Review Article

EMULSION TECHNOLOGY AND RECENT TRENDS IN EMULSION APPLICATIONS

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Article Received on: 27/05/14 Revised on: 28/06/14 Approved for publication: 07/07/14

DOI: 10.7897/2230-8407.0507108

ABSTRACT

Emulsions are thermodynamically unstable heterogeneous biphasic system. There are certain parameters which if an emulsion follows are considered as stable. There are lots of signs of physical and chemical instability of emulsion such as creaming, cracking, phase inversion, flocculation. There are several methods of detecting stability of prepared emulsion. Rheological assessment, macroscopic examination, globule size analysis and accelerated stability test. Many types of emulsifying agents are interfacial tension, film formation and electric potential and emulsion rheology. Emulgents form three types of films around dispersed phase globules: monomolecular, multimolecular and particulate film. Regarding the improvement in the effectiveness and stability, several enhancements have been made in emulsion technology: micro emulsion, multiple emulsions, non aqueous emulsions, liposome emulsions, nanoemulsions and emulsions polymerization are few advances with the advancement in application of emulsion incorporated in this review.

Keywords: Emulsion, Creaming, Cracking, Micro emulsion, Physical stability, Liposome emulsion, Nano emulsion.

INTRODUCTION

The term emulsion is derived from the word *emulgeo* meaning “to milk”. Milk is an example of a natural emulsion. An emulsion is a biphasic liquid preparation having two immiscible liquids, which cannot be dispersed for a long period. An emulsifying agent is added, which forms a film around the globules, so that a stable emulsion is produced. The size of globules is 0.25 to 25 μm diameters. Micro-emulsions are the globules of smaller diameter as small as 10 nm, which in appearance is milky and transparent. Transparent emulsion is formed when two phases having same refractive index. Emulsions are thermodynamically unstable and revert back to separate oil and water phase.¹ When two immiscible liquids are mechanically agitated, both phases initially tend to form droplets. When the agitation is stopped, the droplets quickly coalesce, and the two liquids separate. The lifetime of the droplets is materially increased if an emulsifier is added to the two immiscible liquids. Usually only one phase persists in droplet form for a prolonged period of time. This phase is called the internal phase and it is surrounded by the external phase. An assembly of close packed mono-dispersed spherical droplets as the internal phase can occupy not more than approximately 74 % of the total volume of an emulsion. It is evident that the internal phase can exceed 74 % if the spherical particles are not mono-dispersed. A further increase in the ratio of internal and external phase can result if the internal phase is assumed to consist of polyhedra rather than spheres. It is almost universally accepted that the term emulsion should be limited to liquid systems.² Emulsions are normally formed by “mixing” two immiscible liquids. It is necessary that the two phases are heated to ensure that they are liquids during emulsification. The most common types of pharmaceutical or cosmetic emulsions include water as one of the phases and an oil and lipid as the other. Since approximately 1978, two additional types of emulsion classified as multiple emulsions with the characteristics of oil in water in oil (O/W/O) or of water in oil in water (W/O/W) emulsions. Such emulsions

also can invert during inversion, they usually form simple emulsion.³

Ideal properties

An emulsion is called stable if it carries following properties

- It should consist of uniform dispersion of fine and mono-sized droplets of internal phase, which should not aggregate and if they do, must not coalesce to form large droplet.
- The internal droplets should not cream up or down and if they do, the cream layer should be re-dispersible.
- Without phase inversion, it should remain in its original type.
- It should be not regarded by microbes on storage.
- It should be stable at various temperatures.
- It should not rancid or degraded due to oxidation. Exp. Oil and Fats.⁴

Type of Emulsion

Emulsions are of two types

1. Oil in water type (o/w).
2. Water in oil type (w/o).

In oil in water type emulsion, oil is dispersed phase and water is continuous phase. These are mostly used internally. Emulsifying bases used in this type are gum acacia, tragacanth, methyl cellulose, saponins, synthetic substances, etc. When the oil phase is dispersed as globules throughout an aqueous continuous phase, the system is referred to as an O/W emulsion. An O/W emulsion is formed if the aqueous phase constitutes more than 45 % of total weight and if a hydrophilic emulsifier is used. It employs the following emulsifiers: sodium lauryl sulfate, sodium oleate and glyceryl monostearate.¹ In water in oil type emulsion, water is dispersed phase and oil is continuous phase. Emulsifying bases used in this type are wool fat, resins, beeswax and soaps. These are mostly used externally as creams and lotions. It employs the following emulsifiers: spans, cholesterol and

wool fats. When an aqueous phase is dispersed as globules and the oil phase serve as the continuous phase, the emulsion is termed as W/O emulsion.²

