لجان الدفعات

DISPENSING

MORPHINE ACADEMY

MORPHINE ACADEMY

Suspensions

Saja Hamed, Ph.D

Dispersed system:

- **Dispersed system**: contain an un-dissolved or immiscible drug distributed throughout a vehicle
- Dispersed particles and dispersed medium
- A dispersed system could be a colloid, gel, suspension, emulsion, lotion, cream, ointment, suppository, troche, or medication stick
- Important factors that determine which type:

- Size of the dispersed particles: e.g. colloids and gels have the smallest size particles

Dispersed system:

- **The particles of the dispersed phase vary widely in size, from large particles visible to the naked eye down to particles of colloidal dimension, falling between 1.0 nm and 0.5 µm:**

1. Dispersions containing coarse particles, usually 10 to 50 µm, are referred to as *coarse dispersions; they include the suspensions* and *emulsions.*
2. Dispersions containing particles of smaller size are termed *fine dispersions (0.5 to* 10 µm),
3. Dispersion containing particles in the colloidal range (falling between 1.0 nm and 0.5 µm), are termed *colloidal dispersions such as Magmas and gels*.

Dispersed system:

- The particles of the dispersed phase are either:

- solid materials that are insoluble in the dispersion medium as in the case of suspension. ممكن مادة صلبة في مادة سائلة طبعًا ما بذوبوا في بعض

- Or, in the case of ***emulsions***, the dispersed phase is a liquid that is neither soluble nor miscible with the liquid of the dispersing phase. وممكن مادة سائلة في مادة سائلة ثانية

- Or, In the case of an aerosol, the dispersed phase may be small air bubbles throughout a solution or an emulsion. بخاخات وممكن غاز في مادة سائلة

- Or, droplets of a liquid in air. وممكن نقاط من السائل في الهواء زي الندى على أوراق الشجر

Dispersed systems:

Dispersing medium	Dispersed phase		
	Solid	Liquid	Gas
Liquid (L)	Colloidal system (sol), Suspension S/L	Emulsion L/L	Foam G/L
Solid (S)	سبائك Alloys, minerals S/S	Solid emulsion, gel L/S	Porous bodies, solid foam G/S
Gas (G)	Smoke (aerosols), dust (S/G)	ضباب Fog, mist (aerosol) L/G	-

COLLOIDS

Examples of colloidal systems from daily life


Foams


Milk


Fog, smoke


Detergents


Aerogel


Blood


Paints


Cosmetics

Colloids

Colloid-- A mixture of two phases of matter

emulsions	*aerosols*
smoke	*fog*
foams	*gels*
milk	*clouds*

Gel & Foam

Clouds

Milk

Dispersed systems: Suspensions

Saja Hamed, Ph.D

Suspensions:

- Suspensions are dispersions of a finely divided insoluble solid that is evenly dispersed (suspended) in a liquid (the dispersing medium)
- A suspension is classified according to particle size to:

1. **Colloidal suspension:** Suspension containing particles between 1 nm to 0.5 µm.
2. **Coarse suspension:** Suspension containing particles between 1 to 100 µm,.

Most of the pharmaceutical suspensions are coarse suspension.

Suspensions

Usage:

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

When they are used?

- When the active drug is not soluble in a solvent
- When the active drug is not stable in a solution. In this instance, the suspension ensures chemical stability while permitting liquid therapy.

Advantages of suspensions

1. An ideal dosage form for insoluble drugs for patients who have difficulty swallowing tablets or capsules (i.e. children, elderly). the liquid form is preferred to the solid form of the same drug because of the ease of swallowing liquids and the flexibility in administration of a range of doses.
2. Mask the undesirable tastes of drugs: The disadvantage of a disagreeable taste of certain drugs in solution form is overcome when the drug is administered as un-dissolved particles of an oral suspension. In fact, chemical forms of certain poor-tasting drugs have been specifically developed for their insolubility in a desired vehicle for the sole purpose of preparing a **palatable** liquid dosage.
3. Drugs are chemically more stable compared to solution
4. Oral suspensions can be given for both local or systemic therapeutic effects

