Packaging Materials

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Introduction

- Pharmaceutical Package is an integral part of pharmaceutical product.
- "An article or device which contains the pharmaceutical product and the container may or may not be in direct contact with the product."

- Packaging should be such that it should:
  - Maintain the integrity of the dosage form
  - Be inert in nature
  - Not be fragile
  - Have good mechanical strength

Types of Packaging Materials

- P'ceutical packaging is most commonly used to store and protect drugs.
- It is essential for identification purposes, for marketing and promoting different brands, for facilitating the use of p'ceutical products.

Classification of packaging materials

1. **Glass:** Type I, II, III and IV glass, colored glass.
2. **Metals:** Aluminium, tin, lead, etc.
3. **Rubbers:** Natural rubber, neoprene rubber, nitrile rubber, butyl rubber, etc.
4. **Plastics:** Polyethylene, polystyrene, polycarbonate, polyvinyl chloride, polyvinylidene
5. **Fibrous materials:** Cotton, paper and jute.com chloride, polychlorotrifluoro ethylene, cyclic olefin copolymers, polypropylene, etc.
6. **Films, Foils and laminates:** Regenerated cellulose, cellulose coatings, foil and paper.

Types of Package

1. Primary package:

- The primary packaging consists of those packaging components and subcomponents which have a direct contact with the pharmaceutical formulation such as bottle, cap, cap liner, label, etc.
- The main functions of the primary package are to contain and to restrict any chemical, climatic or biological or occasionally mechanical hazards that may cause or lead to product deterioration.
- Examples: Aerosol cans, glass and plastic bottles, plastic bags, wrappers, blister and strip packs, envelopes, cushioning, etc.

Types of Package

2. Secondary package:

- The packaging external to the primary package is known as the secondary packaging.
- This package provides additional physical protection necessary during safe warehousing and for refill packaging.
- This packaging is to carry information about drug product
- Examples: Boxes, leaflets, cartoons, shrink-wraps, corrugated shippers, pallets, etc.

Types of Package

3. Tertiary package:

- Tertiary packaging facilitates the protection, handling warehousing, storage and transportation of a series of sales units or secondary packaging in order to group everything into unit loads during transit.
- It is used to protect not only the products for shipping in the distribution process or storing but also its secondary and primary packaging.
- This type of packaging is rarely seen by the consumer.

Components of Packaging

1. **Container:** Container is a part of package in which the formulation is placed and enclosed that remains in direct contact with the drug.

2. **Closure:** Closure is a part of some packaging's that tightly packs the container to exclude oxygen, carbon dioxide, moisture, and microorganisms and prevent the loss of water and other volatile substances from the product.

Components of Packaging

3. **Carton/outer:** Carton is the outer covering of package, which provides secondary protection against mechanical and other environmental hazards which also serves to display of written information. The cartons are made up of cardboard, molded wood pulp and expanded polystyrene.
4. **Box:** It is used to pack multiples of products. The box provides primary defense against external hazards and have shock absorbing features. The boxes are made up of thick cardboard and wood.

Type	Uses
Glass	Bottles, vials, ampoules, syringes, cartridges, parentral containers, aerosol container.
Plastic	Bottles, syringes, parentral containers, tubes, bags, laminate, pouches, lids, tapes, aerosol, container (dip tube, gasket housing button, stems).
Metals	Collapsible tubes, foils, needles, aerosol container, cans.
Rubber	Closures, vial wrappers, caps, plungers.
Paper/Cardboard	Labels, inserts, display units, pouches, laminates, cartons, boxes, foils, gum tapes, paper drums.

Advantages of Packaging

1. Packaging helps to maintain stability of the product.
2. It protects the product from physical impacts such as hitting, wetting, and bruising.
3. It helps for the product to reach the consumer in economic way with ease of storage.
4. It provides with ease of choice and usage with the information it holds.
5. The package with details written on label provides convenience to the consumer.
6. Decreases product costs by packaging in small quantities.
7. Packaging provides hygiene.

