5. PACKAGING MATERIAL AND DRUG CONTAINERS

Packaging materials are materials which are used to protect from external influences, store and transport. Drug containers are protective and conservator materials which are contained in the pharmaceutical form for pharmaceutical use and some of which are in direct contact with it.

Glass, metal, plastic, cellulose based materials and various synthetic materials are used in the production of packaging materials and drug containers. Drug containers consist of main body and parts in various structures such as bottle, blister, box, tube, jar, bag, lid, valve, stopper, paper.

In the choice of packaging materials and drug containers, selection is made for properties of convenience, ease of processing and production, volume and weight, cost, ease of supply and the structure and form of the medicine are taking into consideration.

The drug container should be release its drug content and should be produced to maintain the product's nature at various degrees of protection and drug loss in its content, depending on the extent of its deterioration and its destruction. Drug containers must not interact with the drug in any way physically, chemically or biologically in order to change the quality beyond the specified limits.

Drug containers and packing material are labeled as main container (bottle, blister, jar, tube, etc.) that is in direct contact with the drug, a protective outer container (such as cardboard box or wrapping paper) in which the main container is placed, (Large cardboard boxes, wooden chests, etc.).

Drug containers are classified according to the forms of use and the nature of the medicament contained therein as follows:

- Single dose containers: A single dose container holds the drug for use in whole or in part in a single administration. The remaining medicine is not taken from this container again.
- Multi-dose containers: A multi-dose container contains two or more doses of the drug.
- Well-sealed containers: A well-closed container normally protects the drug is inside from contamination of solid or liquid that may come from outside or from the loss of its substance during storage and transport.
- Tightly closed containers: Normally, they will not penetrate from the inside or outside during storage and transport of solids, liquids and gases. If the container is designed to open more than once, it should be designed to maintain air tightness when it is closed again.
- Hermetically sealed containers: These vessels are very tightly closed by fusion of the material forming the vessel.
- Non-tampering containers: These are vessels that have a cover that shows it is open or can not closed again.
- Protective containers for children: They are covered with a lid to prevent them from being opened by children.

5.1 CONTROLS OF RUBBER STOPPER

Rubber stoppers are elastic, translucent or opaque and it does not have a specific color as it changes depending on the additives used. They are almost insoluble in tetrahydrofurane, but may swell up to a significant amount. They are homogeneous, They do not contain prominent foreign materials (eg, fibers, foreign particles, residual rubber particles).

Rubber stoppers used in containers containing liquid preparations for parenteral use are made from the material obtained by vulcanization (crosslinking) of macromolecular organic substances (elastomers) using suitable additives. These properties also apply to lyophilized products and plugs used in powdered containers. These features do not apply to stoppers made of silicone elastomer, multilayer stoppers and lacquered stoppers. Elastomers are produced from natural or synthetic materials by polymerization, polycondensation and polyaddition. The nature of the essential components and additives (e.g. vulcanizers, accelerators, stabilizers, pigments) depends on the desired properties of the finished product.

Rubber stoppers can be classified into two types:

- Type I stoppers provide the desired properties at the highest level and are generally preferred.
- Type II stoppers have the necessary mechanical properties for special uses (such as many punctures) and due to their chemical composition they can not meet the rigid requirements as the first class stoppers.

5.1.1. Physical Controls (TS 5540)

1. Size examination

Dimensions of the stoppers less than 0.5 cm are measured at a sensitivity of 0.01 mm; greater than 0.5 cm are measured at a sensitivity of 0.1 mm.

2. Appearance and construction

There should be no burrs, cuts, holes, other defects and foreign materials on the plugs which can not be removed by washing as dusting, fiber, nodule, roughness, paint stains, oil and the color of the plugs should be homogeneous. The place where the needle will enter the top surface of the stoppers with inlet channels should be obvious. Coated type stoppers must be covered at least the surfaces of the plug that enter the bottle and in contact with the bottle.

3. Extraction solution is prepared so that some physical controls such as hardness test, resistance to sterilization and particle delivery test can be done.

