

COARSE DISPERSION

By,

Dr. Vaibhav G. Bhamare

Ph. D, M. Pharm, MBA

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INTRODUCTION

- Coarse dispersions are heterogeneous dispersed systems, in which the dispersed phase particles are larger than 1000 nm
- Coarse dispersions are characterized by relatively fast sedimentation of the dispersed phase caused by gravity or other forces.
- Dispersed phase of coarse dispersions may be easily separated from the continuous phase by filtration.

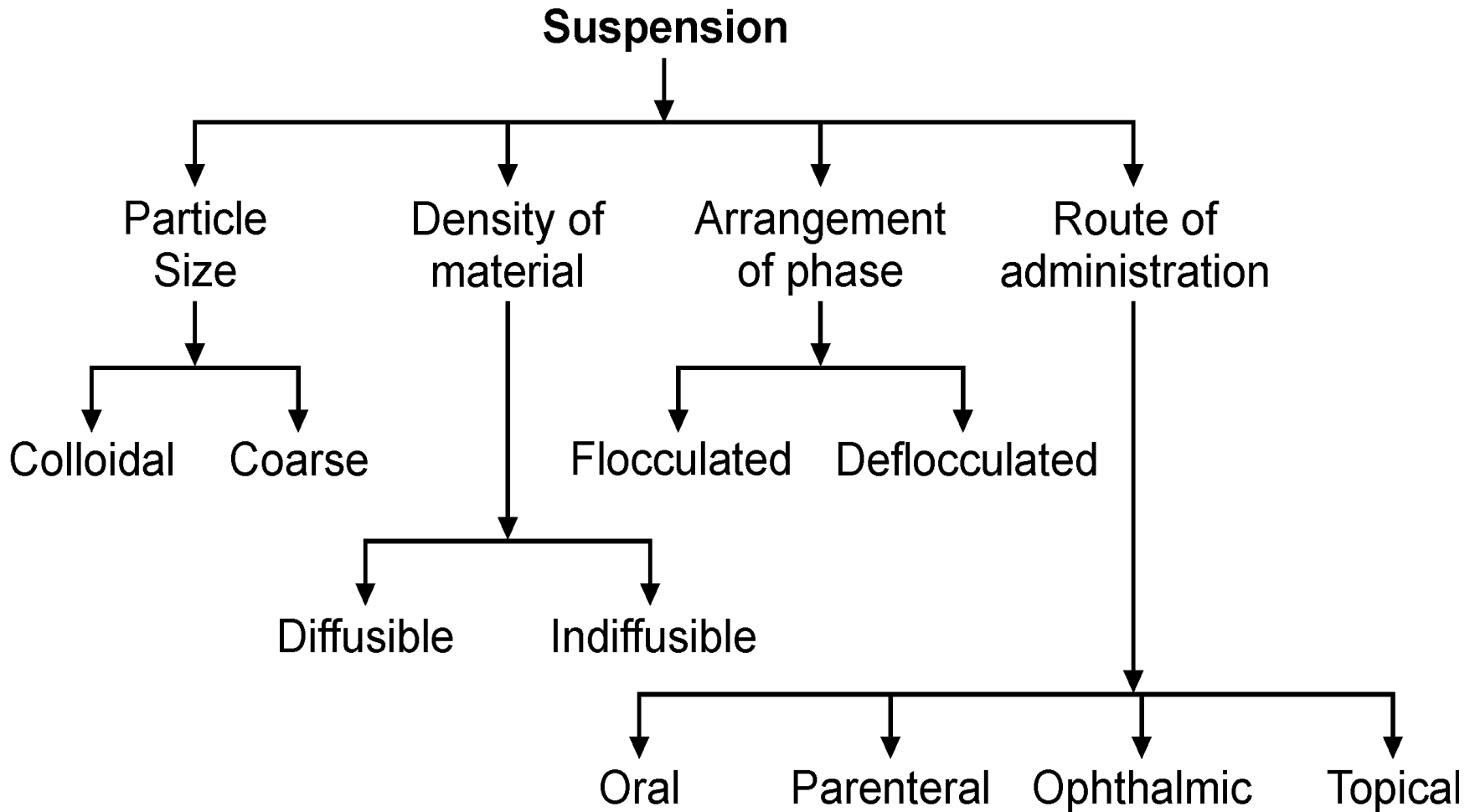
SUSPENSION

- Suspension can be defined as heterogeneous biphasic liquid systems in which insoluble solid particles are suspended in a liquid medium.
- A suspension of liquid droplets or fine solid particles in a gas is called an aerosol.
- The suspended insoluble particle is referred to as external or discontinuous or dispersed phase whereas the liquid phase is referred to as external or continuous or dispersion medium.
- Suspensions are thermodynamically unstable and to make them stable, these may require the inclusion of stabilizer, suspending agent.

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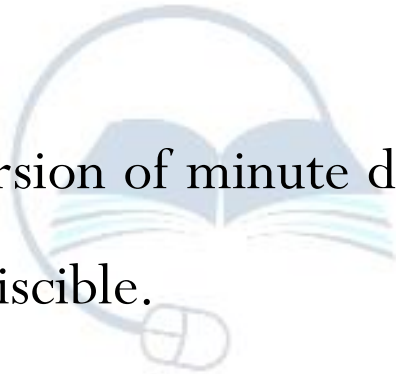
- Surfactants or suspending agents are molecules which possess two fundamental properties as adsorption and aggregation.
- On the one hand, surfactant tends to be located preferentially at the interface between a polar and a non-polar phase. The phenomenon according to which a molecule comes from the bulk of a solution to place itself at the interface is called adsorption and is characteristic of many amphiphilic molecules.
- On the other hand surfactant molecules in solution exhibit a tendency to self-associate to produce aggregation polymer called micelles, as well as other structures.

Classification of Suspension



EMULSION

- An emulsion can be defined as a biphasic liquid dosage form in which two immiscible liquids are mixed with force and stabilizing it by adding surfactants or emulsifier.
- An emulsion is a fine dispersion of minute droplets of one liquid in another in which it is not soluble or miscible.
- Depending on the continuous phase two liquids can form different types of emulsions.
- The type of emulsion that forms depends largely on the volume ratio of the two materials, with the more abundant phase forming the continuous phase.

