Pharmaceutical Quality Management

CHAPTER 3

Quality Control tests for Oral Liquid Dosage forms

By:

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SYRUP:

"Syrups are concentrated aqueous preparations of a sugar or sugar substance with or without flavoring agents and medicinal substances."

Components of Syrup

- Sugar (sucrose) or its substitute
- Flavors
- Colors
- Preservatives

Quality Control Tests for syrups

- *1. Clean and purified vehicle (water)*
- *2. Microbial Contamination*
- *3. Uniformity of Mass*
- *4. Visual Inspection*
- *5. Content Uniformity*
- *6. Sucrose concentration*
- *7. Physical stability in syrups*
- *8. pH Measurement*
- *9. Light Transmittance Test*

1- CLEAN & PURIFIED VEHICLE (WATER):

- The water is filtered and purified at the plant to destroy any micro-organisms and to remove particles from the water. Quality control technicians test the water frequently to ensure that it is clean and pure

before the syrup is made. The syrup is also thoroughly filtered before filling in bottles.

- Water Testing Lab ensures the purity of water.

2- MICROBIAL CONTAMINATION:

- Ensure that all ingredients are of appropriate quality
- Minimize the risk of microbial contamination

  (*See recommendations in chapter MICROBIOLOGICAL QUALITY OF NON-STERILE PRODUCTS: RECOMMENDED ACCEPTANCE CRITERIA FOR PHARMACEUTICAL PREPARATIONS of the supplementary information section****)***
- Minimize the risk of cross-contamination

Route of administration	Total aerobic microbial count (CFU/g or CFU/ mL)	Total combined yeasts/moulds count (CFU/g or CFU/ mL)	Specified microorganism
Non-aqueous preparations for oral use	10^3	10^2	Absence of Escherichia coli (1 g or 1 mL)
Aqueous preparations for oral use	10^2	10^1	Absence of Escherichia coli (1 g or 1 mL)

3- ***UNIFORMITY OF MASS:***

- Liquid preparations for oral use that are presented as single-dose preparations comply with the following test. Weigh individually the contents of 20 containers, emptied as completely as possible, and determine the average mass. Not more than 2 of the individual masses deviate by more than 10% from the average mass and none deviates by more than 20%.

- **Uniformity of mass of doses delivered by the measuring device**

  The measuring device provided with a multidose liquid preparation for oral use complies with the following test. Weigh individually 20 doses taken at random from one or more multidose containers with the measuring device provided and determine the individual and average masses. Not more than two of the individual masses deviate by more than 10% from the average mass and none deviates by more than 20%.

4- VISUAL INSPECTION:

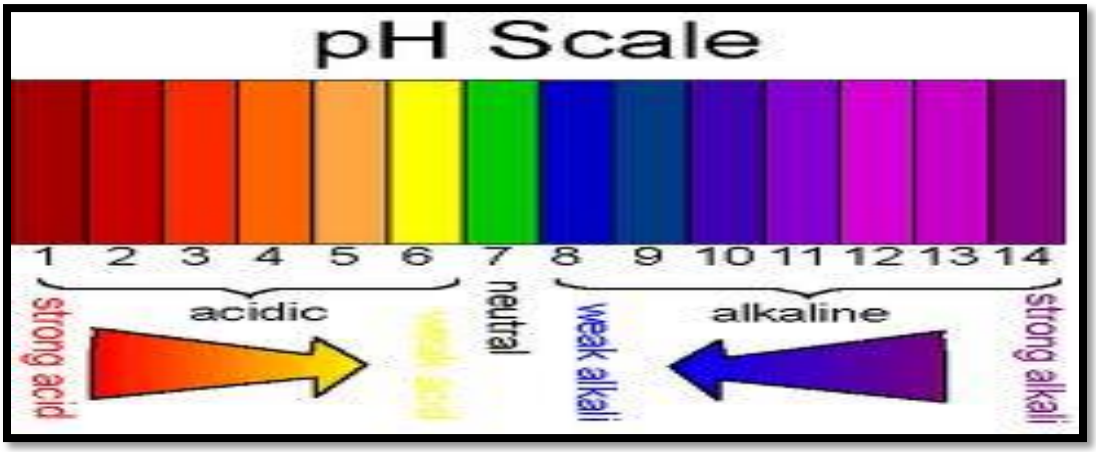
- Inspect the solution. It should be clear and free from any precipitate. A change in colour or cloudiness of solutions may indicate chemical degradation or microbial contamination.
- With visual inspection, the ingredients and the final products are carefully examined for purity and for appearance.
- Physical appearance of products for patient adherence and compliance is critical so it should be
    - Good looking
    - Elegance in appearance

5- LIGHT TRANSMITTANCE TEST:

- A light transmittance meter is a newer tool that is used to check syrup color.
- In a light transmittance meter, a syrup sample is checked for color by passing the light through the sample. The percent of light transmission is compared to light transmission rates set for different grades.
- When using one, you need to be sure there are no fingerprints on the syrup test bottle, and that the syrup sample has no bubbles or cloudiness. Any of these conditions may diminish the light that is transmitted through the sample and therefore lowers the grade of the sample.

6- pH MEASUREMENT:

- The measurement and maintenance pH is also very important step in the Quality control testing.
- Generally there are two different types of methods used in the measurement of pH.



- **Methods for pH Measurement:**

- The simplest and cheapest is to dip a piece of pH paper into the sample. The paper is impregnated with chemicals that change colour and the colour may be compared to a chart supplied with the paper to give the pH of the sample.
- If greater accuracy is required a pH meter should be used. A typical pH meter consists of a special measuring glass electrode connected to an electronic meter that measures and displays the pH reading

7- PHYSICAL STABILITY:

- The syrups are must be stable physically e.g.
  - its appearance (no crystallization and microbial growth)
  - Color must be completely soluble with other ingredients.
  - Odor and taste (palatable)
  - Solid material is completely miscible in liquid.

8- SUCROSE CONCENTRATION:

- The determination of sucrose concentrations is also very important in Quality control testing of syrups.

