





LIGHT SOURCE



SOLUTION



COLLOID



SUSPENSION

LIGHT BEAM:

NOT VISIBLE

VISIBLE

VISIBLE

EXAMPLE:

WATER

MILK

FLOUR AND WATER

Biphasic Liquids

EFFECT

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THE TYNDALL EFFECT IS THE SCATTERING OF LIGHT BY PARTICLES IN A COLLOID OR SUSPENSION.



Introduction

- Biphasic liquid dosage forms such as **suspension** and **emulsion**.
- Many of their properties are due to the presence of a **boundary region** between two phases.
- In suspension liquid and insoluble solid form **interface**.
- In emulsion, two immiscible liquids form an **interface**.
- **The following thermodynamic energy describes the energy at the interface:**

$$\Delta G = \gamma \cdot \Delta A$$

- **ΔG** (change in free energy) = surface tension (**γ**). Change in surface area of the interface (**ΔA**)

$$\bullet \Delta G = \gamma \cdot \Delta A$$

- So ΔG represents the change in free energy of the system accompanying a change in interfacial area and surface tension (temperature and pressure are assumed to be constant). So increase in A will lead to an increase in G .
- Because the preparation of dispersed systems involves **decreasing the particle size** of the dispersed phase (and eventually **increasing** its surface area, i.e. increasing the interfacial area) \rightarrow This means that these biphasic systems are **unstable** because of high positive free energy.

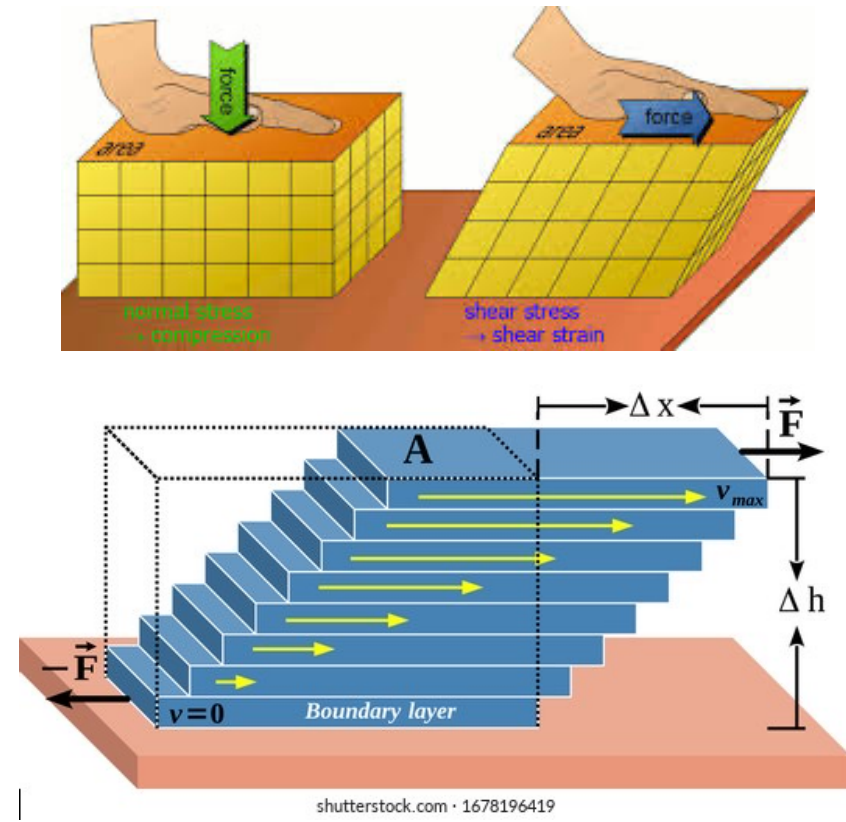
Introduction



- These systems are **trying** to be stable by **lowering the surface area** of the interphase (i.e. formation of a **single large particle** in suspension or a single large **one-layer** of oil on one layer of water).
- This can occur **spontaneously** (**instability pathway**) by agglomeration or in a controlled way as we will discuss later.
- The **focus** of our class is to understand how to avoid instability and how to control the behavior of biphasic systems.
- The main goal of the formulation of a biphasic liquid is to lower this positive interfacial free energy (G) to about zero (**controlled way**)
 1. One approach is to **aggregate (flocculate)** the particles as in suspension
 2. Another approach is to add a surfactant that changes the surface tension and controls particle aggregation.

