

# Pharmaceutics I

صيدلانيات ١

Unit 5

Dispersed systems

# *dispersed system*

- Liquid preparations containing **undissolved or immiscible drug** distributed throughout a vehicle.
- In these preparations, the substance distributed is referred to as the ***dispersed phase***, and the vehicle is termed the ***dispersing phase*** or ***dispersion medium***.
- **Suspension:** The particles of the dispersed phase are usually solid materials that are insoluble in the dispersion medium.
- **Emulsions:** the dispersed phase is a liquid that is neither soluble nor miscible with the liquid of the dispersing phase.
- In the case of an **aerosol**, the dispersed phase may be small air bubbles throughout a solution or an emulsion.

- The particles of the dispersed phase vary widely in size,
- Dispersions containing **coarse particles**, usually **10 to 50  $\mu\text{m}$** , are referred to as *coarse dispersions*; they include the *suspensions* and *emulsions*.
- Dispersions containing particles of **smaller** size are termed *fine dispersions* (0.5 to 10  $\mu\text{m}$ ) **colloidal range**, *Magma*s and *gels* are fine dispersions .
- if the particles are in the colloidal range, *colloidal dispersions*.

- **Complete and uniform redistribution** of the dispersed phase is essential to the accurate administration of uniform doses.
- For a properly prepared dispersion, this should be accomplished by moderate agitation of the container.

# **Coarse Dispersions**

- Suspensions
- Emulsions

# Suspensions

- Suspensions containing finely divided drug distributed somewhat uniformly throughout a vehicle in which the drug exhibits a minimum degree of solubility.
- A pharmaceutical suspension is a coarse dispersion in which insoluble solid particles are dispersed in a liquid medium.
- The particles have diameters for the most part greater than 0.1  $\mu\text{m}$ ,

- Some suspensions are available in ready-to-use form, that is, already distributed through a liquid vehicle with or without stabilizers and other additives.
- Other preparations are available as **dry powders** intended for suspension in liquid vehicles.
- Generally, this type of product is a powder mixture containing the drug and suitable suspending and dispersing agents to be diluted and agitated with a specified quantity of vehicle, most often purified water (**reconstitution**).
- Drugs that are unstable if **maintained for extended periods** in the presence of an aqueous vehicle (e.g., many antibiotic drugs) are most frequently supplied as dry powder mixtures for reconstitution at the time of dispensing.



# REASONS FOR SUSPENSIONS

- certain drugs are chemically unstable in solution but stable when suspended. In this instance, the suspension ensures chemical stability while permitting liquid therapy.
- This is particularly advantageous for infants, children, and the elderly.
- preparing a palatable liquid dosage form: The disadvantage of a disagreeable taste of certain drugs in solution form is overcome when the drug is administered as undissolved particles of an oral suspension.

- For example, erythromycin estolate is a less water-soluble ester form of erythromycin and is used to prepare a palatable liquid dosage form of erythromycin, the result being Erythromycin Estolate Oral Suspension, USP.
- For the most part, oral suspensions are aqueous preparations with the vehicle **flavored** and **sweetened** to suit the anticipated taste preferences of the intended patient.

# **FEATURES DESIRED IN A PHARMACEUTICAL SUSPENSION**

- 1. Should be therapeutic active , chemically / physically stable, and esthetic appeal.**
- 2. Must remain sufficiently homogeneous for at least the period of time necessary to remove and administer the required dose after shaking.**
- 3. A properly prepared pharmaceutical suspension should settle slowly and should be readily redispersed upon gentle container shaking .**
- 4. The particles which settle to the bottom of the container must not form a hard cake.**
- 5. The particle size of the suspended particles should remain fairly constant throughout long periods of undisturbed standing.**
- 6. The suspension should pour readily and evenly from its container.**

# SEDIMENTATION RATE OF THE PARTICLES OF A SUSPENSION

- The various factors involved in the rate of settling of the particles of a suspension are included in the equation of **Stokes law**,

$$\frac{dx}{dt} = \frac{d^2(\rho_i - \rho_e)g}{18\eta}$$

## Stokes law

$$\frac{dx}{dt} = \frac{d^2(\rho_i - \rho_e)g}{18\eta}$$

$dx/dt$  is the rate of settling,  
 $d$  is the diameter of the particles,  
 $\rho_i$  is the density of the particle,  
 $\rho_e$  is the density of the medium,  
 $g$  is the gravitational constant, and  
 $\eta$  is the viscosity of the medium.

- **A number of factors can be adjusted to enhance the physical stability of a suspension, including the diameter of the particles and the density and viscosity of the medium.**

# Example

- A powder has a density of 1.3 g/cc and an average particle diameter of 2.5  $\mu\text{m}$  (assuming the particles to be spheres).
- Calculate the SEDIMENTATION RATE OF THE PARTICLES OF A SUSPENSION in Cm / Second

$$\frac{(2.5 \times 10^{-4})^2 (1.3 - 1.0) (980)}{18 \times 0.01} = 102 \times 10^{-4} \text{ cm/seconds}$$

# Home work

- If the particle size of the powder is reduced to 0.25  $\mu\text{m}$  and water is still used as the dispersion medium,
- Calculate the SEDIMENTATION RATE OF THE PARTICLES OF A SUSPENSION in Cm / Second
- If a different dispersion medium, such as glycerin, is used in place of water, Glycerin has a density of 1.25 g/mL and a viscosity of 400 cP.
- Calculate the SEDIMENTATION RATE OF THE PARTICLES OF A SUSPENSION in Cm / Second



- **EXAMPLE : A powder has a density of 1.3 g/ml**

CONDITION	RATE OF SETTLING (CM/S)
2.5 $\mu\text{m}$ powder in water	$1.02 \times 10^{-4}$
0.25 $\mu\text{m}$ powder in water	$1.02 \times 10^{-6}$
2.5 $\mu\text{m}$ powder in glycerin	$4.25 \times 10^{-8}$
0.25 $\mu\text{m}$ powder in glycerin	$4.25 \times 10^{-10}$

- the greater the density of the particles, the greater the rate of sedimentation
- Because aqueous vehicles are used in pharmaceutical oral suspensions, the density of the particles is generally greater than that of the vehicle, a desirable feature.
- If the particles were less dense than the vehicle, they would tend to float and floating particles would be quite difficult to distribute uniformly in the vehicle.

- The rate of sedimentation may be appreciably reduced by **increasing the viscosity** of the dispersion medium,
- However, a product having too high a viscosity is not generally desirable, because it pours with difficulty and it is equally difficult to redisperse
- Therefore, if the viscosity of a suspension is increased, it is done so only to a modest extent

- **The viscosity characteristics of a suspension may be altered by:**
- **the vehicle used,**
- **the solids content. As the proportion of solid particles in a suspension increases, so does the viscosity.**
- **Suspending agents, viscosity enhancers.**

- **Suspending agents : agents employed to thicken the dispersion medium and help suspend the particles.**
- **Carboxymethylcellulose (CMC),**
- **methylcellulose,**
- **microcrystalline cellulose,**
- **polyvinylpyrrolidone,**
- **xanthan gum,**
- **bentonite**

- When **polymeric substances** and **hydrophilic colloids** are used as suspending agents, appropriate tests must be performed to show that the agent does not interfere with availability of the drug.
- These materials can bind certain medicinal agents, rendering them unavailable or only slowly available for therapeutic function.
- Also, the amount of the suspending agent must not be such to render the suspension too viscous to agitate (to distribute the *particles*) or to pour.

