PHARMACY INDIA

# MODEL PAPER

# B.PHARMA

# 5th SEMESTER

## INDUSTRIAL PHARMACY-I

## (BP-502T)

# INDUSTRIAL PHARMACY-I MODEL PAPER

## SECTION A

### VERY SHORT ANSWERS TYPE QUESTIONS (10 × 2 = 20)

**1. Distinguish drugs on the basis of BCS classification.**

**Answer**

| | | |
|---|---|---|
| **Class-I** | High Permeability, High Solubility | Metoprolol, Diltiazem, Verapamil, Propranolol |
| **Class-II** | High Permeability, Low Solubility | Glibenclamide, Ezetimibe, Phenytoin, Nifedipine |
| **Class-III** | Low Permeability, High Solubility | Cimetidine, Acyclovir, Captopril |
| **Class-IV** | Low Permeability, Low Solubility | Hydrochlorothiazide |

**2. Classify tablets based on route of administration.**

**Answer**

| Tablets ingested orally | Tablets used in the oral cavity | Tablets administered by other route | Tablets used to prepare solution |
|---|---|---|---|
| 1. Compressed tablets or standard compressed tablets<br>2. Multiple compressed tablets<br>○ Layered tablets<br>○ Compression coated tablet<br>3. Chewable tablet<br>4. Sugar and chocolate coated tablet<br>5. Film coated tablet<br>6. Repeat action tablet<br>7. Delayed action tablet & enteric coated tablet<br>8. Controlled release tablets | 1. Buccal & sublingual tablets<br>2. Troches & lozenges<br>3. Dental cones | 1. Implantation tablet<br>2. Vaginal tablet | 1. Effervescent tablet<br>2. Dispensing tablet<br>3. Hypodermic tablet<br>4. Tablet triturates |

**3. Enlist various steps involved in the palletization process.**

**Answer**

- Palletization involves three consecutive steps:
  - Nucleation
  - Transition and
  - Ball growth

**4. Determine the base absorption and minim per gram factor in capsules.**

**Answer**

**Base Absorption**

- Weigh a definite amount (40 g is convenient) of solid into 150 ml tared beaker. In a separate 150ml tared beaker, place about 100g of the liquid base. Add small increment of base to thesolid and using the spatula, stir the base into the solid after each addition until the solid is completely wetted & uniformly coated with base.
- This should produce a mixture that has a soft ointment like consistency. Continue to add liquid and stir until the mixture flows steadily from the spatula blade when held at a $45^{o}$ angle above the mixture.

**Base adsorption = weight of base/weight of solid**

**Minim per gram**

- The minim per gram factor is calculated by dividing the weight of the base plus the gramof solid base (BA+S) by the weight of the mixture (W) per cubic centimeter or 16.23 minims (V).

**(BA+S) x V/W = M/g**

- Thus lower the base absorption of the solids and higher the density of the mixture, thesmaller the capsule will be.

**5. Classify propellants used in aerosols.**

**Answer**

**1. Liquefied Gases:**

(a) **Halogenated Hydrocarbons**: (Chlorofluro Carbons), Hydrofluorocarbons

Examples: Fluorinated chlorinated Hydrocarbons
Trichloro mono fluoro methane (11)
Dichloro difluro methane (12)
Dichloro tetra fluoro ethane (114)

**(b) Hydrocarbons:** Examples: Propane, Butane, Isobutane

**2. Compressed Gases:**

**(a) Soluble gases: Examples:** Carbon dioxide, Nitrous oxide

**(b) Insoluble gases: Examples:** Nitrogen

**6. Explain significance of isotonicity in ophthalmic preparations.**

**Answer**

**Significance of Isotonicity**

- An isotonic solution is one that exhibits the same effective osmotic pressure as blood serum.
- Isotonicity is important for parenteral preparation because if the solution is isotonic with blood, the possibility of product penetrating the RBC and causing haemolysis is reduced.
- For hypertonic solution crenation and for hypotonic solution haemolysis will occur.

**7. Enlist the methods used for preparing soft gelatin capsules.**

**Answer**

**Methods used for preparing Soft Gelatin Capsules**

1. Plate process
2. Rotary die process
3. Reciprocating die process
4. Accogel capsule filling machine

**8. Classify all types of glass used in pharmaceutical packaging.**

**Answer**

**Types of Glass**

| CONTAINER TYPE | GENERAL DESCRIPTION |
|---|---|
| Type I | Borosilicate glass |
| Type II | Treated soda- lime glass |
| Type III | Soda-lime glass |
| Type NP | General purpose sodalime glass |

**9. Define pre-formulation studies.**

**Answer**

- Preformulation may be defined as a stage of the research and development process where the Preformulation scientist characterizes the physical, chemical, biopharmaceutical and mechanical properties of a new drug substance, in order to develop stable, safe and effective dosage form.

**10. Define SPF.**

**Answer**

- SPF is a measure of how much solar energy (UV radiation) is required to produce sunburn on protected skin (i.e., in the presence of sunscreen) relative to the amount of solar energy required to produce sunburn on unprotected skin.