Figure 1: Types of Emulsion

Instability of Emulsion

Thermodynamic stability of emulsions differs from stability as defined by the formulators or the consumers on the basis of entirely subjective judgments. Acceptable stability in the pharmaceutical dosage form does not require thermodynamic stability. If an emulsion rises or cream down or sediments, it may still be pharmaceutically acceptable as long as it can be reconstituted by a modest amount of shaking. According to this, the instability of the emulsion can be divided into two parts.²

Instability of Emulsion

Physical Instability of emulsion

Probably the most important consideration with respect to pharmaceutical and cosmetic emulsions is the stability of the finished product. The stability of a pharmaceutical emulsion is characterized by the absence of coalescence of the internal phase, absence of creaming and maintenance of elegance with respect to appearance, odor, color and other physical properties. Some workers define instability of an emulsion only in terms of agglomeration of the internal phase and its separation from the product. Creaming, resulting from flocculation and concentration of the globules of the internal phase, some times is not considered as a mark of emulsion.²

Symptoms of instability

As soon as an emulsion has been prepared, time and temperature dependent processes occur to effect its separation during storage; an emulsion's instability is evidenced by creaming, reversible aggregation and irreversible aggregation.

- Cracking
- Creaming
- Phase inversion
- Flocculation

Cracking

Cracking of an emulsion refers to separation of dispersed phase and continuous phase, due to coalescence of dispersed phase globules which are difficult to re-disperse by shaking. Coalescence is a growth process during which the emulsified particles join to form large particles. This process is also

known as cracking. Any chemical, physical or biological effects that change the nature of the interfacial film of an emulsifying agent may cause cracking. Coalescence, the complete fusion of droplets leads to a decrease in the number of droplets and the ultimate separation of the two immiscible phases. Aggregation precedes coalescence in emulsions; however, coalescence does not necessarily follow from aggregation. Aggregation is to some extent, reversible. Although it is not as serious as coalescence, it will accelerate creaming or sedimentation, because the aggregate behaves as a single drop. Cracking of the emulsion may be due to Addition of an emulsifier of opposite nature, Decomposition or precipitation of emulsifier, Addition of a common solvent in which both oily and aqueous phases are miscible, Extremes of Temperature, presence of Micro organisms and due to Creaming.^{1,5}

Creaming

Creaming may be defined as the upward movement of dispersed globules to form a thick layer at the surface of the emulsion. Creaming is a temporary phase because it can be re-distributed by mild shaking or stirring to get again a homogeneous emulsion; as far as possible creaming of an emulsion should be avoided because it may lead to cracking with complete separation of two phases. Under the influence of gravity suspended particles or globules tend to upward movement, known as creaming while downward movement of particles or droplets is called sedimentation. Creaming or sedimentation depends on the differences in specific gravity between the phases. The rate at which a spherical droplet or particle sediments in a liquid is governed by Stokes' law. Other equations have been developed for bulk system, but Stokes' equation is still useful because it points out the factors that influence the rate of sedimentation. These are diameters of the suspended droplets, the viscosity of the suspending medium and the difference in densities between the dispersed phase and dispersion medium.^{2,5} According to Stokes' law, the rate of creaming depends on the number of factors which can be explained by the following equation

$$V = \frac{2r^2(\Delta\rho)g}{9\eta}$$

V = Rate of creaming, R = Radius of globules, G = Gravitational constant,
 $\Delta\rho$ = Density difference between the two phases,
 η = Viscosity of the continuous phase.

The rate of creaming is

- Directly proportional to the density difference between the oil and water phase ($\Delta\rho$)
- Directly proportional to the square of the radius of globules r^2
- Inversely proportional to the viscosity of dispersion medium η

Phase inversion

When controlled properly during the preparation of an emulsion, phase inversion often results in a finer product, but when it gets out of hand during manufacturing or is brought about by other factor after the emulsion is formed it can cause considerable trouble. Phase inversion means the change of one type of emulsion into the other type that is oil in water emulsion changes into water in oil type and vice versa. The temperature at which the inversion occurs depends on the emulsifier concentration and is called Phase Inversion

Temperature (PIT). An o/w emulsion stabilized by a non-ionic polyoxyethylene-derived surfactant contains oil-swollen micelles of the surfactant as well as emulsifying oil. Inversion often can be seen when an emulsion, prepared by heating and mixing the two phases, it being cooled. This takes place presumably because of the temperature dependent changes in the solubility's of the emulsifying agents. It may be due to following reason

- By the addition of an electrolyte
- By changing the phase-volume ratio
- By temperature change
- By changing the emulsifying agent

The phase inversion can be minimized by keeping the concentration of dispersed phase between 30 to 60 percent storing the emulsion in a cool place and by using proper emulsifying agent in adequate concentration^{1,2,5}

