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Surface Active Agents as Excipients in Semi-Solid Dosage Forms

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Abstract

Surface phenomena involve surface tension, adsorption at interfaces, wettability and contact angle as well as adhesive and cohesive forces. This paper focuses on surface tension and factors that affect it. While developing new dosage forms and aiming at improving drug stability and bioavailability, technologists rely on papers concerning surface tension, the application of hydrophilic-lipophilic balance value and the central role of surfactants. Research into surface phenomena improves our understanding of molecular interactions between phase particles. Surfactants have a central role in many surface phenomena. In semisolid preparations the resulting structures are very complex. In this review paper numerous examples of surfactants application in semisolid drug forms are presented with respective evaluation of surfactant type, and hydrophilic-lipophilic balance values.

Keywords: surface phenomena, hydrophilic-lipophilic balance, surfactants, semi-solid pharmaceutical preparations

1. Introduction

The collected literature data concerning surface phenomena is largely based on papers published between 1940s and 1960s which have become obsolete due to significant advances in research methodology. Rather few papers concerning surface phenomena are published currently in the area of semi-solid drugs forms, which may stem from the fact that respective studies are now carried out in commercial laboratories. Surface phenomena involve surface tension, adsorption at interfaces, wettability and contact angle as well as adhesive and cohesive forces [1]. This paper focuses on surface tension and factors that affect it. While developing new dosage forms and aiming at improving drug stability and bioavailability, technologists rely on papers concerning surface tension, the application of hydrophilic-lipophilic balance (HLB) value and the central role of surfactants. Surfactants and carbohydrates such as glucose, lactose and other hydrophilic substances change the surface tension [2]. Surface phenomena are physical in nature and occur on the surface of the condensed phase. The studies of surface phenomena are of great importance for physics, medical sciences and medical industry. Surface phenomena are examined in experiments drawn from mechanics and thermodynamics [3]. They occur in dispersed systems such as emulsions, colloids, suspensions and microparticles and are important for the development and stability of dosage forms, foodstuffs and cosmetics. They also affect the drug's pharmacokinetics in the organism. Surface phenomena result from differences in thermodynamic parameters of individual phases of the system [4]. Research into surface phenomena improves our

understanding of molecular interactions between phase particles [5]. Surfactants have a central role in many surface phenomena. In semisolid preparations the resulting structures are very complex, as it is presented on microscopic picture on Figure 1.

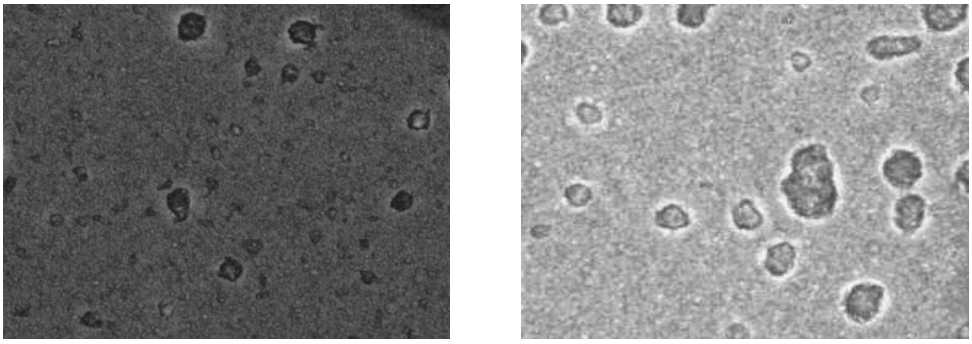
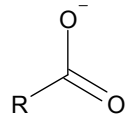
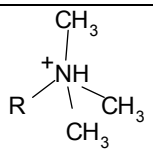
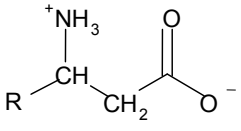
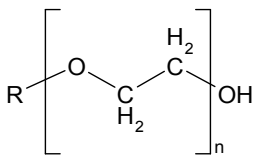


Figure 1. Microscopic pictures of semisolid pharmaceutical preparation, prepared with complex surfactant systems, and high and low content of highly viscous lipophilic base (non-published original study of the authors), the bar represents 50 μm.

2. Application of selected surfactants in multiphase systems

The abbreviation "surfactant" presents surface-active agent. When added to a system at low concentration, a surfactant adsorbs on the surface of the system or at interface and changes the surface tension at interface. An interface is defined as a boundary between two immiscible phases and a surface means that a gas (most often air) is one of the phases. Surfactants are amphiphilic compounds containing specific structural groups [6]. Surface active agents are grouped according to the nature of the hydrophilic group. Table 1 lists types of surfactants as reported in the literature [6, 7].

Table 1. Types of surfactants reported in the literature

Surfactant type	Structure	Source
Anionic – surface active portions of the molecule bear a negative charge.		[8, 9, 10, 11]
Cationic - surface active portions of the molecule bear a positive charge.		[8, 12, 13, 14]
Amphoteric – surface active portions of the molecule carry a charge that varies depending on the pH of the solution.		[10, 15, 16]
Non-ionic – surface active portions of the molecule bear a neutral charge.		[9, 17, 18, 19]