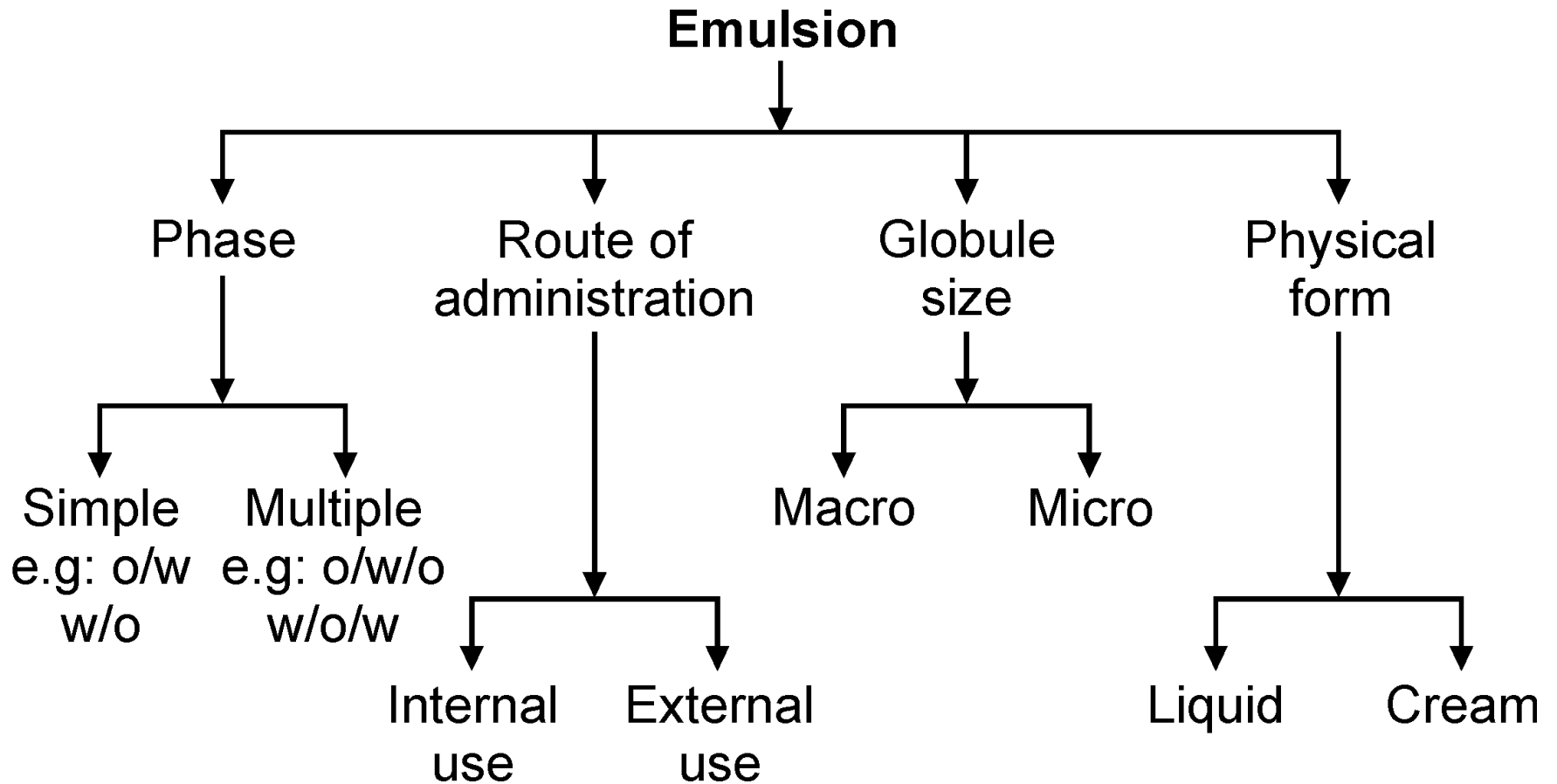


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- As an example, oil and water can form, first, an oil-in-water emulsion, wherein the oil is the dispersed phase and water is the continuous phase.
- Second, they can form a water-in-oil emulsion, wherein water is the dispersed phase and oil is the continuous phase.
- Multiple emulsions are also possible, including a "water-in-oil-in-water" emulsion and an "oil-in-water-in-oil" emulsion.
- As mentioned, emulsions are stabilized with surfactants (emulsifying agents) that have affinities for both phases; these decrease the energy required to make new surfaces between the two phases, the interfacial surface tension.

Classification of Emulsion

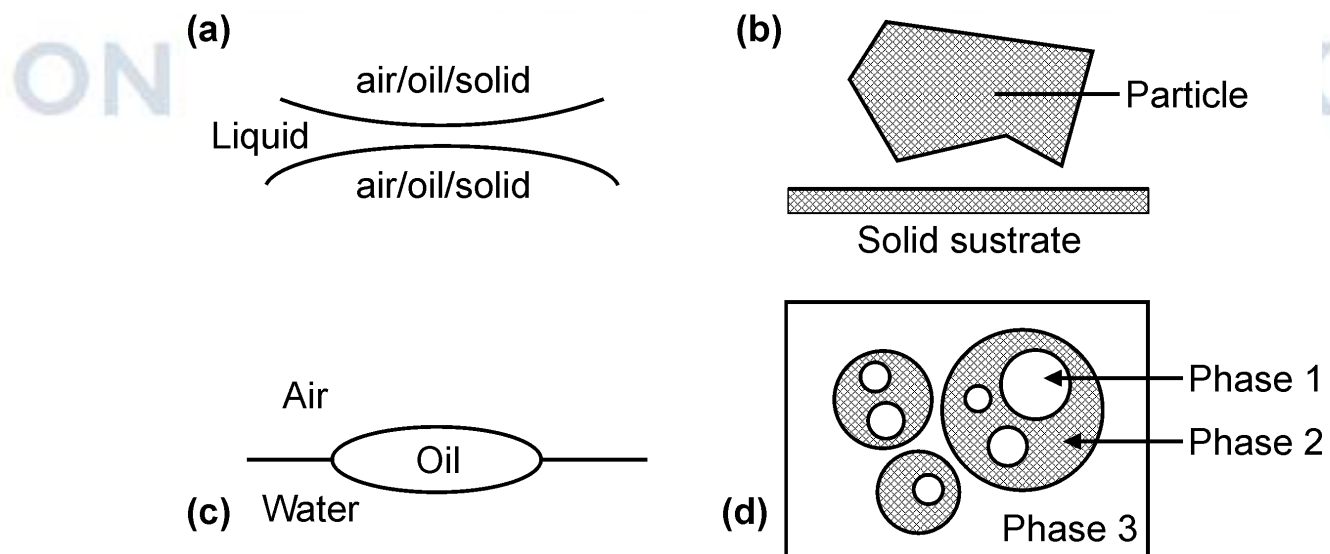


INTERFACIAL PROPERTIES OF SUSPENDED PARTICLES

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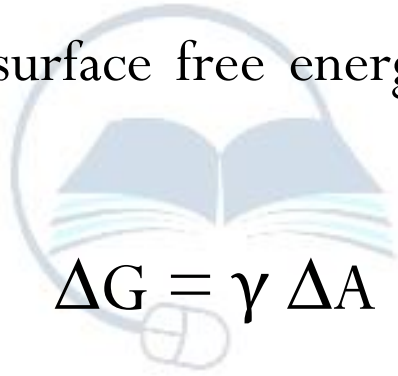
- In pharmaceutical suspensions, the solid phase remains as finely divided particles in the dispersion medium. Therefore, a large amount of interface is involved in the formation, which, in turn, affects the stability of suspension preparations. The interfacial properties, therefore, play a vital role in modifying the physical characteristics of dispersion.



