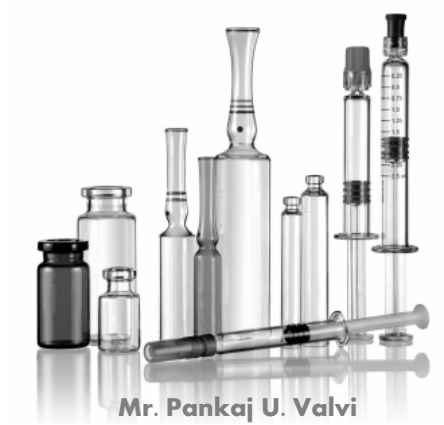
Parenteral Packaging



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❖ Introduction

The container must:

- Maintain the quality, safety and stability of the medicine.
- Protect the product against:
  - ✓ Physical damage,
  - ✓ Chemical and microbial contamination,
  - ✓ Light, moisture and oxygen as appropriate
- Be user friendly, easy to open and reclose.
- Other factors such as cost and the need for both child resistant closures and tamper –evident seals.

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Each container is labelled with the :

- Identity and quantity of the medicine.
- Batch no.
- Appropriate storage instructions.
- Directions for use.
- Product mfg and expiry date.
- Requirements for handling and storage.

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❖Primary and secondary packaging

1. Primary packaging: Which are in direct contact with the product (bottle, closure, blister…..).

Primary containers must:

- Protect the medicine from damage and from extraneous chemical and microbial contamination.
- Support use of the product by the patient.

Primary containers must NOT:

- Allow product leakage,
- Chemically react with the product,
- Release components
- Uptake product components.

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2. Secondary packages:

- Are additional packaging materials that improve the appearance of the product and include outer wrappers or labels that do not make direct contact with the product.
- Also can also supply information about the product and its use.
- They should provide evidence of tampering with the medicine.

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Types of primary and secondary packaging materials and their use

Material	Type	Examples of use
Glass	Primary	Metric medical bottle, ampoule, vial
Plastic	Primary	Ampoule, vial, infusion fluid container, dropper bottle
Plastic	Secondary	Wrapper to contain primary pack
Board	Secondary	Box to contain primary pack
Paper	Secondary	Labels, patient information leaflet

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The selection of packaging for a pharmaceutical product is dependent on the following factors:

- **The nature of the product itself**: its chemical activity, sensitivity to moisture and oxygen, compatibility with packaging materials
- **The type of patient:** is it to be used by an elderly or arthritic patient or by a child?
- **The dosage form**
- **Method of administering the medication**
- **Required shelf life**
- **Product use**, such as for dispensing or for an over-the counter product.

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❖Glass:

- Glass is the preferred packaging material.

Advantages:

- It is inert to most medicinal products,
- Impervious to air and moisture,
- It allows easy inspection of the container contents,
- It can be colored to protect contents from harmful wavelengths of light,
- Easy to clean and sterilize by heat,
- It is available in variously shaped containers.

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Disadvantages:

- Fragile: glass fragments and cracks
- Expensive in comparison to plastic.
- Heavy (transport cost)
- Certain types of glass release alkali into the container contents

The chemical stability of glass for pharmaceutical use is given by the resistance of the glass to the release of soluble minerals into water contacting the glass. This is known as **hydrolytic resistance.**

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Leaching and Flaking

- The basic structural network of glass is formed by the silicon oxide tetrahedron.
- The oxides are only loosely bound, are present in the network interstices, and are relatively free to migrate.
- These migratory oxides may be leached into a solution in contact with the glass, particularly during the increased reactivity of thermal sterilization.
- The oxides dissolved may hydrolyze to raise the pH of the solution and catalyze or enter into reactions. Additionally, some glass compounds will be attacked by solutions and, in time, dislodge glass flakes into the solution.
- Such occurrences can be minimized by the proper selection of the glass composition.

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❖Classification of Glass:

- **Type I, a borosilicate glass;**
- **Type II, a soda-lime treated glass;**
- **Type III, a soda-lime glass; and**
- **Type IV, NP, a soda-lime glass not suitable for containers for parenterals.**

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Type I, a borosilicate glass:

❖ **Composition:** Neutral glass, borosilicate glass composed of silicon dioxide, SiO_2 and boron oxide.

❖ **Advantages:**

- It possesses a high hydrolytic resistance.
- It is the most inert type of pharmaceutical glass.
- It has the lowest coefficient of thermal expansion (and hence suitable for sterilization by heat…..for ampoules and vials).

