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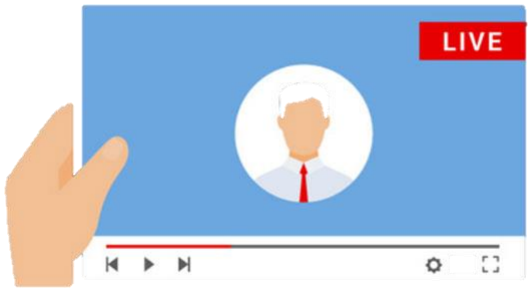

Welcome to "Live online class"

Lecture: Pharmaceutics Parenteral – 2

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Agenda

Today's Topic: **Parenteral**

- Introduction
- Advantages and disadvantages
- Routes of administration
- Excipients
- Containers and Closures
- Manufacturing of parenteral products
- Evaluation of parenteral products
- Ophthalmic products

Solve **6-7 GPAT Questions**

Definition

- Parenteral (Gk, para enteron, beside the intestine) are injected directly into body tissue through the primary protective systems of the human body, the skin, and mucous membranes
- They must be exceptionally pure and free from physical, chemical, and biological contaminants

UNIQUE CHARACTERISTICS OF PARENTERAL DOSAGE FORMS

- All products must be sterile.
- All products must be free from pyrogenic (endotoxin) contamination.
- Injectable solutions must be free from visible particulate matter.
- Products should be isotonic. (IV infusions must be isotonic.)
- All products must be stable, not only chemically and physically like all other dosage forms, but also 'stable' microbiologically
- Products must be compatible

Advantages and disadvantages

Advantages

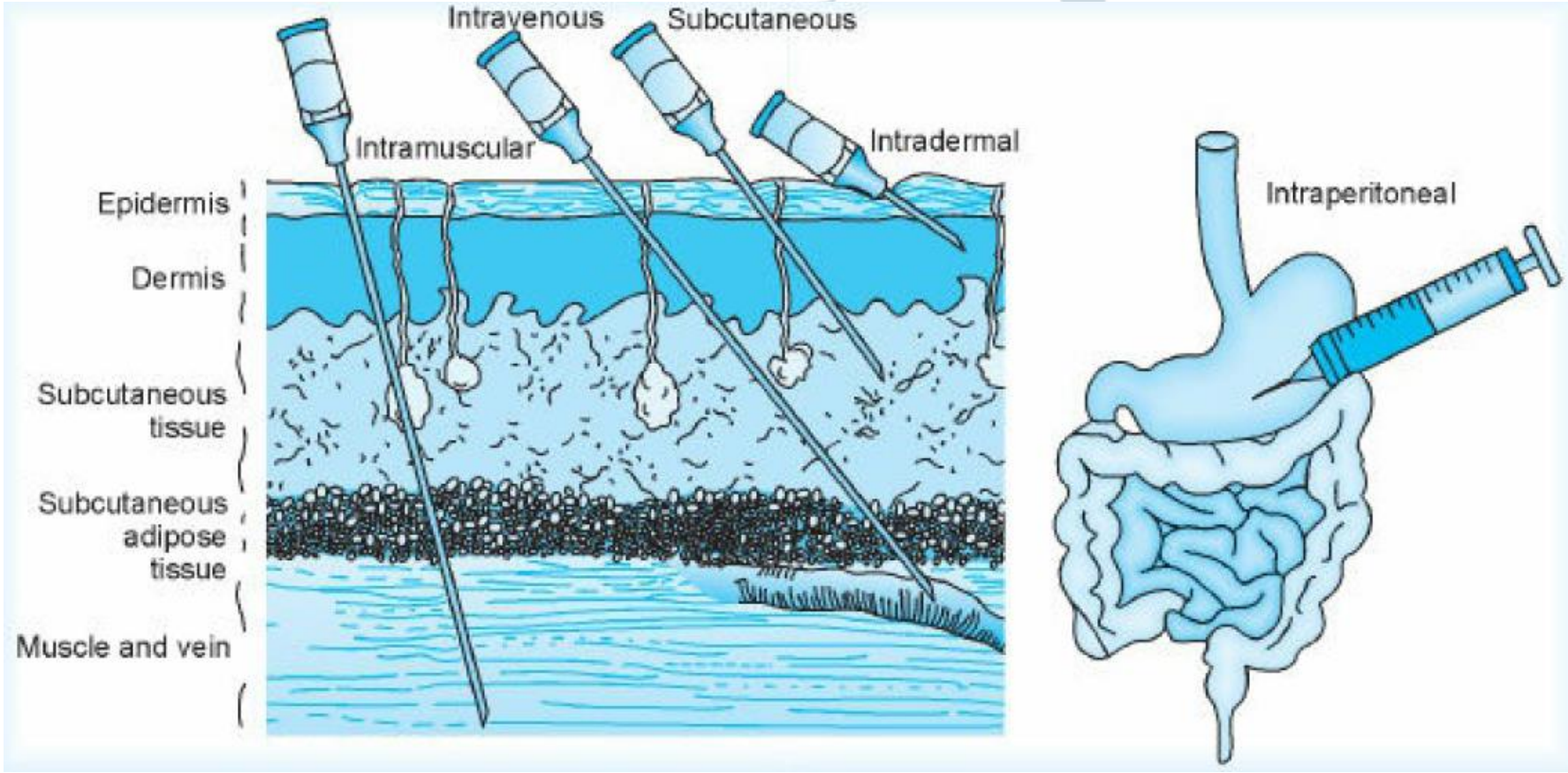
- Useful for drugs that require a rapid onset of action
- Useful for patients who can not take drugs orally
- Suitable for the drugs which are not administered by oral route
- Useful for emergency situations
- Useful for unconscious or vomiting patients
- Duration of action can be prolonged by modifying formulation
- Suitable for the drugs which are inactivated in GIT or CI(GI fluid)