## SECTION B

### LONG ANSWERS TYPE QUESTIONS (2 × 10 = 20)

**1. Analyze the processing problems encountered during manufacturing of coated tablets and suggest remedies to resolve the same.**

**Answer**

**TABLET DEFECTS**

| PROCESS RELATED | FORMULATION RELATED |
|---|---|
| • Capping<br>• Lamination<br>• Cracking<br>• Chipping | • Sticking<br>• Picking<br>• Binding |

## CAPPING

- The upper or lower segment of the tablet separates horizontally, either partially or completely from the main body and comes off as a cap, during ejection from the tablet press, or during subsequent handling.

**Reason:**

Due to the air–entrapment in a compact during compression, and subsequent expansion of tablet on ejection of a tablet from a die.

**Causes and Remedies of Capping**

| S. NO | CAUSES | REMEDIES |
|---|---|---|
| 1. | Poorly finished dies | Polish dies properly.<br>Investigate other steels or other material |
| 2. | Deep concave punches | Use flat punches |

## LAMINATION

- Separation of a tablet into two or more distinct horizontal layers.

**Reason:**

- Air–entrapment during compression and subsequent release on ejection.
- The condition is exaggerated by higher speed of the turret.

**Causes and Remedies of Lamination**

| S. NO. | CAUSES | REMEDIES |
|---|---|---|
| 1. | Large number of fines in the granulation | Remove some or all fines through 100 to 200 mesh screens |
| 2. | Not thoroughly dried granules | Dry the granules properly |

## CHIPPING

- Breaking of tablet edges, while the tablet leaves the press or during subsequent handling and coating operations.

**Reason:**

- Incorrect machine settings, especially mis-set ejection take off.

**Causes and Remedies of Chipping related to 'Formulation'**

| S. NO. | CAUSES | REMEDIES |
|---|---|---|
| 1. | Sticking on punch faces | Dry the granules properly or increase lubrication |
| 2. | Too dry granules | Moisten the granules to plasticize. Add hygroscopic substance |

## CRACKING

- Small, fine cracks observed on the upper and lower central surface of tablets, or very rarely on the sidewall are referred to as 'Cracks'.

**Reason:**

- It is observed as a result of rapid expansion of tablets, especially when deep concave punches are used.

**Causes and Remedies of Cracking related to 'Formulation'**

| S. NO. | CAUSES | REMEDIES |
|---|---|---|
| 1. | Large size of granules | Reduce granule size. Add fines |
| 2. | Tablets expand | Improve Granulation. Add dry binders |

## STICKING

- Tablet material adhering to the die wall.
- Filming is a slow form of sticking and is largely due to excess moisture in the Granulation.

### Reason

- Improperly dried or improperly lubricated granules.

### Causes and Remedies of Sticking related to 'Formulation'

| S. NO. | CAUSES | REMEDIES |
|---|---|---|
| 1. | Granules not dried properly | Dry the granules properly. Make moisture analysis to determine limits |
| 2. | Too little or improper lubrication | Increase or change lubricant |

## PICKING

- Small amount of material from a tablet is sticking to and being removed off from the tablet-surface by a punch face.
- The problem is more prevalent on the upper punch faces than on the lower ones.

### Causes and Remedies of Picking related to 'Formulation'

| S. NO. | CAUSE | REMEDIES |
|---|---|---|
| 1. | Excessive moisture in granules | Dry properly the granules, determine optimum limit |
| 2. | Too little or improper lubrication | Increase lubrication, use colloidal silica as a polishing agent so that material does not cling to punch faces |

## BINDING

- Sticking of the tablet to the die and does not eject properly out of the die.
- Tablets adhere, seize or tear in the die.
- A film is formed in the die and ejection of tablet is hindered.
- With excessive binding, the tablet sides are cracked and it may crumble apart.

### Causes and Remedies of Binding related to 'Formulation'

| S.NO | CAUSES | REMEDIES |
|---|---|---|
| 1. | Too moist granules and extrudes around lower punch. | Dry the granules properly. |
| 2. | Insufficient or improper lubricant. | Increase the amount of lubricant or use a more effective lubricant. |

**2. Explain the preparation of dry powder by lyophilization. Evaluate the quality control tests for Parenterals.**

**Answer**

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## Preparation of Dry Powder by Lyophilization

- Lyophilization or freeze drying is a process in which water is removed from a product after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapor without passing through a liquid phase.
- Dissolving the drug and excipients in a suitable solvent, generally water for injection (WFI).
- Sterilizing the bulk solution by passing it through 0.22-micron bacteria-retentive filter.
- Filling into individual sterile containers and partially stoppering the containers under aseptic conditions.
- Transporting the partially stoppered containers to the lyophilizer and loading into the chamber under aseptic conditions.
- Freezing the solution by placing the partially stoppered containers on cooled shelves in a freeze-drying chamber or pre-freezing in another chamber.
- Applying a vacuum to the chamber and heating the shelves in order to evaporate the water from the frozen state.
- Complete stoppering of the vials usually by hydraulic or screw rod stoppering mechanisms installed in the lyophilizers. There are many new parenteral products, including anti-infectives, biotechnology derived products, and in-vitro diagnostics which are manufactured as lyophilized products.
- Additionally, inspections have disclosed potency, sterility and stability problems associated with the manufacture and control of lyophilized products.

