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**Review Article**

# A Comprehensive Review on Parenterals

**Rutuja Giram*, Diptee Bhagwat, Ashvini Kakad, Aarti Nimse**

*Anuradha College Of Pharmacy Chikhli, Maharashtra, India.*

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## ABSTRACT

Parenteral drug delivery systems, administered via injection, are crucial in modern healthcare, offering rapid therapeutic effects, precision dosing, and bioavailability. This review comprehensively explores the principles, formulations, manufacturing, and quality control aspects of parenterals. Key topics include types of parenteral formulations (solutions, suspensions, emulsions, and implants), the role of excipients, and advancements in drug delivery systems such as liposomes, nanoparticles, and sustained-release formulations. It examines sterilization methods, container systems, and regulatory requirements ensuring safety and efficacy. Emerging trends like biologics, personalized medicine, and innovations in delivery technologies are highlighted. This synthesis underscores the importance of parenterals in treating chronic diseases, acute conditions, and delivering biologics, paving the way for future research and clinical advancements.

## INTRODUCTION

In medicine and pharmacy, enteral administration is the term used to describe drug administration by the gastrointestinal tract. Majority of medicines are administered orally by this route in the form of tablets, capsules, or liquids. NDDS is the system for the delivery of drugs other than the conventional route. The enteral route also encompasses rectal administration utilizing dosage forms such as suppositories, or rectal ointment. In novel drug delivery systems, the parenteral route is the most common and effective for delivering the active ingredient, to express its therapeutic activity. A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance in the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body . This process includes the administration of the therapeutic product, the release of the active ingredient by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action. The term therapeutic substance also applies

***Corresponding Author:** Rutuja Giram
**Address:** Anuradha College Of Pharmacy Chikhli ,Maharashtra,India.
**Email** ✉: rutujagiram04@gmail.com
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to an agent such as gene therapy that will induce in vivo production of the active therapeutic agent. Gene therapy can fit in the basic and broad definition of a drug delivery system. Gene vectors may need to be introduced into the human body by novel delivery methods. However, gene therapy has its special regulatory control. A drug delivery system is an interface between the patient and the drug. It may be the formulation of a drug, to administer it for a therapeutic purpose, or a device used to deliver the drug. In practice, however, parenteral administration is commonly taken to mean drug administration by injection. The word parenteral is derived from the two words "para" and "enter on" means to avoid the intestine According to USP 24/NF19, the parenteral articles are defined as those preparations intended for injection through the skin or other external boundary tissue, rather than through the alimentary canal, so that the active substances can be administered directly into a blood vessel, organ, tissue, or lesion. In today's health care scenario, the key component of therapy for hospitalized patients is parenteral products. Parenteral route of administration i.e. Subcutaneous, intramuscular, intravenous, intradermal and intra-arterial, etc. also possess good absorption characteristics and provide good bioavailability of drugs The route has a plethora of advantages for patients who cannot take the drug orally and require rapid onset of action i.e. in case of unconscious patients Hospitalized and bedridden patients are dependent on parenteral nutrition like fluids, electrolytes, or nutrients by parenteral route. Now a days novel parenteral drug delivery systems like biodegradable implants, transdermal patches, colloidal drug carriers like liposomes, nanoparticles, intramuscular depot injections, are playing a major role. Novel preparations provide sustained, targeted and controlled drug delivery to the patients with less dosing frequency.Despite so many benefits of parenteral formulations are more expensive and costly than conventional formulations. It requires specialized equipment, devices, and techniques to prepare and administer parenteral formulations Despite all these problems, parenteral formulations hold a top place for the treatment of hospitalized patients. Since parenteral products are meant to be introduced directly into the blood for which they should be properly sterile and free from pyrogens.

**Definition: -**Parenteral preparations are sterile, pyrogen free liquids or solid dosage forms packaged in either single dose or multidose containers.

**Table No 1: Advantages and Disadvantages of Parenteral Products:**

| Advantages | Disadvantages |
|---|---|
| Rapid onset of action. | Difficult to reverse an administered drug effect. |
| Useful for patients who cannot take drugs orally. | Pain on injection |
| Useful in emergency situations. | Sensitivity or allergic reaction at site of injection. |
| Provide sustain drug delivery. | More expensive and costly to produce. |
| Target drug delivery. | Trained person is required. |
| Complete bioavailability [upto 100%]. | Required specialized equipment device and technique to prepare and administer drugs. |
| Drug which is unstable in GIT can be given. | Requires strict control of sterility and non pyrogenicity than other formulation. |
| Prolonged drug action is possible. | Local discomfort as a result of needle insertion |

**Routes Of Parenteral Administration:** It can be categorized as

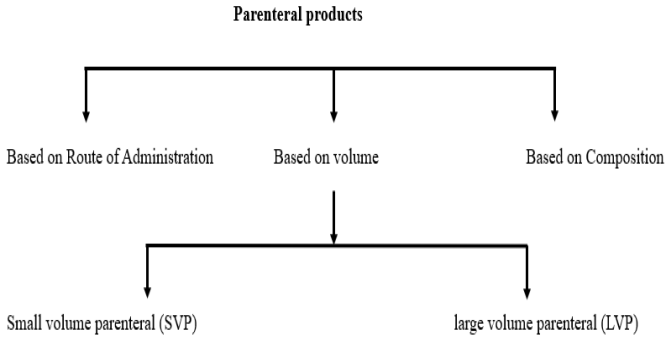
Small scale dispensing – Usually one unit at a time.

