ABSTRACT

Packaging is used to keep a product contained and prevent it from interacting with the environment. Protection, identification, and information must be provided against physical damage, loss of content or ingredients, and entrance of undesired environmental components such as water vapour, oxygen, and light. Pharmaceutical packaging plays an important role in transforming a formulation into an appealing and marketable product. Packaging is one area that not only aids in the creation of wealth, but also extends the shelf life of products. Packaging materials are chosen for their efficacy and performance in protecting the quality, potency, and safety of pharmaceutical medicines. Advancement in pharmaceutical development research has always been reliant on packaging technologies. The quality of packaging ensures the integrity of drugs during storage, shipment, and delivery. This article examines current pharmaceutical packaging patterns and makes predictions about future packaging results.

INTRODUCTION[2-4]

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. Packaging means a collection of different packaging materials which encase the pharmaceutical product from the time of manufacturing to the end of the user. 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

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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 day because of eco-friendly nature. Bio degradable packaging materials on decomposition act as a soil fertilizer. The most widely used biodegradable 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, pollutant etc.

Types of pharmaceutical packaging materials

Packaging materials for pharmaceutical use are many which can be categorized as follows:

Primary packaging materials

Because they come into direct contact with the medication formulation, primary packaging materials are highly sophisticated. Environmental (moisture, temperature, light), chemical, mechanical, and other risks are all protected by these materials. Critical packaging components are also known as primary packaging materials.

Primary packaging materials can be made of glass, plastic, metal, rubber or fusion of plastic & metal.

Table 1: Primary packaging materials with package Name and Photos.

<table>
<thead>
<tr>
<th>Primary packaging materials</th>
<th>Name of Package</th>
<th>Photos of Package</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glass</td>
<td>Ampoule, Vial, Bottle etc.</td>
<td></td>
</tr>
<tr>
<td>Material</td>
<td>Examples</td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>Plastic</td>
<td>Dropper Bottle, Plastic Bottle, Infusion Bag, Plastic Film, Plastic cap &amp; stopper etc.</td>
<td></td>
</tr>
<tr>
<td>Rubber</td>
<td>Rubber stopper, Liner, Plunger Gasket &amp; Syringe Tip etc</td>
<td></td>
</tr>
<tr>
<td>Metal</td>
<td>Blister foil, Collapsible tube, ROPP cap,</td>
<td></td>
</tr>
</tbody>
</table>

Secondary and Tertiary Packaging Materials: Secondary packaging materials are typically used to cover primary packaging. Secondary packaging, such as leaflets, cartons, and boxes, give additional protection during warehousing and also provide information about the drug product. Tertiary packaging materials are huge boxes or cartons that are used to hold a large number of secondary packages for storage in a warehouse. These materials offer additional protection to drug products during storage and delivery.
Table 2: Secondary Packaging Materials with Package Name and Photos.

<table>
<thead>
<tr>
<th>Secondary and Tertiary Packaging materials</th>
<th>Name of Package</th>
<th>Photos of Package</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paper</td>
<td>Label, Patient Information Leaflets</td>
<td><img src="image" alt="Paper Packages" /></td>
</tr>
<tr>
<td>Cardboard</td>
<td>Inner Cartons, Boxes</td>
<td><img src="image" alt="Cardboard Package" /></td>
</tr>
<tr>
<td>Paperboard, Corrugated Line</td>
<td>Master Carton</td>
<td><img src="image" alt="Paperboard Package" /></td>
</tr>
</tbody>
</table>

Pharmaceutical primary packaging made of glass\[^7\]

Glasses are very sophisticated materials that have been used for packaging medicinal drug content/products since antiquity. Ampoule, injection vial, syringe, and infusion bottle for blood products or any other sterile injectable medicines are among the most common principal packages constructed of glass. The major packaging materials composed of glass are designed to come into direct touch with the medicine(s). Glass used in pharmaceuticals is either borosilicate or soda-lime-silica.

