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OVERVIEW ON QUALITY CONTROL TEST OF PRIMARY AND SECONDARY PACKAGING MATERIAL

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ABSTRACT

The quality is normally understood as an index or measurement. It is the degree of excellence, a degree of conformation to standard. It is also the distinctive inherent features, property and virtue. Quality Control or Quality evaluation is the operational techniques to fulfill the requirement of quality. Testing is considered to be as a tool for the quality evaluation through the measurement of different qualitative parameters with respect to physical, Chemical, mechanical and optical properties of packaging materials. Pharmaceutical package is an integral part of Pharmaceutical product. An ideal package protects the product from harmful effects of environmental gases, moisture, microbes etc. Primary package is in direct control with the product and secondary package is the package which surrounds the primary package. Containers are tested by many methods of which commonly used test for glass are Crushed glass test, Whole-Container test, Chemical resistance of test, Water Attack Test etc. Similarly test. Closure materials are tested by Transparency test Penetrability Fragmentation test Self seal ability test, Extractive test etc. The requirement of packaging material testing is set according to specification of regulatory agencies like WHO GMP, USFDA and ICH guidelines. [01,03,09]

KEY WORDS : *Blister package, Closures, Primary package, Glass, ,Secondary package*

1.INTRODUCTION

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 the 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. The commonly used packaging materials are Container, Closure, Carton or Outer and Box. The containers may be made of glass, plastic, matel or paper. The material for closure may include Cork, Glass, Plastic, Metal or rubber. pharmaceutical packaging is the means of providing protection, presentation, identification, information and convenience to encourage compliance with a course of therapy.

2. DEFINATION

2.1) Primary Packing Material

- Packaging that directly protects or houses the product is known as primary packaging.
- Primary packaging is the packaging that comes in direct contact with the product itself. A cereal box wouldn't be considered primary packaging, but the bag inside the box would, since it's the part that actually holds the contents of the box. The material which Comes in direct contact with the product..
- Primary packaging is the first layer of protection for your product. It's in direct contact with the product and designed to protect it from damage, tampering, or spillage.

Example :- Bottles, Vials, Ampoules, Tin, etc . [05,08]

2.1.1) Types of Primary Packaging

- Flexible Packaging
- Rigid Packaging
- Semi-rigid Packaging

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2.1.1.1) Flexible Packaging :- Flexible packaging uses materials like foil, cellophane, and paper. It's often used for food items like chips, candy, and personal care products like shampoo and conditioner. Flexible packaging is easy to mold around a material.

1. Pouches: Stand-up, flat-bottom, or spout pouches for liquids, powders, or solids.
2. Bags: Paper, plastic, or foil bags for snacks, coffee, or tea.
3. Sachets: Small, single-dose packets for pharmaceuticals, cosmetics, or food.
4. Wraps: Flexible wrapping materials (e.g., plastic, paper, or foil) for snacks or food.
5. Labels: Adhesive labels for product identification.

2.1.1.2) Rigid Packaging :- Rigid packaging uses more complex materials that keep their shape like glass, metal, and plastic. Rigid packaging can be used for products that need protection from impact or temperature changes, such as electronics, beverages, and pharmaceuticals.
1. Bottles: Glass or plastic containers for liquids, tablets, or capsules.
2. Jars: Glass containers for food, cosmetics, or pharmaceuticals.
3. Cans: Metal containers for food, beverages, or chemicals.
4. Tubs: Rigid plastic containers for food, cosmetics, or pharmaceuticals.
5. Vials: Glass containers for pharmaceuticals or laboratory samples. [07,09]

2.1.1.3) Semi-rigid Packaging :- Semi-rigid packaging is a hybrid of flexible and rigid packaging, and uses shape-holding materials like foam and cardboard. Semi-rigid packaging materials can easily be bent or molded, and are usually used for products that need some protection from impact like eggs or wine bottles.
1. Trays: Plastic or paper-based packaging for food, pharmaceuticals, or medical devices.
2. Blister Packs: Pre-formed plastic and foil packaging for tablets or capsules.
3. Clamshells: Hinged plastic packaging for food, cosmetics, or pharmaceuticals.
4. Foldable Containers: Paperboard or plastic containers for food, cosmetics, or pharmaceuticals.
5. Thermoformed Containers: Molded plastic packaging for food, pharmaceuticals, or medical devices. [12]

