COLLOIDS and COLLOIDAL DISPERSIONS

WEEK 3

DISPERSE SYSTEMS

- The term «colloid» include a wide range of substances such as suspensions of solids in liquids, emulsified liquids, gels, solutions of soap.

- These compounds are not crystallized and they diffuse very slowly when dissolved or dispersed in water.

- Colloidal dispersions consist at least two discrete phases, thus they are called colloidal dispersions.

Dispersed system:

- They consist of particulate matter, known as the **dispersed phase** (internal phase), distributed throughout a **dispersion medium** (continuous phase, external phase or vehicle)

What is phase?

- It is a physically distinct part of a system, separated by boundaries from other parts of the system.

  Ex: Water and vapour are phases for water vapour system

- The dispersed material may range in size from particles of atomic and molecular dimensions to particles whose size is measured in millimeters.

Possible types of colloidal dispersions are shown in the accompanying table.

Dispersion medium	Dispersed phase	Colloid type
Solid	Solid	solid sol
Solid	Liquid	solid emulsion
Solid	Gas	solid foam
Liquid	Solid	sol, gel
Liquid	Liquid	emulsion
Liquid	Gas	foam
Gas	Solid	solid aerosols
Gas	Liquid	liquid aerosols

* Gas in a gas always produces a solution

Types of Colloidal Dispersions

Dispersions can be classified in various ways;

- Molecular or Micellar
- According to their particle shape
- According to their particle size
  Molecular/colloidal/coarse
- According to the interaction of dispersed phase with the medium.
  Lyophilic/lyophobic/amphiphilic

Disperse Systems

*****Dispersion**

Molecular dispersions <1 nm	Colloidal dispersions 1 nm - 0.5 µm	Coarse dispersions > 0.5 µm

- Based on the size of the dispersed phase, dispersed systems are generally considered as:

a) **Molecular dispersions,**

b) **Colloidal dispersions,**

c) **Coarse dispersions.**

EMULSIONS

Emulsion

Emulsions are heterogeneous systems with homogeneous appearance, formed by dispersing at least two unmixable liquid phases in droplets by using an **emulsifying agent**.

The globular phase is called the dispersed or inner phase or discontinous phase

The other phase is the dispersion medium or external phase or contionus phase

- Pharmaceutical emulsions are in the colloidal state, i.e. the disperse phase sizes range from nanometres to the visible (several micrometres).

Appearance of Emulsions

Droplet size	Appearance
1 μm <	White
0.1-1	Blue-White
50-100 nm	Semitransparent
50 nm >	Transparent

Emulsion components

- Oil phase (resins, waxes, hydrocarbon, etc.)
- Water phase (aqueous solutions of salts and organic or colloidal substances)
- Emulsifier

Advantages of Emulsions

- Mask the bad taste and smells of the ingredients
  - For example: Fish oil, castor oil, oil soluble vitamins (A, E)
- Improve the absorption of active agents;
  - For example: They can increase the gastrointestinal absorption of macromolecules such as insulin, heparin
- Improve the chemical stability of active agents

- They form a thin layer on skin after topical application and can be easily washed
- The thixotropic emulsion forms rapidly penetrate through skin
- IV emulsion forms are used as lipid nutrient
- Multiple emulsions are used for extended drug release and IM reservoir systems
- Radiopaque emulsions are used for diagnostic purposes

Emulsion types
1- Classical Emulsions- Macro Emulsions

- Oil in water type (o/w): Oil droplets are dispersed within aqueous phase. Commonly used for oral and topical applications

- Water in oil type (w/o): Water droplets are dispersed within oil phase. Commonly used for topical applications

Emulsion types
2- Multiple Emulsions

These type of emulsions contain two type of emulsion within one system. They are also defined as «the emulsion of emulsion». W/O/W-O/W/O

It is a complex type of emulsion system in which the oil-in-water or water-in-oil emulsions are dispersed in another liquid medium. In this way 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

Emulsion types
3- Microemulsions

- Microemulsions are homogeneous transparent systems of low viscosity which contain a high percentage of both oil and water and high concentrations (15–25%) of emulsifier mixture.
- Microemulsions form spontaneously when the components are mixed in the appropriate ratios and are thermodynamically stable.
- In their simplest form, microemulsions are small droplets (diameter 5–140 nm) of one liquid dispersed throughout another. The droplet size is therefore very much smaller than that of normal emulsions (which is why microemulsions are transparent) and the droplets are very much more uniform in size.

- To achieve the very low interfacial tension required for their formation it is usually necessary to include a second amphiphile (the cosurfactant) such as a short-chain alcohol in the formulation. This cosurfactant is incorporated into the interfacial film around the droplets.

