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भारतीय मानक मसौदा

होम्योपैथिक औषधि के निर्माण, पैकेजिंग और वितरण हेतु ग्लास कंटेनर व क्लोज़र – विशिष्टि

Draft Indian Standard

Glass Containers and Closures for Manufacturing, Packaging & Dispensing of Homoeopathic Medicine - Specification

Homoeopathy Sectional Committee, AYD 07 **Last Date of Comments: 29-09-2023**

FOREWORD

Glass is used in homoeopathy from very beginning for preparation, storage and dispensing of Homoeopathic medicines.

Glass is an amorphous solid made from natural and abundant raw materials (sand, soda ash and limestone) that melts at very high temperature to form a new material i.e., glass. At high temperature it is structurally like liquids, however at ambient temperature it behaves like solids. Without exception, it also has leaching effects to considerable extent due to the de-alkalization process it undergoes, which is alarming as any packaging materials must not interact physically or chemically with a packaged article in a manner that causes its safety, identity, strength, quality, or purity concern.

In view of the present scenario of Homoeopathy where the globalization of the Homeopathic products takes place; there is a need for standards which should be followed by Homeopathic industries regarding their product to facilitate their product acceptance among consumers.

Being cost-effective, eco-friendly, and recyclable, glass containers are widely used in Manufacturing, Primary packaging and Storing of Homoeopathic medicines by the industry, dispensing chemists, and clinics. The leaching effect is also minimal for long storage and dispensing. This document has been prepared to standardize the specifications for the preparation of Glass containers for manufacturing, primary packaging and dispensing of Homeopathic medicines.

In the formulation of this standard due weightage has been given to the international standards and practices prevailing in different countries in addition to the practices followed by the homoeopathic industry in this country. Assistance has also been extracted from United State Pharmacopoeia (USP 660/1660), as it is widely accepted among the pharmaceutical industries.

Also, due consideration has been given to the provisions of the Drug and Cosmetics Act, 1940 and Rules framed thereunder. However, this standard is subject to the restrictions imposed under these Rules and Regulations, wherever applicable.

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Glass Containers and Closures for Manufacturing, Packaging & Dispensing of Homoeopathic Medicine - Specification

1 SCOPE

This standard prescribes the requirements, methods of sampling and testing of Glass Container used in Manufacturing, Packaging & Dispensing of Homoeopathic Medicines.

2. REFERENCES

The standards below contain provisions that may be applied here as suitable. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this standard are encouraged to investigate the possibility of applying the most recent editions of these standards.

IS No.	Title
IS 4905: 2015	Random Sampling and Randomization Procedures
IS 6506: 1972	Methods for Thermal Shock Tests on Glassware
IS 6654: 1992	Glass Containers - Glossary of Terms
IS 1382: 1981	Glossary of Terms Relating to Glass Industry (First Revision)
IS 6945: 1973	Code of Practice for Packaging Glass and Glassware
IS 8932: 1978	Specification for Preformed Metal Screw Caps for Glass Containers
IS 10497: 2018	Method of Test for the Determination of Brimful Capacity of Glass Containers by Gravimetric Method
IS 2303: (Part 1/Sec 1): 2021	Grading Glass for Alkalinity- Determination and classification of hydrolytic resistance at 98°C
IS 2303: (Part 1/Sec 2): 2021	Grading Glass for Alkalinity- Determination and classification of hydrolytic resistance at 121°C
IS 2303: (Part 2): 2018	Grading Glass for Alkalinity-Determination by Titration Method and Classification
IS 1108: 1975	Specification for pharmaceutical glass containers (Second Revision)
IS 9806: 2001	Methods of test for and permissible limits of toxic materials released from ceramicware, vitreous enamelware, glassware and glass-ceramicware in contact with food

USP 659	Packaging and Storage Requirements
USP 660	Containers-glass
USP 1660	Evaluation of the Inner Surface Durability of Glass Containers

3. TERMINOLOGY/DEFINITIONS

For the purposes of this standard, the definitions given in IS 1382:1981 and IS 6654: 1992 shall apply.

