PHARMACEUTICAL PACKAGING MATERIALS: A BRIEF REVIEW

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ABSTRACT
Pharmaceutical packaging material plays a vital role in the stability of the pharmaceutical dosage form. Packaging should be such that it should maintain the integrity of the dosage form, should be inert in nature, should not be fragile, should have good mechanical strength. The glass is most widely used packaging material. The selection of packaging material is very important parameter during the study of stability testing of the dosage form. Different packaging materials used in the packaging of the pharmaceutical dosage forms are aluminium foil, glass, plastic etc. Now a days biodegradable polymers are used in the manufacturing of the packaging material. So that problem of increasing pollution can be minimized.

KEYWORDS: Packaging material, Pharmaceutical dosage form, biodegradable polymers, packaging, product.

INTRODUCTION: The process by which the pharmaceuticals are suitably placed so that they should retain their therapeutic effectiveness from the time of their packaging till they are consumed is termed as packaging.[1] Packaging means a collection of different packaging materials which encase the pharmaceutical product from the time of manufacturing to the end of the user.[2] Packaging is a multiple user means provide presentation, protection, identification information, about a product during storage, carriage, display and until the product is consumed. The choice of primary and/or secondary packaging materials will depend on the degree of protection required, compatibility with the contents, the filling method and cost, but also the presentation for over-the-counter (OTC) drugs and the
convenience of the packaging for the user (e.g. size, weight, method of opening/reclosing (if appropriate), eligibility of printing). Containers may be referred to as primary or secondary, depending on whether they are for immediate use after production of the finished product or not. Both single-dose and multi-dose containers exist. The use of biodegradable polymers in the manufacturing of packaging material is getting more attention now a days because of eco-friendly nature. Bio degradable packaging material on decomposition act as a soil fertilizer. The most widely used bio-degradable material used for packaging is hydrocolloids and lipids. The examples of biodegradable packaging materials are as follows.

Paper boards, cellulose, xylan, chitin, protein, gluten, zein, soy, casein, whey, gelatin, collagen, keratin, polylactic acid, pullulan etc.

DEFINATIONS

Packaging: 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: 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 is called as pharmaceutical packaging.

TYPES OF PACKAGING SYSTEM

Primary package system: The packaging system made up of those package components & subcomponents that come into direct contact with the product, or those that may have a direct effect on the product shelf life.

Secondary or tertiary package system: Includes cartons, corrugated shippers & pallets.

IDEAL REQUIREMENTS OF PHARMACEUTICAL PACKAGING MATERIAL

- Protect the preparation from environmental conditions.
- Non-reactive with the product and so does not alter the identity of the product.
- Does not impart tastes or odours to the product.
- Nontoxic.
- FDA approved.
- Protect the dosage form from damage or breakage.
- Meet tamper-resistance requirements, wherever applicable.
Adaptable to commonly employed high-speed packaging equipments\(^4\)

**The ideal container or package should**
1. Protect the contents from the following environmental hazards
2. Protects the content from the following mechanical hazards
3. They must not add or permit loss to its contents.
4. Must have a pharmaceutically elegant appearance.

**SELECTION OF PACKAGING MATERIAL**
The ideal characteristics of packaging material should comply following properties.
- They must protect the preparation from environmental conditions.
- They must not be reactive with the product,
- They must not impart tastes or odours to the products,
- They must be non-toxic,
- They must be FDA (Food & Drug Administration) approved,
- They must meet applicable tamper-resistance requirements
- They must be adaptable to commonly employed high-speed packaging equipment. and
- They must have reasonable cost in relation to the cost of the product.\(^4\)

**CRITERIA FOR SELECTION OF PACKAGE TYPES AND PACKAGING MATERIALS**
1. Stability
2. Compatibility with the contents
3. Strength of container and the degree of protection desired
4. Moisture-proofness
5. Resistance to corrosion by Acids or Alkalis
6. Resistance to grease
7. Protection against salt
8. Resistance to microorganisms
9. Resistance to insects and rodents
10. Resistance to differences in temperature
11. Protection against light, fire and pilferage
12. Odour retention and transmission
13. Aesthetic effect
14. Cost
15. Machine suitability of packaging and the filling method.[1]

CONTAINERS OF PHARMACEUTICAL PACKAGINGS

- AMPOULE
- Bag
- BLISTER
- BOTTLE
- CARTRIDGE
- GAS CYLINDER
- INJECTION NEEDLE
- Injection syringe
- PRESURIZED CONTAINER
- SINGLE DOSE CONTAINER
- A MULTIPLE DOSE CONTAINER
- TUBE
- VIAL.[5]

