A NEW ERA ON PACKAGING OF PHARMACEUTICAL PRODUCT

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ABSTRACT
Packing consists of enclosing an individual item, or several items, in a container, usually for shipment or delivery. This operation is mostly done by hand and machine. Pharmaceutical packaging means the combination of components necessary to contain, preserve, protect & deliver a safe, efficacious drug product, such that at any time point before expiration date of the drug product, a safe & efficacious dosage form is available. Packaging is responsible for providing life-saving drugs, medical devices, medical treatments, and new products to deliver every type of product to the people the world over. So the important role of pharmaceutical packaging is to transform the formulation into an attractive and marketable product. It is transparent to the end user when done well and is open to criticism from all quarters when done poorly. So many issues regarding the pharmaceutical product like stability, sale, patient compliance etc are related with the packaging which is indicating a key for sale, safety and success. Advancement in research of pharmaceuticals development had always been dependent on the packaging technology. Maintaining integrity of pharmaceuticals during storage, shipment, and delivery is assured by quality of packaging available. In this regards, the present article reviewing on the various advancements in the packaging techniques and selection of packaging material, machinery & predicting the packaging outcomes in future.

KEYWORDS: Pharmaceutical packaging, Materials, Machinery, Current trends.

INTRODUCTION
Pharmaceutical Packaging is a challenging and diverse area of package design, development and engineering. According the need of the product and convenience of the end user, significant changes are being undergone. It is one of the responsibilities of the pharmaceutical manufacturers to provide their products safely to the customers. Since, Packaging material sometimes play a major role in maintaining stability and therapeutic efficacy of the drug product. The problems related to the drug product for both manufacturing and packaging depend on the type of chemical compounds (Drug) being administered to the patient. The drug molecules, both traditional chemical compounds and larger biopharmaceutical molecules possess inherent problems related to stability, purity and sterility. Manufacture of product and development of its packaging must fulfil all these requirements.\[1,2\]

The term Packaging is defined as a means of enclosing, protecting a product, and providing the information about the product. Packaging can be defined as an art, science and technology to ensure the safer delivery of the product throughout its journey from manufacturing to the end use. A Pharmaceutical Package container is an article or device which contains the Pharmaceutical Product and the container may or may not in direct contact with the product. The container which is designed for pharmaceutical purpose must be stable. According to the WHO, all the medicinal products are required to be protected and hence packed in the container that meet the prescribed standards, particularly with respect to exclusion of moisture and light and prevention of leaching of extractable substances into the contents and of chemical interaction with the contents. However, the limits of acceptability in these various respects depend on the environmental storage conditions.\[1,2\]

Packaging is the most important component for various drug formulations in pharmaceutical industry and packaging of pharmaceutical dosage forms has close relationship between a pharmaceutical preparation and its package concern to the drug stability and safety. The stability of pharmaceutical drugs in solid and liquid dosage forms depends on the efficacy of the packaging materials to protect from chemical degradation and changes in physical characteristics such as appearance, hardness, friability, dissolution, disintegration, weight variation, moisture contents and mechanical durability. Glass, plastics, metal and paper are the most commonly used packaging materials in pharmaceutical industries. The selection of Packaging material to pack pharmaceutical dosage forms are made on the basis of its efficacy and performance characteristics to preserve the quality, potency and safety of the pharmaceutical
products. Packaging should provide protection, identification, information, convenience and compliance for a product during storage, carriage, display and until such time the product is consumed. It has been observed that considerable degradation of the drug resulting in undesirable physical and chemical changes along with some toxic effects which may be highly hazardous to the patient. So the material selected for packing pharmaceutical drugs must be not reactive with products; protective from environmental condition; not impart to the products tastes or odours; non-toxic; FDA approved; meet applicable tamper- resistance requirement; adaptable to commonly employed high-speed packaging equipment. It is intended to evaluate the shelf lives of the products stored in different packaging materials and examine their efficacy and performance characteristics in maintaining the product integrity for a prolonged period of storage.[2,3]

The process of Packaging mainly indicates
- Protection
- Preservation
- Presentation

This is widely known as 3P concept. The latest inclusion of the 4th P is Promotion of the product.

Role of Packaging[4]
- Protection – against light
  - Against reactive gases.
  - Against moisture
  - Against microbes
  - Against physical damage
- Against pilferage and adulteration
- Identification.
- Information.
- Compatible.
- Convenience.

Ideal Qualities of a Pharmaceutical Package[4,5]
1. It should have sufficient mechanical strength so as to withstand handling, filling, closing and transportation.
2. It should not react with the contents stored in it.
3. It should be of such shape that can be elegant and also the contents can be easily drawn from it.
4. It should not leach alkali in the contents.
5. The container should not support mould growth.
6. The container must bear the heat when it is to be sterilized.
7. The contents of container should not be absorbed by the container.
8. The material used for making the container should be neutral or inert.
9. Any part of the container or closure should not react with each other.
10. Closure should be of non-toxic nature and chemically stable with container contents.
11. Protect the preparation from environmental conditions.
12. Does not impart tastes or odours to the product
13. Adaptable to commonly employed high-speed packaging equipment’s.

Criteria for the Selection of package type and package material[2,4,6]
1. On the facilities available, for example, pressurized dispenser requires special filling equipment.
2. On the ultimate use of the product. The product may be used by the skilled person in hospital or may need to be suitable for use in the home by a patients.
3. On the physical form of the product. For example solid, semi – solid, liquid or gaseous dosage form.
4. On the route of administration. For example, oral, parenteral, external etc.
5. On the stability of the material. For example, moisture, oxygen, carbon di oxide, light, trace metals. Temperature or pressure or fluctuation of these may have a deleterious effect on the product.
6. On Compatibility with the contents. The product may react with the package such as the release of alkali from the glass or the corrosion of the metals and the inturn the product is affected.
7. On the cost of the product. Expensive products usually justify the expensive package.
8. Stability
9. Strength of container and the degree of protection required
10. Machine suitability of packaging and the filling method
11. Convenience of the packaging for the physician, pharmacist and finally the patient (size, weight, method of opening/re-closing, legibility of printing).

Factors affecting the selection of packaging materials
Mechanical Factors
- Shock
- Compression
- Puncture
- Vibration

Environmental Factors
- Temperature: Resistance to differences in temperature
- Pressure
- Light
- Moisture
- Gases
- Contamination: Resistance to microorganisms, insects, or any other salts etc.
- Odour retention and transmission

TYPES OF PACKAGE[1,5]
1. Primary Packaging
Primary packaging are those package which are in direct contact with the Pharmaceutical formulation. The main
Aim of primary package is to protect the formulation from environmental, chemical, mechanical and/or other hazards. This is the first packaging envelope which is in touch with the dosage form or equipment. The packaging needs to be such that there is no interaction with the drug and will provide proper containment of pharmaceuticals.

Examples: Blister packages, Strip packages, etc.

Possible interactions between primary packaging materials and the included pharmaceutical product:
- The release of chemicals from components of the packaging materials.
- The release of visible and/or sub-visible particles.
- The absorption or adsorption of pharmaceutical components by the packaging materials.
- Chemical reactions between pharmaceutical product & the packaging materials.
- The degradation of packaging components in contact with the pharmaceutical products.
- The influence of the manufacturing process (e.g. sterilization) on the container.

