

Emulsions and emulsifiers

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Abstract - Emulsions are heterogeneous systems of one liquid dispersed throughout another in the form of droplets usually exceeding 0.1 μm in diameter. Emulsions are generally categorised into single emulsions which include water-in-oil and oil-in-water and multiple emulsions including water-in-oil-in-water and oil-in-water-in-oil. Emulsions are prepared by phase inversion method, membrane emulsification method, dry gum method, and wet gum method. Continental/dry gum method or bottle/general method are most commonly employed techniques for emulsification. Membrane emulsification method which is based on principle of dispersing one immiscible phase (dispersing phase) into another phase (continuous phase) by applying pressure is used for the preparation of multiple emulsions. Emulsifier / emulgents is a substance which stabilises the emulsion by increasing the kinetic energy. Emulsifiers are generally classified based on their chemical structure into four types including synthetic, natural, finely divided solids, and auxillary agents; by mechanism of action into three categories including monomolecular films, multimolecular films, and solid particle films. There are different theories which help in understanding emulsification process which include surface tension theory, surface orientation theory, and plastic/interfacial film theory. Stability of emulsion is one of the critical parameter which is difficult to attain. The instability of emulsions is categorised into flocculation, creaming, coalescence, and breaking which were further detailed in the text.

Key words - Emulsions, Emulsifiers, Water-in-oil, Microemulsion

How to cite this paper - Sarathchandraprakash, N.K., Mahendra, Chandrika, Prashanth, S.J., Manral, Krishan, Babu, U.V. and Gowda, D.V.S. (2013). Emulsions and emulsifiers. *Asian J. Exp. Chem.*, 8 (1&2): 30-45.

Paper history - Received : 21.06.2013; Accepted : 28.11.2013

Emulsions are normally defined as are heterogeneous systems of two immiscible layers, one liquid dispersed throughout another in the form of droplets usually exceeding 0.1 μm in diameter. An emulsion is a thermodynamically unstable two-phase system consisting of at least two immiscible liquids, one of those liquids which is dispersed in the form of small droplets throughout the other, and with the help of an emulsifying agent. And dispersed liquid is known as the internal or discontinuous phase, whereas the dispersion medium is known as the external or continuous phase. Whereas oils, petroleum hydrocarbons, and waxes are the dispersed phase, and the water or an aqueous solution is the continuous phase, the

system is called an oil-in-water (o/w) emulsion. The oil in water emulsion is generally formed if the aqueous phase constitutes > 45% of the total weight, and an emulsifier is used. Conversely, where the water or aqueous solutions are dispersed in an oleaginous medium, the system is known as water-in-oil (w/o) emulsion. These emulsions are generally formed if the aqueous phase constitutes < 45% of the total weight and a lipophilic emulsifier is used.

Many routes of administration are used in Emulsions. Patients generally object to the oily feel of emulsions in the mouth when administered orally. But sometimes, to mask the taste of a very bitter drug emulsions are the formulation of choice. Emulsions were also considered when the oral

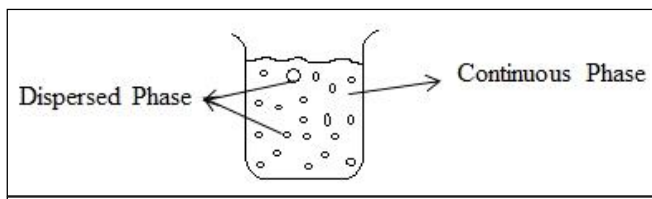


Fig. 1 : Representation of general emulsion

solubility or bioavailability of a drug is to be dramatically increased.

Creams which have emollient properties were used as topical emulsions. Emulsions are also used as bases in lotions, as are suspensions. The term "lotion" is often used to describe fluid liquids affianced for topical use. Lotions which have lubricating effect are intended to be used in areas where the skin rubs against itself such as between the fingers, thighs, and under the arms. Emulsions are also used an ointment bases and intravenously administered as part of parenteral nutrition therapy. Emulsions vary from easily pourable liquids to semisolid creams in terms of their consistency.

Their consistency will depend upon:

- The internal phase volume to external phase volume ratio.
- In which phase ingredients solidify.
- What ingredients are solidifying.

Stearic acid creams (sometimes called vanishing creams) are o/w emulsions and have a semisolid consistency but are only 15% internal phase. And at the same where many emulsions have internal phases that account for 40% - 50% of the total volume of the formulation. Water in oil emulsions tend to be not miscible in water, water washable, will not absorb water, and are occlusive, and also "greasy." Reason might be; oil is the external phase, and will repel any of the actions of water. The oil will not allow water to evaporate from the surface of the skin forming occlusiveness. Conversely, o/w emulsions are water washable, miscible with water; absorb water, nonocclusive, and nongreasy. As water is the external phase it readily associates with actions of water.

Emulsions tend to separate into two distinct phases or layers over time as they are physically unstable. When dispersed oil droplets merge and rise to the top of an o/w emulsion or settle to the bottom in w/o emulsions creaming occurs. The emulsion can be easily redispersed by shaking in the above two cases. Coalescence is the complete and irreversible separation and fusion of the dispersed phase. Finally, this phenomenon known as phase inversion or a change from w/o to o/w (or vice versa) may occur.

Types of emulsions:

- Single Emulsions.

- Oil-in-water.
- Water in oil
- Double or Multiple Emulsions.
- Water in oil in water
- Oil in water in oil
- Microemulsions.
- Pickering emulsions.

Single emulsions:

If the Emulsions are dispersed, multiphase systems consisting of at least two insoluble or immiscible liquids. The dispersed phase is present in the form of droplets in continuous phases. Depending on the emulsification process, the diameter of the droplets lies between 0.1 μm and 0.1 mm. Emulsions of this kind are thermodynamically unstable, which means there is a tendency to reduce the interface (as a result of a relatively high interfacial tension), causing the droplets to coalesce and therewith decreasing the total amount of interface.

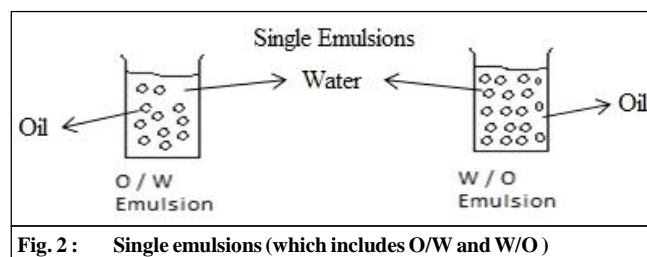


Fig. 2 : Single emulsions (which includes O/W and W/O)

Oil in water emulsion:

The emulsions which are being used in Pharmaceuticals consist of mixtures of aqueous phase with various oils and waxes. The oil droplets are dispersed throughout the aqueous phase, the emulsion is termed oil-in-water (O/W) as shown above. Fats and oils for oral preparations, either as medicaments for vehicles for oil soluble drugs, are always formulated as oil in water (O/W) emulsions [2]. They are non-greasy and are easily removable from the skin surface and they are used externally to provide cooling effect and internally to also mask their taste of oils. Water soluble drugs are more quickly released from oil in water emulsion. These O/W emulsion give a positive conductivity test as the water gives, so the external phase is a good conductor of electricity [3].

