Expert Opinion

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Interest of glycolipids in drug delivery: from physicochemical properties to drug targeting

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Importance of the field: The need for new products derived from natural sources for the replacement of the commonly used non-ionic surfactants containing ethylene oxide units with degradable carbohydrate headgroups has become an important area of research. Glycolipids offer a wide range of applications in the pharmaceutical and cosmetic fields and can compete with the most commonly used surfactants. Involved in molecular recognition mechanisms at the surface of cells, glycolipids are also used for drug targeting.
Areas covered in this review: The structure and pharmaceutical applications of the main glycolipid categories are summarized. The review focuses on marketed glycolipids, biosurfactants and compounds developed at laboratory scale for applications such as self-assembly or drug targeting.
What the reader will gain: This article aims to provide an overview of the different sugar-based surfactant classes and their potential uses.
Take home message: Beside their use as surfactants or absorption enhancers in basic formulations, glycolipids can build gels, niosomes, hexosomes and cubosomes, whose structure is directly related to lyotropic properties. These systems allow solubilization and entrapment of drugs. In innovative delivery systems, glycolipids are also used for drug targeting because their sugar moieties can be specifically recognized by carbohydrate-binding proteins exposed at the surface of cells.

Keywords: adhesions, biosurfactants, cubosomes, drug targeting, gelators, hexosomes, lectins, liposomes, surfactants

Expert Opin. Drug Deliv. (2010) 7(9):1031-1048

1. Introduction

Glycolipids have been the object of growing interest in ingredients, and the pharmaceutical and cosmetic industries for the last two decades. In the context of sustained development with the need of new products derived from natural resources, replacement of the commonly used non-ionic surfactants containing ethylene oxide units by degradable carbohydrate headgroups has become an important area of research. Alkylglycosides and alkylpolyglycosides are the major groups of these new surfactants. They combine advantages of natural or semi-natural origin with effective surface properties [1-3]. Variations in the nature and number of carbohydrate moieties and hydrocarbon chain length determine their surface-active properties and applications. In basic formulation, glycolipids are mostly used for their good detergency, emulsifying, foaming and dispersing properties in a large variety of cosmetic and pharmaceutical forms. They can also promote oral drug absorption in a nonspecific way [4]. The other interesting feature of these compounds is that in nature, carbohydrate headgroups are involved in cell recognition and antibody responses. They interact with saccharide receptors with high specificity [5]. They can promote

10.1517/17425247.2010.511172 ISSN 1742-5247

Article highlights.

- Many marketed glycolipids are available for a wide range of uses, from API solubilization to the stabilization of emulsions or preparation of microemulsions.
- Produced by microorganisms, sugar-based biosurfactants are an interesting alternative to the synthetic ones thanks to their natural origin, low toxicity, antimicrobial activity, biodegradability and possible applications in many kinds of formulation (emulsions, microemulsions, liposomes, etc.).
- More specific glycolipids are designed in research laboratories in order to control their self-assembly properties or to obtain efficient drug targeting.

This box summarizes key points contained in the article.

bioadhesion, which makes them and the other glycoconjugates very promising additives for targeted drug delivery. Originally, the concept of bioadhesion was developed to improve the bioavailability of drugs delivered by the oral route [6,7]. Polymers with mucoadhesive properties were used [8]. However, for minimizing the side effects of drugs, it later appeared more valuable to favor direct cell membrane adhesion, by exclusively targeting the cells that actually require treatment. In this biomimetic strategy, one approach is to use the potential of proteins (lectins) able to bind sugar moieties on a cell membrane, and the other is to use glycolipids to target endogenous lectins exposed at the surface of cells [9-15]. In this review, after a brief presentation of glycolipids in the biological context, their different classes are described as a function of their origin (natural or synthetic), availability (marketed or laboratory scale) and uses (surfactants, self-assembling properties, drug targeting, etc.).

2. Nomenclature, definitions and organization of natural glycolipids

The term glycolipid designates any compound containing one or more saccharide residues bound by a glycosidic linkage to a hydrophobic moiety such as an acylglycerol, a sphingoid or a ceramide (*N*-acylsphingoid) (**Figure 1**). They are collectively part of a larger family of substances known as glycoconjugates, comprising glycoproteins, glycopeptides, peptidoglycans, proteoglycans, glycolipids and lipopolysaccharides [16].

Glycolipids can be found in membranes of bacteria, fungi, plants and animals. They originate from the transfer of sugar residues to sterols, ceramides and diacylglycerols by glycosyltransferases [17]. The term glycoglycerolipid is used to designate glycolipids comprising one or more glycerol residues. Glycosphingolipids (GSLs) contain at least one monosaccharide residue linked to a sphingoid (long-chain aliphatic amino alcohols) or a ceramide (*N*-acylated sphingoid) [16]. They are classified according to their carbohydrate composition: i) neutral glycosphingolipids with one or more uncharged sugars such as glucose, galactose, *N*-acetylglucosamine, *N*-acetylgalactosamine, or fucose; ii) acidic glycosphingolipids with ionized functional groups (phosphate or sulfate) attached to neutral sugars or charged sugar residues such as sialic acid (*N*-acetyl or *N*-glycoloyl neuraminic acid) – the latter are called gangliosides, they have roles in the maintenance and repair of nervous tissue; iii) basic glycosphingolipids; and iv) amphoteric glycosphingolipids [18-20]. Glycosphingolipids are essential structural components of the membrane and reside mostly at the cell surface.

The structures in which fatty acyl/alkyl groups are linked directly to a sugar backbone are saccharolipids, also named acylaminosugars because of the replacement of a hydroxyl group by an amine group in the sugar moiety of most compounds [18,21]. In these lipid derivatives, a sugar (trehalose, glucose or sucrose) replaces the glyceryl group of the glycerolipids and glycerophospholipids. Well-known members of this category are precursors of the lipid A component of the lipopolysaccharides in Gram-negative bacteria.

In biological membranes, glycolipids take a stable conformation by means of relatively weak forces, such as electrostatic interactions, hydrogen bonding, hydration and long-range van der Waals interactions. Depending on their chemical structure, their mixing properties with lipids, especially phospholipids, may vary [13,22,23]. Both the length of their lipid chains and the location of their sugar moieties (in the plane of the polar groups of the phospholipids or protruding in the aqueous medium) affect the organization of the lipids and proteins surrounding them, determining domains with specific properties and, consequently, functions. Ewers *et al.* [24] have shown that GM1 tail length could influence both the degree of lipid ordering of the glycolipid receptor-enriched membrane domains, and the mechanical properties of the membrane such as bending rigidity and spontaneous curvature. Crystal structures of membrane proteins suggested that glycolipids, especially glycosphingolipids, are indispensable at very specific sites for protein/lipid interactions [25].

In normal and pathological processes, including cell–cell recognition, cell adhesion, signal transduction and protein sorting, cells must be able to receive signals from the extracellular medium and deliver them to the inside of the cell. Enacting these processes, glycolipids orientate their carbohydrate moieties towards the extracellular medium, where they can be recognized specifically by receptors or complimentary carbohydrates. The positioning and accessibility of the sugar moieties are crucial [13,26]. They may be affected by the conformation and configuration of the glycolipid in the lipid matrix [24,27,28]. Moreover, binding specificity depends not only on the carbohydrate sequence but also on the character of the lipid moiety itself. There can be *allosteric* mechanisms where changes in the structure in a distal part of the molecule result in alteration of the orientation or conformation of the carbohydrate moiety at the interface, allowing or restricting ligand binding [29,30-32].