2. Secondary Packaging
The package external to Primary package is known as secondary package. This package provide additional protection during warehousing and also provide information about drug product for e.g. Leaflets. This is consecutive covering or package which stores pharmaceuticals packages in it for their grouping. Examples: Cartons, boxes, etc.

3. Tertiary Packaging
It is outer package of secondary packaging & prevents damage to the products. It is used for bulk handling & shipping. This is to provide bulk handling and shipping of pharmaceuticals from one place to another.

Examples: Containers, barrels, Barrel, crate, container, pallets, slip sheet.

Table 1: Types of Primary & Secondary Packaging Materials

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Material</th>
<th>Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Glass</td>
<td>Primary</td>
<td>Ampoules or Vial</td>
</tr>
<tr>
<td>2.</td>
<td>Plastic</td>
<td>Primary</td>
<td>Ampoules, Vial &amp; Dropper bottle</td>
</tr>
<tr>
<td>3.</td>
<td>Metal</td>
<td>Secondary</td>
<td>Wrapper to contain primary pack</td>
</tr>
<tr>
<td>4.</td>
<td>Cardboard</td>
<td>Secondary</td>
<td>Carton box</td>
</tr>
<tr>
<td>5.</td>
<td>Paper</td>
<td>Secondary</td>
<td>Labels, patients information leaflet</td>
</tr>
</tbody>
</table>

With respect to method of closure, the B.P.C defines four types of containers:6,7
- Well closed container.
- Air tight container.
- Securely-closed container.
- Hermetically-sealed container.

Well-closed container: This container protects the contents from contamination with extraneous solids under normal conditions of handling, storage and transport, prevents unintentional release of the contents.

Example: antacid suspensions, syrup, elixirs, closure can be detached many times used for with draw of multiple dosage forms.

Airtight container: This container gives protection from extraneous solids, liquids and vapours under normal conditions of handling, storage and transport, prevents changes due to efflorescence, deliquescence and evaporation.

Securely-closed container: This is an airtight container with a means of preventing unintentional displacement of the closures.

Example: Eye drops, Eardrops, Multidose vials. In this case, if tip of closure is opened it should be used with in a specific period of time. Other should be discarded.

Hermetically-sealed container: This container is impervious to air and other gases under normal conditions of handling, storage and transport.

Example: Glass Ampoule sealed by infusion.

Components of Packaging

Container: A Pharmaceutical container is a device that holds the drug and may be in direct contact with product. If the container is in direct contact with the drugs it is called an immediate container. (or) It is a device which holds the drug (or) the drug product either directly (or) in indirect form. In some of the containers product may not be in direct contact with i.e. Each unit is packed in a sachet and all of them are stored in containers. Ampoules packed in a container. The containers refer in which the product/ medicine is placed & enclosed. It is direct
contact with drug.

Closure: It is a device which protects the drug (or) drug product by preventing the entry of air, moisture, particulate matter, and microorganisms etc., thereby keeping the product in a safe condition and also assists in proper use & of the drug. It is tightly packs the container to exclude oxygen, carbon dioxide, moisture & prevents the loss of water and volatile substances from the products.

Carton/outer: Which gives secondary protection against mechanical and other environmental hazards. It is outer covering. Cartoons are made up of cardboard, wood pulp etc.

Box: In this multiples of products are packed. It provides primary defence against external hazards. The boxes are made up of thick cardboard and wood.

Desirable Features of Containers and closures[7,9]

1. The container must be rigid enough to prevent damage to the contents eg:- fracture of tablets and crushing of capsules.
2. The materials of construction must not react with contents.
3. The closures must prevent-
   A. Loss of moisture eg: to moisture sensitive tablets and, because their shells are hygroscopic to capsules.
   B. Loss of moisture from cream and from water-containing ointments and creams.
   C. Unintentional escape of the content, and
   D. Entry of direct (or) other contaminants such as odorous vapours that might cause
4. The closure must be easily removed and replaced.
5. It must not be difficult to abstract the content (or) empty the container completely.
6. For many products, protection from light must be given.
7. It must be easily to label the container correctly.
8. It must have a pharmaceutical-elegant appearance.
9. They should be inert and should not interact with the drug product.
10. They should have uniform distribution of the product for easy usage and handling.
11. They must be available in form by which they are suitable for a dosage form eg:- ear drops, nasal drops.
12. They should be able to protect the drug from environment hazards.
13. They should be made in such a way that they have to resist/withstand stocks and abrasions while they are under handling and transport.
14. Containers, used for parental products should be to withstand high sterilization conditions (temperature pressure).
15. The containers used for pharmaceutical purposes should be available in a highly economic rate.
16. Containers used for aerosol packing should be able withstand high pressures.
17. Containers should be available in different size and shapes for easy identification by the patients.

Packaging Materials[8]
The materials selected for packaging must have the following characteristics:
- Mechanical properties.
- Physico-chemical properties.
- Biological properties.
- Economical aspects.
- Pharmaceutical properties.
- They must be non-toxic.

Types of packaging materials
The following materials are used for the construction of containers and closures.

![Fig. 2: Types of Packaging Materials](image)

GLASS[3,10]
Glass is generally the first choice of packaging for all types of pharmaceutical products. Glass is the only packaging material rated ‘GRAS’ or ‘generally regarded as safe’ by the U.S. Food & Drug Administration. In the European and the United States pharmacopeia’s various grades of glass are classified as official based on their chemical characteristics and efficacy within the packaging of pharmaceuticals.

Glass containers also are beneficial from the economical point of view as glass is abundantly present in nature and because of its capability to be sterilized and hence be recycled.

When compared to other packaging materials, the glass container lies in the unique combination of durability, inertness and transparency. The container chosen for a given preparation shall be such that the glass material does not release substances in quantities sufficient to affect the stability of the preparation or to present a risk of toxicity. 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.

Preparation of glass[10]: Glass is composed principally of sand, soda-ash and lime stone. Glass made from pure silica consists of a three dimensional network of silicon atoms each of which is surrounded by 4 oxygen atoms in
tetrahedral way to produce the network.

Primarily there are four processes involved in the manufacturing of glass – blowing, drawing, pressing and casting. In the blowing process compressed air is used to make the molten glass in the cavity of a mold made of metal. This mold is used to manufacture most of the bottles and jars using automating machines. In the drawing process, the molten glass is drawn through dies or roller to give shape of soft glass. By this process the rods, tubes, sheet glass of uniform diameter or thickness are produced. The molten glass is pressed in the process of pressing by a mechanical force against the side of mold. The molten glass is casted in the cavity of mold using centrifugal or gravitational force.

Properties
1. It is very hard
2. Chemically resistant
3. Structure is less rigid so low melting point.
4. Glass made of pure silica.

Advantages
1. They protect the drug (or) drug product from environment hazards.
2. They improve stability of product by starting them in glass container.
3. They are prepared by moulding process.
4. Some of the drugs are highly sensitive to light can be protected by using different kinds of coloured glasses
   Examples: Amber coloured, Green coloured.

Disadvantages
1. They are highly fragile in nature.
2. They undergo leaching process (glass may contain alkalis which may get leach in to drug).
3. They undergo weathering process/clouding process (due to exposure to adverse climatic conditions, If moisture gets stuck to glass surface. It takes away alkali. If further condensation occurs dull form of the container can be observed.
4. If undergoes flaking process (if strength of glass. is decreased, blanking of the particles from the glass occurs).