# Types of suspension

## **Flocculated Suspensions:**

Suspension in which particles are weakly bonded, settle rapidly, do not form a cake and are easily resuspended with a minimum of agitation.

## **Deflocculated Suspension:**

Suspension in which particles settle slowly, and eventually form a sediment in which aggregation occurs with the resultant formation of a hard cake which is difficult to resuspended.

## Flocculated Suspension





**Deflocculated  
Suspension**



**flocculated  
Suspension**

- The velocity of fall of a suspended particle is greater for larger particles than it is for smaller particles,
- Reducing the particle size of the dispersed phase produces a slower *rate* of sedimentation
- The reduction in particle size produces slow, more uniform rates of settling. However, one should avoid reducing the particle size too much, because fine particles have a **tendency to form a compact cake** upon settling to the bottom of the container.
- The result may be that the cake resists breakup with shaking and forms rigid aggregates of particles

- To avoid formation of a cake, intentional formation of a **less rigid or loose aggregation** of the particles held together by comparatively weak particle-to-particle bonds are formed.
- Such an aggregation of particles is termed a *floc* ,
- **flocculated particles** form a type of agglomeration that resists complete settling (although flocs settle more rapidly than fine, individual particles) and thus are less prone to compaction than unflocculated particles.

# Interfacial Properties of Suspended Particles

- The large surface area of the particles that results from the grinding is associated with a surface free energy that makes the system *thermodynamically unstable*, by which we mean that the particles are highly energetic and tend to regroup in such a way as to decrease the total area and reduce the surface free energy.
- 
- The particles in a liquid suspension therefore tend to *flocculate*, that is, to form light, fluffy conglomerates that are held together by weak van der Waals forces.

- The flocs settle to form a higher sediment volume than unflocculated particles, the loose structure of which permits the aggregates to break up easily and distribute readily with a small amount of agitation.

Deflocculated



flocculated

- Under certain conditions—in a compacted cake, for example—the particles may adhere by stronger forces to form what are termed *aggregates*.
- Caking often occurs by the growth and fusing together of crystals in the precipitates to produce a solid aggregate.

# **Sedimentation in different systems**

## **In flocculated systems:**

- The flocs tend to fall together (fast sedimentation due to large size)
- A distinct boundary between the sediment and the supernatant.
- The liquid above the sediment is clear because even the small particles present in the system are associated with the flocs

## **In deflocculated systems (with a range of particle sizes):**

- in accordance with Stokes' law, the larger particles sediment more rapidly than the smaller particles.
- No clear boundary is formed (unless 1 particle size is present)
- the supernatant remains turbid for a longer period of time.

## **Indication of a flocculated or deflocculated system:**

Whether or not the supernatant liquid is clear or turbid during the initial stages of settling.



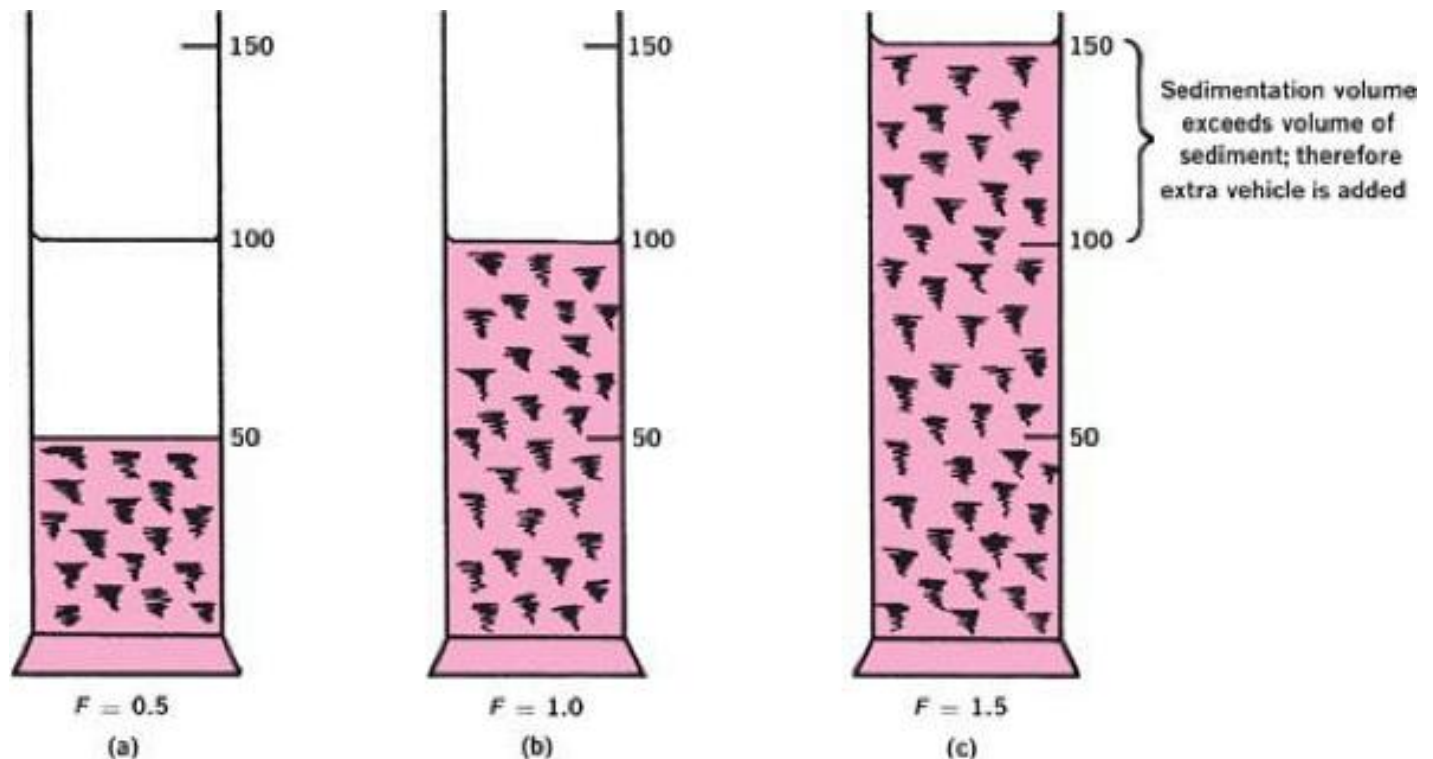
## ***Sedimentation Parameters***

- The sedimentation volume,  $F$ , is defined as the ratio of the final, or ultimate, volume of the sediment,  $V_u$ , to the original volume of the suspension,  $V_o$ , before settling