VARIOUS PACKAGING CLOSURES AND SYSTEMS

I] TYPES OF PACKAGING MATERIAL

1. Glass: - (i) Type-I  Borosilicate glass
   (ii)Type-II  Treated soda-lime glass
   (iii)Type-III  Regular soda-lime glass
   (iv)Type-NP  General purpose soda lime glass
   (v)Coloured glass


3. Plastics  (a) Thermosetting resins.  (i) Phenolics.
   (ii) Urea
   (b) Thermoplastic resins.
      (i) Polyethylene
      (ii) Polypropylene
      (iii) Polyvinylchloride (PVC)
      (iv) Polystyrene
      (v) Polycarbonate
      (vi) Polyamide (Nylon)
(vii) Acrylic multipolymers
(viii) Polyethylene terephthalate (PET)

4. Rubber
(i) Natural rubber
(ii) Neoprene rubber
(iii) Butyl rubber.

GLASS

**Preparation of glass:** Glass is principally composed of sand (silica-$\text{SiO}_2$), soda-ash (Na$_2$CO$_3$ - sodium carbonate) and lime-stone (Ca CO$_3$-calcium carbonate) and cullet. Cullet is broken glass which acts as a fusion agent.\[6\]

**TYPES OF GLASS**
Type I – Borosilicate Glass.
Type II – Treated Soda-Lime Glass.
Type III – Regular Soda-Lime Glass.
Type NP – General Purpose Soda-Lime Glass.

**Type I: Borosilicate Glass.**
1. Highly resistant glass.
2. A substantial part of the alkali & earth cations are replaced by boron and/or aluminum & zinc.
3. It is more chemically inert than the soda-lime glass (which contains either none or an insignificant amount of these cations).
4. It is used to contain strong acids & alkalies as well as all types of solvents.
5. The addition of approx 6% boron to form type I glass reduces the leaching action.

**Type II: Treated Soda-Lime Glass.**
1. 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.
2. Type II containers are made of commercial soda-lime glass that has been de-alkalized or treated to remove surface alkali.
3. The de-alkalizing process is known as “sulphur treatment” and virtually prevents “weathering” of empty bottles.

4. Some manufactures expose the glass to an atmosphere containing water vapour & acidic gases. This results in a reaction between gases & surface alkali, which makes it resistant to attack by water.

5. The alkali removed from the glass appears on the surface as a sulphate bloom, which is removed when the containers are washed before filling.

6. Thus sulphur treatment neutralizes the alkaline oxides on the surface & thus rendering the glass more chemically resistant.[1]

**Type III – Regular Soda-Lime Glass:** Containers are untreated & made up of commercial soda-lime glass of average or better-than-average chemical resistance. This glass is not recommended for parenteral preparations.

**Type NP – General Purpose Soda-Lime Glass:** Containers made up of soda-lime glass are supplied for non-parenteral products, those intended for oral or topical use.

**Table: Types of glass, their composition, properties and uses[7]**

<table>
<thead>
<tr>
<th>Type of glass</th>
<th>Main Constituents</th>
<th>Properties</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type-I</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borosilicate glass</td>
<td>SiO₂ ≥ 80%</td>
<td>Has high melting point so can withstand high temperature.</td>
<td>Laboratory glass apparatus. For injections and, for water for injection.</td>
</tr>
<tr>
<td>e.g. Pyrex, Borosil</td>
<td>B₂O₃ ≥ 12</td>
<td>Resistant to chemical substances.</td>
<td></td>
</tr>
<tr>
<td>Al₂O₃ - 2%</td>
<td>Na₂O+CaO - 6%</td>
<td>Reduced leaching action.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>The surface of the glass is fairly resistant to attack by water for a period of time.</td>
<td>Used for alkali sensitive products Infusion fluids, blood &amp; plasma. large volume container</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sulfur treatment neutralizes the alkaline oxides on the surface, thereby rendering the glass more chemically resistant.</td>
<td></td>
</tr>
<tr>
<td><strong>Type-II</strong></td>
<td>Made of soda lime glass. The surface of which is treated with acidic gas like SO₂ (i.e. dealkalised) at elevated temperature (500°C) and moisture.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated soda-lime glass</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type-III</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular soda-lime glass</td>
<td>SiO₂</td>
<td>It contains high concentration of alkaline oxides and imparts alkalinity to aqueous substances. Flakes separate easily. May crack due to sudden change of temperature.</td>
<td>For all solid dosage forms (e.g. tablets, powders). For oily injections Not to be used for aqueous injection Not to be used</td>
</tr>
</tbody>
</table>
Advantages of glass container

