IJMPR 2018, 7(1), 29-37

International Journal of Modern Pharmaceutical Research

www.ijmpronline.com

ISSN: 2319-5878

IJMPR

Review Article

PHARMACEUTICAL PACKAGING –AN ART OF PROTECTION, PRESERVATION AND PRESENTATION- AN EXHAUSTIVE REVIEW

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Received on: 03/01/2018

Revised on: 24/01/2018

Accepted on: 14/02/2018

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ABSTRACT

Pharmaceutical Packaging is the art of designing & science of protecting the drug content by enclosing in an authentic and suitable package for presentation, preservation, promotion & desired use. Product packages & analysis of packaging materials means a lot to pharmaceutical professionals to release quality packaging materials for production department. Due to advancement of Pharmaceutical Analysis, It has been noticed that most of serious issues like product stability, safety, sell, market complaint & product quality may occur just because of Packaging materials. The selection of the packaging materials for a particular drug content is based on the physical and chemical characters of that content. The stability of a drug in its solid, liquid, gel or paste form is mostly depend on the ability of the packaging materials intended to be used to protect the content from chemical degradation. A chemical degradation of drug may affect its physical properties like appearance, hardness, friability, dissolution, disintegration, moisture content & weight variation. The main purpose of this review is to provide all essential information regarding pharmaceutical packaging science & packaging materials.

KEYWORDS: Packaging, Glass, Plastics, Metals, Rubber, Caps & Closures, Paper & Paperboard.

INTRODUCTION

Packaging of drug content is a critical part of overall manufacturing process, where preparation and maintenance of Batch Packaging Record (BPR) is a must. Dosage forms need extra care in their packaging as it will remain in that pack for a long time. A meaningful definition of Pharmaceutical Packaging is "An economical means of providing protection, presentation, identification, information and convenience for a pharmaceutical product from its production until it is used. Physical & chemical nature of drugs helps in selecting proper packaging material. Pharmaceutical products are many including sterile preparations, biotechnologically developed products. Packaging of them is a practical art and analysis of that packaging materials is essential for product safety & stability. Packaging materials for pharmaceutical use are many which include primary packaging materials, secondary packaging materials & tertiary packaging materials. Different types of materials belong to these groups. Glass, Plastic, Metal, Rubber are the most important example for making pharmaceutical packaging materials. The selection of material depends upon the products which is to be stored in the container.

Function of Pharmaceutical Package

The various functions of packaging are divided into primary, secondary functions. In contrast with the primary functions, which primarily concern the technical nature of the packaging, secondary functions relate to communications. Primary, secondary and tertiary functions are divided into the following sub-functions[11]

Primary Functions

a. Identification Function
b. Protective Function
c. Storage, Loading & Transport Function

Secondary Functions

a. Sales Functions
b. Promotional Functions
c. Service Functions

Identification Function: A product can be identified by its package as packaging provide information regarding product such as brand name & generic name, batch no.,

date of manufacturing & expiry, use, registration number (given by respective drugs authority).

Protective Function: Moisture, temperature, light can degrade drug content resulting the patient might have therapeutically failure or toxic action within body. A package can protect the product from these environmental hazards. Packaging must also reliably be able to withstand the many different static and dynamic forces to which it is subjected during transport, handling and storage operations. It protects the product from biological hazards too.[6]

Storage, Loading & Transport Function: Drug product may remain in quarantine or in a drug shop for a while to long time. A package plays an important role to keep the product stable. Convenient goods handling entails designing transport packaging in such a manner that it may be held, lifted, moved, set down and stowed easily, efficiently and safely. The size, shape & strength of the package should be meaningful so that the package can be handle easily & withstand the stress found during handling & transportation. The shape and strength of packages should be such that no voids may be showed after a long period of their storage.[6,11]

Ideal Qualities of Pharmaceutical Package:[11]

1) They must be good in appearance & design for perfection of aesthetic value.
2) They must contain desired information including registration number.
3) They must not react with the content stored.
4) They must be non-toxic & non-irritant.
5) They must not interfere with the product odor & color.
6) They must have sufficient mechanical strength so that can withstand possible stress while handling, filling, sealing & transportation.
7) The package should not support microbial growth.
8) The container must tolerate the heat while it is subjected to be sterilized.
9) The container closure system should be good as well.
10) The package should not absorb the content.
11) The container (specially for glass ampoule, vial, bottle) should not leach excess of alkali in the content.
12) They must meet applicable temper-resistant requirements.