Selection Criteria for Packaging Materials

- The choice of packaging materials may depend on the degree of protection required, compatibility with the formulation contents, the filling method, and its cost of production, presentation and the convenience of the packaging for the user such as size, weight, method of opening and reclosing and eligibility of printing.
- The selection of the proper packaging material depends on requirements such as protection against light reactive gases, moisture, microbes, physical damage, pilferage and adulteration presentation, identification, information, compatibility and convenience.
- There are a number of factors that influence selection of packaging material in respect of materials, etc. packaging features such as size, shape, design, surface graphics, color schemes, labeling,

Selection Criteria for Packaging Materials

(1) Physical Characteristics:

Packaging material selection decisions are influenced by certain physical characteristics of the product like the physical state, weight, stability, fragility, rigidity, surface finish etc. to be packaged.

(2) Facilities available:

Selection of packaging material depends upon facilities required to convert these materials in to packaging components. For examples, pressurized dispenser requires special filling, sealing and labeling equipment.

Selection Criteria for Packaging Materials

(3) Formulation components:

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 destabilized. Thus, stability and compatibility with the formulation contents are major concerns.

(4) Stability:

Certain environmental factors like moisture, oxygen, light, flame, bacteria, fungi, chemical action, etc., affect stability of formulation.

Selection Criteria for Packaging Materials

Therefore, stability of the formulation and compatibility with the formulation contents are major concerns in selecting packaging materials judiciously.

(5) Economy:

In pharmaceutical packaging, quality of packaging is very important in view of product stability as well as marketing, Aesthetic value of product and cost are related parameters as good aesthetic (expensive) products usually use expensive packaging.

Selection Criteria for Packaging Materials

(6) Convenience:

Packaging must necessarily possess the quality of convenience from the point of view of consumers, distributors and producers.

Thus, apart from the functional requirement, a selection of packaging material is made based upon its certain features like suitability to produce packaging systems for ease to open and close, ease to dispense, ease to dispose of, ease to recycle, ease to identify, ease to handle, convenience to pack, convenience to stack, convenience to display, etc.

Selection Criteria for Packaging Materials

(7) Miscellaneous criterion:

A packaging material selection may also be influenced by a number of other criterions, for example, if there is any statutory rule in respect of packaging, it will have to be abided by.

The socio-cultural factors may also influence material selection. In addition, consumer attitudes also have to be given due consideration.

The growth of consumerism in a number of countries suggests that selection should be made with meticulous care.

Selection Criteria for Packaging Materials

(8) Regulations:

Packaging and labeling may be subject to government regulation in the countries.

Some countries have specified packaging standards for certain products.

If such regulations and standards are to be strictly followed, the products need to be packaged in containers made up of recommended materials.

Selection Criteria for Packaging Materials

(9) Buyer Specifications:

In some cases, buyers like the exporters to give packaging specification. While incorporating such specifications it should also be ensured that packaging satisfies other requirements.

(10) Socio-cultural criterion:

While designing the packaging for a product, socio-cultural factors relating to the important country like customs, traditions, beliefs etc, should also be considered.

Selection Criteria for Packaging Materials

(11) Retailing characteristics:

The nature of retail outlets is a very important consideration packaging decision. For instance as pointed out earlier, in some of the foreign markets as a result of the spread of supermarkets and discount houses, a large number of products are sold on self-service basis.

The package has, therefore, to perform many of the sales tasks and hence it must attract attention, describe the product features, give the consumer confidence and make a favorable overall impression.

Selection Criteria for Packaging Materials

(12) Environmental criteria:

Packaging material selection decisions are also influenced by certain environmental factors like weather and climate factors.

The impact of such factors in the place where the product originates, while the product is in transit and while in the market etc, should be considered.

The packaging material should be capable of withstanding the stresses and hazards of handling and transportation, stacking, storing etc., under diverse conditions globally.

