Pharmaceutical Technology for 3rd year students
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Suspensions

Suspensions

✓ Are coarse dispersion containing finely divided insoluble materials suspended in liquid medium **or** available in dry form to be distributed in the liquid when desired.

✓Disperse system (insoluble solid), Dispersion system (aqueous or oily vehicle).

✓***Ready–to–use Suspensions*** or ***Oral Suspension***

whereas ***USP*** designated title of the form "***for Oral Suspension"***

Why suspensions being prepared??

Ex.,

(unstable) *oxytetracycline HCL* ⇒ (stable) calcium salt

A drug that degraded in the presence of water ⇒ can be suspende in non- aqueous vehicles ⇒ *Phenoxy methyl pencillin*/coconut oil and *Tetracycline HCL*/ oil

2- for many patients, 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.

3- the disadvantage of a disagreeable taste drug is overcome when administered as undissolved particles of an oral suspension,

Suspension Classification

1- Based On General Classes

2- Based On Size Of Solid Particles

3- Based On Proportion Of Solid Particles

4- Based On Electro-kinetic Nature Of Solid Particles

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Features Desired in a Pharmaceutical Suspension

a few other features apply more specifically to the pharmaceutical suspension:

1-A properly prepared pharmaceutical suspension should settle slowly and should be readily ***redispersed*** upon gentle shaking of the container.

2-The particle size of the suspensoid should remain fairly constant throughout long periods of undisturbed standing.

3-The suspension should pour readily and evenly from its container (it should not be too viscous to pour (i.e., pour ***freely*** through the orifice of the container).

4-The product should have an agreeable taste, odor and color and must not decompose or support mold growth during storage.

Application of Pharmaceutical Suspensions

1. Suspensions as oral drug delivery systems

Insoluble drugs or **poorly soluble** drugs which required to be given orally in liquid dosage forms (in case of children, elderly, and patients have difficulty in swallowing solids dosage forms).

2. 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.
- ✓It may also be possible to suspend a powdered drug in an emulsion base, as in Zinc Cream.

3. Suspensions for parenteral use

Suspensions are formulated for parenteral administration in order to control the rate of absorption of the drug

4. Suspensions for ophthalmic use:

5. Suspensions in aerosol Inhalation therapy;

6. X-ray contrast media;

Theory of Sedimentation & Rate of Sedimentation

$$v = d^2 (\rho_s - \rho_o) g/18 \eta_o$$

$$\frac{dx}{dt} = \frac{d2\,(pi - pe)g}{18\eta}$$

Where,

dx/dt is the rate of settling,

d is diameter of the particles in cm,

$\boldsymbol{\rho_i}$ – density of the particle, $\boldsymbol{\rho_e}$ – density of the medium,

g is gravitational constant,

and $\boldsymbol{\eta}$ – viscosity of the medium in poise.

- ✓The effect of changing these is illustrated in the following example;

EXAMPLE

A powder has a density of 1.3 g/mL and an average particle diameter of 2.5 μg (assuming the particles to be spheres). According to the Stokes equation, this powder will settle in water (viscosity of 1 cP assumed) at this rate:

$$\frac{(2.5\times10^{-4})^2\ (1.3-1.0)\ (980)}{18\times0.01}=1.02\ \times 10^{-4}\text{cm / s}$$

If the particle size of the powder is reduced to 0.25 μm and water is still used as the dispersion medium, the powder will now settle at this rate:

$$\frac{(2.5\times10^{-5})^2\ (1.3-\ 1.0)(980)}{18\times\ 0.01}=1.02\times10^{-6}\ \text{cm / s}$$

As is evident, a decrease in particle size by a factor of 10 results in a reduction in the rate of settling by a factor of 100. This enhanced effect is a result of the d factor in the Stokes equation being squared.

If a different dispersion medium, such as glycerin, is used in place of water, a further decrease in settling will result. Glycerin has a density of 1.25 g/mL and a viscosity of 400 cP. The larger particle size powder (2.5 μm) will settle at this rate:

$$\frac{(2.5\times10^{-5})^2(1.3-1.25)(980)}{18\times4}=4.25\times10^{-10}\text{cm/s}$$

The smaller particle size (0.25 μm) powder will now settle at this rate:

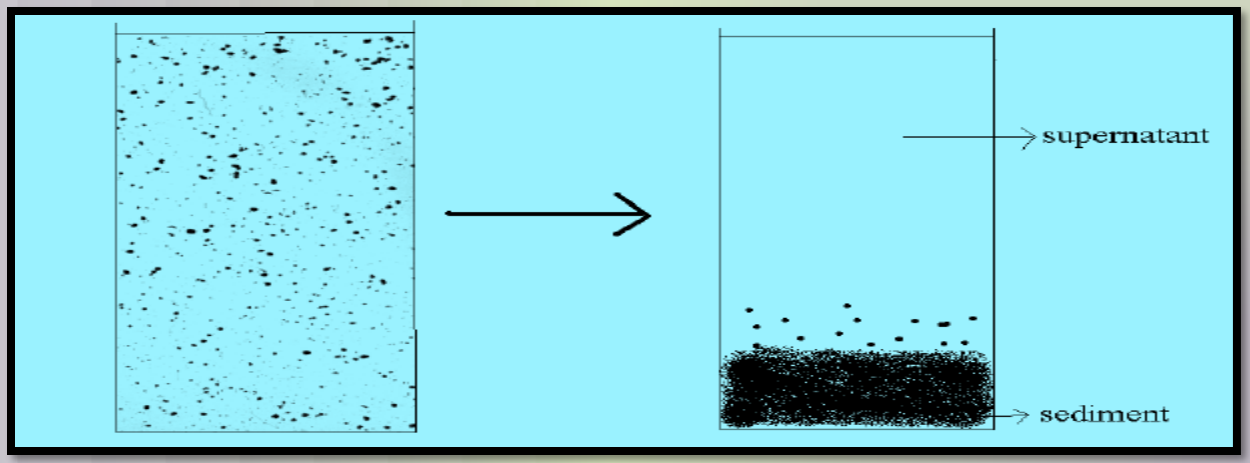
$$\frac{(2.5\times10^{-6})^2(1.3-1.25)(980)}{18\times4}=4.25\times10^{-10}\text{ cm/s}$$

A summary of these results is shown in the following table:

CONDITION	RATE OF SETTLING (CM/S)
2.5 μm powder in water	1.02×10^{-4}
0.25 μm powder in water	1.02×10^{-6}
2.5 μm powder in glycerin	4.25×10^{-8}
0.25 μm powder in glycerin	4.25×10^{-10}

As is evident from this table, a change in dispersion medium results in the greatest change in the rate of settling of particles. Particle size reduction also can contribute significantly to suspension stability. These factors are important in the formulation of physically stable suspensions.

- Stokes' equation **does not apply** precisely to the usual pharmaceutical suspension in which the suspensoid is **irregularly shaped** and of **various particle diameters**, fall of the particles **does** result in both turbulence and collision, and also particles may have some affinity for the suspension medium.



- ✓ The greater the density of the particles, the greater the rate of descent.

- ✓ 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.

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

- ✓ As the proportion of solid particles in a suspension increases, so does the viscosity.

✓For the most part, the **physical stability** of a pharmaceutical suspension appears to be most appropriately adjusted by ***an alteration in the dispersed phase*** rather than through great changes in the dispersion medium.

✓These adjustments are concerned mainly with ***particle size***, ***uniformity of particle size***, and ***separation of the particles*** so that they are not likely to become greatly larger or to form a solid cake upon standing.

Physical Features of the Dispersed Phase of the Suspension

Probably the most important single consideration in a discussion of suspensions is the size of the particles. Generally, ***particle size reduction*** is accomplished by dry milling prior to incorporation of the dispersed phase into the dispersion medium.

1- Micropulverization

Micropulverizers are high–speed attrition or impact mills.

2- ***Jet Milling/Micronizing***

for still finer particles, < 10 µm,

3- Spray Drying

for producing an extremely small dimensions a cone– shaped apparatus named spray dryer into which a solution of a drug is sprayed,

- According to the Stokes' equation, the reduction in the particle size of a suspensoid is beneficial to the ***stability*** of the suspension ***because the rate of sedimentation is reduced as the size decreased.***

➢The latter form a tenacious sediment cake on standing that could not be redistributed, whereas the former did not cake upon standing.

- ✓ a ***less rigid/ loose aggregation together by comparatively weak particle– to –particle bonds*** termed a ***floc or floccule,*** with flocculated particles forming a type of lattice that resists complete settling (although flocs settle more rapidly than fine, individual particles) and thus are less prone to compaction than unflocculated particles.

- ✓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.

1- An oral suspension of a drug, clays such as diluted bentonite magma are employed as the flocculating agent, where their structure assists the suspension by helping to support the floc once formed.

