Pharmaceutical Technology for 3rd year students

2nd Course, 1st Lec.8

By:
Dr. Esra`a Ghazy

Lecturer at
Al-Rasheed University College, Department of Pharmacy,
2021

Pharmaceutical Emulsion

- Introduction
- Types of emulsions
- Emulsifying agents
- Methods of Preparation of Emulsions
- Tests for emulsion types
- Emulsion Stability
- Phase Inversion
- Emulsion Breaking
- General Guidelines

- ✓ Emulsion; is a dispersion in which the dispersed phase is composed of small globules of a liquid distributed throughout a vehicle in which it is immiscible.

Emulsions encountered in everyday life!


Pesticide


Asphalt

Skin cream


Metal cutting oils


Margarine


Ice cream

Dispersion Systems

Emulsion is a dispersion in which the dispersed phase is composed of small globules of a liquid distributed throughout a vehicle in which it is immiscible

Suspension is a two phased system in which a finely divided solid is dispersed in a continuous phase of solid, liquid or gas

- ✓ The dispersed phase ⟶ the internal phase.

  The dispersion medium ⟶ the external or continuous phase.

- ✓ Because the external phase of an emulsion is continuous, an o/w emulsion may be diluted or extended with water or an aqueous preparation and a w/o emulsion, with an oleaginous or oil-miscible liquid.

- ✓ Generally, to prepare a stable emulsion, a third phase, ***an emulsifying agent***, is necessary.

- ✓ Depending on their constituents, the viscosity of emulsions can vary greatly, and pharmaceutical emulsions may be prepared as liquids or semisolids.

Emulsion Classifications

Type of Emulsion	Dispersed Phase or Internal Phase	Dispersion medium or external/ continuous phase
O/W	Oil	water
W/O	water	oil
W/O/W O/W/O	Multiple Emulsion	

- ✓ Based on the constituents and the intended application, liquid emulsions may be employed as;

Oral


Duolax™
Oral Emulsion
100 ml
Duolax™
Magnesium Hydroxide & Liquid Paraffin
Oral Emulsion
Sugar free
SQUARE
Duolax™
Magnesium Hydroxide & Liquid Paraffin
Oral Emulsion
100 ml
SQUARE


GOOD'N NATURAL
Enteric Coated
Oil of Peppermint
50 mg
A Calmative Oil
Once Daily Formula
Dietary Supplement
90 RAPID RELEASE SOFTGELS

Topical


ΔΕΡΜΑΤΟΛΟΓΙΚΑ ΕΛΕΓΜΕΝΟ
DERMATOLOGICALLY TESTED
Biotrin
Hard & Strong
NAILS
Topical Emulsion
ΕΞΩΤΕΡΙΚΗ ΧΡΗΣΗ
EXTERNAL USE
e 20ml
Τοπικό Γαλάκτωμα


EAU THERMALE
Avène
Tolérance
Émulsion · Emulsion
TEXTURE LÉGÈRE · LIGHT TEXTURE
sterile
Peaux sensibles à hypersensibles
For sensitive and hypersensitive skin

Parentral

✓ Many pharmaceutical preparations that are actually emulsions are not classified as such ***because*** they fit some other pharmaceutical category more appropriately. For instance,

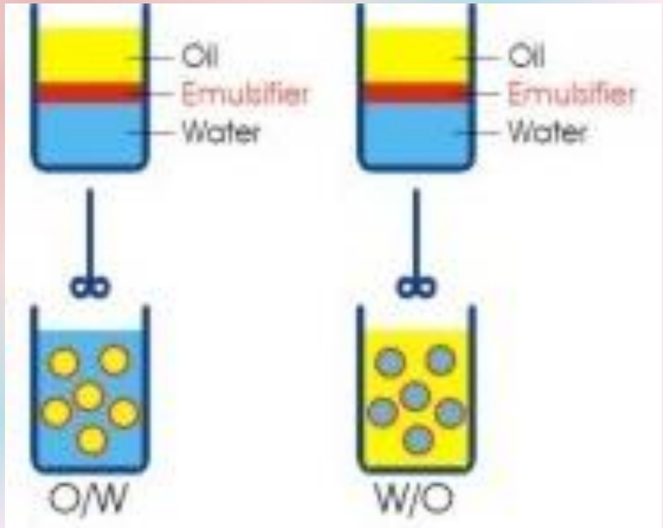
1) Lotions
2) Liniments
3) Creams
4) Ointments
5) Vitamin drops

Emulsion Classifications

A/ *Based on dispersed phase*

1- Emulsions with an oleaginous internal phase and an aqueous external phase are oil-in-water (o/w) emulsions.

