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Micelle-like association of polysaccharides with hydrophobic end groups

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ABSTRACT

New dextran derivatives with hydrophobic end groups were synthesized by reductive amination of dextran chain ends, followed by chemical modification of the dextran main chain by attachment of cationic groups and/or by crosslinking. Properties of the aggregates formed by hydrophobic association of the end groups were studied by fluorescence, dynamic light scattering, atomic force microscopy and transmission electron microscopy and depended on the length of the dextran chain (6, 10, 25 kDa) and the hydrophobicity of the end group (alkyl, dialkyl, bile acid). All neutral derivatives were able to form micelle-like aggregates above a critical aggregation concentration (0.008–0.159 g/dL). Polarity of the micelle hydrophobic core was close to or lower than that of neutral low molecular surfactants (polarity parameter $I_1/I_3 \approx 0.8–1.13$), aggregation number was 20–30 and hydrodynamic radius 20–30 nm. Attachment of cationic groups to the dextran main chain increased critical aggregation concentration and core polarity, but cationic polymeric surfactants with good association ability could be obtained by an appropriate choice of the content and hydrophobicity of the cationic groups. Cross-linking of the micelle shell with divinylsulfone increased micelle stability to dilution.

1. Introduction

Hydrophilic polymers with hydrophobic end groups can associate with formation of different types of interpolymeric aggregates, similar to low molecular surfactants or amphiphilic block copolymers. Double end (or α, ω−) modified polymers form flower-like micelles and are usually called associative telechelic polymers as they can associate in physical networks giving highly viscoelastic fluids at high concentrations. Therefore, these polymers attracted widespread interest due to their applications as thickeners, adhesives, adsorbants, coatings, flocculants, or surfactants. By comparison, single end modified polymers (or α− modified, semi-telechelic) which can associate into spherical (star like) micelles are less extensively studied (Rubinstein & Dobrynin, 1997) despite their potential application in biotechnology and medicine. Among applications foreseen for semi-telechelic amphiphilic polymers one can mention the steric stabilization of liposomes (Pignatello et al., 2013; Torchilin et al., 2001), nano-scaled colloidal drug carriers (Kuskov et al., 2010) or nanoreactors (Patterson, Cotanda, et al., 2013). In comparison with block-copolymers, these block-like telechelic polymers can be prepared by easier, more reproducible and less expensive methods.

Poly(ethylene glycol) was the polymer of choice for the design of both double and single end modified polymers, due to its known hydrophilicity, presence of reactive end groups, biocompatibility and stealth properties (Beaudoin, Hiorns, Borisov, & François, 2003; Chassenieux, Nicolai, & Durand, 1997; Song, Dai, Tam, Lee, & Goh, 2003; Zhou, Zhuang, Yuan, Jiang, & Zhang, 2000). Other polymers modified at one chain end with hydrophobic moieties were poly (N-isopropylacrylamide) (Ishii et al., 2010; Patterson, Kelley, et al., 2013; Winnik, Davidson, Hamer, & Kitano, 1992), poly[N^5-2-(hydroxyethyl) L-glutamine] (Inomata, Doi, Yamada, Sugimoto, & Nakanishi, 2007), poly (vinyl pyrrolidone) (Kuskov et al., 2010; Rizos, Tsikalas, Tsatsakis, & Shtilman, 2006; Torchilin et al., 2001), poly (2-alkyl-2-oxazoline) (Obeid, Maltseva, Thünemann, Tanaka, & Winnik, 2009; Volet, Chanthavong, Wintgens, & Amiel, 2005), polyvinyl alcohol (Uemura, Hirayama, Hatate, & Macdonald, 2001). Ionic polymers such as poly-(sodium 2-acrylamido-2-methylpropanesulfonate) (Mizusaki, Morishima, Raju, & Winnik, 2001; Yusa, Kamachi, & Morishima, 2000), poly(acrylic acid) (Klijn, Kevelam, & Engberts, 2000; Patterson, Cotanda, et al., 2013) or poly(2-(dimethylamino)ethyl methacrylate) (Báñez, Robinson, Vamvakaki, Lascelles, & Armes, 2000) were also used. Most of the end groups were alkyl (C8–C18) but other hydrophobes were also

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attached to polymers, for example fullerene (C60) (Song et al., 2003), cholesterol (Yusa et al., 2000), phospholipids (Auguste, Prud'homme, Ahl, Meers, & Kohn, 2003), azobenzen (Ishii et al., 2010) or pincer ligands (Patterson, Cotanda, et al., 2013; Patterson, Kelley, et al., 2013).

There are also few oligo- and polysaccharides end modified with hydrophobes: cellulose (Enomoto-Rogers, Kamitakahara, Yoshinaga, & Takano, 2011), dextran with very low molar mass (about 1300) (Zhang & Marchant, 1996) or high molar mass (40 kDa) (Hirsjärvi et al., 2013; Richard, Barras, Younes, Monfilliette-Dupont, & Melnyk, 2008), highly branched oligoxyloglucan (Greffe, Bessueille, Bulone, & Brumer, 2005), O-acetyl-galactoglucomannan (Dax et al., 2013; Lindqvist, Holmback, Eosling, & Salminen, 2013). These derivatives were designed for application as surface active agents (Zhang & Marchant, 1996; Dax et al., 2013), surface coatings for lipid nanocapsules, which can increase their blood half-life (Hirsjärvi et al., 2013; Richard et al., 2008), or additives in paper making (Lindqvist et al., 2013). The hydrophobically modified polysaccharides can be perceived as polymeric analogues of commercially available saccharide surfactants, obtained either from pure saccharides (glucose, maltose or sucrose) (Garofalakis, Murray, & Sarney, 2000) or as mixtures of compounds containing alkyl chains of varying lengths and 1–5 condensed glucoside units) (so called alkyl polyglucosides (Biermann, Schmid, & Schulz, 1993; Sulek & Wasilewski, 2006). Due to their low toxicity, these surfactants are commonly chosen as additives for personal care products (von Rybinski & Hill, 1998), for biological membranes solubilization (Biermann et al., 1993), or as drug delivery systems (Abdelrahim, Simerska, & Toth, 2012; Söderlind, Wollbratt, & von Corswant, 2003).

The use of polysaccharides in the design of new semi-telechelic amphiphilic polymers takes the advantage of the presence of only one reactive end group, which makes possible a chemoselective end modification and allows the maintaining of polymer intrinsic biological properties (aqueous solubility, molecular recognition). Besides, the numerous reactive OH groups along the polymer backbone can be further chemically modified by introducing other functionalities (ionic groups, biologically active compounds) or by cross-linking.