R – alkyl group

Thanasukam et al. studied the influence of emulsifier type on the physico-chemical properties of 20 weight % hydrogenated palm o/w (oil-in-water) emulsion. Ethoxylated sorbitan ester based on a natural fatty acid - lauric acid (Polysorbate 20), caseins and whey protein were examined in the experiment. 2.5 wt % Polysorbate 20 stabilised emulsions were unstable at temperatures where the oil phase was partially crystalline, contrary to emulsions stabilised by 1.25 wt % whey protein and 1.25 wt % casein [20]. Whitby et al. described the structure and stability of emulsions containing PLGA (poly(lactic-co-glycolic acid)) i.e. copolymer of polylactic and polyglycolic acid. The composition of the PLGA used was 50:50 lactic to glycolic acid ratio. Molecular weight of the PLGA was 40-75 kDa. The authors obtained stable emulsions with uniform droplet size distribution in the dispersed phase are dependent on stirring time adjustment [21]. Emulsion stabilisation by surface active agents is a complex process. Surfactants reduce the system's internal energy, adsorb at the interface thus reducing intermolecular interaction in the dispersed phase and generate electrical double layer at the interface [22]. Phase behaviour of emulsifier is dependent on the system's temperature. Adding a surfactant to the mixture of water and oil facilitates formation of emulsion, microemulsion and lyotropic mesophase. In each case the water and oil phase are separated by amphiphilic film. Mesophase has a higher surfactant concentration [23]. Amphiphilic film exhibits varied elastic properties and surface tension [24]. O/w emulsions stabilised with non-ionic surface active molecule can undergo phase inversion upon temperature variation. It is related with very low surface tension [23].

3. Formation of microemulsions

Molecules of surface active agents accumulate on the phase surface. Surface tension is reduced to the greatest extent when critical packing parameter (CPP) is attained, represented by the equation 1, where the v is hydrocarbon tail volume, a_0 reflects the optimum head group area, and l_c is critical hydrocarbon length.

$$CPP = \frac{v}{a_0 \cdot l_c} \quad \text{(Eq. 1)}$$

Theoretically, critical packing parameter value less than 1/3 corresponds to spherical micelles, between 4/3 and 1/2 corresponds to rod-shaped micelles and between 1/2 and 1 corresponds to planar structures. The shape of the micelle is determined by the conformation of the surfactant molecules, which are implemented into the microsphere, as it is illustrated on the Figure 2.

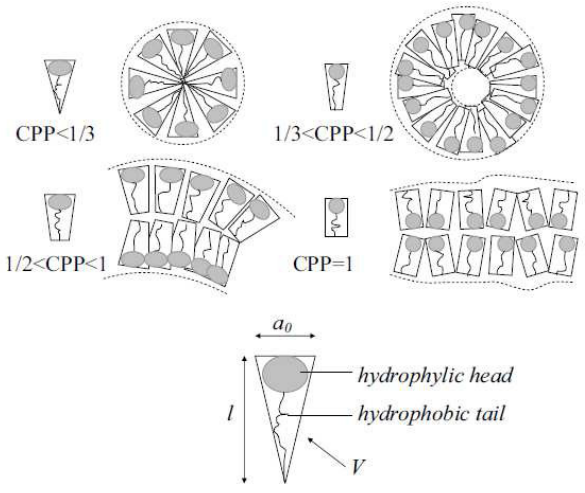


Figure 2. The influence of surfactant particle conformation presented as critical packing parameter (CPP) on the shape of the micelle, house-made picture according to bibliography [25, 26].

In 1969 Adamson concluded that electrical double layer at the interface is partially responsible for the interfacial energy [27]. Garbacia and Rosano discovered that a micro-emulsion is formed spontaneously when interfacial tension is of the order 10^{-4} to 10^{-5} dyn/cm [28]. Scriven [29] further investigated the role of electrical double layer and molecular interactions in microemulsion formation. Ruckstein and Chi examined the stability of such systems. Their experiments brought about information concerning the stability and particle size in the dispersed phase. It was confirmed that microemulsions are formed spontaneously when free phase energy is negative [30]. This theory was modified by Holmberg [31]. He demonstrated that the monolayer that is formed at the interface and is responsible for surface tension can be estimated by Gibbs equation. There are numerous theories concerning microemulsion formation. One of them assumes that microemulsions are formed due to molecule interaction at the interface and reduction of surface tension values of the oil and water phases to zero. However, zero surface tension does not automatically result in microemulsion formation. It is equally likely that cylindrical micelles or lamellar micelles will be formed. Due to their physico-chemical properties, microemulsions stabilised with surfactant monolayer are used as matrices in pharmaceutical products and matrices for nanoparticles synthesis [31]. In recent years amino acid-based surface active agents have been of great interest to researchers. A paper by Yunxiang et al., a result of this trend, is related to glycine, amino malonic acid, aspartic acid and glutamic acid. Further, octyl, ecyl and dodecyl derivatives were synthesized. Alkyl derivatives' critical micelle concentration was approximately 5 times lower than that of acyl derivatives [32]. Soy protein is an important emulsifier used in food industry. Fang et al. reported a study involving soy protein at the concentration of 2-12 mg/ml. The results of the experiment confirm the correlation between rheologic and physico-chemical properties of soy protein stabilised gel emulsions and protein concentration and gelling temperature [33]. Studies into the stability of coconut milk depending on the type of emulsifier were conducted by Tangsuphoom and Coupland. In the experiment the concentration used was 0-1 wt % of sodium caseinate, whey protein, sodium dodecyl sulphate and Polysorbate 20. SLS (Sodium Lauryl Sulphate) increases the rate of flocculation in coconut milk emulsion. A stable system formation was dependent on adding a surfactant in the production process and its concentration [34].

4. Quantitative evaluation of surfactants activity in emulsion system

In a multiphase system liquid particles located deep within an emulsion are surrounded by other particles on all sides. Due to that the forces acting on the particles are identical in value, and symmetrical as regards the direction and sense. The net force is 0. Particles located at the interface are subject to asymmetrical forces. This is due to various forces being active in the liquid and gas phases. The net force is other than zero and directed towards the interior of the liquid. A sphere has the smallest surface to volume ratio and that is why liquid droplets are spherical. Work is needed to increase the free surface of a liquid. If such work is ireversible, isothermal and does not produce a change of volume, it equals free energy of the system.