4. REQUIREMENTS

4.1 Material and Workmanship – Pharmaceutical containers shall be prepared by using either borosilicate (neutral) glass or soda-lime-silica glass, of Type I, II or III glass material, clear or amber colored, and have smooth surface without cracks, pinholes, or sharp edges as per USP 660. The selection of containers should be based on the suitability of the glass type for pharmaceutical products, based on the tests for hydrolytic resistance and stability test data.

4.2 The bottles shall be well annealed and shall not contain strains more than that shown by standard strain disc No. 4 as per IS 1108:1975.

4.3 Neck finish of the container shall be referred by IS 1108:1975, Specification for pharmaceutical glass containers (wherever applicable).

4.4 The containers shall be free from cords, blisters, and stones and as far as possible, free from loading marks.

4.5 The containers shall be well formed with a uniform distribution of glass all over the walls and the base, avoiding any wedge bottom.

4.6 The containers shall be regular in shape and smoothly finished and, when placed on a horizontal plane, shall rest evenly.

4.7 The container shall be manufactured by a suitable process adhering to good manufacturing practice (GMP).

4.8 All bottles shall be thoroughly cleaned immediately before filling by automatic/semi-automatic washing machines. Washing shall be accomplished by pre-rinse and final rinse. For final rinse purified water shall be used. Bottles should be thoroughly drained after final rinse so that strength of medicine is not affected after filling.

4.9 After the final rinse, bottles shall be air dried or vacuum dried properly.

5. DIMENSIONS

5.1 Glass Phials

5.1.1 Capacity: The nominal capacities of the containers shall be:

(1.6, 3, 6) mL

5.2 Glass Bottles

5.2.1 Capacity: The nominal capacity of the container shall be:

(10, 12, 15, 30, 45, 60, 100, 115, 125, 200, 450, 500, 750, 1000) mL.

5.3 Manufacturing vessels

5.3.1 Capacity: The nominal capacity of the vessels shall be:

(500, 1000, 2500, and 5000 or above) mL

5.4 Nominal Capacity and Overflow capacity to be determined as per IS 1108-1975.

TABLE 1 CAPACITIES AND TOLERANCES OF PHARMACEUTICAL GLASS CONTAINERS

NOMINAL CAPACITY (1) ml	BRIMFUL CAPACITY (2) ml	TOLERANCE ON BRIMFUL CAPACITY (3) ml
5	10.0	± 1
10	15.5	± 1
15	19	± 2
30	38	± 3
50	60	± 3
100	115	± 5
115	135	± 6
200	225	± 8
250	280	± 8
450	480	± 10
500	530	± 10
1000	1060	± 15

6. TESTING

6.1 Hydrolytic Resistance of Glass Containers:

6.1.1 Glass Grains Test (USP 660):

APPARATUS

- Autoclave: For these tests, use an autoclave capable of maintaining a temperature of 121 ± 1°, equipped with a thermometer, or a calibrated thermocouple device, allowing a temperature measurement independent of the autoclave system; a suitable recorder; a pressure gauge; a vent cock; and a tray of sufficient capacity to accommodate the number of containers needed to carry out the test above the water level. Clean the autoclave and other apparatus thoroughly with purified Water before use.
- Mortar and pestle: Use a hardened-steel mortar and pestle for pulverizing glass.
- Sieves: A set of three square-mesh stainless steel sieves mounted on frames consisting of US Sieve Nos. 25, 40, and 50.
- Mechanical sieve-shaker or a sieving machine: That may be used to sieve the grains.
- A tempered, magnetic steel hammer
- Weighing bottles & stoppers
- A hot air oven, capable of maintaining 140 ± 5°C.
- Weighing balance: Capable of weighing up to 500 g with an accuracy of 0.005 g
- Desiccator
- Ultrasonic bath/Sonicator.

REAGENTS

- **Carbon dioxide-free water**: This is Purified Water that has been boiled vigorously for 5 min or more and allowed to cool while protected from absorption of carbon dioxide from the atmosphere, or Purified Water that has a resistivity of not less than 18 Mohm-cm.

- **Methyl red solution:** Dissolve 50 mg of methyl red in 1.86 mL of 0.1 M sodium hydroxide and 50 mL of ethanol (96%), and dilute with Purified Water to 100 ml. To test for sensitivity, add 100 mL of carbon dioxide-free water and 0.05 mL of 0.02 M hydrochloric acid to 0.1 mL of the methyl red solution. The resulting solution should be red. NMT 0.1 mL of 0.02 M sodium hydroxide is required to change the colour to yellow. A colour change from red to yellow corresponds to a change in pH from pH 4.4 (red) to pH 6.0 (yellow).