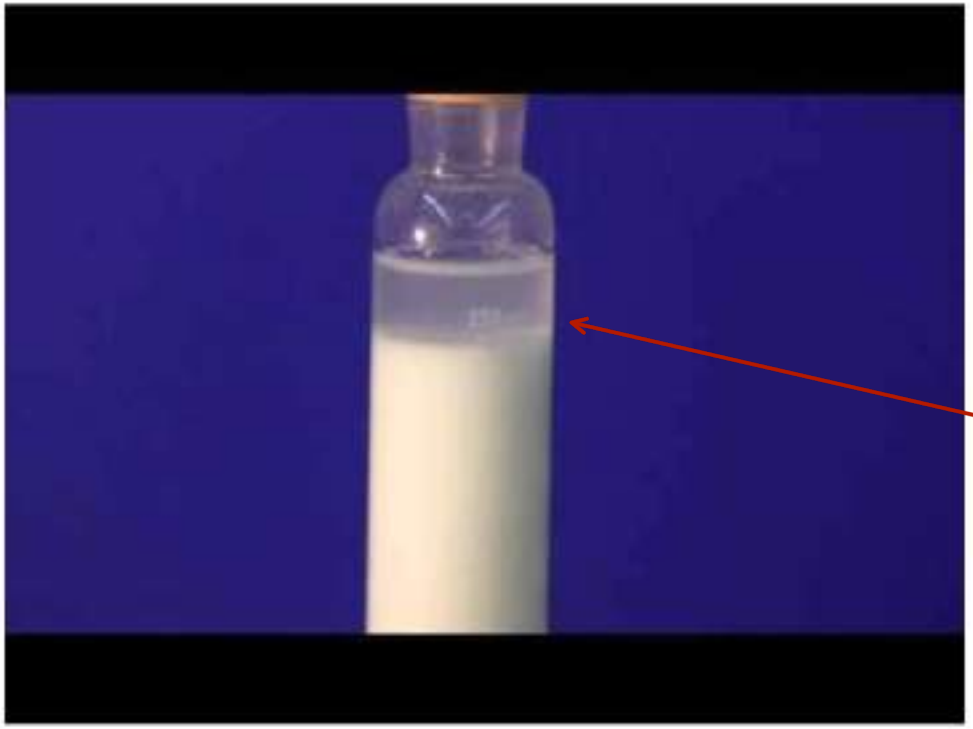
Desirable properties الخصائص المرغوب فيها

1. A properly prepared pharmaceutical suspension should settle slowly and should be readily redispersed upon gentle shaking of the container أن تترسّب ببطء، وأن يمكن إعادة توزيعها بسهولة عند هز العبوة برفق.
2. Of correct viscosity to pour freely from bottles and or to flow through an administration needle أن تكون لزوجتها مناسبة بحيث يمكن سكبها بسهولة من الزجاجات أو مرورها عبر إبرة الإعطاء.
3. The particle size of the suspension should remain fairly constant throughout long periods of undisturbed standing. لازم يضل حجم الجزيئات ثابت طول المدة
4. In dermatology, the suspension must be sufficiently fluid to spread over the skin with no resistance and adhere to skin after application في المستحضرات الجلدية تكون سائلة نوعًا ما وتنفرد بسهولة على الجلد وما تلتصق
5. In ophthalmic suspension, the particle size must be kept to a minimum to prevent irritation of the eye. بحكيلك صغر حجم الجزيئات في منتجات العين عشان ما يصير تهيج

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

Sedimentation (settling properties):



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

How to control the settling properties?

- The rate of sedimentation of a suspended phase depends on several factors which may be controlled by pharmaceutical manipulation.
- Assuming that all dispersed particles are of uniform shape and size and that the particles are sufficiently far apart so that the movement of one does not affect the neighboring particles, the rate of sedimentation can be estimated by Stoke's equation:

$$V = \frac{d^2 (\rho_1 - \rho_2) g}{18 \eta_o}$$

- where **V** is the sedimentation rate (cm/sec), **d** the diameter of the suspended particles (cm), $\mathbf{p_1}$ its density and $\mathbf{p_2}$ is the density of the medium (g/cm^3), **g** is the acceleration of gravity (980.7 cm/sec^2) and $\mathbf{n_o}$ is the viscosity of the external phase in poises (g/cm sec).

حسب قانون (Stok's equation)

كصيدلاني بقدر اتحكم بالمادة عشان أقلل sedimentation rate بقلل (d) الي هي حجم المادة المعلقة عشان التناسب طردي

هسا ممكن نتحكم بكثافة المادة ولكنها صعبة جدًا

بننتقل على اللزوجة (n) والي هي ممكن انزيدها عشان نقلل sedimentation rate حسب التناسب العكسية

How to control the settling properties?

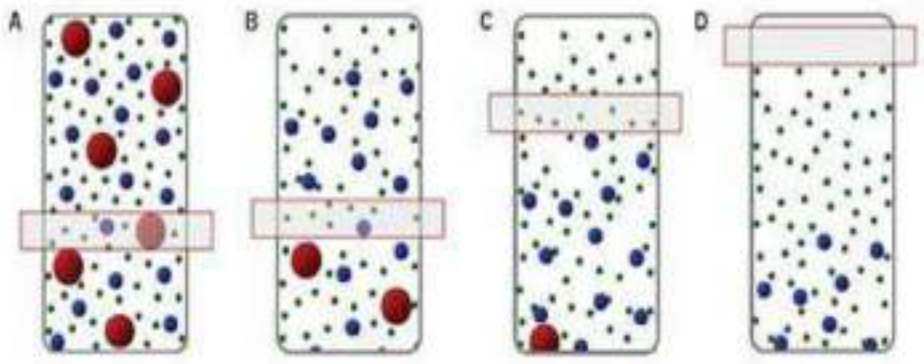
- Stokes' equation gives an approximation of the settling rate and an appreciation of the variables governing the sedimentation process

- For example, by reducing the particle size or by increasing the viscosity and density of the external phase, the rate of sedimentation can be retarded.

