PACKAGING of sterile dosage forms

Prepared by-Mr.GautamKumar
Assistant Professor(Pharmaceutics)
Lord Shiva College of Pharmacy, Sirsa

PACKAGING

- **Packaging** is the science, art, and technology of enclosing or protecting products for distribution, storage, sale, and use.
- Packaging also refers to the *process* of design, evaluation, and production of packages.
- Packaging may also be defined as the collection of different components (e.g. bottle, vial, closure, cap, ampoule, blister) which surround the pharmaceutical product from the time of production until its use.

PACKAGING: BARRIER PROPERTIES

- Pack barrier capabilities may be critical to the viability of a medicine:
- Moisture ingress can lead to hydrolytic degradation or physical instability; high humidity territories may warrant extra precautions

  – Air ingress can lead to oxidative degradation
  – Some products are photo labile and need protection from light
  – Bacteria must be excluded from sterile/ sterilized products
  – Other biological challenges need to be denied ingress, e.g. insects
  – Leaking of liquid products from their pack must be avoided
  – The egress of any volatile excipients must be prevented to maintain integrity of the product

SELECTION CRITERIA FOR PACKAGING MATERIAL

- The product or pack contents
- The application of the product
- Content stability, and the need of protection form any environmental factors
- Content reactivity (with relevant to the packaging material)
- Acceptability of the pack to the consumer or user
- The packaging process
- Regulatory, legal and quality issues

Characteristics of packaging material

- They must protect the preparation from environmental conditions.
- They must not be reactive with the product.
- They must not impart to the product tastes or odors.
- They must be nontoxic.
- They must be FDA approved.
- They must meet applicable tamper-resistance requirements.
- They must be adaptable to commonly employed high speed packaging equipment.

TYPES OF PACKAGING

Primary packaging is the material that first envelops the product and holds it. This usually is the smallest unit of distribution or use and is the package which is in direct contact with the contents.

Examples: Ampoules,Vials ,Containers ,Dosing dropper ,Closures

(plastic, metal) ,Syringe ,Strip package, Blister packaging.

Secondary packaging is outside the primary packaging – perhaps used to group primary packages together.

Example: Paper and boards, Cartons ,Corrugated fibers ,Box manufacture)

Tertiary packaging is used for bulk handling , warehouse storage and transport shipping. The most common form is a palletized unit load that packs tightly into containers.

Apart from primary and secondary packaging, two types of special packaging are currently in use, as follows:

- **Unit-dose packaging**. This packaging guarantees safer medication by reducing medication errors; it is also more practical for the patient. It may be very useful in improving compliance with treatment and may also be useful for less stable products.

- **"Device" packaging.** Packaging with the aid of an administration device is user-friendly and also improves compliance. This type of packaging permits easier administration by means of devices such as prefilled syringes, droppers, transdermal delivery systems, pumps and aerosol sprays. Such devices ensure that the medicinal product is administered correctly and in the right amount

List of packages for sterile dosage forms

- All types of parental
  - ampoules
  - vials
  - i.v. infusion (small vol. + large vol.)
  - s.c injections
  - intra thecal inj.
  - intramuscular inj.
- Oral vaccines
  - tripsules
- Ophthalmic product
  - drops
  - ointment

Using of packaging material

I) Glass - ampule, vials, syringe, SVI, LVI, vaccine storage, dropper (primary packaging)

II) Metals - vials (primary packaging)

III) Rubbers – vials, syringe's plunger, vaccine closer (primary packaging)

IV) Plastics - ampule, vials, syringe, SVI, LVI, vaccine storage, dropper, tripsules, (primary packaging as well as secondary packaging)

V) Fibrous mater- all types of secondary packaging

VI) Films, Foils and laminates –all types of secondary packaging

GLASS:

- Glass has been widely used as a drug packaging material.
- Glass is composed of sand, soda ash, limestone,& cullet.
- Si, Al, Na, K, Ca, Mg, Zn & Ba are generally used into preparation of glass

❖ *Advantages*

- They are hygienic and suitable for sterilization
- They are relatively non reactive (depending on the grade chosen)
- It can accept a variety of closures
- They can be used on high speed packaging lines
- They are transparent.
- They have good protection power.
- They can be easily labeled.