Types Of Glass Containers
According to the hydrolytic resistance characteristics, glass containers are classified as follows: Following four types of glass are accepted for packaging in the USP.

Type I glass containers or borosilicate glass
Neutral glass, with a high hydrolytic resistance due to the chemical composition of the glass itself. It is used to contain strong acids & alkalies as well as all types of solvents. The addition of approx. 6% boron to form type I glass reduces the leaching action.

Main constituents: SiO2-80%, Al203-2%, Na2o, Cao-6%
Uses: Laboratory glass apparatus, for water for injection.
Eg: Pyrex, Borosil.

Type II glass containers or treated sodalime glass
Usually of soda-lime-silica glass with a high hydrolytic resistance resulting from suitable treatment of the surface. The surface of glass is resistant to attack by water for a period of time. When glassware is stored for several months, especially in a damp atmosphere or with extreme temperature variations, the wetting of the surface by condensed moisture (condensation) results in salts being dissolved out of the glass. This is called “blooming” or “weathering” & it gives the appearance of fine crystals on the glass. Type II containers are made of commercial soda-lime glass that has been de-alkalized or treated to remove surface alkali. The de-alkalizing process is known as “sulphur treatment” and virtually prevents “weathering” of empty bottles. Some manufacturers expose the glass to an atmosphere containing water vapor & acidic gases. This results in a reaction between gases & surface alkali, which makes it resistant to attack by water.

Main constituents: Made of soda lime glass. The surface of which is treated with acidic glass like so2 at Elevated temperature and moisture.

Uses: For alkali sensitive products, Infusion fluids, blood, & plasma, large volume container.
Type III glass containers or regular sodalime glass
Usually of soda-lime-silica glass with only moderate hydrolytic resistance. Flakes separate easily, many cracks due to sudden change of temperature.
Main constituents: SiO2, Na2O, Cao.
Uses: Topical use, For oral use, Not for ampoules.

Type IV glass container or Non Parenteral glass or general purpose sodalime glass
Usually lower-quality flint or soda glass (U.S) or not for parental use. Uses: Topical use, for oral use, not for ampoules.

Neutral glass
Lower cost than borosilicate, they are softer & can easily be moulded.
Main constituents: SiO2 -72 to 75%, B2O3 -7to 10, Na2o -6 to 8%, K2o - 0.5 to 2%, Bao -2 to 4%.
Uses: Small vials (25 ml), Large transfusion bottles.

Coloured bottles
Produce amber colour glass, Can resist UV visible radiation from 290-400-450nm. Main constituents: Glass + iron oxide.
Use: for photosensitive products.

Problems With Glass Containers[10,12]
- Leaching.
- Weathering/clouding.
- Flaking.

Leaching
It is the process of liberation of alkali from the surface of glass container in to the drug, product. Due to liberation of alkali, product may undergo instability, and pH of drug gets altered. Finally drug may be come toxic, impotent, decomposition and inactive.

Example Insulin-pH3.5 if stored in glass container for prolonged period. It interacts with glass, and alkali gets liberated. It pH crosses 7 it becomes inactive and doesn't give its effect.

Weathering/Clouding
It is process of loss of alkali from the surface of glass containers. There by clarity of glass gets decreased, cloudiness occurs. It is continuous process. Due to loss of alkalis, strength is decreased, there by clarity is decreased and cloudiness appears.

Flaking
It is the process of release of fine particles of glass in to the drug product. It arises due to exposure of particular container to fluctuated temperature (or) environment conditions.

Exposure to fluctuated temperatures, leaching (or) weathering occurs which ultimately leads to flaking with remaining amount of alkalis, once flaking occur. It should not be used.

Access the strength of glass& amount alkali liberated. they are two types, such as
- Whole-glass test
- Glass pieces test

Whole-Glass Test
A suitable glass container is taken, filled with distilled/purified water closed with suitable closure and the container is subjected to autoclaving process at 121°C for 1hr. Due to high temperature and pressure alkali may get leached in to the water. Glass container is allowed to cool at room temperature and the water taken in glass container is transferred in to conical flask and titrates against 0.2N H2SO4 by using methyl red as an indicator. Amount of alkali assayed shouldn't exceed the limit. it exceed, it shouldn't be used.

Glass-Pieces Test
Glass container is taken crushed to fill powder, sieved and a suitable amount of uniform glass pieces/powder is taken and mixed with some of the purified/distilled water. Mixture is subjected to autoclaving process at121°C for 1/2hr. Mixture is taken out, cooled to room temperature and subjected to either centrifugation or decantation process, to collect the super-nated liquid. This is titrated against 0.2N H2SO4 using methyl red as an indicator. Titration value obtained should be below the normal value given in I.P.

Plastic[5,10]
Plastics are long-chain polymers that can be melted, formed into a desired shape, and solidified during cooling. The general advantages of using plastic materials in pharmaceutical packaging include consumer acceptance, preference, excellent safety characteristics (non fragility), less weight than other materials, moisture barrier properties, gas barrier properties, good puncture resistance, low heat conductivity, good sealant properties, and recyclability. Plastics are inexpensive, lightweight, strong, durable, corrosion-resistant materials, with high thermal and electrical insulation properties, because of these properties plastics are widely used in the pharmaceutical packaging industry. In addition to this it can be easily moulded into the preferred shape and provide protection against contamination and in the storage and transportation.

Types of plastics
Plastics are classified in to 2 groups according to their behaviour when heated.
- Thermosetting type

Thermosetting types are used in packaging industry mainly for bottle and jar closures. These are usually hard and brittle at room temperature and cannot be re-melted at without decomposition during the manufacturing process, raw materials of the any plastic type, when heated to particular undergoes liquefaction. This liquid
when cooled, gets reconstituted to solid form. On heating, they soften to a viscous fluids which hardens again on cooling.

Examples polyethylene—they are off 2 form

a) Low density polyethylene.

b) High density polyethylene.

Polyvinyl chlorides (PVC), polyamides, polyalkyles, polymetacrylates, polypropylene, Polypropylene, Polystyrene, Nylon etc.

Advantages: It can be recycled for many numbers of times and can be used for different purposes. During manufacturing, we may not be satisfied in strength size required for pharmaceutical use. Then the entire mass can be recycled and problem can be rectified by adding suitable additives.

Disadvantages: They melt at low temperature & can’t tolerate high temperature up (or) exposure labour use.

Thermoplastic type

It includes materials which can be converted in to an unlimited range of shapes and sizes by various processes like extrusion, injection moulding casting etc., this type of plastic can be re melted without decomposition. When heated, they may become flexible but they do not become liquid, usually hard and brittle at room temperature.

Examples Low density polythene, high density polyethylene, polyvinylchloride (PVC), polymethyl methacrylate (PMMA), Polystyrene, poly tetra Fluro ethylene (PTFE).

