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Biosurfactants: A New Pharmaceutical Additive for Solubility Enhancement and Pharmaceutical Development

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Abstract

Biosurfactants are structurally diverse group of surface-active substances produced by microorganisms. At present, biosurfactants have gained importance in the pharmaceutical, biomedical, cosmetic and food industry, with a high added value, are still developing.

Surfactants have numerous uses in pharmaceuticals, for solubilization of hydrophobic drugs in aqueous media, as components of emulsion or surfactant self-assembly vehicles for oral and transdermal drug delivery, as plasticizers in semisolid delivery systems, and agents to improve drug absorption and as penetration enhancer. Many pharmaceutical-grade surfactants consist of saccharide- or polyol-fatty acid esters or fatty alcohol ethers that are biosurfactant.

This article describes classical and new biosurfactants' producing bacteria along with their significant role as pharmaceutical additives in development of pharmaceuticals and to encourage its use in solubility or bioavailability enhancement of poorly soluble drugs.

Keywords: Biosurfactant; Biodegradable; Bioavailability; Bioemulsifier

Introduction

Surfactants are amphiphillic molecules that accumulate at interfaces, decrease interfacial tensions and form aggregate structures such as micelles [1]. The present market demand for surfactants is currently met by numerous synthetic, mainly petroleum-based, chemical surfactants. About 54% of the total surfactant output from world is utilized in household/laundry detergents, with only 32% destined for industrial use [2]. Chemical surfactants are available in many forms, and are generally classified based on charge as anionic, non-ionic, cationic and amphoteric. Cationic surfactants are the most toxic and have historically been used as antimicrobials, while anionic are less toxic and are more active against Gram positive than Gram negative bacteria, and non-ionic are often considered nontoxic. Important surfactants include linear alkyl benzene sulfonates (LAS), fatty alcohol ethoxylate (FAEO) and lauryl ether sulfate (LES) [3]. The growing awareness towards the use of renewable-based products and "green products" has stimulated the development of alternatives to these chemical surfactants. Biosurfactants (BS) are an example of such environmental friendly options [4]. Biosurfactants can be obtained either by chemical synthesis from renewable resources, by microbial fermentation processes or by enzymatic syntheses [5].

One important feature of biosurfactant is that they have very low critical micelle concentrations (CMC). This means that biosurfactant are effective at low concentrations, lower than many chemically made surfactants. The fact that only small amounts of biosurfactants are needed to reduce surface tension coupled with their known biodegradability makes them excellent candidates for "green" detergents and surfactants.

Surfactants: Important Components in Pharmaceutical Products

Surfactants, chemical species which lower the surface energy at interfaces between liquid, solid, and/or gas phases, play numerous roles in pharmaceutical products [6,7]. Surfactants are amphiphilic; moreover, their chemical structure contains both hydrophilic and lipophilic domains. Their major function in pharmaceutical processing is to improve the solubility of drugs, particularly those which are poorly soluble in water, which includes an increasing number of new and developing bioactive agents (e.g., small molecular therapeutics, peptides, proteins, vitamins, vaccines, and oligonucleotides), to enable there *in vivo* delivery. They also improve the stability of encapsulated drugs, and possibly the thermodynamic activity and rate of diffusion. They are particularly important to enable the penetration of drugs across cell walls and membranes, skin, and other biological interfaces. Surfactants are also important plasticizers, needed to improve the fluidity and *in vivo* dissolution of semisolid delivery vehicles and viscous excipients such as those employed for suppositories. For example, sucrose-fatty acid esters are important lubricants for tabletting [8]. They can also serve as wetting agents to enable drug incorporation into delivery vehicles and dispersants for powders, granules, and nanoparticles.

