



Department of Pharmacy GP  
(Uttwar)

# Pharmaceutical suspension



(Pharmaceutics II)  
Unit 7

# Introduction

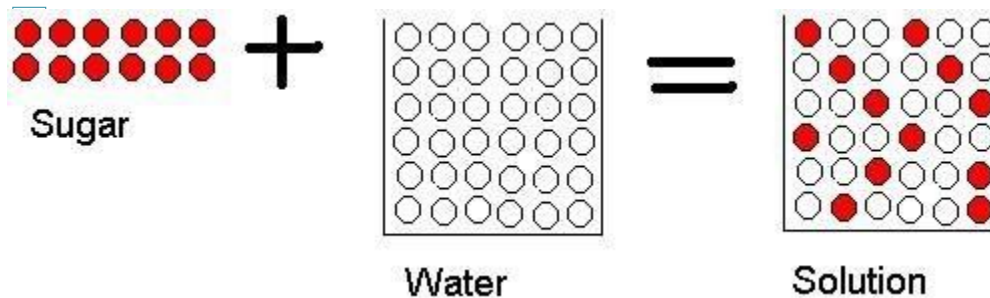
- A Pharmaceutical suspension is a disperse system in which internal phase is dispersed uniformly as finely divided insoluble particles throughout the external phase.
- The internal phase consisting of **insoluble** particles having a specific range of size which is maintained uniformly throughout the suspending vehicle with aid of single or combination of suspending agent.
- The external phase (suspending medium) is generally aqueous in some instance, may be an organic or oily liquid for non oral use.

# Introduction continued

- The term "Disperse System" refers to a system in which one substance (The Dispersed Phase) is distributed, in discrete units, throughout a second substance (the continuous Phase or vehicle).
- Each phase can exist in solid, liquid, or gaseous state .
- . Most suspensions are classified as a coarse suspension which is a dispersion of particles with a mean diameter greater than  $1\ \mu\text{m}$  ( $1$  to  $100\ \mu\text{m}$ ). A colloidal suspension is a dispersion of particles with a mean diameter of less than  $1\ \mu\text{m}$  ( $0.5\ \mu\text{m}$  to  $1\ \mu\text{m}$ ).

# The Difference Between Solution & Suspensions

- When the 2 substances totally mix it is called a solution.
- E.g. Solute + Solvent = Solution
- (sugar) + (water) = Solution



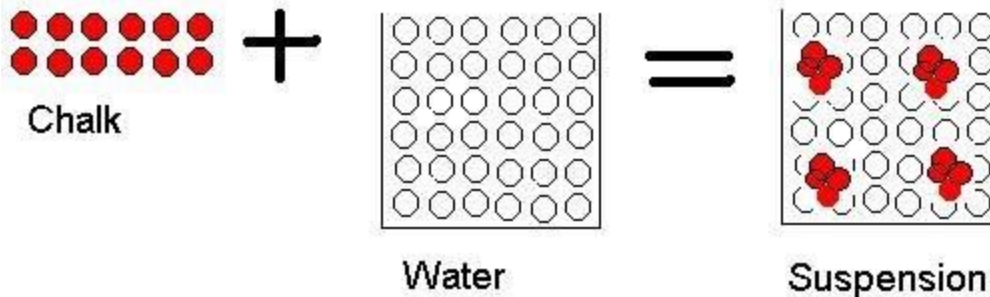
- We then say sugar is soluble in water, it has dissolved.

# The Difference Between Solution & Suspensions

.The particles in a suspension are insoluble

□ Sometimes when we mix substances ~~it~~ stay in clusters. We therefore say it is insoluble in water.

□ E.g. Chalk + Water = Suspension



□ Eventually the particles sink to the bottom to form sediment.

# Types of insoluble solids

There are two types of insoluble solids which constitute the internal or dispersed phase. These are

- I. Diffusible solids – these sediment sufficiently slowly to enable satisfactory dose removal after redispersion. eg. Light kaoline, magnesium tricilicate

# Types of insoluble solids

- **INDIFFUSIBLE SOLIDS-** eg. sulphadimidine and chalk. These sediment too rapidly and require the addition of other materials to reduce sedimentation rate to an acceptable level.

# Sedimentation

- This is a phenomenon which occurs in a dispersed system where the dispersed particles settle to the bottom of the container. This occurs because the particles are too large to remain permanently suspended in the vehicle.
- Therefore suitable suspending agents are added to retard this process.



