MODULE 4: Parentrals
Lecture 1

DISCLAIMER

All the content material provided here is only for teaching purpose

STERILE PRODUCTS

INTRODUCTION TO PARENTERAL DOSAGE FORMS

MODULE 4-L1

PARENTERAL PRODUCTS-DEFINITION

- Parenteral preparations are sterile, pyrogen-free liquids (solutions, emulsions, or suspensions) or solid dosage forms packaged in either single-dose or multidose containers.
- These preparations are administered through the skin or mucus membranes into internal body compartments.
- These includes any method of administration that does not involve passage through the digestive tract.

PARENTERAL PRODUCTS: RATIONAL & ADVANTAGES

- Drug is not absorbed orally.
- Drug is unstable in GIT.
- Drugs undergoing extensive first pass metabolism.
- Patients need rapid drug action in emergency situations.
- Patient is uncooperative/unconscious(accident, surgery etc.).
- Complete drug bioavailability is possible.
- Prolonged drug action is possible.
- Parenteral therapy provides the means of correcting serious disturbances of fluid and electronic balances.
- When food cannot be taken by mouth, total nutritional requirement can be supplied by the parenteral route.
- Patient compliance problems are largely avoided.

Parenteral Products: Disadvantages

- Most inconvenient route of administration /pain upon injection.
- Generally need medical help for administration (like physician or nurse usually in hospital or clinic)
- If administered by patients themselves, need good training.
- It requires strict adherence to aseptic procedures.
- It requires more time than those administered by other routes
- Chances of improper dosing are more.
- Chances of adverse effects are more.
- Danger of blood clot formation is there.
- Drug can not be recovered in adverse conditions.
- The manufacturing and packaging requirements of parenteral dosage forms are more expensive than other dosage forms.

Parenteral Products: Routes of Administration

Intravenous (IV)	**Vein**
Intramuscular (IM)	**Muscle**
Subcutaneous (SC)	**Under the skin**
Intradermal (ID)	**Into the skin**
Intraarticular	Joints
Intrasynovial	Joint-fluid area
Intraosseous	Bones
Intracerebral	Brain
Intraspinal	Spinal column
Intrathecal	Spinal fluid
Intra-arterial	Arteries
Intracardiac	Heart
Endotracheal	Down the trachea
Sublingual	below tounge

PARENTERAL PRODUCTS: ROUTES OF ADMINISTRATION

INTRAVENOUS ROUTE (IV)

- IV drugs are administered directly into the systemic circulation either by direct **injection** (upto 40 ml) or **infusion** (large volume parenteral: upto 1000ml, 2-3ml/min).
- Devices and site of administration must be sterile.
- Vehicle: aqueous solution, mix with blood, should not precipitate. Fat emulsion for TPN with controlled globule size.
- ***No suspension***
- IV is routine route of administration in hospital.
- IV route gives 100 % bioavailability.
- Drug is instantaneously distributed to its sites of action.
- IV route can be used to deliver or withdraw blood.

Parenteral Products: Routes of Administration

Intravenous Route (IV)

- IV administration is frequently complex and confusing.
- It may require dose calculations, dilutions, knowledge of administration rates and compatibilities with other IV solutions.
- IV medicines requires the use of an aseptic technique.
- Is the drug suitable for preparation at ward level or should it be prepared in pharmacy?
- Does it require supporting equipment for example, programmable infusion devices
- Does the drug cause any local reaction when given?
- Is any monitoring required during or after administration?
- Is there any danger of thrombus & embolus formation?
- Is the drug free from particulate matters (no suspensions).?

Parenteral products: routes of administration
Intramuscular route (IM)

- ***Administration***: deep skeletal muscle far from nerves & blood vessels.
- ***Site of injection*** may vary with multiple injections
- Note: during administration plunger of the syringe withdrawn back to assure absence of blood.
- 0.5 - 5 ml syringe \ 20-25 gauge \ 5/8-3" length needle.
- ***Volume***: maximum 5ml in gluteus region and 2ml in deltoid.
- ***Vehicle***: aqueous, oleaginous or suspension – influence duration of action.
- Note : suspensions can be administered.
- Less rapid than IV but has longer duration of action

Parenteral Products: Routes of Administration

Intramuscular Route (IM)

- Intramuscular injections are given at 90 degree to the skin, penetrate deep, aspirate to check whether you have puncture an artery, vein or nerve, if blood comes, withdraw the needle, change position.
- Less rapid than IV but has longer duration of action.
- In general the injection of drugs into the muscle or the adipose tissue beneath the skin allows a deposit or ‘depot’ of drug to become established that will be released gradually into the systemic circulation over a period of time.
- By altering the formulation of the drug, the period over which it is released can be influenced. For example, the formulation of antipsychotic agents such as flupentixol in oil allows them to be administered once a month or every three months.
- ***Danger of IM injections:*** Paralysis, abscess, cysts, embolism, hematoma, scar formation etc.