SAMPLE PREPARATION

- Rinse the containers to be tested with Purified Water, and dry in the oven. Wrap at least three of the glass articles in clean paper, and crush to produce two samples of about 100 g each in pieces NMT 30 mm across. Place in the mortar 30–40 g of the pieces between 10 and 30 mm across taken from one of the samples, insert the pestle, and strike it heavily with

the hammer once only. Alternatively, transfer samples into a ball mill-breaker, add the balls, and crush the glass. Transfer the contents of the mortar or ball mill to the coarsest sieve (No. 25) of the set. Repeat the operation until all fragments have been transferred to the sieve. Shake the set of sieves for a short time by hand and remove the glass that remains on sieves No. 25 and No. 40.

- Submit these portions to further fracture, repeating the operation until about 10 g of glass remains on sieve No. 25. Reject this portion and the portion that passes through sieve No. 50. Reassemble the set of sieves and shake for 5 min. Transfer to a weighing bottle the glass grains that passed through sieve No. 40 and are retained on sieve No. 50. Repeat the crushing and sieving procedure with the second glass sample until two samples of grains are obtained, each of which weighs more than 10 g.

- Spread each sample on a piece of clean glazed paper and remove any iron particles by passing the magnet over them. Transfer each sample into a beaker for cleaning. Add 30 mL of acetone to the grains in each beaker, and scour the grains, using suitable means such as a rubber-tipped or plastic-coated glass rod. After scouring the grains, allow to settle, and decant as much acetone as possible. Add another 30 mL of acetone, swirl, decant, and add a new portion of acetone. Fill the bath of the ultrasonic vessel with water at room temperature, then place the beaker in the rack, and immerse it until the level of the acetone is at the level of the water; apply the ultrasound for 1 min. Swirl the beaker, allow to settle, and decant the acetone as completely as possible; then repeat the ultrasonic cleaning operation. If a fine turbidity persists, repeat the ultrasonic cleaning and acetone washing until the solution remains clear. Swirl, and decant the acetone. Dry the grains, first by putting the beaker on a warm plate, then by heating at 140° for 20 min in a drying oven. Transfer the dried grains from each beaker into separate weighing bottles, insert the stoppers, and cool in a desiccator.

TEST METHOD

Filling and heating: Weigh 10.00 g of the cleaned and dried grains into two separate conical flasks. Pipet 50 mL of carbon dioxide-free Purified Water into each of the conical flasks (test solutions). Pipet 50 mL of carbon dioxide-free Purified Water into a third conical flask that will serve as a blank. Distribute the grains evenly over the flat bases of the flasks by shaking gently. Close the flasks with neutral glass dishes or aluminium foil rinsed with Purified Water or with inverted beakers so that the inner surfaces of the beakers fit snugly down onto the top rims of the flasks. Place all three flasks in the autoclave containing the water at ambient temperature and ensure that they are held above the level of the water in the vessel.

OPERATIONS

1. Insert the end of a calibrated thermometric device in a filled container through a hole of approximately the diameter of the thermocouple and connect it to an external measuring

device. If the container is too small to insert a thermocouple, apply a thermocouple in a suitable, similar container. Alternatively, use the internal thermometer of the autoclave.

2. Close the autoclave door or lid securely but leave the vent-cock open.
3. Start automatic recording of the temperature versus time, and heat the autoclave at a regular rate such that steam issues vigorously from the vent-cock after 20–30 min, and maintain a vigorous evolution of steam for a further 10 min. For autoclaves using a steam generator, it is not necessary to maintain the temperature for 10 min at 100°.
4. Close the vent-cock, and raise the temperature from 100° to 121° at a rate of 1°/min within 20–22 min.
5. Maintain the temperature at 121 ± 1° for 30 ± 1 min from the time when the holding temperature is reached.
6. Cool down to 100° at a rate of 0.5°/min, venting to prevent formation of a vacuum, within 40–44 min.
7. Do not open the autoclave until it has cooled to 95°.
8. Remove the hot samples from the autoclave using appropriate safety precautions and cool the samples cautiously down to room temperature within 30 min, avoiding thermal shock.