2.1.2) Functions of Primary Packaging

- Protection
- Presentation
- Branding
- Information

2.1.2.1) Protection :- Products need protection from the elements, tampering, and damage. Primary packaging keeps your product safe from when it leaves the factory until it reaches the customer.
1. Physical Protection: Prevents damage from shock, vibration, temperature, and humidity.
2. Chemical Protection: Shields contents from chemical reactions, contamination, or degradation.
3. Microbiological Protection: Prevents contamination from bacteria, viruses, or fungi.
4. Moisture Protection: Controls humidity levels to maintain product integrity

2.1.2.2) Presentation :- The way your product looks is important to customers. Primary packaging should be eye-catching and make your product look its best. Well-packaged products are more likely to sell than poorly-packaged ones.[13]

2.1.2.3) Branding :- Primary packaging is often the first thing customers see, meaning it's an excellent opportunity to make a good impression and build brand awareness. Your packaging should be consistent with your branding across all channels, from your website to your social media accounts.[15,17]

2.1.2.4) Information :- Products like food and pharmaceuticals need specific information on the packaging, such as nutrition facts or expiration dates. It's important that this information is legible and easy to find.

2.2) Secondary packing material

- Secondary packaging is generally used to group a certain amount of products together into a cohesive unit that's easy to identify. The SKU, or Stock Keeping Unit, makes it easy for vendors to identify the movement of stock as well as inventory. Secondary packaging makes it possible to group products so that they can be more easily tracked.
  Its design protects multiple products during shipping and storage, and can also be used for branding and marketing purposes. [20,25]
  Example :- Cardboard boxes,Plastic Containers,Shrink Wrap,etc

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2.2.1) Types of Secondary Packaging

- Wrapping
- Boxes
- Containers

2.2.1.1) Wrapping :- Wrapping is a type of secondary packaging that uses materials like paper, plastic, or fabric to enclose a product or group of products. These materials are commonly used for products that need protection from the elements, like food items or personal care products

2.2.1.2) Boxes :- Boxes are a type of packaging that uses materials like cardboard or paperboard to enclose a product or group of products. They're often used for products that need protection from impact, like electronics or glassware.[16,17]

2.2.1.3) Containers :- Containers are a type of packaging that uses materials like plastic or metal to enclose a product or group of products. They're normally used for products that need protection from the elements or tampering, like pharmaceuticals or cosmetics

2.2.2) Functions of Secondary Packaging

- Protection
- Stacking
- Branding

2.2.2.1) Protection :- Secondary packaging protects your products from damage during shipping and storage. It's often made from sturdy materials like cardboard or plastic that can withstand impact.Most secondary packaging contains multiple layers of protection to further protect your products. These layers of protection are most commonly created with foam or bubble wrap

1. Shock Absorption: Cushioning against impacts and vibrations
2. Moisture Protection: Barrier against humidity and water
3. Dust Protection: Prevention of contamination

2.2.2.2) Stacking :- Secondary packaging is often designed to stack on top of each other to improve efficiency during shipping and storage. The stacking feature is especially important for fragile products that need protection from the elements.[27]

1. Stability: Prevents shifting or toppling
2. Load Containment: Secures products during transport

2.2.2.3 Branding) :- Secondary packaging can be used for branding and marketing purposes as it's an opportunity to make a good impression and build brand awareness. Your packaging should be consistent with your branding across all channels. It can feature unique shapes or patterns to entice customers, though the primary purpose of secondary packaging is to hold mass quantities.

1. Visual Identity: Logo, colors, and design consistency
2. Product Differentiation: Distinct packaging for brand recognition
3. Marketing Messaging: Communication of product benefits
4. Brand Storytelling: Emotional connection with customers [25]

2.3) Characteristics of Packaging Material

1. It must be a non –toxic
2. It must be a FDA approved
3. It must be not reactive with the product
4. Material must be protect the preparation from environmental condition
5. It must be not impart to the odor or taste to the product

3. PRINCIPAL INSTRUMENTAL TECHNIQUES EMPLOYED FOR PACKAGING MATERIAL

i. Spectrophotometry
ii. Chromatographic Methods
iii. Thermal analysis techniques
iv. Gas transmission analysis
v. Leak detection
vi. Physical test methods
vii. X-ray Fluorescence Analysis

3.1) Spectrophotometry :

1. Spectrophotometry (UV-Vis, NIR, IR): Measures absorption, transmission, or reflection of light to identify molecular structures, contaminants, and material properties.

