UNIT-5

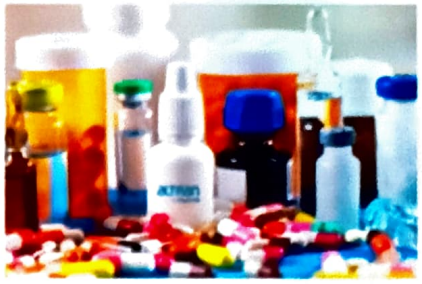
PART-1

Packaging materials for pharmaceutical product development

Points to be covered in this topic

- INTRODUCTION
- PACKAGING DEVELOPMENT MATERIALS FOR PHARMACEUTICAL PRODUCT
- SELECTION OF PACKAGING MATERIALS

❑ INTRODUCTION



- Packaging is an important component in the **pharmaceutical product development,** as it can greatly affect **drug stability, safety and product performance**.
- Packaging can be defined as, "an economical means of providing presentation, protection, and identification of information on containment; convenience and compliance for a product during storage, carriage and display until the product is consumed".
- A package provides protection against various climatic conditions such as; **biological, physical and chemical hazards and keeps them safe until opened by the end user**.
- Packaging is an important feature required at all level of use such as by **manufacturers, stockiest, retailers and consumers** that helps in Packaging must function as a means of drug administration and therefore, **products product identification and separates a particular product from variety of other products.**
- A packaging system protects the product from **spoilage, leakage, microbial growth, design and type of packaging container**, a patient can identify and understand its intended contamination, etc.
- In order to ensure adequate stability of the product throughout the shelf life, packaging materials are chosen on the basis of their efficacy and other characteristics that enable them to **preserve the quality, potency and safety. Recently, packaging is becoming more important both to the successful marketing of products and** to the health and safety of patients.
- Often, the role of packaging is simply as a container for the product, but in some cases wherein, products are unstable in their formulations, due to formulation limitations can be well stabilized with innovative packaging systems, for **example, aerosols.**

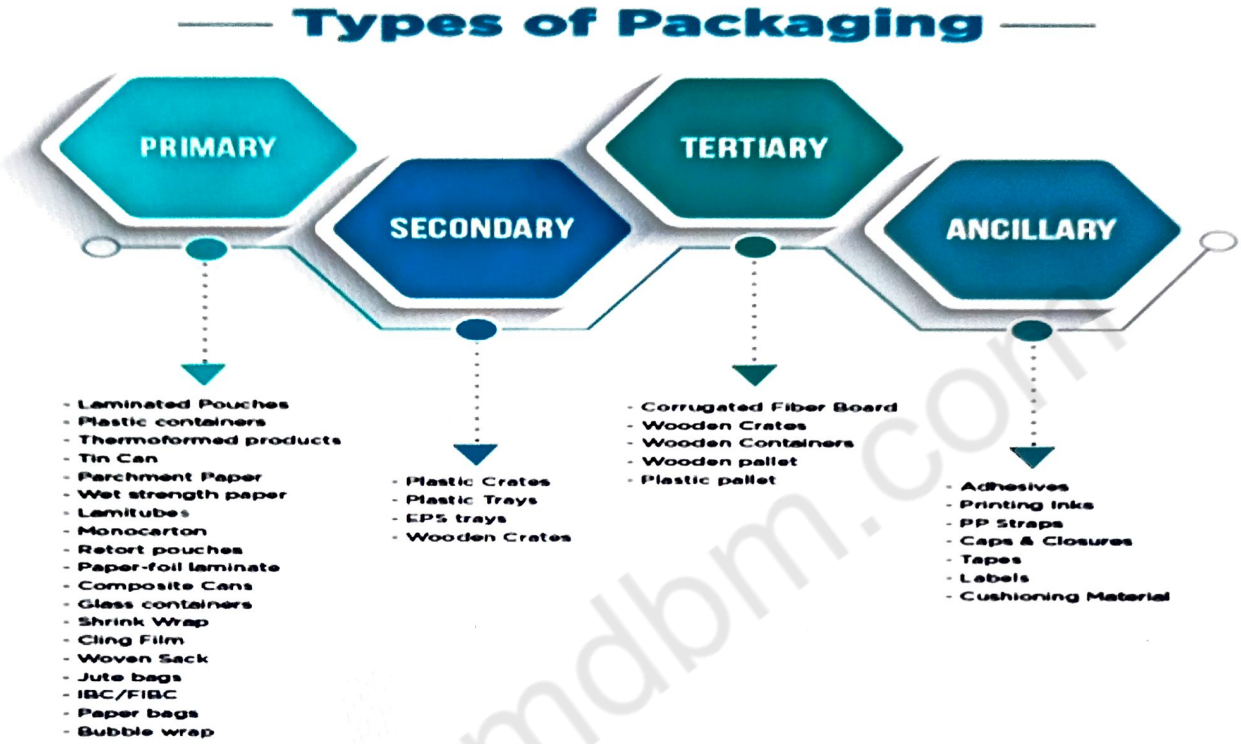
➢ Ideal Characteristics of Packaging Material :