Table 1: Polymers used in the production of Plastic

<table>
<thead>
<tr>
<th>Commonly Used Polymers</th>
<th>Less Commonly Used Polymers</th>
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</thead>
<tbody>
<tr>
<td>Polyethylene</td>
<td>Polyethylene terephthalate</td>
</tr>
<tr>
<td>Polyvinyl chloride</td>
<td>Polymethyl methacrylate</td>
</tr>
<tr>
<td>(PVC)</td>
<td>Aminioformaldehydes</td>
</tr>
<tr>
<td>Polypropylene</td>
<td></td>
</tr>
<tr>
<td>Polystyrene</td>
<td>Polyamide</td>
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</table>

Polyethylene (PE): Polyethylene is available in three different grades including low (LDPE), medium (MDPE) and high (HDPE) density (ranging from 0.91 to 0.96). As the density of PE increases both physical and chemical properties vary. The clarity and translucency depends upon the density of PE. The low, medium and high density PE have oxygen transmission of 500, 250-535 and 185 respectively. High density polyethylene (HDPE) is the most crystalline material and is most widely used for the containers by the pharmaceutical industry for drug packaging because it offers good barrier against moisture but a relatively poor one against oxygen and other gases. HDPE mostly used for solid oral medication in pharmaceutical industry. Polyethylene is the material of choice with polypropylene (PP) as a polymeric material used for on line blow fill seal technology.

Poly-Styrene (PS): The polystyrene is the clear rigid hard material with good tensile strength but is one of the most brittle plastics when dropped. It is resistant to mineral oil, water and alkali but is soluble in organic solvents. It is fairly permeable to moisture and is generally not a suitable packaging material for pharmaceutical products.

Polycarbonate (PC): The poly carbonate material is having good impact resistance with excellent dimensional stability. It has a low water absorption capacity and is heat resistant. PC is used to make membrane filters, reusable bottles and sterilize-able medical packaging.

Polyvinyl Chloride (PVC): PVC used as a forming film is called rigid PVC because it is almost free of softening agents. Currently it is the most widely used forming film and displays ideal forming characteristics. Its water-vapor permeability is very low. The principal advantages of PVC are the low cost and the ease of thermoforming. The main disadvantages are the poor barrier against moisture ingress and oxygen ingress; moreover PVC has a negative environmental connotation due to its chlorine content. In the case of blister packaging the PVC sheet does not contain any plasticizer and is sometimes referred to as Rigid PVC or RPVC. In the absence of plasticizers, PVC blisters offer structural rigidity and physical protection for the pharmaceutical dosage form. On the other hand, the blister cavity must remain accessible by the push-through effect and the formed web may not be too hard to collapse when pressed upon; for this reason the PVC sheet thickness is typically chosen between 200μ to 300μ depending on the cavity size and shape. Most PVC sheets for pharmaceutical blisters are 250μ or 0.250 mm in thickness. Typical values for the Water Vapor Transmission Rate (WVTR or MVTR) of a 250μ PVC film are around 3.0 g/m²/day measured at 38°C/90%RH and the Oxygen Transmission Rate (OTR) is around 20 ml/m²/day. In order to overcome the lack of barrier properties of PVC film, it can be coated with PVDC or laminated to PCTFE or COC to increase the protective properties. Multi-layer blister films based on PVC are often used for pharmaceutical blister packaging, whereby the PVC serves as the thermo formable backbone of the structure. Also, the PVC layer can be coloured with pigments and/or UV filters. The following Factors must be considered when PVC is used for pharmaceutical purpose like stabilizers, plasticizer, monomer, residue, modifiers, lubricants, catalytic residue.

Poly Vinylidene Chloride (PVDC): PVDC-coated PVC has characteristics similar to those of uncoated PVC except that the water vapor permeability of films coated in this way is reduced by a factor of 5-10. The coating is applied on one side and usually faces the product and the lidding material. PVDC is Copolymer of vinyl chloride or vinyl acetate and vinyldene chloride. It is an excellent resistance to permeation by moisture and gas and mostly
widely used as a coating.

**PVC and ACLAR (CTFE):** VC-CTFE films made from PVC and ACLAR (CTFE) have the lowest water-vapor permeability of all the films used for blister packaging. The environmental concerns raised about PVC also apply to PVC-CTFE film. Poly chloro trifluoro ethylene or PCTFE can be laminated to PVC to obtain very high moisture barrier. Typical constructions used for pharmaceutical products are 250μ PVC film laminated to 15μ-100μ PCTFE film. Duplex structures are PVC/PCTFE and triplex laminates are PVC/PE/PCTFE. Deeper cavities can be formed by using the triplex structures with PE. Typical WVTR values are between 0.06 - 0.40 g/m²/day.

**Cyclic Olefin Copolymers (COC):** Cyclic olefin copolymers (COC) or polymers (COP) can provide moisture barrier to blister packs, typically in multi-layered combinations with polypropylene (PP), polyethylene (PE), or glycol-modified polyethylene terephthalate (PET). Cyclic olefin resins are generally amorphous and are noted for good thermoforming characteristics even in deep cavities, leading some to use COC in blister packaging as a thermoforming enhancer, particularly in combination with semi crystalline resins such as PP or PE. Films can be manufactured via co extrusion or lamination. WVTR values of commercial cyclic olefin-based pharmaceutical blister films typically range from 0.20 to 0.35 g/m²/day at 38°C/90% RH. Unlike PVC and other common pharmaceutical barrier resins, cyclic olefin resins do not contain chlorine or other halogens in their molecular structure, being comprised solely of carbon and hydrogen. Cyclic olefin resins are available which comply with pharmaceutical packaging guidelines in the US, Europe, and Japan.

**Polypropylene (PP):** There is an increasing trend towards the use of PP as a support material for blister packages. The water-vapor permeability of uncoated PP is lower than that of PVC and is comparable to the water vapor permeability of PVDC coated PVC. Water- vapor permeability of uncoated PP is lower than PVC, and is comparable to PVDC coated PVC. One problem posed by PP processing is thermoforming. The temperature required for thermoforming PP and the temperature of subsequent cooling process must be precisely controlled. Another problem is warping of package – often resulting in the requirement for PP formed packages to be straightened before cartooning.

**Limitations of Plastic Materials:** [7,10,11]

1. **Permeation**
2. **Leaching**
3. **Sorption**
4. **Chemical modification**
5. **Alteration on the properties of plastics or product**
6. **Deformation**
7. **Entrainment of light rays.**

**Permeation**

The transmission of gases, vapours or liquids from the surrounding environment into the plastic container is known as “Permeation”. Permeation of water vapor & oxygen through the plastic wall into the dosage form can be problematic if the drug is sensitive to hydrolysis and/or oxidation. An increase in temperature, increases permeability of gases. An increase in crystallinity of the material decreases permeability. Hydrophilic plastic materials such as nylon are poor barriers to water vapor, while hydrophobic materials like polyethylene are better barriers. The concentration of drugs in formulations containing volatile ingredients might change when stored in plastic containers because of the permeation of one or more volatile ingredients through the walls of the plastic containers. Plastic containers also affect the physical properties of the product. For example, when water-in-oil emulsion is stored in a hydrophobic plastic bottle, there is a tendency for the oil phase to migrate & diffuse into the plastic. Permeation may also affect the shelf-life of a drug.

**Leaching**

Release of a constituent from the plastic material of the container into the formulation is known as “leaching”. For example, particular dyes which are used as colouring agents may migrate into a product, contaminates the product and may cause a toxic effect.

**Sorption**

The Process of extraction / removal of one or more of the constituents from the formulation by the packaging material are referred to as “Sorption”. Becomes a serious problem particularly for dosage forms that contain drug and/or other important ingredients in the solution form. It may significantly affect the therapeutic efficacy of the formulation containing highly potent drug.