Flocculation and Its Prevention

Flocculation involves the aggregation of the dispersed globules into loose clusters within the emulsion. The individual droplets retain their identities but each cluster behaves physically as a single unit. This would increase the rate of creaming. As flocculation must precede coalescence, any factor preventing or retarding flocculation would therefore maintain the stability of the emulsion. Flocculation in the secondary minimum occurs readily and cannot be avoided. Re dispersion can easily be achieved by shaking. Primary minimum flocculation, however, is more serious and re dispersion is not so easy. The presence of a high charge density on the dispersed droplets will ensure the presence of a high energy barrier, and thus reduce the incidence of flocculation in the primary minimum. Care must be taken to ensure that the effects of any ions in the product are taken into consideration very early in the formulation process. This is particularly important when formulating emulsions for parenteral nutrition which contain high levels of electrolyte.⁶

Chemical instability

Chemical instability of an emulsion causes coalescence of particles of emulsion. It is necessary to insure that any emulgent system use is not only physically but also chemically compatible with the active agent and with the other emulsion ingredients. Anionic and cationic emulgents are thus mutually incompatible. It has already been demonstrated that the presence of electrolyte can influence the stability of an emulsion either by

- Reducing the energy of interaction between adjacent globules
- A salting out effect, by which high concentration of electrolyte can strip emulsifying agents of their hydrated layers and so cause their precipitation.

Change in pH may also lead to the breaking of emulsion. Soap stabilized emulsions are therefore usually formulated at an alkaline pH. Environmental conditions, such as the presence of light, air, contaminating microbes adversely affect the stability of an emulsion. For light sensitive emulsion, light resistance container is used. For emulsion susceptible to oxidative decomposition, anti oxidants may be included in the formulation and adequate label warning provided to ensure that the container is tightly closed to air

after each use. Many molds, yeasts, and bacteria can decompose the emulsifying agent, disrupting the system. Even if the emulsifier is not affected by the microbes, the product can be rendered unsightly by their presence and growth and will not off course not be efficacious from a pharmaceutical or therapeutic point. Because fungi (molds and yeasts) are more likely to contaminate emulsion than are bacteria, fungi static preservatives, commonly combinations of methylparaben and propylparaben are generally included in the aqueous phase of an o/w emulsion. Alcohol in the amount of 12 % to 15 % based on the external phase volume is frequently added to oral o/w emulsion for preservation.⁷ Chemical instability is of three types namely:

- Oxidation
- Microbial contamination
- Adverse storage condition.

Oxidation

Many of the oils and fats used in emulsion formulation are of animal or vegetable origin and can be susceptible to oxidation by atmospheric oxygen or by the action of micro organisms. Oxidation of microbiological origin is controlled by the use of anti microbial preservatives and atmospheric oxidation by the use of reducing agents or more usually, anti oxidants like butylatedhydroxyanisole (BHA) is widely used in the protection of fixed oil and fats at concentration of up to 0.02 % and for some essential oils up to 0.1 %. The efficiency of an anti oxidant in a product will depend on many factors, including: (1) Its compatibility with other ingredients (2) its O/W partition coefficient (3) the extent of its solubilization within micelles of the emulgent (4) its sorption on to the containers and its closure.

Microbial contamination

Microbial contamination of emulsion occurs by micro organisms can adversely effect the physicochemical properties of the product, causing such problem as gas production, color and odor changes, hydrolysis of fat and oils, pH changes in the aqueous phase and breaking of the emulsion. An emulsion can contain many bacteria and if these include pathogens may constitute a serious health hazard and most fungi and many bacteria will multiply readily in the aqueous phase of an emulsion at room temperature. Many moulds will also tolerate a wide pH range. Species of the genus *Pseudomonas* can utilize polysorbates, aliphatic hydro carbons and compounds. Some fixed oils such as arachis oil, can be used by some *aspergillus* and *rhizopus* species, and liquid paraffin by some species of penicillium.^{6,7} Water in oil product have less chances of microbial spoilage as compared to oil in water emulsion as in the latter case the continuous oil phase act as a barrier to the spread of micro organisms throughout the product, and less water there is present the less growth there is likely to be. It is necessary to include an anti microbial agent to prevent the growth of any micro organisms that might contaminate the product. Example, because fungi are more likely to contaminate emulsion than are bacteria, fungi static preservatives, commonly contamination of methyl paraben and propyl paraben are generally included in the aqueous phase of an oil in water emulsion.⁸