- If the concentration Sucrose in the syrup is very high it may crystallize the syrup and less sucrose concentrations give favor for the microbial growth.
- There is no specific method for the determination sucrose in syrup. We use HPLC and UV-SPECTROSCOPY for this purpose.

9- CONTENT UNIFORMITY:

- For oral solutions, suspensions, and syrups in single-unit containers, conduct the Assay on the amount of well-mixed material that drains from an individual container in not more than 5 seconds, and express the results as delivered dose. Where the amount of active ingredient in a single dosage unit differs from that required in the Assay, adjust the degree of dilution of the solutions and/or the volume of aliquots so that the concentration of the active ingredients in the final solution is of the same order as that obtained in the Assay procedure.

▸ **Content Uniformity (Acceptance Criteria)**

- Unless otherwise specified in the individual monograph, the requirements for dosage uniformity are met if the amount of the active ingredient in each of the 10 dosage units as determined from the Weight Variation or the Content Uniformity method lies within the range of 85.0% to 115.0% of the label claim and the Relative standard deviation is less than or equal to 6.0%.
- If 1 unit is outside the range of 85.0% to 115.0% of label claim and no unit is outside the range of 75.0% to 125.0% of label claim, or if the Relative standard deviation is greater than 6.0%, or if both conditions prevail, test 20 additional units. The requirements are met if not more than 1 unit of the 30 is outside the range of 85.0% to 115.0% of label claim and no unit is

outside the range of 75.0% to 125.0% of label claim and the Relative standard deviation of the 30 dosage units does not exceed 7.8%.

- **Applications of Content Uniformity & Weight Variation Tests:**

Table 1. Application of Content Uniformity (CU) and Weight Variation (WV) Tests for Dosage Forms

Dosage Form	Type	Subtype	Dose & Ratio of Drug Substance	
			≥25 mg and ≥25%	<25 mg or <25%
Tablets	Uncoated		WV	CU
	Coated	Film	WV	CU
		Others	CU	CU
Capsules	Hard		WV	CU
	Soft	Suspension, emulsion, or gel	CU	CU
		Solutions	WV	WV
Solids in single-unit containers	Single component		WV	WV
	Multiple components	Solution freeze-dried in final container	WV	WV
		Others	CU	CU
Solutions in unit-dose containers *and into soft capsules+			WV	WV
Others			CU	CU

Viscosity Measurement:

- Viscosity is a property of liquids that is directly related to the resistance to flow.
- Viscosity measurement is very important quality control test in case of syrups and elixirs.
- Viscosity and consistency directly relates with stability of solutions.
- As viscosity increases, chance of stability also increases

  (↑ Viscosity, ↑ chance of stability)

Types of Viscosity

a. *Dynamic (absolute) Viscosity*

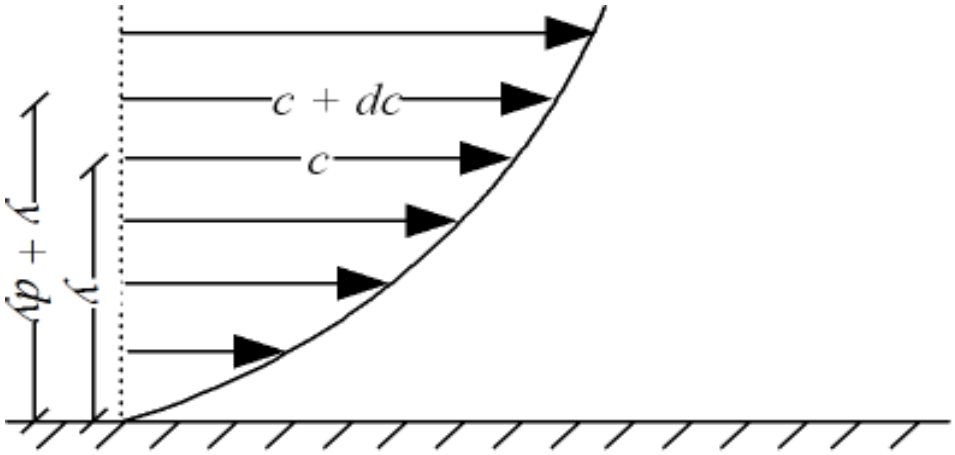
b. *Kinematic Viscosity*

c. *Relative Viscosity*

d. *Apparent Viscosity*

a. DYNAMIC (ABSOLUTE) VISCOSITY:

- Absolute viscosity - coefficient of absolute viscosity - is a measure of internal resistance. Dynamic (absolute) viscosity is the tangential force per unit area required to move one horizontal plane with respect to an other plane - at an unit velocity - when maintaining an unit distance apart in the fluid.
- The shearing stress between the layers of a non turbulent fluid moving in straight parallel lines can be defined for a Newtonian fluid as



- The dynamic viscosity can be expressed

$$\tau = \mu \, dc / dy \qquad (1)$$

Where,

τ = *shearing stress* (N/m^2)

μ = *dynamic viscosity* ($N\ s/m^2$)

dc = *unit velocity (m/s)*

dy = *unit distance between layers (m)*

- Equation *(1)* is known as the ***Newtons Law of Friction***
- In the SI system the dynamic viscosity units are ***N s/m²***, ***Pa s*** *or* ***kg/(m s)*** where,

1 Pa s = 1 N s/m² = 1 kg/(m s)

- Dynamic viscosity may also be expressed in the metric *CGS (centimeter-gram-second)* system as ***g/(cm s)***, ***dyne s/cm²*** or ***poise (p)***

Where,

1 poise = 1 dyne s/cm² = 1 g/(cm s) = 1/10 Pa s = 1/10 N s/m²

- For practical use the *Poise* is normally too large and the unit is often divided by *100* - into the smaller unit ***centipoise (cP)***

b. KINEMATIC VISCOSITY:

- *Kinematic viscosity is the ratio of - absolute (or dynamic) viscosity to density - a quantity in which no force is involved.*
- Kinematic viscosity can be obtained by dividing the absolute viscosity of a fluid with the fluid mass density.

$$\nu = \mu / \rho \qquad (2)$$

Where,

ν = *kinematic viscosity* (m^2/s)

μ = *absolute or dynamic viscosity* ($N\ s/m^2$)

ρ = *density* (kg/m^3)

- In the SI-system the theoretical unit of kinematic viscosity is m^2/s - or ***Stoke (St)***.

where,

1 St (Stokes) = $10^{-4}\ m^2/s = 1\ cm^2/s$

c. RELATIVE VISCOSITY:

- Relative viscosity is an important parameter when testing polymers in solutions.
- For most polymers there is a definite relationship between molar mass and viscosity. You can measure the viscosity to determine the molar mass. The

higher the molar mass is, the more viscous the polymer solution is. Molar mass is one of the most important quality parameters of polymers.

