Surfactants: Pharmaceutical and Medicinal Aspects

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Abstract

Surfactants are amphipathic substances with lyophobic and lyophilic groups and are critical components in pharmaceutical products. Surfactants have several uses in pharmaceuticals, i) for solubilisation of hydrophobic drugs in aqueous media, ii) as components of emulsions ,iii) surfactant self-assembly vehicles for oral and transdermal drug delivery, iv) as plasticizers in semisolid delivery systems, and v) as agents to improve drug absorption and penetration. Non-ionic surfactants such as ethers of fatty alcohols are most commonly used in pharmaceuticals. Cationic surfactants are capable of exerting antibacterial properties by disrupting bacterial cell membranes. In pharmaceutical processing, phospholipid lecithin, bile salts, certain fatty acids and their derivatives have become indispensable since they afford a uniquely effective and efficient mechanism of drug carriage by solubilising the drugs of fatty origin. The antibacterial, antifungal and antiviral activities make biosurfactants relevant molecules for applications in combating many diseases and as therapeutic agents. Biosurfactants have the potential for use as major immunomodulatory molecules, as anti-adhesive biological coating for biomaterials, in vaccines and gene therapy, and they may be incorporated into probiotic preparations to combat urogenetical tract infections and pulmonary immunotherapy. Gemini surfactants are effective potential transfection agents for non-viral gene therapy. Ionic liquids act as secondary surfactants and the use of surfactant/ionic liquid systems should be explored to build specific properties in the organized medium, and to explore pharmaceutical applications of traditional, biosurfactant and Gemini surfactants.

Keywords: Surfactants, biosurfactants, Gemini surfactants, gene therapy, pharmaceutical applications, antimicrobial activity.

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INTRODUCTION

Surface-active agents (usually referred as surfactants, synthetic and bio-based) are active at interfaces and possess both polar (hydrophilic) and non-polar (hydrophobic) characteristics in the same molecule. The hydrophobic part is referred to as the head group and the hydrophobic part as the tail (Corrigan and Healy, 2006); Kjellin and Johansson 2010; Monsteqszia and Haqqueni 2012; Schramm et al. 2003) (Fig. 1).

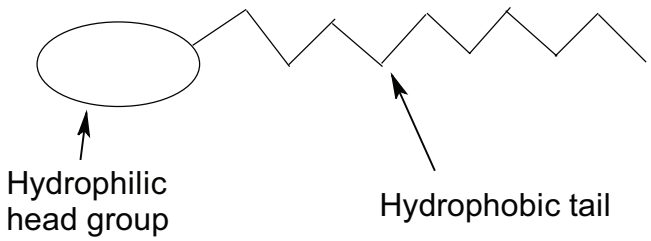


Figure 1: Schematic representation of a surfactant.

For pharmaceutical products poorly soluble in water, the use of surfactants becomes inevitable to reduce the interfacial tension between the medium and the drug and to increase solubility of drugs. In drinks, surfactants are used as solubilizers to dissolve herbal medicinal materials, Vitamin E and other oil ingredients. Rectovaginal and urethral surfacants increase the rate of percutaneous absorption and increase the solubility of medicinal materials in oil- and fat-based materials. Surfactants used in dental, oral, sublingual (under tongue) to form ointments, creams, gels, patches, tapes, and liquids, as well as dissolve, disperse, emulsify, and solubilize medicinal ingredients were found safe and ingestible.

Depending on the nature of the polar group, surfactants can be classified into four groups: cationic, anionic, zwitterionic and non-ionic. Scientists reported a systematic *in vitro* evaluation of the microbicidal, antiviral and contraceptive potential of cationic, anionic, zwitterionic, and non-ionic surfactants (Vieira et al. 2008). Cationic surfactants have a positive charge on their polar head group while anionic surfactants have a negative charge on their polar head group (Hait and Moulik 2002). Zwitterionic surfactants have the potential to have both positive and negative charges, depending on the environment in which they are placed. Non-ionic surfactants have no charge on their head group. Generally, surfactants market is considered fragmented, however, few major players include AkzoNobel N.V. (The Netherlands), BASF SE (Germany), Henkel (Germany) , P&G Chemicals (U.S.), Stepan Company (U.S.), The Dow Chemical Company (U.S.), and Croda, Stepan, Huntsman, ICI/Uniqema/Mona(U.K). Examples of surfactants that are used in pharmaceutical formulation are as follows:

Anionic surfactants

They carry negative charge in hydrophilic part. Examples of anionic surfactants include (a) carboxylates: alkyl carboxylates-fatty acid salts; carboxylate fluoro surfactants, (b) sulfates: alkyl sulfates (e.g., sodium lauryl sulfate); alkyl ether

sulfates (e.g., sodium laureth sulfate), (c) sulfonates: docusates (e.g., dioctyl sodium sulfosuccinate); alkyl benzene sulfonates, (d) phosphate esters: alkyl aryl ether phosphates; alkyl ether phosphates. Sodium lauryl sulphate BP (a mixture of sodium alkyl sulfates, mainly sodium dodecyl sulfate, $C_{12}H_{25}SO_4^-Na^+$) is used pharmaceutically as a preoperative skin cleaner, having bacteriostatic action against gram-positive bacteria, and also in medicated shampoos (Fig. 2). Branched alkyl sulphate is other example of anionic surfactants (Fig. 3).

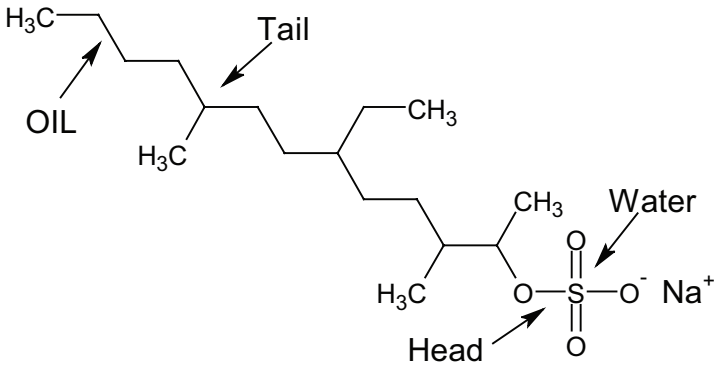


Figure 2: Sodium dodecyl sulphate. Polar head has affinity for water and tail has affinity for oil.

