FACULTEIT FARMACEUTISCHE WETENSCHAPPEN

Evaluation and analysis of sucrose stearate as possible surfactant for oral formulation development in pharmaceutical industry

Hanne Van Den Haute

A master dissertation for the study programme Industrial Pharmacy

Industrial Promotor: Jan Leys

Supervisor: Kim Verwaest

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SUMMARY

This thesis compiles the evaluation and analysis of eight grades containing sucrose stearate retrieved from five different suppliers. Three pharmaceutical grade (SE 5S, SE 11S and SE 15S), four cosmetic grade materials (SP50-C, SP70-C, Tegocare SE 121 MB and Emulgade Sucro Plus) and one cosmetic and food grade material (Crodesta F160) are evaluated. In the first part general properties and the regulatory status of the materials are discussed and compared with specifications to comply with in order to be acceptable for use as excipient in oral pharmaceutical formulations. SE 5S, SE 11S and SE 15S comply with the requirements for use in oral delivery systems. SP50-C, SP70-C and Crodesta F160 are offered as cosmetic grade materials, however they have potential for use in oral formulations as well. Crodesta F160 is already used in capsule coatings and two other types: Crodesta F10 and Crodesta F110 are listed in the FDA IIG list.

The second part includes functional properties of the materials where the solubility is evaluated, and surface tension and critical micelle concentration measurements are carried out. From the experimental part it is seen that solubility is of concern for most materials. For SP50-C, SP70-C and Crodesta F160 more or less clear solutions are obtained in water at 60 °C. The addition of a small fraction of ethanol increases the solubility of the materials, and SE 11S and SE 15S are seen to become soluble in a mixture containing 10 % ethanol. Regarding the reduction in surface tension at concentrations above the critical micelle concentration, no big differences are seen concerning the different materials, regardless of their solubility. For SE 5S and Tegocare SE 121 MB the surface tension deviates fairly from that of the other materials. For neither of the materials, the addition of ethanol did impact the surface tension measured above the critical micelle concentration. When acceptable solubility is obtained, no big differences are measured for the critical micelle concentration. However, the addition of ethanol results in a strong decrease of the critical micelle concentration for the materials that do not show good solubility in water, since the effect of solubility exceeds the effect of ethanol on the critical micelle concentration.

Lastly, an overview of some critical material attributes regarding sucrose stearate materials is listed. The mono-, di-, tri- and polyester content, C16 + C18 content and the free fatty acid content of the materials are considered critical to ensure the desired quality of outcome products.

SAMENVATTING

Deze thesis omvat de evaluatie en analyse van acht verschillende stalen die sucrose stearaat bevatten. Deze stalen werden verkregen bij vijf verschillende leveranciers. Drie stalen voldoen aan de farmaceutische kwaliteitsvereisten (SE 5S, SE 11S en SE 15S), vier stalen worden aangeboden als zijnde cosmetische materialen (SP50-C, SP70-C, Tegocare SE 121 MB en Emulgade Sucro Plus) en één materiaal voldoet aan de cosmetische en voedingskwaliteitseisen (Crodesta F160). In het eerste luik werden algemene eigenschappen en de regulatoire status van de materialen besproken en vergeleken met specificaties waaraan voldaan moet worden om gebruik toe te laten als hulpstof in farmaceutische formulaties. SE 5S, SE 11S en SE 15S voldoen hierbij aan de vereisten voor gebruik via orale toedieningsroutes. SP50-C, SP70-C en Crodesta F160 worden weliswaar beschikbaar gesteld als cosmetische materialen, maar hebben daarnaast ook potentieel om gebruikt te worden in orale formulaties. Crodesta F160 wordt reeds gebruikt in de coating van capsules en twee andere types: Crodesta F10 en Crodesta F110 staan vermeld in de FDA IIG lijst.

Het tweede luik omvat een analyse van de functionele eigenschappen van de materialen waarbij de oplosbaarheid, oppervlaktespanning en de kritisch micellaire concentratie werden bepaald. Op basis van het experimenteel werk werd gezien dat de oplosbaarheid voor de meeste materialen een probleem vormt. Voor SP50-C, SP70-C en Crodesta F160 werden min of meer heldere oplossingen bekomen in water bij 60 °C. Toevoeging van ethanol resulteerde algemeen in een toegenomen oplosbaarheid van de materialen waarbij SE 11S en SE 15 eveneens heldere oplossingen vormden in een mengsel met 10 % ethanol. Betreffende de reductie in oppervlaktespanning boven de kritisch micellaire concentratie werden geen grote verschillen waargenomen tussen de verschillende materialen ongeacht hun oplosbaarheid. Voor SE 5S en Tegocare SE 121 MB werd een oppervlaktespanning gezien die afwijkend is van de andere materialen. De toevoeging van ethanol resulteerde voor geen van de materialen in een gewijzigde reductie van de oppervlaktespanning boven de kritisch micellaire concentratie. Wanneer een aanvaarbare oplosbaarheid wordt bekomen, werden geen grote verschillen gemeten in de kritisch micellaire concentratie. De toevoeging van ethanol resulteert echter wel in een sterke afname van de kritisch micelaire concentratie voor die materiaal die slecht oplossen in water aangezien het effect van oplosbaarheid het effect van ethanol op de kritisch micelaire concentratie overstijgt.

Tot slot werd een overzicht opgelijst met kritische materiaaleigenschappen omtrent materialen die sucrose stearaat bevatten. Hierbij worden de mono-, di-, tri- en polyester hoeveelheid, C16 + C18 hoeveelheid en de hoeveelheid vrije vetzuren aanwezig in de materialen als kritisch beschouwd om de gewenste kwaliteit van eindproducten te verzekeren.

ACKNOWLEDGMENT

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ABBREVIATIONS

ADI	Acceptable daily intake
APG	Alkyl polyglycosides
API	Active pharmaceutical ingredient
BSE	Bovine spongiform encephalopathy
CAS	Chemical abstracts service
CFR	Code of federal regulations
CMA	Critical material attributes
CMC	Critical micelle concentration
CTAB	Cetyl trimethylammonium bromide
EFSA	European Food Safety Authority
EU	European Union
HLB	Hydrophilic-lipophilic balance
INCI	International Nomenclature of Cosmetic Ingredients
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JP	Japanese Pharmacopoeia
LD_{50}	Lethal dosis 50 %
NOAEL	No observed adverse effect level
O/W	Oil-in-water
Ph. Eur.	European Pharmacopoeia
POE	Polyoxyethylene
SEFA	Sucrose esters of fatty acids
SFT	Surface tension
SFT_{CMC}	Surface tension at the critical micelle concentration
$SFT_{>CMC}$	Surface tension above the critical micelle concentration
SLS	Sodium lauryl sulphate
TSE	Transmissible spongiform encephalopathies
USP-NF	United States Pharmacopoeia - National Formularium
W/O	Water-in-oil

1 INTRODUCTION

Surfactants are an important class of chemical compounds possessing both hydrophilic and hydrophobic moieties. Whereas the hydrophilic group shows affinity to aqueous phases, the hydrophobic group shows affinity to oily phases. These amphiphilic molecules are surface active compounds that adsorb to the interface between two phases decreasing the interfacial tension. Surfactants with a stronger tendency to accumulate at the interface are considered better than surfactants which are less surface active [1].

1.1 CLASSIFICATION OF SURFACTANTS

Surfactants can be classified based on the charge of the polar head group as anionic, cationic, zwitterionic or non-ionic [2]. Anionic and cationic surfactants dissociate in aqueous solutions into anions and cations respectively. Zwitterionic surfactants, having a net neutral charge, do not dissociate due to the counterparts being covalently bound [3]. Most ionic surfactants are monovalent but also divalent amphiphiles exist [1].

1.1.1 Anionic surfactants

Approximately 50 % of the rough estimated surfactants produced worldwide are anionic [4]. They are popular because of the ease and low cost of manufacturing. Anionic surfactants are used frequently in detergents and the best detergency is obtained by alkyl and alkylaryl chains in the C_{12} - C_{18} range. While anionic surfactants are excellent for suspending soils, they are not as good at emulsifying oily soils. This class of surfactants typically creates a lot of foam [1]. The most commonly used surfactant in cosmetic products used to aid foaming is sodium lauryl sulphate (SLS, E487). The chemical structure of SLS is illustrated in Figure 1.1 [5].

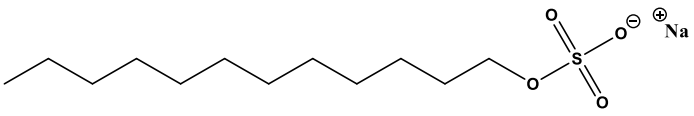
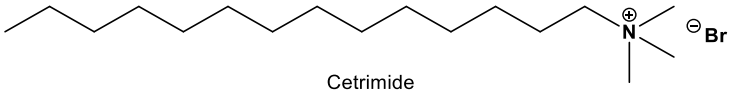


Figure 1.1: Chemical structure of sodium lauryl sulphate.

1.1.2 Cationic surfactants

The class of cationic surfactants accounts for 5-6% of the overall surfactant production. These surfactants are more expensive than anionic surfactants, because a high pressure hydrogenation reaction needs to be carried out during their synthesis. Consequently, these surfactants are only used when no cheaper substitute can be used: (1) as bactericide, (2) as positively charged substance which is able to adsorb on negatively charged substrates to produce antistatic and hydrophobic effects. They are not good detergents nor foaming agents, and they cannot be mixed in formulations which contain anionic surfactants [4]. Both amine compounds, which cannot be used at high pH, and quaternary ammonium based products, which are not pH sensitive, are common. The counterion of cationic surfactants is usually a halide or methyl sulphate. Figure 1.2 shows the chemical structure of the cationic surfactant cetrimide [1].



Cetrimide

Figure 1.2: Chemical structure of the cationic surfactant cetrimide.

1.1.3 Zwitterionic surfactants

Zwitterionic surfactants are quite expensive. Because these surfactants exhibit low eye irritation and have high biological compatibility their use is limited to shampoos and other cosmetics. The dual charges of zwitterionic surfactants cancel each other out creating a net charge of zero. The physicochemical behaviour often resembles that of non-ionic surfactants, meaning these surfactants possess good interfacial activity. Similar to non-ionic surfactants, zwitterionic surfactants function well in high electrolyte formulations [1].

Amphoteric surfactants are only zwitterionic over a certain pH range, because neither the acid nor the base site is permanently charged. The net charge is dependent of the environmental pH. In Figure 1.3 the zwitterionic surfactants betaine and amidobetaine are shown. Imidazoline and the amino acid based sodium lauryl glutamate are examples of amphoteric surfactants [1].

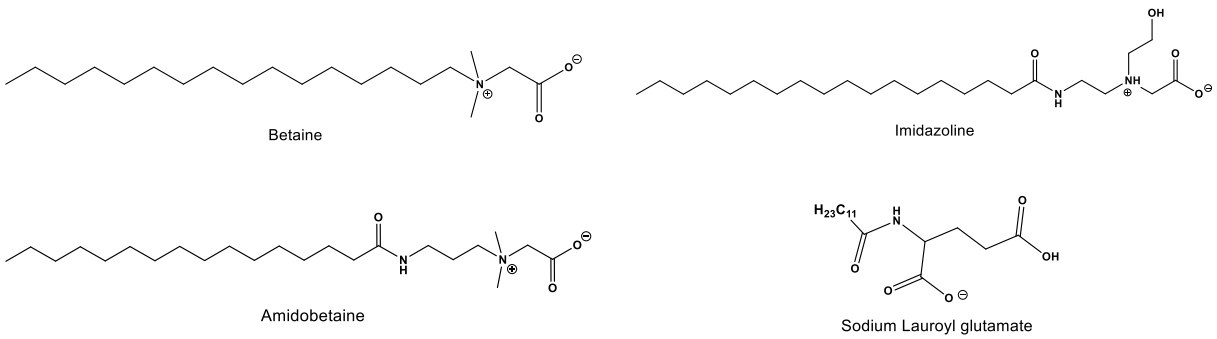


Figure 1.3: Chemical structure of zwitterionic (left) and amphoteric (right) surfactant molecules.

1.1.4 Non-ionic surfactants

Non-ionic surfactants make about 45 % of the overall industrial production of surfactants. Their hydrophilic group is a non-dissociable group, such as alcohol, phenol, ether, ester or amide. These surfactants can be made more hydrophilic by the presence of a polyethylene glycol (PEG) chain, obtained by the polycondensation of ethylene oxide on a hydroxyl or amine group [4]. Contrary to ionic surfactants, non-ionic surfactants are much less sensitive to electrolytes. As non-ionic surfactants are good at emulsifying oils, they are better detergents than the anionic surfactants. To create 'dual-action cleaners' that can both suspend soils, but also emulsify oily soils, non-ionic and ionic surfactants are frequently used together. Besides non-ionic surfactants exhibit very low toxicity levels and are used in pharmaceuticals, cosmetics and food products. A common example of non-ionic surfactants are fatty acid esters of sorbitan (trade name: Span). The sorbitan ester surfactants are edible and hence, useful for food and drug applications where they are useful in stabilizing O/W emulsions. The corresponding ethoxylated products, polysorbates (trade name: Tween), make up the most important type of the non-ionic surfactant class. Figure **1.4** shows the chemical structure of polysorbate 20 and polysorbate 80 which are both commonly used in pharmaceutical industry [6].

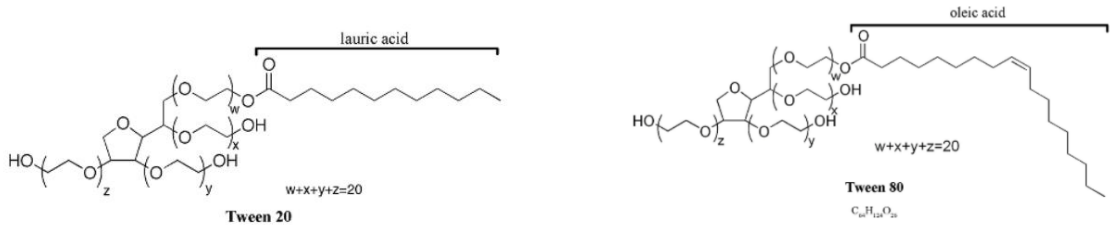


Figure 1.4: Chemical structure of polysorbate 20 (left) and polysorbate 80 (right).

1.2 SURFACTANT CHARACTERISTICS

1.2.1 Wetting properties

When placed on a flat, homogeneous solid surface a drop of liquid comes to equilibrium, having a shape which minimizes the total free energy of the system. This is illustrated in Figure **1.5**. The angle between the liquid and the solid is called the contact angle (θ) and can be calculated from Young's equation given in Equation **1.1** and Equation **1.2** if the interfacial tensions are known [7].

$$\sigma_S = \sigma_{Sl} + \sigma_l . cos\ \theta \qquad \text{Equation 1.1}$$

or

$$cos\ \theta = \frac{(\sigma_S - \sigma_{Sl})}{\sigma_l} \qquad \text{Equation 1.2}$$

Where:
- σ_s: The interfacial tension between the solid and air,
- σ_l: the interfacial tension between the liquid and air,
- σ_{sl}: the interfacial tension between the solid and liquid phase.
- θ: Contact angle of the solid and liquid interface.

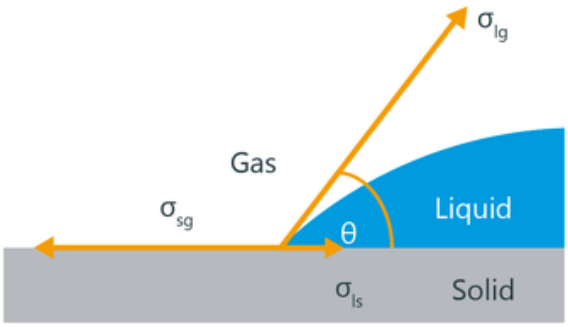


Figure 1.5: Representation of the forces impacting the contact angle at equilibrium [7].

For contact angles below 90° the solid is considered good wettable. For contact angles above 90° on the other hand, it is considered that no good wetting takes place. A contact angle of 0° means complete wetting of the solid and in case of ultrahydrophobic materials the contact angle approaches the theoretical limit of 180°[7].