Water in oil emulsion:

A system in which the water is dispersed as globules in the oil continuous phase is termed water-in-oil emulsion (W/O) as shown in above Figure. Water-in-oil emulsions will have an occlusive effect by hydrating the stratum corneum and inhibiting evaporation of eccrine secretions. And it has an effect on the absorption of drugs from water in oil

emulsions. These W/O emulsions are also useful for cleansing the skin of oil soluble dirt, although its greasy texture is not always cosmetically acceptable [2]. They are greasy and not water washable and are used externally to prevent evaporation of the moisture from the surface of skin like cold cream. Oil soluble drugs are more quickly released from water in oil emulsions. They are preferred for formulation meant for external use like cream W/O emulsion is not given a positive conductivity tests, because of oil is the external phase which is a poor conductor of electricity [3].

Double emulsions:

The double emulsions are defined as an emulsion in an emulsion. Two main types of double emulsions can be distinguished as; water-in-oil-in-water (W/O/W) emulsions, in which a W/O emulsion is dispersed as droplets in an aqueous phase, and oil-in-water-in-oil (O/W/O) emulsions, in which an O/W emulsion is dispersed in the oil phase. W/O/W emulsions are more common than O/W/O emulsions. Double emulsions contain more interfaces and are even more thermodynamically unstable than single emulsions. A two-step emulsification process is used generally for double emulsions preparation by using two surfactants; a hydrophobic one designed to stabilize the interface of the W/O internal emulsion and a hydrophilic one for the external interface of the oil globules (for W/O/W emulsions). The primary W/O emulsion is prepared under high-shear conditions to obtain small droplets while the secondary emulsification step is carried out with fewer shears to avoid rupture of the internal droplets [4]. In generally, conventional emulsification processes high-shear stresses are needed to decrease the droplet size and droplet size distribution of the coarse emulsion. However, external flow (shear) causes internal streaming in the droplets, which increases the frequency of collision (and thus coalescence) of internal droplets with the outer water phase [5]. Besides, elongation of the droplets increases the interface available for release of internal droplets. Therefore, the release rate of internal droplets is dependent on the applied shear stress [6] and only moderate shear can be used for the production of double emulsions if a reasonable percentage of internal phase is required. This is the reason why double emulsions are in general polydisperse.

Florence and Whitehill [7] described as four possible mechanisms for instability of W/O/W emulsions. These four mechanisms are

- Coalescence of the internal aqueous droplets.
- Coalescence of the oil drops.
- rupture of the oil film separating the internal and external aqueous phases.
- Passage of water (water-soluble material, like a

drug) to from internal droplets through the oil layer.

Again the last mechanism is subdivided into two possible mechanisms: via reverse micellar transport and by diffusion across areas where the oil layer is very thin [4].

All the mechanisms are known to occur both during preparation of double emulsions and during storage. They influence the size distributions of the internal and outer droplets, which are important characteristics for double emulsions and the stability thereof. Further, double emulsions are characterized by the entrapment yield of a certain compound in the inner droplet phase and the stability in time. Combinations of surfactants in the outer water phase have a beneficial effect on stability and polymeric surfactants are very suitable emulsifiers (and stabilizers) for double emulsions, because they can protect double emulsions against coalescence by making them resistant to shear [4]. In general it can be stated that the formulation of double emulsions greatly influences the stability and droplet size, and this should be considered in conjunction with the choice of the preparation method.

Multiple emulsions have a high potential for application in the food processing industry to encapsulate or protect sensitive and active food components from the environment (antioxidation) [8], to control the aroma and flavour release [9-11], or to produce foods with a lower oil or fat content [12-15]. The main problem with food related applications, *i.e.* with food-grade emulsifiers and stabilisers, is in preparing such emulsions, especially of the W/O/W type, with prolonged stability and release. Reviews on the behaviour of multiple emulsions have been published by [16-18]. A special review on multiple emulsions in food related applications was published [19, 20].

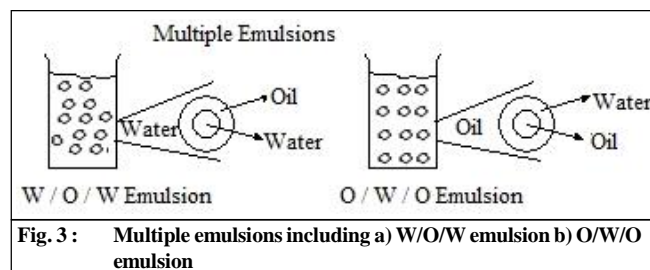


Fig. 3: Multiple emulsions including a) W/O/W emulsion b) O/W/O emulsion

Microemulsions:

These are the systems consisting of water, oil, and surfactant, constituting a single optically isotropic and thermodynamically stable liquid solution. Two types of micro emulsion are available, which they are defined as O/W (oil in water) and W/O (water in oil) micro emulsion. For preparation of O/W microemulsion, w/o emulsion was considered along with a low hydrophilic lipophilic balance (HLB) number surfactant. To this emulsion, an aqueous solution of high HLB number surfactant is added while

stirring at a certain amount of addition, a gel' phase is produced and further addition of surfactant, an inversion into O/W emulsion take place. For W/O microemulsion, O/W emulsion stabilized with an ionic or nonionic surfactant was considered. This emulsion is titrated with a co-surfactant and the emulsion passes through a gel phase, after further addition of co-surfactant result in the production of W/O microemulsion. A drawback of microemulsion is the possibility of disruption of the crystalline structure of stratum corneum. These lead to skin irritation.

Pickering emulsion:

Emulsion stabilizers such as the solid particles in the colloidal size may be used for preparation of this emulsion. Such particles are known as Pickering emulsion. The Pickering emulsions are recently employed in many areas like cosmetics, food, pharma products, oil recovery and waste water treatment [21].

Emulsification process:

Milk a natural emulsion, consists of fatty globules surrounded by a one layer by casein, suspended in water. The theory of emulsification is based on the study of milk. The principal consideration is the same as that of milk for preparation of pharmaceutical emulsions [22].

General method:

The oil phase was completely divided into minute globules and each globule was surrounded with an emulsifying agent and the globules were suspended in the aqueous phase which forms the O/W emulsion. Conversely, aqueous phase was divided into minute globules and each globule was surrounded with emulsifying agent and the globules in the oily phase were suspended forming W/O emulsion [22].

Phase inversion method:

The aqueous phase is first added to the oil phase in this method, to form a W/O emulsion. The addition of more water results in the inversion of emulsion which gives rise to an O/W emulsion at the inversion point [23].

Continental and dry gum method:

Emulsions are usually made by continental or dry gum method. The emulsion is prepared by mixing the emulsifying agent (usually acacia) with the oil. This was then mixed with the aqueous phase. Continental and dry gum methods were same in all the preparation methods except in the proportion of constituents [22].

Wet gum method:

The proportion of the constituents is same as those

used in the dry gum method in this technique; only method of preparation differs. The mucilage of the emulsifying agent (usually acacia) is formed to which oil is added drop by drop by triturating continuously [22].

