SHREE H. N. SHUKLA INSTITUTE OF PHARMACEUTICAL EDUCATION AND RESEARCH

B.PHARM

(SEMESTER –VII)

SUBJECT NAME: QUALITY ASSURANCE

SUBJECT CODE: BP706TT

UNIT 03 (a): QUALITY CONTROL TESTS FOR PACKAGING MATERIALS

Content

Quality Control: Quality control test for containers, rubber closures and secondary packing materials.

Packaging of pharmaceutical products gives an adequate degree of protection, minimizes the loss of constituents and should not interact physically or chemically with products. Any material which is used for packing of product for sale and transportation is said to be packing material.

The commonly used packaging materials are Container, Closure and Carton. The containers mostly made of glass, plastic, metal or paper. The material for closure may include cork, glass, and plastic, metal or rubber.

There are two types of packing materials which are as below.

1. **Primary packaging**
   Primary packing materials which comes directly contact with products. e.g. bottles, vials, ampoules, tin, Blister package, Strip package etc.

2. Secondary Packaging

Secondary Packaging is outside the primary packaging perhaps used to group primary packages together and cover it. e.g. cartons, boxes, etc.

3. Tertiary Packaging

Tertiary Packaging is used for bulk handling, warehouse storage and transport shipping.

QUALITY CONTROL TEST FOR CONTAINERS

❖ Quality Control Tests for Glass containers

1. Chemical Resistance Test
   - **A.** Powdered Glass Test
   - **B.** Water Attack Test
2. Hydrolytic Resistance Test
3. Arsenic Test
4. Thermal Shock Test
5. Internal Bursting Pressure Test

1) **Chemical Resistant Test:**

The following tests are designed to determine the resistance to water attack of new glass containers. The degree of attack is determined by the amount of alkali released from the glass under the influence of the attacking medium under the conditions specified.

A. Powdered Glass Test: It is done to estimate the amount of alkali leached from the powdered glass, which usually happens at elevated temperature. When glass is powdered, leaching of alkali is enhanced, which can be titrated with 0.02 N sulphuric acid using methyl red as an indicator.

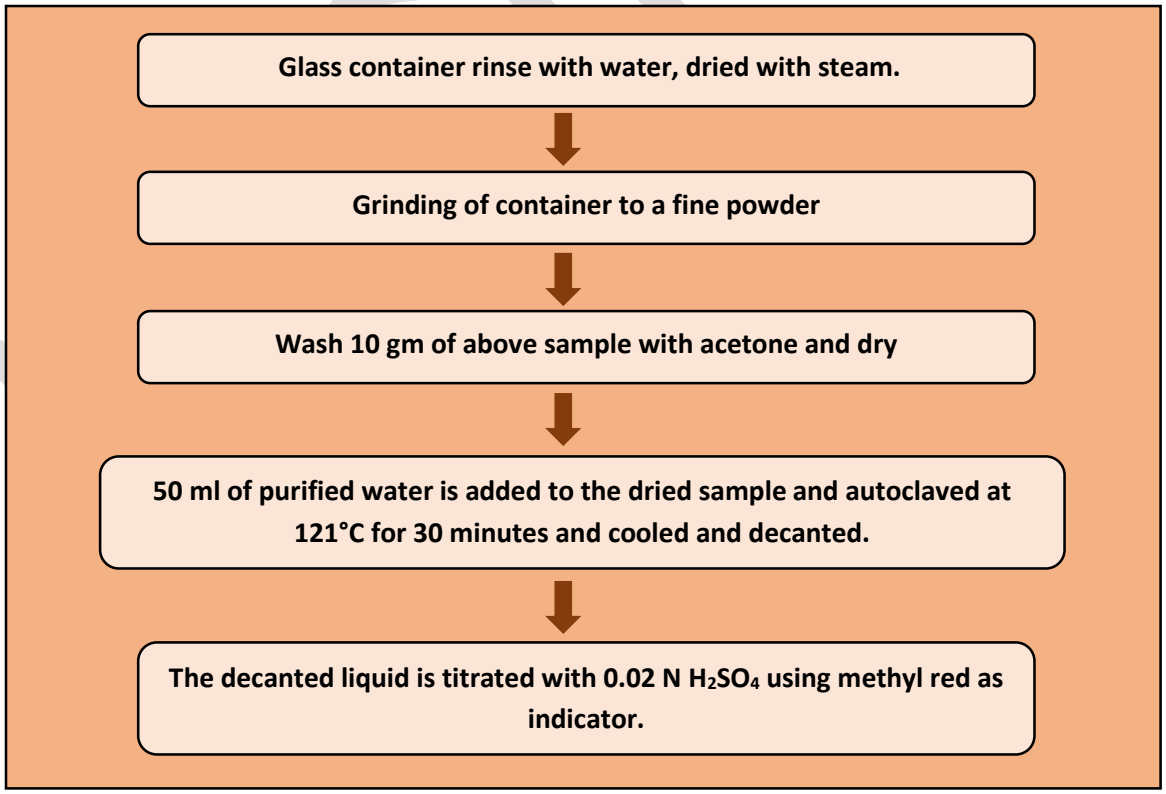
Step 1: Preparation of glass specimen

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:

10 gm 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.