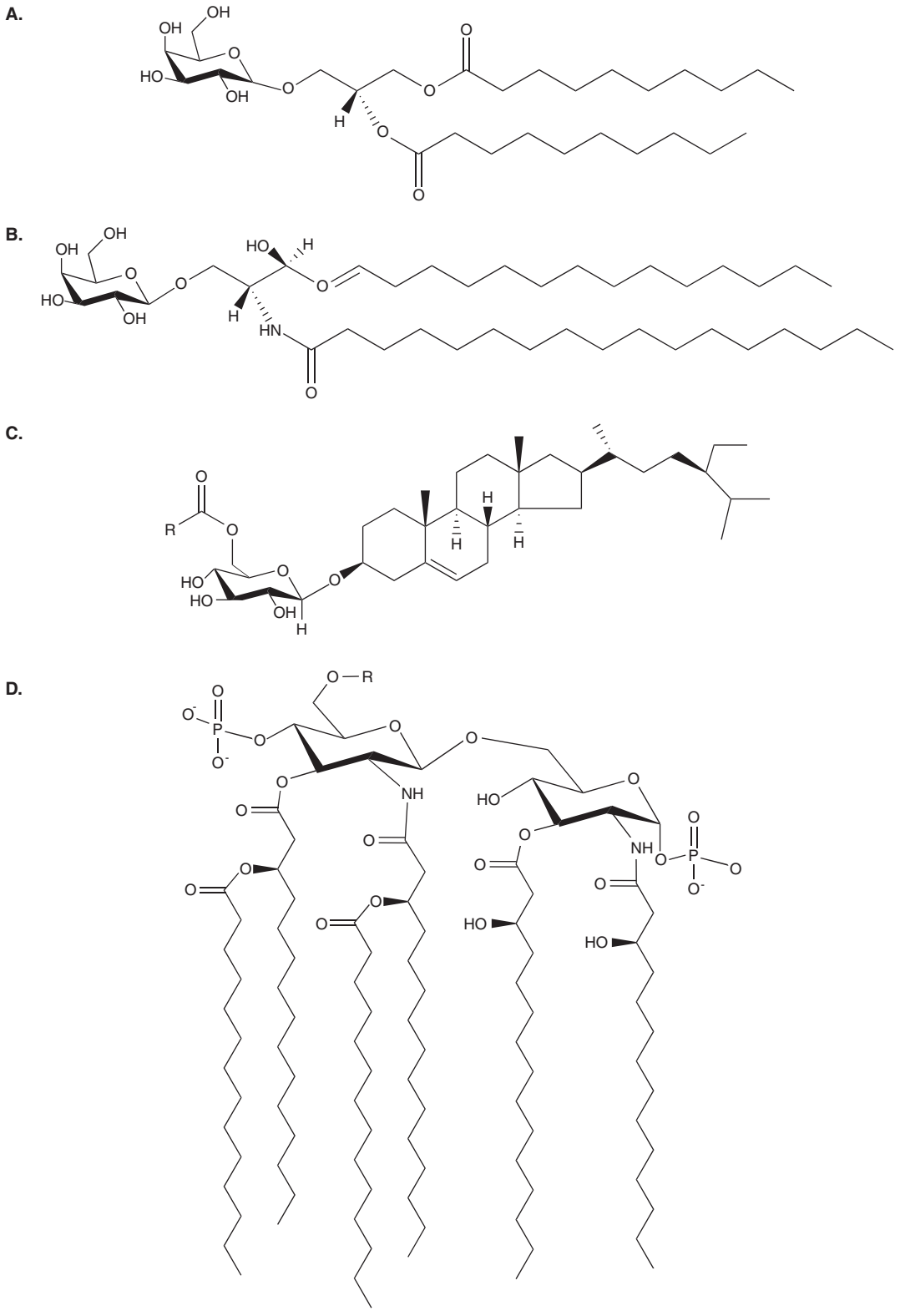

Figure 1. Examples of glycolipid structures. A. Galactosyl-diacylglycerol. **B.** Galactosyl-ceramide. **C.** β-Sistosterol glucoside. **D.** Lipid A.

Knowledge of glycolipids' organization in membranes can be taken advantage of for the development of drug delivery systems.

3. Glycolipids as surface-active agents

3.1 Marketed glycolipids

3.1.1 General aspects

From an industrial point of view, the sugar-based surfactants having the most important potential are alkyl polyglycosides (50,000 t/a), fatty acid *N*-methyl glucamides (40,000 t/a), sorbitan ester (20,000 t/a) and sucrose esters (5000 t/a) (**Figure 2**) [33,34]. As most of them have been described extensively in the literature, only a brief overview will be given in this review.

Alkyl polyglycosides are obtained by the reaction of long-chain alcohols, from C8 to C16, with glucose [35]. The result of the reaction is a complex mixture of alkyl mono-, di-, tri- and oligoglycosides including α- and β-anomers. Depending on Fisher synthesis conditions, the ratio of alkyl monoglycosides to alkyl polyglycosides can be adjusted, and then the hydrophobicity/hydrophilicity of the mixture controlled without further purification. The critical micellar concentrations of alkyl mono- or polyglycosides are in the range 2×10^{-2} – 2×10^{-4} mol/l, comparable to that of typical non-ionic surfactants. The alkyl chain length has a stronger effect on the critical micellar concentration – which decreases as the number of carbon increases – than the number of glucose units. Compared with ethoxylated non-ionic surfactants, alkyl polyglycoside derivatives do not show the phase inversion temperature phenomenon.

Fatty acid glucamides are prepared by reductive alkylation of glucose and then acylation with fatty acids. The longer the alkyl chain length, the lower the surface tension and critical micellar concentration values [36]. Fatty acid *N*-methyl glucamides are essentially used as detergents [33].

Sorbitan esters are derived from sorbitol. Depending on the amount and type of their fatty acid chains (from C12 to C18), many sorbitan esters are available with hydrophilic–lipophilic balance (HLB) values in the range 1 – 8. To increase their hydrophilicity, these compounds have been modified by reaction with ethylene oxide to produce sorbitan ester ethoxylates (polysorbates) with HLB values ranging from 10 to 17, depending on their fatty acid chain length or number of ethoxy units.

Contrary to the above-described surfactants, the market size of sucrose esters tends to increase and their development does not seem to be mature [33]. High-purity sucrose (β-D-fructofuranosyl α-D-glucopyranoside) is available at low cost. The limited use of surfactants derived from this sugar comes from the synthesis routes and the high reactivity of hydroxyl groups, which usually lead to complex mixures of mono- to pentaesters during the transesterification step. The approaches investigated to improve the reaction selectivity or purification methods are still not totally compatible with many industrial applications and require laboratory-scale development [37,38].

Among these marketed glycolipids, the most documented toxicity studies have been done on the alkylglycoside derivatives. The environmental ranking of surfactants is classically based on their biodegradability and aquatic toxicity. Sugar-based surfactants are generally rapidly biodegradable, both in aerobic and in anaerobic conditions, and present low aquatic toxicity compared with classical polyoxyethylene-based non-ionic compounds [39]. Furthermore, it has been shown that 12 principles of the green chemistry could be applied to alkylglycosides. Among these principles, it is possible to cite a less hazardous chemical synthesis, safety concerning solvents and auxilaries, the use of 100% renewable raw materials, or the lack of protection group requirements during the synthesis [40].

3.1.2 Applications

In the pharmaceutical and cosmetic fields, alkyl glycosides are used extensively as surfactant, foamer or viscosity enhancer, and for their detergent properties [33,35]. Sorbitan esters are lipophilic non-ionic emulsifiers in the preparation of creams and emulsions for topical application, but also solubilizing and wetting agents. Most of them are relatively non-toxic by ingestion in acute and long-term studies, mild skin irritants, and non-sensitizing in clinical tests [41]. The hydrophilic polyethylene oxide derivatives of sorbitan esters are used as emulsifiers in oil-in-water emulsions, solubilizers for poorly water-soluble molecules, or suspension stabilizers [34]. Like non-PEGylated sorbitan esters, they are considered safe for human health and are widely used in cosmetic formulations [42].

