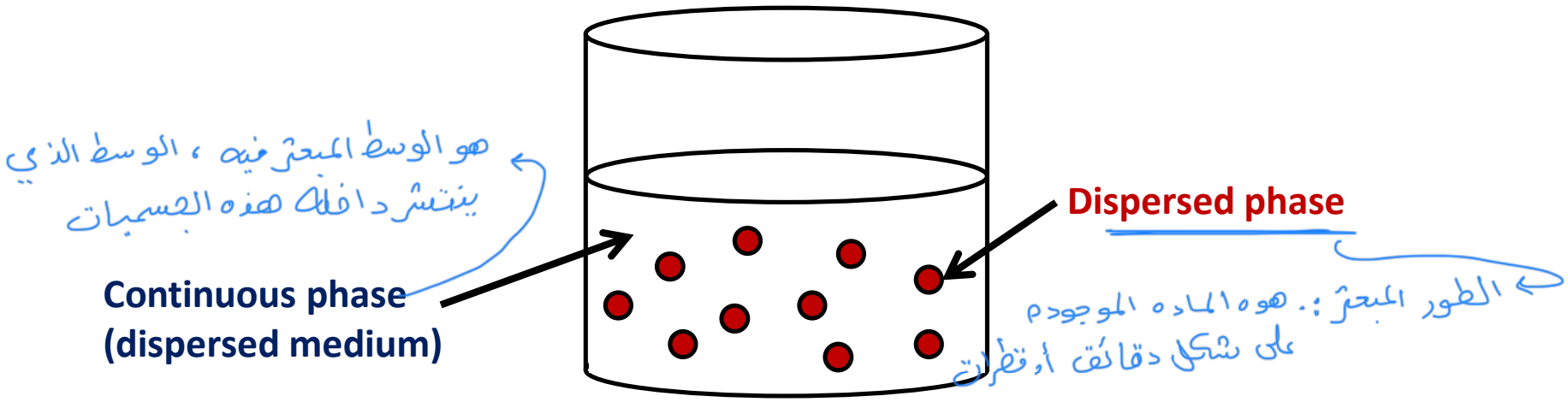
Dispersed systems

What is a dispersed system



- A system in which one component is ***dispersed*** as particles (un-dissolved) or droplets (immiscible) throughout another component.

dispersed medium ينتشر أو يتبعثر داخل ⟸ dispersed Phase *

- A dispersed system could be a colloid, gel, suspension, emulsion, lotion, cream, ointment, suppository, troche, or medication stick.

- Size of the dispersed particles is the important factors that determine the type of dispersion. e.g. colloids and gels have the smallest size particles.

* الاختلاف الأساسي بين هذه الانوع يعتمد على :-

- Particle size ← هو العامل الرئيسي
- Type of dispresed
- Type of dispresed medium
- The final texture of the preparation (القوام النهائي للمستحضر)

Colloidal dispersions

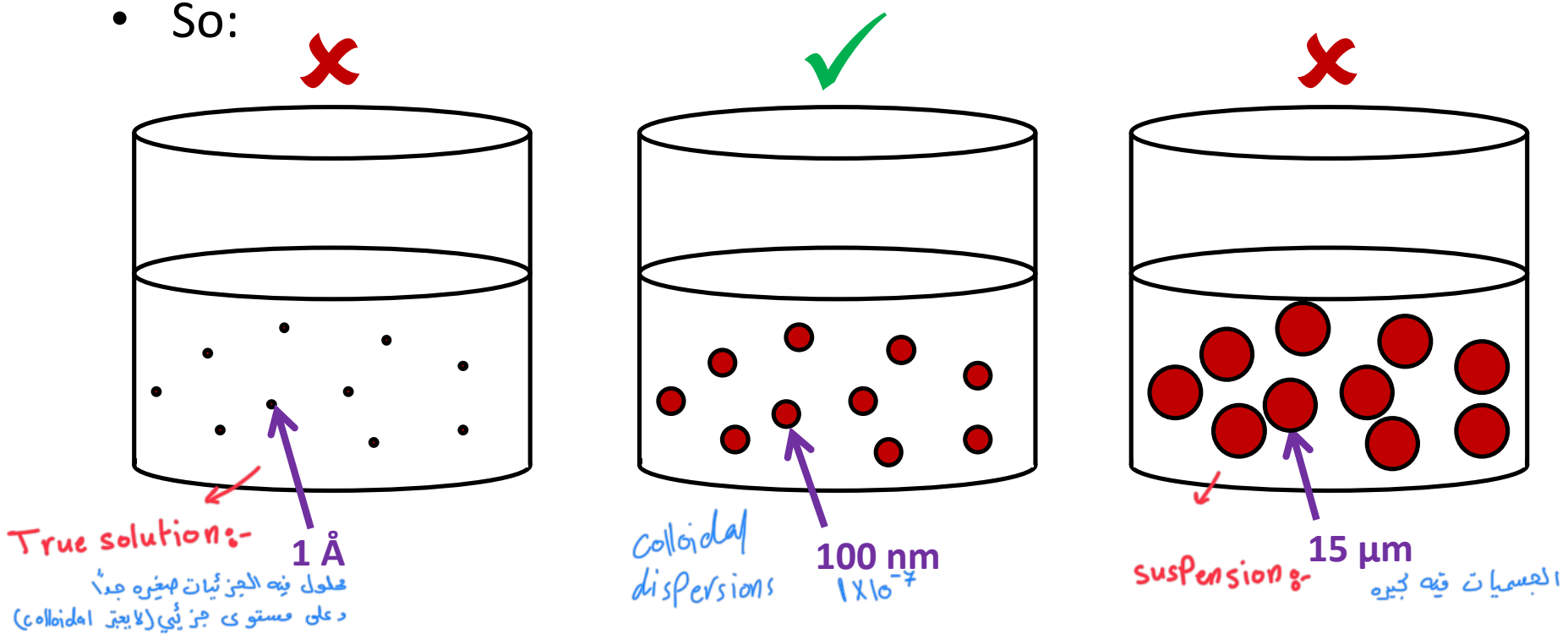
الجسيمات فيه صغيره جداً

- **Colloidal dispersions** are defined as:

  dispersions in which the size of the dispersed particles in the continuous phase is in the range of 10^{-9} – 10^{-6} m

  (1 nm – 1 µm)

- So:



Classification of disperse systems

Dispersed phase	Continuous phase	Name	Example
Liquid	Gas	Liquid aerosol	Cloud قطرات سائله منتشره في الهواء
Solid	Gas	Solid aerosol	Smoke جسيمات صلبه منتشره في الهواء
Gas	Liquid	Foam	Bath foam فقاعات غازيه داخل سائل
Liquid	Liquid	Emulsion	Milk سائل داخل سائل آخر في ممتزج
Solid	Liquid	Suspension	Calamine lotion صلب داخل سائل
Liquid	Solid	Solid emulsion	Ice cream سائل موزع داخل بنيه شبه صلبه

Suspension ⇐ * اذا كانت الماده الصلبه غير ذائبه وموزعه في ماء

Emulsion ⇐ * اذا كان سائل موزع داخل سائل آخر غير ممتزجه

I. Suspension

⤶ غالبًا في المضادات الحيوية

Objectives

- By the end of these lectures, you should be able to:
  - Explain why suspensions are useful dosage form.
  - Describe the properties of a good suspension.
  - Explain with the role of viscosity enhancing, wetting and flocculating agents to stabilise suspensions.
  - Know how to inhibit the problem of caking.

Part 1: Introduction and advantages

Definition

- A **suspension** consists of a dispersion of insoluble **solid particles** in a **liquid**.

* الاجسيمات لا تكون ذائبه ، تبقى منفصله و مرئيه مجهريًا

- In a suspension, the particle size is generally > 1µm.

- Different to a colloidal system, where particle size is < 1 µm.

Solid in liquid colloids *vs*. solutions

- Suppose we add a powder of drug to water. How do I know if I have a colloid or a solution?

- In a true solution, the drug molecules are dispersed on the molecular scale in the solution – each molecule is isolated from all other drug molecules;

- In a colloid, we have ***particles*** of drug – aggregates consisting of many drug molecules.

* True solution ⇐ ذوبان كامل على المستوى الجزيئي (كل جزيء منفصل عن الاخر)

* colloid ⇐ تجمعات صغيره جداً، لا كن ليست ذوباناً حقيقيا كاملاً (جزيئات كثيره متجمعه)

Why use suspensions?

1. To formulate **Poorly soluble** drugs into a liquid form if they cannot be made into solutions.

* اذا كان الدواء لا يذوب في الماء ، لا كن المريض يحتاجه كسائل ، نلجأ للـ suspensions

2. For **taste masking** – unpleasant tastes may be less noticeable in suspension than in solution (Ex. paracetamol). (Why?)