2- A parenteral suspension, frequently a floc of the dispersed phase can be produced by an alteration in the pH of the preparation (generally to the region of minimum drug solubility).

3- Electrolytes as flocculating agents, reducing the electrical barrier between the particles of the suspensoid and forming a bridge so as to link them together.

Interfacial Properties of Suspensoid:

-The particles in a liquid suspension tend to *flocculate*, i.e.; to form light, fluffy conglomerates that are held together by weak van der Waals forces. Thus, the large surface area of the particles that results from the comminution is associated with a ***surface free energy*** that makes the system ***thermodynamically unstable***, i.e.; 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.

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

where γSL is the interfacial tension between the liquid medium and the solid particles.

Sedimentation Parameters

1- Sedimentation Volume, F – is the ratio of the final, or ultimate, volume of sediment, *Vu*, to the original volume of suspension, *Vo*, before settling. Thus:

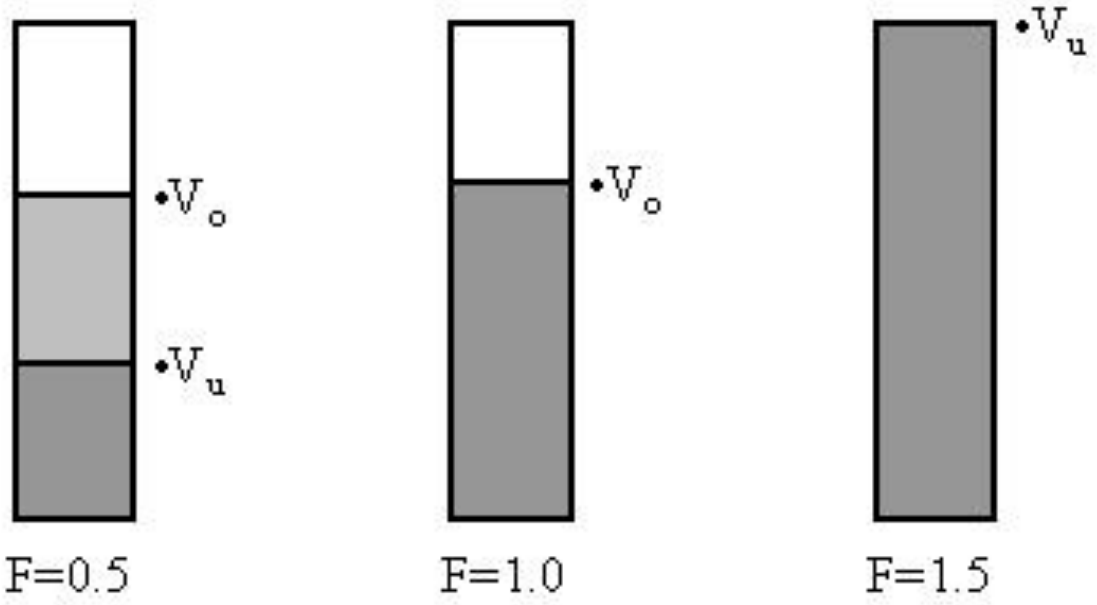
$$F = \frac{Vu}{Vo}$$

F= 1	No sedimentation, no clear supernatant
F =0.5	50% of the total volume is occupied by sediment
F > 1	Sediment volume is greater than the original volume due ????

Evaluation of Suspensions: Sedimentation volume

Sedimentation Volume

F={volume of sediment V_u}/{original volume V_o}



2- *Degree of Flocculation, β* - the sedimentation volume gives only a qualitative account of flocculation because it lacks a meaningful reference point. If a suspension completely deflocculated, the ultimate volume of the sediment will be relatively small:

$$F_\infty = \frac{V\infty}{Vo}$$

where F_∞ is the sedimentation volume of the deflocculated suspension. The degree of flocculation, β, is therefore defined as the ration of F to F_∞, or

