Parenteral Drug Manufacturing

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Abstract-

- *Parenteral preparations are sterile, pyrogen-free liquids (solutions, emulsions, or suspensions) or solid dosage forms containing one or more active ingredients, packaged in either single-dose or multidose containers.*
- *They are intended for administration by injection, infusion, or implantation into the body. The term parenteral derives from the Greek word: para which means outside and enteron which means intestine.*
- *Parenteral preparations may contain excipients such as solvents, suspending agents, buffering agents, substances to make the preparation isotonic with blood, stabilizers, or antimicrobial preservatives.*
- *The addition of excipients should be kept to a minimum. When excipients are used, they should not adversely affect the stability, bioavailability, safety, or efficacy of the active ingredient(s), or cause toxicity or undue local irritation. The manufacturing process should meet the requirements of Good Manufacturing Practice.*
- *The quality of starting materials, the design and maintenance of the equipment and the method of manufacture must be such as to ensure the stability of the active substance and the final product which is sterile and free of pyrogens and particulate matter.*
- *This review describes an overview of parenteral drug delivery system. Firstly, different routes of administration, formulation of parenterals, their types and containers used are pointed out. In the second part, various Preformulation and pharmaceutical factors affecting parenteral administration, general manufacturing procedure and evaluation tests of parenterals are reviewed.*

I. INTRODUCTION

- Parenteral preparations are sterile, pyrogen-free liquids (solutions, emulsions, or suspensions) or solid dosage forms packaged in either single-dose or multidose containers.
- These preparations are administered through the skin or mucus membranes into internal body compartments.
- These include any method of administration that does not involve passage through
- The digestive tract.The term parenteral is derived from the Greek word Para – outside and Enterone –Intestine. It denotes the route other than oral.
- Parenteral (Gk, para enteron, beside the intestine) dosage forms differ from all other drug dosage forms, because they are injected directly into body tissue through the primary protective systems of the human body, the skin, and mucous membranes.
- They must be exceptionally pure and free from physical, chemical, and biological contaminants. These requirements place a heavy responsibility on the pharmaceutical industry to practice current good manufacturing practices (cGMPs) in the manufacture of parenteral dosage forms and on pharmacists and other health care professionals to practice good aseptic practices(GAPs) in dispensing parenteral dosage forms for administration to patients.
- parenteral products have grown in number and usage around the
- world.
- The requirements of this monograph do not necessarily apply to human blood and products derived from human blood, toimmunological preparations, to peritoneal dialysis solutions or radiopharmaceutical preparations.
- Parenteral preparations are sterile preparations containing one or more active ingredients intended for administration by injection infusion or implantation into the body. They are packaged in either single-dose or multidose containers.
- When excipients are used they do not adversely affect the stability, bioavailability, safety or efficacy of the active ingredient(s), or cause toxicity or undue local irritation. There must be no incompatibility between any of the components of the dosage form.
- Water for injections is used as the vehicle for aqueous injections. Sterilization at this stage may be omitted, provided that the
- Unless otherwise specified in the individual monograph, sodium chloride or other

Types of Injectable Drug Products:

Injectable drug products can be developed into several different types depending upon the characteristics of

the drug, the desired onset of action of the drug, and the desired route of

administration. The following presentations are typically used:

 Injectable solution: a drug dissolved in water (or other solvent) that may include additives, known as excipients, to help stabilize it

Injectable suspension: drug crystals are not soluble in water, so the surface of the crystals are wetted to prevent them from floating on the solution surface; this is typically accomplished using a surfactant; suspending agents are then added to prevent the crystals from settling to the bottom and forming a solid (concretion), which is difficult to re-suspend.

 Injectable emulsion: a drug that is not soluble in water so it is dissolved in an oil, which is then added to water with an emulsifying agent.

Pre-Formulation and Formulation Development:-

There is a significant amount of time, effort, and expense required when identifying a new drug molecule, whether it is a small molecule or a large bio-molecule. However, once the molecule is identified and a process to mass produce the molecule is created, the final product development work begins.

The initial goal is to get the product to a semi-formulated state so it can be administered to animals for safety/toxicology studies (pre-clinical). For the early phases of animal and human studies (clinical trials) it is common to use drug products that are not in the final formulated state, as they need to be stable only through the course of the trial. While these early phase studies are conducted, development scientists work to identify the final formulation that willoffer the best stability, safety, and efficacy.