**Chemical reactivity**

Certain ingredients used in plastic container manufacturing may chemically react with one or more components of a drug product. These chemically incompatible substances may also alter the appearance of the plastic or formulation.

**Modification**

The physical or chemical alteration of the packaging material by the drug product is called “modification”. The content may extract the plasticizer, antioxidant or stabilizer, thus changing the flexibility of the container. Permeation, sorption or leaching may also alter the properties of the plastic container.

For example: (1) Oils have a softening effect on polyethylene; (2) Fluorinated hydrocarbons attack polyethylene & PVC.

**Deformation**

This effect occurs if permeation, leaching & sorption occur. On other hand if containers are stored at very
adverse climatic conditions structural deformation occurs.

**Entrainment of light ray**

Just like glass, plastics don’t resist the entrainment of light rays. In complex polymeric chain of plastic, all additives are fixed in to it. Even though a very high complex occurs, fine pores are can appear both the complexes which can allow the light rays to pass that may affect the light sensitive materials gets decomposed.

**Test To Be Performed By Plastics**

Plastic should be tested for fitness. In-vivo tests are to be performed.

- TYPE-1 RABBIT
- TYPE-2 MICE (OR) RAT
- TYPE-3 RABBIT

**TYPE 1 Rabbit**

Plastic containers is shredded to cut in to fine pieces then mixed with water after that suspension is made. A Suspension is to be injected intramuscularly to the rabbit and toxic effects are produced in the rabbit are to be observed. Toxic effects are increase in temperature, convulsions animals, paralysis to particular organ, unconscious, and death of the animal. Intensity of toxic effects should be compared with standard sample of plastic that is injected to another set of rabbits. Intense of toxic effects should be less than the standard sample then it is proved to be best.

**TYPE 2 Mice (or) Rat**

Either mice (or) rats are observed used finely divided pieces of plastic is extracted with water and supernated liquid obtained by extract is collected and injected intraperitoneally to either rats (or) mice then effects are observed. Intensity of toxic effects should be compared with standard sample of plastic that is injected to another set of rabbits. Intense of toxic effects should be less than the standard sample then it is proved to be best.

**TYPE 3 Rabbit**

Extracted solution of plastic is injected intradermally to the rabbit and toxic effects are observed.

**Metal Containers**

Metal is the most adaptable of all the materials used in the packaging; however it is used to dispense only the non-parental medicinal products since it poses the threat of possible shedding of metal particles into the product. Different metals like tin, aluminium and tinplate are used in pharmaceutical industries. Metals provide superior protection against contamination as they impervious to light, moisture and gases. They are also lighter in weight when compared to most materials. The containers made from metals include tubes, packs made from foil or blisters, cans, and aerosol and gas cylinders. The major disadvantage that they pose is that they are highly expensive. The collapsible metal tube is an attractive container that permits controlled amounts to be dispensed easily, with good re closure and adequate environmental protection to the product. The risk of contamination of the portion remaining in the tube is minimal, because the tube does not “suck back.” It is light in weight and unbreakable, and it lends itself to high-speed automatic filling operations. The ductile metals used for collapsible tubes are tin (15%), aluminium (60%), and lead (25%). Tin is the more expensive than lead. Tin is the most ductile of these metals. Tin containers are preferred for foods, pharmaceuticals, or any product for which purity is an important consideration. Tin is chemically inert of all collapsible tube metals. Laminates of tin-coated lead provide better appearance and will be resistant to oxidation. They are also cheaper compared to tin.

**Aluminium**

Aluminium is the most abundant metal on the earth’s surface, but it is one of the most costly constituents in a laminate. Foil is obtained from metal of 99% purity and above. The gauges range from 0.006 mm to 0.040 mm. The foil is annealed to give a soft foil with a ‘dead fold’ property. Hard tempered (non-annealed) foil occasionally finds special applications, i.e. push-through lidding for blister packs. Lubricants are removed from hard foil by either solvent washing or controlled heating. For any nominal gauge +8% variations is normally allowed. For solid dosage form (i.e. tablet, capsules, and powders) aluminium foil is the most commonly used packaging material due to its protective characteristics with respect to the effects of moisture, heat and light. Aluminium offers significant saving in the product shipping costs because of their light weight; they provide the attractiveness to the tin at somewhat lower costs. The different types of aluminium packaging materials include lidding aluminium foil containers, casserole, lid punching machine, disposable kitchen foil, cling film, lidding pharma foil, lidding packaging material, cigarette foil, lidding blister foil, aluminium lidding foil poly, paper laminated foil, heat sealable lidding foil, foil lidding casserole, triple laminate for ORS pouch, strip packing, foil panes, aluminium foil and alufoil lidding. A number of alufoil properties combine to provide a convenient, safe and versatile packaging format for tablets, creams, liquids and powders covering an enormous variety of pharmaceutical products. Alufoil unrivalled barrier properties totally exclude moisture, oxygen and other gases, microorganisms and light, thus maintaining sensitive products in peak condition for long periods.

**Important properties of aluminium foil**

**Barrier:** Alufoil total barrier to light, atmosphere and liquids is the principle reason for its use in pharmaceutical applications.

**Dead fold and mechanical properties**

Alufoil is strong and can be laminated with other materials. By using different alloys alufoil can be given a choice of characteristics, which make it suitable for ‘push through’
lids or pre-formed trays for tablets.

**Hygiene and safety:** Alufoil does not harbour bacteria. It can be supplied in a fully sterile condition. Many suppliers offer alufoil packaging materials produced in hygienic ‘clean-room’ facilities.

**Sustainability:** Alufoil is weight saving, effective and minimizes the amount and diversity of packaging material needed. Added to this reduction at source, it also helps to preserve valuable pharmaceutical products, so cutting waste of materials and energy.

**Applications of aluminium and plastic as packaging material**
The various applications of aluminium as packaging material for pharmaceutical products are given below.

**Blister packs**
Alufoil is particularly suitable for blister packs because of the range of mechanical properties available. Depending on the alloy and its treatment, alufoil can be made more brittle, tougher or more ductile. It can also be combined with other materials like paper or plastics. Blister packs are tamper-evident and can be designed to be ‘child-proof’ or to provide more secure access. Most blister packs consist of a preformed plastic tray with an aluminium foil closure manufactured to facilitate the necessary ‘push-through’ characteristic. A recent development is the all-aluminium blister pack.

**Strip packs**
Strip packs can be produced from Aluminium or in combination with paper or plastics.

A key requirement is that they should be easy to tear open. Alufoil is readily printed and its malleability and dead fold characteristic are important in these applications, allowing the metal to closely form to the shape of the tablet. Strip packs provide economical high barrier performance and can be filled at high speeds on modern, sterile, filling lines.

**Sachets and pouches**
The sensitive nature of most pharmaceutical preparations demands that the packaging provides a perfect barrier to moisture, and often to light. Alufoil laminated sachets provide an effective packaging solution for many products whether in powder, cream or liquid form.

Heat-sealed membranes and closures
Many medicines are supplied in glass, plastic or metal containers. Alufoil, laminated with paper or plastic, is frequently used as a heat-sealed membrane hermetically closing the container, usually under a plastic screw cap. The localized heat needed to affect the sealing process is generated by an electrical induction process after the screw caps are applied on the filling and capping line. The resulting alufoil membrane provides excellent barrier properties preventing moisture or gas transmission and providing tamper evidence.