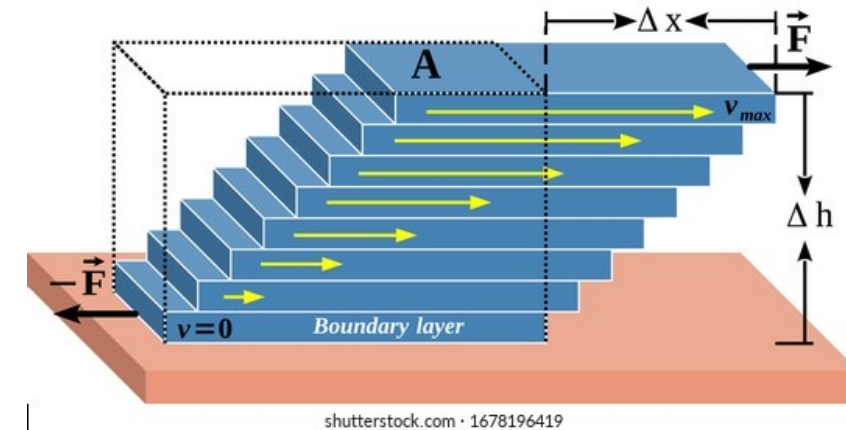
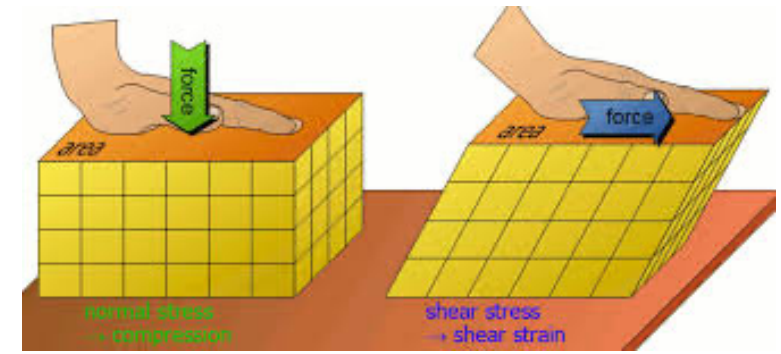
Rheology Background

- **Rheology** studies the flow behavior of liquids and the deformation of solids.
- **Viscosity** is the resistance of a fluid to flow. Higher viscosity implies greater resistance to flow (less fluidity)
- To understand viscosity look at the model to the right:
- The bottom layer is fixed. A Force \mathbf{F} is applied to the top layer to displace it at a velocity \mathbf{V} .
- Friction within the liquid causes the velocity of the lower layers to be less than \mathbf{V} .
- The velocity of the liquid layers **decreases** as the distance from the top layer increases till we get to the bottom layer which is stationary ($\mathbf{V}=0$)
- **Viscosity is a measure of this molecular friction that resists the flow.**



