Sterile/Parenteral Dosage Forms

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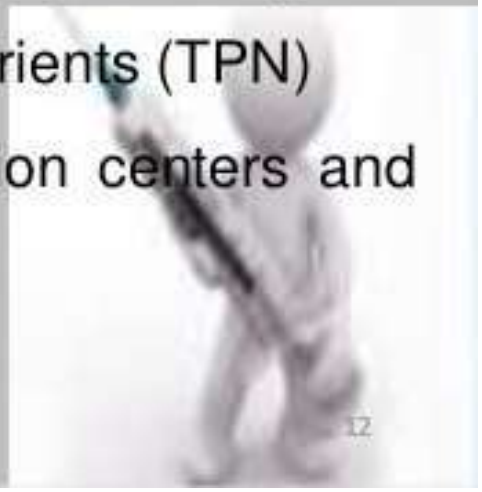
Introduction

- The term derived from Greek word ‘Para’ outside & ‘Enterone’ intestine.
- Parenterals are sterile solutions or suspension of drug in aqueous or oily vehicle that are given by other than oral routes.
- Parenteral drugs are administered directly into the veins, muscles or under the skin or more specialized tissues such as spinal cord by means of syringe and needles.
- Term parenteral used for any drug/fluid whose delivery doesn’t utilize the alimentary canal for entering into the body tissues.

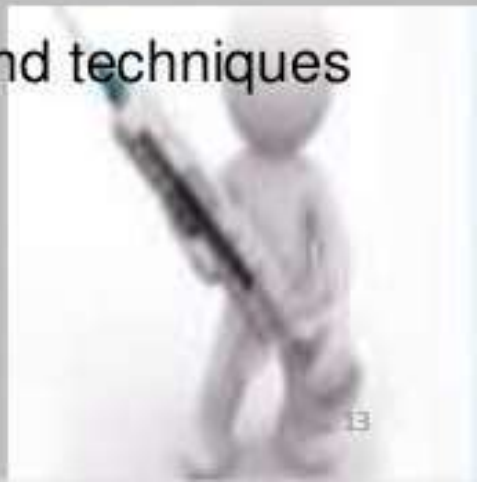
ADVANTAGES

- Useful for patients who cannot take drugs orally
- Rapid onset of action
- Useful for emergency situations
- Providing sustained drug delivery (implants, im depot inj)
- Avoid first pass metabolism
- Can inject drug directly in to a tissue (target drug delivery)
- Useful for delivering fluids, electrolytes, or nutrients (TPN)
- Can be done in hospitals, ambulatory infusion centers and home health care centers
- Complete bioavailability.



DISADVANTAGES

- Pain on injection
- Difficult to reverse an administered drug's effect.
- Sensitivity or allergic reaction at the site of injection.
- Requires strict control of sterility & non pyrogenicity than other formulation.
- Trained person is required.
- Require specialized equipment, devices, and techniques to prepare and administer drugs.
- More expensive and costly to produce.



ROUTES OF ADMINISTRATION

Drugs may be injected into almost any organ or area of the body.

- **Major routes:**

- vein (intravenous, IV),
- muscle (intramuscular, IM),
- under the skin (subcutaneous, SC)

- **Other routes:**

- joints (intra-particular),
- Joint fluid area (intra-synovial),
- spinal cord (intra-spinal),
- spinal fluid (intra-thecal),
- arteries (intra-arterial), and
- in an emergency, even the heart (intra-cardiac).
- skin (intradermal, ID, intra-cutaneous)

Types of Parenteral Preparations

Small Volume Parenterals: An injection that is packed in containers labelled as containing 100 mL or less.

Examples: Solution, Suspension, Emulsion, Dry Powders

Large Volume Parenterals (**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 Parenterals

- **Electrolytes:** 0.9 % NaCl Injection, Multiple electrolyte, Lactated Ringer Injection
- **Carbohydrates:** 5 % Dextrose Injection, 10 % Fructose Injection, 10 % Invert Sugar 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.)

