IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 14, Issue 2 Ser. II (Mar – Apr 2019), PP 01-06
www.Iosrjournals.Org

Role of Excipient's HLB Values in Microemulsion System

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Abstract: *The hydrophilic-lipophilic balance (HLB) system provides distinctive feature in deciding the role of surfactants and co surfactants combinations (S_{mix}), oil content and ratio of aqueous phase in a microemulsion system. Also, it has definitive role in the formulation of different types of microemulsion systems including O/W, W/O and bicontinuous microemulsions asit offers a strategic approach to determine on the choice and selection of suitable emulsifiers.The present study is based on the evaluation of hydrophilic-lipophilic balance (HLB) system in fabrication of various types of microemulsions. Microemulsions can be made through two different methods i.e. Phase titration method wheremicroemulsion can be prepared by a spontaneous emulsification method (phase titration method) and Phase inversion Methodwhere phase inversion of the microemulsion occurs as a result of addition of surplus amount of the dispersed phase. Hence, in this review we studied the effect of HLB values of excipients used in the microemulsion system on the fabrication process.*

Keywords:*Surfactants; Co surfactants; interfacial tension; aqueous phase; amphiphilic.*

Date of Submission: 26-03-2019 Date of acceptance: 11-04-2019

I. Introduction

Microemulsion (ME) system consists of four major components with isotropic property and is prepared by emulsifying oil in an aqueous system with the help of surfactant and co-surfactants. [1] The oil and water phases are immiscible due to the fact that interfacial tension between oil and water is huge, so to overcome this limitation Smix (i.e. Surfactant: co-surfactant) in a certain optimized ratio is added which not only reduce the interfacial tension but form an interface between oil and water. These excipients of microemulsions have a polar head and a tail which gets attached to the aqueous phase and oil phase respectively, forming a strong connection and hence, reducing the interfacial tension between the oil and the aqueous phase thereby blending them both into a clear emulsion[2].ME's are the suitable drug carrier system for almost all the drug administration routes as it solubilizes both hydrophilic or lipophilic drug easily, as it can be formulated either in oil in water (o/w) or water in oil (w/o) types.Nowadays it is been commercially used in many of the transdermal formulations due to its much higher topical drug delivery, deeper penetration, spreading ability, impregnation, and hydration which leads to increased skin penetrations and skin flux.To come up with the perfect combination of a microemulsion can be quite a tedious task as you get to choose over thousands of already existing oils and amphiphiles [3]. But the most important aspect while developing a suitable microemulsion system is to keep a check on HLB (hydrophilic and lipophilic balance) values of the selected components, type of microemulsion system (i.e. O/W and W/O) opted. Similarly, amount of oil and amphiphiles used to formulate a microemulsion, whether they are under the GRAS (Generally regarded as safe) limits and the selected excipients characteristics like – whether they are stable, non-toxic and non-irritating in nature plays a major role. Oil being the major component of a microemulsion constitutes lipophilic active ingredients and are chosen purely on the basis of the nature of drug that will be used for the formulation and the route of administration. Thus, the chosen drug must have high solubilization potential [4]. The aqueous phase comprises of hydrophilic active ingredients and preservatives and sometimes buffer solution [5]. The blending of oil in water or water in oil results in an immiscible suspension as the interfacial tension between the two phases are extremely huge. So, in order to overcome such a limitation an intermediate (surfactant) is required which possess both the lipophilic and lipophobic properties and thus acts as an interface between oil and water as they have a polar head and a tail which attach to the lipophobic and lipophilic phase respectively forming a strong connection.

Surfactants behaviour is dependent on the hydrophilic and lipophilic balance (HLB), so as to form W/O (water in oil) microemulsion surfactants with HLB value from 4-6 are preferred whereas surfactants with HLB from 8-18 are preferred for O/W (oil in water) microemulsion [6]. Mostly surfactant in solitary cannot lower down the interfacial tension and thus co surfactants containing a small polar head group with an alkyl chain of appropriate length have a crucial role in developing a microemulsion system as they fill in the gaps

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Microencapsulation of the drug solely depends on the nature of the drug and is encapsulated in the suitable phase whether it be a lipophilic or lipophobic phase. And thereby, various forms of microemulsions are available which includes Oil in water (O/W) as shown in Figure 1, Water in oil (W/O) as shown in Figure 2 and bicontinuous phase and to achieve the proper fabrication, knowledge of Hydrophilic and lipophilic (HLB) balance plays a crucial and prime role.

