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Alkyl-mannoside derivatives: Glycolipids able to form big size aggregates

C. Sandoval-Altamirano[1] | S.A. Sanchez[2] | N. Pizarro[3] | J. Morales[4] | G. Gunther[1]

[1]Departamento de Química Orgánica y Fisicoquímica, Universidad de Chile, Facultad de Ciencias Químicas y Farmacéuticas, Santiago 1, Chile

[2]Departamento de Polímeros, Universidad de Concepción, Facultad de Química, Concepción, Chile

[3]Departamento de Ciencias Químicas, Universidad Andrés Bello, Facultad de Ciencias Exactas, Viña del Mar, Chile

[4]Departamento de Ciencias y Tecnología Farmacéuticas, Universidad de Chile, Facultad de Ciencias Químicas y Farmacéuticas, Santiago, Chile

Correspondence
G. Gunther, Universidad de Chile, Facultad de Ciencias Químicas y Farmacéuticas, Departamento de Química Orgánica y Fisicoquímica, Casilla 233, Santiago 1, Chile.
Email: ggunther@ciq.uchile.cl

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Abstract

Three different series of alkyl mannoside derivatives have been synthesized, designing the hydrophobic portion to provide different topology to the surfactant and, hence, modulating their aggregation properties. The aggregates formed were characterized using both physical and photophysical methodologies, such as surface tension, dynamic light scattering, and emission of selected fluorescent probes. The non-ionic sugar surfactants have been widely used in studies of membrane solubilization and protein purification. Indeed, mannoside unit, nonionic and hydrophilic, can be selectively recognized by several lectins, which are proteins present in different membranes. Then, the specific interactions of these derivatives incorporated into synthetic bilayers with lectins have been studied and reported. In this work, monoalkyl derivatives with a presumably conical shape and dialkyl derivatives with cylindrical ones, including also a third family with a hydrophilic spacer were studied. These compounds are able to self-aggregate to form micelle like structures or bilayers despite their topology. Additionally, they are able to form bilayers, using cosurfactants like cholesterol.

KEYWORDS

aggregation, alkyl mannoside, micelles, vesicles

1 | INTRODUCTION

Glycolipids are surface active biomolecules composed of a lipid chain (lipophilic) and a monosaccharide or oligosaccharide as hydrophilic group. They are generally non-toxic, easily degradable, with adequate solubility in water and organic solvents.[1] The most common glycolipids contain galactose, mannose, fucose, glucose, glucosamine, galactosamine, or sialic acid as hydrophilic groups.[2] Besides their biological role, their chemical structures make them good candidates for a large and continuously growing number of biotechnological applications such as thermotropic and lyotropic liquid crystals,[3,4] surfactants,[5] lubricants,[1] cosmetics,[6,7] and membrane solubilizing agents.[8–10]

Glycolipids amphiphilic nature allows them to spontaneously aggregate and arrange in structures like micelles,[11] whose capacity to form bilayers and/or vesicles has been also reported.[12] In particular, the aggregation behavior of glycolipids like alkyl polyglycosides, sorbitan esters, and sucrose esters can be found in literature.[13–17]

Because mannoside derivatives can be selectively recognized by several lectins, they could be used in the fabrication of targetable vehicles. In fact, these compounds as monomers were incorporated into synthetic

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liposomes[18,19] or nanotubes.[20,21] Their capability to interact with specific lectins, Concanavalin A (Con A) among them, was demonstrated.[18,19] Mannosides having different structure could modulate the aggregation properties of the targetable vehicle. In this work, a physicochemical characterization of aggregates formed by 3 different families of mannoside derivatives is presented. In these 3 families (see Figure 1), the mannoside is attached to:one alkyl chain (MXM), two alkyl chains with (DXEM) or without (DXM) an ethylene glycol extensor. They were synthetized to provide different topology to the surfactant in order to modulate their aggregation properties.

