**INDUSTRIAL PHARMACY-I**

**UNIT II-TABLETS AND LIQUID ORALS**

**CLASS:17**

**TOPIC** Filling and packaging; evaluation of liquid orals official in pharmacopoeia

- The method used for filling a liquid dosage form depends on following:
- Characteristics of the liquid (viscosity, surface tension, foaming ability)
- Type of package
- Production output

**Three basic methods are used for filling of liquid dosage forms**:

- 1. Gravimetric filling
- 2. Volumetric filling
- 3. Constant level filling

**Gravimetric filling**

- In this, a particular weight of liquid is filled into the container. This type of filling is rare in use
- because it can be used only for highly viscous liquid or to fill large size containers.

**Volumetric filling**

- In this, a given volume of liquid is filled into the container using the displacement piston action.
- Each filling station is equipped with a measuring piston and cylinder. The fill amount is
- measured by the stroke of the piston which can be varied from machine to machine.

**Disadvantages:**

- Highly viscous liquids can block the piston causing loss of fill accuracy
- Highly thin liquids can cause dripping of the drops from the filling point of machine
- If container is oversized then filling appears loose and if container is undersized then

- filling appears overfill, hence container to be filled should have uniform size

**Constant level filling**

- In this, each container is filled to the same level hence it is also called as fill-to-a- level method.
- It uses the container for controlling the filling of each unit which means that any change in size

of the container causes change in the net fill per unit

**Methods for constant level filling**

- In older days, the siphon method was used. But due to slowness of this method, slight
- modifications in siphon method are used which are following:

- Vacuum filling
- Gravity-vacuum filling
- Pressure-vacuum filling

**Vacuum filling**

A container is connected to the bulk liquid tank through vacuum head.

- The connections must be air-tight. Container, on the other hand, is connected to vacuum pump. A vacuum is then developed within the container.
- The developed vacuum causes the liquid to flow from the bulk liquid tank to the container.
- The liquid level rises until it reaches the vacuum tube, which is positioned at the desired constant level.
- If excess liquid is drawn through the vacuum tube, from there the liquid is recycled to the bulk liquid tank.

**Gravity-vacuum filling**

- In this method, the bulk liquid tank is placed a level above the container.
- Connections are made air-tight.
- Vacuum is applied for filling.

- In addition gravitational force also acts to aid filling.

**Pressure-vacuum filling**

- Here also connections are made air-tight.
- Container is connected to vacuum pump and bulk liquid tank is connected to positive pressure inducing pump.
- Vacuum in the container and positive pressure above the bulk liquid synergistically act to fill the liquid.
- Advantage: Suitable for high viscous liquids.

**Filling of liquid dosage form**

- Problem: Foam is produced during the filling with all these methods. This is a severe problem when high production rates are required.
- Solution: The problem of foam formation cannot be totally solved. However the intensity of the problem can be decreased by any of the following techniques;

➢ (a) Using equipment that minimizes product turbulence.

➢ (b) Using closed system filling equipment that prevents the entry of air or other gases which participate in the formation of foam.

➢ (c) Using mechanical defoaming devices.

➢ (d) Using low filling rates

**Packaging**

- most liquid orals are packaged in either amber or flint glass containers with plastic or metal caps Glass is generally inert to aqueous solutions in the pH range appropriate for oral liquids.
- But cap and liner may react.
- Plastic caps may undergo stress cracking on contact with some liquids. Metal caps may undergo corrosion.
- Therefore compatible closures must be selected on an individual basis

**Evaluation of syrup**

**Solubility:**

- The solubility of syrup is determined and it should be soluble in water.

**Refractive index:**

- The refractive index of the syrup is determined and it should be in range of 1.4608-1.4630

**Physical stability**

- 1. Its appearance(no crystallization and microbial growth).
- 2. Colour must be completely soluble with other ingredients
- . 3. Odour and taste(palatable).

4. Solid material is completely miscible in liquid

**Determination of sucrose concentration**

- Concentration of sucrose is very important in syrup because
- high amount of sucrose in syrup may cause crystallization of syrup while
- low amount may cause loss of preservative property of syrup.
- The concentration of sucrose in syrup is determined using analytical tools HPLC or U-V spectrophotometer.

**Content uniformity**

- In this, take 10 containers having syrup and emptied content of each container. Then determine the drug assay of content of each container as per method prescribed in monograph of that drug in Pharmacopoeia.
- The preparation complies with the test if not more than one value is outside the 85%-115% limit of average value and none value is outside the 75-125% limit.
- If 1-3 values are outside the 85-115% limit value but none is outside the 75-125% limit of average value then

test is performed for another 20 containers. Then not more than 3 values should be outside the 85-115% limit and none should be 75-125% limit of average value

**Light transmittance test**

- A light transmittance meter is used to check the color of syrup.
- In this, a syrup sample is checked for color by passing the light through the sample. The percent of transmitted light is compared to light transmittance rates for different grades.

**Quality control tests of elixirs**

- 1. Determination of alcohol conc
- 2. Viscosity measurements

**Determination of alcohol conc**

- 1.elixir usually contains 5 to 40% alcohol.
- 2. The determination of alcohol unless specified in the individual monograph. Cloudy distillates may be clarified by agitation with talc,or with calcium carbonate and filtration. For liquids it is presumed to contain less than 30% of alcohol.

**Viscosity measurements**

- Viscosity is measured by different viscometers. Note: Higher the viscosity =Higher the stability It is used for syrup also.

**quality control tests emulsions**

- The following are the quality control tests done for emulsions:

**Determination of particle size and particle count**: Determination of changes in the average particle size or the size distribution of droplets is an important parameter used for the evaluation of emulsions.