Surface tension is the derivative of the free energy with respect to the area of the liquid phase. It is a measure of specific free surface area of the liquid phase. Surface tension unit is $N \cdot m^{-1}$ or $J \cdot m^{-2}$ [4, 35]. It must be underlined that surface tension is dependent on the type of liquid and temperature [36].

Several methods can be applied to measure surface tension, and most common ones include capillary rise method, maximum bubble pressure method, stalagmometric method and strain gauge method. Capillary rise method is based on the liquid moving up in into a

capillary tube with a convex or concave meniscus being formed. Concave meniscus is produced when adhesion energy, visualized via liquid being attracted to the walls of a capillary tube, is higher than cohesion energy, i.e. intermolecular attraction between molecules. A convex meniscus occurs in the opposite situation [3, 35, 37]. Meniscus is formed as a result of distribution of forces acting on the particles of a liquid which are close to the three phases, namely gas, solid and liquid [38]. Maximum bubble pressure method is based on the measurement of the maximum pressure in a bubble growing at the tip of a capillary immersed into the liquid under study. Surface tension is determined based on the capillary radius and pressure difference required for the bubble to separate from the capillary. strain gauge method involves lifting a thin platinum ring from the surface of a liquid. Surface tension keeps the ring at its outer circumference [35, 37]. Stalagmometric method measures the weight of the drops falling from the glass capillary tube of the stalagmometer or counts the number of drops of the liquid of known density and volume falling out of the tube [35, 37, 39].

5. Application of Hydrophilic – Lipophilic Balance (HLB) system in the preparation of medicinal products

The letters HLB stand for Hydrophilic-Lipophilic Balance. Studies into the hydrophilic-lipophilic balance in emulsion systems were first conducted in the 1940s by William C. Griffin. HLB was developed for use with nonionic emulsifiers [22]. In the 1950s and 1960s extensive studies were conducted in this field. In 1978 Ralph C. Little provided a mathematical relation between solubility parameters and HLB value. The equation has been used for anionic and nonionic surfactants and it is not suitable for use in the case of cationic surface active agents [40, 41]. HLB value is important for several industries and products such as pharmaceutical products, cosmetics, food or chemical products [42]. The HLB value for ionic tensides is between 1 and 20, and nonionic tensides may have a value of over 20. The HLB value determines the surfactants' solubility potential in lipophilic or hydrophilic layer [7]. Each surfactant has a specific HLB value. Surfactants with higher HLB values are more hydrophilic while surfactants with lower HLB values are more lipophilic. Emulsion type is defined by the so-called required HLB. The required HLB values are accurate to within +/- 0.5 HLB units. Optimal HLB value selection is of key importance for ensuring optimal efficiency and cost-effective emulsion production [43].

Literature provides formulas to calculate the HLB value [2, 44, 45]. To calculate the HLB value for a blend of emulsifiers it is necessary to determine a coefficient providing information of percentage ratio of emulsifiers with known HLB to achieve the value required for the complex emulsifier – in presented equation 2, the %(A) and %(B) designate the percentage of emulsifier A and emulsifier B respectively, whereas the X denotes the HLB of mixture of the emulsifiers, similarly HLB(A), and HLB(B) denote the HLB values of emulsifier A and emulsifier B respectively.

$$\%(A)=\frac{100(X-HLB(B))}{HLB(A)-HLB(B)}\ ,\ \%(B)=100-\%(A) \quad \text{(Eq. 2)}$$

For many nonionic emulsifiers and all ionic emulsifiers HLB value must be determined by experimental procedures [46, 47]. In 2013 Meher et al. reported a study where the required HLB was determined for citronella oil to produce a stable cream. A blend of emulsifiers: ethoxylated sorbitan ester based on a natural fatty acid - oleic acid (Polysorbate 80) and biodegradable surfactant based on a natural fatty acid - oleic acid and the sugar alcohol

sorbitol (BOS), was used in the experiment. The composition for 11 systems with the HLB value ranging from 5.0 to 15.0, and then 8 dosage forms with the HLB value ranging from 11.0 to 13.8 were formulated. The obtained formulations were evaluated with respect to stability and droplet size. The results have shown that a stable cream was developed from oil with 10% blend of emulsifiers of HLB value of 12.6. Organoleptic parameters were confirmed as stable during the entire storage period [48].