$$\beta = \frac{F}{F\infty}$$

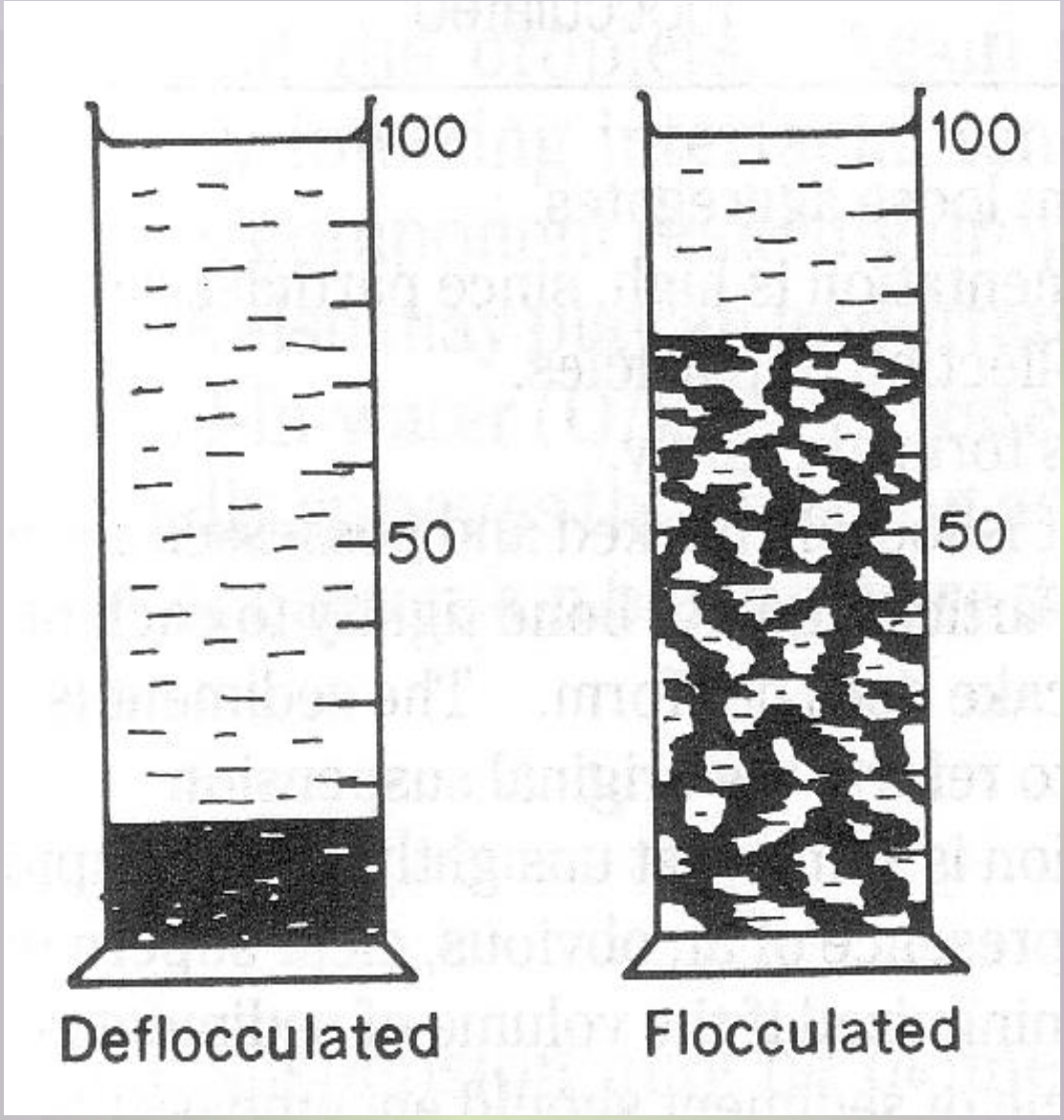
$$\beta = \frac{Vu/Vo}{V\infty/Vo} = \frac{Vu}{V\infty}$$

The degree of flocculation is a more fundamental parameter than sedimentation volume because it relates the volume of flocculated sediment to that in a deflocculated system. Then:

$$\beta = \frac{\text{ultimate sediment volume of flocculated suspension}}{\text{ultimate sediment volume of deflocculated suspension}}$$

- ***3-Re-disperseability:*** This is determined by the number of upside down inversions of the suspension contained in a measure.

Dispersion Medium:



-The solid content of a suspension intended for oral administration may vary considerably, depending on

-1-the dose of the drug to be administered,

-2-the volume of product to be administered and

-3-the ability of the dispersion medium to support the concentration of drug while maintaining desirable features of viscosity and flow.

Preparation of Suspensions:

-In some instance, the dispersed drug has an **affinity** for the vehicle to be employed and is **readily wetted** by it, whereas those do 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 t**o make it more penetrable by the dispersion medium.

