ADVANCE PHARMACEUTICALS

M.PHIL PHARMACEUTICS

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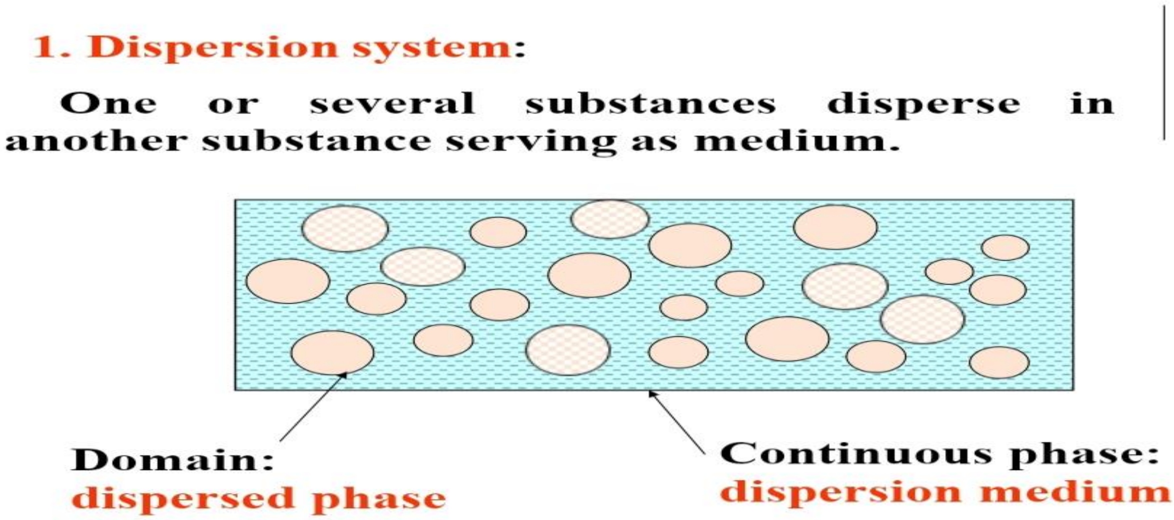
DISPERSE SYSTEM

DEFINITION :
Disperse system is a two part system made up of microscopic particles and the medium in which they are suspended.
An example of disperse system is a foam such as shaving cream.



PHARMACEUTICALS DISPERSIONS:
These are systems where one substance is dispersed within another substance. ... Terms used to describe dispersion components include internal or noncontinuous phase to describe the dispersed phase component (the particles) and the external or continuous phase to describe the dispersion medium.

EXAMPLES:
Milk is a commonly cited example of an emulsion, a specific type of dispersion of one liquid into another liquid where to two liquids are immiscible. The fat molecules suspended in milk provide a mode of delivery of important fat-soluble vitamins and nutrients from the mother to newborn.[8] The mechanical, thermal, or enzymatic treatment of milk manipulates the integrity of these fat globules and results in a wide variety of dairy products.[9]

CLASSIFICATION OF DISPERSE SYSTEM:
Dispersion (dispersed system) is a mixture of two substances,
one of which (dispersed phase) is distributed in form of subdivided particles throughout another substance (continuous phase, dispersion medium). Molecular dispersion is a true solutions of a solute phase in a solvent.
So according to the size of the dispersed phase, there are three types of dispersion system which are as follow,

1.Molecular Dispersion
2.Colloidal Dispersion
3.Coarse Dispersion

1.2 Classification of dispersion systems

According to the size of dispersed phase

r / m	Atom number	name	Phase number	uniformity
$< 10^{-9}$	$< 10^{3}$	Molecular dispersion	Single phase	uniform
$10^{-7} \sim 10^{-9}$	$10^{3} \sim 10^{9}$	Colloidal dispersion	multiphase	uniform
$10^{-7} \sim 10^{-4}$	$> 10^{9}$	Coarse dispersion	multiphase	nonuniform

1.Molecular dispersions

Molecular dispersion is a true solutions of a solute phase in a solvent. The dispersed phase (solute) is in form of separate molecules homogeneously distributed throughout the dispersion medium(solvent). The molecule size is less than 1 nm . The examples of molecular dispersions: air (a molecular mixture of Oxygen, Nitrogen and some other gases), elctrolytes (aqueous solutions of salts), metal alloys Solid solutions.