Parenteral Products: Routes of Administration
Subcutaneous Route (SC)

- Injections in fatty subcutaneous tissues below the skin.
- Small volume injections upto maximum 2 ml
- 1-3 ml syringe \ 25-32 gauge \ 1/2-5/8" length needle
- Site: Abdomen, upper-outer arms, upper-outer thighs, & upper back
- At least 1 inch (2.5 cm) pinched fold of skin and tissue is necessary for administering SC injections.
- Subcutaneous injections, are given by holding the needle at 45 degree angle while piercing the skin, skin is pinched tight.
- Insert needle so that hub of needle shaft touches the skin, aspirate to check the location of needle. If blood is aspirated, withdraw the needle and try at other site, if not gently push the medication into subcutaneous tissue, withdraw needle and gently massage the area to help in absorption

Table 1 Parenteral Routes of Drug Administration

Routes	Usual volume (mL)	Needle commonly used	Formulation constraints	Types of medication administered
Primary parental routes				
Small-volume parenterals				
Subcutaneous	0.5–2	5/8 in., 23 gauge	Need to be isotonic	Insulin, vaccines
Intramuscular	0.5–2	1 1/2 in., 22 gauge	Can be solutions, emulsions, oils, or suspensions, isotonic preferably	Nearly all drug classes
Intravenous	1–1000	Veinpuncture 1 1/2 in., 20–22 gauge	Solutions, emulsions, and liposomes	Nearly all drug classes
Large-volume parenterals	101 and larger (infusion unit)	Venoclysis 1 1/2 in., 18–19 gauge	Solutions and some emulsions	Nearly all drug classes (see precautionary notes in text)
Other parenteral routes				
Intra-arterial: directly into an artery (immediate action sought in peripheral area)	2–20	20–22 gauge	Solutions and some emulsions	Radiopaque media, antineoplastics, antibiotics
Intrathecal (intraspinal; into spinal canal)	1–4	24–28 gauge	Must be isotonic	Local anesthetics, analgesic neurolytic agents
Intraepidural (into epidural space near spinal column)	6–30	5 in., 16–18 gauge	Must be isotonic	Local anesthetics, narcotics α_2-agonists, steroids
Intracisternal: directly into caudal region of the brain between the cerebellum and the medula oblongata			Must be isotonic	
Intra-articular: directly into a joint, usually for a local effect there, as for steroid anti-inflammatory action in arthritis	2–20	1.5–2 in., 18–22 gauge	Must be isotonic	Morphine, local anesthetics steroids, NSAIDs, antibiotics
Intracardial: directly into the heart when life is threatened (epinephrine stimulation in severe heart attack)	0.2–1	5 in., 22 gauge		Cardiotonic drugs, calcium
Intrapleural: directly into the pleural cavity or a lung (also used for fluid withdrawal)	2–30	2–5 in., 16–22 gauge		Local anesthetics, narcotics, chemotherapeutic agents
Diagnostic testing				
Intradermal	0.05	1/2–5/8 in., 25–26 gauge	Should be isotonic	Diagnostic agents

Factors affecting parenteral formulations

- Physicochemical properties of the drug.
  - **Unstable in moisture**
    - Dry
    - Suspension
    - Replace water by other solvent
  - Insoluble in water
    - Non-aqueous solvent
    - Derivative (salt)
- Route of drug administration
  - IV Aqueous
  - Others may not aqueous
- Desired onset of drug action
  - Physical state of the drug (suspension)
  - Vehicle (aqueous or not)
- Duration Oleogenous > suspension > aqueous

CONSIDERATIONS IN PARENTERAL PREPARATION

- Solvents & vehicles must meet special purity & other standard to assure safety.
- Added substances (buffer, stabilizers preservatives) should be approved for parenteral products.
- Prepared in controlled areas under strict sanitation standards & personnel specially trained, clothed to maintain sanitation.
- Packing hermetically sealed container of specific & high purity.
- Volume slightly excess of the labelled size to help administration.
- Volume is limited depending on route and type (single or multiple).
- Dry parenteral should reconstitute fast with ease (Lyophilized).
- The finished product must meet sterility standard.
- Must be pyrogen free.

