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CURRENT ASPECT OF PHARMACEUTICAL PACKING MATERIALS, IMPORTANCE AND IT'S FUTURE TREND - A REVIEW

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ABSTRACT

Packaging is a key for sale, safety and success. Like other packaged goods, pharmaceuticals packaging need to be in such a manner that it will provide speedy packaging, protection, identification, product quality, patient comfort, display and needs of security. Advancement in research of pharmaceuticals development had always being dependent on the packaging technology. Maintaining integrity of pharmaceuticals during storage, shipment, and delivery is assured by quality of packaging available. This article reviewing current pharmaceutical packaging trends and predicting the packaging outcomes in future. Packaging must provide protection against climatic conditions biological, physical and chemical hazards and must be economical. The package must ensure adequate stability of the product throughout the shelf life. The primary packaging consist of those packaging components which have a direct contact with the product (i.e. bottle, cap, cap liner, etc). The main functions of the primary package are to contain and to restrict any chemical, climatic or biological or occasionally mechanical hazards. The packaging external to the primary package is known as the secondary packaging. The secondary packaging mainly provides the additional physical protection necessary to endure the safe warehousing and for refill packaging. Packaging are currently in use, as follows Unit-dose packaging & Device packaging.

Keywords – *Packaging, primary packaging, secondary packaging, shelf life, Packaging's are currently in use, Unit-dose packaging & Device packaging, marketing.*

1. INTRODUCTION

The packaging can be defined as an economical means of providing presentation, protection, identification information, containment, convenience and compliance for a product during storage, carriage, display and until the product is consumed. Packaging must provide protection against climatic conditions biological, physical and chemical hazards and must be economical. The package must ensure adequate stability of the product throughout the shelf life. The primary packaging consist of those packaging components which have a direct contact with the product (i.e. bottle, cap, cap liner, etc). The main functions of the primary package are to contain and to restrict any chemical, climatic or biological or occasionally mechanical hazards. The packaging external to the primary package is known as the secondary packaging. The secondary packaging mainly provides the additional physical protection necessary to endure the safe warehousing and for refill packaging.[1-22, 23]

The selection of the package therefore begins with a determination of the product's physical and chemical characteristics, its protective needs, and its marketing requirement.[1, 2,21,22,23] Packaging is a key for sale, safety and success. Like other packaged goods, pharmaceuticals packaging need to be in such a manner that it will provide speedy packaging, protection, identification, product quality, patient comfort, display and needs of security. Advancement in research of pharmaceuticals development had always being dependent on the packaging technology. Maintaining integrity of pharmaceuticals during storage, shipment, and delivery is assured by quality of packaging available. This article reviewing current pharmaceutical packaging trends and predicting the packaging outcomes in future.

Packaging is defined as a technique which allows containment of pharmaceutical product from the time of production in a unit till its use. Role of pharmaceutical packaging is to provide life saving drugs, surgical devices, blood and blood products, nutraceuticals, powders, poultices, liquid and dosage forms, solid and semisolid dosage forms. Packaging of pharmaceuticals essentially provides containment, drug safety, identity, convenience of handling and delivery. Pharmaceutical packaging has to balance lots of complex considerations. Leaving behind relatively simple issues such as developing good designs and communicating with customers, pharmaceutical packagers are concerned to more pressing concerns which include fighting with counterfeiting, encouraging patient compliance, ensuring drug integrity and balancing child-resistance and accessibility for the elderly. Issue of environment safety is also key concern for both developed and developing countries packaging industry. [3,5,22,23,24]

Packaging documentation [5] includes aspects related to:

— Specifications and quality control, including batch records

— Labels, inks and adhesive materials (e.g. glue)

— Package inserts for patients.

Apart from primary and secondary packaging, two types of special Packagings are currently in use, as follows: [20]

This packaging guarantees safer medication by reducing medication errors; it is also more practical.

Unit-dose packaging: It may be very useful in improving compliance with treatment and may also be useful for less stable products.

Device" packaging: Packaging with the aid of an administration device is user-friendly and also improves compliance. This type of packaging permits easier administration by means of devices such as prefilled syringes, droppers, transdermal delivery systems, pumps and aerosol sprays. Such devices ensure that the medicinal product is administered correctly and in the right amount. The selection of the package therefore begins with a determination of the product's physical and chemical characteristics, its protective needs, and its marketing requirement.

The material selected must have the following characteristics[1, 2, 25,26]

1.They must protect the preparation from environmental conditions.

2.They must not be reactive with the product.

3.They must not impart to the product tastes or odors.

4.They must be nontoxic.

5.They must be FDA approved.

6.They must meet applicable tamper-resistance requirements.

2. CATEGORICALLY DIFFERENTIATING PHARMACEUTICAL PACKAGING [1, 3,4,24]

2.1 **Primary Packaging:** Primary Packaging Material (Also known as Critical Packaging Component).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. E.g. Blister packages, Strip packages, etc.

2.2 **Secondary Packaging**: Secondary Packaging Material (Also known as Non -Critical Packaging Component).This is consecutive covering or package which stores pharmaceuticals packages in it for their grouping.E.g. cartons, boxes etc.

2.3 **Tertiary packaging**: Tertiary Packaging Material (Also known as Non -Critical Packaging Component).This is to provide bulk handling and shipping of pharmaceuticals from one place to another.E.g. Containers, barrels etc.

Table 1:Types of raw materials used in packaging [1,5]

Types of materials	Uses
Cardboard	Boxes, Display units
Paper	Labels ,Leaflets
Glass	Ampoules, Bottles, Vials, Syringes, Cartridges
Plastic	Closures, Bottles, Bags, Tubes Laminates with paper or foil
Metal, e.g. aluminium	Collapsible tubes, Rigid cans, Foils, Needles Gas cylinders, Pressurized containers
Rubber	Closures, including plungers

Table 2: Primary and Secondary packaging material[1, 9, 20, 24]

Material	Type	**Example of use**
Plastic	Primary	Ampoule, vial, infusion fluid container, dropper bottle
Glass	Primary	Metric medical bottle, ampoule, vial
Paper	Secondary	Labels, patient information leaflet
Cardboard	Secondary	Box to contain primary pack

3. HAZARDS ENCOUNTERED BY PACKAGE[1, 9]

Hazards encountered by the package can be divided into three main groups viz. Mechanical hazards, Climatic or environmental hazards and Biological hazards. The only exception is theft, which can be a serious risk with drugs and may demand special protection in certain cases.

