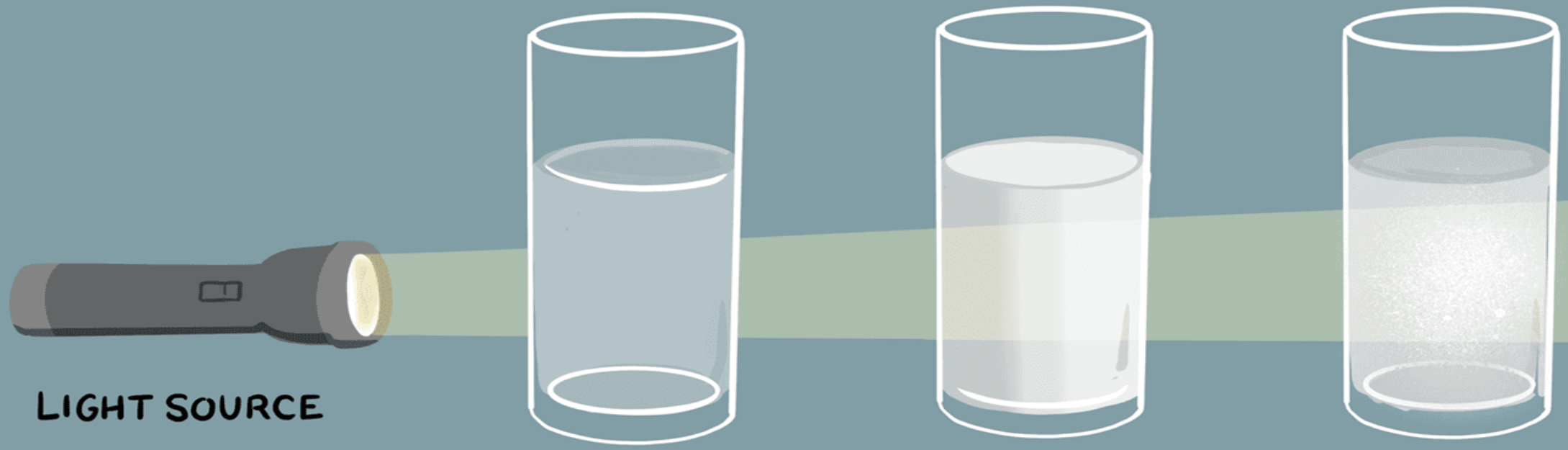


	SOLUTION	COLLOID	SUSPENSION
LIGHT BEAM:	NOT VISIBLE	VISIBLE	VISIBLE
EXAMPLE:	WATER	MILK	FLOUR AND WATER

Biphasic Liquids

Mohammed Albarki, PhD.

THE TYNDALL EFFECT

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:**

$$\Delta G = \gamma . \Delta A$$

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

- $\Delta G = \gamma . \Delta A$

- **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) ➔ This means that these biphasic systems are **unstable** because of high positive free energy.