❖ DISADVANTAGES

- It is relatively heavy
- Glass is fragile so easily broken.
- Release alkali to aqueous preparation

TYPES OF GLASS:

Type I (Neutral or Borosilicate Glass)

Type II (Treated Soda lime glass)

Type III (Soda lime glass)

Type IV (General purpose soda lime glass)

- TYPE I GLASS
- Least reactive.
- Higher ingredients and processing cost therefore used for more sensitive pharmaceutical products such as parenteral or blood products.
- Mostly ampoules and vials are made up of Type I gla

Type II glass:

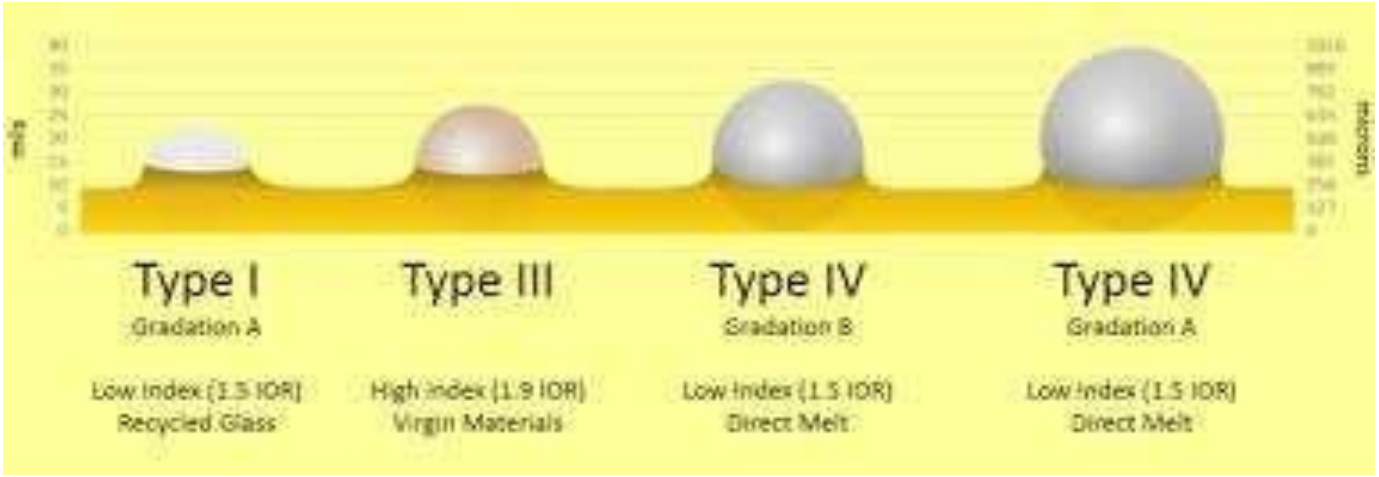
- Higher chemical resistance but not as much as typ
- Cheaper than Type I.
- Acceptable for most products accept blood products and aqueous pharmaceutical with a pH less than 7

Type III glass

- Have *similar composition* and are *distinguished from each other* on the basis of their hydraulic resistance
- **it** has average or slight better than average resistance and is suitable for non- aqueous parenterals and non parenteral products.
- Type III glass containers are normally dry
- sterilized before being filled.

- **Type IV glass:**

  lowest hydraulic resistance and is suitable for solid products, some liquids and semi solids and not for parenteral.



METALS

- Metal containers are used solely for medicinal products for non-parenteral administration.
- Metal is strong, opaque, impermeable to moisture, gases, odors, light, bacteria, and shatterproof, it is the ideal packaging material for pressurized containers.
- It is resistant to high and low temperatures
- They include tubes, packs made from foil or blisters, cans, and aerosol and gas cylinders.
- Aluminium and stainless steel are the metals of choice for both primary and secondary packaging for medicinal products.
- Form an excellent tamper evident containers.

- **ALUMINIUM**
- It is relatively light yet strong
- Barrier to light and chemicals
- Impermeable and easy to work into a variety of formats, depending on its thickness.

- Thickest aluminium is used for rigid containers such as aerosol cans and tubes for effervescent tablets.
- Intermediate thickness are when mechanical integrity is still important but the pack should be capable of being reformed under a reasonable force.
- e.g. Collapsible tubes for semi solid preparations or roll on screw caps.
- Thinnest aluminium is used in flexible foil that are usually a component of laminated packaging material.

- **Disadvantages and their overcome solution**
- Major disadvantage is its reactivity in raw state, although it rapidly forms a protective film of aluminium oxide it is still liable to corrosion (when exposed to some liquids and semi solid formulations, particularly at extreme pH or if the product contains electrolytes.
- To overcome this problem, Aluminium is lined with epoxide, vinyl or phenolic
- resins.
- They are work hardening like collapsible tubes are made by impact extrusion which tends to make aluminium less flexible.
- To overcome, flexibility has to restored by an annealing stage.

RUBBERS (Elastomers)

Excellent material for forming seals, used to form closures such as bungs for vials or in similar applications such as gaskets in aerosol cans.

Categories of Rubbers:

1) Natural rubbers:

Suitable for multiple use closures for injectable products as rubber reseals after multiple insertion of needle.

