SUSPENSIONS

A suspension may be defined as a heterogeneous (biphasic) system comprising of a solid phase (the dispersed phase) uniformly dispersed in a liquid phase (the continuous phase or dispersion medium). A pharmaceutical suspension is a coarse dispersion in which insoluble solid particles are dispersed in a liquid medium. Suspensions often provide a means of supplying an insoluble and often distasteful substance in a form that is pleasant to taste. Chloramphenicol is very bitter and cannot be given in a liquid form to children. Chloramphenicol palmitate, an insoluble salt can be formulated as a suspension suitable for paediatric use. The large surface area of the dispersed drug ensures a high availability of drug for dissolution and absorption. The high surface area also allows good adsorptive or neutralizing action of certain drugs such as kaolin, magnesium carbonate, etc,

Aqueous suspensions are also suitable for parenteral and ophthalmic purposes and are also used for topical application to the skin. When used parenterally, suspensions generally provide a prolonged action by forming a depot at the site of application from which the drug dissolves slowly and gets absorbed. Insulin zinc suspension is a good example of such a preparation. Certain drugs such as antibiotics which are unstable in aqueous solution can be formulated as suspensions in non-aqueous solvents to provide a stable product.

Criteria for a Good Suspension

A good suspension should usually possess the following desirable properties :

(*i*) Suspended matter should not settle rapidly.

(*ii*) The particles which settle should not form a hard cake and should redisperse easily on shaking.

(*iii*) A good suspension should not be too viscous to pour.

(*iv*) In case of parenteral preparations, the suspension should flow out of syringe needle.

(*v*) Suspension for external application should be easy to apply and not run off. Also it should not dry off too quickly.

(*vi*) A good suspension should have a smooth, elegant appearance.

(*vii*) It must have an acceptable colour and odour.

(*viii*) It must be resistant to microbial attack.

(*ix*) The suspended ingredients should not hydrolyse or degrade too rapidly or undergo change in polymorphic form.

Ideally, suspensions should be thixotropic, i.e., these should become viscous on standing and should thin readily on shaking. This prevents sedimentation of the drug during storage and allows its easy withdrawl on shaking.

Interfacial Properties of Suspended Particles

In considering the interfacial properties of suspended particles, two factors must be taken into account. These are the surface free energy increase resulting from the increase in surface area of suspended

particles due to reduction in the size of the particles and the presence of electrical charge on the surface of dispersed particles.

1. Surface Free Energy

During formulation of a suspension, work is done to reduce the particle size (i.e., increase the surface area) or to disperse in a continuous medium. This makes the system thermodynamically unstable. In order to increase the stability, particles either flocculate, i.e., form a light, fluffy conglomerate that are held together by weak *van der Waal's* forces or they settle down to form a compacted aggregate (cake). Caking usually occurs by the growth and fusing together of crystals in the precipitate.

The increase in free energy due to reduction of particle size is given by the equation :

$$\Delta G = \gamma_{SL} \Delta A$$

where,

ΔG is the increase in work or surface free energy.

γ_{SL} is the interfacial tension between liquid medium and the solid particles.

ΔA is the total surface area.

With excess free energy due to the increase in surface area, the system tends to approach a stable state by reducing the surface free energy to zero. When the surface free energy approaches zero, the system becomes thermodynamically stable. Reduction in the surface free energy can be accomplished either by reducing the interfacial tension or by decreasing the interfacial area either through flocculation (desirable) or aggregation (caking — undesirable). The interfacial tension can be reduced by the addition of a wetting agent which gets adsorbed on the surface of the suspended particles. The wetting agent is however not able to reduce the interfacial tension to zero and hence a suspension generally possesses a finite positive interfacial tension as a result of which the suspended particles tend to flocculate or aggregate.

2. Electrical Properties

The forces acting on the surface of the suspended particles also affect the degree of flocculation in a suspension. Forces of attraction arise from *van der waal's* forces while forces of repulsion result from the interaction of electric double layer surrounding each particle. These result in the potential energy of attraction and the potential energy of repulsion. Fig. 6.1 shows the potential energy of two particles plotted as a function of the distance of separation. Shown are the curves depicting the energy of attraction, the energy of repulsion and the net energy curve with a peak and two minima.

When the repulsive energy is high, the potential barrier energy is also high and it prevents the collision of the approaching particles and hence, they remain deflocculated. When these deflocculated particles eventually settle, they tend to be closely packed and the particles at the bottom gets compressed by the weight of the particles in the upper layer as well as by the dispersion medium. At this stage, the energy barrier is overcome and the particles come closer and closer and they enter into primary minimum. As a result, they experience attractive forces and ultimately form a hard cake like

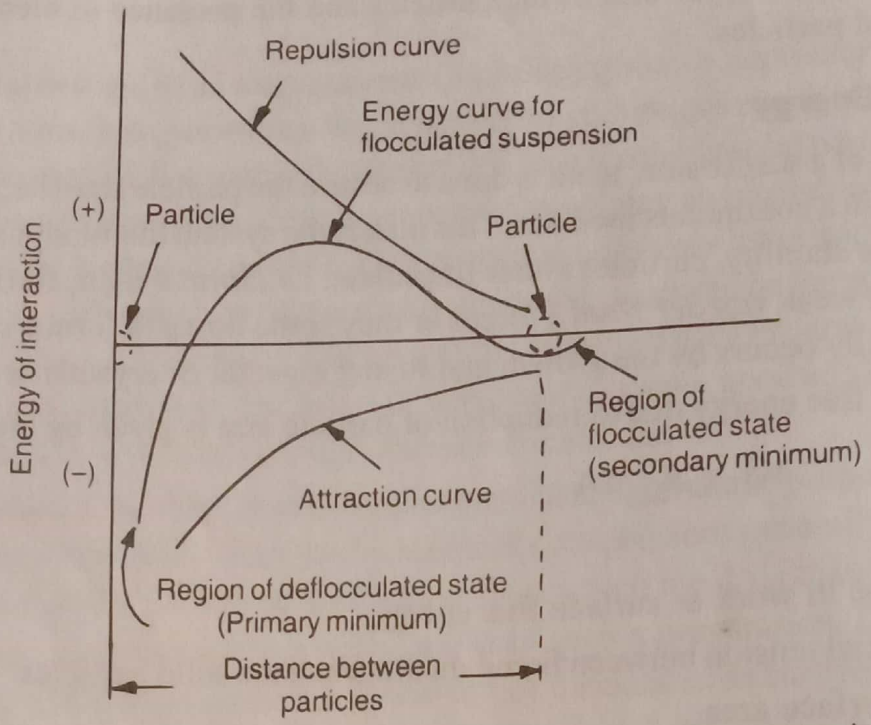


Fig. 6.1. Potential energy curve for particle interactions in suspensions.

sediment. To regain the original energy barrier, a high energy is required. Hence, even or vigorous agitation, the redispersion of the particles is not easily achieved and the particles remain as a cake.

