Packaging materials of pharmaceutical products

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Introduction

Packaging is the process by which the pharmaceuticals are suitably placed so that they should retain their therapeutic effectiveness from the time of their packaging till they are consumed.

Definition: Packing is the art and science which involves preparing the articles for transport, storage, display and use.

Introduction

The ideal container or package should:

1. Protect the contents from the following environmental hazards:

(a) Light - protect the contents from light

(b) Temperature - be capable of withstanding extremes of temperature.

(c) Moisture - be capable of withstanding extremes of humidity.

(d) Atmospheric gases - protect the contents from the effect of atmospheric gases (oxidation).

(e) Particles - protect from particulate contamination.

(f) Microorganisms - protect from microbial contamination.

Introduction

The ideal container or package should:

2. Protects the content from the following mechanical hazards

(a) Vibration - Usually due to transportation

(b) Compression - this usually includes pressure applied during stacking.

(c) Shock - such as impact, drops or rapid retardation.

(d) Puncture - penetration from sharp objects or during handling operations.

3. They must not add or permit loss to its contents:

(a) Protect the contents from both loss and gain of water.

(b) Protect the contents from loss of volatile materials

(c) Must not leach anything to the contents.

Introduction

The ideal container or package should:

4. Must have a pharmaceutically elegant appearance

5. Must be convenient and easy to use by the patient.

6. Must be cheap and economical.

7. Must not react with the content.

8. Must be biodegradable.

SELECTION OF PACKAGING MATERIAL

The materials selected for packaging must have the following characteristics:

1. They must protect the preparation from environmental conditions.
2. They must not be reactive with the product,
3. They must not impart tastes or odors to the products,
4. They must be non-toxic,
5. They must be FDA approved,
6. They must have reasonable cost in relation to the cost of the product.

PACKAGING MATERIAL

The following materials are used for the construction of containers and closures

1. Glass: - (i) Type-I Borosilicate glass
   (ii) Type-II Treated sodalime glass
   (iii) Type-III Regular soda-lime glass
   (iv) Type-NP General purpose soda lime glass
   (v) Coloured glass
2. Metals (i) Tin (ii) Iron (iii) Aluminium (iv) Lead.
3. Plastics (a) Thermosetting resins : (i) Phenolics (ii) Urea
   (b) Thermoplastic resins:
   (i) Polyethylene
   (ii) Polypropylene
   (iii) Polyvinylchloride (PVC)
   (iv) Polystyrene
   (v) Polycarbonate
   (vi) Polyamide (Nylon)
   (vii) Acrylic multipolymers
   (viii) Polyethylene terephthalate (PET)
4. Rubber (i) Natural rubber
   (ii) Neoprene rubber
   (iii) Butyl rubber.

Glass

It is fragile and more weight

Composition: Silicon dioxide, sodium carbonate, calcium carbonate, cullet (all are mixed).

Silicon, aluminum, boron, sodium, potassium, calcium, magnesium, zinc are present as cation.

Reduction in Na results in chemically resistant glass. But without Na/alkali preparation of glass is difficult and expensive to melt.

Boron oxide is added to reduce melting temperature.

Lead is added to make glass clear and brilliant but soft grade glass is produced.

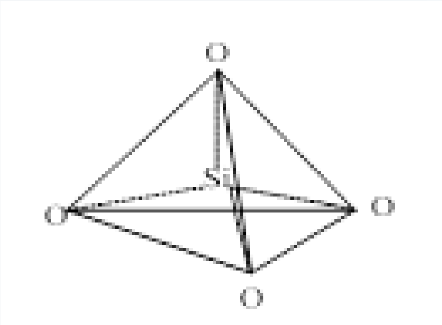
Aluminum oxide (alumina) addition gives hardness and durability (long lasting) and also produce chemically resistant glass.

Glass

Glass is composed principally of sand (silica - SiO_2), soda-ash (Na_2CO_3 - sodium carbonate) and lime-stone ($CaCO_3$-calcium carbonate).

Glass made from pure silica consists of a three-dimensional network of silicon atoms each of which is surrounded by four oxygen atoms and in this way the tetrahedra are linked together to produce the network.

Glass prepared from pure silica require very high temperature to fuse, hence soda-ash and lime is used to reduce the melting point.



Glass

(i) Glass made of pure silica has network (Fig-1)

Properties:

(a) It is very hard and

(b) chemically resistant but

(c) melting point very high so it is very difficult to mould.

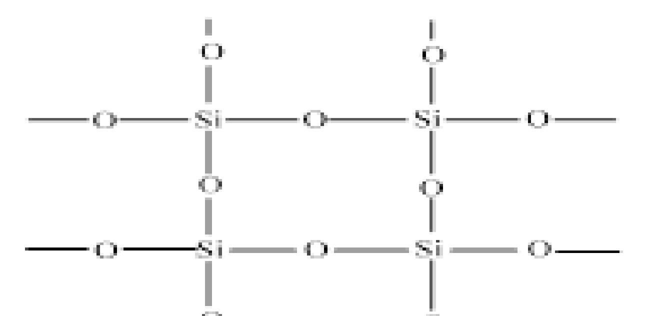


Fig. 1

(ii) Glass made of pure silica + Na_2O (Fig.-2)

(valency of Na = 1)

Properties:

(a)Structure is less rigid so low m.p. and easier to mould

(b) the glass is too rapidly attacked by water and NaOH is leached out of the glass.

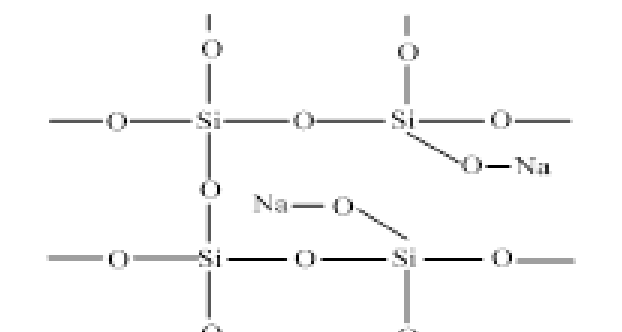


Fig. 2

Glass

(iii) Pure silica + CaO (or BaO, MgO, PbO and ZnO)(Fig.-3)

(valency of Ca, Ba, Mg, Pb, Zn = 2)

(a) It is more rigid than soda-silica network.

(b) Since the bond is more stronger, hence chemical reactivity is lowered.

