# AS-2521

**Model Answer**

## B. Pharm. (Fifth Semester) Examination
## Pharmaceutical Technology-I

**Note: 1. All questions in section A are compulsory. Each question carries 2 marks.** (2x12=24)

**2. Attempts any four questions from section B.** (4x14=56)

## Section A

1. **Capsule weighing machine Rotoweigh used for weight variation testing, is based on**

**Ans**. c. Reflected energy α weight

**2. Ac-Di-Sol is**

**Ans**. c. marketed disintegrant of CMC

**3. Blood carrying bags are generally made up of**

**Ans**. c. Polypropylene

**4. Cerelose is a brand name of**

**Ans**. c. Dextrose

**5. Melting point of cocoa butter reduced by volatile oils can be corrected by adding**

**Ans**. a. Spermaceti

**6. Classify tablets.**

**Ans**. Tablets are classified on the basis of shape and size, process involved in its preparation and route and other characteristics.

**Oral Tablet for Ingestion**
Standard compressed tablets
Multiple compressed tablets
Compression coated tablet
Layered tablet
Inlay tablet

**Modified Release tablet**
Delayed action tablet

**Targeted tablet**
Floating tablet
Colon targeting tablet
Chewable tablet
Dispersible tablet

**Tablet Used In the Oral Cavity**
Lozenges and troches
Sublingual tablet
Buccal tablet
Dental cones
Mouth dissolved tablet

**Tablets Administered By Other Routes**
Vaginal tablet
Implants

**Tablets Used To Prepare Solution**
Effervescent tablet
Hypodermic tablet
Soluble tablet

**7. Why tablet coating is required?**

**Ans**. Tablet coating required:

1. To mask the unpleasant taste of drug
2. Environment protection
3. Separation of incompatible ingredients
4. For site specific delivery e.g. Enteric coating
5. Sugar coating for children

**8. Define salt polishing.**

**Ans**. Salt polishing is a finishing step in the preparation of capsule in which capsules are polished with salt in a coating pan. It is performed to remove adhered particles from capsules.

**9. Give name of the different ointment bases.**

**Ans**. 1. Oleaginous base e.g. hydrocarbon

2. Absorption base e.g. mixed of animal sterols

3. Emulsion base

4. Water soluble base e. g. PEG

**10. Write the qualities of an ideal suppository bases.**

**Ans**. Ideal suppository bases possess following qualities:

1- Melts at body temperature or dissolves in body fluids.
2- Non-toxic and non-irritant.
3- Compatible with any medicament.
4- Releases any medicament readily.
5- Easily molded and removed from the mould.
6- Stable to heating above the melting point.
7- Easy to handle.
8- Stable on storage.

**11. Give name of different types of glass containers.**

**Ans**. Type I : Borosilicate glass

Type II: Treated Soda Lime

Type III: Regular Soda Lime

Type IV: General Purpose glass

**12. Write the merits of enteric coated tablets.**

**Ans.** Enteric coated tablets:

1. Provide site specific absorption of drugs
2. Useful for the drugs that have an irritant effect on the stomach, such as aspirin.
3. Provide stability to the drugs at the highly acidic pH found in the stomach

## Section B

**2. (a) Discuss different equipments used in coating process.**

Three general types of equipments are used in coating process

1. **Standard coating pan**

e.g., Pellegrin pan system

Immersion sword system

Immersion tube system

2**. Perforated pan system**

e.g., Accela cota system

Hi coater system

Glatt coater system

Dria coated system

3. **Fluidized bed coater**

**2 (b) Elaborate film defects in film coating.**

Common defects associated with coated tablets and some likely causes and the remedies.
Twinning
Tablet surface erosion
Edge erosion
Splitting and peeling
Core expansion
Cracking
Tablet to tablet color variation
Within tablet color variation
Orange peel
Logo bridging

***Picking and sticking***

This is when the coating removes a piece of the tablet from the core. Over wetting or examples or excessive film tackiness causes tablets to stick to each other or to the coating pan. On drying, at the point of contact, a piece of the film may remain adhered to the pan or to another tablet, giving a "picked" appearance to the tablet surface and resulting in a small exposed area of the core. It is caused by over-wetting the tablets, by under-drying, or by poor tablet quality. **Remedy:** A reduction in the liquid application rate or increase in the drying air temperature and air volume usually solves this problem. Excessive tackiness may be an indication of a poor formulation

***Twinning***

This is the term for two tablets that stick together, and it's a common problem with capsule shaped tablets.

**Remedy:** Assuming you don't wish to change the tablet shape, you can solve this problem by balancing the pan speed and spray rate. Try reducing the spray rate or increasing the pan speed. In some cases, it is necessary to modify the design of the tooling by very slightly changing the radius. The change is almost impossible to see, but it prevents the twinning problem.