Membrane emulsification method:

This method is based on a novel concept of generating droplets "drop by drop" to produce emulsion. Pressure is applied directly to the dispersed phase which passes through a porous membrane into the continuous phase. In this way the droplets formed are then detached from the membrane surface due to the relative shear motion between the continuous phase and membrane surface [24].

Usages of emulsions:

Oral formulation:

- Enhancing bioavailability.
- Giving controlled rate of drug release.
- Affording protection to oxidation or hydrolysis.

Topical formulation:

- Easily applied and can be formulated to eliminate oiliness and staining.
- Carrying water which is an excellent softener to skin.

Determination of emulsion types:

- By ratio between water and oil phase.
- By order of addition.
- By type of emulsifier.

Choice of emulsion types:

- Fats or oils for oral administration (E.g. O/W is formed to mask the unpleasant taste).
- For i.v administration (O/W or W/O is used).
- For external applications.

O/W emulsion:

- Water soluble drugs.
- Easily washed from skin.
- Non greasy texture.

W/O emulsion:

- Occlusive effect – influence the absorption of drugs.
- Cleansing skin.
- Moisturising creams.

Emulsion theories:

To explain how emulsifying agents can act in promoting emulsification and in maintaining the stability of the resulting emulsion, several emulsification theories were implemented.

Surface tension theory:

The force causing each liquid to resist breaking up into smaller particle is called as an interfacial tension. The Surfactants promote the lowering of this resistance.

Surface orientation theory:

Emulsifying agent having a greater character of hydrophilic than hydrophobic character will promote an o/w emulsion

Plastic or interfacial film theory:

Emulsifying agent is surrounding by the droplets of the internal phase as a thin layer of film adsorbed on the surface of the droplets, prevent the contact and coalescing of the internal phase.

Tests for identification of emulsion types:

It is very difficult to differentiate between o/w or w/o emulsions using naked eye. Thus, the four following methods have been used to identify the type of emulsions.

Dilution test:

This test involves the addition of continuous phase, for example in case of O/W emulsion; the emulsion remains stable upon unlimited addition of water but will become unstable upon unlimited addition of oil, that is, and oil will separate. Likewise is the case with W/O emulsion [25].

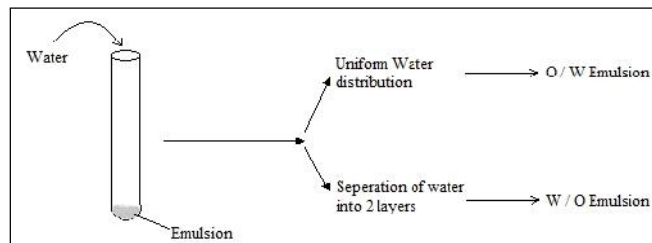


Fig. 4 : Dilution test procedure in schematic representation

Electrical conductivity test:

Water is known as a good conductor of electricity; hence, an emulsion with water continuous phase will readily conduct electricity rather than that with oil continuous phase [2].

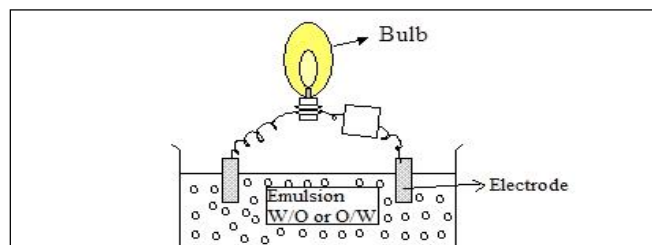


Fig. 5 : Conductivity test apparatus

Staining test/dye-solubility test:

A small amount of water soluble dye, such as Amaranth is added to the emulsion, now if water is the continuous phase (O/W emulsion); dye will dissolve uniformly throughout the system. If oil is the continuous phase, dye will remain as cluster on the surface of the system [26].

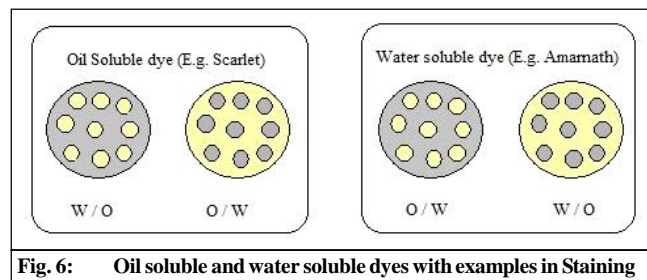


Fig. 6 : Oil soluble and water soluble dyes with examples in Staining

Fluorescence test :

Oils give fluorescence under UV light, whereas water doesn't. Therefore, Oil in water emulsion shows spotty pattern while W/O emulsion fluoresces.

Uses of emulsification:

- To mask the taste.
- O/W is convenient means of orally administration of water-insoluble liquids.
- O/W emulsion facilitates the absorption of water-insoluble compounds comparing to their oily solution preparations (e.g. vitamins).
- Oil-soluble drugs can be given parentally in form of oil-in water emulsion.
- Emulsion can be used for external application in cosmetic and therapeutic uses.

Control of emulsion type during formulation:

- Volume of internal and external phases controls the type of emulsion. The smaller volume will be for the internal phase and the larger volume will be for external phase. In some cases like, internal phases can be more than 50% of the total volume.
- Dominance of polar and non-polar characteristic of emulsifying agents (relative solubility of emulsifying agent in water and oils). The polar part results in formation of oil in water emulsion and dominance of non-polar part results in formation of water in oil emulsion. Note that polar groups are better barriers than non-polar; therefore, oil in water emulsion can be prepared with more than 50 % of oil phase "internal phase".

Pharmaceutical applications of emulsion:

Both macro and micro emulsions were good carriers for hydrophilic and lipophilic drugs.

The size distribution and stabilization phenomenon were being controlled, which creates novel horizons; which resulted in great attention for liquid dispersion systems. An increase the solubility, bioavailability of therapeutic drugs, and the ability to favour the topical transport of hydrophilic drugs is the main advantage of such systems.

For controlled and sustained release of drugs, multiple emulsions, especially W/O/W emulsions are very good candidates. These are also used as an alternate to liposomes as delivery system.

Microemulsions can be formed spontaneously and are thermodynamically stable; they improve drug solubilisation and bioavailability, and also act as potential drug delivery systems by integrating a wide range of drug molecules. Oil in water and W/O/W emulsions are generally employed for intravenous route.

The Lipid emulsions are used for parenteral nutrition's, intravenous drug administration and as oxygen carriers.

Emulsions have been used for many centuries for treating local skin diseases. Generally Oil-in-water emulsions are used for lamination of skin lacerations. The advantages of using the topical emulsions are to avoid gastrointestinal environment and first pass metabolic effect. Emulsions are also being used for oral formulations /route. They are mainly used for enteric nutrition or laxative preparations [27]. In addition to that aforementioned applications, the emulsions may also use, to stabilize hydrolytically susceptible drugs for sustained releases by reduction of irritation or toxicity, possible targeted delivery of drugs to various organs and possible enhanced pharmacological effect [28].