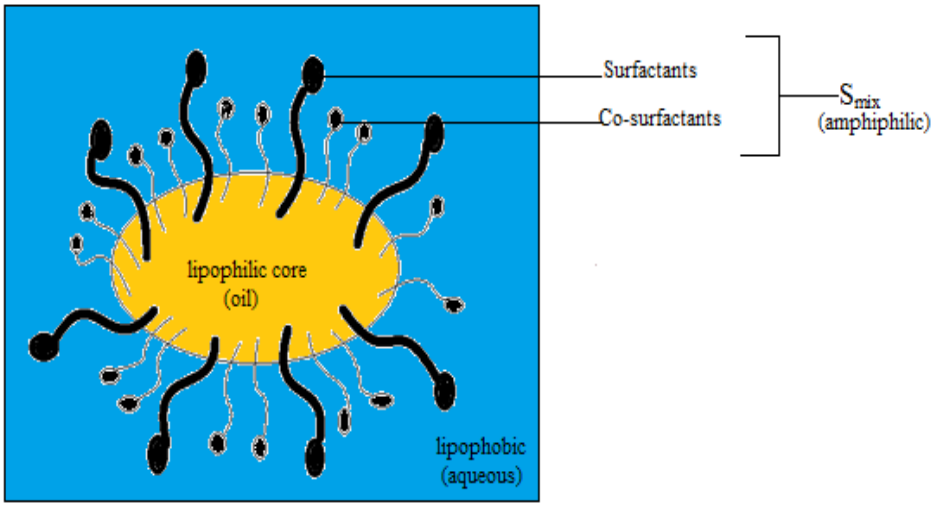

Figure 1: It represents oil in water (O/W) based microemulsion system

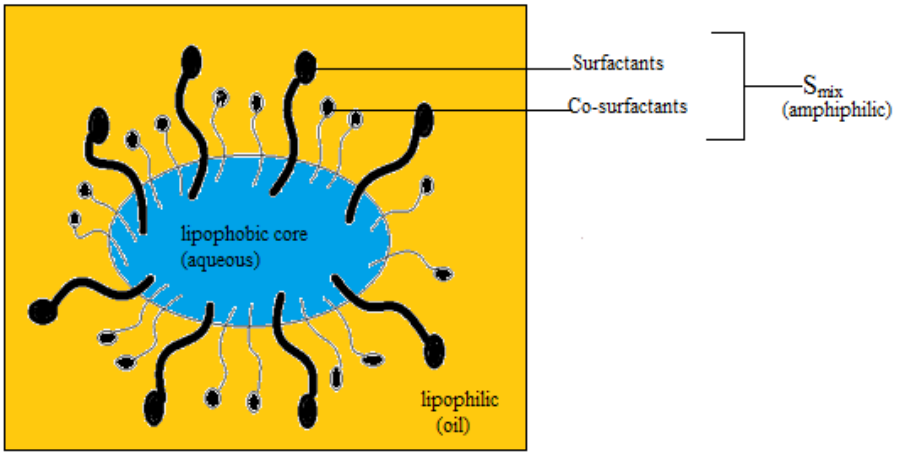

Figure 2: It represents water in oil (W/O) microemulsion system.

Method(s) of preparation:

Two important method(s) are reported for the formulation of a microemulsion. One method is Phase titration Method where microemulsion can be prepared by a spontaneous emulsification method (phase titration method) [33,34] and can be depicted through the phase diagrams that is a practical approach to study the

complicated series of interaction which takes place when different components of the microemulsion are mixed[8]. Preparation of microemulsion involves addition of S_{mix} (surfactant: cosurfactant) in appropriate ratios to the lipophilic (oil) phase and then vortexed followed by the addition of lipophobic (aqueous) phase until the mixture turns clear and another method reported for the formulation is Phase inversion Method where phase inversion of the microemulsion occurs as a result of addition of surplus amount of the dispersed phase[9]. It leads to substantial changes generally the physical changes which includes modification in the particle size which might directly affect in the release of the drug both *in-vitro* and *in-vivo.* In few surfactants [38,39], taking, for instance, the ionic surfactants, phase inversion can be achieved through changes in the temperature i.e. forcing the transition of oil in water microemulsion at low temperature to water in oil microemulsions at high temperature which is commonly known as transitional phase inversion.