Emulsion types
4- Nanoemulsions

- Nanoemulsions are emulsions with droplet size on the order of 100 nm.
- A typical nanoemulsion contains oil, water and an emulsifier.
- The addition of an emulsifier is critical for obtaining small sized droplets as it decreases the interfacial tension i.e., the surface energy per unit area, between the oil and water phases of the emulsion.
- The emulsifier also plays a role in stabilizing nanoemulsions through repulsive electrostatic interactions and steric hindrance.

Administration Routes of Emulsions

- Oral emulsions:
  - Purpose: To mask bad taste
  - Improve the absorption and bioavailability of some active agents. Poorly water soluble drugs can be formulated by dissolving in oil phase, thus improve their bioavailability.
  - They are o/w type emulsions. Laxatives such as liquid paraffin, oil soluble vitamins, oily nutrition preparations
  - Non-ionic surfactants are commonly used as emulsifiers.

Administration Routes of Emulsions

Topical emulsions

- Lotions and liniments.
- Most of them are cosmetic preparations
- Both o/w (local) and w/o (oclusives, skin cleanser) types are used
- Their usefulness depends on their ability to penetrate.

Administration Routes of Emulsions

Parenteral Emulsions

- The oil-soluble active agent is dissolved in a suitable carrier and the mixture is emulsified.
- The droplet diameter should be <1µm.
- -IV emulsions of Vitamins A and K, Hormones,antineoplastic agents are prepared
- IV emulsions;
  - contain 10-20% fat
  - Diameter 0.1-0.5µm
  - pHs are 5.5-8.0
  - o / w type
- Lecithin and poloxamers are used as emulsifiers
- IM emulsions are w/o type (reservior effect)

Administration Routes of Emulsions

- **Ocular Emulsions**
- RESTASİS® ophthalmic emulsion

- Cyclosporine…… 0.5mg (%0.05)
- Glycerol 2.0mg
  Castor 12.5mg
  Polysorbate 80 ..... 10.0 mg
  Carbomer 1342 .....0.5 mg
  Sodium hydroxide……q.s.

Composition of Emulsions

- Polar compounds
- Apolar compounds
- Emulsifier
- Stabilizing agents
- Antimicrobial agents
- Antioxydants
- Active Agents

Polar compounds

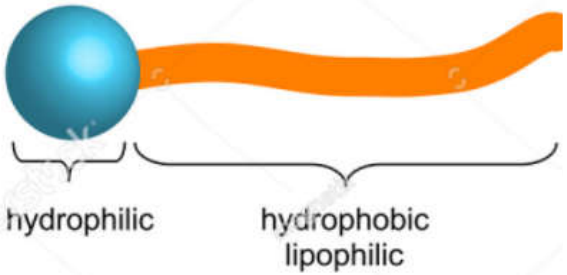
- -Water
- - Polyols
  - Butylene glycol
  - Glycerin
  - PEG
  - Propylene Glycol

Apolar compounds

- - Esters (solid lipids, lanolin, synthetic materials (iso propyl myristate, glyceryl monostearate))
- - Ethers
- - Fatty acids
- - Fatty alcohols
- - Hydrocarbons (butane, propane, squalene)
- - Others (halo hydrocarbons, vegetable / animal waxes, silicone)