When the particles are flocculated, the energy barrier is still too large to be overcome and therefore the particles remain separated by a distance approximately from 1000 to 2000Å in the secondary minimum. This distance is sufficient to form the loosely structured floccules.

Flocculation and Deflocculation in suspensions

The overall charge existing on the suspended particle is the zeta potential and it is a measurable indication of the potential existing at the surface of a particle. Therefore, flocculation and deflocculation may be considered in terms of zeta potential. When the zeta potential is high, the repulsive force between two particles exceed the attractive van der waal's forces and the particles remain dispersed. These are then said to be deflocculated. These particles resist collision due to their high surface potential even if the particles are brought close by way of random motion or agitation.

The zeta potential can be progressively lowered by the addition of an electrolyte whose charge is opposite to that of the suspended particles. At some concentration of the electrolyte, the forces of attraction dominate slightly over the electrical forces of repulsion. Under these conditions the particles approach each other and form loose aggregates commonly called flocs. Such a suspension is said to be flocculated.

If however, a large amount of the electrolyte is added, the suspended particle attain a strong opposite charge by adsorption of the electrolyte and become deflocculated again.

Table 4.1 Difference between flocculated and deflocculated suspension

Flocculated suspension	Deflocculated suspension
In Flocculated suspension, particles form loose aggregates	In Deflocculated suspension, particles remain dispersed
Rate of sedimentation is high	Rate of sedimentation is low
It does not form hard cake	It form hard cake.
On shaking sediment can be easily redispersed	On shaking sediment is difficult to redisperse.
Flocculated suspension is not good in appearance	Deflocculated suspension is pleasing in appeance
Less bioavailablity	More bioavailablity

SETTLING IN SUSPENSION

Theory of Sedimentation

The sedimentation velocity of suspended particles is given by Stoke's law according to which :

$$v = \frac{d^2(\rho_s - \rho_o)g}{18\,\eta_o}$$

where,

v is the rate of settling in cm/sec.,
d is the diameter of the particles in cm,
ρ_s is the density of the dispersed phase,
ρ_o is the density of the dispersion medium,
g is the acceleration due to gravity and
η_o is the viscosity of the dispersion medium in poise

Stoke's law is generally applicable to dilute suspensions containing 0.5 to 2 g solid per 100 ml of liquid. The more concentrated suspension have hindered settling due to collision between the particles. Also 'd' may not be uniform as particles in real suspensions vary in size and shape.

or

$$v = K\,\frac{d^2(\rho_s - \rho_o)}{\eta_o}$$

where K is an experimentally determined constant.

Thus, according to Stoke's law, the rate of sedimentation of particles in a suspension may be reduced by decreasing the particle size provided the particles are deflocculated. The rate of sedimentation can also be decreased by increasing the viscosity of the dispersion medium, for example, by addition of thickening or suspending agents. However, there is an optimum level upto which the viscosity of the dispersion medium can be increased since too much increase in viscosity may hinder the uniform redispersion of the suspended particles after they have settled and would also pose problem for easy flow of suspension out of the container. Another approach to reduce the sedimentation is to narrow down the difference in the density of the dispersed particles and the dispersion medium. Since the density of the suspended particles is constant for a particular substance, the density of the dispersion medium can be altered to bring it closer to that of the dispersed phase. In general, the density of the dispersion medium can be increased by the addition of substances like polyethylene glycol, glycerin, sorbitol, sugar, etc. either alone or in combination.

Brownian movement

When the size of the dispersed particles is very small such as about 2 to 5 μm, brownian motion sets in. However it depends on the density of the particles and the density and viscosity of the dispersion medium. The brownian movement prevents or reduces sedimentation to a considerable extent at room temperature by keeping the dispersed material in random motion.

Effect of flocculation on sedimentation rate

In a deflocculated suspension, the larger particles settle relatively at a faster rate than the smaller particles. As a result, a clear boundary between the sediment and the dispersion medium cannot be easily distinguished and the supernatent liquid remains cloudy for a considerable period of time. However, in the case of flocculated suspension, groups of particles are aggregated into flocs and the flocs tend to fall together while settling resulting in a clear boundary between the sediment and the supernatent liquid. The supernatent liquid in this case is clear because even very small particles present in the system are associated with the flocs and settle with it. Settling in flocculated suspensions depends on the size and porosity of the flocs but it is faster than deflocculated suspensions. Fig. 6.2 depicts the sedimentation in flocculated and deflocculated suspensions.

Sedimentation Parameters

Two parameters namely sedimentation volume and degree of sedimentation are useful while assessing a formulation of suspension in terms of amount of flocculation.

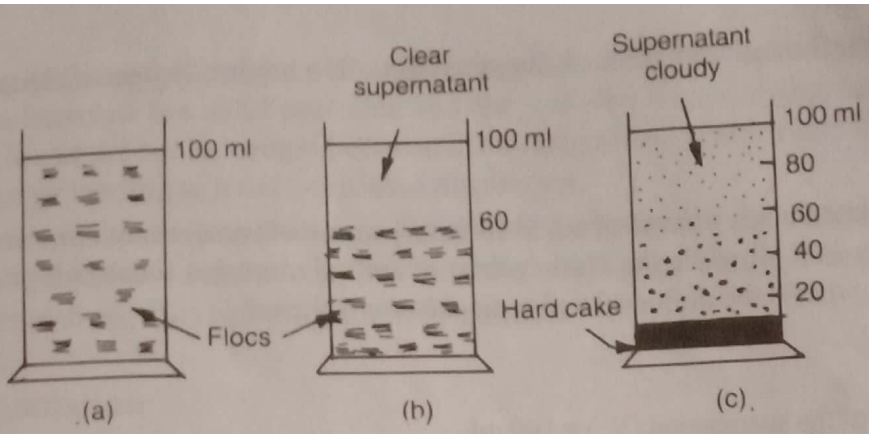


Fig. 6.2. Sedimentation in suspensions. (a) Flocculated suspension – initial state, (b) Flocculated suspension – after storage, (c) Defloculated suspension – after storage.