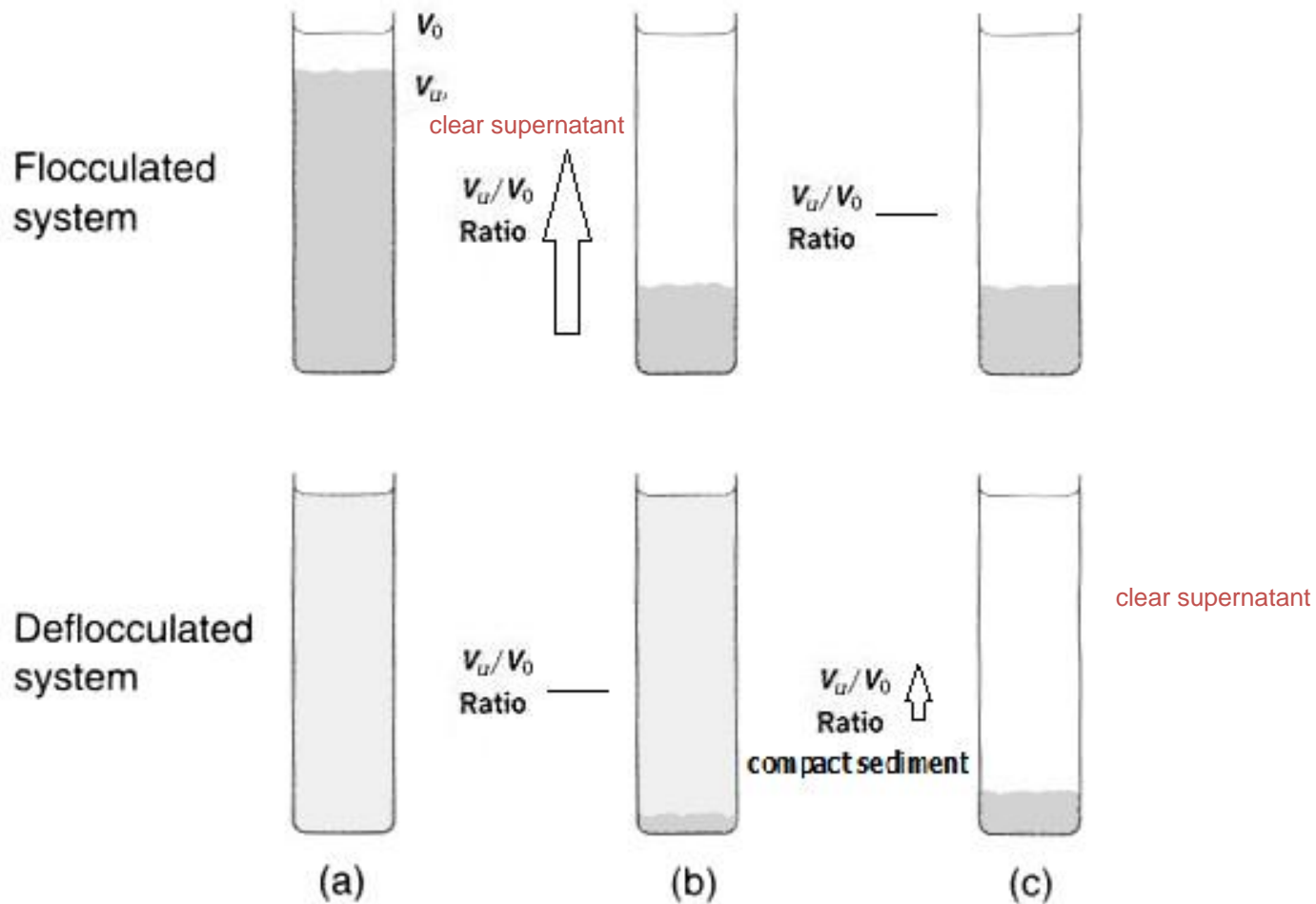
$$F = V_u / V_o \quad (17-4)$$

- if the ultimate volume of sediment is smaller than the original volume of suspension, ,  $F = 0.5$ .
- If the volume of sediment in a flocculated suspension equals the original volume of suspension, then  $F = 1$

- It is possible for  $F$  to have values greater than 1, meaning that the final volume of sediment is greater than the original suspension volume.
- This comes about because the network of flocs formed in the suspension is so loose and fluffy that the volume they are able to encompass is greater than the original volume of suspension.



# The sedimentation behaviour of flocculated and deflocculated suspensions.



## Deflocculated system

- (a) Within a **few minutes** of manufacture there is **no apparent change** within the deflocculated system compared to its initial appearance.
- (b) Even after **several hours** there is **still little obvious change**, except that the concentration of solids in the lower layers has increased at the expense of the upper layers owing to slow particle sedimentation. There is a small amount of a **compact sediment**.
- (c) After **prolonged storage**, depending on the physical stability of the system, the **supernatant has cleared, leaving a compact sediment**.

## Flocculated system

- (a) There is **some clear supernatant with a distinct boundary between it and the sediment**.
- (b) After several hours there is a larger volume of clear supernatant with a relatively large volume of a porous sediment, which does not change further even after prolonged storage (c).

# **Evaluation of Suspensions**

**Evaluation techniques permits the formulator to screen the initial preparations made and also to compare commercial products.**

- 1. Sedimentation volume "F"**
- 2. Redispersability:** This was determined by the number of upside down inversions of the suspension contained in a measure. The smaller the number, the easier would be the redispersability of the sediment. A number greater than 15 inversions indicated caking.
- 3. Rheological Characteristics :** The flow of the acceptable suspension will be either pseudoplastic or plastic & it is desirable that thixotropy be associated with these two types of flow.

	<b>Flocculated</b>	<b>Deflocculated</b>
<b>Sedimented particle</b>	<b>Forms a network like structure</b>	<b>Separate individual particles</b>
<b>Velocity of sedimentation</b>	<b>fast fall together</b>	<b>slow fall according to size</b>
<b>Boundary</b>	<b>a distinct boundary between sediment and supernatant</b>	<b>no distinct boundary between sediment and supernatant</b>
<b>Supernatant</b>	<b>clear</b>	<b>turbid</b>
<b>Suspension</b>	<b>Not pleasing in appearance</b>	<b>Pleasing in appearance</b>
<b>Viscosity</b>	<b>High</b>	<b>Low</b>
<b>Rheology</b>	<b>plastic &amp; pseudoplastic</b>	<b>Dilatent</b>
<b>Sediment</b>	<b>Loosely packed and doesn't form a cake</b>	<b>Closely packed and form a hard cake</b>
<b>Redispersibility</b>	<b>Easy</b>	<b>Difficult</b>

# **INGREDIENTS of SUSPENSION**

# **INGREDIENTS of SUSPENSION**

**I - Insoluble drug.**

**II- Vehicle (suspending medium).**

**III- Wetting agents.**

**IV- Compounds allowing control of stability and sedimentation (Flocculating, Suspending agent)**

**V - Additives used to regulate the flow behavior.**

**VI- pH regulators**

**VII- Other additives ( flavour, colour, taste preservatives).**



## **I- The Insoluble Drug:**

- 1 - Size distribution of the powder.**
- 2 - Ease of wetting.**
- 3 - Surface electric charge of the particles in suspension.**
- 4 - Chemical stability of the drug, and possible interactions and incompatibilities with other suspension constituents.**

## **II- The Suspending Medium or Vehicle:**

- 1 - Distilled water or deionized water.**
- 2 - Water- alcohol**
- 3 - Solution of glycerol.**
- 4 - Nonaqueous vehicles (Topical use).**
- 5 - Structured vehicles are pseudoplastic and plastic in nature, it is desirable that thixotropy is associated.**

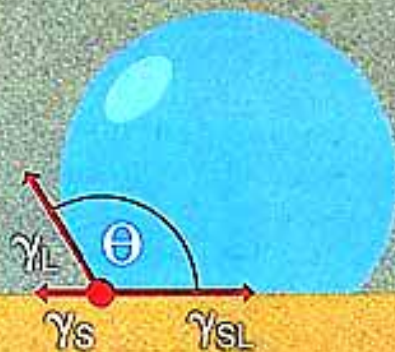
Wetting agents  
Flocculating Agents  
Suspending agents

# wetting agents

- Some **insoluble solids** may be easily wetted by water and will disperse readily throughout the aqueous phase with only minimal agitation.
- Most, however, will exhibit varying degrees of hydrophobicity and will not be easily wetted. Some particles will form large porous clumps within the liquid, whereas others remain on the surface and become attached to the upper part of the container.
- To ensure adequate wetting, the interfacial tension between the solid and the liquid must be reduced so that the adsorbed air is displaced from the solid surfaces by the liquid.

