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## Chemo-enzymatic synthesis of glycolipids, their polymerization and self-assembly

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### Abstract

This paper describes the synthesis of bio-based methacrylated 12-hydroxystearate glucose (MASG), and its (co)polymerization with methyl methacrylate (MMA) by either free- or RAFT radical polymerizations. The obtained amphiphilic p(MMA-MASG) copolymers self-assembled in water into various morphologies depending on the MASG unit content and glycopolymer crystallinity. Finally, as a proof of concept, a hydrophobic dye, Nile Red, was entrapped by co-nanoprecipitation into p(MMA-MASG) nanoparticles, showing their loading capacity and thus demonstrating the potential of such amphiphilic glycolipid-based copolymers in hydrophobic compound encapsulation applications.

### Introduction

Due to the drastic depletion of readily available fossil resources,<sup>1</sup> taking advantage of biomass, a viable alternative carbon source, with a short regeneration time that can be measured in decades instead of million years, becomes a necessity.<sup>2</sup> Consequently, the development of new biobased monomers and polymers and the investigation of their original properties is of interest. In this context, glycopolymers (*i.e.*, polymers containing sugar units, either as intra chain or pending), present an important potential as biosourced materials. The specific interactions between the sugar moieties of glycopolymers and lectins, similar to those occurring at the surface of the cells between carbohydrates and proteins,<sup>3, 4</sup> make them particular good candidates for biomedical<sup>5</sup> and pharmaceutical applications<sup>6</sup> and has motivated the development of several synthetic strategies, as reported in literature reviews.<sup>7-11</sup> Glycopolymers can be synthesized either by functionalization of a pre-existing polymer to introduce sugar moieties,<sup>12, 13</sup> or by polymerizing sugar-bearing monomers.<sup>14</sup> In the design of glycopolymers able to self-assemble in aqueous solution as micelles, worm-like structures or vesicles, the control of amphiphilicity is a key parameter. For this reason, the post-polymerization functionalization methods have several disadvantages, such as limited available coupling reactions, lack of control in terms of efficiency, reproducibility and often involves protection/deprotection steps.<sup>7</sup> Most of amphiphilic glycopolymers are diblock or triblock copolymers,

composed of a synthetic hydrophobic block (vinyl polymers from styrene<sup>15</sup> acrylated<sup>16</sup> or methacrylated monomers,<sup>17, 18</sup> resorbable polymers such as poly(D,L-lactide),<sup>19</sup> polycaprolactone,<sup>20, 21</sup> polycarbonate,<sup>14</sup> or polypeptides<sup>22, 23</sup>) and a hydrophilic sugar-containing block. Consequently, a large range of polymerization techniques was developed, including ionic chain polymerization or ring-opening polymerization but atom-transfer radical polymerization (ATRP) and reversible addition-fragmentation chain transfer (RAFT) polymerizations dominate the literature. Some rare examples of self-assembled gradient or random copolymers, synthesized by free-radical polymerization or RAFT polymerization,<sup>24, 25</sup> have been reported in the literature. Glycolipids are non-ionic surfactants that can be synthesized from a fatty acid moiety and a sugar. Because of their amphiphilic nature, non-toxicity and biodegradability,<sup>26, 27</sup> they find a wide range of applications in many fields such as food,<sup>28</sup> pharmaceutical,<sup>29</sup> detergents and cosmetics.<sup>30, 31</sup> Depending on the chosen carbohydrate and acyl moieties, fatty acid sugar esters have been shown to exhibit antimicrobial<sup>32-34</sup> and potential antitumoral properties,<sup>35</sup> which could make them interesting as starting monomers for glycopolymers for biomedical applications. Besides, they would lead to glycopolymers with a higher biosourced carbon content.

Some examples of sugar-pending linear polymers from glycolipid monomers have been reported, but with low diversity.<sup>36</sup> If our group described in 2012 the synthesis of sugar-pending polyurethanes by polyaddition of isophorone diisocyanate (IPDI) with  $\alpha$ -D-methylglucoside 9,10-dihydroxy stearate or saccharose 9,10-dihydroxy stearate,<sup>37</sup> most of examples in the literature involved radical polymerization, based on an enzymatic approach, first described in 1998 by Tokiwa *et al.*<sup>38</sup> In such a strategy, the authors used a mono-acylated glucose with divinyl adipate in the presence of *Candida antarctica* lipase B to obtain a sugar-bearing vinyl ester, monomer further polymerized by free radical polymerization. This strategy was later applied by other research groups to various vinyl glycolipids from many saccharides (glucose,<sup>39-43</sup> galactose,<sup>41-43</sup> mannose,<sup>41, 43</sup> rhamnose,<sup>44</sup> maltose,<sup>41</sup> lactose,<sup>41</sup> trehalose,<sup>45</sup> raffinose,<sup>46</sup> and maltitol<sup>47</sup>) and from divinyl succinate,<sup>41</sup> divinyl sebacate<sup>46</sup> or divinyl adipate<sup>39</sup> but the diversity of the obtained structures was low.<sup>48</sup> Moreover, those glycolipidic monomers were obtained in quite poor yields (15-72%), and the monomer conversion in all cases was not exceeding 80%. As an alternative strategy, Gross *et al* described the functionalization of the primary alcohol of a lactonic sophorolipid with an acrylate moiety, using vinyl acrylate in the presence of *Candida antarctica* lipase (CALB).<sup>49</sup> A new synthetic strategy to obtain glycopolymers from radical polymerization of glycolipids would be to functionalize the hydroxyl function or double bonds naturally present on some fatty acids, such as oleic, linoleic or ricinoleic acids, to introduce a polymerizable group on the fatty chain. To the best of our knowledge, no example of such methodology has been described in the literature yet. Glycolipids can be synthesized under enzymatic