2 | EXPERIMENTAL SECTION

2.1 | Reagents

1-Octanol, 1-dodecanol, 1-hexadecanol, 1-bromooctane, 1-bromododecane, 1-bromohexadecane BF_3OEt_2, $SnCl_4$ (1 M CH_2Cl_2 solution), 1,6-diphenyl-1,3,5-hexatriene (DPH), glycerol, mannoside, and cholesterol were acquired in Sigma-Aldrich and Laurdan in Molecular Probes. All of them were used without further purification. The mannoside derivatives: *1-octyl-α-D-mannopyranose* ***(MOM)***, *1-dodecyl-α-D-mannopyranose* ***(MLM)***, *1-hexadecyl-α-D-mannopyranose* ***(MPM)***, *1-(2,3-bis(octyl) glycero)-α-D-mannopyranose* ***(DOM)***, *1-(2,3-bis(dodecyl) glycero)-α-D-mannopyranose* ***(DLM)***, *1-(2,3-bis(hexadecyl) glycero)-α-D-mannopyranose* ***(DPM)***, *1-(2-(2,3-bis(octyl) glycero)ethoxy)-α-D-mannopyranose* ***(DOEM)***, *1-(2-(2,3-bis(dodecyl)glycero)ethoxy)-α-D-mannopyranose* ***(DLEM)***, and *1-(2-(2,3-bis(hexadecyl)glycero)ethoxy)-α-D-mannopyranose* ***(DPEM)*** were synthesized as previously described.[22]

Pyrene (Sigma Aldrich) was recrystallized 3 times from methanol; 8-anilino-1-naphthalenesulfonic acid (ANS, Sigma Aldrich) was employed without further purification.

All solvents employed were HPLC quality and water was deionized using a Waters Milli-Q system.

2.2 | Methodology

2.2.1 | Vesicle preparation by ultrasonication

Ultrasonication consists in the application of acoustic energy through a tungsten tip (400 Watts Ultrasonic Homogeneizer, Cole Parmer) or an ultrasonic bath (Liposomicator, Avanti lipids) to a lipid or lipid mixture suspension in water or buffer (Hepes 10 mM pH 7.4 and, 10 mM NaCl, and is widely employed to prepare vesicles. Pressure waves produce unilamellar vesicles with average size below 100 nm when tip is employed[23] and around 200 nm with the ultrasonic bath. When a lipid mixture is required, in order to assure homogeneity, a sample with the appropriate amount of each component is solubilized in a volatile organic solvent (chloroform or methanol) and then evaporated to obtain a homogeneous lipid film. Sample is hydrated with water or buffer and then sonicated.

2.2.2 | Giant vesicle preparation

To obtain unilamellar vesicles with sizes in the micrometric range (GUVs), electroformation method developed by Angelova et al[24] was employed. Two different procedures were selected: (A) GUVs settled on cover slide and (B) GUVs fixed on platinum wire. For both, near