General requirements for Parenterals

- Sterility
- Free from Pyrogens
- Free from Particulate matters
- Isotonicity
- Specific gravity
- Chemical Purity
- Stability

FORMULATION

AQUEOUS VEHICLE :

WATER FOR INJECTION (WFI) USP :

- Highly purified water used as a vehicle for injective preparations which will be subsequently sterilized.
- USP requirement include not more than 10 parts per million of total solids.
- pH of 5.0 – 7.0 .
- WFI may be prepared by either distillation or reverse osmosis.
- Stored in chemically resistant tank.

WATER MISCIBLE VEHICLES

➢The number of solvents that are miscible with water has been used as a portion of a vehicle.

➢Primarily to affect solubility of drugs and to reduce hydrolysis.

Example:

- Ethyl alcohol,
- Liquid propelene glycol
- Glycerine
- Ethyl alcohol used in the case of cardiac glycoside.

NON – AQUEOUS VEHICLES

- Fixed oils (vegitable origin, liquid, and rancid resistance ,unsaturated, free fatty acid content)
  - Peanut oil
  - Corn oil
  - Cotton seed oil (depo-testosterone)
  - Sesame oil
  - Soyabean oil
  - Ethyl oleate
  - Isopropyl myristate.

OTHER ADDITIVES

ANTIBACTERIAL AGENTS

- These are added in multiple dose containers.
- To prevent microorganism growth
- Limitted concenteration of agents are used.
- Phenyl mercuric nitrate and thiomersol 0.01%.
- Benzethonium chloride & benzalkonium chloride 0.01%.
- Phenol & cresol 0.05%.
- Chlorobutanol 0.05%.

BUFFERS

- Added to maintain pH.
- To stabilize a solution from chemical degradation.

- Citrate and acetate buffer.
- Sodium benzoate and benzoic acid
- Sodium tartarate and tartaric acid
- Phosphate buffer.

ANTIOXIDENT

- To protect the formulation from oxidation
- Two types

1. Reducing agents

- Ascorbic acid
- Sodium bisulfite 0.01%
- Thiourea

2.Blocking agents

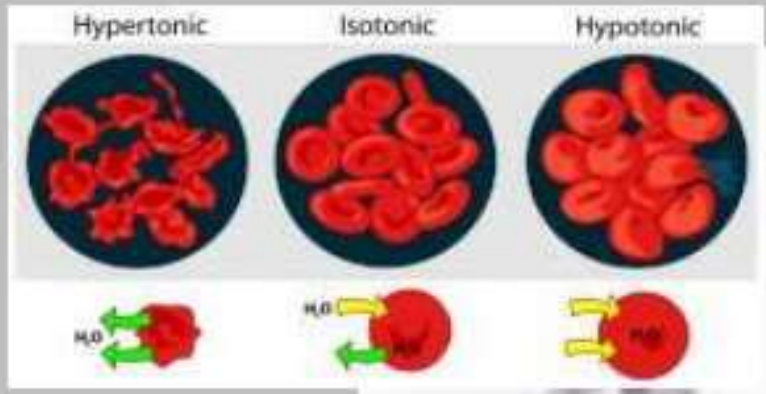
- Tocopherol

SURFACTANTS

- **Solubilise the active ingredient**
  - Polyoxythylene sorbitan monooleate & Sorbitan monooleate

TONICITY AGENTS

- Need isotonic solution to avoid destruction of red blood cells, irritation, and tissue damage
- More important for large volumes, rapidly administered, and extravascular injections
- Reduces the pain on injection
  - NaCl & KCl
  - Dextrose
  - Mannitol & Sorbitol



Effect of different solutions on blood cells

CHELATING AGENTS

- To remove trace elements that catalyse oxidative degeneration
- Ethelene diamine tetra acetic acid

CO-SOLVENT

- Improve solubility
- Prevent potential for hydrolysis

Containers and Closures used for Parenteral Products

Materials:

- Glass
- Plastic
- Metals
- Rubbers

Requirements for Containers and Closures

1. It should not yield foreign substances to the product
2. It should be transparent to allow visual inspection of the content in it.
3. It should not have any adverse effect on the product.
4. It should be compatible (physical and chemical) with the product.
5. It should prevent diffusion in or across the walls of the contaier and closure.