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



Tests	Container	Vol. of 0.02 N H_2SO_4
Powdered Glass Test	Type I	1.0
	Type II	8.5

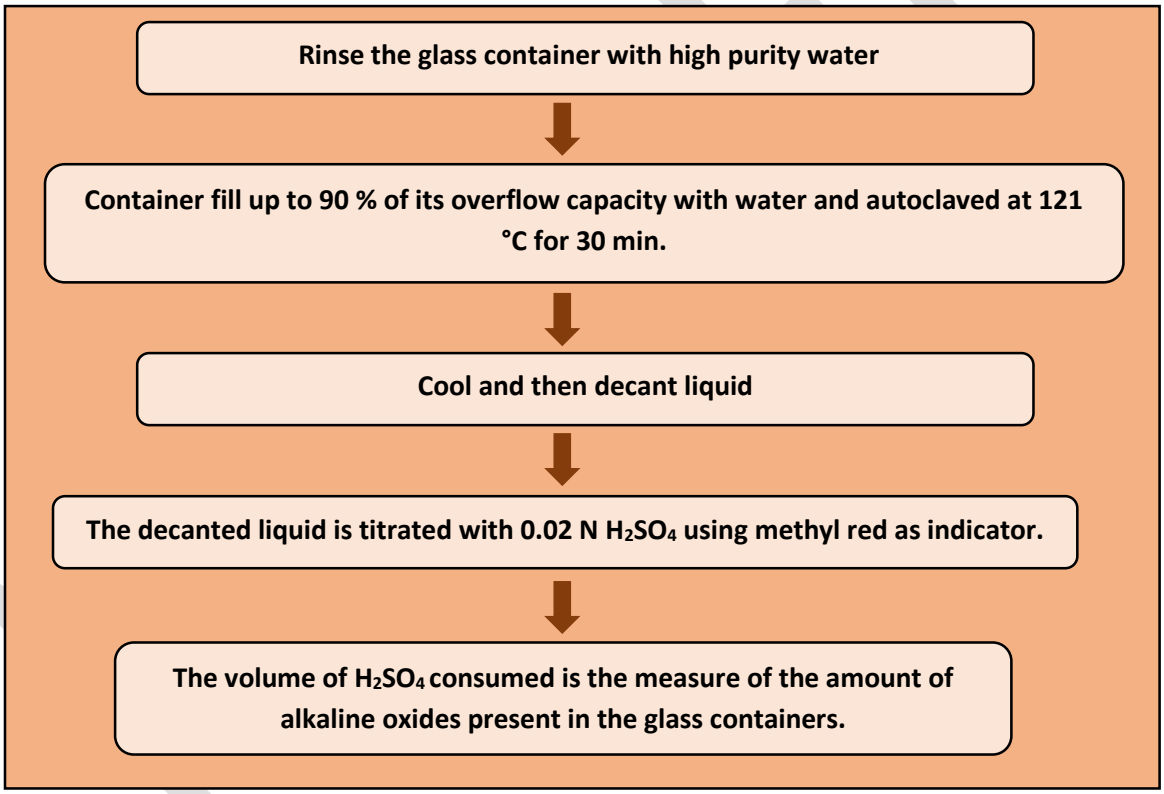
	Type III	15.0

B. Water Attack Test:

This test is used only with containers that have been exposed to sulphur dioxide fumes under controlled humidity conditions. Such a treatment neutralizes the surface alkali. Now the glass becomes chemically more resistant.

Principle: The principle involved in the water attack test is to determine whether the alkali leached form the surface of a container is within the specified limits or not. The amount of acid that is necessary to neutralize the released alkali from the surface is estimated, the leaching of alkali is accelerated using elevated temperature for a specified time. Methyl red indicator is used to determine the end point. The basic is acid-base titration.

Procedure:



Tests to be done on different type of glass materials.

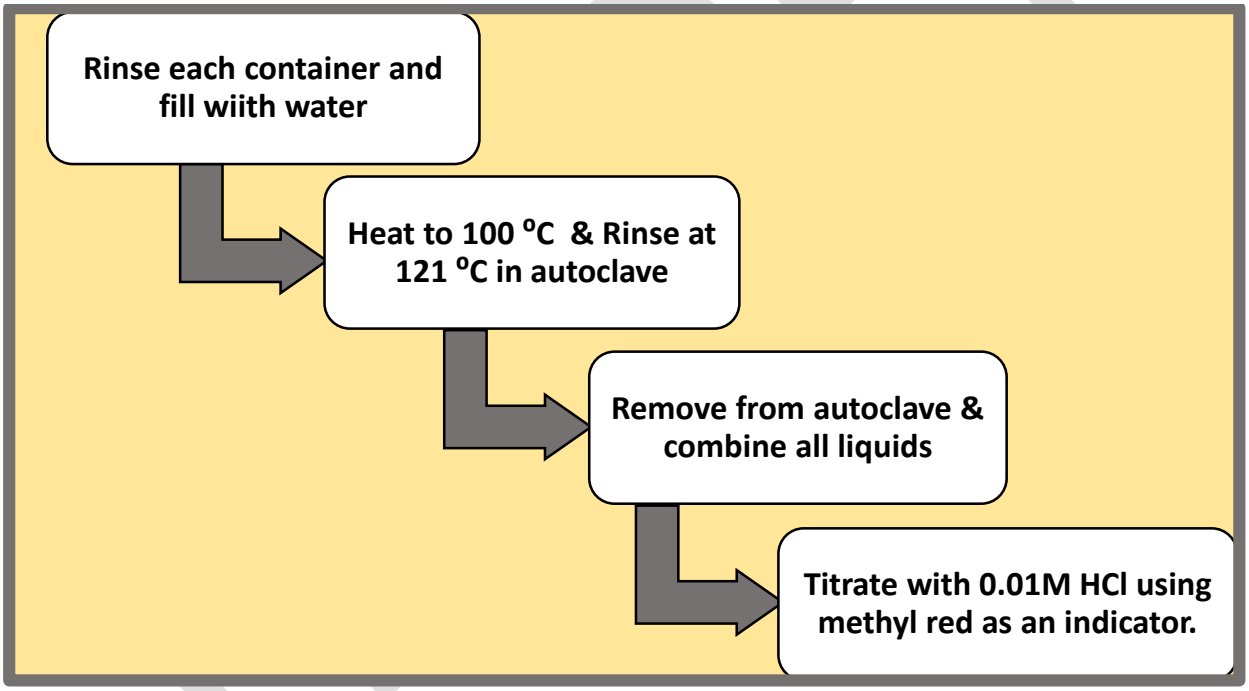
Type	General Description	Type of Test
I	Highly resistant, borosilicate glass	Powdered Glass
II	Treated soda-lime glass	Water Attack
III	Soda-lime glass	Powdered Glass

