UNIT 4: LIQUID ORALS

Syllabus: Formulation and evaluation of suspensions, emulsions and solutions. Stability of these preparations.

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.

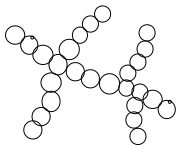


Fig. floccule

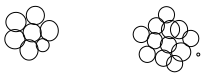


Fig. Coagule

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
ρ_s, ρ_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 ∞ (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 ∞ (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

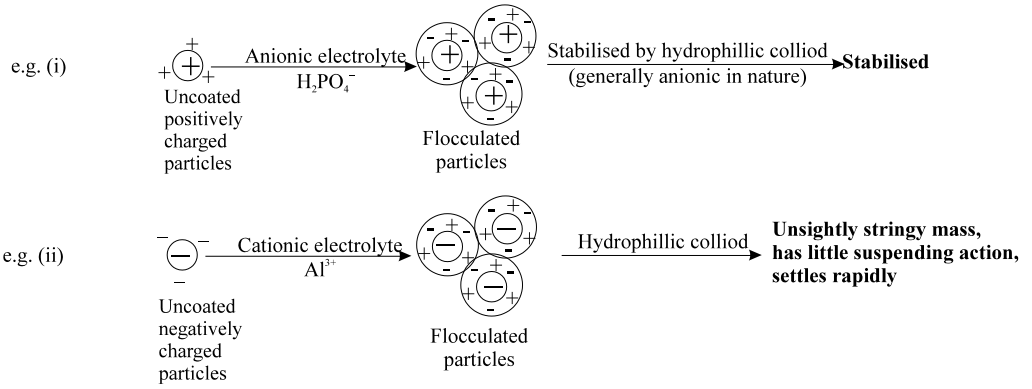
Although the controlled flocculation approach is capable of fulfilling the desired physical chemical requisites of a pharmaceutical suspension, the product can look unsightly if F, the sedimentation volume, is not close to or equal to 1. So a suspending agent is added to retard sedimentation of the flocs. 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

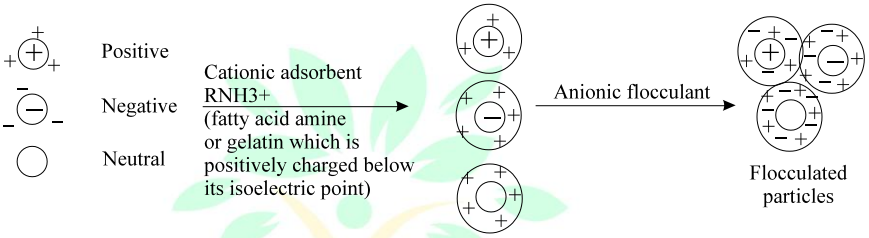
(i) the initial particle charge

(ii) the charge carried by flocculating agent and

(iii) the charge carried by suspending agent.



To overcome this incompatibility the following method is applied



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 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.

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

$F\infty = V\infty / Vo$

$F\infty$ = sedimentation volume of *deflocculated* suspension

$V\infty$ = 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, $\beta = F / F\infty$
$= (V\infty / Vo) / (Vu / Vo)$
$= (V\infty / Vu)$

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

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.

EMULSION

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 and creams, which are semisolid in nature.

The particle diameter of the dispersed phase generally extends from about 0.1 to 10 μm and as 100 μm are 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

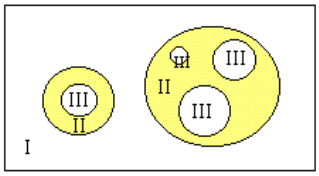
Simple emulsion type:

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.



Photomicrograph of w/o/w emulsion system

I : Continuous phase (External aqueous phase)

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:

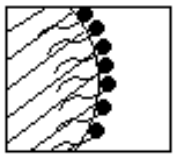
(i) Synthetic emulsifying agent / Surface active agents (SAA) / Surfactants
(ii) Hydrophilic colloid
(iii)Finely divided solids

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:

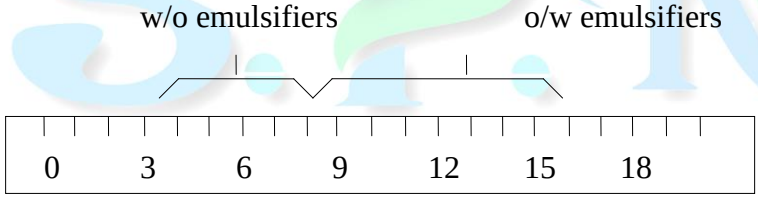
(a) The surface tension should be reduced to a value less than 10 dynes/cm^2.
(b) A complete and coherent film should be formed around the dispersed globules so as to prevent their coalescence.
(c) Should assist in building up the zeta potential and viscosity since both of these phenomena contribute 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

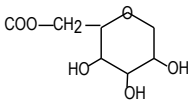
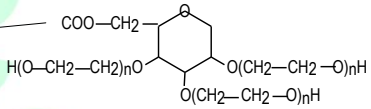
Mode of action of synthetic surfactants

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)	$C_{16}H_{33}$	$N^+(CH_3)_3$	Br^-
(b) Pyridinium compounds	Dodecyl pyridinium chloride	$C_{12}H_{25}$	$N^+C_5H_5$	Cl^-
3. *Ampholytic*				
Amino acids	N-dodecyl alanine	$C_{12}H_{25}$	In alkaline soln.– anionic $NH-CH_2-CH_2-COO^-$	Na^+
		$C_{12}H_{25}$	In acid solution – cationic $N^+H_2-CH_2-CH_2-COOH$	Cl^-
		$C_{12}H_{25}$	At isoelectric point – zwitterion $N^+H_2-CH_2-CH_2-COO^-$	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 sorbitan mono-oleate	$C_{17}H_{33}$		none

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	

Example: Formula of an emulsion is as follows:

Ingredient	Amount	RHLB (o/w)
1. Beeswax	15g	9
2. Lanolin	10g	12
3. Hard paraffin wax	20g	10
4. Cetyl alcohol	5g	15
5. Emulsifier	2g	
6. Preservative	0.2g	
7. Color	q.s.	
8. Water, purified q.s.	100g	

To calculate the overall RHLB of the emulsion the following calculation is carried out:

Oil Phase	Amount	(Amount/Total)xRHLB
1. Beeswax	15g	(15/50)x9 = 2.7
2. Lanolin	10g	(10/50)x12 = 2.4
3. Paraffin	20g	(20/50)x10 = 4.0
4. Cetyl alcohol	5g	(5/50)x15 = 1.5
Total	**50g**	**10.6**

Next, a blend of two emulsifiers is chosen, one with an HLB above 10.6 and the other below 10.6. Let these two surfactants be Tween80 (HLB = 15) and Span 80 (HLB = 4.3). These two surfactants should be mixed in such a ratio that the mixture will have a HLB of 10.6. By aligation method:

HLB of Tween80 → Parts of Tween80 → 15 → 6.3

RHLB → 10.6

HLB of Span80 → Parts of Span80 → 4.3

5.6

Required amount of Tween80 = {6.3/(6.3+5.6)}x Total amount of emulsifier

= 0.53x2 g

= 1.06 g

Required amount of Span80 = {5.6/(6.3+5.6)}x Total amount of emulsifier

= 0.47x2 g

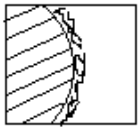
= 0.94 g

Therefore, using 1.06 g Tween80 and 0.94 g of Span 80 we can stabilize the above formula of an emulsion.

