## INDUSTRIAL PHARMACY-I

## UNIT II-TABLETS AND LIQUID ORALS

## CLASS:16

## TOPIC Formulation and manufacturing consideration of syrups and elixirs suspensions and emulsions;

**DEFINITION:**

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 aninsoluble 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 notacceptable, 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 suspensionto mask the objectionable taste. e.g. Chloramphenicol base is very bitter in taste,hence theinsoluble chloramphenicol palmitate is used which does not have the bitter taste

4. **Prolonged action:** Suspension has a sustaining effect, because, before absorption the solidparticles should be dissolved. This takes some time. e.g. Protamine Zinc Insulin and procainepenicillin G.

5. **Bioavailability:** Drugs in suspension exhibit a higher bioavailability compared to other dosageforms (except solution) due to its large surface area, higher dissolution rate. e.g. Antacidsuspensions provides immediate relief from hyperacidity than its tablet chewable tablet form.

## 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 acetatesuspension.

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 **classifie**d as flocculated anddeflocculated.

## DEFLOCCULATED SUSPENSION

In this system, solids are present as individual particles.

## FLOCCULATED SUSPENSION

In this system, particles aggregate themselves by physical bridging. These flocsare light, fluffy conglomerate which are held together by weak van der Waal'sforces 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 calleC **coagule**. They are tightly packed,produced by surface film bonding

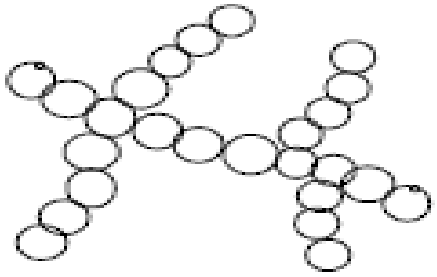


Fig. floccule

Fig. Coagule

*TABLE: Comparison between Deflocculated and Flocculated System*

| **Deflocculated System** | **Flocculated System** |
|---|---|
| 1. Pleasant appearance, because of uniformdispersion of particles.<br>2. Supernatant remains cloudy.<br>3. Particles exist as separate entities<br>4. Rate of sedimentation is slow, as the sizes of particles are small.<br>5. Particles settle independently and separately<br>6. The sedimentation is closely packed andform a hard cake.<br>7. The hard cake cannot be redispersed.<br>8. Bioavailability is higher due to large specific surface area. | 1. Somewhat unsightly sediment.<br>2. Supernatant is clear<br>3. Particles form loose aggregates.<br>4. Rate is high, as flocs are the collection ofsmaller particles having a larger size.<br>5. Particles settle as flocs.<br>6. Sediment is a loosely packed network andhard cake cannot form.<br>7. The sediment is easy to redisperse.<br>8. Bioavailability is comparatively less dueto small specific surface area |

**FACTORS AFFECTING THE STABILITY OF A SUSPENSIONSETTLING 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 suspendingmedium.

ii) and higher viscosity of the medium.

**1. Particle size**

Rate of sedimentation α(diameter of particle)$^2$

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

2. Viscosity of the medium

According to Stoke's law:

Rate of sedimentation α1 / (viscosity of the medium)

The viscosity of suspension should be optimum. Viscosity can be increased by addingsuspending agents or thickening agents. selection of high viscosity have both advantages anddisadvantages.

3. Density

Rate of sedimentation α(density of solid αdensity of liquid medium)

Lesser the difference between the densities of solid particles and liquid medium slower is therate of sedimentation.

The addition of nonionic substances such as sorbitol, polyvinylpyrrolidone (PVP), glycerin, sugar, orone 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 settledownwards, the phenomenon is known as sedimentation. If the density of particle is lesser than thatof 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) Theuse of structured vehicle maintains deflocculated particles in suspension. Structured vehicles are pseudo plastic 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 vehicles 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 between7 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 ofthe 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**

Rheologicconsideration 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 zetapotential 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.

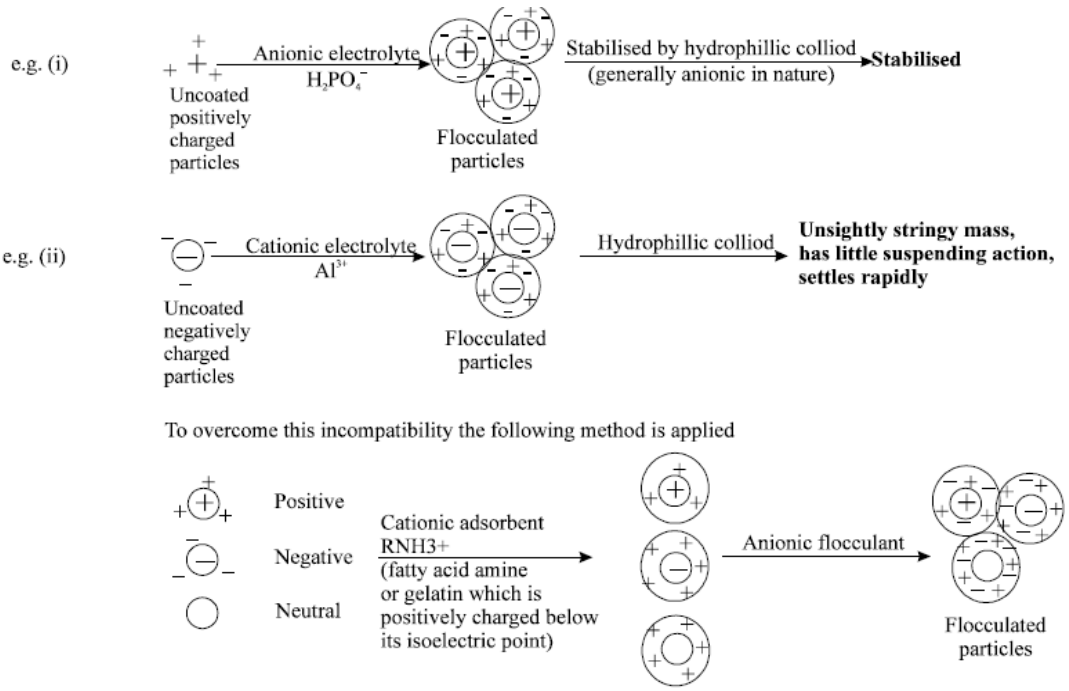
**(iii) Polymers** are long chain, high molecular weight compounds containing active groups spaced along their length. These agents act as flocculating agents because part of the chain is adsorbed on the particle surface, with the remaining parts projecting out into the dispersion medium. Bridging between 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

(i) Organic solvent precipitation

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.

(ii) Precipitation effected by changing the pH of the medium 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 sothat 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 ofsulphurated potash to form a precipitate of zinc polysulphide.

**Dispersion method**

In this case the powder form of the drug is directly dispersed in the liquid medium. The liquidmedium 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 colloidmills. 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 ahomogeneous system, measurement of the sedimentation volume and its ease of redispersion are thetwo common evaluative procedures.

Definition: The sedimentation volume, F, is defined as the ratio of the final, or ultimate volume

of thesediment (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 ina flocculated system equals the original volume of suspension, then F = 1. Such a product is said tobe in 'flocculation equilibrium'.