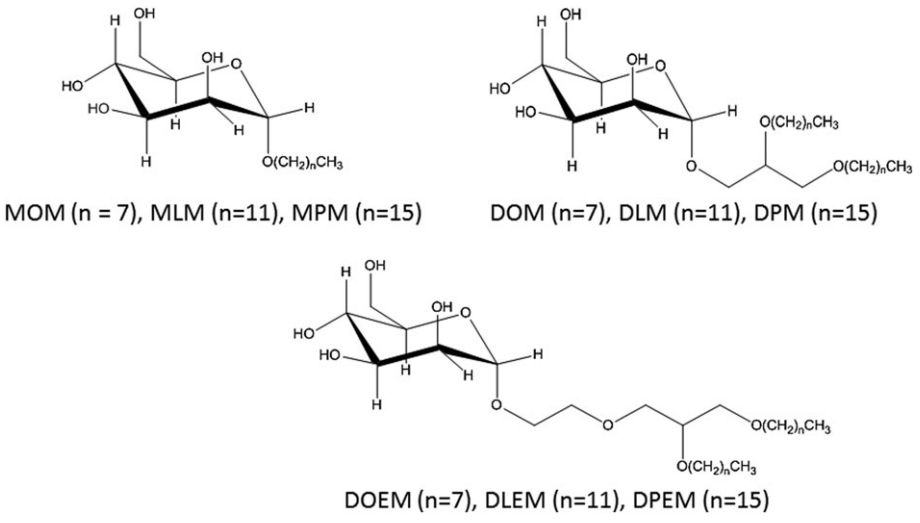

FIGURE 1 Chemical structure of the alkyl mannoside derivatives synthetized

5 μL of a 0.2 mg/mL of lipid solution (pure or mixture) is seeded on platinum wire, and a 100 mM solution of sucrose (case a) or buffer solution (case b) is added at a temperature higher than lipid transition temperature. For 1 hour, keeping temperature constant, a square shaped electric field of 1 Volt and 10 Hz was applied. In case a, to detach GUVs, frequency was reduced to 1 Hz for 15 minutes, then sample is cooled and stored in an Eppendorf. To perform measurements, 50 μL of GUV solution is gently incorporated to an isotonic glucose solution, where denser liposomes sink to the bottom. In case b, sample is just cooled to experiment temperature, and measurements are made "in situ." In Figure 2, Teflon cuvettes employed in both procedures are shown.

Intensity and generalized polarization (GP) images were acquired in a 2-photon microscope (Zeiss Axiovert S100TV) coupled to a Becker and Hick 830 card (Becker and Hickl, Berlin). As excitation source, a Ti:Sapphire laser (Spectra-Physics Mai Tai) with a repetition rate of 80 MHz at 780 nm was used. Fluorescent signal was splitted in 2 channels, each of them with filters of 440/50 nm and 490/50 nm. Data were acquired and treated with SimFCS software developed at Laboratory for Fluorescence Dynamics (www.lfd.uci.edu).

2.2.3 | Steady-state fluorescence measurements

Steady-state fluorescence measurements were performed in a Fluorolog Tau-2 (SPEX, Jobin Ybon), controlled with DMF 300 software and a PC1 (ISS Inc., Champaign, IL), controlled with Vinci software. Aggregates micropolarities were determined with Py scale[25] (pyrene will locate in the hydrophobic core of aggregates). Laurdan GP was employed to stablish water penetration in the structures, because emission of this probe at 490 nm is directly related with its dielectric relaxation.[26–30]

Aggregate microviscosity was determined with fluorescence anisotropy measurements, related with the reorientation of probe dipolar moment during its lifetime. Its magnitude is directly related with the size and shape of the probe (or molecule where probe is attached), and of course, with the restrictions imposed by the fluidity of the microenvironment. Anisotropy of diphenylhexatriene (DPH)[31] has been widely employed to study lipid bilayers in terms of an apparent microviscosity, determined through an empirical scale (constructed with oils of known viscosity).[32] All measurements were performed at controlled temperature, 25.0 ± 0.1°C, with thermoregulated bath Fisons, HAAKE F3, and OMEGAETTE thermocouple.

2.2.4 | Surface tension measurements

Surface tension measurements performed with a DuNoüy tensiometer (K8 Krüss, measurement range 5–90 mN/m with Pt-Ir ring of 20 mm) were used to determine critic aggregation concentration (*cac*) values. From plots of the change surface tension values against surfactant concentration, *cac* was determined from the point of slope change. All described measurements were performed at 25.0 ± 0.1°C.

2.2.5 | Size and size distribution determinations

Dynamic light scattering (DLS) measurements were carried out in a Zetasizer Nano ZS (Malvern, UK), with green excitation (532 nm) and detection at 173°. Data treatment was made with Zetasizer 6.2 software (Malvern).

2.2.6 | Zeta potential determination

The electric potential at the slipping plane was determined in a Zetasizer Nano ZS (Malvern, UK), with green excitation (532 nm) and detection at 173°. Measurements for alkyl mannosyl derivatives were carried out in Hepes buffer (pH 7.4 10 mM and 10 mM NaCl).

FIGURE 2 Teflon cuvettes employed to form GUVS, using procedure (A) and (B)

3 | RESULTS AND DISCUSSION

3.1 | Aggregation of monoalkyl mannoside derivatives

Consequence of its amphiphilic nature, the mannoside glycolipids synthesized are able to form aggregates in aqueous solution, and their critical aggregation concentrations, *cac*, were determined by using both surface tension measurements and fluorescence with ANS as probe. The results obtained for all monoalkyl derivatives studied are shown in Figure 3, being these values on the order of those reported for similar compounds, particularly for octyl and lauryl derivatives.[33,34]

The *cac* values determined for **MOM**, **MLM**, and **MPM** using the du Noüy ring method were 10.0, 0.03, and 0.008 mM, respectively (Figure 3), while by using ANS emission intensity results were 10.0, 0.01, and 0.004 mM, respectively. Despite the differences on *cac* values when physical and photophysical measurements are compared, the trend observed for the *cac* dependence on the number of methylene units is clear and expected.