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.

Examples:

(i) Plant origin: Acacia, tragacanth, alginates, chondrus and pectin.

(ii) Animal source: Gelatin, egg yolk, casein, woolfat, cholesterol and lecithin.

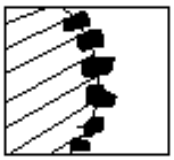
(iii)Synthetic: Methyl cellulose, Hydroxyethyl cellulose, Polyoxyethylene polymer and Carboxyvinyl polymer.

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.

[*For more details see Lieberman & Lachman, Industrial Pharmacy, 3rd Edn. pp 521.*]

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. Thus the use of chelating agents, in a formulation may markedly 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 tetraacetic acid)
   Phenyl alanine
   Phosphoric 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 hydrochloride
   Thioglycerol
   Thioglycollic acid
   Thiosorbitol
   Lipid soluble compounds e.g. Alkyl gallates (octyl, propyl, dodecyl)
   Butylated hydroxy toluene (BHT)
   Butylated hydroxy anisole (BHA)
   α-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
   [N.B. For experimental formulations, use a higher concentration of emulsifier (e.g. 10 to 30% of the oil phase) than that required to produce a satisfactory product.
4. Dissolve the oil-soluble ingredients and the emulsifiers in the oil. Heat, if necessary, to approximately 5 to 10^0C over the melting point of the highest melting ingredient of to a maximum temperature of 70 to 80^0C.
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 5^0C 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.
8. Examine the emulsion and make adjustments in the formulation if the product is unstable.

Large scale industrial method

The preparation of an emulsion requires work to reduce the internal phase into small droplets and disperse them throughout the external phase. This can be accomplished by a mortar and pestle or a high speed emulsifier. The addition of emulsifying agents not only reduces this work but also stabilizes the final emulsion. Emulsions may be prepared by four principle methods:

1. <u>Addition of internal phase to external phase</u>

Let us take a model of o/w emulsion.

(i) The water soluble substances are dissolved in water and the oil soluble substances are dissolved in oil.

(ii) The oil mixture is added in portions to the aqueous preparation with agitation (in a colloid mill or homogenizer).

N.B. Sometimes, in order to give a better shearing action during the preparation, all of the water is not mixed with the emulsifying agent until the primary emulsion with oil is formed; subsequently, the remainder of the water is added.

e.g. *Emulsion using Gelatin-typeA as the emulsifier*.

Gelatin (Type A)	8g	
Tartaric acid	0.6g	
Flavour as desired		
Alcohol		60ml
Oil	500ml	
Purified water, to make		1000ml

Procedure

(i) The gelatin & tartaric acid are added to approximately 300ml water, allowed to stand for few minutes, heated until gelatin is dissolve, then temperature is raised to 98^0C and this temperature is maintained for about 20 minutes. Cooled to 50^0C, flavor and alcohol are added and more water was added to make 500 ml.

(ii) The oil is added to the aqueous phase (i.e. external phase), and the mixture is agitated thoroughly and passed it through a homogenizer or colloid mill.

2. Addition of the external phase to the internal phase

Let us take a model of o/w emulsion.

In this method water (external phase) is first added slowly to the oil (internal phase) to promote the formation of a more w/o emulsion due to the presence of more oil than water. After further addition of water phase inversion to an o/w emulsion should take place.

This method is especially successful when hydrophilic agents such as acacia, tragacanth or methyl cellulose are first mixed with oil, effecting dispersion without wetting. Water is added and, eventually, an o/w emulsion is formed.

e.g. *Mineral oil emulsion*

Mineral oil	500ml	
Acacia, in very fine water	125g	
Syrup	100ml	
Vanillin		40mg
Alcohol		60ml
Purified water, upto	1000ml	

(i) The mineral oil and acacia are mixed in a dry mortar. Purified water, 250 ml (Phase volume ratio o/w = 2: 1) is added and the mixture triturated vigorously until an emulsion is formed.

(ii) A mixture of the syrup, 50 ml of purified water and the vanillin dissolved in alcohol are added in divided portions with trituration

(iii)Sufficient purified water is then added to the proper volume, the mixture well and homogenized.

3. Mixing both phases after warming each

This method is use when waxes or other substances which require melting are used. The oil-soluble emulsifying agents, oils and waxes are melted and mixed thoroughly. The water-soluble ingredients dissolved in the water and warmed to a temperature slightly higher than the oil phase.

The oil phases are then mixed and stirred until cold. For convenience, but not necessity, the aqueous solution is added to the oil mixture.

This method frequently is used in the preparation of ointments and creams.

e.g. *An oral emulsion (o/w) containing an insoluble drug*

1.	Cotton seed oil	460g
2.	Sulphadiazine	200g
3.	Sorbitan monostearate	84g
4.	Polyoxyethylene 20 sorbitan mono stearate	36g
5.	Sodium benzoate	2g
6.	Sweetener	q.s.
7.	Purified water	1000g
8.	Flavor oil	q.s.

Procedure

(i) Heat the first three ingredients to 50^0C and pass through colloid mill.

(ii) Add the next four ingredients at 50^0C to the first three ingredients at 65^0C and stirred while cooling to 45^0C.

(iii) Add the flavor oil and continue stirring until room temperature is reached.

4. Alternate addition of the two phases to the emulsifying agent

Model: Let us prepare an o/w type of emulsion.

(i) A portion of the oil is added to all of the oil-soluble emulsifying agents with mixing.

(ii) Equal quantity of water is added to all of the water-soluble emulsifying agents with mixing.

(iii) Aqueous solution is mixed with oil phase stirred until the emulsion is formed.

(iv) Further portions of water and oil are added alternately until the final product is formed.

N.B. The high concentration of the emulsifying agent in the original emulsions makes the initial emulsification more likely and the high viscosity provides effective shearing actin leading to small droplets in the emulsion.

This method is often used successfully with soaps.

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

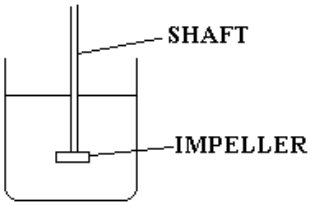
(iii) Simplest operation among all other instruments.

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 of mixing 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.

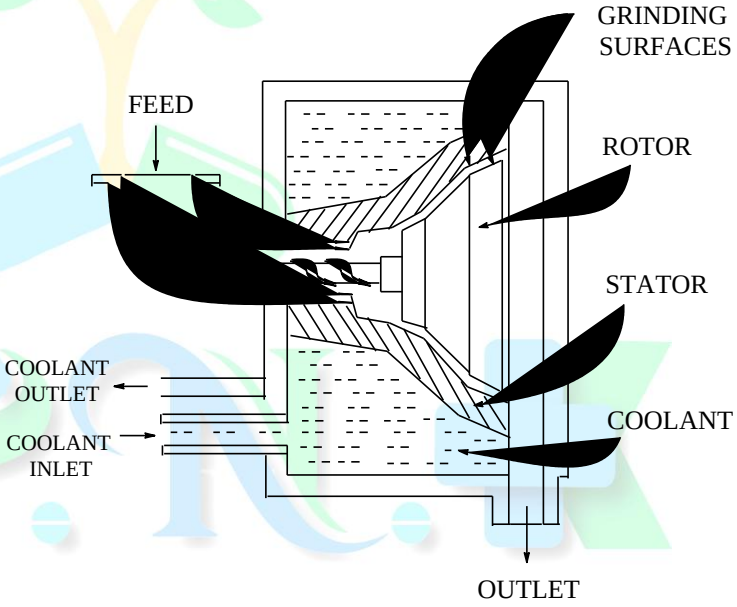
(ii) Can be used for small-scale production and laboratory purpose.