Selection Criteria for Packaging Materials

(13) Disposability:

Attention should also be paid to the aspects relating to the disposal of the containers. One of the qualities required for good package is that it could be easily disposed off or recycled, in some of the developing countries like India many packaging materials easily find some other use or are recycled.

But the situation is different in other countries. Indeed, the disposal of packaging materials is causing environmental problems in a number of countries, Reusable packages have potential risk of misusing it for selling counterfeit products or any other irrational purpose.

Glass

Glass

- Glass containers are commonly used for storing pharmaceutical products because glass possesses superior protective qualities.
- These containers are intended to come into direct contact with pharmaceutical products.
- The hydrolytic resistance, the resistance to release of soluble mineral substances into water, under the prescribed condition of contact between the interior surfaces of the container expresses the chemical stability of glass container for pharmaceutical use.

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Advantages of Glass

1. Glass is impermeable to water vapors, air, etc.
2. It is available in various sizes and shapes.
3. It has efficient mechanical strength and rigidity.
4. It is transparent so the contents can be easily seen from outside.
5. It can be converted into light resistant form by mixing with metal oxides.
6. It has elegant appearance than plastic containers.
7. It withstands high temperature and pressure during sterilization.
8. It can be easily sealed to provide hermetic protection and is easily labeled

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Disadvantages of Glass

1. Glass is heavy thus increasing product transportation cost.
2. It is brittle and thus has high risk of cracking and breaking.
3. It easily leaches out alkali to aqueous product contents, if not chemically treated.
4. It is expensive to manufacture.
5. It has tendency to shedding some part of silica into the formulation.

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Composition of Glass:

- Glass is principally made up of silica (59-80%) with varying degree of calcium oxide (5-12%), sodium oxide (12-17%), aluminium oxide (0.5-3.0%), barium oxide, boric oxide, potassium oxide, and magnesium oxide and cullet.
- The high melting point of glass is due to the presence of silica.
- The melting point and melt viscosity of the glass is modified by the addition of oxides.
- 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.

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- The most common cations found in glass are silicon aluminium, boron, sodium, potassium, calcium, magnesium, zing and barium.

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Process of Forming Glass Containers:

1. **Blowing:** In this method compressed air is used to form the molten glass in the cavity of a mold.
2. **Drawing:** This involves the pulling of molten glass through dies that shape the soft glass into ampoules, vials etc.
3. **Pressing:** Glass container in this method is formed by the use of mechanical force which presses or forces the molten glass against the ride of a mold.
4. **Casting:** In this method the force of gravity or centrifugal force is used to initiate the formation of molten glass in the cavity

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Ampoules

- Ampoules are thin-walled glass containers, which, upon filling are sealed by either tip or pull sealing method.
- The contents are withdrawn after rupture of the glass, or a single occasion only.
- The filled in product is in contact with glass only and the packaging is 100% tamper proof.
- The break system, one point cut or the color break ring offer consistent breaking force. There are varieties of ampoule types available ranging from 0.5 to 50 mL.
- Up to three color rings can be placed on the stem of ampoule for identification. Printed ampoules with heavy metal free colors are also available. Vials are classified as Type B (straight stem), Type C (funnel tip) and Type D (closed)

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Bottles, vials and syringes

- These are more or less thick walled containers with closures of glass or of any other material such as plastic or elastomers. The contents may be removed in several parts at one or more times.

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Types of Glass

(1) Borosilicate glass (Type 1)

1. Contains 80% silica 10% boric oxide, small amount of sodium oxide and aluminium oxide.
2. It is a neutral glass and has a high hydrolytic resistance due to the presence of boric oxide.
3. A substantial part of the alkali and earth cations are replaced by boron and/or aluminium and zinc.
4. It is more chemically inert than the soda-lime glass.
5. Type I glass is suitable as packaging material for most preparations whether parenteral or non-parenteral.
6. They can also be used to contain strong acids and alkalis.