Microemulsions, which consist of microdomains of oil or water stabilized by an interfacial film, are thermodynamically stable and isotropic systems that form spontaneously. Owing to their long-term stability, easy preparation and high solubilization capacity, microemulsions are considered to be very promising liquid vehicles for drug delivery [43]. Sorbitan esters have been used successfully to prepare microemulsions able to reduce the pain of clonixic acid or propofol parenteral administration compared with marketed formulations [44,45]. Microemulsions can also be formed with alkyl polyglycosides [46,47]. They are electrolyte and temperature independent, and can be processed more rapidly than those prepared with other surfactants.

In controlled conditions, hydrated non-ionic surfactant molecules lead to the formation of liposome-like vesicles called niosomes [48,49]. Alkylglycosides were among the first surfactants described for the preparation of niosomes, mostly for cosmetic applications, then for drug delivery. The self-organization of non-ionic surfactant into niosomes obeys the same rules as phospholipids for liposome formation. The preparation methods are also derived from those of liposomes, and additives such as cholesterol and charged lipids are often required to improve the niosomes' stability.

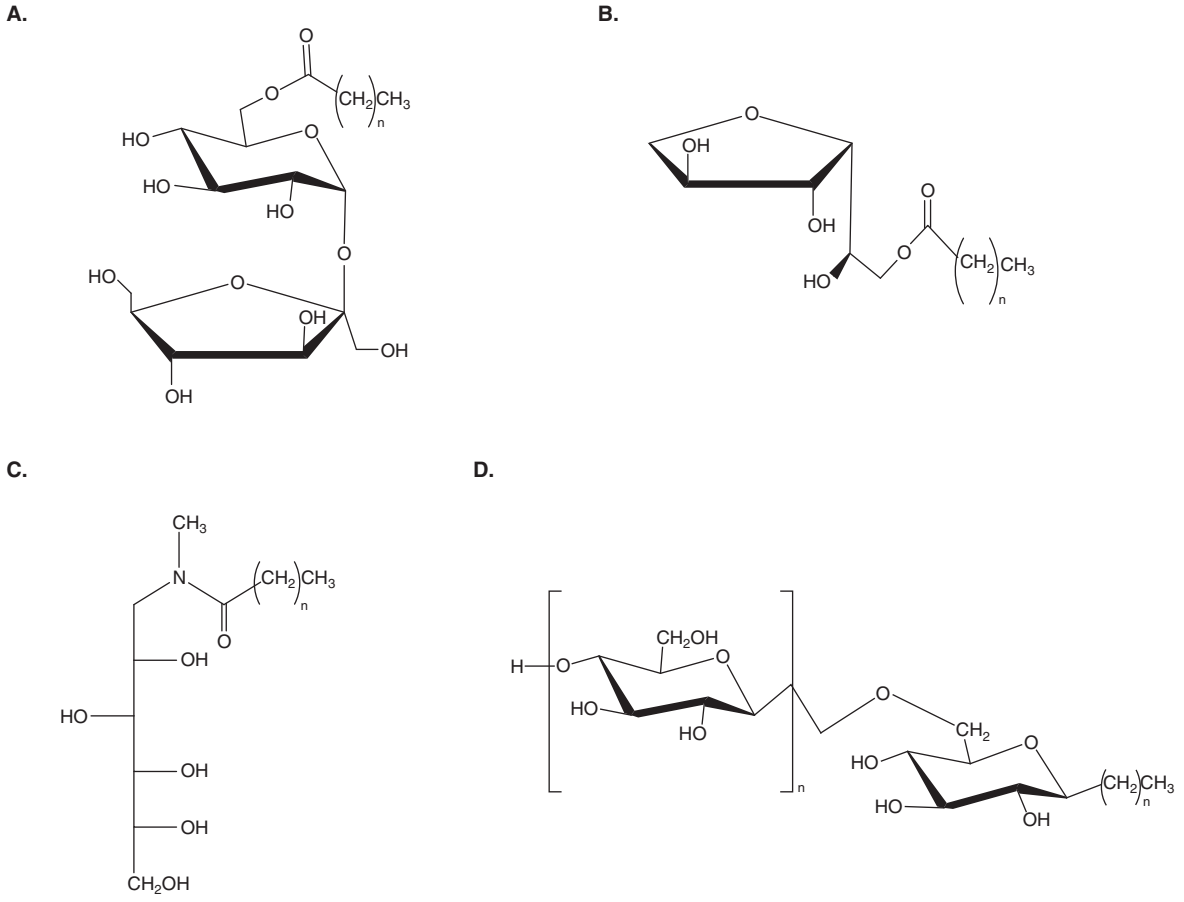

Figure 2. Examples of commercial synthetic glycolipids. A. Sucrose ester. **B.** Sorbitan ester. **C.** *N*-methyl glucamide. **D.** Alkylglucoside.

Cholesterol abolishes the gel-to-liquid phase transition, thus reducing leakage. The charged lipids prevent niosome aggregation. The chemical structure of the glycolipids affects drug loading: the hydration of surfactant headgroups depends on the nature of the sugar moiety, which thus controls the formation of bilayers. The length of the hydrophobic chains influences the phase transition temperature of surfactant molecules. The longer the acyl chain, the higher the phase transition temperature: it increases encapsulation efficiency and niosome stability, and lowers their toxicity. Niosomes have been applied to the delivery of various drugs [49]. Recently, Abd-Elbary and co-workers [50] have developed sucrose stearate-based niosomes for the nebulizable delivery of cromolyn sodium. Sucrose stearate D18-11 (HLB = 11) allowed preparation of effective niosomal dispersions in a mixture with cholesterol and stearylamine in a 7:3:0.3 molar ratio. The modification of the sucrose ester HLB (D18-16) had a pronounced effect on the drug release and nebulization efficiency with respect to sucrose ester ability to reduce surface tension and to modulate the aerosol droplet size.

Sucrose esters have shown solubilizing properties for poorly water-soluble drugs such as nifedipine, phenytoin and spironolactone. However, these properties seem less efficient than those of classical ethoxylated surfactants [51]. Sucrose esters have also been used in the formulation of tablets [52]. Indeed, some authors have described the effect of their hydrophilic–lipophilic properties on drug release rate and suggested a controlled release due to surfactant gelation. Chansanroj and Betz [53] investigated various tablet properties as a function of the proportion of monoesters in a sucrose ester composition. Increasing the amount of monoacylated products resulted in an increase in porosity, elastic recovery and tensile strength of the tablet matrix, facilitating its swelling, and thus modulating the drug release rate. A similar effect was observed by Szuts *et al.* [54], who compared the impact of sucrose palmitate and stearate on the release of paracetamol from hard gelatine capsules. Besides their release control effect, sucrose esters can reduce ejection force during the tableting process or increase tablet hardness, depending on their HLB. Their gelling behavior, which depends on sucrose ester structures, can

control drug release kinetics from thermosensitive drug delivery systems for topical and transdermal applications. Interestingly, transdermal therapeutic systems describing zero-order kinetics could be obtained with adequate formulations [55].

3.2 Biosurfactants

3.2.1 General aspects

Biosurfactants are bio-based amphiphiles produced by microorganisms. Such surfactants are structurally diverse, depending on the producing microorganism and the resource used in fermentation conditions. Thanks to their natural origin, their biodegradability and their low toxicity, these surfactants are of particular interest for pharmaceutic and cosmetic applications. The most classical structures are lipopeptides, phospholipids, fatty acids, polymeric compounds and glycolipids. Among the last category, the most described and used compounds are mannosylerythritol lipids, sophorolipids, rhamnolipids and trehalose-conjugated lipids (**Figure 3**) [56,57].