**poor  
wetting**

$$\theta > 90^\circ$$



**good  
wetting**

$$90^\circ > \theta > 0^\circ$$



**complete  
wetting**

$$\theta \rightarrow 0^\circ$$



$$\gamma_L \times \cos \theta \quad j < 0$$

$$j > 0 \quad \gamma_L \times \cos \theta$$

$$\gamma_S > \gamma_{SL} + \gamma_L$$

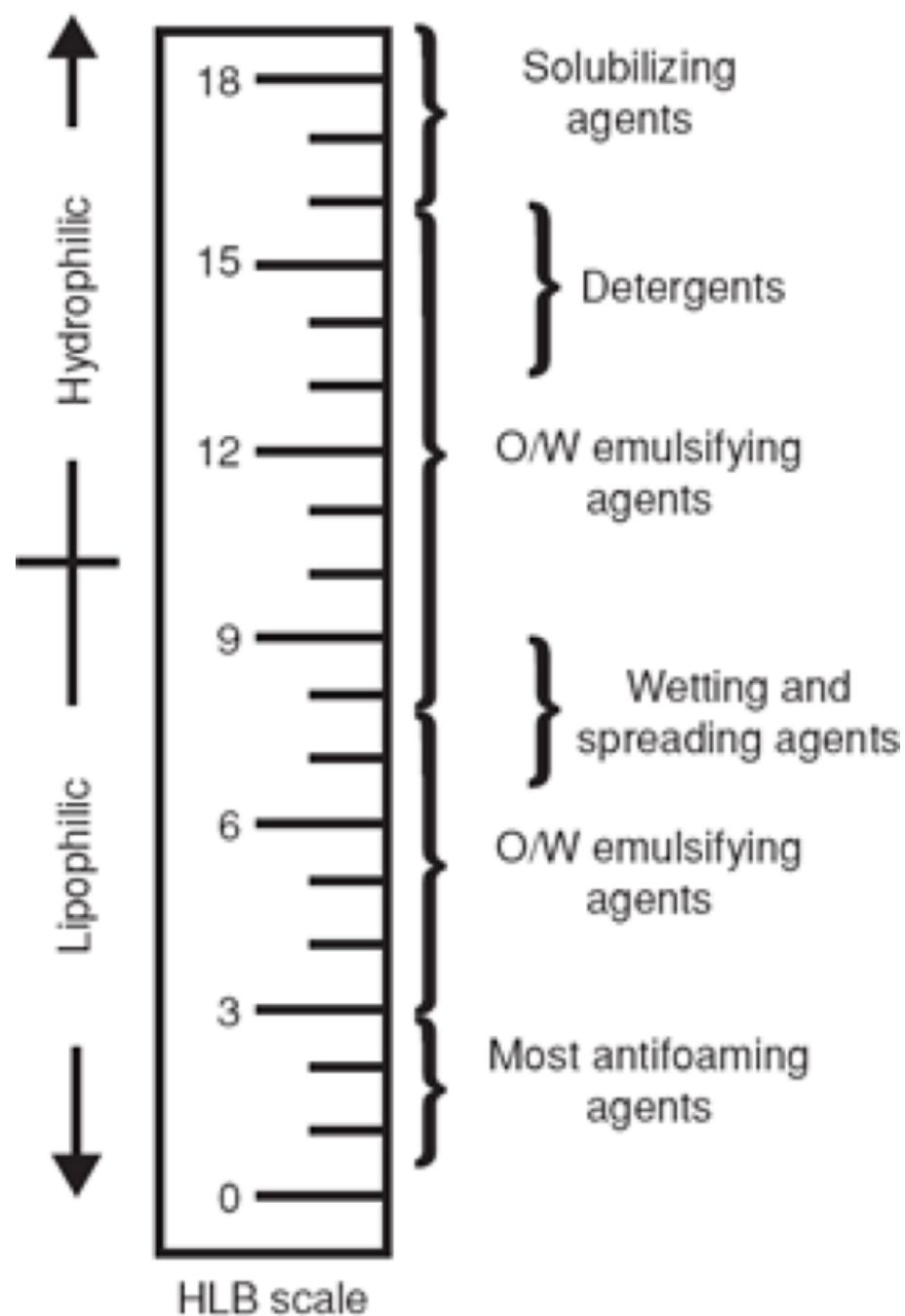
$$\theta = \text{Theta}$$

# wetting agents

- **1. *Surface-active agents:***
- **2. *Hydrophilic colloids***
- **3. *Solvents***

# ***1. Surface-active agents:***

- surfactants possessing an HLB value between about 7 and 9 would be suitable for use as wetting agents.
- The hydrocarbon chains would be adsorbed by the hydrophobic particle surfaces, whereas the polar groups project into the aqueous medium and become hydrated.
- Wetting of the solid occurs as a result of a fall in interfacial tension between the solid and the liquid .



- Most surfactants are used at concentrations of up to about 0.1% as wetting agents and include:
  1. for oral use, the polysorbates (Tweens) and sorbitan esters (Spans).
  2. For external application, sodium lauryl sulphate, sodium dioctylsulphosuccinate and quillaia extract can also be used.
  3. For parenteral use: polysorbates, some of the poloxamers (polyoxyethylene/polyoxypropylene copolymers) and lecithin.



- Disadvantages in the use of this type of wetting agent include excessive foaming and the possible formation of a deflocculated system, which may not be required.