Glass

Type	General Discription	Type of Test	Size (mL)	0.02 N H2SO4 (mL)
I	Highly resistant, Borosilicate Glass	Powdered glass	All	1
II	Treated Sodalime Glass	Water attack	≤ 100 > 100	0.7 0.2
III	Sodalime Glass	Powdered glass	All	8.5
IV (NP)	General Purpose Sodalime Glass	Powdered glass	All	15

Type	Products Packed
I	All SVPs, LVPs that are mildly alkaline
II	LVPs like IV and Irrigating solutions, anticoagulants, blood components, diagnostic preparations, SVPs (Neutral and Acidic)
III	Solutions and suspensions in vegetable oil, sterile dry powders, Several neutral aqueous products
IV (NP)	Cough syrups, elixirs, tinctures, extracts, creams, lotions, tablets, capsules, other dry powders

Plastic

- **Thermoplastic type**

Examples: Polyethylene (PE), Polypropylene (PP), Polyvinyl Cholride (PVC), Polystyrene (PS), Polyamide (PA) (Nylon), Polycarbonate (PC), Polyethylene terephthalate (PET) etc.

- **Thermostting type**

Examples: Phenol-formaldehyde, urea-formaldehyde, melamine-formaldehyde

Metals and Rubbers

Types of Metal

- Tin
- Aluminium
- Lead
- Iron

Types of Rubber

- Butyl rubber
- Nitrile rubber
- Chloroprene rubber
- Silicon rubber

Processing of Parenteral preparations

1. Cleaning of containers, closures and equipments.
2. Collection of materials
3. Pre-sterilization
4. Preparation of parenteral products
5. Filtration
6. Filling
7. Sealing
8. Sterilization
9. Evaluation
10. Labelling and Packaging

Evaluation of Parenteral Preparations

- Sterility test
- Pyrogen test
- Clarity test
- Leakage test
- Assay
- Stability

Sterility Test

Sterility Testing: It is a testing procedure applied to products intended to be sterile before marketing, to check that these products are free from all living microorganisms.

Sterility tests are performed on random samples from the batch and must be carried out under aseptic conditions in order to avoid accidental contamination of the product during the test using, for example, a laminar air flow cabinet.

Growth of microorganisms, if present in samples under test, is usually checked by incubating over specified culture Media at specified temperature for specified time.

Principle:

If bacteria or fungi are placed in a medium which provides nutritive material and water and kept at a favourable temperature, the organism will grow and their presence can be indicated by a turbidity in the clear medium.

Steps involved in sterility testing

1. Selection of sample size.
2. Selection of quantity of product to be used.
3. Method of testing.
4. Observation and Results.

Number of Items in the Batch	Minimum Number of Items to be Tested for Each Medium
Parenteral preparations	
< 100 containers	10% or 4 containers, whichever is the greater
100 - 500 containers	10 containers
> 500 containers	2% or 20 containers, whichever is less
For large-volume parenterals	2% or 10 containers, whichever is less
Antibiotic solids	
Pharmacy bulk packages (<5 g)	20 containers
Pharmacy bulk packages (> 5 g)	6 containers
Ophthalmic and other noninjectable preparations	
Not more than 200 containers	5% or 2 containers, whichever is the greater
More than 200 containers	10 containers

Quantity per Container	Minimum Quantity to be Used
Liquids (other than antibiotics)	
Less than 1 mL	The whole contents of each container
1–40 mL	Half the contents of each container, but not less than 1 mL
40-100 mL	20 mL
>100 mL	10% of the contents of the container, but not less than 20 mL
Antibiotic liquids	1 mL
Other preparations soluble in water or in isopropyl myristate	The whole contents of each container to provide not less than 200 mg
Insoluble preparations, creams, and ointments to be suspended or emulsified	Use the contents of each container to provide not less than 200 mg
Solids	
Less than 50 mg	The whole contents of each container
50 - 300 mg	Half the contents of each container, but not less than 50 mg
300 mg–5 g	150 mg
> 5 g	500 mg

Methods of sterility Testing

1. **Membrane Filtration Method**
2. **Direct Inoculation Method**

1. Membrane Filtration Method

The membrane filtration method requires the test sample to first pass aseptically through a membrane filter capable of retaining microorganisms having normal porosity of 0.45 micron and a diameter of approximately 47mm. After the filtration, the membrane is removed aseptically from the metallic holder and divided into two equal halves. The first half is transferred into 100ml of culture media meant for fungi and incubated at 20-25^{o}C for not less than 7 days. The other half is transferred into 100 ml of fluid thiglycollate medium and incubated at 30-35^{o}C for not less than 7 days. Observe the growth in the media.