Disadvantages:

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.

3. Colloid mill

The principle of operation of the colloid mill is the passage of the mixed phases of an emulsion formula between a stator and a high speed rotor revolving at speeds of 2000 to 18,000 rpm.



The clearance between the rotor and the stator is adjustable, usually from 0.001 inch upward. The emulsion mixture, while passing between the rotor and the stator, is subjected to a tremendous shearing action which effects a fine dispersion of uniform size.

The shearing forces applied in the colloid mill usually raises the temperature within the emulsion. Hence, a coolant is used to absorb the excess heat.

Advantage

(i) Very high shearing force can be generated.

(ii) Very fine particles can be prepared.

(iii) Particularly useful in preparing suspensions containing poorly wetted solids.

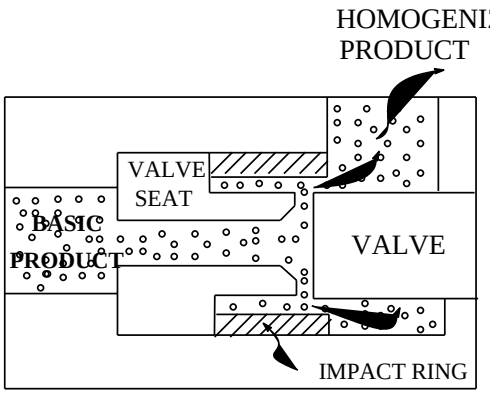
(iv) Useful for the preparation of relatively viscous emulsions.

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:

(i) The ingredients in the emulsion are mixed and then passed through the homogenizer to produce the final product.
(ii) A coarse emulsion is prepared in some other way and then passed through a homogenizer for the purpose of decreasing the particle size and obtaining a greater degree of uniformity and stability.



The coarse emulsion (basic product) enters the valve seat at high pressure (1000 to 5000 psi), flows through the region between the valve and the seat at high velocity with a rapid pressure drop, causing cavitation; subsequently the mixture hits the impact ring causing further disruption and then is discharged as a homogenized product. It is postulated that circulation and turbulence are responsible mainly for the homogenization that takes place.

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

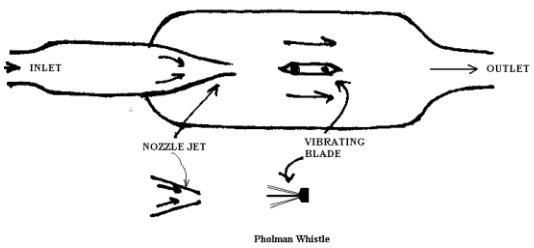
Can be used for low viscosity and extremely low particle size.

Disadvantages

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

Example: Pohlman Whistle

Commercial products may be prepared using ultrasonics based upon the device known as the Pohlman whistle. In this apparatus, the premixed liquids are forced through a thin orifice and are allowed to impinge upon the free end of a knife-edge bar which is made to vibrate.



Pholman Whistle

Ultrasonic waves are produced and areas of compression and rarefaction are formed. Shock waves are produced by the collapse of bubbles which produced a shear effect, thereby producing fine particle sizes.

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

ρ_1 , ρ_2 = densities of dispersed phase and continuous phase respectively

η = viscosity of the continuous medium

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

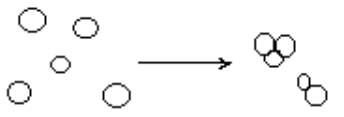
(i) reduction of droplet size

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

(iii)increase in the viscosity of the continuous phase

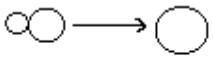
- *Reduction in droplet size* is done by using an efficient homogeniser or colloid mill. There are, however, technical difficulties in reducing the diameter of droplets to below about 0.1 μm.
- Stoke's equation predicts that no creaming is possible if the specific gravities of the two phases are equal. 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


Floccules

Flocculation

Flocculation of the dispersed phase may take place before, during or after creaming.
Flocculation is reversible aggregation of droplets of the internal phase 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 form larger particles.


Coalescence

Any evidence for the formation of larger droplets by merger of smaller droplets suggests that the emulsion will eventually separate completely.
The major factor which prevents coalescence in flocculated and deflocculated emulsions is the mechanical strength of the interfacial barrier. Thus macromolecules and particulate solids forms thick interfacial film – and hence natural gums and proteins are useful as auxiliary emulsifiers when used 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 70^0C 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, and

(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 45^0C.

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 thixotrophic 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

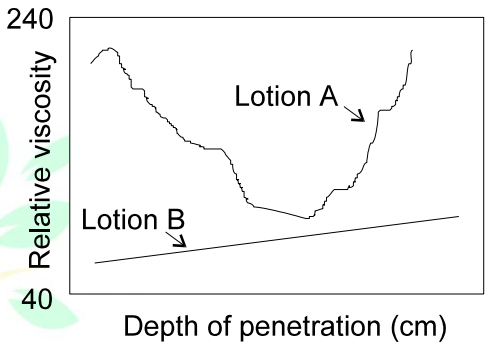
N.B. The Brookfield viscometer determines the resistance encountered by rotating spindle or cylinder immersed in a viscous material. The Helipath attachment slowly lowers the rotating spindle into the medium so that the resistance measured is always that of previously undisturbed test substances.

As a result of emulsion separation, the descending rotating spindle meet varying resistance at different levels and registers fluctuations in viscosity.

Example

Lotion A in the figure contains solids suspended in an emulsion, and the high viscosity near the top is due to non-wetted solid and creamed emulsion; the high viscosity at the lower level is due to sedimented particles.

The addition of polyoxyethylene monooleate (SAA) and methyl cellulose (viscosity enhancer) in lotion B yields a much more uniform viscosity pattern after eight weeks storage.



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

(i) the aid of the moving boundary method or

(ii) more quickly and directly, by observing the movement of particles under the influence of electric 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 50^0C,

(ii) 5 to 6 months at 37^0C and

(iii)12 to 18 months at room temperature.

(iv) After 1 month storage at 4^0C
(v) After 2 to 3 freeze-thaw cycles between –20 and +25^0C.
(vi) After 6 to 8 freeze-thaw cycles between 4 and 45^0C with storage at each temperature for not less than 48 hours.
(vii) No deterioration by centrifuging at 2000 to 3000 rpm at room temperature.
(viii) No deterioration by agitation for 24 to 48 hours on a reciprocating shaker (≈ 60 cycles per minute) at room temperature and at 45^0C.

SOLUTIONS

In pharmaceutical terms, solutions are liquid preparations that contain one or more chemical substances dissolved in a suitable solvent or mixture of mutually miscible solvents.

CLASSIFICATION OF SOLUTION

(i) According to the route of administration

a) *Oral solutions*—through oral route.
b) *Otic solutions*—instilled in the ears.
c) *Ophthalmic solution*—instilled in the eyes.
d) *Topical solutions*—applied over the skin surface.