1. They are quite strong and rigid.
2. They are transparent which allows the visual inspection of the contents; especially in ampoules and vials.
3. They are available in various shapes and sizes. Visually elegant containers attracts the patients.
4. Borosilicate (Type-I) and Neutral glasses are resistant to heat so they can be readily sterilised by heat.
5. Glass containers can be easily cleaned without any damage to its surface e.g. scratching or bruising.
6. Borosilicate type of glass is chemically inert. Treated soda lime glass has a chemically inert surface.
7. As the composition of glass may be varied by changing the ratio of various glass constituents the proper container according to desired qualities can be produced.
8. They do not deteriorate with age, if provided with proper closures
9. Photosensitive drugs may be saved from UV-rays by using amber colour glass.
10. They are cheaper than other packaging materials.
Disadvantages

1. They are brittle and break easily.
2. They may crack when subject to sudden changes of temperatures.
3. They are heavier in comparison to plastic containers.
4. Transparent glasses gives passage to UV-light which may damage the photosensitive drugs inside the container.
5. Flaking: From simple soda-lime glass the alkali is extracted from the surface of the container and a silicate rich layer is formed which sometimes gets detached from the surface and can be seen in the contents in the form of shining plates known as ‘flakes’ and in the form of needles they are known as ‘spicules’. This is a serious problem, specially in parenteral preparations.
6. Weathering: Sometimes moisture is condensed on the surface of glass container which can extract some weakly bound alkali leaving behind a white deposit of alkali carbonate to remain over there, further condensation of moisture will lead to the formation of an alkaline solution which will dissolve some silica resulting in loss of brilliance from the surface of glass called weathering.
   i. To prevent weathering, the deposited white layer of alkali carbonates should be removed as early as possible by washing the containers with dilute solution of acid and then washing thoroughly with water.

Table: Types of Packaging\textsuperscript{[4]}

<table>
<thead>
<tr>
<th>PACKAGE TYPE</th>
<th>TYPE OF FORMULATION CAN BE PACKED</th>
<th>MINIMUM QUALITY OF GLASS THAT CAN BE USED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampoule</td>
<td>Aqueous Injectables Of Any pH</td>
<td>Type I</td>
</tr>
<tr>
<td></td>
<td>Aqueous Injectables Of pH Less Than 7</td>
<td>Type II</td>
</tr>
<tr>
<td></td>
<td>Non-Aqueous Injectables</td>
<td>Type III</td>
</tr>
<tr>
<td>Vial</td>
<td>Aqueous Injectables Of Any pH</td>
<td>Type I</td>
</tr>
<tr>
<td></td>
<td>Aqueous Injectables Of pH Less Than 7</td>
<td>Type II</td>
</tr>
<tr>
<td></td>
<td>Non-Aqueous Injectables Dry Powders For Parenteral Use (Need To Be Reconstituted Before Use)</td>
<td>Type III</td>
</tr>
<tr>
<td>Bottles and Jars</td>
<td>Tablets, Capsules, Oral Solids &amp; Other Solids For Reconstitution.</td>
<td>Type IV</td>
</tr>
<tr>
<td></td>
<td>Oral Liquids (Solutions, Suspensions, Emulsions).</td>
<td>Type IV</td>
</tr>
<tr>
<td></td>
<td>Nasal &amp; Ear Drops.</td>
<td>Type IV</td>
</tr>
<tr>
<td></td>
<td>Certain Types Of External Semisolids (Rubeficients, Local Irritants).</td>
<td>Type IV</td>
</tr>
<tr>
<td></td>
<td>Blood &amp; Related Products</td>
<td>Type I</td>
</tr>
<tr>
<td>Dropper</td>
<td>Auxiliary Packaging Device With Certain Kind Of Products</td>
<td>Type IV</td>
</tr>
<tr>
<td>Aerosol Container</td>
<td>Aerosol product (solution, suspension, emulsion or semisolid type)</td>
<td>Type I</td>
</tr>
</tbody>
</table>
METALS
1. TIN: It is malleable, ductile, highly crystalline, silvery white, non-reactive metal. This metal act as catalyst when oxygen is in solution.\(^7\)

Advantages
1. This metal is very resistant to chemical attack.
2. Readily coats a number of the metals e.g. tin-coated lead tubes combine the softness of lead with the inertness of tin and for this reason it was formerly used for packaging fluoride toothpaste.

Disadvantages: Tin is the most expensive metal among tin, lead, aluminium and iron.

Uses
1. Tin containers are preferred for foods, like milk powder containers are coated with tin.
2. Currently, some eye ointment still packaged in pure tin ointment tubes.