**Rubber**
This is mainly used for manufacturing of closures, filters, cap lines, droppers (pediatric purpose). It avoids leakage and protects external environment. Rubber occurs on two forms. They are
- Natural rubbers.
- Synthetic rubbers.

**Natural Rubber**
Natural rubber is majorly obtained from Kerala Malabar plantation. Natural rubber consists of long chain polymers of isoprene units linked together in the cis portion. Its most important source is the tree Hevea braziliensis from which latex, containing 30 to 40% of rubber in colloidal suspension, exudes when shallow cuts are made in the bark. It exudate juicy gummy material to produce rubber. It is susceptible to microbial contamination. They are not compatible and these cannot achieve desired shapes, strength, capacity and strength.

**Synthetic rubber**
It is mostly used in pharmaceutical field. It contains Isoprene derivatives like neoprene butylated rubber etc.; are used as synthetic rubber depending upon the derivatives blend of additive are added we can get rubber of desired shape, strength, capacity & elasticity.

**Advantages of Rubber as Closures**
1. It is having very good ageing effect (long shelf life).
2. It is having proper elasticity (either contract (or) expand allowing fitting in to any type of container).
3. It will not allow the permeation of air (or) moisture through it.
4. They are available in different sizes and shapes which make them to fit in to neck of different kinds of containers.
5. They are free from fragile nature (if rubber, closure is used for multi-vials and if it is fragile small pieces of rubber can enter in to the drug).
6. They are available in highly economic rate.

**Disadvantages of Rubber as Closures**
1. It undergoes leaching process.
2. It may be influenced by sorption process.
3. It cannot resist high temperature.

**Ideal Characteristics of Rubber**
1. It should have proper ageing effect.
2. It should have proper elasticity and strength.
3. It shouldn’t permeate air (or) water in to it.
4. It should be non-fragile in nature.
5. It should be available in highly economical order.
6. It should be free from leaching.
7. It should be available in different sizes& shapes.
8. It shouldn’t be influenced by sorption process.
9. It should have proper resistance to with stand sterilization conditions.
Tests to be performed for Rubber[7,11]

a) Quality test
We find the quality of product manufactured and enclosed with rubber. Before and after packaging it should possess following
A. It should be thoroughly washed with solvent.
B. It should be subjected to sterilization.
Rubber closure should be stable without producing tackiness under certain conditions. If we want to remove detergent from rubber, it should be heated with hot water (or) cold water (or) detergent water at 60-65% for 1hr. If it is parental then it should be heated at 121°C for 1/2hr.

b) Finish test
During manufacturing of rubber closures, different kinds of additives are used, finished product is obtained, a fine dust layer is that on rubber closure which may enter in to container and contaminate it. To prevent it, rubber closure is immersed in distilled water and heated for 4hr under vacuum conditions.

c) Penetrability
Mainly used for rubber closure intended for IV infusions and multivial injection system. In the above cases, closures are used as rubber. To with draw the sample, needle injection is pierced in to rubber work which should have proper strength & elasticity. Injection needle is kept stationary position and multivial injections closed with rubber closures is fixed to the piercing meter, which allows the bottle to move up and down so as to enable the rubber closure to undergo piercing by the stationary needle. Piercing meter is associated with a gauge which gives us the force required for piercing the rubber closures. Optimum force is required for piercing the rubber is noted. If excess force, not suitable for multivial injections.

d) Test for Permeation
If rubber closure is allowable to permeation, complete damage of the drug may occurs. Stability conditions medicated in the above test are too length. To avoid this, accelerated stability conditions like 50°C with 100% humidity for 3 months should be used. At these conditions, if rubber is compatible with drug, we can use it. If it fails we have to check for ordinary stage conditions at least for 6 months. If it is at 6 months also we can reject it and pierce the needle in to it by moving up and down. If the rubber pieces entered are three in water by conducting test. then it is passed or else it fails.

e) Water Extractive Test
It is mainly to find out total residual mass present in rubber closure. When rubber closure is subjected to various temperature conditions, some of the additives may evaporate, residue remains. When evaporate, residue is contact with drug product, contamination occurs. The test is performed by taking rubber closure in water and subject it to reflux condensation process and condensate is collected and condensate is subjected to evaporation followed by drying and now it is collected and weigh. If it is in limits, it is used or else it is rejected.

f) Leakage Test
Two types of tests are performed, they are Type 1 Test
Type 2 Test

Type 1 Test
Containers are filled with distilled water or drug solution closed with the help of rubber closure. With the help of a syringe needle, the rubber closure is allowed to pierce to collect the solution inside. After withdrawal of syringe, the surface of rubber closure is to be checked. If surface of rubber closure is stained with any water drops or if the surface is wetted with water indicates the presence of leakage. If there are no such observations, indicate that rubber closure is free from leakage.

Type 2 Test
The container is filled with dye or indicator solution such as methylene blue, closed with rubber closure to be tested. Then bottle is placed in distilled water and it is subjected to autoclaving at 121°C for ½ hrs, after autoclaving if the outermost water in which bottle is suspended is coloured indicates the leakage of rubber closure. Otherwise there is no leakage.

g) Test for acids and alkalis
Alkalis and acids are highly reactive, if they react with drug product, decompose occurs. To avoid this, we have to test it before.

Rubber closure are suspended in to water and it is subjected to autoclaving at 121°C for ½ hrs after that, water is collected and it is assayed by using acidimetry or alkaliometry to find out presence of alkalis & acids.

Paper And Paperboard[3,10]

Paper and cardboard is a pillar of traditional packaging materials, consumption of large, wide range of applications, its output accounts for about 45% of the total output value package. Paper and paperboard must be appropriate strength, impact resistance and wear resistance; good sealing and easy to clean; excellent shape and fold, easy to use various processing methods; should be in the mechanization and automation of packaging; have the best printable, easy introduction and landscaping products; lower prices, and light weight, can reduce packaging costs and transportation costs; easy to handle after use, reuse and recycling of recyclable and will not pollute the environment and conserve resources; paper and cardboard containers are mainly large cardboard boxes, cartons, paper bucket, paper bags, paper cans, paper cups, paper plates, etc., are widely

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used in transport packaging sales packaging.

**Caps And Closures**

Closures that form part of the container-closure system are an important component in the packaging of sterile products. They are also known as stoppers or bungs. Closures, which form a part of the primary packaging system, are very important & should be therefore carefully selected. They form essential component of the container & an integral part of the drug preparation. Most commonly an elastomeric closure is used. An elastomer is any material that is able to resume its original shape when a deforming force is removed, which is known as viscoelasticity. The primary function of the closure system is to retain or contain the content, safety and security may be necessary to prevent hazards resulting in leakage, seepage, spillage, pilferage, loss of quality, purity, etc. The ideal closure prevents exposure of the sterile product to both moisture and oxygen thus ensuring the stability of the product and also prevents the contents from escaping the container. The adequacy of the seal is dependent on a number of factors; these include the flexibility of the liner and the torque which is applied. For a closure system to be effective it is essential to consider the nature of material of container, properties of the product and the stability requirements. Closures may be manufactured by a number of means of combination of pressure, temperature and adhesion. The materials used for the formation of closures include: Metals like aluminium, aluminium alloys, tinplate, tin free steel, stainless steel. Glass is used for formation of stoppers. Rubbers and plastics are also and very commonly and widely used for cap and closures. Caps or over seals are used to secure the rubber closure to the container in order to maintain the integrity of the seal under normal condition of handling and storage. These caps are usually made of aluminium and may be equipped with plastic top to facilitate opening.