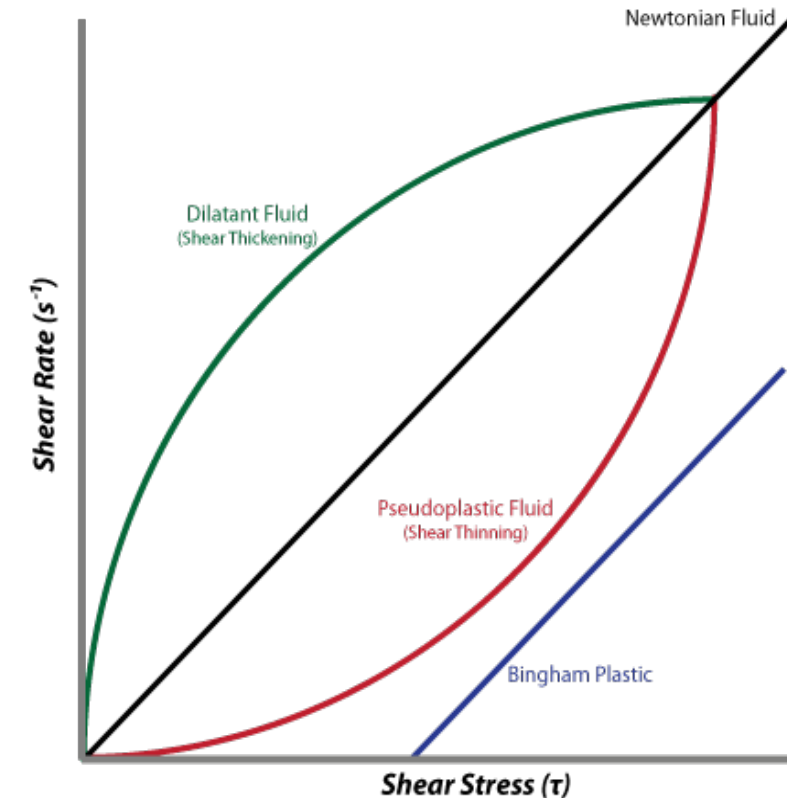
Rheology Background

- So viscosity or the resistance happens when we apply shear force on an area of fluid.
- **Shear stress** = force/area = $F/A = \sigma$ (dynes/cm²)
- **Rate of Shear** = Velocity gradient = change in velocity with distance = $dv/dr = \gamma$ (sec⁻¹)
- Viscosity $\eta = \frac{\text{shear stress } (\sigma)}{\text{Rate of Shear } (\gamma)}$ in poise or (g/cm. sec)



Types of Fluid

- **Newtonian Fluid:** like water where constant viscosity; → the rate of shear increases with shear stress
- **Non-Newtonian fluid:**
 1. **Plastic flow:** a fluid that behaves like Newtonian fluid after a certain shear stress limit (yield value, viscosity is constant after this point). An example is flocculated **suspension** which after **shaking** becomes more easily to flow.
 2. **Pseudoplastic flow:** viscosity is **not** constant (shear **thinning** behavior) (ex Ketchup).
 3. **Dilatant flow** (rare type): viscosity **increases** with shear stress (shear **thickening** behavior) like corn starch solution



https://youtu.be/2mYHGn_Pd5M



Dispersed Systems

- Classification based on the size of the internal phase

Molecular dispersion True solutions. (<1.0 nm)	Colloidal dispersion (1 nm to ~ 0.5 μm)	Coarse dispersion (> 0.5 μm)
Homogeneous	Invisible under ordinary light microscope -may be detectable under ultramicroscope	Particles visible under microscope
Form true solutions	Pass through filter paper but not through semipermeable membrane	Do not pass through normal filter paper or dialyze through semipermeable membrane
Invisible under electron microscope		
Pass through ultrafilter and semipermeable membrane		
Example: Oxygen in water Salt solution	Example: Polymer solutions Microemulsions	Example: Coarse Suspensions Macroemulsions

Suspension (Biphasic Liquids)



Suspension

- Suspensions may be **defined** as preparations containing finely divided drug **particles** distributed throughout the water in which the drug exhibits a **minimum solubility**.
- Some suspensions are available in **ready-to-use** form, that is, already suspended in a liquid such as Panadol suspension.
- Other preparations are available as **dry powders** to be suspended in liquid at the time of dispensing (**powders for reconstitution**).
- Drugs that are **unstable** in the presence of water (e.g., **antibiotics**) are frequently supplied as dry powder for reconstitution.
- Suspensions can be used orally, applied topically to the skin, or given parenterally by injection. However, **oral suspensions** are our focus in this lecture.



Reasons for Suspension Preparation



1. Certain drugs are **chemically unstable in solution** but stable when suspended. The suspension ensures chemical stability while permitting the drug to be administered as a liquid. For example, the calcium salt of oxytetracycline
2. Can formulate **distasteful** drugs into a pleasant-to-taste liquid dosage form when the drug is administered as **undissolved** particles in a suspension.
 - For example, erythromycin estolate is a less water-soluble prodrug of erythromycin and is used to prepare a palatable liquid dosage form of erythromycin.
3. Drug **bioavailability** is better (in most cases) compared to tablets in the first hour of administration. (why?)

The Desirable Features of Suspensions



Advantages	Disadvantages
Allows preparation of liquid dosage forms of drugs with poor solubility	Risk of physical instability (settling) and dose non-uniformity (compared to tablets or capsules)
Taste masking due to undissolved drug (compared to solutions, e.g. Chloramphenicol palmitate oral suspension)	Bulkier products (compared to tablets or capsules)
Easier to swallow (oral administration) even for large doses (compared to tablets)	Drug may be more stable than in a solution but not as stable as in a tablet or capsule
Allows preparation of parenteral formulations (e.g., I.M., I.V. injections) for insoluble	

