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A Review on Formulation and Evaluation of Parenteral Dosage forms

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ABSTRACT

The present study will outline the types, formulation and evaluation tests / quality control tests of the parenteral dosage forms. The parenteral routes of drug administration are used for quick action. It is majorly preferred when patient is uncooperative, unconscious, or not capable of administering oral medication. Parenterals must be sterile, Pyrogen free. Drugs for intravenous injection, sterile water for irrigation and ophthalmic preparations must meet this criteria. In addition other dosage forms might be labeled as sterile, for instance an ointment to a puncture wound or skin abrasion. It is well recognized that the advantages of parenteral injections are immediate systemic drug availability and rapid onset of action.

Key Words: Quality control, injectable, adsorption , Parenterals, Implants.

INTRODUCTION

The word parenteral was derived from the two Greek words “para” and “enteron” means other than the intestine. Parenterals are defined as the preparations intented for injection through the skin [or] other internal body compartments [or] other external boundary tissues. Rather than through the alimentary canal.So that the active substances [or] therapeutic agents can be administered directly into the blood stream,Organ [or] Tissue. Parenterals are sterile products of therapeutics agents that are free of viable microorganisms. In nowadays healthcare system, the major component of therapy for hospitalized patient is parenteral products, because of their high therapeutic activity, more bioavailability, and quick onset of action. The parenteral routes has abundances of advantages for patients who has less compliance in oral route [or] who require rapid onset of action [or] incase of unconscious patients. Bed ridden patients are totally dependent on parenteral nutrition like fluids, electrolytes.

CLASSIFICATION OF PARENTRALS:

1. Based on type of packaging:
   a. Single dose unit : Ampoules, Infusions Prefilled disposable syringes.
   b. Multi dose unit: Multiple dose vials
2. Based on fill volume :
   a. Small volume parenterals: Volume less than 100ml
   b. Large volume parenterals: Volume more than 100ml

ROTUES OF DRUG ADMINISTRATION OF PARENTERAL PRODUCTS:
PRIMARY PARENTERAL ROUTES:

1) **Intravenous/ Intravenous injection**: The drug is directly administered into the veins directly enters into blood stream, hence shows 100% bioavailability. Parenterals ranging from 1ml to 100ml can be injected. The solutions should be isotonic. Ex: All types of drugs.
2) **Intramuscular injection/ Route:** The drug is injected into muscular tissues. The muscles of shoulder, thigh [or] buttock are usually selected .volume ranging 0.5 to 2ml can be administered by the route. Ex. Nearly all drug classes.
3) **Subcutaneous injection/Route:** In subcutaneous administration the drug is injected into the subcutaneous tissue under the skin. The volume ranging 0.52 to 2ml can be administered through subcutaneous route. Ex. Insulin vaccine.

OTHER PARENTERAL ROUTES:

1) **Intra-dermal Route:** In this Route the drug is administered in between the layers of the skin like dermis and epidermis. Generally very small volume 0.1 to 0.2ml of drug can be injected through this route. Ex. Local anesthetics.
2) **Intra-arterial Route:** The drug administered directly into the arteries the volume ranging 2ml to 20ml can be administered through Intra-atreal Route. Ex. Antineoplastics, Antibiotics.
3) **Intrathecal/ Intraspinal Route:** In this Route the drug administered directly into the spinal canal. The volume ranging 1-4ml can be administered through these Routes. Ex. Neurolytics, analgesic.
4) **Intraepidural Routes**: The drug administered into the epidural space near the spinal column volume ranging 6-30ml can be administered. Ex. Narcotics , Steroids.
5) **Intra-articular Routes:** The drug administered directly into a joint usually for a local delivery, volume ranging 2-20ml can be administered. ex: steroids, Local
6) **Intrapleural Route**: The drug is administered directly into the pleural cavity [or] a lung. Volume ranging 2-30ml can be administered. Ex. Local anesthetic, chemotherapeutic agents.

PARENTERAL FORMULATIONS:

Parenteral formulations are three types

1) Parenteral solutions.
2) Parenteral suspensions.
3) Parenteral emulsions.

PARENTERAL SOLUTIONS:

The simplest and most convenient form of drug administration of parenteral product is an isotonic aqueous solution, which has pH similar to that of pH of the human blood(pH 7.4). parenteral solutions includes large volume parenterals (LVP), small volume parenterals(SVP), irrigation solutions. Infusion fluids are aqueous solutions given in large volumes than normally administered intravenous injections.

There are three types of vehicles are used for the preparation of solutions

1) Aqueous vehicle: Ex. Sodium chloride injection, ringers injection.
2) Water miscible vehicles: Ex. Ethyl glycol
3) Non aqueous vehicles: Ex. Fixed oils, cottonseed oil, corn oil.

There are many USP approved marketed formulations used widely for electrolytes replacement.

Table.1: USP approved marketed parenteral solutions.

