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E-Mail :
editor.ijasem@gmail.com
editor@ijasem.org

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Methods for Manufacturing Sterile Dosage Forms

P. KANCHANA, N. NAGA MALLESWARI, G.USHA KIRAN

ABSTRACT:

Patients who are unconscious or otherwise unable to cooperate with oral drug delivery are admitted through the parenteral method.These Medicinal Items Are Another method of medication delivery is through a parenteral formulation.Administration through injection, infusion, or implantation will be required.Injectable pharmaceutical dosage forms are used for medication delivery. Solvents, suspending agents, buffering agents, stabilizers, and antimicrobial preservatives are all examples of the types of excipients used in parenteral preparations.Excipients should not induce toxicity or local irritation, nor should they reduce the stability, bioavailability, safety, or effectiveness of the active ingredients.Parenteral preparation, ocular preparation, and irritant preparation are all examples of sterile products, which are pharmaceutical dosage forms to medicinal substances that are devoid of microorganisms.Ophthalmic medication, including eye drops, eye drops in a bottle, eye ointment, and eye lotion.

KEYWORDS: Parenteral, Sterilization, Administration Route.

I. INTRODUCTION

Parenteral preparations provide a sterile, pyrogen-free alternative to traditional methods of oral dosing.Parenteral comes from the Greek words for "beside" (para) and "intestine" (enterion), therefore it means anything that is administered outside of the digestive system. Subcutaneous, intramuscular, and intravenous are the three most common forms of parenteral administration, although additional routes, such as intracardiac and intraspinal, also exist.[1]Long-acting antipsychotics are sometimes given through intramuscular injection.[2] The device inserted into an intravenous line to provide a steady stream of drugs or fluids. [3] The intravenous

The contaminating bacterium is not present in the preparations. Sterile dosage forms come in both small and big amounts, and are used for things like injectable preparations, irrigation fluids, surgical opening fluids, and dialysis solution. Vaccines, toxoids, and antitoxins are all examples of biological preparations. Due to the close proximity of these attachments to internal bodily fluids or tissues, it is crucial that the preparation be completely sterile. [4]Parenteral dose forms are administered by intramuscular or subcutaneous injection into living tissue. Injectable medications prescribed for parenteral use are prepared in a sterile, pyrogen-free environment.[5]

ROUTEOFPARENTERAL ADMINISTRATION

❖ **Intravenousinjections:-**

Intravenoustheroutes of administration which provide injections orinfusions are administeration directly into the vein.Only the most common parenteral routes employedas hospitals today for the purpose to administrationofdrugs,fluidsand/orelectrolytes.Itis approachableasrapidlyinfusinghighvolumeoffluids . The common indications for use of this routeare:

- Toguaranteedistributionanddeliverywhenhypotensionor shockexists.
- Toimmediatepharmacologicalresponsetoachievethe emergencies.
- Torestorerapidlyfluidandelectrolytebalance.
- To avoid complications forces occur by throughtheotherroutesofadministration.
- To treat serious, life-threatening infections orconditions.
- Chancesofthrombosisarewithorwithoutcomplicating infection at the site of injection orinfusion.
- Theinjectionsaretoxins,microorganisms,particulatematterandair.

Department of PHARMACOLOGY[1,2,3]
NRI College Of Pharmacy,
Pothavarappadu Village, AgiripalliMandal, Krishna Dist,Andhra Pradesh Pin Code:521212

- Theadministrationoffluidsordrugsareuncontrolled andexcessive
- The site of administration are extravasation ofinjectionsandinfusion.[6,7]

❖ **Intramuscular injections:-** Intramuscularthe route of administration by which injection areinjecteddirectlyintothebodythrougharelaxedmuscle.Theroutesareavailableforboththeadministrator and patients particularly as childrens.To provide the route of sustained release of drug toformulated as aqueous, oily solution and suspension.Thisrouteispreferablewhencomparedtosubcutaneous routes when a rapid rate of absorptionis required and over the intravenous route when themedication cannot be administered directly into thevascularcompartment.Althoughthisisaneasyrouteofadministration,precautionsaretakentoavoidtheentryofinjectionstobloodvessels,particularly an artery, which might lead to aninfusion of a toxic agent or toxic vehicle directly toanorganor tissue.[8,9,10,11]

