Applications of Surfactants in Pharmaceutical Formulation Development of Conventional and Advanced Delivery Systems

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***Abstract*—The role of surfactants is very critical in the development of pharmaceutical formulations. The diverse applications in different delivery systems have been highlighted in different reports of formulation development for various conventional and advanced delivery systems. The relevancy of critical micelle concentration and HLB value for the section of surfactants for different drug delivery systems was rationalized with suitable examples. The present attempt is focused on the compilation of all the important aspects of surfactants with a broad discussion of the drug delivery implications. The regulatory status of different investigational surfactants has been criticized relevantly with a compilation of FDA-approved surfactants. The safety aspects of newly developed surfactants must be ensured before their incorporation into therapeutic dosage forms. The properties of different categories of surfactants were discussed with special emphasis on their physicochemical properties. The compiled information will make a firm base for the selection of surfactants for conventional and advanced drug delivery systems. Precise information on surfactant toxicity was also included to check the safe concentrations of these surface-active agents in pharmaceutical formulations meant for administration through different routes of administration. The various pharmaceutical applications of surfactants were also discussed in detail.**

***Index Terms*—Critical micelle concentration, HLB Value, Phase behaviour of surfactants, Surfactant toxicity**

I. INTRODUCTION

When two phases that are immiscible with each other come in contact, then the boundary between them is known as the interface. There are several types of interfaces depending on the types of adjacent phases, such as solid, liquid, or gaseous states. The term surface is commonly used when the interface is formed between either a gas-solid or a gas-liquid interface. Every interface acts as a surface.

In pharmaceutical formulation development, one has to deal with the different interfacial phenomenon that affects the characteristic properties of the dosage form or delivery system under consideration. To deal with such interfacial phenomenon in the pharmaceutical dosage form, surfactants are incorporated in the formulations 1. Surfactants are surface active agents which are amphiphilic. These are interfacially active compounds having both polar (Hydrophilic) and non-polar (Lipophilic) features within the same molecule 2.

The interfacial phenomenon has a significant effect in the field of pharmacy and medicine as it plays a key role in drug absorption onto solid adjuncts in dosage form, molecules penetration through the biological membrane, and the dispersion of immiscible materials to form emulsion 3. Surfactants are also helpful in enhancing the solubility of insoluble therapeutic moiety due to their amphiphilic nature; they possess both oil-soluble and water-soluble characteristics. Surfactants have also shown the capability to be used as drug carriers. Non-ionic surfactants are widely used to form stable solutions of drugs that are poorly soluble in water. Apart from non-ionic surfactants, phospholipids are also used as a tool for drug delivery. To develop a delivery system containing surfactants, the potential and limitations of such systems can be understood by the phase behaviour of the surfactants.

Critical Micelle Concentration: In solution surface, active agents form micelles or aggregates and the process of micelles formation is known as Micellization, in other words, Micellization is a strongly cooperative self-association process occurring at a particular narrow concentration, critical micellar concentration.

The hydrophobic effect is believed to be the main driving force in the self-association. Surfactant reduces the free energy in the system by decreasing the hydrophobic surface area. Furthermore, micelles act as the reservoir for the surfactant molecule as a single monomer unit 4.

TABLE 1: CHARACTERISTIC VALUES OF CMC AND NUMBER OF SURFACTANT MOLECULES PER MICELLE FOR SOME OF THE IMPORTANT SURFACTANTS 4

Name	Type of surfactant	CMC (mmol/m3)	No. of surfactant molecules per micelle
Potassium laureate	Anionic	2.4 × 104	50
Sodium octane sulfonate	Anionic	15×104	28
Sodium decane sulfonate	Anionic	4×104	40
Sodium dodecyl sulfate	Anionic	0.8×104	62
Decytrimethyl ammonium bromide	Cationic	6.3×104	36
Tetradecyltrimethyl ammonium chloride	Cationic	0.3×104	64
Dodecylammonium chloride	Cationic	1.3×104	55
Polyoxyl 8 dodecyl ether	Non-ionic	0.013×104	132
Polyoxyl 12 dodecyl ether	Non-ionic	0.014×104	78
Nonoxynol 10	Non-ionic	0.07×104	276
Nonoxynol 30	Non-ionic	0.024×104	44