2. ALUMINIUM
Advantages
1. Aluminium is a light metal hence the shipment cost of the product is less.
2. They provide attractiveness of tin at somewhat lower cost.
3. The surface of aluminium reacts with atmospheric oxygen to form a thin, tough, coherent, transparent coating of oxide, of atomic thickness, which protects the metal from further oxidation.

Disadvantages
1. Any substance that reacts with the oxide coating can cause corrosion e.g. products with the oxide coating can cause corrosion e.g. products of high or low pH, some complexing agents etc.
2. As a result of corrosion process H\(_2\) may evolve.

Use
1. Aluminium ointment tubes.
2. Screw caps
3. Aluminium strips for strip-packaging of tablet, capsules etc. Sometimes internally lacquered aluminium containers are used to stop the reaction with the content.
3. IRON

**Advantages:** Iron as such is not used for pharmaceutical packaging, large qualities of tin-coated steel, popularly called ‘tin’, combines the strength of steel with the corrosion resistance of tin.

**Disadvantages:** If an aqueous liquid can penetrate a pinhole or other fault in the layer of tin, which is virtually a short-circuited galvanic cell is set up and the intense chemical reaction which results brings about rapid corrosion of underlying steel. As a further measure the tin surface is lacquered.

**Uses:** Fabrication of milk containers, screw caps and aerosol cans.

4. LEAD

**Advantages**
(i) Lowest cost of all the metals used in pharmaceutical containers.
(ii) Soft metal.

**Disadvantages:** Lead when taken internally there is risk of lead poisoning. So lead containers and tubes should always have internal lining of inert metal or polymer.

**Uses:** With lining lead tubes are used for such product as fluoride tooth paste.[1]

PLASTICS

**General properties of plastics**
1. Plastics are synthetic polymers of high molecular weight.
2. They are sensitive to heat, and many may melt or soften at or below 100°C. Nevertheless, several plastics can be autoclaved e.g. nylon, polycarbonate, polypropylene, high density polyethylene (HDPE) etc.
3. Plastic containers are light in weight, they are easier to handle.
4. Mechanically they are almost as strong as metals and therefore, containers can have thinner walls than glass containers.
5. They are poor conductors of heat, a disadvantage if the content is to be autoclaved.
6. Generally, they are resistant to inorganic chemicals but are often attacked by organic chemicals but are often attacked by organic solvents and oils.
7. Plastic contain some additives (e.g. antioxidants, lubricants, plasticizers, stabilizers, filler) which may contaminate the content.
8. Very few types of plastics completely prevent the entry of water vapour and some are permeable to gases like oxygen, carbon-di-oxide.

**TYPE OF PLASTICS:** Plastics are classified into two groups according to their behaviour when heated.

1. **Thermoplastic type:** On heating, they soften to a viscous fluid which hardens again on cooling.
   
e.g. Polyethylene, polypropylene, polyvinylchloride, polystyrene, nylon (polyamide), polycarbonate, acrylic multi-polymers, polyethylene terephthalate etc.

2. **Thermosetting type:** When heated, they may become flexible but they do not become liquid; usually their shape is retained right up to the temperature of decomposition. Because of a high degree of cross-linking they are usually hard and brittle at room temperature.
   
e.g. phenol-formaldehyde, urea formaldehyde, melamine formaldehyde.

**ADDITIVES OF PLASTICS:** Plastics are polymers which are prepared from monomers. Plastics may be used directly to form the finished article, it is usual to add other substances for improved stability, or in-use performance.

1. Stabilizer
2. Antioxidants
3. Pigments
4. Fillers
5. Plasticizers
6. Other agents: Cross-linked agents, curing agents, activators and accelerators etc.[1]

**ADVANTAGES OF PLASTIC CONTAINERS**

1. Low in cost
2. Light in weight
3. Durable
4. Pleasant to touch
5. Odourless and inert to most chemicals
6. Unbreakable
7. Able to retain their shape throughout their use.
DISADVANTAGES OF PLASTIC CONTAINERS

1. Poor physical stability.
2. Stress cracking, a phenomenon related to low density polythene and certain stress cracking agent like wetting agent, detergents and some volatile oils.
3. Crazing a surface reticulation which can occur particularly with polystyrene and PVC have poor resistance.\(^{[6]}\)

Demerits of plastic material

- Permeation.
- Leaching.
- Sorption.
- Chemical modification.
- Alteration on the properties of plastics or product.