The aim of the present work is the synthesis of a new series of block-like amphiphilic polymers by end attachment of hydrophobic moieties (alkyl, dialkyl, bile acids) to a polysaccharide, dextran of different molar masses. Chemical modifications of the polysaccharide main chain (crosslinking, cationic group introduction) were also performed in order to improve stability and applicability of aggregates. The properties of nanoaggregates formed by the modified polymers in aqueous solutions were studied as a function of the polymer chemical structure (nature of the hydrophobic end chain, molar mass of the dextran chain, presence of crosslinks and/or cationic groups). The size, shape, and polarity of aggregates were determined by a combination of different techniques: fluorescence, dynamic light scattering (DLS), atomic force microscopy (AFM), transmission electron microscopy (TEM).

2. Experimental part

2.1. Materials

Dextran samples from Leuconostoc mesenteroides with molecular weights M_r (as indicated by the supplier) 4000 (D4), 6000 (D6), 9000–11,000 (D10) and 15,000–25,000 (D25) were purchased from Sigma. The weight-average (M_w) and number-average molar masses (M_n) determined by size exclusion chromatography are presented in Table 1. (2′-Aminoethylene)-3α,12α-dihydroxy-5β-cholanoamide (NH_2-CH_2-CH_2-NH-CO-DCA) was prepared from deoxycholic acid (DCA) and ethylenediamine (EDA) using the procedure described by Liu et al. (Liu, Avoce, Song, & Zhu, 2001). All the other reagents were from Aldrich and used as received. DMSO and N-methylformamide (MeF) were dried on molecular sieves.

Table 1
Characteristics of dextran samples used for end modification.

Dextran sample	M_w	M_n	*PI*
D4	4250	2820	1.50
D6	6385	4500	1.42
D10	10,700	7955	1.34
D25	22,946	14,900	1.54

2.2. Polymer synthesis

The codes used for synthesized polymer samples and their descriptions are presented in Fig. 1.

2.2.1. Synthesis of end-modified dextran (DM-R_1)

End modified dextrans (DM-R_1) were synthesized by the reaction of reductive polysaccharide end with an amino group terminated hydrophobe. Synthesis of D10-C18 is given as an example. D10 (1 g, 0.122 mmol) was dissolved in dry DMSO (10 mL) at room temperature (r.t.), then $NaBH_3CN$ (0.1 g) was added to obtain the solution A. Another solution (B) was separately prepared from octadecylamine (0.3 g, 1.12 mmol) and dry MeF (5 mL) heated at 60 °C. Solution B was added drop-wise to solution A, under stirring and heating at 60 °C. The resulted homogeneous mixture was stirred for 48 h at 65 °C, and then poured into methanol (100 mL) for polymer precipitation. The precipitate was recovered by filtration and rinsed on the filter with methanol and chloroform. Two other precipitation/rinsing operations were performed in order to remove all unreacted amine. Drying under vacuum led to 0.8 g white powder (79% yield related to dextran). The modification degree was determined from ^{1}H NMR spectrum taken in DMSO-d_6 (Bruker Avance DRX 400 spectrometer) (Fig. 2) using formula: $(A_{dex}/DP_{dex})/(A_{CH3}/3)$, where A_{dex} and A_{CH3} are the integrals of the peaks assigned to the anomeric protons of the dextran (4.7 ppm,) and methyl protons of the alkyl chain (0.85 ppm,), respectively, and DP_{dex} is the dextran degree of polymerization. The obtained value, 1.02, corresponds to 98% end capped dextran chains. UV analysis (325–330 nm) performed on a 0.1 wt% aqueous solution indicated the complete reduction of intermediate Schiff base derivative to amine derivative.

No degradation of dextran chain occurred during reductive amination, therefore the theoretical molar mass of the end-modified derivatives was calculated as a sum of dextran and end group molecular weights (Table 2).

2.2.2. Synthesis of cationic end modified dextrans (DM-R_1-QR_2X)

Attachment of quaternary ammonium groups to the dextran main chain was realized by a procedure previously elaborated for both linear and crosslinked polysaccharides (Nichifor, Stanciu and Simionescu, 2010), based on the reaction of dextran with an equimolar mixture of a tertiary amine and epichlorohydrin (ECH) in an aqueous medium. The synthesis of D10-C18-QBz16 is given here as an example. D10-C18 (1 g) was dissolved in deionized water (10 mL), then N,N-dimethyl-N-benzylamine (2 mL) and ECH (1 mL) were sequentially added. After stirring for 6 h at 40 °C, the mixture was diluted with 5 mL methanol and precipitated in acetone. The precipitate was further purified by redissolution in a mixture water/methanol (10 mL, 2/1, v/v) and precipitation in acetone. The gel-like product was triturated with acetone until a white solid was obtained. After drying under vacuum, 0.9 g of the final product resulted. The degree of substitution ($X = 100x/(x+y)$, mol%) was

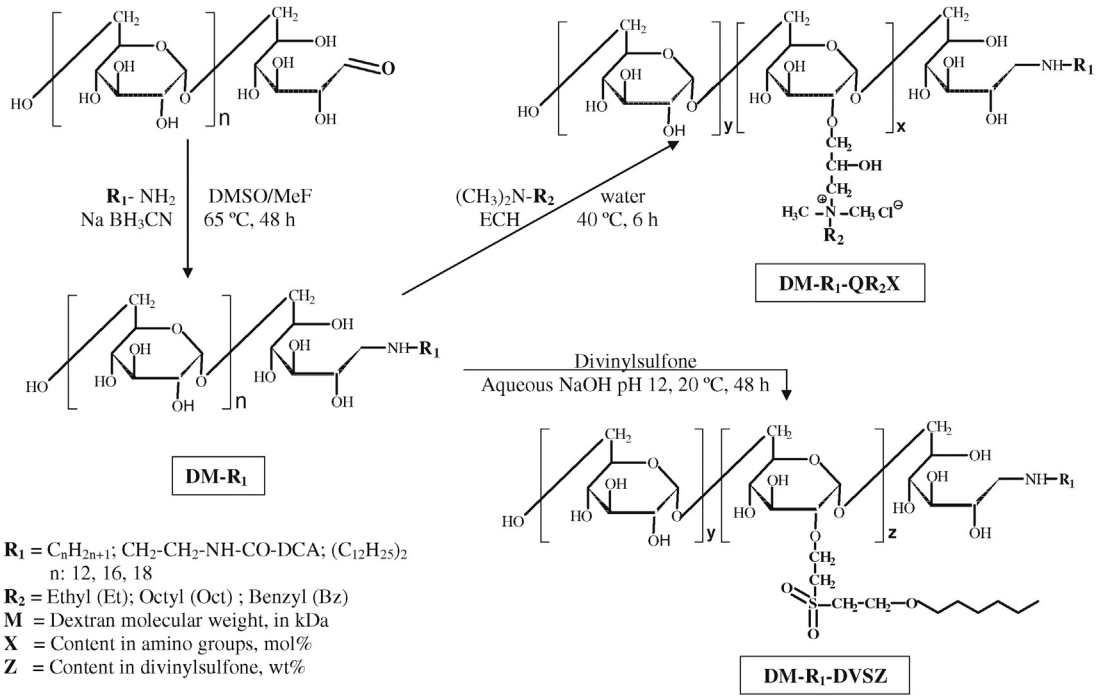

Fig. 1. Synthetic pathways for preparation of end modified dextrans and their cationic and crosslinked derivatives.