Glass Container Classification the ability of glass containers to resist the release of soluble compounds into water under specified conditions of contact between glass and water is
referred to as hydrolytic stability. Titrating released alkali can be used to assess hydrolytic resistance.

**According to their hydrolytic resistance, glass containers are classified as follows:**

**Type I glass containers**\(^8\)
Because of its chemical makeup, neutral (borosilicate) glass has strong hydrolytic and thermal shock resilience. Boric oxide, aluminium oxide, and alkaline earth oxides, primarily calcium oxide, make up Type I glass. The glass is colored with alkaline earth oxide. Most preparations for (human) parenteral use are suitable/preferred in Type I glass containers. Laboratory glass apparatus, ampoules, injection vials, and other Type I glass maid containers are examples.

**Type II glass containers**\(^9\)
Usually made of soda-lime-silica glass with a good hydrolytic resistance due to proper inner surface treatment. Type II glass has a larger salt and calcium oxide content than Type I glass, but it is less resistant to hydrolysis. Most acidic and neutral aqueous preparations for (veterinarian) parenteral use are appropriate for Type II glass containers. Infusion bottle, Vial, and other Type II glass maid containers are examples.

**Type III glass containers**
With only moderate hydrolytic resistance, Type III glass is sometimes known as normal soda-lime glass. Non-aqueous parenteral preparations, powders for parenteral use (excluding freeze-dried preparations), and non-parenteral medications can all be stored in Type III glass containers.

**Type IV glass containers**
Type III glass is a soda-lime glass that can be used for a variety of purposes. Because it is not used for parenteral purposes, this type of glass is also known as Non-Parenteral (NP) glass. Ultraviolet rays are blocked by colored glass, which effectively protects contents from photochemical deterioration.

**Pharmaceutical primary packaging made of plastic**\(^10\)
Plastics are the most used packaging material for pharmaceutical prescription products. Glasses are being phased out in favour of various forms of plastic. Plastics are polymers with a lengthy chain of monomers. Plastics used in packaging systems are made up of homologous
polymers with a variety of molecular weights, as well as additives including antioxidants, stabilizers, lubricants, plasticizers, and colourants. The type of polymer, the polymer's use, and the process used to transform the polymer into components, containers, or packaging systems all influence the nature and amount of additives in plastics used for packaging systems. Plastic (Thermoplastics) can be molded easily to make any form according to desire.

Types of plastic packaging system
Plastic packaging system can broadly be divided into two categories: thermoplastics and thermosets.

Thermoplastics (Thermo-softening Plastics)\cite{11}
Thermoplastics are heat-softening polymers that are stiff at room temperature but can be remelted and remoulded when exposed to high temperatures and pressure. The five most cost-effective plastics - polyvinylchloride, polystyrene, polypropylenes, polyethylene, and polyester – are examples of thermoplastics. Nylon, polyvinylidene chloride, and polycarbonate are among the others.

Thermosets are a type of thermoseal (Thermo-setting Plastics) They're called thermosets because when subjected to high temperatures/heat, they become noticeably infusible or insoluble, and so can't be remelted or remoulded after their initial heat formation. They are made using a polymerization process that includes a curing or vulcanization stage in which the components are heated and pressed into a permanent condition. To get the optimum quality, thermosets frequently comprise extra additives (fillers and strengthening agents). When strong dimensional and heat stability are required, these materials are used as packing materials. Examples of thermoses resins include phenol formaldehyde (originally known as bakelite), urea formaldehyde, melamine formaldehyde, epoxy resins (expoxies), and certain polyesters and polyurethanes. These materials are commonly used in the pharmaceutical industry as closures for glass and/or plastic containers, small cases as one time used for methanol cones, protective lacquers and enamels as applied internally and externally to metal containers and a range of adhesive systems.

Pharmaceutical plastic containers are made from following polymers:

Polyvinyl Chloride (PVC)\cite{12-14}
After polyethylene and polypropylene, PVC (Polyvinyl Chloride) is the world's third most widely produced synthetic plastic polymer.
PVC is a thermoplastic that is made up of 57% chlorine (produced from industrial grade salt) and 43% carbon (generated primarily from oil and gas via ethylene).