# SUSPENDING AGENTS

- Suspending agents are substances that are used to keep finely divided insoluble materials suspended in a liquid media by preventing their agglomeration (coming together) and by imparting viscosity to the dispersion media so that the particles settle more slowly. Care must be taken when selecting a suspending agent for oral preparations as the acid environment of the stomach may alter the physical characteristics of the suspension and therefore the rate of release of the drug from suspension.
- They are various types of suspending agents

# Types of suspending agents

## 1. **NATURAL AGENTS**

This class consists of those from.

- a. Animal source eg Gelatine
- b. Plant source eg. Accacia, Tragacanth, Starch, sea weed (Alginates)
- c. mineral sources.eg Bentonite, Kaoline

## 2. **SEMI-SYNTHETIC AGENTS**

These consist of substituted celluloses (minerals) eg. Hydroxyethylcellulose, Sodium Carboxymethylcellulose, methylcellulose, Microcrystalline cellulose

## 3. **SYNTHETIC AGENTS.**

They are synthetic polymers eg carboxypolymethylene (carbopol), Polyvinyl Alcohol, Polyvinyl Pyrrolidone iodine complex (PVC)

# Types of suspending agents continued.....

- Most suspending agents perform two functions i.e. besides acting as a suspending agent they also imparts viscosity to the solution. Suspending agents form film around particle and decrease interparticle attraction.
- A good suspension should have well developed thixotropy.
- At rest the solution is sufficient viscous to prevent sedimentation and thus aggregation or caking of the particles. When agitation is applied the viscosity is reduced and provide good flow characteristic from the mouth of bottle.

# Classification of suspensions

- **Based On General Classes**

  - Oral suspension

  - Externally applied suspension

  - Parenteral suspension

- **Based On Proportion Of Solid Particles**

  - Dilute suspension (2 to 10%w/v solid)

  - Concentrated suspension (50%w/v solid)

- **Based On Electrokinetic Nature Of Solid Particles**

  - Flocculated suspension

  - Deflocculated suspension

- **Based On Size Of Solid Particles**

  - Colloidal suspension (< 1 micron)

  - Coarse suspension (> 1 micron)

  - Nano suspension (10 ng)

# FORMULATION OF SUSPENSIONS

□ The three steps that can be taken to ensure formulation of an elegant pharmaceutical suspension are:

1. **CONTROL PARTICLE SIZE**. On a small scale, this can be done using a mortar and a pestle to grind down ingredients to a fine powder.
2. Use thickening agent to increase viscosity of the vehicle by using suspending agents or viscosity increasing agents
3. Use of a wetting agent/ surfactants

# Pharmaceutical Applications of suspensions

Suspensions may be used pharmaceutically for a number of reasons. Some are given below;

- Suspension is usually applicable for drug which is insoluble or poorly soluble. E.g. Prednisolone
- suspension To prevent degradation of drug or to improve stability of drug. E.g. Oxytetracycline suspension
- To mask the taste of bitter or unpleasant drug when formulated in solution form. Drugs are formulated in as suspension which will be more palatable  
E.g. Chloramphenicol palmitate suspension
- Suspension of drug can be formulated for topical application e.g. Calamine lotion.

# Pharmaceutical Applications of suspensions

- Suspension can be formulated for parenteral application in order to control rate of drug absorption, E.g. penicillin procaine
- Vaccines as a immunizing agent are often formulated a suspension.E.g. Cholera vaccine
- X-ray contrast agent are also formulated as suspension. E.g. Barium sulphate for examination of alimentary tract
- If the drug is unstable when in contact with the vehicle, suspensions should be prepared immediately prior to handing out to the patient in order to reduce the amount time that the drug particles are in contact with the dispersion medium. Eg Amoxicilin suspension

# Pharmaceutical Applications of suspensions

- Drugs which degrade in aqueous solution may be suspended in a non-aqueous phase. eg. Tetracycline hydrochloride is suspended in a fractionated coconut oil for ophthalmic use.
- Lotions containing insoluble solids are formulated to leave a thin coating of medicament on the skin. As the vehicle evaporates, it gives a cooling effect and leaves the solid behind. eg calamine lotion and sulphur lotion compound.
- Bulky, insoluble powders can be formulated as suspension so that they are easier to take eg Kaolin or chalk