3.1 MECHANICAL HAZARDS

a. Shock or impact damage

Damage due to shock is usually caused by rough handling, during transport etc. Cushioning can be provided and a warning label may be useful. Restriction of movement and more careful handling should be made.

a. Compression

Fragile items may be broken, or collapsible articles crushed by compression, the usual procedure then being to protect with a rigid outer package. Top pressure or loading can distort inside. The crushing of a carton can make a product un- sealable even though no damage has occurred to the contents. This is more likely to occur during stocking in the ware house or during transport where vibration adds a further hazard. Compression can also occur in other situations like capping on a production line, when being carried home by the user etc.

b. Vibration

Vibration consists of two variables-frequency and amplitude. Considerable vibration may occur during transport, especially with exported items. Sometimes screw caps may be loosen or labels or decorations may abrade etc.

c. Abrasion

Although abrasion results from both regular and irregular forms of vibration , it is listed separately as the visual appearance of the product or package can be affected. eg: rectangular bottle in a carton will move up and down and from side to side. A round bottle in the same circumstances will suffer from an additional possibility of rotation.

3.2 CLIMATIC OR ENVIRONMENTAL HAZARDS

Environmental conditions encountered by the package are likely to vary considerably, especially in articles for export to the tropical areas. In general, it is extremes of conditions that give rise to problems, and this is especially true of fluctuating conditions.

a. Temperature

Extreme conditions may cause deterioration, low temperatures leading to aqueous solutions freezing and, hence, to fracture of containers. High temperatures increase diffusion coefficients, accelerating the entry of water vapor into hygroscopic products and the loss of volatile components. In addition, high, temperatures increase reaction rates and product breakdowns either by hydrolysis or oxidation. High temperature coupled with a high relative humidity will produce a slower effect if the temperature is lowered sufficiently to reach dew point. Contamination from liquid moisture can encourage mould and bacterial growth.

b. Moisture

Moisture as liquid or water vapor may cause physical changes (e.g. color fading, softening, hardening etc) or chemical changes (hydrolysis, oxidation, effervescence etc). Although liquid moisture may cause obvious damage, water vapour may penetrate into a package, leading to hydrolysis, without visual changes. It is essential to check the water vapour permeability of materials to be used for packaging moisture-sensitive products; for example, plastics show considerable variation in this property. It may also act as a carrier for other contaminants like moulds and fungi.

c. Pressure

Decrease in pressure, as in mountainous regions or during flight in non-pressurized transport aircraft, may cause thin containers to burst or strip packs to inflate.

d. Atmospheric Gases

Gases from the atmosphere may diffuse into the package, leading to deterioration. Thus, oxygen will encourage oxidation, while carbon dioxide can cause a pH shift (un buffered solution in plastic bottle particularly Low Density Poly Ethylene (LDPE), which is relatively permeable to carbon dioxide) or lead to precipitation of some products (barbiturates from solutions of their sodium salts). Permeation of the common gases through plastic is typically in the ratio of 1:4:20 for nitrogen, Oxygen and Carbon dioxide respectively, nitrogen being more permeable. Odorous gases or volatile ingredients associated with perfumes, flavors and product formulation may also pass into or out of a package. If a volatile ingredient is lost from a flavor, an unpleasant odor or taste may result.

e. Light

Light consist of wavelengths from the UV zones through the visible to infrared. A number of deteriorations are due to photochemical reactions particularly affected by the ultra-violet band of the spectrum. Such changes may not always be visible. Printed or deteriorated packaging materials may also suffer from discoloration (white may go yellow, deeper colors may fade) and this may be seen as implying a change in the product efficacy or strength. Although light can be excluded by using selected material, tin plate, soil etc opacity and/or color may reduce penetration or filter out selected wavelength. The additional use of UV absorbers in plastics may also restrict light rays entering the packed it should also be noted that many products are protected by a carton, outer etc. Alternatively, an opaque outer packaging may be used, with a warming that the advantage that the latter may be transparent, permitting the contents to be inspected.

f. Solid airborne contamination (particulars)

Particulars matters present in the atmosphere will make the containers dirty during transport or storage. This can be prevented by outer wrappers or by anti-static agents.

3.3 BIOLOGICAL HAZARDS

a. Microbiological

The packaging materials must be reasonably clean initially and when put together to form a finished package and restrict any further contamination as much as possible. In the case of sterile products the package and its closure must maintain a 100% effective seal against microbiological contaminants like bacteria, moulds and yeasts. Growth of yeasts is critical with sugar based products as fermentation may occur. Moulds will also grow on cellulose based materials like paper if these are kept under humid conditions. Care should be taken in order to avoid fluctuation in temperature.

b. Chemical Hazards

The main risk of chemical hazard is due to interaction or in compatibility between the product and package. Compatibility investigations must basically cover any exchange that can occur between the product and the package and vice versa. These may be associated with interaction or contamination, covering migration, absorption, adsorption, extraction, corrosion, etc. where by ingredients may either be lost or gained. Such exchange may be identifiable as organoleptic changes, increase in toxicity/irritancy degradation, loss or gain of microbial effectiveness, precipitation, turbidity, color change, PH shift etc. These external influences may catalyze, induce or even nullify chemical changes.