The capability of the surfactant molecule to lower the interfacial surface tension depends on the free monomer concentration at which the formation of micelles starts is known as critical micelles concentration. Micelles are spherical or cylindrical. Ionic surfactant has a higher CMC value than non-ionic because the electrostatic repulsion of the head group makes micellization more difficult. A representative of CMC values and aggregation numbers of surfactant molecules per micelles are listed in Table 1. 5 Phase Behaviour of Surfactant: 6 Route of administration for insertion of surfactant in the body is important, which is better understood by the phase behaviour of surfactants. If surfactants are diluted below their CMC, it may lead to precipitation of drug which is administered. Such kind of precipitation is most commonly seen in the case of intravenous administration. Non-ionic surfactants are preferred over ionic for being used in the delivery system as they possess lower CMC.

A) Equilibrium Phase Structure: As surfactants self-associate in a wide variety of solvents, hence their aggregation varies between solvents. As the continuous phase in most of the delivery systems are water or buffer solutions, it is important to predict the range of equilibrium phase structure that is incorporated in such solutions. Surfactants generally aggregate when dispersed in water above its CMC, aggregation depends on the molecular geometry into any of the four types isotropic micellar phase, liquid crystalline, hexagonal lamellar and cubic phase. Apart from these some of the usual structures are also observed such as helical bi-layers and fiber gels.

B) Modified Phase Structure: Apart from the equilibrium phase, there are some non-equilibrium and modified structures also used in drug delivery. Vesicles are formed by lamellar phase dispersion in excessive water or non-aqueous phases. Reverse vesicles are formed by dispersion over oil. These non-equilibrium structures are prepared using methods such as sonication and will eventually re-equilibrate back into

the lamellar phases from which they originate. Polymerized aggregates are made to use polymerization to stabilize various developing phase structures. Micelles polymerization has the significant *in-vivo* advantage that these structures do not break down on dilution. Because of their size (ranging from tens to hundreds of nm), these aggregates can cause problems as they are not readily excreted from the body, hence such systems will probably have limited clinical use, although they may have a use in oral administration. Biodegradable polymerized aggregates are presently being investigated Hydrophilic-Lipophilic Balance Value: In 1947, Griffith developed a system called hydrophilic-lipophilic balance (HLB) for selecting the surfactants according to their Hydrophilic/ lipophilic nature. Griffith explained the HLB value for a surfactant as the mol% of the hydrophilic group divided by 5. HLB value indicates the polarity of the surfactants. It is also used to describe the functional properties of the surfactants. Concerning formulation under development surfactants having high polarity are assigned higher values while surfactants with low polarity are assigned lower values. The ionic nature of the surfactant is an important consideration for its incorporation in any formulation 4. The function and properties of surfactants can be represented in terms of HLB values Table 2

TABLE 2: PROPERTIES OF SURFACTANTS AND THEIR HLB VALUE

Properties	HLB value
Oil Soluble	<10
Water soluble	>10
Antifoaming	4–8
Water in an oil emulsifier	7–11
Oil in water emulsifier	12–16
Wetting agent	11–14
Detergent	12–15
Stabilizer	16–20

Lipophilic surfactants are used to couple water-soluble material into non-aqueous oil-based systems whereas hydrophilic surfactant is used for solubilization and detergency. The HLB value of surfactants depends on the oil type and the temperature of the solution 7. Identifying the correct HLB number can be done by observing an indication when a small quantity of surfactant is mixed with water and shaken. The appearance of the solution indicates the HLB number. The more the hydrophilic surfactant higher the HLB number 8. Classification of Surfactants: Surfactants are classified into four groups depending upon the charge possessed by their polar group cationic, anionic, amphoteric, and non-ionic. Fig. 1 represents the types of surfactants. Table 3 represents a hydrophilic group of surfactants. The different active drugs for therapeutic delivery possess different natures, *i.e*. the hydrophilic part of the surfactant may have positive, negative, or both charges or may have no charges.