Adverse storage condition

Adverse storage conditions may also cause emulsion instability by increase in temperature that cause increasing

rate of creaming, owing to a fall in apparent viscosity of the continuous phase. Increase in temperature cause an increased kinetic motion, both of the dispersed droplet and of the emulsifying agent at the oil in water interface. Increased motion of the emulgent will result in a more expended monolayer and so coalescence of more likely. Certain macro molecules emulsifying agents may also be coagulated by an increase in temperature. Freezing of the aqueous phase will produce ice crystals that may exert a pressure on the disposed globules and their absorbed layer of emulgent. In addition, dissolved electrolyte may concentrate in the unfrozen water, thus affecting the charge density on the globules. Certain emulgents may also precipitate at low temperature. The growth of micro organisms within the emulsion can cause deterioration and it is therefore essential that these products are protected as far as possible from the ingress of micro organisms during manufacture, storage and use.^{7,8}

Evaluation of Emulsion

Evaluation of an emulsion can be determined by various methods. Some method was given below:

- Dilution Test
- Dye Test
- Conductivity Test
- Fluorescence Test
- Macroscopic examination
- Globule size analysis
- Accelerated stability testing

Dilution test

Emulsions are diluted with water, if it remains stable after dilution, so it is oil in water type, if emulsion breaks after dilution i.e. water in oil type. The test is based on the fact that more of the continuous phase can be added into an emulsion without causing the problem of its stability.

Dye test

In dye test scarlet red dye is used. Red dye is mixed with emulsion. One drop of emulsion place under on microscope slide. If globules appear red and ground is colorless, than the emulsion is water in oil type.

Conductivity test

In this test pair of electrodes connected to a lamp and an electric source is dipped in emulsion. If the emulsion is oil in water type then lamp glows. If lamp does not glow then the emulsion is water in oil type.

Fluorescence test

Many oils exhibits fluorescence when exposed to UV light when water in oil type emulsion is exposed to fluorescence light under a microscope, the entire field fluoresces. If the emulsion is spotty, the emulsion is of oil in water type.^{1,7,9}

Macroscopic examination

Testing of physical stability of an emulsion is examined by degree of creaming or coalescence occurring over a period of time. This is carried out by calculating the ration of volume of the creamed or separated part of the emulsion and the total volume. These values can be compared for different products.

Globule size analysis

If the mean globule size increases with time, it can be assumed that the coalescence is the cause. It is possible to compare the rates of coalescence of a variety of emulsion formulations by this method. Microscopic examination or electronic particle counting device, such as the coulter current or laser diffraction sizing are most widely used.

Accelerated stability testing

A drug substance should be evaluated under storage condition that tests its thermal stability and its sensitivity to moisture. The storage condition and the lengths of the studies chosen should be sufficient to cover storage, shipment and subsequent use. The long term testing should cover a minimum of 12 months duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed retest period. Data from the accelerated storage condition and if appropriate, from the intermediate storage condition can be used to evaluate the effect of short term excursions outside the label storage condition. The accelerated storage condition according to ICH guidelines was given in table below:

Table 1: Storage condition according to ICH guidelines

Study	Storage condition	Minimum time period covered by data at submission
Long term*	25°C ± 2°C/60 % RH ± 5 % RH or 30°C ± 2°C/65 % RH ± 5 % RH	12 months
Intermediate**	30°C ± 2°C/65 % RH ± 5 % RH	6 months
Accelerated	40°C ± 2°C/75 % RH ± 5 % RH	6 months ¹⁰

*It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60 % RH ± 5 % RH or 30°C ± 2°C/65 % RH ± 5 % RH.

**If 30°C ± 2°C/65 % RH ± 5 % RH is the long-term condition, there is no intermediate condition.

Table 2: Drug substances intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C ± 3°C	12 months
Accelerated	25°C ± 2°C/60 % RH ± 5 % RH	6 months

Storage at adverse temperature

Emulsion must be protected from extreme of cold and heat. Freezing and thawing coarsen and emulsion and sometime break it; excessive heat has the same effect. Emulsion products transported in various locations with different climates of extremely high or low temperature. The industry performs tests at 5 °C, 40 °C and 50 °C to determine

the product stability. Stability at 5 °C and 40 °C for three months is considered minimal. Shorter exposure periods at 50 °C may be used as alternative test. Temperature cycles consisting of storage for several hours at about 40 °C, followed by refrigeration or freezing until instability becomes evident, have been used successfully. The continual formation and melting of small ice crystals will disrupt the

absorbed layer of emulgent at the oil in water interface and any weakness in the structure of the film will quickly become apparent.^{7,10}

Emulsifying Agents

Emulgents can impart stability to such systems. Thus the choice of an emulgents is a critical factor since the quality and stability of the emulsion. System can be directly related to the type of Emulgent employed. Emulgents are broadly classified as surfactants like spans and tweens, hydrophilic colloids such as acacia and finally divided solids. Exp. Bentonite and Veegum.^{2,9} Properties of emulgents are

- It should able to reduce surface tension below 10 dyne/cm.
- It should be absorbed rapidly around dispersed phase.
- It should help in building adequate zeta potential and viscosity in the system so impart optimum stability.
- It should be effective in fairly low concentration.

