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Review

Basics of pharmaceutical emulsions: A review

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Pharmaceutical preparations for the treatment of skin conditions and skin care are usually supplied in the form of emulsions. This pharmaceutical dosage form is thermodynamically unstable and must be stabilized by the addition of emulsifying agent. Emulsified systems range from lotions having comparatively low viscosity to creams which are more viscous. There are two basic types of emulsions, that is, oil in water (O/W) and water in oil (W/O). In addition to these two types, a relatively complex emulsion, called multiple emulsions can also be formulated. Emulsions generally have certain advantages over other dosage forms as the drug solubilized may be more bioavailable. Moreover, gastrointestinal problems and first pass metabolic effect are also avoided.

Key words: Pharmaceutical, emulsions, viscosity, skin, oil in water (O/W), water in oil (W/O).

INTRODUCTION

The pharmaceutical term “emulsion” is most time used to indicate preparations prepared for internal use. Emulsions for external use are always given a different title that it focus may indicate their use, e.g. lotion and cream (Christopher and Dawn, 2008).

An emulsion may be defined as a biphasic system consisting of two immiscible liquids, one of which (the dispersed phase) is finely and uniformly dispersed as globules throughout the second phase (the continuous phase). Since emulsions are a thermodynamically unstable system, a third agent, the emulsifier is added to stabilize the system (Agarwal and Rajesh, 2007). Emulsifier stabilizes the system by forming a thin film around the globules of dispersed phase (Javed et al., 2008). Either the dispersed phase or the continuous phase may vary in consistency from that of a mobile liquid to semisolid (Alfred, 2005). Thus, pharmaceutical emulsions range from lotions (low viscosity) to creams (high viscosity). The particle size of the dispersed phase commonly ranges from 0.1 to 100 µm (Agarwal and Rajesh, 2007).

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Types of emulsion

Oil in water emulsion

Pharmaceutical emulsions usually consist of mixtures of aqueous phase with various oils and waxes. If the oil droplets are dispersed throughout the aqueous phase, the emulsion is termed oil-in-water (O/W) as shown in Figure 1. Fats or oils for oral administration, either as medicaments in their own right, or as vehicles for oil soluble drugs, are always formulated as oil in water (O/W) emulsions (Aulton, 1996). 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 the bitter taste of oil. Water soluble drugs are more quickly released from O/W emulsion. O/W emulsion give a positive conductivity test as water, the external phase is a good conductor of electricity (Javed et al., 2008).

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 Figure 2. Water-in-oil emulsions will have an occlusive effect by hydrating the stratum corneum

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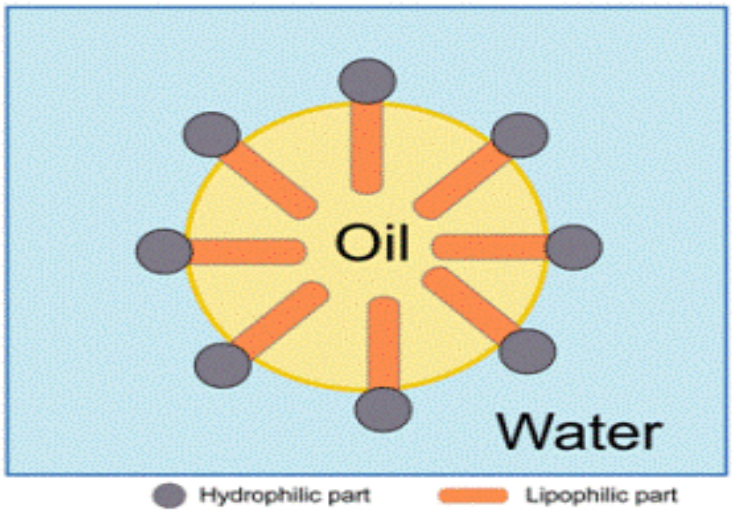

Figure 1. O/W emulsion.