(ii) According to composition and uses

a) *Syrup*—aqueous solution containing sugar.
b) *Elixir*—sweetened hydroalcoholic (combination of water and ethanol) solution.
c) *Spirit*—Solution of aromatic materials in alcohol.
d) *Aromatic Water*—Solution of aromatic material in water.
e) *Tincture / Fluid extract*—Solution prepared by extracting active constituents from crude drugs. e.g. Compound cardamom tincture. They may also be solutions of chemical substances dissolved in alcohol or in hydroalcoholic solvent. e.g. Tincture of Iodine.
f) *Injection*—Certain solution prepared to be sterile and pyrogen-free and intended for parenteral administration.

FORMULATION CONSIDERATION

1) **Solubility**
   a) pH
   b) Cosolvency
   c) Solubilization
   d) Complexation
   e) Hydrotrophy
   f) Chemical modification of the drug molecule
2) **Preservation**
   a) Preservatives
   b) Antioxidants
   c) Reducing agents
   d) Synergists
3) **Organoleptic consideration**
   a) Sweetening agents
   b) Flavoring agents
   c) Coloring agents
   d) Viscosity control
   e) Overall appearance
4) **Stability**
   a) Chemical stability
   b) Physical stability

SOLUBILITY

When a solid solute is dissolved in a liquid solvent two types of interactions are evident—one is the intra-molecular force between the solute molecules and the other is the intermolecular force between the solute and solvent molecules. When a solute dissolves, the substance's intra-molecular forces (cohesive force) must be overcome by the force of attraction between the solute and solvent

molecules (adhesive force).This involves breaking the solute-solute forces and the solvent-solvent forces to achieve the solute-solvent forces attraction.

EXPRESSION OF SOLUBILITY

According to Indian Pharmacopoeia

Descriptive Phrase	Approximate quantities(ml) of solvent by volume for 1 part (1 gm) of solute by weight
Very soluble	less than 1 part
Freely soluble	from 1 to 10 parts
Soluble	from 10 to 30 parts
Sparingly soluble	from 30 to 100 parts
Slightly soluble	from 100 to 1000 parts
Very slightly soluble	from 1000 to 10,000 parts
Practically insoluble	more than 10,000 parts

Solubility

The *solubility* of an agent in a particular solvent indicates the *maximum* concentration to which a solution may be prepared with that agent and that solvent.

Determination of Equilibrium Solubility of a Drug

An excess of the drug (finely powdered to minimize the time required to attain the equilibrium) is placed in a vial along with a specific amount of the solvent. The tightly closed vial is then agitated at constant temperatures (preferably at temperature somewhat higher than room temperature e.g. 30^0C so that constant conditions can be maintained regardless of normal laboratory temperature variations), and the amount of drug in solution is determined periodically by assay (by some chemical method) of a filtered sample of the supernate. Equilibrium is not achieved until at least two successive samplings give the same result.
The *solubility* is generally expressed in mg of solute per ml of solvent at 25^0 C or per 100 ml etc.

Solubility of a drug depends on temperature, solvent, pH and the chemical nature of the molecule itself. By modifying these parameters the solubility of a drug can be manipulated according to the requirement of designing the dosage form.

pH

A large number of drugs are either weak acids or weak bases. The solubility of these agents can be markedly influenced by the pH of the environment. When a weakly acidic drug is dissolved in water it can remain in three states, namely undissolved, dissolved and ionized which can be expressed in the following reaction format:

$$\underset{\text{(Undissolved)}}{DH\ (solid)} \rightleftharpoons \underset{\text{(Undissociated)}}{DH\ (solution)} \rightleftharpoons \underset{\text{(Dissociated / ionized)}}{D^-} + \underset{\text{(Proton)}}{H^+}$$

The relationship between equilibrium solubility of a weakly acidic drug and the pH of the environment can be expressed by Henderson-Hasselbach equation:

$$pH = pKa + \log \frac{[D^-]}{[DH]}$$

where pKa = Dissociation constant of the acid
$[D^-]$ = Molar concentration of ionized drug

[DH] = Molar concentration of unionized drug

The same equation can be written in the following forms:

$$pH = pKa + \log \frac{[ionized]}{[unionized]}$$

$$pH = pKa + \log \frac{[base]}{[acid]}$$

where DH = Acid

D^- = Corresponding base of the acid (DH)

Weak Acid

$DH\ (solid) \rightleftharpoons DH(solution) \rightleftharpoons D^- + H^+$

Dissolved
Unionised

$$pH = pKa + \log \frac{[D^-]}{[DH]}$$

$$pH = pKa + \log \frac{[ionised]}{[unionised]}$$

$$pH = pKa + \log \frac{[base]}{[acid]}$$

DH = acid

D^- = corresponding base of DH

Weak Base

$DOH\ (solid) \rightleftharpoons DOH(solution) \rightleftharpoons D^+ + OH^-$

Dissolved
Unionised

$$pH = pKa + \log \frac{[DOH^-]}{[D^+]}$$

$$pH = pKa + \log \frac{[unionised]}{[ionised]}$$

$$pH = pKa + \log \frac{[base]}{[acid]}$$

DOH = base

D^+ = corresponding acid of the base DOH

To maintain the drug in soluble state the solution of a drug must be done in a suitable buffer solution. The buffer must have the following properties:

1. The buffer must have adequate capacity in the desired pH range.
2. The buffer must be biologically safe for the intended use.
3. The buffer (or its pH range) must have minimum interference on the stability of the final product.
4. The buffer should permit acceptable flavoring and coloring of the product.

e.g. Some commonly used buffer systems are ammonium chloride, diethanol amine, triethanolamine, boric acid, carbonic acid, phosphate buffer, glutamic acid, tartaric acid, citric acid buffer, acetic acid buffer etc.

COSOLVENCY

Weak electrolytes and nonpolar molecules frequently have poor water solubility. These types of solutes are more soluble in a mixture of solvents than in one solvent alone. This phenomenon is known as cosolvency; and the solvents that, in combination increases the solubility of the solute are called cosolvents.

To increase the water solubility of a drug another water miscible solvent in which the drug has good solubility is mixed.

Mechanism of action

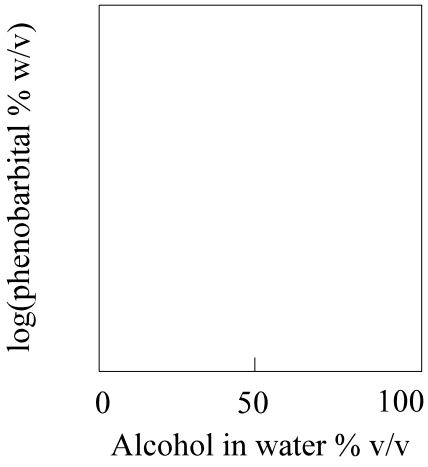
It has been proposed that a cosolvent system works by reducing the interfacial tension between the predominantly aqueous solutions and the hydrophobic solute.

Examples of commonly used cosolvents

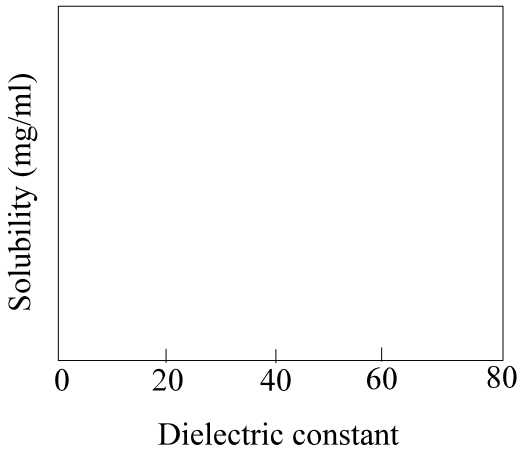
Ethanol, sorbitol, glycerin, propylene glycol and several members of the polyethylene glycol polymer (PEG200) series are the limited number of cosolvents (of water) those are used and are acceptable in oral preparation.