1.2.2 Critical micelle concentration

When adsorption of surfactant molecules takes place at the liquid-air interface the hydrophilic part of the surfactant molecule is directed towards the aqueous liquid and the hydrophobic tail is directed towards the air. As the surfactant concentration increases, more and more surfactant molecules adsorb at the liquid-air interface. During the accumulation the interfacial tension decreases until the surface is fully overlaid [8].

Above the corresponding concentration, micellization occurs, whereby the hydrophobic parts of the surfactants group together in the centre of the structure protected from water and the hydrophilic parts are exposed to water. Therefore, this concentration is referred to as the critical micelle concentration (CMC). Regardless of the amount of surfactant added to the solution, the unimer concentration will never exceed the CMC. The effect of increasing the surfactant concentration on both the surface tension as well as the formation of micelles is illustrated in Figure 1.6 [8].

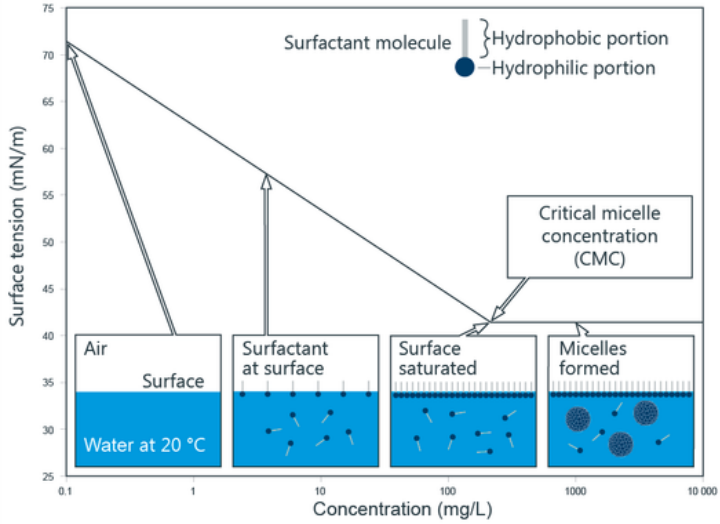


Figure 1.6: Visual representation of the behaviour of surfactant molecules at different concentration levels and their effect on the surface tension [8].

In **Appendix 1**, CMC-values of different surfactants are given. Typically, CMC-values of non-ionic surfactants are lower than those of ionic surfactants. For ionic surfactants the CMC decreases with increasing alkyl chain length of the surfactant. Moreover, the effects of charge of the head group are moderate. For oxyethylene non-ionic surfactants (POE), there is a moderate decrease in the CMC as the polar head becomes larger [1,9].

1.2.3 Critical Packing Parameter

At CMC, surfactant molecules spontaneously self-assemble into many different sizes and shapes. Overall, ionic surfactants form smaller micelles than non-ionic surfactants as for ionic surfactants the electrostatic repulsion between the ionic head-groups is greater than the steric repulsion between non-ionic head groups [1]. On the other hand, the shape of the micelles is strongly influenced by the relative size of the head group and tail group. The equilibrium structure is the result of the competition between the propensity of the head groups for the solvent and the tendency of hydrocarbon tails to minimize contact with the solvent [9].

This critical packing parameter (N_s) is the ratio between the volume of the hydrophobic tail of the surfactant (V) and the product of the surface area of the headgroup (A) with the chain length of the hydrophobic tail of the surfactant (L). This dimensionless ratio gives the best explanation to understand which self-assembly structure will be formed. Therefore mathematically, N_s can be calculated by using the following Equation **1.3** [10]:

$$N_S = \frac{V}{A \cdot L} \qquad \textbf{Equation 1.3}$$

Where: N_S: The cricital packing parameter,

V: The effective hydrocarbon volume,

A: The surface area of the headgroup of the surfactant,

L: The fully extended chain length.

The packaging parameter is < 0.33 for spherical micelles, between 0.33 and 0.5 for cylindrical micelles, between 0.5 and 1 for lamellar structures and > 1 for reverse micelles [10]. These aggregate types are illustrated in Figure **1.7** [11].

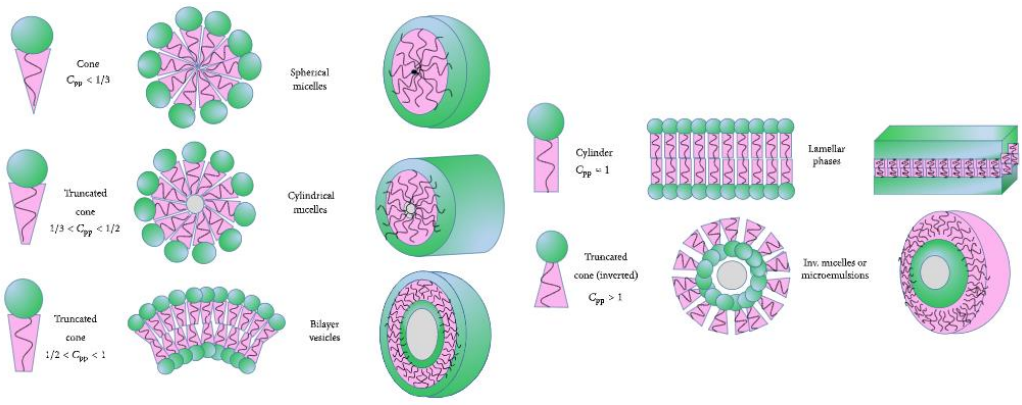


Figure 1.7: Different micelle shapes based on the critical packing parameter of the surfactant molecule [11].

1.2.4 Hydrophilic-lipophilic balance

Whereas ionic surfactants typically are well soluble in aqueous media, the solubility of non-ionic surfactants depends on the balance between the hydrophilic group's affinity towards water and the lipophilic group's affinity towards oil [2]. Griffin undertook a systematic ranking, using numbers, to indicate the hydrophilic-lipophilic balance (HLB). This was done by comparing two important aspects: (1) the type of emulsion formed (O/W or W/O) and (2) the stability of the emulsions formed by using different oils. The scale ranges from 1 to 20, with 1 depicting the most hydrophobic material and 20 being the most hydrophilic material. Surfactants with a low HLB value are typically more soluble in oil whereas surfactants with a high HLB value are more soluble in water. Since HLB indicates the characteristics of the non-ionic surfactants, it is commonly used as an indicator for choosing a surfactant for specific applications, such as wetting agents or emulsifiers, as illustrated in Figure 1.8 [1,6,12].

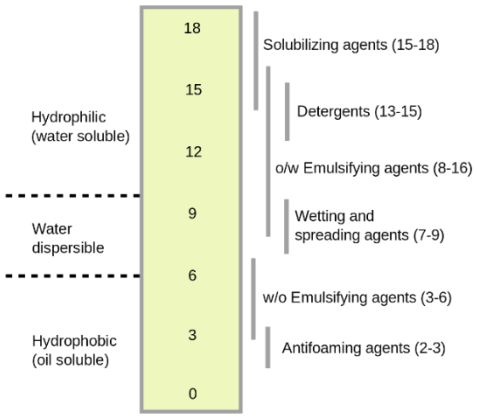


Figure 1.8: Applications of surfactants with different HLB values [12].

Although, the HLB-system has great value, there are some drawbacks against the use of this system as it does not take into account the effect of temperature and the addition of electrolytes. It has been observed that the apparent HLB of ethoxylated non-ionic surfactants decreases with increased temperature as discussed in the following section. Moreover, the addition of electrolytes, such as NaCl, results in salting-out of the surfactant whereby the surfactant molecules become less hydrophilic, and the apparent HLB is decreased [13].

1.2.5 Krafft point and cloud point

The krafft phenomenon is denoted as the increase in solubility of the surfactant by orders of magnitude in a relatively narrow temperature range. The onset temperature of the strongly increasing solubility is known as the krafft point. Generally, at higher temperatures, surfactants display an increased solubility and CMC because an increase in temperature is associated with an increased kinetic energy of the system. The solubility at krafft point is called the CMC of the surfactant [1,9,10]. The temperature dependence of surfactant solubility in the region of the krafft point is illustrated in Figure **1.9** and the correlation between CMC and the temperature is illustrated in Figure **1.10** [1].

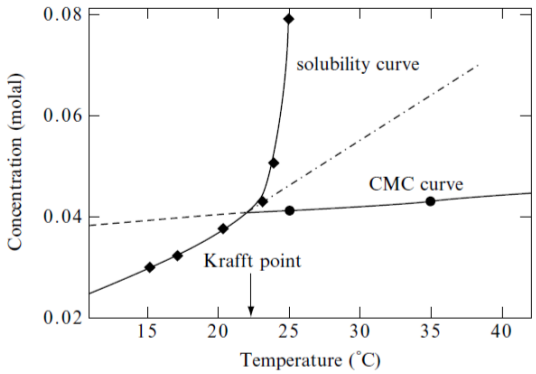


Figure 1.9: Curve showing the determination of Krafft point [1].

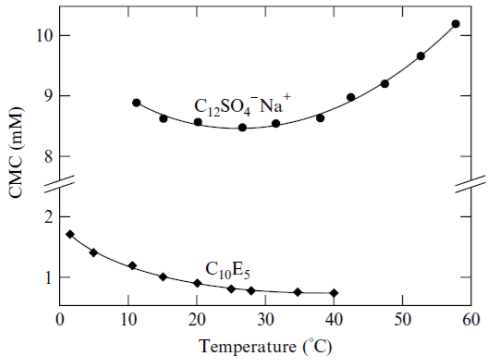


Figure 1.10: Change in critical micelle concentration for SLS and a polyoxyehtylene non-ionic surfactant [1].

However, non-ionic surfactants of the POE-type show inverse solubility and typically display a pronounced decrease in CMC with increasing temperature as illustrated in Figure **1.10**. This phenomenon occurs because the solubility of surfactants of the POE-type is due to the hydrogen bonding to water molecules. The increased kinetic energy causes the hydrogen bonds to break. At the transition temperature, referred to as the cloud point, phase separation occurs and the solution becomes turbid. Above their cloud point, surfactants may start to lose their surface active properties [9]. Electrolytes may either increase or decrease the cloud point due to interaction with the surfactant molecules. The effect is mainly dominated by anions and follows the Hoffmeister lyotropic series [1].

1.3 APPLICATIONS OF SURFACTANTS

Initially surfactants were used mostly in the soap industry, but nowadays surfactants have a wide variety of applications. They are present in pharmaceutical products, cosmetics, foods, drinks, cleaning products, clothes and petrochemical industry. In this thesis the focus will be on the use of surfactants for oral formulation development in pharmaceutical industry [14].

1.3.1 Detergents

The high surface tension of water makes it a relatively poor cleaning detergent. The cleaning efficiency can be increased slightly by increasing the temperature of water as this decreases the surface tension. However, addition of surfactants is needed to have good detergency [15]. Wetting agents that rapidly diffuse and adsorb at appropriate interfaces are most effective. Nowadays, anionic surfactants, particularly alkylbenzene sulfonates, are the most widely used surfactants in detergents. Among the non-ionic surfactants, those of the POE type are the most commonly used. Alkyl polyglucosides (APG) are derived from entirely renewable raw materials and are used in liquid detergents and dishwashing liquids. They are expected to play an important role in the future [16].

1.3.2 Food stability

Typically, in food products some naturally occurring emulsifiers, such as proteins and lipids are present, but they can also be added during the production stage [15]. Some of the most common surfactants used in food industry are lecithins (E 322), polysorbates (E 432 – 436), monoglycerides (E 471), sucrose esters (E 473), polyglycerol esters (E 475), propylene glycol esters (E 477) and sodium stearoyl-2-lactylate (E 481). In most cases, commercial food emulsifiers contain glycerol, sorbitol, sucrose, propylene glycol or polyglycerol as the hydrophilic part and the hydrophobic part is formed by fatty acids derived from fats and oils [17].

1.3.3 Cosmetics

When putting a surfactant solution on surfaces like hair or skin, the oil will be drawn away from the surface into the micelles, since micelles have the ability of suspending oil in water. In emulsion formulas, like creams and lotions an emulsifier is used to help blend and stabilize the mixture. The oil remains suspended in the center of the micelles until the product is applied to the skin or hair where the micelles break open and deliver the oily materials. Non-irritating surfactants can also be used as conditioning agents when left behind on surfaces like skin and hair. The oily part of the molecules is responsible for improving the feel and look of the surface. In addition, some surfactants can be used as a preservative since they have anti-microbial effects [18]. Sorbitan esters and ethoxylated fatty alcohols and fatty acids have applications in many cosmetic products [19].

1.3.4 Pharmaceutical excipient

Among surfactants used in oral pharmaceutical formulations, SLS, polysorbate 20 and polysorbate 80 are some of the most frequently used [20]. Surface tension plays a crucial role in the following pharmaceutical processes:

(i) Solubilisation enhancement

Surfactants in concentrations above the CMC can increase drug solubility. For pharmaceutical products that are poorly soluble in water, the use of surfactants becomes inevitable [3,21]. In aqueous systems, micelles have the ability of solubilising hydrophobic drugs within their interior as non-polar compounds will be more attracted to the non-polar interior of the micelle. Thermodynamically stable isotropic solutions are formed [18]. Sorbitan mono-oleate and polysorbates are examples of surfactants used as solubilizing agents [22].

(ii) Stabilize emulsions

Since surfactants have the property to form stable emulsions, they are included in pharmaceutical, cosmetic, and food formulations [22]. When two or more immiscible liquids are mixed, coalescence occurs to reduce the interfacial energy in the emulsion. By absorbing at the oil-water interface surfactants have the ability of lowering the interfacial energy which prevents coalescence of the drops and thus stabilizes the emulsion. In addition, the surfactant molecules can produce repulsive electrical forces due to an electrical double layer between approaching droplets [18]. W/O-emulsions contain surfactants with low HLB-values such as sorbitan esters and for O/W-emulsions water-soluble surfactants are used. These may be anionic, cationic, zwitterionic or non-ionic [22].

(iii) Wetting of solids

Surface active agents have been widely shown to enhance drug dissolution rates. Consequently, surfactants have been included in tablet and capsule formulations to improve wetting and deaggregation of drug particles and thus increase the surface area of particles available for dissolution. The wetting effect is operative at concentrations below the CMC [22].

In binders for granulation, surfactants are used at concentration levels of 0.1 to 0.5 % m/V. Surfactants are added in the binder solutions for wet granulation to improve wettability of a powder bed by lowering the surface tension and the contact angle of the binder liquid [23]. Wetting and spreading ability of the binder over the substrate is important in good granulation, especially for hydrophobic powders. The work of Krycer et al.

showed that the addition of SLS remarkedly improved the spreadability of a binder solution and granule friability was significantly decreased. However, tablet crushing strength was only modestly influenced. Besides SLS, also polysorbates are typical surfactants which can be added to binder solutions [24].

(iv) Wetting agent in suspensions

Surfactants are used in the formulation of suspensions to aid dispersion of the solid particles in the liquid. This is particularly important if the powder is not readily wetted by the liquid vehicle. Surfactants reduce the interfacial tension between the solid particles and the liquid vehicle which results in a reduction of the contact angle. Consequently, wetting of the solid particles is promoted and the system is said to be deflocculated. The inclusion of a surface active agent to improve powder wettability will often also improve the bio-availability of the formulation. To avoid toxicity, surfactants typically are used at concentrations of maximum 0.5% m/V [22].

1.4 DRAWBACKS OF COMMONLY USED SURFACTANTS IN ORAL FORMULATIONS

SLS and polysorbate 20 are among the most commonly used surfactants in pharmaceutical formulations for oral use [5]. Although SLS is not a permitted food additive in the European Union (EU) and there is no EU regulatory guideline or recommendation regarding acceptable levels of SLS in medicinal products, its use is regarded as safe at low concentrations. In rats an LD_{50} of 800 – 3 100 mg/kg/day is reported [5,25]. SLS is not recommended for use in injectables or ophthalmic routes as this ionic surfactant has shown to cause changes in the permeability of the blood-brain barrier in rats and is irritating for the eyes [5,26]. As ionic surfactants like SLS interact with active pharmaceutical ingredients (APIs) in their salt form or with charged excipients, the combination can become problematic [25].