The most common use of surfactants is for self-assembly systems as drug delivery vehicles. Common surfactant monolayer-based, self assembly structures are emulsions, dispersions of oil-in-water (O/W-) or vice versa (W/O-). Emulsions are not thermodynamically stable, often requiring agitation for their long-term stability, and are relatively large in size, typically on the order of microns to millimeters. Emulsions are also employed in the preparation of aerosols and microencapsulation media. High-pressure homogenization can be employed to prepare

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nanoemulsions (also referred to as "mini-emulsions"), of average size 0.05-1.0 μm, which due to their smaller size can be sterilized by microfiltration and are more likely to avoid physiological clearance, and penetrate interfaces *in vivo*. Nanoemulsions are commonly used in parenteral delivery (Figure 1).

Water-oil-surfactant mixtures often form thermodynamically-stable microemulsions, characterized by nanometer-sized architectures [9,10]. Hydrophilic and lipophilic surfactant systems form O-W- and W/O-microemulsions, respectively, typically consisting of spherical nanodroplets. Surfactant systems possessing balanced hydrophilicity and lipophilicity form either swollen lamellae or bicontinuous microemulsions, dynamic intertwined networks of oil and water separated by surfactant monolayers. Microemulsions (and emulsions) are often formed *in vivo* by delivering a water-free mixture of the components that self-microemulsify (emulsify) upon contact with water.

Surfactants are also employed as therapeutic agents. For instance, saccharide-fatty acid esters, amino acid-based surfactants, and glycolipid biosurfactants possess antimicrobial activity [11,12]. Glycolipid biosurfactants and polyunsaturated fatty acid monoacyl glycerol (MAGs) possess anticancer activity [12,13]. Sophorolipid biosurfactants are effective modulators of immune response [8]. Surfactants are prominent components of several dermatological, cosmetics, and personal care products.

The chemical structures of common surfactants employed in pharmaceutical preparations are given in figure 2 [10,11]. The surfactants shown are highly biocompatible and nonionic. Cationic surfactants are needed for the delivery of oligonucleotides. Biobased cationic derivatives of arginine have recently been shown to be potentially effective as biocompatible, delivery agents [12].

Another common surfactant category is phospholipids. They are the major components of synthetic lung surfactant, used in the treatment of acute and neonatal distress syndrome [14,15] and of spherical vesicles known as liposomes, which can consist of one or more concentric phospholipid bilayers (uni- or multi-lamellar, respectively), which are common delivery vehicles [16-18].

