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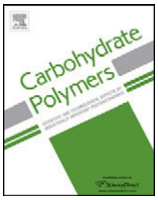

Inverse emulsions stabilized by a hydrophobically modified polysaccharide

Odile Carrier, Rudy Covis, Emmanuelle Marie, Alain Durand*

Laboratoire de Chimie Physique Macromoléculaire CNRS - Nancy-University, ENSIC, 1 rue Grandville, BP 20451, F-54001 Nancy cedex, France

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ABSTRACT

Dextran, a neutral bacterial polysaccharide, was chemically modified by the attachment of n-alkyl chains (hydroxy-2 n-dodecyl) through the formation of ether linkages. The extent of hydrophobic modification was high enough to ensure good solubility of the resulting polymer in organic solvents like chloroform. Furthermore, this polymer was shown to lower interfacial tension between water and dichloromethane with similar effect as to a usual oil-soluble molecular surfactant (Span 80). Submicronic water-in-chloroform emulsions were prepared using the modified dextran as the sole stabilizer with volume fractions of disperse phase up to 30%. The initial average droplet size and storage stability of inverse emulsions was discussed as a function of polymer concentration and volume fraction of disperse phase. Ostwald ripening was shown to dominate emulsion ageing for volume fractions up to 10% while another process accelerated emulsion ageing for higher volume fractions. This process was suggested to be coalescence.

1. Introduction

Dextran is a neutral bacterial polysaccharide consisting of α-1,6 linked glucose rings with a limited fraction of α-1,3 links forming short branches (Nordmeier, 1993). This polysaccharide exhibits valuable properties for biomedical applications like biocompatibility, biodegradability and water-solubility (Lindblad, Sjoeberg, Albertsson, & Hartman, 2007). Dextran properties can be readily modified by performing chemical reactions involving the hydroxyl groups contained in the repeat units (Rodrigues, 2005). It is thus possible to functionalize dextran macromolecules so as to obtain new properties like the ability to adsorb at liquid–liquid or liquid–solid interfaces or to establish specific interactions (Li et al., 2009).

Dextran has been widely studied for the preparation of dextran-covered nanoparticles for drug delivery applications. To that goal, the reactivity of hydroxyl groups within glucose units was used in several ways which can be summarised by distinguishing three strategies. The first strategy involved the use of native dextran directly in the elaboration process. Some chemical reactions (redox for instance) occurred and led to the *in situ* formation of amphiphilic species which were involved in the formation of dextran-covered nanoparticles generally by polymerization in disperse medium (following emulsion polymerization mechanism). This method had the advantage of simplicity and allowed a control of nanoparticle surface characteristics according to the chemical reactions involved (Chern, Lee, & Tsai, 1997; Ladaviere et al., 2007). The second strategy was to synthesize graft copolymers having a dextran backbone and polyester side chains. With convenient number and length of side chains, the resulting glycopolymers were no longer soluble in water and could be used for the preparation of polymeric nanoparticles even without adding any other surfactant. This strategy allowed the preparation of new types of nanoparticles combining polyester and polysaccharide sequences and avoided the need for external surfactant (Gref, Rodrigues, & Couvreur, 2002; Nouvel et al., 2009; Prabu et al., 2008; Rodrigues et al., 2003). The last strategy consisted in converting native dextran into amphiphilic polymers by the attachment of hydrocarbon groups (aliphatic or aromatic) within the polysaccharide backbone (Rotureau, Chassenieux, Dellacherie, & Durand, 2005). These hydrophobically modified dextrans could be used as polymeric stabilizers for the preparation of submicronic oil-in-water emulsions and for adjusting the surface properties of porous or bulk polymeric particles. These properties were applied to the preparation of dextran-covered nanoparticles using several processes like miniemulsion polymerization, emulsion/solvent evaporation and nanoprecipitation (Aumelas, Serrero, Durand, Dellacherie, & Léonard, 2007; Rouzès, Gref, Léonard, De Sousa Delgado, & Dellacherie, 2000). The ageing mechanism of direct submicronic emulsions stabilized by amphiphilic derivatives of dextran has thus been studied in detail (Sadtler, Imbert, & Dellacherie, 2002). On the contrary, the preparation of inverse emulsions using dextran derivatives is rarely considered. Indeed, the reported dextran derivatives generally contain a limited number of hydrocarbon

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* Corresponding author. Tel.: +33 03 83 17 52 92; fax: +33 03 83 37 99 77.
E-mail address: Alain.Durand@ensic.inpl-nancy.fr (A. Durand).