Tests	Container	Vol. of 0.02 N H_2SO_4
Water Attack Test	Type II (100 ml or below) Type II (above 100 ml)	0.07 0.02

2) Hydrolytic Resistance of Glass Containers:

Rinse each container at least 3 times with distilled water and fill with the same to their filling volume. Heat to 100 ºC for 10 min and allow the steam to issue from the vent cork. Rise the temp from 100 ºC to 121 ºC over 20 min. Maintain the temp at 121ºC to 122ºC for 60 min. Lower the temp from 121ºC to 100 ºC over 40 min venting to prevent vacuum.

Remove the container from autoclave, cool and combine the liquids being examined. Measure the volume of test solution into a conical flask and titrate with 0.01M HCl using methyl red as an indicator. Perform blank with water and the difference between the titration represents the volume of HCl consumed by the test solution.



Nominal Capacity of container (ml)	Number of containers to be used	Volume of test solution to be used for titration (ml)
5 or less	at least 10	50.0
6 to 30	at least 5	50.0
More than 30	at least 3	100.0

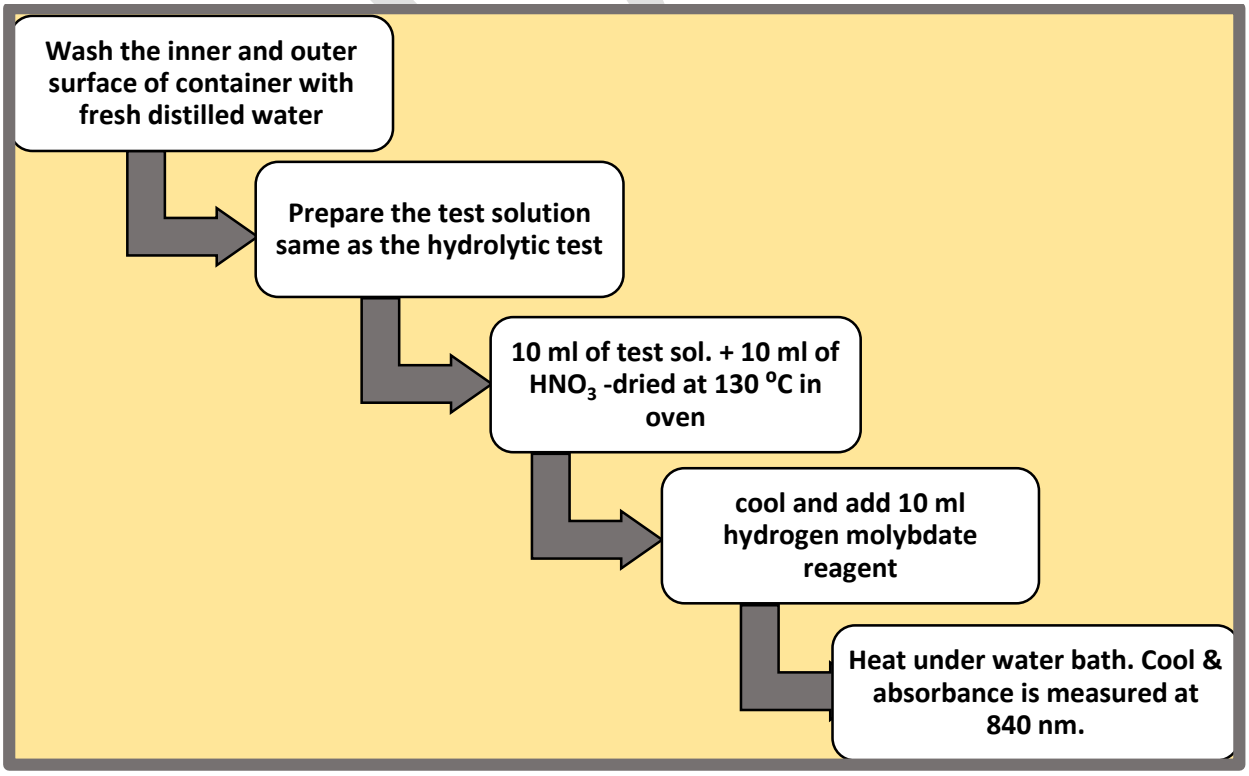
3) Arsenic test:

This test is for glass containers intended for aqueous parenterals.

Wash the inner and outer surface of container with fresh distilled water for 5 min. Then similar steps are followed as performed in the hydrolytic test, previously described, till obtaining the final combined solution.