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2. Fourier Transform Infrared Spectroscopy (FTIR): Analyzes molecular vibrations for material identification, contamination detection, and chemical analysis.
3. Raman Spectroscopy: Detects molecular vibrations for material identification, contamination detection, and chemical analysis.

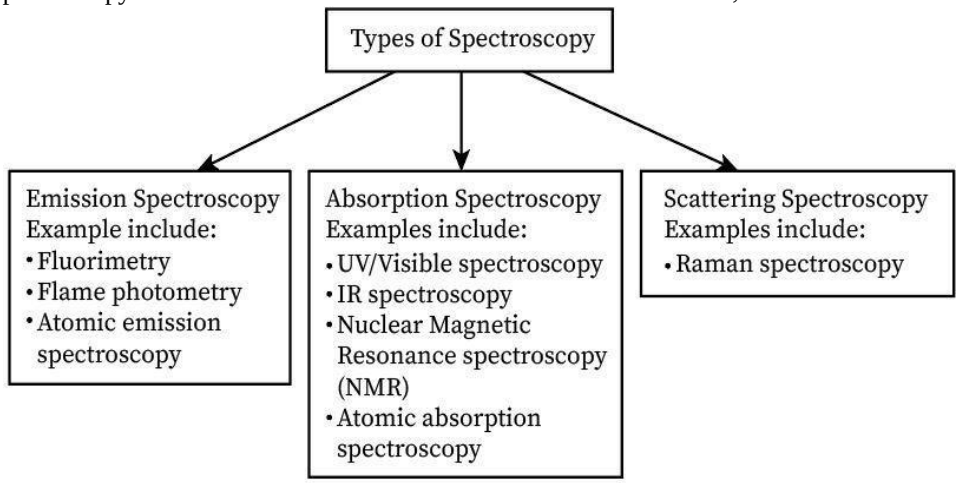


Fig.1 Types of spectroscopy

3.2) Chromatographic Methods

Chromatographic methods separate, identify, and quantify packaging material components. Here are common chromatographic techniques:

3.2.1) Liquid Chromatography (LC)

1. High-Performance Liquid Chromatography (HPLC): Analyzes complex mixtures, additives, and contaminants.
2. Ultra-High-Performance Liquid Chromatography (UHPLC): Provides faster separation and higher resolution.
3. Liquid Chromatography-Mass Spectrometry (LC-MS): Identifies and quantifies molecular structures

3.2.2) Gas Chromatography (GC)

1. Gas-Liquid Chromatography (GLC): Separates volatile compounds.
2. Gas-Solid Chromatography (GSC): Separates gases and volatile compounds.
3. Gas Chromatography-Mass Spectrometry (GC-MS): Identifies and quantifies molecular structures.

3.2.3) Other Chromatographic Techniques

1. Thin-Layer Chromatography (TLC): Separates and identifies compounds on a stationary phase.
2. Paper Chromatography: Separates and identifies compounds on paper.
3. Size-Exclusion Chromatography (SEC): Separates polymers based on molecular size.
4. Ion Chromatography (IC): Separates and identifies ions. [33,36]