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groups which makes them essentially hydrophilic surfactants without any ability to stabilize water-in-oil emulsions. Even if some work has been carried out about the hydrophobic modification of dextran to a large extent, no attention was paid to the ability of such polymers to stabilize inverse emulsions. In addition, the synthesized dextrans were modified with rather short alkyl groups (n-butyl) (Sanchez-Chaves & Arranz, 1983, 1985).

Polysaccharide-stabilized inverse emulsions could find applications in the preparation of hollow colloidal particles for the encapsulation of hydrophilic molecules (via a double emulsion procedure) as well as for the preparation of particles to be dispersed in non polar solvents (like propellants for aerosol applications). Before considering these applications, it was necessary to investigate how highly modified dextrans could stabilize submicronic water-in-oil emulsions in terms of initial droplet diameter as well as shelf life and ageing processes. Previous work about submicronic oil-in-water emulsions showed that during the first weeks, the main ageing process was Ostwald ripening (Sadtler et al., 2002).

In that work we prepared a hydrophobically modified dextran carrying hydroxy-2 n-dodecyl groups with a high extent of modification (more than one alkyl tail per repeat unit on average). The behaviour of that polymer in organic solution and at oil/water interface was characterized. Finally, the polymer was used as the sole stabilizer for preparing water-in-chloroform submicronic emulsions. The average droplet size and stability of these inverse emulsions could thus be compared to those obtained using a common oil-soluble molecular surfactant, Span 80.

2. Experimental

2.1. Materials

Dextran T40© was purchased from Amersham Pharmacia (Uppsala Sweden). The weight-average molar mass was checked by size exclusion chromatography and found close the value given by the supplier (40,000 g/mol). All other reagents were from Aldrich (Saint Quentin Fallavier, France) and used as received. Dialysis membrane Spectra/Por (MWCO: 6–8000) was supplied by Spectrum laboratories, Inc.

2.2. Synthesis of hydrophobically modified dextran

Dextran T40® (5 g) was dissolved in 100 mL of MillQ water. The required amount of tetrabutylammonium hydroxide (TBAOH) was added to the homogeneous medium. The amount of TBAOH was such that the molar ratio to 1,2-epoxydodecane was 1.5. This compound was commercially available under the form of an aqueous solution (40 wt%). The mixture was stirred during 1 h and freeze-dried. The recovered product was dissolved in DMSO at 50 °C. 1,2-Epoxydodecane was then added in such an amount that the molar ratio to glucose units was 2. The reaction medium was stirred over 96 h. The reaction medium was dialyzed against a 1:1 mixture of water and ethanol (in volume) and finally pure water. The modified polymer was recovered and freeze-dried. Further purification was carried out using a Soxhlet extractor with ethanol. The structure was analyzed by ^{1}H NMR in DMSO d_6. The molar ratio of attached n-decyl chains to sugar repeat unit was 1.64 in the recovered polymer.

2.3. Viscometric measurements

Solutions of modified dextran in $CHCl_3$ with concentrations ranging from 5 to 50 g/L were obtained by the dilution of a primary solution obtained by dissolving 2.5 g of polymer in 50 mL of solvent for 6 h. Viscometric measurements of organic solutions were carried out using an Ostwald-type capillary viscometer (0.46 mm diameter). The temperature was regulated by a circulating bath. Prior to measurements, the solutions were filtered through 0.2 μm filters. Polymer concentration was checked by weighting dry extracts obtained after letting the solutions 17 h in an oven at 110 °C. The found values were always about 90% of the calculated ones.

2.4. Interfacial tension measurements

Interfacial (dichloromethane/water) tension measurements were carried out at 25 °C using a K8 surface tensiometer (Krüss, Germany) with a platinum ring. All samples were equilibrated for a sufficient time (15 min to 1 h) to reach constant readings.