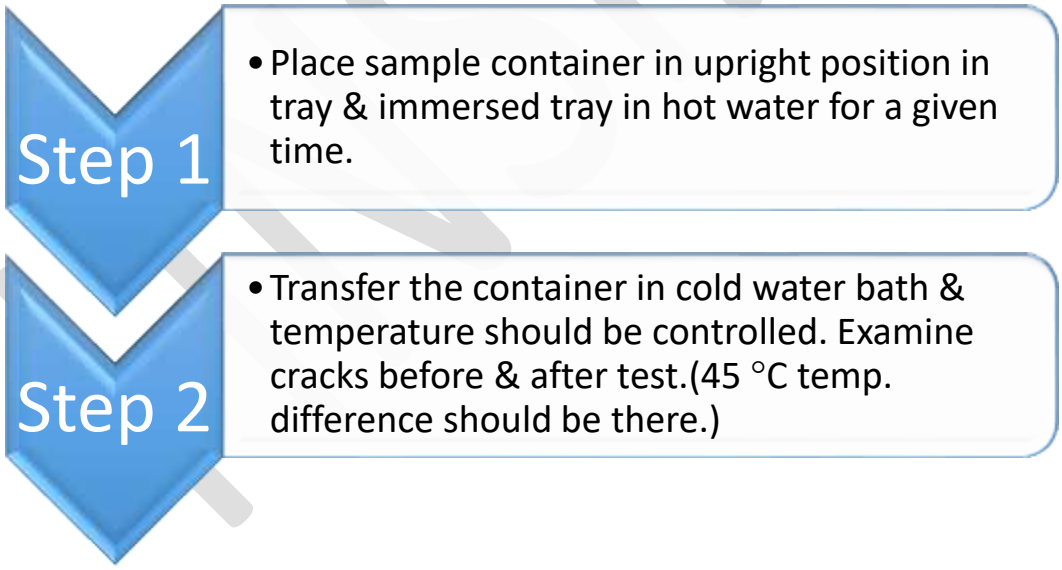
Pipette out 10 ml solution from combined contents of all ampoules to the flask. Add 10 ml of HNO_3 to dryness on the water bath, dry the residue in an oven at 130ºC for 30 min cool and add 10 ml hydrogen molybdate reagent .Swirl to dissolve and heat under water bath and reflux for 25 min. Cool to room temp and determine the absorbance at 840 nm.

Do the blank with 10ml hydrogen molybdate. The absorbance of the test solution should not exceed the absorbance obtained by repeating the determination using 0.1 ml of arsenic standard solution (10 ppm) in place of test solution.



Capacity of container [corresponding to 90 per cent average overflow volume (ml)]	Volume of 0.01M hydrochloric acid per 100 ml of test solution	
	Type I or II glass (ml)	Type III glass (ml)
Not more than 1	2.0	20.0
More than 1 but not more than 2	1.8	17.6
More than 2 but not more than 5	1.3	13.2
More than 5 but not more than 10	1.0	10.2
More than 10 but not more than 20	0.80	8.1
More than 20 but not more than 50	0.60	6.1
More than 50 but not more than 100	0.50	4.8
More than 100 but not more than 200	0.40	3.8
More than 200 but not more than 500	0.30	2.9
More than 500	0.20	2.2

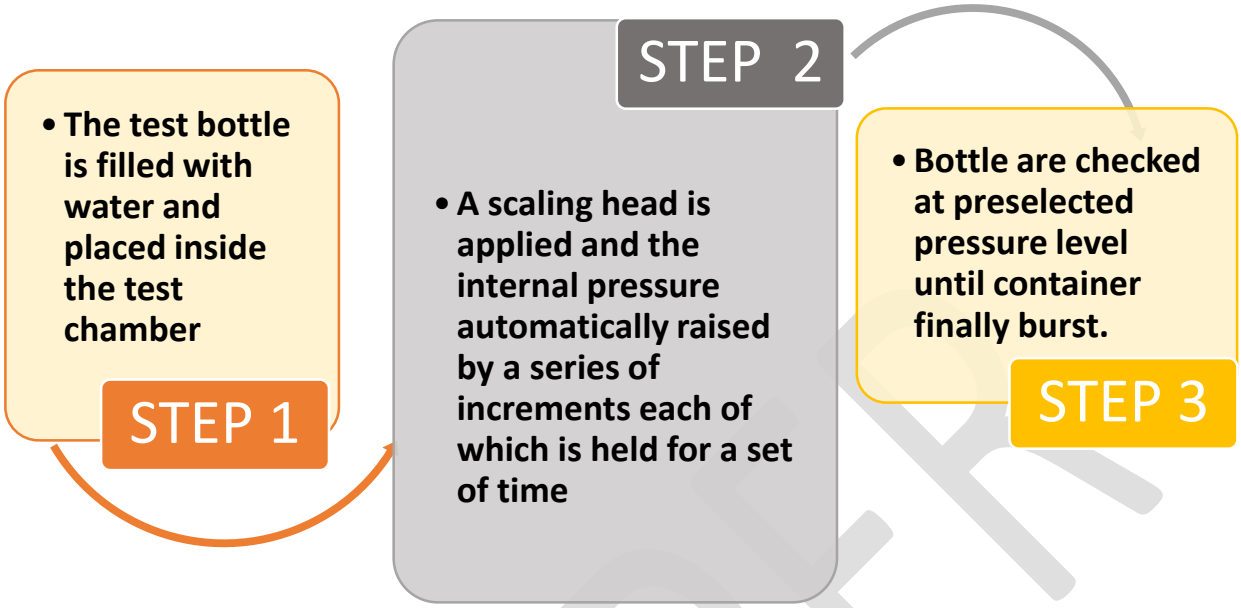
4) Thermal Shock Test:



The amount of thermal shock a bottle can withstand is based on construction. Small bottles withstand a temp differential of 60 °C to 80 °C and 1 pint bottle 30 °C to 40 °C.

5) Internal Bursting Pressure Test

The most common instrument used is American glass research increment pressure tester.



