preparation, primarily those containing epinephrine, and other oxidizable drugs.Example: Sodium bisulphite or metabisulphite are used in concentration up to 0.3% in epinephrine hydrochloride and bitartrate solution.

e) **Surfactants:**

The order of surfactant toxicity is anionic>cationic>>non-ionic. There are several non-ionic surfactant are used in low concentration to add in dispersing steroid in suspensions and to achieve or improve solution clarity. Some of the surfactant which are principally used are sorbiton ether esters of oleic acid (polysorbate or tween 20 and 80).

f) **Preservatives:**

Preservativesareincludedinmultiple-doseeyesolutionsformaintainingtheproduct sterilityduringuse.Preservativesnotincludedinunit-dosepackage.Theuseof preservativesisprohibitedinophthalmicproductsthatareusedattheofeyesurgery because, if sufficient

concentration of the preservative is contacted with the corneal endothelium; the cells can become damaged causing clouding of the cornea and possible loss of vision. The most common organism is Pseudomonas aeruginosa that grow in the cornea and cause loss of vision. Examples:benzalkonium chloride, 0.004% to 0.01%;benzethonium chloride, 0.01%; chlorobutanol,0.5%; phenylmercuric acetate, 0.004%; phenylmercuric nitrite, 0.004%; and, thimerosal, 0.005%to 0.01%.

Formulationofeyedrops:

Ophthalmic solutions are sterile solutions intended for instillation in the eye.In addition to sterility, these dosage forms require the careful consideration of such other pharmaceutical factors as the need for antimicrobial agents, osmolarity, buffering, viscosity, and proper packaging.

Aneyedropformulationcomprisesofthefollowing:

a) Activeingredientstoproducedesiredtherapeuticeffect.
b) Vehicle(AquousorOily).
c) Inertantimicrobialpreservativestopreventmicrobialcontaminationandtomaintainsterility.
d) Inert adjuvants for adjusting tonicity, Viscosity and PH to increase the stability of active ingredients.
e) Suitable container to maintain the preparation in a stable form and provide protection against contamination during preparation, storage and use.
f) Multi dose eye drops are added with an effective antimicrobial preservative system(a single substancecannotbesuccessfullyusedasapreservative inophthalmic solution)thatshould pass the test for efficacy of antimicrobial preservative. Thisensures that the eye drops aresterile and non-contaminated.

FormulationofEyeOintments:

Ophthalmic ointments must be sterile. Like suspensions, ointments can be more difficult to manufacture in sterile form. They can be terminally sterilized, or, alternatively, they must be manufactured from sterile ingredients in an aseptic environment. Filtration through a suitable membrane or dry heat sterilization is often used.

- The ointment base selected for an ophthalmic ointment must be non-irritating to the eye and must permit the diffusion of the active ingredient throughout the secretions bathing the eye.
- Ointment bases utilized for ophthalmics have a melting or softening point close to body temperature.
- Ophthalmicointmentshavealongerocularcontacttimewhencomparedtomanyophthalmic solutions.
- Ointmentbaseissterilizedbyheatandfilteredwhilemoltentoremoveforeignparticulate matter**.**
- It is then placed intoa sterile steam jacketed tomaintain the ointment in amolten stateandexcipients are added.
- One disadvantage to ophthalmicointmentsis the blurred vision that occurs as the ointmentbase melts and spread across the lens.
- Thebaseslike;yellowsoftparaffin,liquidparaffinandwoolfatcanbeusedforthe preparation of eye ointment.

FormulationofEyeLotions:-

Eyelotionsareundilutedaqueoussolutions,appliedtoaneyebath,whichforfirstaid purposes. It is may allow a large volume of fluid to flow quickly over the eye.

Itisiso-osmotictotears,becausecomparedtoeyedrops,lotionscausemuchgreaterdilutionof thelachrymalfluid,hencecausediscomfortifnotadjusted.e.g.Sodiumchloride(NaCl)eyelotion B.P.C.isusedtoremoveforeignsubstancefromtheeye.