لان الدواء في المعلق لا يكون ذائباً بالكامل ، فيكون ملامسته المباشره لمستقبلات التذوق اقل من المحلول

3. The drug may be **more stable** if formulated as a suspension instead of a solution. (Why?)
NOTE: some drug may be more stable as a **solid**, so we make a suspension just before dispensing.

* بعض الادويه تكون اكثر ثباتاً في الحاله الصلبه مقارنه بكونها مذابه

4. Easier to swallow than solid dosage forms. ⇒

* مناسب للأطفال وكبار السن

5. Some materials are required to be present in the GIT in a finely divided forms (ex. Kaolin and $MgCO_3$ are used for the adsorption of toxins).

* ذحتاج المادة على شكل دقائق داخل GIT ، لامتصاص السموم

* بشكل عام suspensions ليس فقط بديلا للمحلول ، بل قد يكون أفضل منه علاجيا وثباتيا

Usage of suspensions:

1. Oral administration (sweetened, flavored).
2. Topical application.
3. Parenteral routes (non-sweetened, non-flavored): intramuscular, intradermal, SC).
4. Intra-oculr and intranasal suspensions (non-sweetened, non-flavored).

Disadvantages of suspensions:

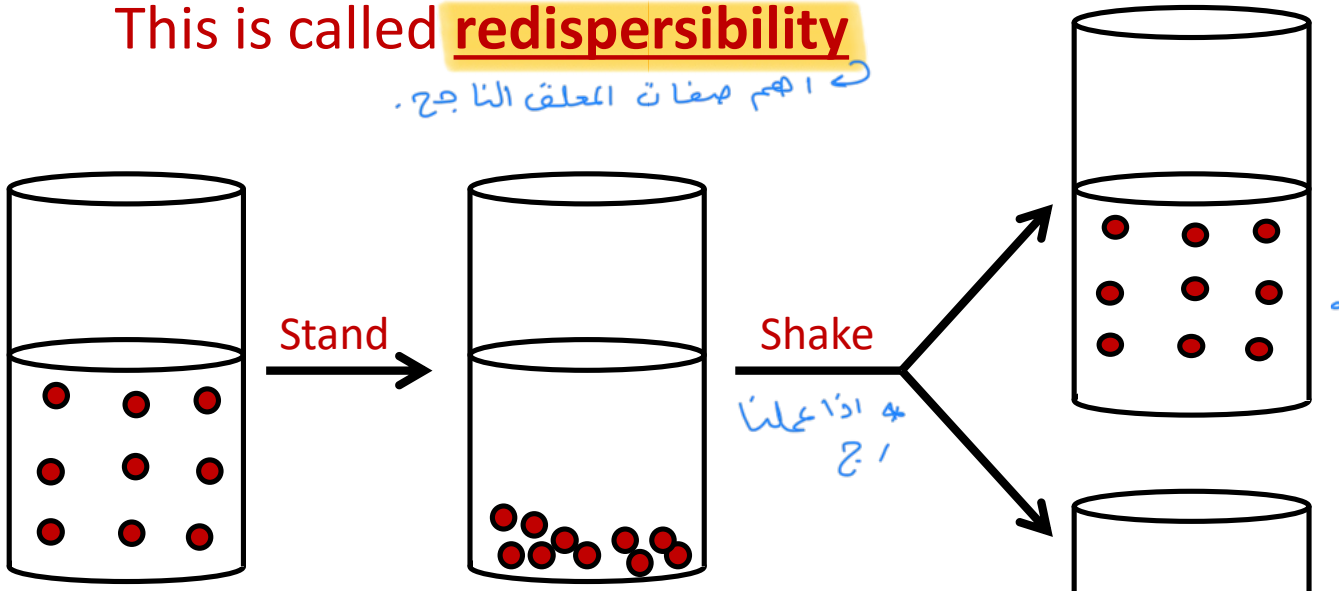
1. Physical instability → settle over time → lack of uniformity of dose → shake before administering each dose.
2. Texture may be unpleasant to patients.
3. Suspension formulations may be bulky and therefore difficult for a patient to carry.

Properties of a good suspension

- The suspension must **be easy to disperse after shaking**:

This is called **redispersibility**

اهم صفات المعلق الناجح.



"Freshly prepared" suspension

* عند تحضير المعلق اول مره تكون الجسيمات موزعه جيداً

Over time, the particles will sink to the bottom of the container

* مع الوقت تبدا الجسيمات بالنزول الى الاسفل بسبب الجاذبيه

* اذا عملنا ج /

A **good** suspension

* في المعلق الجيد تعود الجسيمات للانتشار بسهوله

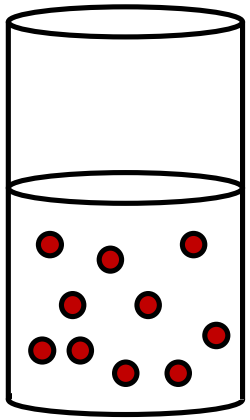
A **bad** suspension

* في المعلق السيئ تبقى متكتله في القاع

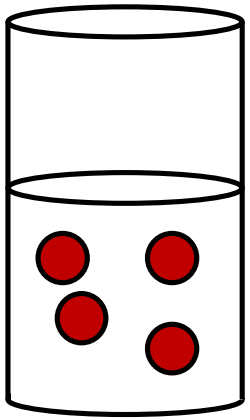
Properties of a good suspension

- The suspension should contain particles which are **small** and of the **same size**. This is to ensure patients do not find the suspension to be **gritty**.

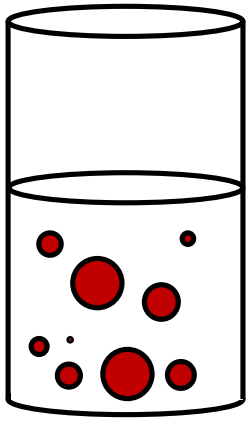
* ليش بتكون صغيره و نفس الحجم ؟ حتى المريض ما يشعر بالخشونه والرمليه
grittiness



A **good** suspension



A **bad** suspension: particles too big

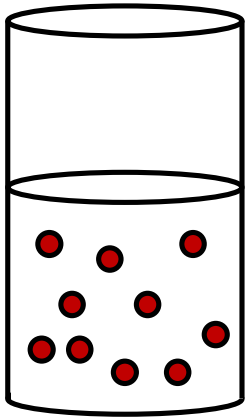


A **bad** suspension: particles are different sizes

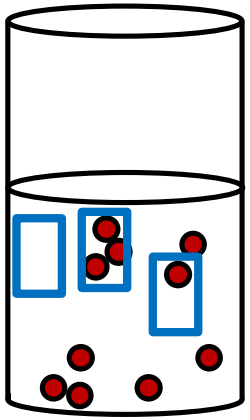
Properties of a good suspension

- The suspension must be **homogeneous**. For the period after shaking and removing the dose, the particles need to be **evenly distributed** throughout the liquid to ensure the **same dose** is given each time.

* لازم لما نرج العبوه ونسحب جرعه ، تكون الجسيمات موزعه بالتساوي في كل السائل ، حتى تكون كل جرعه مساويه للجرعه اللي قبلها



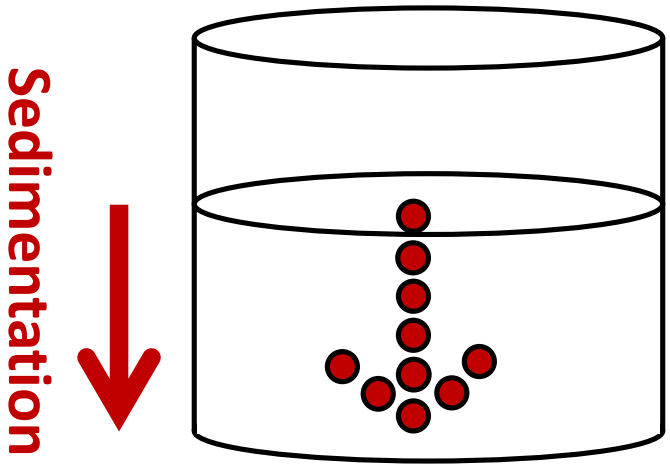
A **good** suspension



A **bad** suspension

The three doses (boxes) contain very different amounts of the drug here.