6) Leakage Test:

Drug filled container is placed in a container filled with coloured solution (due to the addition of dye) which is at high pressure compared to the pressure inside the glass container so that the coloured solution enters the container if any cracks or any breakage is present.

❖ Quality Control Tests for Plastic containers:

- **For Non-injectable preparation:**

1. 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, yield at least 90% of its normal contents at the required rate of flow at ambient temperature.

2. Clarity of aqueous extract:

A suitable container is taken at random, and unlabeled, unmarked and nonlaminated portions is selected.

These portions are cut into strips, none of which has a total surface area of 20 cm^2.

The strips are washed free from extraneous matter by shaking them with at least two separate portions of distilled water for about 30 secs.

The processed sample is taken in to the flask, previously cleaned with chromic acid and rinsed with distilled water.

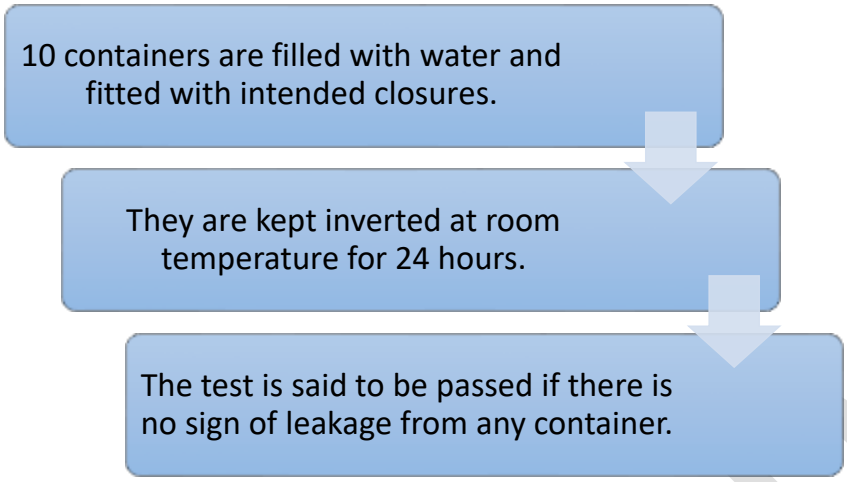
250 ml of distilled water is added to the flask, covered and autoclaved at 121°C for 30 mins.

The extract is cooled and examined. It should be colorless and free from turbidity.

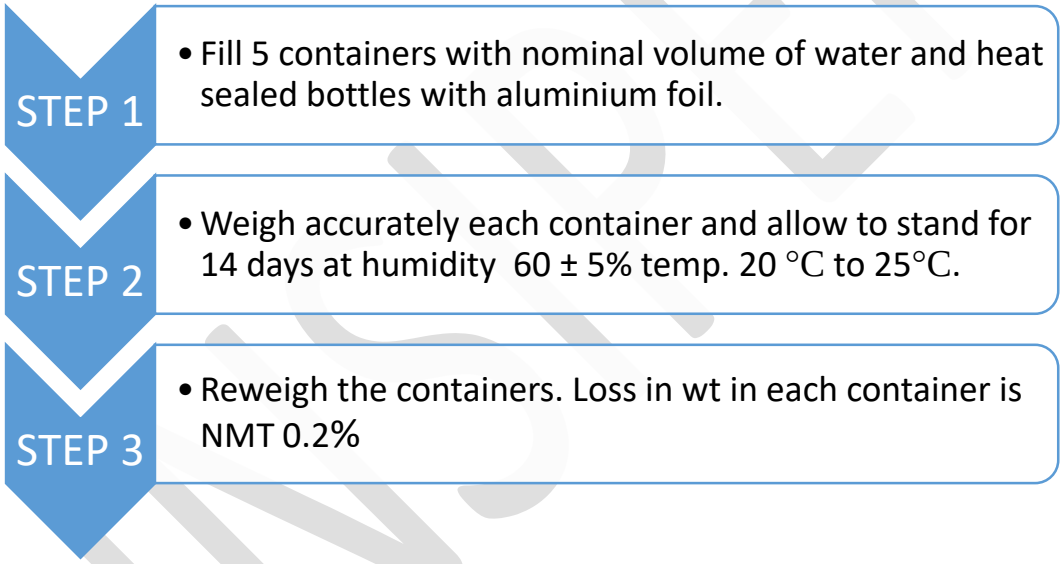
3. Non-volatile residue

Evaporate 100 ml of the extract obtained in the test for Clarity of aqueous extract to dryness and dry to constant weight at 105º. The residue weighs not more than 12.5 mg.

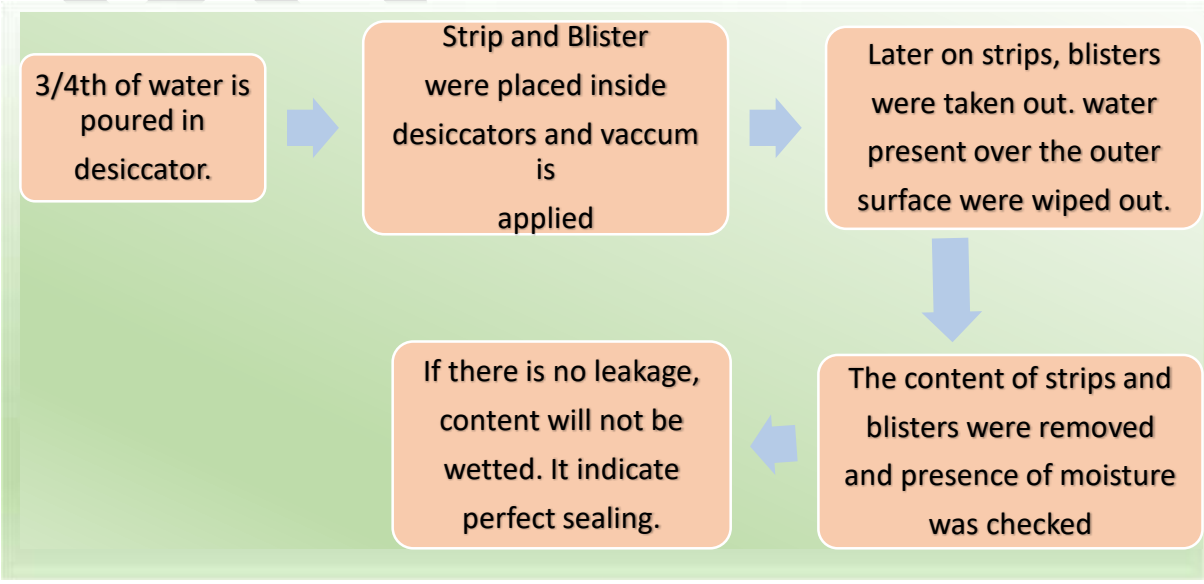
4. Leakage test:



5. Water vapour permeability:



❖ Quality Control Test for Strip and Blister packing



QUALITY CONTROL TEST FOR CLOSURES

1. Sterility Test
2. Fragmentation Test
3. Self-Sealability
4. pH of aqueous extract
5. Light Absorption Test
6. Reducing Substance
7. Residue on Evaporation
8. Penetrability

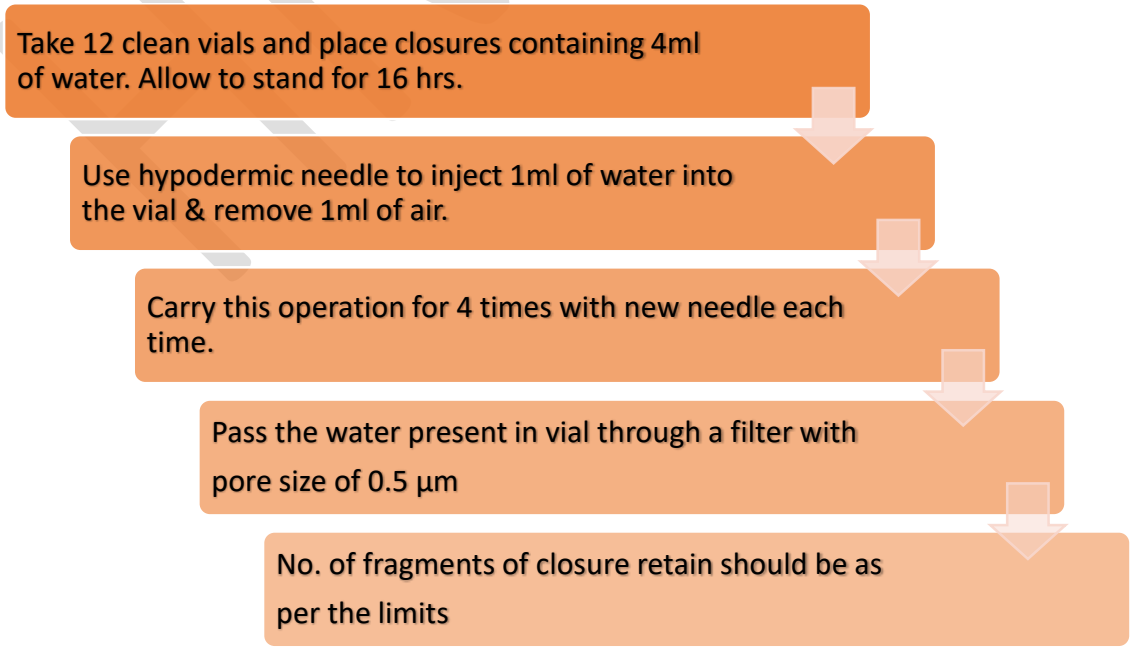
Preparation of sample:

- The closures are washed in 0.2% w/v of anionic surface active agents for 5 minutes.
- Rinsed five times with distilled water and 200 ml water is added.
- Subjected to autoclave at 119°C to 123°C for 20-30 minutes covering with aluminum foil.
- Cooled and solution is separated from closures (Solution A).

1. Sterility Test:

Procedure: When treated closures are subjected to sterilization test at 64-66 ºC and a pressure of about 0.7 KPa for 24 hr., the closures used for the preparation of the sample solution shall not soften or become tacky and there shall be no visual change in the closure.