Stability of emulsion:

A very important parameter for emulsion based products stability pertaining to their emulsion stability. However, the evaluation of emulsion stability is not comparatively easier[29]. An emulsion is considered to be physically unstable in the case of:

- The internal phases tend to form aggregates of globules.
- Large or aggregates of globules rise to the top or fall to the bottom of the emulsion to form a concentrated layer of the internal phase.
- If all or a part of the liquid of the internal phase becomes "unemulsified on the top or bottom of the emulsion.

Pharmaceutical emulsion stability is characterized by the absence of coalescence of their dispersed phase, absence of creaming and retaining its physical characters like elegance, odour, color and appearance. The instability of emulsions can be classified into four types of phenomenon: Flocculation, creaming, coalescence and breaking [26].

Flocculation:

Association of small particles to form large aggregate which is redispersable upon shaking is called flocculation. It is a reversible process in which the droplets remain as an intact. Flocculation is considered as the precursor of coalescence as the presence of excess surfactant in the continuous phase of an emulsion can lead to coalescence of emulsion droplets [30]. Depletion effect is the main reason for the flocculation of emulsion droplets by excess surfactant. It can be explained as, a system containing excess surfactant in the form of micelles.

Creaming:

Creaming is the phenomenon in which the dispersed phase separates out from system, forming a layer on the top of the continuous phase. In creaming, the dispersed phase remains in globules so that it can be re-dispersed on vigorous shaking. The Creaming can be minimized if the viscosity of the continuous phase is increased [22]. The rate of creaming is determined by Stoke's law as follows:

$$V = \frac{D^2 (\rho - \rho_0)g}{18\eta}$$

where, V is the velocity in cm/s, D is representing the diameter of particles of dispersed phase in cm, ρ represents the dispersed phase density, ρ_0 is the continuous phase density, and finally η is the continuous phase viscosity. And also "g" is the gravitational acceleration. Oil in water emulsions generally face upward creaming when the globules of the dispersed phase are less dense than the continuous phase. In more precisely, W/O emulsions face downward creaming when the globules of the dispersed phase are denser than the continuous phase [31].

Coalescence (synonyms: breaking or cracking):

A more subtle type of emulsion instability, coalescence occurs when the mechanical or electrical barrier is insufficient to prevent the formation of progressively larger droplets [30]. Stabilization against coalescence may be achieved by the addition of high boiling point or high molecular weight components to the continuous phase [23]. W/O emulsions are formed only when the film of emulsifying agent in the interface is uncharged and rigid as a result of complex formation was concluded by Newman and Schulman and Cockbain. They were of the view that a W/O emulsion cannot be stabilized against flocculation by charge on the dispersed phase of water droplets, because of an electric diffuse layer cannot be built up as oil being a non-ionizing medium. The surface potential considerably higher than 25 mv is not sufficient to stabilize the droplets of dispersed phase with a radius $\geq 1\mu$ against the flocculation. This is because of their high sedimentation velocities [32].

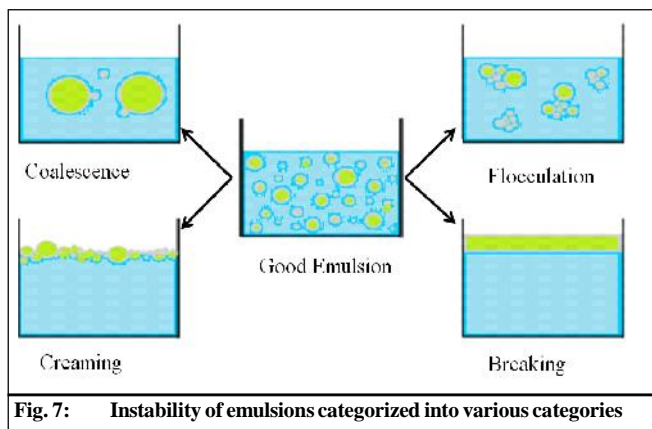


Fig. 7: Instability of emulsions categorized into various categories

Gels and magmas:

Gels are defined as semi-solid systems consisting of dispersions made up of either small inorganic particles or large organic molecules enclosing or interpenetrated by a liquid(s). Magmas / Milks are gels consisted of floccules as small distinct particles. Gels / Magmas are considered colloids because they contain particles within the range of colloidal dispersions.

Examples of magmas and gels:

- Bentonite Magma, NF: Preparation of 5% bentonite, a native, colloidal hydrated aluminum silicate, in purified water.
- Aluminum Hydroxide Gel, (USP): This is an aqueous suspension of a gelatinous precipitate composed of insoluble aluminum hydroxide and hydrated aluminum oxide, equivalent to about 4% of aluminum oxide.
- Milk of Magnesia, USP: This is a preparation containing between 7 and 8.5% of Magnesium hydroxide.

Emulsion stability assessment:

The stability of emulsions must be regarded in terms of physical stability of emulsion system examined and the chemical stability of the emulsion components [23].

Macroscopic examination:

The degree of creaming or coalescence occurring per unit period of time can give the assessment of emulsion physical stability. This is carried out by calculating the ratio of the volume of the creamed part (separated part) of the emulsion and the total volume of the product [2].

Determination of particle size and particle Count/globule size analysis:

Analysis of changes in the average particle size is one of the parameters used for assessing emulsion stability. Optical microscopy, Andresen apparatus and Coulter counter

apparatus are used for this purpose [3].

Determination of viscosity/viscosity changes

A change in the globule size or number or migration of emulsifying agent during aging may be detected by a change in apparent viscosity [2]. Emulsions follow non-Newtonian flow characteristics. So, in O/W emulsions results in an immediate increase in viscosity [3].

Determination of electrophoretic properties:

Zeta potential is an important parameter used for assessing emulsion stability, since electric charges on the particles affect the rate of flocculation [3]. Electrostatically, the emulsion stabilization is due to the mutual repulsion between electrical double layers of both phases. Such type of stability is very very sensitive to the ionic strength of solutions, as the concentration of electrolyte increases the electrical double layer compressed and the distance of electrostatic repulsion is reduced resulting in flocculation.

Hydrophilic lipophilic balance (HLB) scale for emulsions:

A very useful important technique used for the classification of surfactants on the basis of their solubility in water was introduced by Griffin. The numerical values in this system are called hydrophilic-lipophilic balance (HLB) which denotes the relative affinity of the surfactant for oil and water. The Emulsifying agents with HLB values of 3 to 6 are used for w/o emulsions preparations. Whereas the emulsifying agents with HLB values of 7 to 20 are used for o/w emulsions [33]. According to Alfred the type of emulsion is a function of the relative solubility of the surfactants, therefore the phase in which the surfactant is more soluble gives rise to the continuous phase. And also this phenomenon is sometimes referred to as "The Rule of Bancroft" [26].