Sedimentation and suspension



- The **velocity of sedimentation** is given by **Stokes' Law**:

سرعة الترسب

* الجسيمات تترسب اسرع عندما :-
- يكون الحجم الكبير
- يكون فرق الكثافة بين الجسيمات وبين السائل الكبير
- تكون لزوجة الوسط أقل

$$V = \frac{2a^2 g(\sigma - \rho)}{9\eta}$$

a = the radius of the solid particles; (نصف قطر الجسيم)

σ = the density of the solid; (كثافة الجسيم الصلب)

ρ = the density of the liquid; (كثافة السائل)

η = the viscosity of the liquid; (لزوجة السائل)

g = the acceleration due to gravity. (الجاذبية)

Stokes' law

Given that:

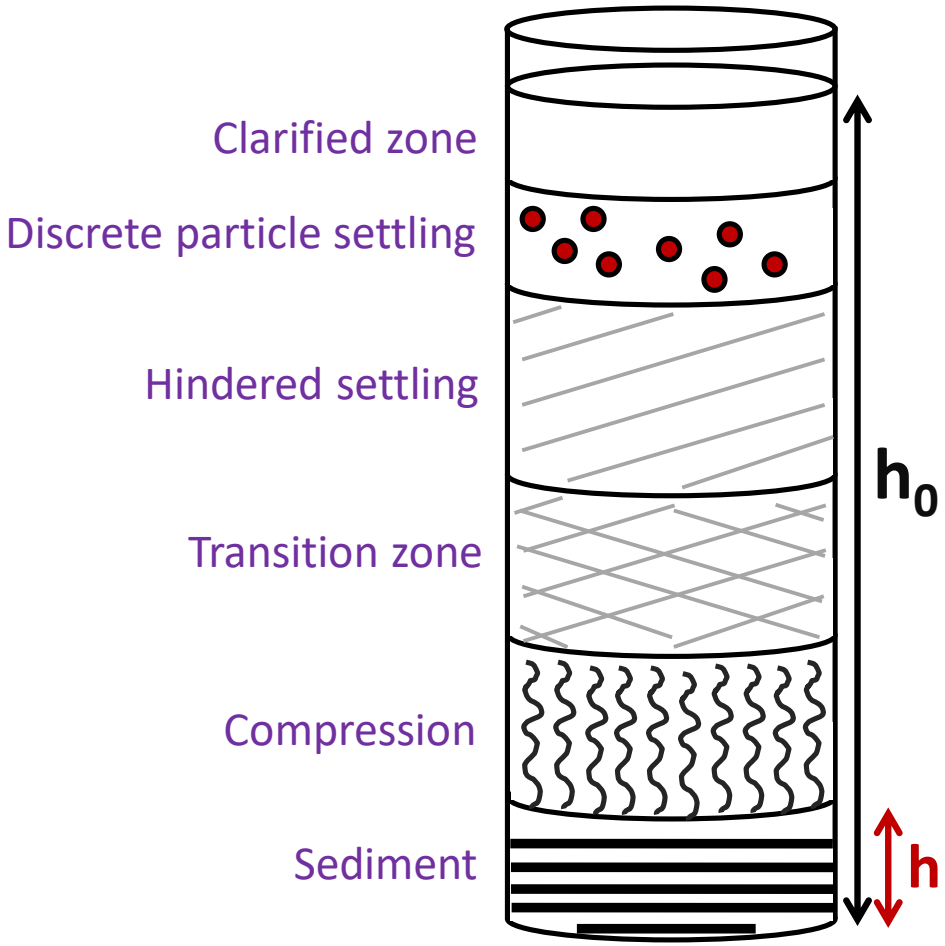
$$V = \frac{2a^2 g(\sigma - \rho)}{9\eta}$$

Will the sedimentation velocity go up or down if we:

- Increase the radii of the particles? تزيد سرعه الترسب
- Increase the density of the solid? تزيد سرعه الترسب
- Increase the density of the liquid? تقلل فرق الكثافه ، تقل السرعه
- Decrease the density of the liquid? يزيد الفرق ، تزيد السرعه
- Increase the viscosity of the liquid? تقل السرعه
- Decrease the viscosity of the liquid? تزيد السرعه

* الترسب يزداد مع :- جسيمات الجم فرق كثافه الجم لزوجه اقل

The sediment ratio



نسبة الترسب

Sediment ratio, R:

حجم الراسب

$$R = \frac{\text{Volume of sedimented layer } (V_s)}{\text{Total suspension volume } (V_t)}$$

الحجم الكلي

Or,

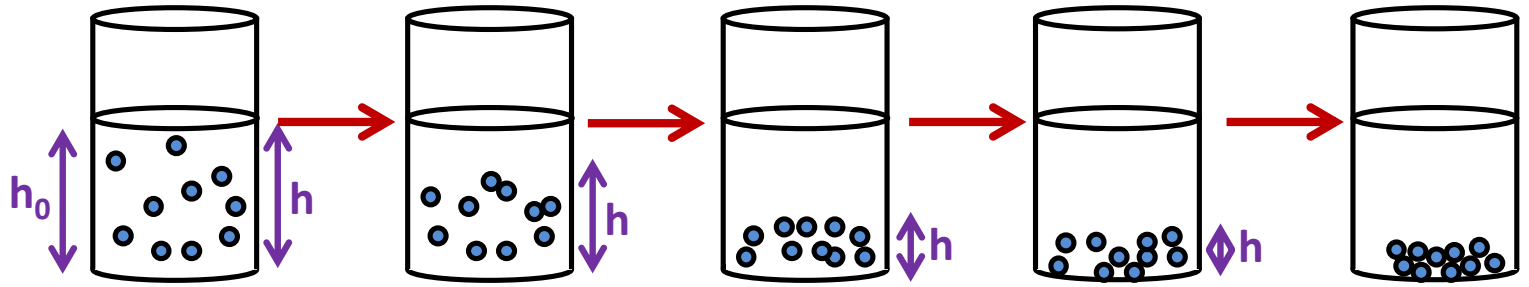
ارتفاع طبقة الراسب

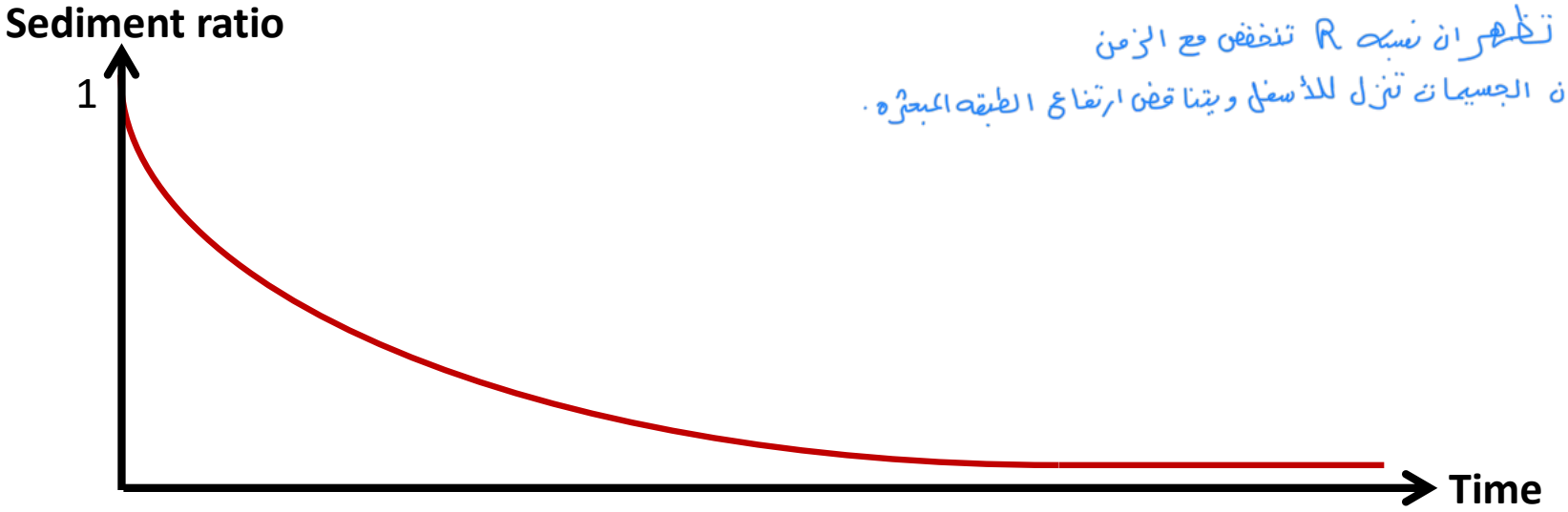
$$R = \frac{\text{Height of sedimented layer } (h)}{\text{Initial height of suspension } (h_0)}$$

الارتفاع الابتدائي للمعلق

The sediment ratio

$$R = \frac{\text{Height of sedimented layer (h)}}{\text{Initial height of suspension}(h_0)}$$





* تظهر ان نسبه R تنخفض مع الزمن
لان الجسيمات تنزل للأسفل ويتناقص ارتفاع الطبقه المبحثره .