Large scale manufacturing – In these hundreds of thousands may constitute one lot of products.

**Table No. 2 : Difference between Large volume parenteral and small-volume parenteral**

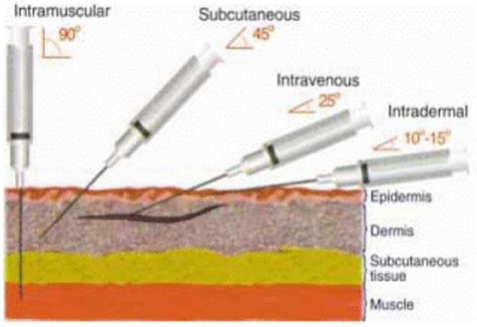
| Parameter | Large volume parenteral | Small volume parenteral |
|---|---|---|
| Volume | 101-1000 ml | 100 ml or less |
| Route | IV | IV,IM,SC |
| Dose unit | Single | Single or multiple |
| Needle | 1 ½, 18-19 gauze | 1 ½, 20-22 gauze |
| Preservatives | Not used | Used |
| Buffer | Not used | Used |
| Formulation | Solution and o/w nutrient emulsion | Solution, emulsion, suspension |
| Use | As nutrition in detoxification Aid during surgery | As therapeutic as diagnosis agents |

**Types Of Parenteral**




**A. Based on route of Administration :-**

1. Intramuscular - Muscle
2. Subcutsneous –under the skin
3. Intradermal-Into the skin
4. Intravenous-vein
5. Intraarticular- joints
6. Intraosseous-bone
7. Intrathecal-spinal fluid
8. Intracardiac-heart
9. Intraspinal –spinal colum
10. Intracerebral-brain
11. Intraarterial-Arteries
12. Endotracheal-down the trachea
13. Intrasynovial-joint fluid area



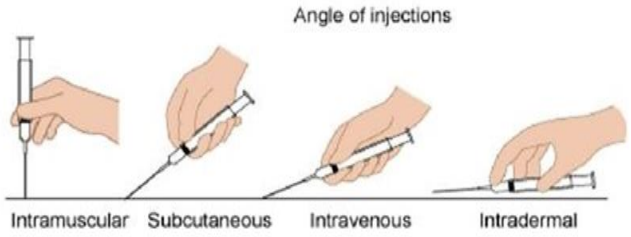



**Figure No. 1 Route of Administrations**

**1. Intramuscular - Muscle :** Intramuscular injections are preferably administered into the tissue of a relaxed muscle. The muscle sites commonly used for intramuscular injections are the thigh or shoulder muscles. Aqueous or oily solutions or suspensions can be administered in volumes of up to 4ml. Drugs administered by the intramuscular route are slowly absorbed from the injection site into the systemic circulation compared to those administered by the subcutaneous route.

**2. Sub cutsneous –under the skin :** The medicine is injected beneath the dermis into the thigh's upper arm or the belly's lower region. Because of the limited subcutaneous area, inject no more than 1ml. This is the most preferred option since it is convenient for both the patient and the doctor. As an example, the Preparation of insulin, rabies, and cholera vaccines the intramus cular approach is quicker than the oral route.

**ADVANTAGE**

Incom paris onto the in travenous approach,the dan ger is reduced. Absorption is smooth and long lasting.

**3. Intradermal-Into the skin :** Intradermal injections are administered between the dermis and the epidermis. The skin on the left forearm was chosen for injection. This channel receives 0.1 to 0.2 ml of parenteral preparation.

**Uses**

BCG vaccination administration for diagnostic test ing, such as susceptibility to specific bacterial infections such as tuberculosis

**4. Intravenous-vein:** Injections are delivered into veins and mixed with blood steam. This method is used for large-volume parenteral injections ranging from 1 to 500 ml. Because it is easily found and links with the arm's vein, the median basilic vein on the anterior surface of the elbow is usually used for administration. ***Advantages***

1. This method is effective in an emergency because the medication enters the system ic circulation quickly. The bioavailability is 100 per cent.
2. This method delivers large amounts of par enteral nutrition.

**DISADVANTAGES**

1. Only aqueous solution drugs were adminis tered intravenously.
2. Because essential organs such as the heart are exposed to overdoses of drugs, this route has the highest danger factor

**5. Intraarticular- joints :** The intra-arterial injection is given directly into the artery. The procedure for intravenous adminis tration is the same as for intravenous administra tion, except that the medicine is administered intra venously

**6. Intraosseous-bone:**

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

**8. Intracardiac-heart :** These are given into the heart muscle or ventricle in anemergency only for example as a stimulant following cardiac arrest.

**9. Intraspinal –spinal colum :** Intraspinal injections are given between the vertebrae of the spine into the area of the spinal cord. Only drugs

in an aqueous solution are administered by this route.

This route can be used for spinal anesthesia. Also, the indication was given to introduce drug substances into the CSF that would otherwise not diffuse across the blood-brain barrier. Typically, this could be antibiotics to treat meningitis or anticancer agents such as methotrexate or cytarabine. Volumes up to 10ml can be administered by Intrathecal injection. Intracisternal injections are given between the atlas and axis vertebrae into the cisterna magna. This route is also used for antibiotic administration into the CSF, or to withdraw CSF for diagnostic purposes**.** Epidural injections or infusions are given into the epidural space between the Dura meter (the outermost protective membrane covering the spinal cord) and the vertebrae. This route is commonly used for spinal anesthesia, for example during childbirth.

