APPLIED ORGANOMETALLIC CHEMISTRY
Appl. Organometal. Chem. 2006; **20**: 235–245
Published online in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/aoc.1051

Siloxane surfactants in polymer nanoparticles formulation

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Carbohydrate-modified cyclosiloxanes were synthesized by hydrosilylation reactions of protected allyl-monosaccharides and subsequent deprotection with a gel-type ion exchanger. They were characterized by ^{1}H and ^{13}C-NMR, FT-IR, GPC and surface tension measurements. These compounds, as well as other water soluble, carboxylate-based siloxanes were tested as stabilizers in nanoparticle formulations, with polydimethylsiloxane (PDMS), poly(*ε*-caprolactone) (PCL) and UDEL polysulfone (PSF) as polymer cores. Owing to their low critical micelle concentrations (cmc), small amounts of surfactants were required. The particle size and granulometric distribution were measured by dynamic light scattering (DLS). Electron microscopy confirmed the DLS results and revealed aggregation phenomena in dry state, depending on the polymer core. In the tested conditions, the glass transition temperature of the polymer seems to be the driving force for the stability of dry nanoparticles.

KEYWORDS: siloxane; monosaccharide; ion exchanger; hydrosilylation; nonionic surfactants; anionic surfactants; nanoprecipitation

INTRODUCTION

Siloxane surfactants are known for their ability to decrease the surface tension of liquids to an extent which is comparable only to some fluorinated compounds.[1,2] Owing to the potential toxicological problems of the latter, siloxane surfactants seem not to have competition for certain applications. This is also due to their other outstanding properties,[3–5] such as physiological inertness, resistance to UV radiation, very low T_g, and good versatility for chemical modification. In this context, it seems that the availability of specifically modified silicones will be more and more important (www.borchers.de).

The most commonly known siloxane surfactants contain alkylene-oxide chains (polyoxyethylene, polyoxypropylene) as hydrophilic parts, in various molecular architectures: block or graft copolymers or trisiloxanes. Their effectiveness in organic systems as well as in water and their use in cosmetics, textile conditioning, foam stabilization, coatings and agriculture has been reported since the 1960 s (DE 19604601, Sanyo Chemical Ind. Ltd, Japan; WP9706777, Mennen Co., USA).[1,6–9]

Recent developments in this research field exhibited new opportunities for employing modified siloxane amphiphiles in high-performance applications, such as nanoreactors, molecular transport, drug delivery systems, microemulsions and reactions in supercritical CO_2.[10–15]

From the synthesis point of view, many new amphiphiles containing siloxane segments have been reported, and their wetting and assembly properties have been discussed, including lyotropic liquid crystalline phases (EP0436359, Dow Corning, USA).[9,16–23] Carbohydrate-modified siloxanes seem to be interesting candidates for surface-active biocompatible materials. They can act as solubility enhancers for hydrophobic drugs and may facilitate the delivery of drugs to the target cell, based on biological recognition procedures.[24–26] Their use as transdermal penetration enhancers,[27] cosmetic formulations (US 5 428 142; EP 958856, L'Oreal, France), surfactants[28–31] and self-assembling polymers[20,21] has also been reported.

In this paper we present the synthesis of glycoside-containing cyclosiloxanes and potassium salts of siloxane–aliphatic carboxylic acids. These water-soluble compounds ensured a significant decrease in water surface tension at critical micelle concentrations (cmc) as low as 10^{-4} M,

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indicating high surface activity. Their use as nonionic and ionic surfactants, respectively, in polymer nanoparticles formulations was tested. Nanoparticle stability in water and in the dry state will be discussed, taking into account the structure and chain flexibility of the two components, namely polymer core and surfactant shell.

EXPERIMENTAL

Materials

D-mannose (mixture of anomers, 99%), D-glucose (99.5%), D-galactose (99%), 1,3,5,7-tetramethylcyclotetrasiloxane (D4H), platinum divinyltetramethyldisiloxane complex [Pt(dvs)] solution in xylenes, 2-allyloxyethanol (AE) and allyl alcohol were high-purity commercial products (Aldrich) and used as received. Pyridine, tetrahydrofuran (THF), *n*-hexane, acetone and methanol were of high purity and used as received unless stated otherwise. Toluene was stored on molecular sieves and azeotrope distilled prior to use in hydrosilylation reactions.

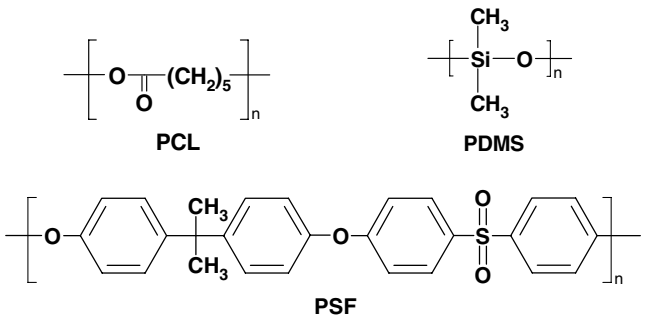
Amberlite IR-120(plus), a strongly acidic gel-type resin with sulfonic acid functionality, having a total exchange capacity of 1.9 meq/ml, was also supplied by Aldrich.

Polycaprolactone (PCL), polydimethylsiloxane (PDMS) and UDEL polysulfone (PSF), the average molecular weights of which are around 30 000 g/mol, were commercial high-purity products and used as received. Their structural units are shown in Scheme 1.

Analyses

^{1}H-RMN and ^{13}C-NMR spectra were registered on Bruker 300 and 400 MHz spectrometers in $CDCl_3$, DMSO-d_6 or D_2O. Infrared absorption spectra were recorded on an FT-IR Nicolet 460 ESP spectrophotometer.

GPC measurements were made in $CHCl_3$ on a PL-EMD 950 evaporative mass detector instrument. The calibration was made with polystyrene standards. Chemical modification (derivatization) was performed before analyzing the final cyclosiloxanes, by acylation with acetic anhydride–pyridine (1 : 2) at room temperature.



Scheme 1. Structural units of the polymers used in nanoparticles formulations.

The thermooptical analysis (TOA) was used to determine the transition temperature of 1 g/l solutions of anionic surfactants. This method is based on the variation of the intensity of light passing through the heated sample, as a result of thermal transitions.[32] TOA was performed on a home-made apparatus under normal light, with a heating rate of 9.6 °C/min.