Parenteral solution	Marketed formulation
Large volume parenteral	0.9% sodium chloride injection., USP 5% sodium chloride injection 5% dextrose injection, USP 10% dextrose injection, USP
Irrigation solutions	0.9% sodium chloride irrigation Tis-u-sol solution pentalyte irrigation 1.5 % glycerine irrigation, USP

PARENTERAL SUSPENSIONS:

Parenteral suspensions are useful dosage forms for administering the drug which are insoluble or poorly soluble in vehicles and not able to administer as solutions. In parenteral suspensions the drug is dispersed as finely insoluble particles in the aqueous or oil phases. The large surface area of dispersed drug particles ensures higher solubility which leads to high absorption and bioavailability. The suspension produce a sustain release than compare to parenteral solutions. Some of the problems associated with suspensions are difficulty in formulation, stabilization of suspension.

Some of the official parenteral suspensions:

1) Ampicillin suspension USP' 2009
2) Procaine penicillin suspension IP' 96

PARENTERAL EMULSIONS:

Parenteral emulsions are the biphasic liquid dosage form in which two immiscible liquids, one of which is dispersed as fine globules throughout the other phase. Parenteral emulsions are generally used in administration of total parenteral nutrition(TPN). Total parenteral nutrition is the practice of feeding patients who are unable to get their nutrition through eating, mainly for

Commercially available emulsions are

1) Intralipid 10 %
2) Lipofundin
3) Lipofundin and liposyn

ADVANTAGES OF PARENTERSLS:

- Onset of action id faster hence it is suitable for emergency.
- Drugs which are unsuitable to administer in GIT
- Drugs which are not absorbed orally can be administered through parenteral route
- Bioavailability is high

DISADVANTAGES OF PARENTERALS:

- Inducing pain during administration
- Drug return is impossible
- Parenterals require aseptic conditions
- Self administration is not possible
- Cause local tissue injury
- Parenterals are expensive

FORMULATION OF PARENTERALS:

1) THERAPEUTIC AGENT:
   Therapeutic agent is a drug or a chemical compound which is responsible for the therapeutic action or pharmacological action.

EXCIPIENTS:

2) VEHICLES OR SOLVENT SYSTEMS:
   a. Aqueous vehicles:
      Aqueous vehicles are officially recognized to which the drug is added at the time of the administration.
      Ex. Sodium chloride injection
      Water for injection
   b. Non aqueous vehicles:
      Non aqueous vehicles are fixed oils. According to USP specifications fixed oils should be of vegetable origin so that they can be metabolized in the body.
      Ex. Cottonseed oil
      Corn oil
3) ANTIMICRONIAL AGENTS:
   Antimicrobial agents in bacteriostatic concentration must be included in the formulation of products packaged in multi-dose vials
   Ex. 1.benzyl alcohol – 0.5 to 10 %
   2. butylparaben – 0.015%
   3. chlorobutanol – 0.25 to 0.5 %
4) SOLUBILIZERS:
   Solubilizers are used to increase the solubility of the drug which are slightly soluble in water.
   Ex. Tweens, polysorbates
5) EMULSIFIERS:
   Emulsifiers are used in the parenteral emulsion to form the emulsion and to maintain stability of the emulsion.
   Ex. Lecithin, sodium phosphates.
6) BUFFERS:
   The degradation of the preparation which is due to the change in the pH be prevented by adding a suitable buffer.
   Ex. Acetic acid – 0.22 %
   Citric acid – 5 %
   Sodium acetate – 0.8%
   Sodium carbonate – 0.06%
7) TONICITY MODIFIERS:

Compounds contributing to the isotonicity of product reduce the pain in areas with nerve endings. Tonicity modifiers maintain the osmotic pressure of the preparation as the osmotic pressure of the human blood
Ex. Sodium chloride- 0.9%
Sorbitol – 2%
Lactose – 0.4 to 2.5%

8) SUSPENDING AGENTS:
Suspending agents are used in the parenteral suspensions to suspend the fine solid particles throughout the liquid phage
Ex. Gelatin -2%
Methyl cellulose- 0.3 to 1.5%
Polyethylene glycol – 2.7 to 3%

9) CHELATING AGENTS:
Chelating agents such as EDTA, and its salts, potassium and its salts are used in formulation to chelate metallic ions if present.
Ex. Edetate sodium – 0.000386 to 0.05%
Edetate calcium disodium – 0.04%

10) ANTIOXIDANTS:
Anti-oxidants are added to the formulation to prevent the oxidation of the product.
Ex. Ascorbic acid – 0.02 to 0.1%
Sodium bisulfite – 0.1 to 0.5 %
Thiourea – 0.005%

11) INERT GAS:
Inert gas is used in the formulation on replace the oxygen and reduces the chance of oxidation
Ex. Argon.

QUALITY CONTROL TESTS FOR PARENTERALS:
The inprocess quality control tests include: 1.Leakage test.
2. Clarity test.
Quality control test for finished products include: 1.Pyrogen test
2. sterility test

1) LEAKAGE TEST

Ampoules are intended to provide a hermetically sealed container for a single dose of a product, thereby completely passing any interchange between the contents of the sealed ampoules and its environment. Should capillary pores or tiny cracks be present, micro organisms or other dangerous contaminants may enter the ampoule or the contents may leak to the outside spoil the appearance of the package.