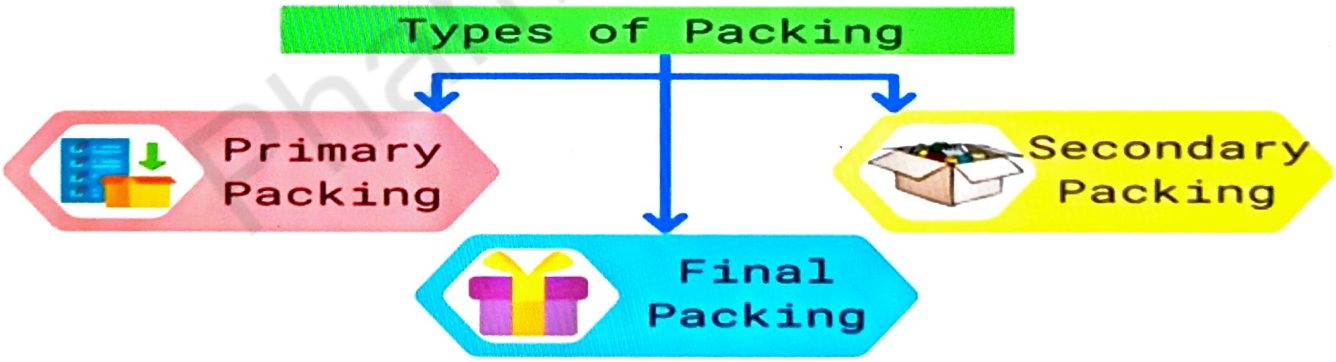
- Ideally, packaging is combination of the **container-closure system**, generally, surrounded by the secondary packaging to provide **protection and stability during the shelf life of the product**.
- The key characteristic of packaging material is the **protection of the product against any possible damage, due to environmental hazards**.
- A packaging material must protect the **product contents from loss or gain of water, loss of any volatile material and leaching anything from the formulation content, etc.**
- In addition to environmental factors, packaging must prevent mechanical hazards like **compression, vibration, abrasion, puncture, shock, etc.**
- Packaging materials **should not react with any of the product component and should preserve the product's inherent features over the shelf life.**
- These materials **should not impart any toxic/immunogenic responses and should be non-irritant to the patient and should be user-friendly**.
- They must be good in appearance and design in terms of product's aesthetic value and must contain desired information including registration number.
- They must have sufficient mechanical strength so that it can withstand various stresses.
- The package **should not support microbial growth and must tolerate the heat while it is subjected to processing such as sterilization**.

- It must deliver the required amount of product requirements and follow the regulatory norms of the specific country where, the product is marketed or planned to be marketed.

➢ Types of Packaging

Pharmaceutical products have mainly three main types of packaging namely; **primary, secondary and tertiary packaging**. The primary and secondary packaging of pharmaceutical products is closely linked to their production and constitutes an integral part of the value- added process.





(1) Primary packaging:

- Primary packaging has a layer of its **material in immediate contact with the formulation.** Since, this package is in direct contact with the product, the stability of the formulation mainly depends on **nature of materials** it is made up of.
- The main function of this package is to contain **formulation components and restrict any hazards** that may cause product deterioration.
- **Examples: Ampoule, vial, strip, blister, bottle, cap, cap liner.**

(ii) Secondary packaging:

- The packaging external to the primary package is known as the secondary packaging.
- The secondary packaging, also known as **outer package**, is mostly used for **inventory management within the pharmacy practice**.
- This type of packaging provides additional physical protection to the product to ensure safe storage and transportation.
- Materials used for secondary packaging never come in direct contact with the formulation that it holds.
- Examples: Show box, cardboard box, paper and plastic crates, etc.