Critical micelle concentrations (cmc) were determined by the superficial tension method, on a K12 Processor Tensiometer, by immersing a Pt plate into the tested solutions, while automatically increasing the surfactant concentration (Wilhelmy plate method).

Nanoparticle average diameter, distribution and polydispersity index were determined by dynamic light scattering on a Malvern Instruments Autosizer Lo-C 7032 Multi-8 Correlator. The mathematical basis of this method is described in Bathfield *et al*.[33]

SEM observations were made on a Tesla BS 301 microscope operating at 15 kV with secondary electrons. The sample were deposited on glass slides, which were fixed on copper supports. Then the samples were covered with a thin layer of carbon-gold.

Synthesis

Nonionic surfactants

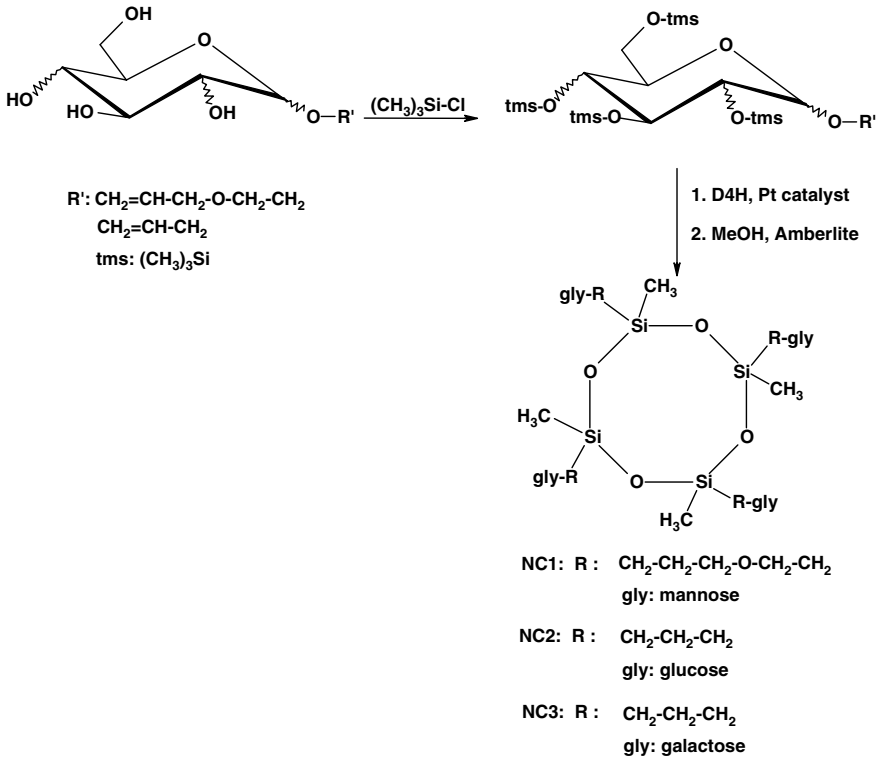
The synthetic path for modified cyclosiloxanes (Scheme 2) is similar to that reported for telechelic and grafted polymers.[34] We describe below in general terms the main reaction steps.

The synthesis of allyloxyethyl-mannoglycoside, allyl-glucoside and allyl-galactoside was carried out by glycosilation of monosaccharides with unsaturated alcohols, in the presence of Amberlite IR 120 (plus) cation exchanger as catalyst, using the general procedure described in Lee and Lee,[35] modified as follows.

The monosaccharide was dissolved in a substantial excess of unsaturated alcohol, then the catalyst (Amberlite IR-120 Plus) was added, without previous drying. In a typical example, 9 g (50 mmol) monosaccharide, 100 ml allyloxyethanol (880 mmol) and 5.45 g ion exchanger were used. The reaction mixture was stirred for 4 h at 90 °C. The ion exchanger was filtered off, and the excess of alcohol was removed by vacuum distillation. The remaining product was repeatedly coagulated in ethyl acetate, in order to remove traces of allyloxyethanol without excessive heating. The final product was recovered after vacuum drying for 5 h, as a viscous yellowish fluid with approximately 90% yield.

^{1}H-NMR (allyloxyethyl-mannopyranoside, D_2O) δ ppm: 5.89–5.98 (m, 1, =CH–); 5.35, 5.30, 5.27, 5.25 (m, 2, $=CH_2$); 4.79, 4.60 (s, 1, H anomeric, 2 isomers); 3.5–4 (m, 12, $-CH_2-$, –CH<).

^{13}C-NMR (allyloxyethyl-mannopyranoside, D_2O), δ ppm: 134.13 (=CH–); 118.94 ($=CH_2$); 101.71, 100.45 (C^1 anomeric, 2 isomers), 73.22 (C^4); 72.23 (C^3); 71.00 (C^2); 70.48 ($\underline{C}H_2$–CH=); 69.12 (CH_2–$\underline{C}H_2$–O); 67.22 (C^5); 66.90 (O–$\underline{C}H_2$–CH_2); 61.41 (C^6).



Scheme 2. Synthesis of nonionic surfactants.

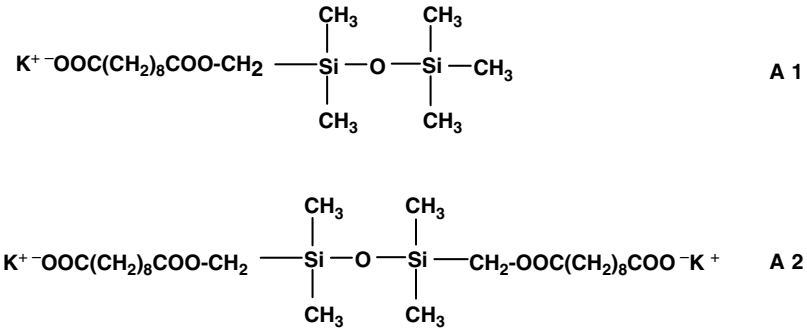
^{1}H-NMR (allyl-glucopyranoside, D_2O) δ ppm: 5.98–5.85 (m, 1, =CH–); 5.32–5.16 (m, 2, $=CH_2$); 4.92, 4.88 (d, 1, H anomeric, 2 isomers); 4.18–3.17 (m, 8, $-CH_2-$, –CH<).
^{13}C-NMR (allyl-glucopyranoside, D_2O), δ ppm: 133.94 (=CH–); 118.50 ($=CH_2$); 97.69 (C^1); 73.48 (C^5); 72.21 (C^3); 71.62 (C^2); 69.97 (C^4); 68.76 ($\underline{C}H_2-CH=$); 60.92 (C^6).
^{1}H-NMR (allyl-galactopyranoside, D_2O) δ ppm: 5.97–5.81 (m, 1, =CH–); 5.31–5.15 (m, 2, $=CH_2$); 4.91, (d, 1, H anomeric); 4.16–3.40 (m, 8, $-CH_2-$, –CH<).