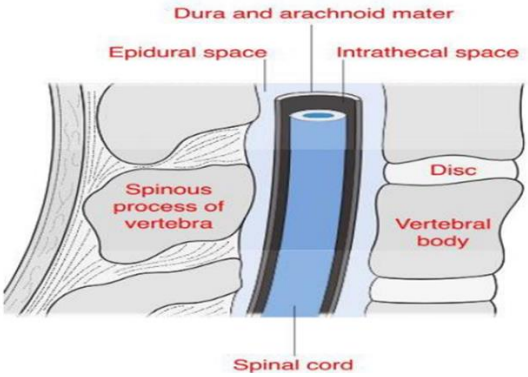



**Figure No. 2: Intraspinal injection**

**10. Intracerebral-brain**

This injection was administered to the cerebrum. Injection of the Pericardium In spinal anesthesia or exceptional instances, the peridural route of admin istration is beneicial. These injections are allo cated between the dura mater and the inner facets of the vertebra. Intravenous Injection Intrathecal injections are administered into the area around the spinal cord. Injection into the Artery A joint is injected by intraarticular injection

**11. Intraarterial-Arteries**

**12. Endotracheal-down the trachea**

**13. Intrasynovial-joint fluid area**

**B. Based on volume:-**

1.Small volume parenteral – An injection that is packed in containers labeled as containing 100 ml or less. Eg- solution ,suspension, emulsion, dry powders 2.Laege volume parenteral- LVP as product in container labeled as containing more than 100 ml of single dose injection intended for administration by IV infusion . These are injected directly into blood stream (IV preparation) poured into open body cavities and surgical area or introduced into body cavity, they must be sterile, non pyrogenic and free from particulate matter .

**C. Based on composition-** These product can be administered by Intra or extra vascular routes. These LVP are packed into either glass or plastic container of 1 lit. capacity.

**Container and Closures Used for Parenteral Preparation**

Containers and closures are the intimate contacts with the parenteral Preparation, and they should be reactive. There are mainly three types of containers have been used

1. Plastic
2. Glass
3. Rubber closure

**Plastic Containers**

Plastics are mainly of two classes [Table 3],

1. Thermosetting plastic is used in manufacturing closures to seal glass and metal containers.
2. Thermoplastics: These are the principal ingredient in the Preparation of plastic

containers. Manufacture additives include lubricants, Anti static agents, plasticizers, Preservatives, and Antioxidants. Most plastics require minimum quantities of additives

**Advantages of Plastics**

1. It is easily carriable.
2. Light in weight.

**Glass Containers**

These are the containers that are widely used containers for parenteral preparations. It mainly com prises silicon dioxide and other oxides such as sodium, magnesium, aluminum, potassium, calcium, and boron oxides. These oxides reduce the intraatomic forces between the silicon and oxygen, lower the glass's melting point, and leeches into Preparation after prolonged contact with preparation results in increased pH [Table 4]

To determine the chemical resistance of the glass containers, the following tests are employed

1. Powder glass test.
2. Water attack test

**Powder Glass Test**

Glass is powdered and transferred into the water for injection. It is maintained at the high temperatures samples collected at intervals to determine the amount of the leached constituents. Water Attack Test Water for injection is placed at high temperatures, and the samples are collected at intervals to deter mine leachable constituents. Based on the chemical resistance, glass containers are classified into four types

1. Borosilicate glass
2. Treated sodalime glass
3. Nontreated sodalime glass
4. General purpose soda lime glass [Table 5]

**Table 3 :Different Polymers and their Properties in the Preparation of Plastic Container**

| Type of Material | Additives | Leachability | Water Vapor Permeability | Gaseous Permeability |
|---|---|---|---|---|
| **Polyethylene** | | | | |
| Low density | Low | Low | High | Low |
| High density | Low | Low | Moderate | Low |
| Polypropylene | Low | Low | Low | Low |
| **Polyvinyl chloride** | | | | |
| Flexible | High | High | High | Low |
| Rigid | Low | Low | High | Low |
| Polycarbonates | Low | Low | High | Low |
| Polyamides | Low | Low | High | Low |
| Polystyrene | Low | Low | High | High |
| PolyTetra Fluro Ethylene(Telon) | Low | Nil | Low | Low |

**Table 4 :Types of Glass Containers and Their Properties**

| Type of Glass | Additives | Leachability | Water Vapor Permeability | Gaseous Permeability |
|---|---|---|---|---|
| **Soda-lime** | **High** | **High** | **Nil** | **Nil** |
| **Boro silicate** | **Low** | **Low** | **Nil** | **Nil** |

**Table 5 : Different Polymers and Their Properties in the Preparation of Plastic Container**

| Types of Glass | Description | Types of Test | Used |
|---|---|---|---|
| Type 1 | Borosilicate | Powder glass | Buffered and unbuffered preparations |
| Type 2 | Treated soda-lime glass | Water attack test | Buffered preparations |
| Type 3 | Non-treated soda lime glass | Powder glass | Dry powders |
| Type 4 | General-purpose soda-lime glass | Powder glass | Tablets, capsules, semisolid preparation |

