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A REVIEW ON PHARMACEUTICAL CONTAINERS AND CLOSURES

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Abstract:

All dispensed medicinal products will need to be dispensed to the patient in a suitable product container. The function of a container for a medicinal product is to maintain the quality, safety and stability of its contents. Although different pharmaceutical preparations will be packaged in different containers depending on the product type, pharmaceutical packaging can largely be grouped. It is device used for providing protection, presentation, identification, information and convenience for pharmaceuticals product from the moment of production until it is used or administered. Drugs need more care in their packaging than do most other product, because any failure in their packing could result in changes in the drug that lead either to a failure to cure, to illness, to injury or even cause death of patient. It should protect the drug product from physical and chemical damage, and also give protection from mechanical and climatic hazards and microbial contamination. It should provide maximum possible information related to the dosage form, provide special precautions specified for different under schedules. Its area not only helps in creation of wealth, preserving product quality, but also lengthens the shelf life of products. This review provides maximum possible information regarding the materials, additives, tests used for manufacturing of containers and closures.

Keywords: *Containers & closures, Additives, Types, Problems & Tests.*

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INTRODUCTION:

Container

A Pharmaceutical container is a device that holds the drug and may be in direct contact with product. If the container is in direct contact with the drugs it is called an immediate container. (or) It is a device which holds the drug (or) the drug product either directly (or) in a indirect form. In some of the containers product may not be in direct contact with i.e.Each unit is packed in a sachet and all of them are stored in containers. Ampoules packed in a container [1].

Closures

It is a device which protects the drug (or) drug product by preventing the entry of air, moisture, particulate matter, and microorganisms etc., thereby keeping the product in a safe condition and also assists in proper use & of the drug.

Desirable Features of Containers and closures

1. The container must be rigid enough to prevent damage to the contents.eg;-fracture of tablets and crushing of capsules.
2. The materials of construction must not react with contents.
3. The closures must prevent-

A. Loss of moisture.eg:-to moisture-sensitive tablets and, because their shells are hygroscopic to capsules.

B.Loss of moisture from creams and from water-containing ointments and creams.

C.unintentional escape of the content, and

D.Entry of direct (or) other contaminants such as odorous vapors that might cause

4. The closure must be easily removed and replaced
5. It must not be difficult to abstract the content (or) empty the container completely.
6. For many products, proctection from light must be given.
7. It must be easily to label the container correctly.
8. It must have a pharmaceutical-elegant appearance.
9. They should be inert and should not interact with the drug product.
10. They should have uniform distribution of the product for easy usage and handling.
11. They must be available in form by which they are suitable for a dosage form.eg:-ear drops, nasal drops.
12. They should be able to protect the drug from environment hazards.
13. They should be made in such a way that they have to resist/withstand stocks and abrasions while they are under handling and transport.
14. Containers, used for parental products should be to withstand high sterilization conditions (temperature pressure).
15. The containers used for pharmaceutical purposes should be available in a highly economic rate.
16. Containers used for aerosol packing should be able withstand high pressures.
17. Containers should be available in different size and shapes for easy identification by the patients.

PHARMACEUTICAL PACKAGING:

Packaging is defined as the collection of different components which surrounds the pharmaceutical product from the time of production until its use [2-3].

