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PHB Education

PHARMACEUTICS

D. Pharm Exit Exam

Chapter -2

PACKAGING OF PHARMACEUTICAL DOSAGE FORMS

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DIPLOMA IN PHARMACY

5.4 PACKAGING OF PHARMACEUTICAL DOSAGE FORMS

PACKAGING OF PHARMACEUTICAL DOSAGE FORMS

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.

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 (e.g. aerial oxidation).

(e) *Particles* - protect from particulate contamination.

(f) *Microorganisms* - protect from microbial contamination.

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.

(e) *Abrasion* - this may create electrostatic effects.

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 shed particles into the contents.

(d) Must not leach anything to the contents.

4. Must have a pharmaceutically elegant appearance:

(a) In a competitive market the appearance of a package first draws the attraction of the consumers than its contents.

(b) Must be easy to label and thus to identify the product.

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 odours to the products,
4. They must be non-toxic,
5. They must be FDA (Food & Drug Administration) approved,
6. They must meet applicable tamper-resistance requirements
7. They must be adaptable to commonly employed high-speed packaging equipment. and
8. They must have reasonable cost in relation to the cost of the product.

PACKAGING MATERIALS

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

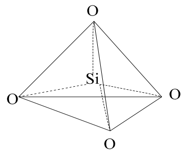
1. *Glass: -*	(i) Type-I	Borosilicate glass		
	(ii)Type-II	Treated sodalime glass		
	(iii)Type-III	Regular soda-lime glass		
	(iv)Type-NP	General purpose soda lime glass		
	(v)Coloured glass			
2. *Metals*	(i) Tin	(ii) Iron	(iii) Aluminium	(iv) Lead.
3. *Plastics*	(a) Thermosetting resins :		(i) Phenolics	
			(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

Preparation of 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 an 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.

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

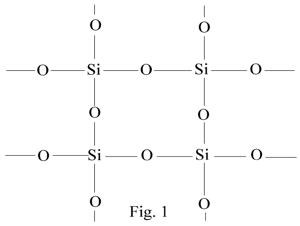


Fig. 1

<u>Properties</u>:

(a) It is very hard and

(b) chemically resistant but

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

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

(valency of Na = 1)

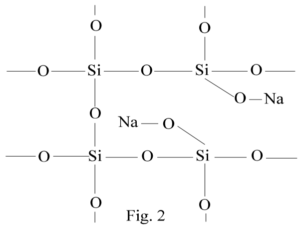
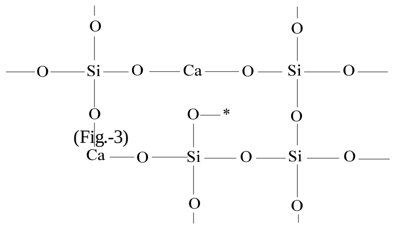


Fig. 2

<u>Properties</u>:

(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.-3)

* Connected to another Ca ion or tetrahedron

Fig. 3

(iii) Pure silica + CaO (or BaO, MgO, PbO and ZnO)

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

<u>Properties:</u>

(a) divalent oxides do not break the network of pure silica, but only push the tetrahedron apart. It is more rigid than soda-silica network.

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

(iv) Pure silica + Boric(B_2O_3) or aluminium oxide (Al_2O_3)

(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.