Mannosylerythritol lipids (MEL) are essentially produced by *Pseudozyma* sp. (*P. antartica, P. aphidis*) and, to a minor extent, by *Ustialgo* sp. MELs have been characterized as a mixture of partially acylated 4-*O*-β-D-mannopyranosyl-*meso*-D-erythriol derivatives containing saturated and unsaturated fatty acid chains from C2:0 to C18:0 and from C10:1 to C18:1, respectively. Depending on the degree of acetylation at the C4 and C6 positions, MEL-A is the diacetylated compound, MEL-B and MEL-C are monoacetylated at C6 and C4, respectively, whereas MEL-D is completely deacetylated [58].

Sophorolipids are obtained from *Candida* species, essentially *C. apicola, bombicola* and *batistae,* from *Wickerhamiella domericquae*, or from *Cryptococcus curvatus.* These compounds are mixtures of 2-*O*-β-D-glucopyranosyl-D-glucopyranose derivatives acetylated at the 6′ and/or 6″ positions while the carboxylic terminal residue is either a free acid or an acid esterified into a lactonic form at the 4″, 6′, or 6″ positions [59].

The rhamnolipids class comprises the monorhamnolipids and dirhamnolipids. The lipophilic part of these glycolipids consists of hydroxyl fatty acids of varying chain lengths from 8 to 14 carbons, in which β-hydroxydecanoic acid is predominant. The major rhamnolipid producers are *Pseudomonas* sp., especially *P. aeruginosa* (ATCC 10145, 47T2 or UG2). Owing to their lower production costs at the industrial scale, rhamnolipids are the best-known and used biosurfactants [60].

Finally, the trehalose-conjugated lipids, containing or not succinoyl residues, are produced by *Rhodoccus* sp., especially *R. erythropolis, R. opacus* and *R. ruber.* Trehalose is a non-reducing disaccharide in which glucose moieties are linked by an α,α-1,1-glycosidic bond. Among the various hydrophobic chains that may be attached to this sugar, some saturated fatty acids (16 – 19 carbons) and α-methyl branched fatty acids are described. In some cases, two mycolic acids are grafted, for example in the cord factor of *Mycobacterium tuberculosis*, whereas it is succinic acid in trehalose-lipid derivatives produced by *R. erythropolis* [61].

3.2.2 Applications of glycolipid-based biosurfactants

Additionally to their antioxidant, antimicrobial and antiviral activities, macrophage-activating, cell-differentiation or fibrinolytic effects [62,63], sugar-based biosurfactants are used in the field of drug delivery. In general, they show good detergency, emulsifying, foaming and dispersing properties. For example, MEL-A has shown a much higher emulsifying activity with soybean oil and tetradecane than polysorbate 80 [56], and an interesting ability to form stable water-in-oil microemulsions without addition of co-surfactant or salt [64]. Sophorolipids are better solubilizers than emulsifiers, but their derivatives containing propylene glycol have excellent hygroscopic properties and are applied as moisturizer or softener in cosmetics. Rhamnolipids and sophorolipids can be mixed with lecithins to prepare biocompatible microemulsions in which the phase behavior is almost insensitive to changes in temperature and electrolyte concentration [65]. Biosurfactants have also been used in more innovative formulations such as liposomes. In 1988, rhamnolipid liposomes were patented as drug delivery systems. More recently, mannosylerythritol lipids were used for gene delivery. Indeed, MEL-A could form thermodynamically stable vesicles when mixed with phosphatidylcholine-containing phospholipids [66]. In water, it self-assembled into a sponge-like structure, which induced curvature in phospholipid lamellar organization. This caused an asymmetric distribution of the two lipids and formation of stable liposomes. MEL-A-containing vesicles dramatically increased transfection efficacy of cationic liposomes, leading to significantly higher levels of gene expression compared with lipid cationic-containing commercially available kits [67,68]. Two mechanisms may explain this synergistic effect: MEL-A might accelerate the fusion between DNA–liposome complexes and plasma membrane, or the dissociation of the therapeutic gene from the complexes by a destabilizing effect on endosome membranes (fusion) in the endocytotic pathway [69,70].

At present, microbial surfactants are still not competitive with synthetic sugar-based surfactants owing to their large production costs and relatively low yields. Perspectives for improving their production processes include the use of recombinant varieties of microorganisms or selected hyperproducing mutants, which can grow on a wide range of cheap substrates [71].

3.3 Neoglycolipids for innovative self-assembled drug delivery vehicles

As already evoked for microemulsions and niosomes, glycolipids self-organize into complex supramolecular structures as a result of their amphiphilic nature, both in solvent (lyotropic properties) or depending on temperature (thermotropic behavior) [72-75]. Thanks to their lyotropic

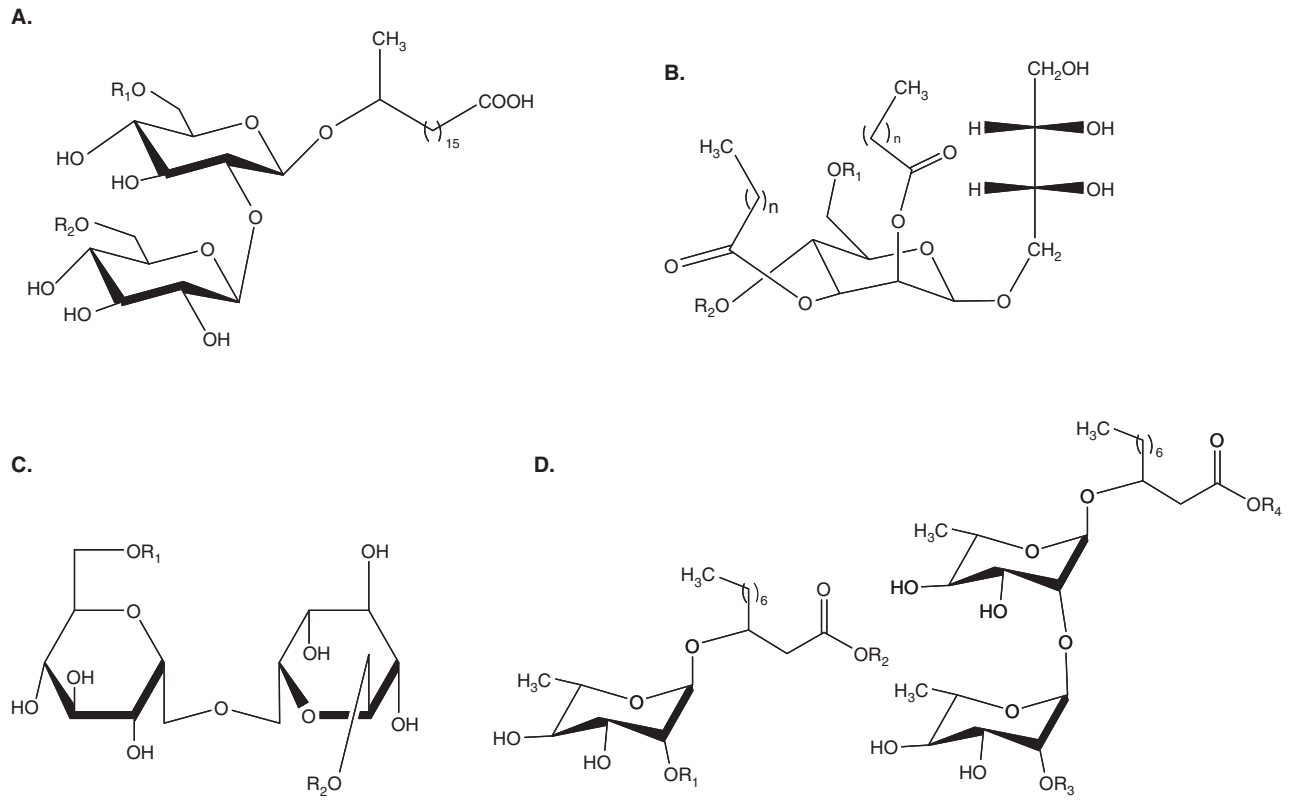

Figure 3. Examples of sugar-based biosurfactant structures. A. Sophorolipid (acid form). **B.** Mannosylerythritol lipid. **C.** Trehalose lipid. **D.** Mono- and dirhamnolipid.

properties, synthetic glycolipids have been specially designed for the preparation of innovative self-assembled drug delivery systems.