2.5. Emulsion preparation

Inverse emulsions were composed of 0.5 M sodium sulfate aqueous solution solutions dispersed in a chloroform solution of $DexC10_{164}$ or Span 80® (5–25 g/L). The stabilizers were previously dissolved in the continuous phase during 20 h. The total volume of the emulsion was kept equal to 10 mL for all experiments while the volume of dispersed phase was varied. Before sonication, the two phases were mixed by the application of a vortex stirrer during 1 min. The mixture was then sonicated (pulsed mode, 10 W, 1 min in an ice bath) using a Vibracell model 600W (Sonics & Materials Inc., Danbury, CT). Emulsions were kept at 4 °C for stability studies.

2.6. Average droplet size measurement

Nanodroplet sizes were measured by dynamic light scattering at low concentration using a HPPS® from Malvern. Quartz cell was used for all measurements. The reported diameters were the so-called *z*-average diameters from cumulant analysis. Three consecutive series of measurements were accumulated leading to total measurement times of about 5 min. Although this apparatus is able to measure relatively concentrated samples, the emulsions were diluted in water-saturated chloroform. For sizes below 500 nm, the values should be considered to be given with an uncertainty of ±5 nm. For sizes between 500 and 900 nm, the experimental uncertainty is ±10 nm. Finally, the values above 900 nm should be considered as good orders of magnitude.

3. Results and discussion

3.1. Synthesis of hydrophobically modified dextran

Native dextran was a commercial sample, T40©, which was further characterized by size exclusion chromatography. Its weight average molar mass was found close to the value given by the supplier (40,000 g/mol). Dextran is only soluble in some polar solvents like water, dimethylsulfoxide (DMSO), formamide and ethyleneglycol. The attachment of hydrocarbon groups onto the polysaccharide backbone has been reported to be possible in water. It is however not possible to reach high enough extents of modification with those conditions. Consequently, the modification was carried out in DMSO following a procedure adapted from previous work and involving 1,2 epoxydodecane as the alkylating agent and tetrabutylammonium hydroxide as the base (Durand & Dellacherie, 2006). The main advantage of DMSO is that it dissolved all reactants and products. In addition, the use of an epoxide led to the synthesis of dextran ethers having good chemical stability even at extreme pH values, which can be useful for some applications. The extent of modification was quantified by the molar ratio of attached n-alkyl chains to sugar units contained in one chain and will be called the *degree of substitution*. The degree of substitution of the studied dextran derivative was determined by ^{1}H NMR analysis (in deuterated

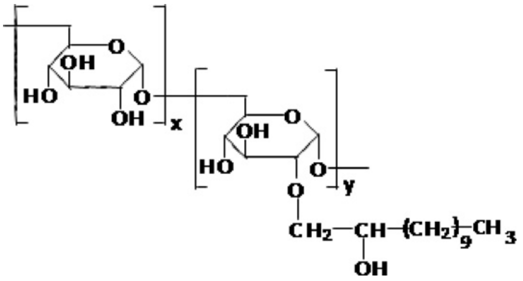

Fig. 1. Chemical structure of the hydrophobically modified dextran noted DexC10$_{164}$. For the sake of clarity only one hydrocarbon tail has been represented (onto the most reactive hydroxyl group). Nevertheless, in the used sample, several hydroxyl groups of each glucose ring were etherified.

DMSO) and found equal to 164%. In what follows, the modified dextran will be denoted DexC10$_{164}$. At this point, we should notice that DexC10$_{164}$ has the same number of hydroxyl groups as the initial unmodified dextran chain since grafting one alkyl chain involves the formation of one hydroxyl group (Fig. 1). Thus, despite the high extent of hydrophobic modification, DexC10$_{164}$ macromolecules should be expected to keep a certain hydrophilic character.

3.2. Solution and interfacial properties of hydrophobically modified dextran

The modified dextran exhibited significant solubility in organic solvents like 1,4-dioxane, tetrahydrofuran (THF), chloroform ($CHCl_3$), dichloromethane and DMSO. Contrary to what has been found previously with other dextran derivatives (obtained by the chemical modification of dextran with phenyl glycidyl ether), DexC10$_{164}$ dissolved in $CHCl_3$ without saturating the solvent with water. This difference may be attributed to the number of carbon atoms contained in the alkyl groups. The solubility characteristics were investigated further by capillary viscometry for solutions in chloroform. Using Huggins equation, we determined an intrinsic viscosity of 12.3 mL/g and a Huggins coefficient equal to 0.7, indicating that DexC10$_{164}$ is in rather good solvent conditions in chloroform. Since native dextran is not soluble in chloroform, this result demonstrates that the solution properties of DexC10$_{164}$ are mainly controlled by the presence of medium length aliphatic groups grafted along the dextran chains. In addition, the good solvent character of chloroform for DexC10$_{164}$ implies that no formation of polymeric aggregates occurs.