The acceptable daily intake (ADI) for polysorbates as food additives was set at 25 mg/kg/day by the European Food Safety Authorisation (EFSA) in 2015. Next to oral formulations, the non-ionic polysorbates 20 and 80 can as well be used in injectables. Polysorbates undergo hydrolysis outside the pH range 3 – 11 and undergo a slow oxidation in the air. The degradation routes of the pegylated polysorbates gives rise to peroxides. Furthermore, a lot of APIs are prone to degradation in combination with the hydrolysis and oxidation products. Due to oxidation reactions with some APIs, the use of polysorbates is not always favourable. Therefore, there is need for non-ionic non-pegylated surfactants which do not suffer from the denoted drawbacks [27].

1.5 NOVEL CLASSES OF SURFACTANTS

Nowadays, studies are carried out in order to find new groups of compounds that could replace surface active agents produced by chemical synthesis due to their high toxicity to the ecosystem and difficulty of being degraded in the environment. Next to the biological and environmental compatibilities of natural surfactants there are papers indicating that they present better physicochemical properties than compounds produced based on non-renewable resources. Currently, fossil fuel-derived feedstocks are less expensive than renewable resources. However, this trend will likely reverse in the future, thereby further enhancing long-term prospects of biobased surfactants [28]. Appendix 2 gives an overview of some novel classes of surfactants, their suppliers and their current field of application [26].

1.5.1 Biosurfactants

Microbial surfactants like rhamnolipids and sophorolipids find versatile applicability in household and industrial sectors. The antibacterial, antifungal and antiviral activities make biosurfactants relevant molecules for applications in combating many diseases and as therapeutic agents. Despite their immense potential their commercial use is still limited due to their high production and recovery cost. Further investigations on human cells and natural microbiota are needed to validate the use of biosurfactants in several biomedical and health related areas [3].

1.5.2 Amino acid based surfactants

Amino acid based surfactants (AAS) are produced from amino acids and natural fatty acids. These surfactants are amphoteric, but not always zwitterionic [1]. The main characteristics are their mild and environmental features. AAS are mainly used for shower gel, facial cleaner and shampoo. It produces creamy and rich foam and it is notable for leaving the skin feeling soft and fresh without making it feel taut [29]. Although AAS can be used in any application where ordinary surfactants are used, they are substantially more expensive than the ordinary surfactants. Consequently, at present, the market size of the classic surfactants is much larger than that of AAS [30].

1.5.3 Gemini surfactants

Gemini surfactants are considered dimers of the conventional surfactants as this novel class of amphiphilic compounds consists of two hydrophilic and two hydrophobic groups per molecule, linked through a spacer chain [31]. Amino acid based gemini surfactants have shown to have low CMC-values, good water solubility and high efficiency in reducing the O/W interfacial tension [32].

1.5.4 Sugar based surfactants

In the past decade sugar based head groups have been introduced in the market in different application areas. Besides their ecological advantages, the starting components of sugar based surfactants are generally plentiful, inexpensive, reproducible and biocompatible. Sugar based surfactants are derived from monomeric, dimeric or polymeric sugar. The hydrophilic head in the molecule is linked glycosidically with a fatty acid by an ester, amine or amide bond. The ester groups form a weaker bond, which is flexible but can be easily hydrolysed in aqueous media at pH outside the 4 – 8 range. The hydrophilic group consists of one or more of the same or different sugar units and the hydrophobic part consists of one, two and even more alkyl chains with the same or different lengths. Sugar esters offer a much wider range of functional properties than other surfactants as this class of non-ionic surfactants is available in a wide range of HLB-values, which is dependent of the degree of esterification and the type of fatty acid used [33].

Regarding pharmaceutical applications, in recent years there has been a focus on three classes of surfactants with sugar or a polyol, derived from sugar, as the polar head group: sucrose esters, alkyl polyglycosides (APG) and alkyl glucamides. Also maltoside based surfactants exist and have potential as permeation enhancer [33].

(i) Alkyl polyglucosides (APG)

APG were described for the first time by Emil Fisher more than 100 years ago and have been produced on a large scale since 1922. These polyol-based surfactants consist of fatty alcohol as the hydrophobic part and a sugar as the hydrophilic part. The hydrophilicity is variable through the degree of oligomerization [1]. Though any reducing sugar can be used as a raw material, glucose or a degraded starch fraction is the start material of choice due to its availability and cost. In Figure **1.11** the chemical structure of β-D-C_{12} glucoside is shown [1].

Whereas APG are stable at high pH, at low pH they hydrolyse to sugar and fatty alcohol. The mildness of APG to the skin and eyes makes this surfactant class attractive for personal care products. Moreover, they are used in detergent formulations. CMC values of APGs are comparable to other non-ionic surfactants, and the CMC decreases with increase in the alkyl chain length. CMC values of some APGs are represented in Table **1.1** [34].

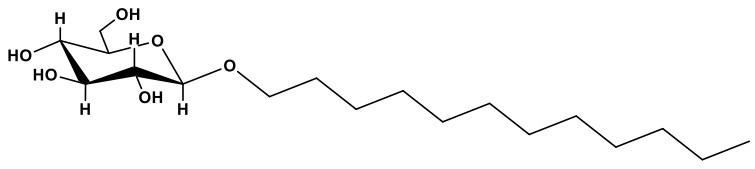


Figure 1.11: Chemical structure of β-D-C_{12} -glucoside.

(ii) Alkyl polyglucosamides

Another type of glucose derivates are the alkyl polyglucosamides. They are obtained from monosaccharides and have the same advantages as APGs and are as well used in detergent formulations. In these molecules the hydrophobic part is an acyl group whilst the hydrophilic part is made up of glucose, whose cycle is opened by hydrogenation. The chemical structure of dodecyl glucosamide is represented in Figure **1.12.** CMC values of some alkyl polyglucosamides are represented in Table **1.1** [16].

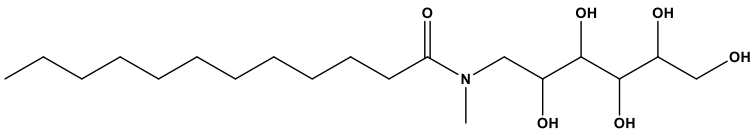


Figure 1.12: Chemical structure of dodecyl glucosamide

(iii) Maltosiden

The non-ionic surfactant *n*-dodecyl-β-D-maltoside is increasingly used for hydrophobic and membrane protein isolation when the protein activity needs to be preserved. The chemical structure of *n*-dodecyl-β-D-maltoside is illustrated in Figure **1.13**. Other maltosides with different lengths of the hydrophobic alkyl chains that exist are *n*-octyl-β-D-maltoside and n-decyl-β-D-maltoside [35].

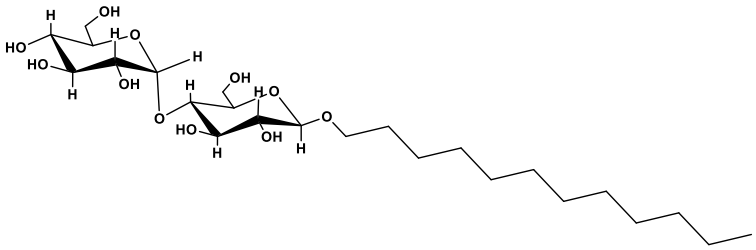


Figure 1.13: Chemical structure of n-Dodecyl-β-D-maltoside.

(iv) Sucrose esters of fatty acids (SEFA)

SEFA are non-ionic surfactants consisting of sucrose as a hydrophilic group and one or more fatty acids as lipophilic group. The lipophilic character increases with an increasing degree of esterification and an increasing chain length of the fatty acid in the ester group. The chemical structure of sucrose monoesters with variable fatty acid chain length is represented in Figure **1.14** [36].

SEFA have a group ADI of 40 mg/kg body weight per day. *Appendix* I gives an overview of the proposed food uses and use levels for SEFA based on the food category system of the GSFA of the Codex Alimentarius Commission (2017) [37].

SEFA are already widely used in the food and cosmetic industries and recently, there has been interest in their applicability in pharmaceutical fields as SEFA display well-known emulsifying and solubilizing behaviour. Currently SEFA find pharmaceutical applications in the enhancement of drug dissolution and drug absorption/permeation. Besides these surfactants are also used in controlled-release systems. Although the number of articles on SEFA is continuously increasing, they have not yet been widely used in the pharmaceutical industry [38].

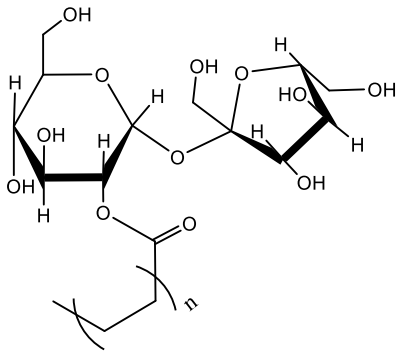


Figure 1.14: Chemical structure of a sucrose ester with variable chain length.

Table 1.1 represents CMC values in water for APG, alkyl glucosamides, maltoside and SEFA of different chain length. The CMC values are more or less similar across the different head groups when comparing the chain lengths [39,40]. In this thesis the focus is on the comparison of different grades of sucrose stearate where CMC determination is part of the experimental work.

Table 1.1: CMC-values (M) for sugar ester compounds with different chain length determined at 25 °C [39,40].

Head group	C_8:0	C_{10}:0	C_{12}:0	C_{14}:0	C_{16}:0	C_{18}:0
Glucoside	$2.5 \cdot 10^{-2}$	$2.2 \cdot 10^{-3}$	$1.9 \cdot 10^{-4}$	-	-	-
Glucosamide	-	$1.3 \cdot 10^{-3}$	$1.5 \cdot 10^{-4}$	$2.4 \cdot 10^{-5}$	$7.7 \cdot 10^{-6}$	$2.9 \cdot 10^{-6}$
Maltoside	$1.9 \cdot 10^{-2}$	$1.8 \cdot 10^{-3}$	$1.7 \cdot 10^{-4}$	-	-	-
Sucrose	-	-	$1.9 \cdot 10^{-4}$	$2.6 \cdot 10^{-5}$	$5.5 \cdot 10^{-5}$	$1.1 \cdot 10^{-5}$

1.6 SUCROSE STEARATE

The focus of this project is on the evaluation and analysis of sucrose stearate as a potential alternative for the use of SLS and polysorbate surfactants in oral pharmaceutical formulations. The hydrophilic group of the non-ionic sucrose stearate is a sucrose molecule and the sucrose stearate contains variable quantities of mono-, di-, tri- and polyesters [41].

Information about the physicochemical behaviour of sucrose stearate is available for the Ryoto sucrose stearate esters from Mitsubishi. Table 1.2 gives an overview of the different Ryoto sucrose stearate esters. These components differ in monoester content which has a reflection on the HLB-value, solubility in water and surface tension at CMC (SFT_{CMC}). From this table it can be denoted that the higher the monoester content, the more hydrophilic the compound and the more decrease in surface tension is observed [42,43].

Table 1.2: Overview of the monoester content, HLB-value, solubility in water and SFT_{CMC} of Ryoto sucrose stearate esters [42,43]. (I: Insoluble, PS: partially soluble or dispersible, S: soluble) *a* Determined with a 0.1 % m/V in distilled water by using the Willhelmy method at 25 °C.

Product	Monoester content (%)	HLB	Solubility in water		SFT_{CMC}[a] (mN/m)
			25 °C	75 °C	
S-570	30	5	I	S	38.1
S-770	40	7	PS	S	37.4
S-970	50	9	PS	S	35.8
S-1170	55	11	PS	S	34.8
S-1570	70	15	S	S	34.7
S-1670	75	16	S	PS	34.7

In this project different grades of sucrose stearate from suppliers other than Mitsubishi, will be evaluated and analysed. The composition and HLB value are evaluated as material attributes in the first part of the project. In the experimental part, next to CMC determination, determination of the surface tension is carried out to gain insight into the functional properties of the materials.

2 OBJECTIVES

The scope of this project is the search for a valuable alternative for the two most commonly used surfactants in pharmaceutical industry: sodium lauryl sulphate (SLS) and polysorbates. SLS and polysorbates suffer from drawbacks as SLS is incompatible with counter charged APIs and/or excipients, whereas the degradation products of polysorbates are sometimes incompatible with the API due to the occurrence of oxidation reactions. A number of novel classes of surfactants have potential, whereby sucrose esters of fatty acids (SEFA) were chosen as the most interesting alternative. This class of surfactants is already widely used in food and cosmetic industry. Furthermore, some SEFA are available and compliant for use in oral pharmaceutical formulations.

Different suppliers of SEFA were contacted to provide samples for analysis. Eventually, 11 samples were retrieved from five different suppliers. An overview of the obtained product samples is represented in Table 2.1. The focus of this thesis lays on the evaluation and analysis of the eight grades containing sucrose stearate: Stelliesters SE 5S, Stelliesters SE 11S, Stelliesters SE 15S, SP50-C, SP70-C, Crodesta F160, Tegocare SE 121 MB and Emulgade Sucro Plus The aim is to assess the suitability of these materials for use in oral pharmaceutical formulations. The other materials are investigated by Michiel Torfs and results are represented in his thesis (Sucrose esters as novel surfactants in oral formulations? An overview of the regulatory status and functional properties of commercial products)

This thesis consists of two parts. The aim of the first part is to provide an overview of some basic properties and the regulatory status of the materials based on product information data sheets and certificates provided by the suppliers. This information is compared with important regulatory requirements for use as pharmaceutical excipients. The different grades will be evaluated regarding their identity, compliance with important purity parameters, physical properties and regulatory and patient safety information.

The second part of the project compromises an evaluation of the functional properties of the materials. The evaluation compromises the solubility of the sucrose stearate grades in milli-Q and milli-Q/EtOH (90:10 V/V), the effect of the composition on the surface tension, the critical micelle concentration, the influence of ethanol on the surface tension and critical micelle concentration and the cross-sectional area per molecule at the surface.

Lastly, based on the collected information, critical material attributes concerning sucrose stearate are listed and discussed.

Table 2.1: Overview of SEFA samples retrieved from different suppliers.

Sucrose ester	Supplier
Sucrose laurate (C12:0)	
L70-C	Sisterna B.V.
Sucrose palmitate (C16:0)	
PS750-C	Sisterna B.V.
Stelliesters SE 15P	Stéarinerie DuBois
Sucrose stearate (C18:0)	
Stelliesters SE 5S	Stéarinerie DuBois
Stelliesters SE 11S	Stéarinerie DuBois
Stelliesters SE 15S	Stéarinerie DuBois
Crodesta F160	Croda GmbH
Tegocare SE 11 MB	Evonik Nutrition & Care GmbH
Emulgade Sucro Plus	BASF Personal Care and Nutrition GmbH
SP50-C	Sisterna B.V.
SP70-C	Sisterna B.V.

3 SUCROSE STEARATE: GENERAL PROPERTIES AND REGULATORY STATUS

Eight grades containing sucrose stearate (CAS n° 25168-73-4) obtained from five different suppliers are discussed. Three grades are obtained from Stéarinerie DuBois: Stelliesters SE 5S, Stelliesters SE 11S and Stelliesters SE 15S, further referred to as SE 5S, SE 11S and SE 15S. All three grades appear as white powder and are offered as pharmaceutical grade materials. Two grades are obtained from Sisterna: Sisterna SP50-C and Sisterna SP70-C, both appearing as white powders and offered as cosmetic grade materials. Crodesta F160-PW-(RB), appearing as a white powder, is obtained from Croda GmbH and is a cosmetic and food grade sucrose stearate material lending it use as component in protective coatings for oral products [44]. Crodesta F160 is already used in the capsule coating of market approved pharmaceuticals. Croda GmbH also releases the cosmetic and food grade materials Crodesta F110 and Crodesta F10 SEFA containing sucrose stearate. According to Croda GmbH these SEFA are listed in the FDA-IID list concerning excipients used in approved new drug application and abbreviated new drug application products [45]. However, only Crodesta F160 is retrieved for analysis. Emulgade Sucro Plus, beige pellets, and Tegocare SE 121 MB, white pellets, are retrieved from respectively BASF Personal Care and Nutrition GmbH and Evonik Nutrition & Care GmbH.