## Quality Control Test for Parenterals

The following are the evaluation test for the parenteral. They are as follows.

1. Sterility test
2. Clarity test
3. Leakers test
4. Pyrogen test

1. **Sterility test:** It is a method carried out to detect confirm absence of any viable form of microbesin product. The method used for sterility tests are
    - Direct transfer method
    - Membrane filtration method

| Direct Transfer Method | Membrane Filtration Method |
|---|---|
| ✓ Open each sample container and with draw the require amount of the sample.<br>✓ Inject one-half of sample in a test tube containing fluid Thioglycolate Medium (FTM).<br>✓ Inject another half in the test tube containing Soyabean-casein digest Medium(SCM).<br>✓ Volume of the medium must be sufficient to promote and expedite microbial growth.<br>✓ Adequate mixing between the sample inoculums and the culture medium must take place to maximize interaction and facilitate microbial growth.<br>✓ If the product to be tested contains any anti-microbial agent, using suitable reagent it should be neutralized before the test. | ✓ This method is employed in the following cases:<br>• Oil & oily preparations<br>• Alcoholic preparations<br>• For preparations miscible with or soluble in aqueous or oily solvents.<br>✓ The steps involved in MF sterility test method are<br>i) The filter unit must be properly assembled and sterilized prior to use.<br>ii) The contents are transferred to the filter assembly under strict aseptic conditions.<br>iii) The membrane is removed aseptically.<br>iv) Membrane is cut in half.<br>v) One half is place in suitable volume of FTM and another in an equal volume of SCM.<br>**Interpretation of results:**<br>• If there is no visible evidence of microbial growth, it may be interpreted that the sample iswithout intrinsic contamination and the product complies the test for sterility.<br>• If microbial growth is found, the product does not comply the test for sterility and the sterilitytest may be repeated. |

**2. Clarity test (particulate matter evaluation): -**

- Particulate matter in parenteral solutions has been recognized as an acceptable.
- Since the user could be expected to conclude that the presence of visible dirt would suggest that, the product is of inferior quality.
- ***In visual method,*** the entire product should be inspected by human inspectors under good light baffled against reflection into the eye and against black and white background. Dark background detects light particles and light background detects dark particles. Any container with visible

particle if seen is discarded.

### 3. Leaker's test: -

- Leaker test for ampoules is intended to detect incompletely sealed ampoules so that they can be discarded in order to maintain sterile condition of the medicines.
- Open capillaries or cracks at the point of seal result in LEAKERS.
- The leaker test is performed by immersing the ampoules in a dye solution, such as 1% methylene blue, and applying at least 25 inches of vaccum for a minimum of 15 mins.
- Detection of leaker is prominent when ampoules are immersed in a bath of dye during autoclaving as this has advantage of acomplishing both leaker detection and sterilization in one operation.

### 4. Pyrogen test: -

- Pyrogens are the metabolic products of microbes. Most bacteria, moulds and viruses produce Pyrogen.
- Most potent pyrogenic substance called endotoxins are produced by gram negative bacteria.
- Pyrogens when injected into a human, shows marked rise in the temperature, chills, body aches, cutaneous vasoconstriction and increased arterial blood pressure. The most likely source of pyrogens are water, contaminated solutes and containers.
- The test involves measurement of the rise in body temperature of rabbits following the IVinjection of a sterile solution into ear vein of rabbit.
- Dose not exceeding 10 ml per kg injected intravenously within a period of not more than 10mins.
- Selection of animals - healthy, adult, not less than 1.5kg.
- Equipment and material used in test - glassware, syringes, needles.
- Retaining boxes - comfortable for rabbits as possible.
- Thermometers - standardized position in rectum, precision of 0.1°C.
- **Preliminary Test (Sham Test):**
    - If animals are used for the first time in a pyrogen test or have not been used during the 2previous weeks, condition them 1 to 3 days before testing the substance by injecting IV 10ml per kg pyrogen free saline solution warmed to about 38.5°c.
    - Record the temperature of the animals, beginning at least 90 mins before injection and continuing for 3 hours after injection.
    - Any animal showing a temperature variation of 0.6° or more must not be used in main test.

- **Main Test:**
  - The main test is carried out by using a group of 3 Rabbits.
  - Dissolve the substance in, ordilute with, pyrogen free saline solution.
  - Warm the liquid to approximately 38.5° beforeinjection.
  - Inject the solution under examination slowly into the marginal veins of the ear of eachrabbit over a period not exceeding 4 mins.
  - Record the temperature of each animal at half hourlyintervals for 3 hours after injection.
  - The difference between the initial temperature and themaximum temperature which is the highest temperature recorded for a rabbit is taken to be its response.