Type of glass	Main Constituents	Properties	Uses
Type-1 Borosilicate glass e.g. Pyrex, Borosil	SiO_2 – 80% B_2O_3 – 12 Al_2O_3 - 2% Na_2O+CaO - 6%	• Has high melting point so can withstand high temperature • Resistant to chemical substances • Reduced leaching action	• Laboratory glass apparatus • For injections and • 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 (500^0C) and moisture.	• The surface of the glass is fairly resistant to attack by water for a period of time. • Sulfur treatment neutralizes the alkaline oxides on the surface, thereby rendering the glass more chemically resistant.	• Used for alkali sensitive products • Infusion fluids, blood & plasma. • large volume container
Type-III Regular soda-lime glass	SiO_2 Na_2O CaO	• It contains high concentration of alkaline oxides and imparts alkalinity to aqueous substances • Flakes separate easily. • May crack due to sudden change of temperature.	• For all solid dosage forms (e.g. tablets, powders) • For oily injections • Not to be used for aqueous injection • Not to be used for alkali-sensitive drugs.
Type NP Non-parenteral glass or General purpose soda-lime glass.			• For oral and • Topical purpose • Not for ampoules.
Neutral Glass	SiO_2 – 72-75% B_2O_3 – 7-10% Al_2O_3 – 6% Na_2O – 6-8% K_2O – 0.5 – 2% BaO – 2-4%	• They are softer and can easily be moulded • Good resistance to autoclaving • Resistant to alkali-preparations (with pH upto 8) • Lower cost than borosilicate	• Small vials (<25 ml) • Large transfusion bottles
Neutral Tubing for Ampoules	SiO_2 – 67% B_2O_3 – 7.5% Al_2O_3 – 8.5% Na_2O – 8.7% K_2O – 4% CaO – 4% MgO – 0.3%	• In comparison to neutral glass its melting point is less. After filling the glass ampoules are sealed by fusion and therefore the glass must be easy to melt.	• Ampoules for injection.
Coloured glass	Glass + iron oxide	• Produce amber colour glass • Can resist radiation from 290 $\longleftrightarrow$ 400 $\longleftrightarrow$ 450nm UV Visible	• For photosensitive products.

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. Visually elegant containers attracts the patients.
4. Borosilicate (Type-I) and Neutral glasses are resistant to heat so they can be readily sterilised by heat.
5. Glass containers can be easily cleaned without any damage to its surface e.g. scratching or bruising.

Chemical aspect

6. Borosilicate type of glass is chemically inert. 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, if provided with proper closures
9. Photosensitive drugs may be saved from UV-rays by using amber colour glass.

Economical aspect

10. They are cheaper than other packaging materials.

Disadvantages:

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.
6. *Weathering*: Sometimes moisture is condensed on the surface of glass container which can extract some weakly bound alkali leaving behind a white deposit of alkali carbonate to remain over there, further condensation of moisture will lead to the formation of an alkaline solution which will dissolve some silica resulting in loss of brilliance from the surface of glass – called weathering.

To prevent weathering, the deposited white layer of alkali carbonates should be removed as early as possible by washing the containers with dilute solution of acid and then washing thoroughly with water.

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 are coated with tin.

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

ALUMINIUM

Advantages:

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

(ii) They provide attractiveness of tin at some what lower cost.

(iii) 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:

(i) Any substance that reacts with the oxide coating can cause corrosion e.g. products with the oxide coating can cause corrosion e.g. products of high or low pH, some complexing agents etc.

(ii) As a result of corrosion process H_2 may evolve.

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.

IRON

Advantages:

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

Disadvantages:

If an aqueous liquid can penetrate a pinhole or other fault in the layer of tin, which is virtually a short-circuited galvanic cell is set up 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.

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.

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 100^0C. Nevertheless, 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 but are often attacked by organic 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 vapour and some are permeable to gases like oxygen, carbon-di-oxide.

TYPE OF PLASTICS

Plastics are classified into two groups according to their behaviour when heated:

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 multipolymers, polyethylene terephthalate etc.

2. Thermosetting type

When heated, they may become flexible but they do not become liquid; usually their shape is retained right upto the temperature of decomposition. 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.

GLASS TRANSITION TEMPERATURE (T_g)

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 (T_g) thermoplastics soften and melt if heated to a considerably higher temperature than T_g. Other plastics are very highly cross-linked and for these thermosetting plastics T_g 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. Plastics may be used directly to form the finished article, it is usual to add other substances for improved stability, or in-use performance.

(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.

(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: whiting, asbestos and mica.

(v) Plasticizers are used to reduce T_g 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.