**Table 6: Different Polymers and Their Properties in the Preparation of Plastic Container**

| Polymers Type | Additives | Leachability | Water vapor permeability | Gaseous permeability |
|---|---|---|---|---|
| Butyl rubber | Moderate | Moderate | Low | Moderate |
| Natural rubber | High | High | Moderate | Moderate |
| Neoprene rubber | High | High | Moderate | Moderate |
| Poly isoprene rubber | High | High | Moderate | Moderate |
| Silicone | Moderate | Moderate | Very high | Very high |

Rubber closures are mainly used to seal vials and infusion bottles. It should be smooth and elastic so the syringe's needle can easily pierce and withdraw from it. Different polymers are used in rubber closure preparation [Table 6]

**General Requirements For Parenterals :-**

1. Sterility
2. Free from pyrogens
3. Free from particular matter
4. Isotonicity
5. Specific gravity
6. Chemical purity
7. Stability

**Consideration In Parenteral Preparations:**

**1. Vehicle:-**

- The vehicles should be pharmacologically inert, non-toxic, compatible with blood, maintain solubility of drug
- Chemically and physically must be stable.
- Pyrogen and microbe free
- Not affected by PH.
- Non aq.may be used to drug of limited water solubility.
- It must be safe in amount administered.
- Eg. fixedoils, peanutoil, Ethyloleate.

**2.Preservatives: -**

- It is a substance that prevents or inhibit microbial growth and extends the shelf life of drug products.

1.Antimicrobial preservative
2.Anti-oxidants
3.Buffer
4.Chelating agents
5.Cryoprotectants
6.Inert gas
7.Surfactant and solubilizing agents
8.Tonicity modifiers
9.Viscosity modifiers

**3. Antioxidant:-**

- To protect formulations from oxidation .
- There are 2 types-
- a. Reducing agents-eg. Thiourea , Ascorbic acid, Sodium bisulfate 0.01%
- b.Blocking agents-eg. Tocopherol
- Added to maintain PH for solubility ,stability and pain reduction.

**4. Cryoprotectants:-**

- Prevent and stabilize denaturation of proteins from effect of freezing.
- Sugar-sucrose,lactose,glucose,trehalose,

- Polyols-glycerol,mannitol,sorbitol
- Amino acid- glycine,alaning,lysine
- Polymers-PEG,dextran,PVP

**5. Lyoprotectants:-**

- Substance which protect drug especially proteins from degradation during drying .
- Sugar-mannitol, lactose, maltose, maltodextrin, trehalose, sucrose
- Amino acid-glycin,histadine,arginine

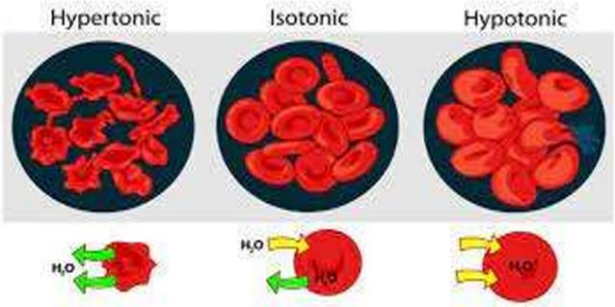
**6. Solubilizing agents and surfactants:-**

- Substance are used extensively in parenteral suspension for wetting powders and provide acceptable syringe ability.(eg- steroid ,fat soluble vitamins)
- Must be purified ,sterile,pyrogen free.
- In limited volume depending on route and type.
- Should not vehicles must have special purity and other std. to assure sterility,stability,and safety
- Eg-sodium oil,PEG,alcohol stat

**Importance of Isotonicity:-**

- Need an isotonic solution to avoid destruction of RBC, irritation and tissue damage.
- More important for large volumes,rapidly administered and extravascular injections.
- Reduce pain on injections.
- Nacl and KCL .
- Dextrose
- Mannitol and Sorbitol
- Tonicity modifiers:- To minimize the tissue damage and irritation reduce hemolysis and prevent electrolyte imbalamce,product should be isotonic

Dextrose (4-5.5%) Nacl (0.5-0.9%)and sodium sulfate (1-1.6%) is used to adjust tonicity.



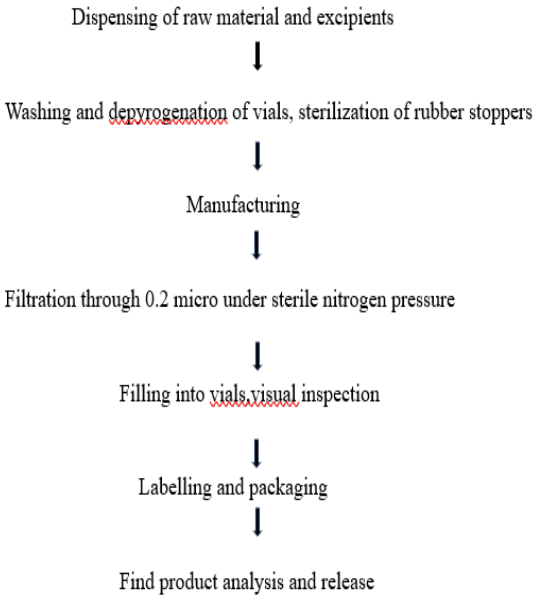

**Formulations :-**

A.Opthalmic preparations
B.Freeze-dried product
C.Long acting formulations:-
1.suspension
2.Emulsion
3.Sterile powders:
a.Sterilerecrystalization
b.Lyophilization
c.Spray drying

**Production Procedure:-**

Production process includes all the steps from accumulation and combining of ingridients of formula to enclosing of product in individual container for distribution. SOP‟s are very important.