Pre-Formulation studies may include:

 pH stability
 pH solubility
 identifying a stability indicating analytical method
 thermal stability
 oxidation potential
 light stability
 hydrolysis potential

Formulation studies may include:

 identifying both the need for and appropriate strength of a buffer system to control pH
 identifying both the need for and appropriate strength of a surfactant
 identifying both the need for and appropriate strength of a stabilizer
 identifying both the need for and appropriate strength of a bulking agent

CONTAINERS:-A container for a pharmacopoeial article is intended to contain a drug substance or drug product with which it is, or may be in direct contact. The closure is a part of the container**.**

1 Plastic Containers:-

(Fig Plastic Container)

Plastic containers suitable for packaging in drugstores are made of polyethylene, polystyrene, polypropylene and polyvinyl chloride. Other plastic safe for pharmacy suitable for specific substances are polyethylene terephthalate and polymethylmethacrylates, among others.

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• Plastic containers are used mainly because:

- Light in weight
- Non-breakable
- When low in additives have low toxicity and low reactivity with products.

Drawbacks:-

• Tissue toxicity can occur from certain polymers, but additives are a more common cause.

Polypropylene:-

- It is the most widely used.
- It is a linear polymer that can be produced to be highly crystalline. Because of its crystallinity, it has a high tensile strength, a high m.p. of 165°C and relatively low permeability to gases and water vapours.
- It is translucent, abrasion-resistant, and has high surface gloss.
- Withstands normal autoclaving temperatures.

USP Procedure for Evaluating the Toxicity of Plastic Materials:-

1. Implanting small pieces of plastic materials intramuscularly in rabbits
2. Injecting eluates using sodium chloride injection with an without alcohol intravenously in mice and injecting eluatesusing PEG400 and sesame oil intraperitoneally in mice
3. Injecting all four eluates subcutaneously in rabbits. The reaction from the test samples must not be significantly greater than non-reactive control samples.

2 Glass Containers

(**Fig** glass container)

As glass is non-reactive, it is often chosen as the safest option.

Another benefit of using glass in pharmaceutical packaging is that it does not leak like certain types of plastic (which can leak a chemical called Bisphenol A or BPA).

PRODUCTION:-

- Production process includes all the steps from accumulation and combining of the ingredients of the formula to the enclosing of the product in the individual container for distribution. Intimately associated with these processes are the personnel who carry them out and the facilities in which they are performed.
- To enhance the assurance of successful manufacturing operations, SOP is very essential.
- Extensive records must be kept to give assurance at the end of the production process that all steps have been performed as prescribed, an aspect emphasized in the FDA's Good Manufacturing Practice.
- In-process control is essential for assuring the quality of the product, since these assurances are even more significant than those from product release testing.
- In the initial step, the formula ingredients, container components and processing equipments that have been released for use are drawn from their respective storage areas. The ingredients are compounded according to the master formula in an environment designed to maintain high level of cleanliness. And if the product is solution, it is filtered during transfer to the asceptic filling room.
- Process equipments and container components are cleaned thoroughly, assembled in a clean environment, sterilized and depyrogenated prior to the use.is then packaged. Outer wrapping of the packages should be loosened. All supplies must be introduced into the aseptic filling rooms.
- After this the containers are sealed.
- It is then transferred to the packaging area. This room must be clean. Packaged products are kept in quarantine storage until all tests have been completed andinprocess control records have been evaluated.

Facilities

- Should be designed for the control of cleanliness environment appropriate for each step.
- Surrounding area should provide a buffer area in which standards of cleanliness are only slightly lower than those for the ascetic rooms.The prevention of contamination must be the primary objective.
- The ceiling, walls, and floors should be constructed of material that is easy to clean and non porous, to prevent the accumulation of debris and moisture.
- For environmental control both the physical and chemical is essentials.

Surface Disinfectant:-

- After thorough cleaning, all surfaces should be disinfected, in the asceptic areas.
- An effective liquid disinfectant should be sprayed or wiped on all surfaces
- UV rays may be particularly useful to irradiate the inside, exposed surfaces of processing tanks, surface under

hoods, surface of conveyor belts, underside of conveyors and the inside of containers.

- Ultraviolet lamps must be kept clean and care must be taken to check for decrease in effective emission, natural occurrence due to a change in the glass structure with aging.