Emulsifier

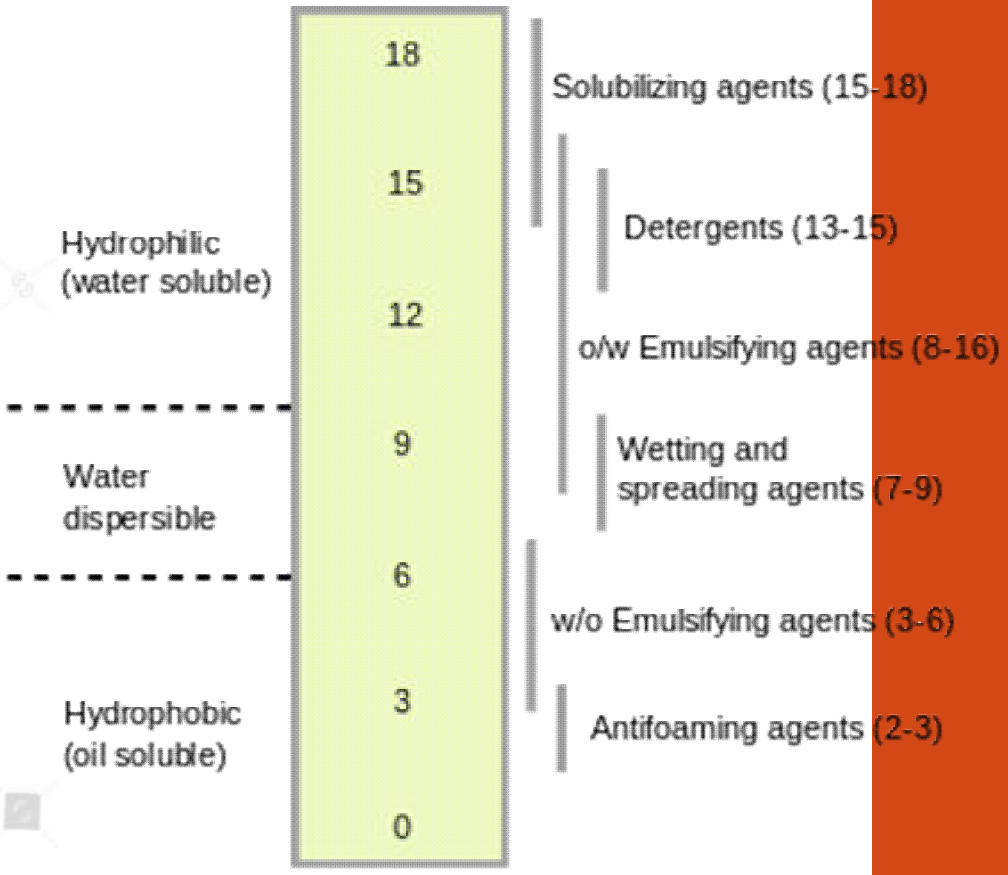
Hydrophilic - Lipophilic - Balance



HLB = 0 to 9 emulsifier is predominantly soluble in oil

HLB = 11 to 20 emulsifier is predominantly soluble in water

HLB = 10 same solubility in water and oil



Stabilizing agents

- Stabilizing agents increase the emulsion stability by :

- - minimizing the phase densities,
- - increasing the external phase viscosity
- - holding onto the o / w interface.

Stabilizing agents

- - Lyophilic colloids (polysaccharides, tragacanth, agar, alginic acid, gelatin, cellulose esters, synthetic-semisynthetic polymers)
- - Particulate powder: Bentonite, Mg-Al Silicate, microcrystalline cellulose, oxides and hydroxides
- - Gelling agents: amino acids, peptides, proteins, lecithin

Preservatives

- It is important to protect emulsions against fungi and yeast.
- Due to microbial contamination following properties may change:
  - odor
  - color
  - Viscosity
  - Chemical structure of the emulsifiers

Stability problems

Preservatives

- - Ethanol (20 %)
- - Sugar (67 %)
- - Polyols (10 %)
- - Glycerin (40-50 %)
- -Sorbitol

Preservative is not needed

Eg:

- Quaternary ammonium compounds
- benzoic acid
- phenyl mercury nitrate
- parabens

Antioxydants

- -In addition to the protection of the active agent, it is also appropriate to add antioxidants to the emulsions for the formulation components such as unsaturated lipids.

- - Besides the addition of antioxidants, the use of tightly closed and opaque containers is also important in terms of preventing system from oxidation.

- -They should be preferentially soluble in the oily phase

Antioxidants

- 1) True antioxydants:
- Inhibits oxidation by rezcting with free radicals and blocking the chain reaction
- Eg: Tocopherols, alkyl gallates, butylated hydroxyanisole (BHA), butylated toluene (BHT), nordihydroguaiaretic acid (NDGA)
- 2) Reducing agents:
- They react with reducing agents.
- Ascorbic acid, Na and K salts of sulfurous acid
- 3)Antioxydant synergists:
- citric acid, tartaric acid, lecithin, EDTA

Colours and Flavourings

- Color is rarely needed in an emulsion, as most have an elegant White colour and thick texture

- Oral emulsions usually contain some flavouring agent.

SUSPENSIONS

-Pharmaceutical suspensions may be defined as uniform dispersions containing finely divided insoluble material suspended in a liquid medium.

-A suspension containing particles between 1 nm to 0.5 μm in size is called colloidal suspension.

-When the particle size is between 1 to 100 µm, the suspension is called coarse suspension.

-Most of the pharmaceutical suspensions are coarse suspension.

Suspensions are heterogeneous systems consisting of two phases:

- The external phase, which is also referred to as the continuous phase or dispersion medium, and the internal or dispersed phase is made up of particulate matter, which is practically insoluble in the external phase.

Most pharmaceutical suspensions consist of an aqueous dispersion medium, although organic or oily liquids are also used in some instances.

