



PARENTERALS – A VERSATILE AND PROMISING DRUG DELIVERY SYSTEM

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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.

Key words: Efficacy, Injection, Pyrogens, Stability, Sterile, Toxicity.

INTRODUCTION

Parenterals are pyrogen free, sterile dosage forms which are administered through routes other than oral route. The term parenteral derives from the Greek word: para which means outside and enteron which means intestine. Injections act rapidly, with onset of action in 15-30 seconds for IV, 10-20 minutes for IM, and 15-30 minutes for SC. They also have essentially 100% bioavailability, and can be used for drugs that are poorly absorbed or ineffective when given orally.^[1] Some medications, such as certain antipsychotics, can be administered as long-acting intramuscular injections.^[2] IV infusions can be used to deliver continuous medication or fluids.^[3] Other advantages include Possibility of accurate dosing, minimized first pass effect and can be administered to unconscious patients, infants, elderly persons and patients who cannot take oral medications.

Disadvantages of injections include potential pain or discomfort for the patient, and the requirement of trained staff using aseptic techniques for administration. As the drug is delivered to the site of action rapidly with IV injection, there is a risk of overdose if the dose has been calculated incorrectly, and there is an increased risk of side effects if the drug is administered too rapidly. Similarly drug when administered through wrong route may produce fatal effect and withdrawal of administered drug is not possible in parenteral route.

ROUTES OF PARENTERAL ADMINISTRATION

Parenteral routes of administration mainly include three primary routes which are commonly employed: intramuscular, subcutaneous and intravenous. To a large extent these three routes satisfy the four main reasons for administering parenterals like, for therapy, for prevention, for diagnosis and for temporarily altering tissue function(s) in order to facilitate other forms of therapy. Under special circumstances, other routes are also employed for parenteral administration.

Intravenous route^[4]

Intravenous route of administration is the route of administration in which injections or infusions are administered directly into the vein. It is one of the most common parenteral routes employed in hospitals today for the purpose of administration of drugs, fluids and/or electrolytes. It is convenient for rapidly infusing large volume of fluids. The most common indications for use of this route are:

- To guarantee distribution and delivery when hypotension or shock exists.
- To achieve an immediate pharmacological response, especially in emergencies.

- To restore rapidly fluid and electrolyte balance.
- To avoid complications which might occur by administration through other routes.
- To treat serious, life-threatening infections or conditions.
- To provide continuous nutrition when patients are unable to be fed by mouth.

There are chances of large number of complications occur using the intravenous routes. They are:

- Chances of thrombosis with or without complicating infection at the site of injection or infusion.
- Injection of toxins, microorganisms, particulate matter, or air.
- The occurrence of physical or chemical incompatibilities between agents prior to or at the time of injection.
- Uncontrolled or excessive administration of fluids or drugs.
- Extravasation of injections or infusions at the site of administration.

Intramuscular route

Intramuscular route of administration is the route of administration in which injections are injected directly into the body through a relaxed muscle. It is the most convenient route available for both the administrator and for the patient, especially for children. This route provides a means of sustained release of drugs formulated as aqueous or oily solutions or suspensions. This route is preferable when compared to subcutaneous routes when a rapid rate of absorption is required and over the intravenous route when the drug 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, especially an artery, which might lead to an infusion of a toxic agent or toxic vehicle directly to an organ or tissue. [5, 6, 7, 8]

Intradermal route

Intradermal route is also known as intracutaneous route. The administration is called intradermal when the injection is given into the dermis which is located just beneath and adjacent to the epidermis. Various diagnostic agents, vaccines and antigens are administered through this route. The volume of injection administered through this route does not exceed 0.1ml. Absorption by intradermal route is very low.

Intra-articular route

The route through which infusion or injection is given into the synovial sacs of different accessible joints is known as intra-articular route. Corticosteroids, lidocaine and antibiotics are mostly administered through this route for infections, inflammations, pain or other problems resulting from inflammatory diseases. Certain agents are administered in a single injection whereas some other agents like certain antibiotics are given via continuous infusion and bathing of the joint. But, there are chances of iatrogenic infection following this route of administration.^[9, 10] The consequence of such injection may lead to destruction of joints.

Subcutaneous route

It is the route through which injection is given into the loose connective and adipose tissue beneath the dermis. Subcutaneous route is mainly preferred 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. Subcutaneously administered medications are insulin, vaccines, narcotics etc. 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. Medications, highly acidic or alkaline, causing irritation, pain, inflammation and/or necrosis of tissues cannot be administered by subcutaneous route.

Intraperitoneal route

The route of administration in which the injection or infusion is given directly into the peritoneal cavity via a needle or indwelling catheter or directly into an abdominal organ, such as the kidney, liver or bladder is known as intraperitoneal route. This route is mostly employed to treat local or wide spread intra-abdominal disease due to tumor or infection; to dialyze and remove different toxic substances from the body when various renal failures prohibits removal; and to determine the patency, as well as the structure of various vascular or collecting systems. There are chances of infection and hemorrhage complications followed by intraperitoneal route of administration. The risk of infection is usually enhanced if an indwelling catheter, rather than a single injection using a sterile needle, is utilized.^[12, 13]

Intra-arterial route

Injection or infusion given into an artery which leads directly to the target organ is known as intra-arterial route of administration. This route is employed generally for the purpose of injecting radiopaque substances for roentgen graphic studies of the vascular supply of various organs or tissues. This route is generally used for organ specific chemotherapy. This route is found to be extremely hazardous; because products administered intra-arterially are not sufficiently diluted nor are they filtered by lungs, kidney or liver before contact with the peripheral tissue(s), vital organs nourished by the artery.