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(2) Treated soda-lime glass (Type II)

1. Type II glass which has high hydrolytic resistance is obtained from treatment of the inner surface of a type III glass with sulfur.
2. Type II glass containers are made of commercial soda-lime glass which is de-alkalized or treated to remove surface alkali.
3. The de-alkalizing process is known as sulfur treatment that prevents weathering of empty glass bottles.
4. Sulfur treatment neutralizes the alkaline oxides on the surface rendering it more chemically resistant.
5. Type II glass has lower melting point when compared to Type I glass and so easier to mould.
6. It is suitable for most acidic and neutral aqueous preparations whether parenteral or non-parenteral.

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(3) Regular soda-lime glass (Type III)

1. This is an untreated soda lime glass that contains silica 75%, sodium oxide 15%, calcium oxide 10%, small amounts of aluminium oxide, magnesium oxide, and potassium oxide.
2. It has average or better than average chemical resistance.
3. Aluminium oxide impacts chemical durability while magnesium oxide reduces the temperature required during moulding.
4. This type of glass used for packaging of those parenteral products or powders that showed suitable stability in this glass.
5. In addition, it can be used for packaging of non-aqueous parenterals and powders with the exception of freeze-dried preparations and for packaging of non-parenteral preparations.

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(4) General purpose soda-lime glass (Type IV or NP)

1. This glass is made up of soda-lime and is used for non-parenteral (NP) products such as those intended for oral or topical use.
2. This type of glass usually has low hydrolytic resistance and therefore it is not used for products that need to be autoclaved as its surface erosion increases with temperature.
3. It is used to store topical products and oral dosage forms.

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Colored glass

- Glass containers for drugs are generally available in clear flint or amber color.
- Only amber glass and red glass are effective in protecting the contents of a bottle from the effects of harmful ultraviolet rays.
- Amber glass meets these specifications, but the iron oxide added to produce this color could leach into the product.
- Therefore, if the product contains ingredients subject to iron-catalyzed chemical reactions, amber glass should not be used.

Plastic

Plastic

1. Plastic containers consist of one or more polymers together with certain additives.
2. These are long-chain polymers that can be melted, formed into a desired shape, and solidified during cooling.
3. Features of plastic materials such as inexpensive, strong, durable, corrosion-resistance with high thermal and electrical insulation properties.
4. In addition, they can be easily molded into the desired shape and provide protection against contamination during storage and transportation.
5. It may contain certain additives such as antioxidants, stabilizers, plasticizers, lubricants, coloring matter and impact modifiers.

Advantages of Plastics

1. Easy to manufacture and are recyclable.
2. Available in various types of quality.
3. Freedom of design to which they lend themselves.
4. Extremely resistant to breakage and good puncture resistance.
5. It has wide consumer acceptance.
6. It is preferred over other packaging materials.
7. These are non-fragile and light in weight.
8. They have an excellent moisture and gas barrier properties.
9. They have low heat conductivity and good sealing properties.

Disadvantages of Plastics

1. Disposable plastics used in packaging for human consumption product contain harmful compounds with ecological risk.
2. Plastics are generally non-biodegradable.
3. Plastics generally have a low melting point and thus cannot provide desired level of protection against heat.
4. Plastics generally have a short useful life compared to metals

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Types of Plastic

(1) Polyethylene (PE)
(2) Polystyrene
(3) Polycarbonate
(4) Polyvinyl Chloride (PVC)
(5) Polyvinylidene Chloride (PVDC)
(6) Polychlorotrifluoro ethylene
(7) Cyclic olefin copolymers:
(8) Polypropylene

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Types of Plastics

(1) Polyethylene (PE)

1. PE is available in three different grades namely low, medium and high density ranging from 0.91 to 0.96 g/mL.
2. Physico-chemical properties such as clarity and translucency of this plastic varies with the density.
3. High density polyethylene (HDPE) is the most crystalline material and is most widely used for the containers by the pharmaceutical industry for drug packaging because it offers good barrier against moisture but a relatively poor one against oxygen and other gases.
4. HDPE is most preferred in packaging of solid oral products.