In 2003 Sepulveda et al. conducted studies with the use of stearyl and cetyl alcohol to optimise cream stability. The emulsifiers used were nonionic surfactants such as Polysorbate 80, Polysorbate 20, Myrj 52, Brij 35, and biodegradable surfactant based on a natural fatty acid - stearic acid and the sugar alcohol sorbitol (BSS). Emulsifiers were used at different percentage ratios and in various combinations. The optimal drug dosage form composed of 30% internal phase of 50% cetyl alcohol and 35% stearyl alcohol, 15% surfactants i.e.: ESO / BSS at the ratio of 3:1, and 70% water was modified by adding hydrocortisone at several concentrations. Dosage forms were technologically modified. Sepuvelda et al. demonstrated that cream stability is dependent on the cetyl alcohol to stearyl alcohol ratio, the concentration of surfactants and the amount of water external phase [49]. Hydrophilic-lipophilic balance was also used in the studies by a team of Indian researchers. Antiseptic cream dosage form was developed with an addition of ocimum oil. A blend of Polysorbate 80 and BOS emulsifiers was used. Creams were evaluated as regards stability, droplet size and turbidity. Having established the required HLB for ocimum oil, dosage forms with two different combinations of surfactants i.e. GMS (Glycerol monostearate) :Polysorbate 80 (1:3:45), SLS:GMS (1:3:68) were prepared and examined as regards antimicrobial activity, viscosity, texture and skin tolerance. As a result of the studies, antiseptic cream was developed with ocimum oil that is well tolerated by the skin, stable and organoleptically uniform, with HLB ranging from 10 to 14 [50]. A few years earlier, studies with BOS and Polysorbate 20 emulsifiers were conducted by a team led by Ferreira. The experiment was to define the stability of emulsion containing Andiroba oil from *Carapa guianensis* as an internal phase. Blends of surfactants with HLB ranging from 4.3 to 16.7 were used. The results have shown that emulsion system containing a blend of BOS and Polysorbate 20 emulsifiers is unstable and phase separation occurs sooner. If Polysorbate 20 is the only surfactant used, the obtained emulsion is stable, which is due to the fact that the required HLB is 16.7, which corresponds to the HLB value for Polysorbate 20 [51].

Shinoda and Saito studied the properties of emulsion containing 3 wt % polyoxyethylene nonylphenylether as functions of temperature, composition, and the hydrophilic-lipophilic balance of emulsifiers. The experiment has demonstrated that emulsion stability is closely correlated with phase inversion temperature. No connection between stability and HLB value was found [52]. Chinese researchers examined the influence of emulsifiers' HLB value on partial coalescence and its influence on the structure of whipped cream. The experiment has shown that if HLB is less than 6, emulsion breaking occurs very slowly, which results in low stability of the whipping cream. HLB value between 6 and 8 was associated with partial coalescence at approx. 60%. Such level ensures ideal structure of whipped cream. Coalescence is too fast when HLB is over 9, which also results in poor stability of the whipped cream [53]. Meisen et al. investigated the influence of emulsifiers of various HLB values on the stability and quality of ice cream. Monoglycerides, sucrose esters, lecithin and BSS were used in the experiments. BSS addition resulted in unstable emulsions and lecithin improved ice cream stability [54, 55]. In 2004 Jansen et al. patented vaccines containing w/o emulsions. Stability tests demonstrated that Arlacel P135, PEG 30, ATLOX® 4912 are the best

emulsifiers [56]. Studies into surface tension and stability of an emulsion in the context of HLB were conducted by a team led by Al-Sabagh. The experiment was conducted with ethoxylated dialkyl amine monostearate esters and ethoxylated polyalkene polyamine. It was determined that emulsion stability is affected by HLB value, surfactant concentration and emulsion generation time [57]. Emulsion with the highest stability can be obtained with the use of an emulsifier or a blend of emulsifiers of HLB value close to the required HLB value. Schmidts et al. examined the effect of polyethoxylated ethers and polyethoxylated esters on the stability of multiple w/o/w emulsion. Liquid paraffin was used as the oil phase. The HLB value of 4.3–4.7 resulted in a stable emulsion [58]. Mutoh et al. examined the effect of adding oil-soluble emulsifier to a cooled cream. 13 emulsifiers were used in the study including stearic acid monoglyceride and lactic acid ester with HLB value ranging from 1.0 to 9.5. Two emulsifiers i.e. sucrose stearate with a low HLB value and citric acid monoglyceride ester with a high HLB value negatively affected cream solidification [59]. In 2006 Macedo et al. reported a methodology for rapid determination of the critical hydrophilic-lipophilic balance of lipophilic emulsion fractions. The surfactant used was a blend of Polysorbate 20 and BOS at various ratios and HLB value from 4.3 to 16.7. The results demonstrated a reverse relationship between HLB values of the surfactants and emulsion stability. Additionally, the critical HLB for Mygliol 812 was established at 15.367 [60]. Orafidiya and Oladimeji found the required HLB for peppermint, eucalyptus and lippia essential oils. They prepared emulsions with BOS and Polysorbate 80 emulsifiers. Seven experimental batches had HLB value from 4.3 to 15.0. The determination of the required HLB for the oils was necessary to obtain stable emulsions [61]. Emulsifiers such as Polysorbate 20, BSS and SLS were used in the studies conducted by Prinderre's team. The experiment aimed at reducing the time and number of stages necessary to obtain a stable emulsion [62]. The goal of the studies carried out by Al-Edresi and Baie was to obtain a cream containing an active whitening ingredient and evaluate its stability. The emulsifier used was Emulium Kappa® containing jojoba oil esters, rice oil esters, stearyl alcohol with propylene glycol. HLB of the system was 10.35. As a result of the experiment a stable cream was obtained of satisfactory physico-chemical properties [63]. HLB-based method for stability evaluation of o/w emulsion prepared with the use of ionic and nonionic surface active agents was also used by Vilasau et al. The nonionic emulsifier was an alkyl chain with 19 carbon atoms of HLB value of 7.6. The ionic surfactant was alkyl amine and carboxylic acid salt with 21 carbon atoms. The experiment demonstrated that emulsions with a high ionic/nonionic surfactant ratio were the most stable ones [64]. One of the stages of the process of developing and introducing new forms of cream into the market is defining its composition. It is worth noting that cosmetic creams can only be o/w, w/o or multiple emulsions. It is necessary to determine the HLB value not only for emulsifiers. Emollients such as coconut oil and dimethicone have the required HLB value, too [65]. Bancroft rule is also related with the hydrophilic-lipophilic balance, according to the rule, the phase in which an emulsifier is more soluble constitutes the external phase [23]. Table 2 gives a list of selected emulsifiers with determined HLB number, reported in the literature.