Fluid Thiglycollate Medium

Components	Quantity
L-cystine	0.5 gm
Sodium Chloride	2.5 gm
Dextrose Monohydrate	5.5 gm
Agar	0.75 gm
Yeast Extract	5 gm
Pancreatic digest of casein	15 gm
Sodium thioglycollate	0.5 gm
Resazurin sodium solution (0.1%)	1 ml
Distilled Water	1000 ml

Medium for Fungi and Aerobic Bacteria (Soyabean Casein Digets Medium)

Components	Quantity
Pancreatic digest of casein	17 gm
Peptic digest of soyabean meal	3 gm
Sodium Chloride	5 gm
Dibasic potassium phosphate	2.5 gm
Dextrose	2.5 gm
Distilled water	1000 ml

2. Direct Inoculation Method

The specified quantity of sample under test is drawn aseptically from the container (The quantity of the substance or preparation to be used for the inoculation varies and is given in IP) and transferred into a vessel of culture medium. Mix the liquid with the medium and incubate for not less than 14 days. Observe the growth of microorganisms in the medium.

Observations and Results

The culture media is examined throughout the incubation period at intervals for macroscopic evidence of microbial growth.

1. If no evidence of microbial growth is found, the product to be examined complies with the test for sterility.
2. There is evidence of microbial growth. So, re-testing is performed using the same number of samples, volumes to be tested and media as in the original test. If no evidence of microbial growth is found, the product to be examined complies with the test for sterility.
3. There is evidence of microbial growth. So, isolate and identify the organism. The second re-test is performed using twice the number of samples. The preparation being examined passes the test for sterility in case there is no evidence of microbial growth. In case there is evidence of microbial growth in the second re-test, the preparation being examined fails the test for sterility.

Pyrogen Testing

Pyrogen testing defines a process used by drug manufacturers to determine if bacterial toxins are present in vaccines and drugs that might cause fever when used on humans.

1. **Sham test**
2. **Rabbit method (Old method, In-Vivo test)**
3. **Limulus Amebocyte Lysate test (New method, In-vitro test)**

1. Sham test: It is performed to select the proper animals for the main test i.e Rabbit method.

Rabbit method (Old method, In-Vivo test)

- A Pyrogen is defined as “a fever producing agent”
- Metabolic products of Microorganisms.

They are

- Soluble
- Filterable
- Thermostable
- Non Volatile

Sources of Pyrogen

- Solvents, drugs, additives apparatus used in manufacture, containers may be sources of pyrogens.
- The method of storage in between preparation and sterilization also may cause the development of pyrogens.
- Hence every item must be apyrogenic and method of storage must not allow any bacterial growth

Rabbit test consists of measuring the rise in body temperature in healthy rabbits after the intravenous injection of a sterile test solution.

Why the Rabbit?

- Other species not predictable
- Rabbit chosen for economic purposes
- Similar threshold pyrogenic response to humans
- Reproducible pyrogenic response

Requirements for the Rabbit Pyrogen Test

- Rabbits must be healthy and mature.
- New Zealand or Belgian Whites used mostly.
- Either sex can be used, each weighing not less than 1.5 kg.
- Must be individually housed between 20 and 23°C.
- Not showing any loss of body weight during the week proceeding the test.
- equipment and material used in test (glassware, syringes, needles etc) must be free from Pyrogens by heating at 250º c for not less then 30 minutes or any other method.
- retaining boxes (comfortable for rabbits as possible).
- Do not use any rabbit having:

1. A temperature higher than 39.8^{o}C.
2. A temperature variation greater than 0.2^{o}C between two successive readings in the determination of initial temperature.

Method

The test is carried out in an AC room. Dissolve the substance being examined in or dilute with a pyrogen free saline solution. Warm the liquids being examined to approximately 38.5^{o}C before injection. The amount of sample to be injected varies according to the preparation being examined and is prescribed in the individual monograph. The volume of injection is not less than 0.5 ml per kg and not more than 1. ml per kg of body weight.