Types of Microemulsion

Winsor developed an approach to classify equilibrium systems consisting of mixed water, oil and surfactants, which is still used to this day [10]. The four categories are oil in water (O/W), water in oil (W/O) microemulsions, bi-continuous and single phase microemulsion as depicted in Figure 3.

In oil in water (O/W) the microemulsion is formed when the surfactant-rich aqueous phase coexists with the oil phase where the surfactant is a monomer.[11]These are recognized as "reverse micelles", where the polar head groups of the surfactants are facing into the droplet of water towards the inner core shell and the fatty acid tails facing towards the lipophobic phase ie towards the outer phase[12]. The water in oil (W/O) microemulsion is formed when surfactant rich oil phase coexists with the aqueous phase where the surfactant is hydrophobic.[18,19] Bi-continuous is a three-phase system where the middle phase that is rich in surfactant coexists with the excess aqueous and the oil phases i.e. the amount of water and oil present are in similar proportion and both water and oil exist as a continuous phase. Such an arrangement of oil and water combined looks like a spongy phase. [13,14] It is non-Newtonian and shows plasticity. These microemulsions are not widely used and successful but few studies determine their usefulness for topical delivery of drugs or for intravenous administration [15]. And lastly, the single phase microemulsion is formed by the addition of the adequate amount of amphiphile [16]. Surfactant molecule may form a single layer at the interface between oil and water, with the hydrophobic tail of the surfactant molecules dissolved in the oil phase and hydrophilic head groups in the aqueous phase [17,20].

