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A Detailed Concepts on Parenteral Preparation

Shivam Harishankar Chaturvedi[1], Chandra Mohan Anand[2]
Lokesh saini[3]
1-Research Scholar, Rameshwaram Institute of Technology & Management, Lucknow, U.P
2-Research Schloar, Sagar Institute Of Technology & Management, Barabanki, U.P
3-Research Schloar, Hygia Institute of Pharmaceutical Education & Research, Lucknow,U.P

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ABSTRACT
Parenteral preparations are defined as solutions, suspensions, emulsions for injection or infusion, powders for injection or infusion, gels for injection and implants. They are sterile preparations intended to be administrated directly into the systemic circulation in human or animal body.
They are required, like any pharmaceutical dosage forms, to meet the pharmaceutical quality standards as described in pharma-copeias and to be safe for the intended purpose of use. In addition to being sterile, parenteral preparations must be pyrogen-free. Sterility can be achieved by different processes of sterilization that should be appropriate to the formulations, while the pyrogen-free aspect will require, if no dehydrogenations process is used during the preparation of the sterile drug products, the use of pyrogen-free pharmaceutical ingredients; drug substances or API (Active Pharmaceutical Ingredient) and excipients. Parenteral Formulations are sterile, pyrogen-free, administered by injection through skin layers. This review highlights all the aspects regarding parenteral products advantages, disadvantages, routes of administration, additives, preparation, types of containers and quality control tests for evaluation.

Keywords: Parenterals, Administration, Contaminants, Pyrogen, Quantity, Types, Method

I. INTRODUCTION

The USP 24/NF19defines parentral articles as "those preparations intended for injection through the skin or other external boundary tissue, rather than through the active substances can be administered directly into a blood vessel, organ, tissue, or lesion" Parenteral route of drug administration generally includes intravenous (IV), subcutaneous (SC), and intramuscular (IM)route, however, lesser-used routes such as intra thecal, intra arterial, convection-enhanced drug delivery and implants are also included under the broad umbrella of parenterals. The pharmaceutical convention, however, is to use the term parenteral for those medicines that are administered by means of an injection. Parenteral products are the mainstay of treatment for hospitalized patient.

This route of drug delivery offers a plethora of advantages for patients who cannot take medications orally or for those who require rapid onset of action.

Parenteral (para–outside enteron-intestine) administration is the introduction into the body of nutrition ,medications ,or other substances other than by the alimentary canal.

Parenteral preparations are defined as solutions, suspensions, emulsions for injection or infusion, powders for injection or infusion, gels for injection and implants. They are sterile preparations intended to be administrated directly into the systemic circulation in human or animal body.

They are required, like any pharmaceutical dosage forms, to meet the pharmaceutical quality standards as described in pharma-copeias and to be safe for the intended purpose of use.[1,2,3] In addition to being sterile, parenteral preparations must be pyrogen-free. Sterility can be achieved by different processes of sterilization that should be appropriate to the formulations,[4] while the pyrogen-free aspect will require, if no depyrogenation process is used during the preparation of the sterile drug products, the use of pyrogen-free pharmaceutical ingredients; drug substances or API (Active Pharmaceutical Ingredient) and excipients.

They are usually supplied in single dose glass or plastic containers (PVC nowadays less recommended, or polyolefin) or more and more in pre-filled syringes or pens to facilitate the ease of use.[1] This article will describe the main challenges encountered during the formulation of parenteral preparations, as well as Roquette's solutions meeting the formulator's needs.

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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.

Certain pharmaceutical agents, particularly peptides, proteins, and many chemotherapeutic agents, can only be given parenterally, because they are inactivated in the gastrointestinal tract when given by mouth. Parenterally-administered drugs are relatively unstable and generally highly potent drugs that require strict control of administration to the patient. Due to the advent of biotechnology, parenteral products have grown in number and usage around the world.1

Characteristics Of Parenteral Dosage Forms

Parenteral products are unique from any other type of pharmaceutical dosage form for the following reasons:

All products must be sterile.

All products must be free from pyrogenic (endotoxin) contamination.

Injectable solutions must be free from visible particulate matter. This includes reconstituted sterile powders.

Products should be isotonic, although strictness of isotonicity depends on the route of administration.