# ADVANTAGES OF SUSPENSIONS

- Suspension can improve chemical stability of certain drug. E.g. Procaine penicillin G
- Drug in suspension exhibits higher rate of bioavailability than other dosage forms. bioavailability is in following order,
  - **Solution > Suspension > Capsule > Compressed Tablet > Coated tablet**
- Duration and onset of action can be controlled. E.g. Protamine Zinc-Insulin suspension
- Suspension can mask the unpleasant/ bitter taste of drug. E.g. Chloramphenicol palmitate

# DISADVANTAGE

- Physical stability, sedimentation and compaction can causes problems.
- It is bulky, therefore sufficient care must be taken during handling and transport.
- It is difficult to formulate
- Uniform and accurate dose can not be achieved unless suspension are packed in unit dosage form

# Basic requirements of suspension

1. The suspended particles should not settle rapidly and sediment produced, must be easily re-suspended by the use of moderate amount of shaking.
2. Satisfactory pourability.
3. Should have an elegant smooth appearance.
4. After gentle shaking, the medicament stays in suspension long enough for a dose to be accurately measured.
5. Constant particle size and size distribution so that the product is free from a gritty texture.

# Theory of Suspensions

## □ Sedimentation Behaviour

- Sedimentation means settling of particle or flocules occur under gravitational force in liquid dosage form.

## □ Theory of Sedimentation

- The factors affecting the rate of sedimentation of a particle are described in **Stoke's equation**

- $$V = \frac{2r^2(\rho_s - \rho_o)g}{9\eta} \quad \text{or} \quad V = \frac{d^2(\rho_s - \rho_o)g}{18\eta}$$

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# Stokes equation

- Where,  $v_{\text{sed}}$  = sedimentation velocity in  $\text{m} / \text{sec}$
- $d$  = Diameter of particle
- $r$  = radius of particle
- $\rho_s$  = density of disperse phase
- $\rho_o$  = density of disperse media
- $g$  = acceleration due to gravity
- $\eta$  = viscosity of disperse medium in poise

# Stokes equation

- The basic consequences of the Stokes equation are that the rate of fall of a suspended particle in a vehicle of a given density is greater for larger particles than it is for smaller particles. Also the greater the difference in density between the particles and the vehicle, the greater will be the rate of sedimentation. Increasing the viscosity of the dispersion medium will reduce the rate of sedimentation. Thus decrease in the rate of sedimentation of particles in a suspension may be achieved by reducing the size of the dispersed particles and by increasing the density and viscosity of the dispersion/continuous phase.

# Factors Affecting Sedimentation

## 1. Particle size diameter (d)

- $V \propto d^2$
- Sedimentation velocity (v) is directly proportional to the square of diameter of particle.

## 2. Density difference between dispersed phase and dispersion media ( $\rho_s - \rho_o$ )

- $V \propto (\rho_s - \rho_o)$
- Generally, particle density is greater than dispersion medium but, in certain cases particle density is less than dispersed phase, so suspended particle floats & is difficult to distribute uniformly in the vehicle.
- If density of the dispersed phase and dispersion medium are equal, the rate of settling becomes zero.

# Factors Affecting Sedimentation

- **Viscosity of dispersion medium ( $\eta$ )**  
 $V \propto 1 / \eta_0$
- Sedimentation velocity is inversely proportional to viscosity of dispersion medium.
- So increase in viscosity of medium, decreases settling, so the particles achieve good dispersion system but greater increase in viscosity gives rise to problems like pouring, syringibility and redispersibility of suspension.



# Advantages and Disadvantages due to viscosity of medium

## Advantages

- High viscosity inhibits the crystal growth.
- High viscosity prevents the transformation of metastable crystal to stable crystal.
- High viscosity enhances the physical stability.

## Disadvantages

- High viscosity hinders the re-dispersibility of the sediments
- High viscosity retards the absorption of the drug.
- High viscosity creates problems in handling of the material during manufacturing.

# The Sedimentation Behavior of Flocculated and Deflocculated Suspensions:

## *Flocculated Suspensions*

**Flocculation** is a condition which occurs as a result of the lowering of electrical forces of repulsion in a dispersed system, so that the force of attraction predominates. Systems under this condition reduced repulsive forces the dispersed particles to approach each other more closely and form aggregates known as flocs

In flocculated suspension, formed flocs (loose aggregates) will cause increase in sedimentation rate due to increase in size of sedimenting particles. Hence, flocculated suspensions sediment more rapidly.

