# SUSPENSION

## DEFINITION

A suspension is a two phase system composed of a solid material dispersed in a liquid. The liquid can be oily or aqueous. However, most suspensions of pharmaceutical interest are aqueous.

## ADVANTAGES

Suspensions offer distinct advantages _ they are as follows:

1. **Stability**: Some drugs are not stable in solution form. In such cases it is necessary to prepare an insoluble form of that drug. Therefore drugs are administered in the form of suspension. e.g. Procaine Penicillin G.
2. **Choice of solvent**: If the drug is not soluble in water and solvents other than water are not acceptable, suspension is the only choice. e.g. Parenteral corticosteroid.
3. **Mask the taste;** In some cases drugs are made insoluble and dispensed in the form of suspension to mask the objectionable taste. e.g. Chloramphenicol base is very bitter in taste, hence the insoluble chloramphenicol palmitate is used which does not have the bitter taste
4. **Prolonged action:** Suspension has a sustaining effect, because, before absorption the solid particles should be dissolved. This takes some time. e.g. Protamine Zinc Insulin and procaine penicillin G.
5. **Bioavailability:** Drugs in suspension exhibit a higher bioavailability compared to other dosage forms (except solution) due to its large surface area, higher dissolution rate. e.g. Antacid suspensions provides immediate relief from hyperacidity than its tablet chewable tablet form.

## TYPES OF SUSPENSIONS

The pharmaceutical suspension preparations are differentiated into suspensions, mixtures, magmas, gels and lotions.

### Suspensions

Simple suspension is the insoluble solid dispersed in a liquid. The stability considerations suggest that the manufacture of drugs in dry form is ideal. They are reconstituted as suspensions using a suitable vehicle before administration.

Few examples are:

i) Dispersible tablets of antibiotic, amoxycillin (e.g. PRESSMOX)
ii) Procaine penicillin G powder (E.G. PENIDURE)

### Gels

Gels are semisolid systems consisting of small inorganic particles suspended in a liquid medium. It consists of a network of small discrete particles. It is a two-phase system. e.g. Aluminum hydroxide gel.

### Lotions

Lotions are suspensions which are intended to be applied to the unbroken skin without friction. e.g. Calamine lotion, hydrocortisone lotion.

### Magmas and Milks

Magmas and milk are aqueous suspensions of insoluble, inorganic drugs and differ from gels mainly in that the suspended particles are larger. when prepared they are thick and viscous and because of this, there is no need to add a suspending agent. e.g. Bentonite magma, milk of magnesia.

**Mixtures**

Mixtures are oral liquids containing one or more active ingredients, dissolved, suspended or dispersed in a suitable vehicle. Suspended solids may separate slowly on standing, but are easily redispersed on shaking. e.g. Kaolin mixture with pectin.

## CLASSIFICATION OF SUSPENSIONS

Based on the proportion of solids, suspensions are empirically classified as dilute or concentrated systems.

i) **Dilute suspensions** : Solid content 2 - 10 % e.g. Cortisone acetate and prednisolone acetate suspension.
ii) **Concentrated suspensions**: Solid content 10 - 50 % e.g. Zinc oxide suspension for external use, Procaine penicillin G injection, Antacid suspension etc.

Depending on the nature and behavior of solids suspensions are classified as flocculated and deflocculated.

## DEFLOCCULATED SUSPENSION

In this system, solids are present as individual particles.

## FLOCCULATED SUSPENSION

In this system, particles aggregate themselves by physical bridging. These flocs are light, fluffy conglomerate which are held together by weak van der Waal's forces of attraction.

If the aggregate is an open network it is called **floccule**. They are fibrous, fluffy, open network of particles. It is loosely packed after sedimentation.

If the aggregate is a closed one - it is called **coagule**. They are tightly packed, produced by surface film bonding.