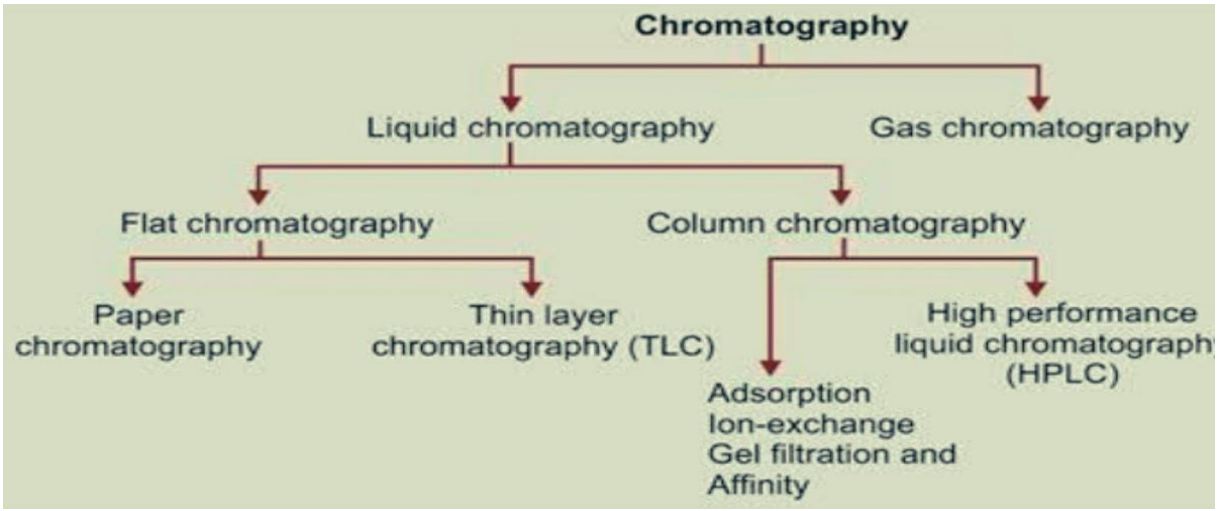


Fig.2 Classification of chromatography

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3.3) Thermal analysis techniques
Thermal analysis techniques analyze packaging materials' thermal properties, stability, and behavior. Here are common techniques:

3.3.1) Calorimetric Methods
1. Differential Scanning Calorimetry (DSC): Measures heat flow, melting points, and glass transition temperatures.
2. Differential Thermal Analysis (DTA): Measures temperature differences between samples and references.

3.3.2) Thermogravimetric Methods
1. Thermogravimetry (TG): Measures mass changes during heating or cooling.
2. Thermogravimetric Analysis (TGA): Measures mass loss, moisture content, and degradation.

3.3.3) Mechanical Methods
1. Dynamic Mechanical Analysis (DMA): Measures mechanical properties, stiffness, and damping.
2. Thermal Mechanical Analysis (TMA): Measures expansion, contraction, and softening.

3.3.4) Other Techniques
1. Thermal Conductivity Measurement: Measures heat transfer properties.
2. Heat Deflection Temperature (HDT): Measures temperature-induced deformation.
3. Vicat Softening Temperature: Measures temperature-induced softening.
4. Dielectric Analysis (DEA): Measures electrical properties.

3.4) Gas transmission analysis :
Gas transmission analysis measures the passage of gases (O2, CO2, N2, H2O) through packaging materials. Techniques:

3.4.1) Methods
1. Oxygen Transmission Rate (OTR): Measures oxygen permeability (ASTM D3985).
2. Carbon Dioxide Transmission Rate (CTR): Measures carbon dioxide permeability (ASTM D5826).
3. Water Vapor Transmission Rate (WVTR): Measures moisture permeability (ASTM F1249).
4. Nitrogen Transmission Rate (NTR): Measures nitrogen permeability.
5. Gas Permeability Testing: Measures gas flow through materials (ISO 2556).

3.5) Leak Detection
1. Vacuum Leak Detection: Detects leaks using vacuum pressure.
2. Pressure Decay Testing: Measures pressure changes.
3. Helium Leak Detection: Uses helium gas to detect leaks.
4. Hydrogen Leak Detection: Uses hydrogen gas to detect leaks.

3.6) Physical Test Methods
1. Tensile Strength Testing: Measures material strength (ASTM D882).
2. Flexural Testing: Measures flexibility (ASTM D790).
3. Impact Testing: Measures impact resistance (ASTM D1709).
4. Compression Testing: Measures compression strength (ASTM D695).
5. Thickness Testing: Measures material thickness (ASTM D374).
6. Density Testing: Measures material density (ASTM D1895).

3.7) X-ray Fluorescence Analysis (XRF) :
1. Elemental Analysis: Identifies elemental composition.
2. Material Identification: Verifies material authenticity.
3. Contamination Detection: Detects impurities.
4. Coating Thickness Measurement: Measures coating thickness. .[24,25]

4. QUALITY CONTROL OF PRIMARY PACKAGING MATERIAL

4.1) CONTAINERS

- A container for a pharmacopoeial 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.

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- 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.

4.1.1) Quality Control tests of Container

4.1.1.1) Airtight Container

These types of containers protect the container from environmental hazards. If these containers are intended to be opened on more than one occasions then they remains airtight after reclosure. These are also known as hermetic sealed containers.A container that is impermeable to solids, liquids and gases under ordinary conditions of handling, storage and transport. If the container is intended to be opened on more than once, it must be so designered that it mains airtight after re-closure.