TITRATION

To each of the three flasks add 0.05 mL of *Methyl red solution*. Titrate the blank solution immediately with 0.02 M hydrochloric acid, then titrate the test solutions until the colour matches that obtained with the blank solution. Subtract the titration volume for the blank solution from that for the test solutions. Calculate the mean value of the results in mL of 0.02 M hydrochloric acid per g of the sample. Repeat the test if the highest and lowest observed values differ by more than the permissible range given in *Table.*

Table 2 Permissible Range for Values Obtained

Mean of the Values Obtained for the Consumption of Hydrochloric Acid Solution per gram of Glass Grains (mL/g)	Permissible Range of Values Obtained
NMT 0.10	25% of the mean
0.10-0.20	20% of the mean
NLT 0.20	10% of the mean

[*Note—Where necessary to obtain a sharp endpoint, decant the clear solution into a separate 250-mL flask. Rinse the grains by swirling with three 15-mL portions of carbon dioxide-free water and add the washings to the main solution. Add 0.05 mL of the Methyl red solution. Titrate, and calculate as before. In this case also add 45 mL of carbon dioxide-free Purified Water and 0.05 mL of Methyl red solution to the blank solution.]*

Table 3 Limits for Glass Grains Test*

Filling Volume (mL)	**Maximum Volume of 0.02 M HCl per g of Test Glass (mL)**	
	Type I	Type II and III
All	0.1	0.85

*The volume does not exceed the values indicated in the table

6.1.2 Surface Glass Test (USP 660): Hydrolytic Resistance of Interior surface of glass

containers can be measured using Surface glass Test should result in values corresponding to that of glass type for Maximum volume of 0.01M HCl per 100ml of test Solution for the given filling volumes as per values given in Table 4 as per method prescribed in IS 2303-Part II / USP 660

Determination of the filling volume: The filling volume is the volume of Purified Water to be added to the container for the purpose of the test. For Phials/vials, bottles, cartridges, and syringes, the filling volume is 90% of the brimfull capacity. For ampuls, it is the volume up to the height of the shoulder.

***Vials and bottles*:** Select six dry vials or bottles from the sample lot, or three if their capacity exceeds 100 mL, and remove any dirt or debris. Weigh the empty containers with an accuracy of 0.1 g. Place the containers on a horizontal surface and fill them with Purified Water to about the rim edge, avoiding overflow and the introduction of air bubbles. Adjust the liquid levels to the brimful line. Weigh the filled containers to obtain the mass of the water expressed to two decimal places, for containers having a nominal volume less than or equal to 30 mL, and expressed to one decimal place, for containers having a nominal volume greater than 30 mL. Calculate the mean value of the brimful capacity in mL and multiply it by 0.9. This volume, expressed to one decimal place, is the filling volume for the container lot. The determination is carried out on unused containers. The volumes of the test solution necessary for the final determination are shown in *Table 4*

Table 4 Volume of Test Solution and Number of Titrations

Filling Volume (mL)	Volume of Test Liquid for One Titration (mL)	Number of Titrations
NMT 3	25.0	1
3-30	50.0	2
30-100	100.0	2
NLT 100	100.0	3

Method

Cleaning: Remove any debris or dust. Shortly before the test, rinse each container carefully at least twice with Purified Water, refilled, and allow to stand. Immediately before testing, empty the containers; rinse once with Purified Water, then with carbon dioxide-free water; and allow to drain. Complete the cleaning procedure from the first rinsing within 20–30 min. Closed ampules may be warmed in a water bath or in an air oven at about 40° for approximately 2 min before opening to avoid container pressure when opening. Do not rinse before testing.

Filling and heating: The containers are filled with carbon dioxide-free water up to the filling volume. Containers in the form of cartridges or refillable syringes are closed in a suitable manner with material that does not interfere with the test. Each container, including ampuls, shall be loosely capped with an inert material such as a dish of neutral glass or aluminium foil previously rinsed with Purified Water. Place the containers on the tray of the autoclave. Place the tray in an autoclave containing a quantity of water such that the tray remains clear of the water. Close the autoclave, and

carry out autoclaving procedure steps 1–8 as described in the Glass Grains Test, except that the temperature is maintained at 121 ± 1° for 60 ± 1 min. If a water bath is used for cooling samples, take care that the water does not contact the loose foil caps to avoid contamination of the extraction solution. The extraction solutions are analysed by titration according to the method described below.