Intracardiac route

Injections given directly into the chambers of heart is called intracardiac route of administration. When better routes of delivery are required this route is preferred. Under unusual circumstances and during certain emergency conditions, such as cardiac arrest, in which the drugs have to reach the myocardium rapidly, intracardiac injections may be used. Precautions should be taken to prevent heart muscle, coronary arteries, or conducting systems from damaging by the trauma of an injecting needle or by the drug injected. There are chances of hemorrhage into the myocardium or pericardium by this route.

Intracisternal route

Injections when given directly into the cisternal space surrounding the base of the brain is called intracisternal route of administration. This route is mainly used for diagnostic purpose. It is mostly used in case of elevated intracranial pressures and the risk of herniation of the brain exists, if fluid is removed from the lumbar sac.

Intralesional route

Injection given directly into or around a lesion, usually located in or on the skin or soft tissues, to achieve a therapeutic effect. This is effective in case of a potential local effect. It is useful in neutralizing various toxins, like tetanus. A similar therapeutic usefulness has been assured for rabies, with direct injections of antisera into and around the site of the bite.

Intraocular route

Injections given directly into the eye cavity are known as intraocular route of administration. Four types of intraocular injections are utilized.

- Anterior chamber: Injections given directly into the anterior chamber of the eye.
- Intravitreal: Injection given directly into the vitreous chamber of the eye.

- Retrobulbar: Injection around the posterior segment of the globe.
- Subconjunctival: Injection given beneath the conjunctive, so that the medication diffuses through the limbus and sclera into the eye.

Intrapleural route

Injection given into the pleural cavity is called as intrapleural route. If dwelling chest tubes are inserted surgically, this route may be used for irrigation purposes or for repeated injections of drugs. At certain conditions, if infections or malignancies involving the pleural cavity, particularly if the disease process is impairing respiratory function, are treated by this route.

Intrathecal route

Injection or infusion given directly into the lumbar sac located at the caudal end of the spinal cord. This route is mostly used for the purpose of diagnostic than for the therapeutic purpose. The treatment frequently comprises of injecting or infusing a suitable chemotherapeutic agent into the lumbar sac and depending on the weight of the substance injected, tilting the patient to encourage distribution over the hemispheres.^[15]

Intrauterine route

Injection or infusion given through a needle inserted percutaneously into the pregnant uterus. It can also be used for delivering calcitonin and insulin. Usually after the sixteenth week of pregnancy, injections or infusions of certain substances like 20% saline, prostaglandin E, or urea to induce labor in medical abortions or to deliver a still born fetus.

Intraventricular route

Injection or infusion given directly into the lateral ventricles of the brain is called intraventricular route of administration. This route is mostly used in cases of infections or malignancies involving the membranes and the cerebrospinal fluid surrounding the central nervous system.

FORMULATION OF PARENTERALS

Formulation of parenterals includes Solutes, Additives or Added substances and Vehicles

SOLUTES

They are dry solids, when added to suitable vehicles yield solutions conforming in all aspects to the requirements for injections. This includes active pharmaceutical ingredient(s) or

drug(s).

ADDITIVES OR ADDED SUBSTANCES

They are suitable substances which may be added to the preparations intended for injections to improve the usefulness or stability, unless prescribed in the individual monograph, provided they are harmless in the amount administered and do not interfere with the therapeutic efficacy of the preparation or with the responses to the specific assays and tests.

a) Antimicrobial agents

Substances that kill or inhibit the growth of micro-organisms like bacteria, fungi or protozoans are termed as antimicrobials. Antimicrobials are mostly grouped according to the micro-organisms they act primarily against. Phenol, thiomersol, benzethonium chloride, benzyl alcohol and chlorobutanol are certain examples of antimicrobial agents. During the shelf-life of a product, the concentration of the antimicrobial added to any multi-dose or single dose parenteral preparations may diminish. Therefore, the lowest level at which it is effective is determined so that the efficacy can be maintained throughout the shelf-life of the product.

b) Buffering agents

They are substances which are added to maintain the pH of the formulation within the pharmacopoeial limit. Maintaining of the pH is very important for avoiding irritations that may be produced if pH is not maintained properly. Some of the commonly used buffering agents are sodium hydroxide, citrates, phosphates etc.

c) Antioxidants

They are substances which improves the stability of the preparation by delaying the oxidation of the API and other excipients present in the formulation. Examples of such antioxidants are ascorbic acid and sodium bisulfite etc. Antioxidants are classified into three groups:

True antioxidants: They inhibit oxidation by reacting with free radicals and blocking chain reactions.

Reducing agents: These substances have lower redox potentials than the API and the excipients that they are intended to protect. Therefore, they get themselves oxidized. They also operate by reacting with free radicals.