Part 2: How to make a suspension

How to make a suspension?

- First, we need the **drug**! It must have small particles of uniform size.

- If the drug is water-insoluble, we may add a **wetting agent**. This breaks the interfacial tension, ensuring the solid particles disperse easily throughout the liquid.

- Interfacial tension is an energy barrier which prevents the liquid spreading around the solid.

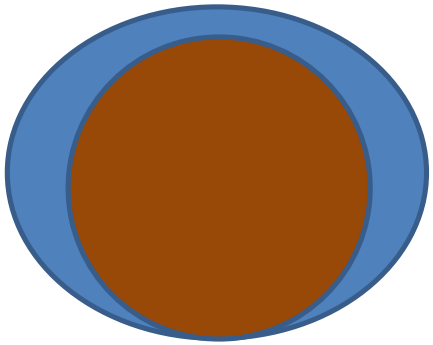
* المشكله ان بعض الاجسام الصلبه خاصه الكارهه للماء لا تبلّل بسهوله ⇐ فتتكتل أو تطفو بدل ان تتوزع داخل الوسط

* wetting agent ⇐ بساعد في انه الجسيمات تتوزع داخل الوسط .
أو
تنتشر

Interfacial tension

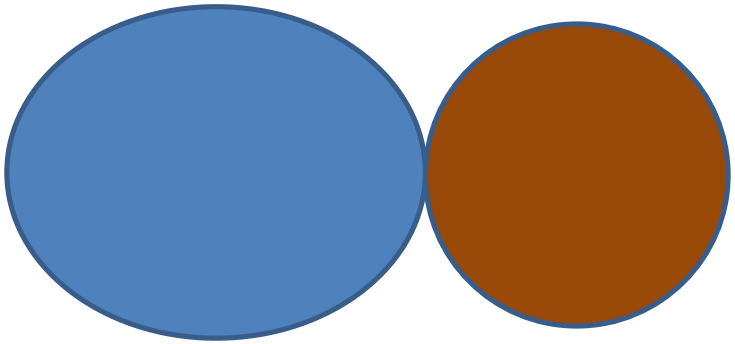
* هي مقاومه تمنع السائل من تغليف سطح الجسيم للذلك تقليلها خطوه اساسيه في تحضير suspension

- Considering a single solid particle:



Low interfacial tension: the liquid spreads around the particle

This should give us a **good suspension.**



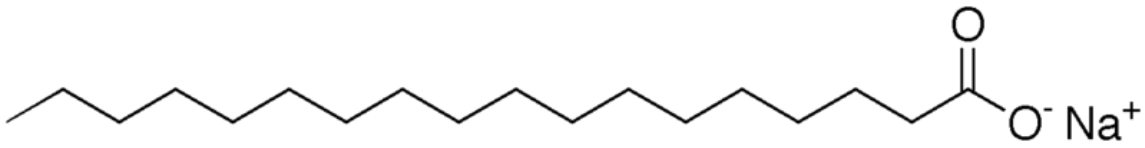
High interfacial tension: the liquid does not spread around the particle

This will give us a **bad suspension.**

Wetting agents

Several types of wetting agents:

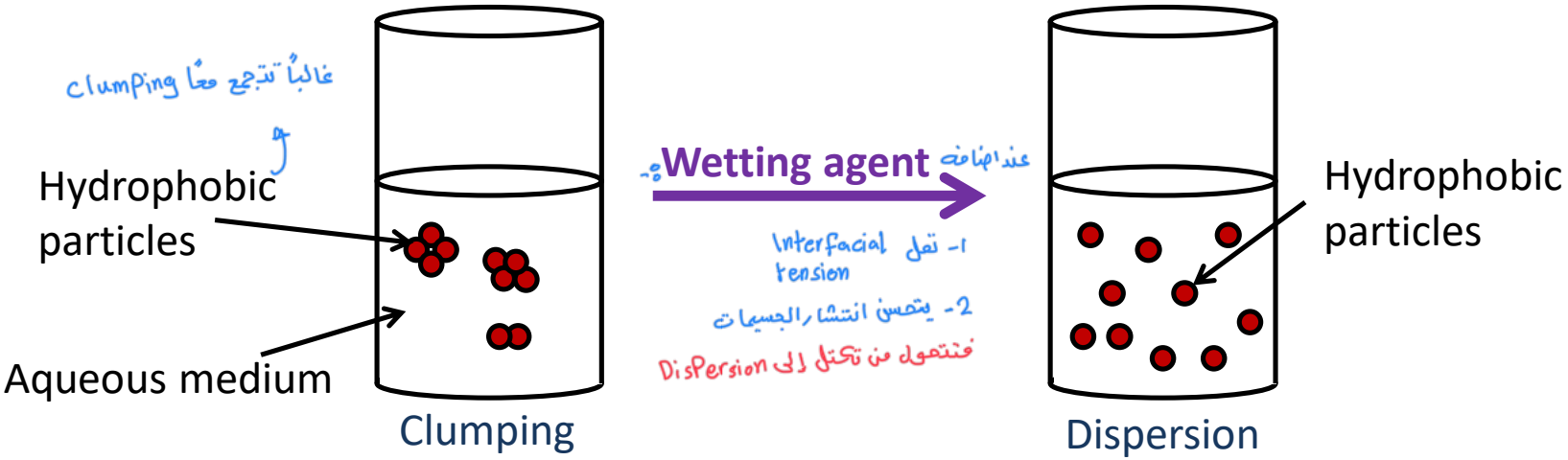
- Surfactants – *e.g.*



- Hydrophilic colloids

- Simple solvents – *e.g.* alcohols, glycerol

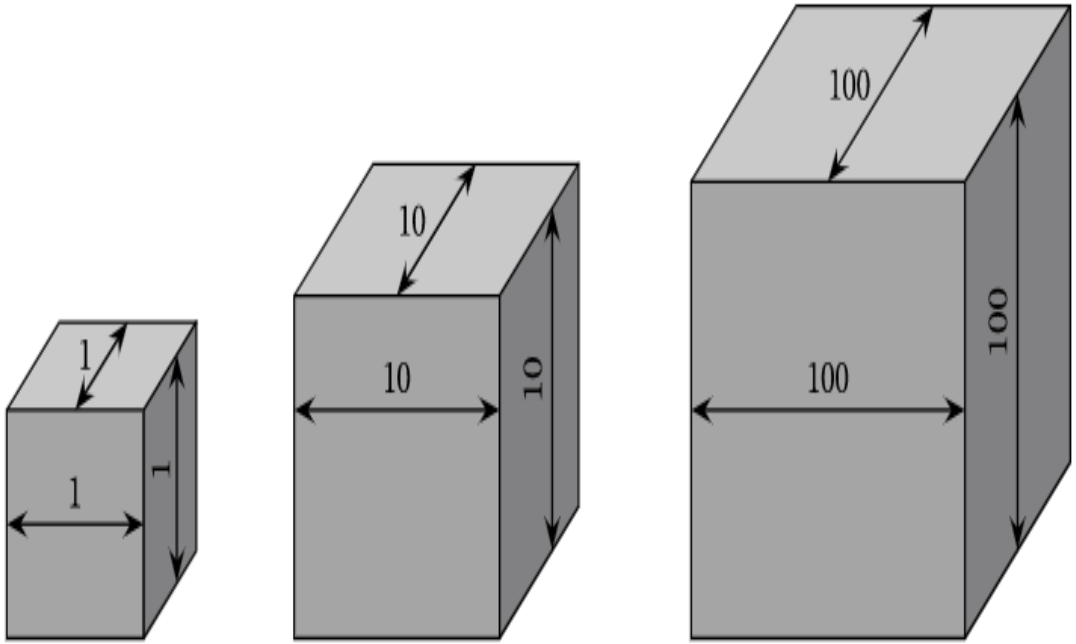
Wetting agents



- Increased wetting of hydrophobic drug particles leads to a **decrease in surface tension**.