Table 3.1 gives an overview of some general information regarding the materials: The International Nomenclature of Cosmetic Ingredients (INCI) name and the Chemical Abstracts Service (CAS) number of the components present in the products is referenced. SE 5S, SE 11S, SE 15S, SP50-C, SP70-C and Crodesta F160 are sucrose esters that mainly compose sucrose stearate. Although the Sisterna SP50-C and SP70-C are offered as cosmetic grade sucrose esters, these materials do also meet the standards, regarding their composition, of the European Pharmacopoeia (Ph. Eur.), United States Pharmacopoeia-National Formularium (USP-NF) and the Japanese Pharmacopoeia (JP) as further discussed in Paragraph 3.2.1. Tegocare SE 121 MB and Emulgade Sucro Plus are mixtures containing a certain fraction of sucrose stearate. Tegocare SE 121 MB contains mainly glyceryl stearate and sucrose stearate is only present for maximum 50 % in the product. Emulgade Sucro Plus mainly consists of sucrose polystearate and besides, 5 – 20 % cetyl palmitate is present. Furthermore, the location of the manufacturing sites is mentioned. In case of Crodesta F160, Croda Europe Limited is responsible for the release, however this product is not manufactured at a Croda facility. Croda does not provide any information about the manufacturing site location [46,47,48,49,50,51,52,53].

Table 3.1: General overview of the different sucrose stearate materials [46,47,48,49,50,51,52,53]. (-: No information available) [a] Sucrose stearate, [b] Sucrose palmitate, [c] Fatty acids, C16-18, C12-18 alkyl esters

Product name	INCI	CAS-number	Grade	Supplier	Manufacturing site
SE 5S	Sucrose distearate	25168-73-4	Pharmaceutical	Stéarinerie Dubois	Route de la creuse 1 36300 Ciron, France
SE 11S	Sucrose stearate	25168-73-4	Pharmaceutical	Stéarinerie Dubois	Route de la creuse 1 36300 Ciron, France
SE 15S	Sucrose stearate	25168-73-4	Pharmaceutical	Stéarinerie Dubois	Route de la creuse 1 36300 Ciron, France
SP50-C	Sucrose stearate	25168-73-4	Cosmetic	Sisterna B.V.	DKS Co. Ltd. Kyoto, Japan
SP70-C	Sucrose stearate	25168-73-4	Cosmetic	Sisterna B.V.	DKS Co. Ltd. Kyoto, Japan
Crodesta F160	Sucrose stearate	25168-73-4	Cosmetic/Food	Croda GmbH	-
Tegocare SE 121 MB	Glyceryl stearate SE Sucrose stearate	11099-07-3 25168-73-4	Cosmetic	Evonik Nutrition & Care GmbH	Evonik Nutrition & care GmbH Goldschmidtstraße 100 45127 Essen, Germany
Emulgade Sucro Plus	Sucrose polystearate Cetyl palmitate	37318-31-3[a] 39300-95-3[b] 95912-87-1[c]	Cosmetic	BASF SE	BASF Personal Care and Nutrition GmbH Carl-Bosch-Straße 38 67056 Ludwigshafen Germany

3.1 PRODUCTION PROCESS

The production process mentioned in the following text describes the general production process for sucrose esters of fatty acids (SEFA) according to Generally Recognized As Safe (GRAS) n° 514: The first step in the manufacturing concerns the preparation of fatty acid methyl esters (FAME). Those methyl esters are formed by reacting fatty acids derived from edible vegetable oils, such as palm oil and coconut oil, with methanol in the presence of a catalyst. Subsequently, fractional distillation is carried out to isolate the FAME. Thereafter, the collected fraction is mixed with water and subjected to a quality check to make sure the FAME meet food grade product standards. To produce SEFA, an interesterification reaction between sucrose, derived from cane or beet, and the purified FAME is carried out, where the ratio of FAME to sucrose determines the degree of esterification. During the interesterification process, dimethyl sulfoxide (DMSO) is used as a solvent. The SEFA obtained are then purified by using food grade solvents as there are: ethyl acetate, ethyl methyl ketone or isopropyl alcohol; or water. The use of water has the advantage of avoiding contact of SEFA with solvents. By carrying out a washing phase the food grade purification chemicals used previously are removed. During the refining step, the obtained product is dried by spray dryers. Lastly, the product undergoes sieving before the product is packed [54].

The production of SEFA from Croda is covered by U.S. Patent No. 3,480.616 were no ethoxylation reaction is carried out [44]. BASF states that no solvents were used in the production of Emulgade Sucro Plus [55]. The manufacturing process of Tegocare SE 121 MB and SE 5S, SE 11S and SE 15S was not provided by the corresponding supplier. For the materials of Sisterna B.V., patents of DKS Co. Ltd. are available [56].

3.2 IDENTITY RELATED MATERIAL ATTRIBUTES

3.2.1 Composition

The non-ionic surfactant sucrose stearate is a mixture of sucrose esters of varying fatty acids chains and variable ester fractions, rather than a single uniform compound. Table 3.2 represents an overview of the pharmaceutical grade sucrose stearate materials and cosmetic grade materials SP50-C and SP70-C together with the results of analysis with regard to their composition and the current compendial specifications. SE 11S, SE 15S, SP50-C and SP70-C match the requirements of the Ph. Eur., monograph 2318 and USP-NF “sucrose stearate, type I” current editions. The monoester fraction in these materials is prominent.

Regarding the materials from Sisterna B.V. there is a lot of missing data. For instance, the exact fraction of lauric, myristic, palmitic or stearic acid ester fatty acid fractions is not specified in the certificate of analysis provided by Sisterna B.V. However, all analyzed product parameters regarding the identity are conform the limits specified by the Ph. Eur, USP-NF and JP [56]. SE 5S matches the requirements of the Ph. Eur. monograph 2318 and USP-NF "sucrose stearate, type II" current editions [46]. Sucrose stearate type II materials contain less monoesters and contain more of the di-, tri- and polyester fraction. In case of "sucrose stearate, type III" mainly the tri- and polyester fraction are present. No sample of this category was available for analysis.

Table 3.3 provides an overview of the composition of Crodesta F160, Tegocare SE 121 MB and Emulgade Sucro Plus as indicated in the product information data sheets. BASF and Evonik do not provide further specification about the ester fractions and no details about the fatty acid composition are available. Emulgade Sucro Plus and Tegocare SE 121 MB both are cosmetic grade and the suppliers state that their product is not suitable for pharmaceutical applications [49,50]. Crodesta F160, Crodesta F110 and Crodesta F10, are all classified as cosmetic and food grade lending them use as component in protective coatings for oral products. Croda specifies Crodesta F160 as a monoester type product, Crodesta F110 as a mixture of mono- and diesters and Crodesta F10 as being a diester type [44].

3.2.2 Identification tests

The identity of each material can be confirmed by two tests described in the Ph. Eur. and USP-NF. These methods provide a conclusive evidence of the identity of the substance. The compendial identification test compromises: [1] the fatty acid composition and [2] the content of mono-, di-, tri- and polyesters, determined through size-exclusion chromatography, which should comply with the limits as indicated in the assay [57]. The Stelliesters from Stéarinerie DuBois have all passed the identification tests A and B and therefore, are in compliance with the identification criteria of the Ph. Eur. and USP-NF [44,46,47,48]. For the SP50-C and SP70-C Sisterna B.V. confirms compliance with Ph. Eur., USP and JP. Emulgade Sucro Plus and Tegocare SE 121 MB do not comply with Ph. Eur. and USP-NF with regard to their composition [49,50]. The identity of both materials should be analyzed to get more insight. However, for Emulgade Sucro Plus, considering that BASF specifies the sucrose stearate present as being polystearate, it is only possible to meet the specifications of type II sucrose stearate. Tegocare SE 121 MB can never meet the minimum amounts of mono-, di-, tri- and polyester fraction of sucrose stearate required in order to comply with one of the three pharmaceutical grade types. Crodesta F160 should be analyzed in order to decide whether or not the identity is compliant with one of the compendial sucrose stearate types.

Table 3.2: Composition of materials meeting Ph. Eur. and USP-NF standards regarding their composition for sucrose stearate [46,47,48,51,52].

(N.A.: Not applicable, -: No information available)

	Type I					Type II		Type III
	Ph. Eur./USP	SE 11S	SE 15S	SP50-C	SP70-C	Ph. Eur./USP	SE 5S	Ph. Eur./USP
Ester fraction								
Monoesters content (%)	≥ 50.0	56.9	66.0	50	70	20.0 – 45.0	32.4	15.0 – 25.0
Diester content (%)	≤ 40.0	27.8	23.3	36	25	30.0 – 40.0	36.7	30.0 – 45.0
Triesters + polyesters content (%)	≤ 25.0	7.3	4.5	14	5	≤ 30.0	27.8	35.0 – 50.0
Fatty acid fraction								
Lauric acid C12:0 (%)	≤ 3.0	0.0	0.4	-	-	≤ 3.0	0.0	≤ 3.0
Myristic acid C14:0 (%)	≤ 3.0	1.3	1.5	-	-	≤ 3.0	0.0	≤ 3.0
Palmitic acid C16:0 (%)	25.0 – 40.0	34.0	38.3	-	-	25.0 – 40.0	34.9	25.0 – 40.0
Stearic acid C18:0 (%)	55.0 – 75.0	64.0	59.2	-	-	55.0 – 75.0	64.5	55.0 – 75.0
C16 + C18 Content (%)	≥ 90.0	98.0	97.5	≤ 100	≤ 100	≥ 90.0	99.4	≥ 90.0
HLB-Value	N.A.	11	15	11	15	N.A.	5	N.A.

Table 3.3: Composition and HLB-value of sucrose stearate materials which are cosmetic and/or food grade [49,50,53]. (*: product limit specified by the supplier)

	Cosmetic/Food grade	Cosmetic grade	
	Crodesta F160-PW-(RB)	Emulgade Sucro Plus	Tegocare SE 121 MB
Composition	Sucrose stearate ≥ 75 %	Sucrose polystearate: 86.5 % (77.0 – 95.0 %)* Cetyl palmitate: 12.8 % (5.0 – 20.0 %)*	Sucrose stearate: 30 – 50 % Glyceryl stearate: 50 – 70 %
HLB-value	14.5	9 – 11	13

3.2.3 HLB-value

As indicated in Paragraph **1.2** HLB values are commonly used as an indicator for choosing a surfactant for a specific application. Table **3.4** gives an overview of theoretical applications of the different products containing sucrose stearate based on their HLB-value and the classification illustrated in Figure **1.8**. SE 5S, which has an HLB-value of 5, is considered as mainly hydrophobic and oily soluble and therefore can be used as W/O-emulsifier. Emulgade Sucro Plus has an HLB-value between 9 and 11 and is intended for use as O/W-emulsifier as indicated by BASF [58]. SE 11S, SE 15S, SP50-C, SP70-C, Crodesta F160 and Tegocare SE 121 MB have high HLB-values and are theoretically mainly hydrophilic and water-soluble lending them theoretically use as wetting agents and as O/W emulsifiers. For Crodesta F160 it is known that O/W-emulsions systems are formed at relatively low temperatures (45 °C) [44]. Crodesta F160, SE 15S and SP70-C can be used as solubilizing agent as well.

Table 3.4: Overview of potential applications with regard to the HLB-value of the sucrose stearate materials.

Product	Grade	Type	HLB	Applications
SE 5S	Pharmaceutical	II	5	W/O emulsifying
SE 11S	Pharmaceutical	I	11	Wetting, O/W emulsifying
SE 15S	Pharmaceutical	I	15	Wetting, O/W emulsifying, solubilisation
SP50-C	Cosmetic	I	11	Wetting, O/W emulsifying
SP70-C	Cosmetic	I	15	Wetting, O/W emulsifying, solubilisation
Crodesta F160	Food/Cosmetic	-	14.5	Wetting, O/W emulsifying, solubilisation
Tegocare SE 121 MB	Cosmetic	-	13	Wetting, O/W emulsifying
Emulgade Sucro Plus	Cosmetic	-	9 – 11	O/W emulsifying

3.3 PURITY RELATED MATERIAL ATTRIBUTES

3.3.1 Physical purity parameters

Some common physical purity parameters are described in Table **3.5**. The results regarding the free sucrose content, acid value, total ash, water content and the appearance are compared to limits specified by monograph 2318 of the Ph. Eur. and USP-NF. The maximum free sucrose content for pharmaceutical grade materials is set at 4.0 % by both, the Ph. Eur. and USP-NF [41,57]. SE 5S, SE 11S, SE 15S, SP50-C, SP70-C and Crodesta F160 (product limit ≤ 2 %) have values below the specified limit. For the cosmetic grade materials Tegocare SE 121 MB and Emulgade Sucro Plus information about the free sucrose content is not available.

The acid value is a measure for the free fatty acids present in 1 g sample. The lower this value, the less free fatty acids that are present in the surfactant product. Both Ph. Eur. and USP-NF have specified a limit of 6 mg KOH/g for pharmaceutical grade materials. Cosmetic grade materials Tegocare SE 121 MB and Emulgade Sucro Plus (product limit ≤ 30 mg KOH/g) have acid values which exceed the set specification. The six other materials have acid value product limits below the specification limit [46,47,48,49,50,51,52]. The results obtained from the certificate of analysis are referenced in the table. For the Crodesta F160 batch the free oleic acid amount was determined to be 1.1 % (product limit ≤ 3.0 %) [53]. For some of the materials the saponification, hydroxyl and iodine value are available, however these are not required to test for in order to comply with the compendia. For Tegocare SE 121 MB and Crodesta F160 the saponification value, defined as the amount of KOH required to saponify 1 g of the product, is available. The hydroxyl value is an indication for the degree of esters present in the sample. For instance, Crodesta F160 is said to have a higher monoester content compared to Crodesta F110 and Crodesta F10, which is reflected by the higher hydroxyl value of the first [44]. The iodine value is a measure of the degree of unsaturation. This value is defined as the amount of iodine that is taken up by 100 g surfactant. As saturated fatty acids do not take up any iodine, SEFA from saturated fatty acids have a iodine value of zero. For Tegocare SE 121 MB the limit for the iodine value is remarkably higher. Therefore, unsaturated fatty acid chains will likely be present in the material [50].

The test for total ash is used for determining the content of inorganic materials in the surfactant materials. The residue on ignition test is a similar test, but the sample is ignited in the presence of sulfuric acid. The results for the pharmaceutical grade materials and the cosmetic grade materials of Sisterna B.V. are compliant with the specified compendial limit [46,47,48,51,52]. The limit for Tegocare SE 121 MB is remarkably higher and for Emulgade Sucro Plus the limit is not specified by the supplier [49,50]. For Crodesta F160 no limit for total ash is specified, however the residue on ignition value of 0.89 % (product specification ≤ 2 %) is lower than the limit of 2 % specified in the residue monograph on SEFA prepared by JECFA in 2017 [53,59]. Regarding the residual water content, both pharmacopoeias state a limit of not more than 4.0 % [41,57]. Tegocare SE 121 MB does not meet this criterium, whereas the seven other materials do meet the criterium of the residual water content [46,47,48,49,51,52,53].

Table 3.5: Common physical purity parameters of the different sucrose stearate materials [46,47,48,49,50,51,52,53]**. Results are based on the CoA of the batches provided for analysis or *: specifications given by the supplier.** (-: No information available), [a] Residue on ignition 0.89 % (specification for sucrose esters of fatty acids defined by JECFA 2017: ≤ 2.0 %)

	Specification limit	SE 5S	SE 11S	SE 15S	SP50-C	SP70-C	Crodesta F160	Tegocare SE 121 MB	Emulgade SucroPlus
Free sucrose content (%)	≤ 4 (Ph. Eur., USP-NF)	0.3	1.1	0.2	0.3	0.4	0.6.	-	-
Acid value (mg KOH/g)	≤ 6 (Ph. Eur., USP-NF)	3.7	2.4	2.9	2.1	2.4	2.1	6.0 – 17.0*	10.7
Saponification value (mg KOH/g)	-	-	-	-	-	-	80 – 140*	72.0 – 92.0*	-
Hydroxyl value (mg KOH/g)	-	-	-	-	-	-	500 – 550*	-	-
Iodine value (g/100g)	-	-	-	-	-	-	≤ 1.0*	≤ 10.0*	-
Water content (%)	≤ 4.0 (Ph. Eur., USP-NF)	0.97	1.69	1.82	0.9	0.8	1.0	1.50 – 4.50*	≤ 3*
Total ash (%)	≤ 1.5 (Ph. Eur., USP-NF)	1.0	≤ 1,5	1.02	0.94	0.86	-[a]	4.50 – 7.50*	N.A.
Colour	White or almost white (Ph. Eur.)	White	White	White	(almost) White	(almost) White	White	Light yellow	Beige

From Table **3.5** it can be concluded that the pharmaceutical grade materials comply with the current compendial specifications. Also, food and/or cosmetic grade materials Crodesta F160, SP50-C and SP70-C are conform the specifications regarding the purity parameters discussed [51,52,53]. Cosmetic grade materials Tegocare SE 121 MB and Emulgade Sucro Plus are not compliant. For both materials the acid value exceeds the specification and for Tegocare SE 121 MB also the water content and total ash limits are not conform the compendial [49,50].