2.Colloids

Colloids are micro-heterogeneous dispersed systems, in which the size of the dispersed phase particles is within the range 1 - 1000 nm. The colloids phases can not be separated under gravity, centrifugal or other forces. Dispersed phase of colloids may be separated from the dispersion medium by micro-filtration. The examples of colloids: milk (emulsion of fat and some other substances in water), fog (aerosol of water micro-droplets in air), opal (colloidal silica), Silica aerogel monolith, Alumina aerogel monolith.

3.Coarse dispersions (suspensions)

Coarse edispersions 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.

EMULSION

Definition:

“Emulsions are heterogeneous, thermolabile biphasic liquids, containing two immiscible liquids which are made miscible by adding emulsifying agent.” Or “Emulsions are a class of dispersed system in which a one immiscible liquid is dispersed uniformly in a liquid dispersion medium.

OR

An emulsion is a colloid of two or more immiscible liquids where one liquid contains a dispersion of the other liquids. In other words, an emulsion is a special type of mixture

made by combining two liquids that normally don't mix. ... The process of turning a liquid mixture into an emulsion is called emulsification.
examples of emulsions include egg yolk, butter, and mayonnaise

Properties of Emulsions

1:Emulsion particles unavoidably form dynamic inhomogeneous structures on small length scale.
2:Emulsions are highly unstable systems and require an emulsifying agent or emulsifier (
3:These are usually surface active agents also known as “surfactants”)
4:Emulsions are prepared by continuous mixing or agitation of the two phases
5:When kept for longer periods of time or in case of absence of an emulsifying agent, the phases in the emulsion tend to separate, resulting in “cracking of emulsion” or ” phase inversion”.

Emulsification:
Emulsification is the process by which a system comprising of two immiscible liquids (usually oil and water), one of which is dispersed as small droplets within the other, is produced.

Mechanisms of emulsification
A number of different chemical and physical processes and mechanisms can be involved in the process of emulsification:[citation needed]

1:Surface tension theory – according to this theory, emulsification takes place by reduction of interfacial tension between two phases
2:Repulsion theory – the emulsifying agent creates a film over one phase that forms globules, which repel each other. This repulsive force causes them to remain suspended in the dispersion medium
3:Viscosity modification – emulgents like acacia and tragacanth, which are hydrocolloids, as well as PEG (or polyethylene glycol), glycerine, and other polymers like CMC (carboxymethyl cellulose), all increase the viscosity of the medium, which helps create and maintain the suspension of globules of dispersed phase

Emulsifiers:
An emulsifier (also known as 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. Emulsifiers are compounds that typically have a polar or hydrophilic (i.e. water-soluble) part and a non-polar (i.e. hydrophobic or lipophilic) part. Because of this, emulsifiers tend to have more or less solubility either in water or in oil.[citation needed] Emulsifiers that are more soluble in water (and conversely, less soluble in oil) will generally form oil-in-water emulsions, while emulsifiers that are more soluble in oil will form water-in-oil emulsions. [18]

Examples of food emulsifiers are:

Egg yolk – in which the main emulsifying agent is lecithin. In fact, lecithos is the Greek word for egg yolk.
Mustard – where a variety of chemicals in the mucilage surrounding the seed hull act as emulsifiers
Soy lecithin is another emulsifier and thickener
Pickering stabilization – uses particles under certain circumstances
Sodium phosphates
Mono- and diglycerides - a common emulsifier found in many food products (coffee creamers, ice-creams, spreads, breads, cakes)