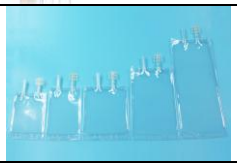
Types of Pharmaceutical Packaging Materials

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

Primary Packaging Materials: Primary packaging materials are very sophisticated materials as they are in direct contact of drug formulation. These materials provide protection against environmental (moisture, temperature, light), chemical, mechanical or any other hazards. Primary packaging materials are also known as critical packaging components.[4]

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

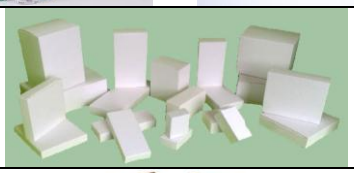
Table 1: Primary Packaging Materials with Package Name and Photos.

Primary packaging materials	Name of Package	Photos of Package
Glass	Ampoule, Vial, Bottle etc.	
Plastic	Dropper Bottle, Plastic Bottle, Infusion Bag, Plastic Film, Plastic cap & stopper etc.	 
Rubber	Rubber stopper, Liner, Plunger Gasket & Syringe Tip etc.	 
Metal	Blister foil, Collapsible tube, ROPP cap,	  

Secondary & Tertiary Packaging Materials: Secondary packaging materials are usually the coverings of primary package. Secondary package provide additional protection during warehousing and also provide information about drug product for e.g Leaflets, cartons, boxes.

Tertiary packaging materials are the large sized boxes or cartons use to hold number of secondary package within it to store at warehouse. These material provide extra protection to drug product during storage and transport shipping.[6]

Table 2: Secondary Packaging Materials with Package Name and Photos.

Secondary & Tertiary packaging materials	Name of Package	Photos of Package
Paper	Label, Patient Information Leaflets	 
Cardboard	Inner Cartons, Boxes	
Paperboard, Corrugated Liner	Master Carton	

Pharmaceutical Primary Packaging Made of Glass

Glasses are very sophisticated materials using for packaging of pharmaceutical drug content/ product from ancient time. Most of the primary package are made of glass including ampoule, injection vial, syringe, Infusion bottle for blood products or any other sterile injectable preparations. Glass made primary packaging materials are intended to come direct contact of medicament(s). Pharmaceutical glass materials are either borosilicate or soda-lime-silica glass.[9]

Classification of Glass Containers

The hydrolytic stability of glass containers is expressed by the capability of resistance to the release of soluble substances into water under prescribed conditions of contact between glass and water. The hydrolytic resistance can be evaluated by titrating released alkali.

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

Type I glass containers: Neutral (borosilicate) glass, with a high hydrolytic and thermal shock resistance due to the chemical composition of the glass itself. Type I glass composed of boric oxide, aluminum oxide & alkaline earth oxides, mainly calcium oxide. Alkaline earth oxide use to make the glass color. Type I glass containers are suitable/preferred for most preparations for (human) parenteral use. Type I glass maid containers exemplified as Laboratory glass apparatus, Ampoules, Injection Vial etc.[9]

Type II glass containers: Usually of soda-lime-silica glass with a high hydrolytic resistance resulting from suitable treatment of the inner surface. Type II glass has higher level of sodium and calcium oxide but has less hydrolytic resistance than Type I glass. Type II glass containers are suitable for most acidic and neutral aqueous preparations for (veterinarian) parenteral use. Type II glass maid containers exemplified as Infusion bottle, Vial etc.[9-10]

Type III glass containers: Type III glass are also called regular soda-lime glass with only moderate hydrolytic resistance. Type III glass containers are in general suitable for non-aqueous preparations for parenteral use, for powders for parenteral use (except for freeze-dried preparations) and for non-parenteral preparations.

Type IV glass containers: Type III glass are general purpose soda-lime glass. This type of glass are also called Non-Parenteral (NP) glass as not used in parenteral purpose.

Colored glass is used to screen out Ultraviolet rays and is thus effective for protecting contents from photochemical degradations.