Types of pharmaceutical packaging

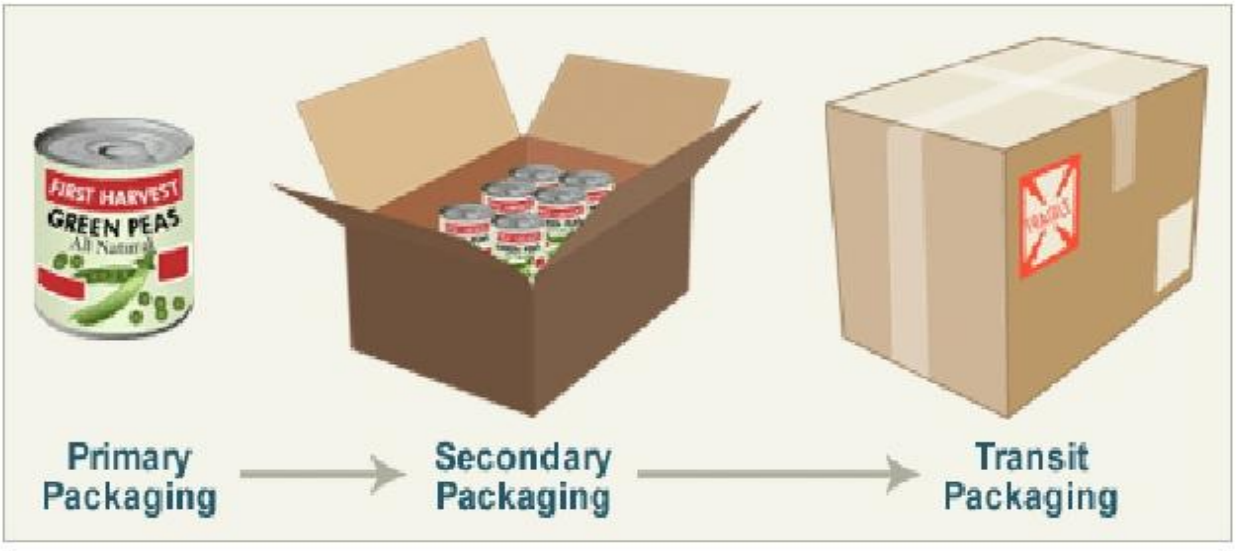

Fig: 1 Types of packing's

Primary Packaging: This is the first packaging envelope which is in touch with the dosage form or equipment. The packaging needs to be such that there is no interaction with the drug and will provide proper containment of pharmaceuticals.
Examples: Blister packages, Strip packages, etc.

Secondary Packaging: This is consecutive covering or package which stores pharmaceuticals packages in it for their grouping.
Examples: Cartons, boxes, etc.

Tertiary packaging: This is to provide bulk handling and shipping of pharmaceuticals from one place to another.
Examples: Containers, barrels, etc.

With respect to method of closure, the B.P.C defines four **types of containers.**

- Well closed container.
- Air tight container.
- Securely-closed container.
- Hermetically-sealed.

WELL -CLOSED CONTAINER:
This container protects the contents from contamination with extraneous solids under normal conditions of handling, storage and transport, prevents unintentional release of the contents [4].

Example antacid suspensions, syrup, elixirs, closure can be detached many times used for with draw of multiple dosage forms.

Airtight container
This container gives protection from extraneous solids, liquids and vapors under normal conditions of handling, storage and transport, prevents changes due to efflorescence, deliquescence and evaporation.

Securely-Closed Container
This is an airtight container with a means of preventing unintentional displacement of the closures.

Example: Eye drops, Eardrops, Multidose voils. In this case, if tip of closure is opened it should be used with in a specific period of time .other should be discarded.

Hermetically-sealed container
This container is impervious to air and other gases under normal conditions of handling, storage and transport.

Example: Glass Ampoule sealed by infusion.

MATERIALS FOR CONSTRUCTION OF CONTAINERS AND CLOSURES:
Different kinds of materials used for the manufacture of containers closures are-Glass, Plastic, Metal (for containers mostly) & Rubber (exclusively used for closures).

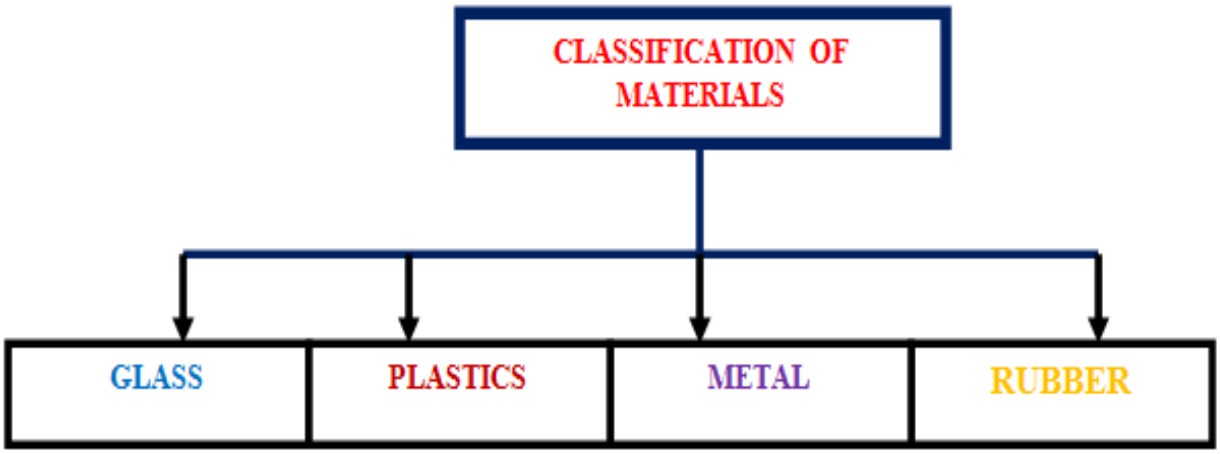

Fig 2: Classifications of Materials

1.Glass

For the post 4 decades glass is used most widely used .due to problems arising now-a-days we used plastic .however 50-60% of products are stored in glass containers. Glass ensures .inertness, visiblity, strength, rigidity, moisture protection, ease in filling .durability, convenience in cleaning and economy.moulded bottles are commonly used in pharmaceutical industry.