4.1.1.2) Hermetically Sealed container :- A container that is impervious to air or any other gas under normal conditions of handling, shipment, storage and distribution, e.g. sealed glass ampoule, gas cylinder etc.

4.1.1.3) Light-resistant container :- A container that protects the contents from the effects of actinic light by virtue of the specific properties of the material of which it is made. These containers protect the contents from light (UV light). These are made up of the materials which do not allow the UV light to pass from them to contents. For e.g : Amber colored glass containers.

4.1.1.4) Single-Dose Container :- A container that holds a quantity of the preparation intended for total or partial use as a single administration. This type of container contain single dose of medicament example are: Glass ampoules,Vials etc.

Fig.3 Single Dose Container



Fig.4 Multi Dose Container



4.1.1.5) Sealed container :- A container closed by fusion of the material of the container.

4.1.1.6) Tamper-evident container :- A container fitted with a device or mechanism that reveals irreversibly whether the container has been opened.

4.1.1.7) Multidose container :- A container that holds a quantity of the preparation suitable for two or more doses. As the name indicates these type of containers holds more than single dose and their contents are withdrawn at various intervals e.g Vials etc.

4.1.1.8) Tightly-closed container :- A tightly-closed container protects the contents from contamination by extraneous liquids, solids or vapours, from loss or deterioration of the article from effervescence, deliquescence or evaporation under normal conditions of handling, shipment, storage and distribution. A tightly-closed container must be capable of being tightly re- closed after use.

4.1.1.9) Well-closed container :- These type of containers provide the protection from foreign particles and loss during transportation, sale etc. A well-closed container protects the contents from extraneous solids and liquids and from loss of the article under normal conditions of handling, shipment, storage and distribution.[39,40]

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4.1.2) Primary Package for solid dosage

4.2.2.1) Strip Package : In this the contents are sealed in a packet. The Package is made up of two layers of film. A strip containing many pockets and each pocket contains single dose of medicament..

4.2.2.2) Blister Package : It is made up of base layer (PVC layer) with cavities which contain Pharmaceutical product. This type of Package provides greater protection than strip package. The lid is made up of aluminium or paper foil. The package is sealed by combining lid and base with the application of heat and pressure.

Fig.5 Tablet Blister



4.1.3) Primary Package for semi solid dosage

Semi- Solid dosage forms include creams, pastes, ointments etc. the containers used for semi-solid dosage forms includes collapsible tubes etc. Plastic Containers are also very popular now a days. Another type of products are also available in market for e.g Pressurized products. For these types of products the package made up of stainless steel, aluminium etc. is used. The package used must be strong enough to withstand pressure built up in the container.



Fig.6 Semi Solid Dosage

4.2 GLASS CONTAINERS

Glass containers may be colourless or coloured. 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 glass containers which are of neutral glass, with a high hydrolytic resistance, suitable for most preparations whether or not for parenteral use,

– Type II 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,

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Fig.7 Glass Container

4.2.1) Quality Control Test For Glass Container

4.2.1.1) 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. 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.[44,45]



Fig.8 Crushed Glass Test

4.2.1.2) 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.

4.2.1.3) Chemical Resistance Of Glass Containers

USP and IP provide two tests to determine the chemical resistance of glass containers.

4.2.1.3.1) Powdered Glass Test : The principle involved in the powdered glass test estimate the amount of alkali leached from the powdered glass which usually happens at the elevated temperatures.



Fig.9 Powdered Glass Test

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.Procedure:-

Sample containers are rinsed with purified water and dried.

I

The containers are grinded in a mortar to a fine powder

and passed through sieve no. 20 and 50.

I

10gm of the sample is washed with acetone and dried.

I

50 ml of purified water is added to the dried sample and autoclaved

at 121°C for 30 min's and cooled and decanted.

I

The decanted liquid is titrated with 0.02 N H_2SO_4 using methyl red as indicator.

4.2.1.3.2) Water Attack Test : This test is used only with containers that have been exposed to sulphur dioxide fumes under controlled humidity conditions. 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.

