Parenteral Products

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Contents

- Definition,
- Types,
- Advantages
- Dis advantages
- Characteristics
- Importance of is tonicity
- Preformulation factors and essential requirements
- Formulation aspects for parenteral product

  Vehicles

  Additives

Defination

- **Parenterals are preparations which are administered by injection through one or more layers of skin tissue.**

- **The word parenteral is derived from the Greek word para and enteron, meaning outside of intestine, and is used for dosage forms administered by routes other than the oral route.**

In general, the parenteral routes are used

- when rapid drug action is desired, as in emergencies;
- when the patient is uncooperative, unconscious, or unable to accept or tolerate oral medication; or
- when the drug itself is ineffective by other routes.

With the exception of insulin injections, which are commonly self- administered by diabetics, most injections are administered by the physician, physician's assistant, or nurse in the course of medical treatment.

Thus, injections are employed mostly in the hospital, extended care facility, and clinic and, less frequently, at home.

Official Types of injections

According to the USP, injectable materials are separated into five general types.

These may contain buffers, preservatives, and other added substances.

1. **Injection: Liquid preparations that are drug substances or solutions thereof (e.g., Insulin Injection, USP).**

2. **For injection: Dry solids that, upon addition of suitable vehicles, yield solutions conforming in all respects to the requirements for injections (e.g., Cefuroxime for injection, USP).**

3. **Injectable emulsion**: Liquid preparation of drug substance dissolved or dispersed in a suitable emulsion medium (e.g., Propofol, USP).

4. **Injectable suspension:** Liquid preparation of solid suspended in a suitable liquid medium (e.g., Methylprednisolone Acetate suspension, USP).

5. **For injectable suspension:** Dry solid that, upon addition of suitable vehicle, yields preparation conforming in all respects to the requirements for injectable suspensions (e.g., Imipenem and Cilastatin for injectable suspension, USP).

Types of Parenteral

Preparations

I Based on Volume:

- **A. Small Volume Parenteral**: An injection that is packed in containers labelled as containing 100 mL or less. Examples: Solution, Suspension, Emulsion, Dry Powders

- **B. Large Volume Parenteral (USP):** LVP as products in a container labelled as containing more than 100ml of a single dose injection intended for administration by IV infusion. These are injected directly into the blood stream (IV preparation), poured into open body cavities and surgical area (Irrigating solution) or introduced into the body cavity (Peritoneal dialysis), they must be sterile, non-pyrogenic and free from particulate matter.

Types of Large Volume Parenteral

- **Electrolytes:** 0.9 % NaCl Injection, Multiple electrolyte, Lactated Ringer Injection
- **Carbohydrates:** 5 % Dextrose Injection, 10 % Fructose Injection
- **Nutritional Solutions:** Proteins, Lipid Emulsions
- Total Parenteral Nutrition (TPN)
- Intravenous admixture
- Peritoneal Dialysis Fluid
- Irrigating Solutions (Any fluid used to rinse an organ or body cavity)

Based on States of Products:

A. Injection: Injections contain sterile solutions and are prepared by dissolving the active ingredient and other substances in Water for Injection or other suitable non-aqueous base or a mixture of both. The solution to be injected may show sediments which can be dispersed easily by shaking the container. The suspension should remain stable in order to deliver a homogenous dose whenever withdrawal is made from the container.

B. Infusions: These parenteral preparations are composed of sterile aqueous solution with water as its continuous phase. The preparations are free from bacterial endotoxins or pyrogens and are made isotonic with blood. They do not contain any antimicrobialPreservatives.

C. Powder for Injection: These are sterile solid compounds that are distributed in their final Volume when the vial or container is shaken to form a clear particle-free solution.

Based on States of products:

D. Concentrated Solutions for Injections:

The concentrated solutions are diluted with water for injection before they are administered through injection or through intravenous infusion.

E. Implants:

These solid sterile preparations are implanted in the tissue in order to release the active ingredient for long periods. They are stored in sterile containers individually.

F. Injectable Emulsion:

These are liquid preparations in which the drug substances are dissolved or dispersed in a suitable emulsion medium. These products provide essential fatty acid and vitamins.

G. Oily Injection:

These are used to prepare parenteral controlled release dosage forms.

Routes of Administration

Parenteral preparation are administered by parenteral routes for following four principle reasons.

- **For therapy (Definitive or Palliative[affording relief])**
- **For prevention**
- **For diagnosis**
- **For temporarily altering tissue functions in order to facilitate other forms of therapy.**