***Color Variation***

This problem can be caused by processing conditions or the formulation. Improper mixing, uneven spray pattern and insufficient coating may result in color variation. The migration of soluble dyes, plasticizers and other additives during drying may give the coating a mottled or spotted appearance.

**Remedy:** 1. The use of lake dyes eliminates dye migration. 2. A reformulation with different plasticizers and additives is the best way to solve film instabilities caused by the ingredients.

***Orange Peel***

This refers to a coating texture that resembles the surface of an orange. Inadequate spreading of the coating solution before drying causes a bumpy or "orange-peel" effect on the coating. It is usually the result of high atomization pressure in combination with spray rates that are too high. This also indicates that spreading is impeded by too rapid drying or by high solution viscosity.
**Remedy:** Thinning the solution with additional solvent may correct this problem.

***Mottled color***

This can happen when the coating solution is improperly prepared, the actual spray rate differs from the target rate, the tablet cores are cold, or the drying rate is out of specification.

***Capping and Lamination***

This is when the tablet separates in laminar fashion. Capping is partial or complete separation of top or bottom crowns of tablet main body. Lamination is separation of a tablet into two or more distinct layers. Friability test can be used to reveal these problems. The problem stems from improper tablet compression, but it may not reveal itself until you start coating.
**Remedy:** Be careful not to over-dry the tablets in the preheating stage. That can make the tablets brittle and promote capping.

***Roughness***

A rough or gritty surface is a defect often observed when coating is applied by a spray. Some of the droplets may dry too rapidly before reaching the tablet bed, resulting in the deposits on the tablet surface of "spray dried" particles instead of finely divided droplets of coating solution. Surface roughness also increases with pigment concentration and polymer concentration in the coating solution.

**Remedy:** Moving the nozzle closer to the tablet bed and reducing the degree of atomization can decrease the roughness due to "spray drying".

***Hazing / Dull Film***

This is sometimes called Bloom. It can occur when too high a processing temperature is used for a particular formulation. Dulling is particularly evident when cellulosic polymers are applied out of aqueous media at high processing temperatures. It can also occur if the coated tablets are exposed to high humidity conditions and partial salvation of film results.

***Bridging***

This occurs when the coating fills in the lettering or logo on the tablet and is typically caused by improper application of the solution, poor design of the tablet embossing, high coating viscosity, high percentage of solids in the solution, or improper atomization pressure. During drying, the film may shrink and pull away from the sharp corners of an intagliation or bisect, resulting in a "bridging" of the surface. This defect can be so severe that the monogram or bisect is completely obscured.
**Remedy:** Increasing the plasticizer content or changing the plasticizer can decrease the incidence of bridging.

***Filling***
Filling is caused by applying too much solution, resulting in a thick film that fills and narrows the monogram or bisect. In addition, if the solution is applied too fast, Over wetting may cause the liquid to quickly fill and be retained in the monogram.

**Remedy:** Judicious monitoring of the fluid application rate and thorough mixing of the tablets in the pan can prevent filling.

***Erosion***

This can be the result of soft or friable tablets (and the pan turning too fast), an over-wetted tablet surface, inadequate drying, or lack of tablet surface strength.

***Peeling and frosting***

This is a defect where the coating peels away from the tablet surface in a sheet. Peeling indicates that the coating solution did not lock into the tablet surface. This could be due to a defect in the coating solution, over-wetting, or high moisture content in the tablet core which prevented the coating to adhering.

***Chipping***
This is the result of high pan speed, a friable tablet core, or a coating solution that lacks a good plasticizer

***Blistering***
When coated tablets require further drying in ovens, too rapid evaporation of the solvent from the core and the effect of high temperature on the strength, elasticity and adhesion of the film may result in blistering.

**Remedy:** Milder drying conditions are warranted in this case.

***Cracking***
It occurs if internal stresses in the film exceed the tensile strength of the film. **Remedy**: tensile strength of the film can be increased by Using higher molecular weight polymers or polymer blends.