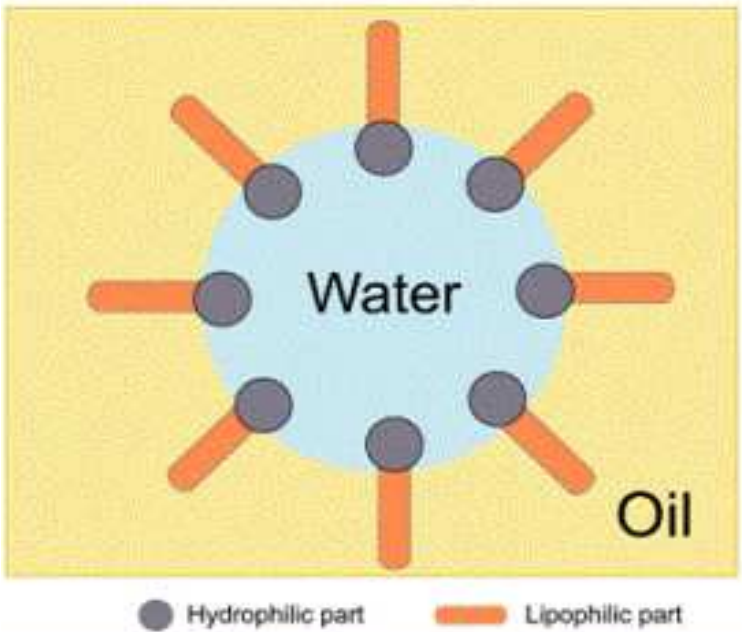

Figure 2. W/O emulsion.

and inhibiting evaporation of eccrine secretions. It has an effect on the absorption of drugs from W/O emulsions. W/O emulsion is also useful for cleansing the skin of oil soluble dirt, although its greasy texture is not always cosmetically acceptable (Aulton, 1996). They are greasy and not water washable and are used externally to prevent evaporation of the moisture from the surface of skin e.g. cold cream. Oil soluble drugs are more quickly released from W/O emulsion. They are preferred for formulation meant for external use like cream W/O emulsion is not given a positive conductivity tests, because oil is the external phase which is a poor conductor of electricity (Javed et al., 2008).

Multiple emulsions

Multiple emulsions are complex systems. They can be considered as emulsions of emulsions, and have been shown been shown to be secured in cosmetic pharma-

ceutical and separation sciences (Figen and Ozlem, 2005). It is a complex type of emulsion system in which the oil-in-water or water-in-oil emulsions are dispersed in another liquid medium. In this way an oil-in-water-in-oil (O/W/O) emulsion consists of very small droplets of oil dispersed in the water globules of a water-in-oil emulsion and a water-in-oil-in-water (W/O/W) emulsion consists of droplets of water dispersed in the oil phase of an oil-in-water emulsion (Agarwal and Rajesh, 2007). Their pharmaceutical applications include taste masking, adjuvant vaccines, an immobilization of enzymes and sorbent reservoir of overdose treatments, and sometimes for the augmentation of external skin or dermal absorption. Multiple emulsions have been formulated as cosmetics, such as skin moisturizer. Prolonged release can also be obtained by means of multiple emulsions. These systems have some advantages, such as the protection of the ensnared substances and the possibilities of incorporating several actives ingredient in the different compartments. Regardless of their importance, multiple emulsions have limitations because of thermodynamic instability and their complex structure (Figen and Ozlem, 2005).

Microemulsions

Microemulsions are systems consisting of water, oil and surfactant, which constitute a single optically isotropic and thermodynamically stable liquid solution. A simple way to formulate a microemulsion was to suggested by Hoar and Schulman. There are two types of microemulsion, one is O/W and the second is W/O microemulsion. For preparation of O/W microemulsion, we start with w/o emulsion using a low hydrophylic-lipophylic 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 solution, an inversion into O/W emulsion take place. For W/O microemulsion, one start with O/W emulsion stabilized with an ionic or nonionic surfactant. This emulsion is titrated with a co-surfactant and the emulsion passes through a gel phase, after which further addition of co-surfactant result in the production of W/O microemulsion. However, a drawback of microemulsion is the possibility of disruption of the crystalline structure of stratum corneum. These lead to facilitated transdermal transport and skin irritation (Tadros, 1992).

Pickering emulsion

The solid particles in the colloidal size may be used as emulsion stabilizers. Such particles are known as pickering emulsion. Pickering emulsions are recently employed in many areas like cosmetics, food, pharmaceuticals, oil recovery and waste water treatment (Fie et al., 2006).