Table 2
The main characteristics of the micelles formed by end modified dextrans.

Polymer code	M_n[a]	*CAC*, g/dL (mM)	$(I_1/I_3)_f$[b]	N_{agg}[b]	D_h, nm[b]
D4-C12	3004	0.012 (0.040)	0.88	70	173
D6-C12	4684	0.037 (0.078)	0.95	39	14
D10-C12	8139	0.075 (0.092)	1.09	36	25
D25-C12	15,084	0.159 (0.105)	1.13	21	30
D6-C16	4740	0.016 (0.034)	0.90	31	20
D10-C16	8195	0.040 (0.048)	1.04	29	23
D25-C16	15,140	0.085 (0.060)	1.05	21	29
D4-C18	3087	0.008 (0.026)	0.80	42	124
D6-C18	4767	0.012 (0.025)	0.81	29	18/76
D10-C18	8222	0.025 (0.030)	0.93	25	20/78
D25-C18	15,167	0.058 (0.041)	1.06	21	21/90
D10-diC12	8309	0.029 (0.055)	1.09	20[c]	20
D10-DCA	8390	0.082 (0.096)	0.85	28	74

[a] Calculated as the sum of dextran and end group molecular weights.
[b] Values measured for 1 g/dL polymer aqueous solutions.
[c] Calculated as a function of chain concentration.

determined by elemental analysis of nitrogen and by potentiometric titration of the chloride ions with $AgNO_3$, and was 16 mol%.

A cationic dextran without hydrophobic end group (D10-QOct30) was prepared by the same procedure for comparison.

Quaternization reactions proceeded in a homogeneous medium over the entire modification process, without any micellization of reagents, leading to an even (statistical) distribution of the cationic groups along the dextran chain. The theoretical molecular weight of cationic derivatives was calculated as the sum of dextran and attached groups (both end and pendent groups) molecular weights (Table 3).

2.2.3. Synthesis of crosslinked end modified dextrans (DM-R_1-DVSZ)

End modified dextrans were crosslinked with divinylsulfone (DVS), in an aqueous solution of pH 12. The synthesis of D10-C18-DVS20 is given as a typical example. D10-C18 (0.1 g) was dissolved in a water solution of pH 12 (prepared with NaOH) (50 mL), under stirring at r.t. The reaction vessel was placed in an ice-bath, stirred for 15 min and then DVS (0.2 mL, 2.7 mol/glucopyranosidic unit, U_g) was added dropwise. The reaction continued under stirring for 48 h, at r.t. Finally, the reaction mixture was dialyzed against water (conductometric control of the external fluid) and freeze-dried. Yield: 0.11 g crosslinked product. Crosslinking degree (Z) was evaluated from the sulfur content (4.99 wt%) determined by EDX (Energy Dispersive X-Ray) and was 20 wt% DVS (14.4% yield related to DVS in the reaction mixture).

2.2.4. Cationic crosslinked end modified dextrans (DM-R_1-DVSZ-QR_2X)

These derivatives were prepared by the same procedure described in Section 2.2.2, using DM-R_1-DVSZ as support.

2.3. Size exclusion chromatography analysis

The weight-average (M_w) and number-average molar masses (M_n) of dextran samples were measured with a Shimadzu HPLC System with refractive index detector, a 10 mm × 250 mm

Table 3
The main characteristics of the micelles formed by cationic or/and crosslinked end modified dextrans.

Polymer code	M_n[a]	*CAC*, g/dL (mM)	$I_1/I_3)_f$[b]	N_{agg}[b]	D_h,[b] nm	Zeta potential,[b] mV
D10-C12-QOct30	11,980	0.100 (0.084)	1.25	6	368	28
D10-C12-QBz30	11,400	0.265 (0.230)	1.37	10	210	26
D10-C12-QBz16	9230	0.202 (0.222)	1.27	13	145	11
D10-C12-QEt30	10,580	0.324 (0.302)	1.43	n.d.	210	43
D10-QOct30	11,634	0.300 (0.257)	1.49	n.d.	346	40
D25-C16-DVS20	–	–	1.18	–	20/125	–
D10-C18-DVS20	–	–	1.04	–	20/92	–
D10-C18-QBz16	9984	0.053 (0.053)	1.15	15	120/330	26
D10-C18-DVS16-QBz16	–	–	1.06	–	33/190	30

[a] Calculated as the sum of dextran and attached groups (both end and pendent groups) molecular weights.
[b] Values measured for 1 g/dL polymer aqueous solutions.

column packed with 5 μm mixed bed linear Jordi DVB Glucose gel (Grace Davison Discovery Science™). Polymer solution (0.5 mg/mL, 100 μL) was injected into column and elution was performed with aqueous 1 N NaOH (0.5 mL/min) at 25 °C. Dextran standards were used for calibration. The results are included in Table 1. The measured M_n values were used for the calculation of polymer molar content and quantitative evaluation of end chain modification from ^{1}H NMR spectra.

2.4. Fluorescence experiments

Steady-state fluorescence emission spectra were obtained with a LS 55 PerkinElmer fluorescence spectrometer, using an excitation wavelength of 337 nm and slits set at 6 and 3 for excitation and emission, respectively. The onset of polymer aggregation, critical aggregation concentration (*CAC*), was determined using polymer solutions with concentrations ranging from 0.001 to 1 g/dL prepared by dilution of polymer stock solutions (2.0 g/dL). Millipore water containing ≈10^{-6} M pyrene (Py) was used for the stock solutions preparation and for their dilution. All solutions were left at room temperature for 24 h prior to measurement. The emission intensities measured at 373 nm (I_1) and 383 nm (I_3), the first and third vibronic peaks in the pyrene fluorescence emission spectra, were used to calculate the ratio I_1/I_3 (polarity parameter) as a function of polymer concentration.