Antioxidant synergists: They have less antioxidant property themselves, but they enhance the antioxidant property of the first group by reacting with the heavy metal, ions that catalyze

oxidation.

d) Tonicity agents

They are substances which are used to maintain the isotonicity, so that the pain of injection is reduced. Examples of tonicity agents are sodium chloride, potassium chloride, dextrose, mannitol, sorbitol etc.

e) Cryoprotectant

Cryoprotectants are used to protect biological tissues from freezing damage. It acts by increasing the solute concentration in cells. Examples are sugars, glycerols, polyols etc.

f) Suspending agents

They are excipients which are added to the formulation in order to improve the stability of the formulation by preventing the sedimentation of the particles. They are mostly used in injectable suspensions. Gelatin and PVP are some examples.

g) Emulsifying agents

Emulsifying agents are added to injectable emulsions in order to increase the stability of the formulation. They are used to prevent separation of two phases. Examples of emulsifying agents are soap, SLS etc.

h) Chelating agents

They are substances which act on metals which catalyze degradation and inactivate them. Example is EDTA, disodium edetate, tetra sodium edetate etc.

i) Co-solvents

Co-solvents are solvents which are added in smaller quantity to the formulation to enhance the solvent power of the primary solvent. Examples of co-solvents are ethanol, PEG, glycerin 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. Generally water for injection is used as vehicle, unless otherwise specified in the

individual monograph. Aqueous vehicles used for the purpose of formulation of small volume parenterals are:

a) 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 pH of water for injection is 5.0 to 7.0. The USP requirement is not more than 10 parts per million of total solids. Reverse osmosis or distillation is used for the preparation of WFI. It is stored in chemically resistant tank for less than 24hrs at room temperature or for longer period at specific temperature. It should not contain any added substances. It should meet USP pyrogen test.

b) Bacteriostatic Water for Injection (BWFI)

Bacteriostatic water for injection is used for making parenteral solutions which are prepared under aseptic conditions and not terminally sterilized. It may contain any bacteriostatic agents when contained in containers of 30ml or less. It should meet USP sterility test.

c) Sterile Water for Injection (SWFI), USP

This is also known as sterile water for irrigation. It is used for washing wounds, surgical incisions or body tissues. Multiple dose containers not exceeding 30ml are mostly used for this. It contains one or more suitable bacteriostatic agents.

Non-aqueous vehicle

Non-aqueous vehicles used for the purpose of formulation of parenterals are of two types: water miscible and water immiscible. The water miscible vehicles used are glycerine, polyethylene glycols, propylene glycols, alcohol. Examples of water immiscible vehicles are corn oil, cotton seed oil, peanut oil, sesame oil etc. The non-aqueous vehicles are used, only in case provided these are safe, in the volume of injection administered, and also provided they do not interfere with the therapeutic efficacy of the preparation or with its response to prescribed assays and tests.

TYPES OF PARENTERALS

Dry powders for injections

Dry powders for injections are the dosage forms which get converted into solutions or suspensions due to the process of reconstitution during administration. Here, drug is filled into reconstituted vials directly. E.g: - Cefuroxime injection.

Liquid injectable systems

They are dosage forms containing liquid injectables for administration. Liquid injections can

be directly administered with or without dilution according to the need. E.g.: Bupivacaine Hydrochloride Injection.

Lyophilized powders for injections

Lyophilized powders for injections are the dosage forms which also get converted into solutions or suspensions after reconstitution during administration. E.g.: Ceftriaxone Injection

Colloidal solution

They are normal solution of sodium chloride at 0.9% w/v concentration, which is close to the concentration in blood. A colloidal solution is a homogeneous solution in which the particles are found to be dispersed in a liquid phase. E.g.: - Iron dextran.

Injectable emulsions

They are liquid preparations of drug substances dissolved or dispersed in a suitable emulsion medium. Injectable lipid emulsions, for decades, have been clinically used as an energy source for hospitalized patients by providing essential fatty acids and vitamins. Recent interest in utilizing lipid emulsions for delivering lipid soluble therapeutic agents, intravenously, has been continuously growing due to the biocompatible nature of the lipid-based delivery systems. E.g.: - Propofol US

Injectable suspension

They are liquid preparations of solids, suspended in a liquid medium. Injectable suspensions are used for the purpose of prolonging the action of the drug. These are mostly used as sustained or controlled release parenteral dosage forms. A suspension usually provides prolonged action when compared to aqueous solution when given subcutaneously or intramuscularly. E.g.: - Methylprednisolone acetate.

Oily injection

Through the use of oily solutions, parenteral controlled release dosage forms can be prepared. Here, the release of drug is controlled by the drug partitioning into the aqueous medium from the oil medium. E.g.: - Dimercaprol injection.

According to the dosing, parenteral preparations are further classified into two types.

a) Single-dose preparations

It can be used only once. Single-dose preparations contain sufficient quantity of the injection which readily permits the withdrawal and administration of the volume specified on the label.

b) Multidose preparations

An antimicrobial preservative in appropriate concentrations will be present in multidose preparations, except in cases where the formulations themselves have adequate antimicrobial characteristics. After partial withdrawal, there are more chances of contamination. Therefore, the containers should be equipped to ensure adequate protection of the contents. The contents of a multidose preparation normally should not exceed 30 ml as the risk of contamination is high with multiple penetrations of closures. ^[18]

TYPES OF CONTAINERS

Glass and plastic containers are used for the packaging of parenteral dosage forms. Glass are original parenteral packaging material, has superior clarity, facilitating inspection for particulate matter. Compared to plastics, glass less frequently interacts with the preparation it contains. Plastic polymers used for parenteral packages include polyvinylchloride (PVC) and polyolefin. Both types of plastic offer several advantages over glass, including durability, easier storage and disposal, reduced weight, and improved safety.

