

# Formulation of ointment and cream



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## **Effects of Pure and Mixed Homologue Alcohols on Non-ionic Creams**

### **1. Introduction**

#### **1.1 General introduction of emulsions**

Emulsions are mixtures of two or more immiscible constituents with the interface being stabilized by the addition of emulsifying agents which may consist of ionic or non-ionic surfactants and fatty alcohols. [Eccleston, 1997; Eccleston et al., 2000] There are two different phases can be found in emulsions, with droplets of one phase dispersed in another phase, termed as dispersed phase and continuous phase respectively. Different types of emulsions like water-in-oil (w/o), oil-in-water (o/w) emulsions or multiple emulsions (w/o/w or o/w/o) can be formed, depending on the nature of the dispersed and continuous phase. [Buszello and Muller, 2000] The thermodynamically unstable structure of emulsions can be stabilized by adsorption of surface active agents at the interface, which work by lowering the interfacial tension to decrease the likelihood of collisions between droplets and hence prevent coalescence. This is important in maintaining the droplets in a dispersed state. [Florence and Attwood, 2006] Figure 1 showed the two different ways of surfactant adsorptions at the interface, i. e. monomeric and micellar adsorption. [Rowe, 1965]

#### **1.2 Structure of creams**

Creams can be described as semisolid emulsions with a relatively fluid viscosity in the presence of excess emulsifiers as these emulsifiers interact with other components in either continuous phase or dispersed phase of emulsions. From the perspective of pharmaceutical and cosmetic industry, the uses of creams are related to their structure properties and they are commonly used as drug delivery agents and cosmetic agents to the skin.

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[Eccleston, 1992; Eccleston, 1997; Eccleston et al., 2000] These have been shown in the studies carried out by Schwarz, Weisspapir and Friedman which indicated that the efficacy of topically administered diazepam, in the form of emulsion cream, depends greatly on the size of oil droplet and to a lesser extent on the type of oil used and formulation composition. These also implied that emulsions can be used as transdermal delivery vehicles of diazepam to generate significant systemic effect of the drug. [Schwarz et al., 1995] There are two different types of creams which known as aqueous creams and oily creams. Aqueous creams are the oil-in-water (o/w) types of emulsions which are non-greasy on use, easily to be spread on skin and tend to produce cooling sensation at the site of application. On the other hand, oily creams are the water-in-oil types (w/o) of emulsions which are less popular than aqueous creams because of the potential of generating greasy feel and sensitization on use. [Buszello and Muller, 2000; Eccleston, 1997; Eccleston et al., 2000]. Thus, aqueous creams are more acceptable than oily creams. It was proposed that there are four different phases present in aqueous creams, i. e. a hydrophilic gel phase, a bulk water phase, a lipophilic gel phase and a dispersed oil phase. This four-phase system was known as gel network system. Further details was discussed under section 1. 3. 4 [Junginger, 1997] Therefore, it can be anticipated that an understanding of complexity and variability of the structure of aqueous creams is essential in characterizing and optimizing specifications of creams to improve the quality of formulated products and hence enhance dermatological drug delivery.

### 1. 3 Emulsifying agent

Emulsifying agents are generally surface-active agents that are exploited during the time of manufacture to enhance emulsification and also to confer long-term stability to products like pharmaceutical creams throughout their shelf-life. All these can be achieved by adsorption of emulsifying agents at the emulsion interface to decrease the interfacial tension and to produce repulsive forces between droplets. [Eccleston, 1992; Florence and Attwood, 2006; Rosen, 1978] As a result, the strong van der Waals forces of attraction between droplets when they come close together are counteracted by these repulsive forces leading to the prevention of coalescence of droplets. In addition, emulsifying agents also play an important role in controlling the rheological properties of formulations by interacting with other components in the system. [Eccleston, 1992; Florence and Attwood, 2006]