Types of Emulsions:
Emulsions can exist as “oil in water” or ” water in oil” of emulsions. The type of emulsion depends upon the properties of the dispersed phase and continuous phase. If the oil phase is dispersed in a continuous aqueous phase the emulsion is known as “oil in water”. If the aqueous phase is the dispersed phase and the oil phase is the continuous phase, then its known as “water in oil”

Whether an emulsion of oil and water turns into a “water-in-oil” emulsion or an “oil-in-water” emulsion depends on the volume fraction of both phases and the type of emulsifier used to emulsify them.
Types of Emulsion
Depending upon the nature of the dispersed phase, the emulsions are classified as;

(i) Oil-in-water emulsions (O/W) : The emulsion in which oil is present as the dispersed phase and water as the dispersion medium (continuous phase) is called an oil-in-water emulsion. Milk is an example of the oil-in-water type of emulsion. In milk liquid fat globules are dispersed in water. Other examples are, vanishing cream etc.

(ii) Water-in-oil emulsion (W/O) : The emulsion in which water forms the dispersed phase, and the oil acts as the dispersion medium is called a water-in-oil emulsion. These emulsion are also termed oil emulsions. Butter and cold cream are typical examples of this types of emulsions. Other examples are cod liver oil etc.

Instabilities in Emulsions

The ability of an emulsion to retain its properties over time is known as the stability of an emulsion. Four types of instabilities generally occur in an emulsion, Let us take a look.

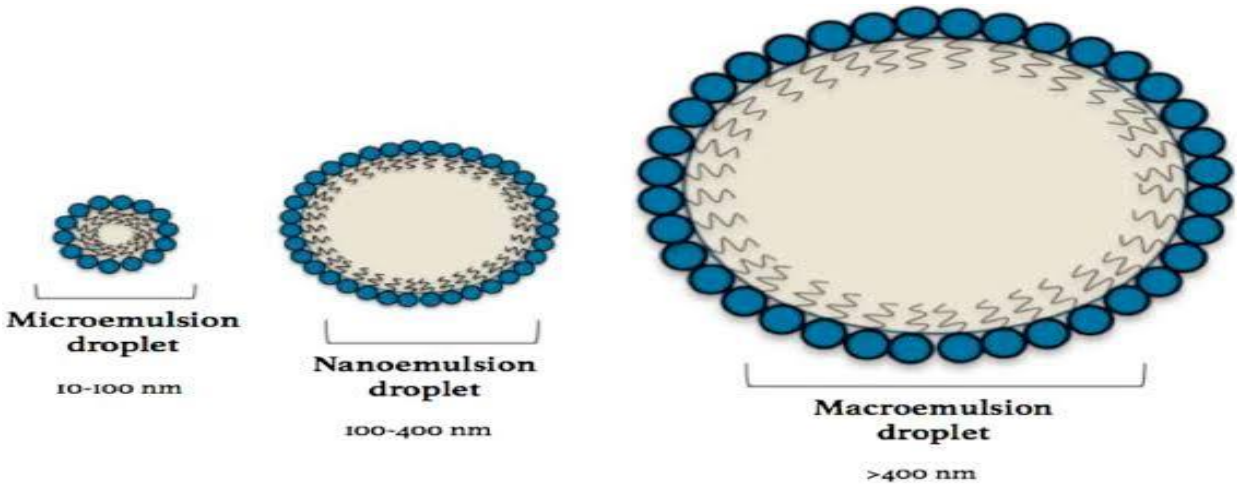
Flocculation – When the particles or droplets of the dispersed phase aggregate together on account of attractive forces, the phenomenon is known as flocculation and results in an unstable system. Flocculation is mainly observed in case of oil in water type of emulsions.
Coalescence – When the droplets of 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.

Creaming – 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
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.