Pharmaceutical Applications of Suspensions

1) Insoluble drugs or poorly soluble drugs which required to be given orally in liquid dosage forms can be formulated as suspensions (in case of children, elderly and patients have difficulty in swallowing solid dosage forms).

2) Suspensions can be prefered to overcome the instability problem of certain drugs in aqueous solutions.

3) Suspensions can be used to mask the unpleasant taste of some active substances.

4) Some materials are needed to be present as finely divided forms to increase the surface area (e.g. Mg carbonate and Mg trisilicate are used to adsorb some toxins)

5) Suspensions can be used in topical applications (Calamine lotion BP)

6) Suspensions can be used for parenteral administration; intramuscular (i.m.) or subcutaneous (s.c.)

7) Suspensions can be used as X-ray contrast media (e.g. oral and rectal administration of propyliodone)

8) Aerosol formulations can be formulated as the suspension of active agents in the mixture of propellants

Depending on their intended route of delivery, pharmaceutical suspensions can be broadly classified as;

-Parenteral suspensions

-Topical suspensions

-Oral suspensions

Also, pharmaceutical suspensions can be applied intranasally, inhaled into the lungs or used for ophthalmic purposes in the eye.

There are certain criteria that a well-formulated suspension should meet:

1) The dispersed particles should not settle readily and the settle should redispersed immediately.

- Ideally, the particles in a suspension should not sediment at any time during the storage period. Unfortunately, the present technology does not allow us to prepare such a suspension. Since the sedimentation of particles cannot be completely avoid, it is desirable that the particles should settle slowly.

** The easy redispersion of sedimented particles in a suspension is important for the uniformity of dose.

2) The particles should not form a cake on settling.

3) The viscosity should be such that the preparation can be easily poured. A highly viscous suspension would make pouring difficult.

4) It should be chemically and physically stable.

5) It should be palatable (for oral suspensions).

6) It should be free from gritting particles (external use).

Factors to be considered in Suspension Formulations

A) Wetting of the particles

- It is difficult to disperse solid particles in a liquid vehicle due to the layer of adsorbed air on the surface.
- Thus, the particles, even high density, float on the surface of the liquid until the layer of air is displaced completely.

* The use of wetting agent allows removing this air from the surface and to easy penetration of the vehicle into the pores.

** Alcohol, glycerin, and propylene glycol are frequently used to remove adsorbed air from the surface of particles when aqueous vehicle is used to disperse the solids.

*** When the particles are dispersed in a non-aqueous vehicle, mineral oil is used as wetting agent.

B) Particle Size

Controlling the size of the particles is very important for suspension stability.

- Finely divided particles are necessary to reduce sedimentation. However, improper control of particle size can create several undesirable consequences.

C) Sedimentation

Sedimentation of particles in a suspension is governed by several factors;

- Particle size
- Density of the particles
- Density of the vehicle
- Viscosity of the vehicle

E) Zeta Potential

The potential difference between the ions in the tightly bound layer and the electroneutral region, referred to as **zeta potential**, has significant effect in the formulation of stable suspension.

* Zeta potential governs the degree of repulsion between adjacent, similarly charged solid dispersed particles.

** If the zeta potential is reduced below a critical value, the force of attraction between particles due to van der Waals' force, overcome the forces of repulsion and the particles come together to form floccules. This phenomenon is known as flocculation. The magnitude of surface and zeta potentials is related to the surface charge and the thickness of the double layer.

F) Flocculation and Deflocculation

When zeta potential is relatively high (25 mV or more), the repulsive forces between two particles exceed the attractive London forces. Accordingly, the particles are dispersed and are said to be deflocculated.

Even when brought close together by random motion or agitation, deflocculated particles resist collision due to their high surface potential.

The addition of a preferentially adsorbed ion whose charge is opposite in sign to that on the particle leads to a progressive lowering of zeta potential. At some concentration of the added ion, the electrical forces of repulsion are lowered sufficiency and the forces of attraction predominate.

Under these conditions the particles may approach each other more closely and form loose aggregates, termed *flocs*. Such a system is said to be *flocculated*.

Commonly Used Ingredients in Pharmaceutical Suspensions

1. Active Pharmaceutical Ingredient

Ideally, the active pharmaceutical ingredient (API) should be insoluble in the continuous phase.

2. Inorganic Clays
3. Water-Soluble Hydrocolloids
4. Bulking Agents (Auxiliary Suspending Agents)
5. Surfactants / Wetting Agents
6. pH Modifiers and Buffers
7. Preservatives, Antioxidants and Chelating Agents
8. Sweetening Agents
9. Flavoring Agents
10. Coloring Agents