- No particulate mater

CONSIDERATIONS IN PARENTERAL PREPARATION: VEHICLES

- Solvents & vehicles must meet special purity & other standard to assure sterility, stability and safety.
- **Vehicle used should be:**
  - ✓ **pharmacologically inert,**
  - ✓ **non toxic and compatible with blood,**
  - ✓ **maintain solubility of the, drug,**
  - ✓ **be physically and chemically stable**
  - ✓ **does not affect the pH.**
  - ✓ **Must be pyrogen free.**
  - ✓ **No particulate mater.**
  - ✓ **The finished product must meet sterility standard.**
  - ✓ ***Water is the ideal vehicle for most injections since aqueous preparations are well tolerated by the body.***
  - ✓ ***Easy visual inspection for particulate contamination, chemical precipitation and colour change.***
  - ✓ ***It may accelerate drug hydrolysis resulting in an inert or toxic products..***

Considerations in Parenteral Preparation Solvents / Vehicles for Injection

- Can be Water, Water-miscible co-solvents or Non-aqueous solvents
- Aqueous is preferred
- Non-aqueous may be used due
  - Drug of limited water solubility
  - Drug susceptible to hydrolysis
  - Desired physicochemical factors (extended release)

CONSIDERATIONS IN PARENTERAL PREPARATION
VEHICLES NOT USED IN PARENTERALS

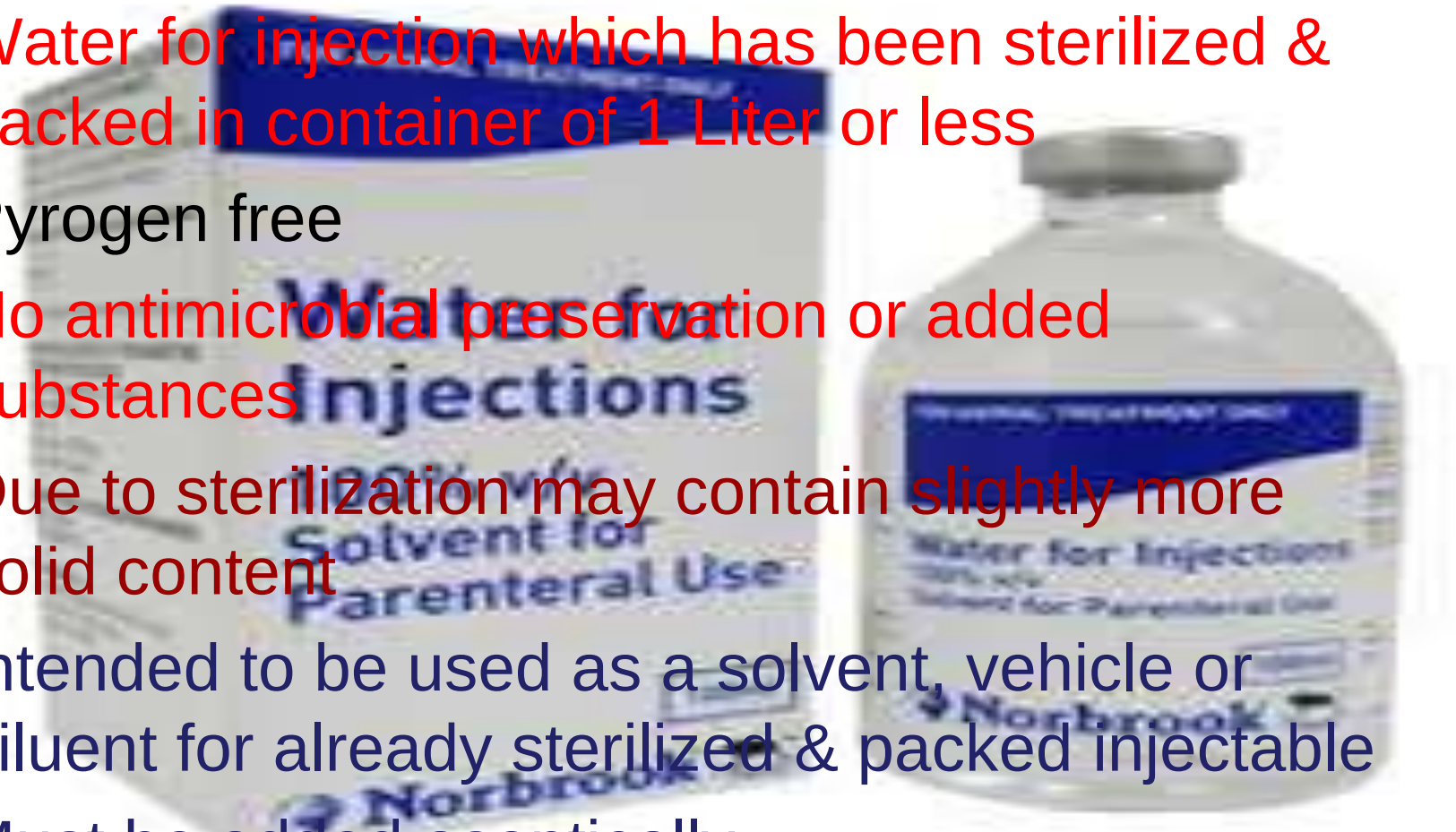
- Natural Water: is not used for drinking or any pharmaceutical formulation. It is highly contaminated.
- Drinking water: may be used in the early stage of chemical synthesis and in the early stages of the cleaning of pharmaceutical manufacturing equipments.
- Purified water: (USP monograph), is used in the preparation of some bulk pharmaceutical chemicals, do not use purified water in preparations intended for parenteral administration.
- Must be protected from microbial proliferation.
- Sterile purified water: Is purified water that is packaged and rendered sterile, contains no antimicrobial agent.
- ***It is not for parenteral administration.***