3.3.2 Inorganic cation content

Stéarinerie DuBois states that no metal catalysts or metal reagents are used during the manufacturing process of the different Stelliesters. For the cosmetic and/or food grade materials this information is not available [46,47,48]. Since metal impurities can act as an oxidation catalyst, level of metals was investigated for the sucrose stearate products and is represented in Table **3.6**. The limits for oral use (µg/g) are with regard to the ICH Q3D guideline for Elemental Impurities [60]. SP50-C, SP70-C and Tegocare SE 121 MB do not meet the limit for oral use for Cd and Pb. It should be noted that these products are offered for cosmetic use, where the limits for Cd and Pb are specified as being respectively 2 ppm and 1 ppm. To assess the suitability of these materials for oral use, regarding the metal content, the exact limits resulting from the production process should be provided [56]. The other materials are in compliance with the specified requirements since the limits indicated by the suppliers do not exceed one of the limits specified in the ICH Q3D guideline [46,47,48,49,50,51,52,53].

Table 3.6: Metal content (ppm) of the different sucrose stearate materials [46,47,48,49,50,51,52,53].
(-: No information available) [a] PDE for Zn is not established in the current ICH Q3D guideline due to low inherent toxicity [60].

Product	Cd	Pb	As	Hg	Co	V	Ni	Sb	Sn	Zn
SE 5S	< 0.01	< 0.05	< 0.1	< 0.005	-	-	< 0.1	-	< 0.2	< 0.5
SE 11S	< 0.5	< 0.5	< 1.5	< 3	-	-	-	-	< 1	-
SE 15S	< 0.005	< 0.1	< 1	< 0.02	-	-	-	-	< 0.8	-
SP50-C	≤ 1	≤ 1	≤ 1	≤ 1	-	-	-	-	-	-
SP70-C	≤ 1	≤ 1	≤ 1	≤ 1	-	-	-	-	-	-
Crodesta F160	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	-	-	-
Tegocare SE 121 MB	< 1.0	< 1.0	< 1.0	< 1.0	< 1.0	-	< 1.0	< 1.0	-	-
Emulgade Sucro Plus	< 2	< 10	< 1	< 1	-	-	< 2	< 5	-	-
Limits oral use	**0.5**	**0.5**	**1.5**	**3.0**	**5.0**	**10**	**20**	**120**	**600**	**1 300[a]**

3.3.3 Residual solvents

For the production of sucrose stearate materials only the following solvents may be used: DMF, DMSO, ethyl acetate, isopropanol, propylene glycol, isobutanol and methyl ethyl ketone. Those solvents are generally recognized as safe in food or regulated for such use. Methanol is a solvent which is not used during the manufacturing, however, it may be formed as reaction product during the production process. Table **3.7** gives an overview of the residual solvent limits as stated by the suppliers and are compared to the limits indicated by the ICH Q3C guideline on residual solvents [61]. The Code of Federal Regulation 21 (CFR 21), specifies criteria for the solvents listed above, which are more strict compared to the ICH Q3C guideline [62]. However, for pharmaceutical grade materials the ICH limits are still the guidance criteria. When a monograph of a sucrose ester, as is the case for sucrose laurate esters, is not available in the compendial, the CFR-criteria offer a good reference for uses in oral pharmaceutical formulations.

SE 5S, SE 11S and SE 15S from Stéarinerie DuBois meet the limits of ICH Q3C, however, they do not meet the criteria of the CFR 21. Since they are in compliance with the currently required standards, these materials are suitable for pharmaceutical applications. Regarding SP50-C and SP70-C, only the limit for DMSO is specified by Sisterna B.V. The limit is in compliance with the CFR 21 criteria [56]. In Crodesta F160, methanol may be present as a by-product to manufacture and DMSO may be present at levels ≤ 2 ppm, however, neither of these solvents form part of the standard specification. No other solvents listed in the ICH Q3C guideline are expected to be present, since they do not form part of the production process and are not present as an impurity in the raw materials. Therefore, these other solvents are not tested for [53].

For Tegocare SE 121 MB no information about limits of residual solvents is available. BASF does not expect any of the listed solvents referenced in Annex I (Art. 2, a) of the Swiss Ordinance on the Incentive Tax on Volatile Organic Compounds, SR 814.018, to be present in Emulgade Sucro Plus at a concentration above 3 000 ppm. The applicable solvent from this list for sucrose stearates is methanol [61].

Table 3.7: Overview of the residual solvents present with comparison to the ICHQ3C concentration limit (ppm) [46,47,48,49,50,51,52,53].
(N.A.: Not applicable, -: No information avalaible) [a] CFR 21 for SEFA; [b] FAO/WHO 2017.

	ICH Q3C limit (ppm)	SE 5S	SE 11S	SE 15S	SP50-C	SP70-C	Crodesta F160	Tegocare SE 121 MB	Emulgade Sucro Plus
Solvent									
Class 1									
	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Class 2									
DMF	880 (1[b])	≤ 880	≤ 880	≤ 880	-	-	-	-	N.A.
Methanol	3 000 (10[a])	≤ 3 000	≤ 3 000	≤ 3 000	-	-	≤ 10	-	≤ 3 000
Class 3									
DMSO	5 000 (2[a])	≤ 5 000	≤ 5 000	≤ 5 000	≤ 2	≤ 2	≤ 2	-	N.A.
Isobutanol	5 000 (10[a])	≤ 5 000	≤ 5 000	≤ 5 000	-	-	-	-	N.A.
Ethyl acetate	5 000 (350[a])	≤ 5 000	≤ 5 000	≤ 5 000	-	-	-	-	N.A.
Isopropanol	5 000	≤ 5 000	≤ 5 000	≤ 5 000	-	-	-	-	N.A.
Methyl ethyl ketone	5 000 (10[a])	≤ 5 000	≤ 5 000	≤ 5 000	-	-	-	-	N.A.

3.4 PHYSICAL PROPERTIES

Some important physical properties are mentioned in Table **3.8**. The materials appear as powders or pellets of white to yellowish colour. For the materials where a pH-value is available, the pH is neutral to alkaline. A pKa-value is not available for any of the materials. Log P values are only available for the pharmaceutical grade materials. For SE 5S, the Log P value is slightly lower compared to SE 11S and SE 15S, which is in relation with the higher hydrophobicity of the first. The melting point of the different samples ranges from 44 to 69 °C. SEFA are typically hygroscopic, therefore these materials must be protected from humidity [46,47,48,49,50,51,52,53].

3.4.1 Solubility

General information about solubility was provided by the suppliers. In water, SP70-C and Crodesta F160 are said to be soluble at 60 °C. SE 15S is said to form an emulsion, although it has the highest HLB-value of the samples analysed. SE 5S has the lowest HLB-value of the discussed materials and is insoluble in water. SE 11S, SP50-C and Tegocare SE 121 MB have moderate HLB-values and are said to be dispersible in water. Emulgade Sucro Plus has also a moderate HLB-value, however, is seen to be insoluble in water. Only Stéarinerie DuBois has determined the solubility of their different Stelliesters in ethanol. Both, SE 11S and SE 15S, are soluble in ethanol, whereas SE 5S is even not soluble in ethanol [46,47,48,49,50,51,52,53].

3.4.2 Stability

The retrieved materials melt at temperatures between 44 and 69 °C depending upon the degree of esterification and the type of fatty acids present for the sucrose stearate. Moreover, the presence of other components will also impact the melt temperatures. Thermal decomposition generates carbon oxides CO and CO_2. Generally, thermal decomposition of SEFA occurs at temperatures above 200 °C [43]. The class of SEFA are stable in the pH-range of 4 to 8. At pH higher than 8 or lower than 4 hydrolysis might occur, whereby monoesters will degrade faster than di- or triesters. When a high electrolyte content is present flocculation may occur. Stearates are seen to be more sensitive than SEFA with shorter fatty acid chain length and those materials with a higher degree of esterification are more sensitive than those with a higher monoester content [63]. Emulgade Sucro Plus is claimed to show good electrolyte compatibility and for Crodesta F160 it is said that the product does not interact with polyvalent salts. For the other materials no concrete information was given. Taken into account that SEFA are non-ionic surfactants, the relevance of the differences in electrolyte compatibility between SEFA with different chain length and different degree of esterification is not mentioned [64].

Table 3.8: Physical properties of the different materials [46,47,48,49,50,51,52,53]. (PS: partially soluble, -: No information available)

	SE 5S	SE 11S	SE 15S	SP50-C	SP70-C	Crodesta F160	Tegocare SE 121 MB	Emulgade Sucro Plus
Physical state (25°C)	Powder	Powder	Powder	Powder	Powder	Powder	Pellets	Pellets
Solubility								
- Water	Insoluble	Dispersible	Emulsion	PS	Soluble at 60 °C	Soluble at 60 °C	Dispersible	Insoluble
- Ethanol	Insoluble	Soluble	Soluble	-	-	-	-	-
pH	-	-	-	± 7.8	± 7.8	7,8	8,5 – 10,5	-
Log P	> 4,2	> 5,8	> 5,8	-	-	-	-	-
Melting point (°C)	60	60	60	51 – 59	54 – 62	44 – 52	55.0 – 69.0	61.4
Hygroscopicity	Protect from humidity	Protect from humidity	Protect from humidity	Protect from humidity	Protect from humidity	Protect from humidity	Protect from humidity	Protect from humidity

3.4.3 Shelf life

Sucrose stearate is sensitive to moisture and therefore should be stored protected from humidity. Generally, the materials should be stored between 5 -30 °C, however, Emulgade Sucro Plus can be stored up to 40 °C. The shelf life of the materials in the unopened original packaging is set at 24 months after production for most materials, except SP50-C and SP70-C from Sisterna B.V. having a shelf life of 36 months. An overview of the shelf life and storage conditions of the different sucrose stearate grades is represented in Table 3.9. If stored as directed no decomposition will occur for neither of the materials [46,47,48,49,50,51,52,53].

Table 3.9: Overview of the shelf life and storage conditions of the different sucrose stearate grades [46,47,48,49,50,51,52,53].
(-: No information available)

Product	Shelf life when unopened in original packaging	Storage conditions
SE 5S	24 months	5 – 30 °C in a dry and ventilated place in original closed packing.
SE 11S	24 months	5 – 30 °C in a dry and ventilated place in original closed packing.
SE 15S	24 months	5 – 30 °C in a dry and ventilated place in original closed packing.
SP50-C	36 months	Container should be kept tightly closed in a dry, cool and well-ventilated place. Kept away from heat, direct sunlight and protected from moisture.
SP70-C	36 months	Container should be kept tightly closed in a dry, cool and well-ventilated place. Kept away from heat, direct sunlight and protected from moisture.
Crodesta F160	12 months	Container should be kept tightly closed in a dry and well-ventilated place.
Tegocare SE 121 MB	24 months	Cool and dry.
Emulgade Sucro Plus	24 months	In original sealed containers at temperatures ≤ 40 °C and protected from moisture.

The Stelliesters from Stéarinerie DuBois are incompatible with strong oxidizers [46,47,48]. For Crodesta F160 no special restrictions on storage with other products are made as the material does not interact with polyvalent salts and adstringents and does not inactivate preservatives, anti-oxidants or other bio-active ingredients. The compatibility for the other materials is not specified in the product data sheets [53].

3.5 REGULATORY AND PATIENT SAFETY INFORMATION

Table **3.10** contains some important regulatory and patient safety information regarding the different grades of sucrose stearate. The sucrose esters from Stéarinerie DuBois and Sisterna B.V. are manufactured from vegetable raw materials. In case of the Stelliesters, Elaeis Guineensis and Beta vulgaris are used to derive the different materials. For those three grades a bovine spongiform encephalopathies (BSE) and transmissible spongiform encephalopathies (TSE) certificate is available. For SP50-C and SP70-C these certificates are not available, however since these materials originate from vegetable raw materials, they are not subjected to monitoring of BSE and TSE *[46,47,48,51,52,56]*. Crodesta F160 is as well obtained from vegetable or plant raw materials. As the product is derived from non-animal sources and does not contain material of bovine, ovine or caprine origin the company confirms that the product presents minimal or no risk of transmitting TSE via medicinal and cosmetic products. According to the manufacturer Tegocare SE 121 MB is produced in the absence of animal derived material of any type. Residual sources of palm oil, rapeseed oil, corn, sugar cane or sugar beet may be present. Since no animal derived materials were used in the manufacturing process, any risk for BSE and TSE can be excluded. For Emulgade Sucro Plus the statement 'non-animal origin' applies exclusively to products manufactured in the European Union (EU), for other regions no information is available. In the EU the Emulgade Sucro Plus batches are from vegetable origin. The fruit of coconut oil or palm kernel oil plants or the cane from sugar cane or beet sugar are utilized to produce the Emulgade Sucro Plus. These are all non-genetically modified plants. Given that for the production of Emulgade Sucro Plus no animal derived materials were used, any risk for BSE and TSE can be excluded *[49,50,53]*.

For SE 5S, SE 11S, SE 15S, SP50-C, SP70-C and Emulgade Sucro Plus both, a halal and kosher certificate, are available. These certificates imply that the materials are made with respect to the Muslim and Jewish faith. Overall, halal and kosher certified pharmaceutical and cosmetic products are gaining awareness and increasing demand. The intent of certifying products as halal or kosher is parallel with the goals of most quality assurance procedures as for instance cGMP. Hence, halal and kosher products must be recognized as an indicator of cleanliness, safety, purity, and quality. Furthermore, as these products are attributed with ethical consumerism and more stringent quality assurance standards, they carry a wider market appeal *[65]*.

Regarding the allergens statement for all materials no ingredient or processing aid derived from a substance or product listed in Annex II of Regulation (EU) No 1169/2011, represented in Appendix **4**, is expected to be present *[66]*. The ingredients listed are typical food allergens that may cause allergies or intolerances.

The cosmetic grade materials, Tegocare SE 121 MB and Crodesta F160, do not contain any of the fragrance allergens listed in Regulation (EC) No 1223/2009 and for Emulgade Sucro Plus it is stated that these are not expected to be present [49,50,53].

3.5.1 Toxicology data

In de FDA inactive ingredient database the use of sucrose stearate is only mentioned for oral and topical use. SEFA have a group ADI of 40 mg/kg/day and overall they are non-irritating for skin and do not cause sensitization. Regarding parenteral safety no concrete information is found to be available. However in 2013, a patent regarding "parenteral formulations compromising sugar based esters and ethers" is granted application [67]. No studies are found verifying the safety of sucrose stearate for ocular uses. The safety assessment report of saccharide esters used in cosmetics CIR (2016) reports a study on rabbits where the effect of a 10 % sucrose laurate solution on the eyes was evaluated. A score of 21 was reported indicating damage to the cornea, since the threshold was set at 20 [68]. Regarding the evaluated materials, for Crodesta F160 the supplier states that contact with the eyes can cause some serious eye irritation. Also, for SE 11S and SE 15S Stéarinerie DuBois mentions eye irritation upon direct contact is possible. For all materials the oral LD_{50} in rat is above 2 000 mg/kg. For sucrose monostearate and sucrose distearate from DuBois the same LD_{50} is reported for dermal administration. The sucrose stearate materials do not cause genetic toxicity and no indication exists that repeated dose exposure causes adverse effects. A NOAEL of ≥ 1 000 mg/kg for sucrose distearate and ≥ 2 000 mg/kg for sucrose monostearate was determined in rat. The oral NOAEL in rat after 90 days exposure was determined to be 3 240 mg/kg/day [46,47,48,49,50,51,52,53].