Procedure :–

Rinse thoroughly with high purity water.

|

Fill each container to 90%of its overflow capacity with water and is autoclaved at 121^0C for 30min

|

cooled and the liquid is decanted which is titrated with 0.02N

sulphuric acid using methyl red as an indicator.

|

The volume of sulfuric acid consumed is the measure of the

amount of alkaline oxides present in the glass containers.

4.2.1.3.3) Hydrolytic Resistance Of Glass Containers:- The hydrolytic stability of glass containers for pharmaceutical use is expressed by the resistance to the release of soluble mineral substances into water under the prescribed conditions of contact between the inner surface of the container or glass grains and water.

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Procedure:–

Rinse each container at least 3 times with CO2 free water

and fill with the same to their filling volume.

|

Fill & Cover the vials and bottles and keep in autoclave.

|

Heat to 100^0C for 10min and allow the steam to issue from the Vent cork Rise the temp from 100^0C to 121^0C over 20min.

|

Maintain the temp at 121^0C to 122^0C for 60min. Lower the temp from 121^0C to 100^0C over 40min 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.

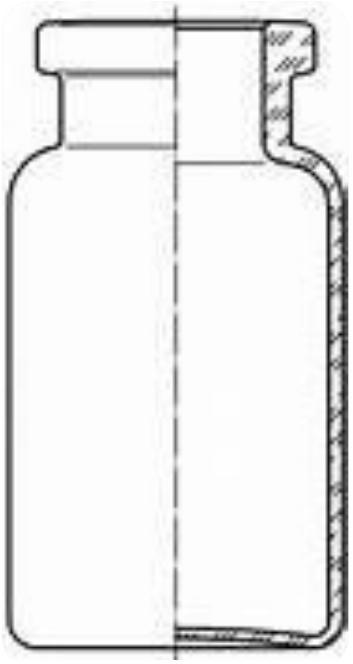


Fig.10 Hydrolytic Resistance Tets

4.2.1.3.4) Arsenic Test :

This test is for glass containers intended for aqueous parenterals. This procedure is designed to determine the presence of trace amounts of arsenic (As) by converting the arsenic in a substance under test to arsine, which is then passed through a solution of silver diethyldithiocarbamate to form a red complex.

Procedure

Wash the inner and outer surface of container with fresh distilled water for 5min.

|

Prepare test for hydrolytic resistance for an adequate no. of samples to produce 50ml.

|

Pipette out 10ml soluteion from combined contents of all ampoules to the flask.



Fig.11 Arsenic Test

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|

Add 10ml of HNO3 to dryness on the water bath,dry the residue in an oven at 130^{0}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 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.

4.2.1.3.5) Thermal Shock Test

Thermal shock testing is the process through which a product is quickly transferred between two extreme temperatures to gauge its durability and identify potential breaking points.

This testing is meant to mimic, in an accelerated environment, the wear and tear a product will encounter in usual conditions or standard use.

Procedure:–

Place the samples in upright position in a tray.

|

Immerse the tray into a hot water for a given time and transfers to cold water bath, temp of both are 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^{0}C and 1 pint bottle 30 to 40^0

A typical test uses 45^{0}C temp difference between hot and cold water.



Fig.12 Thermal Shock Test

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4.2.1.3.6) Internal Bursting Pressure Test

Burst is a condition where internal pressure exceeds pressure loading. Burst can happen in several situations, such as well control, pressure test casing/tubing, pumping operation, etc.

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

Procedure:–

The test bottle is filled with water and placed

inside the test chamber.

|

A scaling head is applied and the internal pressure automatically raised by a series of increments 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.

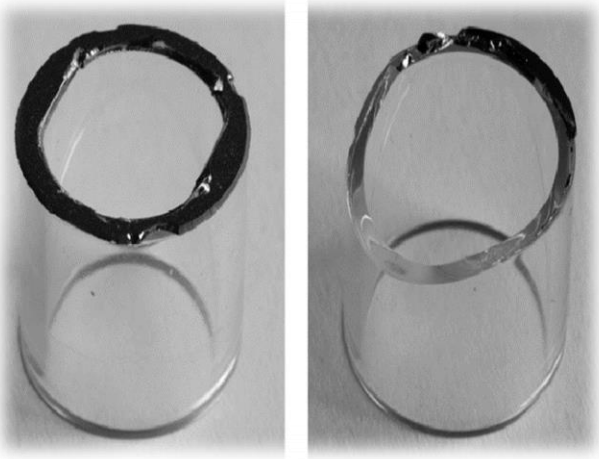


Fig.13 Internal Bursting Test

4.2.1.3.7) Leakage Test:– A leak test is a procedure used to determine if an object, product, or system functions within a specified leak limit. A leak occurs when a gas or liquid flows through an object via an imperfection or manufacturing defect such as a hole, crack or weak seal. These imperfections create high- and low-pressure zones within a product, forcing the gas or liquid to flow from the high-pressure area to the low-pressure area. The primary leak test method discussed in this article uses pressurized air to identify leaks.