Table 2. List of selected emulsifiers with respective HLB value reported in the literature, applied for various internal phases

Emulsifier	HLB value for a stable emulsion	Internal phase	Source
Polysorbate 80 / BOS	12.6	Citronella oil	[48]
Polysorbate 80 / BOS	no data	Cetyl alcohol and stearyl alcohol	[49]
Polysorbate 80 / BOS	10-14	Ocimum oil	[50]
Polysorbate 20	16.7	Andiroba oil	[51]
Polyethoxylated derivatives	4.3 – 4.7	Liquid paraffin	[59]
Emulium Kappa®	10.35	Whitening agent	[63]
BOS, Polysorbate 20, Polysorbate 40, Polysorbate 80	10-12	Argan oil	[65]
Polysorbate 80 / BOS	7,6-14,3	Evening primrose oil	[66]
Polysorbate 80 / BOS	9,6-15	Rice bran oil	[67]
Crill 43 / Softanol 80	9,0-9,9	[2-(acryloyloxy)ethyl]trimethyl ammonium chloride/acrylamide	[69]
Pluronic – 127, Polysorbate 80, SLS	no data	Thyme oil	[70]

6. Influence of soluble salts on emulsion system performance

Experimental studies concerning the effect of pH, ionic strength and temperature of emulsion system are conducted over a limited scope of variables [71]. The few studies conducted have shown that the addition of ionic solutions such as sodium chloride solution to emulsions of high protein concentration, over 2%, improves emulsion stability and slightly reduces drop size in the dispersed phase. In the case of multiphase systems of low protein concentration, below 2%, flocculation accelerates which translates into low emulsion stability [72]. Adding heavier ions such as Ca^{2+}, at higher concentration of over 2 mM, results in irreversible flocculation of the dispersed phase in o/w emulsion. Additionally, emulsion behaviour changes on adding calcium ions to the emulsion [73]. Adding emulsifier or oppositely charged substance to an ionic surfactant stabilised emulsion may result in emulsion breaking i.e. phase separation. This is due to the change of emulsifier solubility or unfavourable change in potential at the interface [7]. In the case of protein-based emulsifiers adding even a small amount of sodium chloride at the concentration of 0 - 400 mM, reduces their solubility and affects the size of drops in the dispersed phase, as demonstrated by the experiment carried out by Onsaard et al. to compare the properties of o/w coconut protein and whey protein stabilised emulsions. In the experiment pH was changed too by adding phosphate buffer. Coconut oil stabilised emulsion had worse stability than whey protein stabilised emulsion over the entire pH range i.e. 3-8 [74]. The influence of pH on o/w emulsion stability containing 20% of sunflower oil stabilised with sodium caseinate was studied by Farshchi et al. The experiment also examined the effect of LBG concentration on emulsion system. Most stable emulsions were obtained at pH 6.0-6.5 and LBG concentration of over 0.2% [75]. The addition of sodium chloride may increase system stability with lower concentration of emulsifier as demonstrated by Ye et al. A system containing NaCl at 50–150 mM and 1% sodium caseinate has a similar stability to systems with high content of sodium caseinate. Similar properties were observed for a system containing 50-150 mM NaCl and 0.5% caseinate [76]. Buffer solution containing 5 mM imidazole and acetic acid in water and pectin was used by Surh et al for studies on stability and physico-chemical properties of o/w emulsion stabilised with sodium caseinate. The experiment demonstrated that depending on

the type of pectin, emulsion stability is reduced or improved depending on the system pH. PH value close to the isolectric point of casein improves system stability while other pH values i.e. pH>pI, pH<pI reduce system stability [77].

7. Conclusions

As shown by literature review above, several active surface agents are used in dosage form technology, and selection of emulsifier for the base has so far been the result of experimental procedures only. Investigators are still on the lookout for methods that would enable to accurately predict the influence of a given emulsifier on the structure of the product and reduce the number of experimental studies.