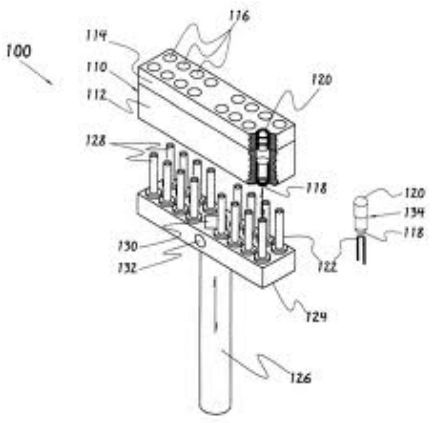
**3 (a) Differentiate hard and soft gelatin capsules. Explain the construction and working of plate and rotary die process.**

Difference between Hard Gelatin and Soft Gelatin Capsules:-

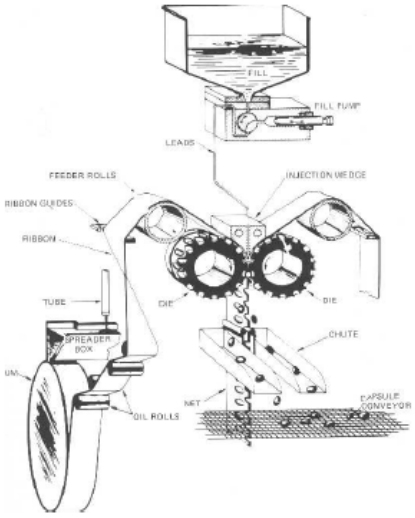
| S. No. | Hard Gelatin Capsule | Soft Gelatin Capsule |
|---|---|---|
| 1 | Hard gelatin capsules shell consists of two parts:-a) Body b) Cap | Soft gelatin capsule shell becomes a single unit after sealing the two halves of the capsules |
| 2 | Hard gelatin capsules are cylindrical in shape | soft gelatin capsules are available in round, oval and tube like shapes |
| 3 | The contents of a hard gelatin capsule usually consist of the medicament or mixture of medicaments in the form of powder, beads or granules | The contents of soft gelatin capsules usually consist of liquids or solids dissolved or dispersed in suitable excipients to give a paste-like consistency |
| 4 | Hard gelatin capsules are prepared from gelatin, titanium dioxide, colouring agent and plasticizer | Soft gelatin capsules are prepared from gelatin, plasticizer (Glycerine or Sorbitol) and a preservative |
| 5 | Hard gelatin capsules are sealed after they are filled to ensure that the medicaments may not come out of the capsule due to rough handling | Filling and sealing of soft gelatin capsules are done in a combined operation on machines. |
| 6 | Traditional friction-fit; mechanical interlock, banding and liquid sealing possible | Hermetically sealed (inherent) |

There are several procedures to prepare soft gelatin capsules, such as the plate process, the rotary die process, and reciprocating die process.

**Plate Process**: A warm sheet of prepared gelatin is laid over the lower plate and the liquid is poured on it. A second sheet of gelatin is carefully put in place and this is followed by the top plate of the mold. The set is placed under the press where pressure is applied to form the capsule which is washed off with a volatile solvent to remove any trace of oil from the exterior.



**Rotary die process:** Most soft gelatin capsules produced in industry are prepared by the rotary-die process (see Figure). In this process, two continuous gelatin ribbons are brought together between twin rotating dies. At the moment that the dies form pockets of the gelatin ribbons, metered-fill material is injected between the ribbons. Then the pockets of fill-containing gelatin are sealed by pressure and heat. The capsules are subsequently severed from the ribbon. As the capsules are cut from the ribbons, they may be collected in a refrigerated tank to prevent capsules from adhering to one another and from getting dull.




**3 (b) Discuss different sealing techniques of hard gelatin capsule.**

1. A hydro-alcoholic fusion process (described in the USP's capsule monograph) is one method of sealing. See Figure 4. This fusion process begins with an application of less than 50 microliters of sealing solution to the cap-body interface. The solution penetrates the overlapping cap and body by capillary action, while a vacuum removes any excess sealing fluid from the capsule. Next, gentle application of warm (40° to 60°C) air fuses the gelatin of the cap and body together and evaporates the sealing solution.
2. Another method entails banding the cap-body interface with a thin strip of gelatin. Banding, however, involves several additional tasks compared with hydroalcoholic sealing.
3. By applying acacia gum etc
4. Heating method
5. Mechanically Interlocking Caps and Bodies

Interlocking rings or bumps molded into the cap and body side-walls e.g. Posilok (Shionogi), Snap-Fit and Coni-snap (Capsugel), Lox-it (Pharmaphil)

**4 (a) Describe testing of suppositories dosage form.**

1- ***Appearance***: This includes odour, colour, surface condition and shape.

2- ***Weight Uniformity***:- Weigh 20 suppositories individually. w1, w2, w3….w20

- Weigh all the suppositories together = W.
- Calculate the average weight = W/20.

Limit: Not more than 2 suppositories differ from the average weight by more than 5%, and no suppository differs from the average weight by more than 10%.

3- ***Melting range test***:- Determines the time taken by an entire suppository to melt when it is immersed in a constant temperature bath at 37°C. The experiment done by using the USP Tablet Disintegration Apparatus.