4. FUNCTION OF PACKAGING[1, 9]

The various functions of packaging are

a. Protective function

Protective function of packaging essentially involves protecting the contents from the environment and vice versa. The inward protective function is intended to ensure full retention of the utility value of the packaged goods. The packaging is thus intended to protect the goods from loss, damage and theft.In addition packaging must essentially be able to withstand the many different static and dynamic forces to which it is subjected during transport, handling and storage operations. The goods frequently also require protection from climatic conditions, such as temperature, humidity etc. The precipitation and solar radiation may require additional packaging measures in the interior portion of the container.The exterior protection provided by the packaging must prevent any environmental degradation by the goods. This requirement is of particular significance in the transport of hazardous materials, with protection of humans being of primary importance. The packaging must furthermore as far as possible prevent any contamination, damage or other

negative impact upon the environment and other goods. The interior and exterior protective function primarily places demands upon the strength, resistance and leak proof properties of transport packaging.

b. Storage function

The materials used for packaging should be stored properly so as to preserve the quality of the material both before packaging and once the package contents have been used.

c. Loading and transport functions

Packaging has a crucial impact on the efficiency of transport, handling and storage of goods. Packaging should therefore be deigned to be easily handled and to permit space-saving storage and stowage. The shape and strength of packages should be such that they may not only be stowed side by side leaving virtually no voids but may also stowed safely one above the other. The most efficient method of handling general cargo is to make up cargo units. Packaging should thus always facilitate the formation of cargo units; package dimensions and the masses to be accommodated should be possibly tailored to the dimensions and load- carrying capacity of standard pallets and containers.

d. Identification

The packaging should give clear identification of the product at all stages. The life of the patient may depend upon rapid and correct identification in emergencies. Packaging also serves as a mean to identify the manufacturer of the product. The manufacturer must consider the packaging requirement for the usage of product in different localities

5. CONTAINERS

A container for pharmaceutical use is an article which holds or is intended to contain and protect a drug and is or may be in direct contact with it. The closure is a part of the container. The container and its closure must not interact physically or chemically with the substance within in any way that would alter its quality. The following terms include general requirements for the permeability of containers.[5]

a. ***Well-closed containers*** must protect the contents from extraneous matter or from loss of the substance under normal conditions of handling, shipment or storage.

b. ***Tightly closed containers*** must protect the contents from extraneous matter, from loss of the substance, and from efflorescence, deliquescence or evaporation under normal conditions of handling, shipment or storage. If the container is intended to be opened on several occasions, it must be designed to be airtight after reclosure.

c. ***Hermetically closed containers*** must protect the contents from extraneous matter and from loss of the substance, and be impervious to air or any other gas under normal conditions of handling, shipment or storage. Substances and dosage forms requiring protection from light should be maintained in a ***light-resistant container*** that — either by reason of the inherent properties of the material of which it is composed, or because a special coating has been applied to it — shields the contents from the effects of light. Alternatively, the container may be placed inside a suitable light-resistant (opaque) covering and/or stored in a dark place[5].

6. PACKAGING MATERIAL

Any material, including printed material, employed in the packaging of a pharmaceutical product, excluding any outer packaging used for transportation or shipment. Primary packaging materials are those that are in direct contact with the product [1, 2, 5,9,20.]

6.1 Selection of the Packaging Materials[1,2]

Selection is based

1.On the facilities available, for example, pressurized dispenser requires special filling equipment.

2.On the ultimate use of product. The product may be used by skilled person in hospital or may need to be suitable for use in the home by a patient.

3.On the physical form of the product. For example, solid, semi-solid, liquids 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 dioxide, light, trace metals, temperature or pressure or fluctuation of these may have a deleterious effect on the product.

6.On 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 in turn the product is affected

7.On the cost of the product. Expensive products usually justify expensive packaging

Primarily two types of containers are used for packaging:

a) Glass Containers
b) Plastic Containers

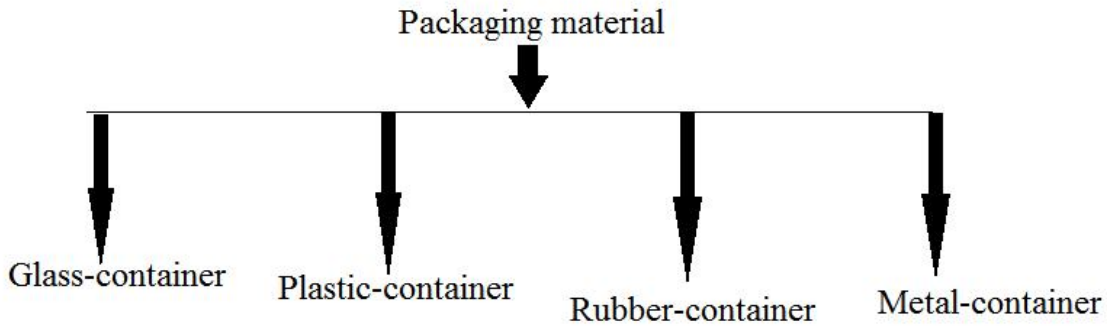

Fig.1 : Classification of packaging materials

A.GLASS CONTAINERS: [2, 3, 23, 24]

i) Advantages

a. Economical

b. Readily available container of variety of sizes and shapes

c. Impermeability

d. Strength and rigidity

e. Has FDA clearance

f. Does not deteriorate with age

g. Easy to clean

h. Effective closure and resolves are applicable.

i. Colored glass, especially amber, can give protection against light when it is required.

ii) Disadvantages[2, 3, 23, 24]

a. Fragility

b. Heavy weight.

iii) Four types of Glass is being used in pharmaceutical industry, [1, 2, 3, 9,11,18,23]