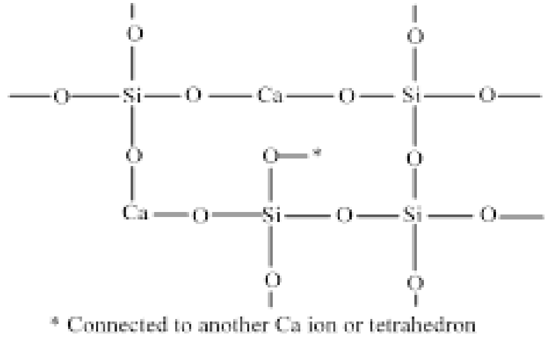


Fig. 3

(iv) Pure silica + Boric(B2O3) or aluminium oxide (Al2O3)

(valency of B and Al = 3, i.e. trivalent)

(a) Since boric oxide, like silica, is acidic. It does not disrupt the network of silica but forms tetrahedron itself; however, these are not the same size as the silicon tetrehedra; as a result the lattice become distorted, and this produces flexibility.

(b) It is chemically resistant.

Glass

Preparation:

Blowing: Melting of glass.

Drawing: Molten glass is shaped to desired size by pulling through any dies.

Pressing: Mechanical force is applied on molten glass against the side of the moulds.

Casting: Gravitational or centrifugal force is applied on molted glass to form the cavity of the moulds.

Glass containers are some time treated internally with silicon fluid to increase hydrophobicity.

Type I and Type II glass are used for acidic, alkali and neutral parenteral preparations.

Type of glasses

Colour glass (light protected glass): Only amber colour or red colour glass can protect harmful light (UV: 2900-4500°A).

Iron oxide is added to produce amber colour glass and it could react with iron sensitive material of the product stored.

Type I (Highly resistant borosilicate glass): Alkali cations are replaced by boron, aluminium or zinc. It is chemically more resistant than soda lime glass. It is used for strong acid, strong base, different solvent, buffered and un-buffered solutions. Reaction with water can produce NaOH as a result of loosely boded Na ions with silicon dioxide. 6% boron treatment may reduce leaching to 0.5PPM per year.

Powder glass test is used for alkalinity test.

Type of glasses

Type II glass (Treated soda lime glass): High temperature and moist environmental condition moisture is condensed to glass surface and solubilize the glass surface salts, it is called Blooming or Weathering.

It is prepared by alkali removal with sulfur treatment (water vapor and sulfur dioxide at high temperature). It is used for buffered solution pH below 7, oleaginous solution and dry powders. It can resists alkali leaching with time dependency. Water attack test used for alkalinity test.

Type III (Regular Soda lime glass): Untreated soda lime glass. It is used for dry powder, oleaginous solution. Powder glass test is used for alkalinity test.

Type IV or Type NP (General purpose Soda lime glass): Soda lime glass. It is used for non parenteral product, oral solutions and suspension, topical products. Powder glass test is used for alkalinity test.

Glass

Type of glass	Main Constituents	Properties	Uses
Type-1 Borosilicate glass	SiO_2 – 80% B_2O_3 – 12 Al_2O_3 - 2% Na_2O+CaO - 6%	1. Has high melting point so can withstand high temperature 2. Resistant to chemical substances 3. Reduced leaching action	1. Laboratory glass apparatus 2. For injections and 3. for water for injection.
Type-II Treated soda-lime glass	Made of soda lime glass. The surface of which is treated with acidic gas like SO_2 (i.e. dealkalised) at elevated temperature (500^{0}C) and moisture.	1. The surface of the glass is fairly resistant to attack by water for a period of time. 2. Sulfur treatment neutralizes the alkaline oxides on the surface, thereby rendering the glass more chemically resistant.	1. Used for alkali sensitive products 2. Infusion fluids, blood & plasma. 3. large volume container
Type-III Regular soda-lime glass	SiO_2 Na_2O CaO	1. It contains high concentration of alkaline oxides and imparts alkalinity to aqueous substances 2. Flakes separate easily. 3. May crack due to sudden change of temperature.	1. For all solid dosage forms (e.g. tablets, powders) 2. For oily injections 3. Not to be used for aqueous injection 4. Not to be used for alkali-sensitive drugs.

Advantages of glass container

Physical aspect

1. They are quite strong and rigid.
2. They are transparent which allows the visual inspection of the contents; especially in ampoules and vials.
3. They are available in various shapes and sizes.
4. Borosilicate (Type-I) are resistant to heat so they can be readily sterilized by heat.
5. Glass containers can be easily cleaned without any damage to its surface e.g. scratching or bruising.

Advantages of glass container

Chemical aspect

6. Treated soda lime glass has a chemically inert surface.

7. As the composition of glass may be varied by changing the ratio of various glass constituents the proper container according to desired qualities can be produced.

8. They do not deteriorate with age

9. Photosensitive drugs may be saved from UV-rays by using amber color glass.

Economical aspect

10. They are cheaper than other packaging materials.

Disadvantages of glass container

Physical aspect

1. They are brittle and break easily.
2. They may crack when subject to sudden changes of temperatures.
3. They are heavier in comparison to plastic containers.
4. Transparent glasses gives passage to UV-light which may damage the photosensitive drugs inside the container.

Chemical aspect

5. Flaking: From simple soda-lime glass the alkali is extracted from the surface of the container and a silicate rich layer is formed which sometimes gets detached from the surface and can be seen in the contents in the form of shining plates- known as ‘flakes’ and in the form of needles- they are known as ‘spicules’. This is a serious problem, specially in parenteral preparations.

Glass screening

Type I&II are used for parenteral preparations. Samples are stored in glass containers under ambient temperature and light. Samples are analyzed at specific time intervals for potency, pH, colour and particulate matter.

Test for glass (USP)

1. Powder glass test
2. Water attack test

Requirements:

i. Highly purified water (6.67 micro-ohm/cm at 25°C)

ii. Methyl red solution: 24 mg in 100 ml purified water solution and neutralize with 0.02N NaOH or 0.02 N sulfuric acid.

iii. Sample glass

iv. Conical flask made by highly resistant glass treated with highly purified water at 90°C for 24h or 121°C for 1h

Powder glass test (USP)

Container is crushed to size that retain on sieve no. 50. Wash with acetone for 30 sec and dry at 140°C for 20 minutes and used within 48h

Take 10 gm of such glass particles in conical flask.

Add 50 ml of highly purified water.

Take one for test and other for control

Place into a autoclave operated at 121±2°C for 30 minutes.

Decant water and titrated with 0.02N sulfuric acid, 5 drops of methyl red solution is used as indicator.

Measure the volume of 0.02N sulfuric acid consumed for titration.

Water attack test (USP)

Container is wash with highly purified water.