3.3.1 *Low-molecular-mass gelators*

Low-molecular-mass gelators are small molecules that can gelify in water and/or organic solvents even at low concentrations (~ 3 – 4 wt%). Sugar-containing gelators are particularly interesting because of their good biocompatibility (**Figure 4A**) [76,77]. Their gelling properties result from a multistage supramolecular organization depending on hierarchical self-assembly from cylindrical primary structures to tridimensional secondary structures. Cui and co-workers carefully investigated the effect of solvent on synthetic 4-(4′-butoxyphenyl)phenyl-β-*O*-D-glucoside [78] and 4″-butoxy-4-hydroxy-*p*-terphenyl-β-D-glucoside [79]. Interestingly, these compounds were able to form gels with large classes of solvents. A different aggregation mechanism was suggested depending on the polarity of the solvent. A combination of hydrogen-bonding interaction between sugar moieties, hydrophobic interaction between lipophilic parts and π–π stacking of aromatic rings would give rise to one-dimensional alignment of gelling molecules. In water, sugar heads would be exposed outside whereas biphenyl groups would be shielded in the core of the aggregates and the butoxy tails interdigitated. In apolar solvent, hydrogen bonding would drive sugar heads' aggregation and butoxy tails would be exposed to the organic medium. John *et al.* showed that, with the number and position of double-bonds, π–π interaction between aromatic rings was involved in the stabilization of nanoassemblies [80]. In their study of monosaccharidic derivatives of 1-*O*-methyl-4,6-*O*-benzylidene, Gronwald and Shinkai observed that the nature of the sugar headgroup affected the gelling properties; the mannoside and galactoside were more efficient than the glucoside [81]. Similar gelling studies have been performed with disaccharide structures bearing one or two alkyl tails [82]. Glycolipid-based gels have been used with API such as plasmid DNA [83]. After inclusion in the gel, DNA showed strong resistance against enzymatic degradation and some data suggested that controlled release could be achieved.

3.3.2 *Cubosomes/hexosomes*

Nanostructured aqueous dispersions are spontaneously self-assembled objects, candidates for delivering active pharmaceutical ingredients (conventional drug, peptides, proteins, etc.) [84]. The fully hydrated bilayers of the amphiphile of interest create a thermodynamically stable network that separates water

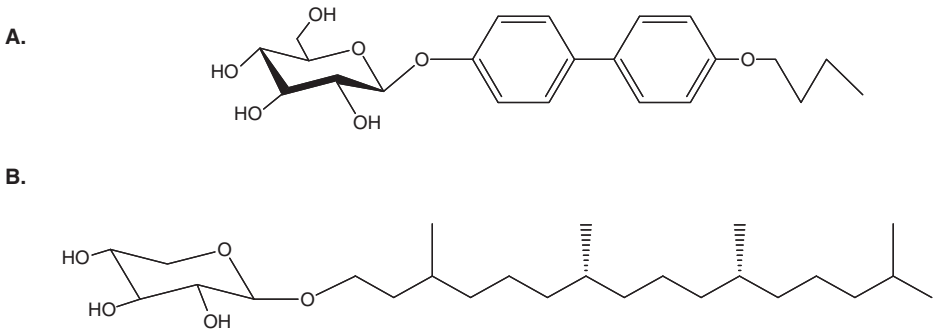

Figure 4. Examples of synthetic glycolipid structures interesting for their lyotropic behavior. A. 4-(4′-butoxyphenyl)phenyl-β-*O*-D-glucoside. **B.** 1-*O*-phytanyl-β-D-xyloside.

channels having pore diameters in the range of a few nanometers. The driving force of these supramolecular organizations is the curvature elasticity and packing frustration of the constitutive compounds. The most important phases in this field are the inverted hexagonal phase (H_2 space group) and the reversed bicontinuous cubic phases ($Pn3m/Q^{224}$ or $Im3m/Q^{229}$) leading to nanostructured aqueous dispersions named hexosome and cubosome, respectively. The main characteristic of these dispersions is their consequent interfacial area, a few hundreds of square meters per gram, allowing the solubilization of large amounts of amphiphilic components as well as hydrophilic or hydrophobic active molecules. Conventional drugs such as indomethacin, cyclosporin A and irrinotecan [85], but also proteins such as insulin, have been loaded in these nanocarriers with certain success. The lipid matrix is generally formed of glyceryl monoleate or phospholipid, stabilized by PEO-PPO-PEO triblock copolymer or polysorbate 80.

Some glycolipids are able to generate inverted hexagonal and reversed bicontinuous cubic phases depending on their hydration. Abraham and co-workers [86,87] investigated this property on 1-*O*-phytanyl-β-D-xyloside (**Figure 4B**). Owing to the large volume of its hydrophobic chain and its small headgroup area, this glycolipid has a critical packing parameter > 1. Furthermore, it has been reported that it is able to form a Pn3m cubic phase in an excess aqueous medium. The difficulty was stabilizing this phase in a dispersed state, using a PEO-PPO-PEO triblock copolymer, in order to obtain bicontinuous cubic nanoparticles.

Several methods have been proposed for the preparation of glycolipid-based cubosomes. Following a classical procedure, a 60:40 β-XP-to-water weight ratio mixture was mixed with the copolymer (5.1 wt%) and stirred in a glass vessel, producing a milky dispersion. After 3 h continuous stirring, particles of size ranging from 200 nm to 6.0 µm were observed, with a mean diameter ~ 1.4 µm [86]. To favor the interaction between the polymer and the glycolipid and improve particle size and distribution, the two compounds were dissolved and premixed in acetone. The solution obtained was then dried by evaporation under vacuum and the resulting binary mixture was hydrated. After a 6 – 12 stirring period, the mean particle diameter reached 650 nm and the size distribution was in the range 100 nm – 1.9 µm [86]. The same group proposed another method in which an aqueous mixture of mixed micelles containing β-XP (2.8 wt%), β-octylglucoside and Pluronic F127 (10.1%) was dialyzed in a cellulose membrane tube against a large volume of water (1:700 ratio) at room temperature [87]. At the end of the 4-day dialysis, octylglucoside was removed and sterically stabilized cubic nanoparticles were obtained. As expected, the indexation of small-angle X-ray diffraction patterns confirmed the cubic Pn3m phase and showed unit cell sizes, a, ~ 9.2 nm. The particles had a size ranging from 170 nm to 3.3 µm with a mean volume diameter of 850 nm. Interestingly, whatever the process used these nanostructured aqueous dispersions were stable for several months at room temperature and showed good stability after dilution in salt solutions. Owing to their lyotropic behavior, mannosylerytritol biosurfactants were also considered as good candidates for the formulation of such self-assembled drug carriers [88].

4. Glycolipids as bioadhesive and drug-targeting agents

Glycolipids have been also considered as ligands for targeted drug delivery. They have been used extensively to modify the surface properties of colloids such as liposomes, niosomes or lipid nanoparticles in order to favor interactions with specific cells and tissues.

4.1 Animal lectins

4.1.1 General overview

Among the dozens of structural families of animal lectins, the most important one is the 'C-type' (**Table 1**). The common features of the C-type lectin superfamily are the presence of one or more C-type lectin-like domains and the coordination bonds with a conserved Ca^{2+} [89]. The asialoglycoprotein receptor, the first lectin identified in animals, belongs to this superfamily [90].