Pharmaceutical suspensions



Suspension	Therapeutic category	Route of administration
Magnesium hydroxide Suspension (Milk of Magnesia®)	Antacid	Oral
NPH Insulin (suspension of crystalline zinc insulin combined with protamine)	Anti-diabetic	Sub-cutaneous
Prednisolone acetate ophthalmic suspension (Pred-Forte®)	Topical Anti-inflammatory	Ophthalmic
Penicillin G Procaine Injectable suspension (Wycillin®)	Antibacterial	Intramuscular
Protein Bound Paclitaxel Suspension Intravenous Nanosuspension (Abraxane®)	Anti-Cancer	Intravenous

Not for save

The Desirable Features of Suspensions



- **How the Suspension should Look Like?**
- In addition to therapeutic **efficacy and stability**, **good suspension** should:
 1. A properly prepared suspension should **settle slowly** and remain homogenous for at least the period between shaking the container and removing the required dose.
 2. The **sediment** produced on storage should be **readily redispersed** upon gentle shaking of the container.
 3. The **particle size** of the suspended drug should **remain constant** throughout long periods and do not show crystal growth (i.e., physically stable).
 4. The suspension **viscosity** must not be very high and it should be **poured easily** from its container.
 5. **Smooth / Grit-Free**: The suspended particle should be **small and uniformly sized** to give a smooth elegant product and free from a gritty texture.



Theoretical Considerations

- Knowing the theories behind suspension technology will help the formulator to choose the best component for manufacturing a stable, effective product.

- **The Sedimentation Rate**

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

$$\frac{dx}{dt} = \frac{D^2 (\rho_{(particle)} - \rho_{(medium)}) * g}{18\eta}$$

- Where:

- $\frac{dx}{dt}$ = sedimentation rate in (cm/s) ; D= particle diameter (cm)

- ρ = **density** in g/ml ; g = **gravity constant** (980.7 cm. s⁻²)

- η = medium **viscosity** in g. cm⁻¹. s⁻¹ or (poise)

- From the equation it is apparent that the velocity of fall (settling rate) of a suspended particle is **greater for larger particles** than it is for smaller particles due to increase effect of Brownian motion.



Theoretical Considerations

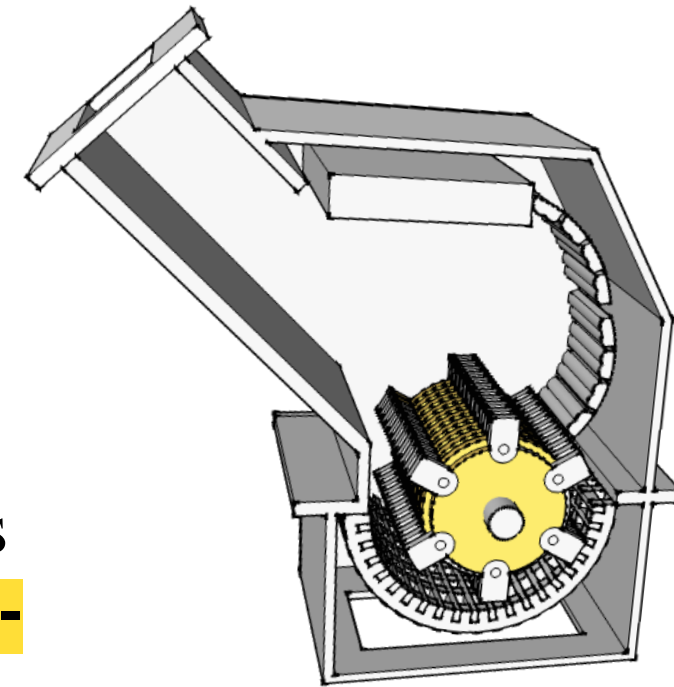
- **Reducing** the **particle size** of the dispersed phase produces a **slower** rate of descent of the particles.
- Also, the greater the density of the particles, the greater the rate of descent.
- The rate of sedimentation may be reduced **by increasing** the **viscosity** of the dispersion medium.
- However, a product having **too high viscosity** is not desirable, because it pours with difficulty and it is difficult to redisperse the suspended particles.
- If the sedimentation rate is 10^{-4} cm/s what will be the the time required for a suspension to settle in a 10 cm length bottle? ~ 28h.
- Note: this equation has some limitations because it assumes a 2g/100 ml max concentration and homogenous particle size.

$$\bullet \frac{dx}{dt} = \frac{D^2(\rho_{(particle)} - \rho_{(medium)}) * g}{18\eta}$$