Fill 90% of overflow capacity with highly purified water and seal.

Place into a autoclave operated at 121±2°C for 60 minutes.

Collect 100 ml water from the container and 5 drops of methyl red solution is added as indicator.

Measure the volume of 0.02N sulfuric acid consumed for titration.

Glass test permissible limits

Type	Description	Test	Size (ml)	Ml of 0.02N sulfuric acid
I	Highly resistant borosilicate glass	Powder glass test	All	1.0
II	Treated soda lime glass	Water attack test	100 or less	0.7
			> 100	0.2
III	Regular Soda lime glass	Powder glass test	All	8.5
NP	General purpose Soda lime glass	Powder glass test	All	15.0

Arsenic test (USP)

After processing of water attack test, same water is used for arsenic test.

Container is wash with highly purified water.

Fill 90% of overflow capacity with highly purified water ad seal.

Place into a autoclave operated at 121 ± 2°C for 60 minutes.

35 ml of water is taken and arsenic test is performed.

Permissible limit ≤ 0.1 µg/gm

Plastics

General properties of plastics

1. Plastics are synthetic polymers of high molecular weight.
2. They are sensitive to heat, and many may melt or soften at or below 100°C. However, several plastics can be autoclaved e.g. nylon, polycarbonate, polypropylene, high density polyethylene (HDPE) etc.
3. Plastic containers are light in weight, they are easier to handle.
4. Mechanically they are almost as strong as metals and therefore, containers can have thinner walls than glass containers.
5. They are poor conductors of heat, a disadvantage if the content is to be autoclaved.
6. Generally, they are resistant to inorganic chemicals but are often attacked by organic chemicals, solvents and oils.
7. Plastic contain some additives (e.g. antioxidants, lubricants, plasticizers, stabilizers, filler) which may contaminate the content.
8. Very few types of plastics completely prevent the entry of water vapor and some are permeable to gases like oxygen, carbon-di-oxide.

Types of Plastics

1. Thermoplastic type

On heating, they soften to a viscous fluid which hardens again on cooling.

e.g. Polyethylene, polypropylene, polyvinylchloride, polystyrene, nylon (polyamide), polycarbonate, acrylic multi polymers, polyethylene terephthalate etc.

2. Thermosetting type

When heated, they may become flexible but they do not become liquid. Because of a high degree of cross-linking they are usually hard and brittle at room temperature.

e.g. phenol-formaldehyde, urea formaldehyde, melamine formaldehyde.

Plastics

GLASS TRANSITION TEMPERATURE (Tg)

The maximum temperature below which a material become rigid, brittle solids and are said to be in ‘glassy-state’.

In this condition they are not crystalline but are super cooled liquids of high viscosity.

Above the glass temperature (Tg) thermoplastics soften and melt if heated to a considerably higher temperature than Tg.

Highly cross-linked thermosetting plastics, Tg is so high that decomposition takes place before the material can soften and melt.

Additives of Plastics

Plastics are polymers which are prepared from monomers.

(i) Stabilizer: Side reactions during polymerization may produce a proportion of unsaturated potentially unstable compounds. So stabilizers are used to stop those side reactions. e.g. octyl tin to stabilize PVC.

(ii) Antioxidants: Plastics are vulnerable to oxidation. The antioxidants binds with the free radicals and stops the oxidation reaction. e.g. N,N'-di-β-napthyl-p-phenylene diamine for stabilizing plastics and rubbers.

(iii) Pigments: These are used for decorative purpose. They may absorb electro-magnetic radiation in UV region and thereby reducing photodegradation. For clear plastics organic absorbers such as 4-biphenyl salicylate are used.

Additives of Plastics

(iv) Fillers are often employed to make the product cheap but in some cases may be essential for correct product performance. e.g. Bakelite, a phenol-formaldehyde resin, is brown brittle material, quite unsuitable for the manufacture of screw caps unless mixed with a filler such as wood flour. Examples of fillers: asbestos and mica.

(V) Plasticizers are used to reduce Tg of a polymer. They do it by directly reducing the attractive forces between polymer chains.

(Vi) Other agents: Cross-linked agents, curing agents, activators and accelerators etc.

Drug-Plastic Consideration

A packaging must protect the drug without altering the composition of the product until the last dose is removed.

Drug plastic consideration have been divided into five separate categories:-

(1) permeation,

(2) leaching,

(3) sorption,

(4) chemical reaction, and

(5) alteration in the physical properties of plastics or products.

Disadvantages of plastic

1. Permeation: Transmission of gas, liquid and vapour through plastic containers is called permeation. It can produce adverse effect on the shelf-life of a drug. Permeation of water vapor and O2 through the plastic wall into the drug can cause a problem if the dosage form is sensitive to hydrolysis and oxidation. Temperature and humidity influences the permeability of oxygen and water.

e.g. Hydrophilic materials are poor barrier for water while hydrophobic materials provide much better barriers. Nylon is hydrophilic and poor water vapour barrier but polyethylene is hydrophobic and a good barrier. Increase in crystallites may reduce the permeation.

Formulations containing volatile ingredients may change when stored in plastic containers due to the permeation of one or two ingredients through the walls of the containers.

Certain w/o emulsions cannot be stored in a hydrophobic plastic bottle, since there is a tendency for the oil phase to migrate and diffuse into the plastic.

Disadvantages of plastic

2. Leaching: Added ingredients like colour, anti-oxidant, modifiers, antistatic agent, plasticizers and stabilizers may leach out into the product stored. Additives those are added in the plastics may also leach into the content.

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, may catalyse some reaction in the solution - decomposing the drug.

Disadvantages of plastic

3. Sorption: Absorption of soluble ingredients by the packaging materials is called sorption. This process involves the removal of constituents from the drug product by the packaging material. Drug substances of high potency are administered in small doses.

In this case losses due to sorption may significantly affect the therapeutic efficacy of the preparation.

A common problem is the loss of 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 influencing the characteristics of sorption from products are:

(i) chemical structure of the solute,
(ii) pH,
(iii) solvent system,
(iv) concentration of solute,
(v) temperature,
(vi) time of contact and
(vii) area of contact.

Disadvantages of plastic

4. Chemical reaction: Certain ingredients that are used in plastic formulations may react chemically with one or more components of a drug.

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.

Modification: The physical and chemical alteration of the packaging materials by the drug product is called modification. Oils have softening effect on polyethylene. Fluorinated hydrocarbons can attack polyethylene and polyvinyl chloride.

Disadvantages of plastic

5. Modification: The physical and chemical alteration of the packaging material by the drug product is called modification.

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.