Table 1. Name, localizations and targets of the most potentially important animal lectins.

Names	Localization	Targeted carbohydrates
C-type lectin		
Mannose receptor	Macrophages, lymphatic and hepatic epithelium, kidney mesangial cells, tracheal smooth muscle cells	Mannose, fucose, *N*-acetylglucosamine
Asialoglycoprotein receptor	Hepatocytes	β-galactose, *N*-acetylgalactosamine
Selectins		
E-selectin (CD62E, ELAM-1, LECAM-2, etc.)	Endothelial cells, leukocytes	Sialyl Lewis x, sialyl Lewis a
L-selectin (CD62L, LAM-1, Mel14-Ag, Leu-8, gp90^{mel}, LECAM-1, etc.)	Leukocytes, circulating lymphocytes monocytes, granulocytes, B cells, T cells	Sialyl Lewis x, sialyl-sulfo-Lewis x
P-selectin (CD62P, LECAM-3, GMP-140, PADGEM, etc.)	Platelets (α-granules), endothelial cells	Sialyl Lewis x, sialyl-sulfo-Lewis x
Collectins		
Dectin-I	Macrophages, splenic T cells, dendritic cells, monocytes, neutrophils	β-Glucan
DC-SIGN	Immature dendritic cells, endothelium, macrophages	Mannose, ICAM-3
Mannan-binding lectin (MBL)	Serum	Mannose, glucose, L-fucose, ManNAc, GlcNAc
Surfactant Prot. A (SP-A)	Lung epithelium, prostate, thymus, intestinal mucosa, paranasal sinuses	Glucose, mannose, *N*-acetylmannosamine, L-fucose
Surfactant Prot. D (SP-D)	Lung and gastrointestinal epithelium	Glucose, mannose, maltose, inosito
Collectin Liver L1	Most tissues	Mannose
Galectins (S-type) Prototypal Gal. (1, 2, 5, 7, 10-types)	Gastrointestinal tract, skeletal and smooth muscles, motor and sensory neurons, keratinocytes	β-Galactose, *N*-acetyllactosamine, GlcNAc, *N*-glycans
Tandem Gal. (4, 6, 8, 9, 12-types)	Intestinal epithelium, lung, liver, kidney, cardiac muscle	
Chimeric Gal. (type 3)	Activated macrophages, respiratory tract, sensory neurons	
Siglecs (I-type) (Sialoadhesin, CD22, CD33, MAG, OB-BP1, AIRM1, etc.)	Macrophages, granulocytes, B cells, monocytes, NK cells, Schwann cells, myeloid precursors	Sialic acid
Fibrinogen-like *Ficolins*		
H-ficolin	Hepatocytes, bile epithelium, type II alveolar cells, ciliated bronchial epithelial cells	GlcNAc, GalNAc, glucose
L-ficolin	Liver	GlcNAc
M-ficolin	Uterus, monocytes	GlcNAc

This receptor, expressed at the surface of hepatocytes, plays an important role in the clearance of desialylated proteins by endocytosis and lysosomal degradation [7]. A mannose receptor (ManR) expressed on macrophages, epithelial and endothelial cells acts as a scavenger from macromolecules (glycoproteins) to pathogenic microorganisms [91]. Collectins are important mediators in nonspecific innate immune responses to pathogens. By binding surface carbohydrate of pathogens, they modify the interaction between pathogens and the immune system, leading to complement activation, phagocytosis or cytokine production [92]. Selectins are transmembrane or soluble proteins that bind to sialylated carbohydrate moieties [93,94]. Depending on the cells in which their genes were initially identified, platelets, endothelium or lymphocytes, P-, E- or L-selectins have been described, respectively. The physiological roles of these glycoproteins are numerous, including neutrophil and monocyte adhesion and rolling over activated endothelium during acute inflammation.

Galectins are sulfhydryl-dependent (S-type) lectins that essentially recognize β-galactose [95]. They are classified into three types: prototypal with two identical binding regions, tandem with two distinct binding domains, or chimeric with only one binding domain. Galectins are widely distributed in animals and have many functions in chronic inflammations, allergic reactions or cell growth regulation.

Ficolins possess a different type of lectin domain, called 'fibrinogen-like', which binds to *N*-acetylglucosamine-bearing containing surfaces in a calcium-independent manner. Ficolin serum types bind to microorganisms and enhance phagocytosis by polynuclear neutrophils and monocytes. In addition to this opsonic activity, they can also activate complement [92].

Lectins are altered in many pathologic situations and overexpressed in some diseases, suggesting them as targets in therapeutics. For example, many epithelial tumors such as colon, thyroid and breast carcinomas express galectin-1, and its overexpression by the tumor is positively correlated with a metastatic phenotype [96]. Neoplasic progression has been correlated with increases in galectin-3 expression in malignancies of neck, head, gastric, thyroid and central nervous system tumors [97]. Galectin-2, -4 and -9 were observed in neural tumor cell lines, and associated with galectin-9 in colorectal tumor cell lines. Selectins, both in soluble or transmembrane form, are also involved in numerous diseases [91,97,98]. Increases in soluble selectin serum levels are observed during acute ischemic stroke, infections (HIV, Plasmodium falciparum, etc.), meningeal leukemia or multiple sclerosis. B-cell chronic lymphocytic leukemia, hairy cell leukemia and mantle zone lymphoma are L-selectin positive. L-selectin can facilitate homing of disseminated tumor cells, resulting in metastasis [94].

4.1.2 *Applications of glycolipids in animal lectin targeting*

Since the 1980s, many studies have been published on glycosylated carriers [99,100]. Only the most significant trends obtained with glycolipid containing formulations are summarized herein.

Mannosylated or galactosylated cholesterol derivatives have been investigated extensively as transfection enhancers for DNA delivery [101]. In a mixture with dioleylphosphatidylethanolamine (DOPE), the mannose-containing derivatives have increased gene expression, due to sugar recognition by the mannose receptor, both *in vitro* and *in vivo* after intraportal injection [102]. A similar implication of ManR has been observed with the same mixture in the presence of alveolar macrophages [103] or after intravenous administration of mannosylated emulsions [104]. The efficacy of all these formulations was strongly reduced by the co-administration of a binding competitor such as Man-BSA or mannan. Similar results on plasmid transfer have been reported with galactosylated liposomes, which were recognized by the asialoglycoprotein receptor instead of ManR [105-108]. More recently, this receptor has been targeted by galactosylated solid lipid nanoparticles [109]. In a systematic comparison, Kawakami and co-workers have shown that owing to the receptor's distribution, galactosylated and mannosylated liposomes were taken up by the parenchymal and non-parenchymal liver cells, respectively [105].

As mentioned previously, the cells of the mononuclear phagocyte system (MPS) are rich in lectin-like receptors able to recognize sugar-conjugated ligands. This property can be taken advantage of to increase the efficacy of anti-HIV or anti-*Leishmania* treatments, by using mannosylated liposomes able to target the MPS, the main reservoir of these pathogens. *O*-palmitoylmannose was synthesized and mixed with stavudine-loaded uncoated liposomes prepared by the reverse-phase evaporation method [110]. Stavudine has a short half-life (0.9 – 1.2 h), and long-term administration results in adverse side effects such as dose-limiting peripheral neuropathy or anemia. Following intravenous administration through the caudal vein of rats, the elimination half-times of liposome-encapsulated stavudine were increased and distribution profiles in favor of MPS were observed with mannosylated vesicles, compared with uncoated formulations. Owing to the site-specific delivery, the dose of the antiviral agent could be reduced, thus limiting its toxicity. More recently, galactosylated liposomes were developed for the same application [111,112]. These formulations maintained a significant level of stavudine in tissues rich in galactose-specific receptors, enhanced the half-life of the drug and its hepatic cellular uptake, and reduced its hematological toxicity. Furthermore, a dose-dependent inhibition of p24 production was observed on treatment on HIV-1 infected MT2 cell line. Loaded with zidovudine, mannosylated liposomes appeared to be a promising vesicular system for enhanced targeting of this drug to lymphatics in AIDS chemotherapy [113]. They also gave interesting results when containing an antibiotic against *Leishmania donovani.* Compared with the free drug or with non-glycosylated vesicles, mannosylated liposomes could eliminate efficiently intracellular amastigotes within splenic macrophages with low toxicities on kidney or liver functions [114].