Disadvantages are;

- It doesn't well tolerate multiple autoclaving becoming brittle and leads to relative degree of extractable material in presence of additives.
- Risk of product absorbing on or in to a rubber.
- It has certain degree of moisture & gas permeation

2) Synthetic rubber:

Have fewer additives and thus fewer extractable and tends to experience less sorption of product ingredients.

Are less suitable for repeated insertions of needle because they tend to fragment or core pushing small particles of the rubber in to the product.

E.g. Silicone, butyl, bromobutyl, chlorobutyl etc.

Silicone is least reactive but it does experience permeability to moisture and gas.

Softer rubbers experience less coring and reseal better, harder rubbers are easier to process on high speed packaging lines.

PLASTICS

According to British standards institutes plastics represents;

" A wide range of solid composite materials which are largely organic, usually based upon synthetic resins or upon modified polymers of natural origin and possessing appreciable mechanical strength. At a suitable stage in their manufacturing, most plastics can be cast, molded or polymerized directly into shape".

Classes of plastics:

index

There are two classes of plastics, reflecting the behavior with respect to individual or repeated exposure to heating and cooling.

Thermoplastics

Capable of being shaped after initial heating and solidifying by cooling.

Resistant to breakage and cheap to produce and providing the right plastics are chosen will provide the necessary protection of the product in an attractive containers.

E.g. Polystyrene, polyethylene and polyvinyl chloride.

Thermosets

They need heat for processing into a permanent shape. During heating such materials form permanent crosslinks between the linear chains, resulting in solidification and loss of plastic flow.

E.g. Phenolic, urea and melamine are representative of thermosets.

Uses

Used for many types of pack including;

rigid bottles for tablets and capsules, squeezable bottles for eye drops and nasal sprays, jars, flexible tubes and strip and blister packs.

Advantages

Least expensive than glasses

Ease of transportation

No risk of breakage

Flexible

Light in weight

Disadvantages

They are not as chemically inert as Type -I glass.

They are not as impermeable to gas and vapour as glass.

They may possess an electrostatic charge which will attract particles.

Types of plastics

- POLYETHYLENE
- This is used as high and low density polyethylene
- Low density polyethylene (LDPE) is preferred plastic for squeeze bottles.
- Properties: Ease of processing , barrier to moisture, strength /toughness, flexibility, ease of sealing.
- High density poly ethylene (HDPE) is less permeable to gases and more resistant to oils, chemicals and solvents.
- Properties: Stiffness, strength / toughness, resistance to chemicals.
- It is widely used in bottles for solid dosage forms.
- Drawback: prone to stress cracking in the presence of surfactants or vegetable or mineral oils.

POLYPROPYLENE

- It has good resistance to cracking when flexed.
- Good resistance to heat sterilization.
- It is colorless, odorless thermoplastic material with excellent tensile properties even at high temperature.
- Excellent resistance to strong acids and alkalis.
- Low permeability to water vapour
- Permeability to gases is intermediate between polyethylene HD and un-plasticized PVC
- Suitable for use in closures , tablet containers and intravenous bottles.

- Plastic bottles made from PP, HDPE and PS

- Bottle- PET and spray- PP

FIBROUS MATERIALS

- The fibrous materials are the important part of pharmaceutical packaging.
- Fibrous materials include: Papers, Labels, Cartons, Bags, Outers, Trays For Shrink Wraps, Layer Boards On Pallets, etc.
- The Applications as well as Advantages of Cartons include:
  - ✓ Increases display area
  - ✓ Provides better stacking for display of stock items
  - ✓ Assembles leaflets
  - ✓ Provides physical protection especially to items like metal collapsible tubes.
  - ✓ Fiberboard outers either as solid or corrugated board also find substantial application for bulk shipments.
  - ✓ Regenerated cellulose film, trade names Cellophane & Rayophane, is used for either individual cartons or to assemble a no. of cartons.

FILMS, FOILS & LAMINATES

- Regenerated cellulose film based on viscose (chemical used for manufacturing of rayon) & laminating two or more types of films, cellulose coatings, foil and paper play diff roles such as supportive, barrier, heat seal & decorative.
- For Example:
- Aluminum foil even in the thinnest gauges offers the best barrier properties, which are not approached even by the most impermeable plastics.
- „Metallization“: A relatively new process whereby particles of metal are laid down onto a surface under vacuum, can significantly improve the barrier properties of a material but these do not approach the properties of a pure foil.
- In the newer technology „Co-Extrusion“, a number of plastic plies are extruded in combination to produce cheaper laminations

- Uses of films, foils, laminations:
  - Strip packs
  - Blister packs
  - Sachets
  - Diaphragm seals for bottles
  - Liners for boxes either attached or loose bag-in-box systems & bags.