❖ **Disadvantages:**

- It has very high glass transition temperature so needs complicated processing and therefore expensive.

❖ **Uses:**

- Type I glass is suitable for packing all pharmaceutical preparations.
- It is widely used as glass ampoules and vials to package fluids for injection.
- In contrast to the other types of glass (type II and III), this type has no/little amounts of basic oxides, so It is used to package solutions that could dissolve basic oxides in the glass.

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Type II, a soda-lime treated glass:

❖ **Composition**: Soda-lime-silica glass.

Soda (Na_2CO_3) is used to decrease the glass transition temperature of silica. However, soda would increase water solubility of silica, so lime (CaO) is used to increase the hydrolytic resistance. This type would also contain other oxides.

❖ **Advantages**:

- This glass has a lower melting point than Type I glass. It is thus easier to produce and consequently cheaper.
- High hydrolytic resistance due to surface treatment of the glass.

❖ **Uses**:

- Type II glass used to package aqueous preparations.
- However, as it contains basic oxides, it is not used to package Parenteral formulations with a pH <7 (i.e. acidic); this would increase the pH of the formulation and could affect the drug stability and potency.
- It is the glass used to produce containers for eye preparations and other dropper bottles.

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Type III, a soda-lime glass:

❖**Composition**:

Soda-lime-silica glass: It has a similar composition to Type II glass but contains more leachable oxides.

❖**Properties and uses**:

Type III glass offers only moderate resistance to leaching and is commonly used to produce dispensary metric medical bottles. It is also suitable for packaging non-aqueous parenterals products and powders for injection.

- ❑ Type II and III glass contains relatively high proportions of sodium oxide and calcium oxide.
- ❑ Type II has lower concentrations of migratory oxides compared to Type III.
- ❑ Type II has been treated under controlled temperature and humidity conditions, with sulfur dioxide or other dealkalizers to neutralize the interior surface of the container.

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Type I Glass	• **USP describes Type I glass as: highly resistant borosilicate glass, and usually used for packaging acidic and neutral parenteral preparations. Also, where stability data demonstrates their suitability.** • **EP describes Type I glass as: neutral glass with high hydrolytic resistance owing to the chemical composition of the glass itself.** • **Type I glass will be suitable for all products, although sulfur dioxide treatment is sometimes used for even greater resistance to glass leachables.** • **Type I is suitable for all preparations whether or not for parenteral use and for human blood and blood components.**
Type II Glass	• **USP: Soda-lime glass that is suitably de-alkalized and is used for packaging acidic and neutral Parenteral preparations, and, also where stability data demonstrates their suitability, is used for alkaline Parenteral preparations.** • **EP: Soda-lime silica glass with high hydrolytic resistance resulting from suitable treatment of the surface. These containers are suitable for acidic and neutral aqueous preparations for parenteral use.**

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Type III Glass	• **USP: These are soda-lime glass containers that are usually not used for Parenteral preparations, except where suitable sensitivity test data indicates that Type III is satisfactory for the parenteral preparations that are packaged therein.** • **EP: These are soda-lime glasses with only moderate hydrolytic resistance. They are suitable for non-aqueous preparations for parenteral use, for powders for Parenteral use, and for preparations not for parenteral use**

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❖Evaluation Studies of Glass:

- **Powdered glass test**
- **Water attack test**
- **Arsenic test**
- **Light transmission test**

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Powdered glass test:

- It is done to **estimate the amount of alkali leached from the powdered glass** which usually happens at the elevated temperatures. When the glass is powdered, leaching of alkali is enhanced, which can be titrated with 0.02N sulphuric acid using methyl red as an indicator
- **Step-1: Preparation of glass specimen:**

  Few containers are rinsed thoroughly with purified water and dried with stream of clean air. Grind the containers in a mortar to a fine powder and pass through sieve no.20 and 50.
- **Step-2: Washing the specimen:**

  10gm of the above specimen is taken into 250 ml conical flask and wash it with 30 ml acetone. Repeat the washing, decant the acetone and dried after which it is used within 48hr.

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❖ Procedure:

- 10gm sample is added with 50ml of high purity water in a 250ml flask. Place it in an autoclave at 121 C±2 C for 30min.Cool it under running water. Decant the solution into another flask, wash again with 15ml high purity water and again decant. Titrate immediately with 0.02N sulphuric acid using methyl red as an indicator and record the volume.