The protection of the unsaturated glycosides was made according to the method described in Ohya *et al*.[36] As a general procedure, the modified glycoside (2 g; 7.5 mmol) was dissolved in a large excess of pyridine (45 ml) and a solution of trimethylchlorosilane (11 ml; 86 mmol) in *n*-hexane (26 ml) was added drop-wise, at 0 °C under argon. The reaction occurred for 4 h, at 0–20 °C. After processing by repeated washings (saturated NaCl solution, water) and filtrations, the silylated product was recovered from hexane (yield 75–80%).

^{1}H-NMR (allyloxyethyl-2,3,4,6-tetra-*O*-trimethylsilyl-mannopyranoside $CDCl_3$) δ ppm: 5.98–5.86 (m, 1, =CH–); 5.33–5.18 (m, 2, $=CH_2$); 4.63, 4.41(s, 1, H anomeric, two isomers); 4.06–3.46 (m, 12, $-CH_2-$, –CH<); 0.17–0.13 [m, 36, $Si(CH_3)_3$].
^{13}C-NMR (allyloxyethyl-2,3,4,6-tetra-*O*-trimethylsilyl-mannopyranoside $CDCl_3$) δ ppm: 134.76 (1, –CH=); 116.8 (1, $CH_2=$); 100.74, 100.32 (1, C^1 anomeric, two isomers), 74.74 (1, C^5); 73.44 (1, C^3); 72.68 (1, C^2); 72.06 (1, $\underline{C}H_2-CH=$); 69.11 (1, $CH_2-\underline{C}H_2-O$); 68.33 (1, C^4); 66.36 (1, $O-\underline{C}H_2-CH_2$); 62.55 (1, C^6); 1.06–0.14 (12, $Si(CH_3)_3$).
^{1}H-NMR (allyl-2,3,4,6-tetra-*O*-trimethylsilyl-glucopyranoside $CDCl_3$) δ ppm: 6.03–5.87 (m, 1, =CH–); 5.37–5.18 (m, 2, $=CH_2$); 4.78 (d, 1, H anomeric); 4.27–3.40 (m, 8, $-CH_2-$, –CH<). 0.22–0.13 [m, 36, $Si(CH_3)_3$].
^{13}C-NMR (allyl-2,3,4,6-tetra-*O*-trimethylsilyl-glucopyranoside $CDCl_3$) δ ppm: 134.48 (1, –CH=); 117.58 (1, $CH_2=$); 97.90 (1, C^1 anomeric), 75.41 (1, C^5); 74.08 (1, C^3); 72.51; 72.56 (2, C^2, C^4); 68.07 (1, $\underline{C}H_2-CH=$); 62.47 (1, C^6); 1.59–0.14 [12, $Si(CH_3)_3$].
^{1}H-NMR (allyl-2,3,4,6-tetra-*O*-trimethylsilyl-galactopyranoside $CDCl_3$) δ ppm: 6–5.86 (m, 1, =CH–); 5.23–5.01 (m, 2, $=CH_2$); 4.82, 4.90 (d, 1, H anomeric, 2 isomers); 4.27–3.39 (m, 8, $-CH_2-$, –CH <). 0.21–0.09 [m, 36, $Si(CH_3)_3$].

The hydrosilylation reactions typically occurred as follows: in a reaction vessel fitted with condenser and argon inlet and outlet, 0.6 g (1.1 mmol) of trimethylsilyl-protected allyl-glycoside and 0.07 g (0.29 mmol) of tetramethylcyclotetrasiloxane (D4H) were dissolved in 1 ml dried toluene. Then 20 µl Karstedt's catalyst were added and the reaction mixture was heated at 70 °C and stirred for 30 h. The modified cyclosiloxane was recovered after distillation of toluene.

^{1}H-NMR of persilylated propyloxyethylene–mannoglycoside cyclosiloxane ($CDCl_3$), δ ppm: 4.63, 4.39 (s, 4H, H anomeric, two isomers); 3.41–3.90 (m, 48H, $-CH_2-$, –CH<);



Scheme 3. Chemical structure of anionic surfactants.

1.60 (m, 8H, C$\underline{H_2}$–CH_2–Si); 0.52 (m, 8H, CH_2–C$\underline{H_2}$–Si); 0.09–0.20 [m, 156 H, Si(CH_3), Si(CH_3)$_3$].

^{1}H-NMR of persilylated propylene–glucoside cyclosiloxane ($CDCl_3$), δ ppm: 4.80, 4.72 (s, 4H, H anomeric, two isomers); 3.17–3.78 (m, 32H, –CH_2–, –CH <); 1.64 (m, 8H, C$\underline{H_2}$–CH_2–Si); 0.54 (m, 8H, CH_2–C$\underline{H_2}$–Si); 0.09–0.23 [m, 156 H, Si(CH_3), Si(CH_3)$_3$].

^{1}H-NMR of persilylated propylene–galactoside cyclosiloxane ($CDCl_3$), δ ppm: 4.82, 4.74 (s, 4H, H anomeric, two isomers); 3.39–4.15 (m, 32H, –CH_2–, –CH <); 1.63 (m, 8H, C$\underline{H_2}$–CH_2–Si); 0.54 (m, 8H, CH_2–C$\underline{H_2}$–Si); 0.09–0.18 [m, 156 H, Si(CH_3), Si(CH_3)$_3$].

The deprotection of the saccharide –OH groups was made according to the following procedure: trimethylsilyl protected modified cyclosiloxane (0.5 g) was dissolved in 1 ml THF, then 1 ml methanol and 0.5 g Amberlite IR 120 (plus) were added and the mixture stirred for 48 h at 70 °C. The ion exchanger was filtered off, and the solvents and side compounds were vacuum distilled. The resulted compound was washed with diethyl ether and dried.