- Foil blisters:

- When sealed with a metal foil-cover, the blister can provide a hermetic pack i.e. an isolated system, which excludes any exchange of gases between the product & surrounding atmosphere.

CLOSURES

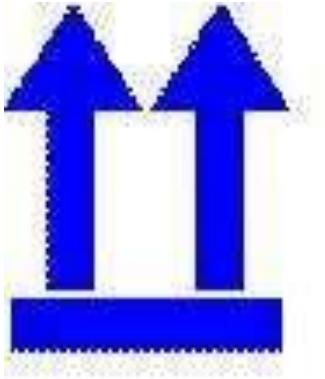
- Closures are the devices by means of which containers can be opened and closed. Proper closing of the container is necessary because
  - It prevents loss of material by spilling or volatilization.
  - It avoids contamination of the product from dirt, microorganisms or insects.
  - It prevents deterioration of the product from the effect of the environment such as moisture , oxygen or carbon dioxide.
- Material used for closures are;

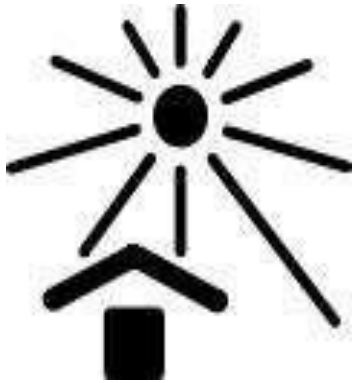
The closures for containers meant for storage of pharmaceutical products are generally made from the following basic materials.

- Cork
- Glass
- Plastic
- Metal
- Rubber

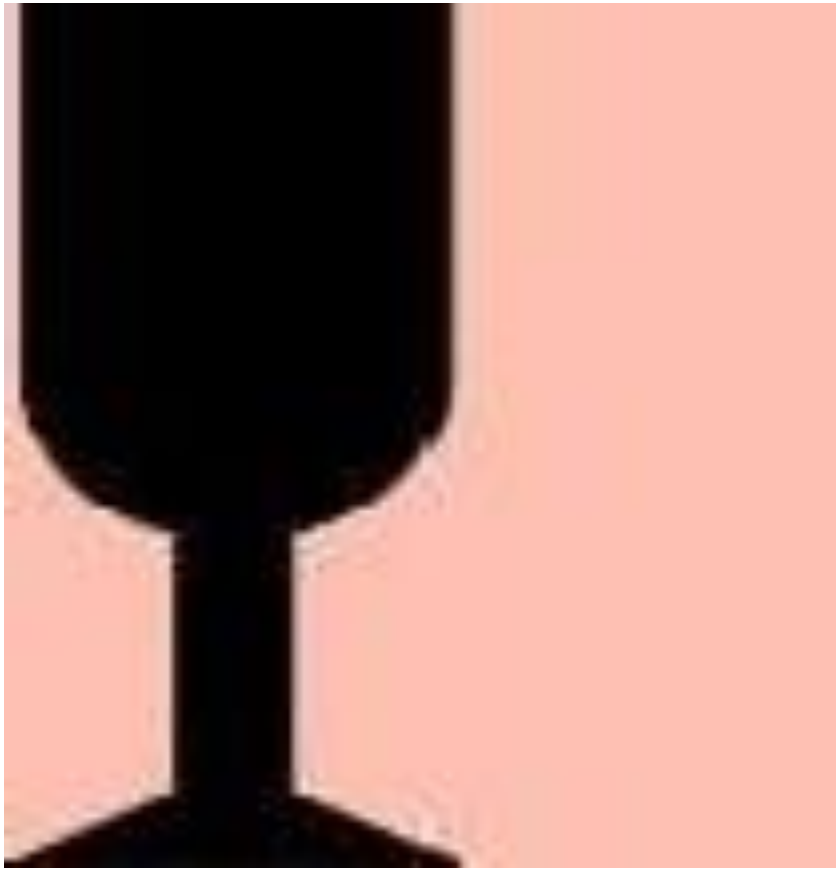
SYMBOLS USED ON PACKAGES AND LABELS

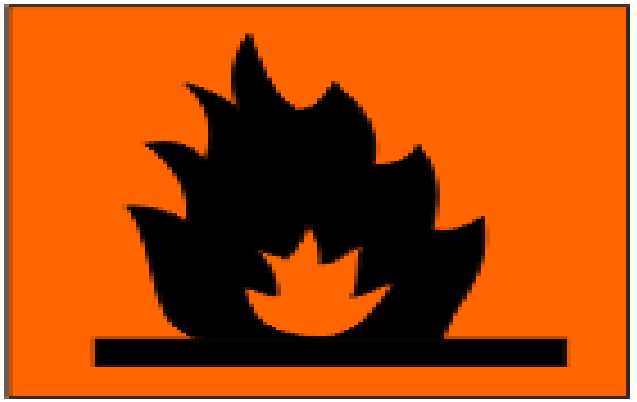
- Many types of symbols for package labeling are nationally and internationally standardized. For product certifications, trademarks, proof of purchase, etc. identification code .