Air Control:-

- A spun glass, cloth or shredded polyethylene filter may be used for preliminary cleaning operation.
- To remove finer debris down to the sub- micron range including microorganism, a High efficiency particulate air (HEPA) filter, as defined as 99.7% efficient in removing particles of 0.3 µm size.
- This class is mostly specified for critical aspects/ clean operations.
- This is expensive and requires effective maintenance and monitoring.
- Class 10,000 rooms are defined as one in which the particle count is no more than 10,000 per cubic foot of 0.5µm and larger in size. Personnel:

Manufacturing:-

- The manufacturing process should meet the requirements of good manufacturing practices (GMP). The following information isintended to provide broad guidelines concerning the main steps to be followed during production.
- The quality and grade of starting materials, the design and maintenance of the equipment and the method of manufacture must be such as to ensure the stability of the active substance and of the final product and that the final product is sterile and free ofpyrogens and particulate matter.
- During development the effectiveness of any antimicrobial preservative present in the preparation shall be demonstrated to thesatisfaction of the relevant regulatory authority.

(Fig manufacturing machine)

- For the sterilization of parenteral preparations follow 5.8 Methods of sterilization. Heating in an autoclave (steam sterilization) itthe method of choice for aqueous preparations and should therefore be used whenever possible. When a parenteral preparation is liable to deterioration due to oxidation the operation of filling may be performed in an atmosphere of suitable sterile inert gas, such as nitrogen, whereby the air in the container is replaced by this gas.
- In the manufacture of preparations containing dispersed particles measures are taken to ensure a suitable and controlled particle size with regard to the intended use. In the manufacture of liquid preparations measures are taken to ensure that the volume of the preparation in the container is sufficient to permit withdrawal and administration of the nominal dose using a normal technique as demonstrated by 5.6

Extractable volume for parenteral preparations:-

- Throughout manufacturing certain procedures should be validated and monitored by carrying out appropriate in-process controls. These should be designed to guarantee the effectiveness of each stage of production.
- In-process controls during manufacture of parenteral preparations should include monitoring of environmental conditions (especially with respect to particulate and microbial contamination), bacterial endotoxins, pH and clarity of solution, freedom from particulate matter and integrity of the container-closure system (absence of leakage, etc.).
- For powders for injections controls should also include uniformity of mass, moisture content and the ease of reconstitution of a solution or suspension.
- The validation of the manufacturing process and the in-process controls are documented.

STORATE AND DISTRIBUTION:-

- The storage and distribution of WFI is as important as production.
- A closed system with air exchange through a filter that removes microorganism, dirt and vapours from the air as the tank is filled and emptied.
- WFI should not be held for more than 24 hr at room temperature before it is used, but if held at 80°C.
- The distribution may be by direct withdrawal from the tank, or in large plants through a pipe system.
- When a pipe system is used precaution must be followed to prevent the contamination/ construction with welded stainless steel pipe, elimination of elbows/ pockets in which water can stagnate for long periods and thorough cleaning/ sanitation at frequent intervals.

Cleaning Equipment and Containers:-

- Equipments and containers to be used should be scrupulously cleaned.
- Debris should be removed by hot detergents. Live steam can sometimes be used to loosen debris effectively, particularly in area where it is not accessible.
- After cleaning, it should be rinsed with WFI.
- A new method for large tanks, pipelines and associated equipments that can be isolated and contained within a process unit has been developed and identified as a CIP (Clean in place) system. Cleaning is accomplished with high pressure rinsing treatments delivered automatically within the equipment which is followed by steam sterilization.
- The glasswares and metalwares is automatically conveyed, usually in an inverted position through a series of rigorous, high pressure treatment including hot detergent, hot tap water and final rinses with distilled water.

Compounding of the Product:-

- The product should be compounded under clean environment conditions.
- The accuracy of compounding should meet the rigid standards accepted in pharmaceutical procedures, regardless of the batch size,recognizing that small multiple errors may be additive.
- Similarly in large batch particular attention must be given to achieve and maintain homogeneity of solutions, suspension and mixtures maintaining a given temperature and accelerating cooling.

Filtration:-

At this point in the manufacturing process the formulated drug product enters the Class A clean room. It remains under these conditions until the product is filled, stoppered, and capped. Only then does the product exit the clean room, unless it is destined to be freeze-dried, at which point the product is aseptically transported to the freeze-dryer.