Titration: Carry out the titration within 1 h of the removal of the containers from the autoclave. Combine the liquids obtained from the containers, and mix. Introduce the prescribed volume (see Table 5) into a conical flask. Transfer the same volume of carbon dioxide-free water, to be used as a blank, into a second similar flask. Add to each flask 0.05 mL of Methyl red solution for each 25 mL of liquid. Titrate the blank with 0.01 M hydrochloric acid. Titrate the test solution with the same acid until the colour of the resulting solution is the same as that obtained for the blank. Subtract the value found for the blank titration from that found for the test solution and express the results in mL of 0.01 M hydrochloric acid per 100 mL of test solution. Express titration values of less than 1.0 mL to two decimal places; express titration values of greater than or equal to 1.0 mL to one decimal place.

Table 5 Limit Values for the Surface Glass Test

Filling Volume (mL)	**Maximum Volume of 0.01M HCl per 100mL of test Solution (mL)**	
	Type I and II	**Type III**
NMT 1	2.0	20.0
1-2	1.8	17.6
2-3	1.6	16.1
3-5	1.3	13.2
5-10	1.0	10.2
10-20	0.80	8.1
20-50	0.60	6.1
50-100	0.50	4.8
100-200	0.40	3.8
200-500	0.30	2.9
NLT -500	0.20	2.2

6.1.3 Surface Etching Test (USP-660): The Surface Etching Test is used in addition to the Surface Glass Test when it is necessary to determine whether a container has been surface treated and/or to distinguish between Type I and Type II glass containers. Alternatively, the Glass Grains Test and Surface Glass Test may be used. The Surface Etching Test may be carried out either on unused samples or on samples used in the Surface Glass Test.

(Note: Type II glass containers are suitable for most acidic and neutral aqueous products for parenteral and non-parenteral uses. Type II glass containers may be used for alkaline products where stability data demonstrate their suitability)

Test Method

Vials and bottles: The volumes of test solution required are shown in Table 3. Rinse the containers twice with Purified Water, fill to the brimful point with a mixture of one volume of hydrofluoric acid and nine volumes of hydrochloric acid, and allow to stand for 10 min. Empty the containers, and rinse carefully five times with Purified Water. Immediately before the test, rinse once again with Purified Water. Submit these containers to the same autoclaving and determination procedure as described in the Surface Glass Test. If the results are considerably higher than those obtained from the original surfaces (by a factor of about 5–10), the samples have been surface treated.

[Note: Distinction between type I and type II glass containers: The results obtained from the Surface Etching Test are compared to those obtained from the Surface Glass Test. For Type-I glass containers; the values obtained are close to those found in the Surface Glass Test. For Type II glass containers, the values obtained greatly exceed those found in the Surface Glass Test; and they are similar to, but not greater than, those obtained for Type III glass containers of the same filling volume.]

6.2 Functionality Test:

Spectral transmission for Colored Glass container (Amber colored): **Spectral Transmission** for colored glass containers for products for non-parenteral use should not exceed 10% at any wavelength in range of 290-450 nm using UV-Vis spectrophotometer as prescribed in Annexure A. This is independent of the type and capacity of the glass container.

6.3 Thermal Shock Test: The bottles shall pass the test when tested by Method A (range) prescribed in IS 6506:1972, with the temperature difference range (t1 - t2) of 45°C. The sample shall be taken to have satisfied the requirements of the test if the bottles show no visible crack after the test.

6.4 Leaching: Leaching of extractable elements lead and cadmium shall be tested as per IS 9806:2001.

6.5 Weathering (Optional Test): This can be observed by methods prescribed in USP 1660: Evaluation of the Inner Surface Durability of Glass Containers using formulations and conditions used to accelerate delamination.

Evaluation of Inner Surface Durability of Glass Container: To evaluate the potential of a drug product to cause the formation of glass particles and delamination.