References

(1) K. CONNORS, S. MECOZZI, Thermodynamics of Pharmaceutical Systems: An introduction to Theory and Applications, 2nd Edition, John Wiley & Sons, Inc., Hoboken, 136, 141 (2010).
(2) P. SINKO, Martin's Physical Pharmacy and Pharmaceutical Sciences: Physical Chemical and Biopharmaceutical Principles in the Pharmaceutical Sciences. Lippincott Williams & Wilkins, 43, 59 (2011).
(3) J. PELLICER, J.A. MANZANARES, S. MAFE, The physical description of elementary surface phenomena: Thermodynamics versus mechanics. Am. J. Phys., 63(6), 542, 547 (1995).
(4) C.O. RANGEL-YAGUI, A. PESSOA JUNIOR, L. COSTA TAVARES, Micellar solubilization of drugs, J. Pharm. Pharmaceut. Sci., 8(2), 147, 163 (2005).
(5) S. IOAN, A.I. COSUTCHI, C. HULUBEI, D. MACCOCINSCHI, G. IOANID, Surface and interfacial properties of poly(amic acid)s and polyimides. Polymer Engineering and Science, 47(4), 381, 389 (2007).
(6) M.J. ROSEN, J.T. KUNJAPPU, Surfactants and interfacial phenomena, 4TH Edition, John Wiley & Sons, 1, 4 (2012).
(7) M. KORHONEN, L. HELLEN, J. HIRVONEN, J. YLIRUUSI, Rheological properties of creams with four different surfactant combinations – effect of storage time and conditions, Int. J. Pharmaceutics, 221, 187, 196 (2001).
(8) N.L. CHAUHAN, J. DAS, R.V. JASRA, Z.V.P. MURTHY, P.A. PARIKH, Synthesis of zeolite ZSM-5: Effect of emulsifiers, Cryst. Res. Technol., 47(7) 746, 753 (2012).
(9) T.M. ALI, A. HASNAIN, Effect of emulsifiers on complexation, pasting, and gelling properties of native and chemically modified white sorghum (Sorghum bicolor) starch, Starch/Stärke, 65 (6), 490, 498 (2013).
(10) S.Y. SHIAU, Effects of emulsifiers on dough rheological properties and the texture of extruded noodles, Journal of Texture Studies, 35(1), 93, 110 (2007).
(11) A. SAJJADI, B.W. BROOKS, Unseed semibatch emulsion polymerization of butyl acrylate: Bimodal particle size distribution, Journal of Polymer Science Part A: Polymer Chemistry, 38(3), 528, 545 (2000).
(12) S.F. YANG, P.T. XIONG, T. GONG, D.P. LU, R. GUAN, St-BA copolymer emulsions prepared by using novel cationic maleic dialkyl polimerizable emulsifier, European Polymer Journal, 12, 2973, 2979 (2005).
(13) S. PEGIADOU-KOEMTJOPOULOU, E. TSATSARONI, M. MYLONA, Pyrymidinium Cationic Surfactants as Emulsifier for Oil-in-Water Emulsions, Journal of Surfactants and Detergents, 499, 502 (1998).
(14) W. QIAO, C. CAO, Y. SUN, H. LIU, X. ZHAO, X. FU, Synthesis and Characterization of a Novel Series of Cationic Fumaric Polymerizable Emulsifiers, J Surfact Deterg, 14, 37, 41 (2011).
(15) N.S. NIELSEN, A.F. HORN, C. JACOBSEN, Effect of emulsifier type, pH and iron on oxidative stability of 5% fish oil-in-water emulsions, Eur. J. Lipid Sci. Technol., 115(8), 874, 889 (2013).
(16) A.F. HORN, N.S. NIELSEN, U. ANDERSEN, L.H. SEGAARD, A. HORSEWELL, C. JACOBSEN, Oxidative stability of 70% fish oil-in-water emulsions: Impact of emulsifiers and ph, Eur. J. Lipid Sci. Technol., 113(10), 1243, 1257 (2011).
(17) H.Y. LIN, I. CAPEK, T.J. HSU, C.-S. CHERN, On the emulsion polymerization of styrene in the presence of a nonionic emulsifier, Journal of Polymer Science Part A: Polymer Chemistry, 37(23), 4422, 4431 (2000).

(18) G. RICHARDSON, M. LANGTON, A. BARK, A.M. HERMANSSON, Wheat starch gelatinization – the effects of sucrose, emulsifier and the physical state of the emulsifier, Starch/Stärke, 55(3-4), 150, 161 (2003).
(19) A. SARAC, H.Y. ERBIL, H. YILDIRIM, Semicontinuos emulsion polymerization of vinyl acetate: Effect of ethoxylation degree of nonionic emulsifiers, Journal of Applied Polymer Science, 86(4), 844, 851 (2002).
(20) P. THANASUKAM, R. PONGSAWATMANIT, D.J. MCCLEMENTS, Influence of emulsifier type on freeze-thaw stability of hydrogenated palm oil-in-water emulsions, Food Hydrocolloids, 18(6), 1033, 1043 (2004).
(21) C.P. WHITBY, L.H. LIM, N.G. ESKANDAR, S. SIMOVIC, C.A. PRESTIDGE, Poly(lactic-co-glycolic acid) as a particulate emulsifier, Journal of Colloid and Interface Science, 375(1), 142, 147 (2012).
(22) J. EASTOE, J.S. DALTON, Dynamic surface tension and adsorption mechanisms of surfactants at the air-water interface, Advances in Colloid and Interface Science, 85(2-3), 103, 144 (2000).
(23) R. STREY, Phase behavior and interfacial curvature in water-oil-surfactant system, Current Opinion in Colloid & Interface Science, 1(3), 402, 410 (1996).
(24) M.A. LOPEZ-QUINTELA, C. TOJO, M.C. BLANCO, L. GARCIA RIO, J.R. LEIS, Microemulsion dynamics and reactions in microemulsions, Current Opinion in Colloid & Interface Science, 9(3-4), 264, 278 (2004).
(25) J. ISRAELACHVILI, The science and applications of emulsions—an overview, Colloids and Surfaces A: Physicochemical and Engineering Aspects, 91, 1, 8 (1994).
(26) D.A. BALAZS, WT. GODBEY, Liposomes for Use in Gene Delivery, Journal of Drug Delivery, 1, 12 (2011).
(27) A.W. ADAMSON, A model for micellar emulsion, J. Colloid Interface Sci., 29(2), 261, 267 (1969).
(28) W. GARBACIA, H.L. ROSANO, Microemulsion: Formation and stabilization, J. Colloid Interface Sci., 44(2), 242, 248 (1973).
(29) L.E. SCRIVEN, Micellization, solubilization and microemulsion, Plenum Press, 1, 877, 893 (1977).
(30) E. RUCKSTEIN, J.C. CHI, Stability of microemulsion, J. Chem. Soc. Faraday Trans., 71,1690, 1707 (1975).
(31) S.K. MEHTA, G. KAUR, Microemulsions: Thermodynamic and Dynamic Properties. [in:] Thermodynamics, InTech, 381, 406 (2011).
(32) L. YUNXIANG, K. HOLMBERG, R. BORDES, Micellization of true amphoteric surfactants, Journal of Colloid and Interface Science, 411(1), 47, 52 (2013).
(33) L. FANG, X. KONG, C. ZHANG, Y. HUA, Rheological properties and permeability of soy protein-stabilised emulsion gels made by acidification with glucono-δ-lactone, J Sci Food Angric, 91(12), 2186, 2191 (2011).
(34) N. TANGSUPHOOM, J.N. COUPLAND, Effect of surface-active stabilizers on the microstructure and stability of coconut milk emulsions, Food Hydrocolloids, 22(7), 1233, 1242 (2008).
(35) H. WENNERSTRÖM, J. BALOGH, U. OLSSON, Interfacial tensions in microemulsions, Colloids and surfaces A: Physicochem. Eng. Aspects, 291(1-3), 69, 77 (2006).
(36) J. RESTOLHO, J.L. MATA, B. SARAMAGO, On the interfacial behavior of ionic liquids: Surface tension and contact angles, Journal of Colloid and Interface Science, 340(1), 82, 86 (2009).
(37) K.H. BAUER, K.H. FRÖMMING, C. FÜHRER: Technologia postaci leku z elementami biofarmacji. MedPharm, 70, 73 (2012).
(38) B. JAWORSKI, A. DIETŁAF, L. MIŁKOWSKA, G. SIERGIEJEW, Kurs fzyki tom 1. Mechanika i podstawy fizyki cząsteczkowej i termodynamiki, PWN (1976)
(39) S.V. CHICHKANOV, V.E. PROSKURINA, V.A. MYAGCHENKOV, Estimation of micelloformation critical concentration for ionogenic and non-ionogenic surfactants on the data of modified stalagmometric method, Chemistry and Computational Simulation. Butlerov Communications, 3(9), 33, 35 (2002).
(40) R.C. PASQUALI, N.S. ACCO, C. BREGNI, The Studies on Hydrophilic – Lipophilic Balance (HLB): Sixty Years after William C. Griffin's Pioneer Work (1949-2009), Lat. Am. J. Pharm., 28(2), 313, 317 (2009).
(41) R.C. LITTLE, Correlation of surfactant hydrophile-lipophile balance (HLB) with solubility parameter, J. Colloid Interface Sci., 65(3). 587, 588 (1978).
(42) J. XIXUAN, D.A. STREETT, Dunlap C.A. DUNLAP, Lyn M.E. LYN Application of hydrophilic-lipophilic balance (HLB) number to optimize a compatible non-ionic surfactant for dried aerial conidia of Beauveria bassiana, Biological Control, 46(2), 226, 233 (2008).