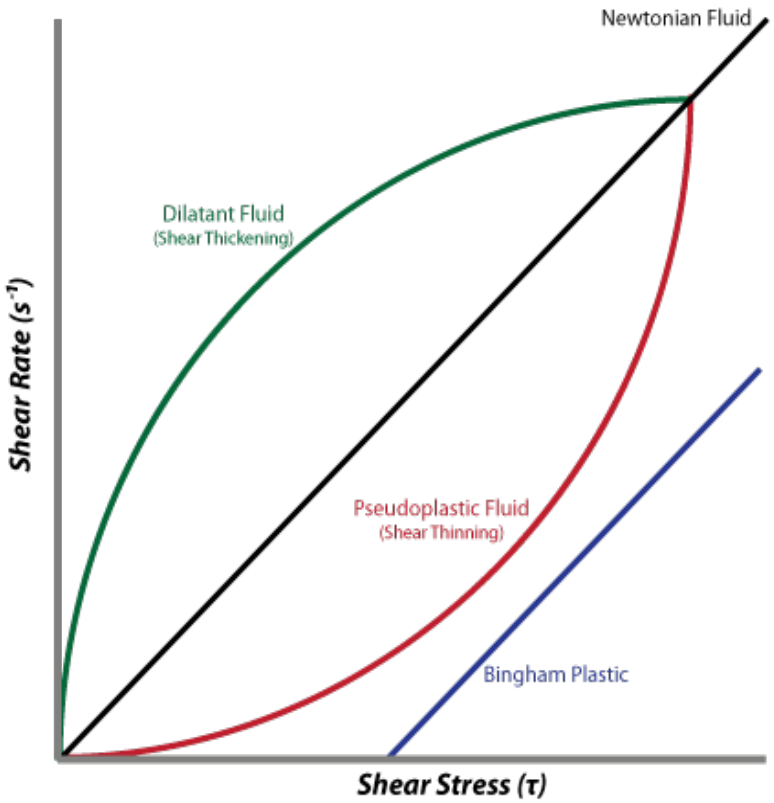
Introduction

- 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.

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

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.**
- 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®)	TopicalAnti-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

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

- Where:
- $\frac{dx}{dt}$= sedimentation rate in (cm/s) ; D= particle diameter (cm)
- ρ = **density** in g/ml ; $\mathcal{g}$= **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.

Theoretical Considerations

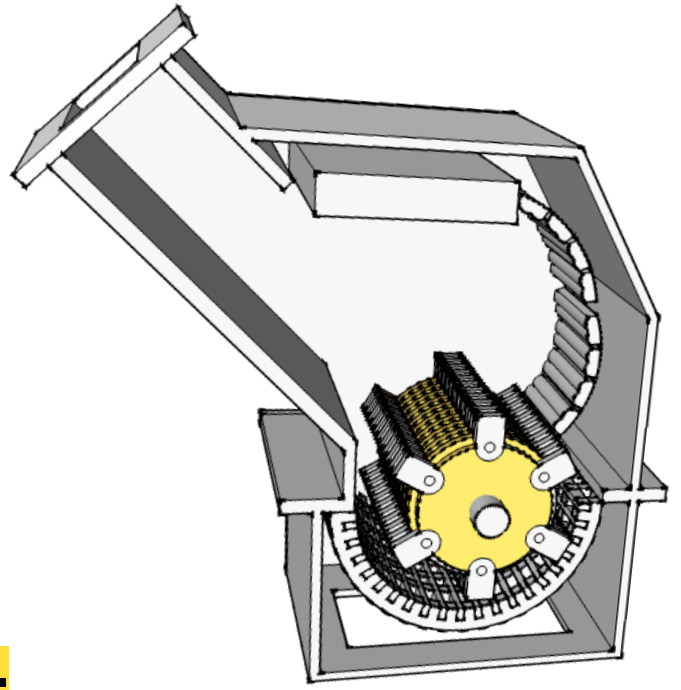
- $\frac{dx}{dt} = \frac{D^2(\rho_{(particle)} - \rho_{(medium)}) * g}{18\eta}$

Increase Sedimentation rate	Decrease Sedimentation rate (remain suspended)
The greater the density of the particles, the greater the rate of descent.	**Reducing** the **particle size** of the dispersed phase produces a **slower** rate of descent of the particles.
	Increasing the **viscosity** of the dispersion medium.

- However, a product with too high a viscosity is not desirable because it pours easil y and it is difficult to redisperse the suspended particles.
- If the sedimentation rate is 10^{-4} cm/s, what will be the time required for a suspension to settle in a 10 cm-long bottle? ~ 28h.