Emulsification process

Milk is a natural emulsion, which consists of fatty globules surrounded by a layer of casein, suspended in water. The theory of emulsification is based on the study of milk. When a pharmaceutical emulsion is to be prepared the principal consideration is the same as that of milk (Christopher and Dawn, 2008).

General method

Generally, an O/W emulsion is prepared by dividing the oily phase completely into minute globules surrounding each globule with an envelope of emulsifying agent and finally suspends the globules in the aqueous phase. Conversely, the W/O emulsion is prepared by dividing aqueous phase completely into minute globules surrounding each globule with an envelope of emulsifying agent and finally suspending the globules in the oily phase (Christopher and Dawn, 2008).

Phase inversion method

In this method, the aqueous phase is first added to the oil phase so as to form a W/O emulsion. At the inversion point, the addition of more water results in the inversion of emulsion which gives rise to an O/W emulsion (Herbert et al., 1988).

Continental and dry gum method

Extemporaneously emulsions are usually made by continental or dry gum method. In this method, the emulsion is prepared by mixing the emulsifying agent (usually acacia) with the oil which is then mixed with the aqueous phase. Continental and dry gum methods differ in the proportion of constituents (Christopher and Dawn, 2008).

Wet gum method

In this method, the proportion of the constituents is same as those used in the dry gum method; the only difference is the method of preparation. Here, the mucilage of the emulsifying agent (usually acacia) is formed. The oil is then added to the mucilage drop by drop with continuous trituration (Christopher and Dawn, 2008).

Membrane emulsification method

It is a method, which is based on a novel concept of generating droplets “drop by drop” to produce emulsion. Here, a pressure is applied direct to the dispersed phase

which seeps through a porous membrane into the continuous phase and 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 (Nita et al., 2009).

Pharmaceutical applications of emulsion

Both macroemulsions and microemulsions are generally well documented as carriers for hydrophilic and lipophilic drugs. Recently, attention has been made on controlling the size distribution and understanding the stabilization phenomenon, which creates novel horizons; this had resulted in great attention for these liquid dispersion systems. The main advantage of such systems is that they increase the solubility and bioavailability of therapeutic drugs as well as the ability to favour the topical transport of hydrophilic drugs. Multiple emulsions, especially W/O/W emulsions are admirable candidate for controlled and sustained release of drugs. Multiple emulsions are used as an alternate to liposomes as delivery system. Microemulsions are isotropic mixture of oil, water and surfactant often with cosurfactant. It has been shown that microemulsions can be formed spontaneously and are thermodynamically stable; on one hand, they improve drug solubilization and bioavailability, and on the other hand, they act as potential drug delivery systems by integrating a wide range of drug molecules. O/W and W/O/W emulsions are generally employed for intravenous route. Lipid emulsions are used for parenteral nutrition, intravenous drug administration and as oxygen carriers. Emulsions have been used for many centuries for treating local skin diseases. Oil-in-water emulsions are used for lamentation of skin lacerations. The main advantage of using the topical emulsions is to avoid gastrointestinal environment and first pass metabolic effect. Emulsions are also available for oral route. They are mainly used for enteric nutrition or laxative preparations (Gilberte and Francoise, 2002). In addition to the aforementioned applications, emulsions may also be used, to stabilize hydrolytically susceptible drugs for sustained release, reduction of irritation or toxicity, possible targeted delivery of drugs to various organs and possible enhanced pharmacological effect (Nasirideen et al., 1998).

Stability of emulsions

A very important parameter for emulsion products is their stability; however, the evaluation of emulsion stability is not easy (Myung, 2000). Pharmaceutical emulsion stability is characterized by the absence of coalescence of dispersed phase, absence of creaming and retaining its physical characters like elegance, odor, color and appearance. The instability of emulsion may be classified into four phenomenons: Flocculation, creaming, coalescence and breaking as shown in Figure 3 (Alfred et al., 2005).