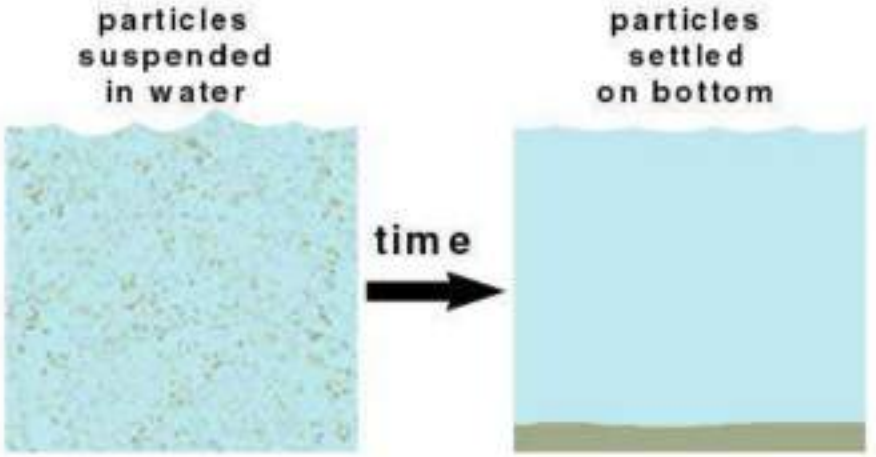
How to control the settling properties?

1. **By reducing the particle size of the dispersed phase produces a slower *rate of sedimentation of the particles.* The velocity of fall of a suspended particle is greater for larger particles than it is for smaller particles.**

$$V = \frac{d^2(\rho_1 - \rho_2)g}{18\,\eta_o}$$



- 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 that are larger and less suspendable.



احنا صحيح بدنا نصغر الحجم بس مش كتير عشان ما يصير هيك يتجمع بالقاع ويعمل زي طبقة كيك صعبة تنشال

How to control the settling properties?

2. ***Also*, the greater the density of the particles, the greater the *rate of sedimentation* , provided the density of the vehicle is not altered.**

$$V = \frac{d^2 (\rho_1 - \rho_2) g}{18 \eta_o}$$

- Because aqueous vehicles are used in pharmaceutical oral suspensions, the density of the particles is generally greater than that of the vehicle, which is 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.

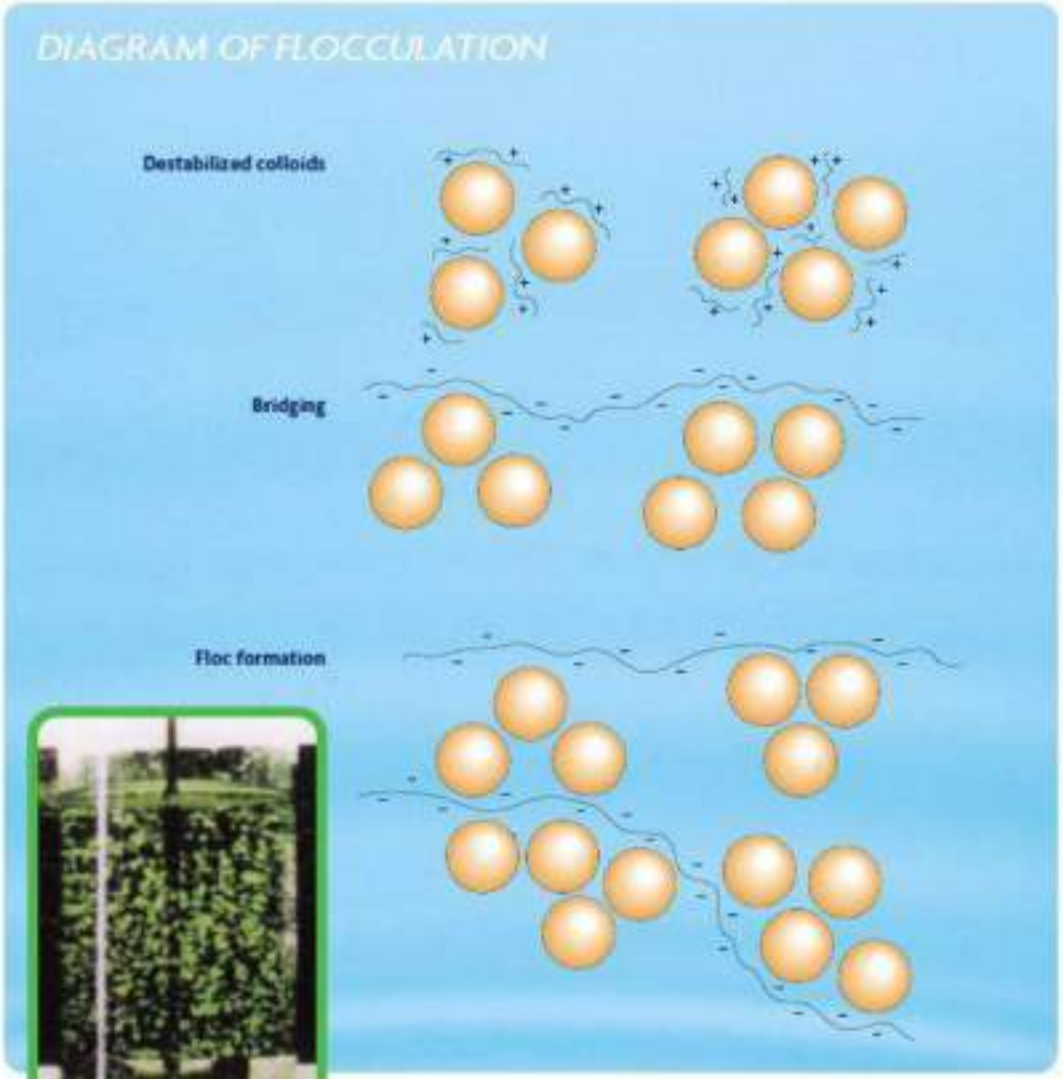
How to control the settling properties?
3. Flocculating agents