Aggregation number of the polymer aggregates (N_{agg}, the number of polymer chains forming an aggregate) was determined by quenching experiments, with Py as a fluorescent probe (1×10^{-6} M) and cetylpyridinium bromide (CPB) as a quencher ([CPB] = 0.01–0.06 mM). Aliquots of methanol solution of the CPB (1 mM) were added to empty vials and the methanol was evaporated with a stream of argon to form a thin film on the bottom of the vials, then polymer solutions (1 g/dL) prepared with water containing ≈1×10^{-6} M pyrene (Py) were added and the vials content was gently stirred. After 24 h at room temperature, the pyrene emission intensity at 373 nm was measured and used to calculate the ratio (I_0/I), where I_0 and I are Py emission intensities at 373 nm in the absence and the presence of the quencher, respectively. The plots of ln I_0/I against [CPB] gave straight lines which allowed the calculation of N_{agg} with Eqs. (1) and (2).

$$\ln \frac{I_0}{I} = \frac{[CPB]}{[M]} \quad (1)$$

$$N_{agg} = \frac{C_p - CAC}{[M]} \quad (2)$$

where [M] – aggregate concentration, C_p – polymer chain concentration and *CAC* are given in mmol/L.

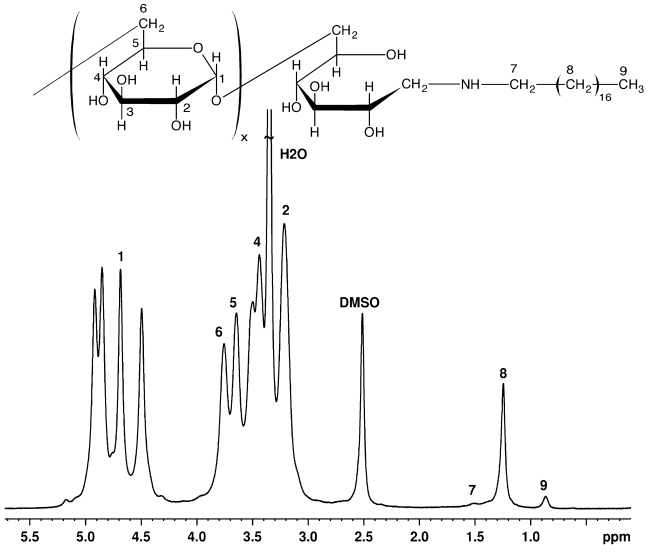

Fig. 2. ^{1}H NMR spectrum in DMSO for dextran derivative D10-C18.

2.5. Aggregate size and Zeta potential determination

The aggregate size (hydrodynamic radius) was measured with a Zetasizer Nano-ZS, ZEN-3500 model (Malvern Instruments) with a He–Ne laser (λ) 633 nm) on 1 g/dL polymer solutions prepared in Millipore water. Solutions were kept at room temperature for at least 12 h prior to analysis. They were filtered through a 0.45 μm Millex Millipore PVDF. The size of particles was determined by cumulant analysis using the software supplied by the manufacturer. The distribution by intensity was mainly used for size evaluation, but distribution by volume was also considered. Distribution by number was very similar to distribution by volume. The same Zetasizer instrument was used to measure zeta potential of aggregates formed in 1 wt% aqueous solutions of cationic polymers. All the reported values are averages of three separate measurements, with a standard deviation of ±4%.

2.6. Atomic force microscopy and transmission electron microscopy

Samples for AFM analysis were prepared as follows: a small amount (20 μL) of a polymer aqueous solution (1 g/dL) was droped on a 22 mm × 22 mm freshly cleaned cover glass (Merrifield, Germany), then water was evaporated at r.t. AFM images were recorded in air with a Scanning Probe Microscope Solver PRO-M (NTMDT, Russia) operated in a tapping mode with a commercially available NSG10 cantilever having a nominal elasticity constant K_N = 11.5 N/m. The samples for TEM measurements were prepared by placing a drop of a polymer solution (2 mg/mL) on a carbon-coated copper grid, then the samples were negatively stained with

an aqueous solution (2 wt%) of phosphotungstic acid and dried at r.t. The TEM images were taken with a HITACHI T7700 microscope (Tokyo, Japan), operated at 120 kV in high resolution mode.

3. Results and discussion

3.1. Polymer synthesis

The synthetic pathways for the preparation of end-modified dextrans and their derivatives are presented in Fig. 1.

3.1.1. End modified dextrans

Any linear polysaccharide has a reducing end aldehyde group, which is prone to reductive amination in the presence of a primary or secondary amine, with formation of an imine (Schiff base) group as an intermediate followed by the conversion of imine to amine in the presence of a reducing agent such as a hydride (Borch, Bernstein, & Durst, 1971). The reducing end is actually in an equilibrium between an open (aldehyde) form and a closed (hemiacetal) form, the later one having a much lower reactivity (Schatz & Lecommandoux, 2010). Therefore, the modification of a polysaccharide end requires large excess of amine derivatives and long reaction times. The reductive amination of dextran samples has been successfully realized in the presence of a large excess of an amine and $NaBH_3CN$ as reducing agent. Generally, a molar ratio end group/primary amine/$NaBH_3CN$ of 1/10/15 was sufficient for a high conversion (95–98% of the polymer chains were end modified) for all primary amine used for synthesis. When a secondary amine–N,N-didodecylamine-has been used, a derivatization in two steps (2 successive reductive aminations) were required in order to completely modify dextran's chain ends, due to lower reactivity of secondary amines comparative to primary amines (Sato, Sakamoto, Miyazawa, & Kikugawa, 2004). Chemical structure and composition were proved by ^{1}H NMR (Fig. 2) and the complete conversion of imine to amine groups was ascertain by UV analysis, which showed the disappearance of the UV absorption peak at 325–330 nm assigned to imine group. The dextran molar mass had no significant influence on the modification degree.

3.1.2. Cationic end modified dextrans

The introduction of ionic groups into the shell of micelle like aggregates can provide new cationic polymeric surfactants with increased application potential due to combination of electrostatic interaction and hydrophobic associations. Cationic polymeric surfactants are recommended as antimicrobial agents, gene delivery vectors or supports for biological compounds. Using a method previously developed for preparation of polysaccharides' cationic derivatives (Nichifor et al., 2010), we introduced pendant quaternary ammonium groups along the dextran main chain and studied the influence of the content (X) and hydrophobicity (given by the substituent R_2, Fig. 1) of these groups on the aggregation ability of the polymers DM-R_1-QR_2X. Ethyl, benzyl or octyl were used in the present study as R_2 substituent, in order the preserve the hydrophilic character of the polysaccharide chain and shell-core like aggregation. A previous study on the aggregation of cationic derivatives DM-QR_2X (Nichifor, Lopes, Bastos, & Lopes, 2004) showed that longer alkyl substituents ($\geq$C12) led to a significant collapse of the polysaccharide by intramolecular hydrophobic interactions, which would prevent the formation of inter-chain micelle-like aggregates.