Advantages and disadvantages

Disadvantages

- More expensive and costly to produce
- Once injected can not be controlled(retreat)
- Injections may cause pain at the site of injection
- Potential for tissue damage upon injection
- Require specialized equipment, devices and techniques to prepare and administer drugs
- If given by wrong route, difficult to control adverse effect
- Difficult to save patient if overdose
- Sensitivity or allergic reaction at the site of injection
- Requires strict control of sterility & non pyrogenicity than other formulation

Routes of administration



Routes of administration

Primary parental routes (*Isotonic)	Volume
Subcutaneous *	0.52 - 2
Intramuscular	0.5 – 2 (Gluteal muscle or Deltoid muscle)
Intravenous	100 and large (Medial basilic vein at anterior surface of elbow)
Intra-arterial *(Directly into an artery)*	2 – 20
Intrathecal, Intraspinal *(into the spinal canal)* *	1 – 4
Intra-epidural *(into epidural space near spinal column)* *	6 – 30
Intra-cisternal *(directly into caudal region of the brain between the cerebellum and the medulla oblongata)* *	6 – 30
Intra-articular *(directly into a joint)**	2 -20
Intra-cardial (*directly into the heart)*	0.2 – 1
Intrapleural *(Directly into the pleural cavity or a lung)*	2 – 30
Intradermal *	0.05

Excipients

- Solvents
- Buffers
- Tonicity modifiers
- Antioxidants
- Chelating Agents/ Complexing Agents
- Preservatives
- Cryoprotectants and Lyoprotectants

Solvents

- A solvent is liquid in which other substances are dissolved
- For drug with poor solubility in a desired solvent, a co-solvent may be used. A co-solvent is a solvent used in combination with another miscible solvent to solubilize a drug

  Eg: Polyethylene glycol (PEG), ethanol, propylene glycol, and glycerin
- Use: Oil-based solvents (used only by IM route)

Excipient	Example
Solvent	Sterile water for injection, USP Bacteriostatic water for injection, USP Vegetable oils (Castor oil, Cottonseed oil, Medium chain triglycerides, Sesame oil, Soybean oil, Safflower oil)

Key points for Water for Injections

	Water for Injections	Sterile water for injection	Bacteriostatic water for Injection
Total solid content	10 ppm	40 ppm for vial < 30 ml 30 ppm for vial >30 but <100 ml 20 ppm > 100 ml	40 ppm
pH	4.5- 7	4.5- 7.5 (5.4)	4.5- 7
Property	Pyrogen should not be more than 0.25 endotoxin units	Sterile and pyrogen free	Sterile and pyrogen free
Method of preparation	Distillation or 2 stage Reverse Osmosis	Reverse osmosis, ion exchange, a solid matrix filter containing activated carbon and zeta adsorbent, a final 0.1 micron pore-size sterilizing filter	