Common Routes of Parenteral Drug Administration

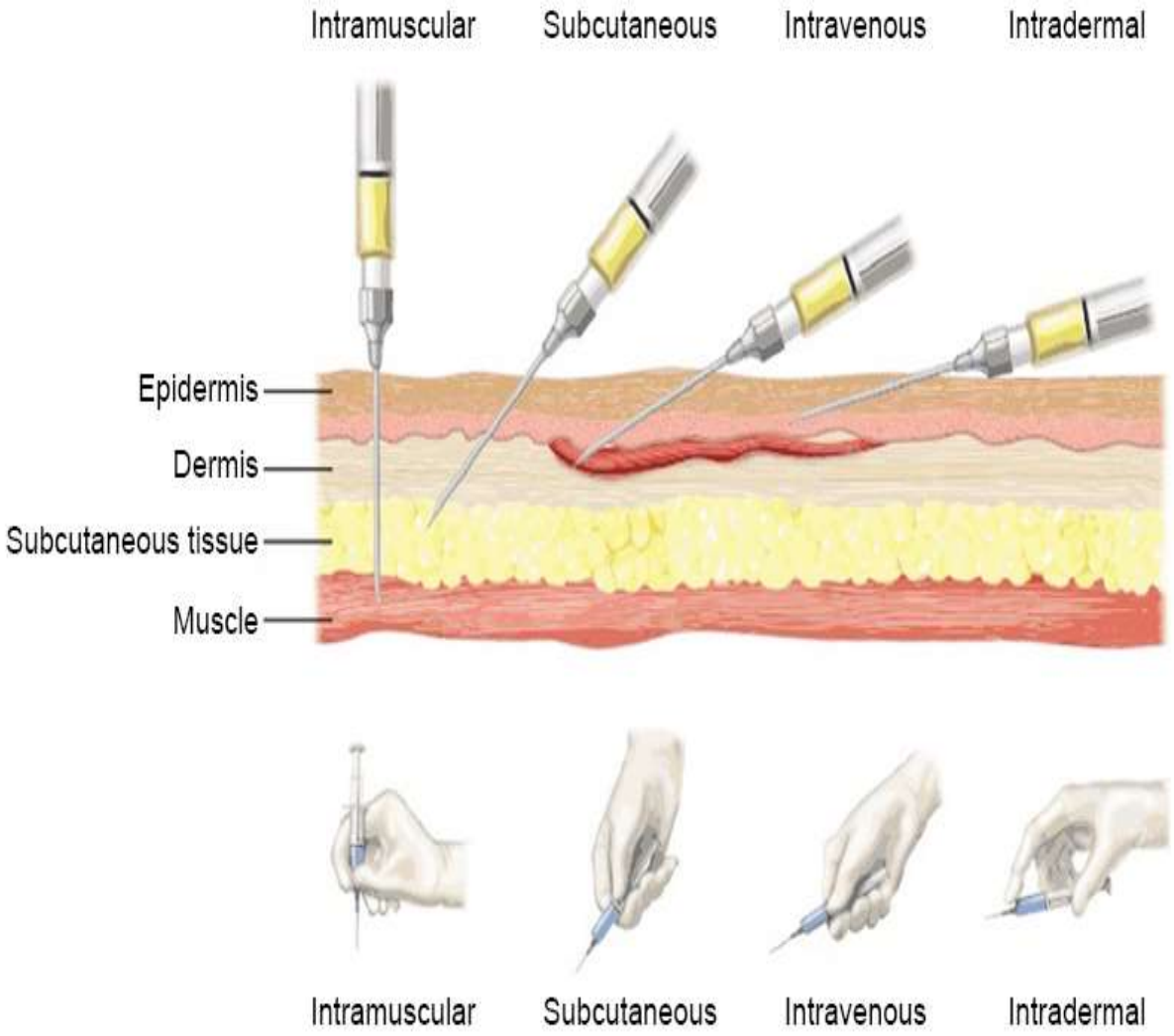


Figure 6 Structure of the skin and subcutaneous layers and common routes of parenteral drug administration.

Primary or Main parenteral routes:-

1. Intramuscular

Site of injection:- **Gluteal muscle in bouttock, deltoid muscle in shoulder and vastus parentrals of thigh. (infant, small children).**

Volume administered:-

- **deltoid muscle- Max. 2ml (rapid absorption)**
- **Gluteal - 5ml (Large volumes can tolerated)**

Aqueous, or oily solution or suspensions

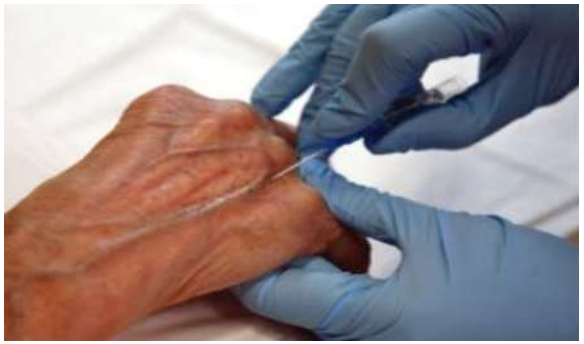
Drug commonly injected:- **Lidocaine, cephalosporins aminoglycosides, diazepam, insoluble salts of penicillin G., Corticosteroids, Narcotics antagonists and Contraceptive steroids.**

Needle specifications:- **1.3 inches, gauge 19-22**

Absorption can be delayed or prolonged by administering the drug as depot preparations using waxes or oils as vehicle.

2. Intravenous:-

- **Site of action:- Superfacial vein, commonly on back of hand or in the flexure of the elbow, superior longitudinal sinus.**
- **Volume administered:- Large or small volume of children for rapid effect.**
- **Solutions of irritating drugs can be given by this route because of their rapid dilution with blood or IV can be used as a diluents.**
- **Solution drugs, oily sub, suspensions, acid or alkaline salts incompatible with blood shouldn't administered by IV route.**

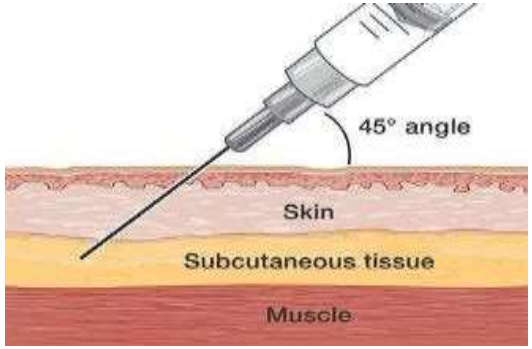


IV Fat Emulsion:-

- **Needle specification:- 20-22 guage, 1-2 inch long**
- **IV infusion are administered usin needle or cathaters, cathaters are inserted into subclavian vein.**
- **Indewelling cathaters contains heparin to avoid clotting and venous thrombosis.**

3. Subcutaneous:- **Abdomen, upper back, lateral upper hips.**

- **Site loose connective and adipose tissue, beneath the skin (demes) into outer surface of arm or thigh.**
- **More rapid absorption than intradermal.**
- **Volume does not exceed 1ml (0.5-1.5 ml)**
- **Needle 24-26, ¼ -5/8 inch long.**
- **Drug like insulin (self medication), vaccines, narcotics, ephiniphrine, vit. B_{12}**