Sedimentation Volume

The sedimentation volume is the ratio of ultimate volume of the sediment to the total volume of the suspension.

$$F = V_u / V_o$$

where,

F is the sedimentation volume

V_u is the ultimate volume of the sediment

V_o is the total volume of the suspension

The sedimentation volume (F) normally ranges from less than 1 to 1 and it may exceed 1. For example, if the sedimentation volume is 0.70, it means that 70% of the total volume of the suspension is occupied by the sediment. When F = 1, the sediment volume and the total volume are equal and such a suspension does not show any clear supernatent liquid on standing. Such a suspension looks elegant and is pharmaceutically acceptable. It is also possible for the sedimentation volume to exceed the total volume of the suspension *i.e.*, for F to become greater than 1. It indicates that the network of flocs formed in the suspension is loose and fluffy and it encompasses a volume greater than the original volume of the suspension.

Degree of Flocculation

The sedimentation volume only gives a qualitative idea regarding the flocculation in suspensions. The degree of flocculation, β, is a better parameter to compare different formulations in terms of flocculation. It is the ratio of the sedimentation volume of the flocculated suspension (F) to the sedimentation volume of the suspension when deflocculated (F_∞)

$$\beta = F / F_\infty$$

Thus, the degree of flocculation refers to the increased sediment volume because of flocculation. For example if β = 2, the sediment volume in the flocculated suspension is twice the volume of the

sediment in the deflocculated state. A suspension with a higher degree of flocculation is to be preferred.

4.5 FORMULATION OF SUSPENSIONS

Three approaches are commonly involved in the formulation of flocculated or deflocculated suspension.

1. Use of structured vehicle
2. Use of controlled flocculation
3. Flocculation in structured vehicle

4.5.1 USE OF STRUCTURED VEHICLE

They are the aqueous solution of natural or synthetic gum. Example: methyl cellulose, sodium carboxy methyl cellulose, acacia, gelatin and tragacanth. They are also called as

suspending or thickening agent. These structured vehicles act by entrap the particle and do not allow the sedimentation of particles. On long storage, deflocculated particles in a structure vehicle form solid hard cake. Therefore during formulation of suspension flocculated particles in structured vehicles are preferred. This provide uniform dosing when poured.

4.5.2 WETTING OF PARTICLES

The dispersion of insoluble powder in a vehicle is major step during the formulation of suspension. Powders those are not easily wetted by water such as sulfur, charcoal and magnesium stearate are called as *hydrophobic* while the powders those are readily wetted by water are called *hydrophilic*. e.g. zinc oxide, talc, magnesium carbonate etc.

For the powders that are not easily wetted, wetting agents such as surfactants, hydrophillic polymers and solvents are used. Surfactants are used to lowers the solid-liquid interfacial tension. They act by displacement of air from hydrophobic material and allow the liquid to surround the particles for proper dispersion. 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 are also used. Solvents such as alcohol, glycerol and glycols which are water miscible are also used to decrease the liquid / air interfacial tension.

4.5.3 USE OF CONTROLLED FLOCCULATION IN CASE OF FLOCCULATED SUSPENSION

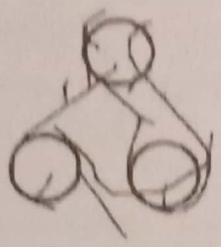
Controlled flocculation of particles is obtained by adding flocculating agents such as electrolytes, surfactants and polymers. The flocs are advantageous because they do not form hard cake and easily redisperse.

(a) **Electrolytes:** They act as flocculating agents. They lessen the electric barrier between the particles and form a bridge between adjacent particles.

Example: Dispersion of bismuth subnitrate in water. As bismuth particles possess large positive charge. Because of the repulsive force between adjacent particles, the system remains in deflocculated state. The addition of small amount of monobasic potassium phosphate (KH_2PO_4) to the suspension causes the adsorption of the negatively charged phosphate anion on positive charged bismuth particles. As a result repulsive force start to decrease and attractive force start to form. The particles come closer to form aggregates or flocs.

(b) **Surfactants:** They are also used for flocculation of suspended particles. They also act as wetting agents to achieve dispersion. Both ionic surfactants (sodium lauryl sulfate) and non ionic surfactants (Tweens) are used.

(c) **Polymers:** They are high molecular weight compounds. These agents also act as flocculating agents. In polymers, part of the chain is adsorbed on the particle surface while remaining parts extruding into the dispersion medium. This lead to formation of flocs.



Large floc
particle forms

Figure 4.3: Formation of flocs

4.5.4 FLOCCULATION IN STRUCTURED VEHICLE

The controlled flocculation approach is essential in the formulation of pharmaceutical suspension. But the product are not so elegant if sedimentation volume is not close to or equal to 1. Therefore a suspending agent is added to prevent the sedimentation or settling of the flocs. The suspending agents such as carboxymethylcellulose (CMC), Carbopol 934, Veegum, tragacanth or bentonite are used. These may lead to physical incompatibilities because of the charge carried by flocculating agent and the charge possess by suspending agent.