Selectins have also been targeted by glycolipid containing formulations. 3-Amino-propyl glycoside of siaLex was used as selectin ligand for merphalan targeting. The results of the tumorigenesis data in mouse have shown that the therapeutic efficacy of the drug increased sharply after its association with sialex liposomes [115]. More recently, doxorubicin-loaded liposomes, decorated with sialyl Lewis x moieties, have led to interesting results to prevent stenosis after angioplasty [116]. The efficacy of these formulations has been attributed to their recognition by E-selectins, which are expressed on injured vessel walls. The selectin recognition has also been used to justify the development of 3′-sulfo-Lewis a-coated vesicles recognizing activated platelets [117], or cisplatin containing glycosylated liposomes [118].

After intravenous injection, it is well known that stealth liposomes circulate in the blood for longer than ordinary liposomes. Zeisig *et al.* [119] have compared the effect of liposome compositions on the inhibition of E-selectin-mediated tumor cell adhesion. Sterically stabilized liposomes with a sialyl Lewis x moiety grafted at the end of the polyethyleneglycol chains, as well as vesicles with the ligand embedded within the PEG layer, were compared with glycosylated liposomes without a PEG crown. The former were the most effective inhibitors of the adhesion of HT29 colon and Lewis lung carcinoma cells on immobilized E-selectin, on CHO cells expressing E-selectin, and on human umbilical vein endothelial cells. These results suggest that the polymer coating did not affect the binding, whereas it completely prevented macrophage uptake compared with uncoated vesicles.

4.2 Adhesins from microorganisms

4.2.1 General overview

In many situations, glycoconjugated derivatives, such as glycoproteins or glycolipids, serve as receptors for microorganisms [91,120,121]. Pathogens use these interactions to initiate adhesion and/or infection. Some examples of microorganism/targeted carbohydrate couples are given in **Table 2**.

Escherichia coli are normal residents of the intestinal flora. However, in some circumstances these bacteria are responsible for diarrhea, sepsis, urinary tract infections and, in the worse cases, newborn meningitis. The binding proteins involved in carbohydrate recognition are named fimbriae and classified according to their specificities. The type 1 includes strains specific for mannose whereas the type S is specific for NeuAcα2-3Galβ1-3Nac and the type P for galabiose (Galα1-4Gal). For example, the interaction between the last oligosaccharide and uropathogenic *E. coli* strains leads to the colonization of the upper urinary tract and pyelonephritis; mannose recognition allows binding to the bladder epithelium [122].

Among other structures, the genital pathogen *Neisseria gonorrhea* specifically binds *N*-acetyllactosamine (Lac*N*Ac). The sequence GalNAcβ1-4Gal is the minimal adhesion moiety of many pathogens, such as *P. aeruginosa, Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumoniae* and *Klebsiella pneumoniae.* This sequence was shown to be present in lung tissue as part of asialo-GM1 and even in higher abundance on cystic fibrosis-affected lung epithelia. This explains the particular pulmonary tropism of the previous microorganisms, especially in cystic fibrosis-infected patients [121].

It is well known that stomachal infections with *Helicobacter pylori*, which have a worldwide prevalence of 50%, lead to chronic inflammation, gastric ulcers and mucosa-associated cancers. The pathogenicity of *H. pylori* depends on several factors, one of them being the adherence to the epithelium gastric by means of multiple adhesins (at least 18) [123-127]. Among the large variety of adhesins, at least two of them, BabA2 and SabA, are outer membrane proteins able to bind to fucosylated oligosaccharides such as the ABO and Lewis b [Leb] antigens and α-2,3-linked *N*-acetyl neuraminic acid containing oligosaccharides such as sialyl Lewis x [sLex] and sialylated Lewis a [sLea] antigens, respectively. These antigens promote infection and inflammatory processes in the gastroduodenal tract [128-130]. It is known that acute and chronic tissue inflammations induce expression of sialyl Lewis x structures, which are used by bacteria to increase their interaction with the gastric epithelium. Furthermore, these two binding proteins have been associated with virulent *H. pylori* strains in several works, confirming their potential role in the pathogenicity of the bacteria.

As with bacteria, cell wall adhesins play a decisive role in fungal virulence, mediating the interaction with host cells [131]. Fungal pathogens as *Candida* sp. are frequent causes for nosocomial infections. These yeasts express several adhesins able to recognize carbohydrate-based ligands. In the special case of *C. galabrata*, the adhesin responsible for the adherence to human epithelial cells is a cell wall protein, which binds to asialo-lactosyl-containing carbohydrates.

4.2.2 Applications

To eradicate *H. pylori*, further approaches are conceivable [132]. One possible option consists of acting against the bacterial adherence, avoiding the chronic infection by *H. pylori.* To get the best efficiency, it would be necessary to treat before the first symptoms and to inactivate as many adhesins as possible, which is in fact very difficult to do. A more realistic alternative consists of using drug-containing particles targeted to *H. pylori* through its membrane adhesins. Several works have been done with carbohydrate-decorated formulations and at least one of them deals with glycolipids. Fucosides of cholesteryl oligoethyleneglycols have been incorporated in PC bilayers [133]. The interaction between the bacteria and liposomes was confirmed by their co-localization and/or aggregation during *in vitro* epifluorescence measurements. The vesicles and the bacteria were labeled with NBD-PC and DAPI, respectively. The most important aggregation was observed for liposomes containing 10% of fucosyled glycolipids in the presence of CCUG 17875 *H. pylori* strain, which expressed the *BabA2* adhesin gene. On the contrary, the aggregation of 149C strain, which did not express *BabA2,* seemed less clear and the superimposition of the two fluorescent dyes was not observable on two *E. coli* and three *Staphylococcus* strains [134]. Further studies have shown that the incorporation of such glycolipids in phospholipid bilayers increased their fluidity in the gel phase, which in turn increased proton permeability [135]. This last point is noteworthy for application in a strongly acid medium, as is the case here.

Biofilms are thin layers of microorganisms adhering to biomaterials or biological surfaces. Bacteria, from a single species or a mixture, aggregate in a hydrated polymeric matrix of their own synthesis. From a medical point of view, the formation of these sessile communities and their inherent

Table 2. List of the most important lectins from microorganisms.

