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Preparation of polymeric nanoparticles using a new polymerizable surfactant

Short Communication

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Abstract: A novel polymerizable surfactant (so-called surfmer) was synthesized and characterized according to its structure, surface activity and polymerization ability. Polymeric micelles (size of 6 and 130 nm) appeared in the polyreaction initiated by free radicals from VA-044. In the presence of the monomer (i.e., methyl methacrylate) microemulsion systems were formed that in turn were transformed into latex entities (size – 40 nm). Additionally, an emulsion polymerization was performed with the use of n-hexadecane as an oil phase resulting in the production of nanocapsules (size in the range – 165–220 nm). The shape and morphologies of the nanoobjects were confirmed using Atomic Force Microscopy (AFM).

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1. Introduction

Submicronic colloidal carriers have attracted considerable interest in the last few years because of their ability to ensure specific targeting of drugs by both the oral and the parenteral route [1]. Different systems have been proposed comprising inorganic or organic nanodevices. In general, some promising nanocontainers are the liposomes, the solid lipid nanoparticles, the polymeric micelles and the polymeric nanoparticles [2]. Templating processes (transcriptive synthesis, morphosynthesis) constitute one of the most important methods of producing nanostructures in which micellar aggregates comprise the most convenient templates [3, 4]. The approach of transcriptive synthesis exploits the external surface of the aggregates bilayer as a receptive surface in the controlled growth of inorganic or organic material. In the case of morphosynthesis, the aggregate interface can be treated as a reaction medium, organized at a molecular level [5]. Both techniques present a unique way to build nanometer particles with a hydrophobic core. In recent years much attention has been devoted to synthesizing polymerizable surfactants, so-called surfmers (surface active substances having an interfacial activity and bearing reactive groups) [6], and to use them [7, 8] as potential building blocks for nanocarriers of active substances [9]. The polymerization process of the micellized polymerizable surfactant (having an interfacial activity and bearing reactive groups) may lead to stable polymeric micelles [10].

Herein, a new concept for the facile preparation of

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stable polymeric nanostructures in dispersion poly-merizations is introduced. The concept involves the use of a new synthesized polymerizable surfactant N-(11-sorbyloylundecyl)-N',N'',N'''-trimethylammonium bromide as a stabilizer of polymerization templates: micelles, microemulsions and nanoemulsions [11]. Preparation and characterization of the surfmer will be described, as well as its subsequent free-radical polymerization.

2. Materials and methods

2.1. Materials

The following materials were used: 2,4-hexadienoic acid (sorbic acid, > 99%, SAFC), thionyl chloride (pure, VEB Laborchemie Apolda), 1-bromoundecan-11-ol ($\geqslant$ 99%, Fluka), trimethylamine (99%, Aldrich), sodium bicarbonate ($\geqslant$ 99.5%, Sigma-Aldrich), magnesium sulphate (anhydrous, 99%, Sigma-Aldrich), hexadecane ($\geqslant$ 99%, Fluka), potassium hydrogen phthalate ($\geqslant$ 99%, Sigma-Aldrich), methyl methacrylate (99%, Sigma) and hydroquinone ($\geqslant$ 99%, Fluka), all of which were unmod-ified and used as purchased. All the solvents utilized (dichloromethane, methanol, diethylether) were pure p. a. grade POCh Gliwice reagents and were used after distillation under reduced pressure. Water taken for experiments was twice distilled with specific conductance at a level below 0.200 μS/cm. The initiator used was 2,2'-azobis[2-(2-imidazolin-2-yl)propane]dihydrochloride (VA-044, WAKO).

2.2. Synthesis

Synthesis of the surfmer was conducted in a way pre-sented in Fig. 1. In the first step (Fig. 1a) sorbyloyl chlo-ride was synthesized according to the procedure described in [12]. Namely, sorbic acid (50 g, 0.446 mol) was dissolved in 50 ml of methylene chloride in a three-necked round bottom flask and was then purged with nitrogen. After re-moving oxygen, the thionyl chloride (53 g, 0.445 mol) was added dropwise (1 ml/min) and the mixture was stirred with a magnetic stirrer (1000 rpm) and refluxed for 24 h. After the reaction was completed the solvent was removed under reduced pressure. Pure product (a pale, yellow liq-uid) was separated in a process of distillation under re-duced pressure (10 mm Hg, 61°C, yield of neat product = 72%). The structures of the prepared compounds were con-firmed by their spectral data. ^{1}H-NMR (300 MHz) spec-tra were recorded using a Bruker DRX 300 spectrometer in CDCl$_3$ solutions containing TMS (tetramethylsilane) as the internal reference. The ^{1}H NMR (CDCl$_3$, TMS)