Eugen Baumann, a German chemist, unintentionally developed PVC in 1872. Inside a flask of vinyl chloride that had been exposed to sunshine, the polymer appeared as a white solid.

PVC is chemically resistant and has strong physical stability. PVC has low heat stability, with melting points ranging from 100 to 260°C. As a result, chemicals that stable the material at higher temperatures are commonly applied to the material throughout the manufacturing process. In comparison to other plastics, polyvinyl chloride is exceptionally thick and consequently quite durable, and it resists impact deformation very well. It has an extremely high tensile strength. In its rigid state, PVC is employed as a forming film (RPVC). The biggest issue is the lack of moisture barrier qualities. To solve this problem, a thin coating of PVdC is applied to the outside of the PVC sheet, with a GSM of 40-90. PVC has various applications in packaging of pharmaceutical products like infusion bag, medical tubing and film for blister packaging.

**High-Density Polyethylene (HDPE)**

High-Density Polyethylene is another name for high-density polyethylene (PE-HD). It is recognized for having a high strength to density ratio of 0.93 to 0.97 g/cm3 (970 kg/m3). HDPE is flexible, translucent/waxy and weatherproof, has good low temperature toughness (to 60°C), is easy to produce by most methods, is inexpensive, and has strong chemical resistance to dilute acids and bases, aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons, and alcohols. Many varieties of pharmaceutical containers and caps are made from HDPE. Containers that are not pigmented are usually transparent and have strong barrier qualities and rigidity. The physical qualities of HDPE vary depending on the moulding process used to create a specific sample; to some extent, the globally standardized testing procedures used to determine these parameters for a certain process are a determining factor. The SPIs Plastic Recycling Code number "2" is assigned to HDPE plastics.

**Low-Density Polyethylene (LDPE)**

The thermoplastic Low-Density Polyethylene (LDPE) is manufactured from the monomer ethylene. The density of LDPE is defined as 0.910–0.940 g/cm3. LDPE has a low chemical reactivity and is resistant to a variety of acids, bases, and alcohols, both dilute and
concentrated. It is a good plastic type that is now employed in the packaging of medicinal products. It's used to make plastic bags, films, ophthalmic containers, sachets, and bottles, among other things.

**Polypropylene (PP)**[18]

Polypropylene is a widely used thermoplastic polymer in the pharmaceutical sector for drug packaging. PP's density ranges from 0.895 to 0.92 g/cm³. PP is chemically resistant to nearly all substances, including strong acids, alkalies, and most organic compounds. Because of its high melting point, it can be used in both boilable and sterilizable packaging. Polypropylene is a great vapour and gas barrier. Polypropylene is used to create measuring cups, droppers, infusion bags, and infusion bag ports and stoppers, among other things.

**Pharmaceutical primary packaging made of Rubber and Elastomer**

Rubber is a common material in the pharmaceutical industry for sterile (parenteral) preparation packing. Pharmaceutical sterile preparations are typically packaged in glass containers, such as injection vials and prefilled syringes, which require a closure to close the container's mouth. Stoppers made of rubber are a common type of closure. The first polymer used in pharmaceutical packaging was natural rubber. Then some processed rubber was utilized, such as butyl rubber, nitrile rubber, silicon rubber, and so on. Butyl rubber is widely used because it has a low sorption property and is less expensive than other synthetic rubbers, although it decomposes at temperatures exceeding 130°C. Filler, colourants, plasticizers, and protective agents are some of the third agents that must be used during the rubber manufacturing process. Quality control testing is required before employing rubber as a closure to verify pH and clarity of the solution, acidity/alkalinity, moisture content, and other factors.

**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**.

**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

**Closers**

The container's closing is usually the most vulnerable and crucial component. These are used to seal the container's opening so that the contents within remain safe and contaminant-free. The contents of the container must not be able to escape, and no substance must be able to enter the container. A seal that is completely hermetic and microbiological is provided by a closure.