Microorganisms	Targeted carbohydrates
Fungi	
Fonsecaea pedrosoi	Man; GlcNAc
Aspergillus fumigatus	Sialic acid
Kluyveromyces bulgaricus	Gal
Beauveria bassiana	Galβ1-4Glc; Galβ1-3GalNAc
Saccharomyces cerevisiae	Man, $(Man)_3$
Candida glabrata	Asialo-lactosyl carbohydrates
Virus	
Influenza B virus (human)	
H3 subtype	Neu5Acα2-3Gal
HI subtype	Neu5Acα2-6Gal-4GlcNAc
Influenza A virus (avian)	Neu5Acα2-3Gal
Bacteria	
Actinomyces naeslundii	Galβ3GalNAc
Campylobacter jejuni	Fucα2GalβGlcNAc
Escherichia coli	LacNAc, Galα1-4Galβ1-4Glc
Type 1	Man
Type S	NeuAcα2-3Galβ1-3Nac, GM1
Type P	Galα1-4Gal
K99	NeuAc(a2-3)Galβ4Glc
K1	GlcNAcβ4GlcNAc
F17	GlcNAc
F1C	GalNAcβ1-4Gal
Enterobacter cloacae	Man-GlcNAc
Streptococcus	
S. pneumonia	NeuAcα3Galβ4GlcNAcβ3Galβ4Glc Galβ4GlcNAcβ3Galβ4Glc
S. gordonii	GlcNAcβ3Galβ4Glc Sialic acid
S. suis	Galα1-4Gal, Neu5Acα2-3Gal
Pseudomonas aeruginosa	Galβ3GlcNAcβ3Galβ4Glc L-Fuc
Klebsiella pneumoniae	Man
Staphylococcus saprophyticus	Galβ4GlcNAc
Vibrio cholerae	Galβ1-3GalNAcβ1-4(NeuAcα2-3)Galβ4Glc
Helicobacter pylori	Lewis b, sialic acid, sialyl Lewis x Neu5Acα2,3Galβ1,4Glc
Neisseria gonorrhea	LacNAc, Galβ4GlcNAc, NeuAcα3Galβ4GlcNAc

resistance to antimicrobial agents are at the root of many persistent and chronic bacterial infections. Drug delivery and targeting to bacterial biofilms have recently received much attention. Among several strategies, Vyas *et al.* [136] developed antibacterial drug (metronidazole)-loaded mannosylated liposomes containing different mannan derivatives, namely cholesteryl mannan (CHM) and sialo-mannan (SM). The targeting efficiency in terms of percentage bacterial (*S. aureus*) growth inhibition of both *in vitro* and *in vivo* bacterial biofilms was investigated. During *in vitro* microtiter plate experiments, at 90% of the MIC, biofilm growth inhibition was 98 and 86% with SM- and CHM-anchored liposomes and only 70% with uncoated liposomes. Viable counts of bacteria in a rat pouch-induced biofilm *in vivo* model showed that plain liposomes induced a 1-log reduction only, whereas SM-decorated ones showed the maximum effectiveness with a 3-log reduction. The efficacy of the CHM liposomes was intermediate. The enhancement of the antimicrobial activity observed with sugar-coated liposomes was attributed to their ability to adhere or fuse with the bacterial biofilm. Such interaction would allow: i) a subsequent release of the drug in the environment of the target; and ii) persistence of the active molecule at the site of action.

5. Conclusion

Glycolipids are amphiphilic molecules self-assembling into micelles, gels and other supramolecular structures such as niosomes, cubosomes and hexosomes. As such, they offer a wide range of applications in the pharmaceutical and cosmetic fields and can compete with the most commonly used surfactants. Glycolipids may be synthesized *de novo* or produced by biotechnologies. They exist in nature and are involved in molecular recognition mechanisms at the surface of cells. This property has been taken advantage of for drug targeting. The analysis of the literature shows that, although there is an enormous potential, the complexity of protein–carbohydrate interactions, and the role of the glycolipid structure and microenvironment still limit the development of efficient marketable drug delivery systems based on these compounds.

6. Expert opinion

More than 10 million tons of surfactants are produced yearly in the world for various applications in the fields of textiles, plastics, paper, food, cosmetics and pharmaceutics. Besides the permanent objective of finding ways to minimize production costs for the existing compounds, the market and consumers' pull for green products has been the driving force for new surfactant development in the last few years. Glycolipids possess several advantages regarding the current interest in the ecological impact of surfactants.

Depending on their lipid chain length, the presence and nature of a spacer, and the number of their sugar moieties, glycolipids' polarity and surface properties may vary significantly. They thus offer a large range of molecules for various applications that have interesting properties compared with non-ionic surfactants bearing poly(ethylene oxide) chains. Indeed, their saccharide moieties do not undergo dehydration with increasing temperature, allowing water solubility over a wide temperature interval. Perfectly fitting the 'green constrains', the biosurfactants produced by microorganisms

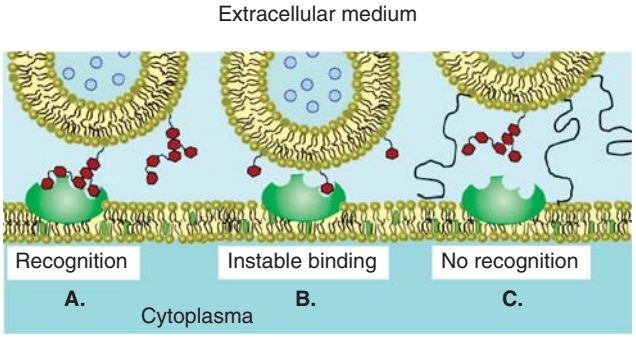

Figure 5. Interaction of a glycoconjugated drug delivery system with a carbohydrate receptor at the surface of cells. A. The glycolipid saccharidic structure fits the multivalent binding site. **B.** Insufficient attachment resulting in instable binding. **C.** Presence of polymer chains hindering carbohydrate–protein binding.

seem to be very promising molecules. Indeed, their detergency, emulsifying, foaming and dispersing properties make them competitive in a wide range of pharmaceutical and cosmetic applications, such as foam, emulsion or suspension formulations.

The role of glycolipids in more innovative formulations, such as cubosomes or hexosomes, must be underlined. The development of these self-assembled structures as drug carriers is relatively new and expanding. Few molecules have been investigated for this application and it seems necessary to find alternative molecules to the monoacylglycerol-type compounds, which have essentially been tried. If some glycolipids have already shown their potential in this field, efforts must be pursued to enlarge the panel of solutions.

Targeting by nanotechnologies is a great challenge of the research on innovative drug delivery systems. The carbohydrate-binding proteins, which can be specific to some tissues, cells or pathologies, have great potential as biological targets. Glycolipids designed for this purpose should, however, possess some general features allowing stable binding to the proteins, such as specificity, accessibility and affinity (**Figure 5**). Each sugar group should be as mobile as possible to increase the odds of interacting with the target protein. This has been the object of many early works and it is well known now that incorporation of a spacer of adequate length between the lipid anchor and the sugar improves sugar freedom. The choice of the length and hydrophobic/hydrophilic character of the spacer, however, must be adapted for each lectin-glycoconjugated drug delivery system.

Affinity of a monovalent sugar for a lectin is generally weak. In nature, the weakness of the affinity between microbial lectins or selectins and carbohydrate is compensated by multivalency, which enhances binding stability. In general, affinities in the millimolar range are observed for lectin binding to monosaccharides, whereas the micromolar range could be reached with oligosaccharides. This implies that to increase the effectiveness of ligands decorating the drug carriers, the synthesized saccharidic structures should be complex, exposing, if necessary, several saccharide moieties to the binding site. If the accessibility has been improved by the development of structures having a small spacer between the sugar and the lipid anchor, the production of an oligosaccharidic headgroup has yet to be ameliorated. This is the difficult part. The more complex the structures are, the longer the synthesis and purification steps are, and the less easy the chemical characterization. Many works are in progress in an attempt to reduce the number of synthesis steps by using bacterial enzymes, and to increase the reaction yield and production volumes. Eventually, a reflection should be led on the lipophilic anchor balancing the hydrophilicity of a headgroup owing to the presence of the spacer and oligosaccharide. Very often, researchers consider the glycolipid headgroup only, with or without a spacer. The hydrophobic anchor is neglected, as it represents just the hook to the drug delivery device. Careful analysis of glycolipids in their natural context (the biological membrane) shows that the efficiency of sugar–protein recognition processes relies on the overall structure of the glycolipids, including that of the hydrophobic anchor.

Building a drug delivery device intended to favor glycolipid–lectin interactions is a difficult task and necessitates the consideration of many parameters with a biomimetic approach. Fortunately, nature provides many examples, which are the basis for very active and promising research.

Acknowledgment

The authors thank A Makky for the schematic representation of the glycolipids.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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