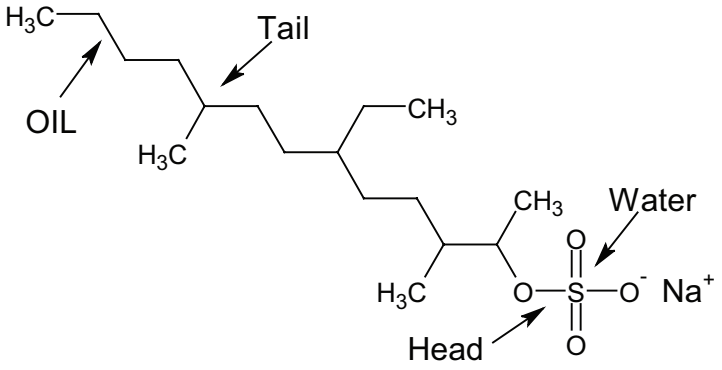


Figure 3: Branched chain alkyl sulphate.

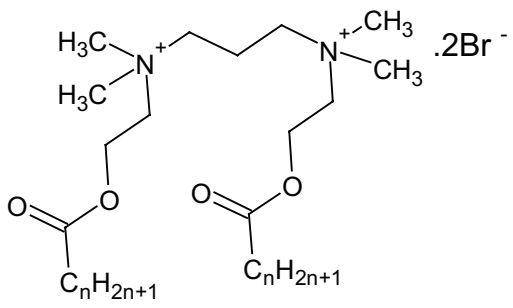


Figure 4: Example of ester-quat

Zwitterionic(amphoteric) surfactants

They can be anionic (negatively charged), cationic (positively charged) or non-ionic (no charge) in solution, depending on the acfidity or pH of the water. These surfactants are very mild and have excellent dermatological properties. Both +ve and –ve charges may be present on the surface active portion. For example, $RN^{+}H_2CH_2COO^{-}$, $RN^{+}(CH_3)_2CH_2CH_2\ SO_3^{-}$, Phospholipids: Phosphatidylcholine (Lecithin)

Cationic surfactants

The surface active portion bears a +ve charge, for example $RN^{+}H_3Cl^{-}$(salt of a long-chain amine), $RN^{+}(CH_3)_3Cl^{-}$(quaternary ammonium chloride also known as quats). The quaternary ammonium and pyridinium cationic surfactants have bactericidal activity against a wide range of gram-positive and some gram-negative organisms. They may be used on the skin, especially in the cleaning of wounds. Spermicidal jellies also contain quaternary ammonium salts. Ester-quats are most common type of cationic surfactants in which ester bond is introduced (Fig. 4).

Non-ionic surfactants

The non-ionic surfactant can be classified as polyol esters, polyoxyethylene esters, poloxamers. polyol esters includes glycol and glycerol esters and sorbitan derivatives. Fatty acid esters of sorbitan (generally referred to as Spans) and their ethoxylated derivatives (generally referred to as Tweens) are perhaps one of the most commonly used non-ionics.

Some examples are given below:

Sorbitan monolaurate – Span 20

Sorbitan monopalmitate	– Span 40
Sorbitan monostearate	– Span 60
Sorbitan mono-oleate	– Span 80
Sorbitan tristearate	– Span 65
Sorbitan trioleate	– Span 8

Some examples of Tween surfactants are given below.

Polyoxyethylene (20) sorbitan monolaurate	– Tween 20
Polyoxyethylene (20) sorbitan monopalmitate	– Tween 40
Polyoxyethylene (20) sorbitan monostearate	– Tween 60
Polyoxyethylene (20) sorbitan mono-oleate	– Tween 80
Polyoxyethylene (20) sorbitan tristearate	– Tween 65
Polyoxyethylene (20) sorbitan tri-oleate	– Tween 85

The most commonly used non-ionic surfactants are ethers of fatty alcohols (Zhang et al. 2009). The Sorbitan esters are insoluble in water, but soluble in most organic solvents (low hydrophile–lipophile balance (HLB) value and are used as water-in-oil emulsifiers and as wetting agents. The ethoxylated products are generally soluble in water and have relatively high HLB numbers ((greater than about 12). The nonionic surfactants products mainly serve as emulsifier, wetter, solubilizer and dispersant in pharmaceutical industry. As gelling agent and foaming agent, they are used in the manufacture of several forms of drugs such as emulsion, cream, suppository, tablet and capsule etc. The most frequently used surfactants are Polsorbate 20 and Polysorbate 80 and Poloxamer 188 in a concentration range between 0.001% and 0.1%.

Poloxamers are synthetic block copolymers of hydrophilic poly(oxyethylene) and hydrophobic poly(oxypropylene) with the general formula $E_mP_nE_m$, where E = oxyethylene (OCH_2CH_2) and P = oxypropylene ($OCH_2CH(CH_3)$) and the subscripts m and n denote chain lengths. They are supplied commercially as Pluronics and are labelled using the Pluronic grid, for example as F127 or L62, where the letter indicates the physical state (F, P or L, denoting solid, paste or liquid, respectively). The last digit of this number is approximately one-tenth of the weight percentage of poly(oxyethylene); the first one (or two digits in a three-digit number) multiplied by 300 gives a rough estimate of the molecular weight of the hydrophobe (Attwood and Florence (2012). Poloxamers (188, 407, 338, 184), poloxamine (304, 904, 908). Other examples include: Polyoxyethylene 15 hydroxystearate - Solutol HS15; Polyoxyethylene alkyl ethers – Brij; Polyoxyethylene stearates – Myrj; Polyoxyethylene castor oil derivatives - Cremophor EL, ELP, RH40 (Niazi 2004; Rowe et al. 2006).