2- Emulsions with an aqueous internal phase and an oleaginous external phase are termed water-in-oil (w/o) emulsions.



B/ Based on size of liquid droplets

1- Macroemulsions (Kinetically Stable); ranges from 0.2 – 50 mm.

2-Microemulsions (Thermodynamically Stable) ranges from 0.01 – 0.2 mm.

Or;

Macroemulsion	Microemulsion	Nanoemulsion
Coarse or ordinary emulsion, P.S. more than 400nm	100-400nm	Less than 100nm
White opaque appearance	Cloudy-translucent tyndal effect	Homogeneous transparent system
Thermodynamically unstable system, while kinetically stable	Thermodynamically stable system	Thermodynamically stable system

Purposes of Emulsions and of Emulsification

1-Emulsification enables the pharmacist to prepare relatively stable and homogeneous mixtures of two immiscible liquids.

2-Emulsion permits administration of a liquid drug in the form of minute globules rather than in bulk.

3-For orally administered emulsions, the o/w type permits palatable administration of an otherwise distasteful oil by dispersing it in a sweetened, flavored aqueous vehicle.

4-The reduced particle size of the oil globules may render the oil more digestible and more readily absorbed, or more effective in its task, e.g., the increased efficacy of mineral oil as a cathartic when emulsified.

5-Emulsions to be applied to the skin may be o/w or w/o, depending on such factors;
as the nature of the therapeutic agents,
the desirability for an emollient or tissue-softening effect, and the condition of the skin.

6-Medicinal agents that irritate the skin generally are less irritating in the internal phase of an emulsified topical preparation than in the external phase, from which direct contact with the skin is more prevalent.

- ✓Naturally, the miscibility or solubility in oil and in water of a medicinal agent dictates to a great extent **the vehicle, and its nature** in turn suggests the **phase of the emulsion** that the resulting solution should become.

- ✓ On the unbroken skin, a w/o emulsion can usually be applied more evenly, because: -

1-The skin is covered with a thin film of sebum, and this surface is more readily wetted by oil than by water.

2-A w/o emulsion is also more softening to the skin, because it resists drying and removal by contact with water.

- ✓ On the other hand, if it is desirable to have a preparation that is easily removed from the skin with water, an o/w emulsion is preferred.

- ✓ Also, absorption through the skin (percutaneous absorption) may be enhanced by the diminished particle size of the internal phase.

Theories of Emulsification

- ✓ Many theories have been advanced in an attempt to explain how emulsifying agents promote emulsification and maintain the stability of the emulsion.

- ✓ Although certain of these theories apply rather specifically to certain types of emulsifying agents and to certain conditions (e.g., the pH of the phases of the system and the nature and relative proportions of the internal and external phases), they may be viewed in a general way to describe the manner in which emulsions may be produced and stabilized.

These theories include;

1) Surface Tension Theory
2) Oriented-Wedge Theory
3) Plastic / Interfacial film theory

1- <u>Surface Tension Theory</u>

✓Liquid drops have a tendency to assume a spherical shape, which having the minimal surface area exposed. Therefore; liquid drops possess internal forces that tend to promote association of the molecules to resist distortion of the sphere.

✓If two or more drops come into contact, the tendency to coalesce, making one larger drop having a smaller surface area than the total surface area of the individual drops.
✓The surrounding of the liquid is air, it is referred to as the liquid's *surface tension*. The liquid is in contact with a second liquid in which it is insoluble and immiscible, the force is called *interfacial tension*.

✓Surface tension – lowering substances - are *surface active* (surfactant) or *wetting agents* that reduce this resistance encourage a liquid to break up into smaller drops or particles.

✓The use of these substances as emulsifiers and stabilizers can;

1- lower the interfacial tension of the two immiscible liquids,

2- reducing the repellent force between the liquids and

3- diminishing each liquid's attraction for its own molecules.

✓*Thus, the surface – active agents facilitate the breaking up of large globules into smaller ones, which then have a lesser tendency to reunite or coalesce.*

2- ***Oriented Wedge Theory***

✓Monomolecular layers of emulsifying agent orient themselves and curved around a droplet of the *internal phase* of the emulsion in a manner *reflective of their solubility in that particular liquid.*

✓In a system containing two immiscible liquids, the emulsifying agent is *soluble* and *embedded* in one phase than the other. Substances molecules (e.g. soaps) based on this theory have a hydrophilic portion and a hydrophobic portion, then molecules orient themselves into each phase.

- ✓ Depending on the *molecules shape*, *size*, *solubility and orientation*, the wedge shape envisioned for the molecules causes either

oil globules or *water globules* to be surrounded.

