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A Review on Sterile Dosage Form

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ABSTRACT:
The route of parenteral administration is given into quick onset of actionis unconscious and uncooperation emergencies patient to admit not able to allow oral medication.These Pharmaceutical product are Parenteral preparation is further other route of drug administration.To be needed for injection and infusion or implantation with route of administration.The pharmaceutical dosage forms for conveying of a drug areinjected in to the body. The excipient should be parenteral preparation are such as solvent, suspendingagents and buffering agents areprepared to isotonic blood, stabilizers and antimicrobial preservative.When used for excipients should not adversely affect of stability, bioavailability, safetyand efficacy of the activesubstances as cause toxicity or local irritation.The sterile product are pharmaceutical dosage form to therapeutic agents that are free of microorganism are included in parenteral preparation, ophthalmic preparation and irritating preparation.Ophthalmic preparation such as eye lotion, eye ointment,eye suspension and eye drop.

KEYWORDS: Route of Administration, Parenteral, Sterilization.

I. INTRODUCTION

The parenteral preparation are pyrogen free and sterile dosage form to through other route of oral administration.[1]The term of parenteral is derived from the Greek Word PARA (beside) and ENTERON (Intestine),which together indicate something done outside of the intestine and not by way of the alimentary tract. They are three route of parenteral administration: subcutaneous, intramuscular and intravenous they are other route of administration such as intracardic and intraspinal.[2]Some medication for antipsychotics is long- acting are administered in to the intramuscular injection.[3] The used for IV Infusion to deliver the continuous medications or fluids. [4] The parenteral preparations are free from the contaminating microorganism. The small and large volumes of sterile dosage form are injectable preparation, irrigation and fluid to be needed for body wounds, surgical opening and dialysis solution. Biologic preparations are included that vaccine, toxoid and antitoxin. The sterility of the preparation is essential, easily infection for arise because these placed are attached in to the internal body fluids or tissues. [5]Parenteral dosage forms of a drug are directly injected into body tissue through further other route of administration. The parenterally administration to be needed for injections are sterile and pyrogen free preparation.[6]

ROUTE OF PARENTERAL ADMINISTRATION

❖ **Intravenous injections:-**Intravenous the routes of administration which provide injections or infusions are administeration directly into the vein. Only the most common parenteral routes employed as hospitals today for the purpose to administration of drugs, fluids and/or electrolytes. It is approachable as rapidly infusing high volume of fluids. The common indications for use of this route are:

- To guarantee distribution and delivery when hypotension or shock exists.
- To immediate pharmacological response to achieve the emergencies.
- To restore rapidly fluid and electrolyte balance.
- To avoid complications forces occur by through the other routes of administration.
- To treat serious, life-threatening infections or conditions.

➢ Chances of thrombosis are with or without complicating infection at the site of injection or infusion.
➢ The injections are toxins, microorganisms, particulate matter and air.

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- The administration of fluids or drugs are uncontrolled and excessive
- The site of administration are extravasation of injections and infusion.[7]

❖ **Intramuscular injections:-** Intramuscular the route of administration by which injection are injected directly into the body through a relaxed muscle. The routes are available for both the administrator and patients particularly as childrens. To provide the route of sustained release of drug to formulated as aqueous, oily solution and suspension. This route is preferable when compared to subcutaneous routes when a rapid rate of absorption is required and over the intravenous route when the medication cannot be administered directly into the vascular compartment. Although this is an easy route of administration, precautions are taken to avoid the entry of injections to blood vessels,particularly an artery, which might lead to an infusion of a toxic agent or toxic vehicle directly to an organ or tissue. [8,9,10,11]

❖ **Subcutaneous injections:-**It is the route through which injection is given into the loose connective and adipose tissue beneath the derm. Subcutaneous route is mainly preffered if the drug cannot be administered orally due to various reasons like inactivation of the drug by the GIT or lack of absorption or if the patient is unable to ingest medication(s) by mouth or if self-medication of parenterals is desired. Compared to the oral route, drug is more predictably and rapidly absorbed by this route but when compared with intramuscular route absorption and predictability is less for subcutaneous route. The administration of Subcutaneous medications are insulin, vaccines and narcotics etc. subcutaneous administration are special form of Hypodermoclysis,namely the large amount of fluid into the subcutaneous tissue at the site of not available for intravenous. Hypodermoclysis is a special form of subcutaneous administration, namely, the infusion of large amounts of fluid into the subcutaneous tissues when intravenous sites are not available. These Medications are highly acidic or alkaline causing irritation, pain, inflammation and necrosis of tissues cannot be route of administration. [12,13]

❖ **Intradermal injection:-** These are given in between dermis and epidermis. Skin of the left Forearm is usually selected for given injection. Gennerally, 0.1 to 0.2 ml of parenteral solution is injected by this route.The route are used to diagnostic purposes and the sensitivity of the injectables for testing.[8]

❖ **Intra-Arterial injections:-**These injection are comparable to intravenous injection and sometimes the used for immediate effect in a peripheral area. The injections are administered directly in to the artery.