There are four primary types of filters used in the parenteral and biopharmaceutical industry (the type of filter chosen depends on the type of material to be removed). The filter types include:

- clarifying filters—large particles
- microfilter—bacteria and yeasts (used for injectable drug products)
- ultrafilter—viruses
- nanofilter—small organic compounds and ions

The injectable drug industry uses microfilters to remove particles in the 0.1 to 10 micron size range from the formulated drug product. Several different types of membranes are available in this pore size range to accommodate different types of formulations, including water based formulations (hydrophilic) and solvent based formulations (hydrophobic). It is up to the development scientist to conduct studies for

(**Fig** Filtration Machine)

filter compatibility in order to determine thecorrect filter and filter surface area for the particular product. For most parenteral products, a hydrophilic (water loving) filter is used and may include:

- cellulose acetate
- cellulose nitrate

egenerated cellulose
- modified regenerated cellulose
- polyamide (nylon)
- polycarbonate
- polyethersulfone
- polysulfone
- polyvinylidene difluoride (PVDF)

The next step in the process is to sterilize the solution using one of the filters listed above. Note that products that are either suspensions or large particle-sized Filling and sealing machines are packaging equipment that uses flexible, heat-sealable, plastic film to form packages that can be filled with a product and then sealed, and cut.

- There are many types of filling and sealing machines. Filling machines load previously formed packages with a specific product quantity, but do not provide closing or sealing action. Seal-only equipment wraps or secures products, but does not form packages or fill them. Equipment that combines form, fill and seal functions is also available.
- Filling and sealing machines are used to process liquids, granules, powders, and sprays for consumer, bulk and original equipment manufacturer.
- Filling and sealing machinery are capable of packing different kinds of liquids, pastes, granules, powders categorized as shampoo, ketchup, oil, lube, petroleum jelly (cream), spices, tea coffee, liquor and other related products.

Filling Equipments for Solids: -

- The rate of flow of solid materials tends to be slow and irregular whereas small, granular particles flow most evenly.Containers with large openings must be used even the filling rate is slow and the risk of spillage is present.
- When the solid is obtained in relatively free-flowing form, machine methods of filling may be employed. This method involves the measurement and delivery of volume of solid material which has been calibrated in terms of weight desired.
- Another filling machine consists of an adjustable cavity in the rim of the filling wheel which is filled by vacuum as the wheel passes under the hopper.Thecontents are held by vacuum until the cavity is inverted over the container when
- a jet of sterile air discharges the dry solids.

Sealing Ampoules:

- Ampoules may be closed by melting a portion of the glass of the neck to form either bead-seals (tip seals) or pull 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.
- 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. It is a slower process but the seals are more reliable than that form tip-sealing.
- The heating with high temperature gas-oxygen flame must be even and carefully controlled to avoid distortion of the seal.**Granulation Process** Pharmaceutical granulation is necessary to overcome the significant compression difficulties and erratic flow properties of many active pharmaceutical ingredients (API, s) that limit the successful production of these dosage forms.

Current Solid Dosage Manufacturing Technologies Orally administered solid dosage forms constitute a blend of several pharmaceutical excipients. These include diluents, binders, disintegrants, glidants, lubricants, and the API's. Successful production of these types of products is dependent on the ability of the production process to adequately mix and or granulate these products to ensure that the resultant solid

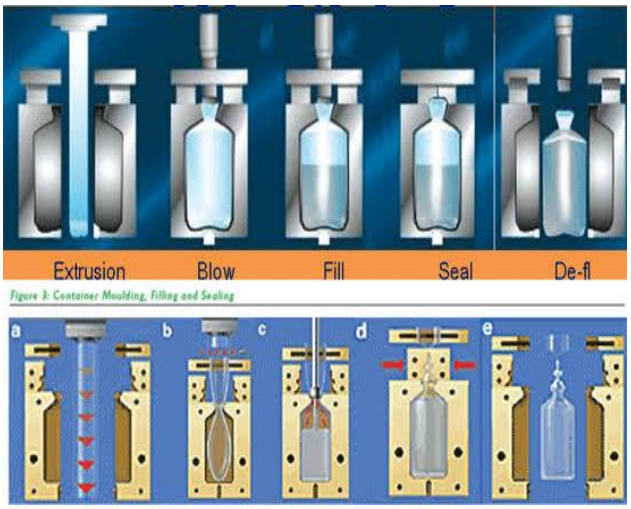
agglomerates posses high fluidity , compressibility and in addition avoid de-mixing during the following post granulation processes such as tablet compression and capsule filling processes.

Manufacturing Equipments The production equipment forms a critical part in the success of the process. They must be able accurately determine, define and release product in accordance to the calibrated quantities without altering any properties of the products. Some of the solid dosage manufacturing equipments include; Storage Tanks, Jacketed Vessels, tablet coating machine, vibro-sifters, multi mills, de burring, de dusting machine, oscillating granulator, granulating machine, tablet coating, pan tablet coating machine, strip packing machines, blister packaging machinery, liquid filling machinery, liquid manufacturing plants and many more.