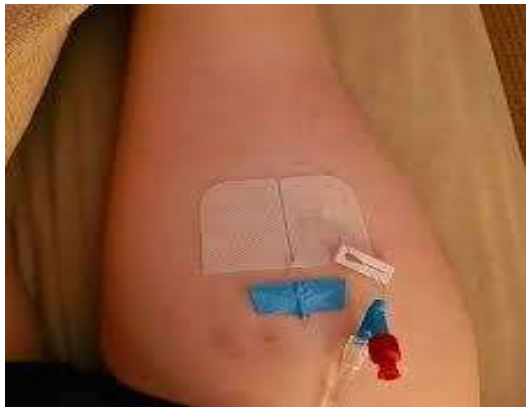
4. Intradermal:-

- **Site- superficial layer of skin just beneath the epidermis usually at the anterior foreman**
- **Volume administered 0.1 ml**
- **Needle size 3/8 inch, 23-26 guage**
- **Various agents for diagnostic determination, desensitization or immunizations (limited number of vaccines) e.g. smallpox, antigents, tuberculin. Absorption by this rout is very slow i.e. slow onset of drug action.**

Secondary parentral routes

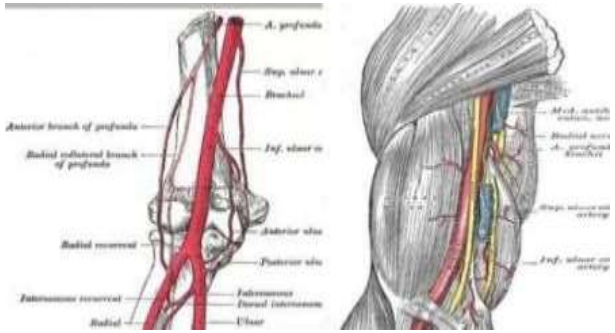
1. Hypodermoclysis:-

- **Hypodermoclysis is a form of SC injections that permits slow administration of large amounts of fluids as isotonic saline or glucose solution when IV sites are not available. This is rarely used today but in the recent past it was commonly used in infants and young children to counteract dehydration.**
- **Site- Interior or lateral position of thigh, in infants best site is SC tissue at the base of either scapula.**
- **An enzyme hyaluronidase may be added to enhance absorption.**
- **Fluid injected- Lactated ringer, dextrose 2.5% in 0.45% saline, Normal saline for maintain or restoration of fluid and electrolyte balance.**



2. Intra-arterial injection

- **Injection or infusion into an artery which leads directly to target organ.**
- **Used for diagnostic purpose like injecting radio-opaque sub for roento genographic studies of vascular supply of various organs or tissues. Such as coronary, pulmonary, renal, enteric or peripheral arteries.**



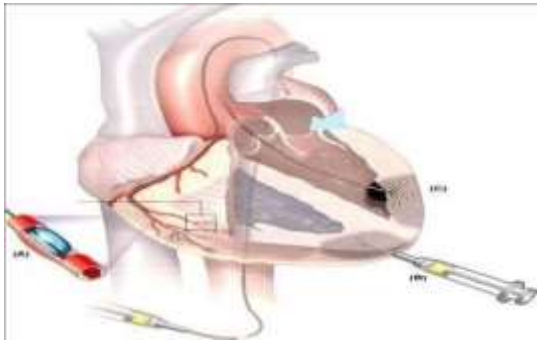
- **Use of intra-arterial route for treatment purpose is infrequent and limited generally to organ specific chemotherapy such as treating certain localized cancers (malignant melanomas of lower extremities) where high concentration of toxic drugs may be perfused through the artery for regional perfusion in the limbs, where IV administration may cause serious systemic reaction.**
- **Suitable sized smooth bored stainless steel needle or short flexible plastics catheter used.**

3.Intra-articular:-

- **synovial sacs of various accessible joints.**
- **Needle 17-22 gauge**
- **Site of action- knee, ankle, wrist, elbow, shoulder, phalangeal, sternoclavicular, acromioclavicular joints, hip joints is entered with difficulty.**
- **Drugs- antibiotics, lidocaine, corticosteroids, esters, administered into body ligands for treatment of infection, pain, inflammation or other problems reaching from inflammation diseases e.g. Rheumatoid arthritis, trauma,**

4.Intra-cardiac:-

- **Site- directly into chambers of heart**
- **Needle- 18-21 gauge, 4-6 inch long**
- **Used in emergency condition like cardiac arrest in which drugs have to reach myocardium immediately.**



5.Intra-cisternal:-

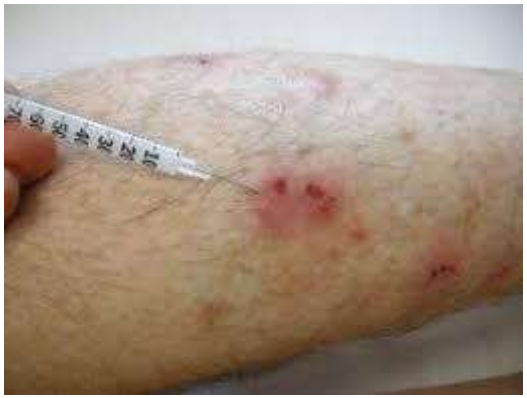
- **Directly into the cisternal space surrounding the space of brain.**
- **Used when intracranial pressures are elevated and risk of herniation of brain exist, if fluid is removed from langer sac.**
- **Used for diagnostic purpose.**

6.Intra-abdominal or Intra-peritonial:-

- **Injection or infusion given directly into peritoneal cavity via needle or indwelling catheter, directly into an abdominal organs like liver, kidney, bladder**
- **Needle- 16-18 gauge.**