Pharmaceutical Primary Packaging Made of Plastic

Plastics are most familiar material for packaging of pharmaceutical drug product. Now a days, use of glasses are being replaced by different types of plastic. Plastics are long chain polymer of distinct monomer. The plastics used in packaging systems are composed of homologous polymers with a range of molecular weights and contain additives such as antioxidants, stabilizers, lubricants, plasticizers, colorants, and others. The nature and amount of additives in the plastics used for packaging systems are dictated by the type of polymer, the polymer's use, and the process used to convert the polymer into components, containers, or packaging systems. Plastic (Thermoplastics) can be molded easily to make any form according to desire.[18]

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

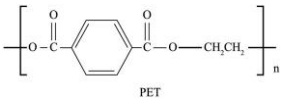
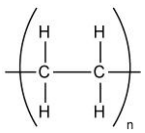
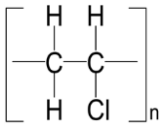
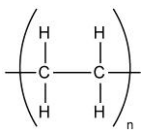
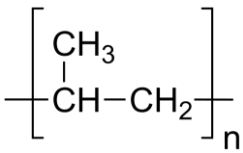
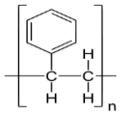
Thermoplastics (Thermo-softening Plastics)
Thermoplastics are heat softening materials which are usually rigid at room temperatures but can be remelted and remoulded when exposed to high temperature and pressure. Examples of thermoplastics include but are not limited the five most economical plastics – polyvinylchloride, polystyrene, polypropylenes, polyethylenes, and polyester. Others include nylon, polyvinylidene chloride, polycarbonate etc.[19]

Thermosets (Thermo-setting Plastics)
They are called thermosets because they get distinctly infusible or insoluble when exposed to high temperature/ heat, and thus cannot be remelted and remoulded after their initial heat forming. They are produced by polymerization process involving a curing or vulcanization stage during which the materials become 'set' to a permanent state by heat and pressure. Thermosets usually contain additional additives (fillers and reinforcing agents) to obtain best quality. These materials are used as packaging material when good dimensional and heat stability are required. Examples of thermoset 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.[19]

Pharmaceutical plastic containers are made from following polymers:

Polyethylene Terephthalate (PET, PETE)
The term PET stands for **Poly-Ethylene Terephthalate.** PET is clear, tough material and it's provide good moisture, oxygen and water barrier properties. PET made container & film has optically smooth surfaces. Polyethylene terephthalate is a condensation polymer formed by reaction of terephthalic acid or dimethyl terephthalic acid with ethylene glycol. In many countries, PET plastics are coded with the SPIs Plastic Recycling Code number "1". It as a useful package for syrup, suspension, emulsion, mouth washes and other products.[20]

Table 3: Plastic Recycling Code with Chemical Structures and Photos.

Symbol	Chemical Structure	Photos of materials/ containers
01 PET		
2 HDPE		
03 PVC		
4 LDPE		
05 PP		
06 PS		

High-Density Polyethylene (HDPE)

High-density polyethylene is also called Polyethylene high-density (PE-HD). It's known for its high strength to density ratio which is range from 0.93 to 0.97 g/cm^3 or 970 kg/m^3. HDPE is Flexible, translucent/waxy, weatherproof, good low temperature toughness (to -60'C), easy to process by most methods, low cost and most importantly has good chemical resistance against dilute acids and bases, aliphatic hydrocarbons, aromatic hydrocarbons, halogenated hydrocarbons and alcohols. HDPE is used to make many types of pharmaceutical containers & caps. Usually un-pigmented containers are translucent and have good barrier properties and stiffness. The physical properties of HDPE can vary depending on the molding process that is used to manufacture a specific sample; to some degree a determining factor are the international standardized testing methods employed to identify these properties for a specific process. HDPE plastics are coded with the SPIs Plastic Recycling Code number "2".[21]

Polyvinyl Chloride (PVC)

The term PVC stands for "Polyvinyl Chloride" is the world's third-most widely produced synthetic plastic polymer, after polyethylene and polypropylene.[5]

PVC is a thermoplastic made of 57% chlorine (derived from industrial grade salt) and 43% carbon (derived predominantly from oil / gas via ethylene).[22]