- The smaller the fragments of the dispersed phase, the larger is the interfacial area and as a consequence, the more important the interfacial phenomena.
- When the proportion of the discontinuous phase is large in the dispersed systems, another phenomenon becomes important, that is the approach of the interfaces of two fragments of the dispersed phase.
- When the two fragments of a dispersed phase approach at some close distance, Van der Waals attractive forces can become important. (fig.(a)).
- On the other hand, if the two interfaces are different, the Van der Waals adhesive forces can be quite different from the cohesive forces and the situation become extremely complex (fig b and fig c).
- Some even more complex cases can occur as called multiple emulsions, where there are two or more dispersed phases or when the drops of the dispersed phase contain even smaller droplets of another phase (fig d). These complex cases are very common as far as the practical applications are concerned.
- The particle tends to communicate with another particle, the 'surface area' of the particle increases and thereby it becomes highly unstable with a 'large amount of energy'. Hence these particles get a lot of energy and try to agglomerate with another particle to reduce the surface area around them and to stabilize their thermodynamic instability. Adding of surfactants in this group can reduce the amount of tension between them.

i) Surface Free Energy

- A large surface area offered by finely divided solid materials is typically associated with a large amount of free energy on the surface.
- The relation between the surface free energy and the surface area can be expressed by,


$$\Delta G = \gamma \Delta A$$

where,

ΔG is the increase in surface free energy,

ΔA is the increase in surface area and

γ is the interfacial tension between the solid particles and the dispersion medium.

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- The smaller is the ΔG , the more thermodynamically stable is the suspension. Therefore, a system with very fine particles is thermodynamically unstable because of the high total surface area. Thus, the system tends to agglomerate to reduce the surface area and thereby the excess free energy.
- Surface free energy may also be reduced to avoid the agglomeration of particles, which can be accomplished by reducing interfacial energy.
- When a wetting agent is added to the suspension formulation, it is adsorbed at the interface. This will result in a reduction of the interfacial tension, making the system more stable.

ii) Surface Potential

- The stability of lyophobic colloidal systems can generally be explained based on the presence or absence of surface potential. This theory can also be extended to suspension systems.
- The surface potential exists when dispersed solid particles in a suspension possess charge surrounding the liquid medium.
- Solid particles may become charged in different ways. If the suspension contains electrolytes, selective adsorption of a particular ionic species by the solid particles is a possibility. This will lead to the formation of charged particles.
- Occasionally, the surface-active agents, which are already adsorbed at the solid-liquid interface, may ionize to give the particles positive or negative charge.
- Solid particles can also be charged by ionization of functional group of the particles. In this case, the total charge is a function of the pH of the surrounding vehicle.

SETTLING IN SUSPENSION

- Settling/sedimentation of particle takes place gradually over a prolonged period, due to gravitational forces.
- Ideally, the internal phase should be dispersed uniformly within the dispersion medium and should not sediment during storage. However this is practically not possible because of the thermodynamic instability of the suspension.
- Particles in the suspension possess a surface free energy that makes the system unstable leading to particle settling.
- To minimize the free energy, the system tends to decrease the surface area, which is achieved by the formation of agglomerates. This may lead to flocculation or aggregation, depending on the attractive and repulsive forces within the system.

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- The rate of sedimentation of particles can be determined by Stokes' law:

$$V = \frac{d^2 (\rho_1 - \rho_2) g}{18 \eta_0}$$

where,

V is the terminal velocity of sedimentation (cm/s),

d is the diameter of the particle (cm),

ρ_1 and ρ_2 are the densities of the suspended particles and the medium, respectively,

g is the acceleration due to gravity and

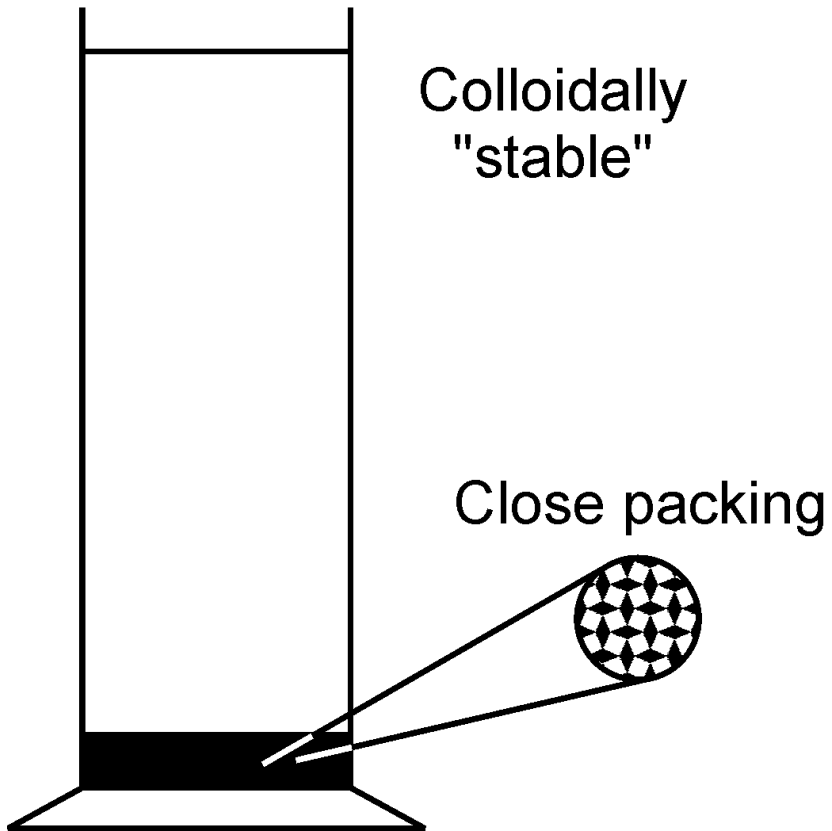
η_0 is the viscosity of the medium.