(iii) Tertiary packaging:

- It is outer package to the secondary package.
- It prevents damage to the products and therefore, used for bulk handling and shipping.
- The tertiary package is usually used for **logistical purposes**, for **example, for distribution from the wholesaler to the pharmacy. Usually, this type of packaging is removed by retailers before products are displayed for sale**.
- This packaging plays **crucial role during the transportation of packaged products from manufacturer to distributors to retailers**.
- It protects the product from damage which may occur during the transportation.
- Examples: Wooden box, shipper, carton box, shrink wrap, etc.

(iv) Formulation packaging:

- Some medicinal products need to be reconstituted under sterile/aseptic conditions before being administered to the patient.
- In such situations, the active substance of the medicinal product is distributed in a formulation package, for example, injectable device, that is ready for use.

➢ Functions of packaging

- **Product Identification:-** Packaging greatly helps in identification of products.
- **Product Protection:-** Packaging protects the contents of a product from spoilage, breakage, leakage, etc.
- **Facilitating the use of product:-** Packaging should be convenience to open, handle and use for the consumers.
- **Product Promotion:-** Packaging is also used for promotional and attracting the attention of the people while purchasing.

➢ Properties of Packaging Materials

In order to provide required protection, the materials from which the packaging components are made must possess following properties:

(i) Mechanical properties:

The packaging material must possess sufficient **mechanical strength to withstand during handling, filling, closing and processing.** They must **remain and maintain their shapes during transport, storage and at the time of usage.**

(ii) Physical properties:

(1) The material should be impervious to any possible contaminants such as **foreign solid particles, liquids, gases and vapors or micro-organisms.**

(2) The packaging must be able to withstand during usual processing and storage temperature variations.

(3) The surface of packaging material must be **capable of labeling.**

(4) Packaging material can be moulded into suitable size and shape.

(5) These materials must **protect formulation from environmental factors such as heat and light.**

(iii) Chemical properties:

(1) The packaging system components **should not react with each other.**

(2) The product formulation components **should not react with the packaging components.**

(3) The packaging system **should not leach any chemical component and should have chemical resistance to these components.**

(iv) Biological properties:

The packaging material must be able to withstand attack by insects and flies if this hazard is encountered. In addition, packing system should not support any microbial growth.

❑ PACKAGING DEVELOPMENT MATERIALS FOR PHARMACEUTICAL PRODUCT

➢ **Types of packaging materials used for pharmaceutical packaging**

- ✓ Glass
- ✓ Plastics
- ✓ Rubbers
- ✓ Paper/card boards
- ✓ Metals

✓ GLASS:

Glass has been widely used as a drug packaging material.

Advantages

- They are transparent.
- They have good protection power.
- They can be easily labelled.
- Economical
- Variety of sizes and shapes

Disadvantages

- Glass is fragile so easily broken.
- Release alkali to aqueous preparation

COMPOSITION OF GLASS:

- **Sand (silicon dioxide) Soda ash (sodium carbonate) Limestone (calcium carbonate) Cullet (broken glass)** - aluminium, boron, potassium, magnesium, zinc, barium,
- **Amber:** light yellowish to deep reddish brown, carbon and sulphur or iron and manganese dioxide
- **Yellow:** Compounds of cadmium and sulphur
- **Blue:** Various shades of blue, cobalt oxide or occasionally copper (cupric) oxide
- **Green:** iron oxide, manganese dioxide and chromium dioxide

MANUFACTURE OF GLASS:

The four basic processes used in the production of glass are:

- **Blowing uses compressed air form the molten glass in the cavity of metal mold.**
- **In drawing, molten glass is pulled through dies or rollers that shape the soft glass.**
- **In pressing mechanical force is used to press the molten glass against the side of a mold.**
- **Casting uses gravity or centrifugal force to cause molten glass to form in the cavity of mold.**

TYPES OF GLASS

- **Type I-Highly resistant borosilicate glas**
- **Type II-Treated soda lime glass**
- **Type III- Soda lime glass**
- **NP-soda glass (non parenteral usage)**

Glass as Packaging Material

Type I- Borosilicate glass

- Alkalinity is removed by using boric oxide to neutralized the oxide of potassium and sodium
- It is highly resistant glass.
- It has high melting point so can with stand high temperatures.
- It is more chemically inert than the soda lime glass
- It can resist strong acids, alkalies and all types of solvents. Reduced leaching action.

Uses:

- Laboratory glass apparatus.
- For injection and water for injection.