Use of cosolvents

Cosolvents are used to increase the solubility of weak electrolytes, non-polar molecules and volatile constituents used to impart a desirable flavor and odour to the product.



The solubility of phenobarbital in a mixture of alcohol & water



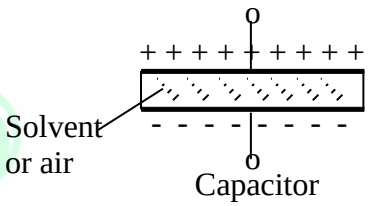
Caffeine in dioxane-water mixtures at solubility (mg/ml) plotted vs. dielectric constant of dioxane-water system.

DIELECTRIC CONSTANT

One property of a solvent system is its dielectric constant. The dielectric constant of a solvent can be defined as the ratio of the capacitances of a capacitor filled with the solvent and air respectively.

$$\text{Dielectric constant } (\varepsilon) = \frac{\text{C solvent}}{\text{C air}}$$

where, C is the capacitance of the condenser filled with respective medium (solvent or air)
e.g dielectric water is 78.5



Every solute shows a maximum solubility in any given solvent system, at one or more specific dielectric constants.

To determine the relationship between solubility of a solute with dielectric constant(s) at which maximum solubility is attained is noted.

Pharmaceutical formulations of comparable dielectric constant can thus be prepared, and the most appropriate solvent system can be selected on the basis of solubility, stability and organoleptic characteristics requirements.

SOLUBILIZATION

spontaneous increase of solubility of a poorly water-soluble solute molecules into an aqueous solution of surface active agents (or surfactants) in which a thermodynamically stable solution is formed.

Mechanism

When surfactants are added to water at low concentrations, they tend to orient at the air-liquid interface.

As additional surfactant is added, the interface becomes fully occupied, and the excess molecules are faced into the bulk of the liquid.

At still higher concentrations, the molecules of surfactant in the bulk of the liquid begin to form oriented aggregates or micelles, this change in orientation occurs abruptly (suddenly).

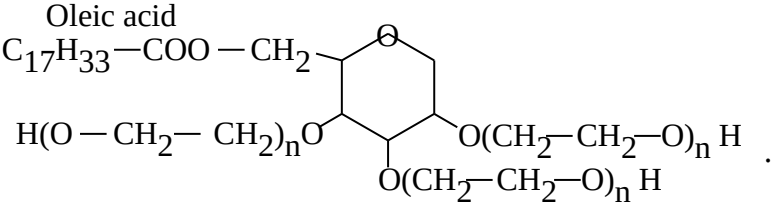
The concentration of surface active agent at which micelles occurs is called critical micelle concentration .

Solubilization is thought to occur by virtue of the solute dissolving in or being adsorbed onto the micelle. The water solubility of the solute increases with the concentration of the micelles.

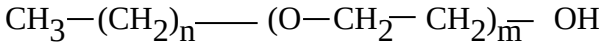
Examples of some solubilizing agents:

Polyoxyethylene sorbitan fatty acid ester (Tween series)

Oleic acid



Polyoxyethylene mono alkyl ether (BRIJ, MYRJ series)



n = 15 to 17 m = 20 to 24

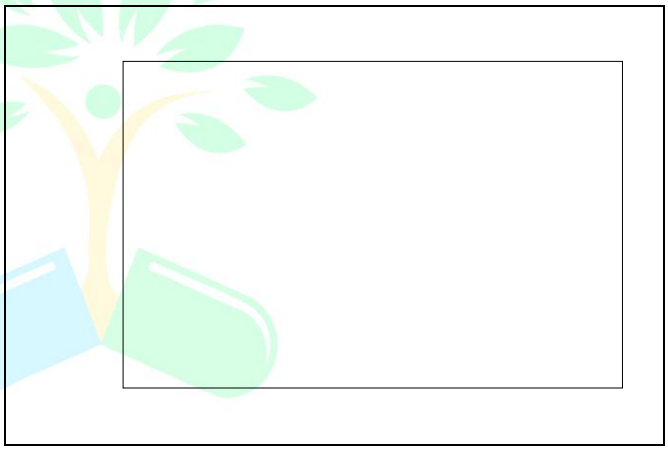
Other examples are Sucrose monoesters, Lanolin esters etc.

It has generally been found that surface-active-agents having HLB (Hydrophilic Lipophilic Balance) values higher than 15 acts better as solubilizing agents.

COMPLEXATION

Solubility of a compound may be increased by complexing with a complexing agent. e.g. solubility of para amino benzoic acid (PABA) may be increased by complexing with caffeine.

When an insoluble compound forms a complex which is more soluble in the solvent - the total solubility is equal to the inherent solubility of the uncomplexed drug plus the concentration of drug-complex in solution.



When a certain amount of drug is mixed in water some amount will get dissolved (A) and some amount will remain undissolved. If a complexing agent is added to it some drug will be complexed and become soluble in water. So the total solubility will be will be increased.

When more complexing agent is added total solubility will increase; at a certain concentration of complexing agent the solution will become saturated with respect to free drug and the complex (B). After this point if still complexing agent is used then remaining drug (undissolved) will form complex and the excess complex will be precipitated (C). When no drug is left for complexation, complexes of higher order may be formed.

e.g. I_2 is sparingly soluble in water. To dissolve it KI (potassium iodide) is added which makes a complex $KI.I_2$ (i.e. KI_3). After point C it forms $KI.2I_2$, $KI.3I_2$ etc.

HYDROTROPHY

The term hydrotrophy has been used to designate the increase in solubility in water of various substances due to the presence of large amounts of additives.

Mechanism of action

Not clear yet. Some workers have speculated that this phenomenon is more closely related to complexation involving a weak interaction between the hydrotrophic agent and the solute.

Another view is that the phenomenon must be due to change in solvent character because of the large amount of additive needed to bring about the increase in solubility.

Examples

Since a large concentration of hydrotrophic agent is required (in the range of 20 to 50%) to produce a modest increase in solubility, hence its pharmaceutical applications are very less in number.

Drug	Hydrotrophic agent
1. Benzoic acid	Sodium benzoate
2. Theophylline	Sodium acetate and sodium glycinate
3. Iodine	Polyvinyl pyrrolidone (PVP)
4. Adrenochrome mono semicarbazone	Sodium salicylate

SOLVENTS FOR ORAL PREPARATIONS

The solvents those are usually used in the oral liquid preparations are purified water, alcohol, glycerin and propylene glycol.

PURIFIED WATER (H_2O)

Naturally occurring water exerts its solvent effect on most substances. In oral preparations the water used is potable water or Purified Water USP.

Specifications of Purified Water USP

Method of preparations : By distillation or by ion-exchange.
Total solid : Less than 10 parts per million (ppm)
pH : Between 5 and 7.

ALCOHOL (ETHANOL)

Next to water, alcohol is the most useful solvent in pharmacy.