**Interpretation of Result:**

a). The test is carried out on the first group of 3 rabbits; if necessary on further groups of 3 rabbitsto a total of 4 groups, depending on the results obtained.

b). Intervals of passing or failing of products are on the basis of summed temperature response.

If the difference is negative, the result is counted as zero response.

| No. of Rabbits | Individu alTemp. Rise($^{O}$C) | Temp. Rise ingroup ($^{O}$C) | Test |
|---|---|---|---|
| 3 Rabbits | 0.6 | 1.4 | Passes |
| (If above not Passes)-: 3+5=8 Rabbits | 0.6 | 3.7 | Passes |
| If above Test not passes,the sample is said to Pyrogenic. | | | |

- **Bacterial Endotoxin Test (BET) or Limulus Amoebocyte Lysate Test (LAL Test):-**
  - The bacterial endotoxin test (BET) is a test to detect or quantify endotoxins from gram negative bacteria using Amoebocyte lysate from the horse shoe crab (Limulus polyphemus or Tachypleustridentatus).
  - The endotoxins of gram-negative bacteria form a firm gel within 60 mins in the presence of lysateof amebocytes of limulus polyphemus of horseshoe crab, when incubated at 37◦ c. Hence, the test is only effective with gram-negative bacteria, which constitute the majority and the most potent of the pyrogens.
  - The addition of a solution containing endotoxins to a solution of a lysate produces turbidity, precipitation or gelation of the mixture.

**3. Describe the basic components of a valve and aerosol container and broadly cite their importance.**

**Answer**

**CONTAINERS FOR AEROSOLS**

- The containers used for manufacture of aerosol must withstand pressures as high as 140 to 180 Psig at 130o F.
- The following aerosol containers have been used to package aerosol products.

| | | | |
|---|---|---|---|
| **Metal Containers** | **Tin plated steel:**<br>• Side-seam (Three-piece)<br>• Two-piece or draw<br>• Tin free steel | **Aluminium:**<br>• Two-piece<br>• One-piece (extruded or drawn) | **Stainless steel** |
| **Glass Containers** | 1. Uncoated glass<br>2. Plastic-coated glass | | |

**Metal Containers**

**1. Tin-plated Containers:**

- In order to produce an aerosol container which is light and relatively inexpensive, tin-plated steel is used for aerosol containers.
- The tin-plated steel container consists of a sheet of steel plate that is electroplated on both sides with tin.

**2. Aluminum Containers:**

**Manufacture:**

- These are produced by an impact extrusion process. Hence the container is seam less.
- This will give added strength to the container.
- Containers made in this way are available in sizes ranging from 15 ml to 150 ml.
- **Resistance:**
  - Many existing pharmaceuticals are packaged in aluminium containers, because these containers have lesser danger of incompatibility due to seamless nature and greater resistance to corrosion.
  - However, aluminium is corroded by pure water and pure ethanol.
  - The combination of ethanol and propellant-11 in an aluminium container has been shown to produce hydrogen, acetyl chloride, aluminium chloride, propellant-21 and other corrosive products.
  - Resistance can be given to container by coating the inside of a container with organic materials such as epoxy, vinyl and phenolic resins.

**3. Stainless Steel Containers:**

(i) These containers are limited to the smaller sizes, owing to production problems as well as cost.
(ii) The containers are available in sizes ranging from 5ml to 30ml.
(iii) They are extremely strong.
(iv) They are resistant. In most cases, no integral organic coating is required.
(v) These containers are used for inhalation aerosols.

**Glass Containers:**

Following two types of glass containers are available:

1. **Uncoated glass containers:** These containers have the advantage of decreased cost and high clarity. The contents can be viewed at all times.
2. **Plastic coated glass containers:** These are protected by a coating, which prevents the glass from shattering in the event of breakage.
   (a) The plastic coating adheres the container totally (except for the neck ring) and becomes an integral part of the container.
   (b) The plastic coating fits over the glass container

**VALVES**

**Continuous Spray Valve Aerosols**

- It consists of many parts made up of different materials.
- These parts are assembled using high-speed production techniques.

| | |
|---|---|
| **Ferrule or Mounting Cup** | • Ferrule is made up of tin-plated steel (rarely aluminium).<br>• Ferrule is used to mount the valve properly to the container. |
| **Valve Body or Housing** | • The housing is made from nylon or delrin.<br>• The housing contains an opening at the point of attachment of the dip tube, which ranges from about 0.013 to 0.08 inch. |
| **Stem** | • The stem is made from nylon, delrin, Brass, SS.<br>• The stem contains one or more orifices. |
| **Gasket** | • Gasket is made from Buna-N and Neoprene rubber. |
| **Spring** | • The spring is made from SS<br>• The spring serves to hold the gasket.<br>• When the actuator is depressed and released, the spring returns the valve to its closed position. |
| **Dip Tube** | • Dip tube is made from polyethylene or poly propylene.<br>• It conveys the liquid from the bottom of the container to the dispensing valve at the top. |
| **Actuator** | • Actuator is a specially designed button fitted to the valve stem. |