Type II-treated soda lime glass

- Type II containers are made of commercial soda lime glass that has been dealkalized or treated to remove surface alkali
- The de-alkalizing process is know as sulphur treatment.
- Sulfur treatment neutralizes the alkaline oxides on the surface, rendering the glass more chemically resistant.

Uses:

- Used for alkali sensitive products. Infusion fluids, blood and plasma. Large volume container.

Type III glass-Regular soda-lime glass

- This is a type of untreated glass that has average or better-than-average (moderate) hydrolytic resistance.
- This glass is suitable for non-aqueous preparations for parenteral use, powders for parenteral use (except for freeze dried preparations) and non-parenteral preparations.

Type IV glass-Non-parenteral glass

- This is a general purpose soda-lime glass and is not used for parenteral products but for oral or topical formulations.
- Type IV colored glass is used to provide protection to the formulation contents against ultraviolet rays that prevent photochemical degradations.

✓ PLASTIC:

Plastics may be defined as any group of substances, of natural or synthetic origins, consisting chiefly of polymers of high molecular weight that can be moulded into a shape or form by heat and pressure.

Advantages

- Less weight than glass,
- flexible
- Variety of sizes and shapes
- Essentially chemically inert, strong, rigid Safety use, high quality, various designs
- Extremely resistant to breakage

Disadvantages

- Absorption permeable to moisture
- Poor printing, thermostatic charge

TYPES OF PLASTICS

Thermosetting type -

- When heated they may become flexible but they do not become liquid

e.g. Urea formaldehyde (UF),Phenol formaldehyde, Melamine formaldehyde (MF), Epoxy resins (epoxides), Polyurethanes (PURS)

Thermoplastics type-

- On heating they are soften to viscous fluid which harden again on cooling.

e.g. Polyethylene (HDPE - LDPE), Polyvinylchloride (PVC), Polystyrene Polypropylene, Nylon(PA), Polyethylene terepthalate(PET),Polyvinylidene chloride(PVDC), Polycarbonate Acrylonitrile butadiene styrene(ABS)

✓ METALS:

Metals are used for **construction of containers**. The metals commonly used for this purpose are **aluminium,tin plated steel, stainless steel, tin and lead**

Advantages:

- They are impermeable to light, moisture and gases.
- They are made into rigid unbreakable containers by impact extrusion.
- They are light in weight compared to glass containers.
- Labels can printed directly on to their surface.

Disadvantages:

- They are expensive.
- They react with certain chemicals

COLLAPSIBLE TUBES METAL

- The collapsible metal tube is an attractive container that permits controlled amounts to be dispensed easily, with good reclosure, and adequate protection of the product.
- It is light in weight and unbreakable and lends itself to high speed automatic filling operations.
- Most commonly used are **tin, aluminium and lead.**

✓ RUBBER:

Rubber is used mainly for the **construction of closure meant for vials, transfusion fluid bottles, dropping bottles** and as washers in many other types of product.

Butyl rubber:

Advantages:

- Permeability to water vapour.
- Water absorption is very low.
- They are relatively cheaper compared to other synthetic rubbers.

Disadvantages:

- Slow decomposition takes place above 130 - C.
- Oil and solvent resistance is not very good.

Nitrile rubber:

Advantages:

- Oil resistant due to polar nitrile group. Heat resistant.

Disadvantages:

- Absorption of bactericide and leaching of extractives are considerable.

Chloroprene rubbers:

Advantages:

- Oil resistant. heat stability is good

Silicon rubbers:

Advantages:

- Heat resistance.
- Extremely low absorption and permeability of water.
- Excellent aging characteristic.
- **Disadvantages:**
- They are very expensive.

✓ PAPER AND PAPER BOARD

- The paperboard (cellulose fiber) materials are a significant part of pharmaceutical packaging.
- Paper is rarely used on its own as a **primary package**.
- Cartons are used for **increasing display area, providing better display of stock items and the collating of leaflets**.
- Cartons also provide physical protection to metal collapsible tubes and therefore are traditionally used material for packaging.
- **These days it is being substantially replaced by orientated polypropylene film. Paper even when waxed has relatively poor protective properties against moisture.**

❑ SELECTION OF PACKAGING MATERIALS

- The external appearance of the package not only compliment product confidence, but also provides **clear and concise product identification**.
- Package should assist in patient compliance and should preferably have an **aesthetically acceptable design**.
- Package should protect the formulation components **against biological contamination and all adverse external factors like moisture, light, oxygen, mechanical shock, temperature, etc.,** which can alter the physical and chemical properties and pharmacological effect of the formulation.
- This alteration in the properties leads to the formation of new chemicals that are less active or inactive and has toxic by-products with adverse reactions.
- Thus, in order to handover products safely to the patient selection of packaging materials is very important to make sure **drug safety**.
- In order to achieve this goal, it is important to know the list of packaging Materials used in the **pharmaceutical industries, factors to be considered when selecting packaging material for a drug product and the possible interactions between the primary packaging materials and the dosage forms.**