3.5.2 Paediatric acceptability

Currently, there is growing concern about the increased consumption of sugars in medications by children as it may contribute to dental caries [69]. Dental caries is initiated by acid end-products of the microbial metabolism. Especially the acids produced from sucrose and glucose by the metabolic activity of Streptococcus mutans initiate dental caries. Inhibiting of the growth of S. mutans species is established *in vitro* at a concentration of 1 600 mg/L for L70-C, containing sucrose laurate, however SP70-C has not shown to be effective. For the other materials containing sucrose stearate no information regarding the inhibition of S. mutans is available [63]. However, SEFA are authorised food additives in the EU with intake limits represented in Appendix 3: [36]. According to EFSA the current exposure estimates to SEFA exceed the ADI of 40 mg/kg/day for many population groups; especially for toddlers and children [36].

Table 3.10: Some regulatory and patient safety information regarding the different grades of sucrose stearate [46,47,48,49,50,51,52,53]. (N.A.:Not applicable, -: No information available) [a] Applies exclusively to products manufactured in the European Union, for other regions no documentation is provided.

	SE 5S	SE 11S	SE 15S	SP50-C	SP70-C	Crodesta F160	Tegocare SE 121 MB	Emulgade Sucro Plus
Attribute								
Animal/human origin	NO	NO	NO	NO	NO	NO	NO	NO[a]
BSE/TSE status	Compliant	Compliant	Compliant	Compliant	Compliant	Compliant	-	-
GMO present	NO	NO	NO	NO	NO	-	NO	NO
Halal certificate	YES	YES	YES	YES	YES	NO	NO	YES
Kosher certificate	YES	YES	YES	YES	YES	NO	NO	YES
Phtalates present	Not expected	-	Not expected	-	-	-	-	-
Additional ingredients causing intolerances								
Preservatives	-	-	-	-	-	-	Not present	-
Latex (natural rubber) or synthetic rubber	Not expected	Not expected	Not expected	-	-	-	Not expected	Not expected
Ingredients from yeast or mold	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
Allergens								
Regulation (EU) No 1169/2011 Annex II (*Appendix* **1.2**)	Not expected	Not expected	Not expected	Not present	Not present	Not expected	Not expected	Not expected
Regulation (EC) No 1223/2009	-	-	-	Not present	Not present	Not present	Not present	Not expected

4 SUCROSE STEARATE: FUNCTIONAL PROPERTIES

4.1 METHODS

4.1.1 Krüss Force Tensiometer K100

The Krüss Force Tensiometer K100 is used for analysing surfaces and interfaces. It performs reliable measurements of the interfacial tension between liquid and air, referred to as surface tension (SFT), as well as critical micelle concentration (CMC) measurements. These measurements are performed with high precision and can be carried out automatically. The Force Tensiometer K100 has a high precision force sensor leading to a resolution of 0.001 mN/m. The setup of the Krüss K100 is illustrated in Figure **4.1** [70].

Figure 4.1: Setup of the Force Tensiometer Krüss K100 [70].

4.1.2 Surface tension measurements

With the Willhelmy plate method the SFT is measured by using the wetting force of a liquid at a rectangular platinum plate (PL01). When a liquid solution touches the vertically suspended plate a force F, correlating with the SFT and the contact angle (θ), acts on the plate [71]. A schematic representation is illustrated in Figure **4.2**.

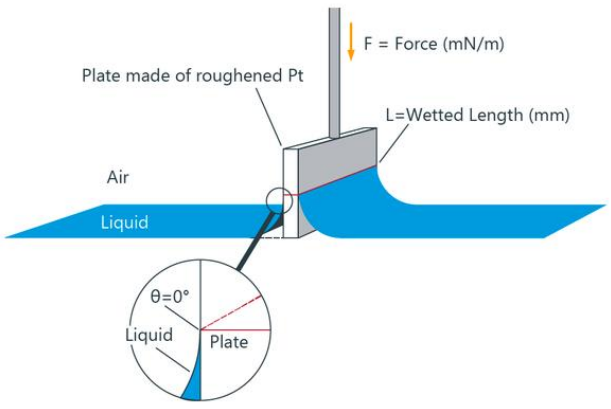


Figure 4.2: Schematic view of the Willhelmy plate method [71].

The SFT is measured by using Equation **4.1**. The wetted length (L) of the plate is equal to 40.2 mm and to measure the force (F), the plate is attached to a force sensor. As plate material, platinum is chosen for measuring the SFT as it is chemically inert and easy to clean. Besides the platinum plate can be optimally wetted through its very high surface free energy. Therefore, it generally forms a contact angle (θ) of 0° with liquids. Since Cos 0° is equal to 1, this term does not influence the SFT measured. Consequently, σ can be calculated directly from the measured force [71].

$$\sigma = \frac{F}{L \cdot cos\theta} \qquad \textbf{Equation 4.1}$$

Where:

σ: Surface tension (mN/m),

F: Force (mN),

L: The wetted length of the plate ($40.2 \cdot 10^{-3}$ m),

θ: The contact angle (°).

Measurements of the SFT with the Willhelmy plate method are carried out by using the standard procedure illustrated in Figure **4.3**. The plate method makes it possible to record the change in SFT over time until the SFT has reached equilibrium. Usually, the standard deviation is used as a stabilization criterion [71].

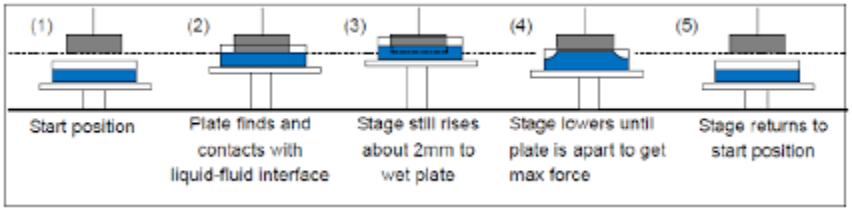


Figure 4.3: Schematic representation of the Willhelmy plate method procedure: (1) Zero the force sensor with the attached plate in air. (2) Detection of the sample surface. (3) Immersion of the plate for prewetting (4) move back to the detected surface. The actual measurement is now carried out. (5) Movement of the sample stage downwards in order to remove the measuring probe and the sample vessel.

4.1.3 Critical micelle concentration measurements

The Willhelmy plate method makes it possible to carry out CMC-measurements by the measurement of the SFT of a concentration series of the sample. To perform fully automated CMC-measurements, micro dispensers are used. These micro dispensers are positioned at the left and right side of the measuring device in Figure **4.1**. One is used for dispensing the liquid into and the other one to aspirate the same volume out of the vessel containing the sample solution. This setup enables to create a concentration series fully automatically. A desired number of cycli is selected to measure the CMC very accurately. Each measuring point represents the mean SFT at each concentration that was analysed. The manual denotion of two regression lines enables the system to calculate a CMC-value based on the intercept of the two regression lines [70].

The cross-sectional area per molecule at the interface (A) is calculated from Equation **4.2** and Equation **4.3** by using the left regression line on the curve [72]:

$$\Gamma = - \frac{d\gamma / d\ln C}{RT} \qquad \textbf{Equation 4.2}$$

$$A = \frac{1}{(N_A \cdot \Gamma)} \qquad \textbf{Equation 4.3}$$

Where:

Γ: The surface excess (mol/m^2),

$d\gamma/d\ln C$: The first derivative of the SFT (N/m) over the concentration (mol/m^3),

R: The universal gas constant (8.3 J/K · mol),

T: The absolute temperature (K),

N_A: The Avogadro number (6.023 . 10^{-23} deeltjes/mol),

A: The cross-sectional area per molecule at the interface (Å^2).

4.2 MATERIALS

Table **4.1** provides an overview of the sucrose stearate products that are analysed together with the corresponding suppliers and the lot number of the retrieved batches. In addition, the solvents used during the sample preparation and cleaning of the PL01-plate are listed in this table.

Table 4.1: Overview of the products, solvents and instruments used.

Product name	Supplier	Lot n°
Stelliesters SE 5S	Stéarinerie DuBois	18122101
Stelliesters SE 11S	Stéarinerie DuBois	19042105
Stelliesters SE 15S	Stéarinerie DuBois	18092114
Sisterna SP50-C	Sisterna B.V.	648714
Sisterna SP70-C	Sisterna B.V.	648952
Crodesta F160-PW-(RB)	Croda GmbH	0001622333
Tegocare SE 121 MB	Evonik Nutrition&Care GmbH	D719505616
Emulgade Sucro Plus	BASF SE	0020972105
Solvent	**Supplier**	**Lot n°**
Ethanol (EtOH)	Merck	K51871183
Isopropyl acetate	Merck	S7803160
Instrument	**Supplier**	**Serial n°**
Krüss K100	Krüss GmbH	30009801
SV20 Glass Ø70mm	Krüss GmbH	-
PL01-plate	Krüss GmbH	-

4.3 SAMPLE PREPARATION AND MEASUREMENTS SETTINGS

To get an idea of the solubility of the different samples, 100 mg of each sample is dissolved in milli-Q and diluted to 100 mL with milli-Q (0.1 % m/V). These samples are stirred at 250 rpm and heated at 100 °C to improve the dissolution. Afterwards, the samples are cooled down to room temperature. A second experiment is done where 100 mg of each sample is diluted with a mixture of milli-Q/EtOH (90:10 V/V) to 100 mL (0.1 % m/V). The samples are as well stirred and heated at 100 °C during 30 min – 2 h at 250 rpm after which they are cooled down to room temperature.

For the SFT-measurements a dilution series of 5 concentrations is made: 0.5 %; 0.1 %; 0.01 %; 0.001 % and 0.000 1 % m/V. To obtain the 0.5 % m/V-solution, 1 000 mg of each product is dissolved in milli-Q and diluted to 200 mL. The samples are stirred at 250 rpm and heated at 100 °C to improve the dissolution. After 30 min – 2 h, the 0.5 % m/V samples are cooled down to room temperature and the dilution is carried out to obtain the other concentrations. To test the SFT, a minimal volume of 37.5 mL is put into the SV20 Glass Ø70mm vessel and the Willhelmy plate method is applied. SFT are measured at a set temperature of 25 °C. Each recorded SFT-value is the mean of the SFT measured during 900 s; 0.2 Hz with acceptance criterium a standard deviation of 0.02 mN/m over ten consecutive recorded data points. Between different SFT-measurements the PL01-plate is cleaned with milli-Q and isopropyl acetate and heated up with a gas burner.

CMC-measurements are performed by using the reversed-concentration method, with the SV20 Glass Ø70mm vessel containing 50.00 mL of the start concentration, which is the highest concentration. A start concentration of 1 000 mg/L (0.1 % m/V) is used for SE 5S, SE 11S, SE 15S, SP50-C, SP70-C and Crodesta F160. For Emulgade Sucro Plus a start concentration of 5 000 mg/L is used. For samples dissolved in milli-Q and samples dissolved in milli-Q/EtOH (90:10 V/V), the dispenser is filled with respectively, milli-Q and milli-Q/EtOH (90:10 V/V) to dilute the sample concentration over time. For Emulgade Sucro Plus 46 cycli were carried out to dilute the 5 000 mg/L start concentration to 0.5 mg/L. The CMC of SE 11S and SE 15S in milli-Q are measured by using respectively 43 and 57 cycli. The CMC of SE 5S, SP50-C, SP70-C and Crodesta F160 is measured by using 21 cycli. For all measurements in milli-Q/EtOH (90:10 V/V), 21 cycli are carried out to dilute the start concentration from 1 000 mg/L to 0.1 mg/L. Analysis is done at a set temperature of 25 °C and each measurement is carried out for 500 s; 0.2 Hz with acceptance criterium a standard deviation of 0.02 mN/m over ten consecutive recorded data points.

4.4 RESULTS AND DISCUSSION

4.4.1 Literature results regarding functional properties of sucrose stearate esters

4.4.1.1 Solubility

Generally, SEFA are sparingly soluble in water and are soluble in ethanol. Given that SEFA with longer fatty acid chain length exhibit less hydrophilic properties and are thus less soluble in aqueous media, sucrose stearate (C18:0) is less water-soluble compared to sucrose palmitate (C16:0) and sucrose laurate (C12:0). Regarding the degree of esterification, a higher monoester content results in higher hydrophilicity [31]. The latter observation is seen for the Ryoto sucrose stearate esters from Mitsubishi-Kagaku and is already represented in Table 1.2. In 2016, a study investigated the solubility of ten SEFA products that are commercially available worldwide as food additives. The study showed an increased solubility in water and alcohol when the samples were heated due to an increase in the molecular movement of the hydrophobic groups [73]. Information regarding the solubility of the retrieved samples in water and ethanol was provided by the suppliers and is represented in Table 3.8.

4.4.1.2 Surface tension and the influence of alcohol addition

Table 1.2 illustrates that the reduction in surface tension regarding Ryoto sucrose stearate materials of Mitsubishi-Kagaku compared to water (72.0 mN/m) is mainly dependent of the monoester content. The higher the monoester content the higher the reduction in surface tension is observed [43]. The effect of alcohol addition in aqueous micellar solutions of various surfactants has not been studied on a large scale. For the cationic surfactant cetyltrimethylammonium bromide (CTAB) and the non-ionic polysorbate 20 the effect of an increase in the alcohol carbon chain on the $SFT_{>CMC}$ was analysed and the results are presented in Table 4.2. It was seen that the $SFT_{>CMC}$ decreased sharply as the hydrocarbon chain length of the alcohols becomes larger. Therefore, the more hydrophobic the alcohol, the more decrease in $SFT_{>CMC}$ is seen [74].

Table 4.2: Surface tension values (mN/m) at CMC for PS20/CTAB systems as a function of the mole fraction of polysorbate 20 in different alcohol solutions at 25 °C [74].

Polysorbate 20/CTAB	10 % Methanol	10 % Ethanol	10 % Propanol	10 % Butanol
0	40.5	39.9	33.9	24.5
1	32.2	37.2	33.5	24.6

4.4.1.3 Critical micelle concentration and the influence of alcohol addition

The tendency of surfactant molecules to form micelles is in relation with their hydrophobicity. The longer the hydrophobic chain, the lower the concentration at which a surfactant starts to form micelles as the hydrophobic parts group together to have a lower energy level. Besides, a higher degree of esterification increases the hydrophobicity of the material. For sucrose monostearate a CMC of 6.7 mg/L is found in literature [39]. To be surface active surfactants need to be in dissolved state [31]. Therefore, good solubility of surfactants is crucial as it will influence the CMC-determination. As sucrose stearate esters are sparingly soluble in aqueous media, the addition of ethanol can help increase the solubility and consequently could result in more representative CMC-values. When mixed with water, alcohols do dissolve well as they are polar liquids and have electrostatic interaction [75]. Consequently, for alcohols micelle formation is not seen. Whereas the SFT of the water-air interface at 25 °C is 72.8 mN/m, the SFT of the ethanol-air interface, ± 22 mN/m, is much lower. Since the presence of 10 % ethanol in water decreases the SFT (± 51 mN/m), surfactants do tend to form micelles at higher concentrations when dissolved in a water/ethanol mixture [76].

4.4.1.4 Cross-sectional area at the surface

The steeper the left regression line, the smaller the estimated cross-sectional area taken per molecule at the surface (*A*). As only dissolved surfactant molecules determine the results of the SFT-values obtained in the CMC-experiments, the real concentration and therefore the solubility will impact *A*. Previous studies have shown that *A* is mostly influenced by the identity of the bulky head group. For SEFA *A*-values around 40 - 50 Å^2 were found for alkyl chains ranging from seven to 11 methylene units. For longer alkyl chains an important increase is observed. For instance, for sucrose palmitate an *A*value above 100 Å^2 is observed [77]. In addition, the stereochemistry and packing of the structure impact *A*. Surfactant molecules with geometry which allow closer packing at the interface will in general have lower *A*-values. Therefore, SEFA containing a higher proportion of monoesters result in lower *A*-values than those with a higher di- and triester fraction since the latter have more bulky three-dimensional structures [72,78].

4.4.2 Experimental results

4.4.2.1 Solubility

The solubility of the materials containing sucrose stearate in milli-Q and a mixture of milli-Q/EtOH (90:10 V/V) is represented in Table 4.3. At room temperature neither of the materials are seen to form clear solutions in milli-Q. After heating, the solubility of the materials increases where SP50-C, SP70-C and Crodesta F160-PW-(RB) are seen to be soluble. However, the other materials remain partially soluble and after cooling down to room temperature white precipitates are observed. When dissolved in a mixture of milli-Q/EtOH (90:10 V/V), SE 11S and SE 15S become soluble after heating and remain soluble after cooling down to room temperature. Since the other materials do not form clear solutions, these are still considered to be partially soluble, with Emulgade Sucrose Plus showing the greatest turbidity.