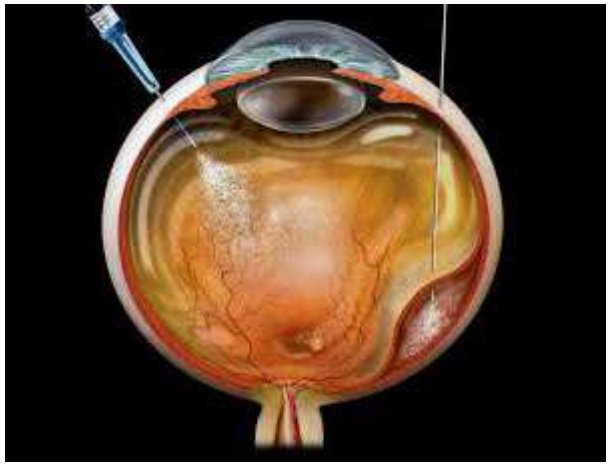
7.Intra-lesional:-

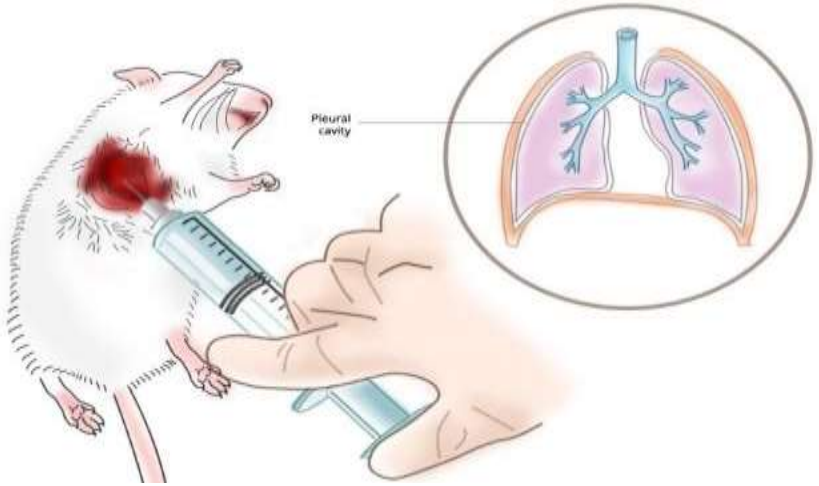
- **Directly into or around a lesion usually located in or on the skin or soft tissues to achieve therapeutic effect.**
- **Needle- 24-26 gauge**
- **Small volume less than 1ml injected**
- **Dermatologist commonly used this route to treat psoriasis, lichen simplex, sarcoid, lichen plains hyper tropics, herpes zoster, cystic or nodular acne with local steroid.**



8.Intraocular:-

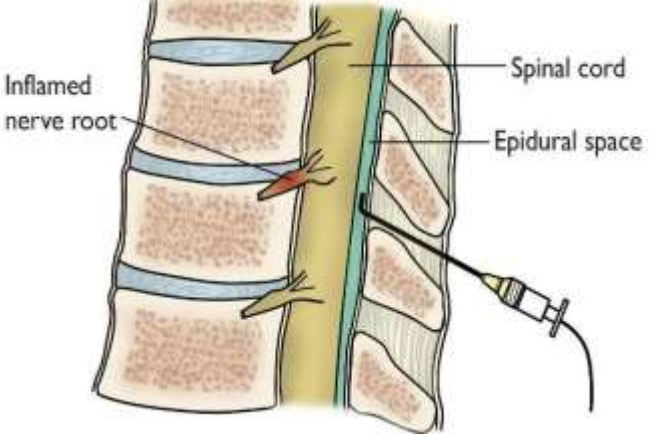
- **In anterior chamber, vitreous cavity of eye, around the posterior segment of the glow and sub conjunctival i.e. beneath the conjunctiva, so that drug diffuse through the limbus and sclera into the eye.**
- **Needle- anterior chamber 25 gauge or smaller, vitreous 25 gauge, retrobulber 1:2 inch long 25 gauge**
- **Subconjuctival injection do not exceed 0.5ml mainly used to treat cortical abscesses.**





9.Intrapleural:-

- Injection into pleural cavity
- Needle 13-18 gauge
- Infections or malignancies involving pleural cavity particularly if diseases process is impairing respiratory function are treated by this route.
- Enzyme such as streptokinase and streptodornase injected to liquefy thick empyema which may not be removed by aspiration or reabsorb naturally. If such empyema are not treated may result in fibrosis, addition thickening of the flora and restriction of breathing.
- Carcinomatous spread or mesotheliomas involving pleura are treated by local Intrapleural injection of antitumor or sclerosing agents.



10.Intra-thecal or Intra-spinal:-

- **Also referred as subarachnoid, intra-cisternal, epidural, peridural injection.**
- **Infusion and injection are directly into the lumbar sac located at the caudal end of the spinal cord or into the subarachnoid space. These injections are made by inserting needle through the vertebral interspinus species into spinal fluid usually by lumber puncture.**
- **Less than 20ml solution can be injected and specific gravity of the injection should be adjusted.**