PLASTIC MATERIALS

MATERIAL	ADVANTAGES	DISADVANTAGES	TYPICAL USES
High density polyethylene (HDPE) $\rho = 0.955$ g/cc	Inert, low cost, low water vapour transmission, tough.	Semi-opaque, transfer of taste ingredients, absorb dilute solutions.	Detergents, bleaches, milk, foods, cleansing powders, drugs & cosmetics.
Low density polyethylene (LDPE) $\rho = 0.920$ g/cc.	Squeeze property, inertness, low cost.	Relatively poor barrier to non-polar molecules and high water vapour transmission.	Cosmetics, personal products, foods.
Polystyrene $\rho = 1.05$ g/cc.	Clarity, stiffness, low cost.	High water vapor transmission, susceptibility to cracking, poor impact.	Dry drugs, petroleum jelly.
Rigid polyvinylchloride (PVC) $\rho = 1.35$ g/cc.	Clarity, stiffness, O_2-barrier, retention of non-polar molecules.	10-12 additives may be present, difficult to process, susceptible to organic solvent.	Shampoo, bath oil, detergent.
Polypropylene $\rho = 0.90$ g/cc.	Inert, low cost.	Low temperature brittleness, high concentration of stabilizer is present.	Drugs, cosmetics, syrups, juices.
Polyamide (Nylon6,10) $\rho = = 1.10$ g/cc.	Good barrier for non-polar molecules, tough, good O_2-barrier, sterilizable.	High cost, water absorption	Foods, drugs, cosmetics, aerosols
Polycarbonate $\rho = 1.20$ g/cc.	Very tough, clear, sterilizable	Cost, susceptibility to solvent cracking, poor barrier for water and O_2.	Drugs, cosmetics.
Acrylic polymers (PMMA =Polymethyl methacrylate) $\rho = 1.10$ g/cc.	Clarity, good for oils	Poor water vapor transmission, poor barrier for O_2.	Drug cosmetics.
Polyethylene terephthlate (PET)	Excellent strength, good barrier for gas and aroma.		Bottle for carbonated waters, mineral waters, mouth washes, cosmetics.

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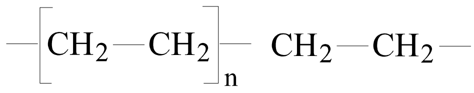
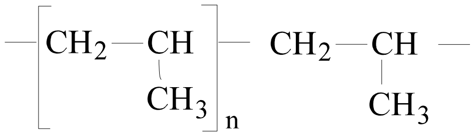
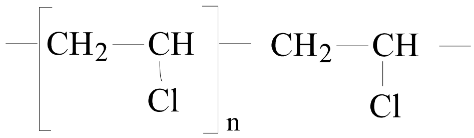
Structures of some common plastics



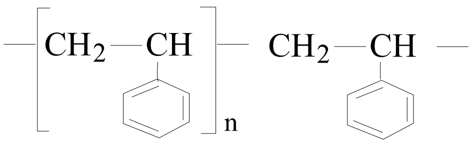
Polyethylene ($T_g = -120^0C$)



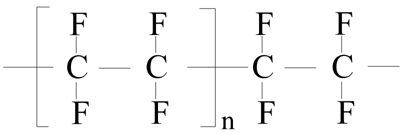
Polypropylene ($T_g = -27^0C$)



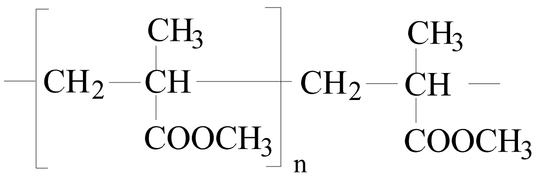
Polyvinylchloride ,PVC ($T_g = 80^0C$)



Polystyrene ($T_g = 100^0C$)

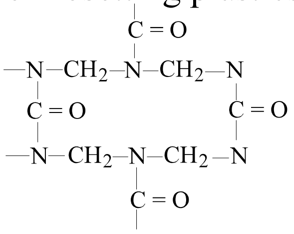


Polytetrafluroethylene ($T_g = 126^0C$)

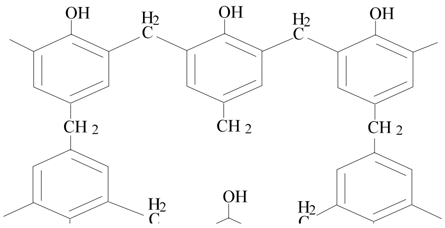


Polymethylmethacrylate, PMMA ($T_g = 110^0C$)

Thermosetting plastics



Urea formaldehyde



Phenol formaldehyde

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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.

1. PERMEATION

The transmission of gases, vapours or liquids through plastic packaging materials can have an adverse effect on the shelf-life of a drug.