Emulsifiers:

Emulsifiers are a group of [34] organic compounds that encompasses two dissimilar structural groups like water soluble and a water insoluble moiety in the same molecule. The surface activity of a compound is determined by their composition, The solubility properties, location and relative sizes of these dissimilar groups in relation to the overall molecular configuration. All emulsifying agents must be inert and chemically non-reactive with other components of the emulsion. Emulsifier must be chemically stable in the system. It should be nontoxic and nonirritant. They should also be odorless and relatively cheaper. Emulsions are stabilized by adding an emulsifier or emulsifying agent. These agents possess both hydrophilic and a lipophilic part in their chemical structure. All emulsifying agents are concentrate at and are adsorbed onto the oil : water interface and provide

a protective barrier around the dispersed droplets. Emulsifiers also stabilize the emulsion by reducing the interfacial tension of the system. Some emulsifiers improve stability of emulsion by imparting a charge on the droplet surface thereby reducing the physical contact between the droplets and hence decreasing the potential for coalescence. Some of the commonly used emulsifying agents include tragacanth, sodium lauryl sulfate, sodium dioctylsulfosuccinate, and polymers known as the Spans® and Tweens®.

Emulsifiers has their applications in agriculture, building and construction, elastomers and plastics, foods and beverages, industrial cleaning, leather, metals, paper, textiles, paints industry and etc. Emulsifiers derived from non-hydrogenated fats [35,36] apart from stabilizing emulsions also help in maintaining sensory characteristics of food such as texture, flavor, and taste which are usually lost due to fat reduction. This characteristic of making healthier products similar in taste to fat containing products has enabled emulsifiers in gaining huge acceptance in the market.

Classification of emulsifiers [37]:

Emulsifying agents are classified based on their chemical structure and mechanism of action. Based on chemical structure, emulsifiers are classified as synthetic, natural, finely dispersed solids, and auxiliary agents. Classes based on mechanism of actions which include monomolecular, multi-molecular, and solid particle film(s).

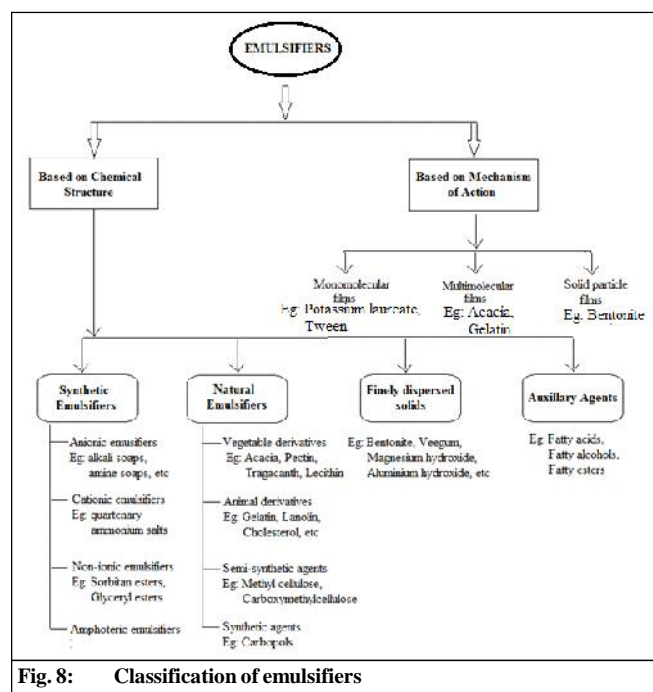


Fig. 8: Classification of emulsifiers

Synthetic emulsifiers:

These are further classified into anionic, cationic, no-

ionic and amphoteric emulsifiers. Each of these classes is described below.

Anionic emulsifiers [38]:

Anionic surfactants, the hydrophilic moiety is a polar group which is negatively charged in aqueous solutions or dispersions. It is either a carboxylate, sulphonate, sulfate or phosphate group in commercial products. In neutral or acidic media or in the presence of heavy metal ions the solubilizing power of the carboxylate group is markedly less than that of the other groups [39].

Anionic surfactants and its associated ionic environment influence the properties of their solutions. The salts of Sodium and potassium are generally more soluble in water and less soluble in hydrocarbons. And conversely the calcium barium and magnesium salts are more compatible with hydrocarbon solvents and less with water. Ammonium and amine salts e.g. tri-ethanolamine improves the compatibility of anions with water and hydrocarbons. These are widely used in emulsification and detergent applications. Higher total ionic strengths of anionic surfactants are usually associated with lower solubilities. To improve the solubility, molecular weight of the hydrophobe is lower in products designed for use at higher electrolyte concentrations. Micellar solubilisation by anionics is markedly affected by total ionic strength [40].

The anionic surfactants are divided into four groups according to their anionic groups as

Carboxylates Sulphonates, Sulfates and Sulfated Products and finally Phosphate Esters.

Carboxylates:

Carboxylate class of surfactants includes soaps and a small volume of amino carboxylates are the only anionic surfactants commercially available.

Soaps:

Soaps especially amine salts have applications such as emulsifiers, dispersants and solubilizing agents with a wide range of industrial uses. And also soaps have an emollient action in contact with the skin and leave a soft feel on textile fabrics.

Amino carboxylates:

Two types of amino carboxylate surfactants *N* acylsarcosinates and acylated protein hydrolytes are produced.

N Acylsarcosinates:

Sodium *N* lauroylsarcosinate and sodium *N* acylsarcosinate derived from coconut fatty acids are a type of soap like detergents with good lathering properties. *N*

Oleoysarcosinate is used as a textile auxiliary and detergent.

Acylated protein hydrolysates:

Fatty acyl aminocarboxylates are prepared from protein hydrolysates by acylation of fatty acid chlorides or by direct condensation with fatty acids. Derivatives of the incompletely hydrolyzed peptides have a great tolerance for hard water but their effectiveness as surfactants is less.

Sulfonates:

The most effective structures for an anionic surfactants are sulfonate group of the general formula RSO_3Na where R is a biodegradable hydrocarbon group in the surfactant molecular weight range which can be alkyl or alkyl aryl and product can be a random mixture of isomers as long as it does not contain chain branching which interferes with its biodegradability. Sulfonation processes can usually be adjusted to either slightly increase or decrease the degree of substitution of the solubilizing group on the hydrophobic part on surfactant raw materials.

Neutralization is another parameter for modification of properties of the hydrophobe. Sulfonates are usually obtained in the production process as free acids which can be neutralized to form alkali metal salts, alkaline earth metal salts or amine salts.

Sulfates and sulfated products:

The hydrophilic group in these emulsifying agents is SO_3 attached through an oxygen atom to a carbon atom in the hydrophobic moiety(s). The additional oxygen makes the sulfate a stronger solubilizing group than the sulfonate but the C-O-S linkage of the sulfates is hydrolysed more easily than the C-S linkage of the sulfonates. Sulfates are susceptible to hydrolysis. Optimum solubility balance is obtained by the solubilisation of hydrophobes through the combination of ethoxylation and sulfation

The commercial importance of surfactants in this groups are alkyl benzene sulfonates petroleum sulfonates di alkyl sulfosuccinates naphthalene sulfonates N acyl N alkyltaurates 2 sulfo ethyl esters of fatty acids and olefin sulfonates.