Fig 3 : Types of Glass

Advantages

1. They protect the drug (or) drug product from environment hazards.
2. They improve stability of product by starting them in glass container.
3. They are prepared by molding process.
5. Some of the drugs are highly sensitive to light can be protected by using different kinds of colored glasses

Examples: Amber colored, Green colored.

DISADVANTAGES

1. They are highly fragile in nature.
2. They undergo leaching process (glass may contain alkalis which may get leached in to drug).
3.They undergo weathering process/clouding process(due to exposure to adverse climatic conditions, If moisture gets sticked to glass surface .It takes away alkali .if further condensation occurs dull form of the container can be observed.
4. If undergoes flaking process (if strength of glass. is decreased, blanking of the particles from the glass occurs).

Table: 1 Types of Dosage forms and containers [5-6]

SNO	PREPARATION	CONTAINER	IMPORTANT AUXILIARY LABELS	SUGGESTED DISCARD DATE
1	Capsules	Amber tablet bottle with CRC	See BNF for advisory labels recommended for active ingredient	3 months
2	Creams & Gels	Amber glass jar and collapsible metal tube	For external use only	4 weeks
3	Dusting powders	Plastic jar preferably with a perforated, reclosable lid	For external use only not to open wounds or raw weeping surfaces Store in a dry place	3 months
4	Ear Drops	Hexagonal amber fl uted glass bottle with a rubber teat and dropper closure	For external use only	4 weeks
5	Elixirs	Plain amber medicine bottle with CRC		4 weeks
6	Emulsions	Plain amber medicine bottle with CRC	Shake well before use	4 weeks
7	Enemas	Amber fl uted bottle with CRC	For rectal use only	4 weeks
8	Gargle & Mouth washes	Amber fluted bottle with CRC	Not to be taken Do not swallow in large amounts	4 weeks
9	Inhalations	Amber fl uted bottle with CRC	Not to be taken Shake the bottle	*4 weeks
10	Linctuses	Plain amber medicine bottle with CRC		4 weeks
11	Liniments and Lotions	Amber fluted bottle with CRC	For external use only Shake the bottle Avoid broken skin	4 weeks

Continue…….

12	Mixtures and Suspensions	Plain amber medicine bottle with CRC	Shake the bottle	4 weeks
13	Nasal Drops	Hexagonal amber fluted glass bottle within rubber teat and dropper closure	Not to be taken	4 weeks
14	Ointments	Amber glass jar	For external use only	3 months
15	pastes	Amber glass jar	For external use only	3 months
16	Pessaries	Wrapped in foil and packed in an amber glass jar	For vaginal use only	*3 months
17	Powders (individual)	Wrapped in powder papers and packed in a cardboard carton	Store in a dry place Dissolve or mix with water before taking See BNF for advisory labels recommended for active ingredient	3 months
18	Suppositories	Wrapped in foil and packed in a amber glass jar	For rectal use only See BNF for advisory labels recommended for active ingredient	3 months

- BNF – British National Formulary; CRC – Child Resistant Closure

Fig 4: Amber Colored Bottle

Fig 5: Amber Fluted Bottle

Different kinds of glass are commercially available are

a) Soda lime glass.
b) Borosilicate glass.
c) Neutral glass.
d) Sulfurated/treated soda lime glass.
e) Neutral tubing for Ampoules
f) Coated soda lime glass.
g) Lead free glass.
h) Silicone-treated containers.

a) Soda-Lime Glass

Soda lime glass are used for glass media bottles and many other commercial purposes, contain approximately 75%sio2,15%Na2o and 10%cao and with small amounts of H2O,Mgo,Al2o3.The aluminum oxide improves mechanical strength or chemical durability and makes melting easier. it is prepared by silica or silicon dioxide with calcium (or) sodium oxides. Which are fused to get uniform mass and molded.

Disadvantages

It undergoes leaching process due to presence of huge amount of alkalis.

b) Borosilicate Glass

Borosilicate glass (or) resistance glass is mainly for chemical glassware, ovenware and containers for alkali sensitive preparations. In this aluminum oxide usually present and silica content is slightly increases .The approximate composition of borosilicate glass is

80%sio2,12%B2o372Al2o3,6Na2o+cao+other oxides. It is prepared by using silica &silicon dioxide with boron oxides .In this country, because of the development of neutral glass, borosilicate is not widely used for Injection containers, but some antibiotic vials are made from it. Less alkaline in nature [7].