Buffers/Tonicity modifiers

Excipients	Example
Buffers (used primarily to stabilize a solution against chemical degradation or, especially for proteins, physical degradation (ie, aggregation and precipitation) that might occur if the pH changes appreciably	Acetic acid/acetate Citric acid/citrate Phosphoric acid/phosphate Histidine

Note: Buffers are not used for LVPs

Tonicity adjusters (to adjust the tonicity of the solution)	Sodium chloride
Important: intradermal and intraspinal injections	Mannitol
Osmolarity of blood: 250-350 mosmol/litre.	Glycerin
Osmolarity of sodium chloride: 300-308 mosmol/litre.	

Antioxidants/Chelating Agents

- Antioxidants work by decreasing the rate of oxidation (retardants) or by prolonging the period before oxidation is initiated (inhibitors)
- Chelating agents are incorporated into solutions to complex trace metals, thereby improving the efficacy of preservatives and antioxidants

Mechanism	Example
Compounds that break the free radical chain reaction	Butylated hydroxyanisole (BHA), Butylated hydroxyl toluene (BHT), Tocopherols (Vit E) (Oil soluble)
Compounds that are preferentially oxidized and react with free radicals, due to their low redox potential	**Ascorbic acid, Sodium ascorbate, Sodium bisulfate, Sodium metabisulfite,** Sodium formaldehyde sulfoxylate, Thiourea
Chelating agent (i.e., chelation of trace metals)	EDTA, Citric acid, Fumaric acid, Tartaric acid

Preservatives

- Preservatives help prevent microbial growth in a solution

Category	Name (%)	Comments
Alcohols	Ethanol Benzyl alcohol	• Contraindicated in pediatric patients less than 2 years • Antimicrobial activity is reduced by nonionic surfactants
Acids	Benzoic acid Sorbic acid	
Esters	Parabens (propylparaben and methylparaben)	• Antimicrobial activity increases as chain length of alkyl moiety increases • Binds to nonionic surface active agents, which can decrease activity • Used with propylene glycol or other antimicrobial agents to enhance efficacy
Quaternary ammonium compounds	Benzalkonium chloride	• Incompatible with anionic compounds and can bind to nonionic surfactants • Used in preparations for external use • Used with 0.1% edetate disodium to enhance antimicrobial activity against pseudomonas

Large-volume, single-dose containers may not contain an added preservative
IV infusions (toxicity due to large quantities); Intraocular injections (toxicity to delicate eye tissues); Intraspinal injections (damage nerve fibres / CNS side effects); Intradermal injections (interfere with diagnostic tests)

Cryoprotectants and Lyoprotectants

Excipients	Example
Cryoprotectants and Lyoprotectants (to protect biopharmaceuticals from adverse effects due to freezing and for drying of the product during freeze dry processing)	Non-reducing sugars (sucrose or trehalose) Amino acids (glycine or lysine) Polymers (liquid polyethylene glycol or dextran) Polyols (Mannitol or sorbitol)

GPAT QUESTION

Preservatives should not be added to _____

A. IV infusions

B. Intraocular injections

C. Intraspinal injections

D. All of above

GPAT QUESTION

Which of the following excipient is used to adjust tonicity of formulations?

A. Citrate

B. Phosphate

C. Histidine

D. Mannitol

Containers and Closures: Types of packaging

PLASTIC CONTAINERS

- Most widely used: **Polypropylene and polyethylene**
- Except Low density polyethylene & Polystyrene, all plastics are autoclavable
- Polyamides and Polystyrene have high reactivity due to sorption as they have high permeability for water vapors.
- **Flexible polyvinyl chloride → Use in intravenous solutions**
- **Polyethylene containers → Use in ophthalmic solutions**

Test procedure for evaluating toxicity of plastic materials* implanting small pieces of plastic material to intramuscularly in rabbits**

Containers and Closures: Types of packaging

GLASS CONTAINERS

- Glass is supercooled liquid of viscosity greater than 10^{13} poise
- It is composed of SiO_2 (65-75 %), Tetrahedron modified physicochemically by oxides of Na^{+}, K^{+}, Ca^{+2}, Mg^{+2}, Al^{+3}, and B^{+3}
- It is relatively brittle and has very high melting point (1700 C)
- Leaching and flake formation (alkaline solution) enhanced during autoclaving