spectra recorded for sorbyloyl chloride are as follows: δ 1.91 [t, 3H, CH_3-CH], 5.96 [d, 1H, CH$_3$-CH=CH], 6.30 [m, 1H,CH$_3$-CH=CH-CH], 6.36 [d, 1H, CH-CH-C=O], 7.43 [m, 1H, CH-CH-CH-C=O].
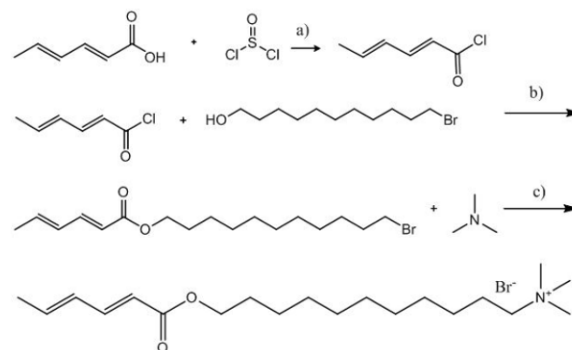
Figure 1. Scheme of the surfmer synthesis.

The product of the first reaction was used as an acylat-ing agent in the second stage (Fig. 1b) of the synthesis [13]. 10 g of 1-bromoundecan-11-ol in 30 ml of methylene chloride was stirred on a magnetic stirrer and cooled in an ice bath. The system was closed and purged with in-ert gas in order to remove any possible oxidating agents. Afterwards the acidic chloride (5.2 g) was added dropwise to soluted alcohol (1 ml/min), and finally the system was refluxed for another 24 h. The odd gases were collected in scrubbers filled with an aqueous solution of NaHCO$_3$. The obtained bromide was separated by triple extraction (pure water, saturated solution of NaHCO$_3$, pure water) and then dried with neutral magnesium sulphate. The pu-rified semi-product was kept with a small addition of an in-hibitor (hydroquinone, 200 ppm) at 4°C (pale yellow waxy solid). The ^{1}H NMR (CDCl$_3$, TMS) spectra recorded for sorbyloyl undecyl bromide are as follows: δ 1.38 (m, 14H, -CH$_2$-(CH_2)$_7$-CH$_2$), 1.64 (m, 2H, -CH_2-CH$_2$-Br), 1.84 (m, 5H, -O-CH$_2$-CH_2-, CH_3-CH-), 3.40 (t, 2H, Br-CH_2-CH$_2$-), 4.12 (t, 2H, -O-CH_2-CH$_2$-), 5.75 (d, 1H, -CH=CH-C), 6.15 (m, 2H, CH$_3$-CH=CH-CH=), 7.24 (m, 1H, -CH=CH-C). In the next step (Fig. 1c), using methanol (40 ml) as a reaction medium, sorbyloylundecyl bromide (10 g) was used as a trimethylamine (1.7 g) quaternizing agent. After 80 h of stirring and refluxing a solvent was removed under reduced pressure, the product was precipitated and crystallized from methanol/diethyl ether mixture with a yield of 69%. ^{1}H NMR (CDCl$_3$, TMS) spectra for N-(11-sorbyloylundecyl)-N',N'',N'''-trimethylammonium bromide (SorbUAB) are as follows: δ 1.37 (m, 14H, -CH$_2$-(CH_2)$_7$-CH$_2$), 1.75 (m, 2H, -O-CH$_2$-CH_2-CH$_2$-),

1.95 (d, 3H, CH_3-CH-), 2.11 (m, 2H, N$^+$-CH$_2$-CH_2-CH$_2$-), 3.05 (t, 2H, -CH$_2$-CH_2-N$^+$), 3.45 (s, 9H, CH_3-N$^+$), 4.50 (t, 2H, -O-CH_2-CH$_2$-), 5.78 (d, 1H, -CH=CH-C), 6.15 (m, 2H, CH$_3$-CH=CH-CH=), 7.25 (m, 1H, -CH=CH-C). The obtained surfactant (a pale orange powder) was stored in −20°C, subsequently examined (surface tension isotherm) and used in polyreactions.