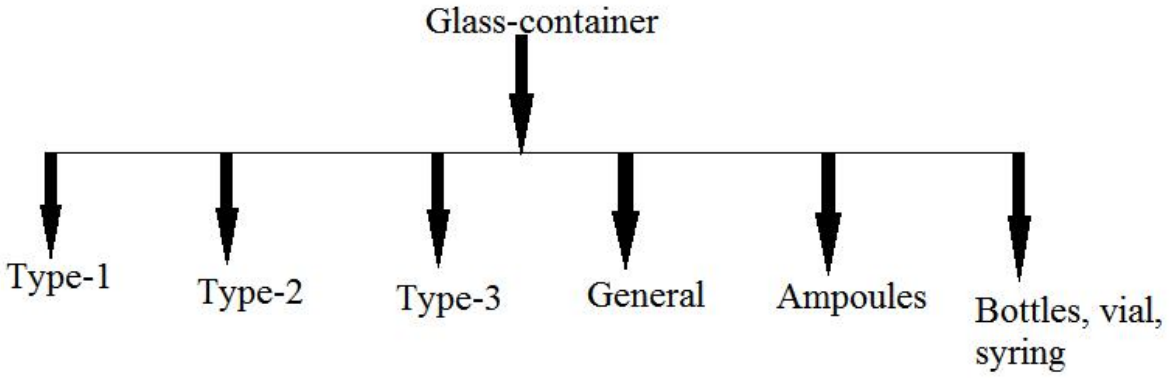

Fig.2: Classification of glass containers

a. **Type I-Borosilicate glass:** Highly resistant and chemically inert glass. Alkali's and earth cations of glass are replaced by boron and/or aluminum and zinc. These are used to contain strong acids and alkalis.
b. **Type 2-Treated soda-lime glass:** These are more chemically inert than Type I glass. The glass surface is de-alkalized by "Sulfur treatment" which prevents blooming/weathering from bottles.
c. **Type III- Regular soda lime glass:** Untreated soda lime glass with average chemical resistance.
d. **Type IV- General Purpose soda lime glass:** Glass is not used for parenterals, used only for products intended to be used orally or topically.

iv) Manufacturing of glass [1,2]

Four basic processes are used in the production of glass:-

Blowing ⟹ Drawing ⟹ Pressing ⟹ Casting.

Blowing uses compressed air to form the molten glass in the cavity of a metal mold. Most commercial bottles and jars are produced on automatic equipment by this method. In drawing, molten glass is pulled through dies or rollers that shape the soft glass. Rods, tubes, sheet glass, and other items of uniform diameter are usually produced commercially by drawing. Ampoules, cartridges, and vials drawm from tubing have a thinner, more uniform wall thickness, with less distortion than blow-molded containers. In pressing, mechanical force is used to press the molten glass against the side of a mold. Casting uses gravity or centrifugal force to initiate the formation of molten glass in the cavity.

v) Composition of glass [1, 2, 9,11,18]

The only anion of consequence is oxygen. Many useful properties of glass are affected by the kind of elements it contains. Reduction in the proportion of sodium ions makes glass chemically resistant; however, without sodium or other alkalies, glass is difficult to melt and is expensive. Boron oxide is incorporated mainly to aid in the melting process through reduction of the temperature required. Lead in small traces gives clarity and brilliance, but produces a relatively soft grade of glass. Alumina (aluminum oxide), however, is often used to increase the hardness and durability and to increase resistance to chemical action. Glass is composed principally of silica with varying amount of metal oxides, soda-ash, limestone, and cullet. The sand is almost pure silica; the soda-ash is sodium carbonate, and the limestone, calcium carbonate. Cullet is broken glass that is mixed with the batch and acts as a fusion agent for the entire mixture. The

composition of glass varies and is usually adjusted for specific purposes. The most common cations found in pharmaceutical glassware are silicon, aluminum, boron, sodium, potassium, calcium, magnesium, zinc, and barium

B.PLASTIC CONTAINER [1,2]

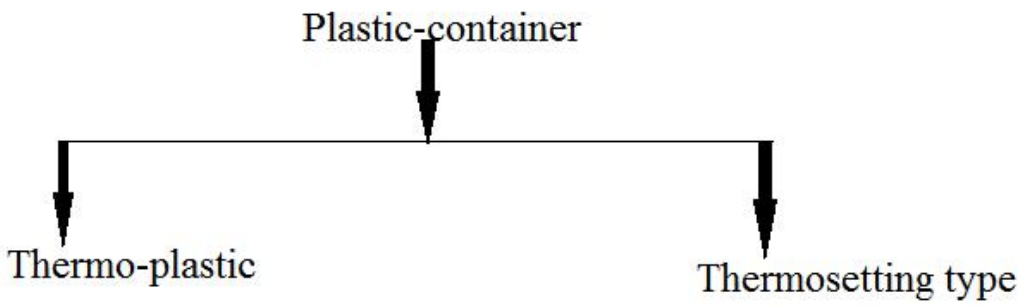

Fig. 3: Classification of plastic containers

i) Thermoplastic type

On heating, they are soften to viscous fluid which hardens again on cooling. e.g. polyethylene ,PVC Polystyrene ,polypropylene ,Polyamide ,Polycarbonate.

ii) Thermosetting type

When heated, they may become flexible but they do not become liquid. Phenol formaldehyde , urea formaldehyde, melamine formaldehyde Plastics in packaging have proved useful for a number of reasons, including the ease with which they can be formed, their high quality, and the freedom of design to which they lend themselves. Plastic containers are extremely resistant to breakage and thus offer safety to consumers along with reduction of breakage losses at all levels of distribution and use. Plastic containers for pharmaceutical products are primarily made from the following polymers: polyethylene, polypropylene, polyvinyl chloride, polystyrene, and to a lesser extent, polymethyl methacrylate, polyethylene terephthalate, polytrifluoroethylene, the amino formaldehydes, and polyamides. Plastic containers consist of one or more polymers together with certain additives. Those manufactured for pharmaceutical purposes must be free of substances that can be extracted in significant quantities by the product contained. Thus, the hazards of toxicity or physical and chemical instability are avoided.

Advantages of Plastic Containers

Plastic containers have a number of inherent practical advantages over other containers or dispenses. They are

a. Low in cost
b. Light in weight
c. Durable
d. Pleasant to touch
e. Flexible facilitating product dispensing
f. Odorless and inert to most chemicals
g. Unbreakable
h. Leak proof
i. Able to retain their shape throughout their use.
j. They have a unique 'suck-back' feature, which prevents product doze.

Disadvantages

Plastics appear to have certain disadvantage like interaction, adsorption, absorption lightness and hence poor physical stability. All are permeable to some degree to moisture, oxygen, carbon dioxide etc and most exhibit electrostatic attraction, allow penetration of light rays unless pigmented, black etc. Other negative features include:

• *Stress cracking*

A phenomenon related to low density polythene and certain stress cracking agents such as wetting agents, detergents and some volatile oils.

• *Paneling or cavitation*

Where by a container shows in ward distortion or partial collapse owing to absorption causing swelling of the plastic or dimpling following a steam autoclaving operation.

• *Crazing*

A surface reticulation which can occur particularly with polystyrene and chemical substances (e.g. isopropyl myristate which first cause crazing and ultimately reaches of total embitterment and disintegration).