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Types of Plastics

(2) Polystyrene

1. The polystyrene (PS) is the clear rigid hard material with good tensile strength.
2. The major limitation it has is its brittleness. Although it is resistant some of the mineral oils, water and alkali it solubilizes in the organic solvents.
3. Since, it has fair permeation for moisture it is not commonly used for pharmaceutical packaging.

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Types of Plastics

(3) Polycarbonate

1. The polycarbonate (PC) has good impact resistance and excellent dimensional stability.
2. It has a low water absorption capacity and is heat resistant Generally, it is used in making membrane filters, reusable bottles and sterilizable medical packaging.

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Types of Plastics

(4) Polyvinyl Chloride (PVC)

1. Polyvinyl chloride (PVC) most widely used film forming plastic displaying ideal forming characteristics.
2. PVC used in the film formation is called rigid PVC or RPVC as it is almost free of softening agents.
3. It has very low water-vapor permeability.
4. The advantages of using PVC are low cost and the ease of thermoforming.
5. The poor barrier against moisture and oxygen ingress and negative environmental degradation due to its chlorine content are its major limitations.
6. When it is used in blister packaging it does not contain any plasticizer and thus blisters offer structural rigidity and physical protection to the dosage form.

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Types of Plastics

(5) Polyvinylidene Chloride (PVDC)

1. Polyvinylidene chloride (PVDC) is copolymer of vinyl chloride or vinyl acetate and vinylidene chloride.
2. It is an excellent resistance to permeation by moisture and gas and mostly widely used as a coating.
3. The coated PVC has characteristics similar to uncoated PVC except that the water vapor permeability of coated films is reduced by a factor of 5-10.
4. The coating is applied on one side and usually faces the product and the lidding material

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Types of Plastics

(6) Polychlorotrifluoro ethylene

1. Polychlorotrifluoroethylene (PCTFE) can be laminated to PVC to obtain very high moisture barrier.
2. PVC-CTFE films have the lowest water-vapor permeability of all the films used for blister packaging. Because of some environmental concerns
3. PVC is applied to PVC-CTFE film.
4. Double layered structures are of PVC/PCTFE and triple layered laminates are of PVC/PE/PCTFE.

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Types of Plastics

(7) Cyclic olefin copolymers:

1. Cyclic olefin copolymers (COC) or polymers (COP) in multilayered combinations with polypropylene (PP), PE, or glycol modified polyethylene terephthalate (PET) can provide moisture barrier to blister packs.
2. Cyclic olefin resins are amorphous and have good thermoforming characteristics and thus are used in blister packaging as a thermoforming enhancer in combination with PP or PE.
3. Films can be manufactured via co-extrusion or lamination.

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Types of Plastics

(8) Polypropylene

1. PP is used as a support material for blister packages.
2. Problem with this polymer is its thermoforming processing. The temperature of thermoforming and subsequent cooling are critical parameters that need to be controlled.
3. While warping of with PP packages need be straightened before cartooning.

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Metals

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Metals

1. Metal is the most versatile of all the materials used in the packaging.
2. Metals are strong, relatively unbreakable, opaque, and impervious to vapors, gases, odour and microorganisms.
3. It is used only in packaging of non-parental pharmaceutical products due to its particle shedding properties.
4. They are usually resistant to temperature variation.
5. The commonly used metals in pharmaceutical packaging include tin, aluminium and tinplate.
6. Packs made from metal foil are strips and blisters and container packs are aerosol cans and gas cylinders.
7. Metallic tubes are light in weight, unbreakable, and are suitable for high-speed automatic filling operations.

Advantages of Metals

1. Some metals are light in weight.
2. Metals provide superior protection against contamination.
3. Form excellent tamper-evident containers.
4. Metals are strong and shatter proof.
5. Suitable for pressurized packaging

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Disadvantages of Metals

1. Metals are highly expensive.
2. Some metals are heavy in weight.
3. They show chances of toxicity.
4. They are reactive to certain chemicals and are susceptible to corrosion.