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.
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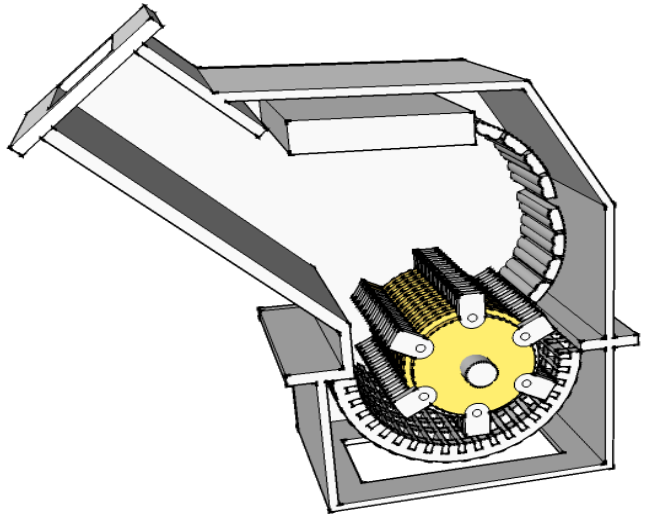
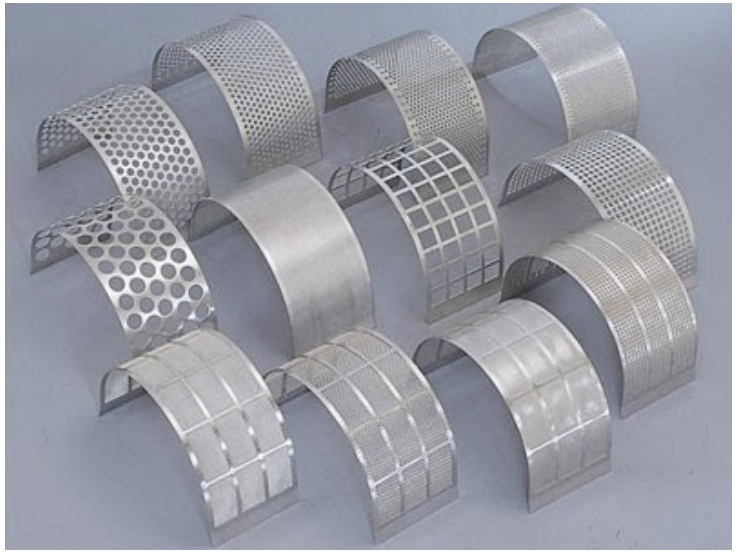
- https://youtu.be/e6trUtoIOZE



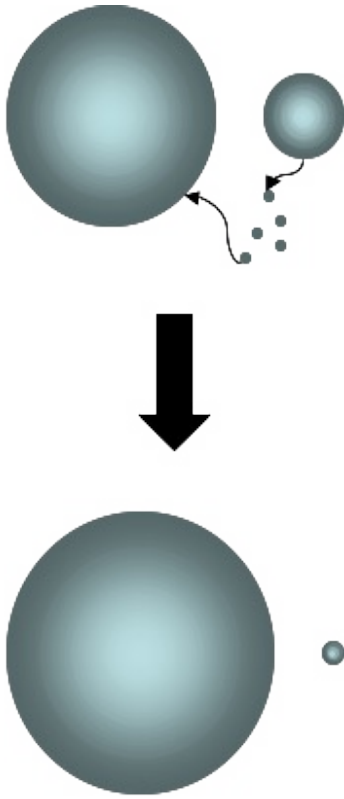
- **Jet Mills**: For still finer particles, under 10 μm, ***jet mills are used*** (also called *micronizers)*, it is quite effective.
- https://youtu.be/J0WEeE_I1i0



- **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**:



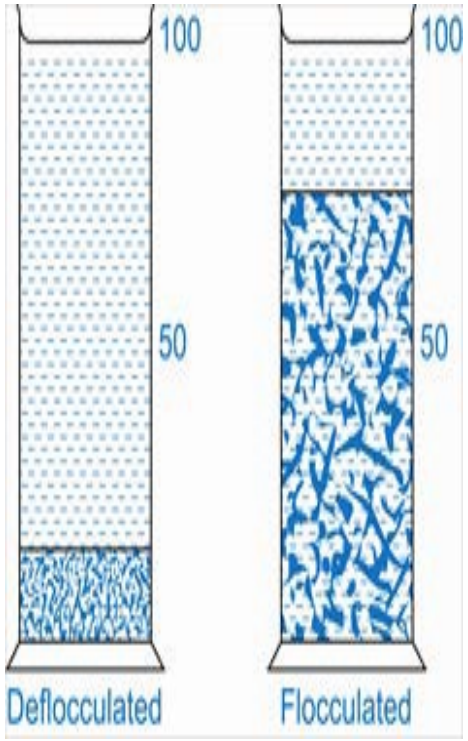
1. **Ostwald Ripening**: different particle sizes of the suspended particle will have different dissolution and "solubility" (solubility change is within certain limit) so the small particle will dissolve faster and make a bridge between larger particles.
2. **Polymorphic transformation**: polymorph 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.

Formulation Components of Orally Administered Suspension

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

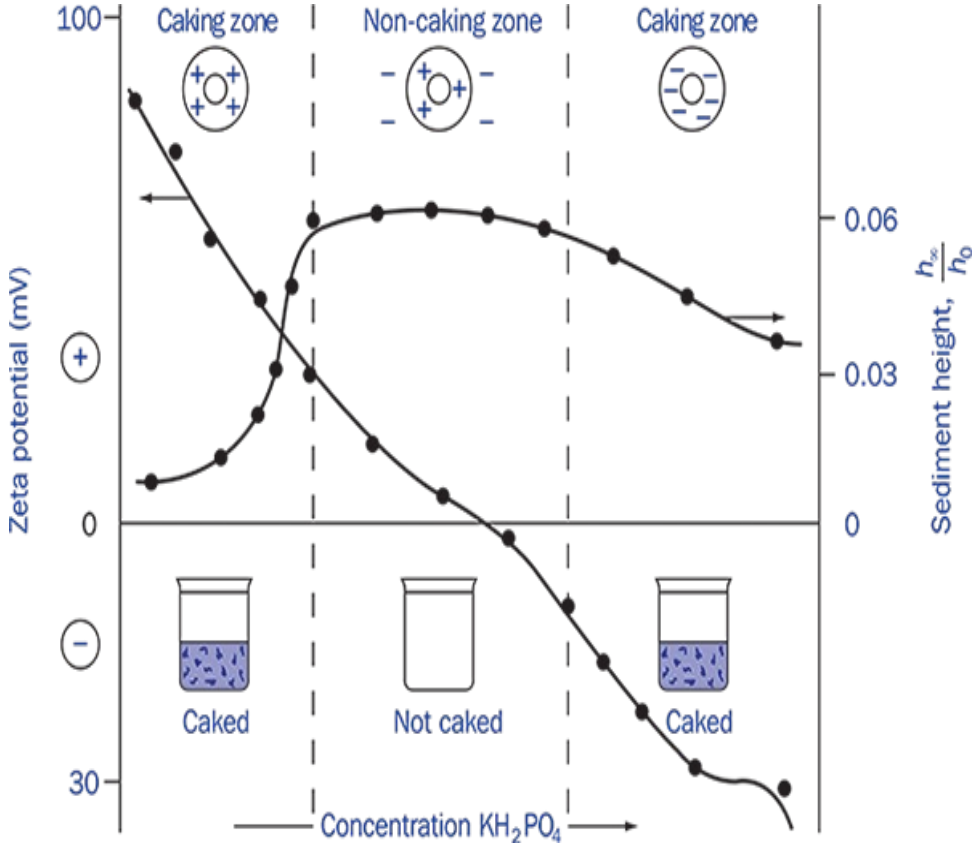
Flocculated	Deflocculated
Particles form **loose aggregates**	Particles exist in suspension as **separate particles**
The sedimentation rate is **high** and particles **settle as floc (or floccule),** which is a collection of particles (larger particles settle faster).	The sediment **rate is slow** because each particle settles separately
Sediment is **loosely packed** –easily and readily redisperses	Suspension **appears uniform** and well dispersed much longer than flocculated systems
Suspension may **not appear attractive** because of rapid sedimentation (–separates into two phases –a clear liquid and flocculated particles).	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**.