## ***2.Hydrophilic colloids***

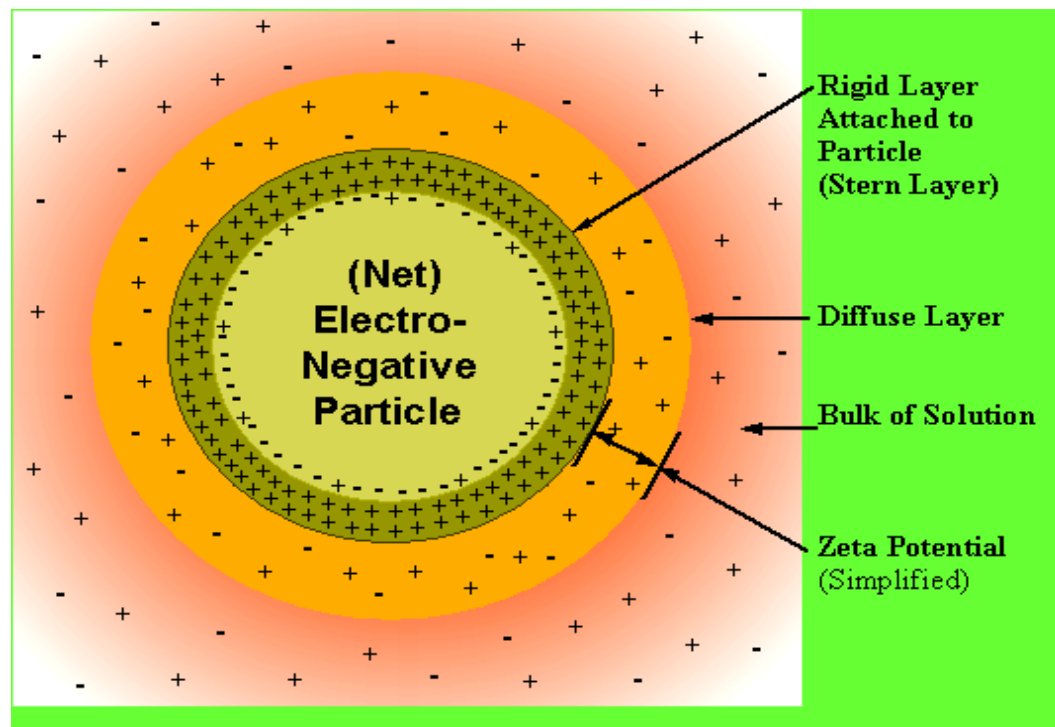
- These materials include acacia, bentonite, tragacanth, alginates, xanthan gum and cellulose derivatives, and will behave as **protective colloids by coating the solid hydrophobic particles** with a multimolecular layer.
- This will impart a hydrophilic character to the solid and so promote wetting.
- These materials are also used as suspending agents and may, like surfactants, produce a deflocculated system, particularly if used at high concentrations.

### ***3. Solvents***

- Materials such as alcohol, glycerol and glycols, which are water miscible, will reduce the **liquid/air interfacial tension**.
- The solvent will penetrate the loose agglomerates of powder **displacing the air** from the pores of the individual particles, so enabling wetting to occur by the dispersion medium.
- Alcohol, glycerin, propylene glycol, and other hygroscopic liquids are employed as wetting agents when an aqueous vehicle is to be used as the dispersion phase.

# *Flocculating agents*

- The next stage of the formulation process, after the addition of the wetting agent, is to ensure that the product exhibits the correct degree of flocculation.
- Controlled flocculation is usually achieved by a combination of particle size control, the use of electrolytes to control zeta potential, and the addition of polymers to enable crosslinking to occur between particles.
- Some polymers have the advantage of becoming ionized in an aqueous solution, and can therefore act both electrostatically and sterically.
- These materials are also termed **polyelectrolytes**.



Zeta potential is therefore a function of the surface charge of the particle. Because it reflects the effective charge on the particles and is therefore **related to the electrostatic repulsion** between them, the zeta potential has confirmed to be extremely related to the colloidal stability and maintains colloidal dispersion.

# **Flocculating agents**

- **1- Electrolytes**
- **2- Surfactants**
- **3- Polymers**
- **4-Alteration in the pH of the preparation (generally to the region of minimum drug solubility).**

# *1. Electrolytes*

- The addition of an inorganic electrolyte to an aqueous suspension will **alter the zeta potential of the dispersed particles** and, if this value is lowered sufficiently, flocculation may occur.
- the ability of an electrolyte to flocculate hydrophobic particles depends on the **valency** of its counter-ions.

- Although they are more efficient, **trivalent** ions are less widely used than mono- or divalent electrolytes because:

1. they are generally more **toxic**.

2. If hydrophilic polymers, which are usually negatively charged, are included in the formulation they may be **precipitated** by the presence of trivalent ions.

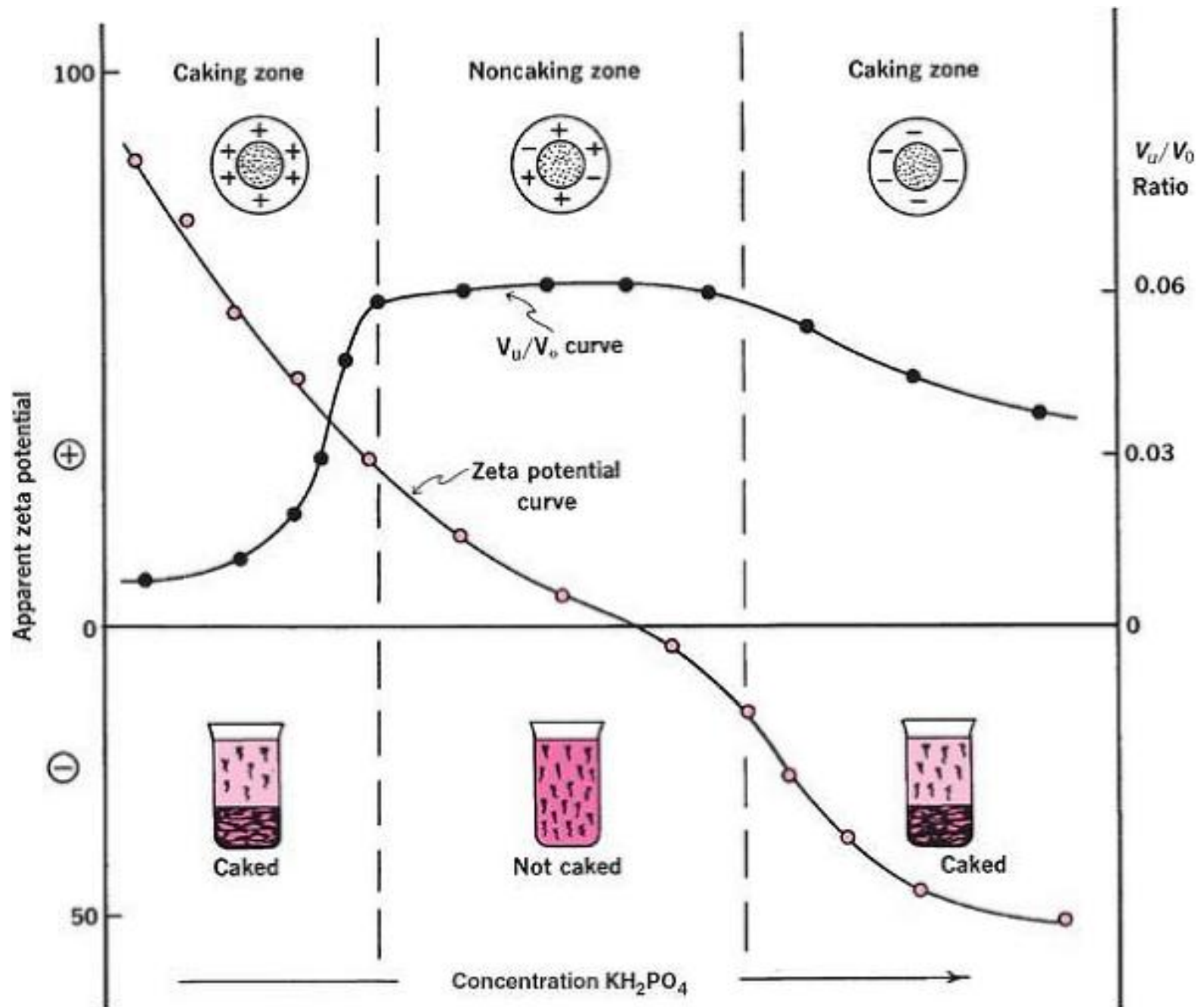


- The most widely used electrolytes include the **sodium salts of acetates, phosphates and citrates**, and the concentration chosen will be that which produces the desired degree of flocculation.
- Care must be taken not to add **excessive electrolyte or charge reversal may occur on each particle**, so forming, once again, a deflocculated system.