FLOCCULATED SYSTEM DEFLOCCULATED SYSTEM

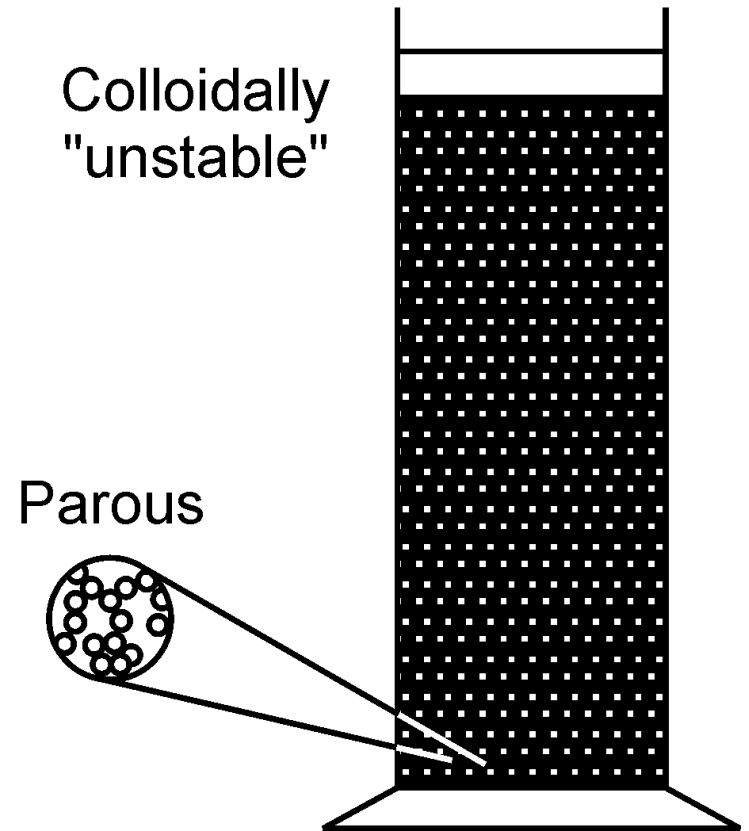
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Deflocculated



Flocculated



Flocculated Suspension	Deflocculated Suspension
Particles forms loose aggregates with network like structure.	Particles exist as separate entities.
Rate of sedimentation is high.	Rate of sedimentation is slow.
Sediment is rapidly formed.	Sediment is slowly formed.
Sediment is scaffold like loosely packed and doesn't form a compact cake.	Sediment is very closely packed and a compact cake is formed.
Sediment is easy to re-disperse.	Sediment is difficult to re-disperse.
Suspension is not pleasing in appearance.	Suspension is pleasing in appearance.
The floccules stick to the bottle wall.	They don't stick to the sides of the bottle.
Supernatant liquid is generally clear.	Supernatant liquid is generally cloudy.
Bioavailability is comparatively less due to small specific surface area.	Bioavailability is higher due to large specific surface area.

FORMULATION

- To prepare an ideal suspension, one should prepare a suspension with partial flocculation.
- The particle size distribution in the finished drug product dosage form is a critical parameter that significantly impacts the bioavailability and pharmacokinetics of the product.
- In addition to therapeutic efficacy and stability, other features apply specifically to the suspensions:
 - A properly prepared suspension should settle slowly and remain homogenous for at least the period between shaking the container and removing the required dose.
 - The sediment produced on storage should be readily redispersed upon gentle shaking of the container.
 - The particle size of the suspended drug should remain constant throughout long periods and do not show crystal growth.
 - The suspension viscosity must not be very high and it should be poured easily from its container.

i) Suspending Agent

- Suspending agents are substances used to make the particles suspended in the vehicle for a longer time and slow down their settling by increasing the viscosity of the medium.
- The amount of the suspending agent must not be very high to render the suspension too viscous to agitate or to pour.
- Surfactant is a general name for materials that possess surface activity; in solution they tend to orient at the surface of the liquid.
- There are several general classes of surfactants: anionic, cationic, amphoteric and non-ionic.
- Surfactants are amphiphilic molecules, i.e. part of the molecule is hydrophilic, and part is lipophilic. This combination of the two opposite affinities in the same molecule causes them to orient to the interface and thereby reduce the interfacial tension between the continuous and disperse phases, such as in emulsions and suspensions.
- Ionic surfactants work primarily through electrostatic forces, whereas non-ionic surfactants work primarily through steric forces.

ii) Flocculating Agent

- Flocculating agents are suspending agents which help to entrap particle and reduce sedimentation of particles. Flocculating agents are added to enhance particle redispersability. The best approach to prepare stable suspension is to achieve a controlled flocculation of the particles. Controlled flocculation of particles is achieved by adding flocculating agents such as electrolytes, surfactants and polymers.
- **Electrolytes:** Electrolytes acts as flocculating agents by reducing the electrical barrier between the particles, thus, decrease the zeta potential. This leads to decrease in repulsion potential and makes the particle come together to form loosely arranged structure (flocules).

continued...

- **Surfactants:** Surfactants are used to control flocculation. Optimum concentrations of surfactants bring down the surface free energy by reducing the surface tension between liquid medium and solid particles. The particles possessing less surface free energy are attracted towards each other by Van der Waal forces and forms loose agglomerates.
- **Polymers:** Natural polymers are long chain, high molecular weight compounds containing active groups spaced along their length. These polymers act as flocculating agents. One part of the chain is adsorbed on the particle surface while the other projecting out in the dispersion medium. Bridging between these portions leads to the formation of floccules. Polymers exhibit pseudo-plastic flow in solution promoting the physical stability of suspension.

iii) Wetting Agent

- Wetting agents are added in suspension to reduce interfacial tension between solid particles and dispersion liquid. Hydrophilic solid particles are easily wetted by water while hydrophobic particles are easily wetted by non-polar liquids. The extent of wetting by water is dependent on the hydrophilicity of the solid particles. If the particles are more hydrophilic it finds less difficulty in wetting by water. Wetting agents work by reducing the contact angle and interfacial tension between the dispersed phase and dispersed medium. A liquid phase containing suitable wetting agent helps to displace air at the surface particles.
- Alcohol and glycerine may be employed as wetting agents. They function by displacing the air on the surface of the particles thereby allowing penetration of water into the powder.

FORMULATION PRINCIPLE

- Settling/sedimentation of particle takes place gradually over a prolonged period, due to gravitational forces. Ideally, the internal phase should be dispersed uniformly within the dispersion medium and should not sediment during storage. However this is practically not possible because of the thermodynamic instability of the suspension.
- Particles in the suspension possess a surface free energy that makes the system unstable leading to particle settling.
- Many factors must be considered in the course of developing a suspension dosage form. The basic concern involves the fact that suspension settles, and it is necessary to redistribute them before using.

i) Effect of particle size

- Smaller particles can have a greater effect on increasing the viscosity of the system because they have a higher specific surface area than the larger particles.
- The particle size plays a key role in the formulation of suspension. Care must be taken that the particles must be of small size.
- Reduction in particle size decreases rate of sedimentation of the suspended particles. Particle size can be reduced by milling, sieving, and grinding.
- Particle size has effects on rate and extent of drug absorption, dissolution, and distribution of the drug in the body. Size reduction has a limiting value that beyond particular size reduction lead to formation of a compact cake upon sedimentation.

ii) Crystal Growth

- Also known as Ostwald ripening, crystal growth sometimes is very important for suspension sedimentation, physical stability, re-dispersibility, appearance and bioavailability.
- Size of all particles in dispersion may not remain constant throughout its shelf life. One reason for that change would be crystal formation.
- Metastable (i.e., the least stable form of the drug) is the most soluble. As the metastable form changes to a more stable form, solubility decreases and crystallization occurs. This problem can be avoided by excluding the metastable form from the dispersion and by using the most stable polymorph of the drug.

iii) Use of Structured Vehicle

- Structured vehicles are also called as thickening agents.
- Structured vehicles are vehicles containing thixotropic polymers like acacia which are pseudo-plastic or plastic in nature. These polymers form a three-dimensional gel network structure which entrap the particles in order to avoid particle settling. During shaking, the gel network is completely destroyed so that administration is facilitated. Structured vehicles are used only in deflocculated suspensions.
- In addition, Structured vehicle should possess some degree of Thixotropic behaviour viz., the property of GEL-SOL-GEL transformation. Because during storage it should be remained in the form of GEL to overcome the shear stress and to prevent or reduce the formation of hard cake at the bottom which to some extent is beneficial for pourability and uniform dose at the time of administration.