2.3. Surface tension measurements

Surface tension of the surfmer was measured using the Wilhelmy plate method. Measurements were conducted at 22 ± 0.1°C. The critical micelle concentration (CMC) values were taken at the intersection of the linear portion of the surface tension plot against the logarithm of the surfmer concentration. The maximum amount of adsorbed surfactant Γ at the air/water interface was calculated using the Gibbs adsorption equation [14]:

$$\Gamma = \frac{1}{nRT}\left(\frac{\delta\gamma}{\delta\ln c}\right), \qquad (1)$$

where R is the gas constant (8.314 J/(mol×K)), T is the absolute temperature (K), γ = surface tension [N/m], c is the surfactant concentration (mol/l), and $\frac{\delta\gamma}{\delta\ln c}$ is the slope below the CMC in the surface-tension plots. The value of n (the number of species at the interface, whose concentration at the interface changed along with a change in surfactant concentration) was taken as 2 because in the studied case the surfactant is of divalent type. The area occupied by a surfactant molecule at the air/solution interface was obtained from the saturated adsorption as follows:

$$A = \frac{10^{18}}{N\Gamma_{CMC}}, \qquad (2)$$

where N is the Avogadro's number, and Γ_{CMC} is the maximum surface excess at CMC concentration.

2.4. Polymerization in micellar systems

To evaluate the surfmer homopolymerizability [15], SorbUAB solutions were polymerized using a VA-044 as a free radicals source. Different concentrations (see Table 1) of the surfmer in D$_2$O were examined. The polymerization was conducted under a nitrogen atmosphere by heating in a 60°C bath and stirring on a magnetic stirrer. The process of polymerization was monitored by ^{1}H NMR (Bruker DRX 300 spectrometer) and UV-Vis (Spectrophotometer Metertech SP 8001) measurements. In order to avoid misinterpretation of the solution's spectra caused by micelles, micellar solutions were diluted 50 times in D$_2$O

before NMR measurements. The final monomer conversion was calculated by measuring the peak height at the beginning and at the end of the reaction.

Table 1. Recipes of polymerizing systems and product characteristics.

System	Formulation contents					Size analysis	
	Surfmer [mg]	H$_2$O [mg]	MMA^a [mg]	HXDN^b [mg]	Initiator VA044 [mg]	Size [nm]	PDI^c
PM1	14.2	5000	–	–	10	6; 128	0.498
PM2	371.4	2500	–	–	10	133	0.178
NL1	10.2	5000	115.0	–	10	39	0.217
NL2	10.8	5000	152.0	–	10	40	0.065
NL3	11.0	5000	187.0	–	10	45	0.085
NC1	10.2	5017	14.3	16.3	10	165	0.066
NC2	79.0	3000	24.0	25.0	50	192	0.100
NC3	79.0	3000	24.0	25.0	100	224	0.078

^{a}methyl methacrylate
^{b}hexadecane
^{c}polidispersity index

2.5. Polymerization in microemulsion

Microemulsions made of surfmer, methyl methacrylate (MMA) and distilled water were used to obtain a nanolatex. Stable, opaque emulsions prepared in the process of pre-mixing on a magnetic stirrer and, later on, by sonication, were polymerized using the previously described apparatus. The emulsions were purged with nitrogen and heated to 60°C. The initiator VA-044 in water (10% w/w) was added and the process run for 24 h. After that time samples were collected for characterization.

2.6. Nanoemulsion – templated polyreaction

Nanoemulsions were prepared in the same way as the microemulsions, the only difference being that apart from the methyl methacrylate, hexadecane (HXDN) was added as a hydrophobic agent. An oil was pre-blended with MMA and then added to the surfmer-in-water solution. After stirring with magnetic bar and sonication, the dispersions were purged with nitrogen, placed in a bath and heated to 60°C. When the temperature was high enough, a solution of the initiator was added and the process was continued for 24 h. A route was confirmed using UV-Vis spectrophotometry. Afterwards, the reaction samples were washed 5 times with water. The upper part of the samples containing nanocapsules were collected for further analysis (DLS, AFM) and the lower part examined for the presence of unpolymerized surfmer. The amount of unreacted

SorbUAB was calculated from titration results. A potassium hydrogen phthalate, in the presence of crystal violet [16], was used as the titrating agent.