**Flow Chart:**




**Parenteral Dosage Forms:**

**Solutions:** Most injectable products are solutions. Solutions The simplest and most convenient form of presentation of an injectable product is an isotonic aqueous solution, which has a pH close to that of blood and body tissues (pH 7.4). Parenteral solutions include large volume parenterals (LVP), small volume parenterals (SVP), and irrigation solutions. Infusion fluids are aqueous solutions given in larger volumes than those normally administered by intravenous injection. Infusions generally include preparations used for basic nutrition, restoration of electrolyte balance, fluid replacement, etc. The formulation aspect of solutions includes vehicles and added substances. There are three types of vehicles used for the preparation of injectable solutions. One is aqueous vehicles which are officially recognized to which drug is added at the time of administration i.e. sodium chloride injection, ringer's injection, dextrose injection, lactated ringer's injection, etc. The second one is water-miscible vehicles that are used to partially dissolve the drug in combination with water i.e. cardiac glycosides solutions are prepared in ethyl alcohol and glycols are used for dissolving barbiturates but these preparations are given intramuscularly. The third and last category involves non-aqueous vehicles which are fixed oils. According to USP specifications, fixed oils should be of vegetable origin so that they can be metabolized easily in the body i.e. cottonseed oil, corn oil. Added substances in parenteral solutions may involve antimicrobial agents, buffers, chelating agents, etc

**Suspensions:** Parenteral suspensions are a useful dosage form for administering insoluble or poorly soluble drugs. The drug is dispersed in the aqueous/oily solution for aqueous/oily suspensions respectively. The main property, a suspension should possess for parenteral delivery is that it should not produce tissue irritation on injection. The larger surface area of dispersing drug ensures higher solubility which helps in providing a high degree of availability for absorption of the drug. The parenteral suspension provides more prolonged release as compared to the solution from the injection site. This system is used through the subcutaneous and intramuscular routes. Suspensions are better than solutions as they provide increase resistance to hydrolysis and oxidation as the drug is present in solid form. Despite all these benefits, many problems are associated with suspensions like difficulty in formulation, stabilization of suspensions for the

period between manufacture and use, and chances of nonuniformity of dose at the time of administration. Some of the official parenteral suspensions include sterile ampicillin suspension USP'2009, sterile aurothiglucose suspension USP'2009 - vegetable oil suspension, tetanus toxoid adsorbed USP'2009, IP'96, betamethasone acetate suspension USP'2009 aq. suspension, Insulin inc suspension USP'2009, IP'96 aq. suspension and procaine penicillin suspension IP'96 etc. The formulation aspect of suspension involves drug and added agents like wetting agents (particularly surfactant of 7-9 HLB values), buffers, viscosity-increasing agents (natural gums like tragacanth, acacia), preservatives, etc. Some workers prepared a pharmaceutical aqueous suspension formulation for parenteral administration having substantially stabilized pH, comprising a steroidal compound with an effective concentration of L-Methionine (pH controlling agent).

**Emulsions:** An emulsion is a two-phase system prepared by combining two immiscible liquids, one of which is dispersed uniformly throughout the other and consists of globules that have diameters equal to or greater than those of large colloidal particles. Emulsions are generally used in the administration of total parenteral nutrition (TPN). TPN is the practice of feeding patients who are unable to get their nutrition through eating, mainly for the coma patients, etc. It is normally used during surgical recoveries. Emulsions generally fall into two categories i.e. a heterogenous system comprised of a drop of organic liquid immersed/surrounded in an aqueous solution that is known as oil in water emulsion (o/w type) and a heterogeneous system comprised of a drop of water immersed/surrounded in organic solutions that are known as water in oil emulsion (w/o type). The formulation view of emulsion includes pharmaceutical oils (as mentioned in non-aqueous vehicles in solutions), pharmaceutical emulsifiers (surface-active agents, natural polymers, finely divide solids), preservatives, and antioxidants. Steps in emulsion formulation depend upon the type of formulation, whether an o/w emulsion or w/o emulsion, internal phase is selected in which drug is mixed. In the external phase, the pharmaceutical emulsifier is added to stabilize the droplets that form during emulsification. A mixture of drug and internal phase is poured in a mixture of emulsifier and external phase with a high-pressure homogenization, to break the internal phase droplets. Emulsifier covers the whole surface to stabilize the droplet of the internal phase. The major problem associated with emulsions is that these are thermodynamically unstable because of the increase in surface free energy of the system, which depends on the total surface area, and interfacial tension which increases by increasing the surface area of the system during emulsification. Parenteral emulsions are administered through subcutaneous and intramuscular routes. Commercially available oily emulsions are intralipid 10%, lipofundin, and liposyn. The major focus on recent literature has been in the area of parenteral drug delivery like subcutaneous, intramuscular, intraperitoneal delivery, etc. Park et al. evaluated the potential of flurbiprofen microemulsions in parenteral delivery. The pharmacokinetic studies yield a 1.5 to 2 folds increase in half-life, area under the curve, and mean residence time of flurbiprofen from microemulsions. Drugs in emulsion form provide sustained release i.e., buprenorphine emulsions. An oil-in-water buprenorphine formulation including buprenorphine and a surfactant that emulsifies the buprenorphine in oil, wherein oil concentration controls the drug release. A buprenorphine oil formulation including a buprenorphine salt suspended in pharmaceutically acceptable oil.