Thus these preparations should be very simple as wellas the mostcommon eye lotionconsists ofsterile normal saline. This preparation demonstrate the requirements of an eye lotion which are:

- Sterileaswellasusuallycontaining nopreservative.
- Isotonictolachrymalfluid
- NaturalpH
- Largevolumebutnotgreater than200ml
- Non-irritanttooculartissue.

MethodsofPreparation:

1) PreparationoftheSolution:Theaqueouseyedropsvehiclecontainingsuitablepreservative ,antioxidant ,stabilizer, tonicitymodifier , viscositymodifier,orbuffershouldbe prepared,andaddedwith theactiveingredientandthevehicleto makeupthe volume.
2) Clarification:sinteredglassfiltersormembranefiltershaving0.45-1.2µmporesizes shouldbeused.Theclarified solution is either fillieddirectly intothefinalcontainers whicharesealedbeforeheatsterilisationoristemporarilyfilledintoasuitable containerbeforefiltration.Clarifiedcontainersvehicleisusedtoprepareeyedrop suspensionsfilledintofinalcontainersandsealed beforesterilisation.
3) Sterilisation: Thiscan beachievedby autoclavingat115°Ctemperature for30minutesor 121°Ctemperaturefor15minutes .Filtration into sterile containers through a membrane filter having 0.22µm pore size is also a suitable method for sterililisation.Dry heat sterilisation at 160°C temperature for 2 hours is best suited for non-aqueous preparations such as liquid paraffin eye drops.
4) After sterilisation, the eye drop containers should be covered with a readily breakable seal to distinguish between opened and unopened containers.

Labeling:-

Thelabelshouldinclude:

(1) Thenameofthepharmaceuticalproduct;
(2) Thename(s)oftheactiveingredient(s);InternationalNonproprietaryNames(INN)shouldbe used wherever possible;
(3) The concentration(s) of the active ingredient(s) and the amount orthe volume of preparation inthe container;
(4) Thebatch(lot)numberassignedbythemanufacturer;
(5) Theexpirydate,theutilizationperiod,and,whenrequired,thedateofmanufacture;
(6) Anyspecialstorageconditionsorhandlingprecautionsthatmaybenecessary;
(7) Ifapplicable,theperiodofuseafteropeningthecontainer;
(8) Directionsforuse,warningsandprecautionsthatmaybenecessary;
(9) The name and address of the manufacturer or the person responsible for placing the product onthe market;

(10) If applicable, the name(s) and concentration(s) of antimicrobial agent(s) and/or antioxidant(s) incorporated in the preparation; and
(11) Thestatement"Thispreparationissterile".

Storage:

Ophthalmic preparations should maintain their integrity throughout their shelf-life when stored at the temperature indicated on the label. Special storage recommendations or limitations are indicated in individual monographs.

Containers:

Traditionally, ophthalmic liquid products were packed in glass containers fitted with an eye dropper. Today, glass containers have limited use where product stability or compatibility issues exclude the use of flexible plastic containers made of polyethylene or polypropylene. Most liquid ophthalmicproductsonthemarketarepackagedinplasticcontainersfittedwithnozzlesfrom which, by gentle squeezing, the contents may be delivered as drops.