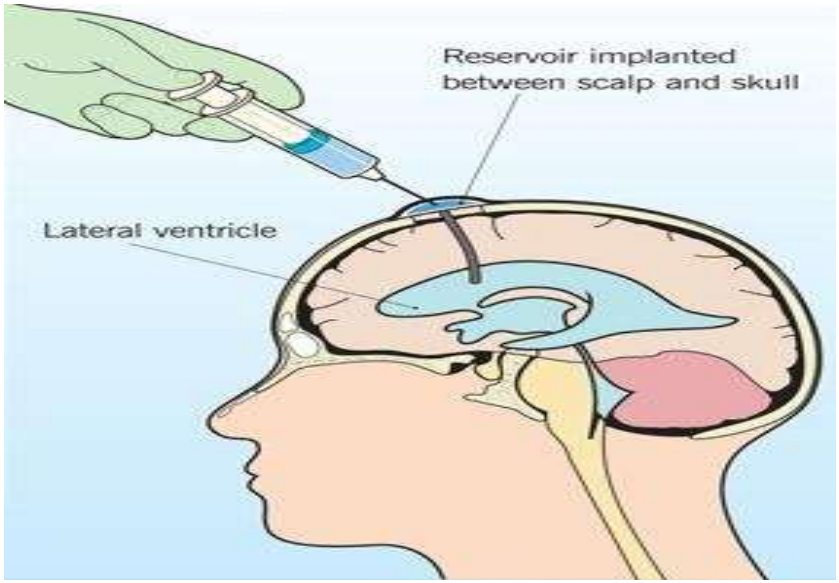
- **This route mainly used for diagnostic purpose and sometimes also utilize for treating the infections and tumors of subarachnoid space along the cord.**
- **Used for infectious type of meningitis or to produce spinal anesthesia or for introduction of radiopaque contrast media into subarachnoid space to visualize spinal cord (myelography)**
- **Needle- 20-22 gauge 3-5 inch long needle.**

11.Intrauterine:-

- **Infusion or injection via needle inserted percutaneous into the pregnant uterus**
- **Injection of infusion of 20% saline, prostaglandin E or urea into pregnant uterus to induce labour in medical abortions or to deliver stillborn fetus.**
- **Sometimes used to inject contrast material for roentogenographic studies to study potential congenital anomalies.**
- **Needle 18-20 gauge, 3-5 inch long**

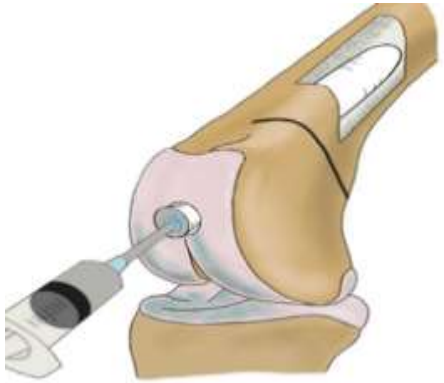
12.Intra-ventricular

- **Lateral ventricles of the brain**
- **This route is employed to treat infections such as bacterial or fungal meningitis (amphotericin B), ventrilytis or malignancies such as leukemic infiltrates (methotrexate) of meninges or carcinometosis involving the membranes and CSF surrounding the CNS**
- **Radio opaque, radiolabelled or dyes injected into intra-ventricular space to study anatomy or flow of CSF**
- **Needle 3-5 inch long, 18 gauge**



13.Intramedullary

- **Injection directly into bone marrow**
- **Rapidity or availability is comparable with IV injection.**
- **Whole blood normal saline or glucose can be injected.**



Advantages of Injectables:

1. Useful when degradation occurs in GIT ex-insulin.
2. Useful when patient is unconscious, unable to swallow, nauseous or uncooperative.
3. Rapid action specially useful in cardiac arrest asthma, shock
4. Greater predictability and reproducibility of drug absorption.
5. Patient returns to physician for further doses therefore no overdosing or under dosing is possible.

6. Also useful for local effect when desired ex- in dentistry.
7. Prolonged drug action is also possible. Ex- long acting steroids.
8. Useful for immediate treatment of serious disturbances of fluid and electrolyte balance.
9. When fluid cannot be taken by mouth, total nutritional requirements can be supplied by parenteral route.
10. New drugs in preliminary stages of clinical trial are prepared in parenteral dosage form because with this dosage form it is possible to control the dose more precisely.

Disadvantages:

- Should be administered by trained person.
- Administration requires more time.
- Requires strict adherence to aseptic procedure during manufacturing and administration.
- Pain on injection is unavoided.
- Once administered, it is difficult to reverse the physiological effect.
- More expensive because of stringent manufacturing and packaging requirements.
- There may be complications of septicemia, fungal infection, IV admixture incompatibility etc.
- Contamination of particulate matter in injection is hazardous.

Characteristics of parenteral dosage forms

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

1. **All products must be sterile.**
2. **All products must be free from pyrogenic (endotoxin) contamination.**
3. **Injectable solutions must be free from visible particulate matter.**
4. **This includes reconstituted sterile powders.**
5. **Products should be isotonic, although strictness of isotonicity depends on the route of administration.**

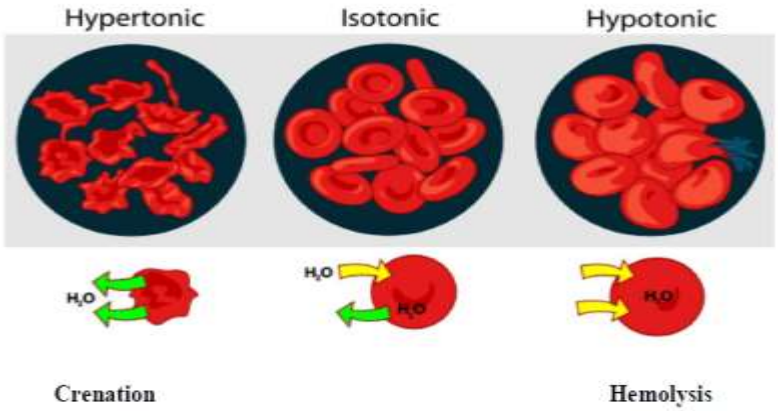
6. Products administered into the cerebrospinal fluid must be isotonic.
7. Ophthalmic products, although not parenteral, must also be isotonic.
8. Products to be administered by bolus injection by routes other than intravenous (IV) should be isotonic, or at least very close to isotonicity.
9. IV infusions must be isotonic.
10. Products must be compatible, if applicable, with IV diluents, delivery systems, and other drug products co-administered.
11. All products must be stable, not only chemically and physically like all other dosage forms, but also 'stable' microbiologically (i.e. sterility, freedom from pyrogenic and visible particulate contamination must be maintained throughout the shelf life of the product).

