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A REVIEW ON PHARMACEUTICAL PACKAGING MATERIAL

Praveen Nasa*

Department of Pharmaceutical Education & Research, Bhagat Phool Singh Mahila Vishwavidyalaya, Bhainswal Kalan (Sonipat), India.

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***Correspondence for Author**
Praveen Nasa
Department of Pharmaceutical Education & Research, Bhagat Phool Singh Mahila Vishwavidyalaya, Bhainswal Kalan (Sonipat), India..

ABSTRACT

Pharmaceutical package is an integral part of Pharmaceutical product. An ideal package protects the product from harmful effects of environmental gases, moisture, microbes etc. Primary package is in direct control with the product and secondary package is the package which surrounds the primary package. Tertiary package is the package used for transportation purpose.Pharmaceutical package provides the hermetic seal which do not contaminate the Pharmaceutical product. Glass, Plastic, Metal and rubber are the important component of container closure system. Various types of glass, plastic, metal packaging material are used for construction of containers and closures. The selection of these material depends upon the products which is to be stored in the container. Closure is also an important part of Pharmaceutical packaging and it is direct contact with the pharmaceutical preparation. So container and closure material should be carefully selected which do not affect the therapeutic efficacy of the products. This review article mainly focused on the Pharmaceutical packaging material properties, their use and their limitations.

KEY WORDS: Blister package, Closures, Primary package, Glass, Plastic.

What is a Pharmaceutical Package?

A Pharmaceutical Package container is an article or device which contains the Pharmaceutical Product and the container may or may not in direct contact with the product. The container which is designed for pharmaceutical purpose must be stable. [1]

Ideal Qualities of a Pharmaceutical Package

1. It should have sufficient mechanical strength so as to withstand handling, filling, closing and transportation.
2. It should not react with the contents stored in it.
3. It should be of such shape that can be elegant and also the contents can be easily drawn from it.
4. It should not leach alkali in the contents.
5. The container should not support mould growth.
6. The container must bear the heat when it is to be sterilized.
7. The contents of container should not be absorbed by the container.
8. The material used for making the container should be neutral or inert.
9. Any part of the container or closure should not react with each other.
10. Closure should be of non toxic nature and chemically stable with container contents.
11. It should provide desired degree of protection from environmental hazards. [2, 3]

Function of Package

1. Protective Function

A good package protects the container from static and dynamic force during transportation and storage. Vibration is mainly responsible for cracking of emulsion which can be inhibited by using good package. It also protects the contents from biological hazards. It protect the container from moisture ,temp, environmental gases, humidity etc. light sensitive material can be protected from light by using primary packing of amber colored bottles.

2. Identification Function

A packaging provide information regarding product such as date of manufacturing, expiry date, use, batch no., warnings if any etc. It also provide an ease of identify the product for e.g colored flutted bottles are used for packaging external preparation.

3. Storage and transport Function

Packaging plays an important role in storage and transportation of product. Package shape should be such that it can be handled easily. It must be so designed that they can be stored in efficient manner i.e safely one above the other. The dimensions of package should be according to the pellets.

4. Other Functions

Other functions of package includes protection from theft, compression, impact etc., patient compliance, effective tool for marketing. [3-6]

Types of Package

1. Primary Package

Primary package are those package which are in direct contact with the Pharmaceutical formulation. The main aim of primary package is to protect the formulation from environmental, chemical, mechanical and/or other hazards.

2. Secondary Package

The package external to Primary package is known as secondary package. This package provide additional protection during warehousing and also provide information about drug product for e.g Leaflets.

3. Tertiary Package

It is used for warehouse storage and transport shipping. The most common form is a palletized unit load that packs tightly into the container.