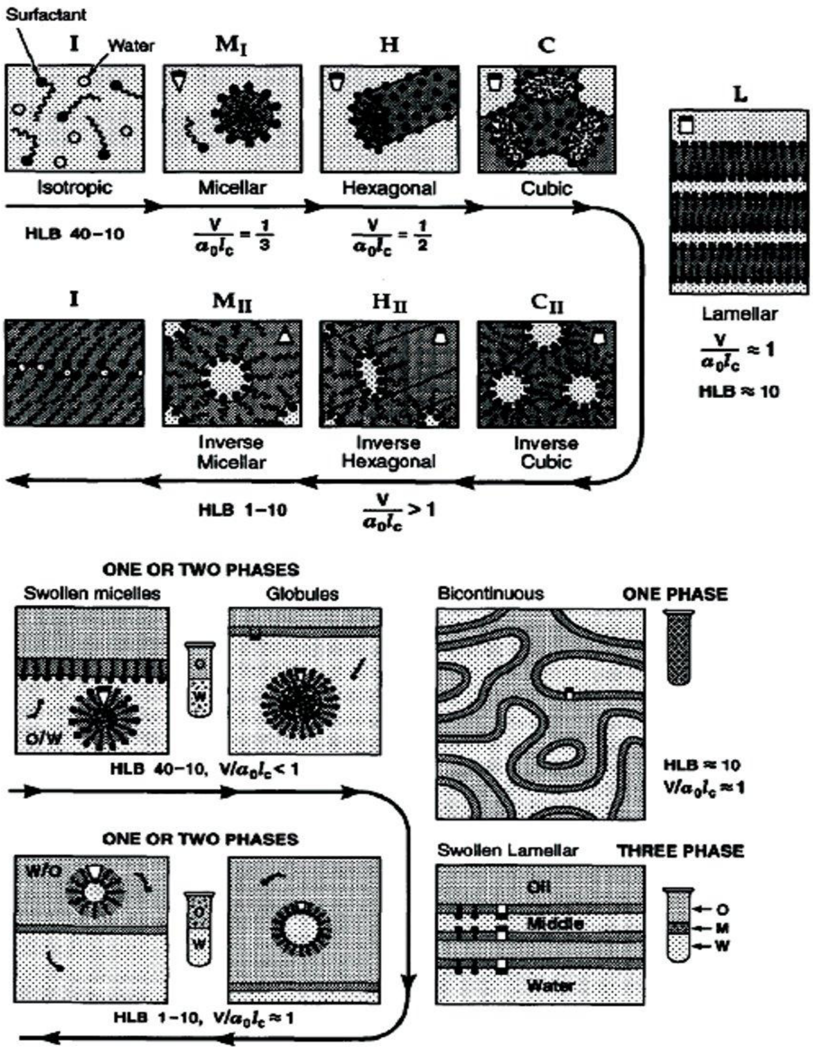

Figure 1: Surfactant self-assembly structures formed in: a) water surfactant and b) water-surfactant-oil systems as a function of the surfactant's hydrophilic-lipophilic balance.

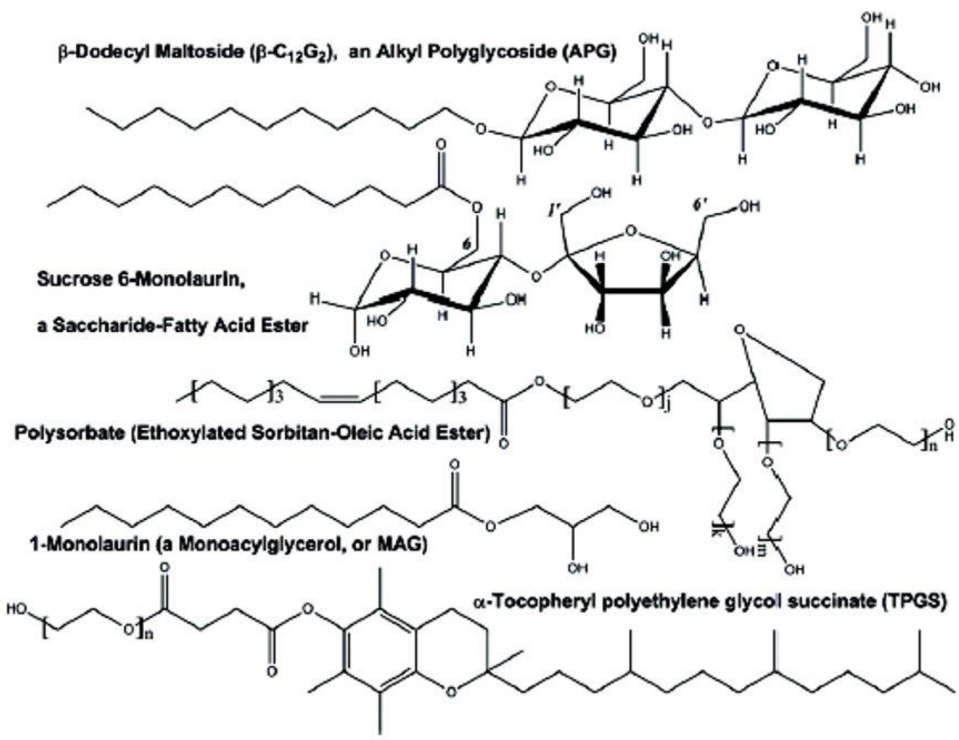

Figure 2: Commonly employed surfactants in pharmaceutical products.

Advantages of Biosurfactants

Biosurfactants have many advantages when compared to their chemically synthesized counterparts, some of these are:

Biodegradability

Biosurfactants are easily degraded by microorganism [6].