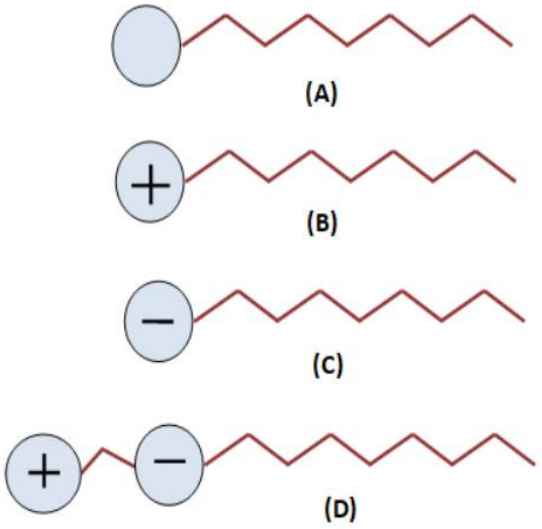

FIG. 1: TYPES OF SURFACTANT (A) NON-IONIC (B) CATIONIC (C) ANIONIC (D) AMPHOTERIC

A) Anionic Surfactants: These surfactants possess a negative charge on their head group while the straight tail chains are composed of saturated/unsaturated C12-C18 aliphatic group. The potential for aqueous solubility of these surfactants depends on the double bonds present in the molecule. Owing to their superior hair conditioning property, anionic surfactants are preferred for the formulation of shampoos meant for oil removal from hairs. Deactivation of anionic surfactants is observed when mixed with water due to the higher concentration of cations (Ca++ and Mg++) present in water 9. Anionic surfactants can be classified based on functional groups at their head, *e.g*. sulfonate, phosphate, sulfate, and carboxylate 10.

B) Cationic Surfactants: These surfactants possess a positive charge on their head. Cationic surfactants that

have having single long alkyl group exhibit good aqueous solubility while surfactants with multiple long alkyl groups (hydrophobe) are dispensable in water and exhibit solubility in organic solvents 11.

C) Amphoteric Surfactants: The head of these surfactants is composed of both positive and negative charge groups. They are also known as zwitterionic surfactants. These are soluble in water but have minimal solubility at the isoelectric point. They are stable at both alkaline and acidic pH of the solution in which they are dissolved 12. These surfactants acquire a positive charge in an acidic pH solution and show characteristics similar to cationic surfactants while at alkaline pH they acquire a negative charge in the alkaline pH and show characteristics of the anionic surfactant. It can be explained as:

$N^+....COOH \iff N^+....COO^- \iff NH....COO^-$

Acidic pH<3 Isoelectric point Alkaline pH>6

The surface activity of the amphoteric surfactants depends on the distance between the charged groups. Hence, shows maximum surface activity at the isoelectric point. The most commonly used class of amphoteric surfactant is N-alkyl betaine which is derived from trimethyl glycine, *e.g*. lauryl amido propyl dimethyl betaine. Other classes are N-alkyl amino propionates and alkyl imidazoline. Zwitterionic surfactants are best used in dermatological products. They have low eye and skin irritability, hence used in shampoos and cosmetics. They show good antistatic properties and are foam boosters 13.

D) Non-Ionic Surfactant: These do not produce ions in aqueous solutions. Hence, they are compatible and excellent candidates to enter complex mixtures. These are less sensitive to electrolytes, particularly divalent cations than ionic surfactants can be used with high salinity. These are good emulsifiers and wetting agents and have good foaming properties. They exhibit low toxicity levels. The most commonly used non-ionic surfactants are ethers of fatty alcohols. The sorbitan esters are water-insoluble whereas soluble in alcohol and have low HLB value 14. Surfactant Protein: A total of 10% of the protein by weight has been isolated from the surfactant. Major parts of these proteins have serum protein, *i.e*. about 80% and the remaining 20% are specific to surfactant.

TABLE 4 TYPES OF SURFACTANT PROTEINS, THEIR MOLECULAR CHARACTERISTIC, AND FUNCTIONS 16

Type	Molecular Characteristic	Main Function
SP-A	Lectin/collagen hybrid	Supports alveolar macrophage activities and regulates surfactant secretion
SP-B	Disulfide bridge	Optimize surface activity
SP-C	Rich in hydrophobic valine	Optimize surface activity
SP-D	Lectin/collagen hybrid	Interacts with alveolar macrophage and regulates surfactant secretion