- flocculation refers to process which leads to aggregates that are loose or open

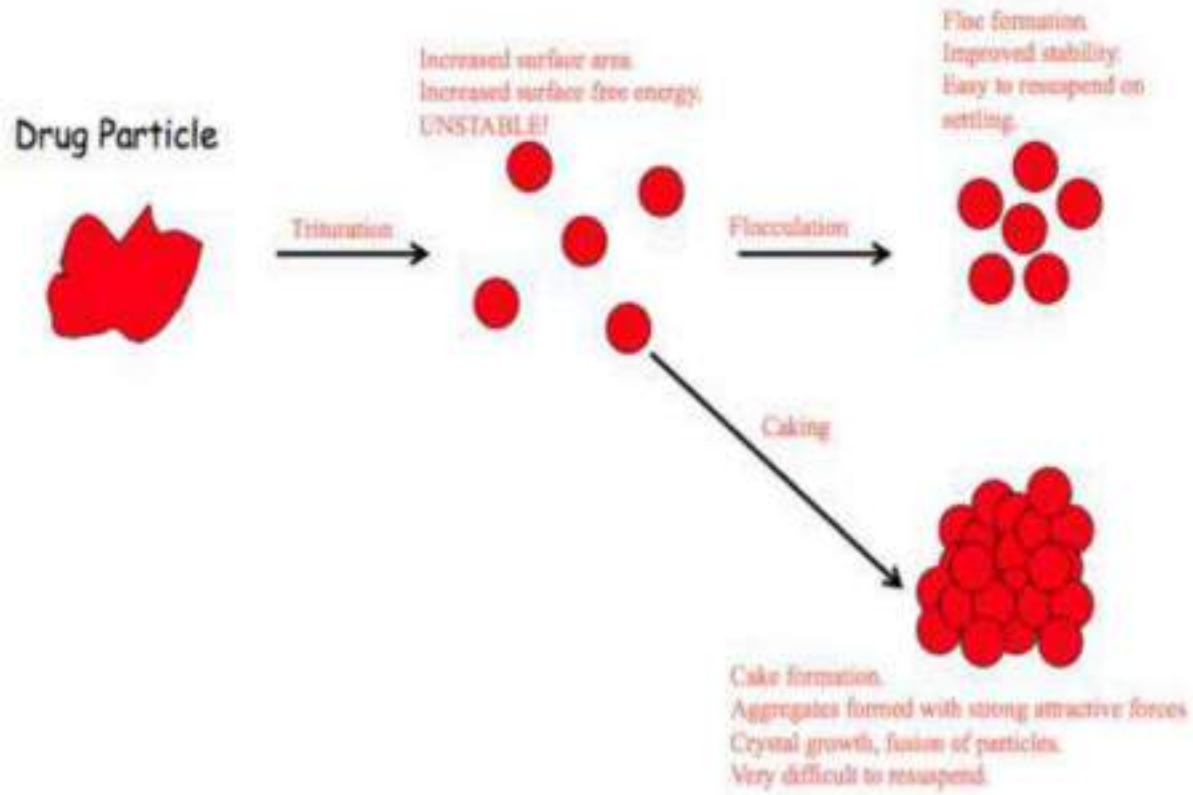
تجمعات

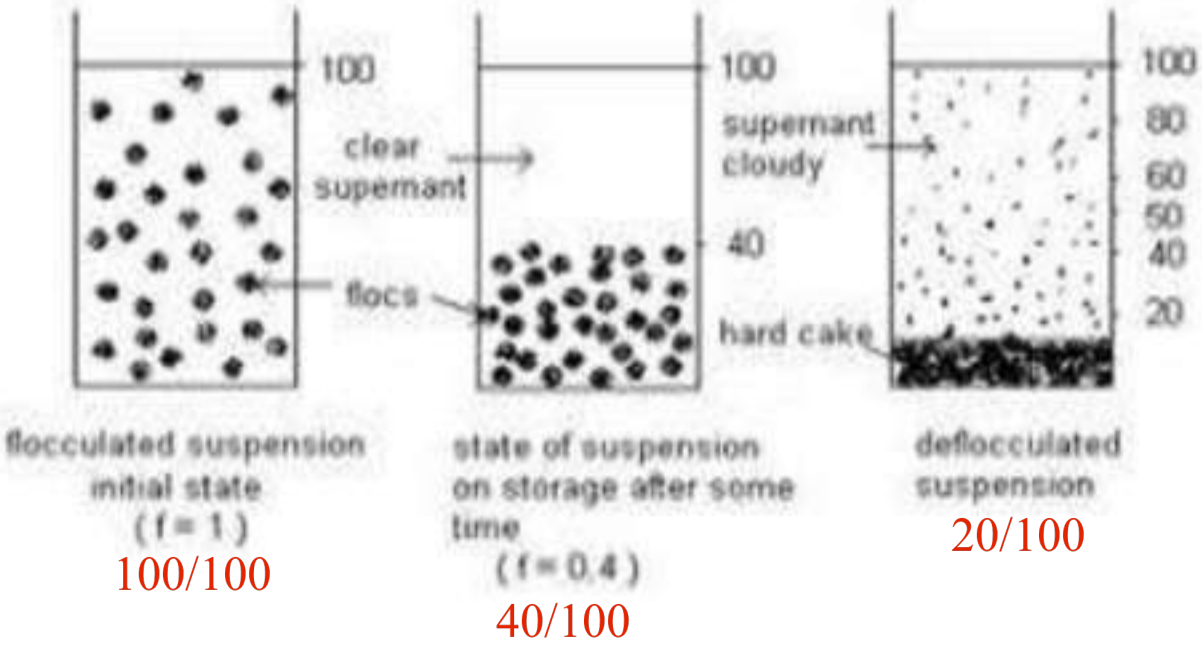
يعني بتكون مفتوحة والسائل بكون بيناتهم

- Flocculating agents are electrolytes that carry an electrical charge opposite from that of the net charge on the suspended particles
- Electrolytes act as flocculating agents, apparently by reducing the electrical barrier between the particles of the suspensoid and forming a bridge so as to link them together.