There are many factors which need to consider when selecting a suitable type of pack for the product:

- The product or pack contents
- The application of the product
- Content stability, and the need of protection from any environmental factors
- Content reactivity (with relevant to the packaging material)
- Acceptability of the pack to the consumer or user
- The packaging process
- Regulatory, legal and quality issues

UNIT-5

PART-2

Packaging materials for pharmaceutical product development

Points to be covered in this topic

- QUALITY CONTROL TESTING OF PACKAGING MATERIALS
- REGULATORY CONSIDERATIONS

❑ QUALITY CONTROL TESTING OF PACKAGING MATERIALS

- The materials used for **fabricating all types of packaging systems** may have certain interactions with formulation components.
- In addition, suitability of these materials in terms of ease of **administration, storage and stability over shelf life is of much significance**.
- Also, both primary packages and shipping containers have a risk of being dropped or being impacted by other items and in such cases package **integrity and product protection are important packaging functions**.
- Therefore, quality control tests are performed to measure the resistance of packages and products to controlled laboratory shock and impact in addition to safety testing.
- There are various tests for determination of **quality, integrity and compatibility of packaging materials.**
- The specification and requirement of quality testing depends on type of pharmaceutical materials used.
- The requirement of packaging material testing is set according to specification of regulatory agencies like **WHO GMP, U.S. FDA and ICH guidelines.**

➢ Testing of Packaging Materials

- Tests applied to packaging materials are **physical, chemical, mechanical and environmental.**
- **In physical testing,** physical appearance of formulation and packaging components is tested which should be retained during the shelf life of formulation at specified storage conditions. A visual appearance change is the first indication of instability. Physical changes include but **are not limited to discoloration, deformation, breakage, leakage, etc.** Physical changes can be easily detected by visual observation or using optical microscopy.

- **Chemical testing** includes **pH test, test for chloride and sulphate in case of paper or board, test for alkalinity of glass, compatibility test with drug and excipients, etc.**

- **Mechanical testing** uses standard tests available for the effect of **creasing, folding, hot tack test, tensile test and coefficient of friction.**

- In **environmental testing,** materials may be tested for absorption of **water, permeability to water vapour, gases, oils, odour, etc. and for light transmission.**

➢ Quality Control Tests for Packaging Materials

(a) Tests for identification:

- Identification of raw material quality for packaging components is a **prime quality testing requirement.**
- Identification test confirms the **quality of packaging components against the specifications.**

(b) Tests for dimensions:

- Every **packaging system is manufactured with different components** which are assembled with each other for intended use.
- It is important that all dimensions of these components and assembled packaging system should be within the acceptable limits to perform the respective function during **shelf life and at its intended** use.
- In case of **pediatric oral drops, calibrated** droppers are used to avoid compromised efficacy to avoid underdosing and toxicity in case of overdosing.

(c) Tests for formulation volume in container:

- Liquid formulations have a definite **fill volume in the packaging system which is generally aimed to provide the labeled quantity to the**

patient in a single dose or in uniformly divided doses.

(d) Tests for deliverable volume/ dose:

- Each formulation needs to be delivered in the recommended dose by the intended route of administration. Many pharmacopoeias provide **deliverable volume tests for different formulations**. Deliverable volume depends on the packaging components primarily associated with **formulation characteristics such as viscosity and surface tension**.

(e) Tests for extractable, leachable and delamination:

- Primary packaging materials are prepared by using some chemicals such as stabilizers to provide necessary characteristics as per requirements.
- These chemicals may get extracted into the drug formulation. The extractables, or leachables or delamination causes potential toxicity after administration. Studies need to be done during the laboratory scale stability batches and/or exhibit batches.
- Packaging material plays an important role in **keeping the formulation safe and unchanged.**

(f) Testing for formulation protection:

- A container intended to provide protection from **light or offered as a light-resistant container must meet the requirements of the U.S.P. light transmission test.**
- The procedure requires the use of a spectrophotometer, with the required sensitivity and accuracy, adapted for measuring the amount of light transmitted by the plastic materials used for the container.