The magnitude of the critical aggregation concentration is strongly dependent on the stereochemistry of the anomeric center at C4. Higher *cac* values have been reported for β than for α derivatives,[34] consequence of the direct interaction between the hydroxyl group at C6 with the first methylene group, which results in a decreased hydrophobicity of the alkyl chain.[35] This stereochemical effect can be clearly seen for 3 different monoalkyl monosaccharides (mannoside (Man), glucoside (Glc), and galactoside (Gal)) with *cac* $C_8\alpha Man \approx C_8\alpha Glc < C_8\alpha Gal$.[33,34]

Surface tension measurements also allow determining several interesting parameters of surfactants. If the aggregation behavior is described by Gibbs adsorption model, the surface excess and the molecular area in the interface were calculated where a linear dependence between surface tension and concentration natural logarithm before *cac* was observed. The surface excess values depend inversely on the hydrocarbon chain length. As can be seen, the values determined for A (cross-sectional area per molecule), not only depend on the balance of the hydrophilic head (sugar plus solvation sphere) and hydrophobic tail, but also on packing of whole molecule (Table 1).

Table 1 includes the values of the limiting surface tension, γ_{lim}, observed after aggregation; this value is a measure of the surfactant ability of each compound. The γ_{lim} values determined for the studied compounds are similar to those reported for nonionic surfactants with sugar heads.[36]

The critical packing parameter, Cpp, which only considers interaction forces between amphiphilic molecules