Alkyl sulfates are used as high foaming detergents, strong wetters, emulsifiers and dispersants. Some of other the products are used as leathering and cleansing agents in shampoos and dentifrices. Others are used as detergent and wetting agents for textile processing industry. Another use of the alkyl sulfates is as emulsifiers and dispersants in emulsion polymerization.

Sulfated natural fats and oils:

Olive oil was the first oil to be sulfated other than soap to obtain a commercial surfactant. Polyunsaturated fatty acid

moieties are undesirable components of glycerides for sulfation since the resulting surfactants are usually dark in colour and sensitive to oxidation.

Cationic emulsifiers:

Cationic surfactants are classified as quaternary ammonium compounds [41]. In solution, the head of the cationic surfactant is positively charged and they are mostly used as disinfectant and preservatives as they have good bactericidal properties. They are used on skin for cleansing wounds or burns. Widely used cationic surfactants are cetrimide which has tetra-decyltrimethyl ammonium bromide with minimum amount of dodecyl and hexadecyl compounds.

Other cationic surfactants are benzalkonium chloride, cetylpyridinium chloride etc. The quaternary ammonium compounds are being used in the cosmetic industry because of their germicidal properties. There are a large variety of materials available and a large number of hydrophobic groups being used. The use of quaternary ammonium compounds in cosmetic formulations is limited due to their low compatibility with anionic surface active chemicals and certain other chemicals, e.g. sodium citrate, zinc salts, etc. The list of incompatible materials could also include pectins, gum tragacanth, and sodium carboxymethyl cellulose. These materials may be used as sensitizing agents to cationic systems. Precipitation of an anionic/cationic complex is normally indicated by the cloudiness of a solution, but some complexes are water-soluble and others are easily solubilized by an excess of either constituent. It is, therefore necessary to check for the absence of incompatibility in a product by measuring specifically. This is particularly important in formulae utilizing the bactericidal activity of quaternary ammonium compounds, and it should never be assumed that the activity of the product will be equivalent to the content of quaternary incorporated.

Non-ionic emulsifiers [42]:

These are a type of surfactants that do not possess any electrical charge(s), which can make them resistant to water hardness deactivation. These are less irritant than other anionic or cationic surfactants.

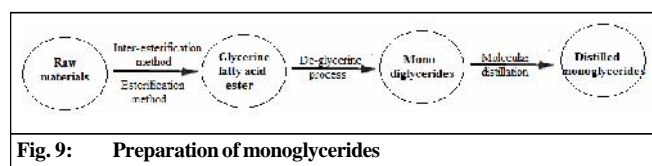
The hydrophilic part contains the poly oxy ethylene, poly oxy propylene or polyol derivatives [43]. The hydrophobic part contains saturated or unsaturated fatty acids or fatty alcohols. They are excellent grease/oil removers and emulsifiers. Non-ionic surfactants contribute to making the surfactant system less hardness sensitive.

The non ionic surfactant can be classified as Poly olesters, polyoxyethylene esters, poloxamers. The polyol esters includes glycol and glycerol esters and sorbitanderivatives [44] Polyoxyethylene esters includes

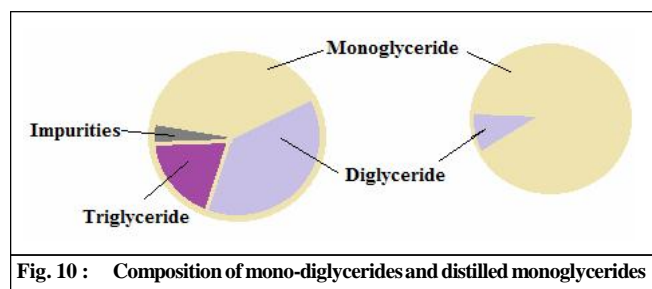
polyethylene glycol (PEG 40, PEG -50, PEG- 55).The most commonly used non-ionic surfactants are ethers of fatty Alcohols.

Glycerine fatty acid esters (Monoglyceride, MG) [45]:

Glycerine fatty acid ester is obtained from glycerine and animal and plant oils/fats or their fatty acids. These are generally produced by the Inter-esterification method. Glycerine has three hydroxyl groups, one of which is esterified with the fatty acid and an ester is called mono glyceride. Di- and tri-glyceride have two and three fatty acid groups esterified at hydroxyl groups.

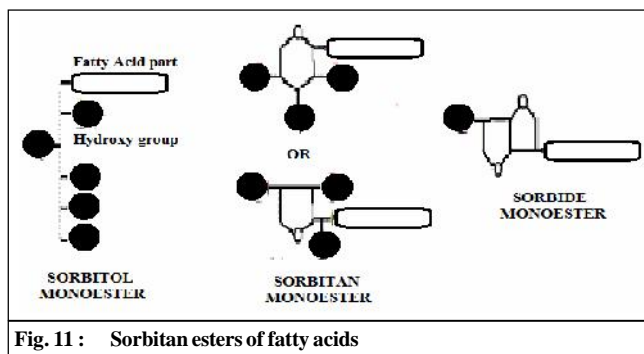


Glycerine fatty acid ester produced by inter-esterification is a mixture of glycerine and these glycerides. Since mono glyceride with a strong surface activity is suitable as an emulsifier, then mono and di-glyceride is produced by removing the glycerine from the mixture. Furthermore, to enhance functionality, a highly-purified mono glyceride, called Distilled Mono glyceride, is produced by molecular distillation which is used as an emulsifier for foaming agent, anti-foaming agent, starch-modifying agent and anti-bacterial agent.



Sorbitan esters of fatty acids (Sorbitan ester) [46]:

Sorbitan ester which is sorbitan esters of fatty acid is produced by the esterification of sorbitol and fatty acid. Sorbitan ester is a mixture of sorbitol ester and sorbide ester. There are many types of sorbitan esters with different kinds of fatty acids and various degrees of esterification. These are generally used as an emulsifier in creams and lotions. It has a limited number of applications other than emulsifier. However, it is widely used as a major emulsifier in combination with other co emulsifiers with different functions.



Amphoteric/Zwitterionic emulsifiers [47]:

These are a type of surfactants which are very mild, thereby making them particularly suitable for use in personal care preparations over sensitive skins. They can be anionic (negatively charged), cationic (positively charged) or non-ionic (no charge) in solution(s), depending on the acidity or pH of the water. These emulsifiers may contain two charged groups of different sign among which the positive charge is almost always ammonium but the source of the negative charge may vary (carboxylate, sulphate and sulphate(s)). These surfactants have excellent dermatological properties. Because of their high foaming properties, they are frequently used in shampoos, other cosmetic products and also in hand dishwashing liquids.

Natural emulsifying agents [48]:

A variety of emulsifiers are natural products which are derived from plant or animal tissue. And Most of the emulsifiers form hydrated lyophilic colloids (called hydrocolloids) that form multimolecular layers around emulsion droplets. Hydrocolloid type of emulsifiers have little or no effect on interfacial tension, but exert have a protective colloidal effect, reducing the potential for coalescence, so they're by

- Quality of providing a protective sheath around the droplets.
 - The imparting a charge to the dispersed droplets (so that they repel each other).
 - Quality of swelling to increase the viscosity of the system (so that droplets are less likely to merge).
- Hydro colloidal emulsifiers may be classified as:
- vegetable derivatives, Examples like acacia, agar, pectin, carrageenan, lecithin.
 - animal derivatives, for examples lanolin, cholesterol
 - Semi-synthetic agents, like methylcellulose, carboxy methyl cellulose.
 - Synthetic agents, like Carbopols®.