* الفكرة :-

كلما صغر حجم الجسيم ← زادت المساحه السطحيه بالنسبه للحجم ← تزداد تلامسه مع الوسط ← يتحسن التبخر والبلل



Surface area = 6 cm^2
Volume = 1 cm^3
Surface area : volume
6 cm^2 : 1 cm^3
= 6/cm

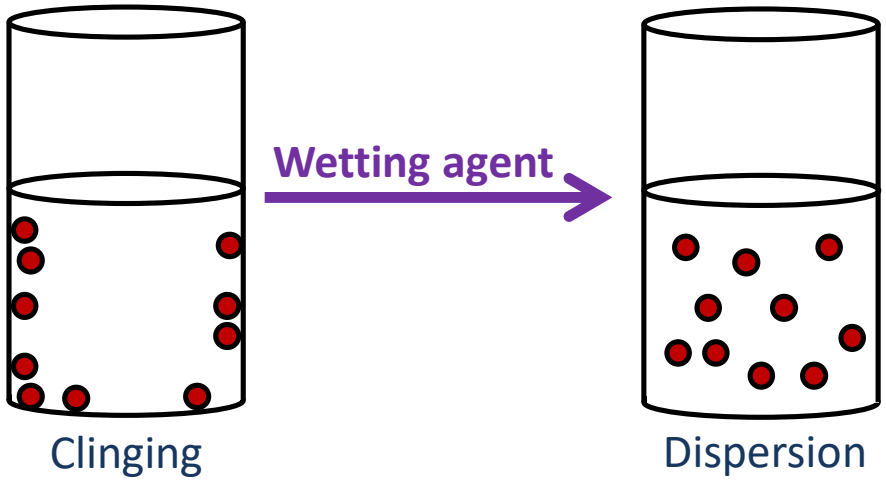
Surface area = 600 cm^2
Volume = 1 000 cm^3
Surface area : volume
600 cm^2 : 1 000 cm^3
= 0.6/cm

Surface area = 60 000 cm^2
Volume = 1 000 000 cm^3
Surface area : volume
60 000 cm^2 : 1 000 000 cm^3
= 0.06/cm

Wetting agents

- Wetting agents also **decrease adsoption** of particles to the container by applying a **repellent coating** to the particles in the suspension.

- Without a wetting agent, particles tend to **stick to the container**.

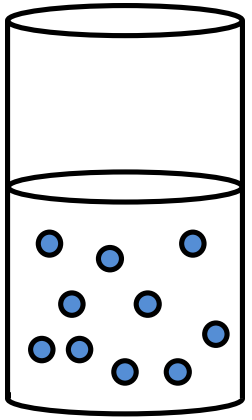


Flocculation

Once we have a suspension, we need to determine if it is:

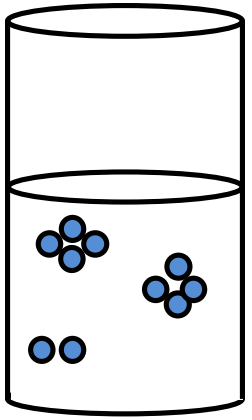
- **Deflocculated**, where the particles remain as separate units.

* الجسيمات تبقى منفصلة
لـ وحدات مستقلة



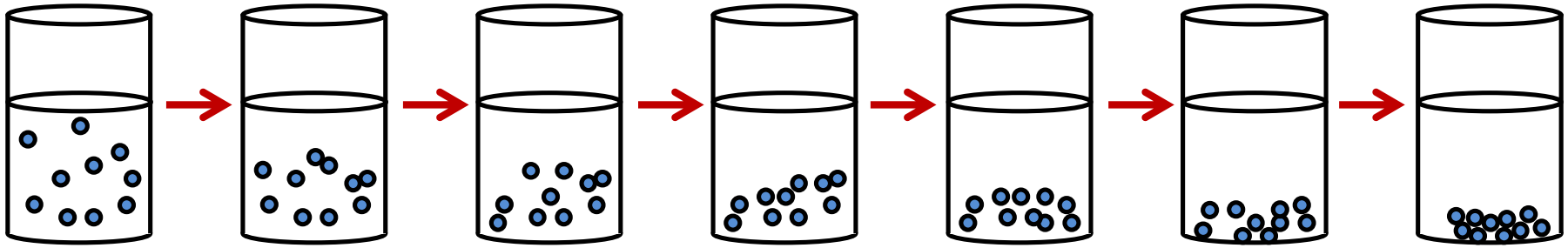
- **Flocculated**, where the particles exist as loose aggregates.

* الجسيمات تتجمع في تجمعات رخوة
losse aggregates.



Deflocculation

- In a **deflocculated system**, the rate of sedimentation depends on the particle size, but generally is **slow**.

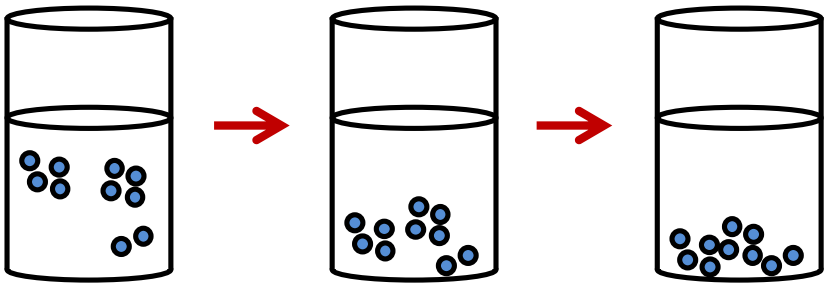


- A slow rate of settling prevents liquid entrapment in the sediment, which becomes **compact** (**"caked"**) and is very difficult to redisperse.

* الترسب البطيء ليس دائماً جيداً، لانه قد يؤدي إلى caking

Flocculation

- In a **flocculated system**, the aggregates settle quickly. This leads to liquid entrapment in the sediment, which tends to be fairly easy to redisperse.



* لا كن الراسب الناتج :-
- يكون فضفاضاً نسبيًا
- يحتجز سائلاً داخله
- يسهل إعاده تبثره

- So, in pharmaceutics, flocculated suspensions are better then deflocculated ones (why do you think this is?)!

لأن الأهم ليس فقط تأخي الترسيب ، بل منع تكون cake صلب غير قابل للرج

Flocculated *vs.* deflocculated

Flocculated system	Deflocculated systems
Loose **aggregates** of particles	Particles exist as **discrete units**
Large volume of final sediment	Small volume of final sediment
Rapid sedimentation rate	Slow sedimentation rate
Suspension clears quickly	Suspension remains cloudy for a prolonged period of time
Entrapment of liquid within sediment	Liquid entrapment in the sediment is prevented
Easy to redisperse sediment	Difficult to redisperse sediment

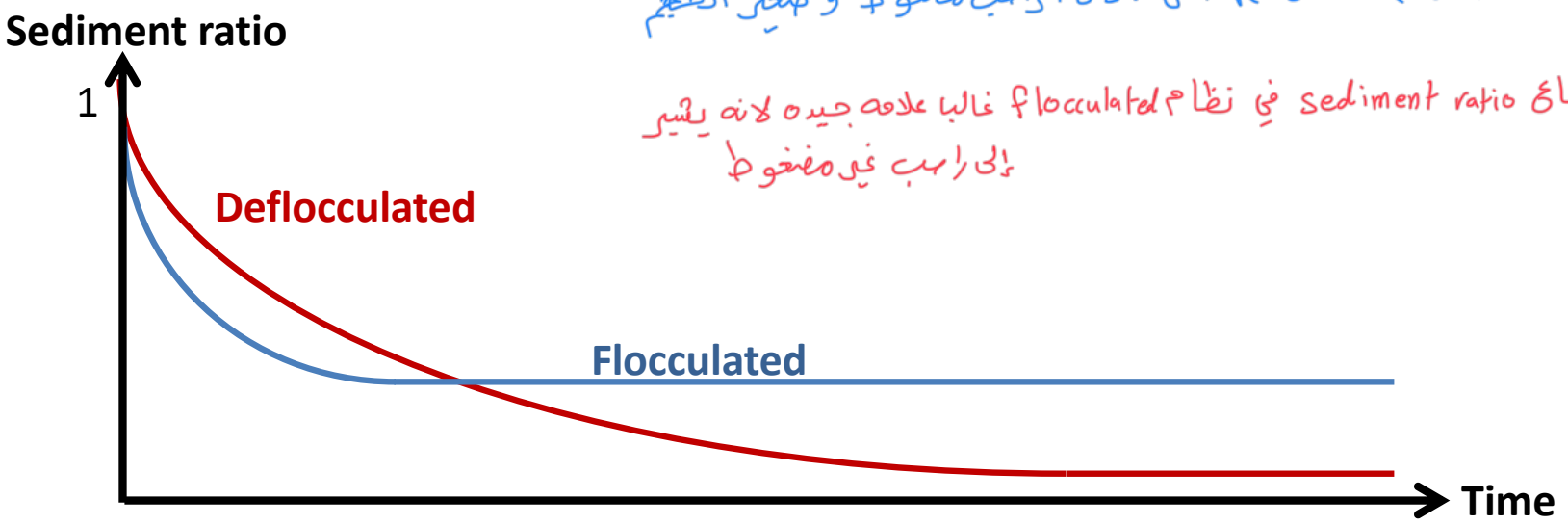
Flocculated *vs.* deflocculated

$$R = \frac{\text{Height of sedimented layer (h)}}{\text{Initial height of suspension } (h_0)}$$