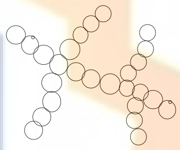


Fig. floccule

Fig. Coagule

*TABLE: Comparison between Deflocculated and Flocculated System*

| Deflocculated System | Flocculated System |
|---|---|
| i) Pleasant appearance, because of uniform dispersion of particles. | i) Somewhat unsightly sediment. |
| ii) Supernatant remains cloudy. | ii) Supernatant is clear |
| iii) Particles exist as separate entities | iii) Particles form loose aggregates. |
| iv) Rate of sedimentation is slow, as the size of particles are small. | iv) Rate is high, as flocs are the collection of smaller particles having a larger size. |
| v) Particles settle independently and separately | v) Particles settle as flocs. |
| vi) The sedimentation is closely packed and form a hard cake. | vi) Sediment is a loosely packed network and hard cake cannot form. |
| vii) The hard cake cannot be redispersed. | vii) The sediment is easy to redisperse. |
| viii) Bioavailability is higher due to large specific surface area. | viii) Bioavailability is comparatively less due to small specific surface area. |

## FACTORS AFFECTING THE STABILITY OF A SUSPENSION

### SETTLING IN SUSPENSIONS

**Brownian movement**

Brownian movement of particles prevents sedimentation. In general, particles are not in a state of Brownian motion in pharmaceutical suspensions, due to

i) larger particle size (Brownian movement is seen in particles having diameter of about 2 to 5 μm (depending on the density of the particles and the viscosity and the density of the suspending medium.

ii) and higher viscosity of the medium.

**Sedimentation**

The rate of sedimentation of particles can be expressed by the Stoke's law, using the following formula:

$$\text{Sedimentation rate} = \frac{d^2 (\rho_s - \rho_l) g}{18\eta}$$

Where d is the particle diameter

$\rho_s$, $\rho_l$ are densities of a particle and liquid respectively.

g is the acceleration of gravity.

η is the viscosity of the medium.

Stock's law is applicable if:

i) particles are spherical; but particles in the suspension are largely irregular.

ii) Particles settle freely and independently.

In suspensions containing 0.5 - 2 % (w/v) solid, the particles do not interfere with each other during sedimentation - hence free settling occurs.

Most pharmaceutical suspensions contain 5 - 10 % or higher percentages of solid. in this cases particles interfere with one another as they fall - hence hindered settling occurs and Stoke's law no longer applies.

Stoke's law is applicable to deflocculated systems, because particles settle independently. However, this law is useful in a qualitative manner in fixing factors which can be utilized in formulation of suspensions.

**1. Particle size**

Rate of sedimentation ∞ $(\text{diameter of particle})^2$

So smaller the particle size more stable the suspension. The particle-particle interaction results in the formation of floccules or coagules where the sedimentation rate increases. The particles are made fine either by **dry milling** prior to suspension or **wet-milling** of the final suspension in a colloid mill or a homogenizer.

**2. Viscosity of the medium**

According to Stoke's law:

Rate of sedimentation ∞ 1 / (viscosity of the medium)

The viscosity of suspension should be optimum. Viscosity can be increased by adding suspending agents or thickening agents. selection of high viscosity have both advantages and disadvantages.

Advantages

i) Sedimentation rate is retarded, hence enhances the physical stability of the suspension.

ii) Inhibits crystal growth, because movement of particles is diminished.

iii) Prevents the transformation of metastable crystals to stable crystals.

Disadvantages

i) Redispersibility of the suspension on shaking is difficult.
ii) Pouring out of the suspension from the container may be difficult.
iii) Creates problems in the handling of materials during manufacture.
iv) May retard absorption of drugs from the suspension.

**3. Density**

Rate of sedimentation $\propto$ (density of solid – density of liquid medium)

Lesser the difference between the densities of solid particles and liquid medium slower is the rate of sedimentation. Since it is very difficult to change the absolute density of the solid particles so the density of the liquid medium can be manipulated by changing the composition of the medium. The addition of nonionic substances such as sorbitol, polyvinylpyrrolidone (PVP), glycerin, sugar, or one of the polyethyleneglycols or combination of these may be helpful in the manipulation.