Tetramethyltetra(propyloxyethylene-mannoglycoside) cyclosiloxane NC1, m.p. 132 °C: ^{1}H-NMR (D_2O) δ ppm, 4.69, 4.59 (s, 4H, H anomeric, 2 isomers); 3.17–3.77 (m, 48H, –CH_2–, –CH <); 1.50 (m, 8H, C$\underline{H_2}$–CH_2–Si); 0.43 (m, 8H, CH_2–C$\underline{H_2}$–Si); 0.00 [m, 12 H, Si(CH_3)].

^{13}C-NMR (D_2O): δ ppm, 101.19, 100.30 (C^1 anomeric, two isomers), 73.07 (C^5), 72.88 (C^2), 70.89 (C^3), 70.26 ($\underline{C}H_2$–O–CH_2), 67.09 (O–$\underline{C}H_2$–CH_2–CH_2–Si), 66.77 (C^4), 62.89 (C^6), 61.29 ($\underline{C}H_2$–CH_2–O), 22.87 (CH_2–$\underline{C}H_2$–CH_2–Si), 11.51 (CH_2–CH_2–$\underline{C}H_2$–Si), 0.47 (Si–H_3).

Tetramethyltetra(propylene-glucoside) cyclosiloxane NC2, m.p. 125 °C: ^{1}H-NMR (DMSO-d_6) δ ppm, 4.69, 4.58 (s, 4H, H anomeric, two isomers); 3.11–3.75 (m, 32H, –CH_2–, –CH<); 1.60 (m, 8H, C$\underline{H_2}$–CH_2–Si); 0.55 (m, 8H, CH_2–C$\underline{H_2}$–Si); 0.13 [m, 12 H, Si(CH_3)].

Tetramethyltetra(propylene-galactoside) cyclosiloxane NC3, m.p. 120 °C: ^{1}H-NMR (D_2O) δ ppm, 4.73, 4.66 (s, 4H, H anomeric, two isomers); 3.29–3.87 (m, 32H, –CH_2–, –CH <); 1.54 (m, 8H, C$\underline{H_2}$–CH_2–Si); 0.48 (m, 8H, CH_2–C$\underline{H_2}$–Si); 0.00 [m, 12 H, Si(CH_3)].

Anionic surfactants

Sebacomethylpentamethyldisiloxane and bis-(sebacomethyl) tetramethyldisiloxane (Scheme 3) were synthesized following in general terms the method described in C 07/1 124 823 (Dow Corning, USA).

For the synthesis of sebacomethylpentamethyldisiloxane, 2.62 g (12.9 mmol) sebacic acid, 3.58 g (12.9 mmol) potassium sebacate and 5.07 g (25.8 mmol) pentamethylchloromethyldisiloxane were dispersed in 15 ml DMF. After 22 h stirring at 130 °C, the resulting KCl was filtered off, and the crude acid was recovered by precipitation in water, filtration and washing. The acid was purified by washing with diethyl ether and subsequent extraction with benzene. The corresponding dicarboxylic acid was obtained in a similar way. The potassium salts of these acids, which were used in this study as anionic surfactants A1 and A2 respectively, were obtained by titration, using 0.1 M KOH solution, followed by removal of water.

Nanoparticle formulation

A nanoprecipitation method was used for obtaining polymer nanoparticles, as described here in a typical example: 6 ml of aqueous surfactant solution (1 g/l) were slowly stirred and 3 ml of 1% solution of PCL in acetone were rapidly injected into the vessel. The stirring was continued very slowly for 15 min, then the suspension was left at room temperature for 30 min, before removing the solvent and part of aqueous phase by rotary evaporation. The remaining suspension was thus concentrated to about 2% polymer.

In a similar way, PDMS and PSF nanoparticles were obtained, using THF as organic solvent, instead of acetone.

RESULTS AND DISCUSSION

Monosaccharide-modified cyclosiloxanes

Cyclic siloxanes bearing different monosaccharide units were synthesized by hydrosilylation with D4H of trimethylsilyl-protected mannose, glucose or galactose with an allyl double bond on the glycosidic site, and subsequent deprotection in

heterogeneous medium. The main reaction steps are shown in Scheme 2.

Allyl-containing monosaccharides were obtained by Fischer glycosilation with allyloxyethanol or allyl alcohol, using Amberlite IR-120 Plus cation-exchange resin as catalyst, following in general terms the method described in Lee and Lee.[35] In order to avoid side reactions during hydrosilylation and to enhance the organic solubility of the monosaccharides, the –OH groups were transformed into trimethylsilylether, using trimethylchlorosilane as a protective agent. The complete silylation was checked by IR spectroscopy, following the disappearance of OH absorption band at about 3500 cm^{-1}, as well as the appearance of $Si–CH_3$ deformation absorption band at 1260 cm^{-1} and $Si(CH_3)_3$ characteristic absorption bands at 840 and 760 cm^{-1}. ^1H and ^{13}C-NMR spectroscopy confirmed the silylation reaction by the displacement of the anomeric signals and the appearance of the $Si(CH_3)_3$ signals.

The monosaccharide-modified cyclosiloxanes were obtained by hydrosilylation reactions in the presence of Karstedt's catalyst. The hydrosilylation reaction time was determined by IR spectroscopy, following the disappearance of the Si–H absorption band at 2155 cm^{-1} and of the double bond absorption at 1670 cm^{-1}. Complete addition occurred after a rather long reaction time, typically around 30 h, probably due to sterical hindrance.

The structure of the reaction products was confirmed by ^1H-NMR spectroscopy, as shown in Fig. 1. The disappearance of the double bond signals (around 6 and 5.3 ppm) from the modified saccharides and of the Si–H proton at 4.7 ppm from the D4H, as well as the presence of all the other signals for the protons in the expected compounds, were taken into account. Based on ^1H and ^{13}C-NMR data, only anti-Markovnikov addition occurred.

According to the literature data,[37] the mild and easy deprotection method by incubation or refluxing in methanol is generally used to regenerate the saccharide –OH groups. Nevertheless, it is interesting to note that, in the case of the previously synthesized polymers,[34] this method did not give the expected results, so that we had to use an acidic medium, provided by the gel resin Amberlite IR-120 Plus, in order to cleave the Si–O–C links, while not attacking the Si–O–Si ones. Owing to the large number of protective groups in the cyclosiloxanes, the employment of the same deprotection route seemed appropriate for complete desilylation.