Ultraviolet rays are completely filtered by using amber color bottles which mainly contains iron oxide

Containers and Closures: Types of packaging

USP Glass Type	Description	Type of test	Test limits – Size (mL)	Test - mL of 0.02 N H_2SO_4	General use
I	Highly resistant borosilicate glass	Powdered Glass	All	1.0	Buffered & unbuffered aqueous solutions
II	Treated soda lime glass	Water Attack test	100 or less over 100	0.7 or 0.2	Buffered aq. Solutions (pH < 7), Dry powders, oleaginous solutions
III	Soda lime glass	Powdered Glass	All	8.5	Dry powders, oleaginous solutions
NP	General purpose soda lime glass	Powdered Glass	All	15.0	Not for parenteral. For tablets, oral liquids & external liquids

Containers and Closures: Types of packaging

Rubber

- Usually used as closures, sufficiently elastic to allow the puncture to reseal when the needle is withdrawn and protect the contents from airborne contamination for multidose (bromobutyl, chlorobutyl, butyl)

Types of rubber	Made up of
Natural	Polyisoprene latex of tree Hevea brasiliensis
Grey butyl (widely used)	Polyisobutylene (synthetic)
Nitrile rubber (Hycar)	Butadiene acrylonitrile
Chloroprene	Neoprene (synthetic)
Silicone rubber	Polymethylsiloxane

If there is a formation of rubber particles with insertion of needle → causing contamination of the product. This is called coring

GPAT QUESTION

Which of the following parenteral container material shows the highest Gas permeation?