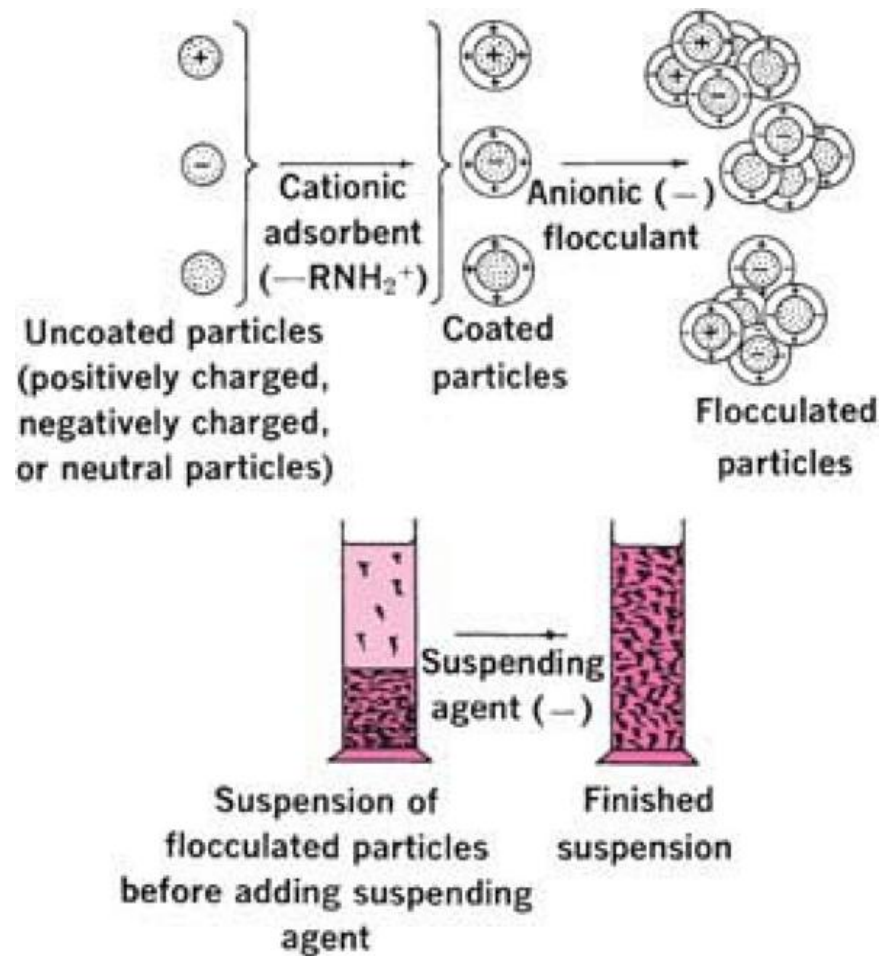
## ***Controlled Flocculation***

- *Electrolytes* act as flocculating agents by reducing the electric barrier between the particles, as evidenced by a decrease in the zeta potential and the formation of a bridge between adjacent particles so as to link them together in a loosely arranged structure.

- If we disperse particles of bismuth subnitrate in water, we find that they possess a large positive charge, or zeta potential.
- Because of the strong forces of repulsion between adjacent particles, the system is deflocculated.
- The addition of monobasic potassium phosphate to the suspended bismuth subnitrate particles causes the positive zeta potential to decrease owing to the adsorption of the negatively charged phosphate anion.
- With the continued addition of the electrolyte, the zeta potential eventually falls to zero and then increases in the negative direction,
- at a certain positive zeta potential, maximum flocculation occurs and will persist until the zeta potential has become sufficiently negative for deflocculation to occur once again.
- The onset of flocculation coincides with the maximum sedimentation volume determined.  $F$  remains reasonably constant while flocculation persists, and only when the zeta potential becomes sufficiently negative does the sedimentation volume start to fall.



# The sequence of steps involved in the formation of a stable suspension



## 2. Surfactants

- Ionic surface-active agents may also cause flocculation by **neutralizing the charge on each particle**, thus resulting in a flocculated system.
- Non-ionic surfactants will, of course, have a negligible effect on the charge density of a particle but may, because of their linear configurations, adsorb on to more than one particle, thereby forming a loose flocculated structure.

### 3. *Polymeric flocculating agents*

- *Polymeric flocculating agents* Starch, alginates, cellulose derivatives, tragacanth, carbomers and silicates are examples of polymers that can be used to control flocculation.
- Their linear branched-chain molecules form a gel-like network within the system and become adsorbed on to the surfaces of the dispersed particles, thus holding them in a flocculated state.
- Although some settling can occur, the sedimentation volume is large, and usually remains so for a considerable period.

*Viscosity modifiers* (suspending agents )



## *Viscosity modifiers (suspending agents )*

- unless a high concentration of disperse phase is present the **viscosity of the suspension may not be sufficient to prevent rapid settling**, particularly if a surfactant or an electrolyte is present as a flocculating agent.
- In these cases suspending agents may be used to increase the apparent viscosity of the system.

- Suitable materials are the **hydrophilic polymers**
- These exert their effect by entrapping the solid dispersed particles within their **gel-like network**, so preventing sedimentation.
- At low concentrations many suspending agents can be used to control flocculation, and it must be realized that if large quantities are to be used to enhance viscosity the degree of flocculation may also be altered.

# suspending agents

## **1. Polysaccharides**

- *Acacia*
- *Tragacanth*
- *Alginates*
- *Starch*
- *Xanthan gum (Keltrol)*

## **2. Water-soluble celluloses**

- *Methylcellulose (Celacol, Methocel)*
- *Hydroxyethylcellulose (Natrosol)*
- *Carmellose sodium (sodium carboxymethylcellulose)*
- *Microcrystalline cellulose*

## **3. Hydrated silicates**

- **bentonite, magnesium aluminum silicate and hectorite**

## **4. Carbomers (carboxymethylcellulose )**

## **5. Colloidal silicon dioxide (Aerosil)**

# *1. Polysaccharides*

- *Acacia*
- *Tragacanth*
- *Alginates*
- *Starch*
- *Xanthan gum (Keltrol)*



- *Acacia*
- This natural material is often used as a suspending agent for extemporaneously prepared suspensions.
- Acacia is **not a good thickening agent**
- Acacia is **not very effective for dense powders**.
- it is often combined with other thickeners such as tragacanth, starch and sucrose in compound tragacanth powder.

- acacia mucilage **becomes acidic on storage** as a result of enzyme activity, and it also contains an oxidase enzyme which may cause **deterioration of active agents** that are susceptible to oxidation.
- This enzyme can, however, be inactivated by heat.
- Because of the stickiness of acacia it is rarely used in preparations for external use.



