INDUSTRIAL PHARMACY-I

UNIT IV-PARENTERALS

CLASS:30

TOPIC Containers and closures selection, filling and sealing of ampoules

CONTAINERS

- No interaction between the contents and container.
- Should withstand high temperatures especially during sterilisation.
- Should protect the contents from harmful light radiations.
- Must be suitable for repeated use and easy to clean.
- Should be transparent and colourless.
- Containers are in intimate contact with the product.
- No container presently available is totally non reactive, particularly with aqueous solutions .
- Both the chemical and physical characteristics are given primary consideration in the selection of a protective container .
- Glass containers traditionally have been used for sterile products , many of which are closed with rubber stoppers.
- Interest in plastic containers for parenterals is increasing and such containers are being used for commercial ophthalmic preparations and IV solutions.

PLASTIC

THERMOPLASTIC

- On heating, these soften to a viscous fluid which hardens again on cooling.
- Hardness depends on degree of cross linkage or intermolecular attraction.
- They include:

➢ Polyethylene

➢ HDP

➢ PVC

➢ PMMA

➢ Polystyrene

➢ PTFE

➢ Polypropylene

➢ Polyamide

➢ Polycarbonate

THERMOSETTING

- When heated, these may become flexible but they do not become fluid.
- They are usually hard and brittle at room temperature because of high degree of cross-linking.
- They include:

- Phenol- formaldehyde
- Urea- formaldehyde

  Melamine- formaldehyde

- Plastic consists plasticizers, fillers,antistatic agents,antioxidants and other ingredients not usually chemically bound may migrate out to the plastic into the container
- Low density poly ethylene and poly propylene can be autoclaved when formulated with low amount of plasticizer
- Advantages
- Light in weight
- Non-breakable
- Low in additives have low toxicity and low reactivity

HIGH DENSITY POLYTHENE

- More rigid, handling and filling of containers is easier.
- Permeability to gases is low and resistance to oil is high.
- Can be sterilised by autoclaving because of higher melting point.
- Used for disposable syringes, packaging of infusion fluids, Flexible polyethylene-opthalmic preparation
- Polyvinyl chloride-I,v bags
- A relatively new group of plastics, the **polyolefins**, deserve special mention.
- The two of interest today in the parenteral field are **polypropylene** and the copolymer **polyethylene-polypropylene.**
- Polypropylene is the most widely used. It is a liner polymer that can be produced to be highly crystalline.
- Because of its crystallinity, it has a high tensile strength, a high melting point of 1650c and a relatively low permeability to gases and water vapours.

  It is translucent, abrasion resistant and has a high surface gloss

- It withstand normal autoclaving temperatures. It must be stabilized with an antioxidant, however the type and concentration of which must be carefully controlled to avoid leaching on one hand and degradation of the plastic on the other.
- Flexible polyethylene containers are used for ophthalmic solutions to be administered in drops and flexible polyvinyl chloride bags for IV solutions.
- The latter have particular advantage over glass bottles in that no air from the patient's bedside need enter the container as the liquid flows out, the bag simply collapses.

USP procedure to evaluate toxicity of preparation

- Implanting small pieces of the plastic material intramuscularly in rabbits
- Injecting eluates using sodium chloride injection with or without alcohol
- Injecting eluates peg400 and seasame oil intraperitonally in mice
- Injecting all four eluates s.c to rabbits

The reaction from the test samples must not be significantly >non-reactive control samples

GLASS

- Preferred material for containers for injectable products
- Composed principally of silicon dioxide
- Replaced with other oxides of sodium,potassium,calcium,magnesium,Aluminium,boron

Two types of glass

- Borosilicate glass
- Treated soda lime glass
- The glass that is most resistant chemically is composed almost entirely of silicon dioxide, but it is relatively brittle and can only be melted and molded at high temperatures.
- Boric oxide somewhat modified the above characteristics as it enters the structural configuration, but most of the other oxides apparently enter the spaces within the structure and reduce the strength of intraatomic forces between the silicon and oxygen.
- Therefore the latter oxides lower the melting point of the glass and are comparatively free to migrate.
- Consequently, they also lower the chemical resistance of the glass, i.e. they May migrate into a product over a prolonged period of contact, particularly with aqueous solutions.

Table 23.5: USP glass types, test limits and selection guide

Type	General description	Type of test	Test limits: Size (ml)	Test limits: ml of 0.02 N H_2SO_4	General use
I	Highly-resistant borosilicate glass	Powdered glass	All	1.0	Buffered and unbuffered aqueous solutions. All other uses
II	Treated soda-lime glass	Water attack	100 or less over 100	0.7 0.2	Buffered aqueous solutions with pH below 7.0. Dry powders, oleaginous solutions
III	Soda-lime glass	Powdered glass	All	8.5	Dry powders, oleaginous solutions
NP	General-purpose soda-lime glass	Powdered glass	All	15.0	Not for parenterals. For tablets, oral solutions and suspensions, ointments, and external liquids

U.S.P. Glass Types and Test Limits

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Chemical resistance

The USP provided the powdered glass and water attack test for evaluating chemical resistance of glass.