Surfactants have been employed as permeation enhancer in transdermal drug delivery of various drugs (Som et al. 2012). Moreover, biological surfactants perform a vital role in the metabolic processes of living organisms. For instance, the pathological effects of sucrose like dental cavities and also higher caloric contents have led to the use of certain surfactants e.g. the non-ionic sorbitol as sugar substitutes in some confection. Surfactants applications include artificial implants, gene transfection, biomembranes, ophthalmology, and pharmaceuticals (Abraham 2003).

Nonionic sufactants are most useful for humans. In the United States, the most commonly used vaginal spermicide is the neutral agent nonoxynol-9. However, octoxynol is also fully approved by the FDA. In other parts of the world, the surfactants benzalkonium chloride (cationic) and docusate sodium (anionic) are also used for contraception (Kirkman and Chantler 1993).

Drugs as surfactants

Many drugs have surface-active properties including the antihistamines and the tricyclic depressants (Florence and Attwood 2006; Attwood and Florence 2012). Diazepam was found to be the most surface active substance in aqueous solutions, chlorpromazine was less active and the lowest activity was found for haloperidol (Pawelek et al. 1976).

Aerosolized surfactants

Surfactant replacement therapy has been the core of treatment for preterm infants with respiratory distress syndrome for more than twenty years. Aerosolized surfactants for neonatal respiratory distress syndrome may prevent the need for endotracheal intubation (Mazela et al. 2007). Noninvasive ventilation has led to novel approaches of administration (Gupta and Donn 2012). The recent development of vibrating membrane nebulizers coupled with appropriate positioning of the interface device indicated that efficient delivery of aerosolized surfactant is a realistic goal in infants (Jane Pillow and Minocchieri 2012). AEROSURF® is a drug-device product that consists of the entire technology system for the delivery of aerosolized surfactant to premature infants for respiratory distress syndrome: KL4 Surfactant, Capillary Aerosol Generator, and a proprietary nCPAP compatible patient interface (http://www.discoverylabs.com/aerosurf.php).

Silicon surfactants

Silicone surfactants are becoming increasingly important in the pharmaceutical industry. Silicones (more accurately called polysiloxanes) are mixed

inorganic-organic polymers with the chemical formula $[R_2SiO]_n$, where R is organic groups such as methyl, ethyl, and phenyl. The polydimethylsiloxanes, compared to other polymers, are very permeable to the diffusion of active drugs**.** The hydrophobic and amorphous low-density properties of polydimethylsiloxanes have also made it the material of choice in the drug delivery implant called Norplant**.** The preparation, properties and application of carbohydrate-modified silicone surfactants such as glucosamide-containing and glycoside-containing silicone surfactants have been reported (Han et al. 2012).

Fluorinated Surfactants

Hemifluorinated surfactants could potentially aid in the development of new strategies for contraception (Rajni 2010).

Surfactant proteins

The role of the surfactant system for the development of the human lung is known to be essential. Pulmonary surfactant is a complex mixture of lipids and proteins that regulates dynamically the alveolar surface tension. There are four main surfactant proteins, known as surfactant protein (SP)-A, B, C, and D. SP-A and D are hydrophilic while SP-B and C are hydrophobic (Goldmann et al. 2009). SP-A, the most prominent among four proteins in the pulmonary surfactant-system, is expressed by alveolar epithelial cells type II as well as by a portion of non small cell lung carcinomas. Surfactant proteins fulfil several different functions in the human body. The first vaginal microbicide nonoxynol-9 acted as a surfactant (Weber et al. 2005). Surfactant protein SP-A is an essential component of the host-defence system in the lung as well as in vagina (MacNeill et al. 2004). Surfactant proteins B (SP-B) and C (SP-C) are well-documented genetic disorders. Surfactant proteins B and C (SP-B and SP-C) are small hydrophobic proteins of pulmonary surfactant that are essential for lung function. Deficiency or abnormal protein expression due to SP-B and SP-C gene mutations has been linked to various acute and chronic lung diseases (Beers. and Muluget 2006). Surfacant protein-D is present throughout the female genital tract (Leth-Larsen et al. 2004).

Pulmonary surfactant

Pulmonary surfactant is a surface-active lipoprotein complex (phospho-lipoprotein) formed by type II alveolar cells. The proteins and lipids that comprise the surfactant have both a hydrophilic region and a hydrophobic region. Synthetic pulmonary surfactants include: Exosurf - a mixture of

DPPC with hexadecanol and tyloxapol added as spreading agents; Pumactant (Artificial Lung Expanding Compound or ALEC) - a mixture of DPPC and PG; KL-4 - composed of DPPC, palmitoyl-oleoyl phosphatidylglycerol, and palmitic acid, combined with a 21 amino acid synthetic peptide that mimics the structural characteristics of SP-B; Venticute - DPPC, PG, palmitic acid and recombinant SP-C. Animal derived surfactants include: Alveofact - extracted from cow lung lavage fluid; Curosurf - extracted from material derived from minced pig lung; Infasurf - extracted from calf lung lavage fluid; Survanta - extracted from minced cow lung with additional DPPC, palmitic acid and tripalmitin. Exosurf, Curosurf, Infasurf, and Survanta are the surfactants currently FDA approved for use in the U.S (Taeush 2002).

Surfactant proteins have also been discovered in non-pulmonary tissues such as skin epidermis (Mo et al 2007), nasal mucus membrane (Vaandrager and van Golde 2000; Woodworth et al. 2007), and tear fluid (Brauer 2007a; Brauer 2007b). Peptide-containing surfactant provides clinical efficacy in the treatment of respiratory distress syndrome and offers promise for treating other lung diseases in infancy Donn and Sinha 2008; Halliday 2008; Mazela et al. 2006).

Surfactant proteins are an important part of the human immune system for fighting bacterial pathogens. It has now shown that the surfactant proteins also exist in pathogenic bacteria (Bräuer et al. 2013). Researchers have now shown these proteins to exist in two pathogenic types of bacteria, *staphylococcus aureus* and *pseudomonas aeruginosa*, which are both germs that can cause severe infections of the lungs and other organs. Latherin, a surface active protein from horse sweat causes the foaming of a sweating horse, particularly where harness and saddle rub. Its function is to wet the hair and facilitate the rapid translocation of sweat water from the skin to the surface of the pelt to allow evaporative cooling. The recombinant form of the protein is also highly surface active. It is also produced in the salivary glands of horses, and that it is also made by zebras, onagers and wild asses.