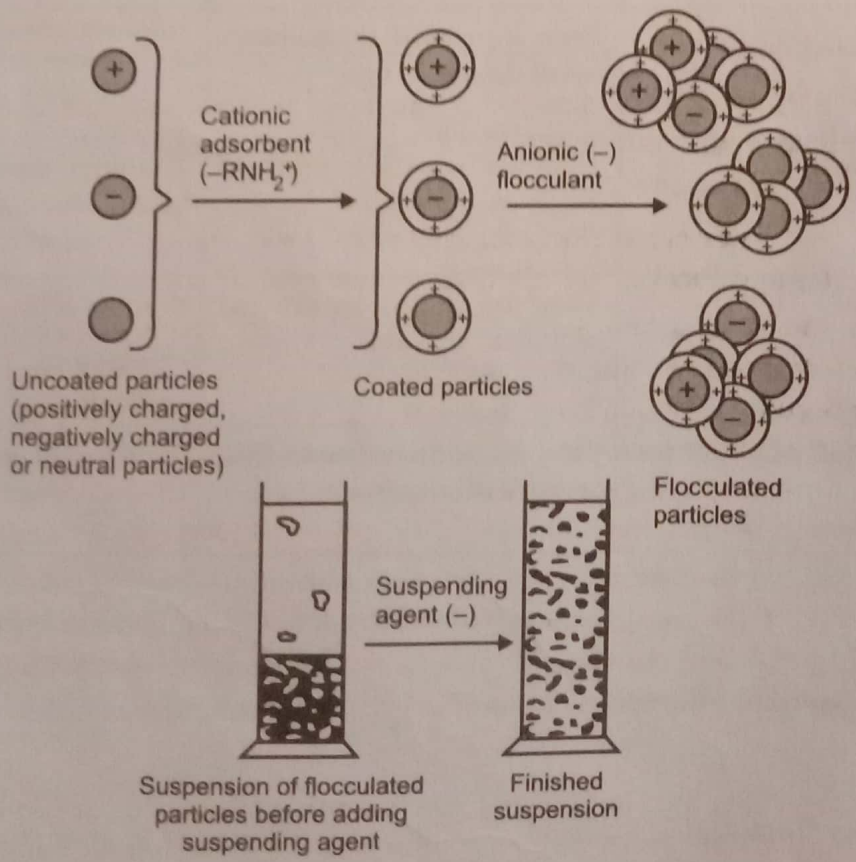


Figure 4.4: Controlled Flocculation in structured vehicle

Table 4.2 Ingredients used in the formulation of suspension

Ingredient	Action	Example
Wetting agents	They are used in suspension for dispersion of solids in continuous liquid phase.	Ionic and Non Ionic surfactants
Flocculating agents	They are added to cause aggregation or formation of flocs of the drug particles. They act by reducing zeta potential of charged particles in suspension	Neutral electrolytes, polymers, sulphate, citrate and phosphate salts
Thickeners	They are added to increase the viscosity.	Acacia, tragacanth, sodium alginate
Buffers	They are added to maintain pH of desired range.	Acetates, citrates
Coloring agent	They are used to improve elegance	Titanium dioxide, Brilliant blue, Tartarazine
Preservatives	They are added to prevent microbial growth.	Benzoic acid. Propylene glycol. Disodium EDTA
External liquid vehicle	They are added to make final volume of suspension	Water

Rheological Considerations

Rheological considerations are important in pharmaceutical suspensions since they affect the viscosity of the suspensions which in turn affects the settling and redispersion of the dispersed particles. Rheological attributes also influence the flow property of the suspensions when the containers are shaken and when the product is poured from the bottle. Rheology is also important in the case of external preparations which are suspensions as they must spread properly over the affected area when applied.

Most of the pharmaceutical suspensions exhibit plastic or pseudoplastic characteristics along with thixotropic properties. The rheological properties depend on the degree of flocculation of the dispersed phase as well as on the type and quantity of the suspending and thickening agent added to the system.

The preferred rheological behaviour for a pharmaceutical suspension is that of pseudoplasticity along with thixotropy. The product thus becomes thick on standing. This prevents or reduces the settling of suspended particles and elegance of product improves. On shaking the product becomes fluid and pouring of the suspension from the bottle and hence dosing becomes easier. Thixotropic character of the product ensures a slow recovery after shaking so that the particles in the product can remain suspended.

Proper selection of the rheological characteristics also improves the physical stability of the suspension and problems like settling, caking and particle growth can be avoided.

EMULSIONS

An emulsion may be defined as a biphasic system consisting of two immiscible liquids one of which (the dispersed phase) is finely subdivided and uniformly dispersed as droplets throughout the other (the continuous phase). Since such a system is thermodynamically unstable, a suitable emulsifying agent is required to stabilize the system.

The dispersed phase or continuous phase can range in consistency from a mobile liquid to a semisolid. Thus pharmaceutical emulsified systems range from lotions and oral emulsions of relatively low viscosity to ointments and creams which are semi-solid in nature. The particle size of the dispersed phase generally ranges from 0.1 to 100 μm.

TYPES OF EMULSIONS

1. Oil-in-Water Emulsions

In pharmaceutical emulsions, one phase is usually water and the other an oil, fat or waxy substance. Systems in which oil is the dispersed or discontinuous phase and water is the continuous phase are termed as oil-in-water (o/w) emulsions. Such emulsions are usually preferred for oral use since the disagreeable taste and odour of the oil is generally masked by emulsification. Additionally, the oil being in a finely dispersed state gets easily assimilated in the body. Emulsions for intravenous administration should also be of o/w type. Oil-in-water emulsions are also useful for preparations for

external use such as creams, lotions and liniments since they provide a non-greasy feeling to the product and can easily be washed off from the skin.

2. Water-in-Oil Emulsions

Water-in-oil (w/o) emulsions are those in which oil forms the continuous or external phase while water is the dispersed or discontinuous phase. Such emulsion are mostly used externally as creams and lotions. Such emulsions have an occlusive effect on the skin and are useful for the preparation of moisturising creams. They are also useful as cleansing creams since they solubilize the oil-soluble dirt from the surface. Certain medicaments such as antiseptics are more effective when used in the form of w/o emulsions. These emulsions are however not always acceptable cosmetically because of their greasy feeling.

3. Multiple Emulsions

In addition to the two types of emulsions discussed above there are certain complex, multiple emulsions in which the oil-in-water or water-in-oil emulsions are dispersed in another liquid medium. Thus, an oil-in-water-in-oil (o/w/o) emulsion consists of very small droplets of oil dispersed in the water globules of a water-in-oil emulsion and a water-in-oil-in-water (w/o/w) emulsion consists of droplets of water dispersed in the oil phase of an oil-in-water emulsion. More complex systems, such as water-in-oil-in-water-in-oil-in-water emulsions, have also been developed. The preparation of multiple emulsions involves two stages. For example, a w/o/w emulsion is prepared by first forming a water-in-oil system and then dispersing this primary emulsion in a second aqueous phase. Multiple emulsion have been proposed as potential candidates for sustained release dosage forms since the drug entrapped in the innermost phase has to pass through two other phases before being released for absorption.