Withhold water during the test. Clinical thermometer is inserted into the rectum of the rabbit for recording the body temperature. Two normal readings of rectal temperature should be taken prior to the test injection at an interval of half an hour and its mean is calculated, which is the initial temperature of the rabbit.

The solution under test is injected slowly through an ear vein in a volume of 0.5-10 ml /kg of body weight. Record the temperature of each rabbit In an interval of 30 minutes for three hours after the injection. The difference between the initial temperature and the maximum temperature recorded for a rabbit is taken to be its response. When this difference is negative, the result is counted as a zero response.

Interpretation of results

- If the sum of the responses of the group of three rabbits does not exceed 1.4°C and if the response of an individual rabbit is less than 0.6°C, the preparation being examined passes the test.
- If the response of any rabbit is 0.6°C or more or if the sum of the responses of three rabbits exceeds 1.4°C, continue the test using five other rabbits. If not more than three of the eight rabbits show individual responses of 0.6°C or more, and if the sum of the responses of the group of eight rabbits does not exceeds 3.7°C, the preparation being examined passes the test.

LAL Test

Limumus: Genera of crab

Amebocyte: Active component is derived from crab blood cell

Lysate: The component is obtained by separating amebocytes from the plasma and then lysing them.

LAL test is in-vitro method used to detect the presence and conc. Of bacterial endotoxins in drugs and biological products.

The lysate is collected by puncturing the hearts of mature crab.

This method is simple, rapid and of greater sensitivity than the rabbit test.

Procedure

- The preparation being examined is added to the lysate (0.1 ml test sample and 0.1 ml LAL reagent) derived from blood cells of horseshoe crab. Incubate for 1 hour at 37^{o}C and mixture is analyzed. The result of the reaction is turbidity, precipitation or gel formation of mixture. This is used for quantitative measure to estimate the endotoxin (pyrogen) content.
- The rate of reaction depends on conc. Of endotoxins, pH, temp. and presence of clotting enzyme and proteins in lysate

ADVANTAGES OF LAL TEST

- Less variable
- In vitro test
- Easier to perform
- More sensitive
- Less Expensive
- Less Time consuming
- Can give Quantitative result

Clarity test

Particulate matter is defined as unwanted mobile insoluble matter other than gas bubbles present in the given product. The presence of foreign matter in parenteral preparations is very dangerous especially when its particle size is larger than the size of RBC. It can block the blood vessel.

Permitted limits of particulate matter as per IP

Particle size (um) (equal to or larger than)	Maximum number of particles per ml
10	50
25	5
50	Nil

Methods

- **Visual method:** Against black and white board
- **Coulter counter method:** Increase in resistance is observed between two electrodes as the particle approaches and passes through the orifice.
- **Filtration method:** Filter and analyze the particles.
- **Light blockage method:** Blocks the path of light.

Methods for identification of particles:

Microscopy, X-ray powder diffraction, mass microscopy, polarised light microscopy, SEM

Leakage test

- It is desirable that all the parenteral preparation which are filled in ampoules must be hermetically sealed.
- The ampoules are immersed in 1% methylene blue solution in a vaccum chamber under negative pressure. When the vaccum is released the coloured solution will enter those ampoules having defective sealing. The presence of dye in the ampoule confirms the leakage and hence rejected.

IV Admixtures

- IV **admixture** as "the preparation of pharmaceutical product which requires the measured addition of a medication to a 50 mL or greater bag or bottle of **IV** fluid."
- One or more sterile products are mixed with an iv fluid for administration, the mixture is called **Intravenous Admixture.** It is done in hospitals where drug is added to the bottles of large volume transfusion fluids. Care should be taken to observe microbial contamination, incompatibility, physical or chemical changes. Necessary knowledge is required.
- The characteristics of sterile products like sterility, freedom from particulate matter, pyrogens are necessary to maintain. Aseptic handling is required.