❖ **Subcutaneousinjections:-** Itistheroutethroughwhichinjectionisgivenintotheloosec onnectiveandadiposetissuebeneaththederm.Subcutaneous route is mainly preffered if the drugcannot be administered orally due to various reasonslike inactivation of the drug by the GIT or lack ofabsorptionorifthepatientisunabletoingestmedication(s)bymouthorifself-medicationofparenterals is desired. Compared to the oral route,drug ismorepredictably andrapidly absorbedbythis route butwhen comparedwith intramuscularrouteabsorptionandpredictabilityislessforsubcutaneousroute.TheadministrationofSubcutaneous medications are insulin, vaccines andnarcoticsetc.subcutaneousadministrationarespecial form of Hypodermoclysis,namely the largeamount of fluid into the subcutaneous tissue at thesiteofnotavailableforintravenous.Hypodermoclysis is a special form of subcutaneousadministration,namely,theinfusionoflargeamounts of fluid into the subcutaneous tissues whenintravenoussitesarenotavailable.TheseMedicationsarehighly acidicoralkalinecausingirritation, pain, inflammation and necrosis of tissuescannotberouteofadministration.[12,13]

❖ **Intradermal injection:-**These are given inbetweendermisandepidermis.SkinoftheleftForearmisusuallyselectedforgiveninjection.Gennerally, 0.1 to 0.2 ml of parenteral solution isinjectedbythisroute.Theroutareusedtodiagnosticpurposesandthesensitivityoftheinjectablesfor testing.[8]

❖ **Intra-Arterial injections:-**These injectionarecomparabletointravenousinjectionandsometimestheusedforimmediateeffectinaperipheral area.Theinjectionsareadministereddirectlyintothe artery.

❖ **Intracardiacinjections:-** Theseinjectionsare made into the cardiac muscle or ventricle in anemergencyonlyforexampleasastimulantfollowingcardiac arrest.

❖ **Intrathecalinjections:-** Theseinjectionsaremadeinto subarchnoidspinalanaesthesia.

❖ **Intracisternal injections:-**These injectionsaregivenintothefirstandsecondcervicalvertebrae.Therouteisusedfordiagnosticpurposes.

❖ **Intra-Articularinjections:-** Thesearegiven into the liquid that lubricate the articulatingendsofbonesina joint.

❖ **Intracerebral injections:-**These are giveninto brain. [14]

CLASSIFICATIONOFPARENTERALPREPARATIONS

Classified into various type of Parenteralpreparations

1. Readyforsolutiononinjection.
2. Readyfor Suspensiononinjection.
3. Emulsionappropriateforparenteralrouteof administration.
4. Drysolubleproductisdirectlydissolvedinsolventbeforeitsadministration.
5. Dry insolubleproductsaresharedwithoppositevehiclebefore itsadministration.[15]

ADVANTAGES;

- Quickonsetofaction.
- Suitableforthedrugscannotbeadministeredbyoral route.
- Usedfortheuncooperative,nauseousanduncons ciouspatients.
- Usedfortheemergencysituation.
- Durationofactionwhichareprolongedbymodifying formulation.

DISADVANTAGES;

- Onlyrequiredfortrainedpersonnel.
- Painoninjection.
- ToDifficultarereversephysiologiceffectofdrugs.
- Sensitivityorallergicreactionatsiteofinjection.
- Moreexpensiveandhighcost[16]

GENERAL REQUIREMENT OFPARENTERALPREPARATION

- Sterility
- Freeofpyrogensandtoxins
- Freeofforeignparticles
- Isotonic
- Chemicalpurity[17,18]

FORMULATIONOFPARENTERALS:

1. Activedrug
2. Addedsubstances

- Antimicrobialagent
- Buffer
- Antioxidant
- Tonicityagent
- Chelatingagent
- Complexingagent
- Solublizers

3. Vehicle-Aqueous-Non-aqueous

Active drug :-It is active pharmaceutical ingredient.The properties of the active drug or essential of drugis developing a stable and safe of parenteral dosageform.[19]

Addedsubstances:-

○ **Antimicrobial agent:-**growth of microbesthat kill and slow the added Substance. The sterilityoftheproductismaintainedwithAntimicrobialagent during its shelf life and use. They are requiredinpreparationsintendedformultipledosingthesame container because of the finite probability ofaccidental contamination during repeated use. Theyare also included in some single dose products toprovideadditionalassuranceofproductsterility.Mostcommonlyusedparenteralantimicrobial preservative includes phenylmercuricnitrateandthiomersol0.01%,benzethoniumchlorideandbenzalkoniumchloride,phenolorcresol 0.5%, chlorobutanol 0.5%, methyl paraben,propylparaben.[20,21]