4. Microemulsions

Normal emulsions generally contain globules ranging from 0.1 to 100 μm in diameter. Microemulsions are emulsions that contain globules having diameters of less than 0.1 μm. Droplets of such dimensions cannot refract light and, as a result, are invisible to the naked eye. Microemulsions therefore appear as transparent solutions and are more acceptable physically in comparison to conventional emulsions. Microemulsions have been employed for preparation of both external as well as internal formulations where they have exhibited better bioavailability than conventional emulsions.

IDENTIFICATION OF EMULSION SYSTEMS

A number of tests have been proposed to determine the type of emulsion. However, the results from one test should not be taken to be conclusive and the identity of an emulsion type should always be confirmed by at least two test procedures.

1. Dilution Test

The type of emulsion may be determined by diluting an emulsion with oil or water. An oil-in-water emulsion can be easily diluted with an aqueous solvent (e.g., milk, an o/w emulsion can be easily

diluted with water) whereas a water-in-oil emulsion can be diluted with an oily liquid. Addition of the wrong liquid will cause cracking of the emulsion.

2. Conductivity Test

This test is based on the principle that an emulsion with an aqueous continuous phase will transmit an electrical current whereas one with an oily continuous phase will not. In this test, a pair of electrodes connected to a lamp and an electrical source is generally dipped into an emulsion. If the emulsion is o/w type, the lamp glows. Conductivity tests, however, may give false results with non-ionic oil-in-water emulsions.

3. Dye Solubility Test

When a water-soluble dye such as amaranth is mixed with an emulsion and examined under a microscope, the continuous phase will appear coloured if the emulsion is o/w type while the globules will appear coloured in case of w/o type. Similarly, the continuous phase of a w/o emulsion and the globules of a o/w emulsion would appear coloured by an oil-soluble dye such as Sudan III.

4. Cobalt Chloride Test

If a filter paper soaked in a cobalt chloride solution and allowed to dry turns from blue to pink on exposure to an emulsion, it indicates that the emulsion is of the o/w type. This test however may not work if the emulsion is unstable or breaks in the presence of electrolytes.

5. Fluorescence Test

If a drop of an emulsion is exposed to ultraviolet radiation and observed under a microscope a water-in-oil emulsion should show continuous fluorescence while an oil-in-water type would show only spotty fluorescence. This is because many oils have the property to exhibit fluorescence on exposure to ultraviolet light.

6. Direction of Creaming Test

The direction of creaming in an emulsion can help in the identification of the emulsion type if the densities of the aqueous and oil phases are known. Water-in-oil emulsions would normally cream downwards as oil is generally less dense than water. On the other hand, o/w emulsions would normally cream upwards.

PHARMACEUTICAL APPLICATIONS OF EMULSIONS

(*i*) Emulsions can be used to administer orally unpleasant tasting drugs such as liquid paraffin, cod liver oil and castor oil in a palatable liquid formulation.

(*ii*) Oil soluble as well as water soluble materials can be formulated into a single dosage form as an emulsion. For example, oil soluble vitamins, A, D and E and water soluble ones such as vitamins B and C can be formulated as a palatable fine emulsion. Such a formulation also leads to better absorption of vitamins.

(*iii*) Radio-opaque emulsions are used for diagnostic applications such as X-ray examination.

(*iv*) O/w type emulsions have been used for intravenous administration of oils and fats with high calorific value to patients who are unable to ingest food by oral route.

(*v*) Emulsions of both o/w and w/o types have extensively been used to prepare pharmaceutical preparations for external use and cosmetic preparations such as creams and lotions.

(*vi*) Emulsification has also been used in aerosol products to prepare foams.

(*vii*) Drugs which are susceptible to oxidation or hydrolysis can sometimes be stabilized by formulating them in the form of emulsion..

(*viii*) Bioavailability of certain poorly soluble drugs can also be improved by dissolving them in oil and emulsifying.

THEORIES OF EMULSIFICATION

When one liquid is broken into small particles, the interfacial area of the globules constitutes a surface that is enormous compared with the surface area of the original liquid. There is an enormous increase in free energy associated with the large increase in surface area of the oil and hence system becomes thermodynamically unstable and separates into two phases due to coalescence of oil droplets.

In order to stabilize the emulsion, emulsifying agents are added. These act by reducing the interfacial tension between the two phases and forming a stable interfacial film between the two. The stability of a prepared emulsion is primarily determined by the strength and nature of the interfacial film formed.

An ideal emulsifying agent for pharmaceutical use should be stable, inert and free from toxic and irritant properties. It should preferably be odourless, tasteless, colourless and should produce stable emulsions of the desired type at very low concentrations.

Emulsifying agents can be broadly classified into three groups :

(*i*) Surfactants which get adsorbed at the oil-water interface to form monomolecular film and thereby reduce interfacial tension.

(*ii*) Hydrophilic colloids which form a multimolecular film around the dispersed droplets of oil in an oil in water emulsion.

(*iii*) Finely divided solids which get adsorbed at the interface between the two immiscible liquid phases and form a film of particles around the dispersed globules.

I. Monomolecular Adsorption

Surfactants are substances containing both hydrophilic and lipophilic regions in their molecular structure. These act by getting adsorbed at the oil-water interface in such a way that the lipophilic nonpolar groups are oriented towards oil while the hydrophilic polar groups are oriented towards the water thus forming a stable film. This film acts as a mechanical barrier to coalescence of the globules of the dispersed phase. A good emulsifying agent also reduces the interfacial tension which in

turn reduces the surface free energy and hence the tendency for coalescence. An additional effect promoting stability is the presence of surface charge which will cause repulsion between adjacent particles. The presence of charges on the surface of oil globules creates an electrical double layer around each globule. Overlapping of these double layer gives rise to a repulsion which opposes the *van der Waals* forces of attraction.