Oils have a softening effect on polyethylene and PVC.

(ii) Fluorinated hydrocarbons attack polyethylene and PVC. In some cases the content may extract the plasticizers, antioxidant or stabilizer, thus changing the flexibility of the package.

(iii) Plasticizers when extracted by some solvents renders the wall stiff.

Plastics

Plastic containers: It is extensively resistant to break and freedom for design. With plastic material, colour, anti-oxidant, modifiers, antistatic agent, plasticizers and stabilizers are used.

Polyethylene: It is susceptible to oxidation. BHT or dilauryal thiodipropionate is added at 100PPM. Antistatic agent like PEG or long chain fatty amides at a concentration 0.1-0.2% is used to prevent air born dust accumulation.

Polypropylene: It does not stress crack under any condition except hot condition and halogenated solvent. Due to its high melting point, it is sterilisable. It is a god barrier to vapour and gas. At low temperature it becomes brittle. It has lack of clarity.

Plastic

Polyvinyl chloride: It is good barrier for oxygen and oils (fixed oils, volatile oils, fixed alcohols, petroleum solvents). It is degraded at 280°C and corrosive products are produced. Under UV-light and heat, it becomes yellow colour, to maintain its clarity stabilizer like dactyl tin mercapto acetate or maleate is added. Stabilizers like sulphur, calcium and zinc salts make plastic yellow colour. Vinyl chloride may cause cancer. Glass bottle inside is coated with vinyl chloride.

Polystyrene: It has high water vapour transmission and oxygen permeability. It is used for dry product packaging.

Plastic

Nylon (Polyamide): It is highly impermeable to oxygen and not a good barrier to water vapour. To make it water resistant, it is laminated with polyethylene.

Polycarbonate: It is more expensive. It is sterilisable repeatedly. It is rigid like glass and possible replacement of glass vials or syringes. It is resistant to chemicals, fair moisture barrier, impact strength and strain, heat and flame, dilute acid, oxidizing and reducing agents, salts, fixed and volatile oils, grease and aliphatic hydrocarbons. It has low water absorption and it is transparent. It is susceptible to alkalis, amines, ketones, aromatic hydrocarbons and some alcohols.

Plastic

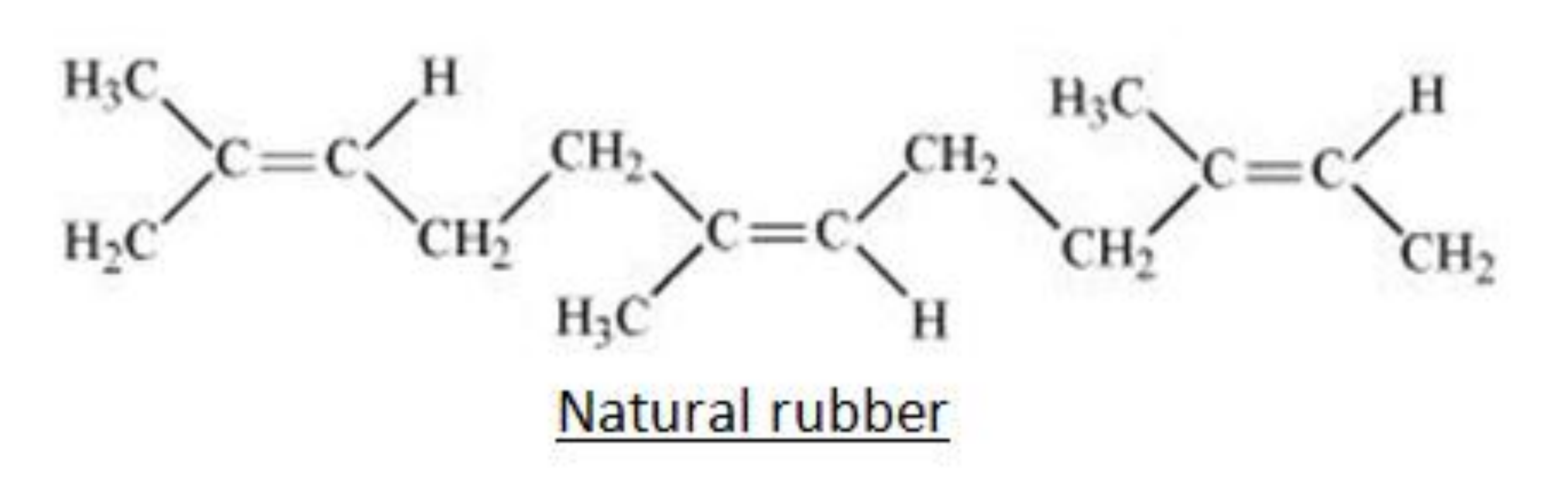
Acrylic multi-polymers (Nitrile polymers): It is high gas barrier, good chemical resistant, excellent strength and safe disposability. It is resistant to oils and grease.

Polyethylene terephthalate: It is a product of terephthalic acid and ethylene glycol. It is used for storing of carbonated beverage.

Low density polyethylene and polystyrene are sterilisable in autoclave and these are used for packaging of parenteral products. Polypropylene, polyethylene-polypropylene copolymers are widely used for parenteral products packaging. Flexible polyethylene is used for ophthalmic products packaging. Flexible polyvinyl chloride is used for i.v. fluid products packaging.

Rubber

Natural rubber consists of long chain polymers of isoprene units.



Its most important source is the tree Hevea braziliensis from which a latex, containing 30 to 40% of rubber in colloidal suspension.

Rubber

Solid rubbers are prepared in two ways:

(i) Smoked sheet

Rubber is negatively charged, so it is coagulated by adding a little acetic or formic acid.

On standing the rubber forms a spongy mass.

It is passed through rollers to make sheets.

The sheets are washed and smoked with wood fire.

Phenolic compounds from wood fire makes the material brown and acts as a preservative and protect rubber from mold growth.

Since it contains non-rubber materials hence, are not used in pharmaceutical purpose.

Rubber

(ii) Pale crepe

The spongy coagulam is thoroughly washed.

It is torn up and then continually sprayed with water while it is squeezed between rollers.

As a result it has less of non-rubber constituents-hence pale crepe is used for pharmaceutical purpose.

Compounding rubbers:

Some of the properties of raw rubber (e.g. poor elasticity and sensitivity of temperature change) makes it unsuitable for the production of most rubber articles.

Rubber

Rubber is used as closures to seal the openings o cartridge, vials and bottles. The closures should have soft material ad elastic enough. Physical and chemical properties of rubber are altered by the addition of some additives.