Sealing Bottles, Cartridges and Vials:-

- Rubber closures must fit the opening of the container snugly enough to produce a seal.
- A faster hand method involves picking up the closure and inserting it into a vial by means of a tool connected to a vacuum line.
- When closures are inserted by machine, the surface of the closure is usually halogenated or coated with silicone to reduce the friction.
- Aluminum caps are used to hold rubber closures in place. Single caps contains hole/ center that is torn away at the time of use to expose the rubber closures.

Whereas the double aluminum caps usually have an inner cap with permanent center hole, which in use is exposed when the entire outer cap is torn off. The triple aluminum caps are used for large bottles with rubber closures having permanent holes for attachment to administration sets.



(fig.filling& sealing)

Stoppering:-

Once the vials have been filled, they travel down the filling line to have pre-sterilized stoppers inserted. If the product is not scheduled to be freeze-dried, a stopper is fully inserted into the neck of the vial and the vial is transported to the capping station. If the product is going to be freeze-dried, a special stopper with a vapor port is partially inserted into the neck of the vial.

The freeze-drying process, described in more detail below, allows for the removal of water; the ice created during the freezing phase of the process is converted to water vapor, which leaves the product via the open port in the specialized lyophilization stopper.

Capping:-

If the vials are not scheduled to be freeze-dried they travel down the filling line to the capping station. Caps are used to secure the stopper in the neck of the vial to prevent the stopper from coming out either over time or during handling. The caps are comprised of a plastic cap and an aluminum skirt

(Fig.aluminium cap)

- The caps are fed down a chute to the vials as the vials travel down the filling line. One cap is loosely placed on the top of each vial.
- The vials then travel to the crimping station where rotating blades crimp the bottom of the aluminum skirt around a lip on the neck of the vial, producing a tight fit that locks the stopper into the neck of the vial. At the time of use the plastic cap is removed; this exposes the top of the stopper, which is then pierced with a needle to remove the contents inside the vial. At this point in the production process the vials exit the Class A environment through a port in the wall and are ready for inspection and final packaging.

Sterilization of Product :-

Freeze-drying: -

- It is a drying process applicable to the manufacture of certain pharmaceuticals and biological that is thermolabile or otherwise unstable in anaqueous solution for prolonged storage periods, but is stable in dry state.
- The rate of drying depend on the thermal conductance of the frozen product, rate at which the vapour can diffuse through the progressively thicker layer of dried porous material and the rate of transfer of vapour through the system to the condenser surface.

(Fig Sterlization machine)

- In production, large freeze driers are usually operated by an automatic control system. The product is usually processed until there is less than 1% moisture in the dried material.
- Freeze driers also may be equipped for stoppering vials within the drying
- Numerous biologic preparations, tissue sections and viable microorganism are being preserved in the freeze dried state. Multiple vitamin combinations, antibiotics, hormones are other examples.

Labeling:-

Once the product is released from Inspection by Quality Assurance, it moves to Labeling. Labeling is performed in order to provide accurate information regarding the product and avoid misrepresentation of the ingredients or effects of a drug, whether accidental or intentional. Stringent controls are placed on the printing and handling of labels in order to prevent errors.

(Fig.labeling)

- Both the label and the information on the label must be approved by the FDA, and each batch of labels to be used for a drug product must be inspected, approved, and released by QA before labeling begins.
- Small batches of drug product may be labeled by hand, but in most cases labeling machines are used. The machines also inspect the labels and insure they are placed correctly and contain the correct information.

Packaging :-

- The package is an extremely important part of the product, for it presents the product to the user.
- It must be particularly dignified, neat and attractive appearance if it is to convey to the user the quality, purity and reliability.
- The labeling should be legible and the identity and strength of the drug should be distinguishable.
- The packaging should protect the product against physical damage during shipping, handling and storage and should protect light-sensitive substances from ultraviolet radiation.

(Fig Packaging)

Conclusion:-

There are also significant benefits related to successful parenteral drug production, including:

- Knowing that you helped produce medication that will save a life or will fight life-threatening diseases.
- Becoming a skilled employee with multiple options in the bio tech industry; an industry forecasted to continue to grow significantly in the future.Aseptic processing of parenterals involves a number of interesting challenges, including:
- Protecting the sterility of the product as it moves through several phases of formulation, filtering, filling, and packaging.
- Development of the experience and technical knowledge to trouble-shoot issues as they occur.
- Maintaining consistent compliance with CGMP regulatory requirements to protect product SISPQ

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