- Plastic containers have several advantages over the glass-dropper combination such as minimizing the risk of the contents being contaminated with microorganisms by the replacement of the dropper which may have become contaminated by touching the infected eye or any other surfaces. Also, plastic containers are cheap, light in weight, more robust to handle and easier to use than glass-dropper type containers.
- Some plastic materials such as polyethylene can absorb some antimicrobial preservatives(e.g. benzalkonium chloride), or some drugs. They may also leach plasticizers into the product, or printing inks from the label can migrate through the plastic into the product.
- The challenge is to develop a packaging system for preservative-free products that maintains the sterility of the product throughout its shelf-life and during use.
- Unit-dose systems offer the easiest technical solution to this problem but have the disadvantage of higher cost of manufacture and of not being as compact as a multidose product containing equivalent doses.
- An alternative approach is to develop a multidose preservative free system. The container is required to be collapsible, and the suck-back of air, which could contain bacteria, has to be avoided. Containers are being developed that contain a valve mechanism to achieve this
- Plastic containers can also be permeable to water vapor and oxygen over prolonged periodsof storage. This can lead to gradual loss of liquid product or oxidation of an unstable drugover time.
- Polyethylene containers are not able to withstand autoclaving and are usually sterilized by ethylene oxide or by irradiation before being filled aseptically with pre-sterilized product. Polypropylene containers can be autoclaved, but are not as flexible as polyethylene for eyedropper use.

- Semi-solid products have been traditionally packed in collapsible tin tubes. Metal tubes are a potential sourceof metal particles in ophthalmic products, and so the tubes have to becleaned carefully prior to sterilization.
- Collapsible tubes made from laminates of plastic, aluminum foil and paper are good alternative to tin tubes. Laminate tubes fitted with polypropylene caps can be sterilized by autoclaving.

Evaluationofophthalmicpreparations:-

Ophthalmicpreparationsareevaluatedasfollows:

1) **Sterility:** The ophthalmic products should meet the standard requirements. If the ingredients used do not lend themselves to routine sterilization, ingredients that meet the sterility requirements should be used. The container for ophthalmic preparations should be sterilizedat the time of filing and closing. They should be sealed and tamper-proof to maintain their sterility.
2) **Antimicrobial preservatives:** These should be added to multiple-dose containers, unless there are different directions provided in the individual monograph for multiple productwithdrawal, the substance contains a radionuclide with a physical half of less than 24hours,he product itself is sufficiently microbicidal, or the added ingredients meet the requirementsof antimicrobial agent content. Thus, acceptance criteria for the content of antimicrobial preservative in multiple-unit products should be established.
3) **Uniformity of Dosage Units**: This test should be performed for single-dose containers to evaluate the mass of dosage form as well as the content of the drug substance(s) in thedosages form. The test is performed by either content uniformity or weight variation.
4) **Uniformity in Containers:** Semisolid drug products undergo physical separation during manufacturing and /or during the storage period. To ensure the drug product integrity, the uniformity of the finished product at the time of batch release and throughout its shelf-life should be evaluated.
5) **Leachable and Extractables:** The packaging system and the preparation should not undergo any physical or chemical interaction to alter the strength, quality, or purity of the drugproduct. The packaging system should meet the requirements in elastomeric closures for injection, and glass or plastic containers.
6) **Container Closure Integrity:** The packaging system should be closed or sealed to prevent contamination or loss of contents. It should also be tamper-proof. Validation of container integrityshoulddemonstratenopenetrationofmicrobial,chemicalorphysical contaminants.

7) **Viscosity:**The residence time of the product in eyes increases in viscosity;but the diffusionofdrugfromtheformulationintotheeyeisinhibited.Theophthalmicointmentshavea very high viscosity to prolong their residence time in the eyes.
8) **Antioxidant Content:** The content of antioxidants (if added in the drug product) should be established unless oxidative degradation can be detected by another test method such as impurity testing. Acceptance criteria for antioxidant content should also be established based on the levels of antioxidant required to keep the product stable throughout its shelf-life.
9) **ParticleSizeand Particle Size Distribution:**The potential for any changes in the particle sizeof ophthalmic suspensions and emulsions should be evaluated through stability testing. the drop size for ophthalmic drops ranges from 20-70µm.However,the drop size should be controlled and maintained throughout the product shelf-life. Suitable substances should be added to the ophthalmic products to increase their stability, provided they do not cause any harm in the amounts administered and do not interfere with the therapeutic efficacy or responses to the specified assays and tests.

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