1. Permeation

1. The transmission of gases, vapours or liquids from the surrounding environment into the plastic container is known as “Permeation”.
2. Permeation of water vapour & oxygen through the plastic wall into the dosage form can be problematic if the drug is sensitive to hydrolysis and/or oxidation.
3. An increase in temperature, increases permeability of gases.
4. An increase in crystallinity of the material decreases permeability.
5. Hydrophilic plastic materials such as nylon are poor barriers to water vapor, while hydrophobic materials like polyethylene are better barriers.
6. 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.

2. Leaching

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

3. Sorption

1. The Process of extraction / removal of one or more of the constituents from the
formulation by the packaging material are referred to as “Sorption”.

2. Becomes a serious problem particularly for dosage forms that contain drug and/or other important ingredients in the solution form.

3. May significantly affect the therapeutic efficacy of the formulation containing highly potent drug.

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

5. Modification
   1. The physical or chemical alteration of the packaging material by the drug product is called “modification”.
   2. The content may extract the plasticizer, antioxidant or stabilizer, thus changing the flexibility of the container.
   3. 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.

**RUBBER:** Natural rubber consists of long chain polymers of isoprene units linked together in the cis-position. Its most important source is the tree *Hevea braziliensis* from which a latex, containing 30 to 40% of rubber in colloidal suspension, exudes when shallow cuts are made in the bark.

**Compounding rubbers:** Some of the properties of raw rubber (e.g. poor elasticity and sensitivity of temperature change) makes it unsuitable for the production of most rubber articles. Physical and chemical properties of rubber are altered by the addition of some additives, such as.

1. **Vulcanizing agent:** Raw rubber has poor elasticity, so its strength is poor. It hardens when cold and becomes soft and sticky when warm. It dissolves in many solvents. Vulcanizing increases greatly the range of stress and temperature over which the material is elastic.
Sulphur is a vulcanizing agent and it forms cross-links between the long rubber molecules.

2. **Accelerators**: These reduce the time of vulcanization and the amount of sulphur required. e.g. 2-mercapto benzothiazol (MBT).
   tetra methyl thiuram disulphide (TMT) [ S is not required].
   zinc dimethyl dithiocarbamate [vulcanize with s at room temperature].

3. **Activators**: These are used to increase the activity of accelerators e.g. Stearic acid or zinc stearate for MBT and zinc oxide for TMT.

4. **Fillers**: Two classes of fillers are added to rubber. Reinforcing fibres are used to improve physical properties. e.g. carbon black (very finely divided carbon), zinc oxide, magnesium carbonate and calcium carbonate.
   Extending fillers are added mainly as diluents to reduce cost and partly to facilitate manufacture. e.g. talc and asbestos.

5. **Softeners**: These facilitates the incorporation of fillers, make the compound easier to manufacture. e.g. Pine oil, mineral oil, tar-fractions.

6. **Antioxidants**: The chains are broken at the double bonds and S-links by oxidation, causing softening and weakening. Deterioration is slowed down by including antioxidants. e.g. phenyl betanaphthyl amine and para-hydroxy diphenyl.

7. **Pigments**
e.g. Oxides of iron and sulphides of cadmium and antimony.
Coal tars dyes.

8. **Lubricants**: To assist the removal of rubber products from the mould e.g. zinc stearate, talc are dusted before moulding.

**TYPES OF RUBBERS**
1. **BUTYL RUBBER**: These are copolymers of isobutylene with 1-3% of isoprene or butadiene.
2. NITRILE RUBBER.
3. CHLOROPRENE RUBBERS (NEOPRENE): These are polymers of 1:4 chloprene.
4. SILICONE RUBBERS.

PAPERS AND BOARDS
1. Paper-based materials include: Labels, Cartons, Bags, Outers, Trays For Shrink Wraps, Layer Boards On Pallets, etc.
2. The Applications as well as Advantages of Cartons include.
   - Increases display area
   - Provides better stacking for display of stock items
   - Assembles leaflets
   - Provides physical protection especially to items like metal collapsible tubes.
3. Fiberboard outers either as solid or corrugated board also find substantial application for bulk shipments.
4. Regenerated cellulose film, trade names Cellophane & Rayophane, is used for either individual cartons or to assemble a no. of cartons. [4]