The deprotection reactions required a long time for completion (48 h), established by IR and ^1H-NMR spectroscopy. In IR spectra, the presence of a large band centered at 3500 cm^{-1} assigned to associated OH groups, as well as the disappearance of the trimethylsilyl band at 840 and 760 cm^{-1}, was the major modification that showed the cleavage of the Si–O–C bonds.

Complete deprotection was proved by ^1H-NMR spectra, following the modifications of the chemical shift of the siloxane region, at 0–0.1 ppm and of the anomeric proton. The ^1H-NMR spectra of mannose-modified cyclosiloxane, before and after deprotection (NC1) are presented in Fig. 1.

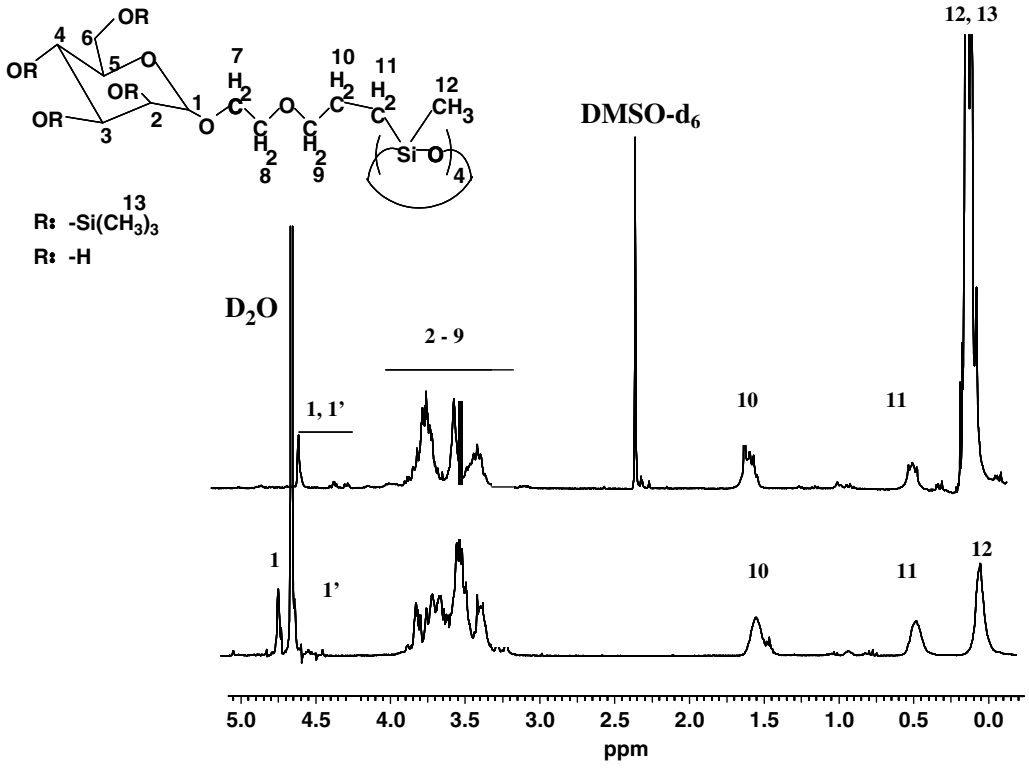


Figure 1. ^1H-NMR spectra of NC1: protected (top) and deprotected (bottom).

In theory, side reactions may occur in the deprotection conditions, since it is known that ion exchangers catalyze the ring-opening polymerization of cyclosiloxanes.[38] We must also consider that, in the presence of methanol, trimethylmethoxysilane is released, and traces of water may favor its condensation to hexamethyldisiloxane. These monofunctional compounds are known to act as chain transfer agents in ring-opening polymerization, thus limiting the chain growth. As in deprotection of monosaccharide-containing cycles a great amount of trimethylmethoxysilane is formed (16 moles per mole of NC), one can expect a complete fragmentation of the cyclotetrasiloxanes to occur in the presence of the acid catalyst, having as a result the formation of MD′M compounds (were M is the usual notation for monofunctional trimethylsilyl-, and D′ for modified difunctional siloxane units). We did not find any information that would support such a hypothesis. The ^{1}H-NMR results showed that, after deprotection with Amberlite gel cation exchanger, the integrals of the $Si(CH_3)$ peaks were in agreement with the expected structure, and no additional protons were found [which would be assigned to $Si(CH_3)_3$ groups, showing the formation of trisiloxane or disiloxane compounds]. The GPC analyses of the derivatized cyclosiloxanes (acylation with acetic anhydride–pyridine) gave molecular weights close to the calculated values. Furthermore, attempts were made to polymerize deprotected cyclosiloxanes in solution (DMSO or methanol), with and without hexamethyldisiloxane as end-blocker, in the presence of a macroporous strong acid ion exchanger (Purolite CT175). This catalyst had been largely employed in the synthesis of polysiloxanes,[38–40] but for saccharide-containing cyclosiloxanes no ring-opening occurred in the tested conditions, as observed by GPC and NMR analyses. A possible explanation for the stability of the modified cycles could be their amphiphilic nature, as well as the sterical hindrance provided by the glycoside units.

Potassium salts of disiloxane acids

Sebacomethylpentamethyldisiloxane and bis-(sebacomethyl) tetramethyldisiloxane were obtained by condensation reactions starting from sebacic acid, its potassium salt, and chloromethylpentamethyldisiloxane or bis-(chloromethyl) tetramethyldisiloxane, in DMF (C 07/1 124 823, Dow Corning, USA).

The potassium salts (A1 and A2, Scheme 3) of mono- and bifunctional disiloxane–ester–sebacic acids were obtained by titration of the corresponding acids with KOH. They were water-soluble compounds, but their aqueous solutions presented a pronounced opalescence, even at concentrations as low as 1 g/l.

Aqueous solution properties and surface activity of the siloxane surfactants

Micelle formation and cmc

The amphiphilic nature of the described compounds is the 'sine qua non' condition for surfactant behavior. For the monosaccharide-modified cyclosiloxanes (nonionic surfactants), the hydrophile–lypophile balance (HLB) was calculated with the formula:

$$\text{HLB} = (\%\ \text{wt of hydrophile part})/5$$

This number, as it was introduced by Griffin,[41] was a criterion for the employment of nonionic surfactants in emulsion applications, based on an empirical scale.[42] According to this scale, the obtained values (Table 1) would insure the use of our nonionic surfactants into the domain of 'oil in water emulsion' (HLB = 10–15).