* flocculated ⇐ تكون قيمه R النهائيه اعلى ، لان الراسب حجمه أكبر والكثر رخاوه

* deflocculated ⇐ تكون R أقل ، لان الراسب مضغوط و صغير الحجم

- ارتفاع sediment ratio في نظام flocculated غالبا علامه جيده لانه يشير الى راسب غير مضغوط



Viscosity enhancing agents

- Remember:

$$V = \frac{2a^2 g(\sigma - \rho)}{9\eta}$$

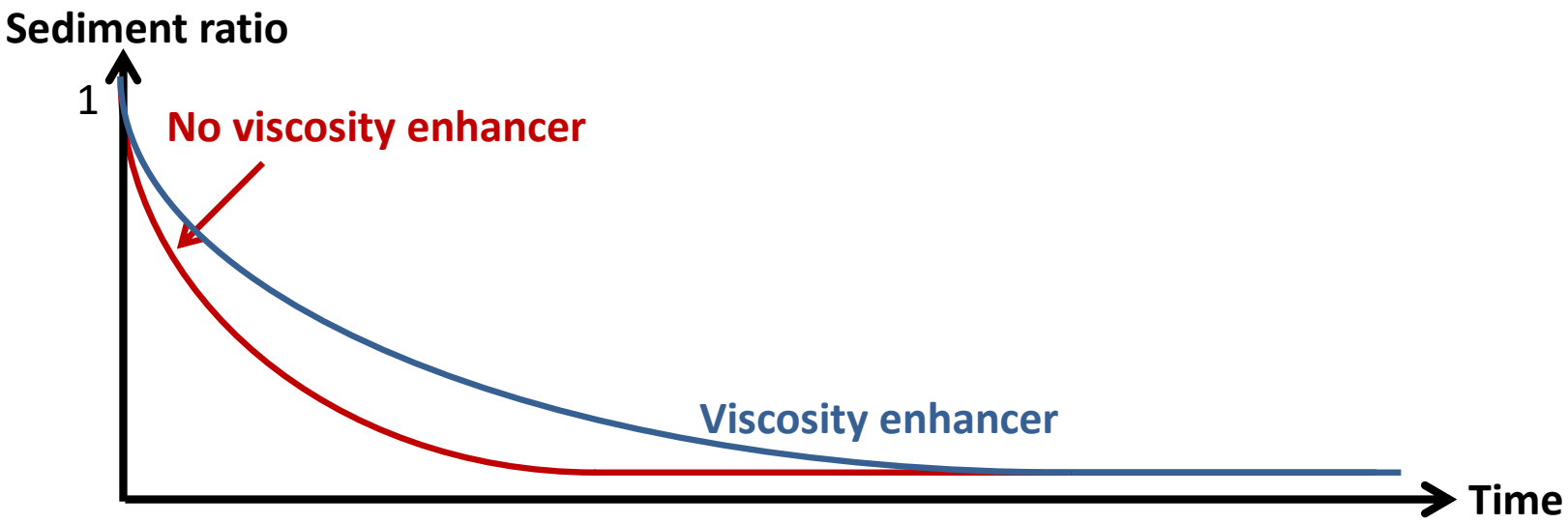
- If we increase viscosity (η) of the liquid phase, the rate of sedimentation is **reduced**.

- For this reason, materials may be added to a suspension with the aim of increasing viscosity.

* رفع اللزوجة لا يمنع الترسب تمامًا ، لكنه يجعله أبطأ

Viscosity enhancing agents

$$R = \frac{\text{Height of sedimented layer (h)}}{\text{Initial height of suspension } (h_0)}$$



Viscosity enhancing agents

Examples of viscosity enhancing agents include:

- **Polysaccharides** (acacia, alginates, tragacanth, starch, xanthum gum).
- **Celluloses** (methylcellulose, hydroxyethylcellulose, sodium carboxymethylcellulose).
- **Hydrated silicates** (bentonite, magnesium aluminium silicate).
- **Carbomers** and **silicon dioxide** (Aerosil).

Viscosity enhancing agents

- We need to take care when using these – if a suspension is very viscous, then it may have poor pourability.

- Also, although sedimentation is **delayed**, it is not **stopped**... so we need to consider using flocculating agents too in some cases.

Caking

- Caking **cannot be eliminated** by reduction in particle size, or by increasing the viscosity of the continuous phase;
- These **delay** sedimentation and caking, but do not prevent it;
- To prevent caking, we need to consider **flocculating agents**.

* caking لا يمكن منعه فقط بواسطة :- تصغير الجسيمات أو زيادة اللزوجة

لماذا ؟ لان هذه الوسائل فقط تؤخر الترسب والتكتل ، لكنها لا تمنع حدوثه

الحل الحقيقي :- استخدام flocculating agents

Part 3: How to avoid caking?

Flocculation

- In Pharmacy, flocculation is preferred , whereas caking is not.
- Why?

* المطلوب ليس منع الترسب بالكامل ، لان ذلك شبه مستحيل ، بل :-
1- السماح بترسب مناسب
2- تكون راسب على شكل مفكك
3- سهل إعاده بعثرته

- To achieve flocculation, we often need to add additional components to a suspension.

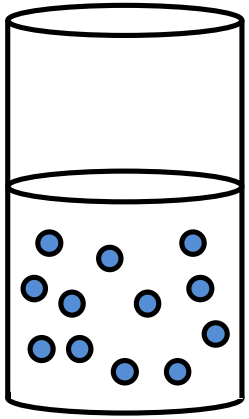
Flocculating agents

- **Flocculating agents** act to **minimise the extent of caking** in a suspension.

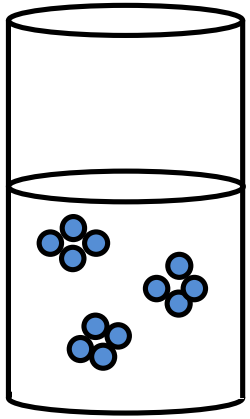
caking تقليل حدوث

- Ideally, we want a **partially deflocculated** system. →

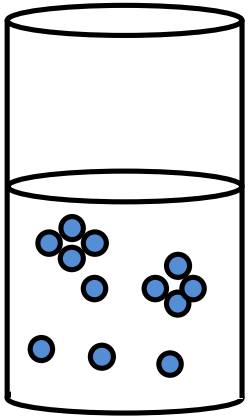
بمعنى انه :-
1- ليس منفصلا تماما
2- ليس متلبدا بشده مبالغ فيها (متماسك)
3. توازن مناسب بين الثبات وسهوله إعاده التبعثر



Too deflocculated



Too flocculated



Partially deflocculated: just right!

Flocculating agents

Examples:

- Electrolytes (sodium acetate, phosphate, citrate).
- Surfactants (ionic or non-ionic).
- Polymers (starch, alginates, cellulose derivatives).
- Carbomers or silicates.

Part 4: How to avoid caking II?