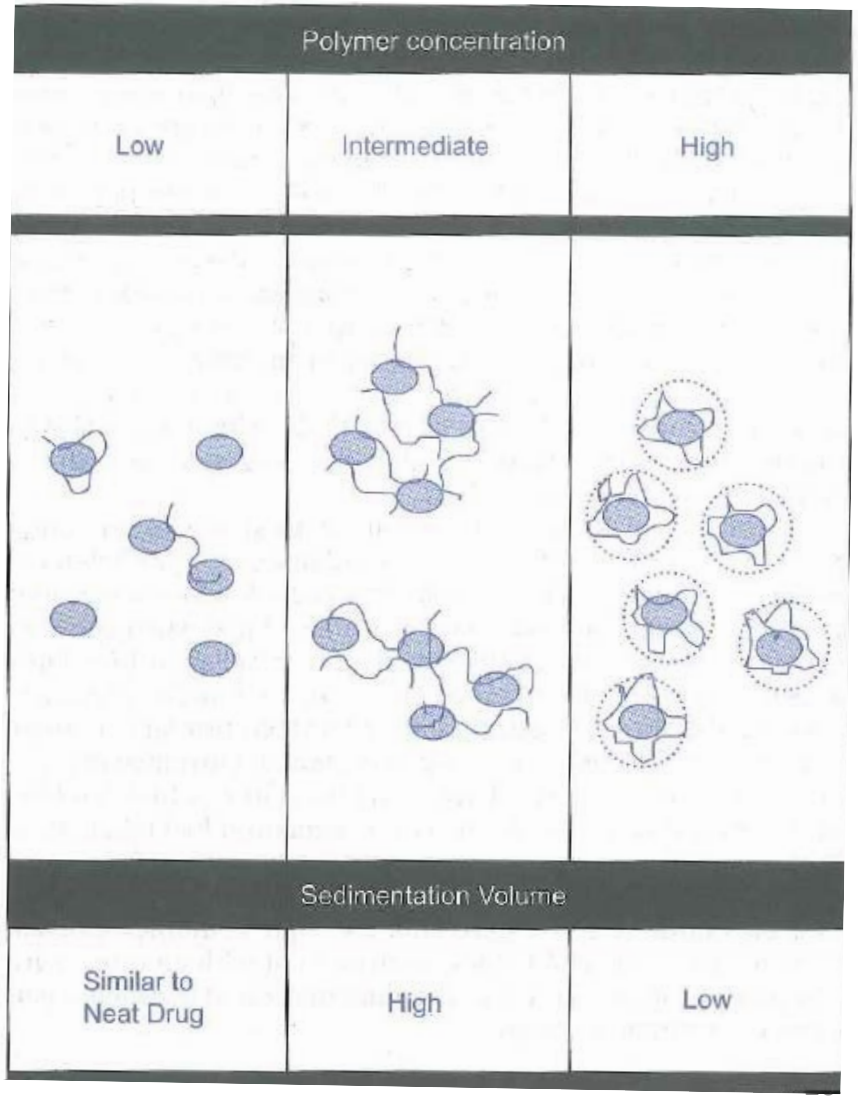
1. **Electrolytes:** neutral electrolytes that are capable of reducing the zeta potential of suspended charged particles to zero.
   - Their effect appears in the graph to the right.
   - At high (positive and negative) zeta potentials the suspension is **deflocculated and caking** eventually occurs 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