- ✓ Generally, an emulsifying agent having a greater hydrophilic character will promote an o/w emulsion, and a w/o emulsion results from use one more hydrophobic.

3- ***Plastic / Interfacial Theory***

- ✓Places the emulsifying agent at the interface between the oil and water, surrounding the droplets of the internal phase as a thin layer of film adsorbed on the surface of the drops.

- ✓The formation of an o/w or a w/o emulsion depends on the degree of solubility of the agent in the two phases.

Theories of Emulsification

Surface Tension Theory:
- lowering of interfacial tension.

Oriented-Wedge Theory:
- mono molecular layers of emulsifying agents are curved around a droplet of the internal phase of the emulsion.

Interfacial film theory:
A film of emulsifying agent prevents the contact and coslescing of the dispersed phase.

- ✓ In actuality, it is unlikely that a single theory of emulsification can explain the means by which the many and varied emulsifiers promote emulsion formation and stability.
- ✓ It is more than likely that even within a given emulsion system, more than one of the aforementioned theories play a part.
- ✓ For instance, lowering of the interfacial tension is important in the initial formation of an emulsion, but the formation of a protective wedge of molecules or film of emulsifier is important for continued stability.
- ✓ No doubt certain emulsifiers are capable of both tasks.

PREPARATION OF EMULSIONS

1- *Emulsifying Agents;*

- ✓Is a substance which stabilizes an emulsion .
- ✓***Selection of the Pharmaceutically acceptable emulsifiers, they ;***

1- must be able to promote emulsification
2- maintain the stability of the emulsion for the intended shelf life of the product.
3- stable .
4- compatible with other ingredients .
5- non – toxic .
6-possess little odor , taste , or color .
7- not interfere with the stability of efficacy of the active agent .

Types of Emulsifying Agents (EA)

1- Carbohydrate materials – e.g.; acacia, tragacanth, agar, chondrus and pectin are hydrophilic colloids when added to water produce ***o/w emulsions***.

✓Acacia is frequently used in extemporaneous emulsions.

✓Tragacanth and agar are employed as thickening agents in acacia – emulsified products.

✓MCC is employed in suspensions and emulsions as a viscosity regulator to retard particle settling and provide dispersion stability.

2- Protein substances – e.g.; gelatin, egg yolk and casein produce ***o/w emulsions***.

The disadvantage of gelatin, the emulsion frequently is too fluid and becomes more fluid upon standing.

3- High – molecular – weight alcohols – e.g.; stearyl alcohol, cetyl alcohol and glyceryl monostearate primarily as thickening agents and stabilizers for ***o/w emulsions*** of certain lotions and ointments used externally.
Cholesterol and cholesterol derivatives employed in externally used emulsions to promote ***w/o emulsions.***

4- Finely divided solids – e.g.; colloidal clays, including bentonite, magnesium hydroxide and aluminum hydroxide form ***o/w emulsions*** when the insoluble material is added to the aqueous phase as its volume greater than the oleaginous phase and vs.

- The relative volume of internal and external phases of an emulsion is important, regardless of the type of emulsifier used.
- As the internal concentration of an emulsion increases, so does the viscosity of the emulsion to a certain point, after which the viscosity decreases sharply. At this point, the emulsion has undergone ***inversion;*** i.e., it has changed from an ***o/w emulsion to a w/o,*** or vice versa.

- In practice, emulsions may be prepared without inversion with as much as about 75% of the volume of the product being internal phase.

Wetting agents - anionic, cationic or nonionic agents contain both hydrophilic and lipophilic groups.

✓In anionic agents, lipophilic portion is negatively charged, but in the cationic agents, it is positively charged. *Owing to their opposing ionic charges, anionic and cationic agents tend to neutralize each other and are thus considered incompatible.*

✓The ionic nature of a surfactant is a prime consideration.

A/ Nonionic surfactants are effective over pH range of 3 to 10;
B/ cationic surfactants are effective over pH range of 3 to 7;
C/ and, anionic surfactants require a pH greater than 8.

- Anionic surfactants:

These dissociate to produce negatively charged ions with surface – active activity. ***They are comparatively more toxic than other categories and this limits their use to external formulations.***
E.g.; *Sodium / potassium salts of fatty acids*
Sodium oleate, sodium stearate and ammonium oleate.

Amine salts of fatty acids

✓These are typically formed in situ in pharmaceutical emulsions, e.g. triethanolamine stearate.

✓They form o/w emulsions.

✓Akin to sodium/potassium salts of fatty acids, their emulgent properties are pH – dependent and may be negated in the presence of electrolytes.