**Procedure:** The suspension is taken in a measuring cylinder up to a certain height and left undisturbed.The particles will settle gradually. The value of F is determined from the ratio of the volume of thesediment at that instant of time (Vu) and the original volume of the suspension (Vo). The value of Fis plotted against time (t). The plot will, will start at 1.0. at time zero. The curve will either runhorizontally 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 betterformulation 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,

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

sedimentation volume of *flocculated* suspension (F)

sedimentation volume of *deflocculated* suspension (F□)

F□ = V□ / Vo

F□ = sedimentation volume of *deflocculated* suspension

V□ = ultimate sediment volume of *deflocculated* suspension

Vo = original volume of suspension

F = Vu / Vo

F = sedimentation volume of *flocculated* suspension

Vu = ultimate sediment volume of *flocculated* suspension

Therefore, □ = F / F□

□ (V□ / Vo) / (Vu / Vo)

= (V□ / Vu)

ultimate sediment volume of *flocculated* suspension (Vu)

□ =

ultimate sediment volume of *deflocculated* suspension (V□)

**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 processand 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 ofthe vehicle and particle structural features for purposes of comparison. The structure of thesuspension 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 helipathstand. The T-bar spindle is made to descend slowly into the suspension, and the dial reading on theviscometer is then a measure of the resistance the spindle meets at various level in the sediment. Inthis technique, the T-bar is continually changing position and measures undisturbed samples as itadvances down in the suspension This technique also indicates in which level of the suspension thestructure is greater, owing to the particle agglomeration, because the T-bar descends as it rotates, andthe 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 ofturns of the spindle. The result indicates how the particles are setting with time. In a screening studythe better suspensions show a lesser rate of increase of dial reading with spindle turns, i.e. the curveis 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 observedcaking and certain zeta potential produced more stable suspensions because aggregation wascontrolled and optimized.

**Particle Size Changes**

During storage or transport the product may experience a fluctuation of temperature which may leadto crystal growth or physical incompatibilities. Normally it may take time to check the stabilityregarding crystal growth. So to accelerate this effect ***freeze-thaw cycling*** technique is particularlyapplicable. The product is put into refrigerator and again brought into room temperature  this typeof temperature cycling promotes the growth of particle size. The growth of particle and sizedistribution are estimated by microscopic means.

*Example(i)* The crystal growth of sulfathiazole in suspensions is found to accelerate after temperature

*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-thawI sodium carboxybenzyl alcohol Caked badlymethylcelluloseII carboxy methyl methyl paraben,No cakingcellulose propyl paraben*Example (iii)* Gelatin solidifies at low temperature and methyl cellulose is precipitates in hot water.

EMULSIONS

DEFINITION :

An emulsion is a thermodynamically unstable dispersed system consisting of at least two immiscible liquid phase, one of which is dispersed as globules in the other liquid phase.

The system is stabilized by the presence of an *emulsifying agent*.

Emulsified systems range from lotions of relatively low viscosity to ointments andCreams, which are semisolid in nature.

The particle diameter of the dispersed phase generally extends from about 0.1 to 10 m and as 100 m is not uncommon in some preparations.

TYPES OF EMULSIONS

(I) Ordinary emulsion systems / Primary emulsion systems / Simple emulsion systems

(i) o/w type oil dispersed in water

oil dispersed phase
water continuous phase

(ii) w/o type water dispersed in oil

water dispersed phase
oil continuous phase

(II) Special emulsion systems

(i) Multiple emulsions —— w/o/w type
└ o/w/o type

(ii) Micro emulsion

**Simple emulsion type:**

o/w- type of emulsion is a system in which the oil is dispersed as droplet throughout the aqueous phase. Most pharmaceutical emulsions designed for oral administration are of the o/w type; emulsified lotions and creams either of o/w or w/o type depending on their use.

Certain foods such as butter and some salad creams are w/o type emulsions.

**Multiple emulsion type**

These multiple emulsions have been developed with a view to delay the release of an active ingredient. In this type of emulsions three phases are present, i.e. the emulsion has the form w/o/w or o/w/o. In these "emulsions within emulsions", any drug present in the innermost phase now has to cross two phase-boundaries to reach the external continuous phase.

I : Continuous phase (External aqueousphase)

II: Middle oil phase

III: Inner aqueous phase

*Advantages of multiple emulsions*

(i) Prolongation of drug action
(ii) Location of drug in the body.

**Micro emulsions**

Microemulsions are liquid dispersion of water and oil that are made homogeneous, transparent and stable by the addition of relatively large amount of a surfactant and a co-

surfactant. They appear to represent a state intermediate between thermodynamically unstable emulsions and solubolised systems.

Unlike emulsions, they appear as clear transparent solution, but unlike solubilised systems micro-emulsions may not be thermodynamically stable.

Microemulsions containing droplets (w/o or o/w types) with the globule size 10 to 200nm and the volume fraction of the dispersed phase varies from 0.2 to 0.8.

DETERMINATION OF EMULSION TYPE

Several methods are commonly used to determine the type of emulsion. The types of emulsion determined by one method should always be confirmed by means of second method.

**(1) Dye solubility test**

A small amount of a water soluble dye (e.g. methylene blue or brilliant blue) may be dusted on the surface of the emulsion.

If water is the external phase (i.e. o/w type) then the dye will be dissolved uniformly throughout the

media.

If the emulsion is of the w/o -type then particles of dye will lie in clumps on the surface.

**(2) Dilution test**

This method involves dilution of the emulsion with water. If the emulsion mixes freely with the water, it is of o/w -type. Generally, addition of disperse phase will crack an emulsion.

**(3) Conductivity test**

This test employs a pair of electrodes connected to an external electric source and immersed in the emulsion. If the external phase is water, a current will pass through the emulsion and can be made to deflect a volt-meter needle or cause a light in the circuit to glow. if the oil is the continuous phase then the emulsion will fail to carry the current.

*Methods for determination of emulsion type:*

| Test | Observation | Comments |
|---|---|---|
| 1. Dilution test | Emulsion can be diluted only with External phase. | Useful for liquid emulsions only. |
| 2. Dye test | Water-soluble solid dye tints only o/w emulsion and reverse. Microscopic observation usually is helpful. | May fail if ionic emulsifiers are present. |
| 3. Conductivity test | Electric current is conducted by o/w emulsions, owing to the presence of ionic species in water. | Fails in nonionic o/w emulsions. |
| 4. Fluorescence test | Since oils fluoresce under UV-light, o/w emulsions exhibit dot pattern, w/o emulsions fluoresce throughout. | Not always applicable |
| 5. $CoCl_2$ / filter paper test | Filter paper impregnated with $CoCl_2$ and dried (blue) changes to pink when (o/w) emulsion is added. | May fail if emulsion is unstable or breaks in presence of electrolyte. |

FORMULATION OF EMULSION

In developing the formula of an emulsion the crucial decisions are related to the choice of the aqueous and oil phases and of the emulgents and their relative proportions. There can be no general guideline in this respect and the choice of phases and emulgents should be related to the qualities desired for the final product. Usually, ingredient selection is made on the basis of the experience and personal tastes of the formulator and by trial and

error.

CHEMICAL PARAMETERS

**Chemical stability**

All the ingredients of an emulsion should be chemically compatible.

e.g. a soap cannot be used as an emulsifier in a system having a final pH of less than 5.

e.g. some lipids are subjected to chemical changes due to oxidation (rancidity); so in general it is simpler to avoid their use than to depend on antioxidants

**Safety**

All the ingredients should pass the toxicological tests. It is essential, therefore, for the formulator to depend heavily on toxicologic information from suppliers or in the scientific literature, and on regulatory activities by governmental agencies.

**Choice of lipid phase**

The choice of lipid phase depends on the ultimate use of the product.

(i) If the oily phase is the active-ingredient itself (e.g. liquid paraffin emulsion) the formulator has nothing to chose from.

(ii) The drug in a pharmaceutical preparation should not be too soluble in lipid phase then it will reduce the

rate of transfer of the drug molecule to other phases.

(iii)Emulsions prepared for topical purpose (e.g. cosmetics and pharmaceutical emulsions) should possess a good “feel”. Emulsions normally leave a residue of the oily components on the skin after the water has evaporated. Therefore, the tactile characteristics of the combined oil phase are of great importance in determining consumer acceptance of an emulsion

**Phase - volume ratio**

The ratio of the internal phase to the external phase is frequently determined by the

**solubility** of the active ingredients, which must provide the required dose.

If this is not the primary criteria, the phase ratio is normally determined by the desired **consistency** of the product. For liquid emulsions the limits of internal phase vary from 40 to 60%, since with such amounts a stable and acceptable emulsion can be prepared. Lower amounts of internal phase (i.e. disperse phase) gives a product of low viscosity with pronounced degree of *creaming* while higher percentage may produce highly viscous emulsions with tendency of *phase inversion*.