PVC was accidentally synthesized in 1872 by German chemist Eugen Baumann. The polymer appeared as a white solid inside a flask of vinyl chloride that had been left exposed to sunlight.[11] PVC has good physical stability and chemical resistance. The heat stability of PVC is very poor and its melting point range from 100 - 260°C. For this reason additives which stabilize the material at higher temperatures are typically added to the material during production. Polyvinyl Chloride is very dense and thus very hard and resists impact deformation very well relative to other plastics. It has very good tensile strength. PVC is used as forming film in its rigid form (RPVC). The main disadvantage is poor barrier properties against moisture. To overcome this issue, particular thin layer of PVdC is used on outside of PVC film where GSM of PVdC may vary from 40-90. PVC has various application in packaging of pharmaceutical products like infusion bag, medical tubing, film for blister packaging.

Low-Density Polyethylene (LDPE)

Low-Density Polyethylene (LDPE) is a thermoplastic made from the monomer ethylene. LDPE is defined by a density range of 0.910–0.940 g/cm^3. LDPE has low chemical reactivity and good resistance to different dilute and concentrated acid, base and alcohol. Now a days, it's a good plastic type used in packaging of pharmaceutical product. It is used to prepare plastic bag, plastic films, ophthalmic container, sachet, bottles etc.[6]

Polypropylene (PP)

Polypropylene is a very popular thermoplastic polymer using in pharmaceutical industry for packaging of drug content. The density of PP is between 0.895 and 0.92 g/cm³. PP 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. Polypropylene is an excellent gas and vapor barrier. Polypropylene is used to make measuring cup, dropper, infusion bag, port & stopper for infusion bag etc.[15]

Polystyrene (PS)

Polystyrene is a clear and rigid material which has good tensile strength. It's synthesized from polymerization of styrene. Polystyrene made materials are look like glass and it's a brittle plastic. Polystyrene has moderate resistance to acid, alkali & other chemical substances that's why it's not a suitable material for packaging of pharmaceutical product specially for making of primary container. Different acrylic compounds may added with polystyrene to make it strengthen.

Pharmaceutical Primary Packaging Made of Rubber and Elastomer

Rubber, a key material used extensively in pharmaceutical industry for packaging of sterile (parenteral) preparations. Pharmaceutical sterile preparations are mainly packaged in glass container including injection vials and prefilled syringes, where a closure need to close the mouth of that container. Rubber made stoppers are widely used form of closure. Natural rubber was the first polymer used in pharmaceutical packaging. After than that, some processed rubber were used namely butyl rubber, nitrile rubber, silicon rubber etc. Butyl rubber is very commonly used because it has low sorption property and also they are cheaper than other synthetic rubber but it decompose above 130ºC. Some third agents need to use during manufacture of rubber which includes filler, colorants, plasticizers, protecting agents. Before using rubber as closure, quality control testing is a must to check pH and clarity of solution, acidity/alkalinity, moisture content etc.[6]

Figure 1: Pharmaceutical Rubbers.

Pharmaceutical Primary Packaging Made of Metal and Metal-Plastic

Metals are now widely used material for pharmaceutical packaging. Number of metal can be used to make primary package where aluminum is the metal of choice. Aluminum made foils are extensively used material for blister packaging. In recent pharmaceutical trend, aluminum is one of the most important part of all lidding material type. Lidding material provides main structure of a blister package, that acts as a potential barrier for moisture and light. A pharmaceutical lidding material has two side, dull side and bright side. Because of technological advancement, a lidding material designed in such a way where dull side printed with stable ink and bright side contain a heat sealable lacquer (HSL). The selection of material depends on the size, shape, weight and nature of the product.