catalysis in the presence of lipases by direct esterification of a fatty acid, this reaction is known to be slow, and the so-formed water has to be removed from the medium to reach high conversions by shifting the equilibrium. The transesterification of fatty acid vinyl esters is well described in the literature as an interesting alternative to direct esterification.<sup>50-53</sup> The reaction subproduct in this case is not water but vinyl alcohol, immediately converted into acetaldehyde by tautomerism, causing an *in situ* equilibrium shift toward the glycolipid formation and leading to reaction kinetics and conversion rates much higher compared to direct esterification.<sup>54, 55</sup> Fatty acid vinyl esters can be easily prepared by fatty acids transvinilation in the presence of vinyl acetate.<sup>56, 57</sup> In our previous studies,<sup>58, 59</sup> the enzymatic synthesis of glycolipids from glucose and fatty acid vinyl esters was investigated. It was shown that nearly full conversion could be obtained for fatty acid vinyl ester of 12 carbons and higher, starting from a 1:1 glucose:fatty acid ratio, at 5%-wt loading of *Candida antarctica* lipase B (CALB) and without molecular sieves.<sup>59</sup> In this study, we describe the chemo-enzymatic synthesis of an original methacrylate-bearing glycolipid from 12-hydroxystearic acid, that can be obtained from renewable ricinoleic acid and glucose. This monomer was then homopolymerized and copolymerized with methyl methacrylate, either by free radical polymerization or RAFT polymerization. The self-assembly properties in water of all these amphiphilic glycopolymers were investigated and their potential for drug vectorization was evaluated by trapping Nile Red as a proof of concept.

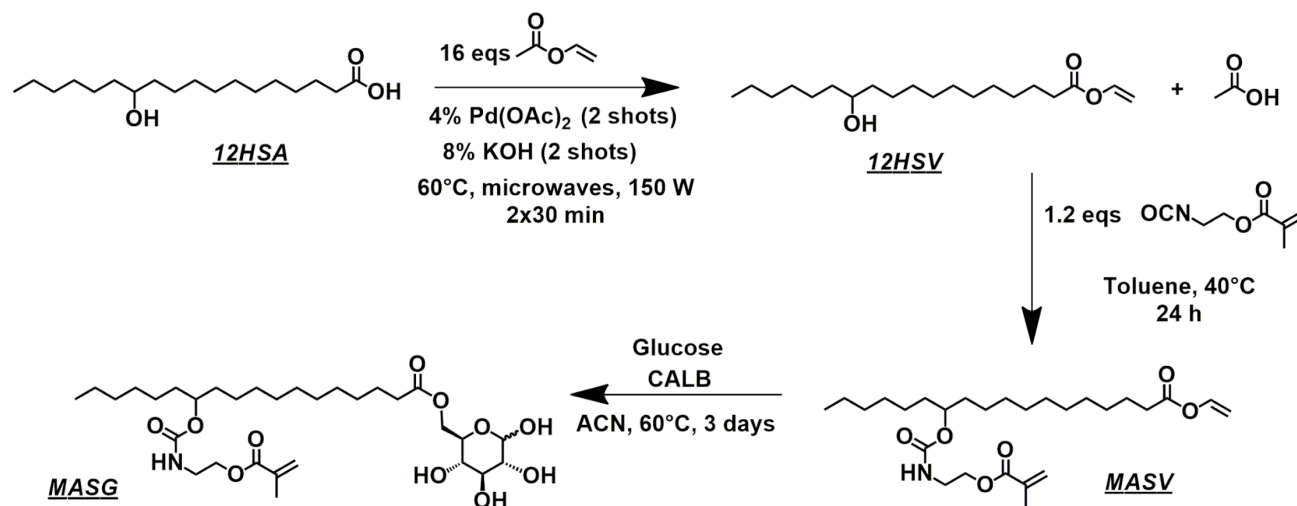
## Results and discussion

### *Glycolipid monomer synthesis*

MASG was synthesized from 12HSA in three steps (**Scheme 1**). First, 12HSA was activated by transvinilation under microwaves in the presence of vinyl acetate, using palladium acetate as a catalyst, to yield the corresponding vinyl ester 12HSV. As the reduction of Pd(II) into Pd(0) under high temperatures generally leads to a drop of its catalytic activity, the latter was used in large amounts. A study from Deleuze and coworkers on transvinilation of several diacids showed that successive additions of palladium led to higher conversions than from a one-shot addition.<sup>57</sup> Transvinilation of 12HSA was thus performed in the presence of 4% of palladium acetate added in two shots (2% at the reaction start and 2% after 30 minutes). The reaction was completed in one hour. A full conversion of 12HSA into 12HSV was confirmed by <sup>1</sup>H NMR with the appearance of resonance signals at 4.65 ppm, 4.80 ppm and 7.20 ppm corresponding to the vinylic protons and the downfield shift of the CH<sub>2</sub>-C(O)-O- triplet from 2.18 to 2.40 ppm. (**Figure 1A**)