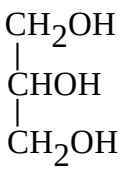
- It is used as a primary solvent for many organic compounds.
- With water it acts as a cosolvent and increases the solubility of drugs. Alcohol is often preferred because of its miscibility with water and its ability to dissolve many water-insoluble ingredients, including drug substances, flavorants, and antimicrobial preservatives.
- Alcohol is frequently used with other solvents, as glycols and glycerin, to reduce the amount of alcohol required.
- It also is used in liquid products as an antimicrobial preservative alone or as a co-preservative with parabens, benzoates, sorbates and other agents.

Disadvantages

It produces pharmacologic and potential toxic effects of alcohol when ingested in pharmaceutical products particularly by children. Hence, it should not be given to children below 6 years. For OTC (over the counter) oral product for children the recommended alcohol-content limit is 0.5 %.

Age of the patient	Permitted alcohol content
For children below 6 years	0.5 %
For children between 6-12 years	5.0 %
Children over 12 years and adults	10.0%

GLYCERIN (Glycerol)

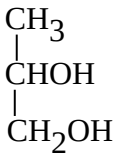


- Glycerin is a clear syrupy liquid with a sweet taste.
- It is miscible both with water an alcohol.
- Glycerin has preservative qualities.

Disadvantages

As a solvent, it is comparable to alcohol, but because of its viscosity, solutes are slowly soluble in it unless it is rendered less viscous by heating.

PROPYLENE GLYCOL



It is a viscous liquid, is miscible with water and alcohol. It is useful solvent with a wide range of application and is frequently substituted for glycerin in pharmaceutical formulation.

BUFFERS

A buffer is a compound or mixture of compounds that, by its presence in solution, resists changes in pH upon addition of small quantities of acid or base.

Buffering agents are necessary to resist the change of pH upon dilution or addition of acid or alkali in the liquid preparation.

The usual buffering agents used in oral liquid preparations are *acetate buffer* and *phosphate buffer*.

Buffer	**Mixture of**	**Buffering Range**
Acetate buffer	Glacial acetic acid Potassium, sodium, ammonium salt of acetic acid	pH 2.8 to 6.0
Phosphate buffer	Potassium dihydrogen phosphate Di-sodium hydrogen phosphate	pH 2.0 to 8.0

Buffering is required to:

1. Keeping weakly acidic or basic drug in solution
2. Increase the stability of the drug
3. Resist the change of pH upon dilution or addition of acid or alkali (e.g. leaching or alkali from glass container).

SWEETENERS

Solutions come in immediate contact with the taste buds (on the tongue). Drugs and other adjuvants are generally not good to taste (i.e. not palatable). To enhance palatability and to mask the taste of the drugs etc. sweeteners are used.

Example: Sucrose (sugar), saccharin, aspartame, liquid glucose.

Sucrose

Source Commercially sucrose is obtained from sugarcane, beet root and shorgum.

Advantages

1. It is soluble in aqueous medium.
2. It is available in highly purified form at reasonable price.
3. It is chemically and physically stable in the pH range of 4.0 to 8.0.
4. It is frequently used in conjunction with sorbitol, glycerin and other polyols.
5. Above 66.7 % mold growth will not take place.

Disadvantages

Concentration of sucrose solution above 66.7% (w/w) the sucrose crystallize making the solution hazy (i.e. reducing the gloss of the solution).

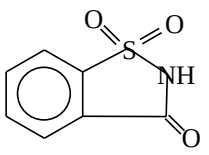
Caps of the containers are generally found to be locked due to this crystallization. Sorbitol, glycerin or other polyols are used to reduce the crystallization.

Liquid Glucose

Liquid glucose is an extremely viscid substance that imparts both body (i.e highly viscous) and sweetness to liquid formulations.

Preparation Partial hydrolysis of starch with strong acid produce liquid glucose. Its main component is dextrose and maltose.

Saccharin (Sodium and Calcium salts are soluble)



Advantages

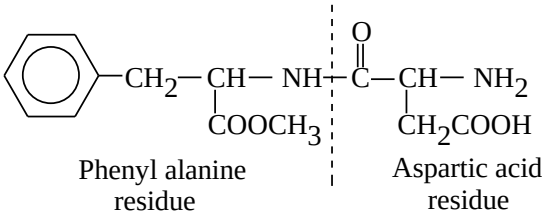
1. Saccharin is used to supplement sugars and polyols as sweeteners.
2. It is approximately 250 to 500 times as sweet as sugar.
3. It has no calorie value, hence can be given to obese patients and diabetic patients.

Disadvantages

It has a bitter after taste.

Aspartame

Aspartame is the methyl ester of aspartic acid and phenylalanine.



Advantages

1. It is approximately 200 times sweeter than sugar.
2. No bitter after taste.
3. Solubility in water is adequate for formulation purpose.

Disadvantage

Although it is very stable as dry powder, its stability in aqueous solutions is pH and temperature dependent. it is stable at pH between 3.4 and 5.0 and at refrigerated temperature.

COLORANTS

To enhance the appeal of the vehicle, a coloring agent is generally used which matches well with the flavour employed in the preparation e.g. green with mint, brown with chocolate flavor etc. The colorant used is generally water soluble, non-reactive with other components, and color-stable at the pH range and under the intensity of light that the liquid preparation is likely to be exposed during its shelf-life.

N.B. From the psychological point of view the scheme may be as follows:

Color Red → Orange → Yellow → Green → Blue → Violet

Psychological reactions → Exciting → Cheerful → Tranquilizing → → Subduing

Desirable properties of a coloring agent

1. Must be harmless, should have no physiological activity
2. It should be a definite compound because then its coloring power will be reliable, its assay practicable.
3. Its tinctorial (coloring) power should be high so that only small quantities are required.
4. It should be unaffected by light, temperature, micro-organisms, pH changes.
5. It should not interfere with other adjuvants.
6. I must be free from objectionable odour and taste.
7. it must by inexpensive.

Example

- Coal tar colors e.g. Amaranth
- The permitted colors do not always give satisfactory shades when used alone but most popular tints and shades can be obtained by blending

e.g. Green S and Tartrazine Solution B.P.C. contains GreenS (greenish blue) and Tartrazine (Yellow green)

PRESERVATION

Specific organisms generally recognized as undesirable in oral liquids include *Salmonella* species, *Escherichia coli*, *Enterobacter* species, *Pseudomonas* species (commonly *Pseudomonas aeruginosa*), *Clostridium* and *Candida albicans*.

Source of contamination:

Raw materials, processing containers and equipment, the manufacturing environment, operators, packaging materials and the user.

Characteristics of an ideal preservative

1. It must be effective against a broad spectrum of microorganisms.
2. It must be physically, chemically and microbiologically stable for the life-time of the product.

3. It must be nontoxic, non-sensitizing, adequately soluble, compatible with other formulation components, and acceptable with respect to taste and odour at the concentrations used.