Advantages

1. Never undergo leaching process.
2. Widely used in pharmaceutical operation.

Disadvantages they are expensive.

1. They are difficult to melt & mould.

Uses

1. Aqueous injectables of any PH
2. Solution, suspension, emulsion and semisolid type
3. Blood and related products

c) Neutral-Glass

It is prepared by using silicon (or) sio2 with combination of both ca(or)Na oxides and boron oxide. The typical composition is 72-75%of sio2,7-10%B2o3.4-6%Al2o3,6-8%Na2o,0.5-2%K2o 2-4%Bao.They have good resistance to autoclaving, weathering and the solutions of pH-8 and also resistance to alkali alkaline preparations.

Advantages

1. Never undergo leaching process.

Disadvantages

2. Very soft, don't undergo shocks abrasions.

d) Sulfurated (Or) Treated Soda lime Glass (type 2 glass)

It is a soda lime glass treated with so2 at500c.untill a precipitate of alkali sulphates is produced. Then surface is thoroughly washed to remove precipitate of excess alkali there by reducing leaching process, but strength of gas may be decreased.

Advantages

1. Very cheap
2. Highly inert

Disadvanges

1. Can be used only once
2. High Thermal Coefficient of Expansion
3. My undergo Leaching Process

Uses

1. Aqueous injectables of PH less than 7.

e) Neutral Tubing for Ampoules

After filling, ampoules are sealed by fusion ad therefore the glass must be easy to melt .consequently the amounts of alkaline and aluminum oxides are slightly. Increased and the content of boric oxide and silica reduced. the composition are 67%of sio2,7-5% of b2o3,8-5%Al2o3,8-7%Na2o,4% cao & 3%Mgo.

f) Coated Soda lime Glass

Instead of eliminating excess of alkali sulphates, inner surface of glass is coated with sio2, thereby preventing leaching process.

g) Lead free glass

Lead Monoxide is used in the manufacture of certain type of glass, but lead is used as cumulative poison. so lead free containers are desirable for pharmaceutical preparations intended for liquids. Sodium calcium edetate and trisodium edetate injections. The medicaments which are used as sequestering agents and also used as lead poisoning &hypercalcium in respectively.

h) Silicon-Treated container

Silicones are organic compounds containing silicon. They are polymers composed of long chains of alternating oxygen and silicon atoms with organic groups attached to the later. Silicone treated glass is coated with silicone on the inner surface of the container. Although it is not popular in pharmaceutical industry. It is less sensitive to alkali is suitable for alkali sensitive products.

Following four types of glass are accepted for packaging in the USP.

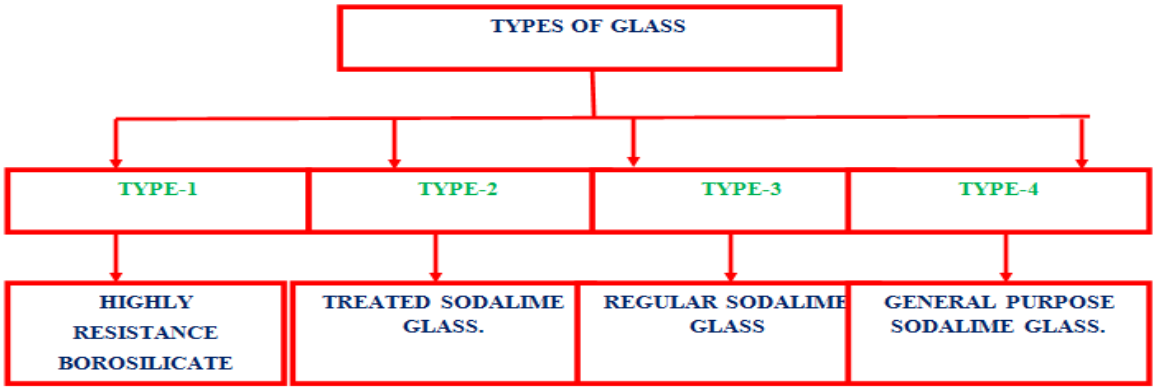

Fig 6: Classification of types of Glass according to USP

PROBLEMS WITH GLASS CONTAINERS

- Leaching.
- Weathering/clouding.
- Flaking.

Leaching

It is the process of liberation of alkali from the surface of glass container in to the drug, product .Due to liberation of alkali, product may undergo instability, and pH of drug gets altered. Finally drug may be come toxic, impotent, decomposition and inactive.

Example Insulin-pH3.5 if stored in glass container for prolonged period. It interacts with glass, and alkali gets liberated. It pH crosses 7 it becomes inactive and doesn't give its effect.