Table 1: Types of Primary and secondary packaging material

Types of primary and secondary packaging material			Images of Examples
Material	**Type**	**Example of use**	
Glass	Primary	Ampoule, vial etc.	
Plastic	Primary	Ampoule, vial, infusion fluid container, dropper bottle	
	Secondary	Tray, Wrapper to contain primary pack	
Metal	Primary	Ointment tubes, pastes etc.	
Cardboard	Secondary	Box to contain primary pack	
Paper	Secondary	Labels, patient information leaflet	

Cardboard, Plastic	Tertiary	Shippers, Pellets.	

Types of containers which are used as primary package are as follows

Primary Package for liquid orals is

1. Well closed containers

These type of containers provide the protection from foreign particles and loss during transportation, sale etc.

Fig.1: Well closed containers

2. Air tight containers

These types of containers protect the container from environmental hazards. If these containers are intended to be opened on more than one occasions then they remains airtight after reclosure. These are also known as hermetic sealed containers.

Fig.2: Air tight containers

3. Single Dose Containers

This type of container contain single dose of medicament example are: Glass ampoules,Vials etc.

Fig.3: Single dose containers

4. Multi Dose Containers

As the name indicates these type of containers holds more than single dose and their contents are withdrawn at various intervals. For e.g Vials etc.

Fig.4: Multi dose containers

5. Light Resistant Containers

These containers protect the contents from light (UV light). These are made up of the materials which do not allow the UV light to pass from them to contents. For e.g : Amber colored glass containers.

Fig.5: Light resistant containers

Primary Package for solid dosage forms

1. Strip Package

In this the contents are sealed in a packet. The Package is made up of two layers of film. A strip containing many pockets and each pocket contains single dose of medicament.

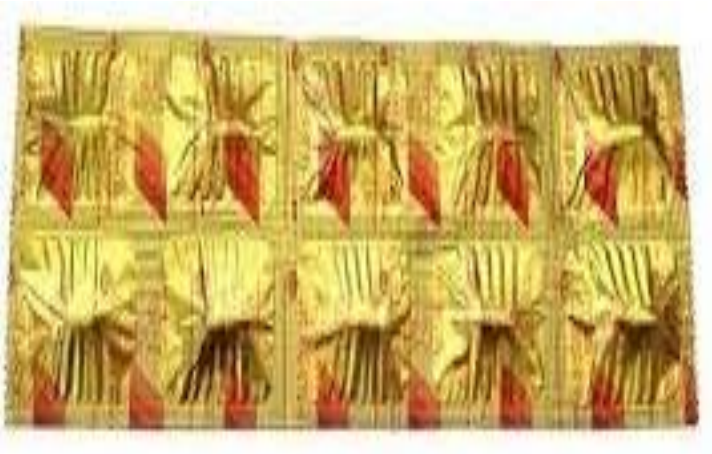


Fig.6: Strip Package

2. Blister Package

It is made up of base layer (PVC layer) with cavities which contain Pharmaceutical product. This type of Package provides greater protection than strip package. The lid is made up of aluminium or paper foil. The package is sealed by combining lid and base with the application of heat and pressure.

Fig.7: Blister Package

3. Primary Package for semi solid dosage forms

Semi- Solid dosage forms include creams, pastes, ointments etc. the containers used for semi-solid dosage forms includes collapsible tubes etc. Plastic Containers are also very popular now a days. Another type of products are also available in market for e.g Pressurized products. For these types of products the package made up of stainless steel, aluminium etc. is used. The package used must be strong enough to withstand pressure built up in the container. [3, 7-9]

Fig.8: Collapsible Tubes

Materials used for Packaging Glass

Glass containers are very commonly used for storing pharmaceutical products. These containers are intended to come into direct contact with pharmaceutical products. Glass containers are used because of their following advantages.

1. They are impermeable to water vapors, air etc.
2. They are available in various sizes and shapes.
3. They have efficient mechanical strength and rigidity.
4. They are transparent so the contents can be easily seen from outside for e.g in case of parental products.
5. They can be converted into light resistant glass by mixing with metal oxides.
6. They have elegant appearance than the plastic containers.
7. They are able to withstand temperature and pressure during sterilization.
8. They can be easily labeled.
9. They can be easily sealed which can provide hermetic sealing.