Vegetable derivatives :

Naturally occurring plant hydrocolloids have the

advantages of being a non-expensive, easy to handle, and nontoxic. Their disadvantages include they require relatively large quantities to be effective as emulsifiers, and they are usually prone to microbial growth and this is overcome by using a preservative systems. Vegetable derivatives are generally limited to use as emulsifiers in o/w emulsion.

Acacia[49]:

Chemically, acacia (also called as Gum Arabic) is a complex mixture of macro molecules of different size and its composition mainly includes carbohydrates and proteins. The properties and features of acacia have been explored widely and developed. It is being used in a wide range of industrial sectors like ceramics, textiles, lithography, cosmetics and pharmaceuticals, encapsulation, food, etc. In food industry, it is being used as a stabilizer, a thickener and/or an emulsifier agent (examples like, soft drink syrup, gummy candies and creams). In the industry of pharmaceutical, acacia is used as an emulsifier in pharmaceutical preparations and as a carrier of drugs since it is physiologically inert. It also possess anti-oxidant properties [50].

Carrageenan [51] :

This is a natural emulsifier which will be used for various applications. Carrageenan is a family of linear sulfated polysaccharides which are extracted from red seaweeds. There are many varieties of carrageenan. A variety called Kappa-carrageenan has gelling nature. Lambda carrageenan is a non-gelling in nature which assists in binding; it retains moisture, and contributes to viscosity in preparations. Applications of carrageenan include its use as binder, thickening agent, and as a stabilizer in medications, toothpastes and foods.

Pectin [52]:

Pectin is a natural substance and it is a component of middle lamella and primary cell wall of all fruits and vegetables. It is hydrocolloid in nature and has good swelling ability. Pectin is poly galacturonic acid which is mainly formed with D-galacturonic acid molecules which are linked to each other by a (1, 4)-glycosidic bonds. The carboxyl groups of pectin are partially esterified with methanol. In some cases the secondary alcohol groups of the pectins also carry acetyl groups. The hydrocolloid pectin is widely used as gelling and thickening agent in the food industry for many years.

Animal derivatives:

Lecithin [53] :

Lecithins are natural compounds prepared by extracting and purifying phospholipids [54] from naturally occurring

products such as sunflower, soybeans, eggs and canola seeds. These are amphiphilic (they do have different affinities for oil and water), and also their low production costs make them invaluable in a broad range of manufacturing processes. These are used mainly as emulsifiers. They are surface-active; simultaneous hydrophilic (water-loving) and hydrophobic (water-repelling) properties enable lecithin to make stable blends of materials which otherwise do not mix easily and tend to separate.

The animal derivatives general form water in oil (w/o) emulsions. The Lecithin and cholesterol form a monomolecular layer around the emulsion droplet instead of the typically multimolecular layers. Lanolin consists of approximately 95% esters, 4% free alcohols, and free fatty acids and hydrocarbons. The ability of lanolin to form w/o emulsions is due to the free alcohol and fatty acid content. Cholesterol is a major constituent of wool alcohols and it gives lanolin the capacity to absorb water and form a w/o emulsion. Lecithin [55] (a phospholipid derived from egg yolk) produces o/w emulsions because of its strong hydrophilic character. An animal derivative is more likely to cause allergic reactions and is subjected to microbial growth and also rancidity. Their advantage(s) is in their ability to support formation of w/o emulsions.

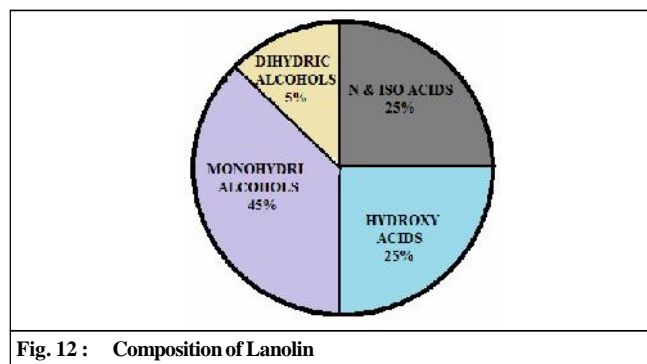


Fig. 12 : Composition of Lanolin

Semi-synthetic agents [56]:

These are stronger emulsifiers, nontoxic, and are less prone to microbial growth. These include methylcellulose and carboxy methyl cellulose.

Methylcellulose (MC) [57]:

It is one of the most widely used cellulose. This polymer is a white powder having little or no odour or taste. Methylcellulose has no ionic charge; hence, the viscosity of its solutions is mostly not affected by pH. However, small amounts of salts can increase the viscosity of solutions. It is considered as stable for many applications over a pH range of 3 to 11. The degree of water retention ranges from 5 to 12% by weight. The polymer will form a clear, flexible film which acts as a barrier to oils and greases. Most commercially

available methyl celluloses have a relatively high degree of substitution, which makes them comparatively enzyme-resistant.

In industry, MC is used as a thickener, as a binder and lubricant, and as a suspension aid and emulsifier. It is metabolically inert and hence used in pharmaceuticals and prepared foods.

Carboxy methyl cellulose [58]:

Cellulose is commonly converted into other useful derivatives by the method of etherification. Carboxy methyl cellulose (CMC) which is a water soluble derivative, has many applications in the food, cosmetics, pharmaceutical and detergents industries, and so on., The modified cellulose is a linear, long chain, water-soluble, anionic, polysaccharide. Purified CMC is a white to cream colored, tasteless, odorless, free-flowing powder. CMC is useful in systems where hydrophilic colloids are involved, where they show ability to suspend solids in media of aqueous, stabilize emulsions, absorb moisture from the atmosphere, solubilize proteins (milk proteins, egg proteins), thicken solutions (sugar solutions, paints) and form films. CMC also gives good enteric coatings for powders and tablets.

Synthetic agents:

Synthetic hydrocolloids are the strongest emulsifiers, which are nontoxic, and do not support microbial growth. Most of the synthetic agents are generally limited to use as o/w emulsifiers.

Carbopol[59]:

These are all classified as polymers of acrylic acid which are cross-linked with polyalkenyl ethers or divinyl glycols. They are all produced from primary polymer particles whose average diameter was about 0.2 to 6 micron. Each primary particle can be viewed as a network structure of polymer chains which are interconnected by cross-linkages. Without of these the cross-links, the primary particle would be a collection of linear polymer chains intertwined but not chemically bonded. Carbopol polymers are all cross-linked along with Pemulen and Noveon polymers. They swell in water up to 1000 times their original volume and upto 10 times their original diameter to form a gel when exposed to a pH environment more than 4.0 to 6.0.

The readily water-swell able polymers (Carbopol) are used in a diverse range of pharmaceutical applications as follows

- These polymers are used to provide controlled release of drug in tablets.
- They also provide bio adhesion in ophthalmic, intestinal, nasal, vaginal, and rectal applications.