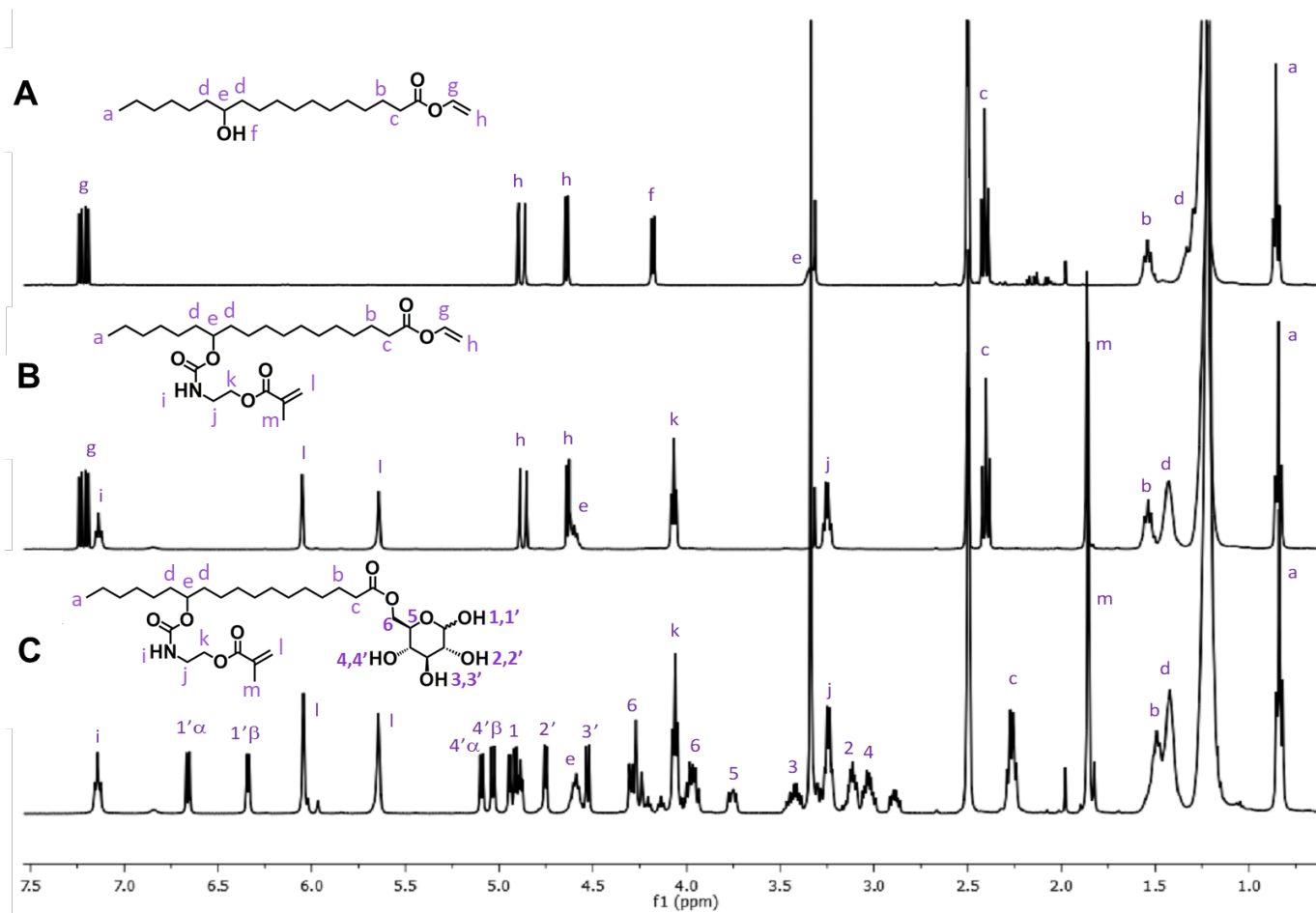
In a second step, 12HSV reacted with IEMA to add a methacrylate moiety and to form MASV. After toluene evaporation, the obtained oily mixture, composed of MASV, remaining IEMA, and traces of 12HSV, was found to be extremely unstable and an irreversible gelification was observed. This

phenomenon could be due to an oligomerization of MASV and residual IEMA, combined with the formation of a hydrogen bonded 3D-network. Gelification was avoided by carrying out this reaction on small 12HSV amounts, between 1 and 3 g and by storing the MASV/IEMA mixture dissolved in a minimum amount of toluene at 4°C. After purification by flash chromatography, MASV was isolated as a solid powder, stable at room temperature over months. The carbamation was confirmed by <sup>1</sup>H NMR by the disappearance of the signal from the hydroxyl labile proton and the appearance of characteristic signals at 1.8, 3.2, 4.6, 5.7 and 6.1 ppm. (Figure 1B)



**Scheme 1. Synthetic route to glucose-bearing methacrylate monomer MASG from 12HSA.**

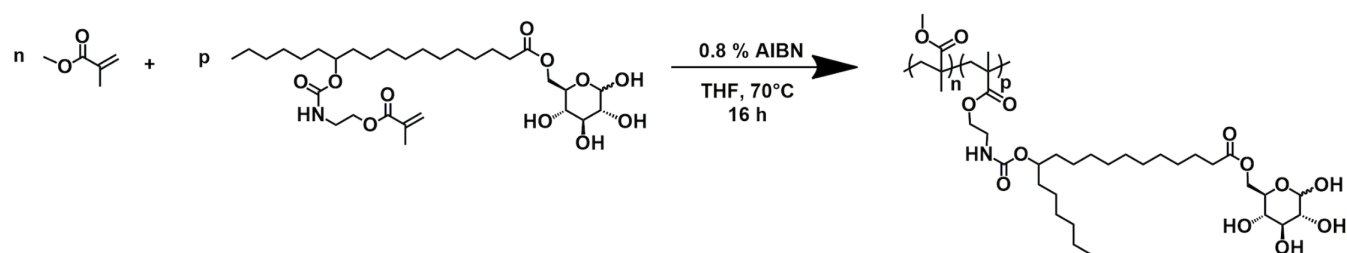
Finally, MASG was obtained by transesterification in the presence of glucose. Based on our previous study,<sup>59</sup> the glycolipid synthesis was catalyzed by immobilized *Candida antarctica* lipase B (CALB) in anhydrous acetonitrile, in the presence of glucose. The reaction was monitored by <sup>1</sup>H NMR and a final conversion of 94% was reached after 3 days. The reaction mixture was filtered on a Büchner to remove the CALB and remaining glucose and then concentrated under vacuum. The so-formed MASG was purified by flash chromatography. The MASG formation was confirmed by <sup>1</sup>H NMR, through the appearance of glucose characteristic signals and the shift from 2.40 to 2.26 ppm of the CH<sub>2</sub>-C(O)-O triplet. The remaining signals from all glucose secondary alcohols demonstrated its monoacylation. (Figure 1C)



**Figure 1.**  $^1\text{H}$  NMR spectra in  $\text{DMSO-}d_6$  of isolated 12HSV (A), MASV (B) and MASG (C).

### Polymerization reactions

MASG was homopolymerized or copolymerized with methyl methacrylate (MMA) in THF in the presence of AIBN (**Scheme 2**). For each feed composition, three polymerization reactions were carried out: regular free radical polymerization (NC) (except for 40:60 and 20:80 MMA:MASG ratios), free radical polymerization in the presence of 2 mol-% of benzyl mercaptan (BM) and RAFT polymerization in the presence of 2 mol-% of 2-cyano-2-propyl benzodithioate (2C2PB). The notation used for all the performed polymerizations are summarized in **Table 1**.