Disadvantages

1. They have heavy weight which increases their transportation cost.
2. They are breakable.
3. They can easily leach alkali to aqueous solutions if not properly treated with chemical.

Composition of Glass

Glass is made up of silica with varying degree of metal oxides, limestone and cullet. Cullet is mainly the broken glass which acts as fusing agent. The common cations which are found in pharmaceutical glassware are silicon, zinc, boron, alumina, sodium, potassium, zinc etc. the only anion present is oxygen.

Manufacturing Process of glass

It includes mainly three steps.

1. Blowing

It uses compressed air to form the molten glass in the cavity of a mold.

2. Drawing

In this molten glass is pulled through dies that shape the soft glass. The containers manufactured by this process includes ampoules, vials etc.

3. Pressing

In this mechanical force is used to press or force the molten glass against the ride of a mold.

4. Casting

This includes use of gravity or centrifugal force to initiate the formation of molten glass in the cavity.

Types of Glass

Type I Glass: Borosilicate Glass (Pyrex)

This type of glass is composed of boric oxide, aluminium oxide and alkali and/or alkaline earth oxides. Except for type I glass containers, glass containers for pharmaceutical preparations are not to be re-used. It has a high hydrolytic and thermal shock resistance.

It is chemically more inert than soda lime glass. It is mainly used in preparation of laboratory glass apparatus and containers for injection and water for injection.

Fig.9: Borosilicate Glass

Type II Glass: De alkalized soda lime glass

It has higher level of sodium and calcium oxide. It is less resistant to leaching property as compare to type I glass but more resistant than type III. It is used to store infusion fluids, plasma and alkali sensitive products.

Fig.10: De alkalized soda lime glass

Type III: Regular soda lime glass

This type of glass contains metal oxides, sodium oxides, aluminium, earth oxides mainly calcium oxides. The main disadvantage is that it can leach alkali in the preparation. So it is used to store liquid formulations which are not alkali sensitive. It is also used to store all types of solid dosage forms.

Fig.11: Regular soda lime glass

USP type NP Glass: Non-Parentral

As the name indicated this type of glass is used to store non parentral formulations where heat shock are not a factors. These formulations are used to store capsules, tablets, topical products. This type of glass is not used for autoclaved products because autoclaving will accelerate the glass erosion reaction. Dry heat sterilization arise not a problem for type III containers. [10,11,22]

Fig.12: NP Glass: Non-Parentral

Plastics

Plastics are very commonly used for packaging Pharmaceutical products. These constitute about 20% of weight of all pharmaceutical packaging. Plastics can be easily molded to required shape.

Fig.13: Plastic containers

Advantages

1. They are unbreakable.
2. They have less wt. than glass and so their transport cost is also very less.
3. They are available in various size and shapes.
4. They can be easily molded into desired shape.
5. They provide good protection power against chemical hazards.
6. They do not have alkali leaching property as in glass containers.
7. They also have suck back feature.

Disadvantages

1. The main disadvantage is permeation. The atmospheric gases, vapors or liquid from surrounding environment can easily migrate into plastic container.
2. Permeation causes problem of oxidation and/or hydrolysis and can degrade the product which is sensitive to hydrolysis and/or oxidation.
3. They also have leaching problem, for e.g dyes which are used as coloring agent may migrate into product from the container.
4. Another problem is sorption; sorption is the process of removal of one or more constituents from the product by packaging material. This can affect the therapeutic efficacy of the product.
5. Preservative can also be absorbed by the container material. This may change the flexibility of the container. [10,12,13]

Materials used for making Plastic containers

1. Polyethylene

Polyethylene is very commonly used polymer. It is available in high density, medium density and low density grades. Mainly high density polyethylene is used for pharmaceuticals. It provides protection against moisture but poor protection against oxygen & other environmental gases. The containers prepared from polyethylene cannot be sterilized by heat but can be easily sterilized by autoclave. Polyethylene's have melting point range of 120-150ºc. It has an excellent chemical resistance, it means it provide protection against strong acid & alkali. It is used to prepare plastic bag, plastic films, bottles etc.