In practice, combinations of emulsifying agents are often used and they are normally consisting of ionic or non-ionic surfactants and lipophilic fatty amphiphiles like fatty alcohols or fatty acids, can be described as mixed emulsifiers. Moreover, the emulsifying waxes are commercial blends of mixed emulsifiers in which the weight ratio of fatty amphiphile to surfactant is nine parts : one part in the mixtures. Example of emulsifying waxes including Emulsifying Wax B. P. and Cetrimide Emulsifying Wax B. P. C. [Barry, 1971; Eccleston, 1997]

Table 1. Examples of commonly used surfactants and fatty amphiphiles. [Eccleston, 1992; Eccleston, 1997]

Surfactants	Fatty amphiphiles
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Sodium lauryl sulphate	Cetostearyl alcohol
Cetrimide	Cetyl alcohol
Cetomacrogol 1000	Stearyl alcohol
PEG 1000 monostearate	Glyceryl monostearate
Triethanolamine stearate	Stearic acid
Sodium stearate	Phosphatidylcholine

Table 2. Examples of commercial and pharmacopoeial emulsifying waxes with respective components. [Eccleston, 1992; Eccleston, 1997]

Emulsifying wax	Components
Emulsifying wax BP	Cetostearyl alcohol, sodium lauryl sulphate
Emulsifying wax USNF	Cetyl alcohol, polysorbate
Cationic emulsifying wax BPC	Cetostearyl alcohol, cetrimide
Glyceryl monostearate S. E.	Glyceryl monostearate, sodium stearate

Cetomacrogol emulsifying wax BPC	Cetostearyl alcohol, cetomacrogol 1000
Polawax	Cetyl alcohol, non-ionic surfactant
Lecithin	Phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidic acid

### 1. 3. 1 Schulman and Cockbain theory

Nowadays, many pharmaceutical literatures reviewed and cited the classical works of Schulman and Cockbain which published nearly 70 years ago as the emulsifier mixtures (combination of ionic surfactants and fatty alcohols) studied are similar to ionic emulsifying waxes that are currently used in formulations. [Eccleston, 1992] According to Schulman and Cockbain theory, it was revealed that molecular interactions arising at a "nujol" (oil-droplet)/water interface were correlated with the molecular interactions at an air/water interface which had been investigated by Schulman and Rideal in 1937. In this context, the stability of interfacial film of "nujol"-in-water emulsions was running correspondingly to the stability of the monolayer interfacial film at the air/water interface which normally composed of a stable complex of two components, i. e. oil soluble substance and water soluble substance. The stability of this condensed interfacial film at air/water interface depends upon the interactions between polar head groups of the components and van der Waals forces of attraction between the respective non-polar parts. Thus, the changes in nature and stereo chemical properties of the components may result in alteration of molecular packing and stability of interfacial films which in turn influences the stability of "nujol"-in-water

emulsions, as shown in Figure 2. Hence, it can be concluded that the understanding of the nature and properties of complex film at the air/water interface is important in deducing the stability of emulsions. [Schulman and Cockbain, 1940]

The greater stabilities of the mobile model emulsions were described in Schulman and Cockbain's publications, however, the detailed mechanism of stabilization of an emulsion was not explained evidently. Thus, Schulman and Cockbain theory cannot be directly imposed into the manufacturing of pharmaceutical emulsions in which the presence of excess emulsifiers above that necessary for a monolayer film, interact with other constituents in the system, either at the droplets interfaces or in the bulk water, to produce a complex multiple phase formulation. [Eccleston, 1992; Schulman and Cockbain, 1940]

### **1. 3. 2 Non-ionic surfactants**

Surfactants, which are one of the constituents of emulsifiers, can be classified into three different categories, such as ionic surfactant, non-ionic surfactant and amphoteric surfactant. Non-ionic surfactants would be the main focus in this study. Non-ionic surfactant is the largest group of surfactant if compared with anionic, cationic surfactant and amphoteric surfactant. This group of surfactant does not bear any charge on their molecule and they are less irritating to eyes and skin if compared to anionic or cationic surfactant. Proportions of hydrophilic or hydrophobic groups in the non-ionic surfactant molecule are crucial in determining the characteristics of this group of surfactants. Generally, the hydrophobic part of molecules contains saturated or unsaturated fatty acids or fatty alcohols

whereas the hydrophilic part of molecules includes the polyoxyethylene, polyoxypropylene or polyol derivatives and the hydroxyl group. Compounds with a wide range of hydrophilic-lipophilic balance (HLB) can be obtained by varying the number of hydrophilic groups or the length of lipophilic chains in the molecules. [Nielloud and Marti-Mestres, 2000]