Microemulsion

Microemulsion are clear, thermodynamically stable, isotropic liquid mixtures of oil, water and surfactant, frequently in combination with a cosurfactant. The aqueous phase may contain salt and/or other ingredients, and the "oil" may actually be a complex mixture of different hydrocarbons and olefins.

Emulsions are stable dispersions of immiscible liquids, but they are not thermodynamically stable. We say that they are kinetically stable. These type of dispersions are sometimes called macroemulsions. Microemulsions, on the other hand, are thermodynamically stable.

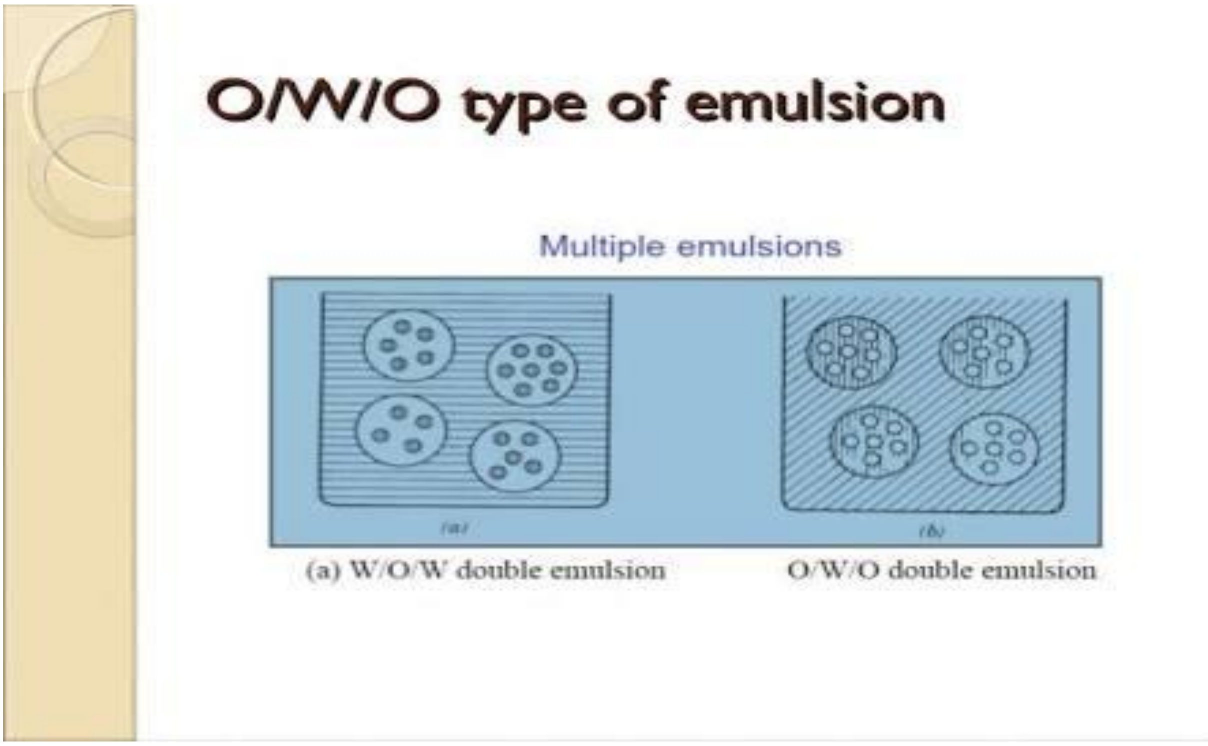


Microemulsions have many commercially important uses:

Water-in-oil microemulsions for some dry cleaning processes
Floor polishers and cleaners
Personal care products
Pesticide formulations
Cutting oils
Drugs

Multiple Emulsion:
Multiple emulsions are complex systems where both oil in water and water in oil emulsion exists simultaneously which are stabilized by surfactants respectively. Among water-in-oil-in-water (w/o/w) and oil-in-water-in-oil (o/w/o) type emulsions, the first one is much more widely used in many applications. Various factors affect the stability of these emulsions. Wide range of applications in controlled or sustained drug delivery, targeted delivery, bioavailability enhancement, and enzyme immobilization are found and these are promising

research areas. Multiple emulsions can be employed as an intermediate step in the microencapsulation process and those are used in oral drug delivery. We can expect that a novel carrier system for drugs, cosmetics, and pharmaceutical agents is provided with the advancement in techniques for preparation, stabilization, and rheological characterization of multiple emulsions.