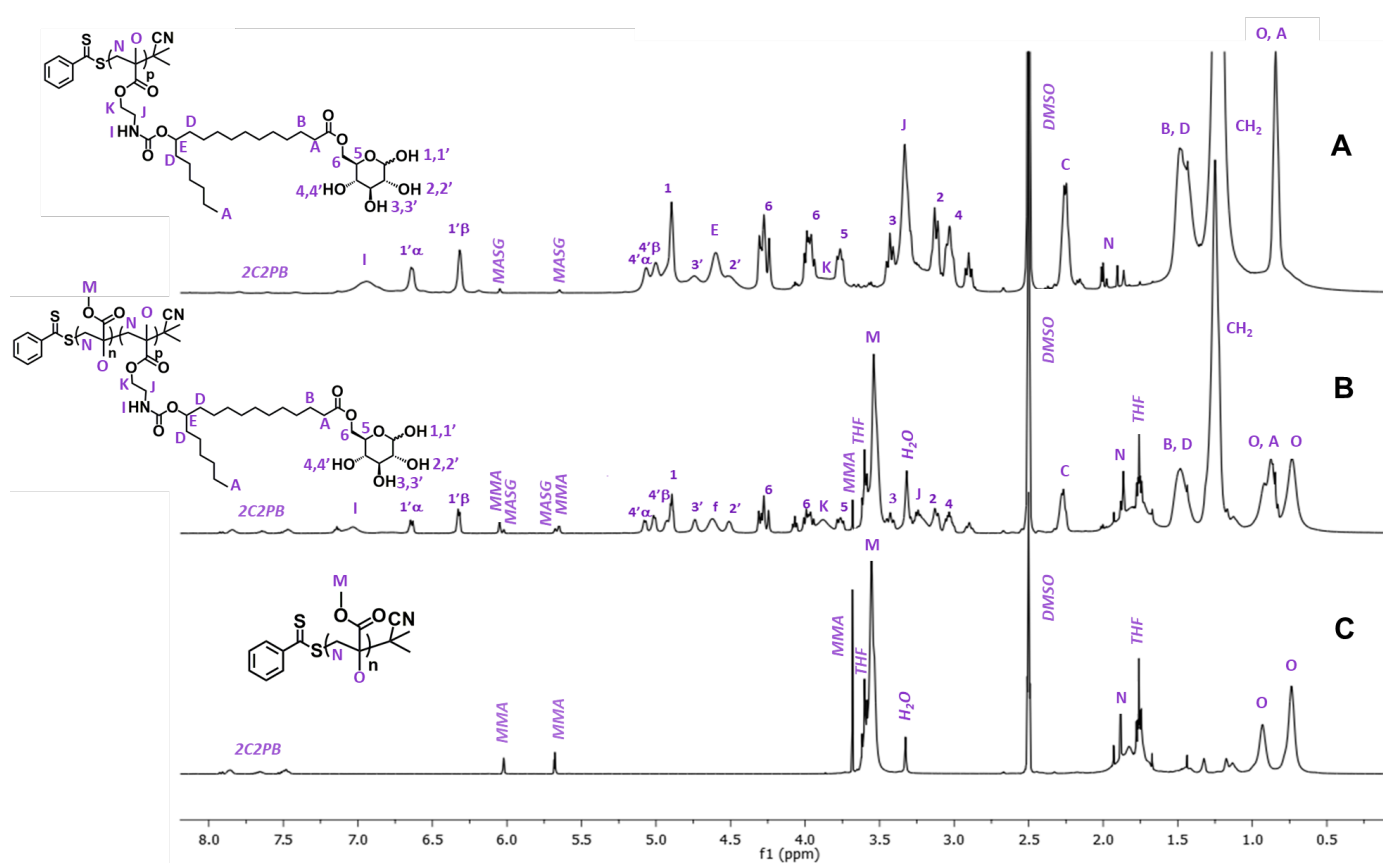
**Scheme 2.** General scheme of the radical copolymerization of MASG with MMA.

**Table 1. Notation for the synthesized (co)polymers based on the MMA:MASG feed ratio**

<b>MMA:MASG</b>	<b>NC</b>	<b>BM</b>	<b>RAFT</b>
100:0	P(MMA) <sub>NC</sub>	P(MMA) <sub>BM</sub>	P(MMA) <sub>RAFT</sub>
80:20	P(MMA <sub>0.8</sub> -MASG <sub>0.2</sub> ) <sub>NC</sub>	P(MMA <sub>0.8</sub> -MASG <sub>0.2</sub> ) <sub>BM</sub>	P(MMA <sub>0.8</sub> -MASG <sub>0.2</sub> ) <sub>RAFT</sub>
70:30	P(MMA <sub>0.7</sub> -MASG <sub>0.3</sub> ) <sub>NC</sub>	P(MMA <sub>0.7</sub> -MASG <sub>0.3</sub> ) <sub>BM</sub>	P(MMA <sub>0.7</sub> -MASG <sub>0.3</sub> ) <sub>RAFT</sub>
40:60	NS	P(MMA <sub>0.4</sub> -MASG <sub>0.6</sub> ) <sub>BM</sub>	P(MMA <sub>0.4</sub> -MASG <sub>0.6</sub> ) <sub>RAFT</sub>
20:80	NS	P(MMA <sub>0.2</sub> -MASG <sub>0.8</sub> ) <sub>BM</sub>	P(MMA <sub>0.2</sub> -MASG <sub>0.8</sub> ) <sub>RAFT</sub>
0:100	P(MASG) <sub>NC</sub>	P(MASG) <sub>BM</sub>	P(MASG) <sub>RAFT</sub>

NS = not synthesized

After 16h of polymerization, the reaction mixtures from p(MMA)<sub>NC</sub> and p(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>NC</sub> syntheses, and all those from BM and RAFT polymerizations were soluble in DMSO-*d*<sub>6</sub>. It was then possible to determine the consumption of the methacrylate functions and thus the conversion rates of MASG and MMA by <sup>1</sup>H NMR. Respective MMA and MASG final conversions were calculated from the <sup>1</sup>H NMR spectra of the reaction medium after 16h at 70°C, by integration of the methacrylate proton signal from residual MMA and MASG monomers, at 5.7 and 6.0 ppm (**Figure 2** and **Figure S1** in Supporting Information). The values obtained are listed in Table 2. Insoluble gels were obtained for p(MMA<sub>0.7</sub>-MASG<sub>0.3</sub>) and p(MASG). The complete monomer consumption was deduced from FTIR spectroscopy by the complete disappearance of the peak at 1630 cm<sup>-1</sup>, characteristic of the acrylate double-bond (**Figure S2**).



