QUALITY CONTROL OF CONTAINERS

A container for a pharmacopoeia article is intended to contain a drug substance or drug product with which it is, or may be in direct contact. The closure is a part of the container. Containers must be chosen with care and after taking into consideration the nature of the articles and the likely effects of transportation and storage, even for short periods of time. A container should be designed so that the contents may be removed in a manner suitable for the intended use of the article in it. It should also provide an adequate degree of protection, minimize the loss of constituents and should not interact physically or chemically with the contents in a way that will alter their quality to an extent beyond the limits given in the individual monograph, or present a risk of toxicity.

GLASS CONTAINERS

Glass containers may be colorless or colored. Neutral glass is a borosilicate glass containing significant amounts of boric oxide, aluminum oxide, alkali and/or alkaline earth oxides. It has a high hydrolytic resistance and a high thermal shock resistance. Soda-lime-silica glass is a silica glass containing alkali metal oxides, mainly sodium oxide and alkaline earth oxides, mainly calcium oxide. It has only a moderate hydrolytic resistance.

According to their hydrolytic resistance, glass containers are classified as:

Type I (Borosilicate) glass containers which are of neutral glass, with a high hydrolytic resistance, suitable for most preparations whether or not for parenteral use.

Type II (Treated soda lime) glass containers which are usually of soda-lime-silica glass with high hydrolytic resistance resulting from suitable treatment of the surface. They are suitable for most acidic and neutral, aqueous preparations whether or not for parenteral use.

Type III (Soda lime) glass containers which are usually of soda- lime-silica glass with only moderate hydrolytic resistance. They are generally suitable for non-aqueous preparations for parenteral use, for powders for parenteral use (except for freeze-dried preparations). Glass containers intended for parenteral preparations may be ampoules, vials or bottles.

Type IV (General purpose soda lime) Containers for parenteral preparations are made from uncolored glass except that colored glass may be used for substances known to be light - sensitive; in such cases, the containers should be sufficiently transparent to permit visual inspection of the contents. Glass is a common material to be used in either no sterile or sterile liquid dosage forms. It leaches alkali from its surface. Leaching of alkali can be reduced but cannot be

zero. Hence, a limit test for alkalinity is to be performed before using it for a particular product.

EVAUATION PARAMETERS: -

(A) Crushed – glass test:

This test is official in USP. The container is crushed and sieved to produce uniform particles of which a definite weight of taken. The control of the particle size and weight of powder ensures that a constant surface area is exposed to the solution. Because all of the glass (not just the surface layer) is examined and extraction is enhanced by the rough surfaces of the particles, this is a severe test, and, if a glass passes, it is unlikely that containers made from it will give trouble while is use. Nevertheless, the technique is tedious and is not applicable to surface treated containers (sulphured or siliconed) because crushing would expose the alkaline glass below the surface. This test can be used for determining the nature of a glass or for distinguish between two types of glasses, such as neutral or surface – treated.

(B) Whole-Container test:

This test is official in European, British and International Pharmacopoeias. it is used in the USP for treated soda-lime containers only. The containers are simply filled with the test solution and exposed to the test conditions. Glassware may pass the whole container test more easily because the surface layer of a container is smooth and less reactive. In this test, surface area does not increase as much as volume with the increase in container size, consequently, the small sized containers are more attacked by the leaching of the alkali from the surface. Container Surface area which supplies alkali to each milliliter of the solution. Ampoule (1 ml.) 5.9 cm2 Ampoule (10 ml.) 2.9 cm2 Bottle (1000 ml) 0.5 cm2

(C)Powdered Glass Test:

From the glass containers, alkaline constituents (oxides of sodium, potassium, calcium, aluminum, etc.) are leached into purified water under conditions of elevated temperatures. When the glass is powdered the leaching of alkali can be enhanced in the powdered is critical. The principle involved in the powdered glass test in estimate the amount of alkali leached form the glass powder. The amount of acid that is necessary to neutralize the released alkali (a specified limit) is specified in the pharmacopoeia. The basic analysis is acid-base titration using methyl red indicator.

(D)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. 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. Since the inner surface is under test entire container (ampoule) has to be used. 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.

(E) THERMAL SHOCK TEST:

Place the samples in upright position in a tray. Immense the tray into a hot water for a few time & transfers to cold water bath, temp. of both is closely controlled. Examine cracks or breaks before and after the test. The amount of thermal shock a bottle can withstand depends on its size, design and glass distribution. Small bottles withstand a temp. differential of 60 to 80°C. A typical test uses 45°C temp. difference between hot and cold water.