CONSIDERATIONS IN PARENTERAL PREPARATION SOLVENTS / VEHICLES FOR INJECTION

- **WATER FOR INJECTION, USP**
- Most frequently used for parenteral formulation
  - Purified water underwent distillation or reverse osmosis
  - Clear, colourless, odourless and having a pH of 5 -7.
  - Total dissolved solids not more than 1mg in 100ml
  - No added substances
  - May not sterile
  - Pyrogen free
  - Collected in sterile & pyrogen free container (glass or glass lined)
  - Must store in tight container at suitable temperature
  - Must be used within 24 hour
  - For products to be sterilized after preparation

CONSIDERATIONS IN PARENTERAL PREPARATION
SOLVENTS / VEHICLES FOR INJECTION

- ***STERILE WATER FOR INJECTION***
- Water for injection which has been sterilized & packed in container of 1 Liter or less
- Pyrogen free
- No antimicrobial preservation or added substances
- Due to sterilization may contain slightly more solid content
- Intended to be used as a solvent, vehicle or diluent for already sterilized & packed injectable
- Must be added aseptically.



CONSIDERATIONS IN PARENTERAL PREPARATION SOLVENTS / VEHICLES FOR INJECTIO

- Sterile water for injection with suitable antimicrobial agent(s).
- Filled in vials/syringe in volume not more than 30ml.
- Name & concentration of preservative must be stated.(benzyl alcohol)
- Intended for small volume injectable (multidose vials).
- Not to be used with large volume parenteral (usually with 5ml or less).
- Concern chemical compatibilities

CONSIDERATIONS IN PARENTERAL PREPARATION SOLVENTS / VEHICLES FOR INJECTION

- **Sodium chloride injection, USP**
  - Sterile, isotonic NaCl in water for injection
  - No antimicrobial agent
  - Na^+, Cl^- 154meq of each
  - Used as vehicle in preparing solutions/ suspension for parenteral administration

- **Bacteriostatic sodium chloride injection, USP**
  - Sterile, isotonic NaCl in water for injection
  - Contain one or more antimicrobial agents (specify in label).
  - Volume not more than 30 ml (5ml preferred).
  - Concerns compatibility.
  - “not for use in newborns”