FILMS, FOILS & LAMINATES
1. Regenerated cellulose film based on viscose (chemical used for manufacturing of rayon) & laminating two or more types of films, cellulose coatings, foil and paper play diff roles such as supportive, barrier, heat seal & decorative.
2. For Example.
3. Aluminium foil even in the thinnest gauges offers the best barrier properties, which are not approached even by the most impermeable plastics.
4. Metallization: A relatively new process whereby particles of metal are laid down onto a surface under vacuum, can significantly improve the barrier properties of a material but these do not approach the properties of a pure foil.
5. In the newer technology „Co-Extrusion“, a number of plastic plies are extruded in combination to produce cheaper laminations. Uses of films foils, laminations.
6. Strip packs
7. Blister packs
8. Sachets
9. Diaphragm seals for bottles
10. Liners for boxes either attached or loose bag-in-box systems & bags.
11. Foil blisters.
12. When sealed with a metal foil-cover, the blister can provide a hermetic pack i.e. an isolated system, which excludes any exchange of gases between the product & surrounding atmosphere.\textsuperscript{[3]}

**ADHESIVES AND INKS**

1. Some substances, such as cements and lacquers used as label adhesives, are not water-based emulsions. They are usually dissolved in toluene, alcohol, naphtha, methyl ethyl ketone, or other organic solvents.
2. When an adhesive of this type is used on plastics or elastomers, the solvent may allow migration of adhesive components into the formulation. Therefore, appropriate testing should be performed to determine whether adhesive and ink components migrate through the container. If they do, adequate information to justify the use of the container system in combination with the drug product should be submitted.
3. For all containers, testing should be conducted on the effectiveness of the adhesive under appropriate challenge conditions (e.g., temperature and humidity).
4. If direct label imprinting is used on containers, such as on containers of injectable drug products, it is necessary that resistant ink be used so that the imprint having the required information resists the normal handling of the containers during their customary conditions of purchase and use.\textsuperscript{[3]}

**PACKAGING MATERIALS WITH RESPECT TO DIFFERENT DOSAGE FORMS:**

a) Solid dosage forms

1. Tamper resistant packaging
   1. Film wrappers
   2. Blister package
   3. Strip package
   4. Bubble pack
   5. Shrink seal and bands
   6. Foil paper or plastic pouches
   7. Bottle seals
   8. Tape seals
   9. Breakable caps
10. Sealed tubes
1.1. Strip packages: A strip package is a form of unit dose packaging that is commonly used for the packaging of tablets and capsules. A strip package is formed by feeding two webs of a heat-sealable flexible film through either a heated crimping roller or a heated reciprocating plate. The product is dropped into the pocket formed prior to forming the final set of seals. A continuous strip of packets is formed, generally several packets wide depending on the packaging machine's limitations. The strip of packets is cut to the desired number of packets in length. Different packaging materials are used for strip packaging based on their properties for high-barrier applications; a paper/polyethylene/foil/polyethylene lamination is commonly used.

![Strip packages](image1)

1.2. Blister packages

The blister package is formed by heat-softening a sheet of thermoplastic resin and vacuum-drawing the softened sheet of plastic into a contoured mold. After cooling, the sheet is released from the mold and proceeds to the filling station of the packaging machine. The semi-rigid blister previously formed is filled with product and lidded with a heat-sealable backing material. The backing material, peelable type is usually heat-seal-coated aluminium foil. The coating on the foil must be compatible with the blister material to ensure satisfactory sealing, both for product protection and for tamper resistance. Materials commonly used for the thermo-formable blister are poly vinyl chloride (PVC), PVC/polyethylene combinations, polystyrene and polypropylene. In tropical areas blister packages with an additional aluminium membrane is used which provide greater protection against high humidity.
1.3. Child Resistant Containers

Child resistant containers are commonly referred to as CRC’s, which are designed to prevent the child accessing to potential hazarding products.\[2\]

Legally: “at least 80% of children between the ages of 20 and 42 months forming a test panel are unable to open the packaging within 5 minutes of receiving it”. Up to now, all standards for testing for child-resistant compliance give a definition of such a package as being the immediate packaging which is resistant to opening by children (under 52 months old), but which does not pose difficulties for the elderly (over 65 years) to open and, where appropriate, to re-close properly.\[4\]

1.4. Bubble Pack

The bubble pack can be made in several ways but is usually formed by sandwiching the product between a thermo formable, extensible, or heat-shrinkable plastic film and a rigid backing material. This is generally accomplished by heat-softening the plastic film and vacuum-drawing a pocket into the film in a manner similar to the formation of a blister in a blister package. The product is dropped into the pocket, which is then sealed to a rigid material such as heat-seal-coated paperboard. If a heat-shrinkable material is used, the
package is passed through a heated tunnel, which shrinks the film into a bubble or skin over the product, firmly attaching it to the backing card[2].

**Bubble packs**

1.5. **Film wrapper**
A transparent film with a distinctive design is wrapped securely around a product or product container. The film must be cut or torn to open the container and remove the product. Substrates options include ultra destructible films, voidable films that provides image when removed. e.g., Solvent sensitive papers.