(g) Tests for formulation and packaging material compatibility:

- A leachability test is performed to evaluate the amount and/or nature of any chemical that migrate from the plastic material in to the pharmaceutical formulation vehicle for the length of shelf-life claim. The drug product is evaluated at regular intervals, such as at 1, 3, or 6 months or at 1 or 2 years, until the length of the shelf life claim has been met.

(h) Tests for product safety:

- Packaging system components should not leach any harmful or undesirable amounts of substances into the formulation which a patient will be exposed during treatment. Determining the safety of a packaging component is not a simple process, and a standardized approach has not been yet well established.

(i) Tests for package performance:

- Package performance is an important attribute for its suitability to be used as container closure system for the accurate drug delivery. It depends upon its ability to function in the manner for which it is designed. The major considerations when evaluating package performance are its functionality (to improve patient compliance), minimizing waste, or improving ease of use and delivery of drug in right amount or at right rate.

➢ Specific Quality Control Test for Packaging Materials

(A) Tests for Glass:

(i) Glass alkalinity test:

(a) Crushed glass test:

- This is a severe test official in U.S.P used to check quality of glass container wherein, **the containers are crushed and sieved to produce uniform particles amongst which a definite weight of particle is taken.**
- In this test, complete glass is tested and extraction is **enhanced because of rough surfaces of the particles**.
- This test can be used for **determining the nature of a glass and to distinguish between types of glass.**

(b) Whole-container test:

- This test is official in **EP. B.P. and International Pharmacopoeia**.
- It is used to test treated **soda-lime containers** only.
- The containers are filled with the test solution and exposed to the prescribed test conditions. Often the containers pass this test because the surface layer of a glass container is smooth and comparatively less reactive.
- The **small sized containers are more attacked for the leaching of the alkali from the surface**.

(ii) Chemical resistance of test:

U.S.P. and I.P. provided following first two tests to determine the chemical resistance of glass containers.

(a) Powdered glass test:

- Under the conditions of elevated temperatures, alkaline constituents

from the glass containers such as **oxides of sodium, potassium, calcium, aluminum, etc.,** are leached into purified water.

(b) Water attack test:

- This test is used only for those containers that have been exposed to **sulphur dioxide fumes under controlled humidity conditions.**
- This treatment neutralizes the surface alkali making glass chemically more resistant.
- The principle involved in the water attack test is to determine whether the alkali leached from the surface of a container is within the specified limits or not.

(c) Arsenic test:

- This test is used for glass containers used for **aqueous parenteral formulations.**
- The inner and outer surfaces of containers are washed with fresh distilled water for 5 min. Each container is rinsed for at least **3 times with CO_2 free water and again filled with same fresh CO_2 free water to their filling volume, covered and kept in autoclave. It is heated to 100 °C for 10 min and allowed the steam to release from the vent.**

(d) Thermal shock test:

- Samples are placed in the **upright position in a tray.**
- The tray is immersed into a **hot water for a specified time and transferred to cold water bath.** The temperatures of both the baths are closely controlled. Containers are closely examined for cracks or breaks before and after the test.

(e) Internal bursting pressure test:

- The most common instrument used is **American glass research is an increment pressure tester.**
- The test container is filled with water and placed inside the test chamber.

(f) Leakage test:

- This testing is conducted by filling the container with **coloured solution (dye)** which is maintained at high pressure compared to the pressure inside the glass container so that the **coloured solution enters the container if any cracks or breakage is present.**

(g) Annealing test:

- Annealing is a process of **slowly cooling hot glass container** after they have been formed, to relieve residual internal stresses introduced during manufacture.
- The sample glass container is examined using **polarized light in either a polariscope or strain viewer.**

(h) Vertical load test (VLT):

- This measures the **vertical load strength of glass containers, simulating capping and stacking loads.**
- It is used in **conjunction with the Agr ramp pressure tester.**

(B) Tests for Plastic:

(i) Test for plastic containers for parenteral and non-parenteral use:

(a) Leakage test:

- A container is filled with 10 mL water and is closed by fitting intended closure and kept inverted at room temperature for 24 h. There should be no signs of leakage from the containers.

(a) (b) Collapsibility test:

- This test is applicable to containers which are to be squeezed in order to withdraw product contents. A container upon collapsing inwards should yield at least 90% of its nominal contents at the required flow rate at ambient temperature.