Surfactant Polymers

The general classification of polymeric surfactants (homopolymers, block and graft copolymers), their solution properties, stabilization of suspensions and nanoemulsions using INUTEC®SP1 have been reported (Tadros 2009). General applications of polymeric surfactants include pharmaceuticals and personal care products. Polymeric surfactants offer many performance advantages over traditional surfactants, especially in the challenging parental administration of drugs, which can be prone to physical instability (Tadros 2009).

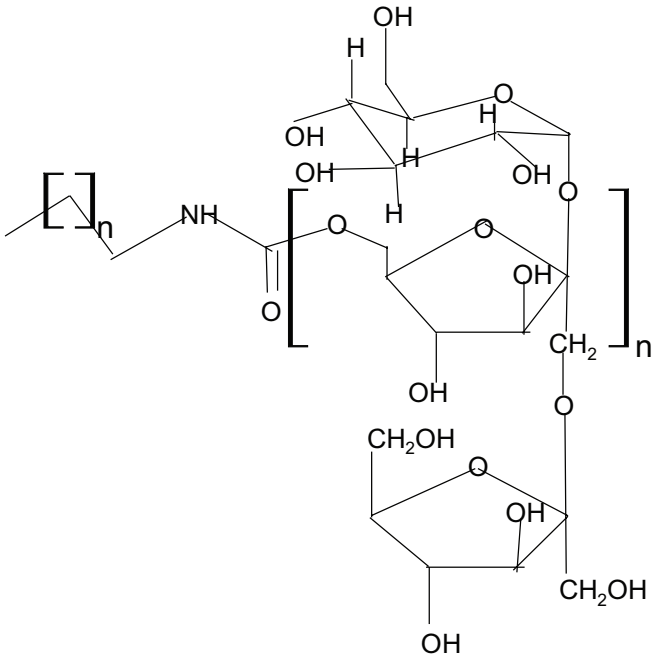


Figure 5: Structure of INUTEC®SP

Hydroxypropyl methylcellulose is a non-ionic polymer extensively used in Pharmaceutical formulations. The polymeric surfactant is useful for stabilising the interface in emulsions or dispersions (Michael 2010). Many useful properties of polyelectrolyte surfactant complexes come from the highly ordered structures of surfactant self-assembly inside the polyelectrolyte aggregate and polyelectrolyte surfactant complexation may be helpful for pharmaceutical and biological applications. Researchers have demonstrated the role of hydroxypropyl methylcellulose-anionic surfactant interactions during the dissolution of non-ionic hydrophilic polymer based solid dispersions and have highlighted the potential relevance of this to a fuller understanding of drug solubilisation/stabilisation *in vivo* (Qi et al. 2013). Inutec SP1 (Fig. 5 and Fig. 6) is a non-ionic, polymeric-based surfactant system derived from chicory inulin (http://www.beneo-bbc.com/Our-Products/INUTECA). It is a graft copolymer based on a naturally occurring polysaccharide, namely inulin (polyfructose) that has been hydrophobically modified by introducing several alkyl groups on the linear polyfructose chain (Van den Mooter et al. 2006). The superior dissolution behaviour of the drugs from Inutec® SP1-based

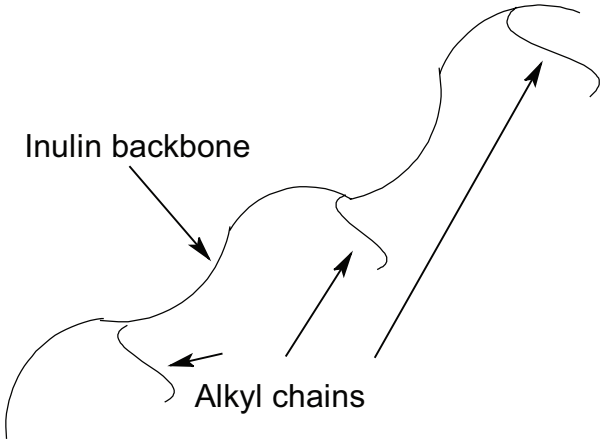


Figure 6: Schematic representation of INUTEC®SP1 polymeric surfactant.

solid dispersions could be ascribed to its surface-active nature (Srinarong et al. 2011). The spherically agglomerates crystals of felodipine with Inutec SP1 were reported for enhanced dissolution rate properties of this drug by spherical crystallization technique (Tapas et al. 2009).

The dissolution rate of etodolac at pH 1.2 and 6.8 was found improved containing polymeric surfactant inutec-etodolac system compared to that of the pure drug and physical mixtures. Inutec-based coevaporate based formulation of etodolac chewable tablets showed significantly higher mean C_{max} and shorter mean T_{max} (about 2 h earlier) and about 1.32-fold higher mean $AUC_{0–24}$ values for the F3 chewable tablets compared to etodolac-filled capsules (Ibrahim et al. 2010).

Alkylpolyglucoside surfactant

The alkyl polyglucosides are derived from reacting corn starch with a fatty alcohol to produce highly biodegradable new surfactants. Low ethoxylated monoglycerides - like PEG-7 cocoate - and alkyl polyglucosides - like Plantaren (decyl glucoside), Plantapon LGC Sorb (sodium lauryl glucose carboxylate), and Plantasol CCG (caprylyl capryl glucoside) are known. PEG-7 glyceryl cocoate is a non-ionic, low ethoxylated monoglyceride that can behave as an skin conditioner. A comparative study of the ocular irritation potential of various alkyl polyglucoside surfactants showed a good correlation between the proportion of C_{10} alkyl polyglucoside and the eye irritation potential Q score. Alkyl polyglucoside bases could be considered as preferential option in drug compounding related to

the conventional ones (Jaksic et al. 2012). Results indicated a good safety profile of alkylpolyglucoside surfactant (Savić et al. 2007).