**Figure 2.**  $^1\text{H}$  NMR spectra in  $\text{DMSO-}d_6$  of (A)  $\text{p(MASG)}_{\text{RAFT}}$ , (B)  $\text{p(MMA}_{0.8}\text{-MASG}_{0.2})_{\text{RAFT}}$ , and (C)  $\text{p(MMA)}_{\text{RAFT}}$ .

All the glycopolymers were synthesized with high monomer conversions, above 85 %, both for MMA and for glycolipidic MASG (**Table 2**). Complete monomer consumption was reached for all NC polymerizations and for copolymers from BM and RAFT with content of MASG in the feed higher than 60%. These results can be explained by a Trommsdorff effect due to a much higher viscosity of the reaction mixture for those samples which limits the diffusion of radical species and partly inhibits the occurrence of termination reactions, especially in free radical polymerization.<sup>60</sup> Overall, these results highlight the good polymerizability of the MASG monomer by free radical polymerization.



**Table 2. MMA and MASG final conversion values obtained from <sup>1</sup>H NMR calculations.**

MMA:MASG feed ratio	NC Platform			BM Platform			RAFT Platform		
	MMA conversion	MASG conversion	%MASG	MMA conversion	MASG conversion	%MASG	MMA conversion	MASG conversion	%MASG
<b>100:0</b>	97%	-	-	93%	-	-	69%	-	-
<b>80:20</b>	100%	100%	20.0%	97%	98%	20.1%	87%	90%	20.5%
<b>70:30</b>	Insoluble gel			100%	100%	30.0%	91%	97%	31.2%
<b>40:60</b>	NS			100%	100%	60.0%	99%	100%	60.1%
<b>20:80</b>	NS			100%	100%	80.0%	100%	100%	80.0%
<b>0:100</b>	Insoluble gel			-	100%	-	-	100%	-

NS = not synthesized

SEC analyses were performed in THF for p(MMA)<sub>NC</sub>, p(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>NC</sub>, p(MMA)<sub>BM</sub>, p(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>BM</sub>, p(MMA<sub>0.7</sub>-MASG<sub>0.3</sub>)<sub>BM</sub>, p(MMA)<sub>RAFT</sub>, p(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>RAFT</sub>, and p(MMA<sub>0.7</sub>-MASG<sub>0.3</sub>)<sub>RAFT</sub>. For each polymer, number-average molar masses were determined using its exact refractive index increment value (**Table S1**). For the glycopolymers synthesized by RAFT polymerization,  $\overline{M}_n$  values were also calculated from <sup>1</sup>H NMR spectra. The results are reported in **Table 3**. **Figure S3** shows the SEC chromatograms of p(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>), p(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>BM</sub>, and p(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>RAFT</sub>.

**Table 3. Absolute number-average molar masses determined by SEC in THF and by <sup>1</sup>H NMR (for RAFT polymers only).**

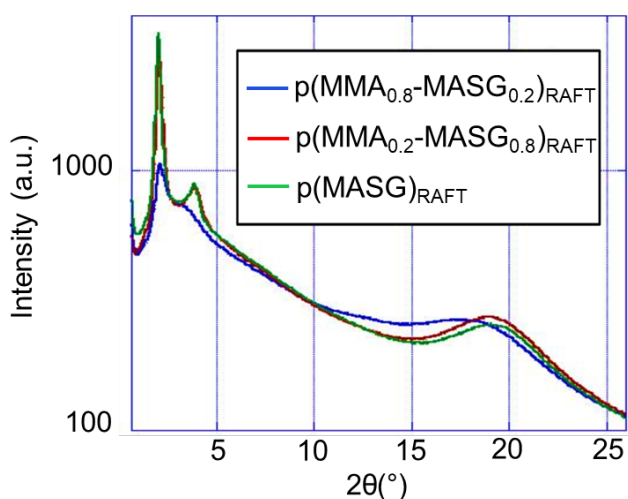
MMA:MASG Feed ratio	NC platform	BM platform	RAFT platform <sup>a</sup>		
	$\overline{M}_n$ SEC (g.mol <sup>-1</sup> ) (dispersity)	$\overline{M}_n$ SEC (g.mol <sup>-1</sup> ) (dispersity)	$\overline{M}_n$ SEC (g.mol <sup>-1</sup> ) (dispersity)	$\overline{M}_n$ <sup>1</sup> H NMR (g.mol <sup>-1</sup> )	DP <sup>1</sup> H NMR
<b>100:0</b>	52,100 ( <i>D</i> = 1.8)	16,900 ( <i>D</i> = 1.9)	8,560 ( <i>D</i> = 1.1)	4,200	42
<b>80:20</b>	70,450	18,800	11,630	11,200	55

	( $D = 1.9$ )	( $D = 1.3$ )	( $D = 1.2$ )		
<b>70:30</b>	Not soluble	17,700	17,370	18,900	74
		( $D = 1.2$ )	( $D = 1.1$ )		

<sup>a</sup> [2C2PB]:[monomers] = 1:50, expected DP = 50.

As expected, the molar masses and  $D$  values obtained by free radical polymerization were significantly higher than those obtained in presence of BM as transfer agent and by RAFT polymerization, highlighting an uncontrolled polymerization process. The addition of BM improved the control while RAFT copolymerization conditions led to both narrow  $D$  of 1.1-1.2, and molar masses close to expected values.