Composition:

- Rubber: Natural rubber, synthetic rubber
- Vulcanizing agent: Crosslinking agent (Sulfer)
- Accelerator: Increase rubber production (2-mercapto benzothiazole)
- Activator: Activate rubber molecules (ZnO)
- Filler: Improve mechanical strength and air tightness (carbon block, lime stone)
- Antioxidant: BHT, BHA
- Lubricant: Mineral oils
- Pigments

Vulcanizing agent

Raw rubber has poor elasticity, so its strength is poor.
It hardens when cold and becomes soft and sticky when warm.
It dissolves in many solvents
Vulcanizing agent increases greatly the range of stress and temperature over which the material is elastic.
Sulfur is a vulcanizing agent and it forms cross-links between the long rubber molecules.
Procedure of vulcanization
(i) Heat vulcanizing
The mixture of rubber and sulfur is heated for about 6 hours at 150°C.
(ii) Cold curing
Rubber is treated in the cold with sulfur monochloride as a vapor or a solution in carbon-di-sulphide.
Small amount of HCl may remain as residue, hence this rubber cannot be used in certain types of medical products.

Accelerators, Activator & Fillers

Accelerator: These reduce the time of vulcanization and the amount of sulfur required.

e.g. 2-mercapto benzthiazol (MBT), tetra methyl thiuram disulphide (TMT), zinc dimethyl dithiocarbamate

Activators: These are used to increase the activity of accelerators.

e.g. Stearic acid or zinc stearate for MBT and zinc oxide for TMT.

Fillers: Two classes of fillers are added to rubber. Reinforcing fibres are used to improve physical properties.

e.g. carbon black (very finely divided carbon), zinc oxide, magnesium carbonate and calcium carbonate.

Extending fillers are added mainly as diluents to reduce cost and partly to facilitate manufacture. e.g. talc and asbestos.

Accelerators, Activator & Fillers

Softeners: These facilitates the incorporation of fillers, make the compound easier to manufacture.

e.g. Pine oil, mineral oil, tar-fractions.

Antioxidants: The chains are broken at the double bonds and S-links by oxidation, causing softening and weakening. Deterioration is slowed down by including antioxidants.

e.g. phenyl betanaphthyl amine and para-hydroxy diphenyl.

Pigments: To make colorful rubber it is used.

e.g. Oxides of iron and sulphides of cadmium and antimony.

Lubricants: To assist the removal of rubber products from the mould

e.g. zinc stearate, talc are dusted before moulding.

BUTYL & SILICONE RUBBER

BUTYL RUBBER: These are copolymers of isobutylene with 1-3% of isoprene or butadiene.

Advantages:-

(i) They are most resistant to aging and chemical attack.

(ii)Permeability to water vapour and air is very low.

(iii) Water absorption is very low.

(iv) They are relatively cheaper compared to other synthetic rubbers.

Disadvantages

(i) Slow decomposition takes place above 130°C.

(ii) Oil and solvent resistance is not very good.

SILICONE RUBBERS

Advantages

(i) Heat resistance (upto 250°C).

(ii)Extremely low absorption and permeability of water.

Excellent aging characteristics due to their saturated chemical structures. Poor tensile strength.

Disadvantage: They are very expensive.

NITRILE & CHLOROPRENE RUBBER

NITRILE RUBBER

Advantages:

(i) Oil resistant due to polar nitrile group.
(ii)Heat resistant.

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

CHLOROPRENE RUBBERS (NEOPRENE)

Advantages

(i) Due to the presence of -Cl group close to the double bond so the bond is resistant to oxidation.
(ii)This rubber is more polar hence oil resistant.
(iii) Heat stability is good (upto 150°C).
(iv) Water absorption and permeability are less than for natural rubbers.

Closure screening

400 ml product is taken in a Type-I glass container. Closures of 200 cm2 surface area washed with detergent, rinse with water followed by autoclaving at 121°C for 30 minutes and dried under vacuum. Closures are placed in the product container and exposed under room temperature and 35°C for 2 weeks with low rpm. Samples are examined weekly for pH, colour, clarity, particulate matter, potency and physical dimension of the closure.

Metals

TIN

Advantages:

(i) This metal is very resistant to chemical attack.

(ii) Readily coats a number of the metals e.g. tin-coated lead tubes combine the softness of lead with the inertness of tin and for this reason it was formerly used for packaging fluoride toothpaste.

Disadvantages:

Tin is the most expensive metal among tin, lead, aluminium and iron.

Uses:

(i) Tin containers are preferred for foods, like milk powder containers.

(ii) Currently, some eye ointment still packaged in pure tin ointment tubes.

Metals

ALUMINIUM

Advantages:

(i) Aluminium is a light metal- hence the shipment cost of the product is less.

(ii) The surface of aluminium reacts with atmospheric oxygen to form a thin, tough, coherent, transparent coating of oxide, of atomic thickness, which protects the metal from further oxidation.

Disadvantages: Any substance that reacts with the oxide coating can cause corrosion

Use:

(i) Aluminium ointment tubes.

(ii) Screw caps

(iii) Aluminium strips for strip-packaging of tablet, capsules etc. Some times internally lacquered aluminium containers are used to stop the reaction with the content.

Metals

IRON

Advantages:

Iron as such is not used for pharmaceutical packaging, large qualities of tin-coated steel, combines the strength of steel with the corrosion resistance of tin.

Disadvantages:

If an aqueous liquid can penetrate a pinhole of tin and the intense chemical reaction which results brings about rapid corrosion of underlying steel.

As a further measure the tin surface is lacquered.

Uses:

Fabrication of milk containers, screw caps and aerosol cans.

Metals

LEAD

Advantages:

(i) Lowest cost of all the metals used in pharmaceutical containers.

(ii) Soft metal.

Disadvantages:

Lead when taken internally there is risk of lead poisoning.

So lead containers and tubes should always have internal lining of inert metal or polymer.

Uses:

With lining lead tubes are used for such product as fluoride tooth paste.