TABLE 1: *Ingredients for oil-phase of emulsions*

| **Class** | **Identity** | **Consistency** |
|---|---|---|
| Hydrocarbon | Mineral oils | Fluids of varying viscosity |
| Hydrocarbon | Petrolatum | Semisolid |
| Hydrocarbon | Polyethylene waxes | Solids |
| Hydrocarbon | Microcrystalline waxes | Solids |
| Ester | Vegetable oils | Fluids of varying viscosity |
| Ester | Animal fats | Fluids or solids |
| Ester | Lanolin | Semisolid |
| Ester | Synthetic (e.g. isopropyl myristate) | Fluids |
| Alcohols | Long chain (natural & synthetic) | Fluids or solids |
| Fatty acids | Long chain (natural & synthetic) | Fluids or solids |
| Ethers | Polyoxypropylenes | Fluids of varying viscosity |
| Silicones | Substituted silicones | Fluids of varying viscosity |
| Mixed | Plant waxes (e.g. Candellia) | Solid |
| Mixed | Animal waxes (e.g. Beeswax) | Solid |

**Choice of emulsifying agents / Emulsifiers / Emulgents**

Emulsifying agents are broadly classified into three classes:

(i) Synthetic emulsifying agent / Surface active agents (SAA) / Surfactants

(ii) Hydrophilic colloid

(iii)Finely divided solids

When an emulsifier is used alone to stabilize an emulsion it is called *primary emulsifier.* Some times a second emulsifier is used to help the primary emulsifier in stabilizing the system the second emulsifier is known as *auxiliary emulsifier*. Generally emulsifiers from (ii) and (iii) category are used both as primary and auxiliary emulsifier.

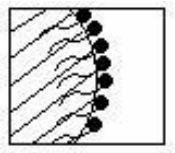
A successful emulsifier must possess some or all of the following characteristics:

(a) The surface tension should be reduced to a value less than 10 dynes/cm$^2$.
(b) A complete and coherent film should be formed around the dispersed globules so as to prevent their coalescence.

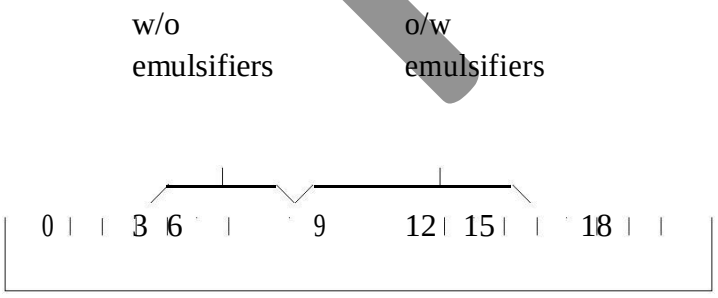
(c) Should assist in building up the zeta potential and viscosity since both of these phenomena contribute to the stability.

**Choice of synthetic surface active agents / Surfactants:**

Molecules and ions that are absorbed at interfaces are termed surface-active-agents or surfactants. An alternative expression is *amphiphile*, which suggests that the molecule or ion has a certain affinity for both polar and nonpolar solvents. Due to the amphiphilic nature of surfactants they absorb at the oil-water interface.



Griffin devised an arbitrary scale of values to serve as a measure of the hydrophilic-lipophilic balance (HLB) of surface-active -agents.




Griffin's HLB Scale

Mode of action of synthetic surfactants

This group of emulsifiers form a flexible film on the oil-water interface. They lower interfacial tension markedly and this contribute to the stability of emulsion. In case of ionic surfactants surface charge is developed, increasing the zeta-potential, which will cause repulsion between two adjacent globules.

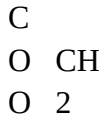
e.g. Sodium lauryl sulphate

Polyoxyethylene sorbitan mono oleate (Polysorbate 80).

***Classification of synthetic Surface Active Agents***

| Class | Surface Active Agent | Chemical formula (in aqs. soln.) | | |
|---|---|---|---|---|
| | | Lipophilic group | Hydrophilic group | Surface inactive ion |
| 1. *Anionic* | | | | |
| (a) Alkali soap | Potassium stearate | $C_{17}H_{35}$ | COO | $K^+$ |
| (b) Organic sulphates | Sodium lauryl sulphate (Sod. dodecyl sulphate) | $C_{12}H_{25}$ | $OSO^3$ | $Na^+$ |
| (c) Organic sulphonates | Sodium cetyl sulphonate (Sod. hexadecane sulfonate) | $C_{16}H_{33}$ | $SO^3$ | $Na^+$ |

| | | | | |
|---|---|---|---|---|
| 2. *Cationic* | | | | |
| (a) Quaternary ammonium compounds | Cetyl trimethyl ammonium bromide (or cetrimide) | C16H33 | $N^{+}(CH_3)_3$ | Br |
| (b) Pyridinium compounds | Dodecyl pyridinium chloride | C12H25 | $N^{+}C_5H_5$ | Cl |
| 3. *Ampholytic* | | | In alkaline soln. anionic | |
| Amino acids | N-dodecyl alanine | C12H25 | $NH\ CH_2\ CH_2\ COO$ | $Na^{+}$ |
| | | | In acid solution cationic | |
| | | C12H25 | $N^{+}H_2\ CH_2\ CH_2\ COOH$ | Cl |
| | | | At isoelectric point zwitterion | |
| | | C12H25 | $N^{+}H_2\ CH_2\ CH_2\ COO$ | none |

| Class | Surface Active Agent | Chemical formula (in aqs. soln.) | | |
|---|---|---|---|---|
| | | Lipophilic group | Hydrophilic group | Surface inactive ion |
| 4. *Non-ionic* | | | | |
| (a) Alcohol-polyethylene glycol ethers | Polyethylene glycol 1000 monocetyl ether (cetomacrogol 1000) | $CH_2$ $(CH_2)n$ (n= 15 to 17) | $(O\ CH_2\ CH_2)m\ COO$ (m = 20 to 24) | none |
| (b) Fatty acid-polyethylene glycol ethers | Polyethylene glycol 40 Monostearate | $C_{17}H_{33}$ | $CO\ (O\ CH_2\ CH_2)_{40}$ OH | none |
| (c) Fatty acid-polyhydric alcohol esters | Sorbitan mono-oleate (TWEEN) | $C_{17}H_{33}$ |  | none |
| | Polyoxyethylene | $C_{17}H_{33}$ |  | none |

| | | | | |
|---|---|---|---|---|
| | sorbitan<br><br>mono-oleate | | O 2<br>O<br><br>H O(<br>( CH2 CH CH<br>O CH2)nO 2 2<br><br>O(CH2 O)<br>CH2 nH | |

## HLB SCALE

The HLB number of surfactants may vary from 40 (sodium lauryl sulfate) to 1 (oleic acid). Emulsifying agents, sometimes used singly, are preferably a combination of two emulsifying agents, which will give a weighted HLB of 8 to 16 which is satisfactory for o/w emulsions and an HLB 3 to 8 for w/o emulsions. NOTE: The HLB required for emulsifying a particular oil in water can be determined by trial and error method; i.e. by preparing appropriate emulsions with emulsifiers having a range of HLB values and then determining that HLB values that yields the "best emulsion". That HLB value is named as Required HLB or RHLB".

TABLE: Required HLB value for some oil phase ingredients

| **Oil** | **RHLB for o/w** | **RHLB for w/o** |
|---|---|---|
| Cottonseed oil | 6-7 | |
| Petrolatum | 8 | |
| Beeswax | 9-11 | 5 |
| Paraffin wax | 10 | 4 |
| Mineral oil | 10-12 | 5-6 |

| | | |
|---|---|---|
| Methyl silicone | 11 | |
| Lanolin, anhydrous | 12-14 | 8 |
| Carnauba wax | 12-14 | |
| Lauryl alcohol | 14 | |
| Castor oil | 14 | |
| Kerosene | 12-14 | |
| Cetyl alcohol | 13-16 | |
| Stearyl alcohol | 15-16 | |
| Carbon tetrachloride | 16 | |
| Lauric acid | 16 | |
| Oleic acid | 17 | |
| Stearic acid | 17 | |

**Choice of hydrophilic colloids**

The naturally occurring gums and synthetic hydrophilic polymers are used as either primarily or (mainly) auxiliary emulsifiers.