Procedure:-The suppository is completely immersed in the constant temperature water bath, and the time for the entire suppository to melt or disperse in the surrounding water is measured. The suppository is considered disintegrated when:

A- It is completely dissolved or

B- Dispersed into its component part.

C- Become soft "change in shape" with formation of core which is not resistant to pressure with glass rod.

4- **Liquefaction Time or Softening Time Test**:- In this test a U tube is partially immersed in a constant temperature bath and is maintained at a temperature between 35 to 37°C. There is a constriction in the tube in which the suppository is kept and above the suppository, a glass rod is kept. The time taken for the glass rod to go through the suppository and reach the constriction is known as the liquefaction time or softening time.

Another apparatus is there for finding "softening time" which mimics in vivo conditions. It uses a cellophane tube, and the temperature is maintained by water circulation. Time taken for the suppository to melt is noted.

5- **Breaking Test (Hardness)**: - The breaking test is designed as a method for measuring the fragility or brittleness of suppository.

1-The suppository is placed in the instrument.

2- Add 600 g; leave it for one min. (use a stop watch).

3- If not broken, add 200 g every one min. until the suppository is broken.

**6- Dissolution test**:- By using different types of apparatus such as wire mesh basket, or dialysis tubing is used to test for in vitro release from suppositories.

**7- Stability testing**:-Cocoa butter suppositories on storage, "bloom"; i.e., they form a white powdery deposit on the surface. This can be avoided by storing the suppositories at uniform cool temperatures and by wrapping them in foils.

- Fat based suppositories harden on storage, i.e., there is an upward shift in melting range due to slow crystallization to the more stable polymorphic forms of the base.

- The softening time test and differential scanning calorimetry can be used as stability indicating test methods.

- If we store the suppositories at an elevated temperature, just below its melting range, immediately after manufacture, the aging process is speeded up.

**4 (b) Discuss various factors affecting absorption from suppositories.**

**Physiological factors affecting rectal absorption:**

***1- Quantity of fluid available:***

The quantity of fluid available for drug dissolution is very small (approximately 3 ml). Thus the dissolution of slightly soluble substances is the slowest step in the absorptive process.

***2- The properties of rectal fluid:***

The rectal fluid is neutral in pH (7 – 8) and has no buffer capacity.

***3. Contents of the rectum:***

When systemic effects are desired, greater absorption may be expected from an empty rectum as the drug will be in good contact with the absorbing surface of the rectum.

***4- Circulation route:***

The lower hemorrhoidal veins surrounding the colon receive the absorbed drug and initiate its circulation throughout the body, bypassing the liver. Lymphatic circulation also assists in the absorption.

**Physicochemical factors of the drug and suppository base affecting rectal absorption:**

***1- Drug solubility in vehicle:***

- The rate at which a drug is released from a suppository and absorbed by the rectal mucous membrane is directly related to its solubility in the vehicle or, in other words, to the partition coefficient of the drug between the vehicle and the rectal liquids.

- When drugs are highly soluble in the vehicle the tendency to leave the vehicle will be small and so the release rate into the rectal fluid will be low.

Drug solubility and suppository formulation

Solubility in

| Fat | Water | Choice of base |
|---|---|---|
| low | high | Fatty base |
| high | low | Aqueous base |
| low | low | Indeterminate |

***2-Particle Size:***

- For drugs present in a suppository in the undissolved state, the size of the drug particle will influence its rate of dissolution and its availability for absorption.

- The smaller the particles size the more readily the dissolution of the particle the greater chance for rapid absorption.

***3- Nature of the base:***

- The base must be capable of melting, softening, or dissolving to release its drug components for absorption.

- If the base interacts with the drug inhibiting its release drug absorption will be impaired or even prevented.

- Also, if the base is irritating to the mucous membranes of the rectum it may initiate a colonic response and a bowel movement incomplete drug release and absorption.

***4- Spreading Capacity:***

- The rapidity and intensity of the therapeutic effects of suppositories are related to the surface area of the rectal mucous membrane covered by the melted base : drug mixture (the spreading capacity of the suppositories). This spreading capacity may be related to the presence of surfactants in the base.

**5 What are emulsion creams? Explain with examples different raw materials used in the formulation of cream.**

A **cream** is a topical preparation usually for application to the skin. Emulsion creams are o/w or w/o emulsion. Emulsion cream are advantageous as they are non greasy, organoleptically acceptable, both oil and water soluble ingredients can be incorporated in one system etc.