- The addition of the flocculating agent, at some critical concentration, negates the surface charge on the suspended particles and allows the formation of floccules or clusters.
- Floccules assume the charge of the flocculating agent, they will **not cake** and may be **easily redispersed** by shaking the suspension.



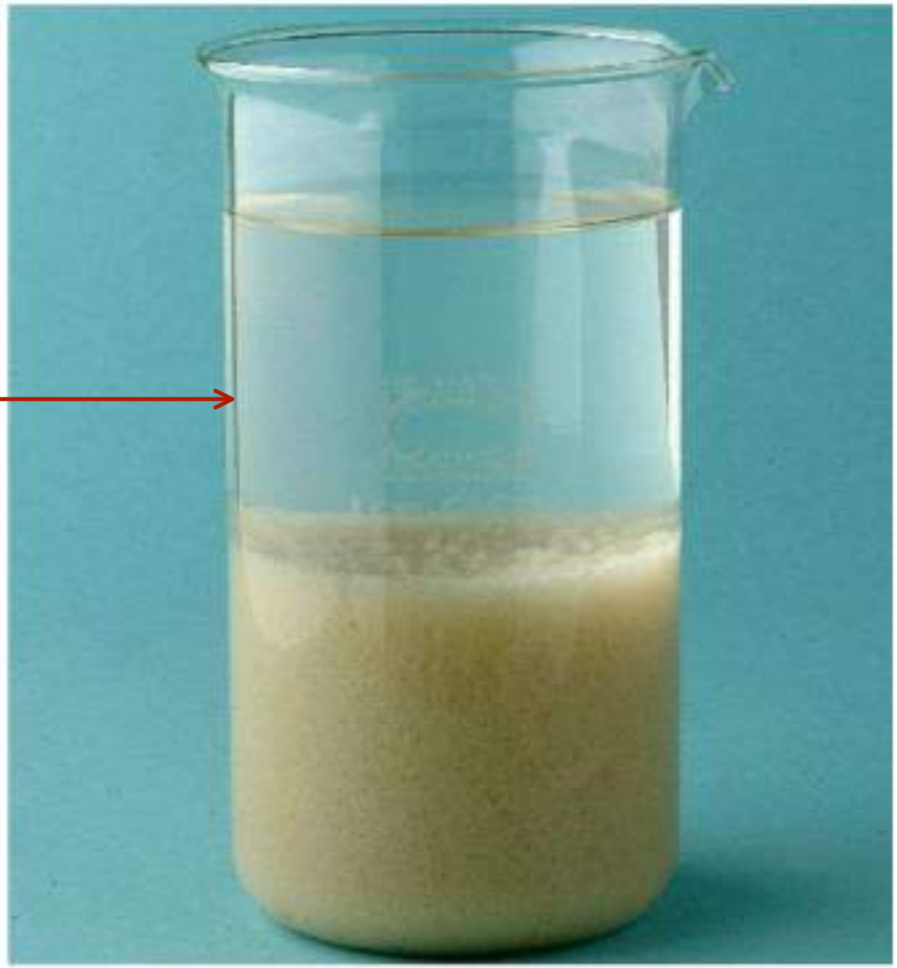
بكل بساطة هي
المادة المعلقة بتكون
مشحونة بشحنة مثلاً
موجبة ووما بتحب
بعض بس انا بدي
اياهم يتجمعوا
فبحطهم بسائل
عكس الشحنة تبعتهم
لانه هذه الطريقة
مناسبة عشان ما
يصير الها كيك