*Mode of action*

(i) They do not reduce the surface tension but forms a rigid film on the oil droplets and form a stable o/w emulsion thus inhibits coalescence of droplets.

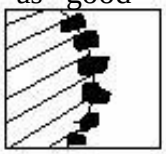
(ii) As an auxiliary emulsifier they increase the viscosity of the continuous phase so that movement of dispersed phase is reduced.

Acacia, tragacanth, alginates, chondrus and pectin. Gelatin, egg yolk, casein, woolfat, cholesterol and lecithin.Methyl cellulose, Hydroxyethyl cellulose, Polyoxyethylene polymer and Carboxyvinyl polymer.

The natural gums exhibit some type of incompatibility or instability depending on the presence of various cations, on pH, or on a second hydrophilic polymer.

**Choice of finely divided solid particles**

The compounds most frequently used in pharmacy are the colloidal clays: bentonite (aluminium silicate) and veegum (magnesium aluminium silicate). They act as good emulsifiers, especially in combination with surfactants or viscosity building agents.



*Mode of action*

(i) They tend to absorb at the oil-water-interface and form thick impenetrable films.
(ii) Sometimes increases the viscosity of water (as continuous phase).

Generally finely divided solids are used in conjunction with a surfactant to prepare o/w emulsions but both o/w and w/o preparations can be prepared by **adding the clay to the external phase first**.

They are used frequently for external purposes such as lotion or cream.

**Specific formulation consideration: Consistency**

Once the desired emulsion and emulsifiers have been chosen, a consistency that provides the desired stability and yet has the appropriate flow characteristics must be attained.

The sedimentation or creaming rate of suspended spherical particles is inversely proportional to the viscosity in accordance with Stoke's law.

Since emulsions should flow or spread easily and since higher viscosity favors stability so thixotrophy in an emulsion is desirable (thixotrophy = phenomenon in which the viscosity of a preparation is reduced by agitation but increases after agitation has been stopped.

Viscosity of emulsions responds to the following changes:

1. When the viscosity of the continuous phase is increased the viscosity of emulsion is also increased. o/w emulsion: Viscosity of water is increased by using gums, clays and viscosity building agents. w/o emulsion: Viscosity of oil is increased by addition of polyvalent metal soaps or the use of high melting waxes and resins.
2. The greater the volume of internal phase, (i.e. greater phase volume ratio) the greater is the apparent viscosity.
3. The viscosity and stability of an emulsion is increased by reducing the size of droplets and by formation of floccules or clumps.
4. It is routinely observed that viscosity of emulsions increases upon aging. Hence, it is recommended that a newly formulated emulsion be allowed to rest undisturbed for 24 hours before checking its viscosity.

**Choice of an antimicrobial preservative**

*Sources of contamination:*

(i) Contaminated raw materials
(ii) Poor sanitation during preparation
(iii) Contamination by the end users

*Substrates of contamination:*

(i) Mainly the water phase is a good medium for microbial growth.
(ii) Some ingredients, such as carbohydrates, pectin, proteins, sterols, and phosphates readily supports the growth of a variety of microorganisms.

*Remedies:*

(i) Use of uncontaminated raw materials
(ii) Careful and through cleaning of equipment with steam.
(iii) Addition of preservatives

*Preservatives commonly used:*

Chlorocresol, chlorobutanol, mercurials [e.g. phenyl mercuric nitrate (PMN), phenyl mercuric acetate (PMA), esters of parahydroxy benzoate (methyl, propyl, butyl, benzyl paraben), sodium benzoate, sorbic acid etc.

Since microorganisms can reside in the water or the lipid phase or both, the preservative should be available at an effective level in both phases. So it is advisable to add an oil soluble and an water soluble preservative simultaneously.

A good example is methyl and propyl paraben. In this case methyl paraben is soluble in water while propyl and higher esters are almost water-insoluble.

Preservatives sometimes *interact* with some ingredients. e.g. phenolic preservatives are especially susceptible to interaction with compounds containing polyoxyethylene groups. Sometimes preservatives are solubilized by the surfactants. The bound or complexed or solubilized preservative can not act as preservative.

**Choice of antioxidants**

The inclusion of an antioxidant in an emulsion formulation may be necessary to protect, not only an active ingredient but also formulation components (e.g. unsaturated lipids) which are oxygen labile.

Oxidation occurs spontaneously under mild conditions generally involved some free radical reactions. Kinetic measurements of fat oxidation in o/w emulsions indicate that the rate of oxidation is dependent on

(i) the rate of oxygen diffusion in the system,
(ii) oxygen pressure (i.e. oxygen content)
(iii)trace element of metal such as Cu, Mn, or Fe or their ions may catalyze the oxidative reactions. improve product stability.

(iv) Some oxidative degradation is pH dependent. So the pH stability profile of the drug and of protective formulation should be established during product development.

*List of selected antioxidants for emulsion system:*

1. *Chelating agents* e.g. Citric acid, EDTA (Ethylene diamine tetraaceticacid)

Phenyl alaninePhosphoric acid ($H_3PO_4$) Tartaric acid

2. *Preferentially oxidized compounds (Reducing agents)* e.g. Ascorbic acid, Sodium sulphite ($Na_2SO_3$) Sodium bisulfite ($NaHSO_3$) Sodium metabisulfite $Na_2S_2O_5$)

3. *Chain terminators*

*Water soluble compounds* e.g. Cystine hydrochlorideThioglycerol Thioglycollic acid Thiosorbitol

*Lipid soluble compounds* e.g. Alkyl gallates (octyl, propyl, dodecyl)Butylated hydroxy toluene (BHT) Butylated hydroxy anisole (BHA) -tocopherol

(Vit-E), Hydroquinone

*Deaeration :*The formulator may wish to deaerate the system by :

(i) Bubbling $N_2$ gas through the liquids to remove dissolved $O_2$.
(ii) boiled before use
(iii) Exposure to vacuum during ultrasonic agitation

(iv) the end space above the container can be flushed with $N_2$ just before sealing.

*Reducing agents:* e.g. Ascorbic acid (Vit-C), Sulphites etc.

They preferentially get oxidized before the oxidation of oil takes place.

*Uses:*

(i) BHA, BHT, Vit-E and the alkyl gallates are particularly popular in pharmaceuticals and cosmetics.
(ii) BHA and BHT have a pronounced odour and should be added at low concentration.
(iii) Alkyl gallates have a better taste.

(iv) L-tocopherol (Vit-E) is well suited for edible or oral preparations, such as those containing Vitamin A.
(v) Some trace metals like copper, iron, manganese ions catalyze the auto-oxidation reaction; therefore, a small amount of sequestering agents like citric acid, EDTA, tartaric or phosphoric acid reduce the reaction rate.

**PREPARATION**

After the purpose of the emulsions has been determined, i.e oral or topical use, and the type of emulsions, o/w or w/o, and appropriate ingredients selected and the theory of emulsification considered experimental formulations may be prepared by a method suggested by Griffin.

*Experimental method*

1. Group the ingredients on the basis of their solubilities in the aqueous and nonaqueous phase.
2. Determine the type of emulsion required and calculate an approximate HLB value
3. Blend a low HLB emulsifier and a high HLB emulsifier to the calculated value
4. Dissolve the oil-soluble ingredients and the emulsifiers in the oil. Heat, if necessary, to approximately 5 to $10^0$C over the melting point of the highest melting ingredient of to a maximum temperature of 70 to $80^0$C.
5. Dissolve the water-soluble ingredients (except acids and salts) in a sufficient quantity of

water. Heat the aqueous phase to a temperature which is 3 to $5^0$C higher than that of the oil phase.
6. Add the aqueous phase to the oily phase with suitable agitation.
7. If acids or salts are employed, dissolve them in water and add the solution to the cold emulsion.