Weathering/Clouding

It is process of loss of alkali from the surface of glass containers. There by clarity of glass gets decreased, cloudiness occurs. It is continuous process, Due to loss of alkalis, strength is decreased, there by clarity is decreased and cloudiness appears.

Flaking

It is the process of release of fine particles of glass in to the drug product. It arises due to exposure of particular container to fluctuated temperature (or) environment conditions. Exposure to fluctuated temperatures, leaching (or) weathering occurs which ultimately leads to flaking with remaining amount of alkalis, once flaking occur. It should not be used.

TESTS FOR GLASS CONTAINERS [8-9]

Access the strength of glass& amount alkali-liberated. they are two types, such as

- Whole-glass test
- Glass pieces test

WHOLE-GLASS TEST

A suitable glass container is taken, filled with distilled/purified water closed with suitable closure and the container is subjected to autoclaving process at 121c for 1hr.Due to high temperature and pressure alkali may get leached in to the water.

Glass container is allowed to cool at room temperature and the water taken in glass container is transferred in to conical flask and titrates against 0.2N H2so4 by using methyl red as an indicator. Amount of alkali assayed shouldn't excess the limit. it exceed, it shouldn't be used.

GLASS-PIECES TEST

Glass container is taken crushed to fill powder, sieved and a suitable amount of uniform glass pieces/powder is taken and mixed with some of the purified/distilled water. mixture is subjected to autoclaving process at121c for 1/2hr.Mixture is taken out, cooled to room temperature and subjected to either centrifugation(or)decantation process, to collect the supernated liquid. This is titrated against 0.2N H2SO4 using methyl red as an indicator. Titer value obtained should be below the normal value given in I.P.

2. PLASTICS [9]

Plastics are a group of organic polymers usually synthetic, which are molded, cast, extruded, drawn (or) laminated in to various forms. Plastics are very commonly used in pharmaceutical and medical packaging especially for disposable type of container such as syringes, tubing devices etc.

Fig 7: Types of Plastic Containers

Advantages

1. They are very light weight in nature.
2. They are unbreakable in nature.
3. They are flexible and available in different shapes sizes.
4. They can be easily molded and can be produce different types of containers.
5. They are very cheap.

Disadvantage

1. They undergo structural deformities due to stress.
2. They undergo permeation process(in case of glass moisture (or) undergoes only condensation on surface but in plastic condensation follows permeation)
3. They undergo leaching process.
4. They undergo sorption process{they may be either absorb(or)adsorb any substance.
5. Light rays can pass through the container and may affect the light sensitive drugs.

Plastics are available in two forms. they are

1) Thermosetting
2) Thermoplastics.

Thermosetting Type

Thermosetting types are used in packaging industry mainly for bottle and jar closures. These are usually hard and brittle at room temperature and cannot be remelted at without decomposition during the manufacturing process, raw materials of the any plastic type, when heated to particular undergoes liquifaction.This liquid when cooled, gets reconstituted to solid form.

Examples polyethylene-they are off 2 form

a) Low density polyethylene.
b) High density polyethylene.

Polyvinyl chlorides (pvc), polyamides, polyalkyles, polymetacrylates,polypropylene.

Advantages

It can be recycled for many numbers of times and can be used for different purposes. during manufacturing, we may not be satisfied in strength size required for pharmaceutical use. Then the entire mass can be recycled and problem can be rectified by adding suitable additives.

Disadvantages

They melt at low temperature& can't tolerate high temperature up (or) exposure labor use

Thermoplastic Type

It includes materials which can be converted in to an unlimited range of shapes and sizes by various processes like extrusion, injection molding casting etc., this type of plastic can be remelted without decomposition.

Examples Low density polythenes, high densitypolythene, polyvinylchloride (pvc) polymethyl metacrylate (PMMA), Polystyrene, polytetrafluroethylene (PTFE).

Fig 8: Types of polymers stored Plastic Containers

Additives Used in Manufacturing Containers &Closures Made of Plastics

Additives are used to achieve desired characters like flexibilty, stability etc

a) Stabilizers.
b) Plasticizers
c) Filters
d) Static agents.
e) Colours&dyes.

a). Stabilizers

Organic polymers are not generally stable for processing and long term use. almost all of them are improved by the addition by the addition of small quantities of stabilizers, generally 0.1 to10%

Stabilizers includes i) Antioxidants
ii) Preservatives

i) Antioxidants

Antioxidants are used to prevent deterioration of preparations by oxidation.