The type of emulsion produced i.e., whether o/w or w/o depends on the hydrophilic-lipophilic balance (HLB) of emulsifier. For example, o/w emulsions are formed when the HLB of the emulsifier is in the range of 9 to 12 whereas w/o emulsions are formed when the range is 3 to 6. Tweens which have a high HLB value give o/w emulsions and Spans which have low HLB values give w/o emulsions. From a practical point of view, a blend of emulsifiers which give the required HLB value for the oil phase give stable emulsions.

The type of emulsion formed is a function of relative solubility of the emulsifier. The phase in which the emulsifier is more soluble becomes the continuous phase. This is referred to as *Bancroft's rule*. As mentioned above, Tweens with high HLB values are soluble in water and lead to the formation of an o/w emulsion and Spans with low HLB value and poor aqueous solubility give w/o emulsion.

II. Multimolecular Adsorption

Hydrophilic colloids generally act by forming multimolecular layers at the interface. The formed layers or films are strong and resist coalescence. They do not cause appreciable lowering of interfacial tension. An additional effect of these hydrocolloids is the significant increase in the viscosity of the medium which in turn decreases coalescence. Since they are hydrophilic, they promote only o/w type emulsions. Their use is limited because of availability of large number of synthetic surfactants. The mechanical strength of gel barrier is increased by adding gelatin which is more effective at isoelectric point. With anionic hydrocolloids such as carboxy methyl cellulose, gelation is induced at low pH and the film formed is rigid.

Solid Particle Adsorption

The finely divided solid particles adsorb at the oil-water interface and form a rigid film of closely packed solids (Figure 11-4b). This film acts as a mechanical barrier and prevents the coalescence of globules. These tend to produce coarse emulsions. Depending on the affinity of the

emulsifier to a particular phase, one can prepare both types of emulsions. Examples are:

Bentonite (hydrated aluminum silicate, pH-9) — *o/w* and *w/o*
Veegum (magnesium aluminum silicate, > 1%) — *o/w*

The stability of an emulsion depends on the finer state of subdivision of solid particles, irregular surface and charge on the surface.

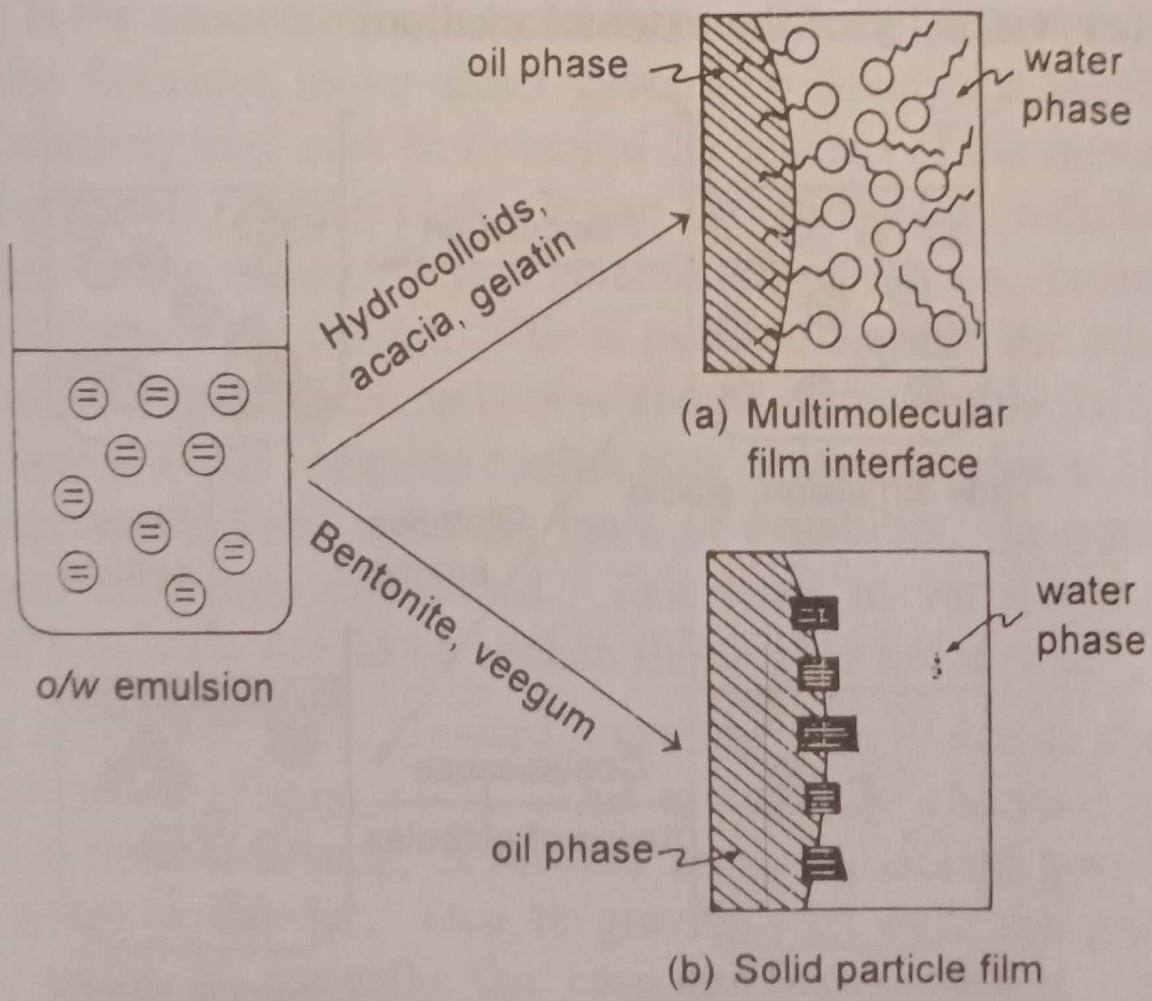


Figure 11-4. Film formation at the *o/w* interface. A. Multimolecular film, B. Solid particle film.