- If the additive injection contains a photosensitive drug, adequate protective measures, eg. Wrapping the container with light resistant paper aluminium foil is necessary.
- If the drug is not stable in aqueous medium needs to be reconstituted before use. Handling of antineoplastic drugs adequate awareness regarding hazards and necessary preventive measures to be taken.
- Process of mixing an additive with an IV fluid varies from excipient to excipient.
- Parenteral Incompatibilities: During admixture mixing of additives may change the characteristics of drug and lead to incompatibilities such as physical such as change in colour, odour, evolution of gas, chemical such as degradation of drug or therapeutic nature. Most of the incompatibilities are due to change in acid-base envirnment, change in pH. Parenteral incompatibilities can be neither predicted but can be minimized.

Total Parenteral Nutrition

Total Parenteral Nutrition became widely accepted after 1967. The 1970s saw wide use of TPN as the predominant route of nutrition. This concept of partial Parenteral Nutrition (PN) would include nearly 90% of the surgical inpatients and 100% of the patients being anaesthetised, as they would be receiving intravenous fluids.

Parenteral nutrition means feeding someone via their blood stream ‘intravenously’, TPN means feeding a patient solely via the intravenous route.

INDICATIONS

- When patient gastrointestinal tract is paralysed and nonfunctional, as in the case of small bowel obstruction
- When >7 days of nothing-by-mouth (NPO) status is anticipated, as in the case of inflammatory bowel disease, critically ill patients and so on
- When the baby's gut is too immature or has congenital malformations
- When the patient is suffering from chronic diarrhoea and vomiting or is extremely undernourished and needs to have surgery, chemotherapy and so on
- When patients in the early postoperative period

ENERGY REQUIREMENTS AND RECOMMENDATIONS

The caloric requirements should be individualised with respect to the degree of stress, organ failure and percentage of ideal body weight. The calories should be provided in the form of carbohydrates, proteins and fats, in the right mixture.

A reasonable and well-accepted recommendation is to initiate it with 25 cal/Kg/day and 1.25 – 2 g protein/Kg/day.

This should be augmented according to the stress levels of the patients.

FLUID REQUIREMENT

Fluid management in PN depends on the hydration status of the patient and the clinical conditions, such as, renal failure, congestive heart failure and so on.

PROTEIN REQUIREMENTS

The provision of adequate protein as an energy source is necessary for the proper utilisation of amino acids. Healthy adults require 0.8 – 1.0 gm of protein per kilogram per day. The amino acid profile is based on the World Health Organisation (WHO) recommendations for adequate essential amino acid proportions.

Critically ill patients, without any hepatic or renal dysfunction, would need about 1.5 gm of protein per kg per day, while patients with chronic renal failure should be given 0.6 – 0.8 gm/kg/day and patients with acute hepatic encephalopathy should have a temporary restriction of protein to 0.8 gm/kg/day. Patients on haemodialysis or peritoneal dialysis would require 1.2 – 1.3 gm/kg/day. Patients who receive renal replacement therapy have daily protein requirements of up to 2.5 gm/ kg/day in order to meet the nitrogen balance and protein losses during filtration.

CARBOHYDRATE REQUIREMENTS

The maximum glucose utilisation rate in critical illness is 5 – 7 mg/kg/min, and providing carbohydrates in excess can lead to hyperglycemia.

Dextrose monohydrate, in concentrations from 2.5 to 70%, is the most common form in which carbohydrate is administered parenterally.

Fructose, sorbitol, xylitol and glycerol as carbohydrate sources for parenteral nutrition have been and are being studied, but none of them have been seen to have any decisive advantage over dextrose and do not have the US Food and Drug Administration (USFDA) approval for use.

FAT REQUIREMENTS

Lipids in parenteral nutrition are used to provide calories and prevent essential fatty acid deficiency (EFAD), which may develop within three weeks of fat free parenteral nutrition. Soybean / safflower oil, egg yolk phospholipids in 10, 20 and 30% concentrations are the common sources for lipids in TPN.

MICRONUTRIENT REQUIREMENTS

Electrolytes, trace elements and vitamins come under micronutrients. Sodium 100 – 150 mEq, Potassium 50 – 100 mEq, Magnesium 8 – 24 mEq, Calcium 10 – 20 mEq and Phosphorous 15 – 30 mEq are recommended per litre of parenteral infusion solution. A total of less than 40 mEq is recommended for calcium and phosphorous to prevent precipitation.