- They act as thickening agent at very low concentrations (less than 1%) and can be used in topical lotions, creams and gels, oral suspensions, and in transdermal gel reservoirs.

- They are used in emulsifying topical oil-in-water systems permanently, even at elevated temperatures, with essentially no need for irritating surfactants.

Advantages of natural emulsifiers over synthetic emulsifiers :

- Natural products are easily available, cost effective, and biocompatible.

- Naturally available materials are often similar, if not identical to macromolecular materials; the biological environment can recognize and process through metabolic pathways.

- Naturally available materials can function biologically at the molecular level, not just macroscopic level.

- The Inflammatory response invoked by synthetic material is suppressed with natural materials.

- Some of the synthetic emulsifiers are used in the topical applications like Betaine, carbomer, carboxymethyl cellulose, cetaryl alcohol, cocobetaine, ethyl acetate, glyceryldialate, PEG family, sorbitane stearate etc., generally these Emulsifiers can have a mild skin & eye irritant. They can react with nitrites to form highly potent carcinogenic nitrosamines. These Nitrosamines have been shown to readily penetrate the skin.

- Detergents like DEA-based, the most commonly used chemicals in cosmetics under the names Cocamide DEA or MEA, Lauramide DEA etc. It is present in all kinds of detergents, liquid soaps, polishers, cutting oils, and lubricating liquids, as a solvent for numerous drugs and household cleaning products. It is a mild skin and severe eye irritant and can react with nitrites to form highly potent carcinogenic nitrosamines. They have been shown to readily penetrate the skin. NDELA (a nitrosamine) was found in 27 of the 29 products tested in 2 surveys in 1991. Repeatedly skin applications of DEA-based detergents resulted in a major cancers like liver and kidney cancers. NTP (Federal National Toxicology Program) emphasized that not only DEA readily absorbs through the skin, but also accumulates in organs such as the brain, where it can produce toxic effects.

Due to safety concerns of the synthetic emulsifiers the importance of Natural Emulsifiers has been increased.

Finely divided or finely dispersed solid particle emulsifiers [60] :

These agents form a particulate layer around the dispersed particles. Most of these agents usually swell in the dispersion medium thereby increasing viscosity and

reducing the interaction between dispersed droplets. Most commonly these agents support the formation of o/w emulsions, but some may also form w/o emulsions. These agents include bentonite[61], veegum, magnesium hydroxide, hectorite, aluminum hydroxide and trisilicates of magnesium.

Bentonite:

It is chemically aluminium phyllosilicate which is used as an adsorbent. It is an impure clay consisting mostly of montmorillonite. There are different types of bentonite, which are named after the respective dominant element, such as potassium (K), sodium (Na), calcium (Ca), and aluminium (Al). The larger surface area of bentonite is utilized for its applications as a chemical, insecticide carrier. Surface area is also of primary importance towards bentonite application as an emulsifier and as an emulsion stabilizer.

Auxillary:

A variety of fatty acids (stearic acid), fatty alcohols (stearyl or cetyl alcohol), and fatty esters (glyceryl mono stearate) are being used to stabilize emulsions through their ability to thicken the emulsions. Since these agents have poor emulsifying properties, So, they are always used in combination with other co - emulsifiers.

A system called the HLB (hydrophile-lipophile balance) system [62] has been developed to make decisions about amounts and types of surfactants needed to be used in stable products. The system has an arbitrary scale of 1 - 18. These HLB numbers are experimentally determined for various emulsifiers. If an emulsifier has a low HLB number, it implies that there is low number of hydrophilic groups on the molecule and it possesses more lipophilic character. The higher HLB number indicates that emulsifier has a large number of hydrophilic groups on the molecule and therefore would be more hydrophilic in character. The Tweens have higher HLB numbers and they are also use as water soluble agents. Because of their water soluble character, Tweens make the water phase predominate and form an o/w emulsion.

The combinations of emulsifiers can produce more stable emulsions than using a single emulsifier with the same HLB number. The HLB value for a combination of emulsifiers can be calculated as follows:

$$\text{HLB} = \frac{(\text{Quantity of surfactant 1})(\text{HLB surfactant 1}) + (\text{Quantity of surfactant 2})(\text{HLB surfactant 2})}{\text{Quantity of surfactant 1} + \text{quantity of surfactant 2}}$$

Classification based on mechanism of action:

Monomolecular adsorption [63]:

Emulsifier is a molecule with two parts, one is hydrophilic and the other one is hydrophobic. In monomolecular adsorption, upon addition of emulsifier, tend to form a monolayer film at the oil/water interface.

Multimolecular adsorption:

The category of this includes hydrophilic colloids which stabilize the emulsions by forming multimolecular adsorption at the oil/ water emulsions interface. They have low effect on the surface tension. They mainly act as emulsion stabilizers by forming a coherent multi-molecular film which is strong and resistant to coalescence. They also exert their effect by increasing the viscosity of dispersion medium. Most of the hydrophilic colloids form oil-in-water emulsions.

Solid particle adsorption:

In this mechanism of stabilization of emulsion, finely divided solid particles are adsorbed at the surface of emulsion droplet thereby stabilize it. These particles are wetted by both oil and water (but not dissolved) and form a particulate film that prevent the coalescence. Particles that are wetted preferentially by water form o/w of emulsion(s), whereas those wetted more by oil form w/o emulsion.

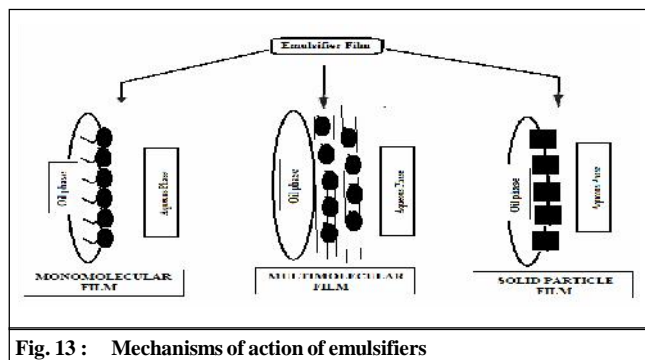


Fig. 13 : Mechanisms of action of emulsifiers

Conclusion:

From the above studies, it can be concluded that emulsions are a very wide category of dosage forms which helps in delivery of drugs. With the help of these emulsions, one can achieve complete biodegradability, increasing drug dosing intervals, and also taste masking of bitter drugs. It is important to note that with emulsions we can entrap both hydrophilic and hydrophobic drugs. It was also found that the drugs can be protected from endogenous factors by preparing them as emulsions. Further studies are to be carried out to overcome the problem of short shelf life of emulsions. A marketing artifice if possible has to be developed as these emulsions are packed only in plastic or glass containers.

Acknowledgement:

Sincere thanks to The Himalaya drug company, Bangalore and also special thanks to Dr. DVS Gowda, professor, JSS Pharmacy college and Dr. KrishanManral, Head-Analytical cosmetic (R&D), The Himalaya Drug company, Bangalore.

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