Differential Scanning Calorimetry (DSC) traces (**Figure S4**) showed glass transition temperature ( $T_g$ ) values of 80°C for p(MMA)<sub>RAFT</sub> polymers and falling to a short range from 42°C to 49°C for the different p(MMA<sub>n</sub>-MASG<sub>p</sub>)<sub>RAFT</sub> copolypeptides. Under the conditions used, it was not possible to determine potential melting temperatures. For this reason, the crystallinity of glycopolymers were investigated by X-ray Diffraction Wide-angle X-ray scattering (WAXS) (**Figure 3**). The WAXS profiles obtained show two diffraction peaks, for angles  $2\theta$  of 1.5° and 3.5°, with an increasing intensity as the glycolipid MASG unit content increased, showing that pendant glycolipid chains have a trend to form ordering packings, increasing the crystallinity, as previously reported.<sup>61</sup>



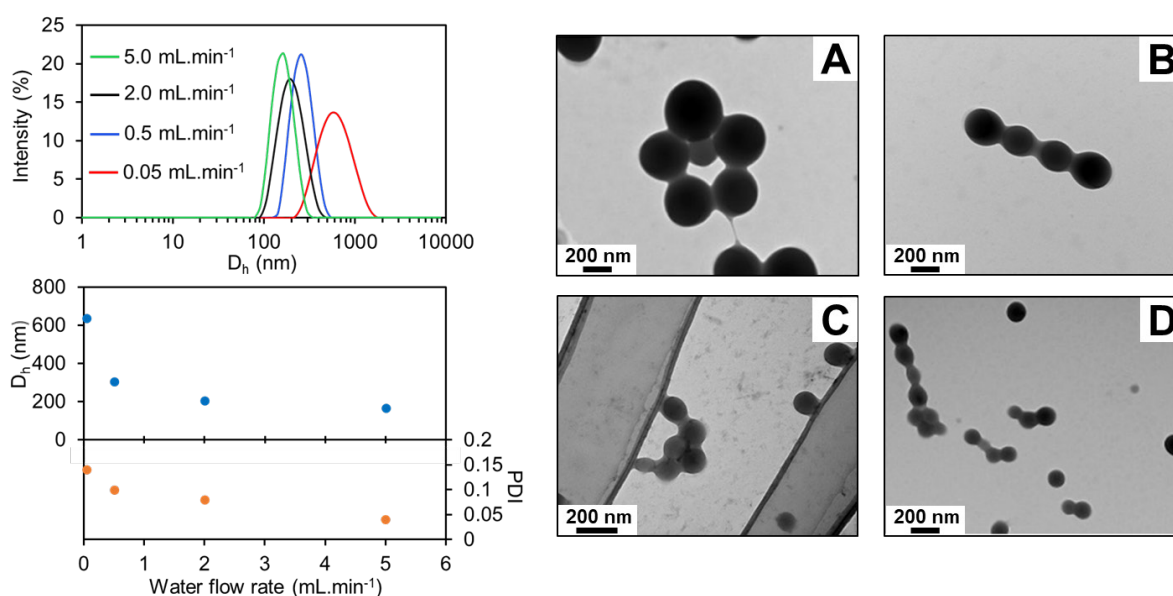
**Figure 3. WAXS traces of p(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>RAFT</sub>, p(MMA<sub>0.2</sub>-MASG<sub>0.8</sub>)<sub>RAFT</sub> and p(MASG)<sub>RAFT</sub> glycopolymers showing the influence of the MMA:MASG unit ratio on the crystallization behavior.**

#### *Self-assembly study in water*

As described in the experimental part, the self-assembly properties of the amphiphilic p(MMA-MASG) glycopolymers were studied using a solvent displacement method. Water, a non-solvent for

the hydrophobic part, was added dropwise at a controlled addition rate into a solution of glycopolymer in THF to induce nanoprecipitation. THF was then removed by evaporation. The influence of several parameters on the self-assembly was investigated: the water addition flow rate, the glycopolymer chain length and dispersity by using P(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>) from free radical polymerization (NC), radical polymerization with BM and RAFT polymerization and finally the influence of MMA/glycolipidic MASG units ratio in the glycopolymer. The resulting self-assembled structures were characterized using two complementary techniques, mono-angle dynamic light scattering at 90° and transmission electron microscopy (TEM) allowing to determine respectively their hydrodynamic diameter ( $D_h$ ) and polydispersity index (PDI), and their shape.

**Figure 4 (up left)** shows the hydrodynamic diameter distributions of P(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>NC</sub> nanoparticles obtained for various water flow rates, from 0.05 mL.min<sup>-1</sup> to 5 mL.min<sup>-1</sup>. The  $D_h$  decreased from 640 nm to 160 nm when increasing the flow rate (**Figure 4, bottom left**), first drastically from 0.05 mL.min<sup>-1</sup> to 0.5 mL.min<sup>-1</sup> and then moderately up to 5 mL.min<sup>-1</sup>. The corresponding PDI followed a similar trend with values in a 0.04-0.16 range, indicating low polydispersities. The values are given in **Table S2**.

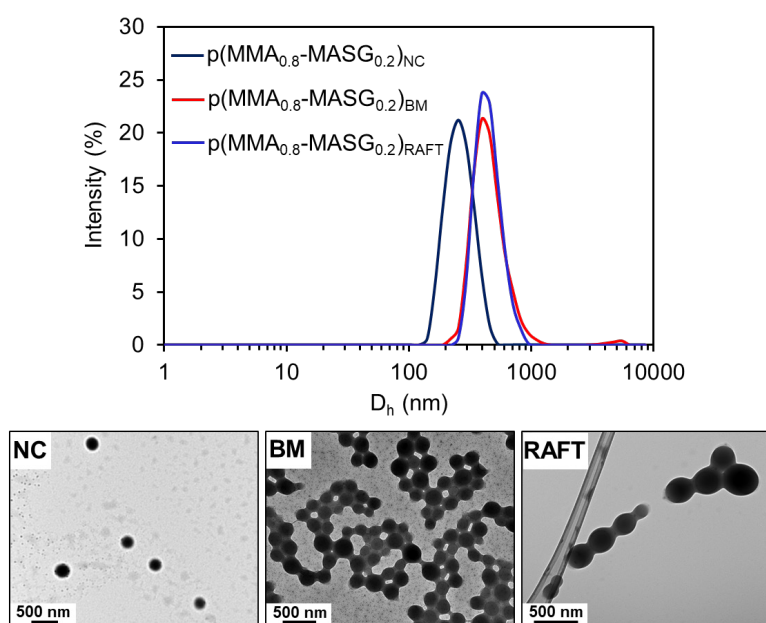


**Figure 4. Influence of the water addition flow rate on the self-assembly of p(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>NC</sub>: hydrodynamic diameter distribution ( $D_h$ ) measured by DLS (top left), evolution of  $D_h$  and PDI as a function of the flow rate (bottom left) and TEM micrographs of nanoparticles (A) 0.05 mL.min<sup>-1</sup>, (B) 0.5 mL.min<sup>-1</sup>, (C) 2.0 mL.min<sup>-1</sup>, (D) 5.0 mL.min<sup>-1</sup>.**