Ampoules

Ampoules are for single use only. They are opened by breaking at a score line on the neck of the glass. The product should be filtered before administration as there are chances of dislodging of glass particles during ampoule opening. The use of ampoules has been reduced due to their unsuitability for multiple-dose use, the need to filter solutions before use and other safety considerations.

Vials

Vials are glass or plastic containers which are closed with a rubber stopper and sealed with an aluminium crimp. Certain drugs which are unstable in solution form are packaged in vials in powder form and must be reconstituted with sterile sodium chloride for injection before use. The advantages of vials over ampoules are that vials can be designed to hold multiple doses (if it is formulated with a bacteriostatic agent), Removal of the product is easier and the contamination of the product with the glass particles during the process of opening gets eliminated with the use of vials. However vials have certain drawback such as coring of rubber stopper, microbial contamination may occur due to multiple withdrawals.

Prefilled syringes

Prefilled syringes are designed for quickest and convenient administration. When packaged in

these prefilled syringes, the drugs can be administered in an emergency (e.g., atropine, epinephrine) and may be available for immediate use.

Infusion solutions

Infusion solutions are used for the intermittent or continuous infusion of drugs or fluids. These are divided into two types: small volume parenterals (SVP), those having a volume of 100 ml or less; and large volume parenterals (LVP), those having a volume of 100 ml or greater.

Cartridges

Cartridge injection system is a convenient and easy to use method of injection that facilitates sterility and accuracy. The device consists of a plastic cartridge holder syringe and a prefilled medication cartridge with needle attached. The medication in the cartridge is premixed and premeasured. Therefore, it saves time and helps to ensure an exact dose.

Automatic injector

It is a medical device designed to administer a drug at a single dose. Most of the auto injectors are spring loaded syringes. These are easy to use and are intended for self administration by patients or any untrained personnel.

PREFORMULATION FACTORS AFFECTING PARENTERAL MEDICATIONS

Preformulation is the study of physical and chemical properties of drug prior to formulation. The preformulation research is related to analytical and pharmaceutical investigations that both precede and support formulation development efforts for all dosage forms. These studies are performed under stressed conditions of temperature, humidity, light and oxygen so that the reactions are accelerated and potential reactions can be detected. There are various physicochemical properties which affect a drug substance. They are

Color

Color is a property of inherent chemical structure of drug which indicates intensity or level of unsaturation. Color intensity depends on the extent of conjugated unsaturation, also the presence of chromophores such as $-\text{CO}$, $-\text{NO}_2$ and $-\text{NH}_2$. Certain saturated compounds also exhibit color due to minute traces of highly unsaturated, intensely colored impurities and / or degradation products. During highly stressed conditions of heat, light and oxygen, most of these compounds tend to produce color. Mostly, a significant color change becomes a

limiting factor to the shelf life of a parenteral product even before a significant change in chemical stability is noted.

Odor

The odor of a new drug substance is examined by cautiously smelling the headspace of the drug container which has been previously closed in order to allow concentration of volatiles. The presence and description of any odor is recorded.

Molecular structure and weight

Molecular structure and weight are the basic characteristics of the drug which must be determined. From the molecular structure, potential properties and reactivities of functional groups can be determined.

Particle size and shape

These characteristics are usually determined by microscopic evaluation by using a scanning electron microscope or an optical microscope with polarizing attachments. For the purpose of comparing with the future batches, the morphological characteristics of the drug substances should be recorded either by a sketch or, more accurately, by a photomicrograph as a permanent record. The crystalline and amorphous character of a drug can be determined by using a polarizing microscope. Polarized lights are refracted by crystalline materials and are thus visible when polarization attachments in the ocular and objectives are crossed at a 90° angle, whereas amorphous or glassy substances become invisible.

Thermal Analytical profile

Samples may have been exposed to changes in temperature environment during synthesis and isolation which may be exhibited as a thermal profile, when the sample is heated between ambient temperature and its melting point. The sample will neither absorb nor give off heat prior to its melting point, if no thermal history exists for the compound. The basic technique used to study this phenomenon is called differential thermal analysis (DTA). Melting or fusion, crystalline structure changes such as polymorphic transitions, boiling, sublimation and desolvation are certain examples of characteristic endothermic transitions that can be detected by this technique. Differential Scanning Calorimetry (DSC) is a similar process. Thermogravimetric analysis (TGA) is also a thermal analytical method used to detect the existence and stability of solvated drug molecules.

Melting point

Thermodynamically, the melting point of a substance can be defined as the temperature at

which the solid and liquid phases are in equilibrium. Melting point determination is a primary indication of purity since the presence of relatively small amounts of impurity can be detected by a lowering and widening in the melting point range.

Hygroscopicity

Hygroscopicity is the phenomenon of absorption of moisture by compounds under specific conditions of moisture and humidity. The physical and chemical properties of a drug substance can be adversely affected by high degree of hygroscopicity, making it pharmaceutically difficult or unsatisfactory to work with. These studies are conducted over a range of humidity conditions relevant to the general laboratory and manufacturing areas as well as uncontrolled storage environment.