Flocculation

It is the association of small emulsion particles to form large aggregate which is redispersable upon shaking. It is a reversible process in which the droplets remain intact. Flocculation is considered as the precursor of coalescence (Gilbert and Christopher, 2002). This is because the presence of excess surfactant in the continuous phase of an emulsion can lead to flocculation of emulsion droplets. The flocculation of emulsion droplets by excess surfactant occurs because of the so-called "depletion effect". The depletion mechanism can be explained as, a system containing excess surfactant in the form of micelles, when the dispersed emulsion droplets approach each other to distances closer than the diameter of the surfactant micelles, segregation of micelles from the interparticle space that occurs because of the loss in configurational entropy of the micelles. This phenomenon results in an attractive force between the droplets due to the lowering of osmotic pressure in the region between the droplets, and accordingly, flocculation of droplets occurs (Rajinder, 1997).

Creaming

Creaming is the phenomenon in which the dispersed phase separates out, forming a layer on the top of the continuous phase. It is notable that in creaming, the dispersed phase remains in globules state so that it can be redispersed on shaking. Creaming can be minimized if the viscosity of the continuous phase is increased (Christopher and Dawn, 2008). The rate of creaming is determined by Stoke's law as follows:

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

where V is the velocity in cm/s, D is the diameter of particles of dispersed phase in cm, ρs is the dispersed phase density, ρo is the continuous phase density, η is the continuous phase viscosity and g is the gravitational acceleration.

O/W emulsions generally face upward creaming when the globules of the dispersed phase are less dense than the continuous phase. In contrast, W/O emulsions face downward creaming when the globules of the dispersed phase are denser than the continuous phase (Agarwal and Rajesh, 2007).

Coalescence (synonyms: breaking or cracking)

A more subtle type of emulsion instability, coalescence

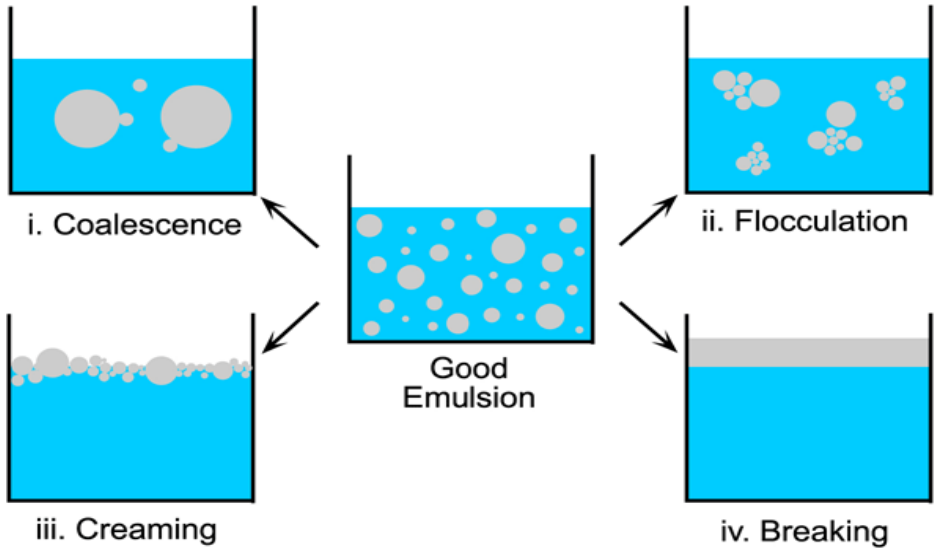

Figure 3. Instability types of emulsion.

occurs when the mechanical or electrical barrier is insufficient to prevent the formation of progressively larger droplets (Gilbert and Christopher, 2002). Stabilization against coalescence may be achieved by the addition of high boiling point or high molecular weight components to the continuous phase (Herbert et al., 1996). Newman (1914) and Schulman and Cockbain (1940) experimentally concluded that 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. 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 an electric diffuse layer cannot be built up as oil being a nonionizing medium. A surface potential considerably higher than 25 mv is not sufficient to stabilize the droplets of dispersed phase with a radius ≥1 µ against flocculation. This is because of the high sedimentation velocities (Albers and Overbeek, 1959).

Stability of W/O emulsions against coalescence

According to Newman (1914) and Schulman and Cockbain (1940) a charged film is not able to prevent coalescence, because due to the repulsion between emulsifying molecules in the interface, no interlinked solid thick film can be formed (Albers and Overbeek, 1959).