Fig.14- Polyethylene Plastic containers

2. Polypropylene

It is very popularly used in Pharmaceutical container. It has many qualities of polyethylene. It has mpt. Of 170ºc which is higher than polyethylene and make it suitable for sterilization at high temp. It has very good resistance power to almost all types of chemicals. It is superior to low density polyethylene. The main drawback of polypropylene is its less clarity which can be improved by making thin walls containers. Other drawback is its brittleness at low temp. which can also be improved by mixing it with some proportion of polyethylene.

Fig.15: Polypropylene Plastic containers

3. Polyvinylchloride (PVC)

It has high clarity and good oxygen barrier. It is third most widely produced polymer after polyethylene & polypropylene. It can be made softer & flexible by incorporation of plasticizers. The heat stability of PVC is very poor and its mpt. is 160ºc. It has good insulation properties but inferior than polyethylene & polypropylene. PVC can be used for making containers used for blood & blood components, catheters, bypass sets, hemodialysis sets etc. The main advantages of PVC include its transparency, light wt., softness, suitability for sterilization and biocompatibility.

Fig.16: PVC Plastic containers

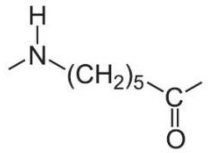
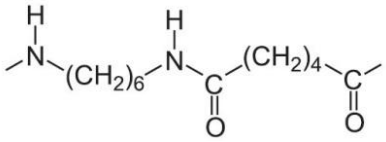
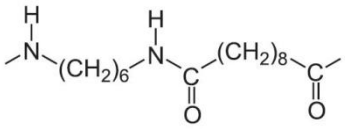
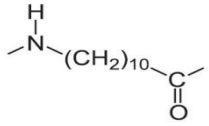
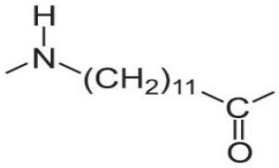
4. Polyamide (Nylon)

It is macromolecules having repeated units linked by amide bonds. Nylon is mainly artificially made. It can be produced by interaction of a diamine and a dicarboxylic acid. It has main advantage of good chemical resistance, high strength, good toughness, high heat resistance, good water resistance etc. it can be autoclaved easily. The main disadvantage is high moisture absorbtivity, attacked by oxidizing agent, strong acids & alkalis etc.

Fig.17: Polyamide Plastic containers

Various grades are available and approved by FDA. Some of these are as follows.

Table 2: - Various grades of Polyamides with their structur

Polyamide (nylon)	Repeating unit
6	
6,6	
6,10	
11	
12	

5. Polystyrene

It is made from petroleum. It is non biodegradable, light and rigid. Its main advantages are that it is inexpensive, resistant to acids, strong alkalies & strong oxidizing agents, high heat resistance, expandable etc. The main disadvantage is that it can leach styrene & benzene when come in contact with warm food, oils, alcohols etc. which causes contamination of product.

Fig.18: Polystyrene Plastic containers

6. Polycarbonate

Polycarbonate is resistant to dilute acids, oxidizing or reducing agents, salts, oils (fixed and volatile), greases, and aliphatic hydrocarbons. It is attacked by strong acids, reducing agents, amines, ketones, aromatic hydrocarbons, and some alcohols. It has highest impact strength and inexpensive. It is clear and very good heat resistance power. It is mainly used for manufacturing of surgical equipments. [14-18]

Fig.19: Polycarbonate Plastic containers

Metal containers

Metals are very commonly used as packaging material for pharmaceutical containers. Examples of metals used for this purpose include mainly aluminium, lead, tin etc.

Advantages of metals

1. They are light in weight than glass.
2. They are strong.

3. They are resistant to light, moisture and gases.
4. They are elegant in appearance.
5. Labels are not required to be pasted because labels can be printed directly on the surface.