○ **Antioxidant:-**The most of the antioxidantusedinaqueousparenteraltheSaltsofsulfurdioxideareincludingbisulfite,metabisulfiteandsulfite. These antioxidants tomaintain the stabilityof the product which are oxidized and during theshelflifeoftheproduct.Irrespectiveofwhichsaltsisaddedtothesolution,theantioxidantmoietydepends on the final concentration of the compoundand thefinalpHoftheformulation.[22]

○ **Complexing and surface active agent:-** ToIncreasing and maintaining the drug solubility. ForexampleasComplexingagentsorsurfaceactiveagents. The most used for Complexing agents thatarecyclodextrinsisincludingcaptisol.Themostusedforsurfaceactiveagentsarepolyoxyethylenesorbitanmonolaurate(tween20)andpolyoxyethylenesorbitanmonooleate(tween80).[23]

○ **Buffer:-**Buffers are added to a formulationtoadjustthepHinordertooptimizationofsolubilityandstability.Theselectionofbufferconcentration (ionic strength) and buffer species areimportant.Citrateandacetatebuffer,phosphatebuffer.[24]

○ **Chelatingagent:-** Onlyafewextentofchelatingagentsareusedinparenteralproducts.Chelating agentsmay potentin antimicrobial andantioxidantactivity.Disodiumedta,citricacid,tartaric acid and some amino acids also can act aschelatingagents.[25]

○ **Tonicity agents:-**which substance are usedtomaintaintheisotonicity,sothatthepainofinjectionisreduced..Examplesoftonicityagentsare sodium chloride, potassiumchloride,dextrose,mannitol,sorbitoletc.

○ **Suspending agents:-**The formulation areadded to the excipientsin order to improving thestabilityoftheproductbypreventingthesedimentation of the particles.They are mostly usedin injectable suspensions. Gelatin and PVP are someexamples.

○ **Emulsifyingagents:-** Emulsifyingagentsareaddedtoinjectableemulsionsinordertoincreasingthe stability of the PRODUCT. They areused to prevent separation of two phases. Examplesofemulsifyingagentsaresoap, SLSetc.

VEHICLES

Vehicles are the liquid phase used in formulation ofparenterals.Theyare oftwotypes:

Aqueousvehicle

The pyrogen test or bacterial endotoxin test wereperformedforvehiclesforaqueousinjections.Aqueousvehiclesusedforthepurposeofformulationofsmallvolumeparenteralsare:

- **Water for Injection (WFI), USP:-** Waterforinjectionishighlypurifiedwaterwhichissubsequently sterilized and used as vehicle for thepurposeofinjectablepreparation.Thewaterforinjection at PH5.0 to 7.0. The USP requirement fortotal solids not more than 10 parts per million. TheReverseosmosisanddistillationpreparationareused in water for injection. It chemically resistanttankforstoredinlessthan24hrsatroomtemperatureorforlongerperiodatspecifictemperature.ItshouldmeetUSP pyrogentest.
- **BacteriostaticWaterforInjection(BWFI):-**to make the parenteral solutions are usedforbacteriostaticwaterforinjectionwhicharepre

paredundermicroorganismandnotterminally

sterilization. It should be contain any bacteriostaticagentsthatcontainersof30mlor less.

- **SterileWaterforInjection(SWFI),USP:-** sterilearewaterforirrigationitusedforsurgical incision, wishing wounds and body tissues.TheMultipledosecontainersmostlyusedforno texceeding 30ml. the suitable contains one or morebacteriostaticagents.[26,27,28]

Non-Aqueous:

The fixed oil is the important group of non-aqueousvehicles.Theoilsareusedforcornoil,cottonse edoil, peanut oil and sesame oil. Fixed oilsusedforvehiclesascertainhormone(eg.Progester one, testosterone, deoxycorticosterone) andvitamin(eg.Vitamink,VitaminE)preparations.[2 9]

PROCESSOFPARENTERALPREPARATION

Thestepsareinvolvedintheprocessofparenteralprepar ation:

a) Cleaningandwashingofcontainersandclosures.
b) Preparationofsolutions
c) Sterilization(Filtration).
d) Fillingandsealing
e) PackagingandLabelling.