- The relative viscosity is calculated by dividing the viscosity of the polymer solution η by the viscosity of the pure solvent η_s.

$$\eta_r = \frac{\eta}{\eta_s} [1]$$

d. APPARENT VISCOSITY:

- Apparent viscosity (sometimes denoted **η**) is the shear stress applied to a fluid divided by the shear rate.
- For a *Newtonian fluid,* the apparent viscosity is constant, and equal to the Newtonian viscosity of the fluid.
- But for *non-Newtonian fluids,* the apparent viscosity depends on the shear rate.
- Apparent viscosity has the SI derived unit Pa.s (Pascal-second, but the centipoise is frequently used in practice: (1 mPa.s = 1 cP).

$$\eta = \frac{\tau}{\dot{\gamma}}$$

Types of Liquids based on viscosity:

a. *Newtonian Fluids*

b. *Shear-thinning or Pseudo-plastic Fluids*

c. *Dilatant Fluids*

d. *Thixotropic Fluids*

a. NEWTONIAN FLUIDS:

- A fluid where the shearing stress is linearly related to the rate of shearing strain - is designated as a Newtonian Fluid**.**
- A Newtonian material is referred to as true liquid since the viscosity or consistency is not affected by shear such as agitation or pumping at a constant temperature. Most common fluids - both liquids and gases - are Newtonian fluids. Water and oils are examples of Newtonian liquids.

b. SHEAR-THINNINGSOR PSEUDO-PLASTIC FLUIDS:

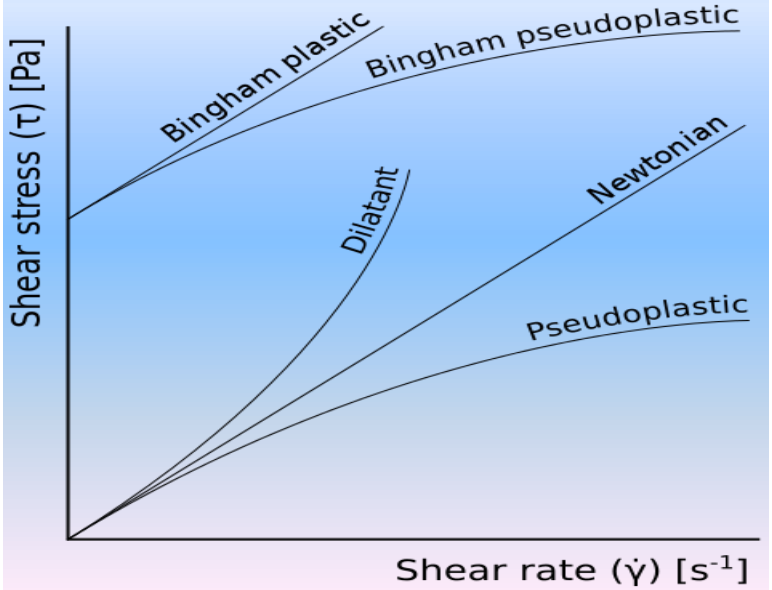
- A Shear-thinning or pseudo-plastic fluid is a fluid where viscosity decreases with increasing shear rate. The structure is time-independent.

c. DILATANT FLUIDS:

- A Shear Thickening Fluid - or Dilatant Fluid - increases the viscosity with agitation or shear strain. Dilatant fluids are known as non-Newton fluids.
- Some dilatant fluids can become almost solid in a pump or pipe line.

d. THIXOTROPIC FLUIDS:

- A Thixotropic fluid has a time-dependent structure. The viscosity of a thixotropic fluid decreases with increasing time - at a constant shear rate.
- They appear thick or viscous but are possible to pump quite easily.



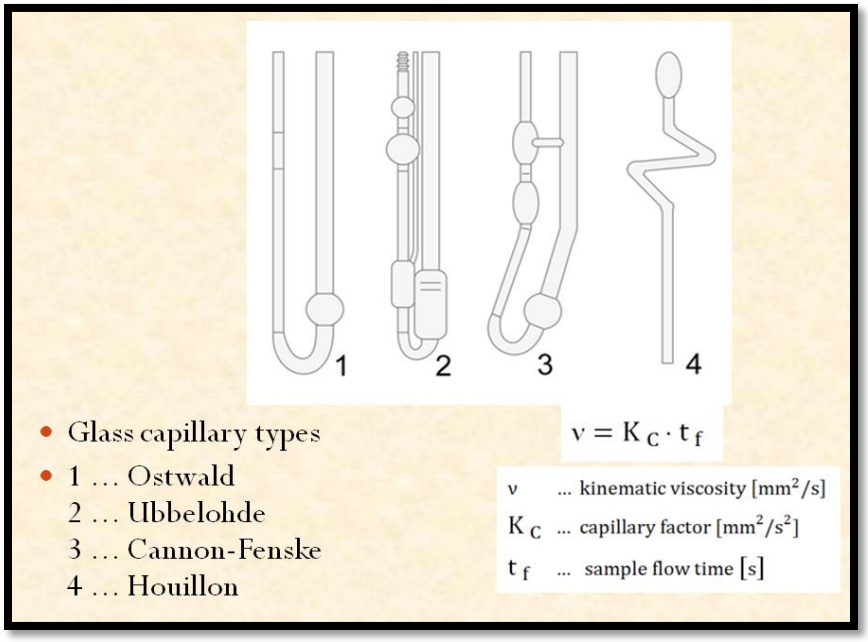
Methods used for Measurement of Viscosity

1) *Gravimetric capillary Principle*
2) *Rotational Principle*
3) *Stabinger Viscometer™*
4) *Rolling / Falling-Ball Principle*

1) GRAVIMETRIC CAPILLARY PRINCIPLE:

- Measurements using capillary viscometers are based on the relation between viscosity and time. They use gravity as the driving force; therefore the results are kinematic viscosity values.