Procedure:–

10 containers are filled with water and fitted with intended closures.

I

They are kept inverted at room temperature for 24 hours.

I

The test is said to be passed if there is no sign of leakage from any container.



Fig.14 Leakage Test

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4.3 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. Plastic containers are containers made exclusively or partially of plastic. Plastic containers are ubiquitous either as single-use or reuseable/durable plastic cups, plastic bottles, plastic bags, foam food containers, Tupperware, plastic tubes, clamshells, cosmetic containers, up to intermediate bulk containers and various types of containers made of corrugated plastic. [47,50]



Fig.15 Plastic Container

4.3.1) Quality Control Test For Plastic Container

4.3.1.1) Physico-chemical Tests :- The sample is extracted in the required extraction media at 70 ± 2°C (water and alcohol) or 50 ± 2°C (hexanes) for 24 ± 2 hours. Other extraction times and temperatures may be used if requested, but the USP General Chapter 661 limits may not be applicable.

For general plastics, all four analyses are recommended using a water extraction. The ROI test is not required when the nonvolatile residue does not exceed 5 mg.

i} Buffering capacity: This test measures the amount of acid or base that is added to the extract which causes a significant change in ion activity (pH).

ii} Nonvolatile residue (NVR): This test quantifies any substances in the extract which do not volatilize at or above a temperature of 105°C.

iii} Residue on ignition (ROI): This test quantifies any substances from the nonvolatile residue test which do not volatilize at or above 600°C in the presence of sulfuric acid. An NVR test must be performed prior to an ROI test.

iv} Heavy metals: This test detects metallic impurities found in the extract that are colored by the sulfide ion. The metals which normally respond to this test are lead, mercury, bismuth, arsenic, antimony, tin, cadmium, silver, copper, and molybdenum. The total amount of heavy metals cannot exceed 1 part per million (ppm).[52,54]

4.3.1.2) Biological Test :- Policies and ethics Bioplastics or bio-based plastics are made from biological sources, a small portion of the worldwide plastic market, and need more research and commercialization.

The USP has provided its procedures for evaluating the toxicity of plastic materials .

i} Implantation test: Implanting small pieces of plastic material intramuscularly in rabbits.

ii} Systemic injection test: Injecting eluates using sodium chloride injection, with and without alcohol intravenously in mice and injecting eluates using poly ethylene glycol 400 and sesame oil intraperitoneally in mice.

iii} Intracutaneous test: Injecting all four eluates subcutaneously in rabbits. The reaction from test samples must not be significantly greater than nonreactive control samples.

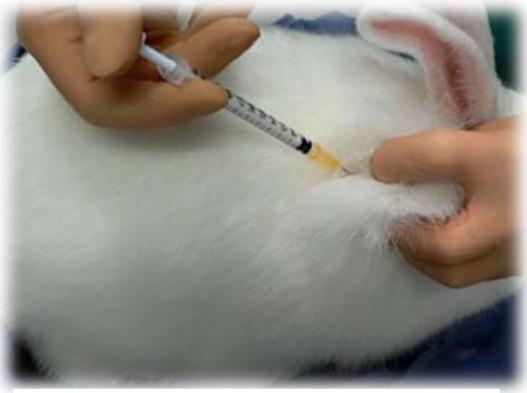


Fig.16 Biological Test on Rabbit

4.3.1.3) Opthalic Test :

Ophthalmic preparations are designed to be instilled on the anterior surface (topical route) of the eye, administered intraocularly (inside the eye), periocularly (subtenon or juxtascleral) or in conjunction with ophthalmic devices

4.3.1.4) Leakage Test : Air leak testing is a common method used for leak testing. It is a flexible test method that can be used to leak test a wide variety of parts and applications.