HLB system is a system invented about 60 years ago by William C. Griffin and it was developed for the use with non-ionic surfactants. All non-ionic surfactants have an HLB value. The HLB values signify an empirical numerical correlation of the emulsifying and solubilizing properties of different surfactants. The higher the HLB number, the more hydrophilic the surfactants; The lower the HLB number, the more lipophilic the surfactants. In other words, the HLB number is an expression of the percentage weight of the hydrophilic portions calculated theoretically from molecular weight. In addition, emulsions and emulsion applications have specific HLB requirements. Therefore, emulsions with optimal performance can be yielded by matching the HLB requirement with the surfactant's HLB value. This correlation can be obtained by performing direct experimental tests, though for some systems the HLB value can be estimated by empirical rules from the analysis of the surfactants.

[Davies, 1957; Eccleston, 1992; Griffin, 1949]

Table 3. Classification of emulsifiers according to HLB values [Davies, 1957; Eccleston, 1992; Griffin, 1949]



Range of HLB values	Emulsion Application
0-3	Antifoaming agents
3 – 6	Water-in-oil emulsifier
7-9	Wetting agent
8-18	Oil-in-water emulsifier
13-15	Detergent
15-120	Solubilizer

In this investigation, polysorbate 60 (Tween 60) was used. Polysorbates are complex mixtures of partial fatty acid esters or sorbitol and its mono- and dihydrides copolymerised with approximately 20 moles of ethylene oxide for each mole of sorbitol and its anhydrides. The polysorbates are miscible with water as reflected in their higher HLB and are used as emulsifying agents for o/w emulsions. The HLB value of polysorbate 60 (polyoxyethylene (20) sorbitan stearate) is 14.9. [Florence and Attwood, 2006]

### 1.3.3 Fatty alcohols

Fatty alcohols are generally functioning as a relatively weak emulsifier when they are used alone to produce unstable and fluid water-in-oil type of emulsions. However, the most commonly used emulsifiers could be formed

from the combination of fatty alcohols and ionic or non-ionic surfactants. As for cetostearyl alcohol BP, it is a mixed homologue alcohol as it composed of mixture of cetyl and stearyl alcohol with the weight ratio of six to one. This homologous admixture was presented in excess which gave rise to a ratio of nine parts by weight of fatty alcohol to one part of ionic surfactant or four parts of fatty alcohol to one part of non-ionic surfactant. [Eccleston, 1997]

The pure long chain alcohols exhibited marked crystalline polymorphism as normally they presented in three forms such as  $\alpha$ -form,  $\beta$ -form and  $\gamma$ -form. In addition,  $\alpha$ -crystalline polymorph was able to create a hydrated crystal in the presence of water via mechanism of limited swelling, as shown in Figure 3.

At room temperature (25 $^{\circ}$ C), mixed homologue alcohols like cetostearyl alcohol existed in a stable  $\alpha$ -modification form whereas pure alcohol such as cetyl or stearyl alcohols in water existed in the form of  $\beta$  and  $\gamma$  crystals.

[Eccleston, 1997; Yoon et al., 1999] This indicated that homologue admixtures are more preferable in producing stable emulsions if compared to pure fatty alcohols.

### **1. 3. 4 Mixed emulsifiers with gel network system**

The consistencies of emulsions are controlled by the concentrations of mixed emulsifiers in a direct proportional manner where at low concentrations of mixed emulsifier, the emulsions formed are liquid and mobile while at moderate or high concentrations of mixed emulsifier, a semi-solid emulsions can be formed. This process can be known as a “ self-bodying” action.