Ionic liquid surfactants

Ionic liquids as surfactants are easier to incorporate into formulations (Smirnova and Safonova 2010). Microemulsions comprising an ionic liquid as surfactant were reported (Zech et al. 2009). The effect of ionic liquids addition on surfactant solution can be regarded as the comprehensive effects of inorganic salt, cosurfactant, and cosolvent on surfactant solution (Shang et al. 2010). When ionic liquids are used in small amounts (say less than 1 wt %), they behave more like "greener" surfactants. Further, ionic liquids look similar to amphoteric surfactants.

Mixed micelles containing more than one type of surfactants are of great importance from the viewpoint of pharmaceutical research. Ionic liquids can be added as cosurfactants or hydrotropes to aqueous solutions of common surfactants, thus affecting the surface activity and the critical micelle concentration of these solutions. Properties of these mixed micelles often strongly depend on the surfactant/ ionic liquids ratio and on the nature of the surfactant head group. . The unique role of ionic liquids in changing properties of aqueous surfactant systems has also been demonstrated (Behera et al. 2009; Behera and Pandey 2009; Brown et al. 2011; Comelles 2012). A series of anionic surfactant ionic liquids has been synthesized based on organic surfactant anions and 1-butyl-3-methyl-imidazolium cations (Brown et al. 2012a). Ionic liquid [bmin][BF_4] favoured early formation of micelle in case of cationic and anionic aqueous surfactant solutions, but slightly prolonged micelle formation in the case of neutral aqueous surfactant solution. However, for curcumin IL [bmin][BF_4] favored strong association (7-fold increase) with neutral surfactant solution, marginally supported association with anionic surfactant solution and discouraged ($\sim$2-fold decrease) association with cationic surfactant solution.

Magnetic ionic liquid surfactants

Magnetic fields may be used to tune the behaviour of the surfactant at the air-water interface. Mixing conventional cationic surfactants with iron salt results in the exchange of the original anion with the iron-containing ion. The resulting ionic liquid surfactant responds to a magnetic field. (Fig.7). The standard surfactant, however, has a bromide ion (Br^-) as counter ion (a), while the modified one has the iron-containing ion $FeCl_3Br^-$ (b). Two other surfactants, 1-decyl-3-methyl imidazolium chloride and didodecyltrimethylammonium

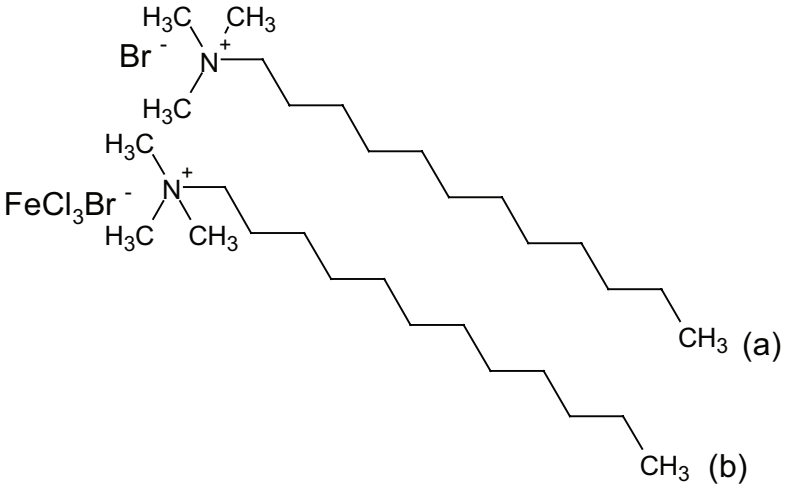


Figure 7: Magnetic ionic liquid surfactants

bromide were also modified using $FeCl_4^-$ and $FeCl_3Br^-$ as counter ions respectively (Brown 2012b). The potential applications of magnetic surfactants are not yet explored.

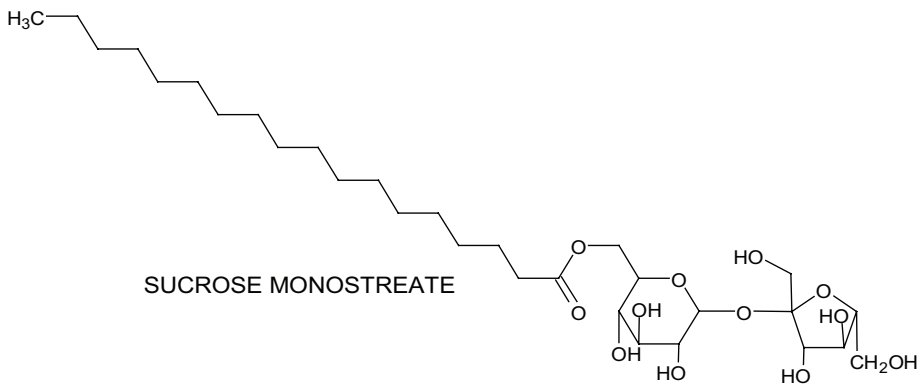
Surfactants from renewable resources

There are many advantages of using natural-based products as raw materials for surfactant applications compared to petroleum-based raw materials. Surfactants based on natural starting materials can often be made more biodegradable, less toxic and less allergenic. Renewable sources of hydrophilic groups include carbohydrates, proteins, amino acids and lactic acid, and sources of the hydrophobic moiety are steroids, monoterpenes, rosin acids, fatty acids and long chain alkyl groups, as well as aromatic compounds (Kjellin and Johansson 2010). Rosin is reputed as green petroleum because it is renewable, not expensive, and environmental friendly. Rosin-based surfactants are commonly used as antibacterial and antifungal agents (Rao 2012).