(i) Permeation of water vapor and O_2 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. Nylons are hydrophilic in nature, and are poor barrier for water while hydrophobic materials as polyethylene provide much better barriers.

(ii) 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. Often, the aroma of cosmetic products become objectionable and the taste of medicinal products changes.

(iii) 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.

2. LEACHING

Additives those are added in the plastics may 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.

3. 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.

4. CHEMICAL REACTIVITY

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.

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 vapours from the environment or by loss of content through the container walls.

(i) 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.

RUBBER

Natural rubber consists of long chain polymers of isoprene units linked together in the *cis*-position. Its most important source is the tree *Hevea braziliensis* from which a latex, containing 30 to 40% of rubber in colloidal suspension, exudes when shallow cuts are made in the bark.

- **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.

(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.

Physical and chemical properties of rubber are altered by the addition of some additives, such as:

1. **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 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 150^0C.

(ii) Cold curing:

Rubber is treated in the cold with sulfur monochloride as a vapour 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.

2. **Accelerators**

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

e.g. 2-mercapto benzthiazol (MBT)

tetra methyl thiuram disulphide (TMT) [S is not required]

zinc dimethyl dithiocarbamate [vulcanize with s at room temperature]

3. **Activators**

These are used to increase the activity of accelerators

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

zinc oxide for TMT.

4. **Fillers**

Two classes of fillers are added to rubber.

<u>Reinforcing fibres</u> are used to improve physical properties.

e.g. carbon black (very finely divided carbon)

zinc oxide, magnesium carbonate and calcium carbonate.

<u>Extending fillers</u> are added mainly as diluents to reduce cost and partly to facilitate manufacture.

e.g. talc and asbestos.

5. **Softeners**

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

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

6. **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.

7. **Pigments**

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

Coal tars dyes.

8/ **Lubricants**

To assist the removal of rubber products from the mould

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

1. BUTYL RUBBER

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

Advantages:-

(i) After vulcanization butyl rubber possesses virtually no double bond, consequently 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 130^0C.

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

2. NITRILE RUBBER

Advantages:

(i) Oil resistant due to polar nitrile group.

(ii) Heat resistant.

Disadvantage

Absorption of bactericide and leaching of extractives are considerable.

3. CHLOROPRENE RUBBERS (NEOPRENE)

these are polymers of 1:4 chloprene.

Advantages

(i) Due to the presence of –Cl group close to the double bond so the bond is resistant to oxidation hence these rubbers age well.

(ii) This rubber is more polar hence oil resistant.

(iii) Heat stability is good (upto 150^0C).

(iv) Water absorption and permeability are less than for natural rubbers.

4. SILICONE RUBBERS

Advantages

(i) Heat resistance (upto 2500C).

(ii) Extremely low absorption and permeability of water.

(iii) Excellent aging characteristics due to their saturated chemical structures.

(iv) Poor tensile strength.

Disadvantages

They are very expensive.

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 of following types;-

(a) <u>Well closed containers</u>:

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.

(b) <u>Air tight container:</u>

Air tight containers are used to protect the container from atmospheric contamination of liquids, solids or vapors. They prevent loss of drugs due to efflorescence, deliquescence or evaporation or oxidation.

(c) <u>Hermetically sealed containers:</u>

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.

(d) <u>Light resistant containers:</u>

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.

(e) <u>Single dose container:</u>

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

(f) <u>Multi dose container:</u>

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

(g) <u>Aerosol containers</u>

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.

2. **Dropper bottles or droptainers:**

Eye drops, ear drops, nasal drops etc. should be dispensed in amber colour glass bottles fitted with a dropper.

Now-a-days manufacturers prefer plastic droptainers. It is a single piece of squeezeable 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.

5. **Vials**

Used for storing multidose indictable 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.

8. **Aerosol containers:**

Gases are made liquid under high pressure. so this type of containers should ensure that pressure.

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 or lug,

(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.

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). Metal caps are usually coated on the inside with an enamel or lacquer for resistance against corrosion.

Lug-cap:

It is similar to screw-cap in principle. It is simply an interrupted thread on the glass Finnish, instead of continuous thread.

It requires only a quarter turn.

Uses: It is used for both normal atmospheric pressure and vacuum-pressure closing. This type of caps are widely used in food industry.