# Flocculated suspension continued

- Here, the sedimentation depends not only on the size of the flocs but also on the porosity of flocks. In flocculated suspension the loose structure of the rapidly sedimenting flocs tends to preserve in the sediment, which contains an appreciable amount of entrapped liquid. The volume of final sediment is thus relatively large and is **easily redispersed** by agitation.
- Most stable pharmaceutical suspensions are flocculated.
- The suspension appear somehow unsight (unappealing) due to its rapid sedimentation and it presents an obvious clear supernatant. This can be minimised by enlarging the volume of the sediments by the use of flocculating agents eg starch, alginates and carboxyvinyl polymers.
- Since the sediment is loosly structured, caking or claying does not occur.

# Deflocculated suspensions


A deflocculated suspension is one in which the electrical repulsive forces between particles exceeds the attractive forces, the particles are kept apart as individuals affected only by the suspending vehicle. Even when brought together by random motion, they resist collision due to the high surface tension.

- In deflocculated suspension, individual particles are settling, so **rate of sedimentation is slow** which prevents entrapping of liquid medium which makes it **difficult to re-disperse** by agitation.
- This phenomenon also called 'cracking' or 'claying'.
- In deflocculated suspension, smaller particles settle slowly and therefore remaining supernatant liquid so supernatant appears cloudy and has a pleasing granular appearance whereby in flocculated suspension, even the smallest particles are involved in flocs, so the supernatant does not appear cloudy.

# Flocculating Agents

Flocculating agents decrease the zeta potential of the suspended charged particle and thus cause aggregation (flock formation) of the particles.

- *Examples of flocculating agents are:*
- Neutral electrolytes such as KCl, NaCl.
- Surfactants
- Polymeric flocculating agents
- Sulfate, citrates, phosphates salts

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- Neutral electrolytes e.g. NaCl, KCl besides acting as flocculating agents, also decreases interfacial tension of the surfactant solution. If the particles are having less surface charge then monovalent ions are sufficient to cause flocculation e.g. steroidal drugs.
  - For highly charged particles e.g. insoluble polymers and poly-electrolytes species, di or trivalent flocculating agents are used.

# Method of Floccules Formation

- The different methods used to form floccules are mentioned below:
- **1. Electrolytes**
- Electrolytes decrease electrical barrier between the particles and bring them together to form floccules. They reduce zeta potential near to zero value that results in formation of bridge between adjacent particles, which lines them together in a loosely arranged structure.

# Method of Floccules Formation

- If we disperse particles of bismuth subnitrate in water we find that based on electrophoretic mobility potential because of the strong force of repulsion between adjacent particles, the system is peptized or deflocculated. By preparing series of bismuth subnitrate suspensions containing increasing concentration of monobasic potassium phosphate co-relation between apparent zeta potential and sedimentation volume, caking, and flocculation can be demonstrated.



# Method of Floccules Formation

- The addition of monobasic potassium phosphate to the suspended bismuth subnitrate particles causes the positive zeta potential to decrease owing to the adsorption of negatively charged phosphate anion.
- With continued addition of the electrolyte, the zeta potential eventually falls to zero and then increases in negative directions.
- Only when zeta potential becomes sufficiently negative to affect potential does the sedimentation volume start to fall.
- Finally, the absence of caking in the suspensions correlates with the maximum sedimentation volume, which, as stated previously, reflects the amount of flocculation.

# Surfactants

- Both ionic and non-ionic surfactants can be used to bring about flocculation of suspended particles.
- ⊗ Optimum concentration is necessary because these compounds also act as wetting agents to achieve dispersion.
- ⊗ Optimum concentrations of surfactants bring down the surface free energy by reducing the surface tension between liquid medium and solid particles. This tends to form closely packed agglomerates.
- ⊗ The particles possessing less surface free energy are attracted towards to each other by van der-waals forces and forms loose agglomerates.

# Polymers

Polymers possess long chain in their structures.

Starch, alginates, cellulose derivatives, carbomers, tragacanth

The part of the long chain is adsorbed on the surface of the particles and remaining part projecting out into the dispersed medium.

Bridging between these later portions, also leads to the formation of flocs.

# Viscosity of Suspensions

- Viscosity of suspensions is of great importance for stability and pourability of suspensions. As we know suspensions have least physical stability amongst all dosage forms due to sedimentation and cake formation.
- So as the viscosity of the dispersion medium increases, the terminal settling velocity decreases thus the dispersed phase settle at a slower rate and they remain dispersed for longer time yielding higher stability to the suspension.
- On the other hand as the viscosity of the suspension increases, its pourability decreases and inconvenience to the patients for dosing increases.
- Thus, the viscosity of suspension should be maintained within optimum range to yield stable and easily pourable suspensions.