❖ **Intracardiac injections:-**These injections are made into the cardiac muscle or ventricle in an emergency only for example as a stimulant following cardiac arrest.

❖ **Intrathecal injections:-**These injections are made into subarchnoid spinal anaesthesia.

❖ **Intracisternal injections:-**These injections are given into the first and second cervical vertebrae. The route is used for diagnostic purposes.

❖ **Intra-Articular injections:-**These are given into the liquid that lubricate the articulating ends of bones in a joint.

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

CLASSIFICATION OF PARENTERAL PREPARATIONS

Classified into various type of Parenteral preparations

1. Ready for solution on injection.
2. Ready for Suspension on injection.
3. Emulsion appropriate for parenteral route of administration.
4. Dry soluble product is directly dissolved in solvent before its administration.
5. Dry insoluble products are shared with opposite vehicle before its administration.[15]

ADVANTAGES;

- Quick onset of action.
- Suitable for the drugs cannot be administered by oral route.
- Used for the uncooperative, nauseous and unconscious patients.
- Used for the emergency situation.
- Duration of action which are prolonged by modifying formulation.

DISADVANTAGES;

- Only required for trained personnel.
- Pain on injection.
- To Difficult are reverse physiologic effect of drugs.
- Sensitivity or allergic reaction at site of injection.
- More expensive and high cost[16]

GENERAL REQUIREMENT OF PARENTERAL PREPARATION

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- Sterility
- Free of pyrogens and toxins
- Free of foreign particles
- Isotonic
- Chemical purity[17,18]

FORMULATION OF PARENTERALS:

1. Active drug
2. Added substances

- Antimicrobial agent
- Buffer
- Antioxidant
- Tonicity agent
- Chelating agent
- Complexing agent
- Solublizers

3.Vehicle - Aqueous - Non-aqueous

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

Added substances:-

- **Antimicrobial agent:-**growth of microbes that kill and slow the added Substance. The sterility of the product is maintained with Antimicrobial agent during its shelf life and use. They are required in preparations intended for multiple dosing the same container because of the finite probability of accidental contamination during repeated use. They are also included in some single dose products to provide additional assurance of product sterility.Most commonly used parenteral antimicrobial preservative includes phenylmercuric nitrate and thiomersol 0.01%, benzethonium chloride and benzalkonium chloride, phenol or cresol 0.5%, chlorobutanol 0.5%, methyl paraben, propyl paraben.[20,21]
- **Antioxidant:-**The most of the antioxidant used in aqueous parenteral the Salts of sulfur dioxide are including bisulfite, metabisulfite and sulfite. These antioxidants to maintain the stability of the product which are oxidized and during the shelf life of the product. Irrespective of which salts is added to the solution, the antioxidant moiety depends on the final concentration of the compound and the final pH of the formulation.[22]
- **Complexing and surface active agent:-**To Increasing and maintaining the drug solubility. For example as Complexing agents or surface active agents. The most used for Complexing agents that are cyclodextrins is including captisol. The mostused for surface active agents are polyoxyethylenesorbitanmonolaurate(tween20) and polyoxyethylenesorbitanmonooleate (tween 80).[23]
- **Buffer:-**Buffers are added to a formulation to adjust the pH in order to optimization of solubility and stability.The selection of buffer concentration (ionic strength) and buffer species are important. Citrate and acetate buffer, phosphate buffer.[24]
- **Chelating agent:-**Only a few extent of chelating agents are used in parenteral products. Chelating agents may potent in antimicrobial and antioxidant activity. Disodium edta, citric acid, tartaric acid and some amino acids also can act as chelating agents.[25]
- **Tonicity agents:-**which substance are used to maintain the isotonicity, so that the painof injection is reduced.. Examples of tonicity agents are sodium chloride, potassium chloride,dextrose,mannitol,sorbitol etc.
- **Suspending agents:-** The formulation are added to the excipients in order to improving the stability of the product by preventing the sedimentation of the particles.They are mostly used in injectable suspensions. Gelatin and PVP are some examples.
- **Emulsifying agents:-**Emulsifying agents are added to injectable emulsions in order to increasingthe stability of the PRODUCT. They are used to prevent separation of two phases. Examples of emulsifying agents are soap, SLS etc.