For betterment of overall barrier properties, specific plastic film (PET, Polyethylene, OPA, PVC) incorporate with hard tempered aluminum foil. This phenomena is same in case of cold forming foil. Use of plastic film with acceptable thickness and GSM is an art as overall film will run in machine along with another thin foil with thickness of about 0.020mm to 0.035 mm.[10]

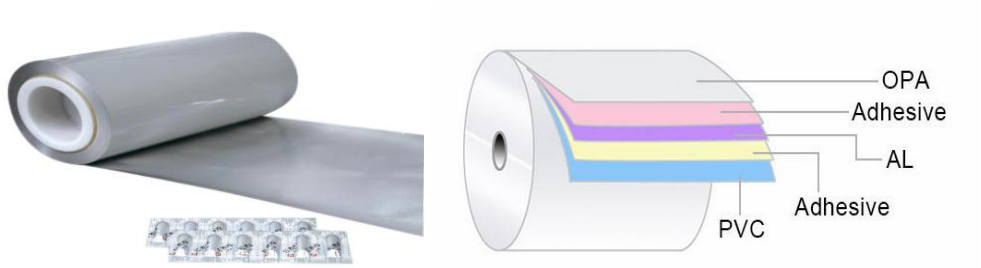


Figure 2: A roll of Aluminum Bottom Foil (Plastic film & Alu. Sheet) and Layer Information.

Metal Collapsible Tube

Metal made tube are extensively used in pharmaceutical industry to pack semi-solid preparation most oftenly preparation to be use on skin and mucous membrane. Pharmaceutical product are very much sensitive towards degradation with respect to moisture and air. After product reaction with air (oxygen) and moisture their shelf life is reduced and may not be used for desired purpose. The Aluminum collapsible tube are impervious for moisture and air (oxygen) also its collapsible or dead fold property does not allow to keep air inside tube, that again reduce the chance of reaction. Quality & uniformity of lacquer coating in collapsible tube, is very important for product compatibility and quality for long term study and use. Different plastic film can be used for better barrier properties & printing.[10]

Closures

The closure is normally the most vulnerable and critical component of a container. These are designed to close the opening of the container so that the content remain safe and contaminant free within it. An effective closure must prevent the contents from escaping and allow no substance to enter the container. A closure provide a totally hermetic and microbiological seal.

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

These are made up of aluminum, tin or plastic. The metal is usually tinplate or aluminum, and in plastics, both thermoplastic and thermosetting materials are used. The screw cap provides physical and chemical protection to content being sealed.

Figure 3: Threaded Screw Cap.

Lug Cap

The lug cap is similar to the threaded screw cap and operates on the same principle. Lug cap usually made of metal. It is simply an interrupted thread on the glass finish, instead of a continuous thread. Unlike the threaded closure, it requires only a quarter turn. The cap is widely used in the food industry rather than pharmaceutical industry.

Figure 4: Lug Cap.

Roll-On and Pilfer Proof Closures

The aluminum roll-on cap can be sealed securely, opened easily, and resealed effectively. It finds wide application in the packaging of food, beverages, chemicals, and pharmaceuticals. The roll-on closure requires a material that is easy to form, such as aluminum or other light-gauge metal. Pilfer proof closure is similar to the standard roll-on closure except that it has a greater skirt length. When the pilfer proof closure is removed, the bridges break, and the bank remains in place on the neck of the container. The torque is necessary to remove the cap.

Figure 5: Roll-On and Pilfer Proof Closures.

Friction Fit Cap

Friction Fit Cap usually plastic made. Some containers have a loose lid for a closure. A friction fit requires some force to close and open, providing additional security. Paint cans often have a friction fit plug.

Figure 5: Friction Fit Cap.

Paper & Cardboard for Pharmaceutical Packaging

Paperboard and cardboard is the pillar of traditional packaging materials. Paperboard is a thick paper-based material. Paperboard made boxes, cartons are widely used in pharmaceutical industry as secondary packaging materials. These materials used for packaging of different primary pack along with drug content, where the primary pack could be blister pack, plastic bottle, glass bottle etc. Board must have sufficient strength, impact resistant capability, easy to clean and fold to form any box or carton, light weight and best to print.

Different types of board can be used for preparing boxes and cartons including Folding Boxboard, Kraft Board, Laminated Board, Solid Bleached/Unbleached Board. Folding Boxboard and Solid Bleached Board are widely used for making boxes, cartons for pharmaceutical use. Solid bleached board contains a middle layer made of chemically bleached pulp with outside and inside coating. In folding boxboard, a mechanical pulp covered with two bleached chemical pulp and there must be an outside coating.