The specimens for physical experiments are washed twice with water at a temperature of about 60 ° C, placed in a suitable beaker and kept at 121 ° C for 30 minutes in autoclave. It is then dried at 60 ° C for up to 60 minutes.

a) Hardness Test (TS 1324)

b) Sterilization Resistance

The samples to be analyzed are kept in the autoclave for 30 minutes at a temperature of 121±1 ^{o}C. After removal from the autoclave, no further defects such as adhesion, deformity, softening, spongeing or other defects that effective on the stopper’s usage shall occur and also there should be no change in its physical properties.

c) Fragmentation Control of Stopper (TS4397)

5.1.2. Physicochemical Controls

The extraction solution is prepared to make the experiments. The specimens for experiments are washed twice with water at a temperature of about 60 ° C. It is dried at 60 ^{o}C for maximum 60 minutes and 200 ml freshly treated water is used for 100±5 cm^2 stopper surface and the mouth is covered with beaker and kept at 121±1 ^{o}C for 30 minutes in autoclave. At the same conditions, the blind extraction solution is prepared as the comparison solution.

1. Appearance (TS 5540)

The blur of the extraction solution should be less than the blur of the comparison solution. The solution should be odorless and colorless.

2. pH (TS 5540)

1 ml of potassium chloride solution (0.1% w / v) are added to 20 ml of extraction solution and 20 ml of blank solution. The pH of the solutions is immediately measured and the difference between them should be less than 0.5.

3. Absorbance (EP 5)

4. Nonvaporized residue (EP 5)

5.1.3. Chemical Controls (EP 5)

The extraction solution is prepared to make the experiments. The specimens for experiments are washed twice with water at a temperature of about 60 ° C. It is dried at 60 ^{o}C for maximum 60 minutes and 200 ml freshly treated water is used for 100±5 cm^2 stopper surface and the mouth is covered with beaker and kept at 121±1 ^{o}C for 30 minutes in autoclave. At the same conditions, the blind extraction solution is prepared as the comparison solution.

1. Acidity and alkalinity

Add 0.1 ml of bromothymol blue to 20 ml of extraction solution. When 0.3 ml of 0.01 M sodium hydroxide is added to this solution mixture, blue color should not occur or when adding than 0.01 M 0.8 ml hydrochloric acid yellow color should not occur.

2. Reducing agent

To a 20 ml extraction and comparison solution, add 1 ml of dilute sulfuric acid solution than add 20 ml of 0.002 M potassium permanganate solution. These solutions are boiled for 3 minutes and cooled. 1 g of potassium iodide is then added to these solutions and titrated to a light brown with 0.01 M sodium thiosulfate solution. After 0.25 ml of 1% starch solution is added as an indicator, titration is continued until the color is gone. Two experimental differences are calculated. For Type I rubber plugs, this difference should not be more than 3 ml and for Type II rubber plugs not more than 7 ml.

3. Extractable heavy metals

4. Ammonium

5. Volatile Sulphides

6. Extractable zinc

7. Self-shutdown test

8. Permeability test

9. Disintegration test (EP 5)

5.1.4. Biological Controls (TS 4397)

1. Toxicity

2. Pyrogenity

3. Hemolytic effect

5.1.5. Identification of properties related to temperature (TS 5540 ve TS 1324)

1. Cooling resistance

2. Resistance to heat

5.2. CONTROLS OF GLASS CONTAINER

Glass containers for pharmaceutical use are glass materials intended to come into direct contact with pharmaceutical products.

Transparent glass is permeable to visible light. Colored glass is obtained by adding small amounts of metal oxides to provide the desired spectral absorption. Neutral glass is borosilicate glass containing significant amounts of boroxides, aluminum or alkaline earth oxides. Because of its neutral glass structure, it has high thermal resistance and very high hydrolytic resistance. Soda-lime-silicium glass is silicium glass that contains alkali metal oxides, sodium oxide and alkaline earth oxides, mainly calcium oxide. The soda-lime-silicon glass has only moderate hydrolytic resistance due to its structure.

The chemical stability of glass containers for pharmaceutical use is indicated by its hydrolytic resistance.

This property is the resistance to the release of substances which contact with inside surface of the container or the substances that pass from the dusted glass to water and to solved. Hydrolytic resistance is assessed by titration of alkalinity.

Glass containers are classified according to their hydrolytic resistance as follows (EP 5):

● Type I glass containers; they are made of neutral glass, they have high hydrolytic resistance due to the chemical structure of the glass used.

● Type II glass containers; they are usually made of soda-lime-silicon glass and have a high hydrolytic resistance as a result of a chemical treatment applied to their surface.

● Type III glass containers; They are usually made of soda-lime-silicon glass and have moderate hydrolytic resistance.

Glass container types which can be used for different pharmaceutical preparations are determined according to the following conditions in the general context. A manufacturer of a pharmaceutical product is responsible for selecting the appropriate container.

● Type I glass containers; whether it is for parenteral purposes or not, it is suitable for all preparations.