Collapsible tube

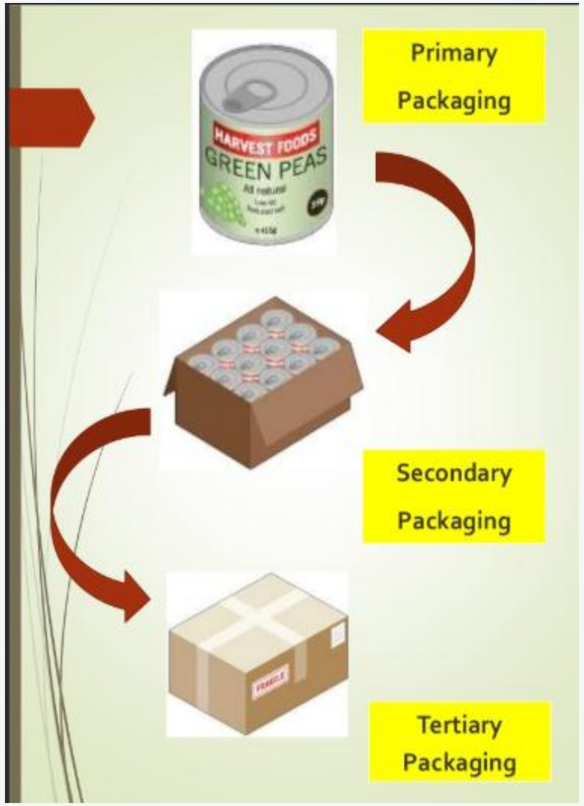
1. Metals: Tin (mostly used), aluminium, lead (for non-food products). Reactive metals are lined with resin or epoxy lining.
2. Plastic: Permeation is a problem associated with plastic. Reactivity and corrosiveness are the problems associated with metals. To avoid these problems lamination is done.

Blister packaging: Made by polyvinyl chloride and combination of polyvinyl chloride and polyethylene.

Strip packaging: Made by paper, polyethylene and aluminium.

Types of Packaging

1. Primary Packaging
2. Secondary packaging
3. Tertiary packaging



Primary Packaging

Primary packaging is the material that first envelops the product and hold it. The package is in direct contact with the contents.

Examples: ampoules, vials, containers, dosing dropper, closures, syringe, strip package, blister package.

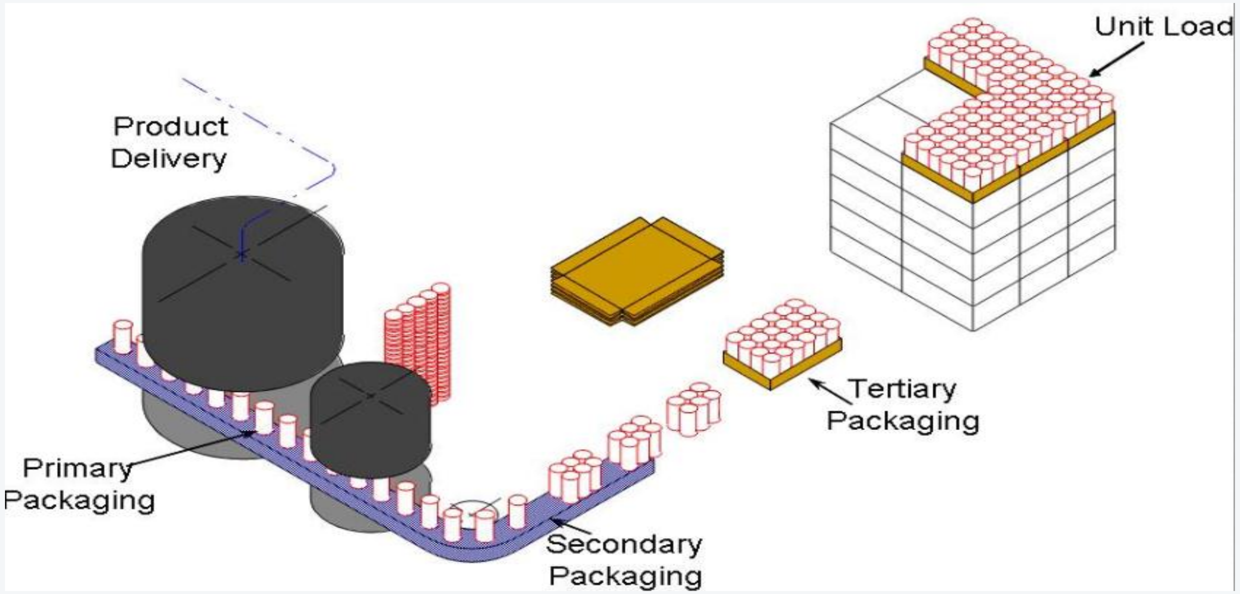
Secondary packaging

Secondary packaging is defined as the packaging outside the primary packaging.

Example: paper and boards, cartons, corrugated fibres

Tertiary packaging

Tertiary packaging is used for bulk handling, warehouse storage, transport and shipping.



PHARMACEUTICAL PACKAGES

1. CONTAINERS

The container is the device that holds the drug. The immediate container is that which is in direct contact with the drug at all times.

According to the method of closure and use, the containers are

(a) Well closed containers

A well closed container is used to protect the preparation from contamination by extraneous solids, to prevent the loss of contents during transport, storage and handling.

PHARMACEUTICAL PACKAGES

(b) Hermetically sealed containers

Hermetically sealed containers is that which does not allow the air and other gases to pass through it. e.g. glass ampoules are sealed by fusion.

(c) Light resistant containers

They are used to protect the drugs which undergo decomposition in the presence of light. Such drugs may be enclosed in amber coloured bottle or opaque container.

PHARMACEUTICAL PACKAGES

(d) Single dose container

They are used to supply only one dose of the medicament. e.g. ampoules.

(e) Multi dose container

A multidose container holds a number of doses e.g. multidose vials.

((f) Aerosol containers

Containers for aerosol must be strong enough to withstand the pressure evolved inside the container at the time of use of the preparation.

Classification of containers according to their shapes

1. Glass/polyethylene bottles.
    - (i) Narrow mouth
    - (ii) Wide mouth
2. Dropper bottles/ droptainers
3. Collapsible tubes
4. Ampoules
5. Vials
6. Polythene packets for i.v. fluid.
7. Polythene / glass bottle for i.v. fluids
8. Aerosol containers

1. Glass / Polyethene bottles

(i) wide mouthed bottles are used for containing solid dosage forms like powder, capsules, tablets. To absorb the moisture sometimes silica-gel bags are given inside the bottle.

(ii) For low viscosity liquids e.g. gargles, mouth washes, mixtures, elixirs narrow mouthed bottle is used. For high viscosity liquids or for suspensions wide-mouthed bottles are used.

(iii) Liquid preparations for external uses like lotion, liniments, paints etc. are supplied in coloured fluted bottles in order to distinguish them from preparations meant for internal use.

Containers

2. Dropper bottles or droptainers: Eye drops, ear drops, nasal drops etc. should be dispensed in amber color glass bottles fitted with a dropper. Now-a-days manufacturers prefer plastic droptainers. It is a single piece of squeezable container having an in built dropper.