Principal of emulsifying agents

Interfacial Tension

Even though reduction of interfacial tension lowers the interfacial free energy produced on dispersion, it is the role of emulsifying agents as interfacial barriers that is most important. Emulsion have tendency to attain a thermodynamically stable state by way of coalescence in the dispersed phase and ultimately separation of the two phases.

If the globules are spheres than:
$$\Delta f = \frac{6 \gamma v}{d}$$

Δf -Increase in surface free energy, V-volume of dispersed phase,
D-Mean diameter of globules, γ -Interfacial tension between dispersed phase globules and dispersion medium

Film formation

The formation of films by an emulsifier on the surface of water or oil droplets has been studied in great detail. The concept of an oriented film of the emulsifier on the surface of the internal phase of an emulsion is of fundamental importance to an understanding of most theories of emulsification. The ability to readily form a film around each dispersed globule is one of the most important requirements of an efficient emulgent. A good film should not thin out and rupture when sandwiched between the globules and if broken it should reform readily. The film can be monolayer, multilayer or particulate one. Film produced additional repulsive force between droplets to contract attractive Vander walls forces and inhibits the close approach of droplets. Provide barriers to coalescence of droplets in close proximity particularly if the film is closed packed and elastic. Surfactant interfacial films also lower the interfacial tension of oil and water. The film pressure that cause the film to collapse in termed the collapse pressure and indicate the strength of film.^{1,2,7,9}

Figure 2: Film Formation

Emulsion forms three type of films that are as follows

1. Monomolecular Film
2. Multi molecular Film
3. Solid Particle Film

Monomolecular Film

Surfactant absorbs at oil in water interface and form monomolecular film. The film rapidly envelopes the droplets as soon as they are formed. Monomolecular film should be compact and strong enough so that it can not easily distributed or broken. Combination of emulgents is used higher today. Combination consists of a pre dominantly hydrophilic emulgent in aqueous phase and hydrophobic agents in the oily phase to form a complex film. It is assumed that they support each other and strengthen the monomolecular film. Surface active agents or amphiphiles, reduce interfacial tension because of their absorption at the oil water interface to form monomolecular film. The reduction in surface free energy is of itself probably not the main factor involved. Of more lightly significance is the fact that the dispersed droplets are surrounded by a coherent monolayer that helps to prevent coalescence between two droplets as they approach one other. Ideally, such a film should be flexible so that it is capable of reforming rapidly if broken or distributed. An additional effect promoting stability is the presence of a surface charge which will cause repulsion between adjacent particles.¹¹ The type of emulsion that is produced, oil in water or water in oil depends primarily on the property of the emulsifying agents. This characteristic is referred to as the hydrophile-lipophile balance (HLB), that is, the polar-non polar nature of the emulsifier. In fact, whether surfactant is an emulsifier, wetting agent, detergent, or solubilizing agent can be predicted from knowledge of the hydrophile-lipophile balance, as discussed in the previous chapter. In the emulsifying agent such as sodium stearate, $C_{17}H_{35}COONa$, the non polar hydrocarbon chain, $C_{17}H_{35}$ is the lipophilic or oil-loving group, the carboxyl group, $-COONa$ is the hydrophilic and lipophilic properties of emulsifier determines whether an oil in water or water in oil emulsion will result. In general, oil in water emulsion are formed when the HLB of the emulsifier is within the range of about 9 to 12 and water in oil emulsions are formed when the range is about 3 to 6.³ This concept is illustrated by the classic study of Schulman and Cockbain. They found that oil in water emulsion stabilized by mixture of sodium cetyl sulfate and cholesterol, which were known from other experiments to form rigid and tightly packed films were extremely stable. When oleyl alcohol was substituted for

cholesterol, however, the steric effect of a double bond resulted in the formation of a poor interfacial complex, and emulsion stability was proportionally low. On the other hand, if this last system was changed somewhat by using sodium oleate and cetyl alcohol, it was possible to obtain a rather poor emulsion, but one that was more stable than that of the previous case. The ability of mixture of emulsifier to pack more tightly contributes to the strength of the film and hence, to the stability of the emulsion. Most emulsifier probably form fairly dense gel structures at the interface and produce a stable interfacial film.^{2,7}

Figure 3: Film Formation (Monomolecular, Multimolecular, Solid Particle)