Disadvantages

1. They may leach metal particles into product.
2. They may react with certain drugs or chemicals and produce toxic product.
3. They are costlier than plastic.

Material used for making metal containers

Aluminium

Aluminium is very commonly used because of its light weight and elegant appearance. They are less expensive than tin. The transparent coating of oxide formed on surface of aluminium on reaction with oxygen protect the metal from further oxidation but some complexing agent & product of high or low pH can cause corrosion on reaction with oxide coating. Aluminium is used for preparation of ointment tube, tablets & capsule strips, screw caps etc.

Tin

It is expensive than amongst other metals used for pharmaceutical containers preparation. It is resistant to chemical attack. It offers a good appearance and it is chemically inert. It is used for preparation for food containers.

Fig.21: Tin Container

Lead

It is inexpensive than amongst all other metals. It is soft in nature. so usually 3% antimony is added in lead to increase its hardness. The main disadvantage of lead is that there is possibility of lead poisoning if taken internally. So, before its use it should be coated with inner lining of inert metal or polymer. It is used for non food products such as paints, inks, lubricants etc.

Fig.22: Lead containers

Types of metal containers

Collapsible Tubes

These are made up of aluminium, tin or lead. They are used to pack semisolid preparation. Aluminium tubes are used for dispensing of tooth paste & creams. Lead is not used for pharmaceutical purpose because of risk of lead poisoning. In case of aluminum collapsible tubes there are chances of minimum contamination of the remaining portion of tube content because of absence of suck back mechanism.

Fig.23: Collapsible Tubes

Metal containers for solid dosage forms

Aluminium is mainly used for this purpose. So the containers for tablets & capsules are light in weight & also strong enough.

Fig.24: Containers for solid dosage forms

Metal Foil

These foils are used for wrapping of individual suppositories or pessaries. Mainly aluminium foil is used for this purpose. Metal foil is also used for strip & blister packing of tablets & capsules. [3,19]

Fig.25:Aluminium Foil (suppositories wrapping)

Secondary Package

Paper and paperboards

Secondary package are used to store primary package containing Pharmaceutical Preparations. Secondary package are directly in contact with the primary package but not with Pharmaceutical preparations. Secondary package mainly contains shippers or cartons which give the physical protection to the primary package. These are prepared of cellulose

fibers obtained from wood. Paperboards are also used as secondary package which are thicker than paper and heavy in weight. Examples of paperboards are white board, solid board, chipboard, fiberboard. These boards are mainly laminated using polyethylene or waxes. chipboard is obtained from recycled paper. Bleached sulphate boards are the example of solidboards which are laminated with polyethylene. [4,20]

Closures

This is the most critical component of a container. An effective closure system prevents the loss of material from the container, prevents the environmental contamination of the product, prevents the microbs to enter inside he container.

Ideal properties of a closure

1. It should be inert.
2. It should be compatible with product & container.
3. It should have the property of re sealable.
4. It should be economical.
5. It should provide an effective seal.
6. It should be easily handable.

Design of closures

Closures are available in five main designs. Their details are as follows.

1. Threaded Screw Type:

These are made up of aluminium, tin or plastic. As the name indicates they contain threads which get engaged with the threads present on the neck of container. These types of closures provide the effective seal which protect the product from physical and chemical reaction. Plastic caps are more popular than metal because plastic are resistant to corrosion.

Fig.26: Threaded Screw Type closure

2. Lug Cap

The difference in lug cap and thread cap is that in thread cap, continuous threads are present but in lug cap threads are present in intermittent fashion. Another difference is that lug cap requires only a quarter turn. Lug caps are mainly used in storage of food products.

Fig.27: Lug Cap

3. Crown Caps

These caps are made up of metal and commonly used for beverages bottles. These also provides an effective seal and cannot be open with hands. These cannot be seal again.