The exact contents of the polymerized systems and the size determination results are presented in Table 1.

2.7. Particle characterization

The size of the obtained nanostructures was determined by dynamic light scattering (DLS) (Zetananosizer Nano series ZS, Malvern Instruments Ltd.) [17]. The average size presented in Table 1 is a Z-average value. Measurements were performed at 25°C at the scattering angle of 173° with an apparatus equipped with a He–Ne laser (632.8 nm) and an ALV 5000 multibit multitau autocorrelator. The AFM imaging was carried out (after drying samples on glass sheets in a vacuum dryer) using the ultra-low-amplitude tapping mode on a Veeco NanoScope Dimension V AFM. Scanning speeds were 0.5 Hz and a low-resonance-frequency pyramidal silicon cantilever resonating at $250 - 331$ kHz was used (force constant: 20–80 N/m).

3. Results and discussion

The aim of the work was to obtain monodisperse nanostructures with well-defined size and shapes. The radical polymerization process of dispersion systems using polymerizable surfactant has been chosen. The new type of surfmer (with two double bonds at hydrophobic terminal) was designed and synthesized according to the scheme presented in Fig. 1 [18].

In the process of a four-step synthesis, a new type of polymerizable surfactant was obtained as a derivative of sorbic acid. The CMC value is relatively small (7 mM) because of the long hydrophobic chain built of 17 carbon atoms. For an analogous non-reactive cationic surfactant CTAB, the CMC value amounts to 8.5 mM [19]. The minimum surface tension γ_{CMC} is 43.5 mN/m. The maximum surface excess Γ calculated from Eq. (1) is 4×10^{-10} mol/cm^2 which is higher than that of CTAB (1.8×10^{-10} mol/cm^2) and is comparable with bigger or more hydrophilic molecules [19]. The minimum surface area occupied by a surfmer molecule A at the CMC point was calculated from Eq. (2) and it is 41.5 Å^2.

Quaternary ammonium salts are widely known for their interfacial activity [20] and also the synthesized surfmer is able to form a wide range of dispersion systems. A compound, containing two reactive groups, was employed to produce various types of nanostructures.

The type of dispersion that occurs is dependant on compo-

sition. Three different dispersed systems were formed for study and are described in detail below. During polyreaction the appearance of samples did not change significantly, which simply means that the size of the originally formed aggregates was preserved.

Polymeric micelles

(PM1, PM2) were obtained in free radical polymerization using micellar solutions as templates. Depending on the system content, small structures of approximately 6 nm or large, approximately 130 nm structures, were formed. This shows that the surfmer used can form various aggregates in different concentrations. During all performed polymerizations, an absorption peak at around 261 nm for the dienoyl group was found to decrease. ^{1}H NMR spectra were recorded before and after polymerization for SorbUAB solutions in D$_2$O. A near-complete conversion was confirmed by loss of the characteristic signals connected with unsaturated bonds ($\delta = 5.78$, 6.15 and 7.25 ppm). Figure 2 presents an AFM image of the polymerized micelles in water, showing fairly small monodisperse, spherical particles with a mean diameter of about 130 nm (see the cross section). The micelle size distribution was confirmed by the dynamic light scattering method (Table 1).
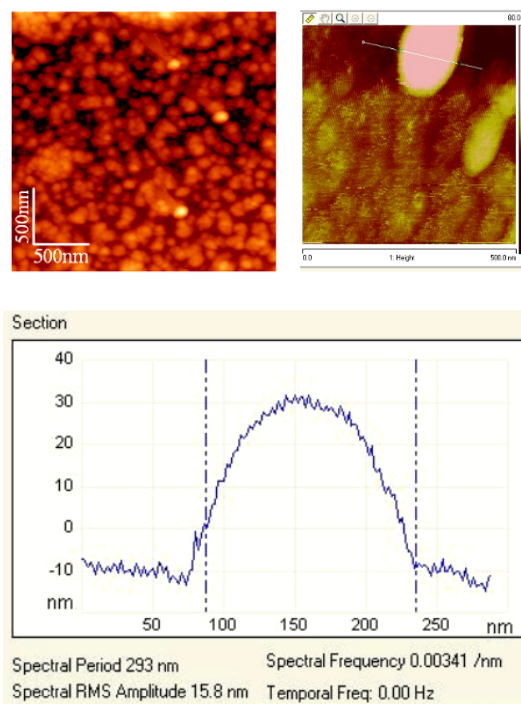

Figure 2. Polymeric micelles (PM1): AFM images and their cross section on a glass plate.