3. Collapsible tubes: Ointments, pastes, gels are packed in plastic or metal tubes.

4. Ampoules: Ampoules are made of special type of neutral glass having low m.p. so that it can be heat sealed at low temperature.

Containers

5. Vials: Used for storing multidose injectable preparation. The needle is passed through the rubber closure, the drug is drawn out. The rubber plug automatically seals the hole. Thus contamination of bacteria is checked.

6. Polyethene packets for infusion fluid: These flexible bags or packets are made of PVC, polyethylene or polypropylene.

7. Glass bottles for i.v. fluids: Previously glass bottles with big rubber stoppers were used.

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CLOSURE AND CLOSURE LINERS

A closure is that part of a package which prevent the contents from escaping and allow no substance to enter the container. Closures are available in five basic designs:

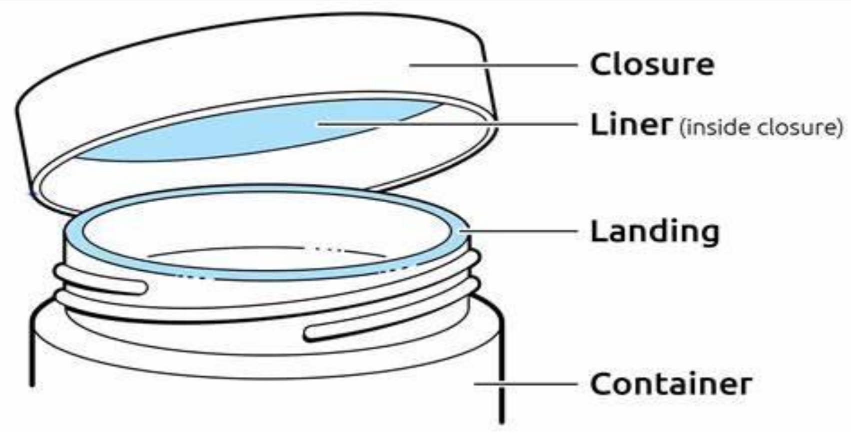
(1) Screw-on, threaded,

(2) Crimp-on (Crowns)

(3) Press-on (snap)

(4) Roll-on and

(5) Friction



Many variation of these basic types exist, including vacuum, tamper-proof, safety, child-resistant and linerless types and dispenser application.

CLOSURE AND CLOSURE LINERS

Threaded Srew Cap: When the screw-cap is placed on the neck of the container, its threads engage with the corresponding threads molded on the neck of the bottle.

A liner in the cap seals the opening of the container.

Screw-caps are commonly made of metals (tinplate or aluminium) and plastics (thermoplastics and thermosetting).

Lug-cap: It is similar to screw-cap in principle. It is simply an interrupted thread, instead of continuous thread.

This type of caps are widely used in food industry.

CLOSURE AND CLOSURE LINERS

Crown caps: This style of cap is commonly used as a crimped closure for beverage bottles.

Crown-caps are made of metals.

Roll-on closures: Roll-on closures are obtained as threadless shell.

This shells are placed on glass bottles having threaded neck.

The shell is placed and then pressed so that a thread is automatically formed.

CLOSURE AND CLOSURE LINERS

Pilfer-proof closures

It is similar to roll-on closures except that it has a greater skirt length.

This additional length extends below the threaded portion to form a bank, which is fastened to the basic cap of a series of narrow metal "bridges".

When the pilfer-proof closure is removed, the bridges break, and the bank remains in place on the neck of the container.

TAMPER RESISTANT PACKAGINGS

A tamper resistant package is provided with an indicator or barrier before entering the package, so that if this indicator or barrier is broken, the buyer immediately gets the evidence that the product has been opened or tampered.

The following packages are approved by FDA as tamper resistant packaging systems:

1. Film wrappers
2. Blister package
3. Strip package
4. Bubble pack
5. Shrink seals and bands
6. Foils, paper or plastic pouches
7. Bottle seals
8. Tape seals
9. Breakable caps
10. Sealed tubes
11. Aerosol containers
12. Sealed cartons.

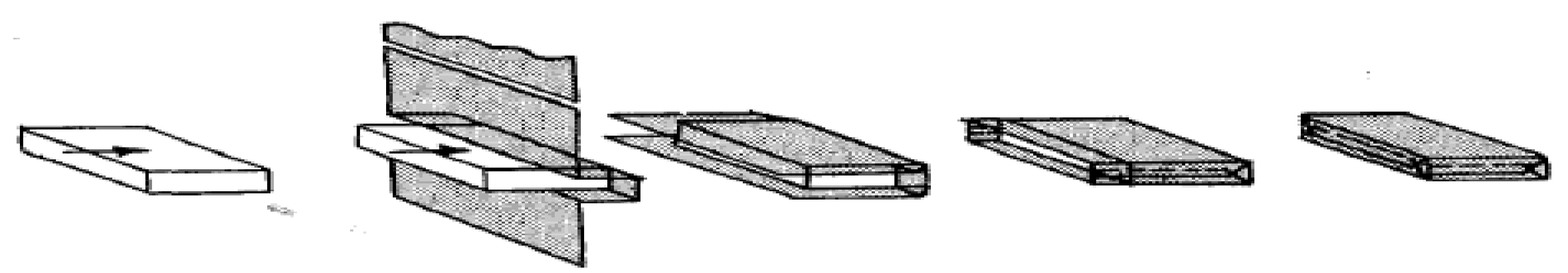
Film wrapper

(i) End-folded wrapper

This is formed by passing the product into a sheet of overwrapping film, which forms the film around the product and folds the edges in a gift-wrap fashion.

The folded areas are heat sealed by passing against a heated bar.

Materials: Cellophane coated in both side by heat sealable polyvinylidene chloride (PDVC) or nitrocellulose-PDVC provides durable moisture barrier.