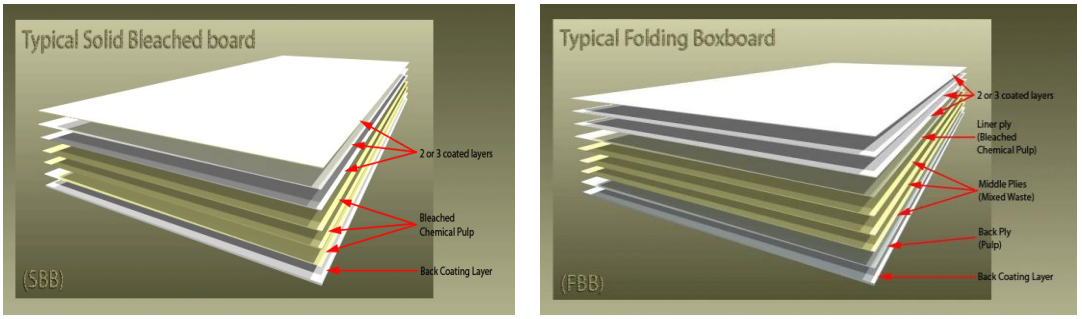


Figure 6: Layers of Solid Bleached Board and Folding Board.

Container board is a type of paperboard used for production of corrugated fiberboard. Corrugated board made shipper cartons are extensively used for packaging of numbers of inner carton and to store in warehouse as well as for transportation countrywide. A shipper carton must contain minimum three layers where a corrugated medium covered with two linerboard. "S" shaped wave in medium is called flute of the board. Flute can be vary depending on the thickness of board.[23]

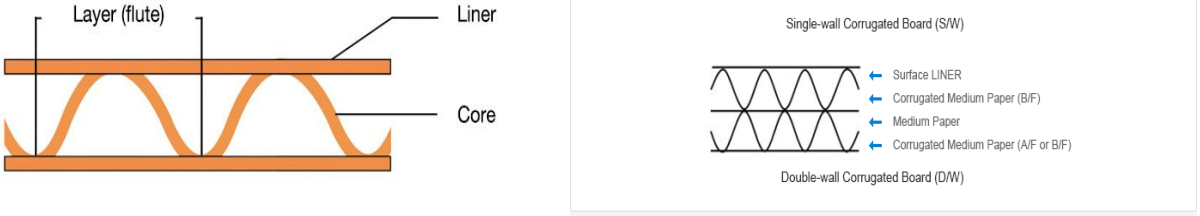


Figure 7: Master Carton Liner Naming.

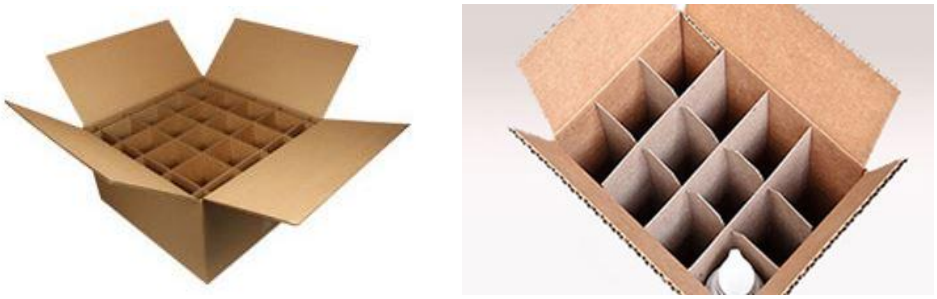


Figure 8: Master Carton with Honeycomb.

Paper made labels and leaflets are the important secondary packaging materials used in pharmaceutical industry.

CONCLUSION

Pharmaceutical packaging materials playing a vital role in pharmaceutical industry as packaging of drug product has close relation to safety and stability of the product. Successful design of pharmaceutical package and packaging itself is the result of the involvement and the work put forward by marketers, designers, and customers. Packaging give Pharmaceutical elegance, Patient compliance which increases marketing of Pharmaceutical product. Though some pharmaceutical packages has many demerits. To overcome that demerits eco-friendly packaging materials are developed and used which are biodegradable in nature and can be reprocessed easily. Domestic Drug Authority and International (FDA/MHRA/TGA) approval is necessary to launch a new package in market. The main objective of this article is to provide adequate information regarding different pharmaceutical packaging materials and packages.

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