• *Poor key of print*

Certain plastics, such as the poly olefins need pre-treating before ink will key. Additives that migrate to the surface of the plastic may also cause printing problem.

• *Poor impact resistance*

Both polystyrene and PVC have poor resistance. This can be improved by the inclusion of impact modifiers such as rubber in case of polystyrene and methyl methacrylate butadiene styrene for PVC.

Materials

Polyethylene

High-density polyethylene is the material most widely used for containers by the pharmaceutical industry and will probably continues to be for the next several years. Polyethylene is a good barrier against moisture, but a relatively poor one against oxygen and other gases. Most solvents do not attack polyethylene, and it is unaffected by strong acids and alkalies. Polyethylene has certain disadvantages that it lacks clarity and a relatively high rate of permeation of essential odors, flavors, and oxygen. Despite these problems, polyethylene in all its variations offers the best all-around protection to the greatest number of products at the lowest cost. The density of polyethylene, which ranges from 0.91 to 0.96, directly determines the four basic physical characteristics of the blow-molded container:

(1) Stiffness

(2) Moisture-vapor transmission

(3) Stress cracking

(4) Clarity or translucency

As the density increases, the material becomes stiffer, has a higher distortion and melting temperature, becomes less permeable to gases and vapors, and becomes less resistant to stress cracking. The molecular structure of high-density material is essentially the, same as that of low-density material, the main difference being fewer side branches.

Polypropylene

Polypropylene has recently become popular because it has many good features of polyethylene, with one major disadvantage either eliminated or minimized. Polypropylene does not stress-crack under any conditions. Except for hot aromatic or halogenated solvents, which soften it, this polymer has good resistance to almost all types of chemicals, including strong acids, alkalies, and most organic materials. Its high melting point makes it suitable for boilable packages and for sterilizable products. Lack of clarity is still a drawback, but improvement is possible with the construction of thinner walls. Polypropylene is an excellent gas and vapor barrier. Its resistance to permeation is equivalent to or slightly

better than that of high-density or linear polyethylene, and it is superior to low-density or branched polyethylene. One of the biggest disadvantages of polypropylene is its brittleness at low temperatures. In its purest form, it is quite fragile at 0°F and must be blended with polyethylene or other material to give it the impact resistance required for packaging.

Polyvinyl Chloride (PVC)

PVC can be softened with plasticizers. Various stabilizers, antioxidants, lubricants, or colorants may be incorporated. Polyvinyl chloride is seldom used in its purest form. PVC is an inexpensive, tough, clear material that is relatively easy to manufacture. PVC must not be overheated because it starts to degrade at 280°F, and the degradation products are extremely corrosive. Polyvinyl chloride yellows when exposed to heat or ultraviolet light, unless a stabilizer is included by the resin supplier. From the standpoint of clarity, the best stabilizers are the tin compounds, but the majority cannot be used for food or drug products Polyvinyl chloride is not affected by acids or alkalis except for some oxidizing acids. Its impact resistance is poor, especially at low temperatures.

Polystyrene

Polystyrene is attacked by many chemicals, which cause it to craze and crack, and so it is generally used for packaging **dry products only.** To improve impact strength and brittleness, general-purpose polystyrene may be combined with various concentrations of rubber and acrylic compounds. Certain desired properties like clarity and hardness diminish with impact polystyrene. The shock resistance or toughness of impact polystyrene may be varied by increasing the content of rubber in the material, and often these materials are further classified as intermediate-impact, high-impact, and super-impact polystyrene.

Nylon (Polyamide)

As a barrier material, nylon is highly impermeable to oxygen. It is not a good barrier to water vapor, but when this characteristic is required, nylon film can be laminated to polyethylene or to various other materials. Its relative high-water transmission rate and the possibility of drug-plastic interaction have reduced the potential of nylon for long-term storage of drugs. Some of the nylon approved by FDA are Nylon 6, Nylon 6/6, Nylon 6/10, Nylon 11, and certain copolymers. Nylon is made from a dibasic acid combined with a di-amine. Variety of nylons can be made with different dibasic acids and amines. The type of acid and amine that is used is characteristic and denotes the type of acid and amine used.e.g. nylon 6/10 has six carbon atoms in the diamine and ten in the acid. Nylon and similar polyamide materials can be fabricated into thin-wall containers. Nylon can be autoclaved and is extremely strong and quite difficult to destroy by mechanical means. Important to the widespread acceptance of nylon is its resistance to a wide range of organic and inorganic chemicals.

Polycarbonate

The plastic is known for its dimensional stability, high impact strength, resistance to strain, low water absorption, transparency, and resistance to heat and flame. Polycarbonate is resistant to dilute acids, oxidizing or reducing agents, salts, oils (fixed and volatile), greases, and aliphatic hydrocarbons. It is attacked by alkalies, amines, ketones, esters, aromatic hydrocarbons, and some alcohols. Polycarbonate resins are expensive and consequently are used in specialty containers. Since the impact strength of polycarbonate is almost five times greater than other common packaging plastics, components can be designed with thinner walls to help reduce cost. Polycarbonate can be made into a clear transparent container. Polycarbonate is expensive and offers some advantage that it can be sterilized repeatedly. The containers are

rigid, as is glass, and thus has been considered a possible replacement for glass vials and syringes. It is FDAapproved,

although its drug-plastic problems have not been investigated adequately. It is only moderately chemically resistant and only a fair moisture barrier.

Acrylic Multipolymers (Nitrile Polymers)

The present safety standard is less than 11 ppm residual acrylonitrile monomer, with allowable migration at less than 0.3 ppm for all food products. These polymers represent the acrylonitrile or methacrylonitrile monomer. Their unique properties of high gas barrier, good chemical resistance, excellent strength properties, and safe disposability by incineration make them effective containers for products that are difficult to package in other plastic containers. Their oil and grease resistance and minimal taste transfer effects are particularly advantageous in food packaging. These type of polymers produce clear container and are less costly. The use of nitrile polymers for food and pharmaceutical packaging is regulated to standards set by the Food and Drug Administration.