3.1.3. Crosslinked end modified dextrans

The stability of polymeric micelles formed by block copolymer or block-like end modified polymers in the blood stream is a very important issue when they have to be used as drug delivery systems. In the blood stream, the micelles are prone to extensive dilution, which can go below the polymer *CAC*. Therefore, the stabilization through covalent intramicellar crosslinking of either the shell or the core of the core–shell micelles can lead to well defined nanostructured materials (Wooley, 2000). Shell cross-linked micelles combine the properties of micelles and nanoparticles with various applications such as targeted drug delivery or entrapment of environmental pollutants (Liu, Weaver, Save, & Armes, 2002). In order to preserve the aggregate form and size, crosslinking of DM-R_1 samples was performed by chemical modification of dextran main chain with DVS in aqueous solution of pH 12. The crosslinking reaction was performed at polymer concentrations (0.1–0.5 g%) higher than its *CAC*, but low enough to avoid inter-micellar cross-linking. DVS has been previously used to selectively crosslink hydroxylated segments in block-copolymers (Liu et al., 2002). The degree of DVS binding (determined from the final content in sulfur) depended on the initial molar ratio DVS/U_g, which should be $\geq$1 in order to obtain stable cross-linked micelles. Only 15% of the DVS amount used in the reaction was bound to polymer, due to reagent involvement in secondary reactions (hydrolysis). ^{1}H NMR analysis of the crosslinked micelles (data not shown) indicated the absence of double bonds.

3.2. Critical aggregation concentration and polarity parameter of aggregates

Fluorescence measurements in the presence of a fluorofore like Py can supply valuable information about the ability of an amphiphilic compound to form aggregates. The variation of Py I_1/I_3 ratio with polymer concentration (Fig. 3) had a sigmoidal profile, with an upper plateau, followed by a gradual decrease of Py parameter toward a lower plateau value. This variation profile clearly indicates the occurrence, above a given concentration, of aggregates with hydrophobic domains able to entrap Py molecules. The polymer concentration corresponding to the onset of the aggregation was defined as critical aggregation concentration (*CAC*, taken as the first inflection point of the curve I_1/I_3 versus concentration), and the I_1/I_3 value corresponding to the final plateau, $(I_1/I_3)_f$, was considered as a measure of the aggregate core hydrophobicity. Lower values of CAC and $(I_1/I_3)_f$ suggest a greater polymer capacity for self-association. The decrease of I_1/I_3 took place over a very large concentration range, a characteristic of amphiphilic polymers which, unlike low molecular weight surfactants, do not assemble cooperatively (Ishii et al., 2010; Mizusaki et al., 2001; Obeid et al., 2009). The cooperativity seems to decrease with increasing alkyl chain length (Fig. 3a), what was also observed for alkylated oligoxyloglucan (Greffe et al., 2005). Both *CAC* and $(I_1/I_3)_f$ depended on the polymer chemical composition. The *CAC* values listed in Table 2 ranged from 0.008 to 0.159 g/dL, an order of magnitude similar to that reported for other polymeric surfactants (Kuskov et al., 2010; Beaudoin et al., 2003; Inomata et al., 2007; Obeid et al., 2009), showing that all these end modified dextrans self-associate even at molar masses as high as 25,000. *CAC* values decreased with increasing monoalkyl chain length and decreasing dextran length. Replacing dodecyl substituent with di-dodecyl led to decrease of *CAC*, but the use of deoxycholic acid had no effect on the value (compare D10-C12 with D10-diC12 and D10-DCA in Table 2). The variation of log(*CAC*) with monoalkyl chain length was linear (Fig. 4), allowing the calculation of the free energy decrease for the transfer of a methylene unit from the bulk phase to the micelle (ΔG_{mic}) using Eq. (3) derived by Rosen (1976) for a homologous series of linear nonionic surfactants.

$$\log CAC = \frac{n\Delta G_{mic}}{2.303RT} + K_{mic} \quad (3)$$

where n is the number of carbon atoms of the alkyl chain and K_{mic} is a constant when the hydrophilic chain is the same. The values

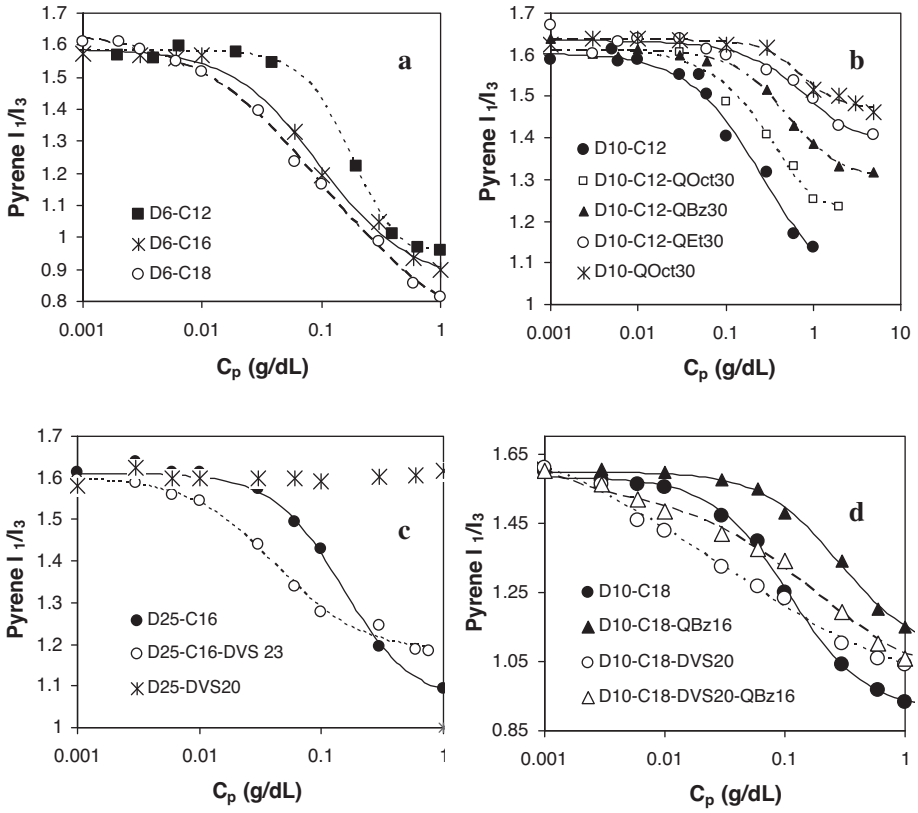

Fig. 3. Variation of pyrene polarity parameter I_1/I_3 with polymer concentration for end-modified dextran derivatives.