Drug Particle
Trituration
Increased surface area
Increased surface free energy
UNSTABLE!
Flocculation
Floc formation
Improved stability
Easy to resuspend on
settling
Caking
Cake formation
Aggregates formed with strong attractive forces
Crystal growth, fusion of particles
Very difficult to resuspend



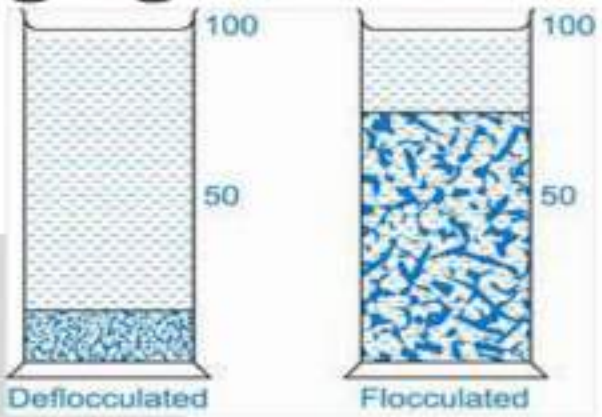
$$f = \frac{\text{حجم السائل لما بترسب}}{\text{حجم السائل وهو موزع بالتساوي}} \quad \text{حجم المادة}$$

كل ما كان السائل
هذا أصفى كل ما
كان الجزيئات أكبر



How to control the settling properties?

3. Flocculating agents



Flocculated

- Particles forms loose aggregates and form a network like structure
- Rate of sedimentation is high
- Sediment is rapidly formed
- Sediment is loosely packed and doesn't form a hard cake
- Sediment is easy to redisperse

يعني بيناتهم فراغات

Non-flocculated (Deflocculated)

- Particles exist as separate entities
- Rate of sedimentation is slow
- Sediment is slowly formed
- Sediment is very closely packed and a hard cake is formed
- Sediment is difficult to redisperse

ملزقة ببعض

How to control settling properties:

4.Viscosity enhancers (suspending agents or thickening agents)

يعني بحكيلك انه لما عملنا flocculation زي كبرنا الجزيئات وهاد زاد من الترسب شو استفدنا بدنا حل ؟!

- flocculation as a means of preventing caking will increase the particle diameter, and thus increase the rate of sedimentation.
- **Now we need some means to reduce this rate of settling, so that the suspension can be accurately dosed before it begins to settle.**

بنرجع للمعادلة وبنحكي في عامل ثاني بنقدر نتحكم فيه وهو اللزوجة

- Practically speaking, the viscosity of the dispersion medium is the only other Stoke's variable affecting sedimentation rate over which the pharmacist can exert any control.
- Suspending or thickening agents are added to suspensions to thicken the suspending medium, thereby reducing the movement (sedimentation) of suspended particles and physically stabilizing the product.
- This is particularly important in flocculated systems in which rapid particle settling is the primary factor leading to physical instability and lack of dosage uniformity in the product.

بسبب الترسيب سريع صار عنا خطأ في الجرعات وعدم استقرار
فشو عملنا زدنا اللزوجة وخلينا اثقل عشان يترسب ابطأ

How to control settling properties:

4. Viscosity enhancers (suspending agents or thickening agents)

- Ideally, the system should (rheologically) be **pseudoplastic**; that is, it should have high viscosity at low shear rates (during storage) and low viscosity at high shear rates (during shaking, pouring, or spreading).

لازم اتكون اللزوجة مناسبة يعني عالية كفاية عشان التخزين وقليلة كفاية عشان لما انرج العلبة

- Thus selecting appropriate viscosity enhancer with desirable rheological properties
- Suspending agents which are pseudoplastic are desirable, since they recover slowly from the deformation that occurs through shearing (i.e. upon shaking, they remain fluid long enough to be poured and spread).

المواد المعلّقة التي تتميز بخاصية اللزوجة الكاذبة (Pseudoplastic)، تكون مرغوبة
لأنها تستعيد لزوجتها ببطء بعد الرج، تبقى سائلة فترة كافية ليتم سكبها.

How to control settling properties:
4. Viscosity enhancers (suspending agents or thickening agents)

- 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 the suspensoid.

- Therefore, if the viscosity of a suspension is increased, it is done so only to a modest extent to avoid these difficulties.