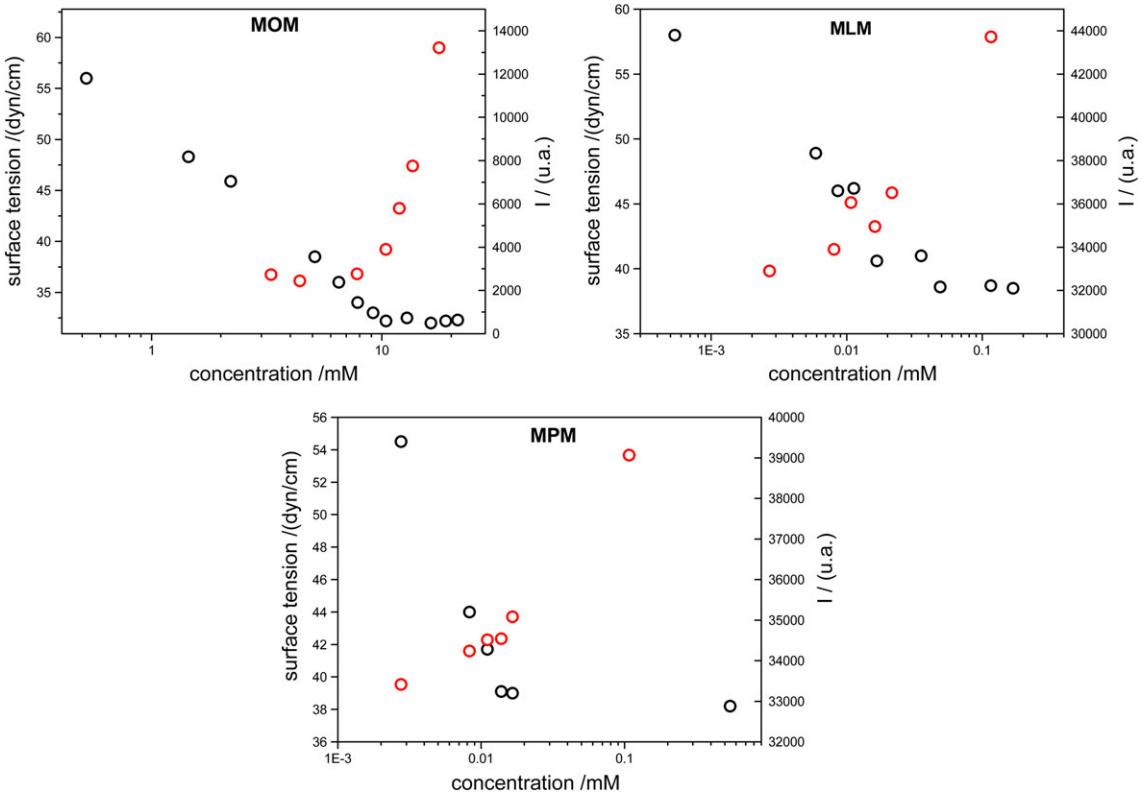

FIGURE 3 Determination of *cac* for monoalkyl mannosides, by using (○) ANS fluorescence intensity and (○) surface tension

TABLE 1 Geometric parameters for **MXM** aggregates

	γ_{lim} / dyn cm^{-1}	Γ /10^{-10} mol cm^{-2}	A/ Å^2 molecule^{-1}	Cpp
MOM	32.2	3.2	51.7	0.40
MLM	38.5	3.0	55.1	0.38
MPM	38.2	4.0	43.5	0.48

within the aggregate and geometrical considerations to minimize free energy,[32] allows to predict that these micro-aggregates would prefer cylindrical geometry.[37]

Cross-section areas determined for **MOM** and **MLM** correspond to the values previously reported for these compounds;[33] however, in the case of palmityl derivative, the reduction on this parameter value indicates a more packed structure.

Table 2 summarizes the physical parameters which characterize the aggregates formed by mono-alkyl derivatives, **MXM**. The size of aggregates in water, r, obtained by DLS measurements, is particularly high for **MLM** and **MPM**, while the value obtained for the octyl derivative **MOM**, 8.4 nm, is in fair agreement with the 6 nm reported value determined by NMR techniques using Stokes-Einstein equation.[34] It must be stated that hydrodynamic radius r determined by DLS assumes spherical particles, if not the case, the estimated radius would correspond to the size of the corresponding spherical particle with a diffusion coefficient equal to the actual aggregates. According to Cpp values, the energetically preferred shape for the aggregates of these compounds is cylindrical, so their longitudinal component could be responsible of an overestimated hydrodynamic radius. Additionally, α mannoside derivatives are reported to be capable of forming bigger structures than β ones, because axial conformation allows them to associate in extended structures (laminar type).[38]

Despite these argumentations, the big sizes determined for **MLM** and **MPM** open the possibility of formation of large vesicles (closed bilayers). Figure 4 shows a giant MPM vesicle fabricated with the electro formation method (described in methods section) in pure water. The intensity signal corresponds to the emission of Laurdan incorporated in the bilayer excited with a 2-photon laser. Regardless several non-ionic surfactants have been reported to form vesicles,[39,40] this is not a widespread observation.

The temperature of phase transition, T_m (Table 2), monitored following the Laurdan GP changes as a function of temperature,[41] can be associated to several phenomena: if aggregates are bilayers, transition corresponds to changes from phases $L_\beta \rightarrow L_\alpha$ (gel to liquid phases); if they are micelles, transition could correspond to shape changes (cylindrical micelles to cubic structures).[42] For **MOM**, this parameter, if exists, probably falls below our experimental range, 5°C to 70°C, following the trend observed for the other derivatives: longer alkyl chains increase interactions, resulting in higher values of T_m.

The absolute value of Zeta potential values, ζ, (Table 2) is straight dependent on the number of methylene chains. The negative values measured for this parameter are directly related with the stability of the colloidal suspension and could be attributed to (a) anion adsorption on the surface of these non-ionic aggregates[43] or (b) due to the difference in dielectric constant between aggregates and dispersing media, water. This behavior is known as Cohen rule, which establishes that the phase with the highest dielectric constant will be charged positively. When water is involved (high dielectric constant), particles (dispersed media) are negatively charged.[43,44]

TABLE 2 Physical parameters of the aggregates formed by monoalkyl mannoside derivatives. Size (r), polydispersity (PI), and zeta potential (ζ) by employing DLS and transition temperature (T_m) by using Laurdan GP

	r, nm	PI	T_m, °C	ζ, mV
MOM	8.36 ± 3.63	0.20 ± 0.074	n.d.	−19.4 ± 1.1
MLM	99.87 ± 1.09	0.11 ± 0.019	10.0 ± 1.0	−43.2 ± 3.0
MPM	84.87 ± 0.89	0.26 ± 0.023	46.4 ± 0.2	−50.7 ± 1.1