Example: Melonoic acid, gallic acid, ascorbic acid, Ascorbyl palmitate, sodium ascorbate, sodium bisulfate and sodium metabisulfite.

ii) Preservatives

The preservatives has adequate stability and will not be reduced in concentration by chemical decomposition (or)volatilization during the desired shelf life of the preparation .The preservative does not adversely affect the preparation container(or) closure.

Example: Phenolic derivatives.

b) Plasticizers

It is component of film-coating solutions to make film more pliable, enhance spread of coat over tablets, beads and granules. It is having high molecular weight monomeric liquids of high boiling point added to vinyl and cellulosic plastics to improve their process ability, flexibilty and softness. They are generally used in conc-20-50%

Examples Diethyl phthalate, glycerin, propylene glycol.

c)Filters

Filters are common inorganic mineral powder is added to improve processing, rigidity, dimensional stability, hiding power and costs. as common natural powders, they do not bring any new health hazards in to plastic industry.

Example: Low density polyethylene (LDPE)
High density polyethylene (HDPE)

LDPE-were bulkiness increases and containers are very light in nature.

HDPE-Highly denser, weight of containers is very high.

Hence contaminations of LDPE+HDPE are used.

d)Static agents

In their long chains of plastics many functional groups may get attached which may be electrically active, posse's tendency to more. If this links of long chains breaks, channels may form and strength can be decrease. These agents prevent the migration of charged ions.

Examples: Electrolytes.

e) Colors & Dyes

Improve elegance by adding suitable color they protect the container from light rays.

Example: Dark color.

EDA approved colors & dyes are usually added to molten mass subjected to molding.

Problems with Plastics

Drug-plastic considerations have been divided in to fire separate categories.

- Permeation.
- Leaching.
- Sorption.
- Deformation
- Entrainment of light rays.

Permeation

The transmission of gases, vapors (or) liquids through plastic. Packaging material can have an adverse effect on the shelf-life of a drug. Permeation of water vapor and oxygen through the plastic wall in to the drug can present a problem. If the dosage form is sensitive to hydrolysis and oxidation, temperature and humidity are important.

Factors influencing the permeability of oxygen and water through plastic. An increase in temperature reflects an increase in the permeability of gas.

Example Two polyethylenes may give different permeability values at various temperatures

Leaching

Any kind of additives may get leached in the product results in the decomposition (or) spoilage of the product, due to leaching process problems may arise with plastics, when coloring agents are added to the formula. Particular dyes are may migrate in to a parental solution and cause toxic effect, release of constituent from the plastic container to the drug product may lead to drug contamination.

Sorption

The process may be either absorption (or) adsorption from product are chemical structure, pH, Solvent system, concentration of active ingredients, temperature, length of contact and area of contact.

If product contains unionized form of ingredients posses' tendency to form bounded neighboring ions there by sorption take place. Due to variation in pH at certain pH may undergo rapid dissolution values. Microbial contamination occurs, if an antimicrobial agent gets adsorbed by any of the container. if colored product are taken ,additives especially filters

adsorbs coloring agents, there by discoloration of product take place.

Deformation

This effect occurs if permeation, leaching &sorption occur. On other hand if containers are stored at very adverse climatic conditions structural deformation occurs.

Entrainment of light ray

Just like glass plastics don't resist the entrainment of light rays. In complex polymeric chain of plastic, all additives are fixed in to it. even though a very high complex occurs, fine pores are can appear both the complexes which can allow the light rays to pass that may affect the light sensitive materials gets decomposed.

Test To Be Performed By Plastics

Plastic should be tested for fitness. In-vivo tests are to be performed.

- TYPE-1 RABBIT
- TYPE-2 MICE (OR) RAT
- TYPE-3 RABBIT

TYPE 1 Rabbit

Plastic containers is shredded to cut in to fine pieces then mixed with water after that suspension is maded. A Suspension is to be injected intramuscularly to the rabbit and toxic effects are produced in the rabbit are to be observed. Toxic effects are increase in temperature, convulsions animals, paralysis to particular organ, unconscious, and death of the animal.

Intensity of toxic effects should be compared with standard sample of plastic that is injected to another set of rabbits .intense of toxic effects should be less than the standard sample then it is proved to be best.

TYPE 2 Mice (or) Rat

Either mice (or) rats are observed used finely divided pieces of plastic is extracted with water and supernated liquid obtained by extract is collected and injected intraperitonially to collect and injected intrapertonially to either rats (or) mice then effects are observed.

Remaining same as type-1

TYPE 3 Rabbit

Extracted solution of plastic is injected intradermally to the rabbit and toxic effects are observed.