(E) Fragile





Quality Assurance Aspects Of Packaging

- To ensure that patients and consumers receive high-quality drugs, the quality management system must take the following considerations into account if the required quality of packaging is to be obtained:
  - — the requirements of the national authorities and the relevant legislation
  - — the product
  - — the production process
  - — the manufacturers' internal policies (safety, marketing, etc.).

- Bad packaging which is the result of deficiencies in the quality assurance system for packaging can have serious consequences, and packaging defects can create problems that may result in drug recalls. Such defects may include breakage, and problems relating to printing or inks, or errors on labels and package inserts (patient information leaflets). The use of GMP and quality control will prevent the release of a defective medicinal product.
- Packaging processes and equipment need validation/qualification in the same way as any other part of processing within a pharmaceutical facility.

Sampling and testing of packaging materials

- **Sampling**
  - To check the correctness of the label, packaging material or container reference, as well as in the acceptance of consignments,
  - Detecting adulteration of the medicinal product, obtaining a sample for rétention, etc.
  - The sampling procedure must take into account the homogeneity and uniformity of the material so as to ensure that the sample is representative of the entire batch.
  - The sampling procedure should be described in a written protocol.

Testing programme

Quality control tests are intended to check the identity of the material concerned. Complete pharmacopoeial or analogous testing may also be carried out, as may special tests, where necessary. All written specifications for packaging materials and containers should include the nature, extent and frequency of routine tests. Routine tests vary according to the type of material and its immediate packaging, the use of the product, and the route of administration. Nevertheless, such tests usually include the following:

- — visual inspection (cleanliness, defects)
- — tests to identify the material
- — dimensional tests
- — physical tests
- — chemical tests
- — microbiological tests

PACKAGE VALIDTAION

Package validation involves two separate validations:

1) The design validation of the package as a component of the device Design validation uses evidence to establish what design specifications will conform with the user needs and the intended to use.

2) The process validation of the packaging process.

Process validation establishes by objective evidence that a process consistently produces a result or product that meets predetermined specifications [820.3(z)(1)].

.

Cont….

- The regulation, of course, refers to establishing evidence that the manufacturing steps involved in packaging the device will consistently produce packaging which meets specifications. For example, the process capability of packaging and sealing equipment should be determined during process validation and documented. Validation of the package design shall be performed under actual or simulated use conditions that show the package conforms to its stated intended uses. Risk analysis shall also be included where appropriate

Design validation results shall include: the design identification, name of the individual(s) performing the validation, method(s) used, and the date.

All of this information should be recorded in the design history file. If any significant change is made in the packaging or packaging operation after validation, the new process will need to be revalidated.

One of the most difficult aspects of package validation is determining how many samples to test. The goal is not to over test because of cost considerations while still running sufficient tests to provide statistically valid sampling.

Statistical methods of analysis are important in process validation. The following decision tree from *Medical Device and Diagnostic Industry*, "Streamlining Package-Seal Validation," October 1992, provides various methods of statistical analysis. The manufacturer is challenged with determining which statistical method is most applicable to their individual needs. The resulting validation plan should identify, measure, and evaluate the key processes and variables that will require assessment to complete a validation or revalidation of the packaging and the packaging process.

Guidelines for packaging:

- **WHO Guidelines**:

1. When programme of packaging is being set up, particular attention should given to minimizing the risk of cross contamination, mix up, or substitution. Different product should not packed in same proximity. Unless there is physical segregation or the use of electronic surveillance.

2. At least 1 to 1.2 meter high special separation should be done between adjacent packaging line.

3. Before packaging operation begun steps should be taken to ensure that the work area, packaging material, printing machine, and other equipment are clean and free from contamination, product, material, documents that previously used and not required in current operation. Check list for performing line clearance…

i) Remove all primary, secondary packaging materials of previous batch.

ii) Avilability of all bulk, primary, secoundary packaging material.

iii) Lower part of conveyer belt many time culprit of traces of previous product.

iv) BPCR should have record of such line clearance

v) The name and batch No. of product being handled should be displayed at all packaging station .

vi) Packaging line should display board witj following details…

packaging line No.- 2

name of product- ranitidine ampoule
strength – 25mg/ml
pack-10 ampoules/pack
date- 26/08/2011

4. Normally filling and sealing should be followed as quickly as possible by labeling . If labeling is displayed appropriate procedure should be ensure that no mix up and cross contamination can occurs.

5. Special care should be taken when cut labels are used and when overwriting is carried out offline and hand packing operation. Roll feed labels are normally preferred avoid mix ups.