Low toxicity

Biosurfactants demonstrate lower toxicity than the chemical-derived surfactants. It was also reported that biosurfactants showed higher EC 50 (effective concentration to decrease 50% of test population) values than synthetic dispersants [7].

Availability of raw materials

Biosurfactants can be produced from very cheap raw materials which are available in large quantities. The carbon source may come from hydrocarbons, carbohydrates and/or lipids, which may be used separately or in combination with each other [8].

Physical factors

Many biosurfactants are not affected by environmental factors such as temperature, pH and ionic strength tolerances. Lichenysin produced by *Bacillus licheniformis* strain was not affected by temperature ranges of up to 50°C, a pH range of 4.5- 9.0, and NaCl concentration of 50g/l and Ca concentration of 25g/l [9].

Surface and interface activity

Sagalowicz et al. [10] stated that a good surfactant can lower surface tension of water from 75 to 35 mN/m and the interfacial tension water/hexadecane from 40 to 1 mN/m. Surfactin possess the ability to reduce the surface tension of water to 25 mN/m and the interfacial tension of water/hexadecane to <1mN/m [9].

Other advantages

Otomo [8] are biocompatibility and digestibility which allows their application in cosmetic, pharmaceuticals and as functional food additives.

Surfactants Employed in Pharmaceuticals are Primarily Biobased

The development of "biobased" surfactants is on the rise due mainly to the increased feedstock cost for petroleum compared to oleochemical starting materials (due to increased global demand and decreased production and availability), and the enhancement of sustainability for utilizing renewable feedstocks [19]. Moreover, dependence upon dwindling production of petroleum (exacerbated by increased global demand) has been linked to environmental damage: the leakage of the "Deepwater Horizon" off-shore oil well in the Gulf of Mexico in 2010 (the largest environmental disaster in US history) and the generation of CO_2 and other greenhouse gases and their impact upon climate change. These factors have increased consumer demand for more sustainable products. In general, the processing cost for preparing biobased surfactants is not significantly different from the production cost of petroleum-derived surfactants. Therefore, the market share of biobased surfactants has increased in recent years, with this trend anticipated to continue.

The majority of the surfactants described in the previous section are at least partially derived from renewable resources [19,20]. The fatty acyl components of saccharide esters, polysorbates, MAG, and fatty acid ethoxylates are derived from oleochemicals, with fatty acid

Glycolipid Type	Producing Organism	Activity	Pharmaceutical/Cosmetic Applications
Sophorolipids	*Candida bombicola*, *Candida apicola*	Antibacterial, Antioxidant, Moisturizing, Wetting, Foaming, Emulsifying, Stimulates dermal fibroblasts	Lotions, body washes, hair products, lip color, eye shadow, acne treatment, deodorants, skin smoothing, anti-wrinkle products
Rhamnolipids	*Pseudomonas aeruginosa*	Antimicrobial, Emulsifying agent	Anti-wrinkle and anti-aging products
Mannosylerythritol lipids	*Candida antarctica*	Antimicrobial, Emulsifying agent, Dispersant	Skin smoothing and anti-wrinkle products

Table 1: Relevance of glycolipid biosurfactants to the pharmaceutical/cosmetic industry [23].

methyl or ethyl esters, the major component of biodiesel, serving as the principal starting material. Therefore, the production of biobased surfactants integrates well with the development and growth of oleochemical biorefineries to produce fuels, chemical intermediates, and biobased products from oilseed crops [19,20]. Feedstocks enriched in C10-C16 saturated fatty acyl groups include palm, palm kernel (particularly palm stearine, a palmitic acyl-rich byproduct from the fractionation of palm kernel oil), coconut, and cuphea oils. Inexpensive sources of 16:0, 18:0, 18:1 and 18:2 fatty acyl groups include tallow, used cooking oils, algal oils, jatropha oil, soapnut oil, and soapstock. Ricinoleic acid is derived from castor oil, grown in India, Brazil, and several other countries worldwide. Medium-chain fatty alcohols, the lipophilic group of APGs (Alkyl polyglycosides), can be derived either from petroleum or from fatty acid methyl ester via heterogeneous catalytic reactions [21]. Phospholipids are directly obtained from soapstock, gums, and other oleochemical processing co-products.