The study is carried out by taking accurately weighed samples of compound into tared containers and placed at different conditions of humidity for time periods up to 2 weeks. Any gain or loss in weight is measured at predetermined intervals until equilibrium is reached. If the drug is found to be very hygroscopic or determined to be unstable in the presence of moisture, the drug would have to be stored under dry conditions and worked with under low humidity. Compounds are grouped according to hygroscopicity classification as below.

CLASS I – Non hygroscopic

At relative humidities of below 90%, essentially no moisture increases occur. Also, the increase in moisture content after storage for 1 week above 90% relative humidity (RH) is less than 20%.

CLASS II – Slightly hygroscopic

At relative humidities below 80%, essentially no moisture increases occur. The increase in moisture content after storage of 1 week above 80% RH is less than 40%.

CLASS III – Moderately hygroscopic

At relative humidities below 60%, moisture content does not increase above 5%. The increase in moisture content after storage for 1 week above 80% RH is less than 50%.

CLASS IV – Very hygroscopic

At relative humidities as low as 40 to 50%, there are chances of moisture. The increase in moisture content after storage for 1 week above 90% RH may exceed 30%.

Solubility

For developing solutions that can be injected either intravenously or intramuscularly,

solubility is of prime importance. In general, solubility is a function of chemical structure; salts of acids or bases represent the class of drugs having the best chance of attaining the degree of water solubility desired. According to the drug moiety the analytical method used for measuring solubility may vary. If unsaturated conjugation is present in the drug structure, enabling it to absorb visible or ultraviolet light, spectrophotometric analysis can be performed. Determination of solubility of compounds that do not absorb uv or visible light can be attempted by transferring filtered aliquot solutions on to previously tared weighing pans, evaporating the solvent, and drying to constant weight under low temperature conditions.

Optical activity

Optical activity is the phenomenon of rotation of plane polarized light by a capable compound. If the compound rotates the beam of light to the right or clockwise by an angle α , the substance is said to be dextrorotatory and if the compound rotates the beam of light to the left or anti-clockwise direction, the substance is said to be levorotatory.

Ionization constant

From the ionization constant, the pH dependent solubility of a compound can be determined. Potentiometric pH titration or pH –solubility analysis is used for determination of pka. The degree of ionization of an acid or base is determined by the ionization constant of the compound.

Partition coefficient

The partition coefficient P is a measure of lipophilicity of a compound. Partition coefficient can be measured by determining the equilibrium concentration of a drug in aqueous phase and oil phase held in contact with each other at a constant temperature. It can be expressed as

$$P = [C \text{ oil}]/[C \text{ water}]$$

PHARMACEUTICAL FACTORS AFFECTING PARENTERAL ADMINISTRATION

Solubility of drug and volume of injection

Before administered by intravenous injection, the drug must be completely solubilized preferably in water. The volume of the injection can be determined by the extent of drug solubility in its intended vehicle and the dose required for the desired therapeutic effect. Except intravenous routes other parenteral routes have limitations regarding the maximum volume of medication administered.

Vehicle character

Drugs in aqueous vehicle can be administered by any parenteral routes whereas drugs in non aqueous vehicles, which may or may not be water miscible, are administered most frequently by intramuscular route. Intravenous routes are mostly used for few drugs in mixed solvent system, but precaution must be taken to prevent drug precipitation at the site of infusion.

Type of dosage form

Solutions, suspensions and sterile solids for reconstitution include parenteral dosage forms. Intramuscular or subcutaneous route is used for suspensions. Particles should not be present in dosage forms administered intravenously or by other parenteral routes in which the medication enters directly into a biological fluid or sensitive organ tissues like brain or eye. Reconstituting diluents are used for completely dissolving sterile solids before they are administered intravenously.

Formulation ingredients

Other than the main therapeutic agents, parenteral formulations may contain various active and inactive excipients for a variety of reasons. For multidose parenterals, antimicrobial agents are added to the formulation for the preservation of sterility. To maintain drug solubility in the solution vehicle, surface active agents like polysorbate 80 are added. The expanding field of sustained or prolonged release of drug delivery employs various formulations and additives that at times aid in achieving the desired duration of drug action. These additives are primarily high molecular weight polymers or oily solvents. Formulations containing these macromolecules are administered by the subcutaneous or intramuscular routes to permit the delayed release of the active ingredient within deeper tissues of the body.

pH and osmolarity of injectable solutions

Injections for administration should be formulated at a pH and osmolarity similar to that of the biological fluids. But, this found to be impossible for many parenteral dosage forms, as many parenteral drugs are unstable at neutral pH. Therefore, such drugs are formulated at pH at which they are most stable. Some parenteral formulations are hyper osmotic with biological fluids and contain a relatively high dose of active ingredient(s) in order to achieve a desired level of biological activity. Hypertonic parenteral dosage forms are contraindicated for subcutaneous or intramuscular injections. The vitreous humour can tolerate only very few narrow ranges of osmotic values from an injected medication. Therefore, although stability and solubility problems may prevent dosage forms from being formulated at physiological

pH, they should be formulated with solute contents approximately equal to those of biological fluids.