Polyethylene terephthalate (PET)

Polyethylene terephthalate is used in food packaging and offers favorable environmental impact system. Polyethylene terephthalate, generally called PET, is a condensation polymer typically formed by the reaction of terephthalic acid or dimethyl terephthalate with ethylene glycol in the presence of a catalyst. Although used as a packaging film since the late 1950s, its growth has recently escalated with its use in the fabrication of plastic bottles for the carbonated beverage industry.

Product-Plastic Interactions

Product-Plastic interactions have been divided into five separate categories:

(1) Permeation

(2) Leaching

(3) Sorption

(4) Chemical reaction

(5) Alteration in the physical properties of plastics or products

1) Permeation

Transmission of gases, vapors, or liquids through plastic packaging materials can have an adverse effect on the shelf-life of a drug. Permeation of water vapor and oxygen through the plastic wall into the drug can present a problem if the dosage form is sensitive to hydrolysis and oxidation. Temperature and humidity are important factors influencing the permeability of oxygen and water through plastic. An increase in temperature reflects an increase in the permeability of the gas. Great differences in permeability are possible,

depending on the gas and the plastic used. Molecules do not permeate through crystalline zones; thus, an increase in crystallinity of the material should decrease permeability. Two polyethylene materials may therefore give different permeability values at various temperatures. Materials such as nylon, which are hydrophillic in nature, are poor barriers to water vapor, while such hydrophobic materials as polyethylene provide much better barriers. Studies have also revealed that formulations containing volatile ingredients might change when stored in plastic containers because one or more of the ingredients are passing through the walls of the containers. Often, the aroma of cosmetic products becomes objectionable, owing to transmission of one of the ingredients, and the taste of medicinal products changes for the same reason.

2) Leaching

Problems may arise with plastics when coloring agents in relatively small quantities are added to the formula. Particular dyes may migrate into a parenteral solution and cause a toxic effect. Release of a constituent from the plastic container to the drug product may lead to drug contamination and necessitate removal of the product from the market.

3)Sorption

It is the process involves the removal of drug content from the product by the packaging material. Sorption may lead to serious consequences active ingredients are in solution. Since drug substances of high potency are administered in small doses, losses due to sorption may significantly affect the therapeutic efficacy of the preparation. Sorption is seen mainly with preservatives. These agents exert their activity at low concentration, and their loss through sorption may be great enough to leave a product unprotected against microbial growth. Factors that influence characteristics of sorption from product are chemical structure, pH, solvent system, concentration of active ingredients, temperature, length of contact, and area of contact.

4) Chemical Reactivity

Certain ingredients that are used in plastic formulations may react chemically with one or more components of a drug product. At times, ingredients in the formulation may react with the plastic. Even micro-quantities of chemically incompatible substances can alter the appearance of the plastic or the drug product.

5) Modification

Polyvinyl chloride is an excellent barrier for petroleum solvents, but the plasticizer in polyvinyl chloride is extracted by solvents. This action usually leaves the plastic hard and stiff. Sometimes, this effect is not immediately perceptible because the solvent either softens the plastic or replaces the plasticizer; later, when the solvent evaporates, the full stiffening effect becomes apparent. The changes in physical and chemical properties of the packaging material by the pharmaceutical product are called modification. Such phenomena as permeation, sorption, and leaching play a role in altering the properties of the plastic and may also lead to its degradation. Deformation in polyethylene containers is often caused by permeation of gases and vapors from the environment or by loss of content through the container walls. Some solvent systems have been found to be responsible for considerable changes in the mechanical properties of plastics. Oils, for example, have a softening effect on polyethylene; fluorinated hydrocarbons attack polyethylene and polyvinyl chloride. In some cases, the content may extract the plasticizer, antioxidant, or stabilizer, thus changing the flexibility of the package.

Constituents of plastic containers

The residues, additives and processing aids that may be used, and therefore possibly extracted from, plastic include:

a. **Monomer residues**
b. **Catalysts**
c. **Accelerators**
d. **Solvents**
e. **Extenders**
f. **Fillers**
g. **Slip additives**
h. **Anti-slip additives**
i. **Antistatic agents**
j. **Anti-blocking agents**
k. **Release agents**

Tests for Plastic containers[1,9,11,18]

Leakage test

The plastic containers (non injectables and injectables 1996 IP): fill 10 plastic containers with water and fit the closure keep them inverted at room temperature for 24 hrs no sign of leakage should be there from any container.

Water Permeability Test

Fill 5 containers with nominal volume of water and sealed weigh each container allows to stand for 14 days at relative humidity of 60% at 20-25°C reweigh the container loss of weight in each container should not be more than 0.2%.

C.METAL-CONTAINER

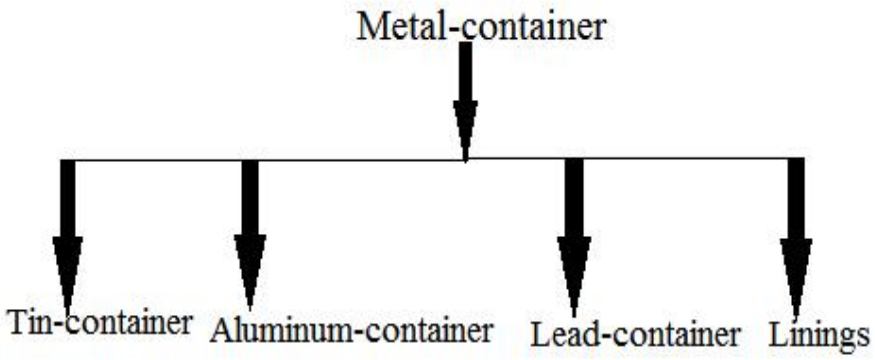

Fig.4 : Classification of metal containers

i) Tin

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. It offers a good appearance and compatibility with a wide range of products.

ii) Aluminum

Aluminum tubes offer significant savings in product shipping costs because of their light weight. They provide good appearance.

iii) Lead

Lead has the lowest cost of all tube metals and is widely used for nonfood products such as adhesives, inks, paints, and lubricants. Lead should never be used alone for anything taken internally because of the risk of lead poisoning. The inner surfaces of the lead tubes are coated and are used for products like fluoride toothpaste.

iv) Linings

If the product is not compatible with bare metal, the interior can be flushed with wax-type formulations or with resin solutions, although the resins or lacquers are usually sprayed on. A tube with an epoxy lining costs about 25% more than the same tube uncoated. Wax linings are most often used with water-base products in tin tubes, and phenolics, epoxides, and vinyl's are used with aluminum tubes, giving better protection than wax, but at a higher cost.