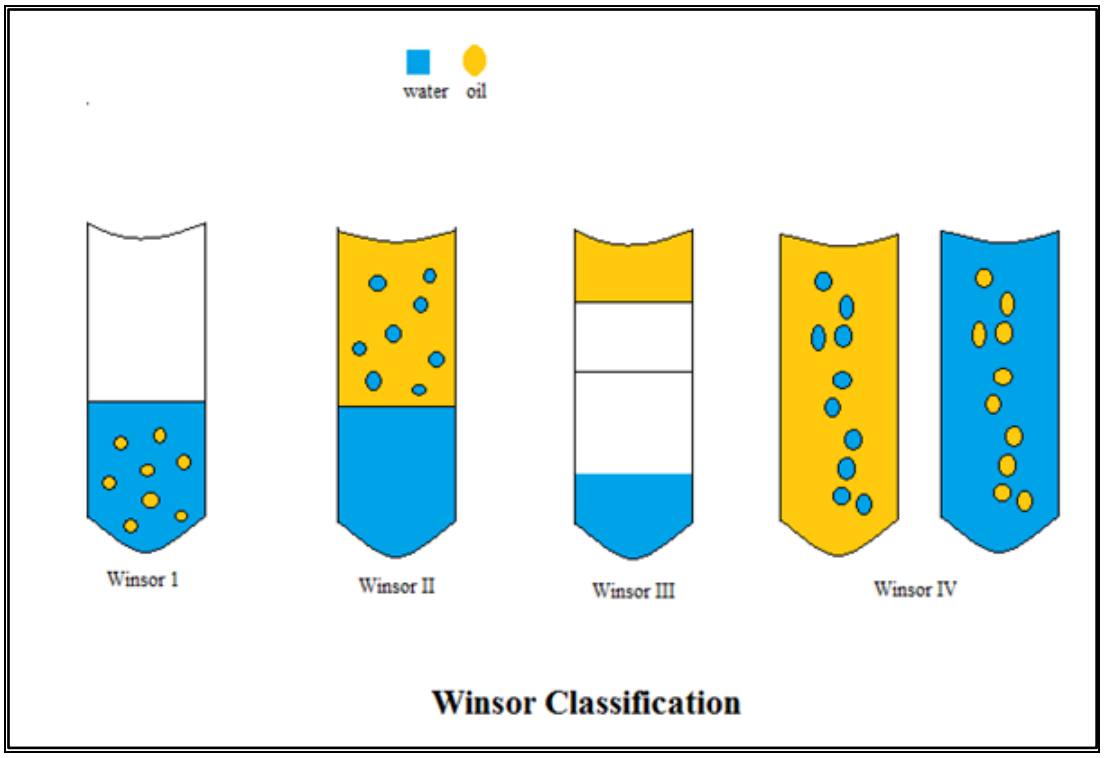

Figure 3: Winsor classification depicting Winsor I as oil in water (O/W), Winsor II as water in oil (W/O) microemulsions, Winsor III as bi-continuous and Winsor IV as single phase microemulsion.

Hydrophilic-Lipophilic Balance (HLB) System

A variety of fatty acids, fatty esters, fatty alcohols serve to stabilize the emulsifiers through their ability to thicken the emulsion, thus, a system was developed to assist in making the decisions about the amounts and types of surfactants needed in stable products [21,23]. The system is called Hydrophilic-Lipophilic Balance System. Emulsifiers or Surfactants are characterized according to the "balance" between the water-loving (hydrophilic) and oil-loving (lipophilic) portions of their molecules. The HLB number stipulate the polarity of the molecules in a range of 1-40, with the most common emulsifiers used in the range of 1-20 [32]. Higher HLB suggests that the emulsifiers have a large number of hydrophilic groups on molecules and therefore is more hydrophilic in nature whereas lower HLB number indicates that the emulsifiers have the lower number of hydrophilic groups on molecules thus imparting lipophilic character as depicted in Figure 4..Hydrophilic-Lipophilic Balance tells about varying degrees of non-polar and polar character[22,35]. Specific oils need emulsifiers with specific HLB (polar or nonpolar character) to be effectively emulsified. Emulsifiers should have similar HLB values to that of the respective oils in order to achieve the maximum stabilization.