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Applications of Metal as Packaging Material

Package	Dosage form	Remarks
Strip, blister	Tablets, capsules	Polymer coated aluminium with various thickness are used to improve the sealability and stability
Collapsible tubes	Ointments, creams, gels and other semisolids	The tubes with internal protective coating of polymers with and without spike are available.
Cans	Aerosols, inhalers, sprays, etc.	Pressure resistant and internal polymer coated aluminum containers are available.

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Types of metals

(1) Aluminium:

1. Aluminium has prominent protective characteristics against the effects of moisture, heat and light.
2. It is used as laminate in strip and blister packaging and is costly component of laminate.
3. Hard tempered (non-annealed) foils are used occasionally for push through lidding for blister packs.
4. Lubricants are removed from hard foil by either solvent washing or controlled heating.
5. This metal is used for packaging of tablets, capsules, and powders. Its light weight offers significant saving in the product shipping costs and when combined with tin it provides the attractiveness.

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6. The excellent properties of aluminium foil provide a convenient, safe and versatile packaging system for variety of pharmaceutical products.
7. Aluminium foil has superior barrier properties that totally excludes moisture, oxygen and other gases, microorganisms and light and thus maintains sensitive products during long term storage.

Types of metals

(2) Tin

1. Tin is chemically inert of all collapsible tube metals.
2. It is the more expensive than lead.
3. Tin is the most ductile of these metals.
4. Tin at 15% used in composition of metal used for collapsible tubes.
5. Laminates of tin-coated lead provide better appearance and is resistant to oxidation.
6. These laminates are cheaper compared to tin alone. The tin that is used for this purpose is alloyed with about 0.5% copper for stiffening.

Types of metals

(3) Lead

1. Lead has the lowest cost of all tube metals and is widely used for adhesives, inks, paints, and lubricants.
2. When it is used as packaging material, about 3% antimony is added to increase hardness.
3. Addition of aluminium hardens it when formed into a tube, and must be annealed to give it the necessary pliability.

Rubber

Rubber

1. Rubber is used in the pharmaceutical industry to make closures, stoppers, cap liners and bulbs for dropper assemblies.
2. Rubber components are made either from either natural or synthetic sources.
3. Natural rubber has got good resealing, fragmentation and coring properties when compared to synthetic rubber.
4. It is poor in respect to ageing and has chances of moisture and gas permeation.
5. It is more susceptible to absorption of preservative systems and sterilization by multiple autoclaving is also not possible.
6. Synthetic rubbers tend to reverse all of these properties,

7. The main types of rubber used for pharmaceutical products include natural rubber, neoprene rubber, nitrile rubber, butyl rubber, chlorobutyl rubber, bromobutyl rubber, silicone rubber etc.
8. Of these, silicone is the most expensive and inert, but is readily permeable to moisture, gases and absorbent to certain preservatives.
9. Rubber components contain more additives and hence product-package interactions should be properly tested before they are used for parentral products.
10. In the injectable drug products, rubber is used for many applications such closures for vials and bottles, seals and plungers for syringes and cartridges, gaskets in manufacturing equipment, and ports on plastic bags and intravenous administration sets.

Properties and Composition

1. Physical and chemical properties of the rubber dictate the best choice of rubber for the product.
2. The physical properties considered in the selection of a particular rubber include elasticity, hardness (durometer), tendency to fragment permeability to oxygen and/or water vapor transfer, pressure to puncture, coring, resealability, break force, vacuum retention, and specific leachables/extractables.
3. The rubber closure is used primarily for multiple dose vials and disposable syringes.

Rubber closure may be classified into two types:

a) **Type I closures:** Meets the strictest requirements and thus are most preferred.

b) **Type II closures:** These have mechanical properties suitable for special use.