Multi molecular Film

The emulsifying agents such as acacia and gelatin tend to form a multimolecular film around the globules and prevent from coalescence. They also reduce the interfacial tension they are effective at high concentration. They also have affinity towards the oil phase and facilitate interfacial absorption. The stability is improved by adding viscosity including agents such as tragacanth, methyl cellulose etc. They differ, however, from the synthetic surface-active agents in that (1) they do not cause an appreciable lowering of interfacial tension (2) they form a multi-rather than a monomolecular film at the interface. Their action as emulsifying agents is due mainly to the latter effect because the films thus formed are strong and resist coalescence. An auxiliary effect promotes stability in the significant increase in viscosity of dispersion medium. Because the emulsifying agents that form multi layer films around the droplets are invariably hydrophilic, they tend to promote the formation of oil in water emulsions.¹⁰

Solid Particle Film

The finally divided solid particles that are wetted to some degree by both oil and water can act as emulsifying agents. This results from their being concentrated at the interface where they produce a particular film around the dispersed droplets so as to prevent coalescence. Powders that are wetted preferentially by water form oil in water emulsion whereas those more easily wetted by oil form water in oil emulsions. Particles absorbed at oil water interface and form a rigid film of closely packed. Solids this film act as a mechanical barrier and prevent the coalescence globules

these tend to produce coarse emulsion depending on affinity of emulsifier to a particular phase. One can prepare both type of emulsions example Bentonite (hydrated aluminum silicate ph.-9 O/W and W/O), Veegum (Magnesium aluminum silicate O/W) etc.^{1,3,9}

Electrical Potential

The same or similar film can produce repulsive electrical forces between approaching droplets. Such repulsion is due to an electrical double layer, which may arise from electrically charged groups oriented on the surface of emulsified globules. The potential produced by the double layer creates a repulsive effect between the oil droplets and thus hinders coalescence. Although the repulsive electric potential at the emulsion interface can be calculated, it can not be measured directly for comparison with theory. The dispersed phase globules are known to acquire an electric charge during the process of emulsification. The globules gather to charge layers around themselves called helmholtz double layer; zeta potential in which the difference in charge potentials between a points on the fixed charge layer on the globule to the point where both positive and negative charge exists. Zeta potential can be measured by zeta meter and helps in the prediction of flocculation behavior of the system. Dispersed phase systems having a zeta potential value higher than 0.25 mV are likely to be stable because the intensity of the charge on the particles repels them from one other.

Figure 4: Electric Potential

Zeta potential for the surfactant stabilized emulsion compares favorably with the calculated double layer potential. The change in zeta potential parallels rather satisfactorily the change in double layer potential as electrolyte is added. These and related on the magnitude of the potential at the interface can be used to calculate the total repulsion between oil droplets as the function of the distance between them.³

Emulsion Rheology

Figure 5: Emulsion Rheology

Emulsified products may undergo a wide variety of shear stresses during either preparation or use. In many of these processes, the flow properties of the product will be vital for the proper performance of the emulsion under the conditions of use or preparation. Thus, spread ability of dermatologic and cosmetic products must be controlled to achieve a satisfactory preparation. The flow of parenteral emulsion through a hypodermic needle, the removal of an emulsion from a bottle or a tube, and the behavior of an emulsion in the various milling operations employed in the large scale manufacture of these products all indicate the need for correct flow characteristics. Most emulsions, except dilute ones, exhibit non-newtonian flow, which complicates interpretation of data and quantitative comparisons among different systems and formulations¹¹

Recent Trends in Emulsion

Following are the advancements in emulsion system:

- Micro Emulsion
- Multiple Emulsion
- Non Aqueous Emulsion
- Liposome Emulsion
- Emulsion Polymerization
- Nano Emulsion.

Micro Emulsions

It may be defined as dispersion of insoluble liquids in a second liquid that appear clear and homogeneous to the naked eyes. Micro emulsions are frequently called solubilized systems because on a macroscopic basis they seem to behave as true solutions. Careful examination of these complex systems has shown that clear emulsions can exist in several differentiable forms. Micro emulsions should not be confused with solutions formed by co-solvency, Exp. the clear system consisting of water, benzene and ethanol. Blending of a small amount of oil with water results in a two phase system because “water and oil do not mix”. If the same small amount of oil is added to an aqueous solution of suitable surfactant in the micelle state, the oil may preferentially dissolve in the interior of the micelle because of its hydrophobic character. This type of micellar micro emulsion, which was observed by MCbain many years ago, has also been called an O/W micellar solution. Micro emulsions having diameter range 100° to 600° Å.¹² The three basic types of micro emulsions are:

1. Direct
2. Reversed
3. Bi continuous.

The term micro emulsion was first used by Jack H. Shulman, a professor of chemistry at Columbia University, in 1959. They are also termed as, transparent emulsion, swollen micelle, micelles solutions and solubilized oil.