THEORIES OF EMULSIFICATION



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Phase Volume Theory

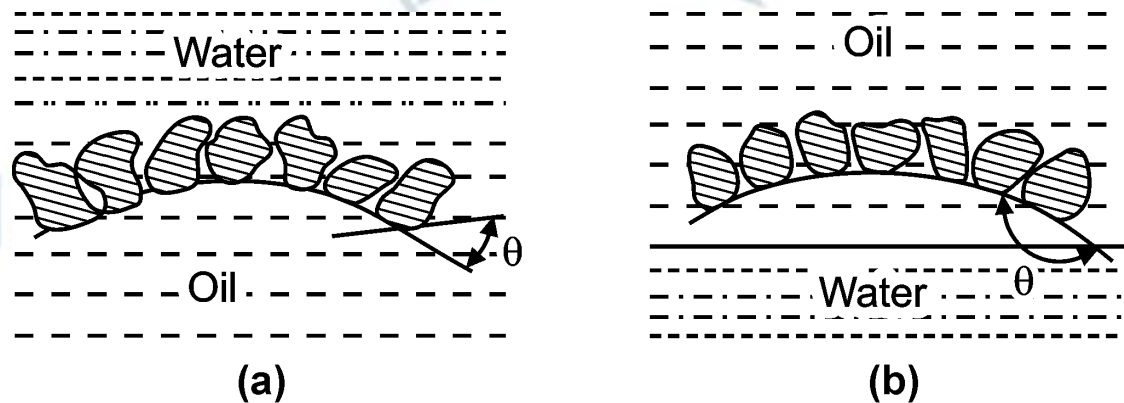
- If the emulsion consisted of an assembly of closely packed uniform spherical droplets, the volume fraction ϕ of the dispersed phase would equal 0.7402 of the total volume, and that of the medium 0.2598.
- Formation of O/W and W/O emulsions would be possible if $\phi = 0.26$ to 0.74.
- If spheres of the same diameter are packed as closely as possible, one sphere will touch 12 others and the volume the spheres occupy is about 74% of the total volume.
- Thus if the spheres or drops of the dispersed phase remain rigid it is possible to disperse 74 parts of the dispersed phase in the continuous phase; but if the dispersed phase is increased to more than 74 parts of the total volume, a reversal of the emulsion will occur.
- However, the dispersed phase does not remain rigid in shape but the drops flatten out where they come in contact with each other, nor are all the dispersed particles the same size, so that it is possible for the dispersed phase to consist of from 1 to 99 per cent of the emulsion.

Oriented Wedge Theory

- It is based upon the concept that the molecules of the emulsifier orient themselves in the interface between the dispersed and continuous phases, forming a wedge, the curvature of which determines the size of the dispersed phase.
- In this theory the surfactant emulsifier molecules are assumed to be shaped like wedges; therefore, it is termed "Oriented wedge" theory.
- Some of the emulsifying agents tend to form film and to penetrate in a medium.
- Based on their miscibility and solubility, the emulsifying agent forms a curve surface over globules which leads to entrapment of
- The orientation is to achieve a maximum interfacial density of emulsifier, thus producing the maximum decrease in free energy and the maximum increase in strength of the interfacial film.

Preferential Wetting Theory

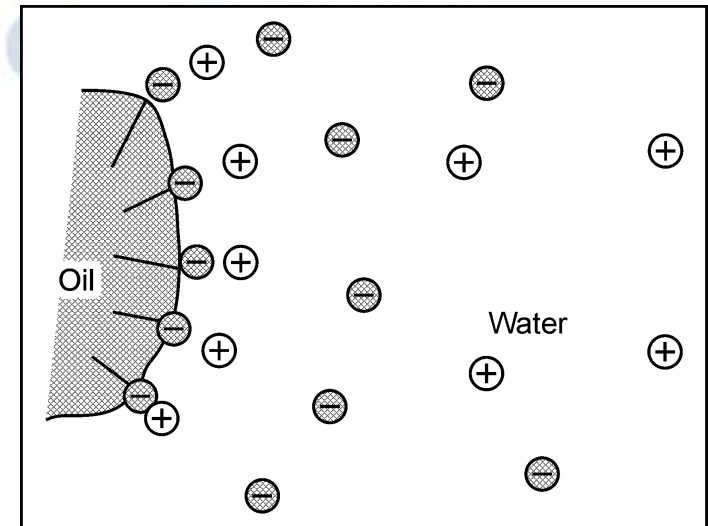
- The most satisfactory general theory of emulsion type is that originally proposed for emulsions stabilized by finely divided solids.
- If the solid is preferentially wetted by one of the phases, then more particles can be accommodated at the interface if the interface is convex toward that phase, that is, if the preferential wetting phase is the dispersion medium, as shown in Fig.



- For example, bentonite clays (which are preferentially wetted by water) tend to give O/W emulsions, whereas carbon black (which are preferentially wetted by oil) tend to give W/O emulsions.

Electric Double Layer Theory

- It is a charge formation over the dispersed phase. Thus, facilitate proper mixing of the dispersed phase into dispersion medium which results in the formation of a proper emulsion.
- The oil globules in O/W emulsion carry a negative charge. The water ionizes so that both hydrogen and hydroxyl ions are present.
- The negative charge on the oil may come from adsorption of the OH ions. These adsorbed hydroxyl ions form a layer around the oil globules.
- The second layer of oppositely charged ions forms a layer in the liquid outside the layer of negative ions.
- These two layers of oppositely charged ions are known as the Helmholtz double layer.
- They are not confined to emulsions but accompany all boundary phenomena.



Hydration Theory

- Fischer and Hooker state that hydrated colloids make the best emulsifiers.
- Fischer states that all permanent emulsions can be explained based on hydrated or lyated colloids. He says that when water changes to a colloid hydrate, its physical constants change; and these include, among others, surface tension, viscosity and adsorption.
- Fischer states the emulsifying agent, by which a permanent emulsion is obtained, invariably "proves to be a hydrophilic colloid when water and oil emulsions are concerned (a lyophilic colloid of some sort when other than aqueous mixtures are under consideration).
- The treatment of the colloid, such as freezing or heating or the addition of substances which alter the water-holding capacity of the colloid may crack the emulsion or lessen its emulsifying ability.