THE EFFECTS OF DIFFERENT PROCESS VARIABLES ON EMULSION STABILITY

The preparation of stable W/O emulsion is critical for the efficient production of final dosage form. The important parameter that can affect emulsion stability is the stirring intensity. It has been concluded that the interfacial area increases with the increase of rotational speed and diameter of the stirrer keeping the diameter of container tank low. Temperature indirectly affects the emulsification as a result of changing the interfacial tension, adsorption of emulsifying agent and viscosity. Higher temperature is favorable for emulsification as both viscosity and interfacial tension decrease with increase in temperature. It has been evidenced that a minute decrease in temperature may cause coagulation of particles thereby result in worsening the emulsion (Gonglun and Daniel, 2005).

Effect of emulsifier concentration

The amount of emulsifying agent is one of the most important factors having an influence on the emulsion stability. Emulsifier concentration has a great impact on emulsion stability. A concentration window existed, out of which the emulsion stability is quickly declined. At low emulsifier concentration, the emulsion is unstable because of agglomeration of the oil droplets. At high emulsifier concentration emulsion instability occurs because of rapid coalescence (Gonglun and Daniel, 2005).

Effect of oil/water ratio

Ostwald concluded that a phase volume above 0.74 for the continuous phase may result either in phase inversion

or breaking (Gonglun and Daniel, 2005).

Effect of stirring intensity

Various types of procedures may be applied for emulsification. Emulsification is usually achieved by applying mechanical energy. In such a process, initially, the interface between the two phases is deformed to extents that large droplets are formed which are subsequently broken into small particles. Stirring is done to form a stable and homogeneous emulsion by converting large droplets into small ones. It is clearly indicating that a more stable emulsion can be prepared with a higher stirring speed but less than 2500 RPM as more than 2500 RPM will lead the emulsifier to break away from the oil-water interface (Gonglun and Daniel, 2005).

Effect of mixing temperature

Emulsions prepared at low temperature are stable; however, more stable emulsions can be prepared at a temperature of 30℃. It is cleared that the surface tension of most liquids decreases with the increase of temperature. Due to this high kinetic energy, the surface molecules tend to overcome the attractive force of bulk liquid. Furthermore, at critical temperature value, the cohesive forces between the liquid molecules become zero; therefore, the surface tension will fade off at critical temperature value (Gonglun and Daniel, 2005).

Effect of mixing time

Mixing time is a key factor during emulsification. According to Gonglun and Daniel, (2005), the radii of the droplets of the dispersed phase decrease with the increase of stirring speed and mixing time. Long mixing time increase the effectiveness of emulsifying agents; however, too much long mixing time will cause a decrease in the effectiveness of emulsifying agents, because severe stirring will cause the emulsifying agents to drop out from liquids interface (Gonglun and Daniel, 2005).

EMULSION STABILITY ASSESSMENT

Emulsion stability must be regarded in terms of physical stability of emulsion system examined and the physical and chemical stability of the emulsion components (Herbert et al., 1996).

Macroscopic examination

The degree of creaming or coalescence occurring per unit period of time can give the assessment of emulsion physical satiability. This procedure 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 (Aulton, 1988).

Determination of particle size and particle count/globule size analysis

Determination of changes in the average particle size is one of the parameters used for assessing emulsion stability. Optical microscopy, Andreasen apparatus and Coulter counter apparatus are used for this purpose (Javed et al., 2008).

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 (Aulton, 1988). Emulsions follow non-Newtonian flow characteristics. Flocculation in O/W emulsions results in an immediate increase in viscosity (Javed et al., 2008).

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 (Javed et al., 2008).
Electrostatically emulsion stabilization is due to the mutual repulsion between electrical double layer of both phases. Such type of stability is very sensitive to the ionic strength of solution, as the concentration of electrolyte increases the electrical double layer compressed and the distance of electrostatic repulsion is reduced resulting in flocculation (Jayme et al., 1999).

TESTS FOR IDENTIFYING EMULSION TYPES

Several tests are used for identifying the emulsion type. Although, such tests may be applied rapidly, the results must be interpreted with caution. It may be possible that such tests can not indicate whether a multiple emulsion has been produced? Such contro-versies may be resolved by microscopic examination (Rawlins, 2005).

Dilution test/miscibility test

Miscibility test involves the addition of continuous phase, e.g. 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, the oil will separate. Vice versa is the case with W/O emulsion (Carter, 2007).