Elastomers

1. The base material for the rubber is the elastomer that is composed of either natural or synthetic rubber.
2. The elastomer determines most of the physical and chemical characteristics of the rubbers.
3. Butyl rubber is the most commonly used elastomer for pharmaceuticals.
4. Sulfur is the most common curing agent for elastomers.
5. An activator, typically a metal oxide with a fatty acid, accelerates the rate at which the sulfur reacts with the unsaturated polymer.
6. The most common activator is zinc oxide combined with stearic acid.
7. Fillers are added to reduce tack, adjust color, and often to increase hardness and durability.

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Advantages of Rubber

1. Rubber is easy to use.
2. Rubber is inexpensive.
3. It exhibits good abrasion resistance and is elastic.
4. It has ability to be removed easily from an article.
5. They are very soft and stretchable.
6. Softer rubbers experience less coring and reseal better.
7. Harder rubbers are easier to process on high speed packaging lines.

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Disadvantages of Rubber

1. Low-cost rubbers generally shrink.
2. Rubber has offensive odour.
3. Some rubbers are sensitive to chemicals, and do not have a long shelf life.
4. They are brittle upon long exposure to heat.

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Manufacturing:

The basic steps in the manufacture of rubber closures involve:

1. Raw materials are tested for identity and purity.
2. Formulation ingredients are weighed within + 1% tolerances.
3. Batch ingredients are mixed and tested to insure cure characteristics.
4. The mixture is placed in an extruder to create pellets, strips, or sheets and molded by injection, compression, or transfer.
5. The molded sheets (stoppers) are trimmed and washed to remove trim and mold lubricants.
6. The stoppers are baked and autoclaved, if applicable.
7. The stoppers are tested for conformance by chemical and physical testing and are packed.

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Manufacturing:

8. The two major steps in the production of rubber products are the compounding of the components followed by curing.
9. In the compounding process, the rubber is masticated, or broken down by heat and shearing with a mixer.
10. Mastication breaks down the polymer, increasing its viscoelasticity, and enables the incorporation of additives such as fillers.
11. Following mastication, the remaining additives, with the exception of the curing agents are added and mixed.
12. Remilling may follow if required to improve dispersion of additives or to modify viscosity.

Manufacturing:

8. The curing system is added during the finish mixing step and the hot mixture is then extruded through a die to form pellets or through a pair of rollers to form a sheet.
9. The rubber is further formed by injection molding or more commonly for stoppers, compression molding, and is then cured or vulcanized.
10. Vulcanization consists of three stages; induction, curing and reversion.

Manufacturing:

(a) Cleaning:

1. Rubber closures are cleaned and depyrogenated by rinsing with numerous amounts of Water for Injection and, if necessary, a cleaning agent like sodium hydroxide, Liquid Safe-Kleen, or tri-sodium phosphate.
2. Many rubber formulations contain polymer surfaces that do not require siliconization and process without difficulty.
3. However, if siliconization is required, it is done prior to sterilization, but after the depyrogenation procedure, and usually in the stopper washer.
4. A pre-determined amount of silicone is added to the stopper washer during a specified period of the washing cycle.

Manufacturing:

(b) Sterilization:

1. Sterilization of rubber closures is done by steam sterilization in an autoclave using a validated cycle.
2. Rubber plungers used in pre-sterilized, ready-to-fill syringes are sterilized by gamma radiation.

(c) Qualification:

1. Physico-chemical and toxicological tests for evaluating rubber closures are described in USP.
2. In-vitro biological reactivity tests for rubber include the agar diffusion test, the direct contact test, and the elution test.
3. In-vivo biological reactivity tests include the systemic injection test, the intracutaneous test, and the implantation test.

Manufacturing:

(d) Siliconization:

1. Rubber closures must be 'slippery' in order to move easily through a rubber closure hopper and other stainless steel passages until they are fitted onto the filled vials.
2. Traditionally, rubber materials are 'siliconized' (silicone oil or emulsion applied onto the rubber) in order to provide lubrication.

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Reference

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