Products administered into the cerebrospinal fluid must be isotonic.

Ophthalmic products, although not parenteral, must also be isotonic. Products to be administered by bolus injection by routes other than intravenous (IV) should be isotonic, or at least very close to isotonicity.

IV infusions must be isotonic.

All products must be stable, not only chemically and physically like all other dosage forms, but also 'stable' microbiologically (i.e., sterility, freedom from pyrogenic and visible particulate contamination must be maintained throughout the shelf life of the product).

Products must be compatible, if applicable, with IV diluents, delivery systems, and other drug products co-administered.2

Properties Of Parenteral Preparations

Parenteral preparations are intended to be administrated through the human or animal body, either by direct injections (for example, bolus intravenous (IV), intramuscular (IM) or subcutaneous (SC)) or by infusion with a controlled infusion rate or by direct implantation through IM or SC. They must meet the following minimum com-pendia criteria:-

- To be sterile and pyrogen-free.
- To be clear or practically exempt of visible particle and to be free from sub-visible particles as required by pharmacopeias EP, USP and JP.
- No evidence of phase separation for the emulsions, or aggregates formation for aqueous dispersions such as injectables Mab (monoclonal antibody) preparations.
- In case of suspensions, the use of appropriate particle size and any sediment should be readily dispersed upon shaking to give stable formulations and ensure the correct dose to be withdrawn and injected.

Parenteral preparations may require the use of biocompatible excipients that are selected according to the specific application and included at the minimum efficient concentration. The functionality of these excipients is as follows:-

- to make the preparation isotonic with respect to blood (glucose/dextrose, mannitol, sodium chloride)
- to adjust the pH to physiological levels (mineral or organic acids or salts)
- to prevent the degradation of the drug substances (stabiliser)
- to ensure or increase the drug substance's solubility
- to provide adequate antimicrobial preservation (only applicable to multidose preparations).

It must be stressed that excipients should not adversely affect the intended medicinal action of the drug product, nor at the concentration used cause toxicity or undue local irritation.3

Classification Of Parenteral Preparation

Injections may be classified in six general categories:-

- Solutions ready for injection.

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- Dry, soluble products ready to be combined with a solvent just prior to use.
- Suspensions ready for injection.
- Dry, insoluble products ready to be combined with a vehicle just prior to use.
- Emulsions.
- Liquid concentrates ready for dilution prior to administration.4

Types Parenteral Products:-. The types of Parenteral products are based on Volume and the state of product according to USP. BasedonVolume:-

- SVP – An injection that is packed in containers labeled as containing 100 ml or less.
- LVP – These are parenterals designed to provide fluid, calories and electrolytes to the body and the volume is more than 100ml are useful in.5

Advantages Of Parenteral Products:-.

- These Unconscious patients.
- Uncooperative and unreliable patients.
- Onset of action of drugs is faster; hence it is suitable for emergency.
- Patients with vomiting and diarrhea.
- These are suitable for irritant drugs and drugs with high first pass metabolism.
- Drugs are not absorbed oral
- Drugs destroyed by digestive juice

Disadvantages Of Parenteral Product:-

- Parenteral preparations should be sterile and expensive.
- They require aseptic conditions.
- Cost
- They can't easily self- administrated.
- Causes local tissue injury to nerves, vessels, etc.

'' Parenteral product formulation depends upon the understanding of several factors that dictate the choice of formulation and dosage form.''6

Development Of Parenteral Preparation:-

Developing a Parenteral product is endowed with challenges such as drug solubility, product stability (crucial for biopharmaceuticals), drug delivery, and manufacturability.

The U.S. Food and Drug Administration (FDA) and Center for Drug Evaluation and Research (CDER) envision modernizing pharmaceutical development and manufacturing so as to enhance product quality.

The increased drug recalls and drug shortages, over a span of time, reflect failures in pharmaceutical quality. The major technical and scientific advancements have further challenged the existing regulatory paradigms (Fisher et al., 2016).

Pharmaceutical development is aimed to develop a product with the desired quality produced using a defined manufacturing process, i.e., robust and reproducible and consistently delivers the product for the intended usage.

The "quality" is built into the pharmaceutical product since the very early research and development (R&D) phase, to ensure that the final product meets the requirements prior to entering the production phase.