(F) INTERNAL BURSTING PRESSURE TEST:

The most common instrument used is American glass research increment pressure tester. The test bottle is filled with water and placed inside the test chamber. A scaling head is applied and internal pressure automatically raised by a series of increment each of which is held for a set of time. The bottle can be checked to a preselected pressure level and the test continues until the container finally bursts.

(G) LEAKAGE TEST:

Drug fill container is placed in a container filled with colored solution (due to the addition of dye) Which is at high pressure compared to the pressure inside the glass container so that the colored solution enters the container. If any cracks or any breakage is present, leakage is there.

PLASTIC CONTAINERS:

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. The containers consist of one or more polymers together with certain additives if necessary. They should be manufactured from materials that do not include in their composition any substances that can be extracted by any contents in such quantities so as to alter the efficacy or stability of the product or to present a toxic hazard. Additives may consist of antioxidants, lubricants, plasticizers and impact modifiers but not antistatic agents and mold- release agents.

Drug Plastic Consideration:

1. Permeation:

The transmission of gases, vapors or liquid through plastic packaging materials can have an adverse effect on self-life of drug. Permeation of water vapor and oxygen through the plastic wall into the drug can present a problem if the dosage form is sensitive to hydrolysis and oxidation. Temperature and humidity are important factors influencing the permeability of oxygen and water through plastic. An increase in the temperature increases the permeability of gas.

2. Leaching:

Since most plastic containers have one or more ingredients added in small quantities to stabilize a specific to the plastic the prospect of leaching or migration from the container to the product is present. Problems may arise with plastics when coloring agents in relatively small quantities are added to the formula. Release of a constituent from the plastic container to the drug product may lead to drug contamination and necessitate removal of the product from the market.

3. Sorption:

It may be defined as bonding of a solute to a plastic. This process involves the removal of constituents from the drug product by the packaging material. Sorption may lead to serious problem for drug preparation in which important ingredients are in solution. Since drug substances of high potency are administered in small doses, losses due to sorption may significantly affects therapeutic efficacy of the preparation.

4. Chemical Reactivity:

Certain ingredients that are used in plastic formulations may react chemically with one or more components of a drug product. At times ingredients in the formulation may react with the plastic. Even micro quantities of chemically incompatible substance can alter the appearance of the plastic or the drug product.

TESTS ON PLASTIC CONTAINER:

1. Leakage test: Fill ten containers with water. Fit with intended closures and keep them inverted at room temperature for 24 hours. There are no signs of leakage from any container.

2. Collapsibility Test: This test applicable to containers. Which are to be squeezed in order to remove the contents. A container by collapsing inwards

during use yields at least 90% of its nominal contents at the required rate of flow at ambient temperature.

3. Clarity of aqueous extract: Select unlabeled, unmarked and non-laminated portions from suitable containers, taken at random sufficient to yield a total area of sample required taking into account the surface area of both sides. Cut these portions into strips none of which has a total area of more than 20 cm^2. Wash the strips free from extraneous matter by shaking them with at least two separate portions of distilled water for about 30 seconds in each case, then draining off the water thoroughly.

4. Transparency test: Fill five empty containers to their nominal capacity with diluted suspension as described in IP 1966. The cloudiness of the diluted suspension in each container is detectable when viewed through the containers as compared with a container of the same type filled with water.

5. Water vapor permeability test: Fill five containers with nominal volume of water and heat seal the bottles with an aluminum foil-poly ethylene laminate or other suitable seal. Weigh accurately each container and allow to stand (without any overwrap) for 14 days at a relative humidity of 60±5% and a temperature between 20 and 25°C. Reweigh the containers. The loss in weight in each container is not more than 0.2%.

QUALITY CONTROL OF CLOSURES

The closure is normally the most vulnerable and critical component of a container as far as stability and compatibility with the product is concerned. Suitable closing of the container is necessary because

1. It prevents loss of material by spilling or volatilization.

2. It prevents the deterioration of product from the effects of environment such as moisture, oxygen, or carbon dioxide.

3. It avoids contamination of the product from dirt, microorganism or insects.

Types of closures: - Thread screw cap, Lug cap, Crown cap, Pilfer proof closures, etc.

Materials used for making closures: - Cork, Glass, Plastic, Metal, rubber.

TEST FOR CLOSURES: -

1. Penetrability: This is measured to check the force required to make a hypodermic needle penetrate easily through the closure. It is measured by using the piercing machine. The piercing force must not exceed a stated value. If it

exceeds that stated value, the hypodermic needle can be damaged as a result of undesirable hardness of the closures.

2. Fragmentation test: This test is performed on 20 closures. Each closure is penetrated with hypodermic needle in a piercing machine five times within a limited area and needle is washed to transfer any fragment present. The contents are filtered through colored paper that contrasts with the rubber and the fragments counted. On an average there should not be more than three fragments per unit.