Online verification of all labels by automated electronic mean can helpful in preventing mix ups but checks should be made to ensure that any electronic code reader, label counter, or similar device are operating correctly.

6. Printed and embossed information on packaging material should be distinct and resistant to fading or erasing .

7. Samples take away from packaging line should not be returned.

8. After completion of packaging operation, any unused batch coded packaging material left, it should be destroyed and recorded the destruction. A document procedure should be followed if uncoated printed material are returned to stock.

Lyophillization

- **Definition**

A stabilizing process in which a substance is first frozen and then the quantity of the solvent is reduced, first by sublimation (primary drying stage) and then desorption (secondary drying stage) to values that will no longer support biological activity or chemical reactions.

Principle

 Lyophilization is carried out using a simple principle of physics
sublimation. Sublimation is the transition of a substance from the
solid to the vapour state, without first passing through an intermediate liquid phase.

 Lyophilization is performed at temperature and pressure conditions below the triple point, to enable sublimation of ice.

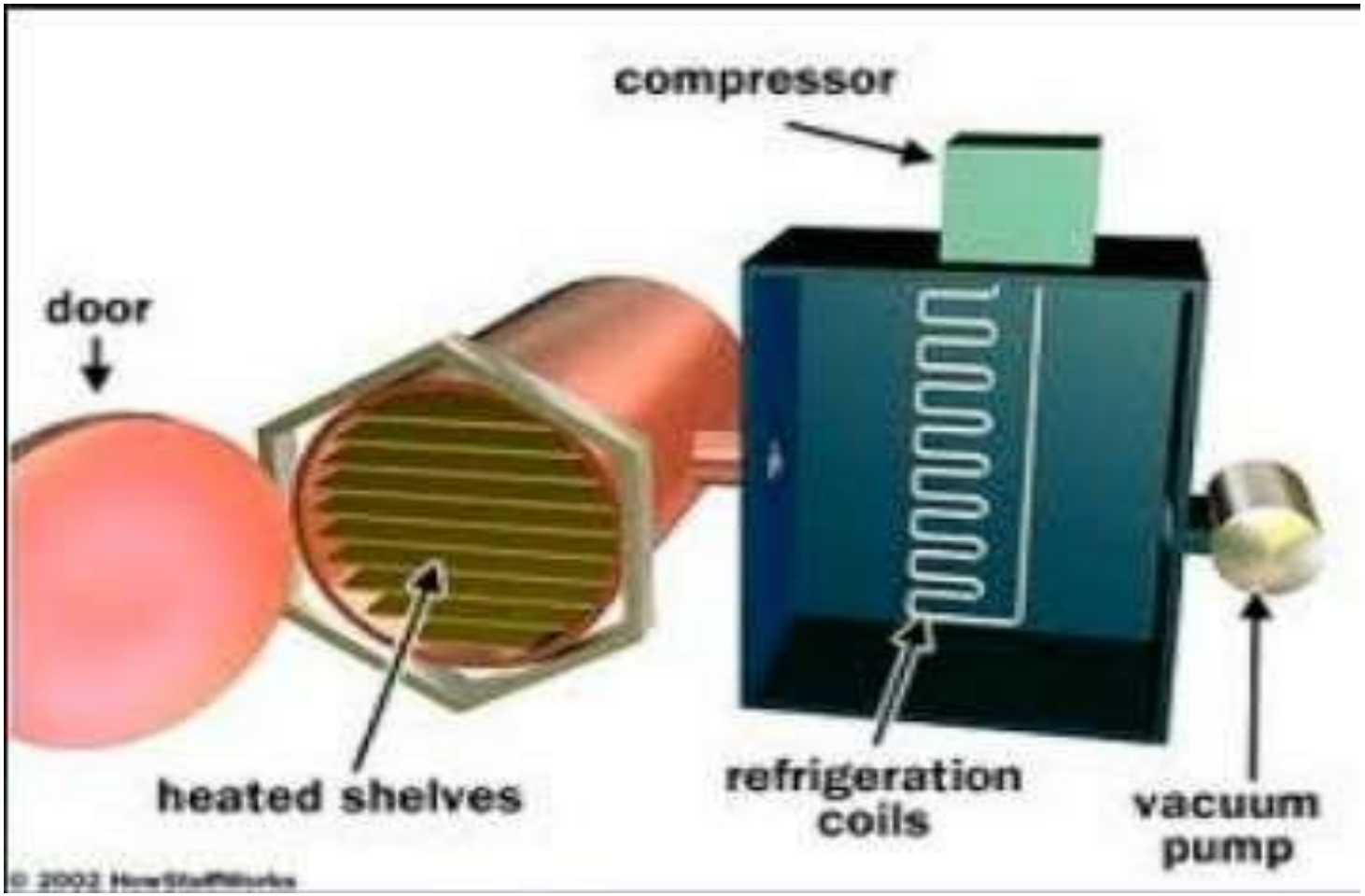
 The entire process is performed at low temperature and pressure by applying vacuum, hence is suited for drying of thermolabile compounds.