[Barry, 1971]

In general, mixed emulsifiers are needed in stabilizing oily dispersed phase with continuous phase in the system. When the presence of these emulsifiers

is surplus to requirements, they interact with each other to form a viscoelastic gel networks in the continuous phase. The formation of this gel networks is related to the stabilities, physico-chemical and rheological behaviours of emulsions. The theory evolved is known as gel network theory. This gel network theory was a result of the study of the types of interaction between surfactant, fatty amphiphile and water of a ternary surfactant-water-amphiphile system. [Eccelston, 1997] Furthermore, the properties and phase behaviours of a range of concentration of mixed emulsifiers and their components in water (ternary system) both below and above the phase transition temperature were investigated and exploited as structural models for the continuous phase of emulsions. [Eccleston et al., 2000] Moreover, it was proposed that the gel network system of non-ionic semisolid cream consisted of four main phases with the similar structural elements as the ionic cream, i. e. a hydrophilic gel phase composed of a hydrated lamellar mixed crystals formed by non-ionic surfactant and fatty alcohol with the incorporation of interlamellarly fixed water, a lipophilic gel phase created mainly by the surplus of fatty alcohol, a bulk water phase and a dispersed oil phase, as shown in Figure 4. [Junginger, 1997]

The swelling properties of gel network system depend on total water content and the chain length of polyoxyethylene (in the case of non-ionic polyoxyethylene surfactant) of the system.[Junginger, 1997] According to study of Junginger, with a non-ionic hydrophilic cream ( PGM20(polyoxyethylated-20-glycerol monostearate) -cetostearyl alcohol - water system ) , at a water content less than 25% w/w, the degree of swelling is minimal due to the inadequate hydration of polyoxyethylene

chains of non-ionic surfactant. On the other hand, at a water content more than 60% w/w, the hydrophilic gel phase of the system becomes unstable because of the excess swelling. Thus, the optimal water content must be in the range of 25-60% w/w in order to allow the continuous swelling of hydrophilic gel phase of the system. [Junginger, 1984] Moreover, the chain length of polyoxyethylene of surfactant influences the ratio of interlamellarly fixed water and bulk water in the system. This ratio is important in affecting the cooling effects of cream, the controlled release of water and the release of active agents from vehicle onto the skin. [Junginger, 1984; Junginger, 1997]

The lamellar phases are phases in which surfactants molecules are arranged in the form of bilayers which separated by layers of water. The hydrocarbon chains of bilayers can present in a few types of different physical states such as liquid crystalline state (disordered state) or gel state (ordered state). However, the liquid crystalline phase could be gradually converted to a desired gel phase under suitable phase transition temperature which allows the melting of hydrocarbon chains without the loss of long-range order, as shown in Figure 5. [Eccleston, 1992; Eccleston, 1997] The presence of homologue admixtures and unsaturated or branched hydrocarbon chains could lower the transition temperature whereas the increase in the length of hydrocarbon chains would increase the transition temperature. According to a study of stabilizing agent of parenteral fat emulsion, the transition temperature of commercial soybean lecithin which possesses a long range of unsaturated C16-C18 hydrocarbon chains was lower than saturated

dimyristyl lecithin, with transition temperature of -21° and 42° respectively.

[Eccleston, 1992]

#### **1. 4 Emulsion Stability**

In practice, the stability of emulsions is generally referring to the ability of components of an emulsion including the dispersed and continuous phase to maintain their original characteristics upon manufacturing throughout a desired shelf life, without the presence of any changes in colour, viscosity, odour, texture, phase behaviour and microbial stability of emulsions on storage.