Crown caps:

This style of cap is commonly used as a crimped closure for beverage bottles and remains unchanged for more than 50 years. 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. Roll-on type of closures are extremely suitable for glass-containers, since these closures allow for dimensional changes in the glass container.

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.

Non-reusable Roll-on Closures:

In some packaging applications a reusable cap is not desired. Vials for ophthalmic products are good example of this type. The aluminium roll-on closures have to be torn-off the tabs.

CLOSURE LINERS

a liner may be defined as any material that is inserted in a cap to effect a seal between the closure and the container.

Factors in selecting a liner:

(i) Chemical inertness – should be chemically inert

(ii) Appearance, thickness etc.

(iii) Gas and water-vapour transmission rates – should be low.

(iv) Torque require to remove the cap – should be optimum.

(v) heat resistance – e.g. during autoclaving should be thermostable.

(vi) Shelf-life – should not change their shape during storage.

(vii)Economics – should be cheap.

Liners are classified into two types:

(a) Homogeneous liner:

These are one-piece liner available either as a disk or as a ring.

they are widely used for pharmaceuticals because their properties are uniform and can withstand high-temperature sterilization.

(b) Heterogeneous or Composite liners:

These are composed of layers of different materials chosen for specific requirements, In general the composite liner consists of two parts: a facing and a backing.

Usually, the facing is in contact with the product, and the backing provides the cushioning and sealing properties required.

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. Especially over the counter products require tamper resistant packaging.

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:

Film wrapper can be categorized into:

(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.

Polypropylene coated with heat sealable acrylic coating or polypropylene is added with heat sealable modifiers.

(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.

In this case heated bars never comes in contact with the package, hence much greater and more consistent sealing pressure can be applied and consequently better sealing integrity can be accomplished.

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

(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)*.

(iv) 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.

The backing material may be of two types:

(i) a push-through type or (ii) peelable type.

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.

For *push through type backing material* aluminium foil coated with heat sealable coating is used.

For *peelable type backing material* polyester or paper is used as a component of the backing lamination. this peelable type backing material is tamper proof and child resistant.

(v) 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.

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.

(vi) Aerosol containers

The aerosol container used for pharmaceutical products is usually made of drawn aluminium. The inside of the container can be specially coated if product compatibility is a problem. A hydrocarbon propellant in its cooled liquid phase is added to the container along with the product, and a spray nozzle contained in a gasketed metal ferrule is crimped over the opening of the aerosol container. A length of polyethylene tube, called a dip-tube, is attached to the inside of the spray nozzle and dips into the product, drawing product into the spray nozzle when the sprayer is activated.

The spray nozzles are usually metered to allow a specific dose to be dispersed with each spray.

N.B. For all other tamper resistant packagings see Liberman, Lachman, *The Theory & Practice of Industrial Pharmacy*, pp. 728-731.

EVALUATION OF PACKAGING MATERIALS

A. TEST FOR HYDROLYTIC RESISTANCE (LIMIT OF ALKALINITY)

Because none of the glasses used for pharmaceutical containers is completely free from extractable alkali a test for its absence is impractical and limit tests must be used:

1. **Crushed glass test**

This test is done on all types of glass containers except surface treated glass (i.e. Type-II, sulfured or siliconed surface). The container is crushed and sieved to produce uniform particle size of which a definite weight is taken. Control of particle size and weight of powder ensures that a constant surface area is exposed to the solution.

The measured amount of glass powder is then taken in a resistant glass beaker, measured amount of distilled water was added, autoclaved for 1/2 an hour at 121^0C. The water was then cooled and filtered. Filtrate is titrated with standard H_2SO_4.

2. Whole container test

In case of surface treated glass container the intact container is taken, filled with distilled water and exposed to the autoclaving condition. The extracts from several containers are pooled and titrated with standard HCl (according to I.P.)