Fig.17 Opthalmic Test on Rabbit

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Procedure:–

10 containers are filled with water and fitted with intended closures.

↓

They are kept inverted at room temperature for 24 hours.

↓

The test is said to be passed if there is no sign of leakage from any container

4.3.1.5) Clearity Of Aqueous Extract :

Procedure:–

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

portions is selected.

I

These portions are cut into strips, none of which has a total surface area of 20cm2 .

I

The strips are washed free from extraneous matter by shaking them with at

least two separate portions of distilled water for about 30 secs.

I

The processed sample is taken in to the flask, previously cleaned with chromic acid

and rinsed with distilled water.

I

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

4.5 METAL CONTAINERS

The materials used for various pharmaceutical drug delivery systems include tin plated steel, mild steel, stainless steel, tin free steel, aluminum and its various alloys..Tin is frequently used in the production of aerosolcans by electroplating it onto sheet steel to improvecorrosion resistance and facilitate soldering. Incontrast; aluminum is used in its pure form as foil.Often, aluminum foil is used as an impermeable layerin a multilayer laminate that may include paper and plasticsas well. Aluminum foil can be formed intorigid containers, semi rigid containers, blister construction,or laminates.. Examples of metals used for this purpose include mainly aluminium, lead, tin etc.[60]



Fig.18 Metal Container

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Plastic containers are containers made exclusively or partially of plastic. Plastic containers are ubiquitous either as single-use or reuseable/durable plastic cups, plastic bottles, plastic bags, foam food containers, Tupperware, plastic tubes, clamshells, cosmetic containers, up to intermediate bulk containers and various types of containers made of corrugated plastic. [47,50]

5. QUALITY CONTROL OF SECONDARY PACKAGING MATERIAL

5.1 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.. 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)



Fig.19 Paper board Box Container

5.2 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. This is the most critical component of a container. An effective closure system prevents the loss of material from the container, prevents the environmental contamination of the product, prevents the microbs to enter inside he container.[56,58]



Fig.20 Closures

Closures are devices used for opening and closing containers. The term closure includes caps, lids, plugs, and covers. Each type of closure refers to the component found at the opening of a container used for sealing product inside. Closures are used in every industry to seal products ranging from food to chemicals. Closures are designed to pair with a variety of containers such as bottles, jars, tubes, pails and more. Different types of closures are selected based on the end user's product application such as resealing for reuse or dispensing a specific amount of product.[59]

Types of closures:-

1. Thread screw cap
2. Lug cap
3. Crown cap
4. Pilfer proof closures

5.2.1) QUALITY CONTROL OF CLOSURES

5.2.1.1) Penetrability test : 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.[77,79]

5.2.1.2) 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 coloured paper that contrasts with the rubber and the fragments counted. On an average there should not be more than three fragments per unit.

5.2.1.3) Self sealability test: Applicable to multidose 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

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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 coloured solution.

5.2.1.4) 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.

5.2.1.5 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.

5.2.1.6) Light absorption : Filter solution A through membrane filter. Measure the light absorbance of filtrate in the range 220 to 360 nm using a blank solution (prepared in the same manner as solution A). The absorbance is not more than2.

7. W.H.O GUIDELINES FOR QUALITY CONTROL OF PACKAGING MATERIALS

1. All the containers and closures intended for use shall comply with the pharmacopoeial and other specified requirements.
2. Suitable sample sizes, specifications, test methods, cleansing procedures and sterilization procedures shall be to suitability of packaging materials.
3. Plastic granules should also comply with the pharmocopeial requirements including physio-chemical and biological tests.
4. All the containers and closure shall be rinsed prior to sterilization with water for injection according to written procedure.
5. The design of the closures, containers and stoppers shall be as such as to make an airtight seal when fitted to the bottles.

10. CONCLUSION

The testing of packaging materials is almost requirement for any pharmaceutical industry. The material of a package affects quality, stability and efficacy of drug product. Thecost of material of a package should be as low as possible without compromising the quality of product. It should pass the specifications of tests before it reached the local markets and made available to the consumers of product. The type of test followed should be according to requirements of regulatory agencies.

Ensuring the quality and integrity of primary and secondary packaging materials is crucial for the safety, efficacy, and stability of pharmaceutical and medical devices. A comprehensive quality control program involves various tests to evaluate material properties, performance, and biocompatibility.

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