- The big advantage of this method is that gravity is a highly reliable driving force. It is not artificially generated, so this avoids potential errors. Because gravity is available everywhere on earth and does not require further technical equipment, this principle is widely established in many standards and standardized practices.
- The disadvantage of this principle is that the driving force cannot be varied. It is too small for highly viscous samples. Further, many different capillaries are required to cover a wide viscosity range with one constant driving force. For example, with Ubbelohde capillaries each can cover a range defined by its minimum viscosity times factor 5 (e.g. type 0B: 1mm^2/s to 5mm^2/s).



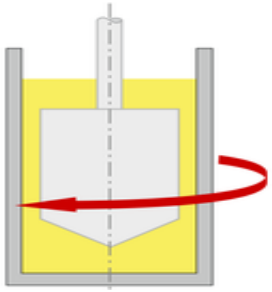
2) ROTATIONAL PRINCIPLE:

- Rotational viscometers use a motor drive. Unlike capillary viscometers, rotational viscometers provide dynamic or shear viscosity results.

- A rotational viscometer consists of a sample-filled cup and a measuring bob that is immersed into the sample.
- There are two main principles in use:
    - ***The Couette Principle***
    - ***The Searle Principle***

The Couette Principle:

- If the bob stands still and the drive rotates the sample cup, this is the Couette principle (named after M. M. A. Couette, 1858 to 1943). Although this construction avoids problems with turbulent flow, it is rarely used in commercially available instruments. This is probably due to problems with the insulation and tightness of the rotating sample cup.



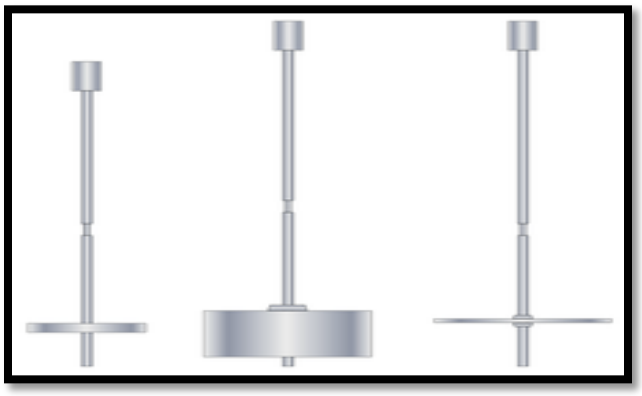
The Searle Principle:

- In most industrially available viscometers the motor drives the measuring bob and the sample cup stands still. The viscosity is proportional to the motor torque that is required for turning the measuring bob against the fluid's viscous forces. This is called the Searle principle (named after G. F. C. Searle, 1864 to 1954).

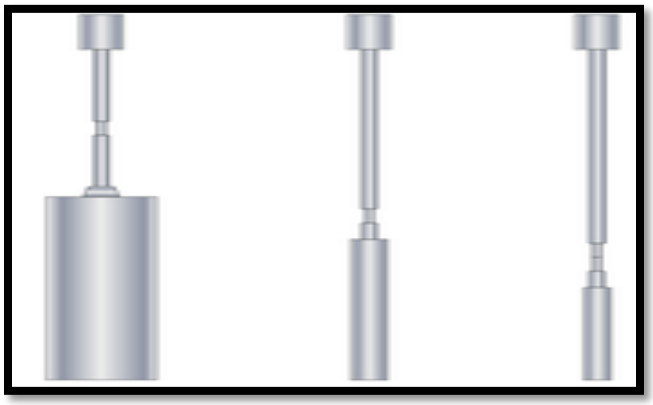
Rotational Measuring Systems:

- By changing the measuring system the rotational viscometer can be adapted to various applications.
- The most common spindles are listed below.
    - ***Disc spindles***
    - ***Cylindrical spindles***
    - ***Spindles with special shapes***
    - ***Coaxial cylinders***

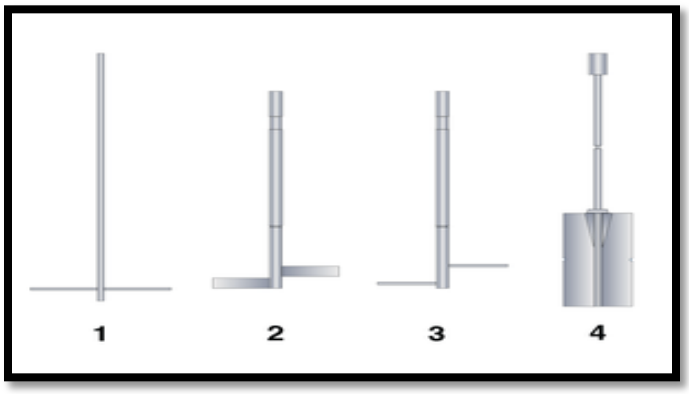
DISC SPINDLES:



CYLINDRICAL SPINDLES:



SPINDLES WITH SPECIAL SHAPES:



Where,

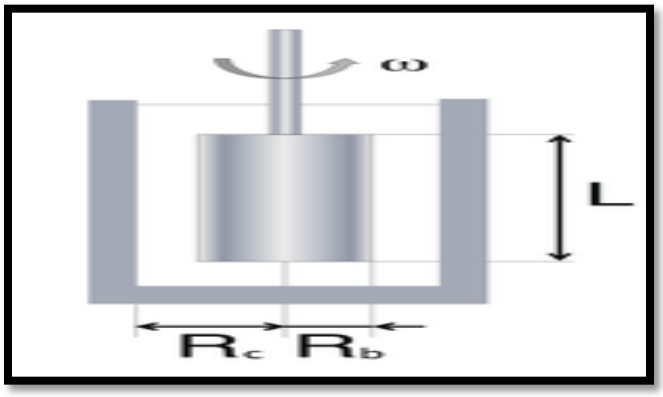
1 … T-bar spindle

2 … Krebs spindle

3 … Paste spindle

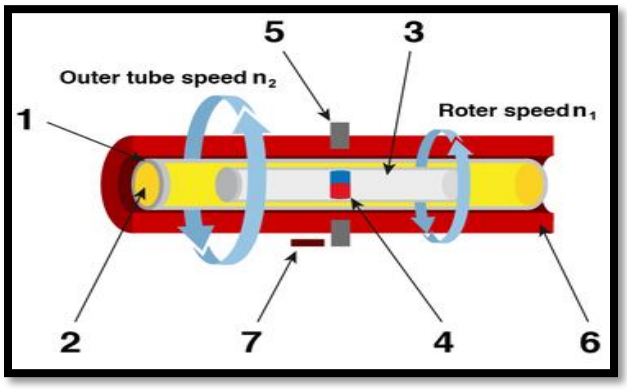
4… Vane spindle

COAXIAL CYLINDERS:



3) STABINGER VISCOMETER™:

- The Stabinger Viscometer™ was first established in the year 2000. It was then an entirely new design, combining the accuracy of kinematic viscosity determination with a wide measuring range. The Stabinger Viscometer™ is a modification of the classic Couette-type rotational viscometer. It consists of two concentric cylinders where the outer one provides the driving force.



Where,

1 ... Outer tube (preset constant speed)

2 ... Sample liquid

3 ... Freely floating rotor (measured speed)

4 ... Magnet

5 ... Soft iron ring

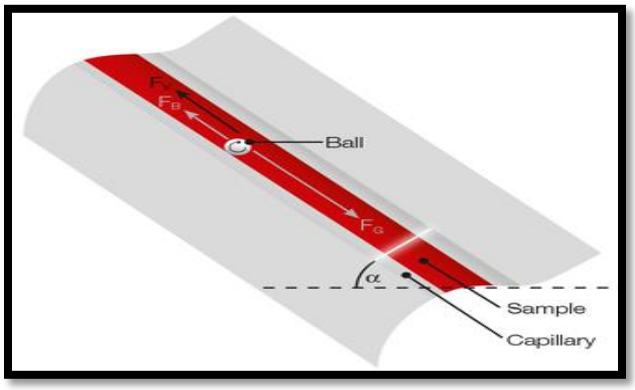
6 ... Copper housing

7 ... Hall-effect sensor

4) ROLLING / FALLING-BALL PRINCIPLE:

- The rolling-ball principle uses gravity as the driving force. A ball rolls through a closed capillary filled with sample fluid which is inclined at a defined angle. The time it takes the ball to travel a defined measuring

distance is a measure for the fluid's viscosity. The inclination angle of the capillary permits the user to vary the driving force. If the angle is too steep, the rolling speed causes turbulent flow. For calculating the viscosity from the measured time, the fluid's density and the ball density need to be known.



Where,

F_G … Effective component of gravity

F_B … Effective component of buoyancy

F_V … Viscous force

Containers

- The containers should be made of material that will not adversely affect the quality of the preparation by, for example, leaching or sorption. Liquid preparations for oral use that contain light-sensitive active ingredients are supplied in containers that are light-resistant.
- Except where indicated in the individual monograph, containers should be made from material that is sufficiently transparent to permit the visual inspection of the contents.
- If the preparation contains volatile ingredients, the liquid preparation for oral use should be kept in a tightly closed container.

ELIXIRS:

- **QUALITY CONTROL TEST FOR ELIXIR**

Determination of alcohol concentration:

- Elixir usually contains 5 to 40% alcohol.
- The determination of alcohol unless otherwise specified in the individual monograph.
- It is suitable for examining most fluidextracts and tinctures and elixirs provided the capacity of the distilling flask is sufficient (commonly two to four times the volume of the liquid to be heated) and the rate of distillation is such that clear distillates are produced.
- Cloudy distillates may be clarified by agitation with talc, or with calcium carbonate. And filtration is done.
- After which the temperature of the filtrate is adjusted and the alcohol content determined from the specific gravity. During all manipulations, take precautions to minimize the loss of alcohol by evaporation.
- Remaining Tests Same as with syrups

SUSPENSIONS

- Pharmaceutical suspensions may be defined as coarse dispersions in which insoluble solids are suspended in a liquid medium.
- The liquid medium is usually water or a water based vehicle.
- The insoluble solid may have size range from 10 to 1000 μm.
- Suspensions are also called heterogeneous systems, or more precisely biphasic systems.

Classification of Suspensions

- **1. Based on proportion of solid particles**
  - a) Dilute suspensions (2 to 10% w/v solid)
  - b) Concentrated suspensions (50% w/v solid)
- **2. Based on electrokinetic properties of solid particles**
  - a) Flocculated suspensions
  - b) Deflocculated suspensions
- **3. Based on general classes**
  - a) Oral suspensions
  - b) Externally applied suspensions
  - c) Parenteral suspensions

IPQC Tests of Suspensions

- 1. Appearance
- 2. Color, odor and taste
- 3. Density
- 4. pH value
- 5. Pourability
- 6.Viscosity
- 7. Rheology
- 8. Photo microscopic examination
- 9. Zeta potential measurement
- 10. Drug content uniformity
- 11. Particle size measurement
- 12. Sedimentation rate and sedimentation volume

- 13. Redispersibility
- 14. Preservative effectiveness
- 15. Compatibility with primary container-closure system

1. APPEARANCE:

- The appearance in a graduated glass cylinder or transparent glass container is noted. It is checked for
    - Uniformity of color and appearance of the sediment
    - Any breaks or air pockets in the sediment
    - Any coagulated material adhering to the inside wall of the container.

2. COLOUR, ODOUR & TASTE:

- These characteristics are especially important in orally administered suspensions. Variation in color often indicates poor distribution and/or differences in particle size. Variation in taste, especially of active constituents can often be attributed to changes in particle size, crystal habit and subsequent particle dissolution.
- Changes in color, odor and taste can also indicate chemical instability.

3. DENSITY:

- Specific gravity or density of the suspension is an important parameter. Decrease in density indicates the presence of entrapped air with in the structure of the suspension.