- **Cleaning and washing of containers andclosures:**The vials are cleaned by soaked in to thedetergentsolutionatovernighttoremovethestickin gparticlesandgrease.andcompletelyremoved for three to four times till the soap solutionis washed with tap water.Toremoved the surface ofalkalinitybyusing1.0%hydrochloricacidandwashe d with again tap water. finally with de-ionizedwateranddistilledwatertosterilizationfor4hrs under200˚C.using1.0%detergentsolutionareboiled with 30 minutes for the Rubber closures andfree from detergent to washed with tap water. Boilwith 1.0%sodium carbonate and wash again. Washthreetofourtimeswithpyrogenfreewater.Sterili zedbyautoclaveat115˚Cfor30minutes.

- **Preparation of solution:** Dissolve the APIinwaterforinjectionwithcontinuouslystirring.Af tercompletelydissolvingthedrug,otherexcipients are added one by one and stirred untildissolved. The pH isadjusted tothe required rangeby using buffering agents like sodium hydroxide andhydrochloric acid.To Make up the volume and mixwith water for injection. The pH is again adjusted ifnecessary[29]

- **Sterilization:**These sterilization processbywhichallviablemicrobesareremovedorkil led.Sterilization is all removal of contaminatingagents fromasurface,apieceofapparatus,foodandbiologic alculturemedium.Thisisvariousfromdisinfecti ons, where only microorganisms that cancausediseaseareremovedbyadisinfectant.In generallyanyinstrumentswhichenteranalready sterilepartofthebodymustbesterilized.Thisequi pment include such as scalpels and hypodermicneedles. Autoclave is the most importantmethod tothesterilization.Whiletherearesomeplasticsd evise that could not remain dimensionally steadyunder autoclave temperature are sterilized by othermethodlikegassterilizationandradiationst erilization.

Variousmethodsofsterilization

1. **Autoclavesterilization:-** autoclavesterilizationareusually a pressurized steamlevel of autoclaveoperatesat121cforat least15min.
2. **Radiationsterilization:-** medicaldevicesareused for this method. That can withstand the attackofgammaraysbombardment.TheRadiationste rilization is used for the polymers are sensitive toheatmoistureandethyleneoxide.
3. **Gassterilization:-** sterilantusedforethyleneoxide itisnontoxic to most plastic. Ethyleneoxidesterilization is used for most of the plasticsyringeandneedles.

Theprocess(thermaland chemical)aredesignedto destroyoreliminatemicro-biologiccontaminantspresent ina product.

1. **Thermalmethods**

❖ Mostcommon,cost-effectiveandrapidmeansofsterilization

❖ Lethaleffectivenessofheatonmicroorganis ms depends upon the degree of heat ,theexposure period,and themoisturepresent.

❖ To the range of sterilizing temperature andtimerequiredtoproduceaeffectofinverselypropo rtionaltothe temperature.

❖ Thesemethodsareeffectedatlowertempera tures in the presence of moisture.**Thermal methods of sterilization may be dividedinto:**

1. Dryheat
2. Moistheat
3. Radiation
4. Filtration

5. Physicalcleaning

2. Chemical method: Chemical methods areusedforsterilization.Heatingprovidesaremostrel iable way to transmissible agents it is not alwaysappropriatebecausetheheatsensitivematerial saredamaged such as biological materials, fiber optics,electronicsandmanyplastics.

a. **Ethylene oxide:** (EO or EtO) Commonly used forsterilizedthataresensitivetotemperaturethegreater than 60°C.The treatment of ethylene oxideare carried out between 30°C and 60°C with relativehumidity above 30% and gas concentration between200 and 800 mg/land generallyfor2 hours.

b. **Nitrogendioxide:**(NO2)Usedforrangeofmicroo rganismareincludingsuchascommonbacteria,viruse sandspores.

c. **Ozone**: Used for industrial sterilization by waterand air. It has benefit of beingable to oxidize mostorganicmatter.

Applicationsofsterilization

- Sterile product may be used for electrons andgammaraysbycontinuousprocess.
- Vitamins, antibiotics and hormones in dry statehave been successfully sterilized by radiation.

II. CONCLUSION:

The preferred method of administration for unconscious patients is the parenteral one, since it ensures complete medication delivery and high bioavailability. We followed the current good manufacturing practice (cGMP) guidelines for every step of the manufacturing process, from raw material procurement through final product labeling and stability testing.

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