Leakage test is employed to test the package integrity. Package integrity reflects its capability to keep the product in and to keep potential contaminant out. Leakage test can be done by dye bath test

DYE BATH TEST:

The test container is immersed in a dye bath vacuum and pressure is applied for some time. The container is removed from the dye bath and washed. The container is then inspected for the presence of dye either visually or by UV spectroscopic method. The dye test can be optimized by use of surfactant and or a low viscosity fluid in the dye solution to increase the capillary migration through the pores.

2) CLARITY TEST:

Clarity test is carried out to check the particulate matter in the sample. In this test the transparent particle or white particles are observed against the black background and the black or dark particles are observed against the white backgrounds.

3) PYROGEN TEST:

PYROGENS: Pyrogens are products of metabolism of micro-organisms. Pyrogens are the fever inducing agent which can increase the body temperature morethan the normal temperature. Water is used in parenteral and irrigation solutions should be free from pyrogens. To achieve this, proper control must be maintained in the preparation and storage of product.

SHAM TEST:
Intravenous injection of sterile pyrogen free saline solution to exclude any animal showing an unusual respone to the trauma[shock] of injection. Any animal showing a temperature variation greater than 0.6℃ is not used in them a intest. All glassware, syringes and needles must be pyrogen free by heating at 250℃ for not less than 30min. Warm the pyrogen free solution up to 38.5℃.

LIMULUS AMEBOCYTE LYCATE (LAL) TEST:
LAL test is an in-vitro test method for pyrogens has been developed utilizing the gelling property of the lysate of the amebocytes of "limulus polyphemus" (the horse shoe crab). Other species of horse crab namely tachyppleus gigas, tachypleus tridentantus and carsinocropius rotundicauda.

The addition of a solution containing endotoxins to a solution of the lysate produce turbidity, precipitation, or gelation of the mixture. However addition of chromogenic substances to a solution of lysate results in the development of colour due to release of chromophore from the substrate upon activation by the endotoxin present in the solution. According to BP there are three techniques for this test.

1. The gel-sol clot technique which is based on gel formation.
2. The turbidimetric technique based upon the development of turbidity after cleavage of an endogenous substrate.
3. chromogenic technique based upon the development of colour after cleavage of a synthetic peptide- chromogen.
4) STERILITY TEST:

All products labeled "sterile" must pass the sterility test, having been subjected to an effective process of sterilization. The test for sterility is intended for detecting the presence of viable form of microbes in the pharmacopoeial preparations. Sterility testing of the products is carried out either by the membrane filtration method or direct inoculation method.

MEDIA TO BE USED IN THE STERILITY TESTS:
Sterility test media should be such that it supports growth of aerobic and anaerobic bacteria and fungi. Fluid thioglycolate medium (FTM) is the primarily intended for the culture of anaerobic bacteria, however it also supports the growth of aerobic bacteria. Soya bean casein medium is suitable for the culture of both fungi and aerobic bacteria.

MEMBRANE FILTRATION METHOD:
A membrane has a nominal pore size not greater than 0.45 microns and diameter of approximately 50 mm is used. This method basically involves filtration of sample through a membrane filter. The filtration is assisted under vacuum, after filtration the membrane is cut into two equal halves. One half is placed in the test tube containing fluid thioglycolate medium and second half is placed in the test tube containing soya bean casein medium. Incubate the media for not less than 14 days. After incubation if the preparation contains any microbes the microbes will grow by using the media and appear as the colonies tested by using bacterial strains. If the preparation is free from any viable microbes there is no colonies formation, so no strains are formed.

DIRFECT INOCULATION METHOD:
Apart from testing oily solutions, creams, ointments, and solid parenteral products is tested for sterility by direct inoculation method. Direct inoculation method is particularly for surgical devices, surgical dressing and sutures in case where membrane filtration method appears difficulty to perform. It involves a direct inoculation of required volume of a sample in two test tubes containing culture media that is one is fluid thioglycolate medium and second one is soya bean casein medium. Volume of preparation under examination is not more than 10%. After inoculation incubate the media for not less than 14 days. After the incubation the media is tested for the presence of microbes by using the bacterial strains. If the preparation contain microbes the microbes grown in the incubation period and formed as colonies and appeared as colour by reacting with strains. If the preparation is free from microbes no colour is observed.

CONCLUSION

It was concluded that parenteral route of drug administration is most effective route for the delivery of the active pharmaceutical substances with narrow therapeutic index. The present article describes the types, formulation and quality control tests for parenterals. Parenteral preparation are the pyrogen free liquids, which are manufactured and stored according to CGMP guidelines. Quality is not an accident this is result of an intelligent effort. To get a product of maximum quality, quality control tests for pharmaceuticals are barely needed. So the cost mentioned in pharmacopoeias for the parenteral preparation must strictly be performed to ensure the proper quality as well a secure human health.

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