- Density measurements at a given temperature should be made using well-mixed uniform suspension.

4. pH VALUE:

- pH of the phases of suspension also contribute to stability and characteristics of formulations. So pH of the different vehicles, phases of suspension before mixing and after mixing are monitored and recorded time to time to ensure optimum pH environment being maintained.
- Different types of methods are used in the measurement of pH.
    a) Dip a piece of pH paper into the sample.
    b) pH meter

5. POURABILITY:

- This test is carried out on the phases of suspension after mixing to ensure that the final preparation is pourable and will not cause any problem during filling and during handling by patient

6. VISCOSITY:

- Stability of a suspension is solely dependant on the sedimentation rate of dispersed phase which is dependant on the viscosity of the dispersion medium. So this test is carried out to ensure optimum viscosity of the medium so a stable, redispersible suspension can be formed.
- The viscosity of the dispersion medium is measured before mixing with dispersed phase and also viscosity after mixing is determined using Brook field viscometer.

- The calculated values are compared with standard values. And if any difference is found necessary corrective action is taken to get optimized viscosity.

7. RHEOLOGY:

- Rheology is the science that concerns with the flow of liquids and the deformation of solids.
- Brookfield viscometer/rheometer is used to evaluate the rheological properties and behaviour of settling of suspensions.
- Brookfield viscometer mounted on helipath stand with T spindle.
- The T bar rotates and descends slowly into the suspension with the help of synchronous motor.
- The path traced by the spindle is a helix. As the T bar moves the sediment offers resistance.
- The dial reading indicates the magnitude of resistance.
- The dial reading is plotted against the number of turns of the spindle.
- Good suspensions show a lesser rate of increase of dial reading as the spindle turns that is the curve is horizontal for a longer period.

8. ZETA POTENTIAL MEASUREMENT:

- Zeta potential is defined as the difference in potential between the surface of the tightly bound layer (shear plane) and electro-neutral region of the solution.
- Zeta potential has practical application in stability of systems containing dispersed particles since this potential governs the degree of repulsion between the adjacent similarly charged dispersed particles.

- Value of zeta potential reflects the future stability of suspension so it is monitored time to time to ensure optimum zeta potential.
- The flocculated suspension is one in which zeta potential of particle is from -20 to +20 mv.
- Zeta potential can be measured by

    a) Zeta meter

    b) Micro-electrophoresis

Electrophoresis

- The principle of electrophoresis is used to determine the sign and magnitude of zeta potential.
- Electrophoresis involves the movement of a charged particle through a liquid under the influence of an applied potential difference.
- An electrophoresis cell is fitted with two electrodes.
- The dispersion is introduced into the cell. When a potential is applied across the electrodes, particles migrate towards oppositely charged electrodes.
- The rate of migration is a function of the charge on a particle.

Zeta potential [mV]	Stability behavior of the colloid
from 0 to ±5,	Rapid coagulation or flocculation
from ±10 to ±30	Incipient instability
from ±30 to ±40	Moderate stability
from ±40 to ±60	Good stability
more than ±61	Excellent stability

9. DRUG CONTENT UNIFORMITY:

- For proper dosing of the dosage form it is necessary that the active ingredient is uniformly distributed throughout the dosage form. Therefore samples are withdrawn from the dispersed phase after micronization and after mixing with dispersion medium and assayed to find out degree of homogeneity.
- If any discrepancy is found out it is suitably corrected by monitoring the mixing step to ensure a reliable dosage formulation.

10. PARTICLE SIZE OF DISPERSED PHASE:

- Optimum size of drug particle in the dispersed phase plays a vital role in stability of final suspension.
- So this test is carried out to microscopically analyse and find out particle size range of drug then it is compared with optimum particle size required.
- If any difference is found, stricter monitoring of micronization step is ensured.

▸ **Particle size measurement**

Particle size can be measured by

a) Optical microscopy

b) Sedimentation method

c) Conductivity method (coulter counter method)

11. PHOTOMICROSCOPIC EXAMINATION:

- The microscope can be used to estimate and detect changes in particle size distribution and crystal shape. Its usefulness can be enhanced by attaching a polaroid type camera to the microscope to permit rapid processing of photomicrographs.
- This can be used to distinguish between flocculated and non-flocculated particles and to determine changes in the physical properties.

a) Optical Microscopy:

- Particle size in the range of 0.2 to 100µm can be measured by optical microscopy.
- This method directly gives number distribution.
- Method: Eye piece of the microscope is fitted with a micrometer.
- The eye-piece micrometer is calibrated using a standard stage micrometer.
- The sample of suspension is mounted on a slide or a ruled cell and placed it on the mechanical stage.
- The size of the particle is estimated with the help of the eye-piece micrometer.
- Around 625 particles must be counted in order to estimate the true mean.
- The size frequency distribution curve is plotted by taking particle size in µm on x-axis and frequency on y-axis.

b) Sedimentation Method:

- Sedimentation method may be used over a size range of 1 to 200 µm.
- Sedimentation of particles are evaluated by

i. **Andreasen pipette method**
ii. **Balance method**
iii. **Hydrometer method**

ANDREASEN PIPETTE METHOD

- Andreasen apparatus consists of a 550 ml cylindrical vessel containing a 10 ml pipette sealed to a ground glass stopper.
- When the pipette is placed in the cylinder its lower tip is 20 cm below the surface of the suspension.
- Transfer the suspension into the Andreasen vessel and place the two-way pipette and securely suspend the vessel in a constant temperature water bath.
- At different time intervals 10 ml of samples are withdrawn using two-way stopcock and collected in watch-glass, evaporated and weighed.
- Particle diameter is calculated from stokes law.