(43) Systematic method for selecting the most effective nonionic emulsifier(s) for any given application, Uniqema (2005)
(44) R.C. PASQUALI, M.P. TAUROZZI, C. BREGNI, Some considerations about the hydrophilic-lipophilic balance system, International Journal of Pharmaceutics, 356(1-2), 44, 51 (2008).
(45) A. FIEBIG, Farmacja stosowana, PZWL, 83, 95 (1987).
(46) The HLB SYSTEM a time-saving guide to emulsifier selection ICI Americas Inc., (1980).
(47) C.C. CHRISTENSEN, Emulsifiers used in food applications, focusing on the meat process industry, Palsgaard Technical Paper, (2011).
(48) J.G. MEHER, N.P. YADAV, J.J. SAHU, P. SINHA, Determination of required hydrophilic-lipophilic balance of citronella oil and development of stable cream formulation, Drug Dev Ind Pharm, 39(10), 1540, 1546 (2013).
(49) E. SEPUVELDA, D.O. KILDSIG, E.S. GHALY, Relationship Between Internal Phase Volume and Emulsion Stability: The Cetyl Alcohol/Stearyl Alcohol System, Pharmaceutical Development and Technology, 8(3), 263, 275 (2003).
(50) N.P. YADAV, J.G. MEHER, N. PANDEY, S. LUQMAN, K.S. YADAV, D. CHANDA, Enrichment, Development and Assessment of Indian Basil Oil Based Antiseptic Cream Formulation Utilizing Hydrophilic-Lipophilic Balance Approach, BioMed Research International, 1, 9 (2013).
(51) M.R.A. FERREIRA, R.R. SANTIAGO, T.P. SOUZA, E.S.T. EGITO, E.E. OLIVEIRA, L.A.L. SOARES, Development and Evaluation of Emulsions from Carapa guianensis (Andiroba) Oil, AAPS PharmSciTech, 11(3), 1383, 1390 (2010).
(52) K. SHINODA, H. SAITO, The stability of o/w type emulsions as functions of temperature and the HLB of emulsifiers: The emulsification by PIT-method, Journal of Colloid and Interface Science, 30(2), 258, 263 (1969).
(53) Z. MOU-MING, Z. QIANG-ZHONG, W.CAI-HUA, F. RUI, Effects of HLB Value of Emulsifiers on the Whipping Properties of the Whipping Cream and Its Mechanism Journal of Food Science and Biotechnology, (2005).
(54) L. MEI-SEN et al., Study on the effect of emulsifiers (HLB>7) on the quality of soft lee cream, Science and Technology of Food Industry, (2006).
(55) L. MEI-SEN, H. WEI-PING, Study on the effect of lower HLB value emulsifiers on the quality of soft-serve ice cream, China Dairy Industry, (2006).
(56) JANSEN et al, Injectable water-in-oil emulsions, Patent Application Publication, (2004)
(57) A.M. AL-SABAGH, N.M. NASSER, M.M. EL-SUKKARY, A.M.F. EISSA, K.I. KABEL, T.M. ABD EL-HAMID, Surface Active and Themodynamic Properties in Relation to the Demulsification Efficiency for Some Ethoxylated Derivatives of Alkyldiamines and Polyalkylenepolyamines. Journal of Dispersion Science and Technology, 34(10), 1356, 1367 (2013).
(58) T. SCHMIDTS, D. DOBLER, A.C. GULDAN, N. PAULUS, F. RUNKEL, Mulitple w/o/w emulsions – Using the required HLB for emulsifier evaluation, Colloids and Surfaces A: Physicochem. Eng. Aspects, 372(1-3), 48, 54 (2010).
(59) T.K. MUTOH, H. KUBOUCHI, M. NODA, Y. SHIINOKI, Y. MATSUMURA, Effect of oil-soluble emulsifiers on solidification of thermally treated creams, International Dairy Journal, 17(1), 24, 28 (2007).
(60) J.P.F. MACEDO, L.L. FERNANDES, F.R. FORMIGA, M.F. REIS, T. NAGASHIMA, L.A.L. SOARES, E.S. EGITO, Micro-emultocrit Technique: A Valuable Tool for Determination of Critical HLB Value of Emulsions. AAPS PharmSciTech, 7(1), 1, 7 (2006).
(61) LO. ORAFIDIYA, F.A. OLADIMEJI, Determination of the required HLB values of some essential oils, International Journal of Pharmaceutics, 237 (1-2), 241, 249 (2002).
(62) P. PRINDERRE, P. PICCERELLE, E. CAUTURE, G. KALANTZIS, J.P. REYNIER, J. JOACHIM, Formulation and evaluation of o/w emulsions using experimental design, International Journal of Pharmaceutics, 168(1-2), 73, 79 (1998).
(63) S. AL-EDRESI, S. BAIE, Formulation and stability of whitening VCO-in-water nano-cream, International Journal of Pharmaceutics, 373(1-2), 174, 178 (2009).
(64) J. VILASAU, C. SOLANS, M.J. GOMEZ, J. DABRIO, R. MUJIKA-GARAI, J. ESQUENA, Stability of oil-in-water paraffin emulsions prepared in a mixed ionic/nonionic surfactant system, Colloids and Surfaces A: Physicochem. Eng. Aspects, 389(1-3), 222, 229 (2011).
(65) Y.S. CHENG, K.W. LAM, K.M. NG, R.K.M. KO, C. WIBOWO, An integrative approach to product development – A skin-care cream, Computers and Chemical Engineering, 33(5), 1097, 1113 (2009).