calculated for each series of end modified dextrans were −0.54, −0.46 and −0.41 kJ/mol for D6-Cn, D10-Cn and D25-Cn, respectively. A value about −3.0 kJ/mol was predicted by Eastoe, Rogueda, Howe, Pitt, & Heenan, 1996 for single chain surfactant homologues, but values of −2 kJ/mol were found for sugar based surfactants (Augé & Lubin-Germain, 2000). The ΔG_{mic} values calculated with Eq. (3) using the *CMC* values reported for some saccharide surfactants such as β-D-monoglucosides-Cn (−3 kJ/mol) (von Rybinski & Hill, 1998) and *N*-alkyl maltonamides (−1.86 kJ/mol) (Zhang & Marchant, 1996) indicate a clear decrease of ΔG_{mic} with increasing the number of saccharide units from 1 to 2. The comparison with other single end-modified polymers is difficult due to the lack of data about such polymeric surfactants with similar molar masses. Using the reported *CAC* values we calculated a ΔG_{mic} value of about −3 kJ/mol for oligoxyloglucan derivatives with $M_n \sim 1600$ (Greffe et al., 2005) and −1.23 kJ/mol for polyoxazoline with a M_n 5550 (Volet et al., 2005). The *CAC* of poly(vinylpyrrolidone) surfactants with M_n 3500 decreases 3 times by increasing the end bound alkyl chain length from 12 to 18 carbons (Kuskov et al., 2010), and the same variation was observed for all DM-Cn, irrespective of M value. All these data support the conclusion about a much lower influence of the length of alkyl tail on *CAC* comparing with low molecular surfactants, and this influence is further reduced by increasing polymer molar mass.

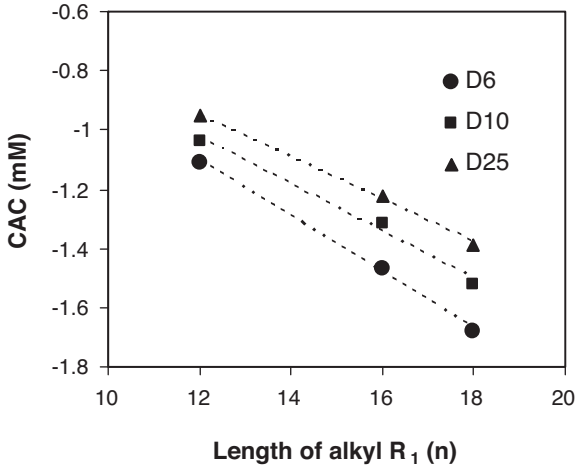

Fig. 4. Variation of critical aggregation concentration, *CAC*, of DM-Cn dextran derivatives, as a function of as a function of the length of alkyl chain (*n*) and dextran molar mass (*M*).

Polarity of the micelle core was influenced by the hydrophobicity of the R_1 end group, and the effect was more evident for lower dextran molar mass. The $(I_1/I_3)_f$ values ranged from 1.13 (D25-C12) to 0.8 (D4-C18). It is worth mentioning that the value 1.13 is still very low and close to that found for SDS and nonionic alkylethylene oxide surfactants (Kalyanasundaram & Thomas, 1977). Presence of an end group with two C12 chains did not change the aggregate core hydrophobicity (as evident by comparing D10-C12 and D10-diC12). By contrary, attachment of a bulky steroid structure (D10-DCA) resulted in a more hydrophobic core than alkyl C18 group (D10-C18).

Attachment of cationic groups along the polysaccharide chain increased both *CAC* values and polarity of the hydrophobic core (Fig. 3b and Table 3), but the loss in association ability was found only when $X > 30$ mol% (data not shown). The increase was enhanced by the hydrophilicity of the R_2 substituent (ethyl > benzyl > octyl) or by a higher content in cationic groups. The cationic group effect on *CAC* was diminished by increasing the length of the end alkyl chain. For example, a comparison of the characteristics obtained for the aggregates formed by D10-C12, D10-C12-QBz16, D10-C18 and D10-C18-QBz16 (Table 2 and 3) shows that the *CAC* increase after the attachment of 16 mol %