Particle Size Reduction Techniques



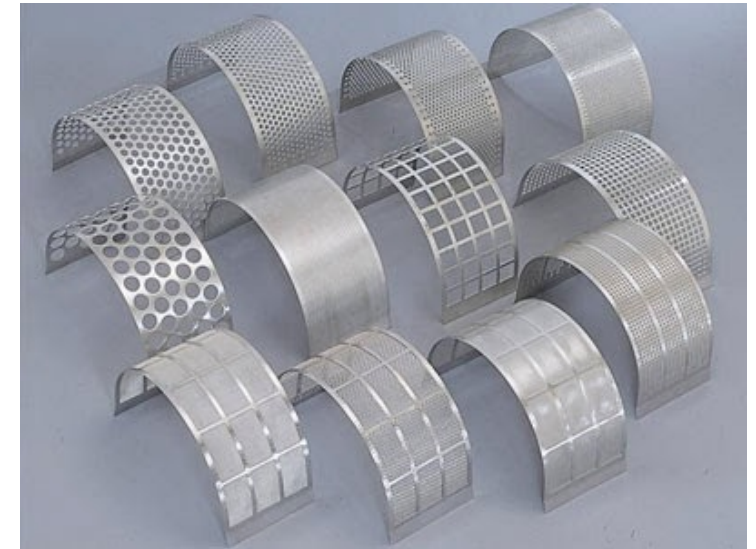
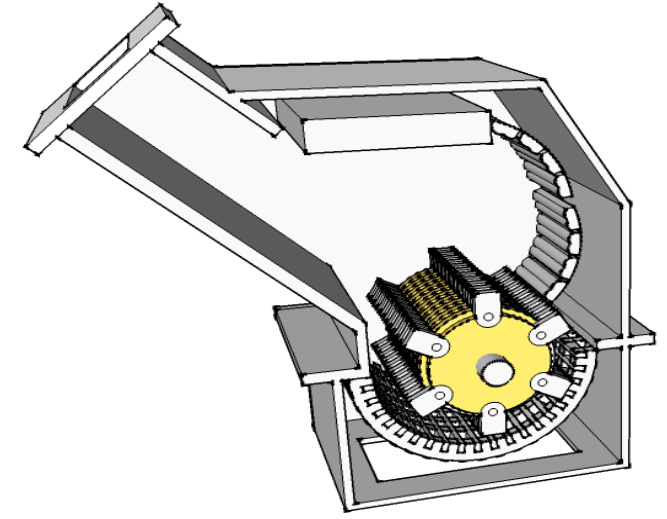
- However, one should avoid **reducing** the particle size **too much**, **because** fine particles tend to form **a compact cake** upon settling to the bottom of the container.
- The most important consideration in suspensions is the size of the particles. In most good suspensions, the particle diameter is **1-50 μm** .
- Generally, **particle size reduction** is accomplished by **dry milling** before incorporation of the dispersed phase into the dispersion medium.
- One of the most rapid, convenient, and inexpensive methods of producing fine drug powders of about 10-50 μm is **micro-pulverization (Hammer Mills)**.



Particle Size Reduction Techniques



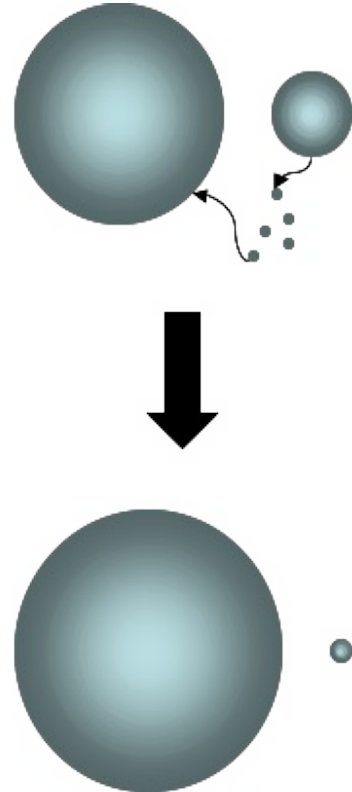
- **Micro-pulverizers** are high-speed mills that are efficient in reducing powders to the size acceptable for most suspensions.
- <https://youtu.be/fSTvbE77ucE>
- <https://youtu.be/e6trUtoIOZE>
- **Jet Mills**: For still finer particles, **under $10\ \mu\text{m}$** , *jet mills are used* (also called *micronizers*), it is quite effective.
- https://youtu.be/J0WEeE_I1i0
- **Spray Dryer**: Particles of extremely small dimensions may also be produced by *spray drying*.