 The concentration gradient of water vapour between the drying
front and condenser is the driving force for removal of water during lyophilization.

Objectives of lyophilization process

- To preserve the biological activity of a product.
- To reduce the product weight to lower the transportation cost.
- To extend the shelf life or stability.
- To dry thermolabile materials.
- To eliminate the need for refrigerated storage.
- To get accurate, sterile dosing into the final product container

Basic components of a Lyophilizer



STEPS INVOLVED IN LYOPHILIZATION

1. FREEZING STAGE
2. PRIMARY DRYING STAGE
3. SECONDARY DRYING STAGE
4. PACKING

Processing

- Fundamental process steps are:

1. Freezing: the product is frozen. This provides a necessary condition for low temperature

2. Vacuum: after freezing, the product is placed under vacuum.

This enables the frozen solvent in the product to vaporize without passing through liquid phase, a process known as *SUBLIMATION.*

3. Heat: Heat is applied to the frozen product to accelerate sublimation.

4. Condensation: Low-temperature condenser plates remove the vaporized solvent from the vacuum chamber by converting it back to a solid. This completes the process

Freeze Drying

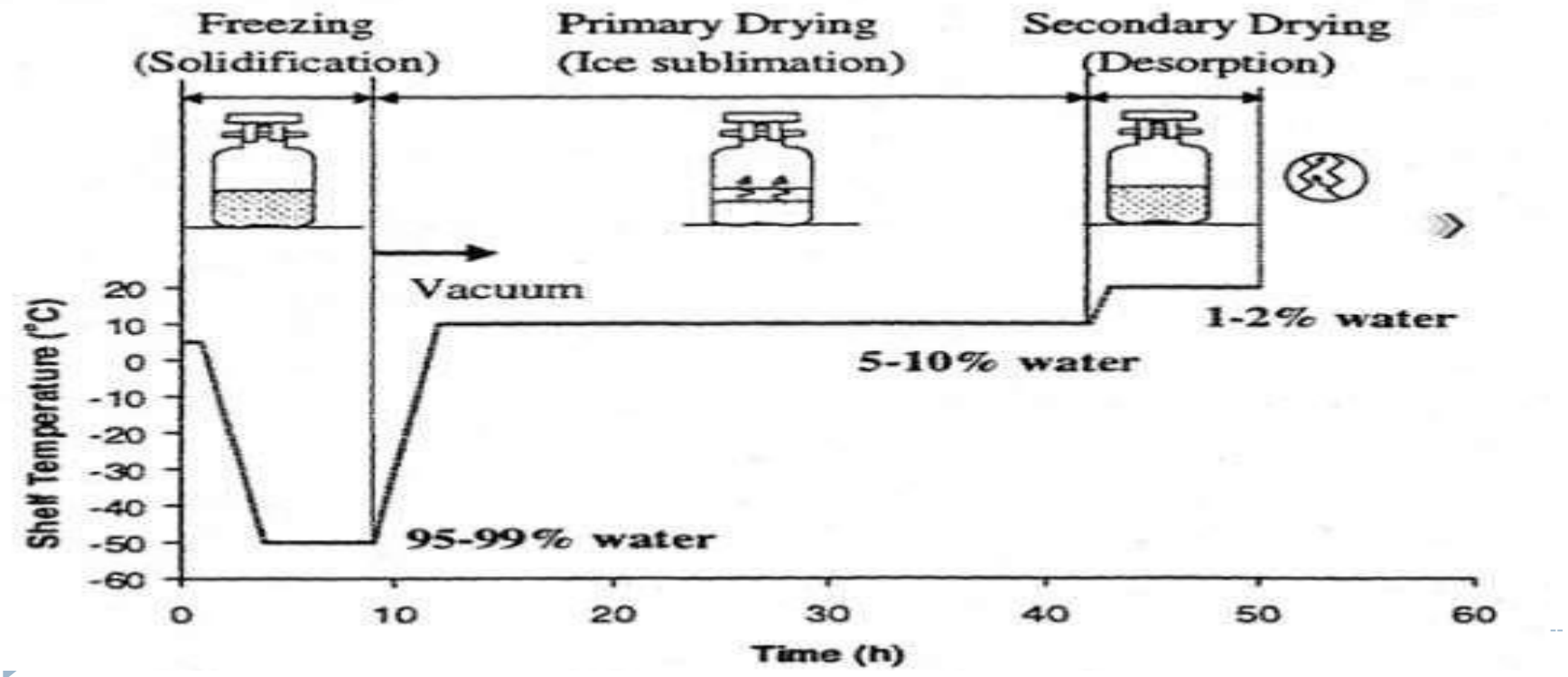
- Freezing the product solution to a temperature below its eutectic temperature.
- Decrease the shelf temperature to -50oc.
- Low temperature and low atmospheric pressure are maintained.
- Freons are used as refrigerant.
- Formation of ice crystals occurs.
- The rate of ice crystallization define the freezing process and efficiency of primary drying.