Examine the emulsion and make adjustments in the formulation if the product is unstable.

**EQUIPMENTS**

The preparation of emulsion requires certain amount of energy to form the interface between the two phases, and additional work must be done to stir the system to overcome the resistance to flow. In addition, heat often is supplied to the system to melt waxy solids and /or reduce the viscosity of the oil phase.

Because of the variety of oils used, emulsifying agents, phase-volume ratio and the desired physical properties of the product, a wide selection of equipment is available for preparing emulsions.

1. Mortar and pestle

It consists of a glass or porcelain mortar and a pestle.

*Advantages:*

(i) Small quantity emulsions can be prepared in the laboratory.

(ii) Low cost

(iii) Simplest operation among all other instruments.

*Disadvantages*

(i) Generally, the final particle size is considerable larger then in other equipments.

(ii) It is necessary for the ingredients to have a certain viscosity prior to trituration in order to achieve a satisfactory shear.

2. Agitators / Mechanical stirrers

An emulsion may be stirred by means of various impellers (propellers: produce axial

movements; turbines produce radial and tangential movements) mounted on shafts, which are placed directly into the system to be emulsified. For low viscosity emulsions propeller type can be used but for higher viscosity turbine type is used.

The degree of agitation is controlled by the rotational speed of impeller, by the patterns of the liquid flow and the resultant efficiency ofmixing are controlled by the type of impeller, its position in the container, the presence of baffles, and the general shape of the container.

*Advantages*:

(i) Agitators are used particularly for the emulsification of easily dispersed, low-viscosity oils.
(ii) Can be used for small-scale production and laboratory purpose.

*Disadvantages:*

(i) Continuous shaking tends to break up not only the phase to be dispersed but also the dispersion medium, in this way, impairs the ease of emulsification.

(ii) Particularly useful in preparing suspensions containing poorly wetted solids.
(iii)Useful for the preparation of relatively viscous emulsions

4. Homogenizers

Impeller type of equipment frequently produce a satisfactory emulsion; however, for further reduction in particle size, homogenizers may be employed.

Homogenizers may be used in one of two ways:

1. The ingredients in the emulsion are mixed and then passedthrough the homogenizer to produce the final product.
2. A coarse emulsion is prepared in some other way and thenpassed through a homogenizer for the purpose ofdecreasing the particle size and obtaining a greater degreeof uniformity and stability

Sometimes a single homogenization may produce an emulsion which, although its particle size is small, has a tendency to clump of form clusters. Emulsions of this type exhibit increased creaming tendencies. This is corrected by passing the emulsion through the first stage of homogenization at a high pressure (e.g. 3000 to 5000 psi) and then through the second stage at a greatly reduced pressure (e.g. 1000 psi). This breaks down any clusters formed in the first step (it is a two stage homogenizer).

5. Ultrasonic devices

The preparation of emulsions by the use of ultrasonic vibrations also is possible. An oscillator of high frequency (100 to 500 kHz) is connected to two electrodes between which placed a piezoelectric quartz plate. The quartz plate and electrodes are immersed in an oil bath and, when the oscillator is operating, high-frequency waves flow through the fluid. Emulsification is accomplished by simply immersing a tube containing the emulsion ingredients into this oil bath.

*Advantages*

Can be used for low viscosity and extremely low particle size.

*Disadvantages*

Only in laboratory scale it is possible. Large scale production is not possible..

**STABILITY OF EMULSION**

The stability of an emulsion must be considered in terms of physical stability of emulsion system and the physical and chemical stability of the emulsion component including pharmacologically active ingredients, if any.

Definition: A physically stable emulsion component may be defined as a system in which the globules retain their initial character and remain uniformly distributed throughout the continuous phase.

Symptoms of instability

As soon as an emulsion has been prepared, time and temperature dependent processes occur to effect its separation. During storage, an emulsion's stability is evidenced by (i) creaming, (ii) flocculation and / or (iii)coalescence.

CREAMING

Creaming is the upward or downward movement of dispersed droplets related to the continuous phase due to the difference of density between two phases.

N.B. The downward creaming is also called sedimentation. Generally the term "sedimentation" is associated with the downward movement of solid particles in suspension.

Creaming is undesirable in a pharmaceutical product where homogeneity is essential for the administration of correct and uniform dose. It may still be pharmaceutically acceptable as long as it can be reconstituted by a modest amount of shaking. However, in case of cosmetic products creaming is usually unacceptable because it makes the product inelegant.

Creaming or sedimentation brings the particle closer together and may facilitate a serious problem of coalescence.

The rate at which a spherical droplet or particle sediments in a liquid is governed by Stoke's equation.

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

where v = velocity of creaming

d = diameter of globule

$\rho_{1,2}$ = densities of dispersed phase and continuous phase Respectively

$\eta$ = viscosity of the continuous medium

A consideration of this equation shows that the rate of creaming will be decreased by:

(i) reduction of droplet size

(ii) a decrease in the density difference between the two phases

(iii) increase in the viscosity of the continuous phase

*Reduction in droplet size* is done by using an efficient homogeniser or colloid mill. There are, however,technical difficulties in reducing the diameter of droplets to below about 0.1 m.

Stoke's equation predicts that no creaming is possible if the specific gravities of the two phases are equal. A few successful attempts have been made to equalize the densities of the oil and aqueous phase. This method is of little use in pharmaceutical practice because, it usually involves the addition of substances those are unacceptable in pharmaceutical preparations.

The most frequently used approach is to raise the viscosity of the continuous phase although this can be done to the extent that the emulsion still can be removed readily from its container

and spread on the body surface conveniently.

FLOCCULATION

Flocculation of the dispersed phase may take place before, during or after creaming.

Flocculation is reversible aggregation of droplets of the internalphase in the form of three-dimensional clusters.

In the floccules the droplets remain aggregated but intact. The droplets can remain intact when the mechanical or electrical barrier is sfficient to prevent droplet coalescence.

e.g. if an insufficient amount of emulsifier is present, emulsion droplets aggregate and coalesce.

The reversibility of this type of aggregation depends on the strength of the interaction between particles, as determined by:

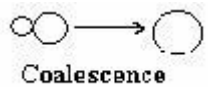
(i) the chemical nature of the emulsifier,
(ii) the phase-volume ratio, and

(iii)the concentration of dissolved substances, especially electrolytes.

The viscosity of an emulsion depends to a large extent on flocculation, which restricts the movement of particles and can produce a fairly rigid network. Agitation of an emulsion breaks the particle-particle interactions with a resulting drop of viscosity; i.e. shear thinning.

COALESCENCE

Coalescence is a growth process during which the emulsified particles join to formlarger particles. Any evidence for the formation of larger droplets by merger of smaller droplets suggeststhat the emulsion will eventually separate completely.


Coalescence

The major factor which prevents coalescence in flocculated and deflocculated

emulsions is the mechanical strength of the interfacial barrier. Thus

macromolecules andparticulate solids forms thick interfacial film and hence natural gums and proteins are useful as auxiliary emulsifiers whenused at low level, but can even be used as primary emulsifiers at higher concentrations.

Any agent that will destroy the interfacial film will crack the emulsion. Some factors

are:

(i) the*addition of a chemical* that is incompatible with the emulsifying agent. Examples include surfactants of opposite ionic charges, addition of large ions of opposite charge, addition of electrolytes such as Ca and Mg salts to emulsions stabilized with anionic surfactants.

(ii) *Bacterial growth*: Protein materials and non-ionic surfactants are excellent media for bacterial growth.

(iii) *Temperature change*: Protein emulsifying agent may be denatured and the solubility characteristics of non-ionic emulsifying agents change with a rise in temperature. Heating above $70^0$C destroys almost all emulsions. Freezing will crack an emulsion; this may be due to the ice-crystals disrupting the interfacial film around the droplet.