- The test results are measures of amount of alkaline constituents leached from the glass by purified water under controlled elevated temperature conditions , the powder glass test are performed on ground, seized glass particles and the water attack test is performed on whole containers.
- The conditionsof the test must be rigidly controlled to obtain reproducible results since the quantity of alkaline constituents leached is small.
- The water attack test is used only with containers that have been exposed to sulfur dioxide fumes under controlled humidity conditions. Such treatment neutralize the surface alkaline oxides thereby rendering the glass more resistant chemically.

- basis of results from the official tests, glass compounds are classified into four types

Physical Characteristics

- The protection of light sensitive products from the degradative effect of ultraviolet rays may be one of the important physical characteristics of a glass container.
- Light sensitive products stored in amber colored bottles
- Amber color can be produced by adding iron oxide,traces of which leached into the product
- Protection from UV rays by means of an opaque carton surrounding a flint glass container
- A low coefficient thermal expansion to withstand the thermal shocks
- Glass Containers are sometimes coated internally with silicon fluid to produce a hydrophobic surface.
- To achieve permanency, the silicon must be baked at a temperature of approximately 150 degree.
- This additional operation is justified for such applications as to reduce the adherence of heavy, costly suspension or emulsions, or to increase the slippage of a plunger in syringe barrel.

Containers use consideration

- Single dose container -1000ml
- Multiple dose containers-30ml
- The particular advantage of these containers is flexibility of dosage offered to the physician. Single dose Containers are intended to provide sufficient drug for just one dose, the integrity of the container being destroyed when opened so that it cannot be reclosed and used again.
- Single dose containers range from 1litre bottles of IV solutions to 1ml or smaller catridges

Rubber

- Rubber closures are used to seal the opening of cartridges, vials, and bottles, providing a material soft and elastic enough to permit entry and withdrawal of a hypodermic needle without loss of the integrity of the sealed container
- consists of long chain polymers of isoprene units linked together in the cis position.

The chief disadvantages of raw rubber are:

- Poor elasticity.
- Poor strength.
- Hardens when cold and becomes soft and sticky when warm.
- Dissolves in many solvents. To give better physical and chemical properties, add:

Vulcanising agent- sulphur which forms cross links between the long rubber molecules thus improving its strength and reducing its susceptibility to temperature changes

- Accelerators- reduces the time and amount of sulphur required, e.g. thiazoles.
- Activators- increase the activity of accelerators, e.g. stearic acid.
- Fillers- they are of two types:
- Reinforcing fillers: improves physical property, e.g. carbon black which increases tensile strength.
- Extending fillers: added mainly as diluents to reduce cost and partly to facilitate
- Softeners- facilitate the incorporation of fillers, make the compound easier and cheaper to manipulate, and influence the hardness of finished product, e.g. mineral oil.
- Anti-oxidants- prevents oxidation of rubber, e.g. aromatic amines and phenols.
- Pigments- originally mineral pigments such as oxides of iron and sulphides of cadmium and antimony were used but these are being displaced by coal tar dyes.
- Special ingredients- examples include:

• **Paraffin wax**: migrates to the surface and produces a protective barrier to oxygen attack and water absorption.

Rosin: increases tackiness.

Lubricants- assists the removal of closures from their moulds after preparation, e.g. zinc stearate, talc.

Rubber closures

- Ideal closures should be completely non reactive with the product
- Compatability problems with rubber
- ➢ Leaching of the ingredients from the rubber compound
- ➢ Removal of the product by sorption by the rubber compound
- ➢ Preliminary compatability usually assessed by placing the rubber closure in intimate contact with the product and maintaining samples at elevated temperatures for planned period of time
- ➢ At prescribed intervals samples examined for qualitative and quantitaive evidence of chemical or physical change in the closure or the product

Physical characteristics

- **Elasticity**-to provide snug fit between closure and the neck and the lip of the glass container
- Must also spring close to the hole made by the needle immediately after with drawl

- **Hardness** must not be hard that require an excessive pressure to insert the hypodermic needle
- **Porosity**:should not permit the easy transfer of water vapor and gases in either direction

Rubber closures

- Minimal water vapour transfer is important, for example to prevent the absorption of water by freeze dried products.
- Plastic or lacquer coatings are sometimes applied to the surface that will be in a contact with the product.
- Plastic or lacquer coating are applied to the surface in contact with the product
- Teflon linings shown to provide an effective barrier against sorption and leaching

Physical shapes

- Common flanged-closures (center)
- Slotted for freeze dried products
- Punctured for attachment of adapters for infusion sets
- Plunger type for catridges

Rubber closures Testing

- Physicochemical tests
- pH
- Turbidity
- Residue on drying
- Iodine number
- Heavy metal content

Biological tests on

- Saline
- Polyethylene glycol 4000
- Cottonseedoil extracts

Include acute and chronic toxicity in mice and rabbits

FILLING AND SEALING

For small volume parentral products(UPTO 100mL):

- Single dose containers(for Ampoule)
- Multi dose containers(for Vials)
- Prefilled syringe