If the density of the particles is greater than the continuous medium the particles will settle downwards, the phenomenon is known as sedimentation. If the density of particle is lesser than that of the liquid medium then the particles will move upward - the phenomenon is known as creaming.

**FORMULATION OF SUSPENSIONS**

The product must
1) Flow readily from the container
2) Possesses a uniform distribution of particles in each dose.

Two approaches are commonly employed to secure the two requirements,
(i) the use of structured vehicle t maintain deflocculated particles in suspension. Structured vehicles are pseudoplastic and plastic in nature; it is frequently desirable that thixotropy be associated with these two type of flow. Structured vehicles act by entrapping the particles so that, ideally no settling occurs. In reality some degree of sedimentation will usually take place. The *shear thinning* property of these vehicle does however facilitate the redispersion when shear is applied.
(ii) and the application of the principles of flocculation to produce flocs that, although, they settle rapidly are easily redispersed with a minimum of agitation.

**WETTING OF PARTICLES**

The initial dispersion of an insoluble powder in a vehicle is an important step in the manufacturing process. Powders sometimes are added to the vehicle, particularly in large scale operations, by dusting on the surface of the liquid. It is frequently difficult to disperse the powder owing to an adsorbed layer of air, minute quantity of grease and other contaminants.

Powders those are not easily wetted by water and accordingly show a large contact angle, such as sulfur, charcoal and magnesium stearate are said to be *hydrophobic*. Powders those are readily wetted by water when free of adsorbed contaminants are called *hydrophilic*. e.g. zinc oxide, talc, magnesium carbonate etc. belong to this category.

When a strong affinity exists between a liquid and a solid, the liquid easily forms a film over the surface of the solid. When this affinity is non-existent or weak, the liquid faces difficulty in displacing the air or other substances surrounding the solid.

Hydrophilic solids usually can be incorporated into suspensions without the use of a wetting agent, but hydrophobic materials are extremely difficult to disperse and frequently float on the surface of the fluid owing to poor wetting of the particles or the presence of tiny air pockets on the surface of the solid particles.

To reduce the **contact angle** between solid and liquid (i.e. increase the wettability) the following agents can be tried out:

1. **Surfactants** Solid-liquid interfacial tension is reduced by incorporating a surfactant with a HLB value between 7 to 9. These are employed to allow the displacement of air from hydrophobic material and permit the liquid, to surround the particles and provide a proper dispersion. The surfactant is mixed with the solid particles if required by shearing. The hydrocarbon chain is

preferentially adsorbed to the hydrophobic surface, with the polar part of the surfactant being directed towards the aqueous phase.

2. **Hydrophilic polymers** such as sodium carboxymethyl cellulose, certain water-insoluble hydrophilic material such as bentonite, aluminum-magnesium silicates, and colloidal silica, either alone or in combination can be incorporated in desired concentration. These materials are also used as suspending agents and may produce a deflocculated system particularly if used at low concentration.
3. **Solvents** such as alcohol, glycerol and glycols which are water miscible will reduce the liquid / air interfacial tension. The solvent will penetrate the loose agglomerates of powder displacing the air from the pores of the individual particles thus enabling wetting by dispersion medium.

**Method of selection of a suitable wetting agent**

In order to select a suitable wetting agent Heistand has used a narrow trough, several inches long and made of a hydrophobic material, such as Teflon, or coated with paraffin wax. At one end of the trough is placed the powder and the other end the solution of the wetting agent. The rate of penetration of the wetting agent solution into the powder can then be observed directly. Greater the rate of penetration of the solution into the powder better is the wetting property of the solution.