The anionic compounds A1 and A2 provided turbid aqueous solutions, which is indicative of self-assembly; for example, the turbidity was linked to the presence of a lamellar liquid crystalline phase (EP0436359, Dow Corning, USA). As thermooptical analysis (TOA) allows the determination of the transition temperatures based on the intensity of the transmitted light, we considered it a reliable tool for assigning the respective values. By this method, the temperatures at which the initially turbid 1 g/l solutions became transparent were found to be 62 °C for A1 and 30 °C for A2.

By dynamic light scattering (DLS), the size of the micelles was estimated for the two anionic surfactants, assuming sphericity, at 60 and 30 nm for A1 and A2, respectively.

For all surfactants, cmc was determined by surface tension measurements. The plot of surface tension vs log(concentration) gave the cmc at the inflexion point. The results presented in Table 1 show very low cmc values, comparable to or smaller than reported values for similar surfactants.[43,44] For nonionics the comparison was made with octyl glycosides and for anionics with potassium salts of fluorinated carboxylic acids. The low cmc values have practical interest in insuring the desired effect by using small surfactant amounts. The comparison with other surfactants having the same hydrophilic part shows the efficiency of siloxane hydrophobes in lowering the water surface tension.

The value of minimal surface tension obtained with propyloxyethylene mannoglycoside-modified cyclosiloxane NC1 is close to polysiloxane surface tension. For the other surfactants, higher surface tensions at cmc were found, probably due to the absence of flexible ether linkage, which led to a different conformation of the surfactant molecules at the interface.

Table 1. Characteristics of siloxane surfactants

cmc, M, literature data[43,44]	Surfactant	cmc, M	cmc, mg/l	Surface tension, mN/m	HLB[39]
10^{-4}–10^{-3}	NC1	0.9×10^{-4}	120	27	13.8
	NC2	1.1×10^{-4}	130	41	12.8
	NC3	1.6×10^{-4}	180	35	12.8
10^{-3}–10^{-2}	A1	2.5×10^{-4}	100	45	
	A2	3.1×10^{-4}	200	42	

Table 2. Average diameter of polymer nanoparticles

Polymer core	Surfactant	Average diameter of freshly prepared particles (DLS), nm	Polydispersity index	Average diameter after 3 months, nm	Observations
PCL	NC1	170	0.2	200	Monomodal distribution, good redispersion
	NC1 + indometacin	190	0.1		
	NC2	150	0.1		
	NC3	180	0.15		
	A1	130	0.2		
	A2	100	0.2		
PDMS	NC1	330	0.3	340	Monomodal distribution
	NC1–2[a]	350	0.7		Bimodal distribution
	NC2	240	0.6		Bimodal distribution
	NC3	400	0.6		Bimodal distribution
	A1	260	0.5		
	A2	250	0.5		
PSF[b]	NC1	100			Very homogeneous particle size
	A1	160			

[a] Initial surfactant concentration 2 g/l.
[b] Average size estimated by SEM.

Polymeric nanoparticles formed with siloxane surfactants

Polymers of the same average molecular weight were tested in nanoparticle formulations using these surfactants. As is known, PDMS is a viscous liquid at room temperature, owing to its very low glass transition temperature ($T_g = -123\,^\circ C$), PCL is a semicrystalline polymer, with $T_g = -64\,^\circ C$ and a low melting point ($T_m = 66\,^\circ C$), while Udel polysulfone is an amorphous polymer, with rigid chain, having high T_g (180 °C).

Owing to very low cmc values of the surfactants, initial solutions of 1 g/l were considered suitable for nanoparticle formulations. Polymer nanoparticles were obtained by nanoprecipitation. The resulting concentrated suspensions of nanoparticles were diluted in order to ensure DLS measurements. In this way, agglomeration in big aggregates was avoided as much as possible, in order to estimate the real size of the particles. Nevertheless, in some cases, aggregation did occur and it was emphasized using multimodal analysis mode (CONTIN analysis). In this way, assuming a polydisperse system, in the size distribution curves we could observe multiple peaks (multimodal distribution) if the aggregation occurred or single peaks (monomodal distribution) indicating the absence of particles agglomeration (Table 2).

On the other hand, for microscopic investigations, the diluted preparations were deposited on microscope slides, and the water was removed by vacuum drying. The obtained materials will be referred to as 'dry state'.

As observed in Table 2, the results depend on the nature of polymer core, since general trends can be traced for all the surfactants within the same series of nanoparticles.

For PCL, particles with 100–200 nm diameter and very low polydispersity index were obtained whatever the surfactant. Some sedimentation occurred during storage, but the dimensional stability was excellent, even after 3 months of storing at room temperature, since the redispersed particles showed practically the same size and distribution curves with single peaks in the multimodal analysis mode. The smallest particles were obtained with the two anionic surfactants. Attempts to encapsulate indomethacin in the PCL core (10 wt %) were made, and the size of particles was found to be slightly higher than for the neat polymer. No agglomeration phenomena were observed by DLS. The same tendency of precipitation as for the neat PCL was noticed, with good redispersion on manual shaking.

In dry state, the scanning electron microscopy (SEM) observations showed the real size and shape of the nanoparticles (Fig. 2). Individualized particles as well as large aggregates were observed. The coalescence process is clearly noticeable in Fig. 2(a) and (b), having as a result the formation of spherical microparticles as well as lamellar aggregates. A completely different appearance was noticed for PCL nanoparticles containing indomethacin. No coalescence was observed by SEM, as shown in Fig. 2(c), which could be explained by a reinforcement of the polymer matrix provided by the crystalline hydrophobic drug.

When using PDMS, bigger particles were obtained in the same conditions, with a more pronounced coalescence tendency, as revealed by multimodal mode analysis of DLS (Table 2). Supposing that the reason for this result was the low surfactant content, an attempt was made to double the initial surfactant concentration. No improvement in particles size was obtained, and further, the polydispersity was doubled, which means that increasing the surfactant content increases the aggregation. The best results were obtained with NC1, if we consider the monomodal aspect of the distribution curves.