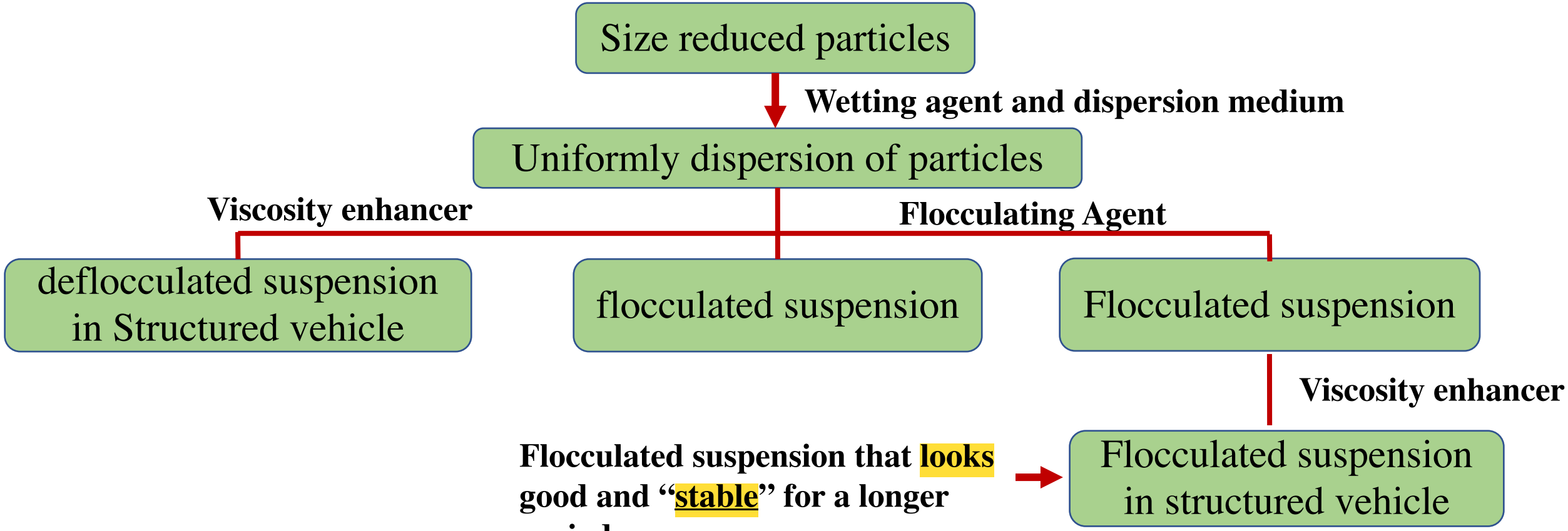
Flocculating Agents:

- **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.



Suspension Preparation Approaches

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



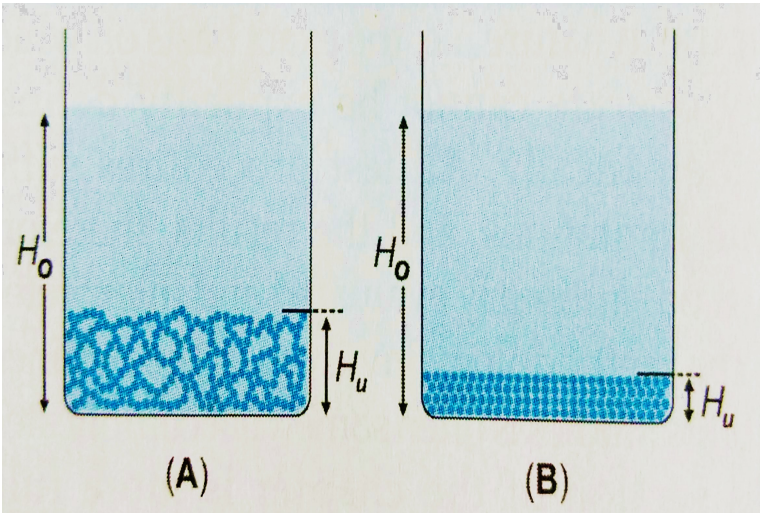
Evaluation of Suspension

- 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 prolong storage at room temperature.