To date, there are four surfactant-specific proteins identified termed surfactant proteins A, B, C and D according to the decreasing order of their molecular weight. Surfactant Protein A is most commonly used and found in the alveolar space 15. Table 4 represents the types of surfactant proteins. Gemini Surfactant: These are dimeric molecules consisting of two head groups linked together with a short spacer and two hydrophobic tails. They have a high affinity for lowering the surface tension and very low CMC. This effect is due to the good packing of the Gemini surfactant molecules at the air/water interface. The use of Gemini surfactant shows special interest in the drug vesicles and gene therapy. GS can be synthesized at low cost and, hence are advantageous for pharmaceutical industries. Cationic-serine-based GS have improved the interfacial properties and lowered toxicity showing potential use in the biological application. GS has more ability than other surfactants in dispersing CNTs. Nimoipine-loaded egg phosphatidylcholine-sodium glycocholate mixed micelles improve the water solubility of nimodipine, thus enhancing their chemical use 17. **Fig. 2** represents the structure of the Gemini surfactant. Srivastava *et al*. observed the synergetic effect of the mixed system due to the hydrophobic interaction between Gemini

surfactant and tetracaine hydrochloride, which were used to stabilize the silver nanoparticles 18.

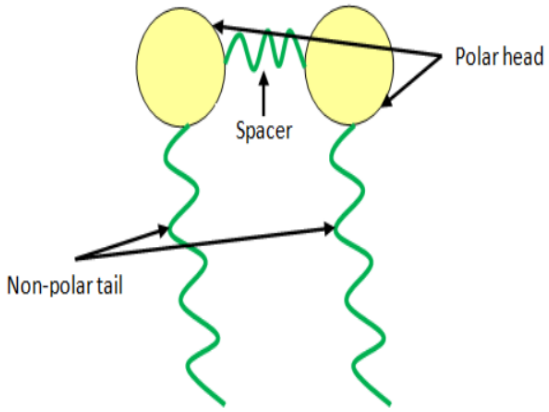

FIG. 2: STRUCTURE OF GEMINI SURFACTANT

Pharmaceutical Application of Surfactants:

A) As Permeation/Absorption Enhancers: Ionic surfactants are enhanced transdermal absorption by disordering the lipid bilayer of the stratum corneum and by denaturation of keratin. Azone (1-dodecylazacycloheptan-2-one or laurocapram) is one of the most efficient enhancers of percutaneous absorption. It enhances the penetration of hydrophilic and lipophilic compounds. Azone leads to the fluidization of the intercellular lipid lamellar part of the stratum corneum 19. Same as with DMSO it reduces the resistance of the lipid barrier and thus increases the lipid fluidity. Alcohol derivatives of N, N disubstituted amine acids, and hexamethylene lauramine also enhance the permeability of the drug 20. B) In Respiratory Distress Therapy: Surfactant preparations are used in the treatment of neonatal respiratory distress syndrome (also known as hyaline membrane disease) in premature infants. These preparations are used in combination with supplement oxygen and mechanical ventilation to facilitate gas exchange for either prophylactic or rescue treatment of neonatal respiratory syndrome 21.

B) As Flocculating Agent: These are used to decrease the rate of sedimentation of floccules Examples of such agents are tragacanth, carbopol 934, methylcellulose, vegum or bentonite used either alone or in combination. The addition of an anionic electrolyte example monobasic potassium phosphate is used for flocculating positively charged particles 21.

C) In Suppository Bases: Several non-ionic surfactants are used in the development of suppository bases. Some of these bases are used in formulating both oil and water-soluble drugs 22. Polyoxymethylene sorbitan fatty acids esters (tween), polyoxymethylene stearates, and sorbitan fatty acid esters (span) are some surface-active agents used in the formulation of suppositories 23.

D) In Suspension Aerosols: These reduce agglomeration thus leading to an increase in the stability of the suspension. These orient at the solid-liquid interface and coat each particle in the suspension aerosols are non-ionic surfactants and those surfactants whose HLB value is less than 10. 24 F) For Contact Lens Cleaning: Surfactants emulsify accumulated oils, inorganic compounds and lipids over the contact lenses, hence are good cleansers. They are used by just placing the drop of surfactant over the lens and gently cleaning the lens back and forth or used with a mechanical washing device. Non-ionic detergents, wetting agents and buffers are used as ingredients for cleaning 25, 21.