**EVALUATION OF EMULSION**

SHELF LIFE

The final acceptance of an emulsion depends on stability, appearance, and functionality of the packaged product. There is no quick and sensitive methods for determining potential instability in an emulsion are available to the formulator. To speed up the stability test program the emulsion is subjected to various stress conditions.

The stress conditions normally employed include:

(i) aging and temperature

(ii) centrifugation,
(iii)agitation

*Aging and temperature*

It is routine to determine the shelf life of all types of preparations by storing them for varying periods of time at temperatures that are higher than those normally encountered. A particularly useful means of evaluating shelf life is cycling between two temperatures preferably between $4^0$ and $45^0$C.

The normal effect of aging an emulsion at elevated temperature is acceleration of the rate of coalescence or creaming, and this is usually coupled with changes in viscosity

*Centrifugation*

Stoke's law shows that creaming is a function of gravity (g), and an increase in gravity therefore accelerates separation. Centrifugation at 3750 rpm in a 10-cm radius centrifuge for a period of 5 hours is equivalent to the effect of gravity for about one year. Thus shelf-life under normal storage conditions can be predicted rapidly by observing the separation of the dispersed phase due to either creaming or coalescence when the emulsion is exposed to centrifugation.

*Agitation*

Droplets in an emulsion exhibit Brownian movement. Coalescence takes place when droplets impinge upon each other. Simple mechanical agitation contributes to the energy with which two droplets impinge upon each other. Thus agitation can also break emulsion. A typical case is the manufacture of butter from milk.

Conventional emulsions may deteriorate from gentle rocking on a reciprocating shaker.

This works in two ways:

(i) increases the rate of impingement of droplets, and

(ii) Reduction of viscosity of a normally thixotropic system.

PHYSICAL PARAMETERS

The most useful parameters commonly are measured to assess the effect of stress conditions on emulsions include

1. phase separation,
2. viscosity,
3. electrophoretic properties, and
4. Particle size analysis and particle count.

***Phase separation***

The rate and extent of phase separation after aging of an emulsion may be observed visually or by measuring the volume of separated phase.

A simple means of determining phase separation due to creaming or coalescence involves withdrawing a samples of the emulsion from the top and the bottom of the preparation after some period of storage and comparing the composition of the two samples by appropriate analysis of water content, oil content, or any suitable constituent.

***Viscosity***

The viscosity of an emulsion for the use of shelf studies is not concerned with absolute values of viscosity, but with changes in viscosity during aging. Since emulsions are generally non-Newtonian systems and the viscosity is measured by viscometer of the cone-plate type are particularly useful for emulsions, but instruments utilizing co-axial cylinders (e.g. cup and bob viscometer) are the easiest to use. The use of a penetrometer is often helpful in detecting changes of viscosity with age.

In case of w/o emulsions flocculation is quite rapid. After flocculation viscosity drops quickly and continues to drop for some time (5 to 15 days at room temperature).

In case of o/w emulsions globule flocculation causes an immediate increase in viscosity. After this initial change, almost all emulsions show changes in viscosity with time which follow a linear relationship when plotted on a log-log scale.

A practical approach for the detection of creaming or sedimentation, before it becomes visibly apparent, utilizes the Helipath attachment of the Brookfield viscometer

***Electrophoretic properties***

If the instability of the emulsion is due to flocculation only (and not due to coalescence)then the zeta potential will have to be measured.

Zeta potential can be determined with

a. the aid of the moving boundary method or
b. more quickly and directly, by observing the movement of particles under the influence ofelectric current.

The zeta potential is especially useful for assessing flocculation since electrical charges on particles influence the rate of flocculation.

The measurement of electrical conductivity has been claimed to be a powerful tool for the

evaluation of emulsion shortly after preparation.

***Particle size number analysis***

Changes of the average particle size or of the size distribution of droplets are important parameters for evaluating emulsions.Particle size determination can be carried out by microscopic method pr by electronic counting machines. (e.g. Coulter counter). Light scattering and related reflectance relationships have been used for particle size determination.The utility of particle size for predicting or interpreting emulsion shelf-life is some what doubtful.

***Practical recommendation for shelf-life prediction in temperate (hot and humid) zone***

A typical test program for an "acceptable: emulsion (in temperate zone) may be as follows: The emulsion should be stable with no visible signs of separation for at least:

(i) 60 to 90 days at 45 or $50^0$C,
(ii) 5 to 6 months at $37^0$C and
(iii) 12 to 18 months at room temperature.

(iv)After 1 month storage at $4^0$C
(v) After 2 to 3 freeze-thaw cycles between 20 and $+25^0$C.
(vi) After 6 to 8 freeze-thaw cycles between 4 and $45^0$C with storage at each temperature for not less than 48 hours.

(vii)No deterioration by centrifuging at 2000 to 3000 rpm at room temperature.

(vii) No deterioration by agitation for 24 to 48 hours on a reciprocating shaker (60 cycles perminute) at room temperature and at $45^0$C.

## ELIXIRS:

Def: Elixirs are clear, sweetened hydro alcoholic solution intended for oral use and are usually flavored to enhance their palatability.

- **Non medicate elixirs** are employed as vehicles and
- Medicated elixirs are used for the therapeutic effect of the medicinal substance.
- Elixir when compared with the
- These are less sweet and less viscous because there will contain lower proportion of sugar so there are less effective than syrups in making the taste of medicinal substance.
- Elixirs are hydro alcoholic because of these both water-soluble and alcohol soluble components can be prepared.

- Elixirs are preferred than syrup because of their stability and ease with which they are prepared.
- Proportion of alcohol in elixir varies widely as the individual components of elixirs have different water and alcohol solubility characteristics so a specific blend of alcohol and water should be selected to maintain all the components in solution
- Elixirs containing poor water solubility components require greater proportion of alcohol
- Other solvents such as glycerin and propylene glycol are used in elixirs as adjunctive solvents.
- Sucrose or sucrose syrup is used to sweeten the elixir other substances like sorbitol, glycerin and artificial sweeteners are also used
- Elixirs containing high alcoholic content uses artificial sweetener such as saccharin, cyclamate which are carcinogenic , so aspartame is used which is about 200 times sweeter than sucrose which is sparingly soluble in water and stable at pH of 4.3

- ✓ Elixirs contain flavoring agents to increase their palatability and coloring agents to enhance their appearance
- ✓ Elixirs containing more than 10 to 12% of alcohol are usually self preserving and do not require the addition of preservative
- ✓ Medicated elixirs are formulated so that a patient receives the usual adult dose of the drug in a convenient measure of elixir one or two teaspoonfuls (5 or 10ml) provides the usual adult dose of the drug
- ✓ Elixirs can be easily administered to patients who have difficulty in swallowing solid dosage forms.
- ✓ **Disadvantage** of elixirs is their high alcohol content

**Preparation of elixirs:**

Elixirs are usually prepared

1. by simple solution with agitation or
2. by admixture of two or more liquid ingredients

Alcohol soluble and water soluble components are dissolved separately in alcohol and purified water, then the aqueous solution is added to alcoholic solution rather than the reverse to maintain high possible alcoholic strength at all time so that to minimize separation of the alcohol – soluble components after mixing two solutions the mixture is made up to the volume with vehicles

Sucrose increases viscosity and decreases the solubilizing properties of water so added after primary solution is formed

Elixirs should be clean but usually the final mixture will be cloudy because of separation of flavoring oils by reduced alcoholic concentration to reduce this effect elixir is permitted to stand for prescribed no of hours to ensure saturation of the hydro alcoholic solvent and to permit the oil globules to coalesce so that they can be easily removed by filtration talc or siliceous earth is usually used as filter aid in the preparation of elixirs, absorbs the excessive amount of oils

Presence of glycerin, syrup, sorbitol and propylene glycol in elixirs contributes to the solvent effect of the hydro alcoholic vehicle, assist in the dissolution of the solute, enhances stability and viscosity of the preparation