**Closures are available in five basic designs**

1. Screw-on, threaded, or lug
2. Crimp-on (crowns)
3. Press-on (snap)
4. Roll-on
5. Friction.

Many variations of these basic types exist, including

Tamperproof,
Child resistant
Dispenser applicators
Threaded screw cap
Aluminum, tin, or plastic are used to make these. Tinplate or aluminium are the most used metals, whereas thermoplastic and thermosetting materials are employed in plastics. The screw cap protects the content being sealed from physical and chemical harm.

Lug Cap
The lug cap is comparable to and works on the same idea as the threaded screw cap. Metal is commonly used for lug caps. Instead of a continuous thread, it's just an interrupted thread on the glass finish. It simply takes a quarter turn, unlike the threaded closing. Rather than the pharmaceutical industry, the cap is frequently employed in the food industry.

Roll-On and Pilfer Proof Closures
The aluminium roll-on cap may be securely closed, conveniently opened, and resealed. Food, beverage, chemical, and pharmaceutical packaging are all examples of where it's used. A material that is easy to shape, such as aluminium or other light gauge metal, is required for the roll-on closure. The pilfer-proof closure is identical to a regular roll-on closure, but with a longer skirt. The bridges break when the pilfer-proof closure is removed, but the bank stays in place on the container's neck. To remove the cap, you'll need to use a lot of torque.
Friction Fit Cap
Friction Fit Caps are usually constructed of plastic. A loose lid is used to close some containers. Friction fittings are more secure since they require some force to close and open. Friction fit plugs are commonly found in paint cans.

- 4 Major trends in pharmaceutical packaging material
  1. Serialization in fine print: Many vendors have now produced various methods to permit serialised printing on both main packaging material and the final dosage form. The bottles, as well as the tablets and capsules, were printed with 2D barcodes using this innovative process. Because of the direct printing on the dosage form, the print is getting even smaller, although it is still a difficult task. This method is used in countries such as Japan and the United States.
2. **Variable global standards necessitate flexibility:** Firms who make pharmaceuticals for various nations on a same processing line must adjust serialised data accordingly. New specialised software can help to simplify things. Another major trend is the use of enhanced vision and inspection systems to ensure quality. This system incorporated advancements in everything from pill making to capsule assembly to vial sealing.

3. **Novel biologics are causing packaging changes:** The growing popularity of new biologic drugs is causing some unacceptably difficult packaging difficulties. These new medications could interact with the packing material. Glass vials and prefilled syringes are two examples of formats that are experiencing alterations in response to market demand. Tungsten-free syringes are attracting more study attention these days.

4. **The beauty of being small:** Previously, the pharmaceutical sector was tasked with dealing with larger dose forms. However, they are currently concentrating on the smaller dose type. The smaller dosage form filling lines are smaller, more modular, more versatile, with a shorter lead time.\[^{16}\]

**International standards on packaging**

The standards on packaging released by the International Organization for Standardization (ISO) as of 10 October 1998 are listed below, beginning with the four main standards and proceeding in number order.

Quality systems are a model for ensuring quality in the design, development, production, installation, and maintenance of products. ISO 9001 is a 1994 international standard.

Quality systems are a paradigm for ensuring quality in production, installation, and maintenance. ISO 9002. 1994 is an international standard.

Quality systems are a paradigm for ensuring quality throughout final inspection and testing. ISO 9003. 1994 is an international standard.


Quality management and quality systems elements. Part 2: Guidelines for service.\[^{17}\]
CONCLUSION

Pharmaceutical packaging materials are important in the pharmaceutical sector since the packaging of drug products is linked to the product’s safety and stability. Marketers, designers, and customers all contribute to the successful design of pharmaceutical packages and packaging. Packaging provides pharmaceutical elegance and patient compliance, resulting in increased pharmaceutical product marketing. Despite the fact that certain pharmaceutical packages have several flaws. To address these drawbacks, eco-friendly packaging materials that are biodegradable and easily recycled have been developed and implemented.

REFERENCES