A. Polypropylene

B. Polystyrene

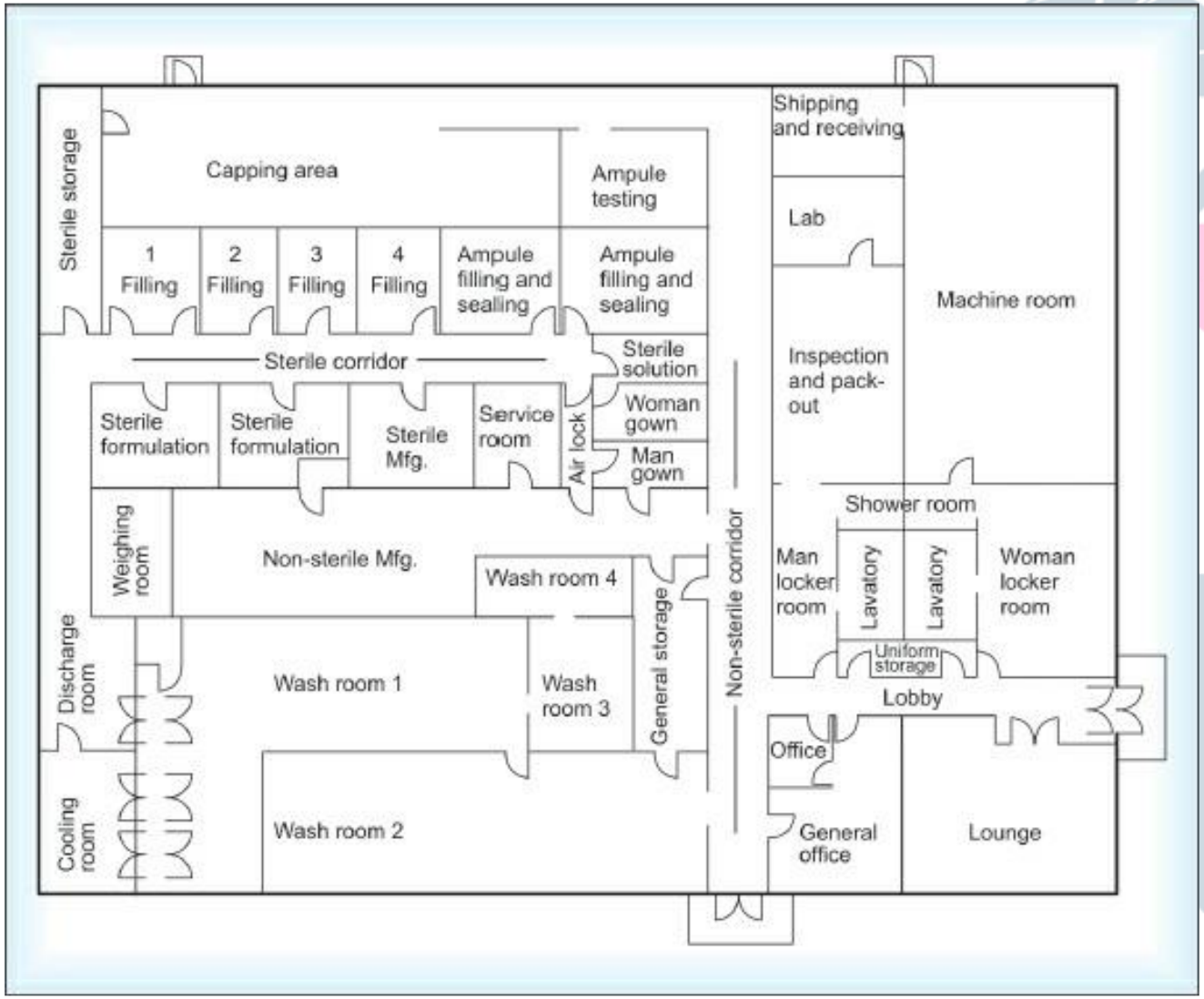
C. Polyisoprene

D. Neoprene

Types of parenteral based upon volume

Name	Type
Small Volume Parenteral (SUV)	Volume < 100 ml or equal to 100 ml
Large Volume Parenteral (LUV)	Volume > 100 ml
Single Dose container	Size is limited to 1000 ml
Multiple dose Container	Size is limited to 30 ml

Key points: Manufacturing Environment



Key points: Manufacturing Environment

Differential pressures

- Positive pressure differential of 10-15 Pascals should be maintained between adjacent rooms of different classification
- Most critical area should have the highest pressure

Air Changes/Airflow patterns

- Air flow over critical areas should be unidirectional (laminar flow) at a velocity sufficient to sweep particles away from filling/closing area

Airflow velocity

- Laminar airflow workstation air speed of approx 0.45m/s ± 20% at working position

Total required area is not less than 60 m² excluding packaging

Manufacturing Environment

WHO GMP	US 209E	US Customary	ISO
Grade A	M 3.5	Class 100	ISO 5
Grade B	M 3.5	Class 100	ISO 5
Grade C	M 5.5	Class 10 000	ISO 7
Grade D	M 6.5	Class 100 000	ISO 8

Grade	At rest		In operation	
	maximum permitted number of particles/m3			
	0.5 - 5.0 µm	> 5 µm	0.5 - 5.0 µm	> 5 µ
A	3 500	0	3 500	0
B	3 500	0	350 000	2 000
C	350 000	2 000	3 500 000	20 000
D	3 500 000	20 000	not defined	not defined

"At rest" - production equipment installed and operating

"In operation" - Installed equipment functioning in defined operating mode and specified number of personnel present

HEPA (HIGH EFFICIENCY PARTICULATE AIR) FILTERS

Parameters	Conditions
Efficiency	99.97%
Particle size	0.3 µm
Efficiency testing	DOP (Dioctyl phthalate) test
Conc. of DOP	66.6 ppm
Alternative to DOP	Liquid paraffin
Reagent used to check efficiency	Hydrocarbon vapours
Flow rate	20 ± 5 ft/min

ULPA (Ultra efficiency particulate air filters)
Efficiency: 99.997%

VEPA (Very efficiency particulate air filters)
Efficiency: 99.999%

Evaluation of parenteral products

Leaker test (Packaging integrity test)

Clarity test (Particulate matter test)

Pyrogen test *(in-vitro and in-vivo)*

Sterility test

Evaluation of parenteral products

Leaker test (Packaging integrity test)

- Applicable to only Ampoules (Not for vials and bottles)
- 1% Methylene Blue dye and vacuum used
- Defective Ampoules becomes blue colored

Evaluation of parenteral products

Clarity test (Particulate matter test)

- Instrument : **Light scattering (Nephelometry) Light absorption, Electrical resistance (Coulter counter)**

1. Solutions for parenteral infusion or solutions for injection supplied in containers with a **nominal content of more than 100 mL**.