Table 4.3: Sucrose stearate from different suppliers solubilized in milli-Q/EtOH (90:10 V/V).
(I: insoluble, PS: Partially soluble or dispersible, S: Soluble)

	SE 5S	SE 11S	SE 15S	SP50-C	SP70-C	Crodesta F160	Tegocare SE 121 MB	Emulgade Sucro Plus
milli-Q								
25 °C	I	PS	PS	PS	PS	PS	PS	I
100 °C	PS	PS	PS	S	S	S	PS	PS
After cooling	PS	PS	PS	S	S	S	PS	PS
milli-Q/EtOH (90:10 V/V)								
25 °C	I	PS	PS	S	S	S	PS	I
100 °C	PS	S	S	S	S	S	PS	PS
After cooling	PS	S	S	S	S	S	PS	PS

The results seen for the different sucrose stearate products are in accordance with the information provided by the suppliers. From these experiments, it can be seen that the higher the monoester content, the better the solubility of the materials. For Tegocare SE 121 MB and Emulgade Sucro Plus the solubility is influenced by the presence of components other than sucrose stearate, glyceryl stearate and cetyl palmitate, respectively.

4.4.2.2 Surface tension

Table **4.4** shows the SFT of the sucrose stearate products dissolved in milli-Q and milli-Q/EtOH (90:10). The SFT above CMC ($SFT_{>CMC}$) for most materials is about 35 to 37 mN/m, except for SE 5S and Tegocare SE 121 MB [42]. Regardless of the turbidity of some samples in milli-Q, only the $SFT_{>CMC}$ for SE 5S and Tegocare SE 121 MB deviate fairly from 35 mN/m. The lower reduction in SFT (higher $SFT_{>CMC}$) for SE 5S is most likely due to its higher composition in di- and triesters. For Tegocare SE 121 MB the presence of glyceryl stearate which is considered more hydrophilic compared to sucrose stearate, could explain the higher reduction in SFT (lower $SFT_{>CMC}$). At a concentration below the CMC (1 mg/L) the SFT in milli-Q increases to values between 48 and 72 mN/m.

Table 4.4: Mean surface tension of a 1 000 mg/L and 1 mg/L solution in milli-Q and 1 000 mg/L milli-Q/EtOH (90:10 V/V) at 25 °C.

		milli-Q		milli-Q/EtOH (90:10 V/V)
	HLB	SFT (mN/m) 1 000 mg/L	SFT (mN/m) 1 mg/L	SFT (mN/m) 1 000 mg/L
SE 5S	5	43.8 ± 1.1	72.3 ± 0.1	42.5 ± 0.7
SE 11S	11	37.5 ± 1.1	57.4 ± 1.5	37.9 ± 0.6
SE 15S	15	37.1 ± 0.3	48.7 ± 0.1	36.6 ± 0.3
SP50-C	11	37.0 ± 0.7	54.6 ± 0.8	-
SP70-C	15	35.2 ± 0.2	53.6 ± 1.3	-
Crodesta F160-PW-(RB)	14.5	35.6 ± 0.3	72.6 ± 0.0	36.2 ± 0.3
Tegocare SE 121 MB	13	27.4 ± 2.0	71.3 ± 0.5	25.7 ± 1.3
Emulgade Sucro Plus	9 – 11	35.2 ± 4.3	72.4 ± 0.1	35.4 ± 0.2

From the obtained results it can be noted that $SFT_{>CMC}$ appears to be similar when the products are dissolved either in milli-Q or in a mixture containing 10 % EtOH. Remarkably, no decrease in SFT is observed which is in contrast with the observations found in literature. However, the similar SFT-values confirm the deviation in SFT that is seen for SE 5S and Tegocare SE 121 MB. Since SP50-C and SP70-C show good solubility in milli-Q, the SFT in milli-Q/EtOH (90:10 V/V) is not measured.

4.4.2.3 Critical micelle concentration

The graphics obtained from the CMC-determination carried out with the CMC Willhelmy plate method for samples dissolved in milli-Q are represented in Appendix **5**. The CMC-measurements for SP50-C, SP70-C and Crodesta F160 show a clear plateau and linear phase. Those materials dissolve (almost) completely in milli-Q after heating and stirring. For SE 5S, SE 11S and SE 15S in pure milli-Q no clear plateau phase is distinguished. Since these materials are seen to be only partially soluble in milli-Q, sinking of dispersed material could explain the course of the curves obtained. When looking at the course of the curve obtained with Emulgade Sucro Plus,

no plateau phase is observed, however a decline in SFT is seen before SFT starts to rise. The decline is likely due to the presence of impurities which are more surface active. Graphic H in Appendix **5** shows the change in SFT over time for the 0.01 % m/V solution. The small bow and the decline after the bow in the curve illustrate the presence of multiple components in the material being surface active. Worth noting is that the SFT at lower concentrations is lower for Emulgade Sucro Plus compared to the other materials. At the end concentration an SFT of 32.2 ± 0.02 mN/m is determined. After cleaning the plate an SFT of 51.8 ± 0.05 mN/m is measured indicating that sticking of surfactant molecules to the plate impacts the automatic measurement for this material.

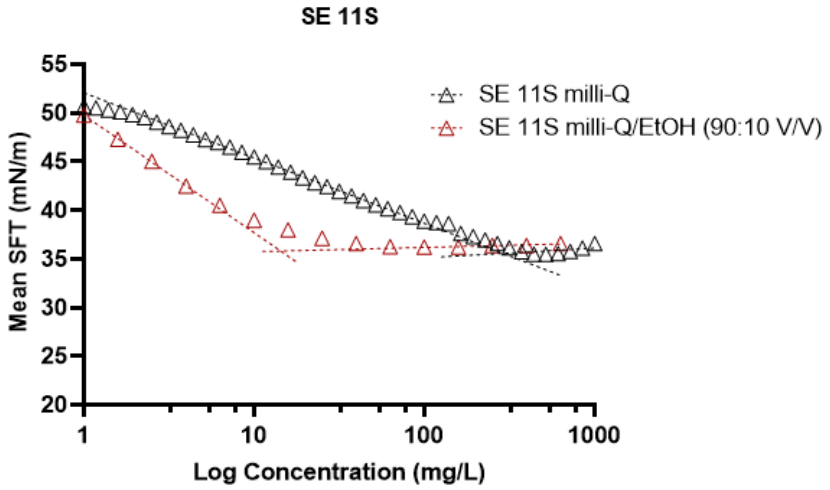
Table **4.5** provides an overview of the obtained CMC, SFT_{CMC} and cross-sectional area at the surface. The SFT_{CMC} for SE 11S, SE 15S and SP70-C and Crodesta F160 are quite similar to the $SFT_{>CMC}$ shown in Table **4.4**. Emulgade Sucro Plus, on the other hand, shows a lower SFT_{CMC} (23.2 mN/m) compared to the $SFT_{>CMC}$ of 35.2 mN/m. Regarding the critical micelle concentration only SP70-C and Crodesta F160 show CMC-values that are not far from the found 6.7 mg/L for sucrose monostearate in literature. The high CMC-values obtained for SE 5S, SE 11S, SE 15S and Emulgade Sucro Plus are likely the consequence of the bad dissolution of these samples in milli-Q .

Table 4.5: Overview of the critical micelle concentration, surface tension at critical micelle concentration and the cross-sectional area per molecule at the surface obtained for the different materials dissolved in milli-Q with the CMC Willhelmy Plate method at 25 °C. For Tegocare SE 121 MB no results are available since the measurement is not carried out. (-: No information available)

Product	HLB	Monoester content (%)	CMC (mg/L)	SFT_{CMC} (mN/m)	A ($Å^2$)
SE 5S	5	32.4	75.6	46.8	132
SE 11S	11	56.9	402.0	35.4	151.9
SE 15S	15	66.0	75.0	35.5	175.6
SP50-C	11	50.0	32.3	36.7	110.0
SP70-C	15	70.0	14.6	35.4	91.5
Crodesta F160-PW-(RB)	14.5	-	12.6	35.4	126
Tegocare SE 121 MB	13	-	-	-	-
Emulgade Sucro Plus	9 – 11	-	607.4	23.2	161.3

4.4.2.4 Critical micelle concentration is influenced by the addition of ethanol

In Appendix **6** Graphic A shows the CMC-results for the pharmaceutical grade materials and Graphic B shows the CMC-result for Crodesta F160. When dissolved in milli-Q/EtOH (90:10 V/V), from the CMC-measurements of SE 5S, SE 11S and SE 15S a plateau and linear phase are distinguished. For SE 11S the result obtained in milli-Q and milli-Q/EtOH (90:10 V/V) are represented in Graphic **4.1**. It can be noticed that the addition of a small fraction of ethanol, resulting in an increased solubility also impacts the CMC-curve obtained. The graphic shows a clear reduction in the measured CMC. Crodesta F160-PW-(RB) appears as a clear solution both in pure milli-Q as well as in milli-Q/EtOH (90:10 V/V), resulting in comparable results for the CMC-measurement. Due to good solubility of SP50-C and SP70-C, CMC is not determined in milli-Q/EtOH (90:10 V/V). For Emulgade Sucro Plus and Tegocare SE 121 MB CMC-measurements in milli-Q/EtOH (90:10) are not carried out due to lack of time and due to the fact that these materials offer no possibility for use in pharmaceutical formulations.



Graphic 4.1: Critical micelle concentration determination for SE 11S in milli-Q and milli-Q/EtOH (90:10 V/V).

Table **4.6** shows the results of the CMC-measurements in a mixture of milli-Q/EtOH (90:10). A strong decrease in CMC compared to the results obtained in milli-Q are seen for SE 11S and SE 15S. The presence of turbid solutions likely explains an overestimation of the CMC-value obtained in milli-Q. Given that surfactant molecules are only surface active in their dissolved state, bad dissolution likely impacts the CMC. Since SFT-determination at 1 000 mg/L is carried out at high concentration, bad dissolution is not likely to impact the SFT. However, for SE 5S a reduction in CMC is not observed.

For Crodesta F160-PW-(RB) a slightly higher CMC is obtained in milli-Q/EtOH (90:10 V/V) compared to milli-Q which is in accordance with the solubility of the material seen in both solvents and the literature results suggesting an increase in CMC in the presence of ethanol. The observation that the CMC for the other materials decreases strongly in the presence of ethanol is in contrast with literature results, however, in this particular case, the effect of increased solubility exceeds the effect of ethanol on the CMC.

Table 4.6: Critical micelle concentration measurements in milli-Q/EtOH (90:10 V/V). (-: No information available)

Product	HLB	Monoester content (%)	CMC (mg/L)	SFT_{CMC} (mN/m)	A (Å^2)
SE 5S	5	32.4	102.4	42.2	170.5
SE 11S	11	56.9	14.9	36.0	81.1
SE 15S	15	66.0	13.9	36.6	137
SP50-C	11	50.0	-	-	-
SP70-C	-	70.0	-	-	-
Crodesta F160-PW-(RB)	14.5	-	13.8	36.0	140.9
Tegocare SE 121 MB	13	-	-	-	-
Emulgade Sucro Plus	9 – 11	-	-	-	-

4.4.2.5 Cross-sectional area at the surface

SP50-C (50 % monoester) and SP70-C (70 % monoester) show a lower *A* compared to the other materials in milli-Q. When comparing the pharmaceutical grades, an increase in *A* is observed going from SE 5S (32.4 % monoester), over SE 11S (56.9 % monoester) to SE 15S (66.0 % monoester), which is in contrast with the assumption that SEFA containing a higher proportion of monoesters result in lower *A*-values than those with a higher di- and triester fraction since the latter have more bulky three-dimensional structures [78]. Emulgade Sucro Plus shows an *A*-value close to those obtained with the pharmaceutical grades, regardless of the presence of mainly sucrose polystearate (86.5 %). A smaller *A*-value than expected is observed where the presence of cetyl palmitate (12.8 %) is likely to have an impact on the observed results. Noteworthy is the fact that SE 5S, SE 11S, SE 15S and Emulgade Sucro Plus appeared as dispersions in milli-Q which impacts the course of the curves obtained and consequently the deviated *A*. When looking at the results obtained for the pharmaceutical grades in the presence of ethanol, it is observed that SE 11S and SE 15S, containing a higher monoester content, have a lower *A* compared to SE 5S, which is in accordance with the literature results. For SE 11S and SE 15S the difference in the monoester content is not outspoken. Although, SE 11S has the lowest monoester content, it also has the highest tri- and polyester content of both, which is likely to impact the observed *A*. When comparing the *A*-values obtained in milli-Q to those obtained in milli-Q/EtOH, a decrease is seen for SE 11S and SE 15S. For SE 5S an increase is observed, regardless of the increased solubility that is seen in the presence of ethanol.

5 CRITICAL MATERIAL ATTRIBUTES

Based on the general and functional properties an overview is made containing some material attributes that are considered critical. To ensure the desired quality of drug products these physical and chemical properties should be kept within an appropriate range. Some effects of the critical material attributes (CMA) are only relevant in liquid formulations [79].

Critical material attributes:

- Degree of esterification
- C16 + C18 content
- Free fatty acid content

The degree of esterification has an influence on the solubility in aqueous media, the reduction in surface tension (SFT), the critical micelle concentration (CMC), melt temperature (T_m), electrolyte compatibility and pH-stability of sucrose stearate materials. The higher the monoester content, the higher the solubility of the sucrose stearate material in aqueous media. When the degree of esterification increases, solubility decreases. In addition, materials with a higher monoester content tend to show more decrease in the SFT and tend to have higher CMC-values. Overall, stearates are seen to be more sensitive to flocculation compared to SEFA with shorter fatty acid chain length. Moreover, those materials with a higher degree of esterification are more sensitive than those with a higher monoester fraction. Monoesters will degrade faster than di- or triesters outside the pH-range 4 - 8 [63].

The amount of C16 + C18 present impacts the solubility of the materials, the reduction in SFT and the CMC-value. The higher the amount of longer fatty acid chain lengths, the lower the solubility and CMC and the higher the SFT.

Furthermore, the free fatty acid content impacts the reduction in SFT and the CMC since these molecules are as well surface active. This CMA becomes more important in liquid formulations since hydrolysis of the ester bonds occurs quite fast in aqueous media. Free fatty acids generally show less solubility and lower CMC-values. Since these molecules are less surface active, the decrease in SFT will be lower [31].

6 CONCLUSIONS

Based on product information data sheets obtained from the suppliers, evaluation and analysis was done for eight grades containing sucrose stearate. Three pharmaceutical grades from Stéarinerie DuBois (SE 5S, SE 11S and SE 15S) are in compliance with the regulatory requirements for use as excipients in oral pharmaceutical formulations. SE 11S and SE 15S comply with the type I requirements according to the Ph. Eur. and USP. SE 5S complies with the requirements for being a type II sucrose stearate material. The two grades from Sisterna B.V. (SP50-C and SP70-C) comply with the limits for type I sucrose stearate materials. However, they do not meet the limits for the elemental impurities Cd and Pb in order to be useful in oral formulations. Further specification by the supplier about the presence of these impurities is needed. The cosmetic and food grade material Crodesta F160 complies with the requirements of the compendial regarding the purity, however the composition and identity should be specified to be acceptable as pharmaceutical excipient. Since it is offered as food grade material, the material is permitted for use in protective coatings for oral formulations, where it is already used in authorised medicinal products. Tegocare SE 121 MB and Emulgade Sucro Plus offer no potential for use in oral pharmaceutical formulations as they do not meet the requirements regarding their composition and purity related material attributes. On top, their corresponding suppliers explicitly state that these materials are not intended to be used in pharmaceutical formulations.

Regarding the functional properties of the materials it can be concluded from the experimental part that solubility is of concern for most materials. For SP50-C, SP70-C and Crodesta F160 more or less clear solutions are obtained in water. For SE 11S and SE 15S the addition of a small fraction of ethanol helps to increase the solubility. Regarding the reduction in surface tension at concentrations above the critical micelle concentration, no big differences are seen concerning the different materials, regardless of their solubility. For SE 5S and Tegocare SE 121 MB the surface tension deviates fairly from 35 mN/m. When acceptable solubility is obtained, no big differences are measured for the critical micelle concentration. However, the addition of ethanol results in a strong decrease of the critical micelle concentration for the materials that do not show good solubility in water, since the effect of solubility exceeds the effect of ethanol on the critical micelle concentration. Ideally, critical micelle concentration measurements should be repeated to perform statistical analysis on the obtained results in order to make better conclusions regarding the functional properties.