Multiple Emulsion Systems

Multiple emulsions are emulsions of emulsions. In these emulsions, the internal and external phases are alike and an intermediate phase separates the two like phases. The intermediate phase is immiscible with the two like phases. For instance, in w/o/w multiple emulsions, a w/o emulsion is dispersed in a water-continuous phase. An emulsifier is present to stabilize the emulsions and various ionic and nonionic surfactants are available for this purpose. Oil-soluble surfactants stabilizes w/o emulsions, whereas water-soluble surfactants stabilizes o/w systems. As referred, applications for multiple emulsions are well-documented and many of these applications have been patented. Applications in cosmetics are promising. For example, in cosmetics they have a fine texture and a smooth touch upon application, and they are aimed for slow and sustained release of active matter from an internal reservoir into the continuous phase. They can serve as an internal reservoir to entrap matter from the outer diluted continuous phase into the inner confined space. They can also improve dissolutions or solubilization of insoluble materials. Due to these properties, multiple emulsions find applications related to protecting sensitive and active molecules. We can expect many more applications to emerge in the near future.

EMULSIFYING AGENTS BASED ON HLB

HLB (Hydrophilic lipophilic balance)

DEFINITION:

Emulsifiers with low HLB value are soluble in oil while high HLB emulsifiers are soluble in water.The HLB is measure of degree to which it is hydrophilic or lipophilic determined by calculating values of the molecule as described by Griffin This is concept of choosing emulsifiers and value of HLB ranges from 1-20.

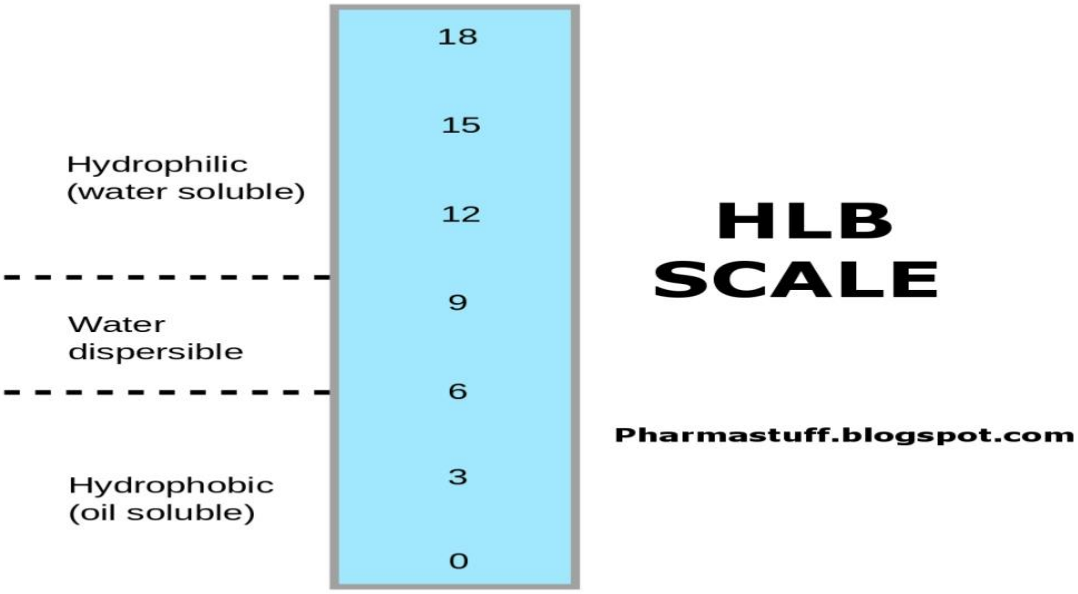
It is the relationship between the hydrophilic portion of the non-ionic surfactant to the lipophilic portion.