Interfacial Tension Theory

- Clayton states that with this theory emphasis is laid upon the fact that emulsification is influenced by
 - the mass of the emulsifying agent present
 - the ease with which this agent is adsorbed at the interfacial surface
 - the nature of the ions adsorbed by the resultant film.
- To form an emulsion, the emulsifier must be adsorbed at the interfacial surface and form a sufficiently coherent film to stabilize the emulsion. The reversal of the emulsion depends upon the nature of the ions adsorbed by this film.
- The emulsifier may be adsorbed by the water or by the oil, but it is usually adsorbed more in one liquid than in the other and thus lowers the interfacial tension of one liquid to a greater extent than that of the other.
- If the tension of the water is lowered more than that of the oil, the water has less tendency to form drops, flows to form a film more readily and becomes the continuous phase.

MICROEMULSION



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INTRODUCTION

- Microemulsions are clear, thermodynamically stable, isotropic liquid mixtures of oil, water and surfactant, frequently in combination with a cosurfactant.
- Microemulsion concept was introduced in the early 1940s by Hoar and Schulman who developed a clear single-phase compound using titration of a milky emulsion with medium-chain alcohol. Schulman and coworkers subsequently coined the term "microemulsion."
- Microemulsions are thermodynamically stable and their formation is facilitated by the ultralow interfacial tension of these systems, which leads to the formation of extremely small droplets of the dispersed phase. The droplet sizes are below 100 nm (and in many cases even smaller).

- Microemulsions at the molecular scale, are a finely balanced system, where the energetics of entropy and surface energies are opposing each other.
- The Entropy of the system is increased by having a higher number of droplets dispersed while the surface areas and correspondingly surface energies are increased with more droplets.
- Additionally, surfactants that have hydrophilic-lipophilic balances (HLBs) of 3–6 tend to promote W/O microemulsions formation, while those with HLB values of 8–10 tend form O/W microemulsions.
- The choice of microemulsion components affects its stability. It has been reported that the formation and stability of microemulsions are dependent on the interfacial tension between the dispersed and continuous phases.

- Microemulsion instability can lead to Ostwald ripening, leading to the dissolution of the small droplets with a resultant increase in the size of the large droplets; therefore, stabilization against Ostwald ripening is critical because the resultant change in droplets sizes could lead to loss of physical stability of the dosage form.
- Microemulsions are prepared by simple mixing of the components and do not require specific preparation conditions.

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DIFFERENCE BETWEEN

Property	Microemulsion	Emulsion
Appearance	Transparent	Cloudy
Optical isotropy	Isotropic	Anisotropic
Interfacial tension	Ultra-low	High
Microstructure	Dynamic	Static
Droplet size	20 – 100 nm	> 500 nm
Phases	Monophasic	Biphasic
Viscosity	Low	high

TYPEs OF MICROEMULSION

There are three kinds of Microemulsions:

(1) Oil dispersed in water (o/w):

The presence of o/w droplets is likely to be a characteristic of microemulsions where the amount of oil is low.

(2) Water dispersed in oil (w/o):

The existence of w/o droplets is a characteristic of microemulsions where the water fraction is low.

(3) Bicontinuous:

Bicontinuous microemulsions may result where the amounts of water and oil are equal.

APPLICATIONS OF MICROEMULSION

- **As the carrier for protein and peptide:** Microemulsions may be used as the carrier for protein and peptide delivery to the GI tract. With all types of microemulsions, water-oil-water type microemulsion offers unique advantages like a reduction in degradation of proteins
- **Topical and transdermal drug delivery:** Microemulsions are known to increase drug absorption on topical application
- **Nanotechnology application in controlled release:** Microemulsions have been proposed as drug delivery systems to enhance the absorption of drug across biological membranes.
- **Colloidal carriers for noninvasive delivery of insulin:** Insulin-loaded microemulsions developed using didecyl dimethyl ammonium bromide (DMAB) and propylene glycol (PG) showed 10-fold enhancement in bioavailability compared to plain insulin solution administered orally.

MULTIPLE EMULSION



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INTRODUCTION

- Multiple emulsions are complex polydispersed systems where both oil in water and water in oil emulsion exists simultaneously which are stabilized by lipophilic and hydrophilic surfactants respectively.
- Multiple emulsions are "emulsion of emulsions", in which the drop of the dispersed phase themselves contain smaller dispersed droplets of miscible liquids.
- Each dispersed globule in the double emulsion forms a vesicular structure with single or multiple aqueous compartments separated from the aqueous phase by a layer of oil phase compartments.
- In multiple emulsion system, solute has to transverse from inner miscible phase to outer miscible phase by the middle immiscible organic phase; it is also known as liquid membrane system.

TYPEs OF MULTIPLE EMULSION

(1) Oil in water in oil (o/w/o) emulsion:

- In O/W/O systems, an aqueous phase separates internal and external oil phases.
- In other words, O/W/O is a system in which water droplets may be surrounded in an oil phase, which in turn encloses one or more oil droplets.

(2) Water in oil in water (w/o/w) emulsion:

- In W/O/W systems, an organic phase separates internal and external aqueous phases.
- In other words, W/O/W is a system in which an oil droplet may be surrounded by an aqueous phase, which in turn is enclosed one or more water droplets.

POSSIBLE DRUG RELEASE MECHANISM

- Diffusion and facilitated diffusion (carrier mediated transport)
- Micellar transport
- Thinning of the oil membrane
- Rupture of oil phase
- Photo-osmotic transport
- Solubilization of internal phase in the oil membrane



APPLICATIONS OF MULTIPLE EMULSION

- **Controlled & sustained drug delivery:** In both systems drug contained in innermost phase partitions through several phases before releasing at the site of absorption and the rate of release is governed by its ability to diffuse through various phases and cross interfacial barriers
- **Enhancing oral bioavailability or oral absorption:** The various drugs have been incorporated in Multiple Emulsions for the enhancement of the increase of oral bioavailability from the stomach. eg: Heparin, Insulin, Griseofulvin etc.
- **Multiple emulsions in cancer therapy:** Most anticancer drugs are used as emulsions because they are water-soluble. In the form of an emulsion, it is possible to control release rates of medicine and suppress strong side effects of the drug.
- **Vaccine/vaccine adjuvant:** The use of w/o/w multiple emulsion as a new form of adjuvant for antigen was first reported by Herbert. These emulsions elicited a better immune response than antigen alone.