E) As an Emulsifying Agent: The lipophilic part of the surfactants is generally responsible for the surface activity. Depending on the individual nature of the surfactant these are used to form o/w and w/o emulsions 26. Non-ionic surfactants are effective at the pH range of 3-10, and the cationic surfactant is effective over pH range of 3-7, here as anionic surfactants are effective at the pH range more than 8. 13, 27 H) As Cerumen Removing Solutions: The waxy deposition in the external auditory canal, which is composed of secretions of sweat and sebaceous gland, is known as cerumen. Some of the synthetic surfactants have been utilized for their cerumenolytic activity to remove the ear wax, e.g. triethanolamine polypeptide oleate-condensate (Cerumenex drops) combination with propylene glycol. Another example is carbamide peroxide in combination with glycerine/propylene glycol (Debrox drops). Carbamide peroxide, when comes in contact with oxygen, destroys the impacted wax, which leads to the easy removal of wax 28.

F) In the Petroleum Industry: Surfactants show great diversity and practical importance in the petroleum industry and are advantageous in the production of petroleum processes like in the reservoir of oil and gas wells, and surface processing operations. CMC is of great importance in the selection of surfactants to be used in the petroleum industry. For example, enhanced recovery of oil process includes the use of surfactant involving micellar, alkali/ surfactant/ polymer (A/S/P) and gas (hydrocarbons, N2, CO2 or steam) flooding. The surfactant must be present in the concentration more than CMC because the effect of surfactant is obtained at the significant CMC whether it is lowering of interfacial tension or promoting the stability 29, 30.

G) Regulatory Status for Surfactants: Any substance that is added to the food is recognized as an additive, which is the subject of approval by the Food and Drug Administration (FDA). Generally Recognised as Safe (GRAS) under sections 201(s) and 409 of the federal Food, Drug, and Cosmetic Act. Under section 201(s) and 409 and FDA's implementing regulations in 21 CFR (Code of Federal Regulations) 170.3 and 21 CFR 170.3, the additive must be GRAS either through scientific procedures or for an additive used in food before 1958. Table 5 shows some FDA-approved surfactants 10.

TABLE 5: FDA-APPROVED SURFACTANTS WITH THEIR COLOUR, MELTING POINT AND HLB VALUE 10

Name	Colour	Melting point	HLB value	FDA status
Sorbitan monostearate	Ivory colored	128 – 132 °F	4.7	Approved
Polyoxyethylene (20) sorbitan monostearate	Yellow oily fluid	600 cp	14.9	Approved
Polysorbate 80	Yellow oily fluid	400 cp	15.0	Approved
Polyoxyethylene (20) sorbitan Tristearate	Tan waxy solvent	~ 92 °F	10.5	Approved
Mono and diglycerides	Ivory white coloured solid	135 – 142 °F	3	GRAS

Surfactant Toxicity: The most common type of toxicity caused by surfactants is in the aspects of dermatology. Surfactants can get adsorbed on the surface of the biomembrane due to the hydrophobic interactions with proteins. It binds on the interface and leads to membrane disruption, which affects the normal functioning of the cell. Interaction of surfactant with red blood cells (RBC) can lead to hemolysis 31. Anionic surfactants are more toxic as compared to non-ionic surfactants example sodium dodecyl sulfate (SDS) used in toothpaste is more irritant than ether sulfate used in hand dishwashing formulations. Some of the amphoteric surfactants such as betaines are also used to reduce the skin irritation caused by anionic surfactant 32.

It has also been reported that the surfactants have shown a negative effect on micro-organisms example phosphate solubilizing *Acinetobacter junii*, and autotrophic ammonia-oxidizing *Nitrosomonas*. SDS and Triton X 100 (non-ionic surfactants) affect the nitrogen-fixing ability and growth of cyanobacteria *Gloecapsa* at concentrations of 50 and 500 ppm. LAS can destabilize the protease and amylase activity of the bacteria *Bacillus licheniformis* at a lower concentration than CMC 11.