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## SECTION C

### SHORT ANSWERS TYPE QUESTIONS (5 × 7 = 20)

**1. Estimate various quality control tests for aerosols.**

**Answer**

**Quality Control Tests for Aerosols**

| | |
|---|---|
| **Flammability and Combustibility Tests** | 1. Flash point<br>2. Flame extension |
| **Physico-chemical Characteristics** | 1. Vapour pressure<br>2. Density<br>3. Moisture content<br>4. Identification of propellants |
| **Performance** | 1. Aerosol valve discharge rate<br>2. Spray pattern<br>3. Dosage with metered valves<br>4. Net contents<br>5. Foam stability<br>6. Particle size determination<br>7. Leakage |
| **Biologic characteristics** | 1. Therapeutic<br>2. Toxicity |

**Flammability and Combustibility Tests**

| | |
|---|---|
| **Flash Point** | Standard tag open cup apparatus is used to determine the flash point of aerosol product. The product is chilled to a temperature of −25° F. This liquid is placed in the tag open cup apparatus. The temperature of the liquid is increased slowly. The temperature at which the vapours ignite is taken as the flash point. |
| **Flame Projection** | The product is sprayed for about 4 seconds in a flame. Depending on the nature of the formulation, the flame is extended. The length of the extended flame is measured. |

**Physico-chemical Characteristics**

| | |
|---|---|
| **Vapour Pressure** | The vapour pressure is determined by pressure gauge. Excess variation of vapour pressure in the containers indicates the presence of air in the headspace. |
| **Density** | The density of an aerosol system may be accurately determined using hydrometer or pycnometer. The hydrometer is placed into glass pressure tube. Sufficient sample is introduced through the valve to cause the hydrometer to rise halfway up the length of the tube. The density can be read directly. |
| **Moisture content** | Karl Fischer apparatus is used to determine moisture content. |

| | |
|---|---|
| **Identification of propellants** | Gas chromatography and infrared spectrophotometry have been used to identify the propellants. The same techniques can also be used to determine the proportion of each component in a blend. |

**Performance**

| | |
|---|---|
| **Aerosol valve Discharge Rate** | The aerosol is weighed (w1 g) and discharged for a known period of time (t). The weight of aerosol (w2 g) after discharge is noted. Then rate is expressed as below;<br>Aerosol valve discharge rate = $w_1 - w_2$/ tg/sec |
| **Spray pattern** | The spray pattern of aerosol valve discharge is determined as follows. An apparatus consists of motor driven rotating disc with an adjustable slit. The filter paper coated with dye talc mixture is attached to rotating disc on one side (depending on the nature of the aerosol, an oil soluble or water soluble dye is used). The aerosol is sprayed on to fitter paper from the other side. The particles that strike the paper cause the dye to go into solution and to be absorbed into the paper. |
| **Dosage with metered valves** | When one attempts to test this, then either of the following must be observed.<br>(i) Reproducibility of dosage each time the valve is depressed.<br>(ii) Amount of medication actually received by the patient. |
| **Foam Stability** | The life of a foam can ranges from a few seconds to one hour or more. To determine the foam stability any one of the following methods is used.<br>(i) Actuate an aerosol to form the foam. Note down the time required for a complete collapse of foam by visual observation.<br>(ii) Actuate an aerosol to form the foam. Note down the time required for a given mass to penetrate the foam. |
| **Particle size determination** | • To determine particle size cascade impactor is used.<br>• Cascade impactor consists of series of nozzles and glass slides.<br>• When aerosol is actuated, larger particles impact first on the lower velocity stage.<br>• Then the smaller particles pass on and impact at next stage i.e., higher velocity stage.<br>• In such a way the particles ranging from 0.1 to 30 microns can be studied. |
| **Leakage** | Pass the crimped aerosol containers through the water bath. If any leaks are present, evolution of air bubbles can be observed and the container is rejected. |

**2. Illustrate the various applications of preformulation studies in**

**development of new chemical compound.**

**Answer**

**Applications of Preformulation Studies**

- To find the necessary physicochemical properties like solubility, crystal form of new
- drug substances.
- To determine kinetic release of drug from dosage form.
- To establish physical characteristics.
- To establish compatibility (no interaction) with common excipients.
- To find out the purity of a sample
- To find out the number of polymorphs and to determine the ratio of each polymorph.
- To determine the heat of solvation
- To find out the thermal degradation of a drug or excipients.
- To determine the glass-transition temperature (tg) of a polymer.
- Desolvation and decomposition processes are monitored.
- Comparing TGA and DSC data recorded under identical conditions can greatly aid in the interpretation of thermal processes.
- Identification of crystalline materials by using their diffraction pattern as a 'finger
- print'.
- To decide the storage condition i.e. at low humidity environment.
- To decide special packaging – e.g. with desiccant.
- Bulk density is required during the selection of capsule size for a high dose drug.