**NON MEDICATED ELIXIRS:**

These are used for the addition of a therapeutic agent to a pleasant tasting vehicle and dilution of an existing medicated elixir

In selecting a liquid vehicle for a drug substance, should be concerned with the solubility and stability of drug substance in water and alcohol if hydro alcoholic vehicle is selected, the proportion of alcohol should be only slightly above the amount needed to effect and maintain the drugs solution

When diluting an existing medicated elixir, the non-medicated elixir with selected as diluents should have the same alcohol concentration the color and flavor should be same

For non-medicated elixir is **Aromatic elixir USP:**

| | |
|---|---|
| Orange oil | 2.4ml |
| Lemon oil | 0.6ml |
| Coriander oil | 0.24ml |
| Anise oil | 0.06ml |
| Syrup | 375ml |
| Talc | 30g |
| Alcohol, purified water | |
| q.s to make | 1000ml |

**Method:**Dissolve the oil in alcohol to make 250ml to this solution add the syrup in several portions, agitating vigorously after each addition and afterward add, in the same manner, the

required quantity of purified water, mix the talc with the liquid and filter through a filter wetted with diluted alcohol, returning the filtrate until a clear liquid is obtained

Alcohol content 21 to 23%

Uses: a pleasantly flavored vehicle, employed in the preparation of many other elixirs

**MEDICATED ELIXIRS:**

Most official and commercial elixirs contain a single therapeutic agent is dose adjustment which is not possible with two or more therapeutic agents

Example of medicated elixirs:

**Phenobarbital elixir:**

| | |
|---|---|
| Phenobarbital | 4g |
| Orange oil | 0.25ml |
| Propylene glycol | 100ml |
| Alcohol | 200ml |
| Sorbitol solution | 600ml |
| Color | q.s |
| Purified water to make | 1000ml |

Dissolve Phenobarbital in alcohol and add orange oil, propylene glycol, sorbitol solution, color and sufficient purified water to produce the required volume, mix and filter if necessary.

**Dry elixirs:**

Dry elixirs has been conducted by Kim and co – workers, dry elixirs containing a non steroidal anti inflammatory drug and ethanol were encapsulated in a dextran wall the dissolution rate constant of the drug from the microcapsules usually increased considerably compared to the drug alone due to the co solvent ethanol

This type of dosage form are useful to improve the solubility, dissolution rate, and bioavailability of the drug

**EVALUATION:**

1. Clean and purified vehicle (water):

The water is filtered and purified at the plant to destroy any microbes and to remove particle from the water.

Quality control technicians test the water frequently to ensure that it is clean and pure before the syrup is made

The syrup is also thoroughly filtered before filling in bottles

2. Light transmittance test:

A light transmittance meter is a newer tool that is used to check syrup colour.

In a light transmittance meter a syrup sample is checked for color by passing light through the sample.

The percentage of light transmission is compared to light transmission rate set for different grades. When using one, you need to be sure there are no finger prints on the syrup test bottle, and that the syrup sample has no bubbles or cloudiness.

Any of these conditions may diminish the light that is transmitted through the sample and therefore lowers the grade of the sample.

1. Viscosity measurement:

Viscosity is a property of liquids that is directly related to the resistance to flow.

Viscosity measurement is very important quality control test in case of syrups and elixir.

Viscosity and consistency directly relates with stability of solutions.

Viscosity increases stability also increases. Viscosity chance of stability.

Types of viscosity:

Absolute viscosity:

Measure when all the specifications and place meter are defines.

Relative viscosity:

Measure when we take any standard and make comparison.

But no decisions are made after taking relative viscosity.

Dynamic viscosity:

The resistance to flow encountered when one layer or plane of fluid attempts to move over another identical layers or planes of fluid at a given speed dynamic viscosity is also called absolute viscosity.

Kinemics viscosity:

Addition and deletion of force is known as the kinematic viscosity method used for measurement of viscosity.

Method 1 (u tube viscometer)

Method 2 (capillary viscometer method)

Method 3 (rotating viscometer method)

Method 4 (concentric cylinder viscometer also known as absolute viscometers )

Method 5 (cone plate viscometer)

Method 6 (spindle viscometers and relative viscometer)

SYRUPS :

Definitions: syrups are concentrated aqueous preparations of a sugar or sugar substituted with or without flavoring agents and medicinal substances.

- When purified water alone is used in making the solution of sucrose it is known as syrup or **simple syrup.**
- Syrup containing flavoring agents without medicinal substances are called **non medicated or flavored vehicles**.

**NON MEDICATED SYRUPS:**

**Examples** of some non medicated syrups are cherry syrup, cocoa syrup, orange syrup etc.

These may contain various aromatic or pleasantly flavored substances and is intended to be used as vehicle or flavor for prescriptions

These non-medicated syrups are intended to serve as pleasant tasting vehicles for medicinal substances to be added in the standard formula for medicated syrup

**MEDICATED SYRUPS:**

The aqueous preparations containing added medicinal substances are called **medicated syrups.**

Examples of some medicated syrups are

Demerol syrup (analgesic)

Bentylsyrup(anti cholinergics)

Benadryl syrup (anti tussive)

Syrups contain little or no alcohol these are used as vehicles of choice in many drugs, sucrose based syrups continuous administration to children may cause an increase in dental caries and gingivitis, to overcome this alternate formulations of the drug either unsweetened or sweetened with non cariogenic substances should be used

Syrups has a promising role in masking properties of bitter or saline drugs, glycrrhize syrup has been used to mask the salty taste of bromides, iodides, chlorides and preparations containing B complex vitamins it is used because of its colloidal character and its sweetness.

Acacia syrup because of its colloidal character is used as a vehicle for masking the disagreeable taste of many drugs

Raspberry syrup BP 1988 is useful in masking the taste of bitter drugs.

**Components of syrups:**

Syrups contains the following components

- Sugar, usually sucrose or sugar substitute used to provide sweetness and viscosity
- Anti microbial preservatives
- Flavoring agents
- Coloring agents
- Purified water

They may also contain special solvents, solubilizing agents, thickeners or stabilizers

**Sucrose and non – sucrose based syrups:**

1. Sucrose is commonly used in syrups it may be replaced with other substances like sorbitol, glycerin and propylene glycol
2. In case of diabetic patients and diet restricted to non glycogenetic substances, substances like methyl cellulose or hydroxyethyl cellulose are used
3. These materials are not hydrolyzed and absorbed into the blood stream and the viscosity resulting from these cellulose derivatives is similar to that of sucrose syrup.
4. Addition of artificial sweeteners makes a true syrup, sucrose and alternative agents are added to syrup in order to impart viscosity, along with this sweetness and flavorants, results in masking the taste of the medicinal agents.

5. When the syrup is swallowed, only a portion of dissolved drug comes in contact with the taste buds, the remaining drug being carried past them and down the throat in the viscous syrup.
6. This type of physical concealment of the taste is not possible for a solution of a drug in un thickened, mobile aqueous preparations.
7. The concentration of sucrose is usually 60 to 80% this is not only for desired sweetness and viscosity but also its stability, as the dilute sucrose solutions is efficient nutrient medium for the growth of microorganisms, yeast and molds
8. Whereas the concentrated sucrose solutions are resistant to microbial growth because the availability of water is very less for the growth of micro organisms
   For example simple syrup is prepared by dissolving 85 g of sucrose in enough purified water to make 100 ml of syrup
9. This syrup does not requires the addition of preservatives when used soon, if it is stored for long time preservatives are added.
10. If the syrup is saturated with the sucrose in cool storage sucrose may crystallize from solution which may affect its stability.
11. When heat is used in the preparation inversion of a slight portion of the sucrose. Sucrose solutions are dextrotary, hydrolysis proceeds, optical rotation decreases and becomes negative as reaction is complete this is termed inversion because invert sugar is formed.