Electrical conductivity test

Water is a good conductor of electricity; hence, an emulsion with water continuous phase will readily conduct electricity while that with oil continuous phase will not (Aulton, 1988).

Staining test/dye-solubility test

In this test, a small amount of water soluble dye, such as methylene blue 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 (W/O emulsion), dye will remain as cluster on the surface of the system (Alfred et al., 1993).

THE HYDROPHYLIC-LIPOPHYLIC BALANCE (HLB) SYSTEM FOR EMULSION FORMULATION

Griffin (1954) introduced a very useful system for the classification of surfactants on the basis of their solubility in water. The numerical values in this system are called hydrophylic-lipophylic balance (HLB) that denotes the relative affinity of the surfactant for oil and water. Emulsifying agents with HLB values of 3 to 6 are used for w/o emulsions. Whereas emulsifying agents with HLB values of 7 to 20 are used for o/w emulsions (Ashok, 2005). According to Alfred the type of emulsion is a function of the relative solubility of the surfactants, thus the phase in which the surfactant is more soluble gives rise to the continuous phase. This phenomenon is sometimes referred to as “The Rule of Bancroft” (Alfred et al., 1993).

Emulsification equipments

Various types of equipments are available for emulsification both for laboratory scale and commercial scale. Usually equipment for emulsification is selected on the basis of resulting emulsion. Equipment for emulsification works on the mechanism to break up or distribute the dispersed phase into the continuous phase so that the size of the droplets of the dispersed phase is sufficiently small to avoid coalescence and instability (Herbert et al., 1996).

Small scale processing

For the laboratory scale or prescription department emulsification of fixed/volatile oils, the most frequently used equipments are Wedgwood or porcelain mortars and pestles (Lewis, 1974).

Shaker mixers/agitators

In shaker mixers for small scale production, the material in the container is agitated by oscillator, whereas for large scale production, the material in the container is agitated by rotary movement similar to that of ball mills (Ashok, 2005).

Propeller mixers

Large and small scale production of emulsion is often made conveniently with the help of propellant mixers operating in suitable mixing container. If preheating of the product is required, the mixing container is made steam jacketed (Rawlins, 2005). Propellant mixers are generally used for low viscosity emulsion preparation and they can be rotated at a speed of about 8000 RPM. Sometime, high speed of propellant mixers is undesirable as it results in vortex formation and air entrapment (Ashok, 2005).

Turbine mixers

Turbine mixers are used for mixing the high viscosity emulsions. They are rotated at a slow rate as compared to the propellant mixers. They are provided generally in a circular disc impeller attachment to short straight or curved blades (Ashok, 2005).

Homogenizers

Modern emulsions can be prepared by a variety of various emulsification equipments, all are working nearly on similar mechanism that is agitated (Yuh-Fun and Chung, 1996). Among all the equipments for emulsification, rotor/stator high pressure homogenizer is the most continuously operated device. High pressure homogenizers are provided with a high pressure pump and homogenizing nozzle. The high pressure pump raises the pressure up to 50 to 500 bar (Michael et al., 2001). During emulsification, the dispersion of two liquids is carried out by forcing them through a small orifice at a high pressure (Leon and Herbert, 2009). The rotor/stator assembly of the homogenizer consists of a rotor with blades and a stator with openings. As the rotor rotates, a vacuum is created drawing the liquid in and out of the assembly, resulting in liquid circulation. The size of the dispersed phase is reduced;

1. Due to the mechanical collision against the walls of

homogenizer because of high liquid acceleration and 2. Due to the shear force occurring within the gap between rotor and stator (Yuh-Fun and Chung, 1996).

Ultrasonifiers

Ultrasonifiers, the transduced piezoelectric instruments are used for laboratory scale emulsion production, however, they have limited output and are expensive. Their mechanism of work is that the dispersion is forced through an orifice at a medium pressure of 150 to 350 psi and is allowed to collide upon a blade (Leon and Herbert, 2009). Ultrasonifiers provide an easy way of agitation for the laboratory scale preparation of constant and reproducible oil-in-water (o/w) emulsions (Lloyd and Toshiko, 1974).