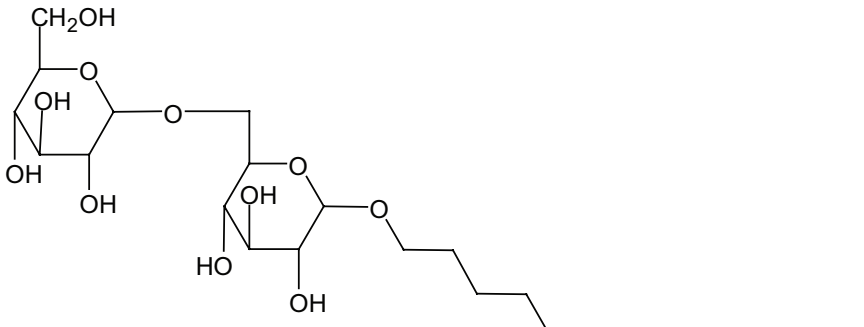
Sugar-based surfactants

Natural surfactants based on plant

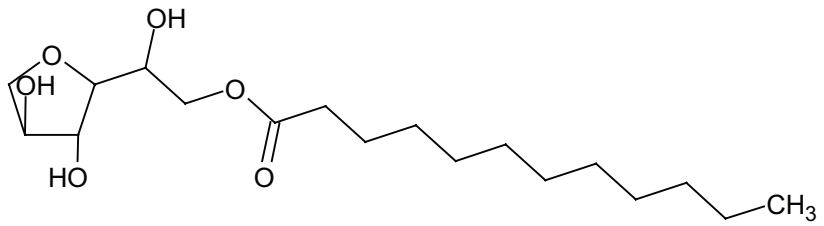
Carbohydrate-based surfactants, being based on plant-derived chemicals, use renewable resources, are readily biodegradable and are non toxic. Structures of three common carbohydrate-based surfactants are shown below (Fig. 8):



SUCROSE MONOSTREATE



LAURYL DIGLUCOSIDE



SORBITAN MONOLAURATE

Figure 8: Carbohydrate-based surfactants in pharmaceutical products.

A few of the currently available carbohydrate-based surfactants include: Alkyl polyglucosides - Triton APGs (Union Carbide), Plantcare (Cognis/Henkel), Lauryl glucoside, Monatrope (ICI/Uniqema); Sorbitan esters - Crills (Croda) and Spans (ICI/Uniqema): Sucrose esters - Crodestas (Croda). Alkylpolyglucoside surfactants are synthesized by reacting corn starch glucose with a coconut oil derived alcohol by the Fischer synthesis. The amphiphilic dextran derivatives have been shown to become convenient drug vehicles (Rotureau et al. 2005; Rotureau et al. 2006a; Rotureau et al. 2006b; Rotureau et al. 2007).

Sugar-based surfactants are more stable and sustainable (Ruiz 2012). Formulations of the alkyl polyglycosides are used in hair and skin care. On an ingredient label they are usually identified as a variety of "glucosides," for example decyl glucoside or lauryl glucoside. **S**ugar-based surfactants complement alkyl polyglycosides that are already on the market. A new family of surfactants based on simple sugars and natural oils hold promise to clean without a long list of environmental side effects (Foley et al 2011). Sugar-based surfactants such as trehalose fatty acid ester, Plantacare 818 and Plantacare 2000 are suitable alternatives to polysorbates in the applied field of low concentration protein formulations (Schiefelbein et al. 2010).

Silicone surfactants

Silicones (more accurately called polymerized siloxanes or polysiloxanes) are mixed inorganic-organic polymers with the chemical formula $[R_2SiO]_n$, where R is organic groups such as methyl, ethyl, and phenyl (Hill 2002). The demand for environmental-friendly surfactants is becoming greater. A composition comprising at least one sugar silicone surfactant and at least one oil-soluble polar modified polymer have pharmacological and/or cosmetic applicability (Bui 2011). There are of course lots of modern surfactants, but products such as sodium laureth sulphate can, on sensitive skin, cause problems. Amino acid-based surfactants on the other hand have been shown to be skin-friendly even when used on a daily basis.

Natural surfactants/biosurfactants

Nature own surfactant include polar lipids, bile salts, phospholipids lecithin, and certain fatty acids and their derivatives. Phospholipids are the major components of synthetic lung surfactant, used in the treatment of acute and neonatal distress syndrome (Acosta et al. 2009) and of liposomes which are common delivery vehicles (Immordino et al. 2006; Shailesh et al. 2009).

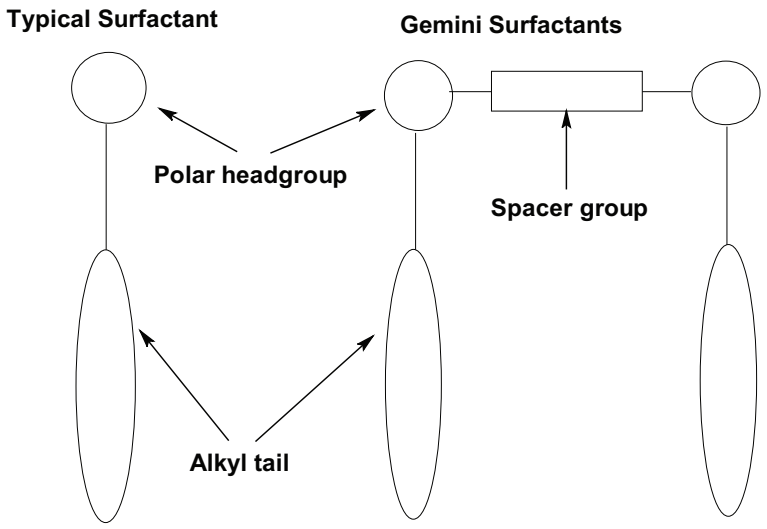
Calfactant, also known as Infasurf is an intratracheal suspension derived from the natural surfactant in calf lungs. This lung surfactant is essential for

effective ventilation as it modifies alveolar surface tension. Neonatal respiratory distress is caused by a lung surfactant deficiency (Tadros 2005).
Natural surfactants include the anionic alkyl polyglucosides (decyl, lauryl, and octyl), which are made from fatty alcohols from coconut or palm and glucose from corn starch. Other natural surfactants include lauryl glucose carboxylate which provides added foaming ability. Glutamate surfactants such as disodium cocoyl glutamate, sodium cocoyl glutamate are mild and made from amino acids. Commonly employed surfactants in pharmaceutical products include: β-dodecyl maltoside (an alkyl polyglycoside), sucrose-6-monolaurin (a saccharide fatty acid ester), polysorbate (ethoxylated sorbitan-oleic acid ester), 1-monolaurin (a monoacylglycerol), α-tocopheryl polyethylene glycol succinate)