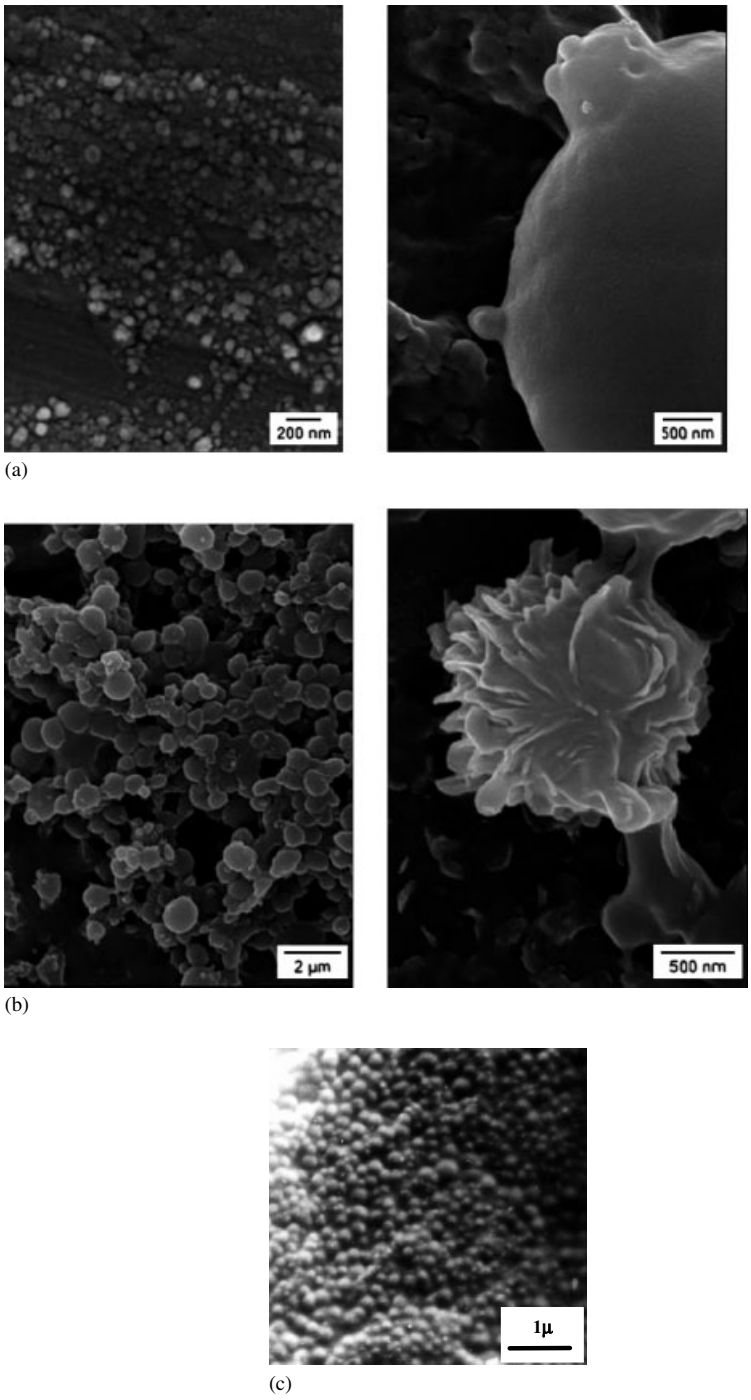


Figure 2. TEM micrographs of PCL nanoparticles: (a) surfactant NC2; (b) surfactant NC3; (c) surfactant NC1, indomethacin encapsulated.

Smaller nanoparticles were obtained again with the anionic surfactants.

In SEM observations (Fig. 3), a dramatic collapse of the particles after removal of water was noticed, which is probably normal if we consider the fact that the polymer is in liquid state at room temperature and that it has a natural tendency of orientation towards the air interface. Interesting results were obtained with anionic surfactants, as shown in Fig. 3(b–d). An organized film was formed after water evaporation from the nanoparticle dispersion. A few domains with nonaggregated nanoparticles remained, but mostly regular convolutions were observed, which are surprisingly similar to the ultrastructure of the surface of Sephadex resins, as described in Kocon *et al*.[45] Such a structuring is probably

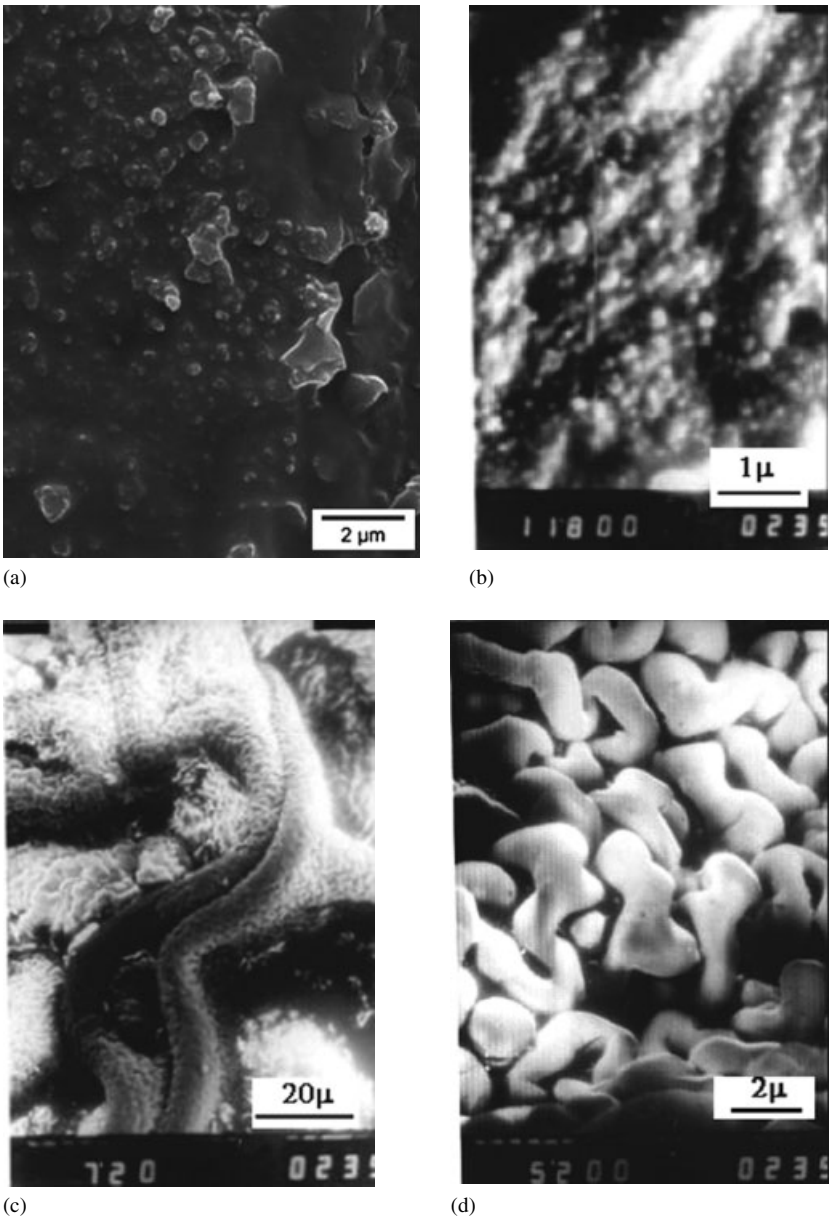


Figure 3. SEM microphotographs of PDMS material after removal of water from nanoparticles: (a) surfactant NC3; (b) surfactant A2; (c) surfactant A1; (d) detail from (c).