- **Multiple emulsions in herbal drugs:** Apart from its targeted sustained release, producing the herbal drug into emulsion will also strengthen the stability of the hydrolyzed materials, improve the penetrability of drugs to the skin and mucous and reduce the drugs stimulus to tissues.
- **Oxygen substitute:** A multiple emulsion of aqueous oxygen-carrying material in oil in the outer aqueous phase is suitable for the provision of oxygen for oxygen transfer processes.
- **Taste masking:** Multiple emulsions of chloroquine, an antimalarial agent, chlorpromazine, an antipsychotic drug has been successfully prepared and had been found to mask the bitter taste efficiently.
- **Drug overdose treatment:** Multiple emulsions can be utilized for the over-dosage treatment by utilizing the difference in pH. In these emulsions, the inner aqueous phase of the emulsion has the basic buffer and when the emulsion is taken orally, acidic pH of the stomach acts as an external aqueous phase.

STABILITY / INSTABILITY in EMULSION



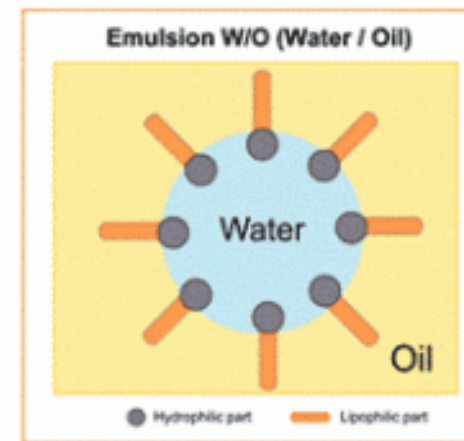
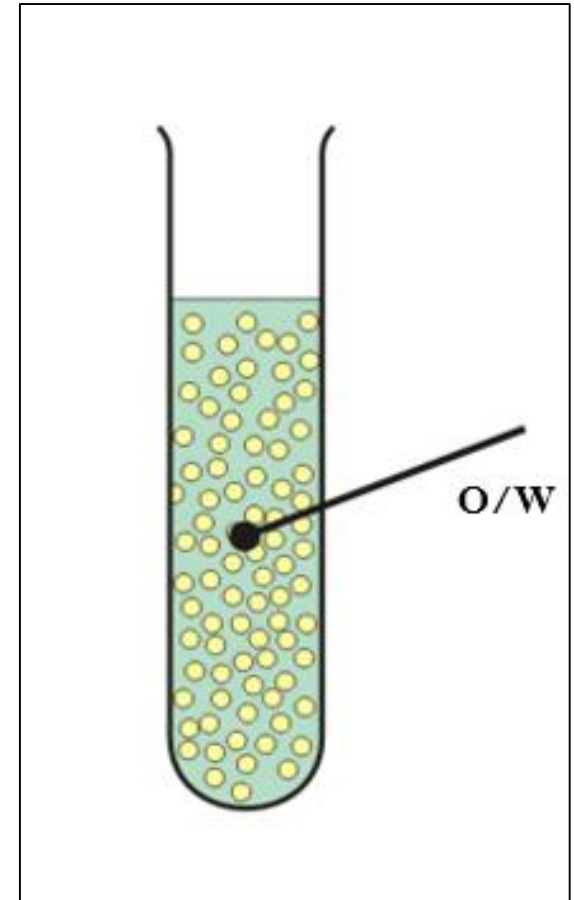
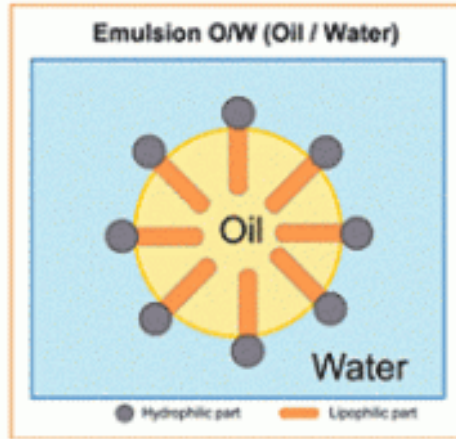
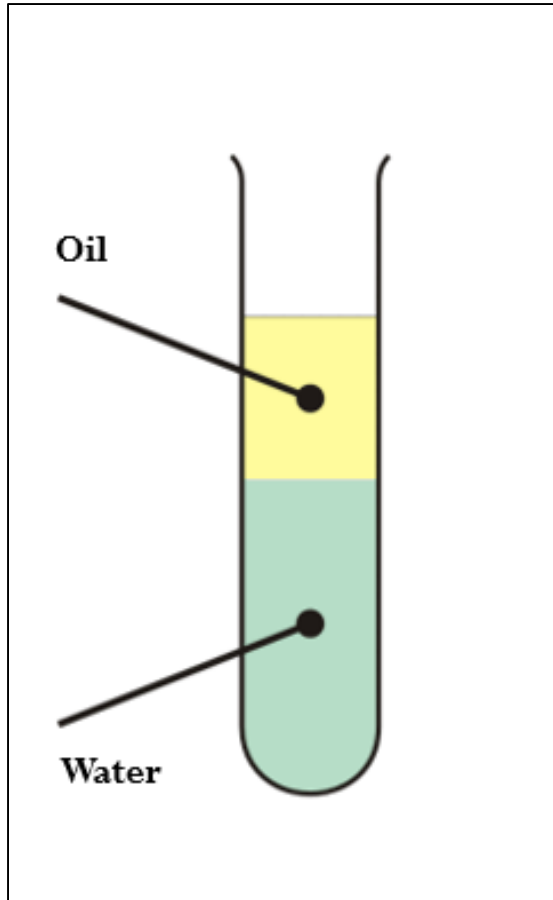
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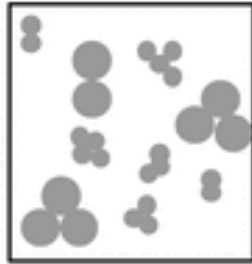


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No change in droplet size and size distribution



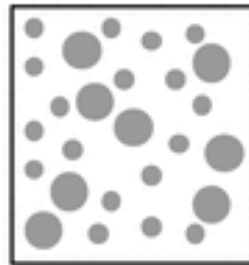
FLOCCULATION



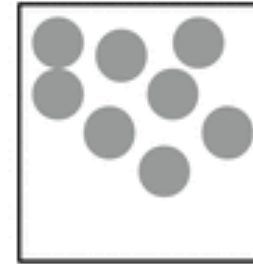
CREAMING



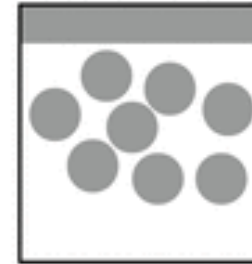
SEDIMENTATION



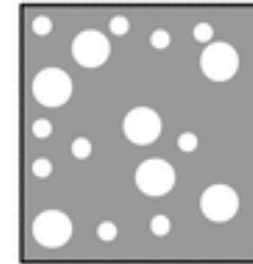
EMULSION



OSTWALD
RIPENING



COALESCENCE



PHASE
INVERSION

Change in droplet size and size distribution



FLOCCULATION:

- When the particles or droplets of the dispersed phase aggregate together on account of attractive forces, the phenomenon is known as flocculation and results in an unstable system.
- Flocculation occurs when there is an attractive force between the droplets, so they form flocs, like bunches of grapes.
- Flocculation is mainly observed in the case of oil in water type of emulsions.
- Flocculation is a process of contact and adhesion whereby the particles of a dispersion form larger-size clusters.
- Flocculation is synonymous with agglomeration and coagulation.