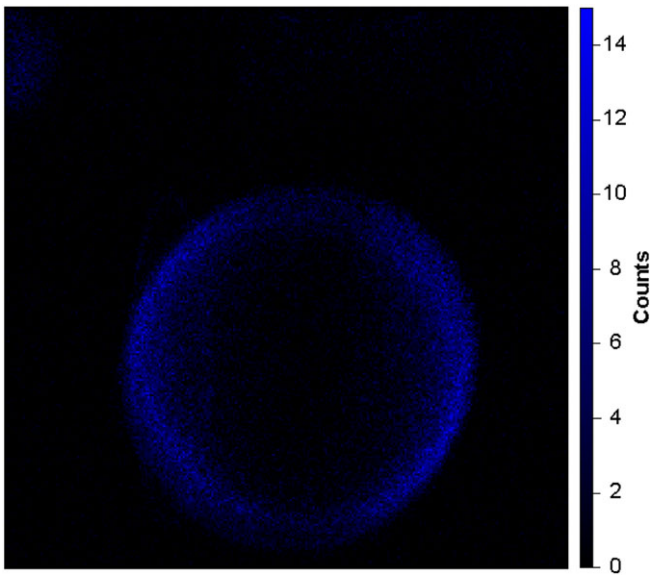

FIGURE 4 Intensity image of Laurdan fluorescence from MPM GUVs

TABLE 3 Values of Laurdan GP and DPH anisotropy (rDPH) at 25°C for the 3 monoalkyl mannoside derivatives

	GP	rDPH
MOM	−0.388 ± 0.007	0.049 ± 0.015
MLM	−0.245 ± 0.027	0.146 ± 0.023
MPM	0.525± 0.040	0.364 ± 0.027

Additionally, aggregates were characterized through steady-state fluorescence determinations, involving Laurdan GP and DPH anisotropy, all of them reported in Table 3. GP and rDPH values follow the same trend, and their values increase as the alkyl chain size increases, so structuration and viscosity around probes are a direct function of the number of methylene units, and both properties are directly related.[45,46] It must be stated that experiments were performed at 25°C, so aggregates are below their transition temperatures. If **MLM** aggregates are able to form bilayers, transition would correspond to a transition involving gel and liquid states. Considering that bilayers formed by **MPM** derivative are under its transition temperature, their GP and rDPH values must be higher.

3.2 | Aggregation of dialkyl mannoside derivatives

Parameters determined for the characterization of aggregates formed by mannoside derivatives with 2 alkyl chains, with and without extensor (**DXM** and **DXEM** families) at 25°C, are summarized in Table 4. Water penetration at the outer region of interphase (as GP values indicate) is blocked as chain length increases. This result indicates that as the number of methylene units increases, interphase structuration increases, too. The presence of an oxyethylene spacer between hydrophilic and hydrophobic segments reduces the GP values, then water access to the Laurdan location is facilitated consequence of an increased hydrophilicity of the head group. The hydrophobic region, sensed by rDPH for both families (**DXM** and **DXEM**), shows a different behavior when compared with previous results. For both families, a maximum value is observed for derivatives with 12 methylene units, and further increase in hydrophobicity of the derivative is buffered by the OE spacer presence which seems to hinder the hydrocarbon chain organization.

TABLE 4 Parameters determined for aggregates of dialkyl mannoside derivatives without and with oxyethylene spacer, in phosphate buffer solution 1 mM pH 7.4 at 25°C

	GP	rDPH	T_m, °C	ζ, mV
DOM	−0.026 ± 0.016	0.088	n.d.	−39.6 ± 0.7
DLM	0.280 ± 0.009	0.383	27.4 ± 0.1	−48.3 ± 0.7
DPM	0.551 ± 0.012	0.342	53.8 ± 1.3	−33.2 ± 4.3
DOEM	−0.180 ± 0.006	0.073	n.d.	−38.9 ± 2.3
DLEM	0.133 ± 0.028	0.308	22.4 ± 0.8	−46.0 ± 2.2
DPEM	0.446 ± 0.057	0.247	59.5 ± 0.5	−44.0 ± 1.5