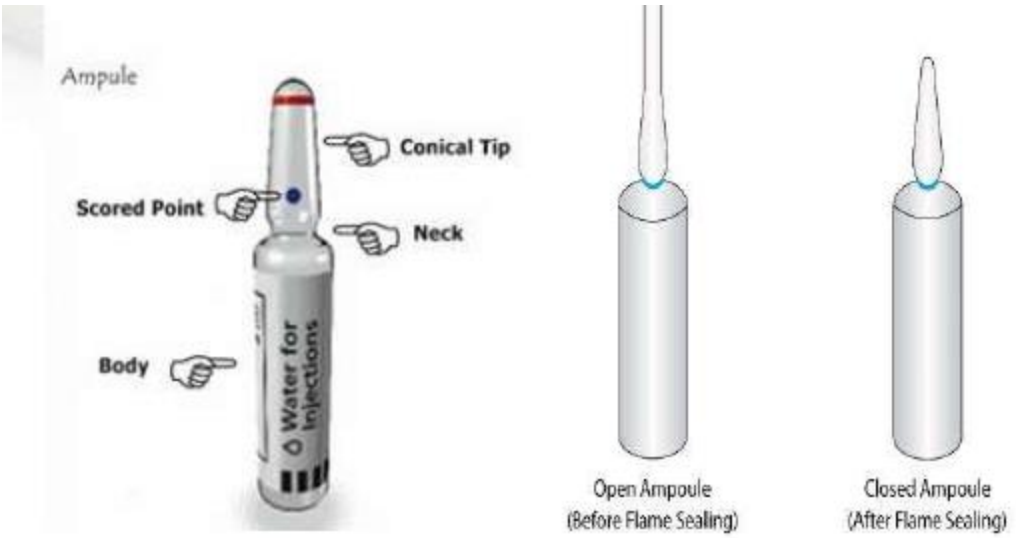
For large volume parentral products:

- Glass bottles
- PVC collapsible bags
- Semi rigid polythene container

AMPOULES FILLING AND SEALING

OPERATION

- Sterilised ampoules are loaded in the tray.
- After that, this tray is directly loaded into slant hopper of unit.
- Now the machine starts to process, while synchronized start wheels start to deliver one at a time moving in the rack in single, twos, fours or sixes.
- The rack stops sequentially and during this period, its every single procedural process is carried out like pre-gassing, filling, post- gassing, pre-heating and finally sealing it out.
- All the sealed ones are then, collected on tray for collection without manual touching



- Ampoule is a parentral product made entirely of glass and intended for single dose use.
- They can be broken at the neck restriction either by scoring or by having a ceramic point that is a weak point meant for breaking site.

HIGH SPEED AUTOMATIC AMPOULE FILLING & SEALING MACHINE

Process Operation

• Empty washed & sterilized ampoules fed into wire mesh conveyor belt from the left hand side of the machine.

• Eight ampoules fed through feeding cassette to receiving rack.

• The moving rack which moves horizontally collect eight ampoules from the receiving rack and transfer the ampoule to the machine in left to right in an inclined position through pre-gassing.

• Pre-gassing, Filling, Post Gassing, Pre-heating & sealing stations completes filling & sealing operations.

• Filled & sealed ampoules are collected automatically in SS tray in upright position without hand touch

Sterile solids

- Sterile solids such as antibiotics are more difficult to subdivide accurately & precisely into individual dose containers than are liquids
- The rate of flow of solid material tends to be slow & irregular, particularly if finely powdered. Small, granular particles flow must be evenly.

- In general, these involve the measurement and delivery of a volume of the granular material that has been calibrated in terms of the weight desired.
- In the machine shown below, an adjustable cavity in the rim of a wheel is filled by vacuum and the contents held by vacuum, until the cavity is inverted over the container.
- The solid material is then discharged into the container by a puff of sterile air.
- **Filling of the parentral solution is done with the help of liquid filling machine.**
- Sealing is a key process in parentral product manufacturing especially ampoules**.**
- **It is sealed by melting a portion of** glass of neck to form a tip seal or pull-seal.
- The heating with a high temperature gas oxygen flame must be even and carefully controlled to avoid gas distortion of seal.

- Tip seals are made by melting sufficient glass at the tip of ampoule neck to form a bead of glass and close the opening.
- Pull-seals are made by heating the neck of rotating ampoule below the tip, then pulling the tip away to form a small , twisted capillary.
- Excessive heating of air and gases in neck causes expansion against the glass with formation of fragile bubbles at point of seal.
- Fracture of neck of ampoules often occurs during sealing if wetting had occurred at the time of filling
- Also wet glass at the neck increases the frequency of bubble formation and of unsightly and contaminating deposits of carbondioxides as a result of the effect of sealing on the droplets of product
- Pull-sealing is a slower process and more reliable than tip sealing.
- It is sometimes necessary to displace the air within the ampoule above product to prevent decomposition.

- This may be done by introducing a stream of inert gas like N2 or CO2 during/after filling the product. Immediately the ampoule is sealed.