General Procedure For Manufacturing Of Parenterals

General procedure for manufacturing of parenterals include planning and scheduling of equipments, material managements, manufacturing requirements like ingredients, drugs etc.The overview of manufacturing process of parenterals is shown below.

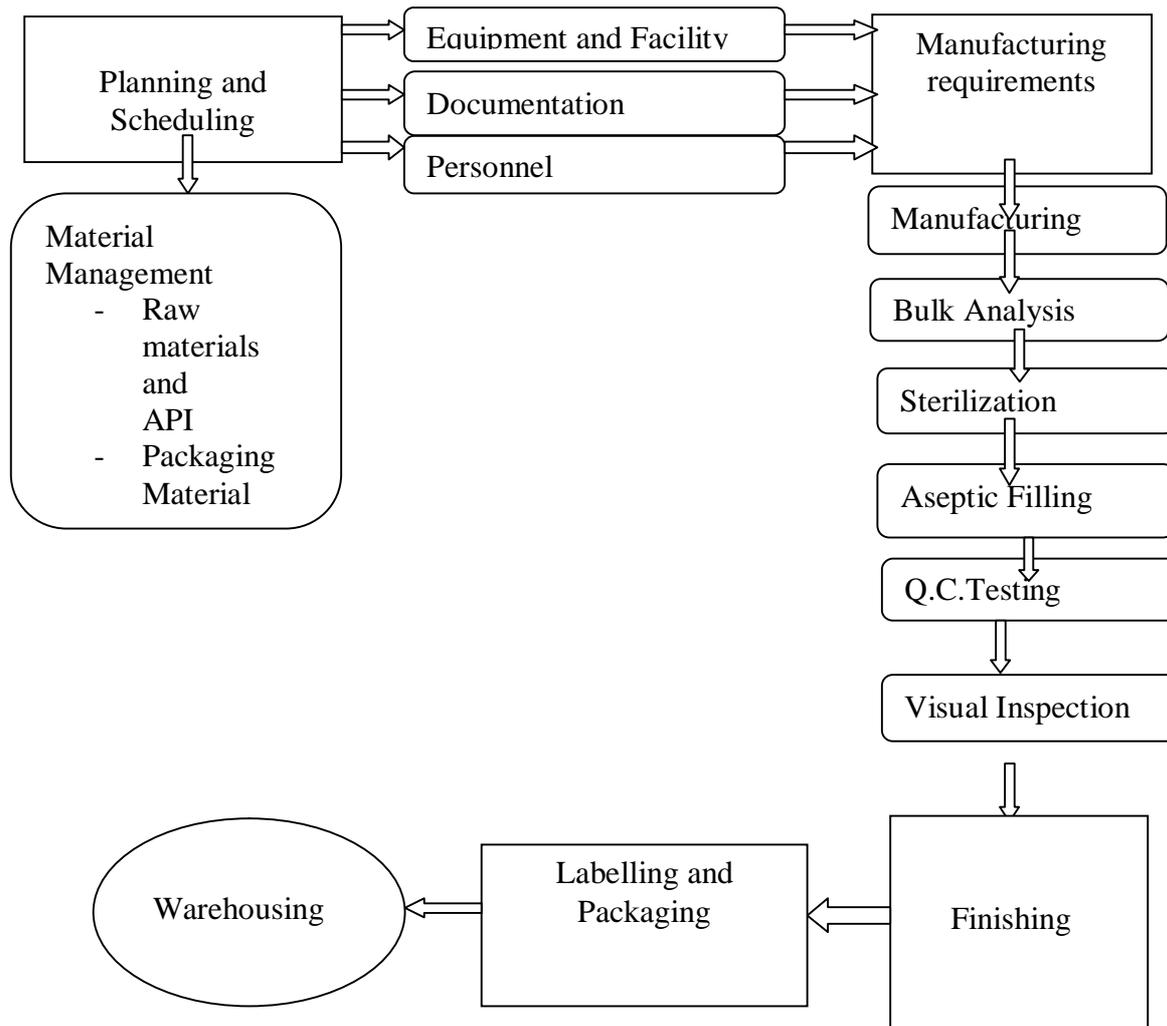


Fig.1 Flow Chart of Manufacturing Process of Parenterals

Steps Involved

The general procedure for manufacture of parenterals includes,

- Cleaning and washing of containers and closures.
- Preparation of solutions.
- Sterilization (Filtration).

d) Filling, Packaging and Labelling.

The passage of materials through various steps of the production process is shown in fig .2