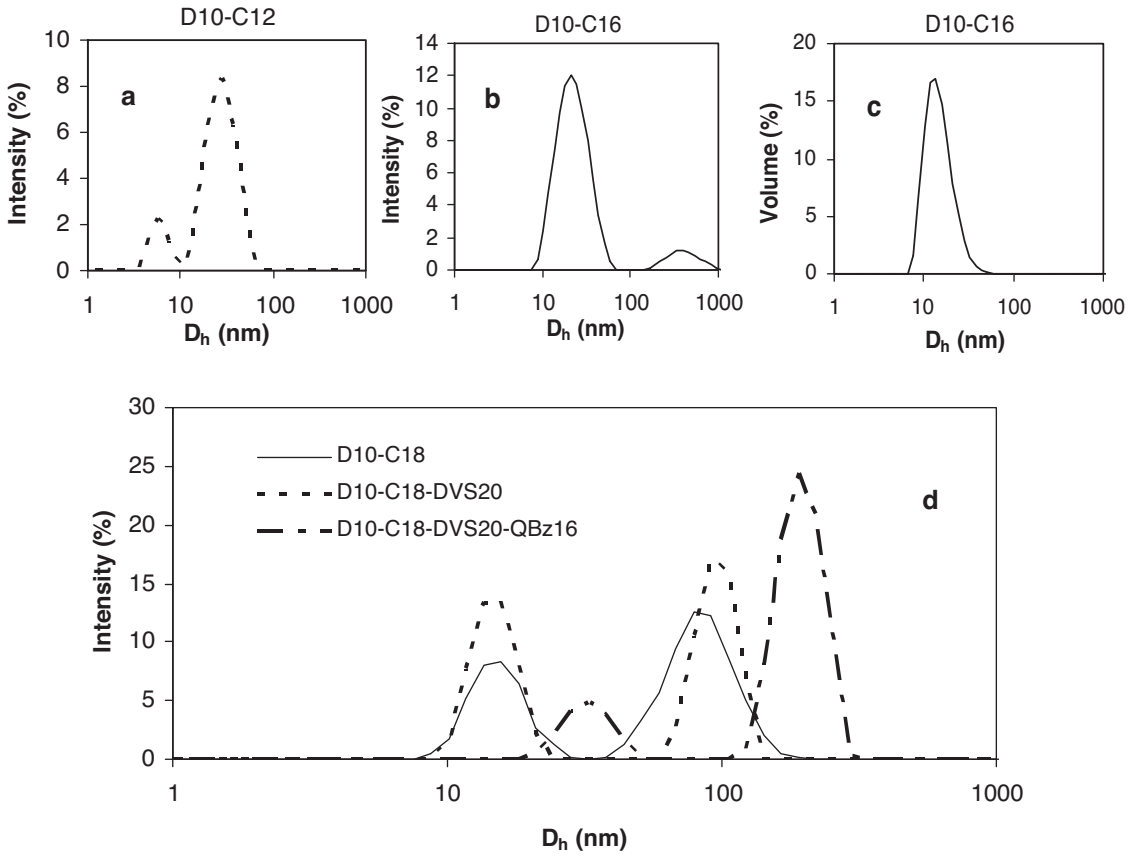

Fig. 5. Hydrodynamic radius distribution for the aggregates formed by end-modified dextran derivatives. Polymer concentration in aqueous solution: 1 wt%.

cationic groups to dextran chains end modified with C12 and C18 alkyl groups was three and two fold, respectively. Among cationic dextrans without end hydrophobic groups (DM-QR_2X), only DM-QOct30 had a slight tendency to self-aggregation (Nichifor et al., 2004, and the present results), but end modification with an alkyl hydrophobe significantly enhanced the polymer self-association (see Fig. 3b, as well as the *CAC* and $(I_1/I_3)_f$ values given in Table 3 for D10-QOct30 and D10-C12-Qoct30). The values of polarity parameter for cationic end modified polymers listed in Table 3 (1.15–1.43) are close to or lower than those reported for cationic surfactants (1.3–1.6, Kalyanasundaram & Thomas, 1977). Positive zeta potential value measured for the aggregates formed by cationic polymers was a supplementary proof for the introduction of cationic groups and their presence at the surface of aggregates. It is evident from these data that cationic polymeric surfactants with good association properties can be obtained by a proper choice of substituents (R_1, R_2) and degree of substitution (X) with cationic groups.

Fig. 3c and d shows the effect of cross-linking on the aggregates formed by end modified dextran. Cross-linking had no influence on aggregation of unmodified dextran (no variation of the ratio I_1/I_3 with concentration of D25-DVS20), but a clear influence was observed on the end modified polymers. Comparing the curves for D25-C16 and D25-C16-DVS20 (Fig. 3c), as well as for D10-C18 and D10-C18-DVS20 (Fig. 3d), three aspects have to be highlighted. First, the I_1/I_3 values are lower than those of non-cross-linked polymer over almost the entire concentration range, indicating that cross-linking did not impair the accessibility of Py molecules inside the hydrophobic core but diminished the influence of the hydrophilic block on core hydrophobicity. Secondly, the curves for cross-linked polymers are much flatter, without a clear inflection point (no clear upper plateau), and this effect is more pronounced for the polymer with C18 end group. Actually, the monotonous variation of I_1/I_3 with concentration of DM-Cn-DVS20 suggests a continuous partition of Py molecules into hydrophobic core of already existing micelles than a discontinuous process (no clear break point corresponding to *CAC* could be observed). The absence of a measurable *CAC* (at least in the concentration range studied) is a proof of increased stability of the cross-linked micelles. Third, the final plateau of the curve for cross-linked polymers corresponds to the I_1/I_3 value found for DM-Cn at the concentration used for its crosslinking (0.2–0.5 g/dL), meaning that the initial density and polarity of the micellar core was preserved in the cross-linked derivative. Moreover, introduction of cationic groups had a much lower effect on the aggregation state of the cross-linked precursor than on the non-crosslinked analogue (Fig. 3d), with hydrophobic core polarity close to that of neutral precursor (Table 3).

3.3. Size and shape of the aggregates

3.3.1. Aggregation number

N_{agg} of DM-Cn was about 20–30 (Table 2), except for the polymers obtained from dextran with the lowest molar mass (D4-Cn), and it was of the same order of magnitude (~16–30) as the N_{agg} values reported for semitelechelic PEO (Ameri, Attwood, Collett, & Booth, 1997) and polyoxazoline (Volet et al., 2005). It decreased slightly with increasing dextran molar mass and with the length of the alkyl hydrophobe. The later finding does not agree with the theoretical model developed for block copolymers (Forster, Zisenis, Wenz, & Antonette, 1996), which predicts an increase of N_{agg} with hydrophobic block length. This rule was obeyed by semitelechelic end alkylated PEO (Ameri et al., 1997) but it was not observed for monoalkylated polyoxazolines (Volet et al., 2005) for which the