TEM images (**Figure 4 A-D**) showed no change in nanoparticle morphology whatever the water addition flow rate as spherical nanoparticles were obtained in each case. As previously reported, rapid

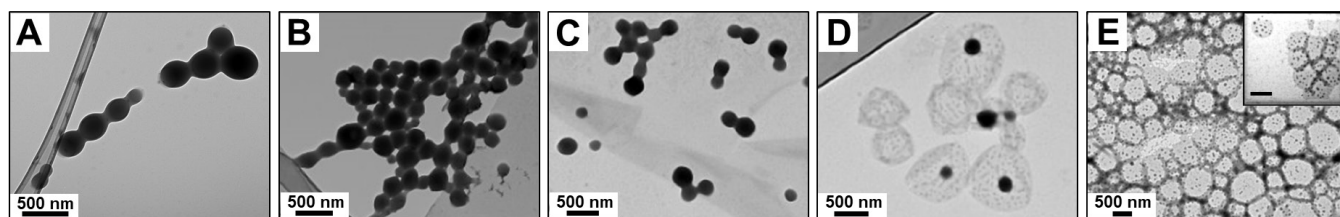
water addition rates reduce drastically the mobility of hydrophobic chains, freezing kinetically the nanoparticle structure while lower flow rates allow dynamic self-assembly leading to larger nanoparticles.<sup>62-64</sup> Consequently, by playing on the self-assembly conditions, the size of the nanoparticles can be tuned while keeping the same shape.

In the following of the study, a flow rate of 0.5 mL.min<sup>-1</sup> was retained. Nanoprecipitation of P(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>NC</sub>, P(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>BM</sub> and P(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>RAFT</sub> allowed the formation of spherical nanoparticles with low PDI value, below 0.15 according to DLS analyses (**Figure 5**). P(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>BM</sub> and P(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>RAFT</sub> nanoparticles showed similar D<sub>h</sub> about 460 nm, while D<sub>h</sub> of P(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>NC</sub> nanoparticles was lower, around 300 nm. Consequently, for the same MMA:MASG unit ratio, high  $\overline{M}_n$  glycopolymer with broad dispersity obtained from free radical polymerization self-assemble into smaller nanoparticles than glycopolymer chains with lower  $\overline{M}_n$  and dispersity.

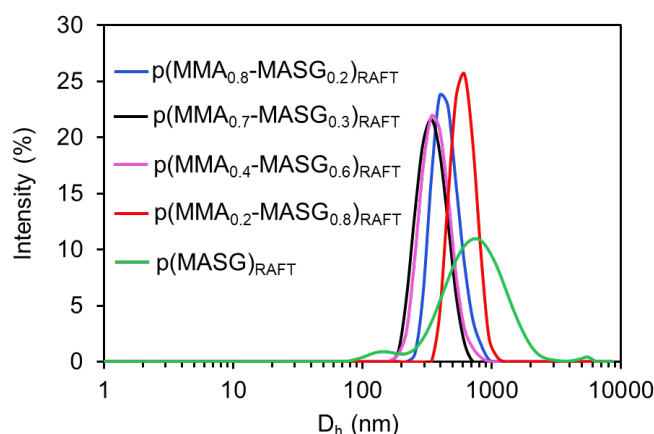


**Figure 5. Hydrodynamic diameter distribution of p(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>NC</sub>, p(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>BM</sub> and p(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>RAFT</sub> nanoparticles and corresponding TEM micrographs.**

Similar spherical nanoparticles with D<sub>h</sub> of 350 nm (PDI=0.05) and 380 nm (PDI = 0.04) were obtained respectively from p(MMA<sub>0.7</sub>-MASG<sub>0.3</sub>)<sub>RAFT</sub> and p(MMA<sub>0.4</sub>-MASG<sub>0.6</sub>)<sub>RAFT</sub>, showing no influence of glycolipidic MASG unit amount on the morphology between 20 % and 60 % (**Figure 6 A-C and Figure 7**).



**Figure 6. Hydrodynamic diameter distribution of  $p(\text{MMA-MASG})_{\text{RAFT}}$  nanoparticles with various MMA:MASG unit ratios.**

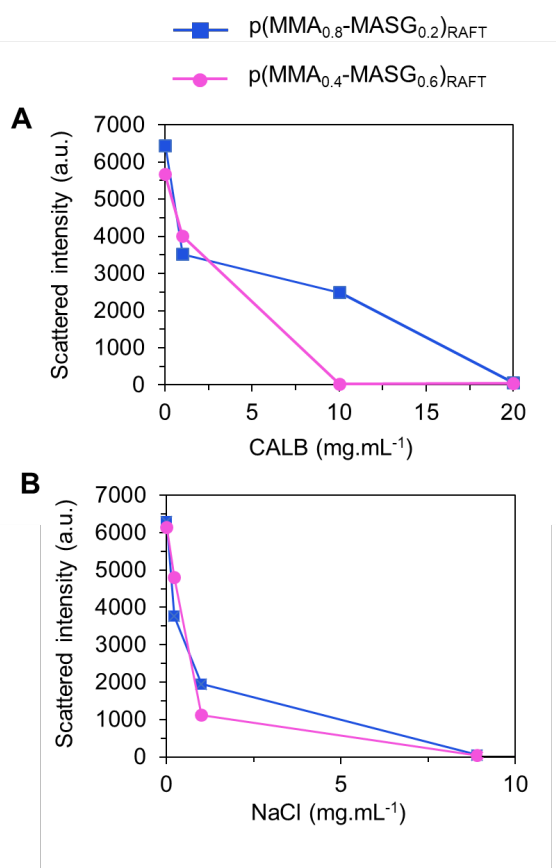


**Figure 7. Hydrodynamic diameter distribution of  $p(\text{MMA-MASG})_{\text{RAFT}}$  nanoparticles with various MMA:MASG unit ratios.**

However, larger hydrodynamic diameters were measured for  $p(\text{MMA}_{0.2}\text{-MASG}_{0.8})_{\text{RAFT}}$  and  $p(\text{MASG})_{\text{RAFT}}$  nanoparticles, with  $D_h$  of 610 nm and 830 nm, respectively. Moreover, if the PDI value of 0.7 for  $P(\text{MMA}_{0.2}\text{-MASG}_{0.8})_{\text{RAFT}}$  is low, the signal obtained for  $P(\text{MASG})_{\text{RAFT}}$  nanoparticles shows a bimodal distribution including a minor population around 150 nm and a broad one between 200 nm and 2000 nm. This result shows that the presence of hydrophobic MMA units ensures uniform self-assembly into low polydispersity nanoparticles and the lipophilic-hydrophilic balance of MASG units alone does not lead to a controlled self-assembly behavior.