Type	Description	Test used	Size (ml)	**Limits** Volume of 0.05 N H_2SO_4 to neutralize the extract from 10g of glass (ml)
I	Highly resistant Borosilicate glass	Crushed glass	All	1.0
II	Treated soda lime glass	Whole container	100 or less	0.7
			Over 100	0.2
III	Soda -lime glass	Crushed	All	8.5

N.P.	General purpose soda-lime glass	glass Crushed glass	All	15.0

B. METAL CONTAINERS FOR EYE OINTMENTS (IP 66)

Metal collapsible tubes comply with the following test for metal particles. According to IP 50 empty tubes are taken, filled with ointment base, sealed and kept and kept overnight.

a metal bacteriological filter assembly fitted with a suitable filter paper and heated to the melting range of the ointment base.

Ointment bases from all the tubes squeezed at a certain rate, pooled and passed through the heated filter under vacuum. The filter paper is washed with chloroform.

The filter paper is dried and observed with magnifying glass under oblique light. The observations are noted as follows:

Particles 1 mm and above	50
Particles 0.5 mm to 1 mm	10
Particles 0.2 mm to 0.5 mm	2
Particles less than 0.2 mm	Nil
Total score	62

The lot of tube passes the test if the total score is less than 100 points. If the score is above 150, the lot fails. If it is between 100 and 150 the test is repeated again with 50 more tubes. This time the lot will pass if total 100 tubes gives 150 points.

C. PLASTIC CONTAINERS

(i) Leakage test

Ten containers are filled with water, fitted with the closures and are kept inverted at room temperature for 24 hours. There should be no signs of leakage from any container.

(ii) Collapsibility test

This test is applicable to containers which are to be squeezed in order to remove the contents. a container, by collapsing inwards during use, yield at least 90% of its nominal contents at the required rate of flow at ambient temperature.

(iii) Transparency test

A 16-fold dilution of a standard suspension described in IP96 is prepared so as to give an absorbance at about 640 nm of 0.37 to 0.43.

Five empty containers were filled to their nominal capacity suspension in each container is detectable when viewed through the containers, as compared with a container of the same type filled with water.

(iv) Water vapour permeability test

Five containers are filled with nominal volume of water and heat sealed with aluminium foil-polyethylene laminate or other suitable seal. Each container is accurately weighed and allowed to stand for 14 days at a relative humidity of 60 ± 5% and a temperature between 20 to 25^{0}C.

After 14 days it is weighed again. The loss in weight in each container is not more than 0.2%.

Other tests include:

*Tests for Barium, heavy metals, tin, zinc, etc.

*Test on extracts:

Specified volume of extracting medium is taken in it. Plastic of specified surface area is cut and extracted. With the extract following tests are carried out:

(i) appearance of the extract - must be colourless.

(ii) Light absorption

(iii) Non-volatile matter.

(iv) Residue on ignition.

(v) Heavy metals

(vi) Buffering capacity

(vii) Oxidisable substances.

Multiple Choice Questions:

Definition and Classification:

1. _______________ is the science, art and technology of enclosing or protecting products for distribution, storage, sale, and use.

A. Tablet

B. Packaging

C. Size Reduction

D. Size Separation

2. Which is/are the type of packaging:

A. Primary Packaging

B. Secondary Packaging

C. Tertiary Packaging

D. All of the above

3. The container used to protect the product from contamination and as well as from loss of contents during use are called:

A. Well-closed containers

B. Air tight containers

C. Light-resistant container

D. Multiple dose container

4. Which of the following materials are used in pharmaceutical packaging?

A. Glass

B. Plastic

C. Metal

D. All of the above

5. Type III glass is also known as:

A. Soda-lime glass

B. General purpose soda-lime glass

C. Borosilicate glass

D. Treated Soda Lime glass

6. Type-1 glass is also known as:

A. Borosilicate glass

B. Regular soda-lime glass

C. Treated soda-lime glass

D. None of the above.

7. Regular Soda-Lime Glass is:

A. Cost-Effective

B. Type-III

C. Type-II

D. Type-I

8. Borosilicate Glass is:

A. Type-IV

B. Type-III

C. Type-II

D. Type-I

9. Treated Soda-Lime Glass is:

A. Type-IV

B. Type-III

C. Type-II

D. Type-I

10. The ideal requirement for packaging is:

A. Toxic

B. FDA approved

C. Reactive with the product

D. Cause of product degradation

11. Which type of glass is suitable for non-aqueous preparations for parenteral use?

A. Type-IV

B. Type-III

C. Type-II

D. Type-I

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

A. Glass

B. Plastic

C. Metal

D. Rubber

13. Which element is/are used for metal container?

A. Tin

B. Aluminium

C. Lead

D. Iron

E. All of the above

14. Which is the thermosetting type plastic?

A. Phenol-formaldehyde

B. Urea formaldehyde

C. Melamine formaldehyde

D. All of the above

Composition of Packaging Materials:

1. Composition of glass is:

A. Sand

B. Soda ash

C. Lime stone & cullet

D. All of the above

2. Plastic containers are generally made from the following material:

A. Polyethylene

B. Polypropylene

C. Polystyrene

D. All of the above

3. Which of the following is used as Vulcanizing agent in the manufacture of rubber closure?

A. Sulphur

B. Activated carbon black

C. Talc

D. Stearic acid

4. The package composed of a base layer having cavities that hold the pharmaceutical product and a lid is called:

A. Strip Package

B. Child resistant package

C. Blister Package

D. Well closed package

5. Soda ash is also known as:

A. Pure silica

B. Sodium carbonate

C. Lime Stone

D. Calcium carbonate

6. Type – I glass consist of:

A. SiO_2 - 80%

B. B_2O_3 - 12

C. Al_2O_3 - 2%

D. Na_2O+CaO - 6%

E. All of the above

7. Which additive used in manufacturing of plastics?

A. Antioxidant

B. Plasticizers

C. Pigments

D. All of the above

Manufacturing Methods:

1. Which of the following methods are used in the production of glass:

A. Blowing

B. Drawing

C. Pressing & casting

D. All of the above

Properties of Packaging Materials:

1. To protect the contents of a bottle from the effects of sunlight by UV rays, which glass is used?

A. Amber Coloured glass

B. Red-coloured glass

C. Both of the above

D. All of the above

2. The Function of packaging is:

A. Target identification

B. Target validation

C. Product Identification

D. Optimization

3. Which type of glass shows, high hydrolytic resistance, suitable for most preparations, not for parenteral use.

A. Type-IV

B. Type-III

C. Type-II

D. Type-I

4. Which type of glasses are resistant to heat so they can be readily sterilized by heat.

A. Type-IV

B. Type-III

C. Type-II

D. Type-I

5. Which metallic container is most expensive?

A. Tin

B. Aluminium

C. Lead

D. Iron

E. All of the above

6. Which containers are preferred for foods, like milk powder containers are coated with tin?

A. Tin

B. Aluminium

C. Iron

D. All of the above

7. Metal is used for inner lining of tubes which are used for such product as fluoride tooth paste?

A. Tin

B. Aluminium

C. Lead

D. Iron

8. Thermoplastic on heating, they soften to a viscous fluid which hardens again on cooling. Example is/ are:

A. Polyethylene

B. Polypropylene, polyvinylchloride

C. Nylon (polyamide)

D. All of the above

9. Chemical used for manufacturing, carbonated waters Bottle, mineral waters Bottle, mouth washes, cosmetics.

A. Polyethylene terephthlate (PET)

B. Poly ethylene

C. Rigid polyvinylchloride (PVC)

D. All of the above

10.Which packaging material used for collapsible tubes?

A. Glass

B. Plastic

C. Rubber

D. Metal

Advantages of packaging materials:

1. The advantages of plastic containers over glass containers are:

A. Easy formation

B. Resistance to breakage

C. Freedom of design

D. All of the above

2. Which of the following packaging material is protect the drug content against the light?

A. Plastic containers

B. Amber coloured glass containers

C. Both of the above

D. None of the above

3. Which packaging material shows have good protection for powder because powder very sensitive against the moisture and Temperature.

A. Glass

B. Plastic

C. Metal

D. All of the above

4. Which is the lowest cost metal used in packaging material?

A. Tin

B. Aluminium

C. Lead

D. Iron

Disadvantages of packaging materials:

1. Major disadvantages of glass as a packaging material are:

A. Fragility

B. Weight

C. Both of the above

D. None of the above

Evaluation of packaging materials:

1. The test for packaging is:

A. Drop test

B. Vibration test

C. Shock test:

D. All of these

2. Method used for plastic container evaluation:

A. Permeation

B. Leaching

C. Sorption

D. Chemical reaction

E. All of the above

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