**3. Depict the manufacturing of Hard gelatin capsules.**

**Answer**

**Manufacturing of Hard Gelatin Capsules**

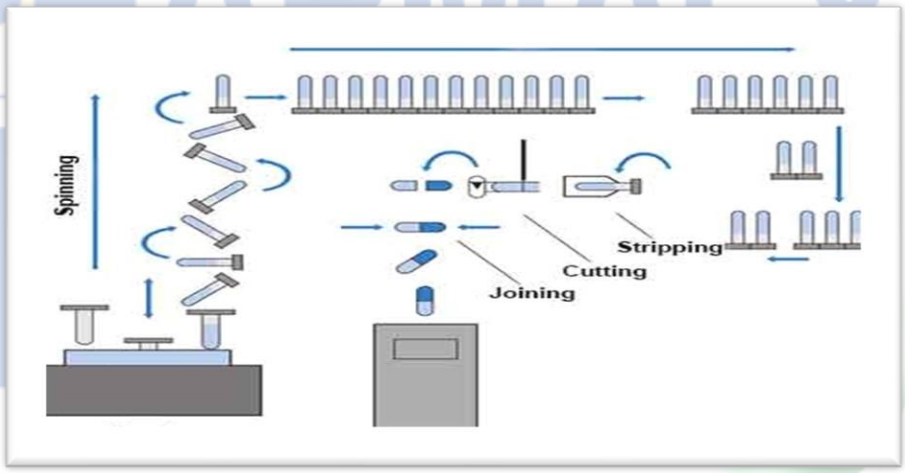
- The mechanism involved for production of hard gelatin capsule shell are
  - Dipping
  - Spinning
  - Drying
  - Stripping & Trimming
  - Joining

- **Preparation of the gelatin solution (dipping solution):** A concentrated solution of gelatin (35- 40%) is prepared by dissolving the gelatin in demineralized water which has been heated to 60–70°C in jacketed pressure vessels. This is stirred until the gelatin has dissolved and vacuum is applied to removed entrapped air bubbles. At this stage, other processing aids may be added like plasticizer, colourant, opaquing agent etc. The viscosity of gelatin preparation has to be controlled as it may affect downstream manufacturing process & very importantly thickness of shell.

- **Dipping:** Capsule shells are manufactured under strict climatic conditions by dipping pairs (body and cap) of standardized steel pins arranged in

rows on metal bars into an aqueous gelatinsolution (25 – 30% w/w) maintained at about 50 ° C in a jacketed heating pan.

- **Spinning of the dip-coated pins:** after adsorption of the gelatin solution on to the surface of the pins, the bar containing the pins is rotated more times to evenly distribute the gelatin solution around the pins, as uniform gelatin distribution being critical for correct and precise capsule wall thickness.
- **Drying of the gelatin-coated pins:** once the gelatin is evenly distributed on the mould, a blast of cool air is used to set the gelatin on the mould. At this point, the gelatin is dried, and the pins arethen passed through several drying stages to achieve the target moisture content.
- **Stripping & Trimming:** After the gelatin is dried, the capsule is stripped off the mould and trimmed tothe proper length.
- **Joining of the trimmed capsule shell:** Once trimmed, the two halves (the cap and body) are joined to the pre-closed position using a pre lock mechanism. At this point, printing is done ifneeded before packing in cartons for shipping.




**Sequence of two-piece hard gelatin capsule shell manufacture**

**4. Illustrate the production facilities and various control for manufacturing of parenteral dosage forms.**

**Answer**

**Production Facilities and Various Control for Manufacturing of Parenteral Dosage Forms**

The manufacturing of parenterals involves the following steps;

1) Cleaning and washing of containers and closures
2) Preparation of solutions
3) Sterilization
4) Filling and sealing
5) Evaluation of parenterals

6) Packaging and labeling

1. **Cleaning of containers and closures: -**
   - All the containers, closures and equipment's which are required during the preparation of parental products are thoroughly cleaned with detergent and washing is done with tap water, followed by clean distilled water and finally rinsed with water for injection.
   - Rubber closures are washed with hot solution of 0.5 % sodium pyrophosphate in water.

2. **Preparation of Solution: -**
   - The various ingredients of the formulation of parental preparations are weighed and collected in the preparation room.
   - The raw materials requiredin the preparation of parenteral products should be pure.
   - Water for injection free from pyrogens and microorganisms are used in preparation of parenteral products.
   - The Industrial pharmacist should decide the order of mixing and exact method of preparation to be followed before preparing the parenteral products.
   - The parenteral preparation must be prepared under strict aseptic conditions.

3. **Sterilization: -**
   - The parental preparations should be immediately sterilized after sealing in its final containers.
   - The sterilization is done by any one of the methods of sterilization, which depends on the nature of Medicaments present in the parenteral preparations.
   - For thermostable medicament, the parenteral product are sterilized either by autoclaving at the temperature of 115°C to 116°C for 30 minutes or 121 degree centigrade for 20 minutesor in hot air oven at 160 degree centigrade for 2 hours.

4. **Filling and Sealing: -**
   - The filtered product is filled into final container such as, ampoules, vials and transfusion bottles, which are previously cleaned and dried.
   - Ampoules are used for feeling single dose whereas, vials are used for filling multidose.
   - The sterile Powders are filled into containers by individual weighing or by using automatic or semi-automatic devices.
   - The filling operation is carried out under strict aseptic precautions.