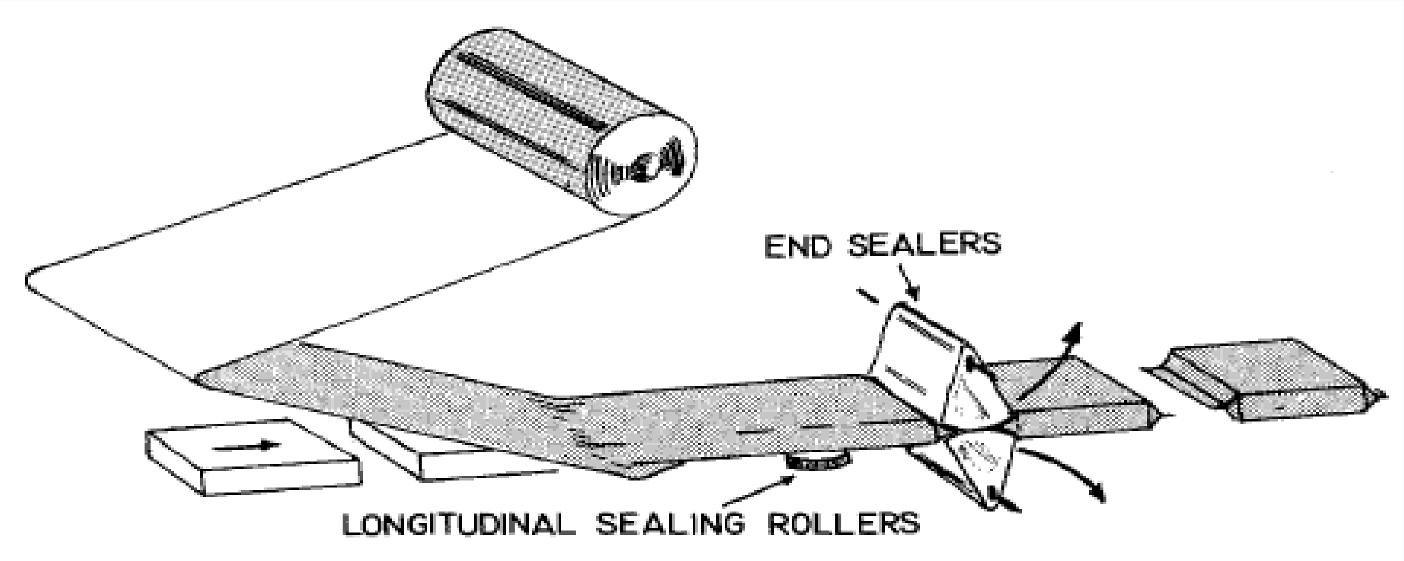


Film wrapper

(ii) Fin seal wrapper

The seals are formed by crimping the film together and sealing together the two inside surfaces of the film, producing a ‘fin’-seal.

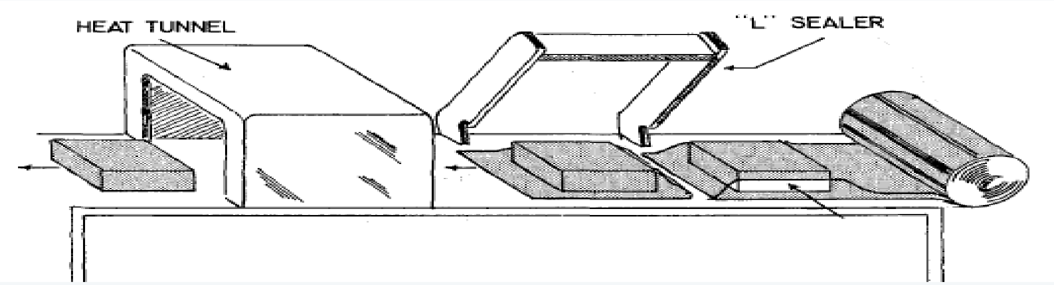
Materials: Polyethylene or Surlyn (Du Pont’s Ionomer resin)



Film wrapper

(iii) Shrink wrapper: In this type of packaging the product is packed within a thermoplastic film that has been stretched and oriented during its manufacture and that has the property of reverting back to its unstretched dimensions once the molecular structure is 'unfrozen' by application of heat. As the film unwinds on the over-wrapping machine, a pocket is formed in the center fold of the sheet, into which the product is inserted. An L-shaped sealer seals the remainder of the overwrap and trims off the excess film.

Materials: Heat shrinkable grades of polypropylene, polyethylene and polyvinylchloride (PVC).

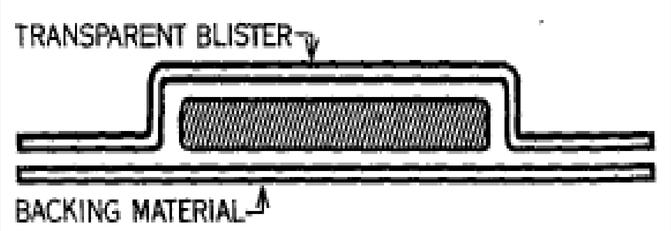


Blister package

The blister package is formed by heat-softening a sheet of thermoplastic resin and vacuum drawing the soften sheet into a contoured mold.

After cooling, the sheet is released from the mold and proceeds to the filling station of the packaging machine.

The semi-rigid blister previously formed is filled with product and lidded with a heat-sealable backing material.



Blister package

Materials

The blister is prepared from polyvinylchloride (PVC)

PVC / polyethylene combinations

polypropylene

polystyrene.

For commercial reason and for machine performance the blisters on most unit dose packages are made of PVC.

For moisture protection PVC may be laminated with polyvinylidene chloride (saran) or polychlorotrifluoroethylene (Aclar) films.

Under extremely humid condition Aclar coated PVC is preferred.

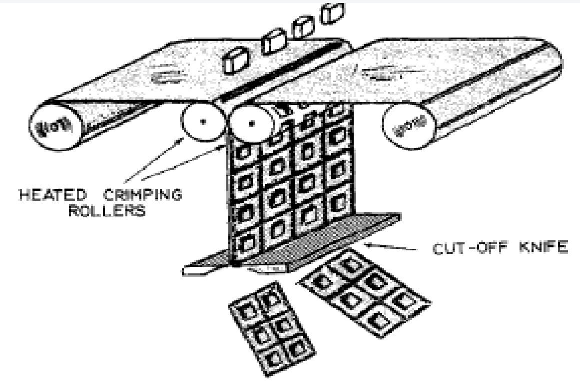
Strip package

A strip package is a form of unit dose packaging that is commonly used for package is formed by feeding two webs of a heat-sealable flexible film through either a heated crimping roller or a heated reciprocating plates.

The product is dropped into the pocket formed prior to forming the final set of seals.

A continuous strip is formed, generally several packets wide.

The strip packets are cut to the desired number of packets in length.



Strip package

The product usually has a seal around each tablet. The seal can be rectangular, or "picture-frame format" or can be contoured to the shape of the product.

Since the sealing is usually accomplished between pressure rollers, a high degree of seal integrity is possible.

Materials:

High barrier materials e.g. foil laminations, saran-coated films.

For higher barrier applications a paper/polyethylene/foil/polyethylene lamination is commonly used.

When product visibility is important a heat-sealable cellophane or polyester can be used.

Thank you