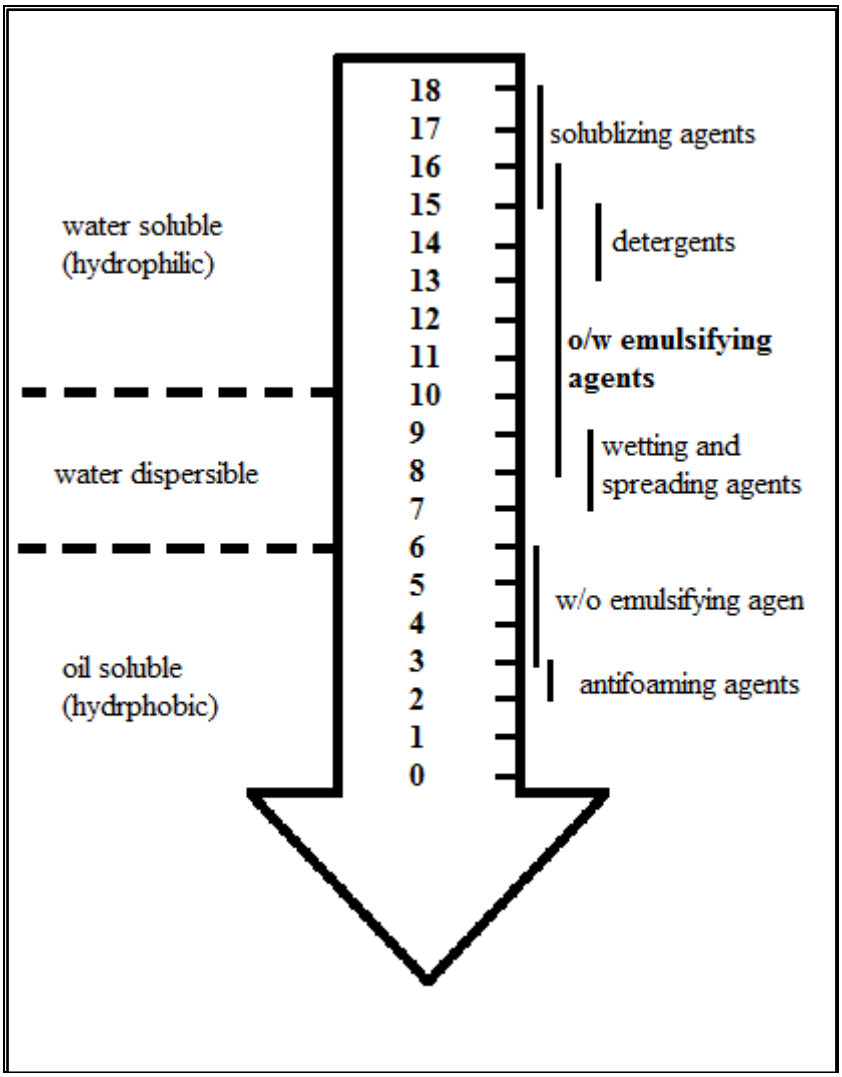

Figure 4: The figure represents the HLB Scale for selecting specific oils which can effectively blend with particular emulsifiers having specific HLB value (polar or nonpolar character) to achieve maximum stabilization.

The HLB number increases with increasing hydrophobicity. Selection for surfactant for an o/w emulsion can be simplified if the HLB system is applied. Oils have required HLB numbers that identify the HLB necessary to give good o/w emulsification. LB of an emulsifier is related to the solubility of microemulsions, therefore, an emulsifier having a low HLB will tend to be oil-soluble, and one having a high HLB will tend to be water-soluble, although two emulsifiers may have the same HLB and yet exhibit quite different solubility characteristics [24,26]. Conventionally, the HLB of oil in o/w microemulsion is taken lower as compared to the w/o microemulsion where oil has remarkably higher HLB. Similarly, Surfactants behaviour

is dependent on the hydrophilic and lipophilic balance (HLB), to form W/O (water in oil) microemulsion surfactants with HLB value from 4-6 are preferred whereas surfactants with HLB from 8-18 are preferred for O/W (oil in water) microemulsions [25].

II. Conclusion

The prime components of microemulsion are chosen on the basis of type of microemulsion and the amount of component used to fabricate the microemulsion system thereby, through extensive literature studies it was concluded that for formulating Oil in water Microemulsion system, the lesser the concentration of oil taken with the higher concentration of $S_{mix,}$ yields a clear and suitable microemulsion. On the other hand, developing water in oil microemulsion the concentration, S_{mix} is lesser than the oil's concentration and thus the system developed is milky in nature or translucent [27,28,30]. The Hydrophilic-Lipophilic value (HLB) plays a significant role in determining the formation of the microemulsion system. If the HLB value is above 10, it signifies the presence of more number of hydrophilic groups in excipients whereas, if HLB value is balanced at 10, it is neutral and lastly if the HLB value is below 10 it signifies the presence of more number of lipophilic groups in the excipients used to formulate the microemulsion system [29,31]. Oil and S_{mix} (Surfactant: cosurfactant) ratio also play a vital role and was concluded that the surfactant ratio must be higher than the cosurfactant in order to broaden the area for the formation of Microemulsion and it was also suggested that various aspects like – role of surfactants, which have amphiphilic properties and thus, it combines with the oil and the aqueous phase by forming an interface between them with its polar head (hydrophilic) towards the aqueous phase and tail ending (lipophilic) towards the oil phase, role of co-surfactants - composed of small polar head group with an alkyl chain of appropriate length which blend into the interfacial films , thereby helping the surfactant to form a sturdy interface between the oil and the aqueous phase and so on.

So, the ideal HLB value for formulating the O/W microemulsion the HLB values must lie in between 9-17 where the chosen oil must have an HLB lower than 10 and the surfactant chosen must be above 12 to yield an appropriate O/W Microemulsion [40]. Similarly, to yield the W/O microemulsion the HLB values must lie in between 4-15 where the chosen oil must have an HLB higher than 10 and the surfactant chosen must be below 7 to yield an appropriate W/O Microemulsion.

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Arushi Pant. "Role of Excipient's HLB Values in Microemulsion System"IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) 14.2 (2019): 01-06.