# Different Approaches To Increase The Viscosity of Suspensions

- Various approaches have been suggested to enhance the viscosity of suspensions. Few of them are as follows:
- **I . Viscosity Enhancers**
- Some natural gums (acacia, tragacanth), cellulose derivatives (sodium CMC, methyl cellulose), clays (bentonite, veegum), carbomers, colloidal silicon dioxide (Aerosil), and sugars (glucose, fructose) are used to enhance the viscosity of the dispersion medium. They are known as suspending agents.

# Thixotropy

- **Thixotropy** is a phenomenon or property exhibited by highly flocculated preparation in which a preparation is sem-solid at rest (in the absence of shearing forces) but becomes so fluid when tapped or shaken and resumes its original structure after only a few minutes of rest.
- A thixotropic suspension is the one which is viscous during storage but loses consistency and become fluid upon shaking.
- A well-formulated thixotropic suspension would remain fluid long enough for the easy dispense of a dose but would slowly regain its original viscosity within a short time.

# Other Formulation Aspects

## □ **Introduciton**

- A perfect suspension is one, which provides content uniformity. The formulator must encounter important problems regarding particle size distribution, specific surface area, inhibition of crystal growth and changes in the polymorphic form. The formulator must ensure that these and other properties should not change after long term storage and do not adversely affect the performance of suspension.
- Choice of pH, particle size, viscosity, flocculation, taste, color and odor are some of the most important factors that must be controlled at the time of formulation.

# Formulation Components

The various components, which are used in suspension formulation, are as follows.

- ❑ **API .....Active drug substances**
- ❑ **Wetting agents .....They are added to disperse solids in continuous liquid phase.**
- ❑ **Flocculating agents .....They are added to floc the drug particles**
- ❑ **Thickeners .....They are added to increase the viscosity of suspension.**
- ❑ **Buffers and pH adjusting agents .....They are added to stabilize the suspension to a desired pH range.**
- ❑ **Osmotic agents .....They are added to adjust osmotic pressure comparable to biological fluid.**
- ❑ **Coloring agents .....They are added to impart desired color to suspension and improve elegance.**
- ❑ **Preservatives .....They are added to prevent microbial growth.**
- ❑ **External liquid vehicle .....They are added to construct structure of the final suspension.**



# wetting Agents

Hydrophilic materials are easily wetted by water while hydrophobic materials are not. However hydrophobic materials are easily wetted by non-polar liquids. The extent of wetting by water is dependent on the hydrophilicity of the materials. If the material is more hydrophilic it finds less difficulty in wetting by water. Inability of wetting reflects the higher interfacial tension between material and liquid. The interfacial tension must be reduced so that air is displaced from the solid surface by liquid.

- **Non-ionic surfactants** are most commonly used as wetting agents in pharmaceutical suspension. Non-ionic surfactants having HLB value between **7-10** are best as wetting agents. High HLB surfactants act as foaming agents. The concentration used is less than 0.5 %. A high amount of surfactant causes solubilization of drug particles and causes stability problem.
- **Ionic surfactants** are not generally used because they are not compatible with many adjuvant and causes change in pH.

# Surfactants

- Surfactants decrease the interfacial tension between drug particles and liquid and thus liquid is penetrated in the pores of drug particle displacing air from them and thus ensures wetting.
- Surfactants in optimum concentration facilitate dispersion of particles. Generally we use non-ionic surfactants but ionic surfactants can also be used depending upon certain conditions.
- Disadvantages of surfactants are that they have foaming tendencies.
- Further they are bitter in taste. Some surfactants such as polysorbate 80 interact with preservatives such as methyl paraben and reduce antimicrobial activity.

# Surfactants

- Polysorbate 80 is most widely used surfactant both for parenteral and oral suspension formulation.
- Polysorbate 80 is also adsorbed on drug particle and decreases its zeta potential. This effect of polysorbate 80 stabilizes the suspension.
- Polysorbate 80 stabilized suspensions through steric mechanism. At low concentration of polysorbate 80, only partial stabilization of suspension was observed.

# Surfactants

- In absence of polysorbate 80, difficulty was observed in re-dispersion of sedimented particles.
- Polysorbate 80 is most widely used due to its following advantages
- It is non-ionic so no change in pH of medium
- No toxicity.
- Safe for internal use.
- Less foaming tendencies however it should be used at concentration less than 0.5%.
- Compatible with most of the adjuvant.