**RHEOLOGIC CONSIDERATIONS**

Rheologic consideration are important in

(i) the viscosity of a suspension as it affects the settling of particles. As viscosity increases rate of sedimentation of the particles reduces.
(ii) the change in flow properties of the suspension when the container is shaken and when the product is poured out off the bottle.
(iii) the spreading quality of the lotion when applied to the affected area.
(iv) during the manufacture of the suspensions.

**Importance of suspending agents**

The particles in a suspensions are experiencing bombardment constantly with each other owing to the Brownian movement. During this type of inter-particular interaction the particles may circumvent the repulsive force between them and form larger particles which will then settle rapidly. Suspending agents reduce this movement of the particles by increasing the viscosity of the medium.
According to Stoke's law rate of sedimentation is inversely proportional to the viscosity of medium. So the settling of the particles , either in flocculated or deflocculated system, can be slowed down by increasing the drag force on the moving particles by increasing the viscosity of the medium.
Hydrophilic polymers such as sodium carboxymethyl cellulose, certain water-insoluble hydrophilic material such as bentonite, aluminum-magnesium silicates, and colloidal silica, either alone or in combination can be incorporated in low concentration as **wetting agent.**
Hydrophilic polymers also acts as **protective colloids** and particles coated in this manner are less prone to cake than are uncoated particles.
**Cellulose polymers** e.g. sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose.
**Proteins** e.g. gelatin.
**Synthetic polymer** e.g. Polyacrylic acid (Carbopol)
**Clays** essentially hydrated aluminum and/or magnesium silicates are also useful in suspension formulation.

**Characteristics of ideal suspending agent**

(i) An ideal suspending agent should have a high viscosity at negligible shear; i.e. during shelf storage; and it should have a low viscosity at high shear rates, i.e. it should be free flowing during agitation, pouring and spreading on the skin.
(ii) Suspending agents should coat the particles which will be less prone to caking than the uncoated particles.

Pseudoplastic substances e.g. tragacanth, sodium alginate and sodium carboxymethylcellulose show these desirable qualities. It is a shear thinning system, i.e. when this type of system is shaken or agitated the viscosity diminishes.
A suspending agent that is thixotropic as well as pseudoplastic should prove to be useful since it forms gel on standing and becomes fluid when disturbed. e.g. Bentonite - Carboxymethylcellulose has both pseudoplastic and thixotropic behavior.

| Suspending agent | Concentration in which generally used |
|---|---|
| Sodiumcarbxymethylcellulose | 0.5 – 2.5 % |
| Tragacanth | 1.25 % |
| Guargum | 0.5 % |
| Carbopol 934 | 0.3 % |

## CONTROLLED FLOCCULATION

Assuming that the powder is properly wetted and dispersed attention may now be given to the various means by which controlled flocculation may be produced so as to *prevent compact sediment which is difficult to redisperse*. Controlled flocculation can be described in terms of the materials used to produce flocculation I suspensions, namely, (i) electrolytes, (ii) surfactants, and (iii) polymers.
**(i) Electrolytes** act as flocculating agents by reducing the electric barrier between the particles, as evidenced by a decrease in the zeta-potential and formation of a bridge between adjacent particles so as to link them together in a loosely arranged structure.
Example: When bismuth subnitrate is suspended in water it has been found (by electrophoretic studies) that they possess a large positive charge, or zeta potential. Because of the strong forces of repulsion between adjacent particles, the system remains in deflocculated (peptized) state. The addition of monobasic potassium phosphate ($KH_2PO_4$) to the suspension causes the positive zeta-potential to decrease owing to the adsorption of the negatively charged phosphate anion. The particles then can come closer to form aggregates.