Some pharmaceutically useful preservative

Class	Preservative	Usual concentration (%)
Acidic	Phenol	0.2 - 0.5
	Chlorocresol	0.05 - 0.1
	o-Phenyl phenol	0.005 - 0.01
	Alkyl esters of parahydroxy benzoic acid (e.g. Methyl and Propyl Paraben)	0.001 - 0.2
	Benzoic acid and its salts	0.1 - .0.3
	Boric acid and its salts	0.5 - 1.0
	Sorbic acid and its salts	0.05 - 0.2
Neutral	Chlorbutanol	0.5
	Benzyl alcohol	1.0
	β-Phenyl ethyl alcohol	0.2 - 1.0
Mercurial	Thiomersal	0.001 - 0.1
	Phenyl mercuric acetate and nitrate (PMA & PMN)	0.002 - 0.005
	Nitromersol	0.001 - 0.1
Quarternary ammonium compounds	Benzalkonium chloride	0.004 - 0.02
	Cetylpyridinium chloride	0.01 - 0.02

Preservatives	Uses
Acidic	
Phenol	Have characteristic odor and unstable when exposed to oxygen, hence used rarely.
Alkyl esters of parahydroxy benzoic acid (e.g. Methyl and Propyl Paraben)	Mostly used Adequately soluble in water Have both antifungal and antibacterial activity Methyl & Propyl ester at a ratio of 10 to 1 produce a synergistic effect.
Sodium salt of benzoic acid Sodium salt of sorbic acid	Mostly used Have antibacterial action and antifungal action Water soluble
Neutral	
Chlorbutanol Benzyl alcohol β-phenyl ethyl alcohol	The are volatile alcohols, hence, have odor and loss of preservative action on aging. Not used in oral liquid preparations. Used in ophthalmic, nasal and parenteral products.
Mercurials	Not used in oral liquid preparations Used in ophthalmic, nasal and parenteral products. *Disadvantage*: Mercurials readily reduced to free mercury.
Quartenary ammonium compounds	Not used in oral preparations Used in ophthalmic, nasal and parenteral solutions. *Disadvantages*: They are inactivated by variety of anionic substances.

SYRUPS

Syrups containing approximately 85% sucrose resist bacterial growth by virtue of their exosmotic effect on micro-organisms. Syrups that contain less than 85% sucrose, a sufficient concentration of polyol (e.g. sorbitol, glycerin, propylene glycol or polyethylene glycol) should be added to have the required osmotic pressure.

It is possible, however, for surface dilution to take place in a closed container as a result of solvent evaporation followed by condensation, with the condensate flowing back onto the liquid surface. The resulting diluted medium for bacterial and fungal growth. A sufficient concentration of preservative or 5 to 10% ethanol should be added to arrest the growth of microorganisms.

FLAVORS

An objectionable taste may lead to nausea, vomiting and refusal to take the preparation regularly or at all. On the other hand, an attractive flavour will encourage continuation of treatment.

The four basic taste sensations are salty, bitter, sweet and sour. A combination of flavoring agents is usually required to mask these taste sensations effectively.

Flavor selection

Taste sensation	Recommended flavor
Salty	Butterscotch, maple, apricot, peach, vanilla, wintergreen mint.
Bitter	Wild cherry, walnut, chocolate, mint combinations, anise etc.
Sweet	Fruit and berry, vanilla
Sour	Citrus flavors, liquorice, root beer, raspberry

Flavor adjuncts

Menthol, chloroform and various salts frequently are used as flavor adjuncts.

Menthol and chloroform are sometimes referred to as *desensitizing agents*. They impart a flavor and odor of their own to the product and have a mild anaesthetic effect on the sensory receptor organs associated with taste.

MANUFACTURING CONSIDERATION

Raw materials

1. Incoming raw materials should be tested against some *specifications* regarding identity, purity, uniformity and freedom from excessive microbial contamination.
2. *Additional processing* may be required e.g. size-reduction or sterilization before manufacturing. It is usually much easier to begin with low microbial counts in the raw materials than to try to reduce these counts substantially during processing.
3. In oral liquid preparations *water* is the main vehicle. It should meet the USP requirements for **Purified water**. It may be obtained by distillation or ion-exchange treatment. To reduce the microbial burden water is passed through UV-rays and constant circulation in piping systems that have “dead ends” where micro-organisms can thrive.

EQUIPMENTS

The following types of equipments may be used in the manufacture of oral liquid solutions:-

1. Mixing tanks (SS 316 Stainless Steel) equipped with an agitator.
2. Measuring devices for large and small amount of solids and liquids.
3. A filtration system for the final polishing - e.g. Sparkler filter.

Cleaning of equipments

All equipments must be thoroughly cleaned and sanitized before use.

Disinfectants used: Dilute solutions of H_2O_2, phenol derivatives and paracetic acid.

Sterilized by: Alcohol, boiling water, autoclaving, steam or dry heat.

Material of construction

- *Tanks* are usually constructed of polished stainless steel and are usually jacketed to allow for heating or cooling of the contents.
- Tanks are covered and equipped with see-through charging ports and illumination for easy observation of the contents. If the tanks are used for compounding of the bulk liquid, they have a built in agitation system.
- The compounded liquid may then be transported to the filling line, either manually by filling into portable transport tanks (fitted with wheels) or by pumping (or gravity flow) through a liquid delivery conduit.
- All the equipments and pipe lines should be easy to disassemble, clean and sanitise.

COMPOUNDING PROCEDURE

Objective Complete solution should usually be confirmed at every stage in the manufacture of a homogeneous liquid.

Formula

1. Active constituent / Drug
2. Vehicle (Water / Alcohol / Glycerol)
   Sweetening agents (viscosity building agents) Syrup, Sorbitol, Glycerol
3. Preservatives
4. Flavors
5. Colors (Dyes)

Steps of preparation

1. Purified water is heated to approximately 50^0C to facilitate the dissolution of the solid solutes. Solid solutes are added to the warm water and stirred to dissolve (e.g. sugar, drug).
2. If any additive is required in small amount then it should be dissolved separately and then mixed with the bulk mixture.
3. Any large volume liquids (e.g. glycerol, sorbitol solution) are added and mixed until homogeneous.
4. Before adding flavors the temperature should be reduced to 30^0C (since most of the flavors are volatile). The flavor should be dissolved in small amount of alcohol (since flavors are generally insoluble in aqueous medium) and then it is mixed with the bulk mixture.
5. Dye should be dissolved n small amount of water. Then transferred to the bulk mixture.
6. Finally volume is made up to the required volume. The total mixture is agitated thoroughly until homogeneity is obtained.
7. Finally the batch is filtered to obtain a polished, clear solution.

ORAL SOLUTIONS

Liquid system where all the solutes remain in dissolved state is known as *solution*. Solutions intended to be taken orally is called *oral solutions*.

Advantages

1. Absorption is instant from the gastro-intestinal tract.
2. Uniform dosage is certain.
3. They provide a safe means of administering substances like potassium iodide that cause gastric pain if taken dry, e.g. as powders or tablets.
4. The attractive appearance of a solution in a well polished bottle has a beneficial psychological effect.

PREFORMULATION

Oral solutions contain

1. Active constituents (Water soluble)
2. Preservative
3. Flavorant

4. Colorant
5. Chemical stabilizers (Antioxidant, reducing agent, synergists)

Dose

Liquid pharmaceuticals for oral administration are usually formulated such that the patient receives the usual dose of the medication in a conveniently administered volume, as 5 ml (one teaspoonful), 10 ml or 15 ml (one table-spoonful).

On the other hand many solutions used in paediatric patients are given by drop, utilizing a calibrated dropper usually furnished by the manufacturer in the product package.

Calculation

The strengths of pharmaceutical preparations are usually expressed in terms of % strength (w/w, w/v, v/v).

Formulation

Some chemical agents may be slowly soluble. In this case rate of dissolution may be enhanced by

1. application of heat: the temperature should not destroy other ingredients.
2. decrease the particle size to increase the specific surface area.
3. by agitation: but dissolution is delayed compared to heat application.