TEM observation of those  $p(\text{MMA}_{0.2}\text{-MASG}_{0.8})_{\text{RAFT}}$  nanoparticles revealed a few small spherical aggregates and non-spherical inhomogeneous structures. The differences of contrast within them suggest a micro-phase separation phenomenon. For  $p(\text{MASG})_{\text{RAFT}}$  nanoparticles, TEM images showed the aggregation of similar structures resulting in a discrepancy in terms of global diameter, as observed by DLS. Nano-phase separations were previously observed in self-assembly structures resulting from polymer architectures combining several levels of hydrophobicity.<sup>65</sup> In our case, local segregation of the three domains: hydrophobic PMMA backbone, lipophilic alkyl chain bearing hydrophilic sugar can be strongly enhanced by the capacity of the pendant glycolipid chains to crystallize when increasing the MASG unit content.

The influence of sugar ester amount in the glycopolymers on the nanosuspension stability towards enzymatic hydrolysis and ionic strength was studied on  $p(\text{MMA}_{0.8}\text{-MASG}_{0.2})_{\text{RAFT}}$  and  $p(\text{MMA}_{0.4}\text{-MASG}_{0.6})_{\text{RAFT}}$ . Their hydrolysis in water was performed under non-ionic catalysis in the presence of supported *Candida antarctica* lipase B (CALB). Indeed, the lipase can catalyze the hydrolysis of primary esters in water. Nanosuspension resistance to ionic strength was investigated by the addition of sodium chloride. After 12h in presence of either CALB or NaCl at different concentrations, the suspension destabilization was monitored by measuring the scattered light intensity by DLS. (Figure 8)

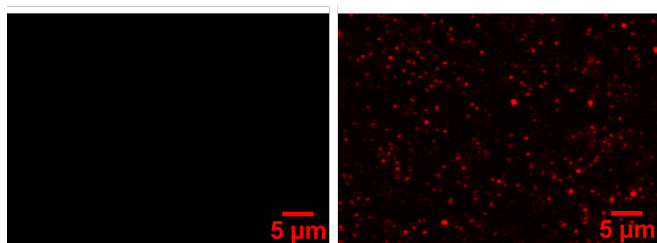


**Figure 8. Influence of the amount of NaCl (A) or CALB (B) on the stability of suspensions obtained from  $p(\text{MMA}_{0.8}\text{-MASG}_{0.2})_{\text{RAFT}}$  and  $p(\text{MMA}_{0.4}\text{-MASG}_{0.6})_{\text{RAFT}}$ .**

Both nanosuspensions were destabilized in the presence of CALB. Nevertheless, a concentration of 20  $\text{mg.mL}^{-1}$  of CALB was required to destabilize completely the  $p(\text{MMA}_{0.8}\text{-MASG}_{0.2})_{\text{RAFT}}$  nanoparticles, against 10  $\text{mg.mL}^{-1}$  for  $p(\text{MMA}_{0.4}\text{-MASG}_{0.6})_{\text{RAFT}}$ . As expected,  $(\text{MMA}_{0.4}\text{-MASG}_{0.6})_{\text{RAFT}}$  nanoparticles, containing three times more sugar ester units than  $p(\text{MMA}_{0.8}\text{-MASG}_{0.2})_{\text{RAFT}}$  are more sensitive to hydrolysis. A clear destabilization of both nanosuspensions was observed in the presence of sodium chloride: the light intensity values drastically fell down from salt concentrations below 1

mg.mL<sup>-1</sup>. At 8.9 mg.mL<sup>-1</sup> of sodium chloride, corresponding to the physiologic ionic strength, the total destabilization was observed indicating that p(MMA-MASG<sub>20</sub>) nanoparticles could be used as carriers for drug delivery applications.

Finally, to explore the so-formed glycopolymers potential for the vectorization of active compounds, their ability to trap Nile Red, a hydrophobic fluorescent dye, was investigated. P(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>BM</sub> was dissolved in THF at 0.5.mL<sup>-1</sup> in the presence of 0.045 μmol of Nile Red. Water was added at a controlled flow rate of 0.5 mL.min<sup>-1</sup> to form Nile Red-loaded nanoparticles. After THF evaporation, a pink, stable nano-suspension was obtained. This suspension was observed by confocal microscopy. **Figure 9** compares images of p(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>BM</sub> suspensions without and with Nile Red. Spherical red aggregates, corresponding to Nile Red trapped by glycopolymer nanoparticles, were observed. This loading experiment was conducted as a proof of concept to demonstrate that hydrophobic dye can be encapsulated inside our glycopolymer nanoparticles.



**Figure 9. Confocal microscopy images of p(MMA<sub>0.8</sub>-MASG<sub>0.2</sub>)<sub>BM</sub> self-assemblies without (left) and with (right) Nile Red.**

## Conclusion

In this paper, we described the 3-step chemo-enzymatic synthesis of MASG, a new glycolipidic methacrylated monomer obtained from renewable resources. MASG was isolated with a total yield of 41% and successfully homopolymerized or copolymerized with MMA by free radical polymerization, in the presence of benzyl mercaptan and by RAFT polymerization, always with a total monomer conversion up to 85%. The obtained amphiphilic p(MMA-MASG) glycopolymers self-assemble in water into different morphologies, from spherical nanoparticles to inhomogeneous aggregates due to MASG unit content and crystallinity increase. Finally, Nile Red, was entrapped by coprecipitation into nanoparticles showing their loading capacity and demonstrating the potential of such amphiphilic glycolipid-based copolymers in active compound encapsulation applications. In addition, the free hydroxyl groups present on glucose offer the possibility of functionalizing the surface of these nano-objects with ligands for active targeting.

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