5. **Evaluation of Parenteral: -** The finished parenteral products are subjected to the following test, in order to maintain quality control.
   a) Sterility test b) clarity test c) Leakage test d) Pyrogen test.

6. **Packaging and labeling: -** After evaluation of the parenteral preparation, the ampoules, vials and transfusion bottles are properly labelled and packed.

## Production facilities and controls

The production area where the parenteral preparations are manufactured can be divided intothe following five sections.

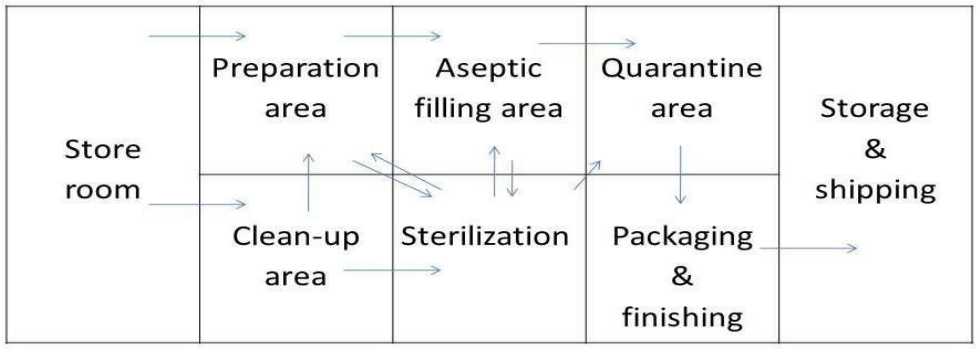
1) Clean-up area
2) Preparation area
3) Aseptic area
4) Quarantine area
5) Finishing & packaging area

### 1. Clean-up area:

- It is not aseptic area.
- All the parenteral products must be free from foreign particles & microorganism.
- Clean-up area should be withstand moisture, dust & detergent.
- This area should be kept clean so that contaminants may not be carried out intoaseptic area.

### 2. Preparation area:

- In this area the ingredients of the parenteral preparation are mixed & preparation ismade for filling operation.
- It is not essentially aseptic area but strict precautions are required to prevent anycontamination from outside.




### 3. Aseptic area:

- The parenteral preparations are filtered, filled into final container & sealed in aseptic area.
- The entry of personnel into aseptic area should be limited & through an air lock.
- Ceiling, wall & floor of that area should be sealed & painted.
- The air in the aseptic area should be free from fibers, dust and microorganism.
- The High efficiency particulate air filters (HEPA) is used for air.

- UV lamps are fitted in order to maintain sterility.

**4. Quarantine area:**

- After filling, sealing & sterilization the parenteral product are held up in quarantine area.
- Randomly samples were kept for evaluation.
- The batch or product pass the evaluation tests are transfer in to finishing or packaging area.

**5. Finishing & packaging area:**

- Parenteral products are properly labelled and packed.
- Properly packing is essential to provide protection against physical damage.
- The labelled container should be packed in cardboard or plastic container.
- Ampoules should be packed in partitioned boxes.

**5. Predict the legal and official requirements for packaging materials.**

**Answer**

**Legal requirements: Pharmaceutical Packaging**

- The regulator sees the pack as having the following characteristics.
- Regulator means the regulatory body, it may be FDA, it may be CDSCO. So, different country and different regulatory agencies in general have the same concept with respect to these factors:

| | |
|---|---|
| **Containing the product** | ▪ Protection of the product<br>▪ Protection of the consumer<br>▪ Dosage control |
| **Carrying the label** | ▪ Legal control of the product<br>▪ Informing the recipient |
| **Contaminating the environment** | ▪ Packaging waste<br>▪ Ozone depletion |
| **Protecting the consumer** | ▪ Child-resistant closures<br>▪ Tamper-evidence. |

- The packaging technologist had been saying for years that packaging development cannot be separated from product development. You cannot separate the packaging development and product development. It had been insisted that it was not possible to separate the pack and product.
- There are several factors, as below
  A. Increasing sophistication of the pack
  B. Increasing sophistication of the product
  C. Incorporating a device into the pack
  D. Cost of development
- These are the four major factors which have separated the packaging development from product development.

**A. Increasing sophistication of the pack**

- Using glass over plastic packaging is the best example
- Glass is preferable because of its inert nature
- Plastics tend to interact with product and destabilizes the formulation
- So regulatory authorities are very cautious about the selection of the right packaging material

**B. Increasing sophistication of the product**

- To develop a new drug is very much time taking and costly process. So industry has shifted its focus of research to the improvement of existing formulation.
- Rather than investing in the new drug development (though it being invested) but their focus has shifted from new drug development to the improvement of the existing formulation.
- So, changing in the packaging or innovative packaging is the most reliable method to improve the stability of product. And by this way they can have the market gain.

**C. Incorporating a device into the pack**

- What is a device into the pack? Aerosol. Aerosol is itself a device into the pack. Rather it's a package as well as the product.
- Metering the dose using advanced containers. We are using the metering the doses with the advances containers in so many ways (you might have seen).
- Nebulizers and insulin syringes are the best examples in this category.
- Painless needles and dry vaccine delivery systems are also under development.