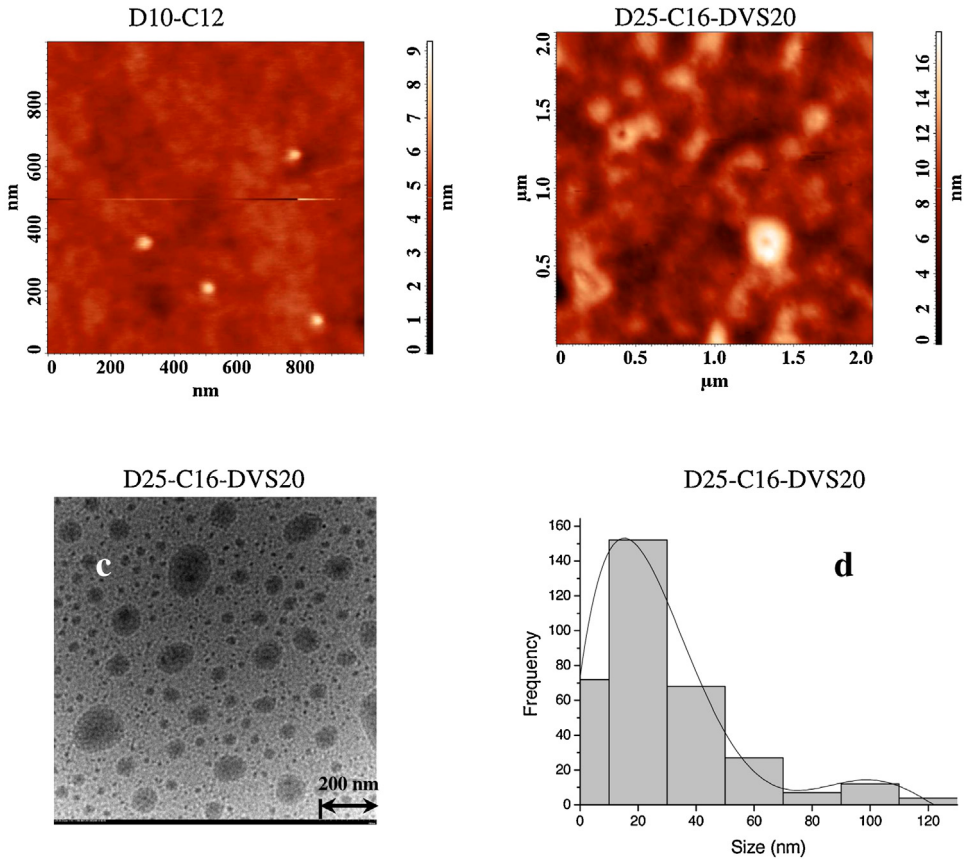

Fig. 6. Microscopic images obtained by AFM (a, b) and TEM (c) for dextran end-modified samples prepared from aqueous solution with 1 wt% (a, b) and 0.2 wt% (c). (d) the size distribution obtained by analysis of the TEM image.

N_{agg} was much lower and decreased with alkyl chain length. In the later case, the low N_{agg} values were explained by higher molar mass of hydrophilic polymer (about 2000 for PEG and 5500–8500 for poly(oxazoline). In case of end-modified dextran derivatives, this behavior might be the result of increasing compactness of hydrophobic core, which may restrict the number of dextran chains in the micelle shell. The N_{agg} of polymers with diC12 and DCA end groups is of the same order of magnitude as for monoalkylated polymers.

The higher N_{agg} values (40–70) observed for D4-Cn derivatives, which are closer to the values reported for classical surfactants, suggests the presence of a threshold in the dextran molar mass, over which the length of the polysaccharide chain is decisive for the final size of the amphiphilic polymer aggregates.

As expected, N_{agg} of cationic derivatives DM-R_1-QR_2X decreased dramatically due to electrostatic repulsion between different charged dextran chains, and the decrease was enhanced by increasing content in cationic groups (Table 3).

3.3.2. Hydrodynamic radius

DLS measurements performed at several polymer concentrations (0.2–1 g/dL, higher than *CAC*) demonstrated a low influence of dilution on aggregate size and size distribution. Therefore, only the results obtained for 1 g/dL aqueous solutions will be discussed in the following.

Hystograms obtained for all the polymeric surfactants studied showed a bimodal distribution, but the size and relative percent of the two populations depended on the alkyl end group length. DM-C12 aqueous solutions contained a main population with a hydrodynamic radius D_h about 20–30 nm and a low percent of very small particles (D_h = 3–6 nm, close to values obtained for unmodified dextrans) (Fig. 5a). The finding suggests an incomplete aggregation of these polymers, leading to the presence of non-associated chains besides aggregates. Polymers with C16 end groups showed also a bimodal distribution, but the smaller particle population had a $D_h \approx$ 20–30 nm and the largest particles had an average D_h higher than 500 nm (Fig. 5b). The bigger particles can be assigned to some clusters of associated micelles, as was shown previously for ω-modified PEGs which can form (in a much lower extent than their α,ω-analogues) some inter-micelle associations proved by a small increase in solution viscosity, compared to unmodified PEG (Chassenieux et al., 1997). Nevertheless, the size distribution by particles volume (Fig. 5c) indicated the preponderant presence of the first population (20–30 nm), therefore in Table 2 only the size corresponding to un-clustered micelles were included. As regarding DM-C18 polymers, the single micelles (about 20 nm) and bigger aggregates (70–90 nm) are present in similar amounts (Fig. 5d, plot for D10-C18), therefore both sizes were included in Table 2. It seems that the tendency to form larger aggregates is enhanced by the presence of longer alkyl chains.

The D_h of single micelles formed by DM-Cn increased slightly with the increase of dextran molar mass and decreased with increasing Cn length. The former variation can be assigned to the increase of the shell thickness due to the presence of longer polysaccharide chains. The influence of Cn length is in agreement with that found for N_{agg}. As expected, the highest aggregates sizes (D_h > 100 nm) were found for D4-Cn. Both N_{agg} and D_h of D10-DCA were much higher than the values reported for micelles of deoxycholic acid (about 10 and 10 nm, respectively) (Mukhopadhyay & Maitra, 2004). This finding deserves a more detailed study and will be the subject of a future work.

Attachment of cationic groups led to much larger aggregates (Table 3), due to extension of each charged dextran chains by intramolecular electrostatic repulsions. According to Fig. 5d, crosslinking resulted in a slight increase in size of particles, with maintenance of a similar polydispersity inside each individual population. Crosslinking prevented a large extension of the cationic dextran chains, as D_h of D10-C18-QBz16 was much higher than that of crosslinked analogue D10-C18-DVS20-QBz16.

3.3.3. AFM and TEM images

Representative AFM images obtained for neutral and crosslinked end-modified dextran derivatives are shown in Fig. 6a and b. The shape of dried aggregates was mainly spherical and their size agreed well with that measured by DLS. A TEM micrograph (Fig. 6c) taken for a diluted aqueous mixture of the crosslinked sample D25-C16-DVS20 clearly revealed the presence of isolated spherical particles. The size distribution obtained by TEM image analysis (Fig. 6d) was bimodal and similar with those obtained by DLS measurements.

4. Conclusions

All synthesized dextran derivatives (neutral or cationic) with a hydrophobic end group (alkyl, dialkyl or bile acid moiety) can form interpolymeric nano-scaled spherical micelle-like aggregates with a hydrophobic dense core and a diffuse polysaccharide corona. The study of aggregates properties by fluorescence, light scattering, atomic force microscopy and transmission electron microscopy revealed that the end group hydrophobicity and dextran molar mass control the aggregation tendency and aggregate properties (core hydrophobicity, aggregation number and hydrodynamic radius). Attachment of less than 30 mol% cationic groups with less hydrophilic substituents (octyl, benzyl) along the dextran chain preserved the micellization ability. Crosslinking of dextran corona stabilized the micelles against dilution. These properties recommend the new dextran derivatives as potential drug delivery systems, antimicrobial agents or surface active agents. The applicability in the mentioned area will be addressed in a future study.

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