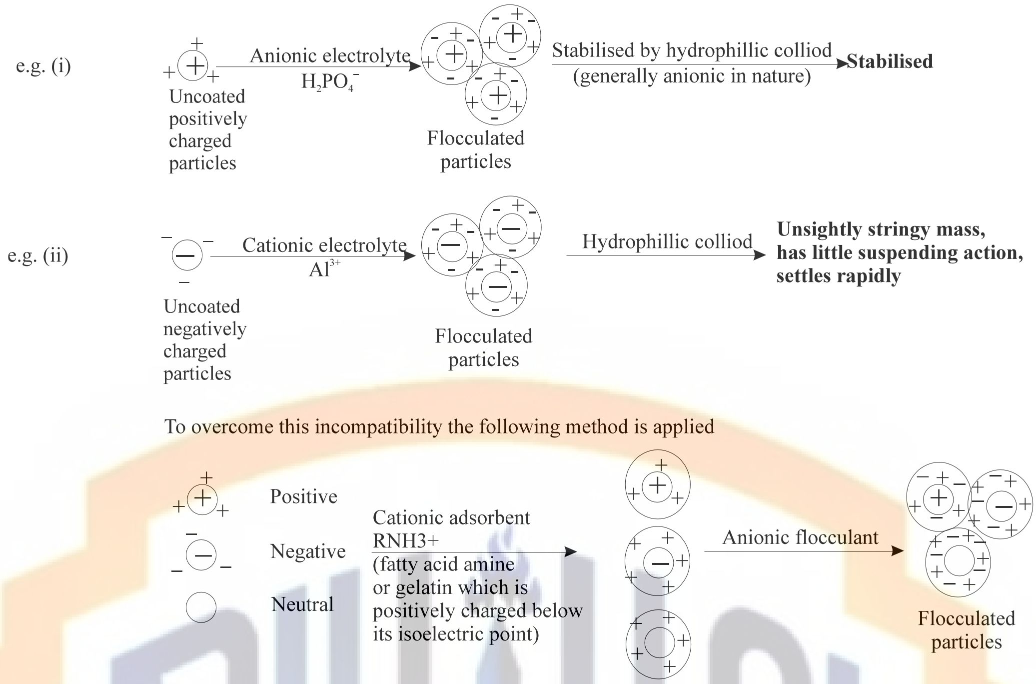
On further addition of $KH_2PO_4$ the zeta potential eventually falls to zero and then increases in a negative direction. Microscopic examination of the various suspensions shows that at a certain positive zeta potential, maximum flocculation occurs and will persist until the zeta potential has become sufficiently negative for deflocculation to occur once again. The onset of flocculation coincides with the maximum sedimentation volume determined. F remains reasonably constant while flocculation persists, and only when the zeta potential becomes sufficiently negative to effect deflocculation.

**(ii) Surfactants** both ionic and nonionic, have been used to bring about flocculation of suspended particles. The concentration necessary to achieve this effect would appear to be critical since these compounds may also act as wetting agents to achieve dispersion.
**(iii) Polymers** are long chain, high molecular weight compounds containing active groups spaced along their length. These agents act as flocculating agents because part of the chain is adsorbed on the particle surface, with the remaining parts projecting out into the dispersion medium. Bridging between these latter portions leads to the formation of flocs.
hydrophilic polymers also acts as protective colloids and particles coated in this manner are less prone to cake than are uncoated particles.

## FLOCCULATION IN STRUCTURED VEHICLE

Although the controlled flocculation approach is capable of fulfilling the desired physical chemical requisites of a pharmaceutical suspension, the product can look unsightly if F, the sedimentation volume, is not close to or equal to 1. So a suspending agent is added to retard sedimentation of the flocs. Such agents as carboxymethylcellulose (CMC), Carbopol 934, Veegum, tragacanth or bentonite have been employed, either alone or in combination.
These may lead to incompatibilities, depending on
(i) the initial particle charge
(ii) the charge carried by flocculating agent and

(iii) the charge carried by suspending agent.




## PREPARATION OF SUSPENSIONS

Method of preparations can be subdivided into two broad categories:

### Precipitation method

There are three methods

1. organic solvent precipitation
2. precipitation effected by changing the pH of the medium and
3. double decomposition

<u>(i) Organic solvent precipitation</u>

Water insoluble drugs can be precipitated by dissolving them in water-miscible organic solvents (e.g. alcohol, acetone, propylene glycol and polyethylene glycol) and then adding the organic phase to distilled water under standard conditions produces a suspension having a particle size in the 1 to 5 μm range.