VEHICLES

Vehicles are the liquid phase used in formulation of parenterals. They are of two types:

Aqueous vehicle

The pyrogen test or bacterial endotoxin test were performed for vehicles for aqueous injections. Aqueous vehicles used for the purpose of formulation of small volume parenterals are:

- **Water for Injection (WFI), USP:-**Water for injection is highly purified water which is subsequently sterilized and used as vehicle for the purpose of injectable preparation. The water for injection at PH5.0 to 7.0. The USP requirement for total solids not more than 10 parts per million. The Reverse osmosis and distillation preparation are used in water for injection. It chemically resistant tank for stored in less than 24hrs at room temperature or for longer period at specific temperature. It should meet USP pyrogen test.
- **Bacteriostatic Water for Injection (BWFI):-**to make the parenteral solutions are used for bacteriostatic water for injection which are prepared under microorganism and not terminally

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sterilization. It should be contain any bacteriostatic agents that containers of 30ml or less.

- **Sterile Water for Injection (SWFI), USP:-**sterile are water for irrigation it used for surgical incision, wishing wounds and body tissues. TheMultiple dose containers mostly used for not exceeding 30ml. the suitable contains one or more bacteriostatic agents.[26,27,28]

Non-Aqueous :

The fixed oil is the important group of non- aqueous vehicles. The oils are used for corn oil, cottonseedoil, peanut oil and sesame oil. Fixed oils used for vehicles as certain hormone (eg. Progesterone, testosterone, deoxycorticosterone) and vitamin (eg. Vitamin k, VitaminE) preparations.[29]

PROCESS OF PARENTERAL PREPARATION

The steps are involved in the process of parenteral preparation:

a) Cleaning and washing of containers and closures.
b) Preparation of solutions
c) Sterilization (Filtration).
d) Filling and sealing
e) Packaging and Labelling.

- **Cleaning and washing of containers and closures:**The vials are cleaned by soaked in to the detergent solution at overnight to remove the sticking particles and grease. and completely removed for three to four times till the soap solution is washed with tap water.To removed the surface of alkalinity by using 1.0% hydrochloric acid and washed with again tap water. finally with de-ionized water and distilled water to sterilization for 4hrs under 200˚C. using 1.0% detergent solution are boiled with 30 minutes for the Rubber closures and free from detergent to washed with tap water. Boil with 1.0%sodium carbonate and wash again. Wash three to four times with pyrogen free water. Sterilized by autoclave at 115˚C for 30minutes.

- **Preparation of solution:** Dissolve the API in water for injection with continuously stirring. After completely dissolving thedrug, other excipients are added one by one and stirred until dissolved. The pH is adjusted tothe required range by using buffering agents like sodium hydroxide and hydrochloric acid.To Make up the volume and mix with water for injection. The pH is again adjusted if necessary[30]

- **Sterilization:**These sterilization processby which all viable microbes are removed or killed.Sterilization is all removal of contaminating agents from a surface, a piece of apparatus, food and biologicalculture medium. This is various from disinfections, where only microorganisms that can cause disease are removed by a disinfectant. In generally any instruments which enter an already sterile part of the body must be sterilized. This equipment include such as scalpels and hypodermic needles. Autoclave is the most important method to the sterilization. While there are some plastics devise that could not remain dimensionally steady under autoclave temperature are sterilized by other method like gas sterilization and radiation sterilization.

Various methods of sterilization

1.Autoclave sterilization:-autoclave sterilization areusually a pressurized steam level of autoclave operates at 121c for at least 15 min.

2. Radiation sterilization:- medical devices are used for this method. That can withstand the attack ofgamma rays bombardment.The Radiation sterilization is used for the polymers are sensitive to heatmoisture and ethylene oxide.

3. Gas sterilization:-sterilant used for ethylene oxide it isnontoxic to most plastic. Ethylene oxidesterilization is used for most of the plastic syringe and needles.[31]

The process (thermal and chemical) are designed to destroy or eliminate micro-biologic contaminants present in a product.

1. Thermal methods

❖ Most common, cost-effective and rapid means of sterilization

❖ Lethal effectiveness of heat on microorganisms depends upon the degree of heat , the exposure period, and the moisture present.

❖ To the range of sterilizing temperature and time required to produce a effect of inversely proportional to the temperature.