3. Self sealability test: Applicable to multi dose containers fill 10 vials with water close them with prepared closures and secure with a cap. For each closure use a new hypodermic needle and pierce 10 times each time at different site immerse the vials upright in methylene blue (0.1%) solution and reduce external pressure for 10 minutes. 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 colored solution.

4.Extractive test: In this test, the closure is boiled with water for four hours under reflux and the water evaporated to dryness. The residue must not exceed the specified amount.

5. Compatibility test: This test is performed to check the compatibility of the rubber closures with various types of the substances, since it is necessary to ensure that there is no interaction between the contents of the bottle and the closure.

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 thiosulphate 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 105ºC.Then weigh the residue NMT 4mg.

QUALITY CONTROL TEST FOR SECONDARY PACKAGING MATERIALS:

Packaging is a process by which the pharmaceuticals are suitably packed so that they should retain their therapeutic effectiveness from the time of packaging till they are consumed. Packaging may be defined as the art and science which involves preparing articles for transport, storage display and use.
Pharmaceutical packaging is the means of providing protection, presentation, Identification, Information and convenience to encourage compliance with a course of therapy.

Primary Packaging: Primary packaging is the material that first envelops the product and holds it. This usually is the smallest unit of distribution or use and is the package which is in direct contact with the contents.
Secondary packaging: Secondary packaging is outside the primary packaging - used to group primary packages together.
Tertiary packaging: Tertiary packaging is used for bulk handling, warehouse storage and transport. Most common form is palletized unit load that packs tightly in to containers.

Secondary packaging designates the packaging used to group various pre-packaged products together. As secondary packaging is not in direct contact with the actual product, its use and application usually differ distinctly from those of primary packaging, although the purpose of both types may at times converge.

PAPER, PAPERBOARD, AND CARDBOARD

The most common applications of paper, paperboard, and cardboard are in blister lidding stock and in over-the-counter (OTC) outer packaging. Because paper, paperboard, and cardboard offer virtually no moisture or gas barrier, they are typically part of the secondary pharmaceutical container. To provide additional protection, paper can be laminated or coated with a variety of materials. More commonly, when paper is involved in critical packaging functions, it is the only one component of a multicomponent system that offers optimal environmental protection to the drug environment. Although paper does not offer high shear strength, its relatively high tensile strength makes it an easy barrier to overcome if one intends to do so, but is an exceedingly confounding one for a child. Paper also simplifies printing on the blister itself. Other uses of paper, paperboard, and cardboard are as secondary packaging or for shipping packaging (e.g., corrugated cardboard).

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

$$\text{Grammage} = 104 \times w/a \times b$$

Where, 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- 1000℃ for 1 hr. Cool to 40-45℃, 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.

$$\% \text{ moisture} = 100(A-B) / B$$

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 8000℃ until all the carbonaceous matter are burnt off. Cool in desiccator, weigh and repeat the experiment to a constant weight (D).

$$\% \text{ Ash} = 100 (C-D)/ D$$

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). \

$$\% \text{ Alkalinity} = 1250 (B-A) \times N/ V \times w$$

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/m2.

Folding endurance: Fold the test piece back and forth until rupture occurs.

Tensile strength: The maximum tensile force per unit width that a paper or board will withstand before breaking. This can be done with an instrument that

pulls the paper apart when force is applied and the amount of force applied is calculated.

Tear strength: The mean force required to continue the tearing of an initial cut in a single sheet of paper

Burst strength: The maximum uniformly distributed pressure, applied at a right angle to surface that a test piece of paper & board will stand under condition of test.

Density: Density is measured for rigid cellular materials.
Density= Mass/ Volume.

Puncture resistance: Energy required to make initial puncture is measured.

Rub resistance: Resistance of printed test piece to withstand rubbing against another similar test piece.

Roughness or smoothness: Important for printability of paper. The printed ink should hold still in the paper after doing rub test.

Ink absorbency: Determination of ink absorbency by K & N ink. The ink should be blotted in test piece and the amount that got absorbed should be calculated.

QUALITY CONTROL TESTS FOR CARTONS

1. Compression: Used to assess the strength of erected package there by estimating the degree of protection that it confers on the contents. This is useful for products with no inherent strength in one plane or another.

2. Carton opening force: The carton should spring open in to its original shape without a need for unreasonable force. If the carton does not spring open or buckles in on itself, it may cause problems on cartooning machine.

3. Coefficient of friction: Both static and kinetic coefficients of friction are determined by sliding the specimen over itself under specific test conditions.

4. Crease Stiffness: This involves testing a carton board piece & folding it through 900 . It will then try to recover its position when bending force is removed.

5. Joint Shear Strength: This is a method of testing glued lap seam on the side of a carton for strength of the adhesive using a tensile testing machine.