Table 2: Types of Polymers and their uses

SNO	NAME OF THE PLASTIC	USES
1	Polyethylene	Used for blister packing (one side of the tablets are sealed with foil, on the other side gaseous made of polyethylene is used).
2	Polypropylene	Used for blister packing disposable syringes strip packing.
3	Poly vinyl chlorides (PVC).	Used for blistering packing, eye ointment tube& IV infusion bags.
4	Polystyrenes	Used for disposable syringes, bottles, ointment&plastic jars.
5	Poly amides	Disposable syringes & packaging
6	Melanin/urea/phenol/ formaldehyde	used for closures

Fig 9: Types of Rubber Closures

3.Rubber

This is mainly used for manufacturing of closures, filters, caplines, droppers (pediatric purpose).it avoids leakage and protects external environment.

Rubber occurs on two forms. They are

- Natural rubbers.
- Synthetic rubbers.

Natural Rubber

Natural rubber is majorly obtained from Kerala Malabar plantation. The botanical name of the plant is Hevea brazilensis from stem it excaudate juicy gummy material to produce rubber. It is susceptible to microbial to contamination .If additives are added. They are not compatible and these cannot achieve desired shapes, strength, capacity and strength.

Synthetic rubber

It is mostly used in pharmaceutical field. It contains Isoprene derivatives like neoprene butylated rubber etc; are used as synthetic rubber depending upon the derivatives blend of additive are added we can get rubber of desired shape, strength, capacity & elasticity.

Advantages of Rubber as Closures

1. It is having very good ageing effect (long shelf life).
2. It is having proper elasticity (either contract (or) expand allowing fitting in to any type of container).
3. It will not allow the permeation of air (or) moisture through it.
4. They are available in different sizes and shapes which make them to fit in to neck of different kinds of containers.
5. They are free from fragile nature (if rubber, closure is used for multi-vials and if it is fragile small pieces of rubber can enter in to the drug).
6. They are available in highly economic rate.

Disadvantages of Rubber as Closures

1. It undergoes leaching process.
2. It may be influenced by sorption process.
3. It cannot resist high temperature.

Ideal Characteristics

1. It should have proper ageing effect.
2. It should have proper elasticity and strength.
3. It shouldn't permeate air (or) water in to it .
4. It should be non-fragile in nature.
5. It should be available in highly economical order.
6. It should be free from leaching.
7. It should be available in different sizes& shapes.
8. It shouldn't be influenced by sorption process.
9. It should have proper resistance to with stand sterilization conditions.

Table 3: Additives used for Manufacture of Rubber Closure

SNO	TYPE OF ADDITIVE	EXAMPLE	APPLICATION
1	Vulcanizing agent	Sulphur	It improves strength &elasticity of rubber. It dissolves in many solvents.
2	Accelerators	Thiazole,Tetramethyl thiura, disulfideT.M.T dilibocarbamates	Improves rate of formation of rubber devices during their manufacturing. It improves strength and resistance to oxidation.
3	Activators	Stearic acid (or) zinc stearate for M.B.T (Mercaptobenthiozole) zinc oxide forT.M.T (Tetra methyl disulphide).	Mainly used to increase the activity of accelerators.
4	Filters	Activated carbon black &zinc oxide and magnesium and calcium carbonates	Increases bulkiness there by reduces the cost of manufacturing devices
5	Softeners	Pine oils mineral oils& tar fractions	To facilitate the incorporation of filters, make the compound easier and cheaper to manipulate and influence the hardness of the finished product.
6	Antioxidants	Phenols&aromatic amines(phenyl betanapthylamine&para-hydroxydi-phenyl)	It prevents oxidative degeneration of raw materials during manufacturing.
7	Lubricants	Talc & Stearates	Allows the rubber closure to fit in to container
8	Special ingredients	Waxes (cheese) now a day's replaced by shellac, Ethylcellulose, Cellulose acetate phthalate (film forming substance).	Forms films onto the surface of the devices & prevents permeation process

Tests to be performed for Rubber

a) Quality test
b) Finish test
c) Compatibility test
d) Extractive test
e) Leakage test
f) Test for acids and alkalis

a)Quality Test

We find the quality of product manufactured and enclosed with rubber. Before and after packaging it should posses following

A. It should be thoroughly washed with solvent after that

B .it should be subjected to sterilization

Rubber closure should be stable without producing tackiness under certain conditions like

I) Purified water II) Warm water.III) Detergent water.