Closures generally require consideration of the following factors

- Resistant & compatible with the product & the product/air space.
- If closure is re-closable, it should be readily openable & effectively resealed.
- Capable of high-speed application for automatic production by high speed machines without loss of seal efficiency.
- Decorative & of a shape which blends in with the main container.
- Offers such additional functions: aid-pouring, metering, administration, child resistance, tamper evidence, etc.
- Prevents exchange with the outside atmosphere to a permissible level.

The majorities of closure systems are incorporated by physical compression or heat sealing. The physical compression system includes:

1) Screw caps – In metal or plastic, preheated or rolled on with or without a wadding system (i.e. wadless).
2) Plug in – A friction push in fit
3) Push over – A flanged or raised ring portion is pressed over a bead or lip.
- Wadless thermoplastic caps using a “crab’s claw” seal or a skirted bore seal are very popular. - Wadded screw caps either contain a wad plus a facing, a disc of resilient plastic or have a flowed-in plastic compound.
- The wad may be of compo-cork, felt-board, and pulp-board or expanded PE, faced with such materials as aluminium foil, tin foil, PE, PVC.
- These have good barrier properties and are reasonably inert, and most widely used these days.
- Foil or waxed foils are less preferable if a higher barrier material is required.
- Rolled on (RO) or rolled on Pilfer Proof (ROPP) aluminium alloy metal caps are popular for security of export products.
- RO and ROPP closure consists of a plain metal shell containing wadding or flowed-in system, which is placed over the container neck & pressure is applied on top to give a good impression on the wad.
- In case of pilfer proof closure; an additional perforated collar is ruled under a lower bead. This type of closure system is capable of maintaining an excellent seal & does not suffer from the occasional tearing of the wad when a conventional screw cap is applied to a substandard bottle finish.

**Types Of Closures**

The basic types of caps and closures include:

a) **Thread Screw**: This provides physical and chemical barrier to the contents in the container. They are either made of plastic or made of metal.

b) **Lug Cap**: This differs from the thread screw closure due to the presence of continuous thread on the container. It is more commonly used in food industries rather than pharmaceutical industry.

c) **Crown Cap**: It is a crimped closure more commonly used in beverage industry.

d) **Rubber Closures**: Rubber consists of several ingredients one of which is an elastomer. Rubber compounds used in pharmaceutical packaging contain only limit number of ingredients which are difficult to extract. These closures do not pose any problem and can be used in contact with a large number of drug preparations.

e) **Roll on Closure**: Pilfer proof; reseal able and non-reseal able type of roll on closures are available. These are dimension specific. Roll on closure hence require an easy to mould material such as aluminium.

f) **Pilfer Proof Closure**: This differs from standard roll on closure in that it has a longer skirt length. When this closure breaks at the bridge, the bank remains at the neck of the container. The closure can be resealed but the broken bank indicates the seal has been broken. It requires torque to remove the cap.
g) Tamper – Evident Closures: Tamper evident closures are designed to prevent accidental and intentional tampering to create safe packaging. The main concept of the tamper-evident packaging is increasingly being recognized in pharmacopoeias. Various types of tamper evident packaging are used in pharmaceutical industries are: Bottles with inner mouth seals, tape seals, Breakable cap ring system etc.

h) Child Resistant Closures: Child-resistant packaging or C-R packaging is special packaging used to reduce the risk of children ingesting dangerous items. This is often accomplished by the use of a special safety cap. It is required by regulation for prescription drugs, over-the-counter medications. In some jurisdictions, unit packaging such as blister packs is also regulated for child safety.

Test For Closures \[1,11\]

Penetrability test: Made to know the power required to make a hypodermic needle infiltrate effectively through the closure.

Fragmentation test: This test is made on 20 closures, every closure is infiltrated with hypodermic needle in a puncturing machine 5 times inside of a constrained region and needle is washed to exchange any part present. The substance is separated with hued paper that appears differently in relation to the elastic and the parts numbered.

Self-saleability test: Made by filling vials with water then closing them with prepared closures, for every closure another hypodermic needle is utilized and after that piercing 10 times every time at various site is done then flood the vials upright in methylene blue (0.1%) arrangement.

Extractive test: Here, we boil the closure with water for 4 hours under reflux and the water vanished to dryness. The build-up must not surpass determined sum.

Compatibility test: This is made to check the comparison of the elastic terminations with different sorts of substances, since it is important to guarantee that there is no communication between the substance of the jug and the closure.

Machinery For Packaging \[1\]
The machinery is an important technique for packing the any medicines or other materials.

1. Strip packing machine

Fig. 4: Strip Packaging Machine.

This model is applied for the packing of tablets, candy and pills in medicine, healthcare, chemical, and foodstuff industry etc with automatic double-aluminium foil hot sealing. Meeting the requirement of sealing for avoiding light, and also it is for double plastic hot sealing packing.

2. Blister Packing Machine

Fig. 5: Blister Packaging Machine.

It is high quality machine, which are suitable for handling automatic loading, filling or none stop feeding. Blister packaging machines are used by pharmaceutical industry to pack capsules and tablets. The packing process initiates with the capsules or tablets being loaded in to a hopper and then in to a feeder which in turn can either be linear feeder or a brush box feeder depending on the shape of the product and also the material to be used.
3. **Cartoning Machine**

This machine is applied to automatically box packing for medicine board, medicine bottle, soft box with palletized granule and ointment. Such as automatically boxing package of medicine, cosmetics. This machine features stable performance, compact structure and beautiful appearance. And it can automatically print stainless steel stamp. It has multi-function identification system. Automatically stopping or elimination when no tablets or vials are available. Cartoners have an output ranging 30 to 300 cartons per minute depending on whether the machine is vertical loading, intermittent Cartoning or a continuous motion model. These machines can handle blister stripes & other pharmaceutical packing.

![Fig. 6: Cartoning Machine.](image)

4. **Ampoule Filling Line**

These high precision machines completely encase the product in the inert glass & don not have a rubber stopper or any other material in direct contact with the drug. The line can be applied to fill 1-20ML amoule with automatic procedures as follows: Ultrasonic washing, three times water washing (twice circulating water washing, plus one time fresh water washing), three times air spraying, drying and sterilizing, cooling, liquid filling and protection gaseous filling (compressed air filling and nitrogen filling).

![Fig. 7: Ampoule Filling Machine.](image)

5. **Liquid Filling Machine**

It features advanced control system, accurate filling, stable performance, excellent appearance.

1. Ideal equipment for filling liquid injection and lyophilization injection.
2. Imported peristaltic pump system has high filling accuracy.
3. Completely 100c purifying laminar flow protection.
4. With function of stop filling without vial.
5. It can automatic count the filled vials.

6. **Syringe Filling Machine**

These machines are high precision & reliable machines used to fill syringes, cartridges and other related containers. Filling is done with the help of rotary piston pumps. The machines format spectrum can range from 0.2 to 29ml. Semi-automatic syringe filling machine: These machines require manual operators for loading the syringes in to the machine which are then filled & capped automatically. Applications include oral dosage syringe& dental gels. Fully automatic syringe filling machine: These high speed and compact machines automatically fill and are used for saline flush syringes, dental gels and oral dose syringe.