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Transfer 10gms of prepared specimen in a 250ml conical flask digested previously with high purity water in a bath at 90°c

Add to conical flask containing 50ml high purity water

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Cap all the flasks and auto clave

↓

Adjust temperature to 150°c

↓

Cold the temperature to 121°c for 30mins

↓

Cool the flasks under running water

↓

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Wash the residue powdered glass(4 times with 15ml purity water)

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Add the decanted washings to main portion.

↓

add five drops of methyl red solution.

↓

Titrate immediately with 0.02N sulphuric acid.

↓

Record the volume of 0.02N sulphuric acid.

↓

Volume does not exceed i.e. indicated in the USP as per the type of glass concerned

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Water attack test for type II glasses:

- This is only for treated soda lime glass containers under the controlled humidity conditions which neutralize the surface alkali and glass will become chemically more resistant.
- Principle involved is whether the alkali leached or not from the surface of the container.

❖ **Procedure**: Rinse thoroughly with high purity water. Fill each container to 90%of its overflow capacity with water and is autoclaved at 121 C for 30min then it is cooled and the liquid is decanted which is titrated with 0.02N sulphuric acid using methyl red as an indicator. The volume of sulphuric acid consumed is the measure of the amount of alkaline oxides present in the glass containers.

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Rinse 3 or more containers with high purity water

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Fill each container to 90%of its over flow capacity

↓

Cap all the container and autoclave for 60mints

↓

Empty the contents and cool the contents in 250ml conical flasks to a volume of 100ml

↓

Add 5 drops of methyl red solution

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Titrate with 0.02N sulphuric acid while warm

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Record the volume of 0.02nsulphuric acid consumed

↓

Volume should not exceed as indicated in USP as for type of glass

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TESTS	CONTAINERS	VOL. (ml) OF 0.02N H_2SO_4
Powdered glass test	Type I	1.0
	Type III	8.5
	Type IV	15.0
Water attack test	Type II(100ml or below)	0.7
	Type II(above 100ml)	0.2

❖ ***The Powdered Glass Test*** **challenges the leaching potential of the interior structure of the glass.**

❖ ***The Water Attack Test*** **challenges only the intact surface of the container.**

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Arsenic test:

- This test is for glass containers intended for aqueous parenterals.
- Wash the inner and outer surface of container with fresh distilled water for 5min.
- Prep test as described in the test for water attack test for an adequate no. of samples to produce 50ml. Pipette out 10ml solution from combined contents of all ampoules to the flask. Add 10ml of HNO3 to dryness on the water bath, dry the residue in an oven at 130 C for 30min cool and add 10ml hydrogen molybdate reagent. Swirl to dissolve and heat under water bath and reflux for 25min. Cool to room temp and determine the absorbance at 840nm.Do the blank with 10ml hydrogen molybdate.
- The absorbance of the test solution should not exceed the absorbance obtained by repeating the determination using 0.1ml of arsenic standard solution (10ppm) in place of test soln.

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Light transmission test:

- Break the container or cut it with a circular saw fitted with a wet abrasive wheel, such as a carborundum or a bonded diamond wheel.
- Select sections to represent the average wall thickness in the case of blown glass containers, and trim them as necessary to give segments of a size convenient for mounting in the spectrophotometer.
- After cutting, wash and dry each specimen, taking care to avoid scratching the surfaces. If the specimen is too small to cover the opening in the specimen holder, mask the uncovered portion of the opening with opaque paper or masking tape, provided that the length of the specimen is greater than that of the slit in the spectrophotometer.

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- Immediately before mounting in the specimen holder, wipe the specimen with lens tissue. Mount the specimen with the aid of a tacky wax, or by other convenient means, taking care to avoid leaving fingerprints or other marks on the surfaces through which light must pass.

❖ **Procedure:**

- Place the section in the spectrophotometer with its cylindrical axis parallel to the plane of the slit and approximately centered with respect to the slit.
- When properly placed, the light beam is normal to the surface of the section and reflection losses are at a minimum.
- Measure the transmittance of the section with reference to air in the spectral region of interest, continuously with a recording instrument or at intervals of about 20 nm with a manual instrument, in the region of 290 to 450 nm.

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	Maximum Percentage of Light Transmission at Any Wavelength Between 290 and 450 nm	
Nominal Size (in mL)	Flame-sealed Containers	Closure-sealed Containers
1	50	25
2	45	20
5	40	15
10	35	13
20	30	12
50	15	10

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❖Plastics:

Two classes of plastics:

Thermosets (screw caps) and **Thermoplastics.**

Advantages:

1. Release few particles into the product
2. Flexible and not easily broken
3. Are of low density and thus light in weight
4. Can be heat sealed.
5. Are easily molded into various shapes
6. Suitable for use as container, closure and as secondary packaging
7. Cheap.