If we want to remove detergent from rubber, it should be heated with hot water (or) cold water (or) detergent water at 60-65% for 1hr. if it is parentals 121c for 1/2hr.

b) Finish test

During manufacturing of rubber closures, different kinds of additives are used, finished product is obtained, a fine dust layer is that on rubber closure which may enter in to container and contaminate it. to prevent it, rubber closure is immersed in distilled water and heated for 4hr under vacuum conditions.

c) Penetrability

Mainly used for rubber closure meant for IV infusions and multivial injection system .In the above cases, closures used as rubber. to with draw the sample needle injection is pierced in to rubber work. to this rubber should have proper strength & elasticity. for this we perform this test. Injection needle is kept stationary position and multivoil injections closed with rubber closures is fixed to the piercing meter, which allows the bottle to move up and down so as to enable the rubber closure to undergo piercing by the stationary needle Piercometer is associated with a gauge which gives us the force required for piercing the rubber closures. Optimum force is required for piercing the rubber is noted. If excess force, not suitable for multi-vial injections.

d)Test for Permeation

If rubber closure is allowable to permeation complete damage of the drug may occurs. Stability conditions medicated in the above test are too length. to avoid this, accelerated stability conditions like 50c with 100% humidity for 3 months should be used. At these conditions, if rubber is compatible with drug, we can use it. If it fails we have to check for ordinary stage conditions at least for 6 months. if it is at 6 months also we can reject it. and pierce the needle in to it by moving up and down. If the rubber pieces entered are three in water by conducting test. then it is passed or else it fails.

e)Water Extractive Test

It is mainly to find out total residual mass present in rubber closure. When rubber closure is subjected to various temperature conditions, some of the additives may evaporate, residue remains, when evaporate, residue is contact with drug product, contamination occurs. The test is performed by taking rubber closure in water and subject it to reflux condensation process and condensate is collected and condensate is subjected to evaporation followed by drying and now it is collected and weigh .if it is in limits, it is used(or)else it is rejected.

f)Leakage Test

Two types of tests are performed, they are

- Type 1 Test
- Type 2 Test

Type 1 Test

Containers are filled with distilled water or drug solution closed with the help of rubber closure. With the help of a syringe needle the rubber closure is allowed to pierce to collect the solution inside. After withdrawal of syringe, the surface of rubber closure is to be checked. If surface of rubber closure is stained with any water drops or if the surface is wetted with water indicates the presence of leakage. If there are no such observations, indicate that rubber closure is free from leakage.

Type 2 Test

The container is filled with dye or indicator solution such as methylene blue, closed with rubber closure to be tested. then bottle is placed in distilled water and it is subjected to autoclaving at 1210c for 1/2 hrs, after autoclaving if the outermost water in which bottle is suspended is colored indicates the leakage of rubber closure. Otherwise there is no leakage.

a) Test for acids and alkalis

Alkalis and acids are highly reactive, if they react with drug product, decompose occurs. to avoid this we have to test it before. Rubber closure are suspended in to water and it is subjected to autoclaving at 1210c for 1/2hrs after that, water is collected and it is assayed by using acidimetry or alkalimetry to find out presence of alkalis & acids.

3. Metals

They are widely used for manufacturing of containers for semisolid dosage forms, aerosols & solid ingredients in bulk and also these metals are used as containers for storing different kinds of food

and milk products. Metals are not used for storing liquid dosage forms, because they are reactive.

Example: Food-Protinex & Farex, some of packed food products & protinized biscuits are packed in metals

Advantages of metals

1. They are light in nature
2. Highly robust for packing of aerosol system
3. They can be molded to different shapes & sizes.
4. They prevent permeation of air, moisture and microbial organisms.
5. Printing can be directly done to the surface.

Disadvantages of metals

1. Highly reactive materials
2. They are costly, when compared to glass & plastics

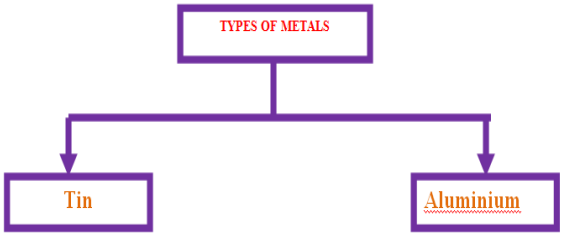

Fig: 12 Classification of Metals

a)Tin

Widely used as packaging material, because of its inertness. Tin coated lead collapsible tubes are widely used as packaging fluoride containing semisolid preparations.

b) Aluminium

Aluminium is also widely used, because of its inertness. An aluminium container up on exposure to environmental conditions reacts with oxygen and forms a thin film of aluminium oxide which protects drug products from external effects as a well as reaction with containers. Epoxy film coated containers are highly suitable for packing highly reactive materials.

CONCLUSION:

Pharmaceutical products must be protected and labeled from the point of manufacture to the final stage of patient use. Proper care should be taken against physical, chemical, climatic and biological hazards. Product quality, safety and stability must be maintained throughout the manufacturing. The packaging must also be convenient in use in order to promote good patient compliance.

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