Figure 6: Micro Emulsion

Uses

- Water in oil micro emulsion for some dry cleaning processes.
- Floor polishers and cleaners
- Personal care products
- Pesticide formulations
- Cutting oils
- Development of Artificial RBC
- Targeting of cytotoxic drugs to cancer cells.¹³

Multiple Emulsions

These are the emulsion system in which the dispersed phase contains smaller droplets that have the same composition as external phase. This is made possible by double emulsification hence; the systems are also called as double emulsion. These are of two types:

Oil in water in Oil (O/W/O) emulsion system

In O/W/O systems and aqueous phase separates internal and external oil phase or O/W/O is a system in which water droplets may be surrounded in oil phase, which in true encloses one or more oil droplets. The immiscible oil phase, which separates two miscible aqueous phases is known as liquid membrane).¹⁴

Water in Oil in Water (W/O/W) emulsion system

In W/O/W systems, an inorganic phase separates internal and external aqueous phases. In other words W/O/W is a system in which oil droplets may be surrounded by an aqueous phase, which in turn encloses one or several water droplets. These systems are the most studied among the multiple emulsions¹⁴. Formulation Example

- Sorbitan monooleate
- Sorbitan trioleate
- Carboxy Methyl cellulose sodium
- Microcrystalline cellulose

Figure 7: Multiple Emulsions

Uses

- Prolonged Action
- Taste Masking
- Improved Stability
- Enzyme Entrapment
- Protection against external environment
- More effective dosage form²⁰

Non Aqueous emulsion

Non aqueous systems are well known as solvents for drugs, suspension vehicles and oleo gels. By far, the vast majority of emulsions used pharmaceutically have water as one phase. It is some time since our group actively investigated oil in water and water in oil in water emulsions but there has been a resurgence of interest in emulsions as delivery vehicles other than for topical delivery, example, micro emulsion formulation of cyclosporine and an intravenous propofol emulsion; emulsions with no aqueous phase used as drug reservoirs as well as templates for the preparation of micro spheres and nanoparticles.

Figure 8: Non Aqueous Emulsions

Drawbacks

There is some challenge in producing stable anhydrous emulsions, which might be useful in formulating hydrolytically unstable drugs or to provide reservoir vehicle for transdermal system. Example, dispersed phase: castor oil and olive oil. Continuous phase: glycerin and silicon oil.¹⁵

Liposome Emulsions

Liposome is those in which chemical and physical characteristics of unique oil-in-water (o/w) emulsions that were produced by using liposomes as the emulsifying agent for stabilizing the oil. two alternative mechanisms: (i) rapid (or slow) release of liposomes containing encapsulated antigen and lipid A for interaction with the immune system at a distant site; or (ii) retention of liposomes in the o/w emulsion as a depot at the site of injection, resulting in gradual ingestion of the liposomes by phagocytic cells attracted to the site by local inflammation.

Figure 9: Liposome Emulsions

Two types of liposome-stabilized o/w emulsions were used in these experiments, stable and unstable. Unstable emulsions

were formulated with liposomes and light mineral oil in a ratio of 10:1 (v/v). Stable emulsions were formulated with liposomes and light mineral oil in a ratio of 7:3 (v/v). Liposomes containing each of the three o/p 140 doses were prepared at two different phospholipid concentrations. The final liposomal phospholipid concentration of the unstable emulsions was 91 mmol/L and the final liposomal phospholipid concentration of the stable emulsions was 125 mmol/L. Example: Lubrizol liposome emulsion.¹⁶

Emulsion polymerization

The name emulsion polymerization is a misnomer that arises from a historical misconception. Rather than occurring in emulsion droplets, polymerization takes place in the latex particles that form spontaneously in the first few minutes of the process. These latex particles are typically 100 nm in size and are made of many individual polymer chains. The particles are stopped from coagulating with each other because each particle is surrounded by the surfactant; the charge on the surfactant repels other particles electrostatically. When water soluble polymers are used as stabilizer instead of soap, the repulsion between particles arises because these water soluble polymers form a hairy layer around a particle that repels other particles because pushing particles together would involve compressing these chains.