![Fig. 8: Liquid Filling Machine.](image)
7. **Automatic Labelling / Gumming / Stickering Machine**

Fully Automatic Labelling machine is useful to place label accurately on round shape of product.

- Full /partial wrap labelling can be possible. A unique feature of machine is if the body diameters changes, then also machine operates without change part.
- Labelling speed is automatically synchronized with conveyor speed to ensure quality.

8. **Pharmaceutical Printing Machine**

This machine is suitable for printing labels, batch number, validity time and series numbers on the surface of cartons, tissue paper, non-ferrous plastic film and aluminium film. No matter with the dry-ink roller or instant liquid ink, it has the features of instant printing and instant drying, and strong adhesion.

**Package Testing**

Package testing or packaging testing involves the measurement of a characteristic or property involved with packaging. This includes packaging materials, packaging components, primary packages, shipping containers, and unit loads, as well as the associated processes. Testing measures the effects and interactions of the levels of packaging, the package contents, external forces, and end-use. It can involve controlled laboratory experiments, subjective evaluations by people, or field testing. Documentation is important: formal test method, test report, photographs, video, etc. Testing can be a qualitative or quantitative procedure. Package testing is often a physical test. With some types of packaging such as food and pharmaceuticals, chemical tests are conducted to determine suitability of food contact materials. Testing programs range from simple tests with little replication to more thorough experimental designs. Package testing can extend for the full life cycle. Packages can be tested for their ability to be recycled and their ability to degrade as surface litter, in a sealed landfill or under composting conditions.

Packaging testing might have a variety of purposes, such as:

- Determine if, or verify that, the requirements of a specification, regulation, or contract are met.
- Decide if a new product development program is on track: Demonstrate proof of concept.
- Provide standard data for other scientific, engineering, and quality assurance functions.
- Validate suitability for end-use.
- Provide a basis for technical communication.
- Provide a technical means of comparison of several options.
- Provide evidence in legal proceedings: product liability, patents, product claims, etc.
- Help solve problems with current packaging.
- Help identify potential cost savings in packaging.

Packaging tests can be used for:

- Subjecting packages (and contents) to stresses and dynamics found in the field.
- Reproducing the types of damage to packages and contents found in actual shipments.
- Controlling the uniformity of production of packages or components.

**Importance of testing**

For some types of products, package testing is mandated by regulations: food, pharmaceuticals, medical devices, dangerous goods, etc. This may cover both the design qualification, periodic retesting, and control of the packaging processes. Processes may be controlled by a variety of quality management systems such as statistical process control, Validation protocols, ISO 9000, etc. For unregulated products, testing can be required by a contract or governing specification. Risk management may involve factors such as

- Costs of packaging.
The purpose of stability testing is to provide evidence of how the quality of an Active Pharmaceutical Ingredient (API) or Finished Pharmaceutical Product (FPP) varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and also to establish the shelf life for the FPP, to determine the storage conditions and the in-use stability. The stability programme also includes the study of product-related factors that influence its quality, for example, interaction of API with excipients, container closure systems and packaging materials. Stability of a pharmaceutical preparation is the capability of formulation in a specific container-closure system to remain within its physical, chemical, microbiological, therapeutically and toxicological specifications throughout its shelf life. The time during which the product retains the same characteristics and properties that it possessed at the time of manufacture.

Stability study is used to:

- Provide evidence as to how the quality of the drug product varies with time.
- Establish shelf life for the drug product.
- Determine recommended storage conditions.
- Determine container closure system suitability.

Stability studies are necessary because of chemical degradation of the product leads to lowering of concentration of the drug in the dosage form and toxic products may be formed due to chemical degradation of the active ingredient.

Stability study to predict shelf life of the product, by accelerating the rate of decomposition, preferably by increasing the temperature of reaction conditions. With the advancement in branch of kinetics, shelf life of a dosage form can be predicted with in months based on the accelerated stability study. In this study, preparations are subjected to high stresses during stability testing. Common high stress are temperature, humidity, light, moisture and of course packaging system.

The concept of accelerated stability testing is based upon the Arrhenius equation

\[ K = A e^{\frac{E_a}{R \cdot T}} \]

Where, \( K \) is the specific rate constant, \( A \) is the frequency factor, \( E_a \) is the activation energy, \( R \) is the ideal gas constant & \( T \) is the absolute temperature.

These equations describe the relationship between storage temperatures and degradation rate. It also explain the effect of temperature on a rate of a reaction. According to Arrhenious, for every 100 rise in temperature, the speed of reaction increases about 2 – 3 times. Using Arrhenius equation, projection of stability from the degradation rates observed at high temperatures for some degradation processes can be determined. When the activation energy is known, the degradation rate at low temperatures may be projected from those observed at “stress” temperatures.

Testing should be done using the container and closures proposed for storage and distribution. The test should include containers and closures used in pharmaceutical packaging for the physician sample, promotion & marketing sample including bulk storage sample. This protocol should provide information about type, size, source of the packaging materials. Extensive studies must be done before selection of containers. The orientation is important for solutions, dispersion systems and semisolid products because of the interaction between the dosage form and container – closure systems. For storage, any one of the following three different positions can be selected. Upright position can be used to study the effect of temperature and relative humidity on the dosage form whereas, inverted and on the side positions can be used to study the interaction between product – container – closure and also to find out adsorption of the product components by the packaging system materials. Accelerated testing should be done for atleast six months according to ICH-QIAR (Oct 99) guidelines, and it suggests sampling points of 0, 3 and 6 months for stable products. The FDA Guidelines suggest sampling intervals of 0, 1, 2, 3 and 6 months intervals.

Who Guidelines for Quality Control of Packaging Materials:[1]

1. All the containers and closures anticipated for use should fulfil the pharmacopoeial indicated requirements.
2. Apt sample sizes, specifications, test methods, cleaning method and sterilization should be suitable of packaging materials.
3. All the containers and closure should be washed before sterilization with water for injection according to the procedure.
4. The design of the closures, containers and stoppers should have an airtight seal when fitted to the bottles.
5. It might be assured that containers and terminations decided for a specific product don’t impact the product.
6. When the glass containers are used, the composed calendar of purging might be set down and followed.
7. Containers of parenteral and ophthalmic preparation should be scrutinized against dark or white background to guarantee freedom from impurities.

CONCLUSION
Packaging is routinely done within manufacturing premises, but it may be required to do in many areas outside a pharmaceutical company. Earlier packaging has been done for contaminant and protection of the product. In most cases both manufacture and the consumer paid little attention to the package systems. Presently the role of packaging is being expanded to include branding, communication, distribution control, anti-counterfeiting, poison protection and much more. Now the concept of packaging is also changing. It is being utilized in the delivery of drug. Moreover the confidence of the user on the authenticity of the drug product is the another big factor to be considered. For this tamper proof packaging are becoming more popular. Science and packaging technology is now being developed within the manufacturing company and its importance is being realized by the consumers. The science of packaging is a combination of disciplines. When stability studies are conducted on an API, the stability also examined to determine the inertness of the packaging materials with excipients and API are needed to be evaluated. Once such testing becomes complete the product and the packaging becomes ready for the best presentation in the market.

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