**Inversion process** occurs rapidly in the presence of acids, the hydrogen ion acts as catalyst in this hydrolytic reaction. Invert sugar under goes fermentation greatly than sucrose and changes to dark color, these two reducing the oxidation of other substances.Invert syrup B.P: it is prepared by hydrolyzing sucrose with hydrochloric acid and neutralizing the solution with calcium or sodium bicarbonate.The sucrose in the 66.7%w/w solution must be at least 95% inverted it when mixed in suitable proportions with syrup, prevent the deposition of crystals of sucrose under storage.The levulose formed during inversion is sweeter than sucrose. The relative sweetness of levulose, sucrose and dextrose is in the ratio of 173:100:74.So invert sugar is 1/100(173+74)1/2=1.23 times as sweet as sucrose .this levulose formed during hydrolysis is responsible for the darking of syrup.Syrup or sucrose is overheated it caramelizes.

**Antimicrobial preservative:** the amount of preservation required to protect a syrup from microbial growth depends on the proportion of water available for growth, the nature of inherent preservative activity of some formulative materials and capability of preservative

eg: flavorings oils that are sterile and posses antimicrobial action.

Commonly used **preservatives** are

Benzoic acid -0.1-0.2%

Sodium-benzoate 0.1-0.2%and

Combinations of Methylparaben,

Propyl parabens,

Butyl parabens of about 0.1%.

Alcohol is also used in syrups to assist in dissolving alcohol soluble ingredients.

**Flavorant:**

Syrups are flavored with synthetic or natural flavoring agents.

Eg: volatile oils eg: orange oil, vanillin, mint.

These are used to render pleasant taste to the syrup.

As syrups are aqueous preparations flavorants must be water soluble and some amount of alcohol is added to solution of a poorly water-soluble flavorant.

**Colorant**:

These are used to enhance the appeal of the syrup, it should correlate with flavorant used.

eg: green with mint, brown with chocolate. These are generally water soluble, non reactive with the other ingreadients, it should be stable at PH range and intensity of light that the syrup encounter during its shelf life.

**Preparation of syrups:**

Syrups are prepared by one of the four general methods, depending on the physical and chemical characteristics of the ingredients.

They are:

1) Solution with the acid of heat.
2) Solution of the ingredients by agitation without the acid of heat.
3) Addition of sucrose to a prepared medicated liquid or to a flavored liquid.
4) Percolation of either the source of the medicating substance or the sucrose.

1. **Solution with the aid of heat:**
   - Syrups are prepared by this method when it is desired to prepare syrups quickly as possible.
   - It is used when components of syrups are not damaged or volatilized by heat. In this method the sugar is added to the purified water and heat is applied until the sugar is dissolved.

- Then other heat-stable components are added to the hot syrup, the mixture is allowed to cool and its volume is adjusted with purified water.
- If heat labile agents or volatile substances , such as volatile flavoring oils and alcohol are added to syrup after sugar is dissolved and the solution is rapidly cooled to room temperature.
- The syrups which are made from an infusion, a decoction or an aqueous solution containing organic matter such as sap from maple trees is heats to the boiling point of syrup to coagulate albuminous matter, this is separated by straining if these are present in the syrup fermentation may occur.
- Saccharo meter are very useful in making syrups by hot process where specific gravity of the syrup can be known. They may be floated in the syrup while boiling so that concentration can be determined without cooling the syrup so that no need to heat It again to concentrate it further.
- Excessive heating causes inversion of sucrose and leads to ferment.
- Syrup cannot be autoclaved for sterilization as caramelization occurs and it will become brownish color.
- Acacia syrup is prepared by this method.

**Ex: Acacia syrup:**

Acacia, granulator powdered ----------100g

Sodium benzoate ----------1g

Vanilla tincture ----------5ml

Sucrose ----------800g

Purifies water, a sufficient quantity to make ----------1000ml

**Procedure**: Mix the acacia, sodium benzoate and sucrose then add 425ml of purified water and min well heat the mixture on a steam bath until solution is completed then cool it remove the scum, add the vanilla tincture and sufficient purified water to make the product measure 1000ml of strain of necessary

Uses: a flavor and demulcent.

**2. Solution by agitation without the aid if heat:**

- This method is used to avoid heat induced inversion of sucrose, syrup is prepared by agitation.
- It is used when components of syrups are not damaged or volatilized by heat. In this method the sugar is added to the purified water and heat is applied until the sugar is dissolved.

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Uses: a flavor and demulcent.

**3. Solution by agitation without the aid if heat:**

- This method is used to avoid heat induced inversion of sucrose, syrup is prepared by agitation.

- On a small scale, sucrose and other formulative agents are dissolved in purified water by placing the ingredients in a vessel larger than the volume of syrup to be prepared in order to provide through agitation of the mixture.

- This is time consuming process but the product has its maximum stability.
- Huge glass-lined or stainless steel tanks with mechanical stirrers or agitators are employed in large scale preparations. When simple syrup or some other non-medicated syrup, rather than sucrose is used as sweetening agent and which other liquids which are soluble in the syrup or miscible with are added and mixed thoroughly to form a uniform product.
- When solids are added to syrup, it should be dissolved first in minimal amount of purified water and add this resulting solution into the syrup.
- When solids are directly added to syrup, they will dissolve slowly because of the viscous nature of the syrup will not permit the solid substance to distribute throughout the syrup to the available solvent and only limited amount of available water is present in concentrated syrups.
- Codeine phosphate oral solution and codeine linctus pc are the syrups prepared by this method and it is given by BP.

**Formulation:**

**Codeine phosphate linctus PC:**

Codeine phosphate ----------3g

Compound tartrazine solution ---------10ml

Benzoic acid solution ----------20ml

Chloroform spirit ----------20ml

Water for preparations ----------20ml

Lemon syrup ----------200ml

Syrup ----------1000ml

**Manufacturing:** dissolve the codeine phosphate in the water, add 500ml of the syrup and mix. Add the other ingredient and sufficient syrup to produce 1000ml for pediatric use 200ml of this linctus is diluted with sufficient syrup to make 1000ml.

In usa the Food and Drug administration (FDA) has banned the use of chloroform in medicines and cosmetics because of its carcinogenicity in animals

**4. Addition of sucrose to a medicated liquid or to a flavored liquid:**

- This method is used in cases where medicated liquids such as tincture or fluid extract, are added to syrup to medicate it
- Syrups prepared by this method usually develop precipitates because alcohol is used as an ingredient, and the resinous and oily substances are dissolved in the alcohol precipitate when mixed with syrup

- a modification of this process consists of mixing the fluid extract or tincture with the water, allowing the mixture to stand to permit the separation of insoluble constituents, filtering and then dissolving the sucrose in the filtrate
- This is not used when the precipitated ingredients are medicinal agent

5. **Percolation:**
   - In this process purified water or aqueous solution is permitted to pass slowly through a bed of crystalline sucrose, thus by dissolving the sucrose syrup is formed.
   - A cotton pledge is placed in the neck of the percolator and the water or aqueous solution added.
   - By means of a stopcock the flow is regulated so that drops appears in rapid succession if necessary, some part of the liquid is recycled through the percolator to dissolve all the sucrose, finally sufficient purified water is passed through the cotton to make the required volume.
   - To get good results using this process following care should be taken.
   - The percolator used should be cylindrical or semi cylindrical and cone shaped as it near the lower orifice.
   - A coarse granular sugar must be used, otherwise it will coalerce into a compact per meat.
   - Purified cotton must be introduced with care of pressed too tightly the cotton will stop the process, of inserted too loosely, the liquid will pass through the cotton rapidly and filtrate will be weak and turbid.
   - This method is preferred for the preparation of syrup USP.

**Simple syrup:**

Sucrose ----------850g

Purified water, a sufficient quantity, to make ----------1000ml

Boiling water may be used for this preparation.

Place the sucrose in a suitable percolator the neck of which is nearly filled with loosely packed cotton, moistened, after packing, with a few drops of water, pour carefully about 450ml of purified water the outflow to a steady drip of percolate return the percolate if necessary until all of the sucrose has dissolved then wash the percolator and the cotton with sufficient purified water to bring the volume of the percolate to 1000ml and mix.