Pharmaceutical quality by design (QbD) is a systematic, risk-based, and pro-active approach to pharmaceutical development that employs quality-improving scientific methods upstream in the research, development and design phases, to assure that quality is designed into the product at an early stage as possible (Singh et al., 2014 and 2015; Beg et al., 2017a,b and 2019).

QbD presents a framework for the understanding and consideration in all pharmaceutical aspects of the drug lifecycle including its development, manufacturing process and the raw materials used therein, distribution, and the inspection and submission/review processes including the pharmacovigilance (Csóka, Pallagi, & Paál, 2018).

The QbD approach offers significant benefits to the drug developers; reduced costs, smoother application approval process, and the regulatory relief when changing the Recent Advances in the Development of Parenteral Dosage Forms 99 CQAs within the design space post-registration and over-the product life cycle (Politis et al., 2017).

Formulation designers seek to optimize the pharmaceutical process so as to assure that the optimal ingredient amounts in the optimal dose are delivered in the right amount, to the right site, at the right rate, at the right time, to obtain a maximum clinical therapeutic effect.

It is highly desirable to optimize the pharmaceutical process which establishes the critical process parameters (CPPs) that result in the manufacturing of the acceptable product incorporating risk assessment and risk management tools, and applying the statistically designed experiments to identify the acceptable operating ranges for both critical and noncritical process parameters (Hakemeyer et al., 2016).

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Design of experiments (DoE) is a basic concept in drug development and has found application in all areas of drug development including, active pharmaceutical ingredient synthesis, drug formulation, analytical method optimization, and stability study.

DoE has emerged as a very helpful tool in drug formulation optimization and development as it significantly reduces the number of experiments, consumption of time and costs. DoE has evolved into the QbD concept.

QbD is adopted by the pharmaceutical legislation as an evidence-based concept for delivering an efficient, safe and effective therapeutic agent of high quality (Savic et al., 2012; Singh et al., 2013).

The product and process optimization using QbD will ultimately lead to patient benefit as they will be more likely to get improved access to high-quality affordable and innovative treatment options.7

Route Of Administration For Parenterals:-

Parenteral therapy (which may be i.m. or i.v.) is preferred for therapy of serious infections because high therapeutic concentrations are achieved reliably and rapidly. Initial parenteral therapy should be switched to the oral route whenever possible once the patient has improved clinically and as long as a suitable oral antibiotic is available and they are able to absorb it (i.e. not with vomiting, ileus or diarrhoea). Many antibiotics are well absorbed orally, and the long-held assumption that prolonged parenteral therapy is necessary for adequate therapy of serious infections (such as osteomyelitis) is often not supported by the results of clinical trials.

Although i.v. therapy is usually restricted to hospital patients, continuation parenteral therapy of certain infections, e.g. cellulitis, in patients in the community is sometimes performed by specially trained nurses. The costs of hospital stays and some risks of health-care-associated infections are avoided, but this type of management is suitable only when the patient's clinical state is stable, oral therapy is not suitable, and the infection is amenable to once-daily administration of a suitable antibiotic (usually one having a prolonged half-life).

Oral therapy of infections is usually cheaper and avoids the risks associated with maintenance of intravenous access; on the other hand, it may expose the gastrointestinal tract to higher local concentrations of antibiotic with consequently greater risks of antibiotic-associated diarrhoea.

Some antimicrobial agents are available only for topical use to skin, anterior nares, eye or mouth; in general it is better to avoid antibiotics that are also used for systemic therapy because topical use may be especially likely to select for resistant strains. Topical therapy to the conjunctival sac is used for therapy of infections of the conjunctiva and the anterior chamber of the eye.

Inhalational antibiotics are of proven benefit for pseudomonas colonisation of the lungs in children with cystic fibrosis (twice-daily tobramycin),
monthly pentamidine for pneumocystis prophylaxis and zanamivir for influenza A and B (if commenced within 48 h). In addition, there is probable benefit for colistin in cystic fibrosis and as an adjunct to parenteral antibiotics for Gram-negative pneumonia,
for aminoglycosides in bronchiectasis, and
for ribavirin for RSV infection in children.