Fig.28: Lug Cap

4. Roll on closures

Roll on closure contains the aluminium roll on cap which can be easily sealed, opened and closed. These are available in re sealable, non- sealable & pilfer proof type forms. These are available for use on glass or plastic bottles & jars for food, beverages, chemicals and Pharmaceuticals.

Fig.29: Roll on closures

5. Pilfer Proof Closures

In this additional length extends below to threaded portion which forms a bridge. When the closure is removed then the bridge break and the additional portion remains in place on neck of container which show its opening. [3, 11, 21]

Fig.30: Pilfer Proof Closures

Material used for construction of closures

Rubber

It is used for construction of closures for vials, transfusion bottle fluids etc. Many types of rubbers are used for this purpose for e.g butyl rubber, nitrile rubber, silicon rubber etc. Butyl rubber is very commonly used because of its low absorption property and also they are cheaper than other synthetic rubber but it decompose above 130ºC. Nitrile rubber has oil resistant and heat resistant property but it can absorb the preservative from the preparation. Silicon rubbers have very low absorption & permeability of water and are stable for a long time. But they are very expensive.

A rubber is prepared by mixing a base polymer with additives. The selection of base polymer & additives depends upon the type of rubber properties to be desired. The resultant rubber is non vulcanized compound.

Fig.31: Rubber Closures

Additives used in preparation of rubber

1. Fillers

Two types of fillers are used. Reinforce for e.g Carbon black and other is non reinforce for e.g Calcium carbonate. Carbon black is mostly used due to this most of the rubbers are black.

2. Plasticizers

They are used to improve the flow of rubber during their processing for e.g Oils & Paraffin's.

3. Vulcanizing agent

Vulcanization is a process of conversion of rubber molecule into a network by formation of crosslinks. Vulcanizing agents are used for introducing crosslinking. e.g of vulcanizing agents are: Sulphur etc.

4. Accelerators

They are used to increase the rate of crosslinking reaction and optimize the vulcanizate properties by reducing sulphur content. For e.g Thiazoles.

5. Activators

They activate the vulcanizing process. Examples are: Zinc oxide, Stearic acid.

6. Pigments

These are used as coloring agent to color rubber compounds. Examples are: Cadmium, iron etc. [22]

Plastic

Two types of plastics are used for construction of closure. These are as follows:

Thermoplatics

This type of plastic gets softened to a viscose fluid on heating and then get hard on cooling. Example includes: Polyethylene, Polypropylene, Polystyrene etc.

Thermosetting

They are firstly softened under heat and then curved before harden to final state. The shape should be required to be achieve during softening because after softening shaping cannot be done. Thermosetting plastics cannot be remelt so the closure which are imperfect or improper in shape must be discarded. Example includes Phenolic compounds and Urea.

Fig.32: Plastic Closures

1. **Phenolic compounds**

   These provides the sturdy and hard product.Phenolic closures provide a tight seal over a prolong period of time. They are rigid, chemically resistant to dilute acids and alkalies.

2. **Urea**

   Closures made from urea have elegant in appearance and chemically inert. They are expensive than Phenolic. They cannot be autoclaved but can withstand high temperature without softening. [10, 11,23]

CONCLUSION

Packaging plays an important role in Pharmaceutical Industries. The pharmaceutical packaging market is constantly increasing with annual growth of at least five per cent per annum in the past few years. Package has a great role in protection of Pharmaceutical

Products. Packaging give Pharmaceutical elegance, Patient compliance which increases marketing of Pharmaceutical product. It also provides valuable information to the patient. Packaging of oral formulations conforms to requirements which includes easy dispensing, child resistance and senior-friendliness, functional and very often hermetically sealed. But most of the Pharmaceutical packaging has many disadvantages. So, now a day's eco friendly packaging components are used which are biodegradable in nature and can be reprocessed easily. FDA approval is necessary before a new package is to be launch in market and after getting approval from FDA no change can be done without prior permission of FDA.

This review article has addressed the important considerations for containers and closures. The article has forced upon the materials used for containers and closures and their advantages and disadvantages and their use.

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