Patents on Surfactants: Holtze *et al*., developed a surfactant system containing a hydrophilic tail used to stabilize aqueous or hydrocarbon droplets in a fluoronic continuous phase. The developed system was composed of a fluorophilic tail and a head group to create a surfactant with a suitable geometry to stabilize the reverse emulsion containing aqueous or lipophilic droplets in a fluorophilic continuous phase. Policello *et al.* worked on trisiloxane compounds to improve the delivery of active ingredients as aqueous solutions. When used in aqueous solutions,

trisiloxane-type compounds have been reported to enable control over wetting, spreading, foaming, and detergency processes to achieve the desired effect. However, these compounds were reported to be effective only in a narrow pH range, *i.e*. from a slightly acidic pH of 6 to a very mildly basic pH of 7.5. Table 6 provides the details about the patents on surfactants.

TABLE 6: PATENTS ON SURFACTANTS

Patent no.	Year	Title	Inventors	Reference
US 9,012,390 B2	2015	Fluorocarbon emulsion stabilizing Surfactants	Holtze *et al.,*	35
9018150	2015	Cleansing composition with cationic surfactants	Kirolos Rizk	36
US 8,197.841 B2	2012	Polymerizable surfactants and comonomers	Linhardt *et al.,*	37
US 8,235,120 B2	2012	Mesophase fluids with extended Chain surfactants for downhole treatments	Quintero *et al.*	38
US 7,935,842 B2	2011	Hydrolysis resistant Organomodified trsiloxane Surfactants	Policello *et al.,*	39

Surfactant-Drug Interaction: Akram M. analyzed that cationic gemini surfactants show stronger binding constant with drug ibuprofen (IBF) than the other surfactants Kb values obtained through the techniques: Intrinsic fluorescence, UV-visible, and CV follow the trend as C12-E2O-C12 > C14-E2O-C14 > C16-E2O-C16 because of higher penetration efficiency of ibuprofen in the looser micelles. Intrinsic fluorescence also illustrates that the hydrogen bonding and van der Waal forces play a dominant role in the exothermic binding of IBF- Cm-E2O-Cm. Surfactants are used to increase the rate of dissolution of some drugs 40. Pan Fang showed that surfactants possess the property of membrane lysis in bacteria. Most of the studied surfactants showed membrane-lytic properties above their CMC, but some like C12TAB and anionic SDS showed membrane-lytic properties below their CMC, causing structural damage to the membrane, mitochondria, and nuclei of bacteria. While with the increase in acyl chain length of SME surfactants showed a sharp decline in membrane lysis and with the physical feature of concentration-dependent also showed cytotoxicity and bactericidal action against *E. coli* and *S. aureus* 41.

Smedt and Raemdonk discussed that pulmonary surfactants could also be used for surfactant replacement therapy for the treatment of respiratory distress syndrome. Surfactant proteins can be used in drug delivery as they modulate the pulmonary distribution of drugs for the treatment of lung cancer and pulmonary lung disease. Accordingly, Wu and Colleagues investigated the conjugation of an anti-SP-C antibody to liposome for a dual purpose, *i.e*. increasing the retention time and targeting microRNA delivery to alveolar type II cells. The intranasal administration of LP-ODNanti-SP-C showed high *in-vivo* specificity for type II cells, with retention time up to 48 h 42. Tozuka prepared an alternate formulation of DCP SDC and DCP-Stevia-G and analyzed the improved properties of micellization when compared to single components. Negative values of interaction parameters and free energy showed that interaction between SDC/stevia-G and DCP forms stable mixed micelles. Also showed increased adsorption of nanosized micelles and mixed micelles in the cell membrane and delivered dug to the target cells. Hence, formulation consisting of nanosized drugs and surfactant showed reduced cytotoxicity and improved the solubility of poorly soluble water-soluble drugs 43. Azum N. Studied the interaction of the antipsychotic drug chlorpromazine (CPL) hydrochloride with mixed surfactant (CTAB and 16-4-16), which are used to reduce the side effects of CPZ. Gemini surfactants are used instead of conventional as they have lower CMC values, which tends to reduce the carrying amount and also increase the amount of drug to be incorporated.

The formation of mixed micelle with negative values of free energy showed that the adsorption process is primary, whereas the process of Micellization is secondary 44.

II. CONCLUSION

For the development of novel and conventional dosage forms, the role of surfactants is well established. However, their rational use according to the different routes of administration is to be closely monitored to avoid toxic effects. Furthermore, extensive safety studies are required to establish the safety profile of newer surfactants at the investigational stage.

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