Other routes used for antibiotics on occasion include rectal (as suppositories), intra-ophthalmic, intrathecal (to the CSF), and by direct injection or infusion to infected tissues.

There are four routes for parenteral medications. Each type of injection requires a specific skill set to ensure the medication is prepared properly and administered into the correct location.8The four types of injections are:

Subcutaneous (SC): This injection places medication/solution the loose connective tissue just under the dermis.

Intradermal (ID): This injection places the medication into the dermis just under the epidermis.

Intramuscular (IM): This injection places the medication into the body of a muscle.

Intravenous (IV): This injection places the medication/solution into a vein through an existing IV line or a short venous access device (saline lock). Medications given by the intravenous route can be given as an IV bolus, as an intermittent (piggyback) medication, or in a large volume continuous infusion.

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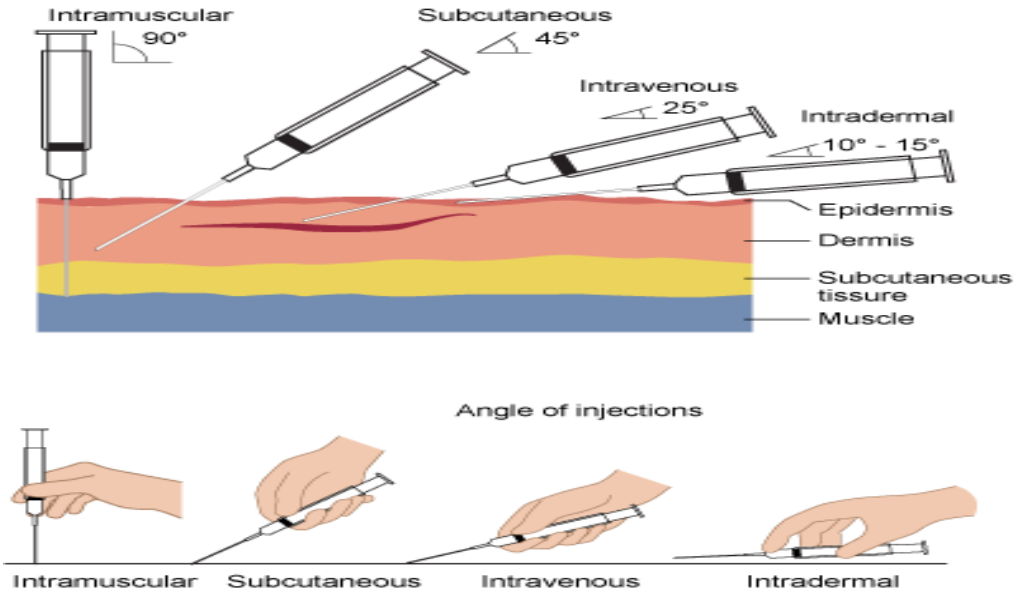

Insertion angles

Formulation Of Parenteral Preparation:-

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.

Vehicles
Additives

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

Vehicles:- - There are two types of vehicles, which are commonly used for the preparation of injections

Aqueous vehicle - water is used as vehicle for majority of injections because water is tolerated well by the body and is safest to administer .The aqueous vehicle used are ;-

- Water for injections .
- Water for injection free from CO2 (carbon dioxide)
- 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.10 Water for injection, contaminated with pyrogens may cause rise in body temperature if injected

Non -aqueous vehicles:- The commonly used non-aqueous vehicles are oils and alcohols. 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 using arachis oil as vehicle. Propylene glycol is used as a vehicle in the preparation of digoxin injection .it is relatively nontoxic but it causes pain on S/C or I/M injection.

Additives:- These substances are added to increase the stability or quality of the product .These additives should be used only when it is necessary

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to use them. While selecting the additives, care must be taken that they should be compatible both physical and chemical with the entire formulation The following additives are commonly used in preparing stable parental preparations-

Solubilising agents:- These are used to increase the solubility of drugs which are slightly soluble in water .the solubility of drug is increased by using surface active agent like tweens and polysorbate or by using co solvents.

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 be prevented by adding a suitable antioxidant such as, thiourea,ascorbic acid ,sodium metabisulphite ,or the product is sealed in an atmosphere of Nitrogen or Carbon dioxide. hydrolysis can be prevented by using a non-aqueous vehicle or by adjusting the pH of the preparation. Antioxidants: Water soluble: Sulfurous acid salts, Ascorbic acid isomers, Thiol derivatives Oil soluble; Propyl gallate ,Butylated hydroxyanisole ,Ascorbyl palmitate, alpha Tocopherol.