Primary Drying (Sublimation)

- Heat is introduced from shelf to the product under graded control by electrical resistance coils or circulating silicone.
- The temperature and pressure should be below the triple point of water i.e., 0.0098°C and 4.58mmHg.
- The driving force is vapor pressure difference between the evaporating surface and the condenser.
- Easily removes moisture up to 98% to 99%.

Secondary Drying (Desorption)

- The temperature is raised to 50°C – 60°C and vacuum is lowered about 50mmHg.
- Bound water is removed.
- Rate of drying is low.
- It takes about 10-20 hrs.

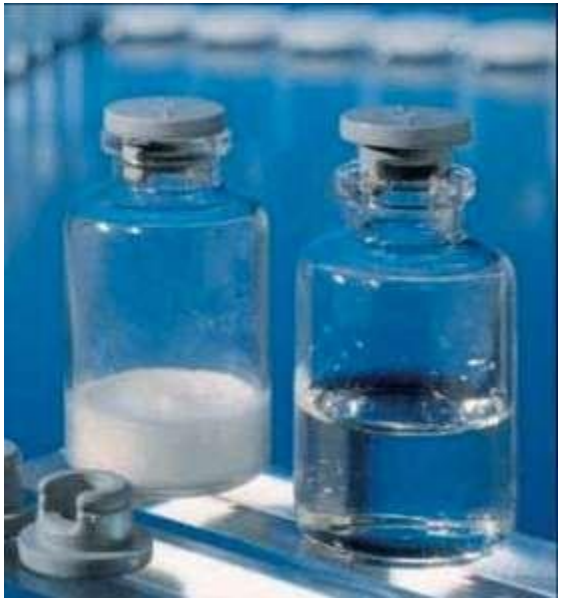


Packing

• After drying the vacuum is replaced by filtered dry air or nitrogen to establish atmospheric pressure

• Ampoules are sealed by either tip sealing or pull sealing method

• Vials and bottles are sealed with rubber closures and aluminum caps



Freeze Dry Product Characteristics

- Sufficient strength
- Uniform color
- Sufficiently dry
- Sufficiently porous
- Sterile
- Free of pyrogens and particulates
- Chemically stable both in dry state and reconstitution

Advantages of Lyophilization

- Removal of water at low temperature
- Thermolabile materials can be dried.
- Compatible with aseptic operations
- More precise fill weight control
- Sterility can be maintained.
- Reconstitution is easy

Disadvantages of Lyophilization

- Many biological molecules are damaged by the stress associated with freezing, freeze-drying, or both.
- The product is prone to oxidation, due to high porosity and large surface area. Therefore the product should be packed in vacuum or using inert gas or in a container impervious to gases
- Cost may be an issue, depending on the product
- Long time process

Common Lyophilized Products

- Pharmaceuticals – large and small molecules
- Bacteria
- Viruses
- Vaccines
- Plasma
- Small zoological specimens
- Fruit
- Coffee
- Flowers
- Water-Damaged documents.

Reference:

- Jain UK, Nayak S and DC Gopale, Pharmaceutical Packaging Technology, 2nd edition, PharmaMed Press, Hydrexpert committee for specification abad.
- Hiremath R Shobharani, Texbook of Industrial Pharmacy, Orient Longman Private Ltd., Chennai.
- Potdar Manohar A, cGMP for Pharmaceutics, , PharmaMed Press, Hydrabad.
- WHO expert committee on specification for pharmaceutical preparation, 36th report, WHO technical report series.
- www.slideshear.net.

- The science and practice of pharmacy by Remington, 21 edition, vol-1. Pg 828-831.

- The Theory And Practice of Industrial Pharmacy by Leon Lachmann, Herbert.A.Lieberman and Joseph I. Kanig, 1991. Pg 62-64, 672-674

.

- Pharmaceutial Engineering – Priniciples and Practices by C.V.S. Subramanyam, J. Thimma Setty, Sarasija Suresh and V. Kusum Devi. Pg 401-405.

- Aulton's Pharmaceutics – The Design And Manufacture Of Medicines by Micheal E. Aulton, 2009. Pg 195.

- The Lyophilization of Pharmaceuticals: A Literature Review by N.A. Williams* and G.P. Polli. Journal of Pharmaceutical science and Technology.