**D. Cost of development**

- The cost of developing a safer and advanced packaging technique is much cheaper than the development of a new advanced chemical entity.

**6. Discuss briefly about formulation of cold cream.**

**Answer**

- These types of emulsions are water-in-oil type of emulsions.
- They produce cooling sensation by the evaporation of water, after application of cream to the skin. Hence, they are known as creams.
- They should produce emollient action by the layer left on the skin after application, should be non-occlusive.

| Formula | Quantity for 100 g |
|---|---|
| Beeswax | 8 g |
| Mineral oil (light liquid paraffin) | 20 ml |
| Borax | 0.5 g |
| Distilled water | 10 ml |
| Perfume | q.s. |

**Method of Preparation of Cold Cream:**

1. Beeswax is melted in a container by using water bath to temperature of about 70°C.

2. The mineral oil is added to the melted beeswax. This is mixture A.
3. In another container water is heated to the temperature of about 70°C and borax is dissolved in it. This is mixture B.
4. Mixture B is added slowly to the mixture A along with stirring.
5. Finally, perfume is added to the formulation.

## 7. Discuss different granulation methods.

**Answer**

- Granulation process may be defined as a process wherein small particles adhere together by forming bonds between them, resulting in the formation of large aggregates called granules.

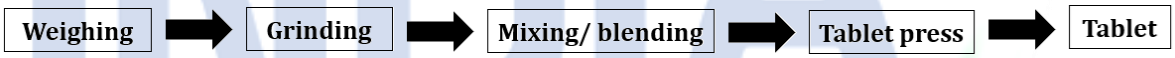
### Methods of Granulation

Some of the available methods in the industrial field for the preparation of granules:

A. Direct compression.
B. Dry granulation methods.
C. Wet Granulation.

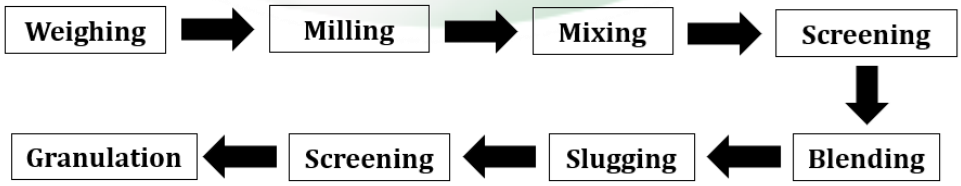
### A. Direct compression

- Direct compression is a dry process where in the powdered material (tablet formulation) is compressed directly into the tablets without the physical nature of the former being modified.
- **Examples:**
  - Formulation of Ascorbic Acid Tablets.
  - Formulation of Chewable Antacid Tablets.
- **Direct compression procedure**



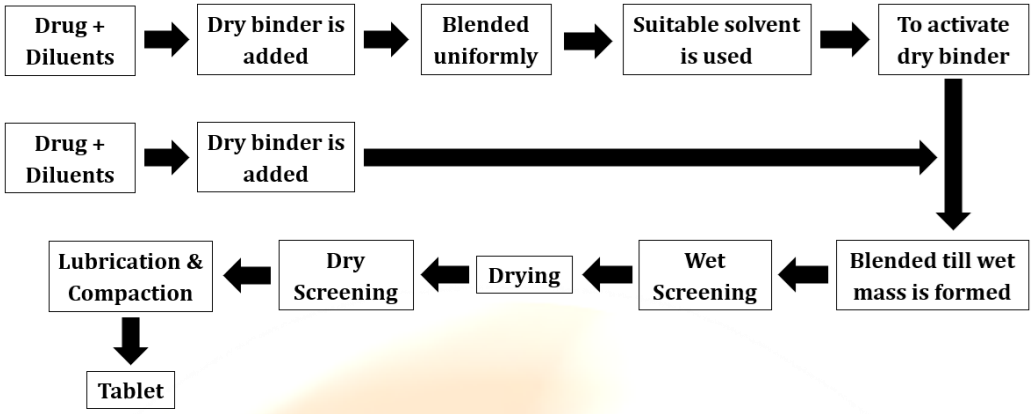

### B. Dry Granulation

- The process of dry granulation is also called Double Compression or Compression
- Granulation or Pre-Compression Granulation.
- The technique of Dry granulation of powdered material can be accomplished by two methods.
  (a) Slugging (slug formation).
  (b) Roller compaction method.




- **Examples:**
  - Formulation of Acetyl Salicylic Acid tablets.
  - Formulation of Vitamin B Complex.

## C. Wet Granulation




- Wet granulation or Moist granulation is the most conventional, versatile and widely used techniques for the manufacture of compressed tablets, as it imparts all the physical properties to the granules.
- This technique differs from the other granulation methods as it involves the usage of liquids to form compact masses.
- **Examples:**
  - Formulation of Acetaminophen tablets.
  - Formulation of Aluminium Hydroxide Chewable tablets.