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 PH.

Ph	Buffer system	Concentration (%)
3.5-5.7	Acetic acid-acetate	1-2
2.5-6.0	Citric acid- citrate	1-5
6.0-8.2	Phosphoric acid- phosphate	0.8-2
8.2-10.2	Glutamic acid- glutamate	1-2

Antibacterial agents:- These substance are added in adequate quantity to prevent the growth of microorganism during storage. so these substances act as preservatives .antibacterial agents are added in single dose containers, where parenteral products are sterilized by filtration method and in multi dose containers to prevent microbial contamination .Some typical preservative used in parenteral suspensions and their commonly used concentrations are as follows.-

- Benzyl alcohol (0.9% to 1.5%)
- Methylparaben (0.18% to 0.2%)
- Propylparaben (0.02%)
- Benzalkonium chloride (0.01% to 0.02%)
- Thiomersal (0.001% to 0.01%)

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	Concentration range (%)
1	EDTA disodium	0.00368-0.05
2	EDTA calcium disodium	0.04
3	EDTA tetrasodium	0.01

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, carboxymethyl cellulose, gelatin and acacia are commonly used as suspending agents .Emulsifying agents are used in sterile emulsions .for this purpose lecithin is generally used .The wetting agents are used to reduce the interfacial tension between the solid particles and the liquid, so as to prevent the formulation of lumps.

Additives	Concentration range (%)
Polyethylene glycol 300	0.01-50.0
Polysorbate 20	0.01
Polysorbate 40	0.05
Polysorbate 80	0.04-4.0

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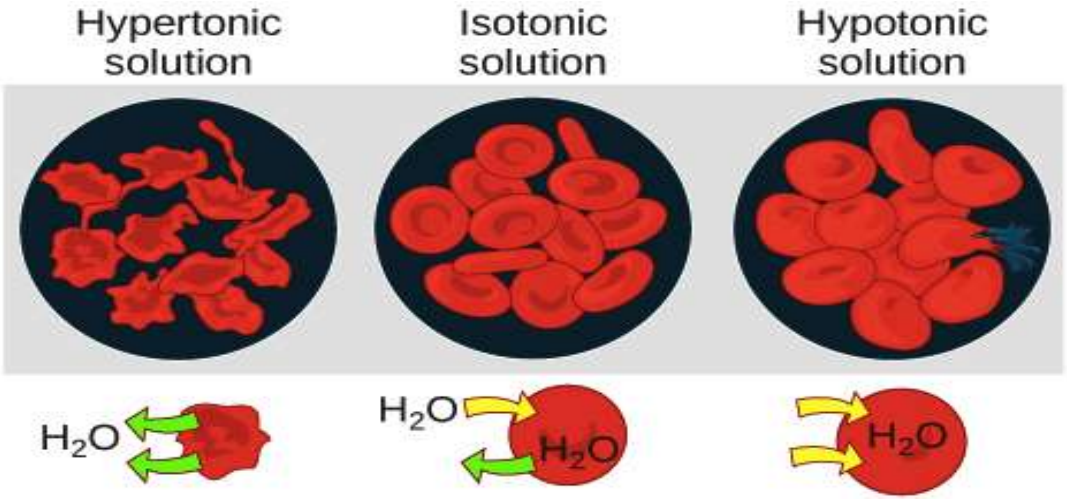
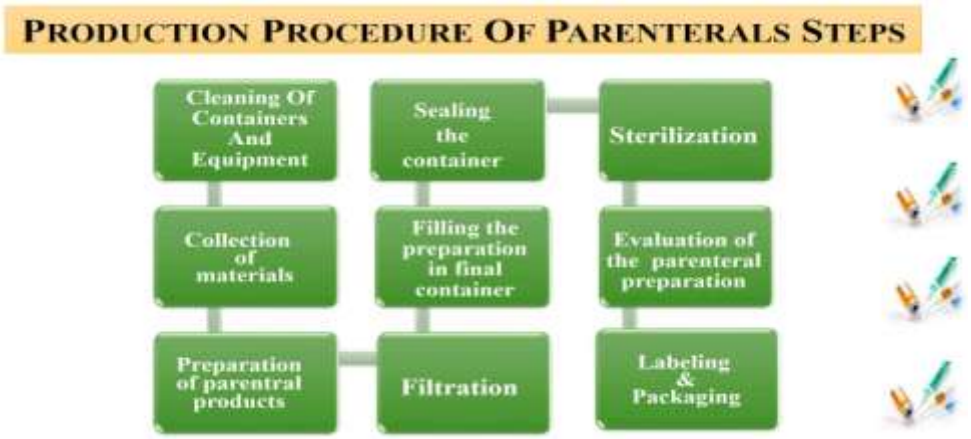
Povidone	0.2-1.0
Propylene glycol	0.2-50.0
Sorbitan monopalminate	0.05
Dimethylacetamide	0.01
Lecithin	0.5-2.3