Andreasen apparatus

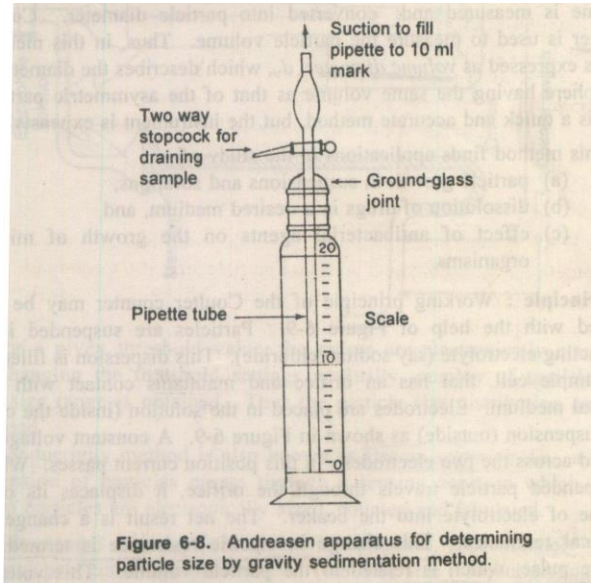


Figure 6-8. Andreasen apparatus for determining particle size by gravity sedimentation method.

12. SEDIMENTATION:

- An ideal suspension can be prepared by preventing the settling of particles.
- The settling of particles can be explained by theories related to sedimentation.

  a) Theory of Brownian movement

  b) Theory of sedimentation
- These theories provide information regarding factors that affect the settling of solids, these factors enable to take appropriate action in the manufacture of suspension.

Theory of Brownian movement

- Brownian movement of particles prevents sedimentation.
- Brownian movement can be observed, if the size of the particle is about 2 to 5µm, provided densities of the particles and viscosity of the medium are favourable.
- Theory of Brownian movement proposes particle size and viscosity as the major factors.

Sedimentation volume

- It is the ratio between “ultimate volume of sediment” to “initial volume of the suspension”.
- F=Vu/V0= ultimate volume of the sediment/initial volume of the suspension
- when a measuring cylinder is used to measure the volume it can be written as Hu/H0
- The F value is between the limits 0 to 1.
- The higher the sedimentation volume the better is the physical stability.

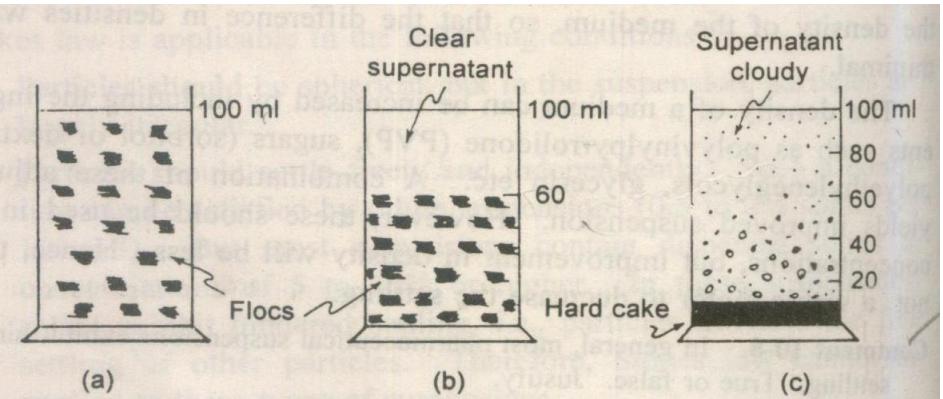


Figure 10-3. Sedimentation parameters of suspensions. Flocculated suspension: (a) initial state (F = 1.0); (b) state of suspension on storage after some time (F = 0.6), and (c) deflocculated suspension.

13. REDISPERSIBILITY:

- If the particles settle they should be easily redispersible by a moderate amount of shaking.

EMULSIONS

- Emulsion systems consisting of at least two immiscible liquid phases, one of which is dispersed as small globules in the other liquid phase.
- The globule diameter may range from 0.1 to 100 µm.
- Emulsions are thermodynamically unstable systems.
- Emulsions are also called as heterogeneous systems, or more precisely biphasic systems.

Classification

1. **Based on nature of dispersed phase**
   1.1. oil-in-water (o/w)
   1.2. water-in-oil (w/o)
   1.3. water-in-oil-in water (w/o/w)
   1.4. oil-in-water-in-oil (o/w/o)
2. **Based on the globule size**
   2.1. Macroemulsion (Droplets size range approximately 5 µm or above)
   2.2. Fine emulsions (0.25 to 25µm)
   2.3. Micro emulsions (0.01µm)

Instability of Emulsions

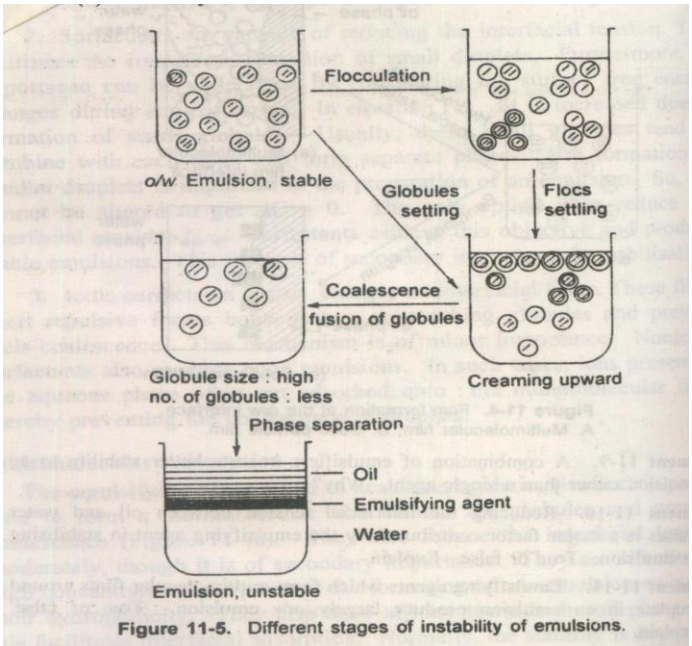


Figure 11-5. Different stages of instability of emulsions.