Copper, zinc, selenium and chromium are the common trace elements that are supplemented in PN.

Molybdenum supplementation is required in neonates / infants on prolonged PN.

INITIATION, MAINTENANCE AND MONITORING OF PARENTERAL NUTRITION

The timing of TPN is a question, it would be prudent to start it as soon as one appreciates that the patient is in requirement of TPN, that is, nutritionally compromised. Strict aseptic precautions should be followed during introduction of the central line; the external dressing should be changed every 48 hours using sterile precautions. The external tubing should be changed every 24 hours starting with the first feed of the day. The lumen being used for TPN should be exclusively reserved for it and no drugs / infusions (except insulin infusion) should be allowed in that lumen.

- Blood sugar levels must be monitored hourly till they are stable, and later six hourly.
- Blood lipid levels may be monitored twice weekly.
- Liver function tests must be monitored weekly.
- Patients on long-term TPN need monthly monitoring of vitamin, mineral and trace element status.

Peritoneal Dialysis Fluid

For patients with end-stage kidney disease, peritoneal dialysis (PD) is the most cost-effective and easiest way to replace kidney function. Peritoneal dialysis fluids contain electrolytes which help to maintain blood composition, an osmotic agent and a pH buffer. Peritoneal dialysis fluid is injected via a permanent catheter into the peritoneal cavity. The peritoneal membrane acts as a dialysis membrane, allowing the removal of waste products from the body into the peritoneal cavity

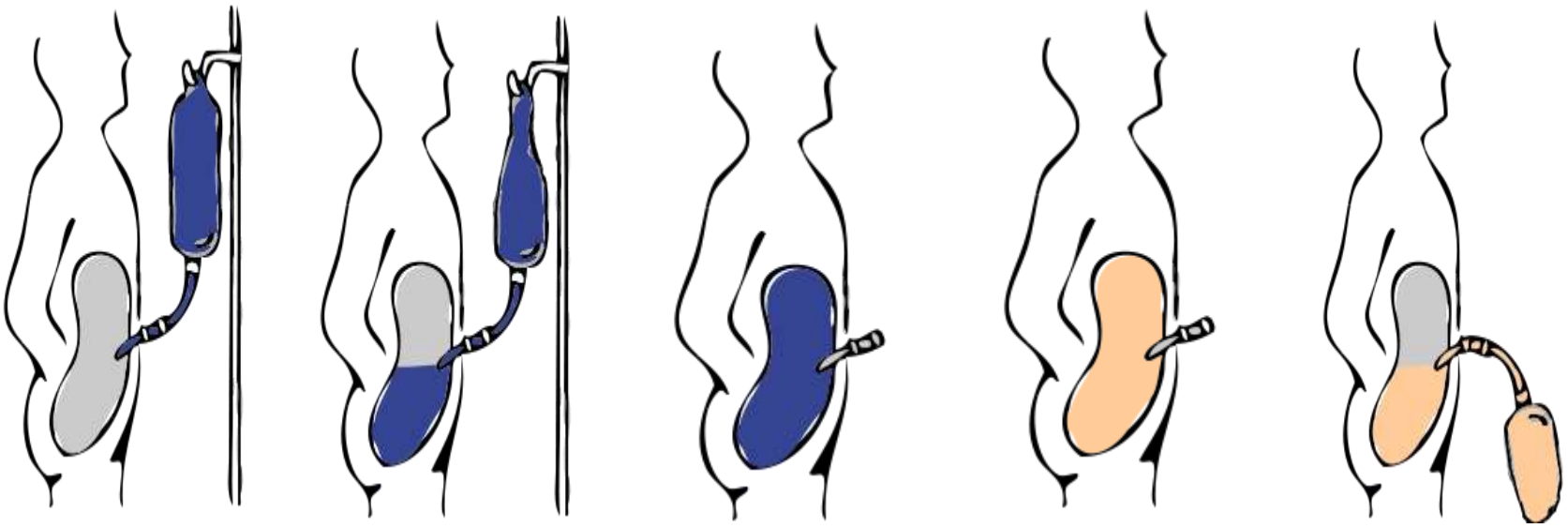
Composition of dialysate or the dialysis 'bath' is: sodium chloride, sodium bicarbonate or sodium acetate, calcium chloride, potassium chloride, and magnesium chloride. This is the general composition of dialysate, but other compounds such as glucose may also be included.