**Dry powders:** Many drugs are too unstable either physically or chemically in an aqueous medium to allow formulation as a solution, suspension, or emulsion. Instead, the drug is formulated as a dry powder that is reconstituted by the addition of water before administration. The reconstituted product is usually an aqueous solution; however, occasionally it may be an aqueous solution (E.g., ampicillin trihydrate and spectinomycin hydrochloride are sterile powders that are reconstituted to form a sterile suspension).

**Freeze drying:** In freeze-drying a solution is filled into vials, a special slotted stopper is partially inserted into the neck of the vial, and trays of filled vials are transferred to the freeze-dryer. The solution is frozen by the circulation of a fluid, such as silicone oil, at a temperature in the range of -35 to about -45°C through internal channels in the shelf assembly. When the product has solidified sufficiently, the pressure in the freeze-drying chamber is reduced to a pressure less than the vapor pressure of ice at the temperature of the product, and heat is applied to the product by increasing the temperature of the circulating fluid. Under these conditions, water is removed by sublimation of ice, or a phase change from the solid-state directly to the vapor state without the appearance of an intermediate liquid phase.

**Microspheres:** Numerous biodegradable polymers have been investigated for the preparation of microspheres as depot formulations. The application of biodegradable microspheres to deliver small molecules, proteins, and macromolecules using multiple routes of administration has been widely investigated and several products have been brought to market in the last 10–20 years. A list of marketed injectable products is shown. For peptide or protein-containing microspheres mainly three processes were studied more intensively, namely the w/o/w –technique phase separation methods and to some extent spray drying. Summarized schematic representation of all three techniques. ABA (PLGA-PEO-PLGA) block copolymer was investigated over PLG polymer by using macromolecular model compounds, such as FITC-dextrans (molecular mass 4-500 kDa). The in vitro release pattern of macromolecules from ABA microspheres was influenced by the molecular mass of the solute and showed continuous release profiles above a threshold level of Ca 20 kDa whereas PLG microspheres yielded biphasic release profile independent of the molecular mass of the solute. Lupron Depot, microsphere containing the LHRH superagonist leuprorelin (leuprolide) acetate with PLGA (75/25)-14000 and PLA-15000, prepared by w/o/w emulsion solvent evaporation method. The microsphere release drug in a zero-order fashion over 1 to 3 months after intramuscular or subcutaneous injection into animals. PLGA microsphere had been also used for delivery of glycoprotein (GP) IIb/IIIa antagonist, plasmid DNA, Interleukin-1α, and prolidase enzyme.

**Liposomes:** In the area of injectable drug delivery systems, research into liposomes played a major role in the past few decades. Lipid complex (Abelcet, Amphoteric) and three liposomal formulations, Ambisome, Daunosome, and a stealth liposome (Doxil) had got approval for human use by regulatory agencies. These products have been developed for intravascular administration, enhancement of circulation times, and reducing toxicity by lipid encapsulation. Nowadays, encapsulation of drugs into multivesicular liposomes (Depo Foam) offers a novel approach to sustained release drug delivery. Drug into unilamellar and multilamellar liposomes, and complexation of drug with lipids, resulted in products with better performance throughout lasting several hours to a few days after intravascular administration whereas Depo Foam encapsulation has been resulting in sustained release lasting over several days to weeks. A

sustained-release depot product (Depocyt) utilizing Depo Foam technology consists of novel multivesicular liposomes characterized by their unique structure of multiple non-concentric aqueous chambers surrounded by a network of lipid membranes. The route of administration most viable for delivery of drugs via Depo Foam formulations includes intrathecal, epidural, subcutaneous, intramuscular, intra-articular, and intraocular. Depo Foam formulations of a protein such as insulin, myelopoietin (Leridistim), and peptide such as leuprolide, enkephalin, octreotide have been developed and characterized. The data show that these formulations have high drug loading, high encapsulation efficiency, low content of free drug in the suspension, little chemical change in the drug caused by the formulation process, narrow particle size distribution, and spherical morphology. Semisolid phospholipid dispersion of vesicular morphology, so-called vesicular phospholipid gels (VPGs) is another approach in liposomal technology. A protein such as erythropoietin and peptide such as Cetrorelix was developed and in vitro evaluated by vesicular phospholipid gels.

**Tests For Quality Control**

**Pyrogen Test:**

**Purpose**: Confirms that the preparation is free from viable microorganisms.

1. Presence of pyrogen may cause fever and alteration in blood coagulation. 2. The tests used for pyrogen detection are:

a) Rabbit test

b) LAL test

**a. Rabbit test:** [Sham test]

- 1.Rabbits are used as the test animal because they show a physiological response to pyrogens, similar to that of human beings.
- 2.Three healthy adult rabbits of either male or female, each weighing not less than 1.5kg are selected

**Method :**

Normal temperature is recorded prior to the test.