1.6. **Shrink seals and bands**
Cap and container union are sealed by the bands or wrappers with distinctive design which are shrunk by heat or drying. The seal must be cut or torn to remove the product. The shrink band concept makes use of the heat-shrinking characteristics of a stretch-oriented polymer, usually PVC. The heat shrinkable polymers are generally prepared as extruded, oriented tube in diameter slightly larger than cap and the neck ring of the bottle to be sealed.[2]

**Shrink seal and bands**

1.7. **Breakable caps** Such caps break when an attempt is made to open it. These caps provide external tamper evidence and can also be combined with the internal seals thereby providing double security.[2]
1.8. Sealed tubes: The mouth of the tube is sealed, and the seal must be punctured to obtain the product.

1.9. Shrink tubing
A packaging concept capable of providing not only a package that is tamper-resistant, but also, by the proper selection of material, a package with a high degree of environmental protection is called as flexible pouch. A flexible pouch is usually formed during the product filling operation by either vertical or horizontal forming, filling and sealing (f/f/s) equipment.
2.0. Containers for semi solid and pressurized products

2.1. Collapsible Metal and Plastic Tubes
A. Its narrow orifice prevents serious contamination of unused parts of contents.
B. Wastage is reduced, since the patient is less likely to remove an excessive amount.
C. When part of the preparation is expelled it is not replaced, as in other containers, by equivalent volume of air; consequently, microbial contamination and oxidative or hydrolytic degradation of the remaining contents are reduced.
D. Nozzle type applicators can be fitted to facilitate administration into body cavities such as nose or vagina. Most collapsible tubes are made of aluminium, although tin, lead, tin coated lead and plastics are also used. Aluminium tubes have good resistance to corrosion because the surface of film of oxide.

![Collapsible metal and plastic tubes](image_url)

2.2. Glass Plastic Pots
Suitable alternatives are wide mouthed squat, cylindrical pots made from glass or suitable plastics having a plastic (or occasionally metal) screw (or, sometimes in case of plastics, slip over cap). Glass pots may either be colorless and either clear or amber color or opal white. Glass is inert, hygienic and provides stability considerations allow transparency, the content can be seen. Unless returned by patient for reuse, they are more expensive than plastics.[2]

2.3. Aerosols: Pressurized packages expel the product through a valve. The pressure exerted for the expulsion of the product is an important consideration while selecting the packaging for any products. Packaging of therapeutic active ingredients in a pressurized system. Aerosols are depends on the power of compressed or liquefied gas to expel the contents from containers. A dose can be removed without contamination of materials. Stability is enhanced
for these substances adversely affected by oxygen and or moisture. When sterility is an important factor, it can be maintained while a dose is being dispensed.\(^2\)

![Aerosol](image)

### Aerosol

3. **Containers for liquids/ Parenterals**

Injectable formulations are packaged in to containers made of plastic or glass. Container system includes ampoules, syringes, vials, bottles, cartridges, bags ampoles are all glass and plastic are all bags. Rubber materials for rubber stoppers for vials and bottles, rubber plungers and rubber seals for syringes, cartridges. Irrigation solutions are packaged in glass bottles with aluminium screw caps. A single-dose container is one that holds a quantity of drug intended as a single dose and when opened cannot be resealed with assurance that sterility has been maintained. These containers include fusion-sealed ampoules and prefilled syringes and cartridges.\(^2\)

![Containers for liquids/ parenterals](image)

4. **Single dose containers**

A container that holds a quantity of the preparation intended for total or partial use as a single administration.
5. **Multi dose containers:** It is a hermetic container which permit withdrawal of successive portions of the contents without altering the strength or endangering the quality or purity of the remaining portions (vials). The device is usually a spoon or a cup of volume of 5ml.

6. **Well closed containers**
Protect the product from contamination with unwanted foreign materials and form the loss of contents during the use.

7. **Air tight containers:** are impermeable to solids, liquids and gases during normal storage.
and use. If the container is to be opened on more than one occasion it must remain airtight after reclosure.