PHYSICAL STABILITY OF EMULSIONS

Stability in emulsions is characterized by the absence of coalescence of the internal phase, absence of creaming and maintenance of elegance with respect to appearance, odour, colour and thus physical properties. The main causes of instability in pharmaceutical emulsion can be classified as follows :

1. Flocculation and Creaming.
2. Coalescence and breaking
3. Physical and chemical changes
4. Phase inversion

1. Flocculation and Creaming

Creaming is a phenomenon characterized by accumulation of droplets of the dispersed phase at the top of the emulsion. The rate of creaming is governed by Stoke's law :

$$v = \frac{d^2(\rho_s - \rho_o)g}{18\,\eta_o}$$

where,

v is the terminal velocity in cm/sec.,

d is the diameter of the particles of dispersed phase in cm,

ρ_s is the density of the dispersed phase,

ρ_o is the density of the dispersion medium,

g is the acceleration due to gravity and

η_o is the viscosity of the dispersion medium in poise

Upward creaming generally results in o/w emulsions when the density of the dispersed phase is less than that of the dispersion medium. Downward creaming (or settling) generally results in w/o emulsions where the density of the dispersed phase is more than the dispersion medium.

Creaming is a reversible phenomenon and except for inelegance and unequal distribution of dose if drug is taken without shaking, it is not such a serious problem. Rate of creaming can be decreased by :

(*i*) Increasing the viscosity of the dispersion medium by the addition of viscosity improvers or thickening agents such as methyl cellulose, tragacanth, sodium alginate, gelatin, etc.

(*ii*) Reducing the particle size of the globules of the dispersed phase by homogenisation.

(*iii*) Minimizing the difference in the density of the two phases. This is however difficult since the density changes with temperature and agents required to increase the density of the oil phase such as a-bromonaphthalein, bromoform, carbon tetrachloride, etc. are toxic for internal use.

2. Coalescence and Breaking

Coalescence is characterized by the merging or aggregation of globules of the dispersed phase and generally occurs due to the rupture of the interfacial film surrounding the dispersed globules. This is an irreversible phenomenon as the coalescence of the dispersed phase results in the breaking up of emulsion and it cannot be reformed easily.

Factors which can reduce the chances of breaking are :

(*i*) Uniformity of particle size of dispersed phase.

(*ii*) Increase in the viscosity of the emulsion to an optimum level since this hinders flocculation and coalescence.

(*iii*) Phase volume ratio : The dispersed phase should be less than 74%; otherwise the oil globules may coalesce and the emulsion may break. A phase volume ratio of 50/50 is likely to give most stable emulsions.

3. Physical and Chemical Changes

Natural gums, starches, etc. used as emulsifiers may contain excessive amount of bacterial load. Bacterial growth may cause change in pH and consequent breakdown of emulsion. Synthetic emulsifiers are comparatively more stable.

Some emulsifiers such as soaps, cationics, etc. carry electric charges. Neutralisation of the charge by an added substance may cause breakdown of the emulsion.

4. Phase inversions

An o/w emulsion prepared with sodium stearate (monovalent soap) can be inversed to the w/o type by adding calcium chloride to form calcium stearate (divalent soap).

Inversion may also be produced by alterations in phase volume ratio. For example, if an o/w emulsifier is mixed with oil and a little quantity of water, a w/o emulsion is produced by agitation. Since water volume is less, it forms w/o emulsion. But when more water is added slowly, phase inversion occurs and an o/w emulsion is produced. Inversion has also been observed when an emulsion, which has been prepared by heating and mixing the two phases, is cooled. It is due to the temperature dependent changes in solubility of the emulsifying agents. Phase inversion can be prevented by choosing proper emulsifying agents in suitable concentrations. Wherever possible, it is better to ensure the internal phase does not exceed 74% of total volume of the emulsion.

Assessment of Stability of Emulsions

Stability of emulsions can be assessed by observing the rate of separation of the disperse phase as a distinct layer from emulsion i.e., by determining the degree of creaming. This method is suitable only for unstable emulsions that exhibit creaming quickly. For accelerating study, the rate of creaming may be increased by centrifugation.

A precise assessment of the physical stability can be made by studying the changes in size distribution of globules in an emulsion with time. Measurement of globule size can be undertaken by using a microscope. In this method, initially, the particle diameters are measured and a size frequency distribution of particles against particle size is obtained as a graph. The size distribution study is carried out at different time intervals. The changes in the shape of the curve shown indicate unstability. Stability can be assessed in terms of rate at which such changes occur. A more reliable result can be obtained by calculating changes in the number of globules per millimetre.

Other methods such as Coulter counting, turbidimetric analysis and temperature tests have also been used to evaluate new emulsifying agents and to determine the stability of emulsion.

PRESERVATION OF EMULSIONS

1. Preservation from Micro-organisms

Preservation of emulsions from micro-organisms is necessary since these can proliferate easily in emulsified systems with a high water content, particularly if carbohydrates, proteins or steroidal materials are also present. Microbial contamination can result in problems such as colour and odour change, gas production, hydrolysis, pH change and eventually breaking of emulsion. Even if there are no visible physical changes due to microbial contamination, the preparation will be unfit for administration. Hence it is necessary that emulsified systems be adequately preserved.

The desirable properties of an efficient preservative for emulsified systems include the following :

(*i*) An ideal preservative should be non-irritant, non-sensitizing and non-toxic in the concentration used.

(*ii*) It should be physically as well as chemically compatible with other ingredients of the emulsion and with the proposed container/closure system for the product.

(*iii*) It should not impart any taste, colour or odour to the product.

(*iv*) It should be stable and effective over a wide range of pH and temperature.

(*v*) It should have a wide spectrum of activity against a range of bacteria, yeast and moulds.

(*vi*) The selected preservative should have a high water solubility and a low oil/water partition coefficient.

(*vii*) It should have bactericidal rather than bacteriostatic activity.

(*viii*) It should be rapidly effective even in the presence of large microbial load.

Examples of antimicrobial preservatives used to preserve emulsified systems include parahydroxybenzoate esters such as methyl, propyl and butyl parabens, organic acids such as sorbic acid and benzoic acid, organic mercurials such as phenylmercuric acetate and phenylmercuric nitrate, quaternary ammonium compounds such as cetrimide, cresol derivatives such as chlorocresol and miscellaneous agents such as sodium benzoate, chloroform and phenoxyethanol.

Since it is the unionized state of the preservative which is able to penetrate the bacterial cell membranes, hence the pH should be low for weakly acidic preservatives such as benzoic acid and mixture of methyl and propyl parabens.