It was invented in 1954 by William C. Griffin.

It is as a guidance to good emulsification performance.

HLB values are calculated for non-ionic surfactants only (non-ionic surfactants posses hydrophilic heads

The HLB value is an indication of the solubility of the surfactant.



GRIFFIN’S METHOD:

In 1954 works, Griffin method for non-ionic surfactant is described as

$$HLB = 20 * M_h / M$$

Where Mh is the molecular mass of hydrophilic portion of molecule

M is the molecular mass of whole molecule, giving a result on a scale 0 to 20.

An HLB value of 0 > a completely lipophilic/hydrophobic.

An HLB value of 20> a completely hydrophilic/lipophobic.

The HLB value can be used to predict the surfactant properties of a molecule:

1 to 3	Antifoaming agents
3 to 6	W/O(water in oil) emulsifiers
7 to 9	Wetting and spreading agents
8 to 12	O?W(oil in water) emulsifiers
12 to 15	Detergents
15 to 20	Solubilisers

HLB AND SOLUBILITY:

Solubility	**HLB range**
No dispersability in water	**1-4**
Poor dispersion in water	**3-6**
Milky appearance	**6-8**
Stable milky appearance	**8-10**
Translucent to clear dispersion	**10-13**
Clear solution	**13+**

DAVIE'S METHOD:

in 1957, Davies suggested a method based on calculating a value based on the chemical groups of the molecule. The advantage of this method is that it takes into account the effect of stronger and weaker hydrophilic groups. The method works as follows

$$HLB = 7 + \sum_{i=1}^{m} H_i - n \times 0.475$$

where:

m - Number of hydrophilic groups in the molecule

H_i - Value of the i^{th} hydrophilic groups (see tables)

n - Number of lipophilic groups in the molecule

SOLUBILIZATION

DEFINITION:

Mc Bain and Hutchinson defined solubilization as,

"A particular mode of bringing into solution substances that are otherwise insoluble in a given medium, involving the previous presence of a colloidal solution whose particles take up and incorporate within or upon themselves the otherwise insoluble material."

This definition is too narrow so broadly it is defined as

"The preparation of thermodynamically stable isotropic solution of the substance normally insoluble of very slightly soluble in the given solvent by the introduction of an additional amphiphilic component(s)."

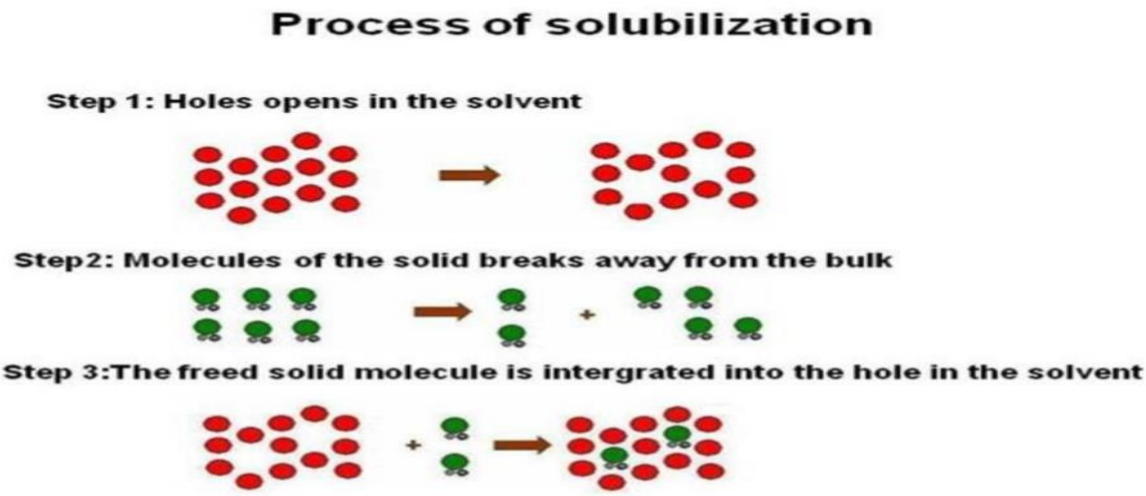
Solubilization - an overview ...