Colloid mills

Colloid mills are suitable for the preparation of emulsions on a continuous basis. Due to intense shearing force, the emulsions produced by colloid mills are of very small globule size (Aulton, 1988). Colloid mills are mostly used for the milling of solids and for the dispersion of very poorly wetable suspensions; however, colloid mills are very useful for the preparation of relatively high viscous emulsions (Leon and Herbert, 2009).

Whisks/churns

These are used for emulsion preparation involving the agitation of emulsion ingredients by blenders fitted in the container. Sometime, the containers may be fitted with a jacket if heating/cooling effects are required (Carter, 2005).

Silverson mixer-emulsifier

Silverson mixer consists of an emulsifying head with blades which are surrounded by stainless steel fine mesh sieves. The emulsifying head is adjustable for insertion into the containers to be used for emulsification. An electric motor is used for rotating the head. The liquid to be emulsified if sucked by the fine mesh sieve into the emulsifying head where they are subjected to intense mixing due to the rotation of blades of emulsifying head (Ashok, 2005).

Micro-fluidizers

For the production of very fine particles, micro-fluidizers are employed. Micro-fluidizers consist of interaction chambers with micro-channels. During emulsion processing, the emulsion is subjected to a high velocity through the micro-channels of the interaction chamber; thus, the particles are subjected to high shear, uproar, collision and cavitation (Paul, 2005).

Foaming during agitation process

The foaming and emulsifying characteristics of emulsion are important characteristics during the production stage, storage, transport and consumer observation of quality and appearance of emulsions. Foaming and emulsifying characteristics and the stability of the resulting dispersion depend on the properties of the emulsifying agent in the system (Cecilio and Juan, 2005). The reason for the formation of foam is that during emulsification, the emulsifying agent also reduces the surface tension at the air-water interface .To avoid foam formation, the emulsification must be carried out in closed system or under vacuum. In addition, continuous mechanical stirring during cooling stage of emulsion may also affect in preventing foam formation (Leon and Herbert, 2009).

Emulsifying agent

Emulsifying agent or surfactant may be defined as" a compound that lowers the surface tension and forms a film at the interface of two immiscible liquids making them miscible". Some commonly used emulsifying agents are shown in Table 1. The efficiency of an emulsifying agent is related to its chemical structure, solubility, pH and physical properties. There are two types of emulsifying agents on the basis of their effect;

1. Primary agents (true emulsifying agents) can form and stabilize emulsions by themselves.
2. Auxiliary agents (stabilizers) alone do not form fine emulsions but assist the primary emulsifying agents (Leon et al., 2004).

Classification of emulsifying agents on the basis of charged groups is as shown in Table 2.

Mechanism of emulsifying agent

Mechanism of action of emulsifying agents depends upon the formation of film they form at the interface of two phases. There are three types of films formed by emulsifying agents (Paul, 2005).

Monomolecular films

Emulsifying agents with stabilizing action form monolayer at the oil-water interface. This monolayer prevents

Table 1. Some commonly used emulsifying agents, their HLB values, characteristics and functions.

Chemical name	HLB	Miscible with H_2O	Function
Oleic acid	1.6	Immiscible	Antifoam
Sorbitan tristearate	2.1	Immiscible	Antifoam
Ethylene glycol monostearate	2.9	Immiscible	Antifoam
Glyceryl monostearate	3.8	Disperses with difficulty	W/O emulsifier
Sorbitan monostearate	4.7	Disperses with difficulty	W/O emulsifier
Sorbitan monopalmitate	6.7	Forms milky dispersion	W/O emulsifier
PEG-4 dilaurate	6	Forms milky dispersion	W/O emulsifier
Sucrose dipalmitate	7.4	Forms milky dispersion	W/O emulsifier
PEG-4 monooleate	8	Forms milky dispersion	W/O emulsifier
PEG-4 monolaurate	9.8	Form milky stable dispersion	O/W emulsifier
Polysorbate 85	11	Form clear dispersion	O/W emulsifier
PEG-8 monooleate	11.4	Form clear dispersion	O/W emulsifier

Table 2. Classification of emulsifying agents on the basis of presence of formally charged groups in their heads.