   The preparation complies with the test if the average number of particles present in the units tested does not exceed ***25 per mL equal to or greater than 10 µm*** *and does not exceed* ***3 per mL equal to or greater than 25 µm***.

Evaluation of parenteral products

Clarity test (Particulate matter test)

2. Solutions for parenteral infusion or solutions for injection supplied in containers with a nominal content of **less than 100 ml**.

The preparation complies with the test if the average number of particles present in the units tested does not exceed ***6000 per container equal to or greater than 10 µm*** *and does not exceed* ***600 per container equal to or greater than 25 µm***

Evaluation of parenteral products

Pyrogen test *(Pyro means 'pyrexia', Gen means 'producing')*

- **In Vitro pyrogen test:** *Bacterial endotoxin test/Limulus Amoebocyte Lysate (LAL) test*
  - The test principle is based on the clotting of lysate of amebocyte (an enzyme obtained from the horse shoe crab) in the presence of pyrogens
  - Amebocyte + Pyrogen ~ Opaque gel
  - The reaction accomplishes within 15-60 minutes, depending on concentration of pyrogens after mixing. The concentrated pyrogens make the gel more turbid and thick
  - It only detects Gram-negative bacteria

Advantages:

- Does not require animal; economical; consume less time; and more accurate

Evaluation of parenteral products

- **In Vivo pyrogen test:** Fever response in Rabbits – if pyrogens are present body temperature rises (Start with 3 rabbits; if fail take more 5 rabbits)

	IP	BP	USP
Animal	Healthy, adult rabbits of either sex	Healthy, adult rabbits of either sex	Healthy, mature rabbits of either sex
Body wt.	Not less than 1.5 kg	Not less than 1.5 kg	Not less than 2 kg
Condition before test	±2 C	Within 3 C	NMT ±3 C
Condition for test	Do not use animals for pyrogen tests more frequently than once every 48 hours	Not used (a) during the preceding 3 days or (b) during the preceding 3 weeks unless the material being examined passed the test	Do not use animals for pyrogen tests more frequently than once every 48 hours
Fail test	0.6°C or more	mean rise exceed 1.2 °C	0.6°C or more

Evaluation of parenteral products

Depyrogenation:

- Depyrogenation is the removal of pyrogen
- Inactivation - Application of very high dry heat (250 °C) for not less than 30 minutes is the desired method for rendering material pyrogen free.

Evaluation of parenteral products

Sterility test

- Method – Membrane filtration or Direct inoculation
- Medium used –
    1. Nutrient broth for Aerobic
    2. Fluid thioglycolate for Aerobic and Anaerobic
    3. Soyabean casein digest for Fungi Aerobic
- Incubation–for 2 weeks at 30 to 35°C (For FTM) and 20 to 25°C (For SCD)

Evaluation of parenteral products

Selection of sample size in sterility testing

Preparation type	No. of items in batch	Minimum no. of items to be used
Injectable	NMT 100 container MT 100 but NMT 500 containers MT 500 containers	10% or 4 containers whichever is greater 10 containers 2% or 20 which ever is less
Ophthalmic	NMT 200 containers MT 200	5% or 2 containers whichever is greater 10 containers
Surgical Devices	NMT 100 packages MT 100 but NMT 500 MT 500	10% or 4 whichever is greater 10 packages 2% 0r 20 packages whichever is less
Bulk solids	LT 4 containers MT 4 containers but NMT 50 MT 50 containers	Each container 20% 0r 4 containers whichever is greater 2% 0r 10 containers whichever is greater

GPAT QUESTION

LAL is an in vitro test and it is used in parental products to detect _____

A. Antigen

B. Pyrogen

C. Antimicrobials

D. All

Definition

- **Ophthalmic products** are the preparations designed for application to the eye either for the treatment of disease, for relief of symptom, for diagnostic purpose or as adjuncts to surgical procedures
- This dosage form is primarily used to treat local conditions of the eye such as infections, allergies, inflammation, glaucoma, and dryness, with the benefit of having limited risk of systemic side effects

- **Otic delivery** is concerned with the local administration to the ear. Similar to the eye, the ear is a delicate and anatomically/physiologically protected organ that requires special formulation approaches to achieve therapeutic delivery