- *Tragacanth*
- This product will form viscous aqueous Solutions.
- Its **thixotropic** and **pseudoplastic properties** make it a better thickening agent than acacia and it can be used both for **internal and external products**.
- Like acacia it is mainly, though not exclusively, used for the extemporaneous preparation of suspensions with a short shelf-life.

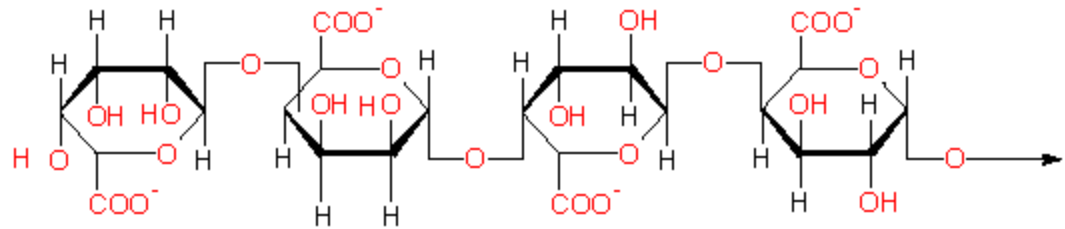


## *Tragacanth Gum*





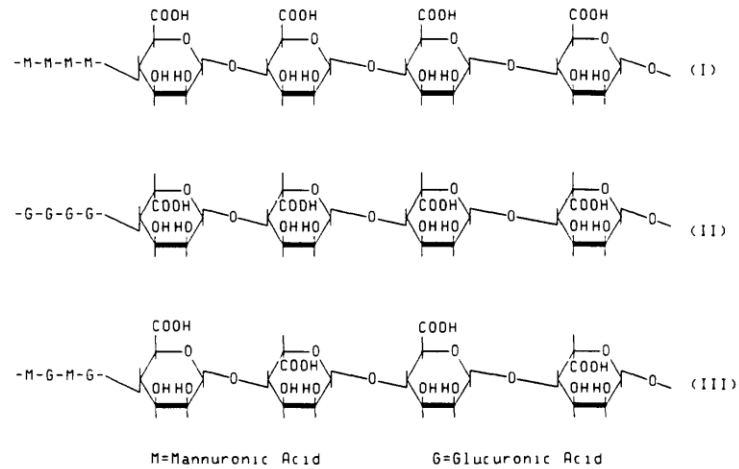
- *Alginates*
- Alginic acid, a polymer of D-mannuronic acid, is prepared from kelp, and its salts have suspending properties similar to those of tragacanth.
- Alginate mucilages must not be heated above 60°C as depolymerization occurs, with a consequent loss in viscosity.
- They are most viscous immediately after preparation, after which there is a fall to a fairly constant value after about 24 hours.



alginic acid



kelp



- Alginates exhibit a maximum viscosity over a pH range of 5-9, and at low pH the acid is precipitated.
- Sodium alginate (Manucol) is the most widely used material in this class but it is, of course, **anionic** and will be incompatible with cationic materials and with heavy metals.
- The addition of calcium chloride to a sodium alginate dispersion will produce calcium alginate, which has a much higher viscosity.
- Several different viscosity grades are commercially available

- *Starch*
- Starch is rarely used on its own as a suspending agent but is one of the constituents of compound **tragacanth** powder, and it can also be used with **carmellose sodium**.
- Sodium starch glycollate (Explotab, Primojel), a derivative of potato starch, has also been evaluated for its use in the extemporaneous preparation of suspensions.

- *Xanthan gum (Keltrol)*
- This is an **anionic heteropolysaccharide** produced by the action of *Xanthomonas campestris* on corn sugars.
- It is **very soluble in cold water** and is one of the most **widely used thickening agents** for the extemporaneous preparation of suspensions for oral use.
- It is used in concentrations up to about 2% and is stable over a wide pH range.

## *2. Water-soluble celluloses*

- *Methylcellulose (Celacol, Methocel)*
- *Hydroxyethylcellulose (Natrosol)*
- *Carmellose sodium (sodium carboxymethylcellulose)*
- *Microcrystalline cellulose*

- ***Methylcellulose (Celacol, Methocel)***
- This is a semisynthetic polysaccharide produced by the methylation of cellulose.
- Several grades are available, depending on their degree of methylation and on the chain length.
- **The longer the chain, the more viscous is its solution.**
- For example, a 2% solution of methylcellulose 20 exhibits an apparent viscosity of 20 millipascal seconds (mPa s) and methylcellulose 4500 has value of 4500 mPa s at 2% concentration.

- *Microcrystalline cellulose*
- It is a widely used suspending agent , This material consists of crystals of **colloidal dimensions which disperse readily in water** (but are not soluble) to produce thixotropic gels.



### *3. Hydrated silicates*

- namely bentonite, magnesium aluminium silicate and hectorite,
- naturally occurring clays.
- They hydrate readily, absorbing up to 12 times their weight of water, particularly at elevated temperatures.
- As with most **naturally occurring materials they may be contaminated with spores**, and this must be borne in mind when considering a sterilization process and choosing a preservative system.

- ***Bentonite***
- **It is used at concentrations of up to 2 or 3% in preparations for external use, such as calamine lotion.**
- **As this product may contain pathogenic spores it should be sterilized before use.**

## 4. Carbomers (carboxypolymethylene)

- This material is a totally synthetic **copolymer of acrylic acid and allyl sucrose**.
- It is used at concentrations of up to 0.5%, mainly for external application, although some grades can be taken internally.
- When dispersed in water it forms acidic, low-viscosity solutions which, when adjusted to a pH of between 6 and 11, become highly viscous.

## ***5. Colloidal silicon dioxide (Aerosil)***

- **When dispersed in water this finely divided product will aggregate, forming a three-dimensional network.**
- **It can be used at concentrations of up to 4% for external use, but has also been used for thickening non-aqueous suspensions.**

# **PREPARATION OF SUSPENSIONS**

# **INGREDIENTS of SUSPENSION**

- I - Insoluble drug.**
- II- Vehicle (suspending medium).**
- III- Wetting agents.**
- IV- Compounds allowing control of stability and sedimentation (Flocculating, Suspending agent)**
- V - Additives used to regulate the flow behavior.**
- VI- pH regulators**
- VII- Other additives ( flavour, colour, taste preservatives).**

- In some instances, the dispersed phase has an affinity for the vehicle and is readily wetted by it.
- Other drugs are not penetrated easily by the vehicle and have a tendency to clump together or to float on the vehicle.
- In the latter case, the powder must first be wetted to make it more penetrable by the dispersion medium
- Once the powder is wetted, the dispersion medium (to which have been added all of the formulation's soluble components, such as colorants, flavorants, and preservatives) is added in portions to the powder, and the mixture is thoroughly blended before subsequent additions of vehicle.
- The suspension is then homogenized.