Transition temperature of the aggregates formed by these derivatives was determined monitoring the Laurdan GP dependence on temperature (Table 4). For the shortest derivatives (8 methylene units), this parameter is below our lower experimental temperature attainable (5°C) and was not measured. The results obtained indicate an increase in transition temperature with the length of alkyl chains, as observed for other lipids.[45] It is already known that this parameter also depends on the presence of unsaturation, the charge and the properties of polar head, among others.[47] The presence of more methylene units implies an increased number of Van der Waals interactions, and more energy is required to unpack the hydrocarbon chains. A transition temperature of 60°C has been reported for an hexadecylglucoside;[48] value similar to the one obtained for **DPEM** and slightly higher than the one of **DPM**. The presence of oxyethylene extensor promotes a fluidization on both regions of bilayer, but transition temperature decreases for lauryl derivatives and increases for palmityl one. A similar trend was determined for zeta potential; for shorter derivatives, its value decreased slightly, and for the longer one, there is an important increase, indicating, if frictional electrostatic charges are involved, that dielectric constants are more affected by the spacer in longer derivatives. The values determined for this parameter (between −33 and −48 mV) account for the stability of these aggregates.

Comparing data given in Tables 3 and 4, aggregates of derivatives with 2 tails (of 8 and 12 methylene units) are less prone to allow the access of water molecules (higher GP values) and present lower micro-viscosity in the inner core (lower anisotropy values), summarizing they are more structured. In the case of **MPM** aggregates, which are over transition temperature, no changes on structuration are detected in this phase. The presence of a second alkyl chain increases transition temperature, but the presence of the OE linker has a fair effect on this parameter.

3.3 | Aggregation of monoalkyl mannoside derivatives in the presence of cholesterol

Niosomes, systems constituted by nonionic surfactants and cholesterol, have received a lot of attention, because they are promising drug delivery systems and a good alternative to phospholipid systems.[39] Surfactants with one long alkyl chain (which present low solubility in water

TABLE 5 Values of Laurdan GP at 25°C, for monoalkyl mannoside niosomes with increasing proportions of cholesterol

	GP			
%Chol	0	25	50	75
MOM	−0.388	0.261	-	0.187
MLM	−0.245	0.369	0.439	0.465
MPM	0.525	0.382	0.396	0.407

TABLE 6 Values of rDPH at 25°C for monoalkyl mannoside niosomes with increasing proportions of cholesterol

	rDPH			
%Chol	0	25	50	75
MOM	0.049	0.200	0.310	0.245
MLM	0.146	0.231	0.237	0.248
MPM	0.364	0.242	0.253	0.244

and low *cac* values) in the presence of cholesterol are able to form bilayers.[39]

In biological membranes, the presence of cholesterol has several functions, like fluidity regulation, reduction of small molecules permeability, and the increase of mechanical force among others.[49] Additionally, in bilayers, it acts as a buffer ordering the liquid phase and disordering the gel phase.[50]

The aggregates formed by **MXM** derivatives and cholesterol were characterized determining Laurdan GP and DPH anisotropy, results that are shown in Tables 5 and 6. The amount of sterol presents in the aggregates of **MOM** and **MLM**, which are below their transition temperatures, promotes, and increases GP and rDPH values until they reach a plateau. On the contrary, for **MPM**, which are in gel phase the effect of cholesterol reduces the values of both parameters. As expected in the liquid phase, the presence of cholesterol promotes structuration, detectable on both, interphase and inner region, while for gel phase promotes fluidization or disorder.[51,52]

4 | CONCLUSIONS

The physicochemical characterization of aggregates formed by alkyl mannoside derivatives in aqueous media was performed. Hydrocarbon chain length and topology play an important role on the modulation of studied properties, which are directly affecting the packing at interphase and in the hydrophobic region. The most hydrophobic monoalkyl derivative (long hydrocarbon chain) is able to aggregate to form giant unilamellar vesicles. The aggregates formed in the presence of cholesterol show the usual behavior when this sterol is present, buffering properties related to fluidity.

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ORCID

G. Gunther http://orcid.org/0000-0002-4733-8426

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