Raw materials used in the preparation of emulsion cream include

1. **Purified Water**: Water should be demonized or distilled. If pure water is not used in creams, discoloration and other defects may be encountered with aging.
2. **Oil, fat and waxes**: Oil, fat, waxes and derivatives comprise an essential portion of a cream.
   Oils may be of two types:- Mineral and Glycerides
   e.g.hydrocarbons, lanolin, petrolatum, stearic acid etc
3. **Humectants**: Humectants are substances which have the capacity to retain water. They also impart viscosity, softness and emolliency to the product. eg Glycerol, PEG, invert sugar etc.
4. **Emulsifier:** Emulsifying agents are an indispensable part of creams as the creams are either o/w or w/o emulsions. The main purpose of these emulgents is to lower the interfacial tension between the water and oil or other water insoluble substances entering the emulsion. Emulsifying agents may be classified as:- Inorganic solids, gums and proteins and surface active agents.
   **eg .** Inorganic solids: bentonite, colloidal kaolin

   Gums and proteins: gum tragacanth, methyl cellulose

   Surface active agents: soaps, TEA
5. **Wetting agents:** To wet the insoluble particles. eg fatty alcohol sulfate
6. **Dispersing agents:** Aids in keeping oil droplets separated when reduced in size.
7. **Opacifier:** For opaque appearance with better hiding power eg $TiO_2$.
8. **Preservatives:** Should always be present if the cream contains substances likely to deteriorate under bacterial or fungal action eg methyl and propyl parabenes
9. **Pigments**: $TiO_2$ and for various color.
10. **Suspending agents:** Suspending agents are required for pigments eg bentinite, cellulose derivatives.d chain fatty acids and esters.
11. **Porositones:** Porositones give porosity to film building materials and allow skin to respire eg branch
12. **Detergents:** In case of cleansing cream eg sodium cetyl sulfate.
13. **Antioxidants**: eg BHT, BHA and propyl gallate
14. **Coloring agents:** Agent that impart color to the product

15. **Flavoring agents:** Agent that impart scent or odor to the product eg rose oil
16. **Vitamins:** Vitamin A, D, E, $B_6$
17. **Special additives**
    **Sunscreen agent:** salts of quinine
    **Urea:** moisturizer, desquamating agent.
    **Antiacne agents:** eg salicylic acid, resorcinol etc

**6 What do you mean by 'Tamper-Resistant packaging? Discuss in detail different tamper-resistant packaging system.**

A tamper-resistant package has an indicator or barrier to entry that, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred. Regulations to implement tamper-resistant packaging on all over-the-counter drugs and certain cosmetics began in February 1983. Tamper-resistant packaging, like child-resistant packaging, may impede access by the elderly and other adults who have mental, motor, and/or sensory disabilities.

Manufacturers and packagers are free to use any packaging system as long as the tamper-resistant standard in the regulations is met. The TRP requirements are intended to assure that the product's packaging "can reasonably be expected to provide visible evidence to consumers that tampering has occurred. Examples of packaging technologies capable of meeting the TRP requirements are listed below. Packaging features must be properly designed and appropriately applied to be effective TRP.

1. FILM WRAPPERS. A transparent film is wrapped securely around the entire product container. The film must be cut or torn to open the container and remove the product. A tight "fit" of the film around the container must be achieved, e.g., by a shrink-type process. A film wrapper sealed with overlapping end flaps must not be capable of being opened and resealed without leaving visible evidence of entry. The use of cellophane with overlapping end flaps is not effective as a tamper-resistant feature because of the possibility that the end flaps can be opened and resealed without leaving visible evidence of entry. The film wrapper must employ an identifying characteristic that cannot be readily duplicated. An identifying characteristic that is proprietary and different for each product size is recommended. Tinted wrappers are no longer acceptable as an identifying characteristic because of the possibility that their material or a facsimile may be available to the public.

2. BLISTER or STRIP PACKS. Dosage units (e.g., tablets or capsules) are individually sealed in clear plastic or plastic compartments with foil or paper backing. The individual compartment must be torn or broken to obtain the product. The backing materials cannot be separated from the blisters or replaced without leaving visible evidence of entry.

3. BUBBLE PACKS. The product and container are sealed in plastic and mounted in or on a display card. The plastic must be torn or broken to remove the product. The backing material cannot be separated from the plastic bubble or replaced without leaving visible evidence of entry.

4. HEAT SHRINK BANDS OR WRAPPERS. A band or wrapper is securely applied to a portion of the container, usually at the juncture of the cap and container. The band or wrapper is heat shrunk to provide a tight fit. The band or wrapper must be cut or torn to open the container and remove the product and cannot be worked off and reapplied without visible damage. The use of a perforated tear strip can enhance tamper-resistance.

Cellulose wet shrink seals are not acceptable. The knowledge to remove and reapply these seals without evidence of tampering is widespread.

The band or wrapper must employ an identifying characteristic that cannot be readily duplicated. An identifying characteristic that is proprietary and different for each product size is recommended.