Tonicity factors: - Parenteral preparation should be isotonic with blood plasma or other body fluids. The isotonicity of the solution may be adjusted by adding sodium chloride, 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.11





Production Procedure - Aseptic Processing For Parenteral:-

- 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.

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- Aseptic processing requirement adds more complication but assures that all dosage forms manufactured are free from any contamination of microbial, endotoxin, and visible particulate matter.
- The manufacturing process initiates with the procurement of approved raw materials (drug, excipients, vehicles, etc.) and primary packaging materials (containers, closures, etc.) and endswith the sterile product sealed in its dispensing package.The manufacturing of parenterals involves the following steps;- 12

Cleaning of containers and closures:- all the containers, closures and equipments which are required during preparation of parental products are thoroughly cleaned with detergent 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.

Preparation of Solution:- The various ingredients of the formulation of parental preparations are weighed and collected in the preparation room. the raw materials required 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 pharmacist should decide the order of mixing and exact method of preparation to be followed before preparing the parenteral products.13 The parenteral Solutions so formed is passed through bacteria proof filter ,such as ,filter candle, seitz filter, membrane filter, and sintered glass filters. 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.

Sterilization:-The parental preparations should be immediately sterilized after sealing in its final containers. For thermostable medicament ,the parenteral product are sterilised either by autoclaving at the temperature of 115°C to 116°C for 30 minutes or 121 degree centigrade for 20 minutes 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 injection in doses exceeding 15 ml ,the bacteriostatic agent should not be used.

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 feeling single dose whereas , vials are used for filling multidoses .bottles are meant for filling transfusion fluids . On small scale feeling is done manually by using hypodermic syringe and needle.The sterile Powders are filled into containers by individual weighing or by using automatic or semi 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 below the neck of ampoules and the solution should not touch the neck of ampoules.14 this will prevent the cracking and stanining of the neck of ampoules at the time of Sealing. The rubber closures are held in place by crimping the aluminium caps which is done manually or by mechanical means.

Evaluation of Parenterals:- The finished parenteral products are subjected to the following test ,in order to maintain quality control.

a) Sterility test
b) clarity test
c) Leakage test
d) Pyrogen test.

Packaging and labeling:- After evaluation of the parenteral preparation,the ampoules ,vials and transfusion bottles are properly labelled and packed. The label should state as :-

a) Name of the preparation
b) Quantity of the preparation
c) Mfg.Lic .no.
d) Batch no.
e) Date of manufacture
f) Date of expiry
g) Storage condition
h) Retail price
i) Manufacturer's add

Production Facilities And Controls:- The production area where the parenteral preparations are manufactured can be following five sections:

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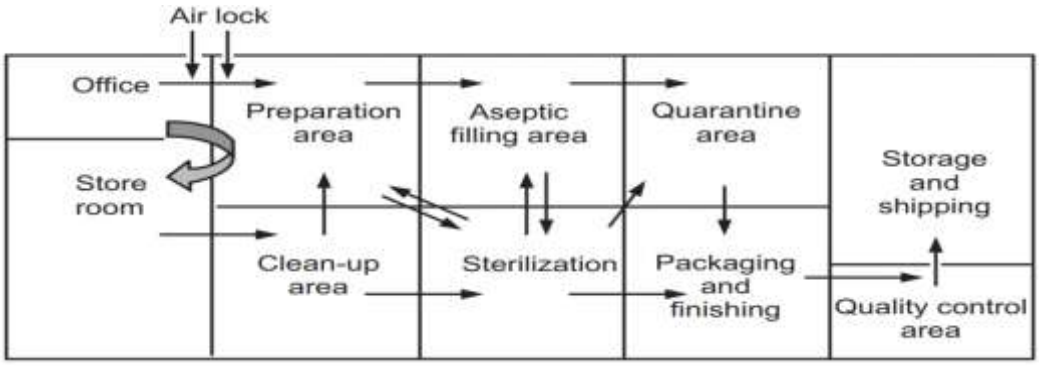

Clean-up area:-
It is not aseptic area.
All the parenteral products must be free from foreign particles& microorganism.
Clean-up area should be withstand moisture, dust & detergent.
This area should be kept clean so that contaminants may not be carried out into aseptic area.15

Preparation area:-
In this area the ingredients of the parenteral preparation are mixed& preparation is made for filling operation.
It is not essentially aseptic area but strict precautions are required to prevent any contamination from outside.

Aseptic area:-
The parenteral preparations are filtered, filled into final container & sealed in aseptic area.
The entry of personnel into aseptic area should be limited & through an air lock.
Ceiling, wall & floor of that area should be sealed & painted.
The air in the aseptic area should be free from fibers, dust and microorganism.
The High efficiency particulate air filters (HEPA) is used for air.
UV lamps are fitted in order to maintain sterility.

Quarantine area:-
After filling, sealing & sterilization the parenteral product are held up in quarantine area. Randomly samples were kept for evaluation.
The batch or product pass the evaluation tests are transfer in to finishing or packaging area.

Finishing & packaging area:-
Parenteral products are properly labelled and packed.
Properly packing is essential to provide protection against physical damage.
The labelled container should be packed in cardboard or plastic container.
Ampoules should be packed in partitioned boxes.

Selection of containers and closures of prenteral preparation
Selection of Containers & Closures should be such that it should ensure that the products must remain its purity, potency & quality during intimate contact with the container throughout its shelf life.

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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 reason.18

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 not suitable for containers for parenteral

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 of the 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.

Type III glass is usually suitable for anhydrous liquids or dry substance.

Plastic:- Plastic packaging has always been important for ophthalmic drug dosage forms and is gaining in popularity for injectable dosage forms. Plastic bottles for large volume injectable (LVIs) have been used for many years. Plastic vials for SVIs may be a wave of the future plastic packing offers such advantages of cost 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:- Rubber formulations are used as rubber closures, rubber plungers and other applications. 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.19 Rubber permits the entry of hypodermic needle into injection vials & also provide resealing of the vial after needle is withdrawn.

Filling and Sealing of Ampoules:- Ampoules are thin-walled glass containers, which after filling, are sealed by either tip 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 break ring offer consistent breaking force. There are wide variety of ampoule types from 0.5 to 50ml volume.

- The measured amounts of liquid deliver from the small orifice into the ampoule by filling machine.
- The size of the delivery tube is governed by opening in the container to be used, the viscosity and density 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 air to 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.
- The solutions are usually filled in the bottle by gravity, pressure or vacuum filling device.
- Emulsion and suspension required specially designed filling equipment because of their high viscosity.

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- Powders such as antibiotics, are more difficult to subdivide accurately and precisely into Individual dose containers than are liquid.
- Container should be sealed in the aseptic area in immediately adjacent to the filling machine.
- It is obvious that a sterile container that has been opened can no longer be considered to be sterile. Therefore, temperature proof sealing is essential.
- Ampoules may be closed by melting a portion of the glass of neck to either form 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. 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.
- 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 seals.20

Evalution Of Parenteral Preparation Product

Quality control shall be concerned with sampling, Specifications, Testing, documentation, Release procedure which ensure that necessary and relevant tests are actually carried out and materials are not release for its use or For sale, until its quality has been judged to satisfactory. The 3 General areas of parenteral quality control are incoming stocks, manufacturing and Finished products. The Basic quality control tests which are performed on sterile parenteral products include:-

Sterility tests:- Sterility is the most important and Absolutely Essential characteristics of Parenteral products. Sterility means complete absence of all viable Micro-organism. It is an absolute term. The methods which are used to perform sterility tests are a) Direct transfer method. B) membrane filtration method.