Peritoneal dialysis (**PD**) is a type of dialysis which uses the peritoneum (abdomen) as a membrane through which fluid and dissolved substances are exchanged with the blood. It is used to remove excess fluid, correct electrolyte problems and remove toxins in those with kidney failure. Peritoneal dialysis has better outcomes than hemodialysis during the first couple of years. Other benefits include greater flexibility and better tolerability in those with significant heart disease.

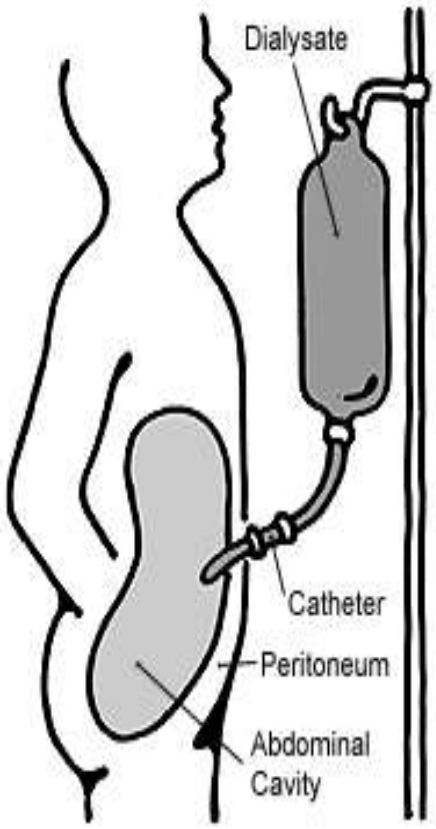
Complications may include infections within the abdomen, hernias, high blood sugar, bleeding in the abdomen, and blockage of the catheter. **PD** is not possible in those with significant prior abdominal surgery or inflammatory bowel disease. It requires some degree of technical skill to be done properly.

In peritoneal dialysis, a specific solution (dialysate) is introduced through a permanent tube/catheter in the lower abdomen and then removed. This may either occur at regular intervals throughout the day, known as continuous ambulatory dialysis or at night with the assistance of a machine, known as automated peritoneal dialysis. The solution is typically made of sodium chloride, hydrogen carbonate and an osmotic agent such as glucose.

Dialysis process



Hookup Infusion Diffusion (fresh) Diffusion (waste) Drainage


Dialysate
Catheter
Peritoneum
Abdominal
Cavity

Formulation of Large Volume Parenterals

LVP formulations have been developed to:

1. Supply water, electrolytes, simple carbohydrates needed by the body.
2. Act as a vehicle for infusion of drugs.
3. Supply nutritional requirements when they cannot be taken orally.
4. Provide solutions to correct acid-base balance in the body.
5. Act as plasma expanders.
6. Promote diuresis when the body is retaining fluids.
7. Act as a dialyzing agent in patients with impaired kidney function.

Formulation Aspects of LVPs

1. **Vehicle:** WFI used to dissolve the drugs
2. **Added substances:** Chelating agents, Buffering agents, Bacteriostatic agents, anti-oxidants are rarely used.
3. **Other ingredients:** Carbohydrates (Fructose, Dextrose), Disaccharides (Sucrose/Maltose), Polysaccharides are used but less common. Oils like soyabean, coconut, palm oil may also be used.
4. **Polyols:** Mannitol, Sorbitol, Glycerol in irrigation solution and also to adjust tonicity in lipid emulsions.
5. **Inorganic salts of Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-** are added to provide necessary electrolytes, adjust tonicity or as alkalizing agent.
6. **Acids and Bases:** HCl, acetic acid, NaOH to adjust pH, as stabilizers.

Formulation Considerations

1. **Physiological Parameters:**

- Osmotic Pressure
- Isotonicity

2. **Physicochemical Parameters:**

- Solubility
- pH
- Vehicles

3. **Physical Parameters:**

- Colour, Odour
- Protection from light

4. **Packaging Parameters:**

ANY

QUESTIONS ?

THANK YOU