8. Light resistant containers

Many pharmaceutical products require light-resistant containers. In most instances, a container made of a good quality of amber glass or a light-resistant opaque plastic will reduce light transmission sufficiently to protect a light-sensitive pharmaceutical. Agents termed ultraviolet (UV) absorbers may be added to plastic to decrease the transmission of short UV rays. A recent innovation in plastic packaging is the coextruded two-layer, high-density polyethylene bottle, which has an inner layer of black polyethylene coextruded with an outer layer of white polyethylene. The container provides light resistance (exceeding amber glass) and moisture protection. It is increasingly being used in the packaging of tablets and capsules protect the contents from the effect of radiation at a wavelength between 290nm and 150nm.\cite{2}

9. CLOSURES

9.1. Threaded Screw Cap

The screw cap when applied overcome the sealing surface irregularities and provides physical and chemical protection to content being sealed. The screw cap is generally made of metal or
plastics. The metal is usually tinplate or aluminium and in plastics, both thermoplastic and thermosetting materials are used. When the screw cap is applied, its thread engages with corresponding threads molded on the neck of the bottle.

9.2. Lug Cap
The lug cap is similar to thread cap. It is simply an interrupted thread on the glass finish, instead of continuous thread. It is used to engage the lug on the cap sidewall and draw the cap down to the sealing surface of the container. It used for both atmospheric as well as vacuum conditions.

9.3. Crown Caps
This style of cap is commonly used as a crimped closure for beverage bottles and has remained essentially unchanged for more than 50 years.\cite{8}
9.4. Roll-On: The aluminium roll-on cap must be sealed securely, opened easily and resealed effectively. It finds wide application in the packaging of food, beverages, chemicals and pharmaceuticals. The roll-on closure requires a material that is easy to form, such as aluminium or other light-gauge metal. Re-sealable, non-re-sealable and pilfer proof types of the roll-on closure are available for use on glass or plastic bottles and jars.

![Roll on closures](image)

9.5. Pilfer proof Closures

The pilfer proof closure is similar to the standard roll-on closure except that it has a greater skirt length. This additional length extends below the threaded portion to form a bank, which is fastened to the basic cap by a series of narrow metal "bridges." When the pilfer proof closure is removed, the bridges break, and the bank remains in place on the neck of the container. The closure can be re-sealed easily and the detached band indicates that the package has been opened. The torque is necessary to remove the cap.[6]

![Pilfer proof closures](image)

Suppositories package

1. Pouch type strip packing, these strips are of 4 ply material [poly+aluminium+poly+paper (inner layer poly and extreme outer layer-paper) strip pack is superior to blister pack in the 3 ways
2. The product i.e. suppository can be removed easily without breakage which happens many times with blister pack.

3. Often blister pack requires refrigeration to avoid deformity in shape this is not the case in strip pack.

4. Strip pack is of 4 ply material including aluminium which has better moisture barrier properties and hence the product is more stable as compared to blister pack which is usually of pvc.

Suppositories: Packaging.

Packaging for liposomes
Generally hermatically sealed containers are used for packaging of liposomes.

Packaging for Liposome

Transdermal patches packaging
Backing Film: Occlusive films of varied composition and/or thickness.

Adhesive: An adhesive layer incorporates the active ingredient; featuring silicone, acrylic and/or polyisobutylene adhesive formulations.

Release Liner: Removable coated film or polymer based protective layer.\textsuperscript{[2]}

✓ 4 Major trends in pharmaceutical packaging material

1. Fine print of serialization: Many suppliers now-a-days introduced different technologies to enable serialized printing on primary packaging material as well as on the final dosage form. This new technique included printing of 2D barcodes on the vials as well as on the pills and capsules. Print is getting even more smaller due to the direct printing on the dosage form, but it is quite challenging one. This technique is adopted in the countries like Japan and America.

2. Varying global standards require flexibility: For the manufacturers producing medicines for multiple countries on a single processing line, serialized data need to be vary accordingly. New specialized softwares can reduce this complexity. The another notable trend is quality assurance through advanced vision and inspection system. This system included advances from pill forming to the proper assembly of capsule to improvements in vial sealing.

3. New biologics driving packaging changes: The rising popularity of new biological medicines continues to fuel some unaccepted packaging challenges. These new drugs may have the interactions with packaging material. The glass vials, prefilled syringe are the examples of the format that is undergoing changes that reflects market requirement and demand. Now a days tungsten free syringes are getting more attention for the research.

4. Small is beautiful: Years back the pharmaceutical industry was engaged in handling the bigger dosage forms. But now they have focused in the smaller dosage form. The filling lines for the smaller dosage form are smaller, more modular, and flexible with shorter lead time.\textsuperscript{[8]}

International standards on packaging

A list is given below of the standards on packaging issued by the International Organization for Standardization (ISO), as of 10 October 1998, starting with the four main standards, after which they are listed in numerical order.

Quality systems —model for quality assurance in design, development, production,
Quality systems —model for quality assurance in production, installation and servicing.
Quality systems —model for quality assurance in final inspection and test. International
Quality management and quality systems elements. Part 2:Guidelines for service[9]

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