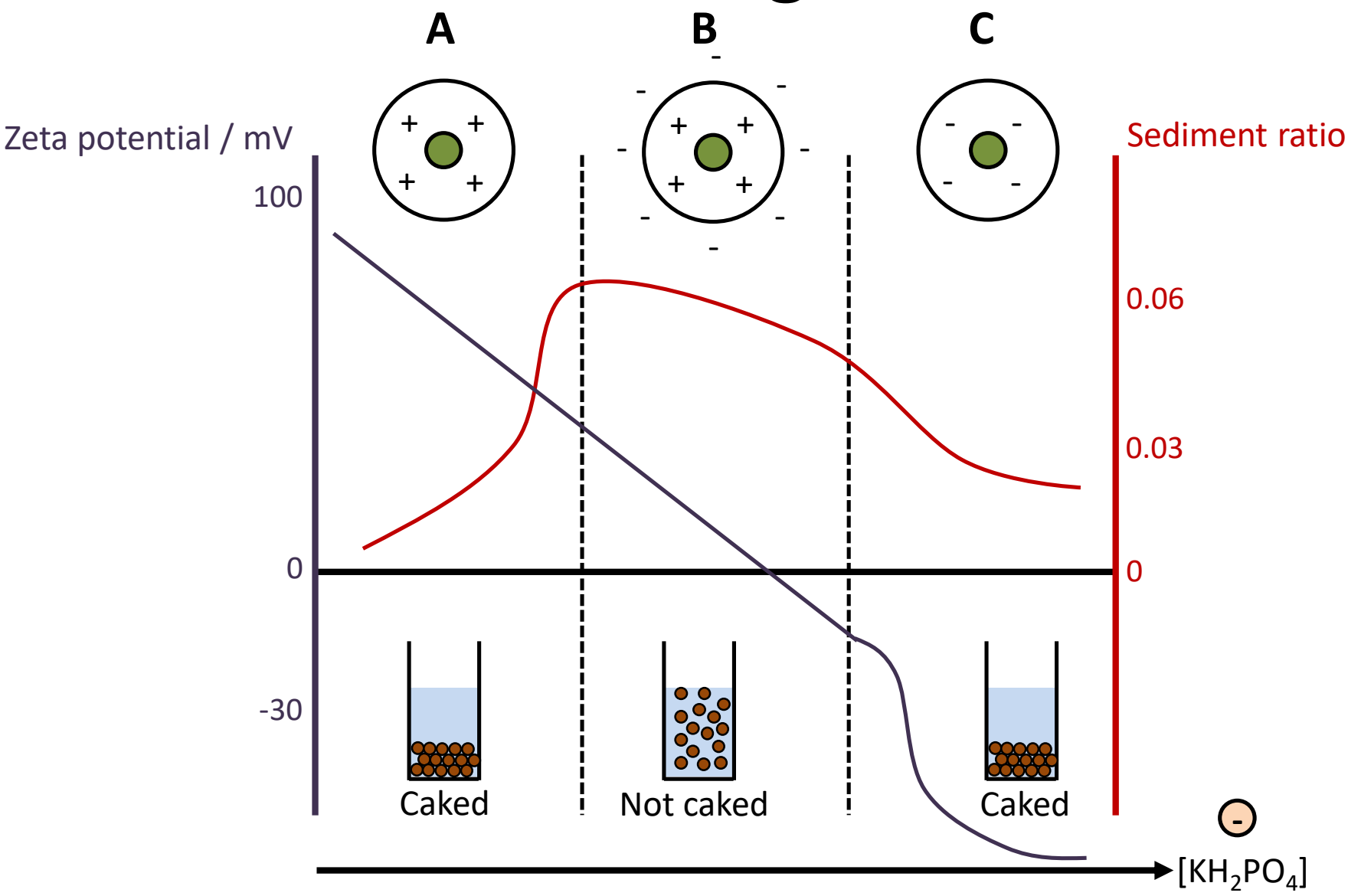
A :- تركيز الالكتروليت منخفض ← جسيمات شحنه (+) عاليه ← جسيمات تتنافر ← تبقى منفصله ← تهبط ببطء ← تصل للقاع ← ترص باحكام تكون راسب صلب

B :- زاد الالكتروليت ← شحنه سطحيه قلت ← تنافر اقل بين الجسيمات ← تكتلات رخويه ← يترسب اسرع قليلاً ← يكون الراسب متفكك سهل اعاده التبعثر (عشالوح)

C :- تركيز الالكتروليت عالي جداً ← الشحنه انعكست أو اقتربت من الصفر لم سالبه ← اختفى التنافر ← جسيمات تندمج بقوه شديده ← تتراص بقوه

الشرح فوق

Caking



Caking

- Bismuth subnitrate particles have **positively charged surfaces**.
- Initially therefore the suspension is **deflocculated**.
- Adding KH_2PO_4 causes a reduction in zeta potential of the particles, because the particles adsorb phosphate anions.

تحتوي ايونات الفوسفات السالبة

- As more KH_2PO_4 is added, the zeta potential reduces to zero and then turns negative.
- To obtain a flocculated non-caking suspension, need to **control** the zeta potential by adding the **correct amount of electrolyte**.

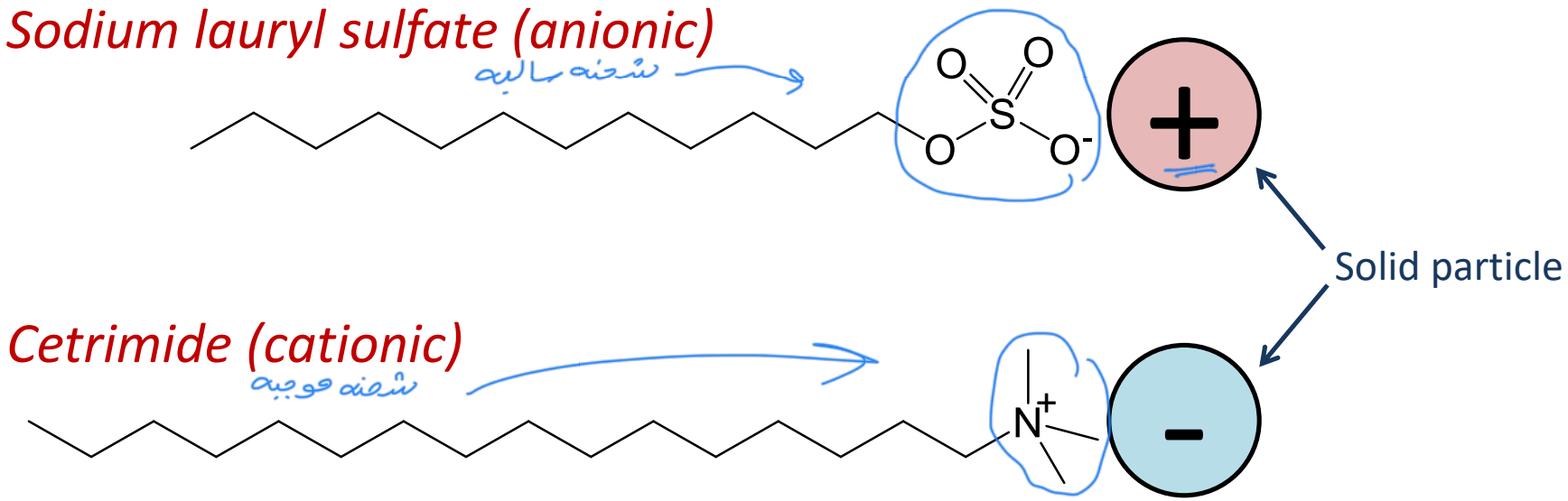
Flocculation وسيلة اساسية للسيطرة على Zeta Potential في التحكم #

مكون من جزئين :-
1- جزء محب للماء (Head) ← يحمل شحنه
2- ذيل دهني (Tail) ← سلسله كربونيه طويله

Surfactants

1- تعادل شحنه سطح الجسيم
2- تقلل التنافر بين الجسيمات
3- تساعد على حدوث flocculation

- Adding a surfactant can neutralise the surface charge of a particle, and hence reduce repulsion between them.



Polymers

- **Starch or Alginate.**

- Chemical groups in the polymer interact with the surfaces of the particles.

- The free end of the polymer attaches to another particle. This gives **interparticle bridging**, leading to **flocculation**.

- If there are no other particles to interact with, the free end of the polymer coats the particle. This leads to restabilisation and a **deflocculated system**;

* اذا لم يجد البوليمر جسيمًا اخر ليرتبط فيه ، فقد يغلف الجسيم نفسه .

- So we need to **carefully control** the polymer concentration.

Rheology of suspensions

Ideally, a suspension will have the properties of:

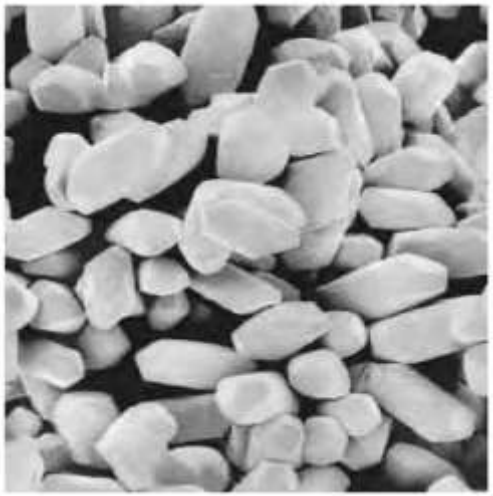
1. **Redispersibility** (dispersed on gentle shaking);
2. **Homogenity** (constant particle sizes);
3. **Pourability** (easy to pour).

- A flocculated system's structure breaks down on shaking, and reforms on standing (*i.e.* the viscosity of the system changes).

The particle shape can also affect caking and product stability:

- It has been shown that symmetrical barrel-shaped particles of calcium carbonate produced more stable suspensions than did asymmetrical needle-shaped particles of the same agent.