● Type II glass containers; whether for parenteral purposes or not, generally suitable for acidic and neutral aqueous preparations.

● Type III glass containers; are suitable for non-aqueous preparations for parenteral administration, parenterally-used powder preparations (except freze-dried preparations) and non-parenteral preparations.

Glass containers with higher hydrolytic resistance than those suggested above may be used for the particular type of preparation.

Colorless or colorless glass containers can be used for non-parenteral preparations. Preparations for parenteral use should be in a colorless glass container. However, colored glass containers can be used for preparations containing substances known to be sensitive to light. It is recommended that glass containers that use for all liquids and powders for parenteral use should be allowed to control the contents. Glass containers for pharmaceutical preparations, except Type I glass containers, shall not be reused. Also, containers for human blood and blood products should not be reused.

5.2.1. Physical Controls (TS 4865)

1. Visual inspection

2. Tolerance of cylindrical parts

3. Height tolerance

4. Curvature control

5. Filling volume

5.2.2. Hydrolytic Resistance Test (EP 5)

A. Test for hydrolytic resistance in powdered glass

10 g of the specimens prepared by powdering as described in EP 5 are transferred into a erlenmeyer and washed with 30 ml of acetone. It is shaken and filtered to suspend the particles. The process is repeated several times. The glass particles are placed in a drying pan, dried at 140 ° C for 20 minutes to allow the acetone to fully evaporate, and allowed to cool.

10 g of dried glass powder, put on a erlenmeyer and add 50 ml of purified water and weigh. In the same way, a second erlenmeyer is filled with 50 ml of purified water to be used as a blank and weighed. Both erlenmeyer are sealed with neutral glassware that is washed with purified water or aluminum foil. It is ensured that the glass particles are uniformly spread on the base. Erlenmeyer is placed in the autoclave and autoclaved at 121 ° C for 30 minutes as specified in EP 5. After getting cool, the caps are opened, the erlenmeyers are carefully dried and brought to their initial weight by the addition of water.

Titration: 50 ml of liquid is added to Erlenmeyer. A blank solution is prepared with 50 ml of purified water in a similar erlenmeyer. Add 0.05 ml of methylene red solution to each well. Titrated with 0.02 M HCl. Titration of the test solution is performed until a color similar to that obtained in the blank solution is obtained. The value obtained from the test liquid is subtracted from the value obtained from the blank solution and the results are given in ml of 0.02 M HCl per gram of glass.

Limit values: The amount of 0.02 M HCl consumed for Type I glass containers should not exceed 1 ml. For Type II and Type III glass containers this should not exceed 8.5 ml.

B. Surface hydrolytic resistance test

The glass containers to be tested for the surface hydrolytic resistance test are cleaned and filled as specified in EP 5 and autoclaved under specified conditions. The samples are removed from the autoclave and cooled according to the pharmacopoeial warnings.

Titration is applied to the containers removed from the autoclave within one hour. The solutions obtained from the containers are combined and mixed. Pre-specified volumes of liquid (Table 5.1) are placed in a erlenmeyer. A purified water of the same amount is put into a similar second erlenmeyer. 0.05 ml of methylene red solution per 25 ml are added to both erlenmeyers. The blank solution is titrated with 0.01 M hydrochloric acid. Titration of the test solution is performed until a color similar to that obtained in the blank solution is obtained. The value obtained from the test liquid is subtracted from the value obtained from the blank solution. The results are expressed in ml of 0.01 M hydrochloric acid at 100 ml. The results should comply with Table 5.2.

Table 5.1. Titration number and volume of test liquid.

Fill volume (ml)	Titration number	The volume of test fluid for a titration (ml)
Up to 3	1	25.0
Above 3 and up to 30	2	50.0
Above 30 and up to 100	2	100.0
Above 100	3	100.0

Table 5.2. Limit values in the test for surface hydrolytic resistance.

Fill volume (ml)	Volume of ml of 0.01 M HCl per 100 ml test fluid	
	Tip I ve II glass	Tip III glass
Up to 1	2.0	20.0
Above 1 and up to 2	1.8	17.6
Above 2 and up to 5	1.3	13.2
Above 5 and up to 10	1.0	10.2
Above 10 and up to 20	0.8	8.1
Above 20 and up to 50	0.6	6.1
Above 50 and up to 100	0.5	4.8
Above 100 and up to 200	0.4	3.8
Above 200 and up to 500	0.3	2.9
Above 500	0.2	2.2