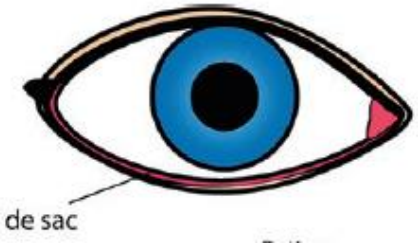
Types

Opthalamic preparations may be categorized into a number of groups

- **Liquid preparations** for application to the surface of eye e.g. eye drop and eye lotions
- **Semi-solid dosage** form e.g. ointments, creams and gels
- **Parenteral products** for subconjunctival or intraocular injection
- Liquid products for irrigation of eye during surgical procedures
- Solid dosage form intended to be placed in contact with surface of eye to produce modified release

Drop size and dosage

- The mean volume of tears in human eye under normal condition is about **7 microlitres**
- Maximum volume that can be held in cut-de-sac without spoilage is about **30 microliters**
- The volume administered by normal dropper as drop is **50 microlitre**



Excipients

Excipients: Viscosity Increasing agents

- An increase in viscosity increase residence time of drug in eye hence its bioavailability
- Commonly used viscosity increasing agents include:

Methyl Cellulose derivatives, Polyvinyl alcohol, Povidone, Dextran, Macrogol.

- Must commercial products have viscosity adjusted in range of **15-25 centipoise**

Excipients: pH and Buffering capacity

- Human tear normally have a **pH of about 7.2** with good buffering capacity and despite the sensitivity of cornea, unbuffered solution with **pH ranges 3.5 and 10.5** can usually be tolerated with little discomfort
- Eye drop should be formulated at physiological pH but in practice drug solubility and stability consideration often necessitate deviation from this ideal
- Eye drop formulated at particular pH require the addition of buffering agent to minimize pH charge during storage
- ***Buffering agents commonly used are borate, phosphate and citrate buffers***

Excipients: Tonicity

- To minimize irritation of eye, ophthalmic solution should locally be isotonic with lachrymal secretion
- To achieve this eye drops should theoretically have tonicity equivalent to **0.9% solution of sodium chloride (eye can tolerate tonicity between 0.7 – 1.5% of sodium chloride)**
- Commonly used tonicity adjuster are: **Sodium chloride, potassium chloride, glucose, glycerol**

Excipients: Wetting and spreading agents

- Some suspension formulations require the inclusion of surface active additives to facilitate the dispersion of the finely divided powdered drug
- Non-ionic surfactants are less toxic to eye than anionic and cationic compounds
- The agents most commonly used surfactant is **polysorbate 80**

Excipients: Stabilizers

- To prevent the drug from oxidative decomposition antioxidants are included in ophthalmic preparations
- The most commonly used antioxidants are **sodium metabisulphite and sodium sulphite**
- Oxidative damage catalyzed by metal impurities can be reduced by incorporating chelating agents such as disodium EDTA

Excipients: Preservation

- The most commonly used preservatives in multiple dose ophthalmic preparations include – **Benzalkonium chrloride, Benzethonium chloride, Chlorobutanol, Phenyl mercuric acetate, Phenyl mercuric nitrate, Thiomersal**

Preservative	Concentration (%)
Benzalkonium chloride	0.004 – 0.01
Benzethonium chloride	0.01
Chlorobutanol	0.5
Phenylmercuric acetate	0.004
Phenylmercuric nitrite	0.004
Thimerosal	0.005–0.01

- ***Mixtures of benzalkonium chloride and polymyxin B or EDTA are effective against most strains of Pseudomonas aeruginosa, a bacterium that can cause ulceration of the eye and blindness***

Sterility

- All ophthalmic solutions should be sterile when dispensed and whenever possible, a suitable preservative should be added to ensure sterility during the course of use
- Ophthalmic solution intended to be used during the surgery or in traumatized eye generally do not contain preservative agent. These solution usually packed in a single dose container.
- Ophthalmic solution are sterilized either by **autoclaving (121 C for 15 minutes) or by bacteria retentive filters**

GPAT QUESTION

Maximum volume that can be held in cut-de-sac is _____

A. 50 microliters

B. 30 microliters

C. 60 microliters

D. All of above

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GPAT QUESTION

Which of the following preservatives are more effective against most strains of *Pseudomonas aeruginosa*?

A. Combination benzalkonium chloride and thiomersal

B. Combination benzalkonium chloride and polymixin B

C. Combination polymixin B and thiomersal

D. All of above

APOMiNd

THANK YOU