- The needle-shaped particles formed a firm sediment cake on standing that could not be redistributed, whereas the barrel-shaped particles did not cake upon standing



Examples of suspensions

Antacid oral suspensions

Antibacterial oral suspension

Rectal suspensions

Sustained release suspensions

* معظم مضادات الحموضه تكون مواد غير ذائبه في الماء وتعمل داخل القناه الهضميه لمعادله الحمض او تهدئه بطانه الجهاز الهضمي

Antacid Oral Suspensions

- Most antacid preparations are composed of water-insoluble materials that act within the gastrointestinal tract to counteract the acid and/or soothe the irritated or inflamed linings of the gastrointestinal tract.

- A few water-soluble agents are employed, including **sodium bicarbonate**, but for the most part, **water-insoluble salts of aluminum, calcium, and magnesium are employed**; these include aluminum hydroxide, aluminum phosphate, dihydroxyaluminum aminoacetate, calcium carbonate, calcium phosphate, magaldrate, magnesium carbonate, magnesium oxide, and magnesium hydroxide.


Rugby
NDC 0536-0025-83
Almacone
Alumina, Magnesia, and Simethicone
Oral Suspension USP
ANTACID
ANTIGAS
VERY LOW SODIUM
SATISFACTION GUARANTEED
Rugby
OR YOUR MONEY BACK
12 fl oz
(355 mL)
COMPARE TO ACTIVE INGREDIENTS IN MYLANTA®
Alcohol: Less than 0.5%
219-06112-2 R0211
Drug Facts
Active ingredients (in each 5 mL teaspoonful)
Purposes
Aluminum hydroxide 200 mg (equivalent to dried gel, USP) ____ Antacid
Magnesium hydroxide 200 mg ____ Antacid
Simethicone 20 mg ____ Antigas
Uses relieves • heartburn • sour stomach • acid indigestion • the symptoms of gas
Warnings
Ask a doctor before use if you have • kidney disease • a magnesium-restricted diet
Ask a doctor or pharmacist before use if you are taking a prescription drug. Antacids may interact with certain prescription drugs.
Stop use and ask a doctor if symptoms last more than 2 weeks
Keep out of reach of children.
Directions • shake well before use • adults and children 12 years and older: take 2 to 4 teaspoonfuls between meals, at bedtime, or as directed by a doctor • do not take more than 24 teaspoonfuls in 24 hours or use the maximum dosage for more than 2 weeks • children under 12 years: ask a doctor
Other information • each 5 mL teaspoonful contains: magnesium 85 mg, sodium 1 mg • store at room temperature • protect from freezing • keep tightly closed • TAMPER-EVIDENT: Do not use if breakaway band on bottle cap is missing or broken.
Inactive ingredients benzyl alcohol, butylparaben, carboxymethylcellulose sodium, flavor (contains alcohol), hypromellose, microcrystalline cellulose, propylparaben, purified water, saccharin sodium, sorbitol solution
Questions or comments?
Call 1-800-645-2158, 9 am - 5 pm E.T, Monday-Friday
• Rugby Laboratories, Inc. is not affiliated with the owner of the registered trademark MYLANTA®.
Almacone® is distributed by Rugby Laboratories, Inc.
Rugby
Duluth, GA 30097
2-919-06112-4 R0211
M 3 0536-0025-83 1

Example

- An example formula for an oral suspension follows. The suspensoid is the antacid aluminum hydroxide, the preservatives are methylparaben and propylparaben, and syrup and sorbitol solution provide the viscosity and sweetness.

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

Antibiotic Oral Suspensions

* بعض المضادات الحيوية تكون فيزجاتيه اذا بقيت فتر طويله في وسط مائي لذلك تكون على شكل

- Dry powder for 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.

- Many antibiotic materials are **unstable** when maintained in solution for an appreciable length of time

* تكون بودرم جافه ، ويضاف لها ماء وقت الاستعمال ، لانه كثير من المضادات الحيوية ١- تتفكك في الماء
2 - تفقد فعاليتها مع الزمن

Rectal suspension

- Colocort is a hydrocortisone rectal suspension indicated as adjunctive therapy in the treatment of ulcerative colitis and is packaged in a convenient disposable single-dose enema designed for self-administration.

- It contains hydrocortisone in an aqueous suspension that contain carbomer, polysorbate 80, purified water, sodium hydroxide, and methylparaben.

Packaging and Storage of Suspensions:

جزء العملي حفظ بعض

1) Should be packaged in wide mouth tight containers having adequate air space above the liquid to permit thorough mixing by shaking and an opening large enough to pour a viscous liquid easily.
2) Should be stored at room temp or refrigerated protected from: freezing, excessive heat & light.
3) Stored in room temperature if it is dry powder (25 ^{0}C). It should be stored in the refrigerator after opening or reconstitution (freezing should be avoided to prevent aggregation).
4) Label: "Shake Well Before Use" to ensure uniform distribution of solid particles and thereby uniform and proper dosage and label to specify whether the medications are for “external” or “internal use”

Preparation of suspensions

Dispersion methods

- In these methods the vehicle is added to the already prepared particles.
- The vehicle must be formulated that it easily wet the particles
- The use of surfactant is desired to ensure uniform wetting of the powder.
- Once the powder is wetted, the dispersion medium (to which have been added all the formulations soluble components such as preservatives, colors and flavors) is added in portions to the powder and the mixture is thoroughly blended.
- The final product is then passed through a colloid mill or other blender to ensure uniformity of mixing.

Preparation of suspensions

Precipitation methods

- Precipitation methods include:

1) Solvent-change method

- In this method water-insoluble drugs can be precipitated by dissolving them in water-miscible organic solvents (ethanol, methanol, propylene glycol, PEGs) and then adding distilled water to the solution.
- Particle size can be controlled by controlling rate of water addition, temperature, agitation,…

2) Precipitation by changing the pH of the medium

- This is applicable to drugs in which solubility is changed by pH value.
- Insulin suspensions may be prepared by this method

Extemporaneous compounding of suspensions

- In some cases, patients are not able to swallow solid medicines such as infants and elderly.
- The pharmacist may have to use a solid dosage form and compound a liquid product.
- A difficulty that confronts that pharmacist is the lack of ready information on stability of drug in liquid vehicle.
- To overcome this information gap, the pharmacist
  - can attempt to contact the manufactruer.of the solid dosage form to attain stability information.
  - Some manufacturers provide in the insert leaflet a formula for preparation of a liquid dosage form.
  - A number of extemoraneous formulas are available in professional literature

Extemporaneous compounding of suspensions

- In formation of an extemporaneous preparation:
  1. The contents of capsules are emptied in a mortar or the tablets are crushed in a mortar with a pestle.
  2. The selected vehicle is slowly added to and mixed with the powder to create a paste and then diluted to the desired volume.

Observing formulations for evidence of instability:

- USP/NF Chapter <1191>

1. Major sign of suspension instability is a "caked" solid dosage that cannot be re-suspended by a reasonable amount of shaking→ no longer flocculated
2. Presence of relatively large particles → excessive crystal growth
3. Microbial contamination (discoloration, turbidity, or gas formation)

Summary

- Pharmaceutical suspensions are a powerful type of formulation which can be applied against a range of diseases, overcoming a number of challenges associated with solutions.
- A “good” suspension should contain small and evenly-sized particles of drug, dispersed a liquid carrier. The suspension must be redispersible upon shaking.
- All suspensions will sediment over time. The rate at which they do so can be controlled through e.g. changing the viscosity of the liquid medium.
- But, ultimately for a deflocculated system the formation of a dense, permanently bound, “cake” will result – this needs to be avoided during the shelf life of the medicine.
- The only way to prevent caking is through using flocculating agents (usually to modulate the V_R forces).

هذا الملف يشرح أن Suspension هو مستحضر دوائي يحتوي على جسيمات صلبة غير ذائبة موزعة داخل سائل. هذا النوع مهم عندما يكون الدواء غير ذائب، أو سيئ الطعم، أو أكثر ثباتًا في الحالة الصلبة. لكن المشكلة الأساسية فيه هي الترسب مع الزمن. لذلك يجب أن يكون المعلق الجيد:

- سهل الرج وإعادة التبعثر
- متجانس
- غير خشن
- سهل السكب

ثم يوضح الملف أن الترسب تحكمه Stokes' law، وأننا نستطيع إبطاءه عبر:

- تصغير الجسيمات
- زيادة لزوجة الوسط

لكن هذه الإجراءات لا تمنع المشكلة الأخطر وهي Caking.
ولذلك نلجأ إلى Flocculation، أي جعل الجسيمات تتجمع في flocs رخوة تترسب بسرعة لكن يسهل إعادة تبعثرها.
ومن هنا تأتي أهمية:

- wetting agents
- viscosity enhancers
- flocculating agents