↓

Dilute the test substance in pyrogen free saline test solution

↓

Warm the solution to $38.5^0$c

↓

Volume of injection is maintained between 0.5-10ml/kg

↓

Test solution is injected through an ear vein

↓

Body temperature is recorded by a clinical rectal thermometer

↓

Record temperature at an interval of 30 mins for 3 hrs

↓

The difference between initial and final temperature is recorded.

The difference in temperature should not be more than $1^0$c.

**LAL Test:**

- This test detects & qualifies the bacterial endotoxin that may be present in the sample using a lysate derived from the amebocytes of the horseshoe crab (Limulus Polyphemus).
- This method utilizes the gelling property of lysate of amebocytes in the presence of pyrogen endotoxin from gram-negative bacteria within 10 minutes when incubated at 37°C.

**Mechanism of LAL test:**

Primitive blood clotting mechanism of horse shoe crab

↓

Enzymes located with the crabs amoebocyte blood cells endotoxins

↓

Initiation of an enzymatic coagulation cascade

↓

Proteinaceous gel

**Advantages**:

- 5 to 10 times more sensitive than rabbit test.
- Less variation &less time-consuming test.
- Quantitative test.

**Leakers test: [containers or closures integrity test]**

Ampoules that have been sealed by fusion must be tested to ensure that a hermetic seal was obtained. The leaker test is performed by immersing the ampoules in a dye solution, such as 1% methylene blue, and applying at least 25 inches (64 cm) of vacuum for a minimum of 15 minutes. The vacuum on the tank is then released as rapidly as possible to put maximum stress on weak seals. Next, the ampoules are washed. Defective ampoules will contain the blue solution

**Clarity Testing and particulate analysis:**

Clarity is performed to ensure that parenteral product is free from foreign particles Constitute the injection as directed on the label.

a) The solid dissolves completely, leaving no visible residue as undissolved matter.

b) The constituted injection is not significantly less clear than an equal volume of diluents for water for injections contained in a similar container and examined in the same manner.

**Sterility test**

It is most important and essential characteristics of parenteral product .Sterility means complete absence of all riable micro- organism.

a.Direct transfer test

b.Membrane filtration test

**a. Direct transfer test:-** It involve the direct incubation of required volume of sample in two test tube containing culture medium ,FTM,SCDM.

**b.Membrane filtration method:-**Filtration of sample through membrane filter 0.22 micron diameter 47 mm with hydrophobic characteristics.

**Limits of membrane filtration:-**

| No. of article in batch (injectable) | No. of articles to be tested |
|---|---|
| Not more than 100 article | article 10% / 4 article |
| More than 100 but not more than 500 | 10 |
| More than 500 | 2% of 20 article |
| For large volume parenteral | 2 % of 20 article |

**The Controlled Environment Required For Parenteral Preparation**

**Clean Room Classified Areas:** Due to the extremely high standards of cleanliness and purity that must be met by parenteral products, it has become standard practice to prescribe specifications for the environments (cleanrooms) in which these products are manufactured

The Critical and General area of the clean room:

The cleanroom divides into:

**1. Critical Area**

The critical area is the area around the point of the production where contamination can gain direct access to the process. This area is often protected by localized laminar flow clean benches and workstations.

**2. General Area**

The General area is the rest of the cleanroom where contamination will not gain direct entry into the product but should be kept clean because of the transfer of contamination into the critical area. The critical area must be cleaned most often with the best cleaning ability without introducing contamination.

**Table No. 7 : Airborne particulate classification for Grade A, B, C, and D**

| | The maximum permitted number of particles/m3 | | | |
|---|---|---|---|---|
| **Grade** | **At rest** | | **In operation** | |
| | 0.5mm | 5mm | 0.5mm | 5mm |
| A | 3500 | 0 | 35000 | 0 |
| B | 3500 | 0 | 350000 | 2000 |
| C | 350000 | 2000 | 350000 | 20000 |
| D | 350000 | 20000 | Not defined | Not defined |

**Table No. 8 : Cleanroom classification**

| FS209 Clean room Classification | ISO 14644-1 Clean room Classification | NMT 0.5µ m particles/m3 | Viable Microbes (cfu/m3) | Average Airflow Velocity (fpm) | Air change/hr |
|---|---|---|---|---|---|
| 100000 | 8 | 3520000 | 100 | 5 to 10 | 5 to 48 |
| 10000 | 7 | 35200 | 10 | 10 to 15 | 60 to 90 |
| 1000 | 6 | 35200 | 7 | 25 to 40 | 150 to 240 |
| 100 | 5 | 3520 | 1 | 40 to 80 | 240 to 480 |

**Types of Parenteral Devices:**

**Syringe**

A sterile device used to inject liquids. A syringe is used to inject or extract secretions from the body. A syringe is a calibrated glass or plastic cylinder connected to a needle. The term ”syringe” is derived from the Greek Syrinx. There are many different types and sizes of syringes available for varied uses. Sizes range from 0.25 to 450 mL. For instance, insulin syringes, medical syringes, and throwaway syringes

*Examples:* - medical syringe, insulin syringe, disposable syringe & tuberculin syringe.

**Needle**

A needle is a thin, sharp object used for injecting, suturing, ligaturing, and puncturing. The hand is reusable for single patients and is almost disposable. It also removes material from an identiiable bulk by aspirating it clinically using a hollow needle attachment.to syringe. A needle gauge indicates the diameter of the needle; different needle lengths are available for different gauges. Example: hypodermic needle, winged needle.