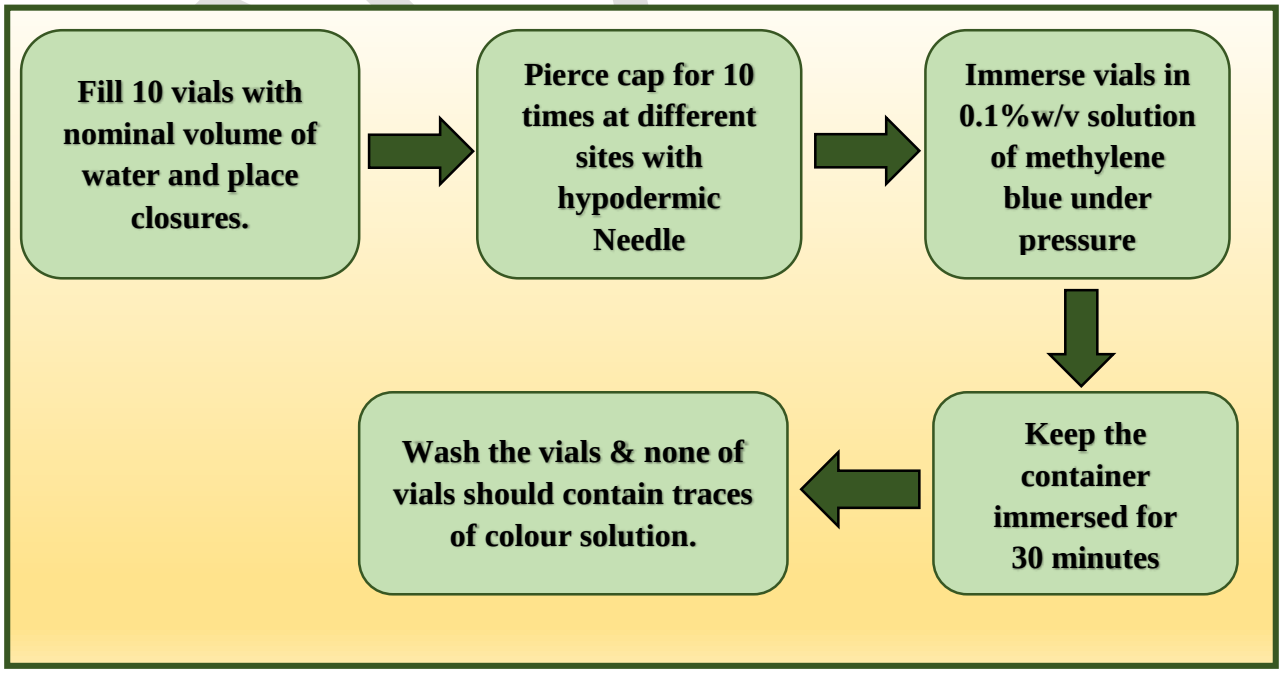
2. Fragmentation Test



No. of fragments is NMT 10 except in the case of butyl rubber closures where the total no. of fragments is NMT 15.

3. Self-Sealability Test

- This test is applicable to closures intended to be used with water close the vials with the 'Prepared' closures
- For each closure, use a new hypodermic needle with an external diameter of 0.8 mm & pierce the closure 10 times, each time at a different site.
- Immerse the vials upright in a 0.1 % w/v solution of methylene blue & reduce the external pressure by 27 KPa for 10 min.
- Restore the atmospheric pressure and leave the vials immersed for 30 minutes. Rinse the outside of the vials.
- None of the vials contains any trace of coloured solution.



4. pH of aqueous extract

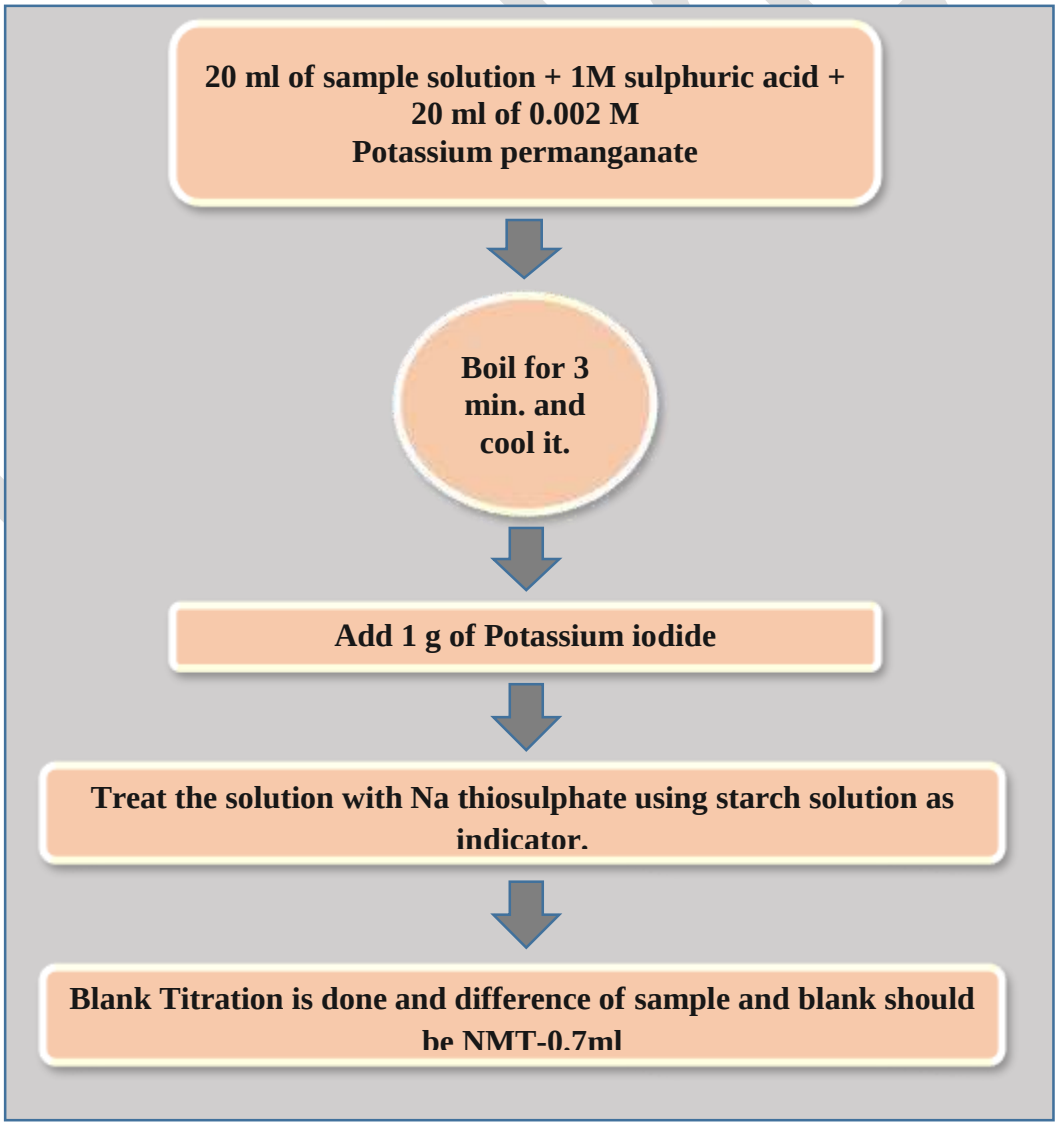
20 ml of solution A is added with 0.1ml bromothymol blue when it is added with a small amount of 0.01M NaOH which changes the colour from blue to yellow. The volume of NaOH required is NMT 0.3 ml and if it is done with HCl, the volume of HCl needed should NMT 0.8ml.