MICELLAR SOLUBILIZATION:

It is the powerful alternative for dissolving hydrophobic drugs in aqueous environments. Surfactants play a vital role in many processes. Surfactants cause the formation of colloidal-sized clusters in solutions known as micelles, which have particular significance in pharmacy because of their ability to increase the solubility of sparingly soluble substances in water. Examples of poorly soluble compounds that use Micellar solubilisation are antidiabetic drugs, gliclazide, glimipride, repaglinid.

PROCESS OF SOLUBILIZATION:
1.Breaking of inter-molecular bonds in the solute.
2.Separation of solute molecules to provide space for the solute
3.Interaction between the solute and solvent molecule or ion.

- Molecules of solids break away from bulk.
- Separation of solvent molecules.
- Freed solid molecules is integrated into the holes of solvent molecule.



FACTORS AFFECTING THE SOLUBILIZATION:
1.PARTICLE SIZE:
It has major factor effecting the solubilisation process.

2.TEMPERATURE:
If solution process absorbs the energy, solubility will increase as temperature will increased.
If solution releases energy, solubility will decrease as temperature will increased.

3.PRESSURE:
For gaseous solutes, increase in pressure increase solubility and vice versa. For solids and liquids solutes, changes in pressure have practically no effect on solubility.

4.NATURE OF SOLID:
Crystalline structures exhibit low solubility while amorphous forms exhibit more solubility.

5.POLYMORPHISM:
The order of dissolution of different solid forms of drug is
Amorphous>Meta stable polymorph>Stable polymer

IMORTANCE:

- Pharmaceuticals
- Detergency
- Emulsion polymerization (30 % of polymer are made through this process)
- Micellar catalysis of organic reaction

PHARMACEUTICAL APPLICATIONS OF EMULSIONS:

Emulsion is used widely in pharmaceutical and cosmetic industries. Pharmaceutical applications are classified according to the route of administration i.e. topical, oral or parenteral. There are following major applications of emulsions in pharmacy.

- **Dermatological Creams and Lotions:**

  Creams and lotions are used topically to the affected area only. Nowadays instead of greasy and semisolids, water washable and non-staining products are being used which are more acceptable to patients.

- **Assist in Diagnosis:**

  Intravenous emulsions of contrast media have been developed to assist in diagnosis.

- **Patient Acceptance and Compliance:**

  Water insoluble compounds are orally administered as o/w emulsion with pleasant taste e.g. vitamin A, E, D and K are absorbed more quickly when emulsified.

- **Mask the Bitter Taste:**

  The unpleasant taste or odor can be masked by emulsification.

- **Bioavailability:**

  Some therapeutic agents show bioavailability more when given in the form of emulsions e.g. Heparin and insulin.

- **Modern Drug Delivery Concept:**

  Non-absorbable macromolecules are absorbed to small extent when given orally as such insulin and heparin and they may even be digested in stomach. But when these agents are given in emulsified form they are not digested and are fully absorbed.

- **Intravenous Fat Emulsion:**

  The intravenous fat emulsions are used to supply or deliver isotonic liquids in small amount i.e. volume to provide large amount of energy to the body. The fat emulsions for intravenous nutrition generally contain vegetable oil, a phospholipid and emulsifying agent.

- **Prolong Release of the Drug:**

  They can be used to prolong the release of the drug and thereby providing sustained release action.

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