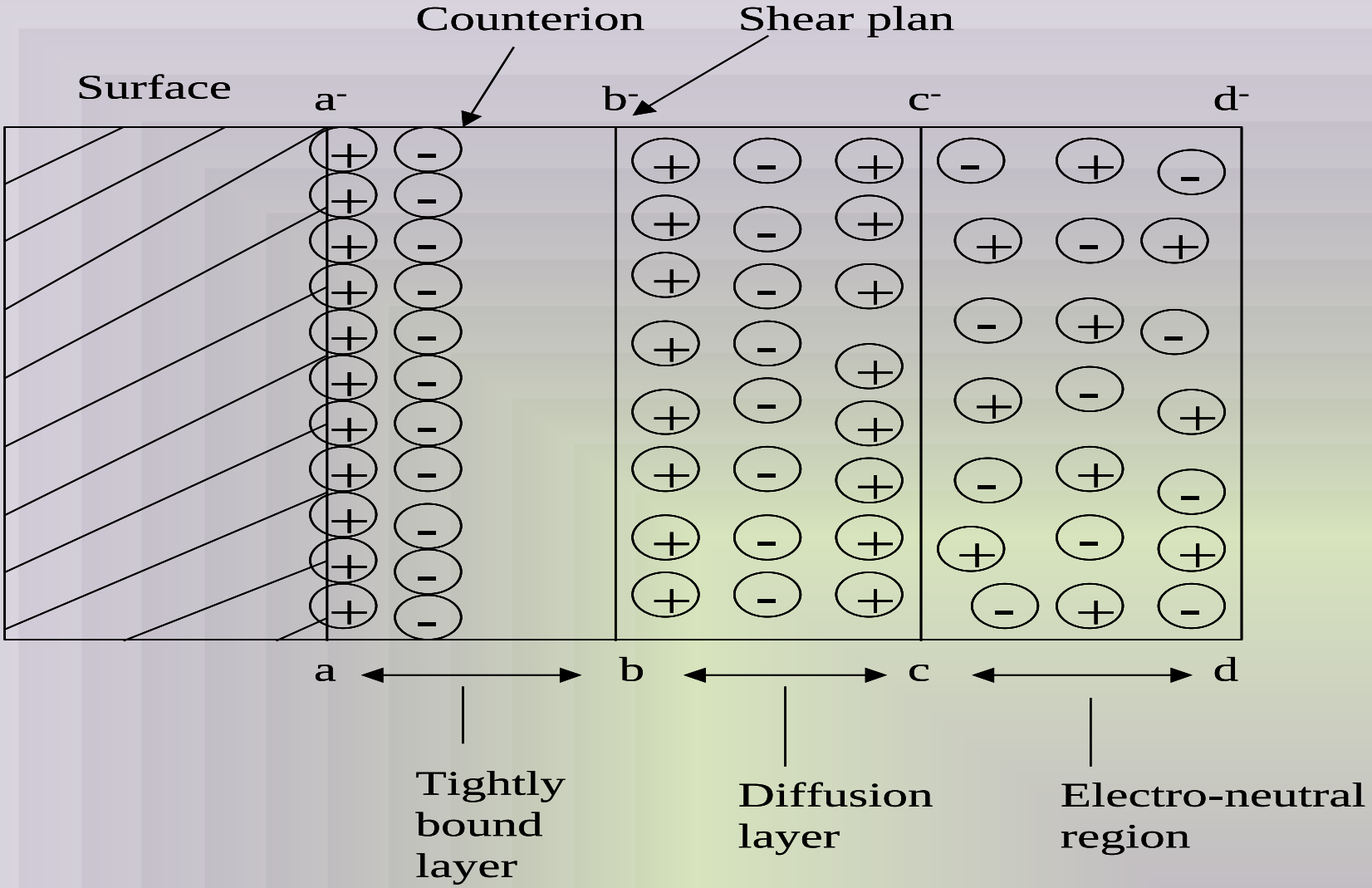
-A portion of the vehicle is used to wash the mixing equipment free of suspensoid, and this portion is used to bring the suspension to final volume and ensure that the suspension contains the desired concentration of solid matter. The final product is then passed through a colloid mill, blender or mixing device to ensure uniformity.

Sustained – Release Suspensions:

-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 G.I.T., e.g. hydrocodone polistirex (Tussionex Pennkinetic Extended – Release Suspension, Medeva).

Flocculating Agents: Electrolytes..



Zeta potential is the potential difference between the ions in the tightly bound layer and the electroneutral region.