IPQC tests for EMULSIONS

- Appearance
- Clarity testing
- pH value
- Viscosity
- Rheology
- Drug content uniformity
- Particle size distribution
- Densities of phases
- Phase volume ratio
- Charge of electrical double layer
- Physical properties of interface
- Temperature fluctuations

- Quality control of water
- Breaking or cracking
- Compatibility of product with container-closure system

1- VISUAL INSPECTION

1.1 - Inspect for Flocculation

1.2- Inspect for creaming

1.3- Inspect for Coalescence

1.4- Inspect for breaking

1.5- Change in color

1.1. <u>Flocculation:</u>

- Neighbouring globules come closer to each other and form colonies in the external phase.
- This is the initial stage that leads to instability
- The extent of flocculation of globules depends on
- a)globule size distribution
- b)charge on globule surface
- c)viscosity of external medium

1.2. <u>Creaming:</u>

- Creaming is the concentration of globules at the top or bottom of the emulsion.
- The floccules move either upward or downward leading to creaming.
- It can be observed by a difference in colour shade of the layers.

- Creaming is influenced by

    a) Globule size

    b) Viscosity of the dispersion medium

    c) Differences in the densities of dispersed phase and dispersion medium

1.3. Coalescence:

- Coalescence is followed by creaming stage.
- In this process the emulsifier film around the globules is destroyed to a certain extent.
- This step can be recognised by increased globule size and reduced number of globules.
- Coalescence is observed due to

    a) Insufficient amount of the emulsifying agent

    b) Altered partitioning of the emulsifying agent

    c) Incompatibilities between emulsifying agents

1.4. Breaking:

- This is indicated by complete separation of oil and aqueous phases.
- It is an irreversible process that is simple mixing fails to re-suspend the globules into an uniform emulsion.
- In breaking the protective sheath around the globules is completely destroyed.

2- VISCOSITY

- As the viscosity increases flocculation of globules will be reduced. simultaneously the Brownian movement of globules will also be hindered

leading to creaming low viscosity also destabilize the emulsion and can promote microbial growth..

- Due to this antagonistic effect an optimum viscosity is desirable for good stability.

- **Measuring Viscosity:**

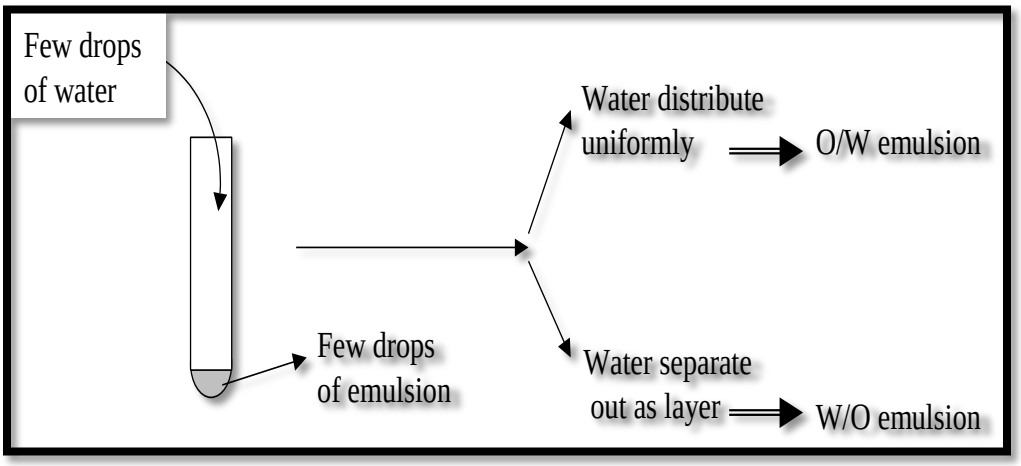
- Ostwald viscometer is a commonly used viscometer, which consists of a U-shaped glass tube held vertically. For more accurate measurements it is held in a controlled temperature bath. It is also known as a glass capillary viscometer. A liquid is allowed to flow through its capillary tube between two etched marks and the time of flow of the liquid is measured using a stopwatch.

3- EVALUATION FOR PHASE INVERSION

- The emulsion is checked for phase inversion.
- Phase inversion means a change of emulsion type from o/w to w/o or vice versa.
- Emulsion type is determined for evaluation of Phase Inversion. Following methods are used for determining emulsion type
    a) Dye Test
    b) Dilution Test
    c) Conductivity Test
    d) Dye test with Microscopic Evaluation

- **DROP DILUTION METHOD:**

- This method is based on the principle that emulsion is always miscible with the external phase. If water is added to water in oil w/o type emulsion, it will not be mixed. On the other hand, oil mixes well.
- Same is the case with o/w type emulsion. If oil is added to oil in water o/w type emulsion, it will not be mixed. On the other hand, water mixes well.



- **DYE SOLUBILITY METHOD:**

- It is based on the solubility of any dye in the external phase. Amaranth, a water soluble dye gives color to oil in water o/w type emulsion, but not to water in oil w/o type emulsion. Same is the case with oil soluble dyes.
- Dye test with Microscopic Evaluation
- Observe dye mixed sample under microscope

4- GLOBULES SIZE DISTRIBUTION:

- Globules of uniform size impart maximum stability.

- In such emulsions globules pack loosely and globule to globule contact is less.
- Globule distribution is effected by viscosity, phase volume ratio, density of phases etc.
- An optimum degree of size distribution range should be chosen to achieve maximum physical stability.
- According to stokes law the diameter of the globule is considered as a major factor in creaming of emulsion. The rate of creaming decreases four folds when the globule diameter is halved.
- Microscopic examination of globule size distribution analysis is an useful tool to evaluate the physical stability.

5- DENSITIES OF PHASES

- By adjusting the density of the phases to the same value we can increase the stability of emulsion.
- Oil phase density can be enhanced by adding brominated oil when the oil is an external phase.

6- PACKAGING MATERIAL CONTROL

- Packaging material should not interact physically or chemically with the finished product to alter the strength, quality or purity beyond specified requirements.
- The following features are to be considered in developing container specifications
    - Properties of container tightness

- Moisture and vapour tightness regardless of container construction
- Compatibility between container and product

7- LABELS CONTROL

- Production control issues a packaging form that carries
  - The name of the product
  - Item number
  - Lot number
  - Number of labels
  - Inserts
  - Packaging material to be used
  - Operation to be performed
  - Quantity to be packaged
- A copy of this is sent to the supervisor of label control, who in turn counts out the required number of labels.