# An example formula for an oral suspension

- **Aluminum hydroxide compressed gel**    **326.8 g**
- **Sorbitol solution**    **282.0 mL**
- **Syrup**    **93.0 mL**
- **Glycerin**    **25.0 mL**
- **Methylparaben**    **0.9 g**
- **Propylparaben**    **0.3 g**
- **Flavor**    **q.s.**
- **Purified water, to make**    **1000.0 mL**



# **PACKAGING AND STORAGE OF SUSPENSIONS**

- **All suspensions should be packaged in widemouth containers having adequate airspace above the liquid to permit thorough mixing by shaking and ease of pouring.**
- **Most suspensions should be stored in tight containers protected from freezing, excessive heat, and light.**
- **It is important that suspensions be shaken before each use to ensure a uniform distribution of solid in the vehicle and thereby uniform and proper dosage.**

# **DRY POWDERS FOR ORAL SUSPENSION**

- **A number of official and commercial preparations consist of dry powder mixtures or granules that are intended to be suspended in distilled water or some other vehicle prior to oral administration.**
- **Most drugs prepared as a dry mix for oral suspension are antibiotics.**

- **The dry products are prepared commercially to contain the antibiotic drug, colorants (FD&C dyes), flavorants, sweeteners (e.g., sucrose or sodium saccharin), stabilizing agents (e.g., citric acid, sodium citrate), suspending agents (e.g., guar gum, xanthan gum, methylcellulose), and preserving agents (e.g., methylparaben, sodium benzoate) that may be needed to enhance the stability of the dry powder or granule mixture or the liquid suspension**

- **When called on to reconstitute and dispense one of these products, the pharmacist loosens the powder at the bottom of the container by lightly tapping it against a hard surface and then adds the label-designated amount of purified water, usually in portions, and shakes the slurry until all of the dry powder has been suspended**

- **It is important to add precisely the prescribed amount of purified water to the dry mixture if the proper drug concentration per dosage unit is to be achieved.**
- **Also, the use of purified water rather than tap water is needed to avoid the possibility of adding impurities that could adversely affect the stability of the resulting preparation.**

# **PHARMACEUTICAL APPLICATIONS OF SUSPENSIONS**

- **Suspensions can be used as:**
  - 1.oral dosage forms,**
  - 2.applied topically to the skin or mucous membrane surfaces,**
  - 3.given parenterally by injection.**

# **Suspensions as oral drug delivery systems**

- The taste of most drugs is more noticeable if it is in solution rather than in an insoluble form.
- Paracetamol is available both in solution as Paediatric Paracetamol Oral Solution and also as a suspension.
- The latter is more palatable, and therefore particularly suitable for children.
- For the same reason chloramphenicol mixtures can be formulated as suspensions containing the insoluble chloramphenicol palmitate.



- **Some materials are required to be present in the gastrointestinal tract in a finely divided form, and their formulation as suspensions will provide the desired high surface area.**
- **Solids such as kaolin, magnesium carbonate and magnesium trisilicate, for example, are used for the adsorption of toxins, or to neutralize excess acidity.**

- **A drug that degrades in the presence of water may alternatively be suspended in a non-aqueous vehicle.**
- **Fractionated coconut oil is used as the vehicle for some formulations of antibiotics for oral use.**
- **The degradation of a drug in the presence of water may also preclude its use as an aqueous solution.**
- **In this case it may be possible to synthesize an insoluble derivative that can then be formulated as a suspension.**
- **For example, oxytetracycline hydrochloride is used in solid dosage forms, but in aqueous solution would rapidly hydrolyse.**
- **A stable liquid dosage form has been made by suspending the insoluble calcium salt in a suitable aqueous vehicle.**

# **Antacid Oral Suspensions**

- **They are also widely employed and sold over the counter (OTC) to patients with acid indigestion, heartburn, and sour stomach.**
- **Most antacid preparations are composed of water-insoluble materials that act within the gastrointestinal tract to counteract the acid**
- **liquid antacids generally are preferred to tablet forms. the liquid suspensions assert more immediate action, because they do not require time to disintegrate.**

# **Antibacterial Oral Suspensions**

- **The antibacterial oral suspensions include preparations of antibiotic substances (e.g., erythromycin derivatives, and tetracycline and its derivatives), sulfonamides (e.g., sulfamethoxazole**
- **Many antibiotic materials are unstable when maintained in solution for an appreciable length of time, and therefore, from a stability standpoint**

- **insoluble forms of the drug substances in aqueous suspension or as dry powder for reconstitution are used.**
- **The antibiotic oral suspensions, including those prepared by reconstitution, provide a convenient way to administer dosages to infants and children and to adult patients who prefer liquid preparations to solid ones.**
- **Many of the oral suspensions that are intended primarily for infants are packaged with a calibrated dropper to assist in the delivery of the prescribed dose.**

- **The dispersing phase of antibiotic suspensions is aqueous and usually colored, sweetened, and flavored to render the liquid more appealing and palatable.**
- **the palmitate form of chloramphenicol was selected for the suspension dosage form not only because of its water insolubility but also because it is flavorless, which eliminates the necessity to mask the otherwise bitter taste of the chloramphenicol base.**

# **Suspensions for topical administration**

- **They can be fluid preparations, such as Calamine Lotion, which are designed to leave a light deposit of the active agent on the skin after quick evaporation of the dispersion medium.**
- **Some suspensions, such as pastes, are semisolid in consistency and contain high concentrations of powders dispersed - usually - in a paraffin base.**
- **It may also be possible to suspend a powdered drug in an emulsion base, as in Zinc Cream.**

# **Suspensions for parenteral use**

- **Suspensions can also be formulated for parenteral administration in order to control the rate of absorption of the drug.**
- **By varying the size of the dispersed particles of active agent, the duration of activity can be controlled.**
- **The absorption rate of the drug into the bloodstream will then depend simply on its rate of dissolution.**



- If the drug is suspended in a fixed oil such as arachis or sesame, the product will remain after injection in the form of an oil globule, thereby presenting to the tissue fluid a small surface area from which the partitioning of drug can occur.
- The release of drug suspended in an aqueous vehicle will be faster, as some diffusion of the product will occur along muscle fibres and become miscible with tissue fluid. This will present a larger surface area from which the drug can be released.

- **Vaccines for the induction of immunity are often formulated as dispersions of killed microorganisms, as in Cholera Vaccine, or of the constituent toxoids adsorbed on to a substrate of aluminium hydroxide or phosphate, as in Adsorbed Diphtheria and Tetanus Vaccine.**
- **Thus a prolonged antigenic stimulus is provided, resulting in a high antibody titre.**

# **Suspensions for inhalation therapy**

- **The adsorptive properties of fine powders are also used in the formulation of some inhalations.**
- **The volatile components of menthol and eucalyptus oil would be lost from solution very rapidly during use, whereas a more prolonged release is obtained if the two active agents are adsorbed on to light magnesium carbonate prior to the preparation of a suspension.**

# Sustained-Release Suspensions

1. coated beads,
2. drug-impregnated wax matrix,
3. microencapsulation,
4. ion exchange resins
5. The use of a combination of ion exchange resin complex and particle coating *has* resulted in product success via the so-called Pennkinetic system. By this technique, ionic drugs are complexed with ion exchange resins, and the drug–resin complex particles coated with ethylcellulose. In liquid formulations (suspensions) of the coated particles, the drug remains adsorbed onto the resin but is slowly released by the ion exchange process in the gastrointestinal tract.

- The ***Pennkinetic system*** is formed by reacting a drug in its ionic state with a suitable polymer matrix.