D.RUBBER

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

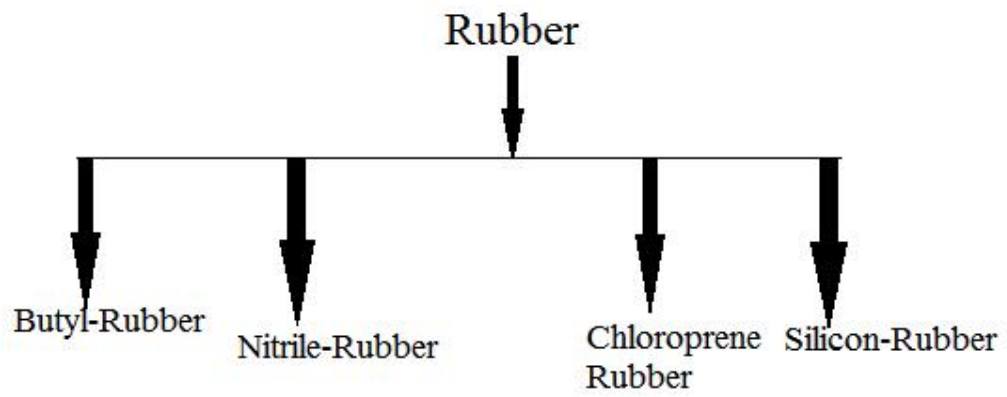

Fig. 5 : Classification of rubber

i) Butyl Rubber

Advantages

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

Disadvantages

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

ii) Nitrile Rubber

Advantages: Oil resistant due to polar nitrile group. Heat resistant.

Disadvantages: Absorption of bactericide and leaching of extractives are considerable.

iii) Chloroprene Rubbers

Advantages: Oil resistant. Heat stability is good.

iv) Silicon Rubbers

Advantages

oHeat resistance. Extremely low absorption and permeability of water.

oExcellent aging characteristic.

Disadvantages:

They are very expensive.

Tests for Rubber Closures

Fragmentation Test

Place a volume of water corresponding to nominal volume-4ml in each of 12 clean vials close vial with closure and secure caps for 16hrs pierce the closure with number 21 hypodermic needle(bevel angle of 10 to 140c)and inject 1ml water and remove 1ml air repeat the above operation 4 times for each closure count the number of fragments visible to naked eye Total number of fragments should not be more than 10.

Self Sealability Test for Rubber Closures Applicable to Multi Dose Containers Only

Fill 10 vials with water to nominal volume and close the vials with closures pierce the cap and closures 10 times at different places with no 21 syringe needle immerse the vials in 0.1 %W/v solution of methylene blue under reduced pressure restore the nominal pressure and keep the container for 30 min and wash the vials none of the vial should contain traces of colored solution.

Blister Packaging Technology

Blister packaging is a type of pre-formed plastic packaging used for small consumer goods. The two primary components of a blister pack are the cavity made from either plastic or aluminum - and the lidding, made from paperboard, paper, plastic or aluminum. The cavity contains the product and the lidding seals the product in the package. Blister packaging helps retain product integrity because drugs that are pre- packaged in blisters are shielded from adverse conditions. Furthermore, opportunities for product contamination are minimal, and each dose is identified by product name, lot number, and expiration date. Therefore, blister packaging ensures product integrity from the producer directly through distribution to the consumer.

Material Used In Blister Packaging

1. PVC

The most basic material for the forming web is polyvinyl chloride (PVC). The principal advantages of PVC are the low cost and the ease of thermoforming.

2. PCTFE: Polychlorotrifluoro ethylene or PCTFE can be laminated to PVC to obtain very high moisture barrier.

3. COC: Cyclic olefin copolymers (COC) or polymers (COP) can provide moisture barrier to blister packs.

Advantages

1. Product integrity.
2. Product protection.
3. Tamper evidence.
4. Reduced possibility of accidental misuse.
5. Patient compliance.

Tamper-evident packaging [14, 20,21]

(TEP) means packaging that has an indicator or barrier to entry which, if breached or missing, can reasonably be expected to provide visible or audible evidence to consumers that tampering may have occurred.

Tamper-Evidence

The degree to which tampering is apparent to the observer.

Tamper-Resistance: The degree to which it is difficult to tamper (and repair) without leaving evidence. A tamper-resistant package has an indicator or barrier to entry which, if breached or missing, can (reasonably) be expected to provide visible evidence to consumers that tampering has occurred.

Tamper- Evident Features

The packaging features listed below are considered to be acceptable forms of TEP provided they are validated in accordance with Clause whilst these forms of TEP are acceptable, they should not be seen to be exclusive of other forms of TEP or to preclude technological innovation. Tamper-evident packaging must not be regarded as replacing or obviating the need for child- resistant packaging wherever the law requires such packaging. In selecting or developing

tamper-evident packaging, consideration should be given to the special.

Film Wrappers

Transparent A transparent film with distinctive design is wrapped securely around the entire product container ensuring the product is completely sealed and a secure tight fit is achieved.

Blister or Strip Packs

Individual doses (for example, capsules or tablets) are sealed in plastic and/or foil. Blister or strip pack seals around individual compartments and the strip as a whole must be intact and complete.

Bubble Packs: The product and container are sealed in a plastic bubble and mounted in or on a display card.

Heat Shrink Bands or Wrappers: Bands or wrappers with a distinctive design are shrunk by heat to tightly seal the union of the cap and container.

Pouches, Sachets and Form Fill Seal Packs

The product is enclosed in an individual pouch or sachet that must be ripped, peeled open or broken to gain access to the product.

Container Mouth Inner Seals

Paper, thermal plastic, polystyrene foam, plastic film, foil, or combinations thereof, with a distinctive design is sealed to the mouth of a container under the cap.