Figure 10: Emulsion Polymerization

Emulsion polymer usually starts with an emulsion incorporating water, monomer and surfactant. The most common type of emulsion polymerization is oil in water emulsion in which droplets of monomer are emulsified in a continuous phase of water. Water soluble polymers, such as certain polyvinyl alcohols or hydroxyl ethyl cellulose, can also be used to act as emulsifier/ stabilizers. A dispersion resulting from emulsion polymerization is often called latex or an emulsion. These emulsions find applications in adhesives, paints, paper coating and textile coatings.⁷

Nanoemulsion

It consists of fine oil in water dispersions, having droplets covering the size range of 100-600 nm. In the present work,

nanoemulsions were prepared using the spontaneous emulsification mechanism which occurs when an organic phase and an aqueous phase are mixed. The organic phase is a homogeneous solution of oil, lipophilic surfactant and water miscible solvent, the aqueous phase consists on hydrophilic surfactant and water. An experimental study of nanoemulsion process optimization based on the required size distribution was performed in relation with the type of oil, surfactant and the water miscible solvent. The results showed that composition of the initial organic phase was of great importance for the spontaneous emulsification process, and so, for the physico-chemical properties of the obtained emulsions.

Figure 11: Nano Emulsion

First, oil viscosity and HLB surfactant were changed, -tocopherol, the most viscous oil, gave the smallest droplets size, HLB required for the resulting oil in water emulsion was superior to 8 second, the effect of water-solvent miscibility on the emulsification process was studied by decreasing acetone proportion in the organic phase. The solvent- acetone proportion leading to the fine nanoemulsion was fixed at 15/85 percent (V/V) with EtAc-acetone and 30/7 percent (V/V) with MEK-acetone mixture. To strength the choice of solvents, physical characteristics were compared, in particular, the auto-inflammation temperature and the flash point. This phase of emulsion optimization represents an important step in the process of polymeric nanocapsules preparation using nano precipitation or interfacial poly condensation combined with spontaneous emulsification technique.¹⁷

Recent Advancement in Applications

Emulsions are sometimes difficult to prepare and require special processing techniques. To warrant this type of effort and to exist as useful dosage form, emulsions must possess desirable attributes and cause a minimum of associated problems. The mixing of immiscible liquids for various purposes has been met by the emulsification process of centuries. Today emulsions continue to have a variety of cosmetics and pharmaceutical applications.

Recent examples of emulsion present in market

Cleviprex Injectable, Propofol (intravenous injection), Soap queen lotion, Amazing Grace firming body emulsion (lotions) Torani syrup, EDEX syrup Memory-Up syrup, Moist full Soothing Cream, Honey Bee BB Cream, Nivea Cream, J. R. Watkins Pain relieving liniments, Arnica Liniment and Cinna Liniment. The latter may be further

classified by route of administration that is topical, oral or parenteral. In Principle, cosmetic applications and topical pharmaceutical applications are similar and together form one of the most important groups of emulsions. The most important application of emulsions is for masking the disagreeable taste of oily liquids by formulating them as oil in water emulsions. Emulsions of oils like liquid paraffin and olive oil enhance the rate and extent of their absorption from the elementary canal due to the fine state of sub division. Similarly water soluble substances having a disagreeable taste can be dissolved in water and water in oil emulsion can be prepared.

Table 3: Marketed Formulation using taste masking drugs

Brand Name	Drug	Company Name
Claritin Redi Tabs	Loratidine 10 mg	Claritin
Feldeme Melt	Piroxican	Pfizer
Pepcid	Famotidine 10 mg	McNeil Products Ltd. ¹⁸

The water in oil emulsion is then further emulsified to yield oil in water emulsion. In such cases the partition coefficient of the drug and flavor should also be taken in the account. Parental emulsions, containing sum fats and medicinal oils, have been formulated for intravenous administration. Cod liver oil, chaulmoogra oil, oil soluble vitamins A, D and K and some hormones have been presented in emulsified form. Sterile, stable, intravenous emulsions containing fats, carbohydrates and vitamins in one formulation have been attempted. Such products are particularly useful for patients unable to assimilate these vital materials. Lotions, liniments and creams can be formulated as either oil in water or water in oil emulsions for external use. Water soluble antiseptics applied as oil in water emulsion are better absorbed as compare to their formulation in greasy base.¹⁹

CONCLUSION

Emulsions are drug of choice for condition such as: medicines having unpleasant taste and odor, protection against environmental condition (polymer emulsion). There is certain limitation of emulsion system which is needed to improve such as thermodynamically instability. There are certain reasons of instability of emulsion which adversely affect formulation. These reasons be studied in detail and rectified to enhance stability of an emulsion to get a therapeutically active emulsion. There are certain recent advances in emulsion technology such as micro emulsion, multiple emulsions to increase stability, effectiveness of emulsion system. The various advancement of emulsion is widely used today in market.

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Cite this article as:

Vani Madaan, Arsh chanana, Mahesh Kumar Kataria, Ajay Bilandi. Emulsion technology and recent trends in emulsion applications. Int. Res. J. Pharm. 2014; 5(7):533-542 <http://dx.doi.org/10.7897/2230-8407.0507108>

Source of support: Nil, Conflict of interest: None Declared