The mechanisms of stabilization are different in various emulsion systems. For liquid emulsions, the stability of system was normally affected by the processes of flocculation and coalescence of dispersed particles in continuous phase which resulted from the forces-orientated aggregation of dispersed droplets and the rupture of thin film of continuous phase respectively. However, these two processes were not applicable for semi-solid emulsions as they were more structurally complex and more concentrated than liquid emulsions in which these characteristics prevented the semi-solid emulsions from being susceptible to the process of flocculation and coalescence and thus stability of the system could be maintained. [Eccleston and Florence, 1985]

In contrast, the stability of semi-solid emulsions was governed by the phase behaviour of emulsifiers on storage. [Eccleston and Florence, 1985] Based on this, the presence of batch variations in the emulsifiers contributed to the instabilities of semi-solid emulsions during storage. In the case of non-ionic

semi-solid creams, the formation of an additional gel phase, which is unwanted for cosmetic use and drug bioavailability, was resulted from the increased hydration of non-ionic polyoxyethylene chains of emulsifiers during storage. As a consequence, the masses of emulsifying wax vanished and the consistencies of the system increased over a period of time on storage. These caused changes in microstructure of the system which in turn rendered instabilities in the system. Besides, the batch variations in polyoxyethylene chain lengths of non-ionic surfactants and in mixed homologue compositions of fatty alcohols gave rise to the alterations of consistency and stability of the system. Hence, structural breakdown of the system would be induced after an extended period on storage. [Eccleston, 1992] The evaluation of stability of semi-solid emulsions must be done at storage temperature under a long period of time as they are liable to phase changes at high temperature condition or on heating. [Flynn, 2002]

### **1. 5 Aims of the study**

In this study, the effects of pure and mixed homologue alcohols on aqueous creams prepared with non-ionic surfactant/ fatty alcohol mixed emulsifiers will be investigated by using microscopic, rheological and thermal techniques. Besides, the suitable ratio by weight of fatty alcohol to non-ionic surfactant in order to produce stable emulsions or creams will also be determined at the end of this study. Tween 60/ fatty alcohol systems were selected for this study. Thus, the overall aim of this study was to examine the detailed microstructure of the Tween 60/ fatty alcohol systems and to relate this structure to rheological properties and stability of creams.

## **1. 6 Analytical procedures and equipment**

### **1. 6. 1 Analytical Procedures**

The influence of pure and mixed homologue alcohols on rheological properties and stability of the standard cream prepared by non-ionic emulsifying wax, i. e. Tween 60 and fatty alcohol, will be examined. Therefore, the very first step to be taken is to prepare a standard cream, before the use of any analytical techniques. The standard cream can be formulated by varying or adjusting the concentration of non-ionic surfactant followed by the adding of fatty alcohol. Different types (pure or mixed homologues alcohols) and different concentrations of fatty alcohols will be used in order to obtain a suitable ratio by weight of fatty alcohol to non-ionic surfactant in formulation of stable cream. Following the addition of fatty alcohols, the gel network formed, as for interlamellar water layers spacing, will be influenced and thus the properties and stability of cream will be affected as well. Different analytical techniques, such as X-ray diffraction, rheometers, DSC (Differential Scanning Calorimetry), thermogravimetric technique, light and electron microscopy, creep analysis, dielectric analysis as well as NMR, had been used in many of the previous studies to examine the microstructure and properties of creams. Yet, in this study, the analysis will be mainly focusing on structure/system of emulsion, viscosity of cream (rheological properties) and transitional temperature (stability of cream). Therefore, light and electron microscopy, rheometer and thermal technique like DSC will be employed to achieve the aims of study.

### **1. 6. 2 Analytical Techniques**

Light and electron microscopes will be exploited to examine the structure/system of emulsion. On the other hand, the viscosity of cream will

be measured by using rotational rheometer as it works effectively in analysing changes in viscosity of non-newtonian fluids. Concentric cylinders rheometer is a preferred rheometer for this study because it is relatively easy to handle and cheaper than other rheometers. [Lapasin and Prici, 1999] Last but not least, transition temperature of cream will be determined with the use of DSC as this technique is able to detect the phase changes (from liquid phase to gel phase) based on the change of enthalpy. If compared with other techniques such as hot stage microscopy and capillary melting, DSC is more widely used and lesser amount of sample is needed in the study.

[Wells, 1988; Laye, 2002]

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