Repeated hydration and dehydration of the layer leads to the cracking of the gel layer and eventual generation of particles. This process is worsened as the gel layer increases in thickness. This phenomenon is well known in glass exposed to ambient moisture (known as weathering). At higher pH values, the mechanism of glass degradation changes from the leaching of alkali elements to the dissolution of the silicate network

If the purpose of the glass screening is to determine the suitability of a given glass container for a specific product, the testing proposed in USP 1660 is insufficient. The exposure conditions are too harsh and do not provide a direct link to the product itself. In these instances, accelerated conditions are still relevant, but they must link to the relevant conditions for the given product. For example, if a product will be stored at 5° and accelerated conditions are 30°, then testing should occur at 30°. Many products or formulations cannot withstand the elevated temperatures. Because lower temperatures are required for actual product testing, the duration of testing must be longer, ranging from weeks to months. A larger number of vials also is appropriate for this scenario because the goal of the testing is to ensure the results are representative of the quality of glass that will be used in the drug product.

Analytical Methods for Screening Studies

Parameter	Test Parameter	Analytical Method
Glass Surface	- Degree of surface pitting - Chemical composition as a function of depth	- DIC Microscopy[a] or EM[b] - SIMS[c]
Extracted elements in solution	- Conductivity/pH - Individual or total extractables • SiO_2 concentration • SiO_2 /B_2O_3 or Si/Al ratio	- Conductivity/pH meter - IC-MS[d] or ICP-OES[e]
Visible and sub visible glass particles	- Particle number and size - Particle morphology and composition	- Particle size analyzer - SEM-EDX[f]

[a]Differential interference contrast microscopy.
[b]Electron microscopy.
[c]Secondary ion mass spectroscopy.
[d]Inductively couples plasma-mass spectrometry.
[e]Inductively couples plasma-optical emission spectrometry.
[f]Scanning electron microscopy-energy-dispersive X-ray spectroscopy.

7. CLOSURES

7.1 Closures for Phials/Bottles shall be provided with suitable inert plastics material (refer to plastic container IS). Closures shall form a liquid-tight seal with the threaded bottle neck.

7.2. For metal closures used in glass bottles refer to IS 8932:1978 (Specification For Preformed Metal Screw Caps For Glass Containers)

8. SAMPLING

8.1 Sampling shall be done as per method prescribed in IS 4905:2015, Methods for Random Sampling.

9. PACKING AND MARKING

9.1 The containers shall be packed as agreed to between the purchaser and the supplier.

9.2 The container shall be packed by using Thermoform or Automatic packaging machine after sterilized in sterilization plant using Ethylene oxide or Gamma radiations (wherever required).

9.3 Each container, except in case of very small size, shall be permanently and legibly marked on its bottom with the manufacturer's name or registered trademark, if any.

BIS Certification Marking: The product may also be marked with Standard Mark.

The use of the Standard Mark is governed by the provisions of the Bureau of Indian Standards Act, 1986 and the Rules and Regulations made thereunder. The details of conditions under which the license for the use of Standard Mark may be granted to manufacturers or producers may be obtained from the Bureau of Indian Standards.

Annexure A

(Clause 6.2)

A.1. Apparatus:

A.1.1. A UV-Vis spectrophotometer is required. It should be equipped with either a photodiode detector or a photomultiplier tube coupled with an integrating sphere.

A.1.2. Circular saw fitted with a wet abrasive wheel to shape the glass

A.1.3. Opaque paper or tape if required

A.1.4. Lens tissue to clean the glass

A.1.5. Mounting Wax

A.2. Preparation:

A.2.1. Break and cut the glass using Circular Saw and select sections that qualify to represent the correct thickness. Trim these selections to become suitable for mounting.

A.2.2. Wash and dry the specimens and wipe with lens tissue.

A.2.3. Mount the specimen in holder using wax, take the aid of opaque paper or tape if the specimen may be too small for the slit.

A.3. Method:

A.3.1. Mount the specimen such that its cylindrical axis is parallel to the slit and the light beam falls perpendicularly to the surface of the section to keep losses to reflection at minimum.

A.3.2. Measure the transmission of the specimen with reference to air in the spectral region of 290–450 nm, continuously or at intervals of 20 nm.

A.4. Results:

Observed spectral transmission for colored glass containers for products intended for non-parenteral use do not exceed 10% at any wavelength in the range of 290–450 nm, irrespective of the type and capacity of the glass container.