# Hydrophilic Colloids

- Hydrophilic colloids coat hydrophobic drug particles in one or more than one layer. This will provide hydrophilicity to drug particles and facilitate wetting.
- They cause deflocculation of suspension because force of attraction is declined.  
e.g. acacia, tragacanth, alginates, guar gum, pectin, gelatin, wool fat, egg yolk, bentonite, Veegum, Methylcellulose etc.

# Solvents

- The most commonly used solvents used are alcohol, glycerin, polyethylene glycol and polypropylene glycol. The mechanism by which they provide wetting is that they are miscible with water and reduce liquid air interfacial tension. Liquid penetrates in individual particle and facilitates wetting.

## Co-solvents Used in suspensions

- Some solvents which themselves have high viscosity are used as co-solvents to enhance the viscosity of dispersion medium:
- Glycerol, propylene glycol, sorbitol.

# MIXING PROCEDURES

## THE DISPENSING OF SUSPENSIONS

- The method of dispensing suspensions is the same for most, with some differences for specific ingredients.
- 1. Crystalline and granular solids should be finely powdered in the mortar. The suspending agent should then be added and mixed thoroughly in the mortar. Do not apply too much pressure, otherwise gumming or caking of the suspending agent will occur and heat of friction will make it sticky.
- 2. Add a little liquid vehicle to make a paste and mix well until smooth and free of lumps. Continue with gradual additions until the mixture can be poured into a bottle. Further liquid is used to rinse all the powder into the bottle where it is made up to volume.
- 3. When water is prescribed as a vehicle, use freshly boiled and cooled water or potable water where permissible

# VARIATIONS

- If the wetting agents are included in the formulation, add them before forming the paste
- If syrup and/or glycerol are in the formulation, use this rather than water to form the initial paste
- If soluble solids are being used, dissolve them in the vehicle before or after making the paste
- Leave addition of volatile components, colouring or concentrated flavouring tinctures such as chloroform spirit, liquid liquorice extract and compound tartrazine solution until near the end



# STABILITY OF SUSPENSIONS

- Factors that contribute to appreciable stability of a suspension include:
  - a) **Small particle size-** reduce the size of the dispersed particle increases the total surface area of the solid. The greater the degree of subdivision of a given solid the larger the surface area. The increase in surface area means also an increase in interface between the solids and liquids leading to an increase in viscosity of a system.

# STABILITY OF SUSPENSIONS

- b). **Increasing the viscosity** — increasing the viscosity of the continuous phase can lead to the stability of suspensions. This is so because the rate of sedimentation can be reduced by increase in viscosity. Viscosity increase is brought about by addition of thickening agents to the external phase. In water these must be either soluble or swell. It is important to note that the rate of release of a drug from a suspension is also dependent on viscosity. Of a product. The more viscous the preparation, the slower is likely to be the release of a drug. Sometimes this property may be desirable for depot preparations.

# STABILITY OF SUSPENSIONS

## C). **TEMPERATURE.**

Another factor which negatively affects the stability and usefulness of pharmaceutical suspensions is fluctuation of temperature. Temperature fluctuations can lead to caking and claying.

# Quality Control of Suspensions

The following tests are carried out in the final quality control of suspension:

- Appearance Color, odor and taste
- Physical characteristics such as particle size determination and microscopic photography for crystal growth
- Sedimentation rate and
- Zeta Potential measurement
- Sedimentation volume
- Redispersibility and Centrifugation tests
- Rheological measurement
- Stress test
- pH
- Freeze-Thaw temperature cycling
- Compatibility with container and cap liner

# Special labels and advice for suspensions

- All pharmaceutical suspensions should be properly labelled.
- The most important additional information in addition to the product name and directions for use is the inclusion of the direction “**shake the bottle well before use**” as some sedimentation of medicament would normally be expected. Shaking the bottle will redisperse the medicament and ensure that the patient can measure the accurate dose.
- Other labelling information include **directions to store in a cool place**, expiry date.

# CONTAINERS FOR SUSPENSIONS

- Choices of packaging of all pharmaceutical products are extremely important aspect of ensuring stability of the product.
- Suspensions should be packed in amber coloured bottles- plain for internal use and ribbed for external use. There should be adequate air space above the liquid to allow shaking and easy pouring. A 5ml medicine spoon or oral syringe should be given when the suspension is for oral use.

# Ideal Requirements of Packaging Material

- It should be inert.
- It should effectively preserve the product from light, air, and other contamination through shelf life.
- It should be cheap.
- It should effectively deliver the product without any difficulty

# Thanking you