Tinted bands or wrappers are no longer acceptable as an identifying characteristic because of the possibility that their material or a facsimile may be available to the public.

5. FOIL, PAPER, OR PLASTIC POUCHES. The product is enclosed in an individual pouch that must be torn or broken to obtain the product. The end seams of the pouches cannot be separated and resealed without showing visible evidence of entry.

6. CONTAINER MOUTH INNER SEALS. Paper, thermal plastic, plastic film, foil, or a combination thereof, is sealed to the mouth of a container (e.g., bottle) under the cap. The seal must be torn or broken to open the container and remove the product. The seal cannot be removed and reapplied without leaving visible evidence of entry. Seals applied by heat induction to plastic containers appear to offer a higher degree of tamper-resistance than those that depend on an adhesive to create the bond.

Polystyrene foam container mouth seals applied with pressure sensitive adhesive are no longer considered effective tamper-resistant features because they can be removed and reapplied in their original state with no visible evidence of entry.

The Agency recognizes that technological innovations may produce foam seals that will adhere to a container mouth in a manner that cannot be circumvented without visible evidence of entry. Container mouth seals must employ an identifying characteristic that cannot be readily duplicated. An identifying characteristic that is proprietary and different for each product size is recommended.

7. TAPE SEALS. Tape seals relying on an adhesive to bond them to the package are not capable of meeting the TRP requirements because they can be removed and reapplied with no visible evidence of entry.

However, the Agency recognizes that technological innovations may produce adhesives which do not permit the removal and reapplication of tape seals. In addition, tape seals may contain a feature that makes it readily apparent if the seals have been removed and reapplied. Tape seals must employ an identifying characteristic that cannot be readily duplicated.

8. BREAKABLE CAPS. The container (e.g., bottle) is sealed by a plastic or metal cap that either breaks away completely when removed from the container or leaves part of the cap attached to the container. The cap, or a portion thereof, must be broken in order to open the container and remove the product. The cap cannot be reapplied in its original state.

9. SEALED METAL TUBES OR PLASTIC BLIND-END HEAT-SEALED TUBES. The bottom of the tube is heat sealed and the mouth or blind-end must be punctured to obtain the product. A tube with a crimped end is capable of meeting the definition of a tamper-resistant feature if the crimped end cannot be breached by unfolding and refolding without visible evidence of entry.

10 SEALED CARTONS. Paperboard cartons sealed by gluing the end flaps are not capable of meting the TRP requirements. However, the Agency recognizes that technological advances may provide sealed paperboard packages that meet the requirements of the TRP regulations.

11 AEROSOL CONTAINERS. Aerosol containers are believed to be inherently tamper-resistant because of their design. Direct printing of the label on the container (e.g., lithographing), is preferred to using a paper label which could be removed and substituted.

12 CANS (BOTH ALL-METAL AND COMPOSITE). Cans may be composed of all metal or composite walls with metal tops and bottoms. The top and bottom of a composite can must be joined to the can walls in such a manner that they cannot be pulled apart and reassembled without visible evidence of entry. Rather than attaching a separate label, direct printing of the label onto the can (e.g., lithographing ) is preferred.

B. CAPSULE SEALING TECHNOLOGIES

Technologies for sealing two-piece hard gelatin capsules are available that provide evidence if the capsules have been tampered with after filling. Such sealing technologies currently in use include sonic welding, banding, and sealing techniques employing solvents and/or low temperature heating. These examples are not intended to rule out the development and use of other capsule sealing technologies. Manufacturers may consult with FDA if they are considering alternative capsule sealing processes.

Sealed capsules are not tamper-resistant packages. They are required to be contained within a package system that utilizes a minimum of one TRP feature.

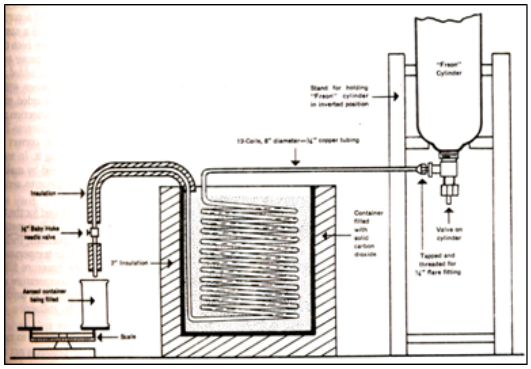
**7 Describe different filling technique of aerosols package and discuss stability testing of aerosols.**

Ans. The manufactured aerosols can be filled in to the containers can be done by following methods and apparatus used.