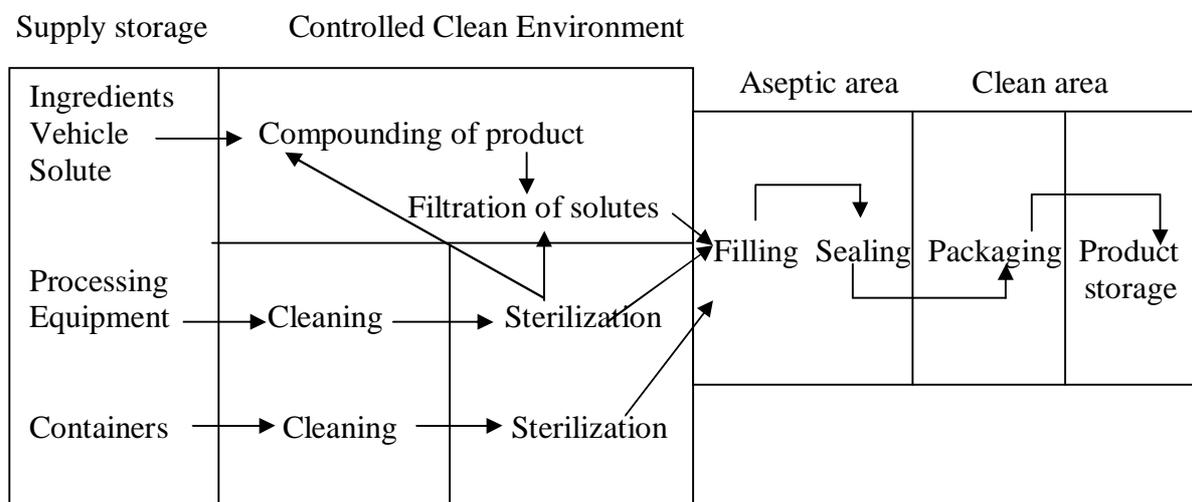


Fig. 2 Flow Chart of Materials through Production Department

a) Cleaning and washing of containers and closures

The vials are cleaned by soaking them in detergent solution overnight to remove any sticking particles, grease etc and wash with tap water three to four times till soap solution is completely removed. Remove surface alkalinity using 1.0% hydrochloric acid and wash again with tap water. Rinse with de-ionized water and finally with distilled water and subjected to sterilization for 4hrs under 200°C. Rubber closures are boiled with 1.0% detergent solution for 30 minutes and wash it with tap water till free from detergent. Boil for 30 minutes using 1.0% hydrochloric acid solution and wash with tap water. Boil with 1.0% sodium carbonate and wash again. Treat them with double strength bacteriostatic solution. Wash three to four times with pyrogen free water. Sterilize by autoclave at 115°C for 30 minutes.

b) Preparation of solution

Dissolve the API in water for injection with constant stirring. After completely dissolving the drug, other excipients are added one by one and stirred until dissolved. The pH is adjusted to the required range by using buffering agents like sodium hydroxide and hydrochloric acid. Make up the volume and mix with water for injection. The pH is again adjusted if necessary.

c) Sterilization

Sterilization is defined as a process of elimination or killing of micro-organism by various means contained in a fluid, present on a surface, in medication, or in a compound such as biological culture media. Sterilization can be achieved by applying chemicals, heat, irradiation, high pressure and filtration.

Processing of sterile products

Processing of sterile products can be performed in three ways. They are as follows:-

1. Terminal sterilization
2. Sterilization by filtration
3. Aseptic preparation

i) Terminal sterilization

It mainly involves preparation, filling and sterilization. It includes usually filling and sealing of product containers under high-quality environmental conditions. The microbial and particulate content of the in-process product is minimized and also it ensures the sterility of the product. Heat or irradiation sterilization process is carried out for products in its final container to ensure sterility.

ii) Sterilization by Filtration

In sterilization by filtration, containers which are previously sterilized are used. Here, filter having a pore size of about 0.22 μm or less is used for the purpose of filtration. Second filtration or double filtration is possible. By filtration sterilization, it is possible to remove bacteria and moulds but removal of virus and mycoplasmas are not applicable.

iii) Aseptic Preparation

The drug product, container, and closure are first subjected to sterilization methods separately and then brought together in an aseptic process. Here there is no process of sterilization of the product in its final container, it is critical that containers should be filled and sealed in an extremely high-quality environment. The individual parts of the final product are generally subjected to various sterilization processes before aseptic assembly into a final product.

d) Filling, Packaging and Labelling

After sterilization procedures the solution is then filled into suitable containers. Bulk preparations are subdivided into unit dose containers during filling. This process forces a measured volume of the preparation through the orifices of a delivery tube designed to enter

the constricted opening of a container by means of gravity, vacuum or with the aid of a pressure pump. After filling, the containers are sealed which will retain the contents of the sterile product and will assure a tamper-proof presentation. When a parenteral preparation is liable to deterioration due to oxidation, the operation of filling may be performed in an atmosphere of suitable inert gas like nitrogen, whereby the air in the container is replaced with this gas.

The best packaging materials used are Tyvek and paper. The packaging should be done in such a way that it maintains product sterility until the time of use and also prevent contamination of content during opening.

The purpose of label is to state the name of the preparation; if liquid preparation, amount of drug in a specified volume or the percentage drug content; in the case of a dry preparation, the amount of active ingredient; the route of administration; the storage conditions; the expiration date; the name and place of business of the manufacturer, packer, or distributor; and identifying lot number. The complete manufacturing history of the specific package, including all manufacturing, filling, sterilizing and labelling operations can be determined from the lot number.