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Disadvantages:

1. They are not as chemically inert as Type I glass.
2. Some plastics undergo stress cracking and distortion from contact with some chemicals.
3. Some plastics are very heat sensitive.
4. They are not as impermeable to gas and vapor as glass.
5. They may possess an electrostatic charge which will attract particles.
6. Additives in the plastic are easily leached into the product.
7. Substances such as the active drug and preservatives may be taken up from the product.

❖ Plastic containers for pharmaceutical products are made from plastics based on the following polymers: **polyethylene (low or high density), polypropylene, polyvinyl chloride, polystyrene and to a lesser extent polyethylene terephthalate.**

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Type of Plastics:

Plastics are classified into two groups according to their behavior when heated:

1. **Thermoplastic type:**

- On heating, they soften to a viscous fluid which hardens again on cooling.

  e.g. Polyethylene, polypropylene, polyvinylchloride, polystyrene, nylon (polyamide), polycarbonate, acrylic multipolymers, polyethylene terephthalate etc.

2. **Thermosetting type:**

- When heated, they may become flexible but they do not become liquid; usually their shape is retained right up to the temperature of decomposition. Because of a high degree of cross-linking they are usually hard and brittle at room temperature.

  e.g. phenol-formaldehyde, urea formaldehyde, melamine formaldehyde.

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The principal plastic materials used in pharmaceutical packaging

Plastic polymer	Properties	Uses	Notes
Low-density polyethylene (LDPE)	Soft, flexible and easily stretched.	Squeeze bottles as eye drop bottles.	Disadvantages. of PE (LDPE and HDPE): •Softened by flavoring agent and aromatic oils, •Unsuitable for packaging oxygen sensitive products, •Adsorb antimicrobial preservative agents, •Crack on contact with organic solvents.
High-density polyethylene (HDPE)	Strong, stiff, less permeable to gases than LDPE.	Bottles for solid dosage forms	
Polypropylene	Strong and stiff, good resistance to cracking when flexed	Used for closures with hinges. Used also for tablet containers and IV bottles	
Polyvinyl chloride (PVC)	Rigid	Laminate (for blisters) and the main constituent of IV bags.	
Polystyrene (PS)	Clear, hard, brittle with low impact resistance.	Used for tubes and amber- tinted bottles. It is also used for jars for ointments and creams with low water content.	Its use in drug packaging is limited due to its high permeability to water vapor

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- **Three principal problem areas exist in using these materials:**

1. **Permeation** of vapors and other molecules in either direction through the wall of the plastic container;
2. **Leaching** of constituents from the plastic into the product; and
3. **Sorption** (absorption and/or adsorption) of drug molecules or ions on the plastic material.

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❖Evaluation Studies of Glass:

1. **Leakage test for plastic containers (non injectables and injectables IP):**

Fill 10 plastic containers with water and fit the closure

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Keep them inverted at room temperature for 24 hrs

↓

No sign of leakage should be there from any container

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2. **Collapsibility test:**

This test is applicable to containers which are to be squeezed in order to remove the contents. A container, by collapsing inward during use, yields at least 90 per cent of its nominal contents at the required rate of flow at ambient temperature.

3. **Light absorption:**

The light absorption in the range 230 nm to 360 nm of solution S using a blank prepared as described under Solution S is not more than 0.20.

(Solution S: Fill a container to its nominal capacity with water and close it, if possible using the usual means of closure; otherwise close using a sheet of pure aluminium. Heat in an autoclave so that a temperature of 121± 2º is reached within 20 to 30 minutes and maintain at this temperature for 30 minutes. If heating at 121º leads to deterioration of the container, heat at 100ºfor 2 hours.)

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4. **Water permeability test for plastic containers (injectable preparations IP):**

Fill 5 containers with nominal volume of water and sealed

↓

Weigh each container

↓

Allow to stand for 14 days at
Relative humidity of 60% at 20-25^{0}c

↓

Reweigh the container

↓

Loss of weight in each container should not be more than 0.2%

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5. **Transparency:**

- Fill the container previously used for the preparation of solution S to its nominal capacity with a 1 in 200 dilution of the standard suspension for a container made from polyethylene or polypropylene.
- For containers of other materials, use a 1 in 400 dilution. The cloudiness of the suspension is perceptible when viewed through the container and compared with a similar container filled with water.