Advantages of Bioprocessing to Prepare Surfactants for Pharmaceuticals

Enzymes can potentially play an important role in the manufacture of many biobased surfactants [19]. Bioprocessing provides many advantages compared to chemical processing, particularly for improving sustainability, lower energy use (due to lower temperatures), lower amounts of waste and byproducts, the absence of toxic metal catalysts or acids/bases, and safer operating conditions. The major disadvantages are the prohibitive costs for enzymes compared to chemical catalysts (although this concern is reduced when enzymes are immobilized to enable reuse) and the lower reaction rates that accompany many enzymatic reactions. In addition, due to the need to reduce any inhibitory agents, the starting materials must be pre-purified; for instance, fatty acyl-containing material must not contain phospholipids, aldehydes/ketones, peroxides, and other contaminants. But, as energy costs increase (as anticipated), the importance of sustainability increases (due to government regulation and/or consumer demand), and the capabilities of enzymes and their production systems increase (due to improved biotechnologies), enzymatic bioprocessing is anticipated to become more cost-competitive and attractive.

Application of Biosurfactant in Pharmaceutical and Cosmetic Industry

In the cosmetic industry, due to its emulsification, foaming, water binding capacity, spreading and wetting properties effect on viscosity and on product consistency, biosurfactant have been proposed to replace chemically synthesized surfactants (Table 1). These surfactants are used as emulsifiers, foaming agents, solubilizers, wetting agents, cleansers, antimicrobial agents, mediators of enzyme action, in insect repellents, antacids, bath products, acne pads, anti-dandruff products, contact lens solutions, baby products, mascara, lipsticks, toothpaste, dentine cleansers, etc [22,23].

Discussion

Biosurfactants can increase the bioavailability of high molecular weight hydrophobic substances, presumably by increasing their surface area, desorbing them from surfaces and increasing their apparent solubility. This property of biosurfactant can be used for the development of pharmaceuticals to enhance the bioavailability.

Although the technological development is in its infancy, significant potential value for bioprocessing approaches to prepare biobased surfactants for use in pharmaceutical products has been demonstrated. Biocatalytic manufacturing is particularly attractive due to its enhancement of sustainability, its higher selectivity toward desired products, and its lower production of byproducts. Biotechnology will need to produce more robust enzymes at lower cost to enable this approach. Scientists and engineers will continue to improve enzymatic bioprocess design and perhaps develop new biobased surfactants for pharmaceutical application as the interest and availability of renewable feedstocks increases.