طبعًا لازم انزيد اللزوجة الي حدٍ معقول عشان ما تصير صعبة لما نحطها على الجلد

How to control settling properties:

4. Viscosity enhancers (suspending agents or thickening agents):

- Viscosity enhancers include agents from each of the following categories. Typically, the concentrations used range from 0.5% to 5%, but the needed viscosity will depend on the suspended particle's tendency to settle:

1. Natural hydrocolloids

Acacia, tragacanth, alginic acid, carrageenan, locust bean gum, guar gum, gelatin.

2. Semisynthetic hydrocolloids

Methylcellulose, sodium carboxymethylcellulose

3. Synthetic hydrocolloids

Carbopol®

4. Clays

Bentonite, Veegum®

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

Preparation of suspension: wetting agents

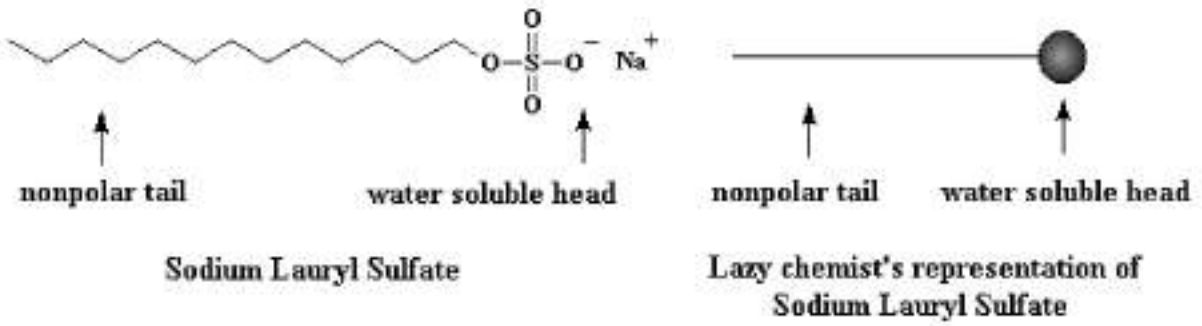
بحكيلك انه في ادوية بتنخلط مع الدواء عادي بس في ادوية ثانية ما بتنخلط وبتطفوا على السطح فبنجيب هذا يخليها تترطب عشان تكون أكثر قابلية للمزج يحل المشكلة

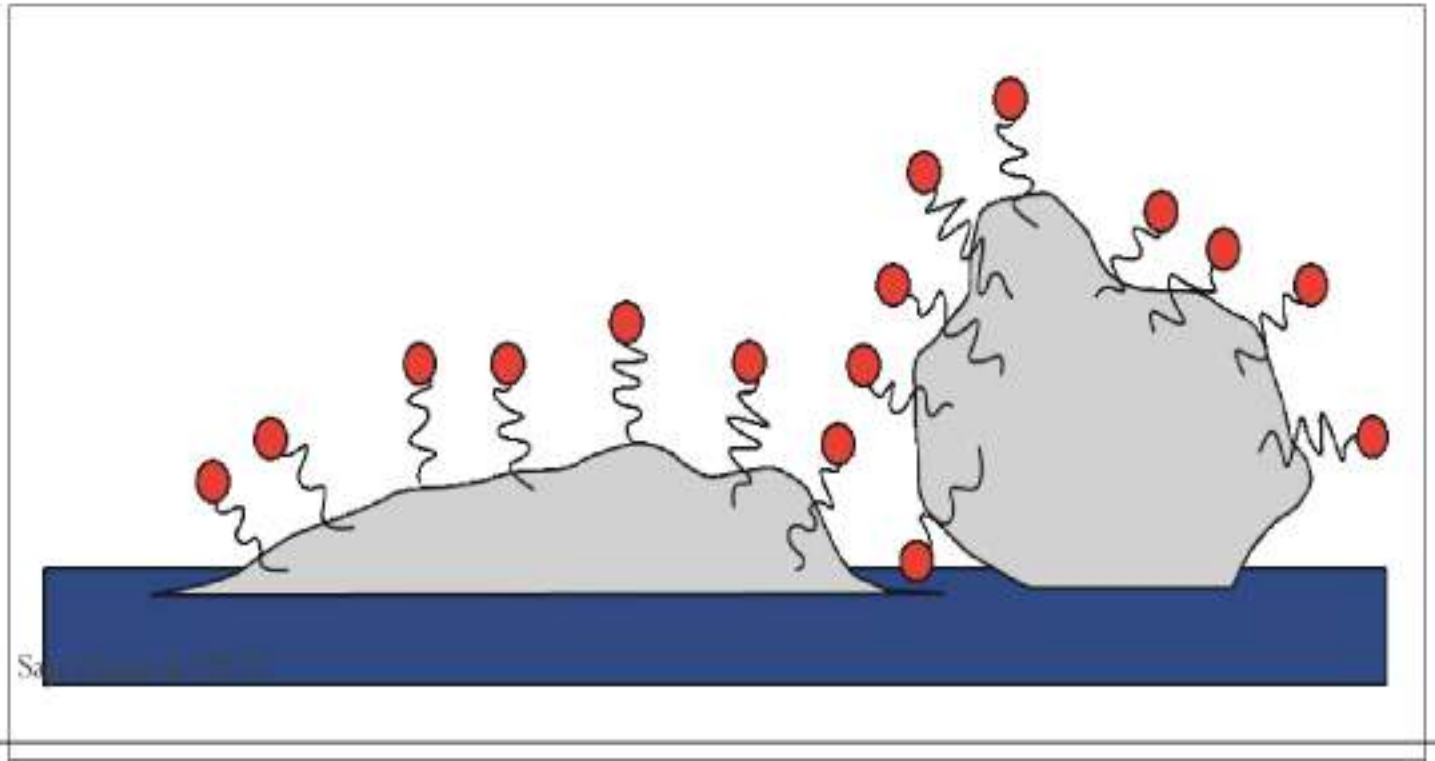
- In some instances, the dispersed phase has an affinity for the vehicle to be employed and is readily wetted by it.
- Other drugs are not penetrated easily by the vehicle and have a tendency to clump together or to float on the vehicle. In this case, the powder must first be wetted to make it more penetrable 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.
- They function by displacing (إزاحة) the air in the crevices of the particles, and by allowing penetration of dispersion medium into the powder.