CONSIDERATIONS IN PARENTERAL PREPARATION
SOLVENTS / VEHICLES FOR INJECTION

- **Ringer's injection**
  - Sterile solution of NaCl, KCl, CaCl2 in water for injection
  - Concentration as physiological concentrations
  - Can be used as vehicle or electrolyte replenishes or fluid extender

- **Lactate Ringer's injection, USP**
  - NaCl, KCl, CaCl2 & Na.lactate
  - Intended to be used as fluid & electrolyte replenishes & systematic alkalyzer

Considerations in Parenteral Preparation

Solvents / Vehicles for Injection

Non Aqueous Vehicle

- Suitable vehicle properties
  - No irritation, sensitization, toxicity or pharmacological activity
  - Should not affect the activity of the drug
  - Should have suitable physicochemical properties for intended use (stability, viscosity, fluidity with temperature, boiling point, miscible with body fluid, low vapor pressure).
  - Purity (ease of purification & standardized).
  - Must remain clear at 10^{o}C

Considerations in Parenteral Preparation
Solvents / Vehicles for Injection
Non Aqueous Vehicle

- Intramuscular
- Must be safe in the amount administered
- Do not interfere with therapeutic activity of the drug
- Selection depend on the formulation
  - Fixed vegetable oils
    - Corn oil, cotton seed oil, peanut oil, sesame oil, castor oil, olive oil
    - Should be properly characterized: purity, iodine number, saponification number
  - Glycerin
  - PEG
  - Propylene glycol
  - Alcohol
  - Less common Ethyl oleate, isopropyl myristate, dimethylacetamide

Fixed oils must never be administered by IV route and injected only by IM route to produce sustained release effect.

Considerations in Parenteral Preparation Solute/Drug

- Full information about the physico-chemical characteristics of the active drug can greatly help in developing a stable and safe parenteral dosage form.
- Crystallinity, polymorphism, particle size, solubility, dissolution, microscopic examination, thermal stability etc.
- chemical form of active drug,chemical and/or microbial potency,, partition coefficient, spectra, dissociation constant, pH profile (Profile of pH versus solubility and versus stability help in predicting the chemical and physical stability of the drug in solutions or suspension as a result of pH changes due to storage or admixing the drug with an infusion fluid.
- Exceptional physical & chemical purity
- Free of microbes & pyrogen
- Stable on storage
- Properly packed & stored to prevent contamination
- The use of whole pack during manufacturing.

Considerations in Parenteral Preparation Additives / Excipients

- **They are substances that are incorporated into the parenteral dosage form to maintain stability, ensure sterility, minimize pain & tissue irritation and aid in parenteral administration.**
- **(1) Antimicrobial preservatives**
- **(2) Anti-oxidants**
- **(3) Buffer**
- **(4) Chelating Agents / Sequestering Agents**
- **(5) cryoprotectants & lyoprotectants**
- **(6)Inert Gas**
- **(7) Solubilizing Agents and Surfactants**
- **(8) Tonicity modifiers**
- **(9) Viscosity modifiers**

CONSIDERATIONS IN PARENTERAL PREPARATION ADDITIVES- PRESERVATIVES (ANTIBACTERIAL S & ANTI OXIDANTS)

- Usually added in multiple dose vials to protect the product from contamination due to repeated dose withdrawal.
- Also added to most unit-dose parenterals which are not terminally sterilized.
- Types of preservatives
- Acidic: Phenols and parabens (Butyl-P-hydroxybenzoate, Methyl-P-hydroxybenzoate).
- Neutral: Alcohols eg Benzyl alcohol
- Mercurial: Thimerosal
- Quaternary ammonium compounds: benzalkonium chloride.
- **ANTIOXIDANTS**:
- prevent oxidation of drug during sterilization.
- Mechanism of action
- Preferentially oxidized: Ascorbic acid & Na bisulfite, metabisulfite or sulfite.
- Blocking an oxidation chain reaction: Ascorbic acid, BHT & Tocopherols.
- Complexing agent with catalyst: EDTA
- Synergistic action: acids (citric, phosphoric, tartaric, ascorbic).