Significance of tonicity adjustment:

- An isotonic solution is one that exhibits the same effective osmotic pressure as blood serum. Isotonicity is important for parenteral preparation because if the solution is isotonic with blood, the possibility of product penetrating the RBC and causing haemolysis is reduced. A parenteral preparation should be isotonic otherwise it may cause crenation or haemolysis of the RBC.

- When a hypertonic (Having high solute concentration) solution is injected then it causes shrinkage of RBC present in blood plasma leading to crenation of the RBC due to flow of fluid from RBC into the solution.

- When hypotonic solution (having low solute concentration) is injected then it causes swelling of RBC leading to haemolysis of the RBC due to flow of fluid from solution into the RBC.



Significance of tonicity adjustment:

- Tonicity is an important factor in the formulation of products intended for application to sensitive mucous membranes of organs like eye, ear and nose.

- Therefore any formulation that comes in contact with sensitive mucous membranes should not result in tissue irritation and pain.

- One of the physiochemical mean by which a formulation may result in pain and tissue irritation is caused by the non physiological concentration of dissolved solutes coming in contact with sensitive tissues.

- **If a small quantity of blood defibrinated to prevent clotting is mixed with 0.9%w/v of NaCl, the red blood cells remain intact and retain their normal size and shape.**
- **The NaCl solution is considered to be isotonic and has essentially same salt concentration as that of red blood cells.**
- **In contrast if blood is mixed with 1.8%w/v NaCl solutions, erythrocytes shrink and become wrinkled and crenated as if the cell content has been sucked out.**
- **Hence the solution is considered hypertonic with respect to RBC contents.**

- It is because the red blood cell contains a lower salt concentration than 1.8%w/v salt solution.
- The opposite phenomena occurs if blood is mixed with 0.45%w/v NaCl solution.
- Water from the surrounding salt solution enters the erythrocytes, causing them to swell and finally burst with liberation of hemoglobin.
- The 0.45%w/v salt solution is considered hypotonic, and the phenomenon is known as hemolysis.
- The crenation and the haemolysis of erythrocytes in hypertonic and hypotonic salt solution respectively can be explained by movement of water across the cell membrane.

- **An isotonic solution is an aqueous solution that generates the same tone or osmotic pressure as the body fluids across biological membranes and thus prevents water flow in either direction and hence nonirritating when injected, instilled, perfused or brought into contact with sensitive mucous membrane.**
- **When a solution is hypertonic or hypotonic, osmotic water flow occurs and tone of the membrane is affected.**
- **Thus formulators need to adjust the tone or tonicity of the solution to be isotonic with physiological fluids.**

- **Thus BP(2001) states that aqueous solutions for large volume infusion fluids, together with aqueous fluids for subcutaneous, intradermal and intramuscular administration, should be made isotonic.**
- **Intrathecal injections must be isotonic to avoid serious changes in the osmotic pressure of the cerebrospinal fluids.**
- **Aqueous hypotonic solutions are made isotonic by adding either sodium chloride, glucose or occasionally mannitol.**
- **The latter two agents are incompatible with some drugs.**
- **If the solution is hypertonic it is made isotonic by dilution.**

- **Some components of injections such as buffer and antioxidants affect the tonicity.**
- **Other components such as preservative which are resent in low concentration have little effect on tonicity**
- **Isotonicity by Sodium chloride Equivalent method**
- **Isotonicity by Freezing point depression method**

Concentration of tonicity adjusting agents

S. No.	Additives	Concentration range (%)
1.	Gelatin	1.6-2.25
2.	Lactose	0.14-5.0
3.	Mannitol	0.4-2.5
4.	Dextrose	3.75-5.0
5.	Sodium chloride	Varies
6.	Sodium sulfate	1.1
7.	Sorbitol	2.0

Pre-formulation factors

- Preformulation involves the study about physical & chemical properties of drug substance prior formulation. These studies are performed under stressed conditions of temperature, humidity; light and oxygen so that the reactions are accelerated and potential reaction are detected. A few physicochemical properties that affect a drug substance are discussed below.

- **Molecular structure and weight:**
- **Colour**
- **Odour:**
- **Particle size, shape and crystallinity**
- **Melting point**
- **Thermal analytical profile:**
- **Hygroscopicity**
- **Absorbance spectra**
- **Solubility:**
- **pH- solubility profile**
- **Ionization constant**
- **Partition Coefficient (P)**

Components or additives

Components of parenteral products

I. Active ingredient,

II. Vehicles

III. Additives

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

Establishing specifications to ensure the quality of each of these components of an injection is essential.