Preparation of suspension: wetting agents

- Hydrophilic powders (e.g. ZnO, MgCO3, talc) can be wetted with water or other polar liquids (alcohol, glycerin) using a mortar and pestle
- Hydrophobic powders (sulfur, charcoal) are wetted with alcohol or glycerin or mineral oil
- Only minimal amount used
- Sometimes a surfactant is needed to ensure sufficient wetting
- Surface active agents that induce wettability are called wetting agents

Preparation of suspension: wetting agents





Preparation of suspension: wetting agents

- Wetting agents are mixed with a mortar and pestle.

- 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 various components, which are used in suspension formulation, are as follows:

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

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

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

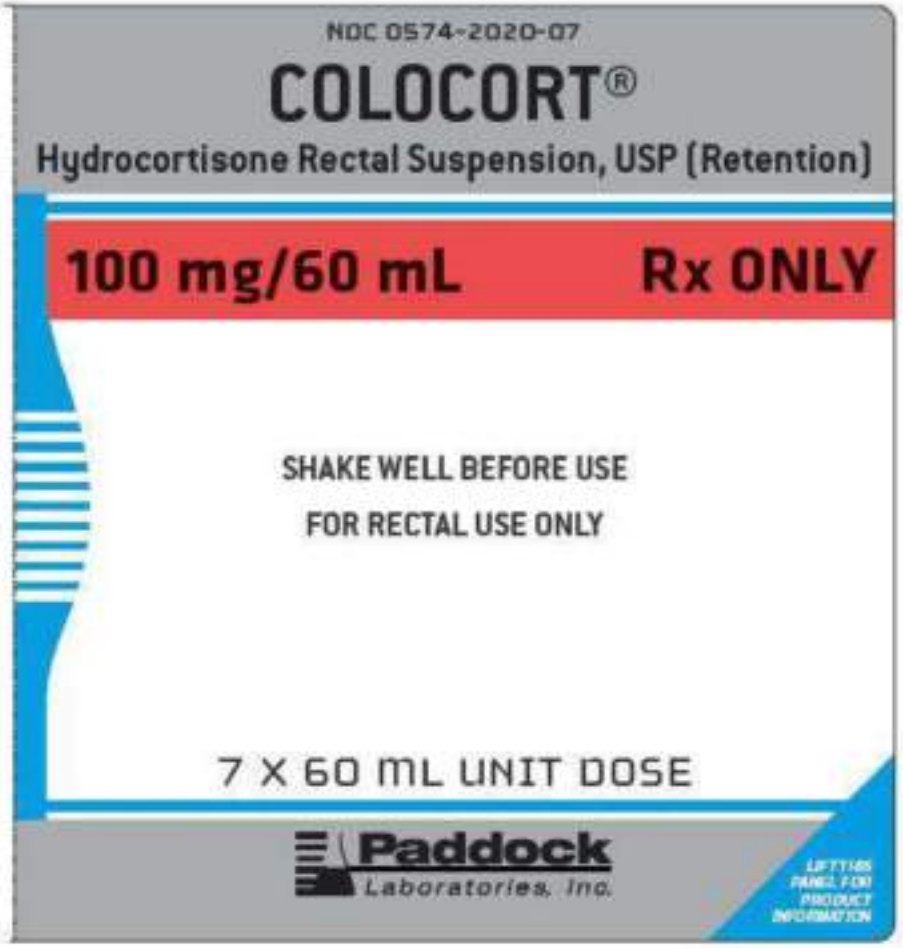
Saja Hamed, Ph.D

Antibiotic Oral Suspensions

- 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

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 solution that contain carbomer, polysorbate 80, purified water, sodium hydroxide, and methylparaben.



Packaging and Storage of Suspensions:

محكمة الغلق

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) 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"
4) 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)

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)