(c) Clarity of aqueous extract:

- To conduct this test unlabelled, unmarked and non-laminated, sufficient portions of suitable containers are selected at random to yield a total sample area required considering the surface area of both sides.
- The selected portions are cut into **strips by controlling these portions in such a way that none has a total area of more than 20 cm^2.**

(d) Transparency test:

- The standard suspension is prepared by adding 1 g hydrazine sulphate to 100 mL water and set aside for 6 h. To 25 mL of this solution 25 mL 10% w/v hexamine is added and left aside for 24 h.

(ii) Tests for Plastic containers for ophthalmic use:

(a) Tests for leakage; collapsibility; clarity of aqueous extract and non-volatile residue:

Comply with the tests described under plastic containers for non-parenteral preparations.

(1) Leakage test: Total 10 containers are filled with water and fitted with intended closures. They are then kept inverted at **room temperature for 24 h.** The test is said to be passed if there is no sign of leakage from any container.

(2) Collapsibility test: This test is applicable to containers which are to be **squeezed in order to remove the contents**. A container by collapsing inward during use, yield at least 90% of its normal contents at the required rate of flow at ambient temperature.

(3) Clarity of aqueous extract: A suitable container is taken at random, and unlabeled, unmarked; and non-laminated portions are selected. These portions are cut into strips, none of which has a total surface area of 20 cm^2.

(b) Systemic injection test:

This test is designed to evaluate systemic responses to the extracts of materials under test following injection into mice. Test animals used are healthy albino mice weighing between 17 and 23 g of the same source. Each of the five mice in a test group are injected with the sample or the blank except to dilute each gram of the extract of the sample prepared with polyethylene glycol 400 and the corresponding blank with 4.1 volumes of Sodium Chloride Injection to obtain a solutions having a concentration of about 200 mg of polyethylene glycol per mL. Animals are observed immediately after injection, and after 4, 24, 48 and 72 h.

(c) Intracutaneous test:

This test is designed to evaluate local responses to the extracts of materials under test following intracutaneous injection into animals. Animals used are healthy, thin-skinned albino rabbits whose fur can be clipped closely and skin is made free from mechanical irritation or trauma. On the test day, loose hairs are removed by means of vacuum and the skin lightly swabbed with diluted alcohol, and dried. For each sample 2 animals are used and each animal is injected intracutaneously on one side the sample and the other side blank. Injection sites are examined for evidence of any tissue reaction such as erythema, edema and necrosis. All animals are observed at 24, 48 and 72 h after injection.

(d) Eye irritation test:

This test is designed to evaluate responses to the instillation of material extract under examination in the rabbit eye. This test follows a standardized protocol for instilling agents onto the cornea and conjunctiva of laboratory animals. A sum of ordinal-scale items of the outer eye gives an index of ocular morbidity. The procedure involves direct instillation of the sample into the lower conjunctival sac of the rabbit eye. The lids should be held open momentarily to ensure contact of the substance with the cornea, and then gently released. While direct corneal application may be justified at times in the assessment of specific hazards, the overall effectiveness of conjunctival sac instillation supports its continued use as the standard procedure.

(iii) Tests on plastic materials:

(a) Physico-chemical tests:

The following tests are based on the extraction of the plastic material. It is essential that the designated amount of the plastic be used. Also, the specified surface area must be available for extraction at the required temperature.

(1) Appearance
(2) Light absorption
(3) pH test
(4) Non-volatile matter
(5) Residue on ignition
(6) Heavy metals
(7) Buffering capacity
(8) Oxidizable substances

(b) Biological tests:

The U.S.P. has provided its procedures for evaluating the toxicity of plastic materials. Essentially the tests consist of three phases:

(1) Implantation test: Implanting small pieces of plastic material intramuscularly in rabbits.

(2) 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.

(3) Intracutaneous test: Injecting all four eluates subcutaneously in rabbits. The reaction from test samples must not be significantly greater than non-reactive control samples.

(iv) Tests for closures:

(a) Penetrability test: Penetrability is measured to check the force required to make a hypodermic needle to 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.

(b) 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

(c) Self sealability test: This test is applicable to multidose containers. The procedure involves filling 10 vials with water and closing them with prepared closures and securing with a cap. For each closure a new hypodermic needle is used. The rubber cap is pierced 10 times, each time at different site, and vials are immersed upright in methylene blue (0.1%) solution and external pressure is reduced for 10 min. When the atmospheric pressure is restored, the vials are left immersed for 30 min and then removed and rinsed from outside. In order to comply with the test none of the vial should contain any traces of the coloured solution.