S/N	Surfactant class	Surface charge	Example
01	Anionic**(**(based on sulfate, sulfonate or carboxylate anions)	The charge is negative	Perfluorooctanoate (PFOA or PFO) Perfluorooctanesulfonate (PFOS) Sodium dodecyl sulfate (SDS), ammonium lauryl sulfate, and other alkyl sulfate salts Sodium laureth sulfate, also known as sodium lauryl ether sulfate (SLES) Alkyl benzene sulfonate Soaps, or fatty acid salts
02	Cationic (based on quaternary ammonium cations)	The charge is positive	Cetyl trimethylammonium bromide (CTAB) a.k.a. hexadecyl trimethyl ammonium bromide, and other alkyltrimethylammonium salts Cetylpyridinium chloride (CPC) Polyethoxylated tallow amine (POEA) Benzalkonium chloride (BAC) Benzethonium chloride (BZT)
03	Zwitterionic (amphoteric)	Two oppositely charged groups	Dodecyl betaine Cocamidopropyl betaine Coco ampho glycinate
04	Nonionic	No charge groups	Alkyl poly(ethylene oxide) Alkylphenol poly(ethylene oxide) Copolymers of poly(ethylene oxide) and poly(propylene oxide) (commercially called Poloxamers or Poloxamines) Alkyl polyglucosides, including: octyl glucoside and decyl maltoside Fatty alcohols, including: cetyl alcohol and oleyl alcohol Cocamide MEA Polysorbates, including: Tween 20 and Tween 80

coalescence of droplets (Paul, 2005).

Multimolecular films

Multimolecular films around the droplets of dispersed phase are formed by hydrophilic colloids. They act as coats around the droplets making them highly resistant to coalescence. They have the ability of swelling to increase the viscosity of the system (so that droplets are less likely to merge) (Paul, 2005).

Solid particle films

Small solid particles like bentonite (Al2O3.4SiO2.H2O), veegum (magnesium, aluminum and silicate), hectorite, magnesium hydroxide, aluminum hydroxide and magnesium trisilicate, 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 particulate film around the dispersed droplets to avoid coalescence (Paul, 2005).

THEORIES OF EMULSIFICATION

Theories of emulsification explain the action of emulsifying agents in stabilizing emulsions. It is the surface or more accurately the interface between the two immiscible liquids that plays the foremost role. Emulsifying agents affect the interface in such a way to obtain stable emulsions (John, 1976). There are several theories proposed to explain the action of emulsifying agents in stabilizing emulsions. Among these theories, some may be applied to specific emulsifying agents under certain conditions like pH of the system and proportion of the two phases. The most well-known theories include surface tension theory, the oriented wedge theory and the interfacial film theory (Paul, 2005).

Surface tension theory

Molecules in a liquid are attracted equally on all sides by the surrounding molecules; however, at the surface, there is inward attraction of molecules due to the imbalance attractive forces. Due to this attraction, a stress or tension is produced known as surface tension (John, 1976). When two immiscible liquids come in contact, the force causing each liquid to resist breakage is known as interfacial tension. In accordance to surface tension theory of emulsification, the emulsifying agents cause a reduction in the interfacial tension of the two immiscible liquids, reducing the repellent force between the liquids and withdrawing the attraction of liquids for their own molecules. In this way, the surfactants convert large globules into small ones and avoid small globules from coalescing into large ones (Paul, 2005).

The oriented Wedge theory of emulsions

According to this theory the oil-like or non- polar ends of the emulsifying agents turn towards the oil and the polar ends towards the polar liquid. The oriented Wedge theory of emulsions indicates that if the non-polar end of the emulsifying agent is smaller, the emulsion will be oil-in-water (o/w) and if the polar end is smaller, the emulsion will be water-in-oil (W/O) (Harkins and Norvil, 1925).

The interfacial film theory

The interfacial film theory suggests that the emulsifying agents make an interface between the two immiscible phases of the emulsion, surrounding the droplets of the internal phase as a thin film. This film prevents the coalescence of the dispersed phase (Paul, 2005).

Conclusion

The basics of emulsions are definitely succeeding and the proficient development and production of excellence pharmaceutical emulsions depends on their basic knowledge of physicochemical properties and stability. This review article provides a critical overview of the most important properties of emulsions, their methods of preparation, instability mechanisms, theories and most suitable emulsifying agents that are of great interest to the researchers and pharmaceutical industries.

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