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❖Rubber Closures:

- The use of silicone to lubricate vial rubber closures, syringe rubber plungers.
- Silicone coating is required for glass syringes and cartridges.
- Most rubber closure formulations are coated rubber to minimize leachables and do not require siliconization.

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Table 12.3 Special properties of rubber

Property	*Advantage gained*
Flexible	Conforms to shape of vial etc.
Resilient	Reseals after needle puncture
Non-thermoplastic	Tolerates most heat sterilising and other processes
Good compression set	Retains seal throughout product life
Can be varied by ingredient choice	Formulations can usually be developed compatible with most drugs

Table 12.4 Typical sulphur cured natural rubber formulation

Category	*Ingredient*	*Mass % (w/w)*
Elastomer	Natural rubber	60.00
Filler	Calcium carbonate	25.0
Pigment	Red iron oxide	4.0
Plasticiser	Paraffin oil	5.0
Processing aid/activator	Stearic acid	1.0
Activator	Zinc oxide	2.5
Vulcanisation system	Accelerator (e.g. sulphonamide, dithiocarbamate, thiuram)	1.5
	Elemental sulphur	1.0

- The elastomer primarily used in rubber closures, plungers, and other rubber items used in parenteral packaging and delivery systems is synthetic butyl or halobutyl rubber.

Table 25-3. Examples of Ingredients Found in Rubber Closures

Ingredient	Examples
Elastomer	Natural rubber (latex)
	Butyl rubber
	Neoprene
Vulcanizing (curing agent)	Sulfur
	Peroxides
Accelerator	Zinc dibutyldithiocarbamate
Activator	Zinc oxide
	Stearic acid
Antioxidant	Dilauryl thiodipropionate
Plasticizer/lubricant	Paraffinic oil
	Silicone oil
Fillers	Carbon black
	Clay
	Barium sulfate
Pigments	Inorganic oxides
	Carbon black

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- The physical properties of rubber considered in the selection of a particular formulation include elasticity, hardness, tendency to fragment, and permeability to vapor transfer.
- **Teflon® & Flurotec®**: Surface coatings to prevent leaching.

Rubber closures are usually washed by mechanical agitation in a tank of hot detergent solution (such as 5% sodium pyrophosphate).

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TESTS FOR RUBBER/RUBBER CLOSURES

1. FRAGMENTATION TEST (IP):

Place a volume of water corresponding to nominal volume-4ml in each of 12 clean vials

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Close vial with closure and secure caps for 16hrs

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Pierce the closure with number 21 hypodermic needle(bevel angle of 10 to 140c)and inject 1ml water and remove 1ml air

↓

Repeat the above operation 4 times for each closure

↓

Count the number of fragments visible to naked eye

↓

Total number of fragments should not be more than 10

2. SELF SEALABILITY TEST FOR RUBBER CLOSURES APPLICABLE TO MULTI DOSE CONTAINERS ONLY (IP):

Fill 10 vials with water to nominal volume and close the vials with closures

↓

Pierce the cap and closures 10 times at different places with no 21 syringe needle

↓

Immerse the vials in 0.1 %W/v solution of methylene blue under reduced pressure

↓

Restore the nominal pressure and keep the container for 30 min and wash the vials

↓

None of the vial should contain traces of colored solution

3. STERILITY TEST:

- When treated closures are subjected to sterilization test at 64-66 C and a pressure of about 0.7 KPa for 24hr.

4. pH OF AQUEOUS EXTRACT:

- 20ml of solution A is added with 0.1ml bromothymol blue when it is added with a small amount of 0.01M NaOH which changes the colour from blue to yellow. The volume of NaOH required is NMT 0.3ml and if it is done with HCl, the volume of HCl needed should NMT 0.8ml.

5. LIGHT ABSORPTION TEST:

- It must be done within 4hrs of preparing solution A. It is filtered through 0.5µ filter and its absorbance is measured at 220 to 360nm.Blank is done without closures and absorbance is NMT 2.0.

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6. REDUCING SUBSTANCES:

- 20ml of solution A is added with 1ml of 1M H_2SO_4 and 20ml of 0.002M $KMnO_4$ and boil for 3min then cool and add 1gm of potassium iodide which is titrated with sodium thio-sulphate using starch as an indicator. Blank is done and the difference between titration volumes is NMT 0.7ml.

7. RESIDUE ON EVAPORATION:

- 50ml of solution A is evaporated to dryness at 105 C.Then weigh the residue NMT 4mg.

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