Chemical interaction

Chemical interactions which may occur between the various components of a solution which may result in a alteration in the preparation's stability and / or potency. For example, it has been demonstrated that esters of p-hydroxy benzoic acid (methyl-, ethyl-, propyl- and butyl- parabens) frequently used preservatives in oral preparations, have a tendency to partition into certain flavoring oils.

SYRUPS

- *Syrups* are concentrated, aqueous preparations of a sugar or sugar-substitute with or without added flavoring agents and medicinal substances.
- Syrups containing flavoring agents but not medicinal substances are called *flavored vehicles* (syrups).e..g Cherry Syrup, Cocoa Syrup, Orange syrup, Raspberry Syrup.
- Syrups containing medicinal agents are called *medicated syrups*. e.g. Chlorpheniramine maleate syrup, Ipecac syrup, Chloral hydrate syrup etc.

Components of syrups

Most syrups contain the following components in addition to the purified water and any medicinal agents present:

1. the sugar, usually sucrose, or sugar substitutes used to provide sweetness and viscosity,
2. antimicrobial preservatives,
3. flavorants, and
4. colorants.

Sucrose and non-sucrose based syrup

Sucrose is most frequently employed in syrups. In special circumstances it may be replaced by sugars, such as, *dextrose*, or non-sugars as *sorbitol*, *glycerin* and *propylene glycol*.

Methyl cellulose or hydroxyethyl cellulose –these two materials are not hydrolyzed and absorbed into the blood stream, and their use results in an excellent syrup-like vehicle.

Taste masking by syrup

The syrup imparts a characteristics "body" (viscosity) and together with the sweetness and the flavorants results in a type of pharmaceutical preparation that is quite effective in making the taste of added medicinal agents. When the syrup is swallowed, only a portion of dissolved drug actually

makes contact with the taste buds, the remainder of the drug being carried past them and down the throat in the containment of the viscous syrup.

In the case of antitussive syrups (e.g. linctus) the thick sweet syrup has a soothing effect on the irritated tissues of the throat as it passes over them.

Preservative action of syrup

Simple syrup NF contains 85% w/v sucrose. At this concentration the syrup is resistant to microbial growth, due to unavailability of the water required for the growth of micro-organisms.

85% w/v syrup has a specific gravity of 1.313

i.e. 100 ml syrup contains 85 gm sucrose

Weight of 100 ml syrup = 100 x 1.313 = 131.3 gm

∴ Weight of water present in 100 ml syrup = (131.3 – 85) gm
= 46.3 gm

Volume of water present in 100 ml syrup =46.3 ml

∴ Volume of sucrose present in 100 ml syrup = (100 – 46.3) ml
= 53.7 ml

∴ 100 ml 85% syrup contains

	Weight	Volume
Sugar	85.0 g	53.7 ml
Water	46.3 g	46.3 ml
Syrup (total)	131.3 g	100.0 ml

The solubility of sucrose in water is 1 g in 0.5 ml

∴ to dissolve 85 g sugar required will be = 85 x 0.5 ml
= 42.5 ml

Thus, only a very slight excess of water (46.3 – 42.5 = 3.8 ml per 100 ml of syrup) is employed in the preparation of syrup. The sight excess of water permits the syrup to remain physically stable under conditions of varying temperature.

If the syrup were completely saturated with sucrose, under cool storage conditions some sucrose might crystallize from solution and, by acting as nuclei, initiate a type of chain reaction that would result in the separation of an amount of sucrose disproportionate to its solubility at the storage temperature. The syrup would then be very much unsaturated and probably suitable for microbial growth. However, the syrup NF is stable and resistant to crystallization as well as to microbial growth.

Preparation of Syrups

Syrups are frequently prepared by one of four general methods; depending upon the physical and chemical characteristics of the ingredients.

1. Solution of the ingredients with the aid of heat
2. Solution of the ingredients by agitation without the use of heat
3. Addition of sucrose to a prepared medicated liquid or to a flavored liquid and
4. by percolation of either the source of the medicating substance or of the sucrose.

Solution with the aid of heat

The sugar is generally added to the purified water, and heat is applied until solution is effected. Then other required heat-stable components are added to the hot syrup, the mixture is allowed to cool, and its volume is adjusted to the proper level by the addition of Purified Water.

The use of heat facilitates the rapid solution of the sugar as well as certain other components of syrups.

If excessive heating occurs then sucrose may be hydrolyzed into dextrose (D-glucose), and fructose (levulose). This hydrolytic reaction is referred to as *inversion*, and the combination of the two monosaccharides is *invert sugar*. When heat is applied in the preparation of a sucrose syrup, some inversion of the sucrose is almost certain. The speed of inversion is greatly increased by the presence of acids, the hydrogen ion acting as a catalyst to reaction.

Invert sugar is more sweeter than sucrose, and normally colorless. Syrup darkens due to the effect of heat on the fructose. When the syrup is greatly overheated, it becomes amber colored due to the caramelization of the sucrose. Syrups so decomposed are more susceptible to fermentation and microbial growth.

Because of the prospect of decomposition by heat, syrups cannot be sterilized by autoclaving.

Solution by agitation without heat

Sucrose and other formulation agents may be dissolved in purified water by placing the ingredients in a vessel of greater capacity than the volume of syrup to be prepared, thus permitting the thorough agitation of the mixture.

Addition of sucrose to a medicated liquid or to a flavored liquid

Medicated liquid such as tincture or fluid extract is employed as the active ingredient in the preparation of syrup.

If the extract contains alcohol soluble ingredients and the alcohol amount is high then sucrose is added directly and stirred.

If alcohol content is low and all the ingredients are water soluble then the liquid extract is directly mixed with a prepared syrup.

Preparation of syrup by percolation

In this method purified water or an aqueous solutionis passed slowly through a bed of crystalline sucrose, thus dissolving it and forming the syrup. If required a poriton of the percolate is recycled.

Preparation of a multivitamin syrup

Formula: Each 15 ml contains

Active ingredients	Vitamin B1	4.5 mg
	Vitamin B2	2.5 mg
	Vitamin B6	1.5 mg
	Niacinamide	30 mg
	D-Pantothenol	5 mg
Sweeteners	Sorbitol	1 gm
	Glycerin	0.5 gm
	Sugar	7 gm
Preservative	Sodium benzoate	0.016 % (w/v)
	Methyl paraben sodium	0.015 % (w/v)
	Propyl paraben sodium	0.0015%(w/v)
Stabilizer	Disodium edetate	0.008%
Taste enhancer	Citric acid	0.008% (w/v)
	Flavours	q.s.
Colours	Caramel	q.s.
Vehicle	Purified water	15 ml

Procedure

1. Primary Syrup is prepared as usual, filtered and cooled to room temperature. The material is transferred to the mixing tank and stirring is started.
2. Vitamin B1 is dissolved in small volume of water and added to the syrup.
3. Vitamin B2 is slightly soluble in water, hence, it is dissolved with the aid of 10% sodium hydroxide. Vitamin B6 is also added to dissolve. The mixture is transferred to the mixing tank.

4. Niacinamide is dissolved in small amount of water and added to the mixing tank.
5. D-pantothenol is dissolved in hot water, cooled and transferred to the syrup.
6. Sorbitol and glycerin are added.
7. All the preservatives are dissolved in small volume of water and added to the syrup.
8. Citric acid and disodium edetate is dissolved separately in water and then mixed to the syrup.
9. Flavors and color are added and the final volume is made up with water.
10. Mixed for 2 hours and filtered.