*Example*: Prednisolone is precipitated from a methanolic solution to produce a suspension in water.

*Disadvantage*: Harmful organic solvents may be difficult to remove.

*Advantage*: In case of parenteral or inhalation therapy very fine particles are required, which can be prepared by this method.

<u>(ii) Precipitation effected by changing the pH of the medium</u>

A drug may be readily soluble at a certain pH and precipitate at another pH. This type of drug is first dissolved in the favorable pH and then the solution is poured in another buffer system to change the pH of the medium and the drug will form a suspension in the medium of the second pH.

*Example 1*: Estradiol suspensions can be prepared by changing the pH of the of its aqueous solution; estradiol is readily soluble in alkali as potassium or sodium hydroxide solutions. If a concentrated solution of estradiol is thus prepared and added to a weakly acidic solution of hydrochloric, citric or acetic acids, under proper conditions of agitation, the estradiol is precipitated in a fine state of subdivision.

*Example 2*: Insulin suspension may also be prepared by pH change method. Insulin has an isoelectric point of approximately pH5. When it is mixed with a basic protein, such as protamine, it is readily precipitated when pH is between the isoelectric points of the two components, i.e. pH 6.9 to 7.3. Protamine-Zinc-Insulin (PZI) contains an excessive quantity of zinc to retard the rate of absorption.

According to the British Pharmacopoeia phosphate buffer is added to an acidified solution of PZI so that the pH is between 6.9 to 7.3 to form the suspension.

(iii) Double decomposition method

In this method two water soluble reagent forms a water insoluble product.

*Example*: White Lotion NF is prepared by slowly adding zinc sulfate solution in a solution of sulphurated potash to form a precipitate of zinc polysulphide.

**Dispersion method**

In this cases the powder form of the drug is directly dispersed in the liquid medium. The liquid medium should have good power of wetting the powder.

1. Small scale preparation method

A suspension is prepared on the small scale by grinding or levigating the insoluble material in the mortar to a smooth paste with a vehicle containing the dispersion stabilizer and gradually adding the remainder of the liquid phase in which any soluble drugs may be dissolved. The slurry is transferred to a graduate, the mortar is rinsed with successive portions of the dispersion medium is finally brought to the final volume.

2. Large scale preparation method

On large scale dispersion method the solid particles are suspended using ball, pebble and colloid mills. Dough mixers, pony mixers and similar apparatus are also employed.

## EVALUATION OF SUSPENSION STABILITY

**Sedimentation volume**

Since redispersibility is one of the major considerations in assessing the acceptability of a suspension, and since the sediment formed should be easily dispersed by moderate shaking to yield a homogeneous system, measurement of the sedimentation volume and its ease of redispersion are the two common evaluative procedures.

Definition: The sedimentation volume, F, is defined as the ratio of the final, or ultimate volume of the sediment (Vu), to the original volume of the suspension (Vo), before settling. Thus

$$F = Vu / Vo$$

The sedimentation volume can have values less than 1 to greater than 1. If the volume of sediment in a flocculated system equals the original volume of suspension, then F = 1. Such a product is said to be in 'flocculation equilibrium'.

Procedure: The suspension is taken in a measuring cylinder upto a certain height and left undisturbed. The particles will settle gradually. The value of F is determined from the ratio of the volume of the sediment at that instant of time (Vu) and the original volume of the suspension (Vo). The value of F is plotted against time (t). The plot will, will start at 1.0. at time zero. The curve will either run horizontally or gradually sloping downward to the right as time goes on.

One can compare different formulations and choose the best by observing the line, the better formulation obviously producing lines that are more horizontal and/or less steep.