Possible Problem in Suspension



- **Particle Size Growth**
- Although the particle size of a drug may be small when the suspension is first manufactured. **But they can grow.**
- This can occur by **different mechanisms**:
 1. **Ostwald Ripening**: different particle sizes of the suspended particle will have different dissolution and “solubility” (**solubility change is within certain limit**) so the small particle will dissolve faster and make a bridge between larger particles.
 2. **Polymorphic transformation**: polymorph will have different solubility which will lead to crystal growth because the more soluble form will go into solution and precipitate.
 3. **Temperature cycling**: temperature change will affect solubility, an **increase in temperature will increase the solubility**, and a decrease in temperature will decrease it and will lead to a supersaturated solution which will precipitate and crystal growth may occur.





1. **Active Ingredients:** Drug.
2. **Wetting agents:** sometimes surfactant is used to increase the wetting of powder in suspensions such as non-ionic surfactant. These compounds decrease the interfacial tension and facilitate dispersion.
 - The wetting is required as **a first step**, so the particle will **immerse** in liquid and not float on the surface. They function by displacing the air on the surface of the particles thereby allowing penetration of water into the powder.
3. **Suspending (viscosity enhancing) agents:** these compounds **do not** lower the interfacial tension but provide a viscous medium to slow down the sedimentation of suspended particles. Examples: Methylcellulose, carbomer.
4. **pH adjusting agents (buffering agents), Anti-microbial preservatives**
5. **Colorant, Sweetener, Purified water**
6. **Flocculating agents (next slides)**

Properties of Deflocculated and Flocculated Systems



Flocculated

Particles form **loose aggregates**

The sedimentation rate is **high** and particles **settle as floc** (or floccule), which is a collection of particles (larger particles settle faster).

Sediment is **loosely packed** –easily and readily redisperses

Suspension may **not appear attractive** because of rapid sedimentation (–separates into two phases –a clear liquid and flocculated particles).

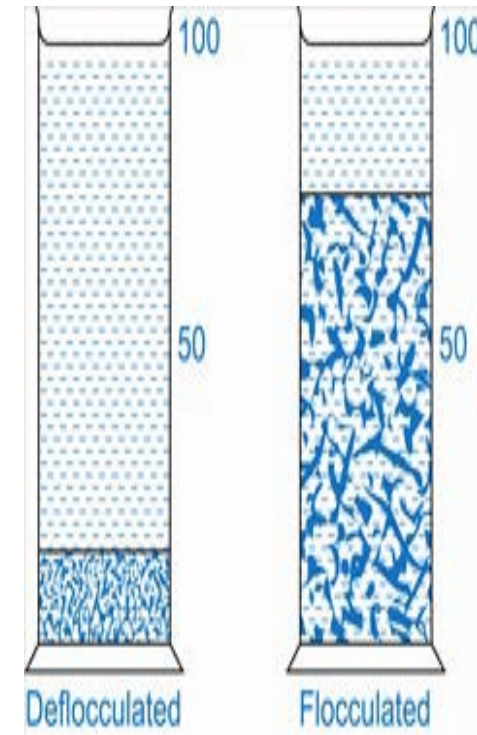
Deflocculated

Particles exist in suspension as **separate particles**

The sediment **rate is slow** because each particle settles separately

Suspension **appears uniform** and well dispersed **much longer than** flocculated systems