Factors which can reduce the preservative activity are binding or complexation of the preservative with one of the components of emulsion and adsorption of the preservative by the container/closure etc. so that the concentration reduces below the minimum inhibitory concentration. Hence, these interactions should be taken care-of while selecting a suitable preservative.

2. Preservation from Oxidation

Many vegetable and mineral oils and animal fats present in emulsified systems are susceptible to oxidative changes such as rancidity and spoilage due to atmospheric oxygen and effects of enzymes produced by micro-organisms. Changes due to atmospheric oxygen can be effectively prevented by the use of suitable antioxidants i.e., agents having a high affinity for oxygen and compete for it with labile substances in the formulation. The ideal antioxidant should be non-toxic, non-irritant, effective at low concentration under the expected conditions of storage and use, soluble in the medium, and stable (to reactions other than oxidation). Antioxidant for use in oral preparations should also be odourless and tasteless. Some of the commonly used antioxidants for emulsified systems include alkyl gallates such as ethyl, propyl or dodecyl gallate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT) and tocopherols.

Rheological Considerations

Most of the emulsion systems encountered in the field of pharmacy such as lotions and creams are non-newtonian except for a very few dilute ones (containing upto 20% of the dispersed phase) which exhibit newtonian behaviour. The fluid emulsions such as lotions containing about 20% to 50% of dispersed phase generally exhibit pseudoplastic behaviour while those approaching semi-solid behaviour such as cosmetic creams containing from 50 to 74% of dispersed phase are plastic and exhibit marked yield values. The semi-solid creams are usually viscoelastic. Different rheological behaviour can be conferred on these emulsion by merely varying the concentration of the dispersed phase and the nature and concentration of the emulsifying agent.

From the point of view of the consumer, shear-thinning emulsions are particularly preferred such as creams. Thus, they have a considerable consistency or body when removed from the pack but spread easily on application to the skin. Thixotropic lotions exhibit considerable consistency when allowed to stand at rest in the bottle. Once the bottle is shaken, they loose their consistency and easily pour from the bottle.

Proper rheological characteristics also confer stability on the emulsified systems and problems like creaming, coalescence and breaking are avoided. Release of drugs from the emulsified systems may also depend on their rheological characteristics.

5.8 FORMULATION OF EMULSION

The formulation of emulsion are related to the selection of the aqueous phase, oil phases and type of emulgents and their relative proportions. The ingredients used in the preparation of an emulsion should be chemically compatible. The ingredients should pass the toxicological tests.

a. Selection of lipid phase

The ingredients used for oil phase emulsion are: Mineral oils, Petrolatum, Polyethylene waxes, Vegetable oils, Animal fats, Lanolin, Substituted silicones, Plant waxes (Candellia) and Animal waxes (Beeswax).

The lipids are prone to oxidation due to chemical changes. The Emulsions prepared for topical purpose should possess a good "feel" but the emulsions containing oil leave oily residue on the skin. Therefore, the optimum volume of oil should be selected.

b. Selection of aqueous phase:

Mostly water is used as aqueous phase. The optimum ratio of aqueous phase should be selected.

c. Selection of emulsifying agents / Emulsifiers / Emulgents:

The selection of emulsifying agents are based on the site of application i.e. either for internal or external use. The examples of emulsifying agents are Synthetic emulsifying agent / Surface active agents (SAA) / Surfactants, hydrophilic colloid and finely divided solids. Non ionic and water soluble emulsifying agents are selected for internal use while ionic and non ionic emulsifying agents are selected for external use. The natural gums exhibit some type of incompatibility or instability and also cause microbial growth. Finely divided solids are used frequently for external purposes such as lotion or cream.

After selection of all components, on small scale, the basic method used in preparation of emulsion are

1. Dry Gum Method: It is also known as Continental method.

The continental method is used to prepare primary emulsion from oil, water, and a gum type emulsifier (usually acacia). It is also called 4:2:1 method because 4 parts oil, 2 parts water, and 1 part emulsifier is used. Mortar and pestle is used to prepare emulsion.

Steps involved in preparation of emulsion are:

1 part gum is levigated or triturated with the 4 parts oil in a dry mortar

↓

Now add 2 parts water all at once

↓

Triturate it continuously until "crackling" sound is produced

↓

At this time the primary emulsion will be creamy white

↓

Then add more quantity of water to the primary emulsion

↓

Solid substances, if any, are added as a solution to the primary emulsion

↓

Oil soluble substance, in small amounts, may be incorporated directly into the primary emulsion

↓

Any substance such as alcohol should be added near to the end of the process to avoid breaking the emulsion

↓

Transfer the primary emulsion to a calibrated vessel

↓

Make the final volume with water

2. Wet Gum Method: It is also known as English Method

The proportions of oil, water, and emulsifier in wet gum method are the same as in dry gum method i.e (4:2:1), but the steps and techniques of mixing are not same. In this method, 4 part oil, 2 part water and 1 part gum is used. English method is more difficult but it produce more stable emulsion.

Steps involved in preparation of emulsion are

1 part gum is triturated or levigated with 2 parts water to form a mucilage

↓

Add 4 parts oil slowly during trituration

↓

Continuously triturate to form the primary emulsion

↓

Add other ingredients, if any, as in the continental method

↓

Transfer the primary emulsion to graduated cylinder

↓

Make the final volume with water

3. Bottle Method: It is also known as Forbes Method

This method is used to prepare emulsions of volatile oils, or substances having very low viscosities. It is not suitable for very viscous oils.

1 part Gum or Powdered acacia is placed in a dry bottle

↓

2 parts of oil are added

↓

Shake the mixture thoroughly after capping

↓

A volume of water (approximately equal to that of the oil) is added in portions

↓

Again shake the mixture thoroughly until the primary emulsion is formed

↓

Dilute it with proper volume of water

On large scale, number of equipments are used for preparation of emulsion such as hand homogenizer, Colloid mill, Propeller and turbine Mixers, ultrasonic devices etc. In hand Homogenizer, due to pumping action, the emulsion pass through a very small orifice. Due to this size of globules get reduced 5 micron or less. The hand homogenizer is not used for emulsions containing a high proportion of solid matter. Colloid mill is also used which reduce size of globules due to shearing action.