The polymerized micelles are stable as prepared and remain stable for more than 1 year after polymerization. They can be evaporated to dryness and then redispersed in water, retaining their original polymerized dimensions. This enhanced stability may be, in part, due to the nature of the polymerized material. Observed stability is similar to that of the described cationic, rodlike polymeric micelles [21].

Nanolatex

Microemulsions of those two components – methyl methacrylate and surfmer – were formed in order to obtain nanoparticles of spherical shape (NL1, NL2, NL3). They were polymerized in a process of radical polymerization, and assessing from the spectrographs, high conversion rates (over 95%) were achieved. The diameter of the obtained nanoparticles was dependent on the amount of the comonomer used for polymerization and increased slightly with MMA concentration. The PDI values (Table 1) were below 0.22, indicating a narrow size distribution of the obtained nanoparticles.

Nanocapsules

(NC1, NC2, NC3) were produced using a similar process to that used to produce nanolatex, but with the addition of oil [22]. As the application of hexadecane as a hydrophobic component is widely discussed in literature [23, 24], we decided to use that hydrocarbon. Starting from nanoemulsions, we were able to produce nanocapsules of spherical shape and size ranging from 160 to 220 nm (see Fig. 3), with low polydispersity index (Table 1). The size of the product depended on starting system droplet sizes and the amount of initiator added. The decrease of diameter with the increase of VA-044 concentration is noticeable. This is certainly connected with the average molecular weight of the forming polymer [25]. Incorporation of surfmer into the polymer lattice was checked using chemical method of titration. There was no cationic surfactant in supernatant, which means that all the surfmer was polymerized into copolymer. It was also confirmed by very high degrees of conversions measured by UV–Vis spectrophotometry.

4. Conclusion

The novel polymerizable surfactant, N–(11-sorbyloylundecyl)–N',N'',N'''–trimethylammonium bromide, was successfully synthesized in a three-step process. The surfmer displayed surface active properties in water, which was confirmed by measurements of surface tension. In water solutions, the surfmer is able to form microemulsions which were produced with the
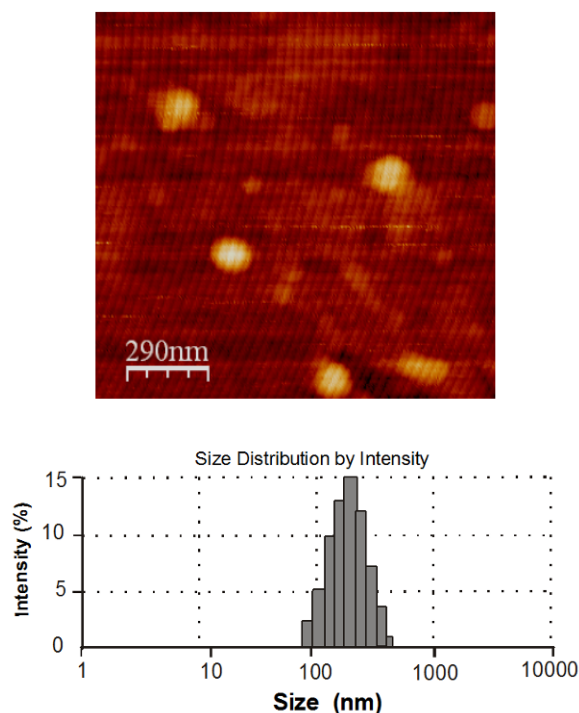

Figure 3. AFM image and particle size distribution of NC1 nanocapsules.

use of methyl methacrylate as a hydrophobic agent, and nanoemulsions obtained with methyl methacrylate and n–hexadecane. A facile and convenient method for the synthesis of polymeric nanostructures has been described. The newly synthesized surfmer was employed as stabilizer and monomer in different types of dispersed systems: micellar solutions, microemulsions and nanoemulsions. By polymerization of three dispersions such structures as polymeric micelles, nanolatex, and nanocapsules were obtained. They were characterized by means of their size and morphologies. Thanks to those results it can be said that using surfmers is an easy and undemanding way of creating nanoobjects. Nascent products are monodisperse, which is very important for their application. In further work, more characteristics of the polymer should be examined, as well as potential application of encapsulation of active substances.

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