Examples: - hypodermic needles, winged needles.

**Cannular**

A cannula (from Latin "little reed"; plural cannulae) or cannula is a tube that can be inserted into the body, often for the delivery or removal of fluid. Cannulae normally come with a trocar attached, which allows puncturing of the body to get into the intended space. There are, however, 11 different kinds of cannulae: Bias Grind, Vet Point, Lancet Point, Deflected point (Anti-Coring), Pencil Point, Closed-End Consistent Wall, Welded "Ball" End, Bullet Point, Razor Edge, Probe Point (Blunt End), and Trocar. Intravenous cannulae are the most common in-hospital use. A variety of cannulae are used to establish cardiopulmonary bypass in cardiac surgery. The nasal cannula is a piece of plastic tubing that runs under the nose and is used to administer oxygen.

*Examples:* Intravenous (IV) cannulation & Nasal cannulation.

**Catheter**

Catheter is a tube introduced into the body through a duct or channel. It enables surgical devices to inject and drain fluids. Catheterization refers to the procedure of inserting a catheter. Most catheters are flexible and thin, with a few exceptions being

more significant solid tube catheters. In ancient times, the Greeks put a hollow tube within the urethra to empty the bladder, and this became known as a catheter

*Examples:* Arterial catheter, Balloon catheter, Cardiac catheterization, Central venous catheter, Dialysis.

**Feeding Tube**

A feeding tube is a medical device used to provide nutrition to patients who cannot obtain nutrition by swallowing. The state of being fed by a feeding tube is called enteral feeding or tube feeding. Placement may be temporary for the treatment of acute conditions or lifelong in the case of chronic disabilities. A variety of feeding tubes are used in medical practice. They are usually made of polyurethane or silicone. The diameter of a feeding tube is measured in French units (each French unit equals 0.33 millimeters). They are classified by site of insertion and intended use.

*Examples:* nasogastric & gastric feeding tube.

**Stents**

In medicine, a stent is a man-made 'tube' inserted into a natural passage/conduit in the body to prevent, or counteract, a disease-induced, localized flow constriction. The term may also refer to a tube used to temporarily hold such a natural conduit open to allow access for surgery. A stent is a wire metal mesh tube used to prop open an artery during angioplasty. The stent is collapsed to a small diameter and put over a balloon catheter. It's then moved into the area of the blockage. When the balloon is inflated, the stent expands, locks in place, and forms a scaffold. This holds the artery open. The stent stays in the artery permanently, holds it open, improves blood flow to the heart muscle, and relieves symptoms (usually chest pain). Within a few weeks of the time the stent was placed, the inside lining of the artery (the endothelium) grows over the metal surface of the stent14 Stents are used depending on certain features of the artery blockage. This includes the size of the artery and where the blockage is. Stenting is a fairly common procedure; in fact, over 70 percent of coronary angioplasty procedures also include stenting.

*Examples:* - drug-eluting stents.

**Prenteral therapy is used to**:

- Easy administration of drugs to the unconscious patient.
- Accurate delivery of the drug to the target tissues.
- create a localized effect.
- The oral route cannot be used for drug administration.
- Quickly accurate fluid and electrolyte imbalance.

**Filling and sealing control of parenteral products:**

GMP practices need that in method quality assurance testing be effectively intended during all stages of manufacturing that some samples have for testing and the type of testing is dependent upon the batch size and the type of parenteral product. If the difference from particular limits occurs the essential corrective action is taken and recorded and a resample is taken and tested to find out whether the quality characteristic of the parenteral product is now inside limits in some instances as in the case of volume examination if the deviation is too much all injectables produced before the corrective action should be isolated accounted for and rejected.

**Packaging:**

Container components for parenteral products must be considered an integral part of the product because they can dramatically affect product stability, potency, toxicity, and safety.

Parenteral dosage forms, especially solutions, usually require more detailed evaluation of packaging components for product compatibility and stability than do other pharmaceutical dosage forms [Common container components in direct contact with the product include various types of

glass, rubber, plastic, and stainless steel (needles), all of which may react with the drug. Maintenance of microbiological purity and product stability, adaptability to production operations and inspections, resistance to breakage and leakage, and convenience of clinical use are factors that must be evaluated when selecting the container.

**Figure No.3 : Packaging of Parenterals**

**Labeling:**

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

**Table No. 9 : List of Marketed Formulations of Parenteral solutions**

| Parenteral Solutions | Marketed Formulation |
|---|---|
| LVPs | 0.9% sodium chloride injection, USP 5%\ sodium chloride injection<br>5% dextrose injection, USP<br>10% dextrose injection, USP<br>Lactated ringers and<br>5% Ringers injection |
| Irrigation solutions | 0.9% sodium chloride irrigation<br>Tis- u- sol® solution pentalyte irrigation 1.5% glycine irrigation, USP |

## CONCLUSION

The parenteral route of Administration is the most effective route for the delivery of active pharmaceutical substance specially drugs cannot be taken orally. The above practice work describes that manufacturing of parenteral products, filling, sealing, storage conditions, evaluation test. It is more important to manufacture good quality of parenteral products. Quality control should be a fundamental segment of parenteral products manufacturing. All the test which are performed are essential and have its own importance in parenteral production. All of these tests ensure that product meet its quality which has been judged to satisfactory also. All the detailed information about the parenteral products and its manufacturing are given in the above practice work.

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