If the suspension is highly concentrated then the suspension is diluted with the continuous medium (liquid phase) and then the sedimentation volume is determined.

### Degree of flocculation

A more useful parameter is the degree of flocculation, β.

Definition: degree of flocculation is the ratio of ultimate sediment volume of *flocculated* suspension to that of *a deflocculated* suspension.

$$\beta = \frac{\text{sedimentation volume of } \textit{flocculated} \text{ suspension (F)}}{\text{sedimentation volume of } \textit{deflocculated} \text{ suspension } (F\infty)}$$

$F\infty = V\infty / Vo$ 	$F\infty$ = sedimentation volume of *deflocculated* suspension

$V\infty$ = ultimate sediment volume of *deflocculated* suspension

$F = Vu / Vo$

Vo = original volume of suspension
F = sedimentation volume of *flocculated* suspension
Vu = ultimate sediment volume of *flocculated* suspension

Therefore, $\beta = F / F\infty$

$= (V\infty / Vo) / (Vu / Vo)$

$= (V\infty / Vu)$

$$\beta = \frac{\text{ultimate sediment volume of } \textit{flocculated} \text{ suspension (Vu)}}{\text{ultimate sediment volume of } \textit{deflocculated} \text{ suspension } (V\infty)}$$

**Redispersibility**

The evaluation of redispersibility is also important. To quantitate this parameter to some extent, a mechanical shaking device may be used. It simulates human arm motion during the shaking process and can give reproducible result when used under controlled conditions.

**Rheologic methods**

Rheologic behavior can also be used to help determine the settling behavior and the arrangement of the vehicle and particle structural features for purposes of comparison. The structure of the suspension changes during storage period. This structural changes can be evaluated by rheologic method.

A practical rheologic method involves the use of a Brookfield viscometer mounted on a helipath stand. The T-bar spindle is made to descend slowly into the suspension, and the dial reading on the viscometer is then a measure of the resistance the spindle meets at various level in the sediment. In this technique, the T-bar is continually changing position and measures undisturbed samples as it advances down in the suspension This technique also indicates in which level of the suspension the structure is greater, owing to the particle agglomeration, because the T-bar descends as it rotates, and the bar is continually entering new and essentially undisturbed material.

Thus using the T-bar spindle and the helipath, the dial reading can be plotted against the number of turns of the spindle. The result indicates how the particles are setting with time. In a screening study the better suspensions show a lesser rate of increase of dial reading with spindle turns, i.e. the curve is horizontal for a longer period.

**Electrokinetic techniques**

*Instrument* : Microelectrophoresis apparatus.

Such instrument permit measurement of the migration velocity of the particles with respect to the surface electric charge or the zeta potential. Zeta potential correlated well with the visually observed caking and certain zeta potential produced more stable suspensions because aggregation was controlled and optimized.

**Particle Size Changes**

During storage or transport the product may experience a fluctuation of temperature which may lead to crystal growth or physical incompatibilities. Normally it may take time to check the stability regarding crystal growth. So to accelerate this effect ***freeze-thaw cycling*** technique is particularly applicable. The product is put into refrigerator and again brought into room temperature — this type of temperature cycling promotes the growth of particle size. The growth of particle and size distribution are estimated by microscopic means.
*Example(i)* The crystal growth of sulfathiazole in suspensions is found to accelerate after temperature cycling

*Example(ii)* the preservative and protective colloid, may have a profound effect on the physical performance of a suspension under freeze-thaw conditions. Two low solid content steroid injectable preparations of following compositions underwent freeze-thaw condition the first preparation showed intense caking while the latter was unaffected.

| Preparation | Protective colloid | Preservative | Result after freeze-thaw |
|---|---|---|---|
| I | sodium carboxy methylcellulose | benzyl alcohol | Caked badly |
| II | carboxy methyl cellulose | methyl paraben, propyl paraben | No caking |

*Example (iii)* Gelatin solidifies at low temperature and methyl cellulose is precipitates in hot water.