Biosurfactants

Biosurfactants are surface-active compounds from biological sources, usually extracellular, produced by bacteria, yeast or fungi (Sekhon 2006; Sen 2010; Xu et al. 2011). Biosurfactants are derived either through the route of microbial fermentations or through the *in-vitro* enzyme catalyzed reactions. Biosurfactants can be classified by their chemical composition, molecular weight and their origin (Okoliegbe and Agarry 2012). They are grouped into three categories of origin: microbially derived surfactants [glycolipids, lipopeptides and phospholipids], animal-derived surfactants [lecithin] and plant-derived biosurfactants [soy protein]. Based on composition, biosurfactants can be divided into different categories: Phospholipid (*T. thiooxidans*); Fatty acids (*Hare corynebacterium*); Lipopeptide and lipoprotein (*Bacillus subtilis & Bacillus licheniformis*); Polymer (LPS) (*B calcium acinetobacter*); Glycolipid: Trehalose fat Paraffin (*arthrobacter & corynebacterium*); Rhamnolipid (*pseudomonas aeruginosa*); Sophorolipid (*Xie Candida lipolytica*); Fiber two glycolipids (*Hung Ping rhodococcus*). In addition, biosurfactants product categories include: Methyl ether sulfonates, Alkyl polyglucosides, Sorbitan esters, Sucrose esters, Fatty acid N-methylglucimides, Methyl glucoside esters, Anionic alkyl polyglucosides derivatives, Alkyl polypentosides Most biosurfactants are either anionic or neutral. Biosurfactants offer the possibility of replacing chemical surfactants (Marchant and Banat 2012a; Marchant and Banat 2012b)).

Biosurfactants have a wide range of applications in pharmaceutical fields (Mukherjee et al. 2006). Several biosurfactants have been reported to possess antifungal, antibacterial, antiviral, antimycoplasma, immunomodulatory and antitumor activities (Desai et al. 2008; Gharaei-Fathabad 2011; Krasowska 2010; Mukherjee et al. 2006; Muthusamy et al. 2008; Okoliegbe and Agarry 2012; Rodrigues et al. 2006; Rodrigues and Teixeira 2010; Seydlová and



Scheme 1. The structure of a typical surfactant and a gemini surfactant.

Svobodová 2008; Sriram et al. 2011; Zhao et al 2010). However, their practical use as therapeutic drugs is to some extent limited by their hemolytic activity and cytotoxicity towards normal animal cell lines (Nasrollahi1 et al. 2012; Rodrigues and Teixeira 2010a; Rodrigues and Teixeira 2010a; Rivardo et al. 2009). Currently, applications of biosurfactant-based microbubbles provide a promising therapeutic approach for targeted treatments (Xu et al. 2011).

Biosurfactants inhibited the adhesion of pathogenic organisms to solid surfaces or to infection sites (Rodrigues et al. 2006). Microbial extracellular glycolipids use as novel reagents for the treatment of cancer cells has been reported (Okoliegbe and Agarry 2012). As immunological adjuvants, bacterial lipopeptides when mixed with conventional antigens improved the humoral humane response (Gharaei-Fathabad 2011; Rivardo et al. 2009). Other applications of biosurfactant include gene delivery and as agents for stimulating stem fibroblast metabolism (Krishnaswamy et al. 2008).

Some advantages of biosurfactants are biodegradability, low toxicity, better surface and interfacial activity while some of its limitations are inability to scale up the production process and patent rights (Fakruddin 2012).

Gemini surfactants

Gemini surfactants (GS) are comprised of two surfactant monomers chemically bonded at or near the headgroups by a rigid or flexible spacer (Scheme 1)

(Ikeda 2003; Sekhon 2004; Wang et al. 2009; Zana 1996). In comparison to their corresponding monomer counterparts, geminis are three orders more surface active, have better wetting properties, and typically exhibit much lower critical micelle concentration strong dependence on spacer structure, special aggregate morphology, and strong hydrophobic microdomain (Menger and Littau 1991; Menger and Littau 1993; Menger and Keiper 2000).

Cationic gemini surfactants exhibit much higher surface activity than their monomeric counterparts. Rapid synthesis of Gemini surfactants (C(12)-C(2)-C(12) and C(14)-C(6)-C(14)) by microwave heating has been reported. The synthesis yields of C(12)-C(2)-C(12) obtained using the 915-MHz equipment were three to four times higher than those obtained using the conventional heating method (Horikoshi et al. 2013). Amino acid-substituted gemini surfactants perform better compared to the surfactants possessing unsubstituted spacers (Yang et al. 2010). Different lyophilization strategies and analytical methods have been established to develop and examine the physiochemical stability of gemini surfactant-based lipoplex (Mohammed Saeid 2012a).

GS are of special interest as drug vehicles and gene therapy. GS are viewed as effective potential transfection agents for non-viral gene therapy and one example of which is Lipofectamine Plus (Invitrogen) (Wettig et al. 2007; Wettig et al. 2009). In addition, GS can be synthesized fairly easily and at low cost, therefore making them advantageous from a pharmaceutical industrial manufacturing and economical perspective (Zana and Xia 2004). Cationic serine-based GSs have enhanced interfacial properties and low cytotoxicities, offering potential use in technical and biological applications (Silva et al. 2013).

Lyophilization significantly improved the physical stability of gemini surfactant-based lipoplexes compared to liquid formulations. Lyophilization also improved the transfection efficiency of the lipoplexes (Mohammed-Saeid et al. 2012 b). The inclusion of 1,2-dioleoyl-*sn*-glycero-3-phosphoethanolamine in gemini surfactant-based lipoplexes significantly increased the transfection efficiency[108]. Gemini surfactant structures capable of inducing a wide variety of polymorphic structures demonstrated higher transfection efficiencies (Wettig et al. 2008). The hemolytic activity of arginine-based gemini surfactants increased with the aliphatic alkyl chain lengths of the hydrophobic tail (Mitjans et al. 2003). Geminis have a superior ability for dispersing CNTs compared to other pharmaceutical surfactants. Nimodipine-loaded egg phosphatidylcholine-sodium glycocholate mixed micelles improve the water solubility of nimodipine, thus making it to be more applicable for clinical use (Song et al. 2012a).