EVALUATION TEST FOR PARENTERALS

Sterility test

It is one of the most and essential characteristics of parenteral product. It indicates complete absence of all micro-organisms.^[22] The methods which are used to perform sterility studies are:

a) Direct transfer method

It involves direct inoculation of required volume of a sample in two test tubes containing a culture medium. This method is theoretically simple but practically tough due to continuous opening of container, sample transferring, and mixing that may cause potential fatigue to the operator and deterioration in operator technique. Because of all these, there are chances for contamination.

b) Membrane filtration method

Membrane filtration method is most widely used method. It requires more skill and knowledge for efficient employment when compared with direct inoculation method. This method basically involves filtration of sample through membrane filters of 0.22 micron and

diameter 47 mm with hydrophobic characters. The filtration is assisted under vacuum. The membrane is cut into two halves and placed in two test tubes containing the culture medium after filtration is completed. If there is no growth of micro-organism in the test tube containing the culture medium, it is interpreted that the sample is without intrinsic contamination. If visible micro-organism growth is seen or the test is judged to be invalid because of inadequate environmental conditions the sterility test is repeated.

Test for pyrogen

Pyrogens are metabolic products of micro-organisms. Most potent pyrogens are produced by gram negative bacteria. These are heat stable, lipopolysaccharides which are capable of passing through bacteria retentive filters. They produce a mark response of fever with body ache and vasoconstriction when injected into the body within an onset of 1 hr. Generally, there are various tests to detect the presence of pyrogen in sterile parenteral products. They are:

a) Rabbit test

Rabbit test mainly involves administration of the sample solution by injection which is to be tested in rabbits through ear vein. The temperature sensing probe like clinical thermometer is inserted into the rectal cavity of rabbit up to a depth of 7.5 cm. The control temperatures of rabbits are determined, prior to 1hr of injecting sample solutions. The test solution must be warmed at 37 degrees prior to injection. Then the rectal temperature is recorded at 1, 2, 3 hr subsequent to the injection. This test is conducted in separate area designed solely for this purpose with environmental conditions similar to animal house. Initially the test is performed on 3 rabbits and if required the test is further repeated on 5 additional rabbits with same sample solution. Use only those rabbits whose control temperature is no vary by more than 1 degree Celsius. If no single rabbit show rise in temperature of 0.5 degree Celsius, the solution is judged to be non pyrogenic, but if this condition is not met then the test is repeated on 5 additional rabbits with same preparation administered to initial first 3 rabbits. The solution is judged to be non pyrogenic, if NMT 3 of 8 rabbits show individual temperature rise of 0.5 degree Celsius.

b) LAL test

This is a recently developed *in vitro* test method for pyrogens utilizing gelling property of lysates of amebocytes of limulus polyphemus which is found only at specific locations along the east coast of North America and along southeast Asia. It is derived from horse

shoe crab. The basic procedure is the combination of 0.1 ml of test sample with LAL Reagent. After incubation for 1 hr at 37 degree Celsius, the mixture is analyzed for the presence of gel clot. If the LAL Test is positive, it indicates that endotoxin is present. This method has several advantages upon Rabbit test as they have greater sensitivity and reliability, specificity, less variation, wider application, less expensive and simplicity.

Clarity test

Clarity is tested by conducting a visual inspection of containers under light and viewed against a black and white background. The instrumental method of evaluation is based on the light scattering principle, electrical resistance and light absorption which are used to count particle and particle size distribution. The visual inspection of a product container is usually done by individual human inspection of each externally clean container under a good light, baffled against reflection into the eyes and viewed against a black and white background, with the contents set in motion with a swirling action. For monitoring particulate matter, two tests are conducted: Light obscuration particle count test which is mostly conducted for large - volume injections, which counts suspended particles; Microscopic particulate count test can be applied to both large and small volume parenterals, where the test enumerates subvisible, essentially solid, particulate matter in these products on a per volume or per container basis after collecting on a micro porous membrane filter.^[24]

Leaker test

Leaker test is performed to determine whether any capillary pores or tiny cracks are present on the vials or ampoules which may lead to microbes or other dangerous contaminants to enter the formulation or may lead to leakage. This may lead to contamination of the content or spoilage of the package. This test is used to detect incompletely sealed ampoules so that they can be discarded in order to maintain the sterile conditions of the preparation. The test is conducted by placing the ampoules in a vacuum chamber and completely submerged in deeply colored dye solution of about 0.5 to 1% methylene blue. A negative pressure is applied within the sample making the dye to penetrate through any opening or pores if present on the ampoule which will be visible after the washing of the ampoule.^[25]

CONCLUSION

The parenteral route of administration is the most common and effective route for the delivery of the active pharmaceutical substances with narrow therapeutic index, poor bioavailability especially for those drugs, prescribed to unconscious patients for quick

response. In general, basic characteristics of parenteral products are sterile, pyrogen-free, particle-free, stable, isotonic, and safety. All of these characteristics are enhanced and ensured by following proper sterile procedures in the preparation of these products. Reduction in number of injections throughout the drug therapy will be truly advantageous not only in terms of compliance, but also in terms of side effects associated with conventional parenteral drug delivery. A number of technological advances have been made in the area of parenteral drug delivery leading to the development of sophisticated systems that allow drug targeting and the sustained or controlled release of parenteral medicines. Controlled and targeted drug delivery systems include implants, oily injections, or particulate systems such as microparticles, nanoparticles, liposomes, micelles etc. Controlled and targeted drug delivery via parenteral route is advantageous in treatment of various disorders but the safety issues and lack of regulations are the major hurdles in their development. The final specifications need to ensure the safety, identity, strength, performance, and quality of the drug product at release and during storage through the end of its shelf-life. Thus the information summarized in the article will be useful as a tool for development of parenteral drug delivery systems.

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