❖ These methods are effected at lower temperatures in the presence of moisture.[32]

Thermal methods of sterilization may be divided into:

1. Dry heat
2. Moist heat
3. Radiation
4. Filtration
5. Physical cleaning [33]

2. Chemical method: Chemical methods are used for sterilization. Heating provides are most reliable way to transmissible agents it is not always appropriate because the heat sensitive materials are

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damaged such as biological materials, fiber optics, electronics and many plastics.

a. **Ethylene oxide:** (EO or EtO) Commonly used for sterilized that are sensitive to temperature the greater than 60°C.The treatment of ethylene oxide are carried out between 30°C and 60°C with relative humidity above 30% and gas concentration between 200 and 800 mg/l and generally for 2 hours.

b. **Nitrogen dioxide:**(NO2) Used for range of microorganism are including such as common bacteria, viruses and spores.

c. **Ozone**: Used for industrial sterilization by water and air. It has benefit of being able to oxidize most organic matter.

Applications of sterilization

- Sterile product may be used for electrons and gamma rays by continuous process.
- Vitamins, antibiotics and hormones in dry state have been successfully sterilized by radiation. [34]

PACKAGING OF PARENTERALS:

Types of containers;

A. Glass container

B. Plastic container

Glass:-TheGlass container materials are choice of the most SVIs. It is composed principally of silicon dioxide with the amounts of other oxides such as sodium, potassium, calcium, magnesium, aluminum, boron, and iron.

Types:-

The USP provides a classification of glass:

• Type I, a borosilicate glass;

• Type II, a soda-lime treated glass;

• Type III, a soda-lime glass; and

• NP, a soda-lime glass the parenteral is not suitable for containers.

○ **Type I glass:They**are suitable for all products ,sometime used for sulfur dioxide treatment is greater resistance to glass leach-ables. Because cost must be considered, one of the other, less expensive types may be acceptable.

○ **Type II glass**may be suitable, for example, for buffer solution bellow at pH7and not reacted with glass.

○ **Type III glass is usually suitable** for dry substances and anhydrous liquids.[35]

Plastic containers:-

Sterile preparation for ophthalmic solutionlarge-volume parenterals and mostly in small volume parenterals are used in thermoplastic polymers as packaging materials. The advantage of plastic container to compare with glass, it is not easily breakable and weight reduction. In large-volumeintravenous fluids is used for flexible bags of PVC (polyvinyl chloride) or select polyolefin.[36]

Rubber Closures:-

Made up of rubber closure are using milling machines by multiple ingredients plasticized and mixed together at an elevated temperature [42]The allergenic proteins from the natural rubber vial closures or stoppers that release into aqueous pharmaceuticals induce some allergic reactions in individuals with latex allergy receiving medications from such vials.[37]

Labeling:-

The package and in particular, the labeling for parenteral dosage forms are integral and critical parts of the product. The labeling must be legible and clearly identify the drug, its concentration, handling or storage conditions and any special precautions, the dose or concentration must be predominantly displayed when other concentrations of the same drug are marketed, proper labeling is difficult with the space limitation dictated by small containers used for many parenteral products. Smaller containers have become increasingly popular because of the unit dose concept. [38]

STERILITY TEST:

The Sterility test of the pharmaceutical product is free from microorganisms with counting all part of the product through a nutrient medium. The character of the test and probabilities to concerning the part of the sample, it is no contaminating microorganism have been found in the sample examined in the situation of the test. it is impossible to show sterility since sampling to select non sterile containers and culture techniques have limited sensitivity.[39]The following methods are used to sterility test a)Direct transfer method b) membrane filtration method.

A) Direct Transfer method: sterility test which involves direct inoculation method are the volume of sample containing a two test tube in culture medium that is FTM, SCDM.The method is simple theory but difficult practice for repetition open container, sampling transfer and mixing increase potential causes fatigue to the operator and detoriation in operator technique.

B) Membrane Filtration method: the method are more popular and widelyusedfor direct transfer method. Successful Employment Requires a more

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skill andknowledge than Direct transfer method. This method basically involves filtration of Samplethrough membrane filters of porosity 0.22 micron and Diameter 47mm with hydrophobiccharacteristics. The filtration is assisted under Vaccum, After filtration completion the membrane is cut into 2 halves and one halve is placed in two test tubes containing FTM, SCDMmedium.[40]

II. CONCLUSION:

Parenteral route is most effective route for 100% of drug delivery and good bioavailability for patient quick response we follow this route especially unconscious patients preferable route. In these article from the preparation to packaging and labeling are cGMP guideline preparation we followed and monitor the stability study to known the effect of activity for long term study.

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