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References

1. Van Hamme JD, Singh A, Ward OP (2006) Physiological aspects. Part 1 in a series of papers devoted to surfactants in microbiology and biotechnology. Biotechnol Adv 24: 604-620.
2. Banat IM, Makkar RS, Cameotra SS (2000) Potential commercial applications of microbial surfactants. Appl Microbiol Biotechnol 53: 495-508.
3. Develter DWG, Lauryssen LML (2010) Properties and industrial applications of sophorolipids. Eur J Lipid Sci Technol 112: 628-638.
4. Vaz DA, Gudiña EJ, Alameda EJ, Teixeira JA, Rodrigues LR (2012) Performance of a biosurfactant produced by a *Bacillus subtilis* strain isolated from crude oil samples as compared to commercial chemical surfactants. Colloids Surf B Biointerfaces 89: 167-174.
5. Syldatk C, Hausmann R (2010) Microbial Biosurfactants. Eur J Lipid Sci Technol 112: 615-616.
6. Chesko JR, Anderson C, Fox L, Kalvodova T, Dutil S, et al. (2009) Nonionic surfactants formulated into drug and vaccine delivery systems, in Non-Ionic Surfactants, edited by P.L. Wendt and D.S. Hoysted, Nova Science Publishers, Hauppauge NY USA 177-197.
7. Mishra M, Muthuprasanna P, Surya Prabha K, Sobhita Rani P, Satish Babu IA, et al. (2009) Basics and potential applications of surfactants-a review, Int J PharmTech Res 1:1354-1365.
8. Otomo N (2009) Biobased Surfactants and Detergents: Synthesis, Properties, and Applications, Hayes DG, Kitamoto D, Solaiman DKY, Ashby RD, (eds.). AOCS Press, Champaign, IL 275-298.
9. Garti N (2003) Microemulsions as microreactors for food applications. Curr Opin Colloid Interface Sci 8: 197-211.
10. Sagalowicz L, Leser ME, Watzke HJ, Michel M (2006) Monoglyceride Self-Assembly Structures as Delivery Vehicles. Trends in Food Science & Technology 17: 204-214.
11. Infante MR, Perez L, Moran C, Pons R, Pinazo A (2009) Synthesis, aggregation properties, and applications of biosurfactants derived from arginine. In: Biobased Surfactants and Detergents Synthesis, Properties, and Applications, Hayes DG, Kitamoto D, Solaiman DKY, Ashby RD, (eds.). AOCS Press, Champaign, IL USA 351-387.
12. Kitamoto D, Morita T, Fukuoka T, Imura T, Konishi M (2009) Self-assembling

properties of glycolipid biosurfactants and their potential applications Curr Opin Colloid Interface Sci 14: 315-328.

13. Fortin S (2010) Polyunsaturated fatty acid monoglycerides, derivatives, and uses thereof. USA Patent 2009-535048, 20100160261.
14. Savić S, Tamburić S, Savić MM (2010) From conventional towards new-natural surfactants in drug delivery systems design: current status and perspectives. Expert Opin Drug Deliv 7: 353-369.
15. Müllertz A, Ogbonna A, Ren S, Rades T (2010) New perspectives on lipid and surfactant based drug delivery systems for oral delivery of poorly soluble drugs. J Pharm Pharmacol 62: 1622-1636.
16. Acosta EJ, Saad SMI, Kang N, Policova Z, Hair ML, et al. (2009) Lung surfactants: formulation, evaluation, and polymeric additives. In: Biobased Surfactants and Detergents: Synthesis, Properties, and Applications, Hayes DG, Kitamoto D, Solaiman DKY, Ashby RD, (eds.). American Oil Chemists' Society Press, Champaign, IL USA 191-229.
17. Shailesh S, Neelam S, Sandeep K, Gupta GD (2009) Liposomes: a review. Journal of Pharmacy Research 2: 1163-1167.
18. Immordino ML, Dosio F, Cattel L (2006) Stealth liposomes: review of the basic science, rationale, and clinical applications, existing and potential. Int J Nanomedicine 1: 297-315.
19. Hayes DG (2009) Biobased Surfactants and Detergents: Synthesis, Properties, and Applications. D.G. Hayes DG, Kitamoto D, Solaiman DKY, Ashby RD. American Oil Chemists' Society Press, Champaign, IL 3-25.
20. Giraldo L, Camargo G, Tirano J, Moreno-Pirajan JC (2010) Synthesis of fatty alcohols from oil palm using a catalyst of Ni-Cu supported onto zeolite. E-Journal of Chemistry 7: 1138-1147.
21. Gielen D, Newman J, Patel MK (2008) Reducing industrial energy use and CO_2 emissions: the role of materials science. MRS Bulletin 33: 471-477.
22. Gharaei-Fathabad E (2011) Biosurfactants in pharmaceutical industry: A Mini-Review. Am J Drug Discov Dev 1-11.
23. Williams K (2009) Biosurfactants for cosmetic application: Overcoming production challenges. MMG 445 Basic Biotechnology 5: 78.