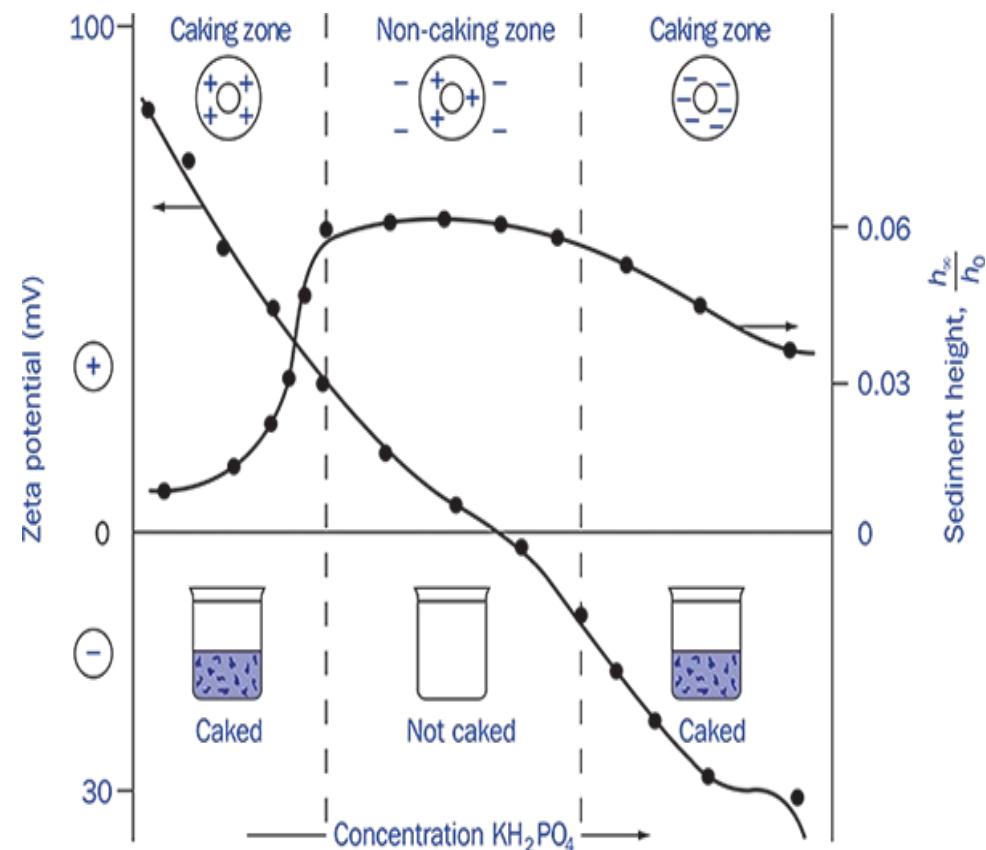
Sediment eventually becomes **closely packed** due to weight of upper layers of sediment -**results in caking**, which is difficult, if not impossible, to re-disperse



Flocculating Agents

- These agents are either **electrolytes**, **polymers**, or **surfactants**.

1. **Electrolytes:** neutral electrolytes that are capable of reducing the zeta potential of suspended charged particles to zero.
 - Their effect appears in the graph to the right.
 - At high (positive and negative) zeta potentials the suspension is **deflocculated and caking** eventually occurs upon sedimentation.
 - At low zeta potential values on either side of zero, the attractive forces are sufficient to form a flocculated suspension as seen by the plateau in the **sedimentation volume** curve.
 - Examples are small concentrations of sodium or potassium chloride (0.01-1% w/v)



Stabilization of bismuth subnitrate particles using monopotassium phosphate flocculating agent

Flocculating Agents:



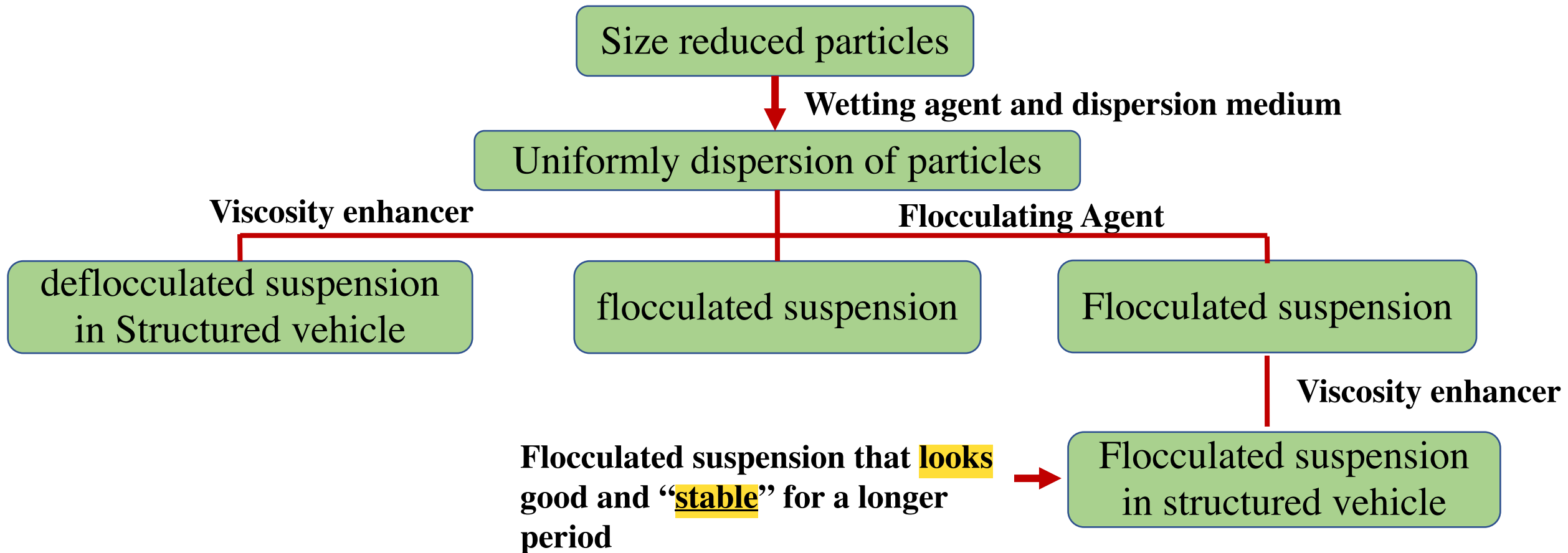
- **Polymers**
- Other flocculating agents are polymers that are partially **adsorbed** on the particle surface and will stabilize the particle due to **inter-particulate polymer bridging**.
- If the polymer is added in a sufficient concentration it will form a flocculated suspension. Example xanthan gum
 - Their branched-chain molecules form a gel-like network within the suspension and become adsorbed onto the surfaces of the dispersed particles, thus holding them in a flocculated state.

Polymer concentration		
Low	Intermediate	High
Sedimentation Volume		
Similar to Neat Drug	High	Low

Suspension Preparation Approaches



- To prepare an ideal suspension, one should prepare a suspension with **partial flocculation**.



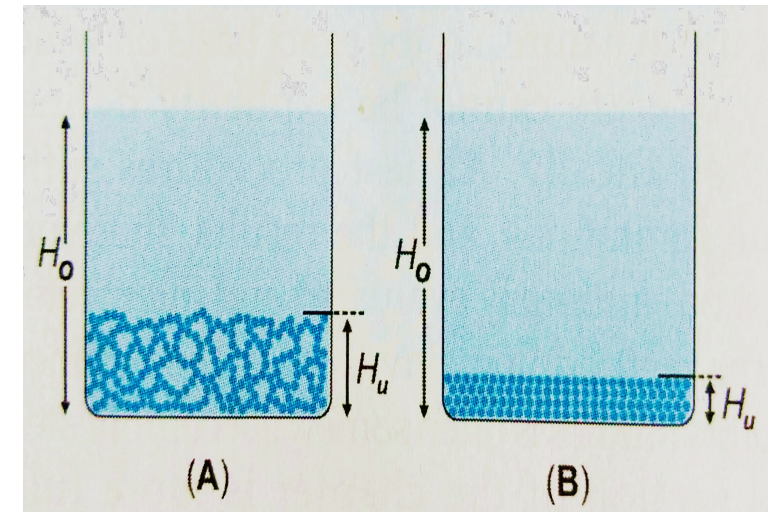
Evaluation of Suspension



- Aesthetic appeal (appearance, color, odor, and taste).
- pH.
- Zeta potential.
- Particle size distribution.
- Rheological behavior.
- **Sedimentation rate.**
- Uniformity of drug content.
- **Stress tests:**
 - 1. (vibration to simulate transportation).**
 - 2. Freeze-thaw cycles.**

Evaluation of Suspension Stability

- **Sedimentation volume (SV):** since particles in suspension tend to settle down and should be re-disperse upon shaking, measurement of sedimentation volume is a common basic evaluation of suspension stability.
- **SV:** It is the ratio of the sediment height to the total height of the suspension (H_u/H_0). The **bigger** the ratio **the better** the suspension.
- At zero time, the $H_u=H_0$ and the sedimentation volume are equal to **1** (highest possible value).
- Upon standing, the suspended solid particles begin to settle and thus sedimentation volume begins to decrease.



Evaluation of Suspension Stability



- **Particle size changes**
- The **freeze-thaw cycling technique** is useful to stress suspensions for stability testing purposes. This technique **promotes particle growth** and may indicate the probable future state after prolonged storage at room temperature.