5. Light Absorption Test

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

6. Reducing Substance

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



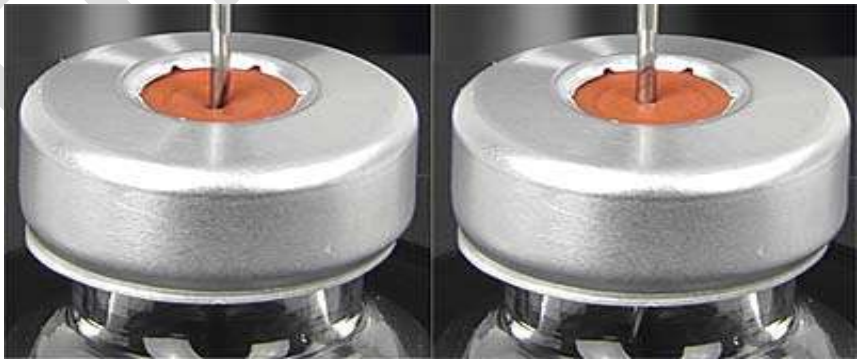
7. Residue on Evaporation

The 50 ml of sample solution is evaporated to dryness at 105 °C. Then weigh the residue.

Residue obtained should not be more than 4 mg.

8. Penetrability Test

- This is to measure the force required to make a hypodermic needle penetrate easily through closure. It is measured by using piercing machine.
- The piercing force must not exceed a stated value, the hypodermic needle can get damage as a result of undesirable hardness of closure.



QC TEST FOR SECONDARY PACKAGING MATERIALS

Different Types of Secondary Packaging materials

- Paper and Boards
- Cartons
- Corrugated fiberboard

Testing of Paper & Board

The test pieces of paper and board are taken for test to be carried out in standard condition

a) Temperature: 23 °C ± 1°C
b) Relative Humidity: 50% ± 2%

Test	Description
Dimensions	The physical dimensions of the given paper board is taken and recorded.
Grammage	A test piece of suitable size (10cm×10cm) is cut and weighed. The grammage of the sample is determined by Grammage = 104×w/a×b w - weight in grams a - length b- breadth
Thickness	Measured with a micrometer. Thickness is related to grammage of paper and its bulk density. It directly influences the physical property of paper like stiffness, varnishing and cutting.
Surface pH	Acidity in paper may be caused by the presence of residual chemical left in the pulp. A drop of distilled water is placed on the top of the test piece and the electrode of pH meter is placed in the drop touching the paper. The reading is taken after 2 min.
PH after Extraction	Cut 1gm of paper & place in a 100 ml flask, fitted with condenser, add 20 ml of boiling distilled water in small portions till the paper is wet. Add 50 ml of distilled water. Reflux and digest with occasional shaking at 95-100 °C for 1 hr. Cool to 40-45 °C, remove the condenser and shake, cool in water bath. Determine the pH of the supernatant with pH meter.
Moisture Content	Conditioned specimen is weighed and heated to a constant weight to expel the moisture. The difference of the two weights gives the moisture content of the paper.

	% moisture = 100(A-B) / B A - Original weight B - Weight after drying.
Ash content	Take about 1g of specimen and make it in to shreds and place in a previously weighed crucible (C). Heat carefully over a burner till completely charred. Transfer the crucible in to a muffle furnace at 800 °C until all the carbonaceous matter are burnt off. Cool in desiccator, weigh and repeat the experiment to a constant weight (D). % Ash= 100(C-D)/D
Alkalinity	Place about 5g (w) of accurately weighed sample, cut into pieces in a stoppered flask containing 250 ml of 0.02N HCl. Allow to stand for 1 hr with occasional shaking. Decant and titrate a measured quantity (v) against 0.1 N NaOH using methyl orange as indicator. Carry out blank (B). % Alkalinity=$\frac{1250\ (B-A)\times N}{V\ x\ w}$ A- Sample reading N- Normality of NaOH
Cobb test	This measures the mass of water absorbed by 1cm2 of the test piece in a specified time under a head of 1 cm of water. It is determined by weighing before and after exposure to the water, and usually quoted in g/m^2.
Folding endurance	Fold the piece back and forth until rupture occurs.
Tensile strength	The max tensile force per unit width that a paper or board will withstand before breaking.
Tear strength	The mean force required to continue the tearing of an initial cut in a single sheet of paper.
Air permeability	Important for using light weight uncoated paper on machine having vacuum pick up system.
Stiffness	Degree of resistance offered by paper/board when it is bent.
Burst resistance	The max uniformly distributed pressure, applied at right angles to the surface that a test piece of paper and board will stand under conditions of test, Hydraulic pressure is applied to diaphragm, bulging it until test piece bursts.