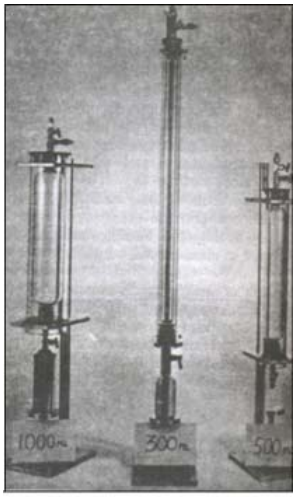
a) Cold filling apparatus b) Pressure filling apparatus

c) Compressed gas filling apparatus d) Rotary filling machine

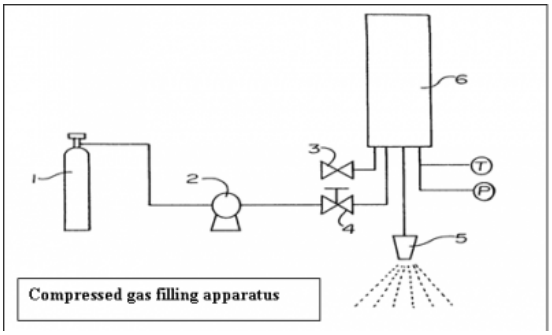
**a) Cold filling apparatus**[1]**:** Cold filling apparatus consists of an insulated box which fitted with copper tubings and filled with dry ice or acetone. The fitted copper tubings increase the surface area and cause faster cooling. The hydrocarbon propellant is not to be stored in the copper tubings as it might cause explosion.



**b) Pressure filling apparatus**[1]: Pressure filling apparatus consists of a metering burette capable of measuring the amount of propellant to be filled to the container. The mixture of propellant or propellant/s is added through the inlet valve present to the bottom of the valve under its own vapour pressure. A cylinder of nitrogen or compressed gas is attached to the top of the valve and the pressure of nitrogen causes the propellant to flow to the container through the metering burette. The propellant flows to the container stops when the pressure of the flowing propellant becomes equal to the pressure of the container.




**c) Compressed gas filling apparatus**: A compressed gas propellant is used. As the compressed gas is under high pressure, so the pressure is reduced by pressure reducing valve. A pressure of 150 pounds per square inch gauge is required to fill the compressed gas propellant in the aerosol container. The product concentrate is placed in the pressure gauge and the valve is crimped in its place. The air is evacuated. The filling head is inserted into the valve opening. Upon the depression of the valve, the compressed gas propellant is allowed to flow into the container. The compressed gas stops flowing when the pressure of the compressed gas flowing to the container from the burette becomes equal to the pressure within the container. In case of increasing the solubility of the gas in the product concentrate and also when an increased amount of compressed gas is required, carbon dioxide and Nitrous dioxide is used. The container is needed to be shaken during and after the filling operation to enhance the solubility of the gas in the product concentrate.




Compressed gas filling apparatus

## EVALUATION OF AEROSOLS

Aerosols are pressurized packages and many tests are necessary to ensure proper performance of the package and safety during the use and storage. For the regulations of aerosols limitation on the pressure within the container, flash point, flame extension and flammability.

Pharmaceutical aerosols can be evaluated by testing physico-chemical, performance and biological tests.

1. **Flammability and Combustibility**
   - Flame Projection and flash back
   - Flash Point
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4. **Biological Testing**
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   - Toxicity
   - Extractable substances

### 1. Flammability and Combustibility

#### *1.1 Flame Projection and flash back*:

- Flame test indicates the effect of an aerosol formulation on the extension of an open flame.
- Aerosol product is sprayed for 4 sec. into open flame.
- Depending on the nature and type of formulation, the fame is extended to some length and exact length was measured with ruler.

#### *1.2 Flash Point*:

- **"Standard Tag Open Cap Apparatus"** is used for determination of flash point.For this the formulation is chilled to temperature of -25 F and transferred to the test apparatus. The temperature of test sample liquid increase slowly, and the temperature at which the vapors of propellant ignite is taken a "flash point". It is calculated for flammable component, which in case of topical hydrocarbon propellants.

## 2. Physico - Chemical Characteristics

### *2.1 Vapour Pressure:*

Vapour pressure is determined by pressure gauges or elaborately through use of a water bath, test gauges and other special equipments. Variation in pressure indicates the presence of air in headscape. Variation in pressure indicates the presence of air in the headscape. For accurate measurement of vapour pressure in aerosol container **can punctuating device** used.

### *2.2 Density of aerosol system:*

- It is determined by **hydrometer or a pycnometer**.
- This method is useful for non aerosols modification to accommodate the liquefied gas preparation.
- In which a pressure tube is fitted with metal fingers and hoke valve of apparatus, which under pressure the liquids are introduced.
- The hydrometer is kept in to the glass pressure tube. Some sufficient amount of sample is added through the valve to cause the hydrometer to rise half way up the length of the tube. The density can be read directly from the apparatus.