Design

During design of TEP, the following aspects must be considered.

1.Suitability of the packaging for its intended purpose.

2.Compatibility of the packaging components.

3.Compatibility of the packaging components with the packaging process.

4.Presence of the required TEP statements on the final pack. The tamper-evident packaging features must be designed to remain intact, when handled in a reasonable manner, during manufacture, distribution and retail display.

7. SPECIFICATIONS

In recognition of the variability of packaging components, the sponsor must ensure that clear and concise specifications are developed and agreed between the packaging material supplier and the product manufacturer. Specifications must include functional / performance criteria and must include reference to approved engineering drawings where appropriate.

Pharmacopoeial Requirements For Containers In Europe, Japan And the USA[20]

Glass Containers

A classification of types of glass for containers for pharmaceutical products does not exist in the Japanese-pharmacopoeia, while those given in the European and United States pharmacopoeias are very similar.

Both the European and United States pharmacopoeias provide specifications for glass containers for injections. The latter publication also gives specific guidance for the packaging, repackaging and dispensing of medicinal products. Both the European and United States pharmacopoeias also provide specifications for light-resistant containers and tightly or well-closed closures for capsules and tablets. The European pharmacopoeia gives a general account of the requirements for glass containers for pharmaceutical use, together with those specifically applicable to glass containers for human blood and blood products.

Plastic Containers

Many different plastics are used for containers for medicinal products and the requirements applicable to them differ greatly in the various pharmacopoeias. It is very difficult to compare the tests described. Other and possibly different requirements may be found in international standards.

Rubber Closures

A comparison of the requirements for rubber closures is as difficult as that for plastic containers. The European and Japanese pharmacopoeias contain special requirements for rubber closures intended for containers of aqueous parenteral preparations. The United States pharmacopoeia describes more generally the use of closures made from elastomers for injection bottles, but does not specify the preparations for which they can be used. Similarities exist between the tests given in the European, Japanese and United States pharmacopoeias, but international standards also exist which differ considerably from one another.

Importance Of Packaging Material In Pharma Industry [13, 14,15]

Drugs need more care in their packaging than do most other product, because any failure in their packing could result in changes in the drug that lead either to a failure to cure, to illness, to injury or even cause death of patient.

8. EXPECTATIONS OF PHARMA INDUSTRY FROM PACKAGING INDUSTRY[13, 14,15]

Packaging Quality must be of a good design relevant to the needs of:

- Product
- Manufacturing and Distribution System (of both Customer & Supplier)

Stability Parameters

1. Protect the Product from Moisture and Gas.
2. Light and Temperature Protection.
3. Microbiological Integrity

4. pH Stability

Compatibility With Packaging Material

Migration from the Medicine to the Packaging Components of :

1)Preservatives

2)Volatile actives

Leaching from The Packaging to the Medicine of :

1)Stabilizers

2)Plasticizers

3)Anti-oxidant

4)Additives etc.

Machine Suitability

1)Line Speed

2)Tolerances

3)Reliability

Legislation

1)Fill Weight

2)Labeling

3)Storage

Marketing Aspects

1)Market Policy

2)Product Code

9. COMPLIANCE WITH INTERNATIONL STANDARDS[13, 14,15]

S. No.	BRITISH STANDARD NUMBER	TITLE
1	BS 795 : 1983	Ampoules
2	BS 2006 : 1984	Aluminium Collapsible Tubes
3	BS 5597 : 1991	Specifications For Non –Refillable Plastic Aerosol Containers
4	BS 6652 : 1985	Specifications For Packaging Resistant To Opening By Children
5	EN 293622 : 1993	Rubber Closures For Injectable Products

10. AN IDEAL PACKAGING MATERIAL INDUSTRY AS PER GMP AND REGULATORY REQUIREMENTS SHOULD BE EQUIPED WITH FOLLOWING QC EQUIPMENTS: [13, 14,15]

1.GSM Measuring Weighing Scale

2.Gauge Meter

3.Viscosity Cup

4.Bond Strength Measuring Unit

5.Bursting Strength Measuring Unit

6.Vacuum Chamber

7.Dart Impact Testing Machine

8.Opacity Meter

9.Pin Hole Checking Table

10.Pantone Shade Card

11.Chemical Analysis Unit

12.VMCH coating machine etc.

11. HOW THE RELATION BEWTEEWN PHARMA AND PACKAGING INDUSTRY CAN HELP EACH OTHER? [6,7, 13, 14,15]

By Providing Product Security: Packaging can help combat Product counterfeiting through authentication and design

By Providing Specific Packaging Material: By Providing Specific Packaging Material which includes prompting and Technology to help patients remember to take their medications

By Building Brands: To partner with customers to develop ideal, effective healthcare solutions to fit their needs &goals

By Ensuring Quality Plants should practice cGMP and Process Control Methods, and undergo audits for continuous process improvements.

12. FUTURE ASPECTS: [4,20,21,22]

Packaging is one of the largest industry sectors in the world, worth $280 billion. Consumer healthcare packaging represents 4% ($11.2 billion) of the packaging industry. As drug manufacturers approach the 21st century, they face a number of challenges that packaging can help them meet. One of the marketing tools that have become popular and important is **packaging** and **packaging design** which allows companies to be different from each other and to have more priorities among competitors. This has become a reason why nowadays there is a big variety of design packages on the supermarkets' shelves. **Plastic packaging systems for pharmaceutical** use include bags, bottles, cartridges, dry powder and metered-dose inhalers, nebulizers, prefillable syringes, vials, and bottles as packaging systems for capsules and tablets. Commonly used plastic materials include polyethylene, polypropylene, polyolefins, polyethylene terephthalate, polyethylene terephthalate G, and poly (vinyl chloride).

13. CONCLUSION

The purpose of this article is to provide information for companies about creating and selecting the right design elements and attributes for their product package. Successful package design and packaging itself is the result of the involvement and the work put forth by marketers, designers, and customers. Hence, packaging is a major instrument in modern marketing activities for consumer goods. Packaging has many functions in different departments. It has its most essential roles in logistics and marketing due to the fact that these two units are strongly connected to the end-users of the product.

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