due to surfactant self-assembling by electrostatic forces, but it seems that there is also a strong interaction with the polymer core, since the PDMS is the only tested polymer to undergo such a phenomenon.

For PSF nanoparticles, the SEM results allowed us to estimate the particle size at about 100–150 nm. No aggregation phenomena were observed in dry state, as shown in Fig. 4. Very homogeneous, individualized particles were noticed even after a month of storage at room temperature.

These results, and especially the microscopy observations, which differ significantly from one polymer to another, led us to the assumption that the polymer thermal properties, and especially their state of phase at room temperature, are very important in nanoparticle stability in the dry state, at least with the tested surfactants. In water, at great dilution, a certain degree of aggregation was noticed only for PDMS, and no such phenomenon for the other polymers, while in the dry state, the aggregation became significant for PDMS but also for PCL, whatever the surfactant.

As different results were obtained using the same surfactant and different polymers, it seems that the reason for this behavior could be the nature of the core polymer, and not the supramolecular aggregation of the surfactant. We can speculate that the aggregation tendency was more pronounced in the case of polymers with low T_g. For flexible polymers, such as PDMS and PCL, the macromolecules are

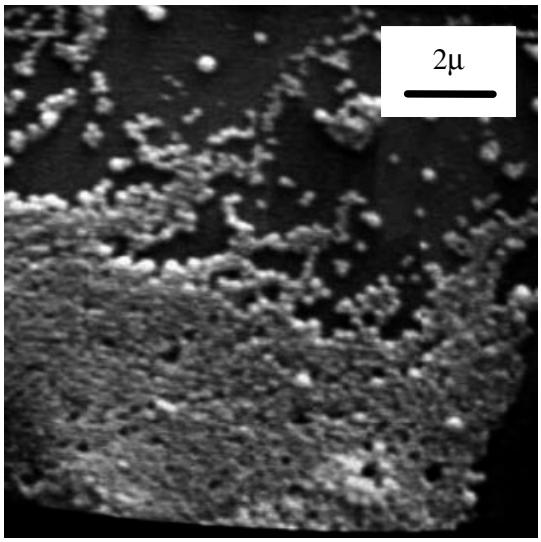


Figure 4. SEM microphotograph of PSF nanoparticles obtained with surfactant A2 (stored for a month at room temperature).

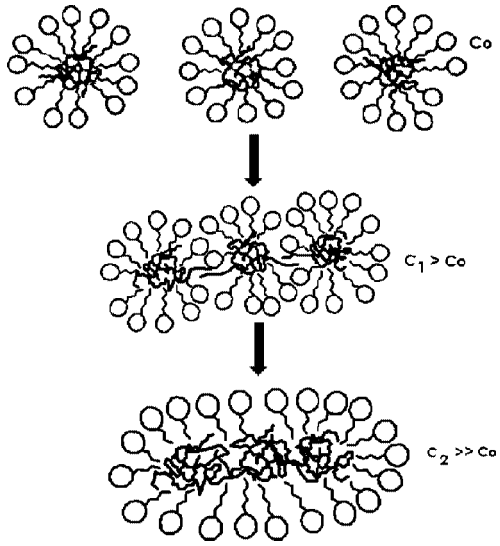


Figure 5. Schematic representation of growth of flexible polymers particles.

able to exit through the surfactant molecules (as schematically represented in Fig. 5), while in the case of the rigid chains of PSF, the thermodynamical conditions for such mobility are not achieved at room temperature. In PCL, intermolecular interactions also have their role, but in PDMS these interactions are practically inexistent, and probably the low T_g and high mobility are the driving force for the collapse of the nanoparticles. The very pronounced hydrophobicity of PDMS could be another key in explaining its behavior. In water, the polymer tends to protect itself as much as possible from the 'hostile' medium, remaining in the hydrophobic cavity of the micelles, despite its aggregation state. After removal of water, PDMS tends to orientate towards air, owing to its very low surface tension. We also have to consider the fact that the hydrophobic part of the surfactant is highly flexible siloxane, which allows the flexible polymer chains to exit from the core. Extensive study is required to verify such a hypothesis, but an interesting argument could be based on the results of Eerikäinen *et al.*,[46] who observed that the coalescence of polymer–drug nanoparticles was related to the thermal properties, and particularly to the decrease in T_g.

The choice of a polymer core for specific applications has to take into account its behavior in the formulation of a complex system. For example, in waterborne systems, any one of the three tested polymers could be used, with the required dimensional limitations. Since the polymers, as well as the surfactants, are nontoxic, these types of nanoparticles could find biomedical utility as water dispersions. In the dry state, PSF nanoparticles could be used without additives, but PCL nanoparticles are stable when reinforced with hydrophobic low molar mass compounds, such as drugs. An interesting approach could be the use of PDMS for water dispersion of micro/nanoparticles, in an environmental friendly formulation, which would be suitable, for example, in cosmetic formulations. Such possible applications deserve to be explored in the near future.

CONCLUSIONS

Cyclic siloxanes with monosaccharide groups were prepared and characterized. These compounds, as well as potassium salts of siloxane–aliphatic carboxylic acids, were investigated for surfactant properties.

The tested surfactants showed different results in stabilizing polymer nanoparticles in water and in the dry state. Flexible polymers, with negative T_g, can form stable monodisperse particles in water, which exhibit a tendency for aggregation after drying. This tendency increases with the increase of polymer flexibility, and it is completely absent for a rigid polymer, such as PSF. The encapsulation of a solid hydrophobic drug can improve the nanoparticles' stability in the dry state.

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