### *2.3 Moisture Content:*

- Karl Fischer method or Gas chromatography method used.

### *2.4 Identification of Propellant/s:*

- Gas chromatography or I.R spectrophotometry methods are used for identification of propellants and also to indicate the proportion of the each component in a blend.

### *2.5 Product Concentrate - Propellant ratio:*

- The proportion of the each component in a blend can be determined by Gas chromatography or I.R spectrophotometry methods are used.

## 3 Performance Test

### *3.1 Aerosol Valve Discharge Rate:*

- It is determined by taking an aerosol with known weight and discharging the contents for given time using standard apparatus. Again reweigh the container, the difference in weight per time release or dispensed is discharge rate. It is expressed as gram per seconds.

### *3.2 Spray Patterns:*

- For this, the method involves the impingement of sprays on a piece of paper, which is treated with dye - talc mixture. Based on the nature and type of the aerosol, an oil soluble

dye or water soluble dye is used. When the particles reach the paper it causes the dye to go into solution and to be absorbed onto the paper. It gives a record of the spray pattern.

***3.3 Dose Uniformity / Dosage Testing with Metered valves:***

- Several points to be considered 1) Reproducibility of dosage each time the valve is dispersed and Amount of medication actually received by the patient.
- Reproducibility has been determined by assay technique and amount of active ingredient is determined. Another method for determination of active ingredient that accurate weighing of filled container then remove contents by dispersing and reweigh the container can and difference in weight divided by Number of doses, gives the average dosage.

***3.4 Net Contents:***

- Weight method used. The tared cans are placed on to the filling line and weighed; the difference in weight is equal to the net contents.
- Te other method is a Destructive method and consists of weighing of a full container, and dispensing the contents. The contents are then reweighed. The difference in weight gives the amount of contents present in the container.

***3.5 Foam stability:***

- The life of a foam ranges from a few seconds (for quick breaking foam) to one hour or more depending on the formulation and type of foam.
- The methods used to determine the foam stability is **Visual evaluation**. Visual evaluation is the
- time for a given mass to penetrate the foam, time for given rod that is inserted into the foam to fall.

***3.6 Particle Size determination:***

- Particle size can be determined by Cascade impactor and Light scattering decay methods.
- **Cascade impactor:**
- Cascade impactor works on the projected through a series of nozzle and glass slides at high velocity. First the larger particles become impacted on the lower velocity stages and then the smaller particles impacted at high velocity stages. The size ranges from 0.1 to 30 u (microns).
- **Light scattering decay:**
- Light scattering method is used to determine the particle size. The aerosol product settle in turbulent condition, Here the particle size is measured by the change in light intensity of Tyndall beam.

***3.7 Leakage Test:***

- Leak test is done by checking the crimping of the valve must be available to prevent defective containers. This is accomplished by measuring the crimp's dimension and ensuring that they meet specifications. Final testing of valve closure is done by passing filled containers through water bath.

## 4. Biological Testing

- The final phase of testing of aerosols involved in a comprehensive research and development program for pharmaceutical aerosols must involve biological testing. These are similar to tests performed for non aerosol pharmaceuticals.

### *4.1 Therapeutic Activity:*

- For Inhalation Aerosols: Therapeutic activity is depends on the particle size.
- For Topical Aerosols: It is determined by applying the active ingredients topically to test areas and the amount of therapeutic active ingredients absorbed is determined.

### *4.2 Toxicity:*

- For Inhalation Aerosols: Inhalation toxicity is studied by exposing test animals to vapor sprayed from Aerosol container.
- For Topical Aerosols: Irritation on the skin & chilling effects are checked. When aerosol is topically applied, thermistor is used to determine the change in skin temperature for a given period of time.

### *4.3 Extractable substances:*

- The pressurized inhalers and aerosols are normally formulated with organic solvents as the propellant or the vehicle. The leaching of extractables from the elastomeric and plastic components into the formulation is a potentially serious problem.
- So, the composition and the quality of materials used in the manufacture of the valve components (e.g., stem, gaskets, housing, container etc.) must be carefully selected and controlled. The container compatibility with formulation components should be thoroughly checked, so as to prevent distortion of the valve components and to minimize changes in the medication delivery, discharge rate, leaks and impurity profile of the drug product over time.
- The extractables profiles of a representative sample of each of the elastomeric and plastic components of the valve should be established under specified conditions and should be correlated to the extractable profile of the placebo or aged drug product, to ensure quality and purity of the drug product. Extractable substance which may include poly nuclear aromatics, nitrosamines, antioxidants, plasticizers, vulcanization accelerators and monomers, etc., should be identified and minimized wherever possible.
- Depends on the specifications and limits for individual components and total extractables from different valve components may require the use of different analytical methods.