(66) A. EL-ABBASSI, M.A. NEVES, I. KOBAYASHI, A. HAFDI, M. NAKAJIMA, Preparation and characterization of higly stable monodisperse argan oil-in-water emulsions using microchannel emulsification, Eur. J. Lipid Sci. Technol., 115(2), 224, 231 (2013).
(67) T.T. LIU, T.S. YANG, Optimization of emulsification and microencapsulation of evening primrose oil and its oxidative stability during storage by response surface methodology, Journal of Food Quality, 34(1), 64, 73 (2011).
(68) H.H. NGUYEN, K.O. CHOI, D.E. KIM, W.S. KANG, S. KO, Improvement of oxidative stability of rice bran oil emulsion by controlling droplet size, Journal of Food Processing and Preservation, 37(2), 139, 151 (2013).
(69) J.R. OCHOA-GOMEZ, F.J. ESCUDERO-SANZ, P.M. SASIA, F. RIO, J. NIETO-MESTRE, J. TORRECILLA, I.A. KATIME, Semicontinuous copolymerization of 80/20 wt% [2-(acryloyloxy)ethyl]trimethyl ammonium chloride/acrylamide in an inverse microemulsion at high comonomer concentrations, Journal of Applied Polymer Science, 114(5), 2673, 2684 (2009).
(70) S.K. CHUNG, J.Y. SEO, J.H. LIM, H.H. PARK, M.J.YEA, H.J. PARK, Microencapsulation of essential oil for insect repellent in food packaging system, Journal of Food Science, 78(5), 709, 714 (2013).
(71) K. DEMETRIADES, J.N. COUPLAND, D.J. MCCLEMENTS, Physicochemical Properties of Whey Protein-Stabilized Emulsions as affected by Heating and Ionic Strength, Journal of Food Sciences, 62(3), 462, 467 (1997).
(72) Y. AIQIAN, M. SRINIVASAN, H. SINGH, Influence of NaCl addition on the properties of emulsions formed with commercial calcium caseinate, Food Chemistry, 69(3), 237, 244 (2000).
(73) Y. AIQIAN, H. SINGH, Interfacial composition and stability of sodium caseinate emulsions as influenced by calcium ions, Food Hydrocolloids, 15(2), 195, 207 (2001).
(74) E. ONSAARD, M. VITTAYANONT, S. SRIGAM, D.J. MCCLEMENTS, Comparison of properties of oil-in-water emulsions stabilized by coconut cream proteins with those stabilized by whey protein isolate, Food Research International, 39(1) 78, 86 (2006).
(75) A. FARSHCHI, R. ETTELAIRE, M. HOLMES, Influence of pH value and locust bean gum concentration on the stability of sodium caseinate-stabilized emulsions, Food Hydrocolloids, 32(2), 402, 411 (2013).
(76) A. YE, M. SRINIVASAN, H. SINGH, Influence of NaCl addition on the properties of emulsions formed with commercial calcium caseinate, Food Chemistry, 69(3), 237, 244 (2000).
(77) J. SURH, E.A. DECKER, D.J. MCCLEMENTS, Influence of pH and pectin type on properties and stability of sodium-caseinate stabilized oil-in-water emulsions, Food Hydrocolloids, 20(5), 607, 618 (2006).