Solvents and vehicles

Water and aqueous vehicles

- **Water for injection**
- **Sterile water for injection**
- **Bacteriostatic water for injection**
- **Sodium chloride injection**
- **Bacteriostatic sodium chloride injection**

Non-aqueous solvents

Fixed vegetable oils

Alcohols

TABLE 15.1 SOME INJECTIONS IN OIL

INJECTION	OIL	CATEGORY
Dimercaprol	Peanut	Antidote to arsenic, gold, and mercury poisoning
Estradiol cypionate	Cottonseed	Estrogen
Estradiol valerate	Sesame or castor	Estrogen
Fluphenazine decanoate	Sesame	Antipsychotic
Fluphenazine enanthate	Sesame	Antipsychotic
Hydroxyprogesterone caproate	Castor	Progestin
Progesterone in oil	Sesame or peanut	Progestin
Testosterone cypionate	Cottonseed	Androgen
Testosterone cypionate and estradiol cypionate	Cottonseed	Androgen and estrogen
Testosterone enanthate	Sesame	Androgen
Testosterone enanthate and estradiol valerate	Sesame	Androgen and estrogen

Water for injection

- **Water for injection is free** from dissolved air, water for injection is sterile water, which is free from Volatile, non- volatile impurities and from pyrogens.
- Pyrogens are by-product of bacterial metabolism. Pyrogens are liposaccharide, thermo stable, soluble in water, unaffected by bactericide and can pass through bacterial proof filters. Pyrogens can be removed from water by simple distillation process using an efficient trap which prevents the pyrogen to enter into the condenser. Immediately after the preparation of water for injection ,it is filled in to the final container, sealed and sterilized by autoclaving .
- Water for injection, contaminated with pyrogens may cause rise in body temperature if injected Hence, test for pyrogen is done to ensure that water for injection is free from pyrogens.

Types of Water for injection

- **Water for injection**
- **Sterile water for injection**
- **Bacteriostatic water for injection**

Preparation of WFI

- The tap water obtained from sources such as well, streams or lakes cannot be employed in the preparation of parent has contaminants like suspended minerals or industrial or agricultural chemical, viable bacteria, bacterial endotoxin, other particulate matter etc.
- Hence portable water must be what are you treated by techniques deionization, filtration etc. to remove the contaminants.
- This pre-treated water is then subjected to either distillation or reverse osmosis for the preparation of water for injection

Reverse osmosis

- As the name suggests, the reverse osmosis system works opposite to that of the natural osmosis process.
- The pretreated water is allowed to permit through a semipermeable membrane in opposite direction that is from high concentration region to low concentration region by applying pressure in order to 200 to 400 PSI to counteract the osmotic pressure.
- The reverse osmosis membranes, which are usually composed of cellulose esters for polyamide, effectively retain macromolecular and micro molecular contaminants present in water to build high quality pure water.

Distillation

- Distillation is the process of converting water into steam which is a pure gaseous water divide of all contaminants. This process is carried out in distillation still made up of stainless steel or neutral glass .
- For small scale production, single effect distillation still with capacity to produce up to 90 litre of water for injection per hour are used. Apart from these Epic impression steel and multiple effect steels are also available which kill about 50 to 1000 gallon of water for injection per hour.
- The distillation still consists of a boiler into which the feed water is fed through the water inlet. The distal end is heated by means of heat source to about 90 degree centigrade as the water heats up the dissolved gases such as CO2 and NH3 in the vapour escape into the atmosphere from the open top of distillation still. The headspace above the boiler contains baffles to reflect the web per so that non volatile impurities are returned to the distillate.
- The distillation unit contains a series of parallel condensing tubes with open ends.
- The vapours while descending from headspace enter into condenser tube where they lose their heat of vaporization and condensed into liquid distillate which is collected from lower end of the steal into pyrogen free glass container or glass lined metal container the distillation still also consists of separation device or the mister to entertain the volatile impurities before they condense. The distillate collected is destroyed in an autoclave or by membrane filtration technique and stored in a tightly closed container at temperature 60 to 80 degree centigrade

1.Water for injection free from CO2

- Classes of organic drugs such as barbiturates and sulfonamide are weak acids and hence are slightly soluble in water.

- The active solubility of these compounds can be enhanced by converting them into their salt form like sodium salt. When such salz are dissolved in water for injection containing dissolved CO2 then they decompose resulting in the precipitation of drug.

- Therefore it is advisable to use water for injection free from CO2 prepared by boiling a pyrogenic water for injection for 10 minutes.

2. Water for injection free from dissolved air

- Most of the drugs are prone to oxidation when they come in contact with air which reduces their stability. Hence it is necessary to make water for injection free from dissolved Air by boiling it for 10 minutes.
- The empty space above the drug solution is replaced with an inert gas such as N2. The containers are then sealed in presence of a nitrogen rich environment.
- Sterile water for injection it is defined as pyrogen free distilled water which is packed in a single dose container
- It does not contain any antimicrobial agent or other additive but shows the presence of higher levels of solids when compared with water for injection. This is due to the incorporation of leached out constituents of glass during sterilization and storage in glass lined containers.
- This water is used as a solvent vehicle or diluent on for reconstitution of already sterilized and packed injectable preparations.

3.Bacteriostatic water for injection

- Bacteriostatic water for injection pyrogen free sterile water for injection which contains one or more bacteriostatic agent. While selecting a bacteriostatic agent its chemical compatibility with the drug should be considered.
- This water is used in preparation of small volume parenteral.
- Large volume parenteral do not employ this water as the bacteriostatic agent present in it may accumulate the result in toxicity.

Storage and distribution

- Distillate is collected in holding tanks for subsequent use.
- The USP also permits the WFI to be stored at room temperature but for a maximum of 24 hours.
- Under such conditions, the WFI is collected as a batch for a particular use with any unused water discarded within 24 hours.
- Such a system requires frequent sanitization to minimize the risk of viable microorganisms being present.
- The stainless-steel storage tanks in such systems are usually connected to a welded stainless-steel distribution loop, supplying the various use sites with a continuously circulating water supply.

• Purity

- The only physical/chemical tests remaining are the new total organic carbon (TOC), with a limit of 500 ppb(0.5 mg/L), and conductivity, with a limit of 1.3 μS/cm at 25°Cor 1.1 μS/cm at 20°C.
- Biological requirements continue to be, for WFI, not more than 10 colony-forming units (CFUs)/100 mL and less than 0.25USP endotoxin units/mL.