It is performed by optical microscopy, sedimentation by using Andersen Apparatus and Coulter counter apparatus.

**Determination of viscosity**: It is done to assess the changes that might take place during aging. Emulsions exhibit Non-Newtonian type of flow characteristics. The viscometers are used eg. Cone and plate viscometers.

**Determination of phase separation**: Phase separation may be observed visually or by measuring the volume of the separated phases

**Determination of electrophoretic properties**: Determination of electrophoretic properties like zeta potential is useful for assessing flocculation since electrical charges

on particles influence the rate of flocculation. O/W emulsion having a fine particle size will exhibit low resistance but if the particle size increase, then it indicates a sign of oil droplet aggregation and instability.

**Stability testing**: Stability testing of emulsions involves determining stability at long term storage conditions, accelerated storage conditions, freezing and thawing conditions. Stress conditions are applied in order to speed up the stability

**Packing of emulsions**

- Depending on the use, emulsions should be packed in suitable containers. Emulsions meant for oral use are usually packed in well filled bottles having an airtight closure. Light sensitive products are packed in amber color bottles. For more viscous emulsions, wide mouth bottles should be used.

**Labelling of Emulsions**

- The label on the emulsion should mention that these products have to be shaken thoroughly before use.
- External use products should clearly mention on their label that they are meant for external use only.

**Storage of Emulsions**

- Emulsions should be stored in a cool place .
- Refrigeration should be avoided as this low temperature can adversely affect the stability of preparation.

**Quality control tests of suspensions**

**Sedimentation Volume (F)**

- **Purpose:** To measure the degree of sedimentation and stability of suspension.
- **Formula:**
- F=V0/Vu Where:
  Vu = final or ultimate volume of sediment
  V0 = total volume of the suspension before settling
- **Interpretation:**
    - F=1: No sedimentation (ideal)

- F<1: Indicates sedimentation (acceptable if redispersible)
- Higher F → better physical stability

**Redispersibility Test**

- **Purpose:** To ensure sedimented particles can be easily redispersed to form a uniform suspension.
- **Method:**
  - Store the sample undisturbed for a specified time.
  - Shake the container manually or mechanically.
  - Observe whether the sediment is easily redispersed without forming lumps.
  - Note the **number of shakes** required for uniform redispersion.

**Particle Size and Distribution**

- **Purpose:** Particle size affects stability, sedimentation rate, and bioavailability.
- **Method:**
  - **Microscopic examination** (Optical/SEM)
  - **Laser diffraction** (for accurate particle size distribution)
  - **Coulter counter** (for particle count and size)
- **Acceptance:** Should remain within specified limits throughout shelf life.

**Particle size**

- The stability of a suspension also depends upon the particle size of the disperse phase. An ideal suspension should have particle size of **0.5- 5µm.**
- According to stoke'sequation, increase in particle size also increases the rate of settling of particles and cause instability of suspension.
- Larger particles settle down rapidly than smaller particles.
- Particles greater than 5µm cause gritty nature to the suspension and may cause irritation if injected or instilled into the eye.
- Particles larger than 25µm cause blockage of the needle if given by parenteral route.

- If particle size is very small then particles form easily hard cake at the bottom of the container. So the particle size of the suspension should neither be too large nor too small.

**Degree of flocculation:**

- Degree of flocculation (β) is the ratio of the sedimentation volume of the flocculated suspension (F) to the sedimentation volume of deflocculated suspension ( F∞ ).
- It can be calculated by:
- β= F/ F∞ β= Hu /Ho/ H∞ /Ho
- β=Hu / H∞

**Rheological Properties / Viscosity**

- **Purpose:** To ensure appropriate viscosity for **pourability**, **suspension stability**, and **dose uniformity**.
- **Instrument:** Brookfield or Rotational Viscometer
- **Observation:**
    - Measure viscosity at different shear rates (since suspensions are often **pseudoplastic** or **thixotropic**).
    - The suspension should show **shear-thinning behavior** — viscosity decreases on shaking.

**Viscosity**

- Viscosity can be determined by stoke's law:
- V=d2(ps-p0)g/18η0
- Where,
- V is the rate of settling of particles
- d is the diameter or size of the particles
- Ps is the density of disperse phase
- Po is the density of disperse medium
- η is the viscosity of the disperse medium

- g is the gravitational constant
- On the basis of this equation, V is inversely proportional to the η (Viscosity). It is clear that on increasing the viscosity of disperse medium, rate of settling of particles decreases. So particles settle down slowly or remain suspended in the medium which form a stable suspension.

**Quality control tests of suspensions**

**pH Measurement**:Calibrated pH meter

**Density / Specific Gravity**:To ensure consistency and control of the formulation.

- Pycnometer or specific gravity bottle.

**Assay / Drug Content Uniformity-**To confirm uniform distribution of drug particles throughout the formulation.

**Method:**

- Take samples from **top, middle, and bottom** of the container.
- Analyze using **UV spectrophotometer** or **HPLC**.
- **Acceptance:** Each sample should contain 85–115% of labeled claim (depending on pharmacopeial standards).

**Zeta Potential**

- **Purpose:** Indicates surface charge on particles, which affects **flocculation and stability**.
- **Instrument:** Zeta potential analyzer
- **Typical range:**
    - **±30 mV or higher** → stable (deflocculated)
    - **Around ±10–20 mV** → optimum for flocculated suspension
- Zeta potential is determined by moving boundary method and micro electrophoresis method. Suspensions having high zeta potential (negative or positive) are electrically stabilized while suspensions having low zeta potential tend to aggregation of solid particles leading to poor stability. Generally at high zeta potential, force of repulsion exceeds the force of attraction causing stable system.