(d) Test for extractive: In this test, the closure is boiled with water for 4 h under reflux and the water is evaporated to dryness. The residue must not exceed the specified amount.

(e) 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.

(f) Light absorption test: A sample solution is prepared by washing closures in 0.2 %w/v anionic surfactant solution for 5 min. These closures are then rinsed 5 times with distilled water and are subjected to autoclaving by immersing them in 200 mL water at 119 to 123 °C for 20 to 30 min covering with aluminum foil.

(v) Tests for collapsible tubes:

(a) Leakage test: Water is filled in the tube and is tightly closed. External surface is wiped off and tube is kept inverted on filter paper at base. It is allowed to stand for 1 h. Filter paper shows absorption at any time during test period, if leaking.

(b) Lacquer curing test:

(1) Power of adhesion: Tube is split along the length and flattened. Cotton wool is soaked in acetone and is rubbed over lacquer surface for 20 min. Lacquer should not lift from surface and cotton wool shall remain colorless.

(2) Flexibility test: The tube is folded in such a manner that internal lacquer surface is outside. The lacquer coating should not be peeled off when the folded position is rubbed with finger.

(c) Lacquer compatibility test:

In all, 10 tubes are taken for the test. Product is filled and crimped and subjected to 45 °C for 72 h. Tubes are allowed to cool and cut lengthwise.

(1) Product compatibility: Content should not show any discolorations or colour or gas formation. change in

(2) Lacquer compatibility: Lifting or peeling of lacquer is checked.

(vi) Tests for metallic tins:

(a) Description: Metallic tins have smooth inner surface. The upper sealed surface consists a clip to break the seal. The lower surface is open.

(b) Dimensions: Measure the height in mm of 10 metallic tin, individually from the lower surface edge to the upper rim. Specimen metallic tin's tolerance is 170 mm ± 10 mm.

(c) Diameter: Inner diameter: Measure the inner diameter of 10 metallic tins. Limit - NLT 98 mm. Outer diameter: Limit - NMT 105 mm. end

(d) Cleanliness: It should not be dirty, damaged, stained or consist of any foreign articles.

(viii) Tests for cartons:

(a) Compression: This method is used to assess the **strength of erected package.**

(b) Carton opening force: The method is used to **hold the flat carton as delivered by its creases between thumb and first finger press.**

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

(d) Crease stiffness: This involves testing a carton board piece and folding. It **tries to recover its former position when bending force is removed.**

(e) Joint shear strength: This is a method of testing the glued lap seam on the side of a carton for strength of the adhesive using a tensile testing machine.

❑ REGULATORY CONSIDERATIONS

- While packaging is important for marketing, pharma packaging is highly regulated. Packaging materials for pharmaceutical use plays crucial roles in the **marketing of pharmaceutical products in a regulated market.**
- It is mandatory for packaging materials to comply with respective regulatory recommendations and guidance. **Regulatory agencies closely monitor the quality of packaging materials used for pharmaceutical drug products by ensuring the adherence of respective manufacturer's compliance with cGMP.** Non- compliance

guidelines results in compromised drug product quality and subsequently recall of drug product from respective market. **Examples of such cases are the recall of drug product due to defective container, mis- packaged, mislabeled container, etc.**

- Packaging components of any drug product has the major role of formulation protection. For **example, in case of ophthalmic aqueous solution, semipermeable LDPE containers should prevent water evaporation during shelf life.** Compromised LDPE containers result in increased drug strength due to reduced volume of ophthalmic solution which may cause toxicity. Drug products are administered by the users in a required dose and route of administration. Packaging components also has major impact on product identification, **dose delivery and ease of administration of drug product**. For safe **administration** of drug product, packaging components should work as per prescribed specifications. Quality of drug product equally depends on packaging components in contact with the formulation.
- The specific U.S. FDA regulation states that **"containers, closures and other component parts of drug packages, to be suitable for their intended use, must not be reactive, additive or absorptive to the extent that the identity, strength, quality or purity of the drug will be affected."** The packaging material must be approved for such use, along with the drug, before its marketing. The drug manufacturer must include data on the container and package components in contact with the pharmaceutical product in its NDA. If the **U.S. FDA determines that the drug is safe and effective, and that the package is suitable, it approves the drug and package.**
- It is critical for the packaging scientist to select the correct packaging materials to **ensure stability of the formulation and to remain in compliance with U.S. FDA regulations.** The U.S. FDA expects that every proposed packaging system should be suitable for its intended use.