Water miscible liquids

- These vehicles were used to effect solubility and to prevent hydrolysis of drugs.
- The most important solvents of this class are: ethyl alcohol, polyethylene glycol, propylene glycol.
- Ethyl alcohol is particularly used in the preparation of solution of cardiac glycosides.
- Glycols are used to prepare the solutions of barbiturates, certain alkaloids and certain antibiotics. These preparations are used for IM administration.

Non -aqueous vehicles

- The commonly used non-aqueous vehicles are oils and alcohols. Fixed oil, such as arachis oil, cottonseed oil, almond oil and sesame oil are used as vehicle .
- The oily vehicles are generally used when a depot effect of drug is required or the medicaments are insoluble or slightly soluble in water or the drug is soluble in oil example dimercaprol injection by using arachis oil as vehicle.
- Ethyl alcohol is used in the preparation of hydrocortisone injection Hydrocortisone is insoluble in water, hence the solution is made in 50% alcohol .Alcohol causes pain and tissue damage at the site of injection. Therefore, it is not used commonly. Propylene glycol is used as a vehicle in the preparation of digoxin injection .It is relatively nontoxic but it causes pain on S/C or I/M injection.
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Additives

a. Solubilizing agents:

Solubilizing agents are used for solubilizing the insoluble or poorly soluble drugs in the vehicle. Solubility can be increased by adding solubilizes like carbonates, tween and polysorbates

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Sr. No.	Additives	Concentration range (%)
1.	Dimethyl acetamide	0.01
2.	Ethyl alcohol	0.61-49.0
3.	Ethyl lactate	0.1
4.	Glycerin	14.6-25.0
5.	Lecithin	0.5-2.3
6.	PEG-40 castor oil	7.0-11.5
7.	Polyethylene glycol 300	0.01-50.0
8.	Polysorbate 20	0.01
9.	Polysorbate 40	0.05
10.	Polysorbate 80	0.04-4.0
11.	Povidone	0.2-1.0
12.	Propylene glycol	0.2-50.0
13.	Sorbitan monopalminate	0.05

b. Stabilizers:

- Drugs present in the injection may undergo hydrolysis or oxidation during preparation and storage. Stabilisers are the substances to prevent these changes in the drugs.
- Since most decomposition is catalysed by hydrogen or hydroxyl ions, adjustment of pH is the most important method of stabilisation of injection. Sometimes water may be replaced by another suitable vehicle to minimize hydrolysis.
- The methods used to prevent oxidation of medicament are use of water for injection free from dissolved air, addition of a reducing agent or antioxidant and replacement of air in the container with an inert gas. Sodium met bisulphite is the most commonly used reducing agent for injections

c. Antioxidant

- Oxidative decomposition is catalysed by metal, hydrogen, and hydroxyl ions. Drugs possessing a favourable oxidation potential will be especially vulnerable to oxidation. For example, a great number of drugs are formulated in the reduced form (e.g., epinephrine, morphine, ascorbic acid, menadione, etc.) and are easily oxidized. By increasing the oxidation potential of the drug, oxidation can be minimized. Salts of sulfur dioxide, including bisulfite, metabisulfite, and sulphite, are the most common antioxidants used in aqueous parenteral. These antioxidants maintain product stability by being preferentially oxidized and gradually consumed over the shelf life of the product

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d. Buffering agents:

pH range is maintained within the desired limits by adding buffering agents. Acetates, citrates and phosphate buffers are used to maintain the pH of injections.

Sr. No.	Additives	Concentration range (%)
1.	Acetic acid	0.22
2.	Adipic acid	1.0
3.	Benzoic acid and sodium benzoate	5.0
4.	Citric acid	0.5
5.	Lactic acid	0.1
6.	Maleic acid	1.6
7.	Potassium phosphate	0.1
8.	Sodium phosphate mono basic	1.7
9.	Sodium phosphate dibasic	0.71
10.	Sodium acetate	0.8
11.	Sodium bicarbonate	0.115
12.	Sodium carbonate	0.06
13.	Sodium citrate	4.0
14.	Sodium tartrate	1.2
15.	Tartaric acid	0.65

e. Antimicrobial agents:

- Antimicrobial preservatives are added in injection to prevent multiplication of microorganisms, which may be accidentally introduced into the preparation during use.
- These preservatives are used in multidose containers and in injections sterilized by filtration.
- Preservatives are not added in single dose containers because they are sterilized after packaging and remain sterile until opened and the solution is injected. Frequently used antimicrobial preservatives are: phenol (0.5%), cresol (0.3%), chlorocresol (0.1%), phenyl mercuric acetate and nitrate (0.001%).

f.Suspending, emulsifying and wetting agents:

- These agents are sometimes used in suspension and emulsion to stabilize the product or to maintain the particle size and prevent lump formation.
- The suspending agents are used to improve the viscosity and to suspend the particles for a long time. Methyl cellulose, carboxyl methyl cellulose, gelatin and acacia are commonly used as suspending agent's .
- Emulsifying agents are used in sterile emulsions .for this purpose lecithin is generally used .
- The wetting agents are used to reduce the interfacial tension between the solid particles and the liquid, so as to prevent the formulation of lumps.

g. Tonicity factors:

- Parenteral formulations should be isotonic with human plasma so as to avoid damage to the tissues. However, not all drugs at their recommended dosage are isotonic with blood, thus requiring the addition of a tonicity adjusting agent to the formulation.
- The parenteral preparation should be isotonic with blood serum or other body fluids where they are injected

h. Chelating agent:-

Chelating agents such as EDTA (Ethylene diamante Tetra acetic acid and its salts ,sodium or potassium salts of citric acid are added in the formulation, to chelate th metallic ions present in the formulation .they form a Complex which gets dissolve the solvent.

Sr. No.	Additives	Concentration range (%)
1.	Edetate disodium	0.00368-0.05
2.	Edetate calcium disodium	0.04
3.	Edetate tetrasodium	0.01