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APPENDIX

Appendix 1: CMC values in water for different ionic and non-ionic surfactants determined at 25 °C.

Appendix 2 Overview sugar-based surfactant classes, possible suppliers and field of application.

Appendix 3: Food uses and use levels for sucrose esters of fatty acids based on the food category system of the GSFA of the Codex Alimentarius Commission (2017).

Appendix 4: Regulation 1169/2011 ANNEX II – Substances or products causing allergies or intolerances

Appendix 5: Graphics critical micelle concentration measurements in milli-Q/EtOH 90:10 V/V)

Appendix 1: CMC values in water for different ionic and non-ionic surfactants determined at 25 °C.

Tabel 1: Critical micelle concentration values in water for different ionic surfactants determined at 25 °C.

Ionic surfactants

Anionic		Cationic	
Surfactant	**CMC (M)**	**Surfactant**	**CMC (M)**
Sodium octanoate	$3.5 \cdot 10^{-1}$		
Sodium decanoate	$9.4 \cdot 10^{-2}$	Decyltrimethylammonium bromide	$6.5 \ 10^{-2}$
Sodium dodecanoate	$2.4 \cdot 10^{-2}$	Dodecyltrimethylammonium bromide	$1.6 \cdot 10^{-2}$
Sodium dodecyl sulfate	$7.4 \cdot 10^{-3}$	Hexadecyltrimethylammonium bromide	$9.2 \cdot 10^{-4}$

Tabel 2: Critical micelle concentration values in water for different non-ionic surfactants containing a polyoxyethylene chain (E) determined at 25 °C.

Non-ionic surfactants

Surfactant	CMC (M)	Surfactant	CMC (M)	Surfactants	CMC (M)
C_8E_5	$9.2 \cdot 10^{-3}$	$C_{10}E_5$	$9.0 \cdot 10^{-4}$	$C_{12}E_5$	$6.5 \cdot 10^{-5}$
C_8E_6	$9.9 \cdot 10^{-3}$	$C_{10}E_6$	$9.5 \cdot 10^{-4}$	$C_{12}E_6$	$6.8 \cdot 10^{-5}$
		$C_{10}E_8$	$10.0 \cdot 10^{-4}$	$C_{12}E_8$	$7.1 \cdot 10^{-5}$

Appendix 2: Overview sugar-based surfactant classes, possible suppliers and field of application.

Tabel 3: Overview sugar-based surfactant classes, possible suppliers and field of application [80].

Surfactant class	Suppliers	Application field
Biosurfactants	Agae technologies, Evonik, Stephan, Jeneil Biotech	Personal care, pharmaceuticals, detergents
Amino acid surfactants	Ajinomoto, Changsha Puji, Clariant, Innospec, Sino Lion, Solvay, Stepan, Zschimmer & Schwarz	Personal care
Sugar based surfactants		
Alkyl polyglycosides	Akzo Nobel, BASF, Cognis, Dai-Ichi Kogyo Seiyaku	Personal care, detergents, agrochemicals
Alkyl polyglucosamides	Lubrizol/Noveon	Detergents, personal care
Maltosides	Anatrace, SAFC, Sigma Tau	Detergents, Research
Sucrose esters	BASF, Cognis, Croda, Dai-Ichi Kogyo Seiyaku, DuBois, Evonik, Mitsubishi-Kagaku, Sisterna	Food, personal care, pharmaceuticals

Appendix 3: Food uses and use levels for sucrose esters of fatty acids based on the food category system of the GSFA of the Codex Alimentarius Commission (2017).

Overview of some food uses and use levels for sucrose esters of fatty acids based on the food category system of the GSFA of the Codex Alimentarius Commission (2017) [37].

Food category	Food use		Use level (mg/kg)
01.0 Dairy products and analogues, excluding products of food category 02.0	01.1.2	Milk (plain)	1 000
0.4.0 Fruits and vegetables (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), seaweeds, and nuts and seeds	04.1.2.8	Fruit preparations, including pulp, purees, fruit toppings and coconut milk	1 500
07.0 Bakery wares	07.1	Bread and ordinary bakery wares	3 000
	07.2	Fine bakery wares (sweet, salty, savoury) and mixes	10 000
13.0 Foodstuffs intended for particular nutritional uses	13.3	Dietetic foods intended for special medical purposes (excluding products of food category 13.1)	5 000
14.0 Beverages, excluding dairy products	14.1.4	Water-based flavoured drinks, including “sport”, “energy”, or “electrolyte” drinks and particulated drinks	200
	14.1.5	Coffee, coffee substitutes, tea, herbal infusions and other hot cereal and grain beverages excluding cocoa.	1 000
	14.2.6	Distilled spiritous beverages containing more than 15 % alcohol	5 000

Appendix 4: Regulation 1169/2011 ANNEX II – Substances or products causing allergies or intolerances.

ANNEX II

SUBSTANCES OR PRODUCTS CAUSING ALLERGIES OR INTOLERANCES

1. Cereals containing gluten, namely: wheat, rye, barley, oats, spelt, kamut or their hybridised strains, and products thereof, except:
   (a) wheat based glucose syrups including dextrose [1];
   (b) wheat based maltodextrins [1];
   (c) glucose syrups based on barley;
   (d) cereals used for making alcoholic distillates including ethyl alcohol of agricultural origin;
2. Crustaceans and products thereof;
3. Eggs and products thereof;
4. Fish and products thereof, except:
   (a) fish gelatine used as carrier for vitamin or carotenoid preparations;
   (b) fish gelatine or Isinglass used as fining agent in beer and wine;
5. Peanuts and products thereof;
6. Soybeans and products thereof, except:
   (a) fully refined soybean oil and fat [1];
   (b) natural mixed tocopherols (E306), natural D-alpha tocopherol, natural D-alpha tocopherol acetate, and natural D-alpha tocopherol succinate from soybean sources;
   (c) vegetable oils derived phytosterols and phytosterol esters from soybean sources;
   (d) plant stanol ester produced from vegetable oil sterols from soybean sources;
7. Milk and products thereof (including lactose), except:
   (a) whey used for making alcoholic distillates including ethyl alcohol of agricultural origin;
   (b) lactitol;
8. Nuts, namely: almonds (*Amygdalus communis* L.), hazelnuts (*Corylus avellana*), walnuts (*Juglans regia*), cashews (*Anacardium occidentale*), pecan nuts (*Carya illinoinensis* (Wangenh.) K. Koch), Brazil nuts (*Bertholletia excelsa*), pistachio nuts (*Pistacia vera*), macadamia or Queensland nuts (*Macadamia ternifolia*), and products thereof, except for nuts used for making alcoholic distillates including ethyl alcohol of agricultural origin;
9. Celery and products thereof;
10. Mustard and products thereof;
11. Sesame seeds and products thereof;
12. Sulphur dioxide and sulphites at concentrations of more than 10 mg/kg or 10 mg/litre in terms of the total SO_2 which are to be calculated for products as proposed ready for consumption or as reconstituted according to the instructions of the manufacturers;
13. Lupin and products thereof;
14. Molluscs and products thereof.

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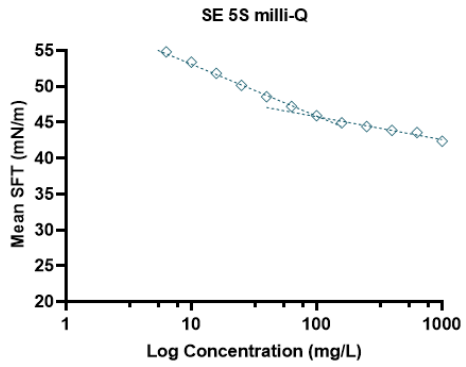
[1] And the products thereof, in so far as the process that they have undergone is not likely to increase the level of allergenicity assessed by the Authority for the relevant product from which they originated.

Appendix 5: Graphics critical micelle concentration measurements in milli-Q.



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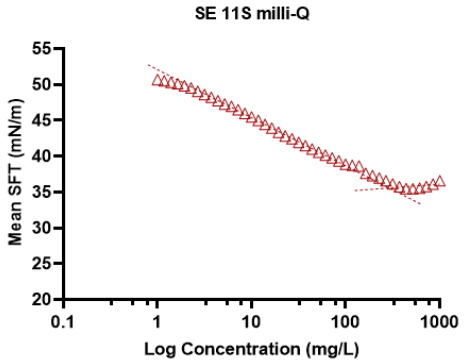

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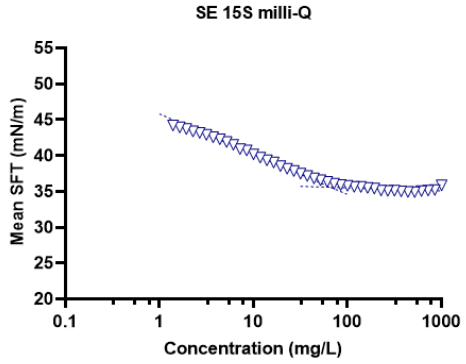

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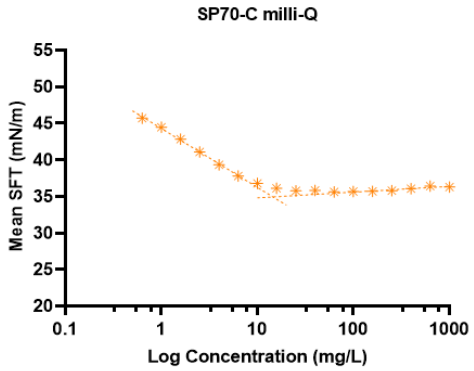

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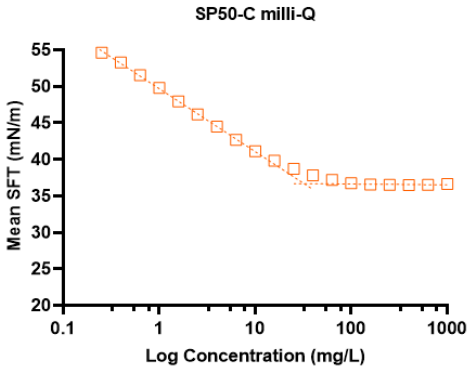

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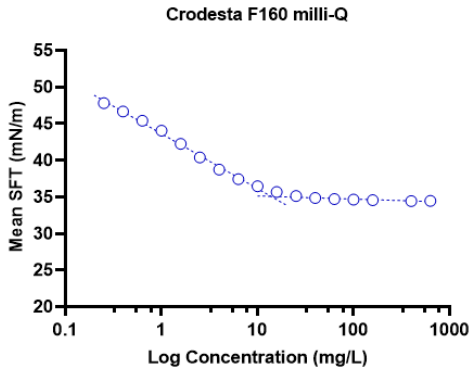

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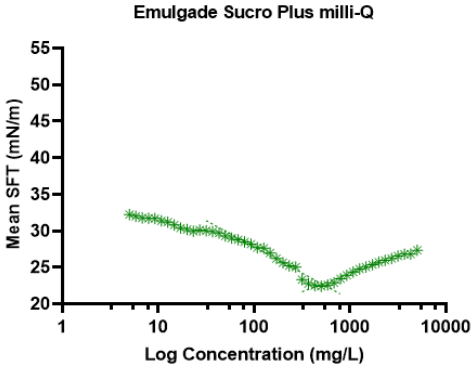

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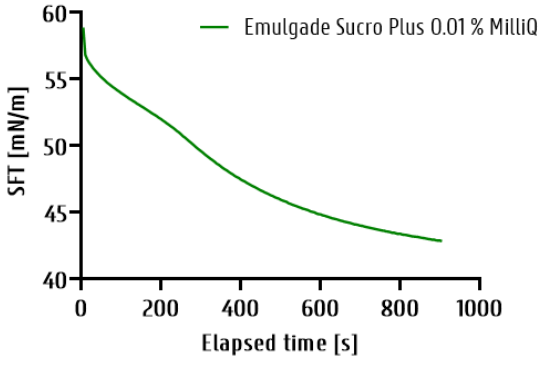
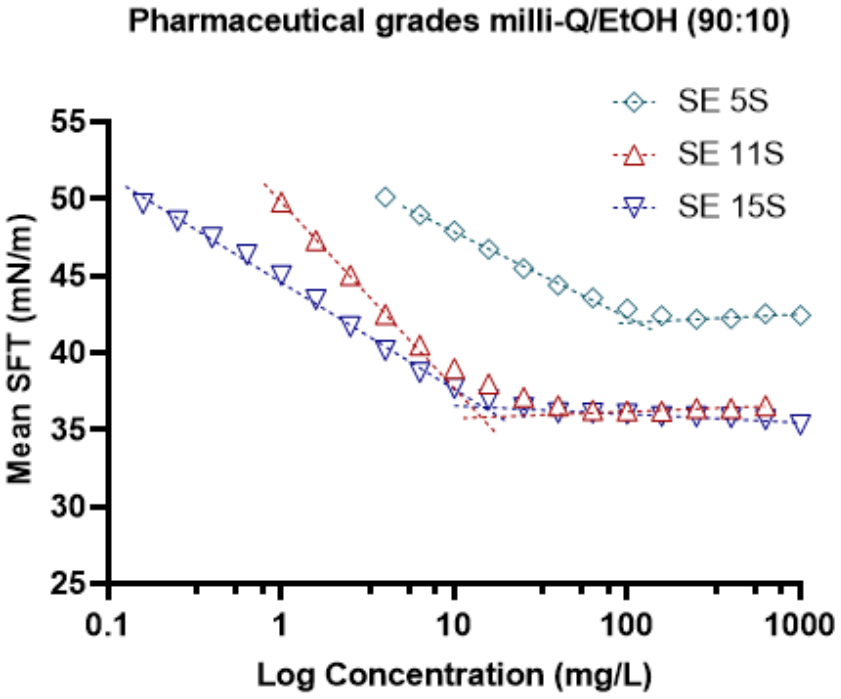


(H)

Appendix 6: Graphics of the critical micelle concentration measurements in milli-Q/EtOH (90:10 V/V).



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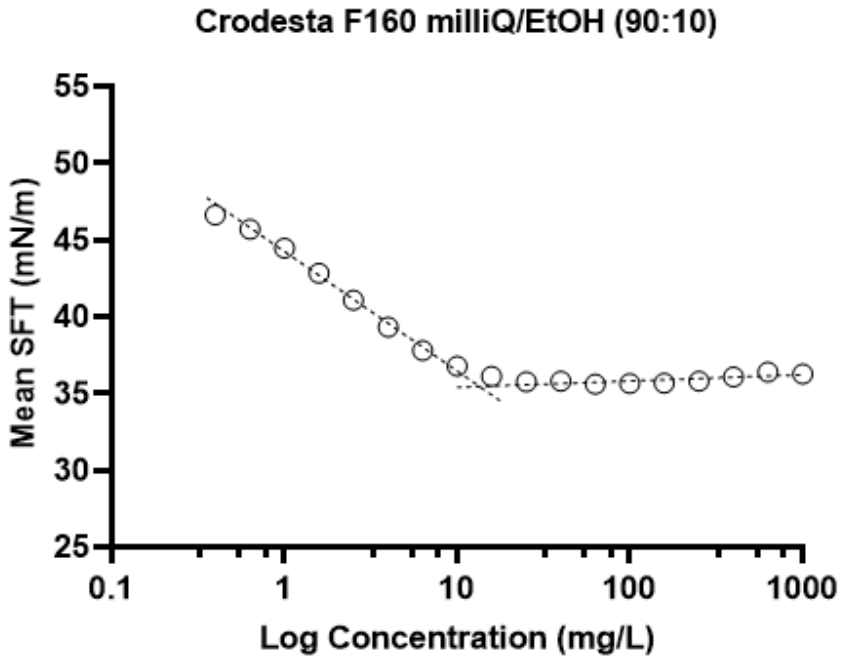

(B)

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The information, conclusions and points of view in this master dissertation are those of the author and do not necessarily represent the opinion of the promoter or his research group.