COALESCENCE:

- When the droplets of the discontinuous phase bump into each other to form a larger droplet thus increasing the average particle size over time, it is known as coalescence which is a form of instability.
- Coalescence is the process by which two or more droplets merge during contact to form a single daughter droplet.

CRACKING (BREAKING):

- Cracking means the separation of two layers of the dispersed and continuous phase, due to coalescence of disperse phase globules which are difficult to redisperse by shaking.
- Cracking may occur due to the following reasons.
 - By the addition of emulsifying agent of the opposite type.
 - By decomposition or precipitation of emulsifying agents.
 - By the addition of common solvent.
 - By micro-organisms
 - Changes in temperature.

CREAMING:

- Creaming may be defined as the upward movement of dispersed globules to form a thick layer at the surface of the emulsion.
- When the droplets in an emulsion rise to the top of the emulsion under the influence of buoyancy or centripetal force, it results in the creaming of emulsion.
- The particles float upwards or sink, depending on how large they are and how much less dense or more dense they are than the continuous phase.
- Creaming is a temporary phase because the layer formed can be re-distributed by mild shaking or stirring to regain a homogenous emulsion.

PHASE INVERSION:

- Phase inversion means the change of one type of emulsion into the other type i.e. oil in water emulsion changes into the water in oil type and vice versa.
- The process of phase inversion occurs when the dispersed droplets unite but retain the formerly continuous material as droplets within the mass.
- This is an "invert emulsion" or "inverted emulsion", in which the formerly continuous phase has become the dispersed phase and vice versa.
- Emulsion inversion differs from emulsion breaking as in that a breaking emulsion tends to separate the two phases into un-emulsified continuous phases.

INVERT EMULSION

- An invert emulsion or “backwards” emulsion refers to an emulsion in which oil is the continuous or external phase and water is the dispersed or internal phase so that, in a given period of time after mixing oil and water phases with the help of an emulsifier, the emulsion may break down and may return gradually to the oil and water split.
- Invert emulsions (water-in-oil type) can be used for many purposes such as formulation of microorganisms, manufacturing of cosmetics and in food additives, in drilling fluid systems etc.

OSTWALD RIPENING:

- It describes the change of an inhomogeneous structure over time, i.e., small crystals or sol particles dissolve and redeposit onto larger crystals or sol particles.
- Ostwald ripening is generally found in water-in-oil emulsions. This results from the finite solubility of the liquid phases. Liquids that are referred to as being immiscible often have mutual solubilities.
- With emulsions, which are usually polydisperse, the smaller droplets will have larger solubility when compared with the larger ones (due to curvature effects). With time, the smaller droplets disappear and their molecules diffuse to the bulk and become deposited on the larger droplets. With time, the droplet size distribution shifts to larger values.

PRESERVATION OF EULSION

- One of the most important properties of emulsions is the stability of the finished product. A stable emulsion is characterised by:
 - 1) The absence of deterioration by microorganisms.
 - 2) The absence of creaming and flocculation.
 - 3) The absence of coalescence of globules and the separation of the internal phase from the emulsion.
 - 4) Maintenance of elegance for general appearance, odour, colour and consistency.

- **Preservation by deterioration by micro-organisms:** Emulsions should be formulated with a preservative as some ingredients of emulsions promote the growth of micro-organisms by providing nutrients. A preservative should be a powerful fungistatic rather than a bacteriostatic agent since it is more likely that fungi (moulds and yeasts) may contaminate emulsions.

- **Preservation by prevention of creaming or sedimentation:** Reduction of droplet size and use of thickeners can be worthy for preservation by prevention of creaming or sedimentation. Below a certain droplet size, the Brownian diffusion may exceed gravity and creaming or sedimentation is prevented. Similarly the thickeners satisfy the criteria for obtaining very high viscosities at low stresses or shear rates. The high value of low shear viscosity prevents creaming or sedimentation.

- **Preservation by reducing (eliminating) flocculation:** Methods for preservation by reducing flocculation are: Charge-stabilized emulsions using ionic surfactants and Sterically stabilized emulsions
- **Preservation by reducing Ostwald Ripening:** Several methods may be applied to reduce Ostwald ripening
 - i) Addition of a second disperse phase component that is insoluble in the continuous medium.
 - ii) Modification of the interfacial film at the O/W interface by using surfactants that are strongly adsorbed at the O/W interface (i.e., polymeric surfactants) and that do not desorb during ripening.

- **Preservation by reducing coalescence:** Several methods may be applied to achieve the following effects:

i) Use of mixed surfactant films: In many cases using mixed surfactants, for example, anionic and nonionic or long-chain alcohols, can reduce coalescence as a result of several effects such as high Gibbs elasticity, high surface viscosity and hindered diffusion of surfactant molecules from the film.

ii) Formation of lamellar liquid crystalline phases at the o/w interface: This mechanism was suggested by Friberg and coworkers, who suggested that surfactant or mixed surfactant film can produce several bilayers that “wrap” the droplets. As a result of these multilayer structures, the potential drop is shifted to longer distances thus reducing the van der

- **Preservation by protection against miscellaneous physical and chemical changes:**
- Care must be taken to protect emulsions against deterioration by light, extreme temperature, oxidative and hydrolytic rancidity of the oil.
- Freezing and thawing result in a coarsening of globules and sometimes breaking of emulsions. High temperatures produce the same effects as well.
- Light and rancidity influence the colour and odour of oils and may destroy their vitamin activity.
- Emulsions should be kept in tight containers and stored at moderate temperature and if they are affected by the light they should be stored in dark containers.

EULSION FORMULATION BY HLB METHOD

- An emulsifier or an emulgent is a substance that stabilizes an emulsion by increasing its kinetic stability. One class of emulsifiers is known as "surface-active agents" or surfactants.
- Surfactants are molecules that have a hydrophobic (oil soluble) and an effective hydrophilic (water-soluble) portion. They act as emulsifiers by significantly lowering the interfacial tension and decreasing the coalescence of dispersed droplets.
- The selection of different surfactants in the preparation of either O/W or W/O emulsions is often still made on an empirical basis.
- The HLB number depends on the nature of the oil.

- **Summary of HLB Ranges and their application**

HLB Range	Application
3–6	W/O emulsifier
7–9	Wetting agent
8–18	O/W emulsifier
13–15	Detergent
15–18	Solubilizer

- Emulsion stability and even its type depend to a large extent on the method of dispersing the oil into the water and vice versa. At best, the HLB number can only be used as a guide for selecting optimum compositions of emulsifying agents.



Dr. VAIBHAV G. BHAMARE

(91)7588176846

vaibhav.bhamre@gmail.com

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