Considerations in Parenteral Preparation Additives- Buffers

- Added to maintain pH for Solubility, Stability and Pain reduction

pH	Buffer system	Conc. (%)
3.5 - 5.7	Acetic Acid/Acetate	1 - 2
2.5 - 6.0	Citric Acid/Citrate	1 - 5
6.0 – 8.2	Phosphoric Acid/Phosphate	0.8 - 2
8.2 – 10.2	Glutamic Acid/Glutamate	1 – 2
> 8.0	Carbonic Acid/Carbonate	> 1

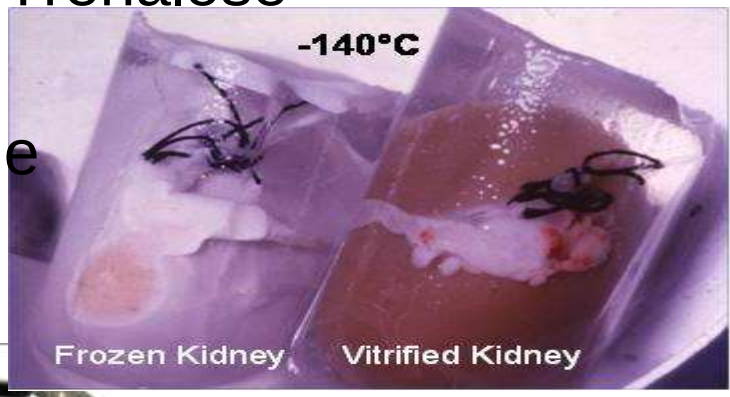
Other systems used in parenterals: Glycine (pH 6.5-7.5), Lactate (pH 3-6), Maleate (pH 2.5-5.0), Tartarate (pH 3-5)

Considerations in Parenteral Preparation Additives- Chelating /Sequestering Agents

- Trace quantities of heavy metal ions often catalyze destructive changes in medicaments.
- For example the breakdown of the sulfur containing ring of benzyl penicillin (copper, lead, mercury and zinc).
- Oxidation of adrenaline (copper, iron and chromium).
- Decomposition of oxytetracyclin (copper).
- Sources of metal contamination are raw material impurities, solvent such as H2O, rubber stopper, container or equipment employed in the manufacturing process.
- The most widely used chelating agents are ethylenediamine tetra acetate (EDTA) derivatives and salts of citric acid and tartaric acids.

CONSIDERATIONS IN PARENTERAL PREPARATION ADDITIVES- CRYOPROTECTANTS & LYOPROTECTANTS

- **CRYOPROTECTANTS :** Stabilize and prevent denaturation of proteins from effect of freezing.
- A hydration shell is maintained around the protein molecules which reduces the denaturing effect of freezing.
- Sugars: Sucrose, Lactose, Glucose, Trehalose
- Polyols: Glycerol, Mannitol, Sorbitol
- Amino Acids: Glycine, Alanine, Lysine
- Polymers: PEG, Dextran, PVP



- **LYOPROTECTANTS**
- Substance which protect drugs espacially proteins from degradation during drying (dehydration).
  - Sugars: Mannitol, Lactose, Maltose, Maltodextrin, Trehalose, Sucrose
  - Amino Acids: Glycin, histadine, arginine.

CONSIDERATIONS IN PARENTERAL PREPARATION ADDITIVES- INERT GAS & SURFACTANTS

- In injections in which oxygen is a serious cause of decomposition, improved stability may be obtained by replacing the air in the final container with an inert gas such as nitrogen or carbon dioxide.
- For best result, the water must be boiled to remove air and purging the container with the used inert gas, prior to filling.
- **SOLUBILIZING AGENTS AND SURFACTANTS:**
- SURFACTANTS are used extensively in parenteral suspension for wetting powders and provide acceptable syringe ability (ex: steroids and fat-soluble vitamins).

REFERENCES

- Indian Pharmacopoeia,2010,Government of India Ministry Of Health and Family Welfare,The Indian Pharmacopoeia Commission,Ghaziabad,Vol-I,p:56-63,36-37,28-33,196-198

- Sandeep Nema, John D. Ludwig (eds.)" Pharmaceutical Dosage Forms: Parenteral Medication", Third Edition, Vol-2,p :122-128, 153-157.

- G.S.Banker & C.T.Rhodes, “Modern Pharmaceutics ", Drugs and Pharm.Sci.Series,Vol.7,Marcel Dekker Inc., p:483-486.

- Lachman.L, Liberman HA, Kaniz JL, The Theory and practice of industrial pharmacy Bombay, Varghese publication House; 1986. P. 673-675.