Direct Transfer method:- it is an traditional sterility test method which involves a direct inoculation of required volume of a sample in two tests tube containing a culture medium that is FTM, SCDM. This method is simple in theory but difficult in practice when the demand for repetition in opening container, sampling Transferring, and mixing increases causes potential fatigue to the operator and detoriation in operator technique.

Membrane Filtration method:- It is official in U.S.P. 1970. It is more popular and widely used method over direct transfer method. Successful Employment Requires a more skill and knowledge than Direct transfer method. This method basically involves filtration of Sample through membrane filters of porosity 0.22 micron and Diameter 47mm with hydrophobic characteristics. 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, SCDM medium.21

Pyrogen Test: - Pyrogens are products of metabolism in microorganisms Gm-ve bacteria produces most potent pyrogens. These are lipopolysacchrides chemically and heat stable and are capable of passing through bacteria retentive filter. When these pyrogens are introduced into a body they produce a mark response of fever with body ache and vasoconstriction within an onset of 1 hour. Basically there are test performed to detect the presence of pyrogens in sterile parenteral products they are C) Rabbit Test D) LAL Test.

Leaker Test:- The leaker test is intended to detect incompletely sealed ampules, so that they may be discarded. Tip sealed ampoules are more prone to leak than pull sealed. In addition to that crack my present around seal or at the base of ampule as a result of improper handling leakers are usually detected by producing negative pressure within the incompletely sealed ampule usually into a vaccum chamber while those ampule are submerged into a colored dye solution of 0.5 to 1% methylene blue. Vials and bottles are not subjected to such leaker test because rubber closure is not rigid however bottles are often sealed while vaccum is pulled so that bottle remains evacuated during its shelf life.

The presence of vacuum is detected by striking at the base of bottle sharply with the heel of hand to produce typical water hammer sound. Another test is to apply a spark tester probe outside to the bottle moving form liquid layer into air space a blue spark discharge occur is air space is evacuated.22

Particulate matter testing:- Particulate matter is primary concern in the parenteral products given by I.V. Route, all parenteral products should be free from insoluble particle. Further U.S.P. states that GMP Requires that all containers be visually inspected and that with visible particle be discarded. It is found that formation of pathologic ganulomes in vital organs of body can be traced to

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fiber, rubber fragment and other solid present in intravenous solutions. The visual inspection is done by holding the ampule by its neck against highly illuminated screens. White screens for the detection of black particle and black screens for the detection of white particles to detect heavy particles it may be necessary to invert container but care must be exercised to avoid air bubble. The instrumental methods are based on principles of light scattering, light absorption, electrical resistance as in coulter counter. A method which utilizes a video image projection could detects a moving particle without destruction of product unit.22

Application Of Parenteral Preparation

1. Parenteral drug are administration directly in to vein ,muscles or under the skin.
2. It is used for emergency situation.
3. It is useful for delivering fluid, electrolytes,or nutrients.
4. It is used for the antimicrobial agent.
5. It is used for the antioxidant agent.
6. It is useful for effective drug delivery system.
7. It is used for the therapy of serious infections.
8. It is used for mild inflammation.
9. It is used for thrombosis (blood clots).
10. It is used for micronutrients deficiency.
11. It is used for hypoglycemia.
12. It is used for chemotherapy.
13. It is used for dextrose provide calories by given intravenously.
14. It is used for metabolic bone disease.
15. It is manage for toxicity.
16. It is used for hyperglycemia. 23

II. CONCLUSION

The optimization of several process and formulation parameters for the production of a parenteral dosage form utilising DOE is the emphasis of this chapter. During formulation development, the researchers face severe technical obstacles, which necessitates the employment of an effective formulation development process. For the optimization of many formulation and process factors, DOE and statistical analysis are viable tools. The significant benefit of using DOE to design pharmaceutical product formulations is that it allows all critical factors to be assessed systematically and precisely. Once the crucial factors have been determined, the best formulations may be finished by employing precise DOE to optimise the values of all critical variables. For researchers, DoE is the first choice for rational pharmaceutical development.

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