Glycyl-lysine substitution in the gemini spacer conferred to the P/12-7NGK-12/L nanoparticles the ability to escape efficiently from clathrin-mediated

endosomes compared to the parent gemini surfactant (Singh et al. 2012). Gemini ester quat surfactants incorporate more easily into the lipid bilayer of the erythrocyte membrane and affect its properties to a greater extent (Łuczyński et al. 2013). Researchers reported heparin determination at the nanogram level in pharmaceutical samples using gemini surfactant (dodecyl polyoxyethylene ether biquaternary ammonium salt. It was found that gemini surfactant reacted with anionic heparin to form an ion-association complex (Song et al. 2012b).

Aquatic toxicity of surfactants

After use, however, surfactants often end up in our environment. Most surfactants are more or less toxic to aquatic organisms due to their surface activity which will react with the biological membranes of the organisms. Generally an increase of the chain length in the range of 10 to 16, leads to an increase in toxicity to aquatic organisms. Aquatic toxicity is an important characteristic of all surfactants (Ardelean et al. 2011; Persson 2012)**.**

pH-sensitive gemini surfactants

pH-sensitive surfactants are often added as a secondary surfactant to enhance performance properties, including solubility, foaming, and mildness to the skin or to the eyes. In addition, pH-sensitive surfactants may be used effectively in novel applications where pH variations can be utilized to control drug release and targeted gene delivery. The lysine-based surfactants showed concentration-dependent and pH-sensitive hemolytic activity, with a significant increase in the hemolysis at pH 5.4 (Nogueira et al. 2011).

The possibility of using pH-sensitive surfactants for endosome disruption could hold great promise for intracellular drug delivery systems in future therapeutic applications. The development of biocompatible lysine-based surfactants conjugates as potential drug delivery systems for pharmaceutical applications is under investigation by various workers. Amino-substituted gemini surfactants are potential components for developing non-viral nanoparticles with enhanced gene delivery for targeting diseases affecting the skin. In this context, gemini nanoparticles were formulated from plasmid DNA, the lipid (dioleoylphosphatidylethanolamine) and surfactants, where the surfactant components are novel pH-sensitive GS derivatives based on the m-7-m (alkyl chain–spacer–alkyl chain, m-s-m) unsubstituted base structure. The incorporation of a pH-active amine group within the spacer of the GSs significantly enhanced transfection efficiency in keratinocytes (Donkuru et al. 2012).

Regulatory aspects of surfactants

The use of surfactants becomes inevitable to reduce the interfacial tension between the medium and the drug. FDA guidelines state that the use of surfactants in a dissolution medium in drug development requires justification. Safety has always been the most important requirement and the most studied when dealing with pharmaceutical drugs. In the United States, the food and drug administration (FDA) has published listings in the code of federal regulations (CFR) for GRAS substances that are generally recognized as safe (U.S. Food and Drug Administration). In general, nonclinical and clinical studies are required to demonstrate the safety of a new surfactant before use. The US FDA has published a guidance document for industry on the conduct of nonclinical studies for the safety evaluation of new pharmaceutical excipients (U.S. Department of Health and Human Services). This guidance not only provides the types of toxicity data to be used in determining whether a potential new excipient is safe, but also describes the safety evaluations for excipients proposed. The document also depicts testing strategies for pharmaceuticals proposed for short -term, intermediate, and long -term use (U.S. Department of Health and Human Services). More importantly, this guidance highlights the importance of performing risk-benefit assessments on proposed new excipients in the drug products while establishing permissible and safe limits for the excipients. It is often possible to assess the toxicology of an excipient in a relatively efficient manner. Existing human data for some excipients can substitute for certain nonclinical safety data. In addition, an excipient with documented prior human exposure under circumstances relevant to the proposed use may not require evaluation with a full battery of toxicology studies (U.S. Department of Health and Human Services).

Conclusions and perspectives

Modern surfactants have to meet market requirements in mildness and naturalness. The synthetic surfactants have drivers such as low price, easy availability, and broadened application areas, whereas drivers for bio-based surfactants are their ecological benefits, availability of a wide range of substrates, increasing awareness towards eco-friendly products. Surfactants are commonly used in upstream and downstream processing and drug formulation. Surfactants of general use increase i) the percutaneous absorption and solubility of medicines and pharmaceutical agents, ii) increase the hydrophilicity of oil bases used in ointments and patches. Surfactants are commonly used in pharmaceutical protein formulations to compete for interfacs that might cause unfolding and aggregation of the API. The application of non-ionic surfactants is found ubiquitary in protein formulations.

Natural surfactants are derived from the carbohydrates sorbitol, sucrose, glucose and from plant oils such as coconut or palm kernel. Lung surfactant contains phospholipids and makes it easier for oxygen to penetrate the lung surface lining and move into the blood. Peptide-containing surfactant provides clinical efficacy in the treatment of respiratory distress syndrome and offers promise for treating other lung diseases in infancy. Biosurfactants offer the possibility of replacing chemical surfactants. They are useful in combating many diseases and act i) as therapeutic agents due to their antibacterial, antifungal and antiviral activities, ii) as anti-adhesive agents against several pathogens.

Gemini surfactant (GS) molecules use as drug delivery systems is one of the more active areas of research. GS are used as transfection agents for DNA delivery. Lyophilization significantly improved the physical stability of GS-based lipoplexes compared to liquid formulations. Lyophilization also improved the transfection efficiency of the lipoplexes. Geminis have shown efficiency in skincare, antibacterial property and are considered as a effective potential transfection agents for non-viral gene therapy. There are substantial differences in the micellization tendencies of mixtures of surfactants as compared with the single pure species. Thus, it is of great importance to evaluate and understand the interactions of Gemini surfactants with common surfactants typically found in pharmaceutical applications. pH-sensitive surfactants for endosome disruption should be further explored for intracellular drug delivery systems in future therapeutic applications.

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