✓*Alkyl sulphates*

✓These are used to produce o/w emulsions (in conjunction with a second non – ionic surfactant of low HLB, i.e. < 6). Fatty alcohols (e.g. cetyl, stearic alcohol) are frequently used for this purpose.

✓Examples of these include **sodium lauryl sulphate** and triethanolamine lauryl sulphate.

Cationic surfactants:

✓These dissociate to produce positively charged ions with surface - active activity.

✓They are primarily used pharmaceutically as preservatives of topical formulations; however, they may be used to form o/w emulsions (when combined with a second non – ionic surfactant of low HLB, i.e. < 6).

- The main example used in topical formulations is **cetrimide**, a mixture of trimethylammonium bromide, with smaller amounts of dodecyl trimethyl ammonium bromide and hexa decyl trimethyl ammonium bromide.

Non – Ionic Surfactants

✓These are by far the most popular category of surface – active agents used for the formulation of pharmaceutical emulsions.

✓They may be used to formulate both o/w and w/o emulsions.

✓Generally combinations of two non – ionic surfactants (one water – soluble and the other oil – soluble) are employed ***to ensure the formation of a stable interfacial film around the surface of the droplets of the disperse phase.***

✓In certain circumstances a single non – ionic surfactant may be used that is of intermediate HLB value.

✓Non – ionic surface – active agents are more stable than ionic surfactants in the presence of electrolyte and / or changes in pH.

✓Generally; molecule hydrophobic portion is composed of a fatty acid or fatty alcohol, whereas the hydrophilic portion is composed of an alcohol or ethylene glycol moieties

E.g.;

Sorbitan esters (e.g.; Span ® series)

➢This is a family of chemically related esters that are produced by esterifying a fatty acid to at least one of the hydroxyl groups of **sorbitan**.

➢Modification of the length of the fatty acid (denoted by the symbol R) will generate a range of surface – active agents with emulsifying properties (and low HLB values).

- By themselves sorbitan esters will form w/o emulsions; however, when combined with the polysorbates, both o/w and w/o emulsions may be formulated.

➢ *Polyoxyethylene fatty acid derivatives of the sorbitan esters (e.g.; Tween ® series)*

➢This family of surface – active agents is prepared by forming **polyoxyethylene esters**

- The emulsifying properties of this series are tolerant of changes in electrolyte concentration and pH.
- Generally they are non – toxic and are used in both parenteral and non – parenteral emulsions.

- *Polyoxyethylene alkyl ethers (macrogols)*
- These are ethers formed between polyethylene glycol and a range of fatty alcohols (lauryl, oleyl, myristyl, cetyl, stearyl).

- Two commercial series of these compounds are *Cremophor* and *Brij*.

- The physicochemical properties of these *non – ionic* surface – active agents may be modified by altering the length of the polyoxyethylene group and the length of the aliphatic chain (denoted as *x* and *y*).

- The macrogols are used as emulsifying agents for both o/w and w/o emulsions.

- Combinations of the more lipophilic and hydrophilic examples of this series are combined to produce stable emulsions.

- For example, **cetomacrogol 1000** is combined with cetostearyl alcohol to produce cream formulations.

- *Polyoxyethylene fatty acid esters*

- These are a series of polyoxyethylene derivatives of fatty acids. The most commonly used derivatives are the stearate derivatives (the *Myrj* series).

- The surface–active properties of these compounds may be modified by varying the length of the ***oxyethylene*** substituent and, in addition, by ***mono - or di – esterification*** of the acid.

- Polyoxyethylene stearates (and related compounds) are non-ionic surfactants, offering a range of HLB values.
- They are frequently combined with stearyl alcohol (or related fatty alcohols) in the formulation of o/w emulsions.

- The emulsifying properties are tolerant of the presence of strong electrolytes.
- *Fatty alcohols* Examples include **cetyl alcohol** and **stearyl alcohol**.

- In addition, cetostearyl alcohol **(**a mixture of cetyl (20–35%) and stearyl (50–70%) alcohols, although other alcohols, e.g. myrisitc alcohol, are present**)** is available.

- Fatty alcohols are generally used in combination with more ***hydrophilic*** surfactants to ***produce stable o/w emulsions***.

- When used alone, fatty alcohols act as ***w/o emulsifiers.***

- Furthermore, the addition of these to a ***hydrophobic base*** will increase the water absorption properties of the formulation.

- In cream formulations excess fatty alcohols interact with the hydrophilic emulsifier to produce ***a viscoelastic external phase***.
- In turn, this increases the viscosity of this phase (thereby decreasing upward/downward sedimentation), producing the consistency expected of cream formulations.

- Fatty alcohols may be used to enhance the viscosity of w/o creams.