The surface active properties of DexC10$_{164}$ were investigated at the dichloromethane/water interface. For comparison, values obtained within the same concentration range with Span 80 were also reported (Fig. 2). The experimental results showed that DexC10$_{164}$ had a strong lowering effect on interfacial tension for polymer concentrations as low as 0.01 g/L. The observed effect was comparable to that of a usual surfactant like Span 80. These results demonstrated that DexC10$_{164}$ had a strong tendency to adsorb at oil/water interface. The polarity of repeat units of dextran and their resulting affinity for the aqueous phase is the most probable driving force of the adsorption of macromolecules at the interface.

All these results confirmed the interest of using DexC10$_{164}$ as a stabilizer for water-in-chloroform emulsions. Indeed the polymer exhibited a strong tendency to adsorb at the liquid–liquid interface (because of the polar repeat units) and may be at the origin of efficient steric stabilization of droplets (through the favourable interactions between grafted repeats units and chloroform).

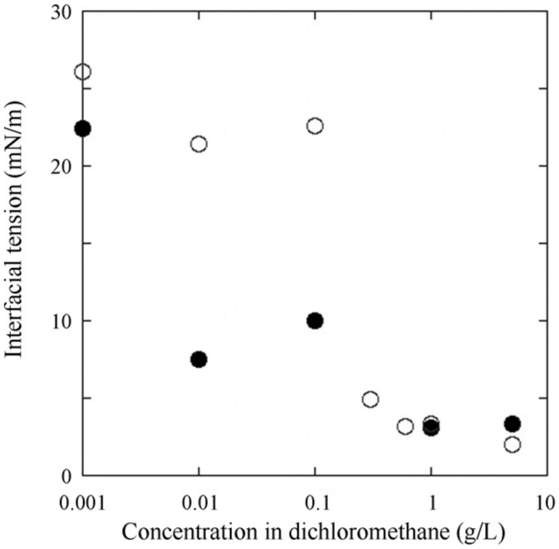

Fig. 2. Interfacial tension between water and dichloromethane as a function of the concentration of DexC10$_{164}$ (bold symbols) or Span 80 (open symbols) in dichloromethane. The temperature was 25 °C.

3.3. Preparation of chloroform-in-water submicronic emulsions

For experimental reasons, chloroform was used instead of dichloromethane for the preparation of emulsions. The higher boiling point of chloroform allowed a complete characterization of the physico-chemical properties of the formed emulsions while dichloromethane evaporated rapidly at room temperature.

3.3.1. Initial droplet diameter

We focused on the preparation of submicronic emulsions considering their potential applications in the design of drug delivery systems. In such disperse systems, it is well known that Ostwald ripening is the main ageing process. As a result it was necessary to prevent Ostwald ripening by adjusting the formulation of emulsions. Indeed, the solubility of water in $CHCl_3$ (6.82×10^{-1} mol% at 20 °C) is high enough to produce a very fast ageing process. Consequently, sodium sulfate was added in the aqueous phase at a concentration of 0.5 mol/L. The low solubility of sodium sulfate in chloroform makes of this salt a good candidate for slowing down Ostwald ripening.

The initial average droplet diameter was first determined as a function of DexC10$_{164}$ concentration in chloroform (Fig. 3). For a water volume fraction of 5%, submicronic emulsions can be readily prepared with average droplet diameters below 200 nm for high enough DexC10$_{164}$ concentrations. When comparing to emulsions prepared with Span 80 in the same conditions, the obtained diameters are similar except at the lowest concentration.

At a given weight ratio of polymer to water phase, the initial average droplet diameter increases with the volume fraction of disperse phase (Fig. 4). This trend has not been observed in the case of oil-in-water emulsions stabilized by low-modified dextrans within the same range of volume fraction (Rotureau et al., 2006a). On the contrary, with oil-in-water emulsions, the initial average droplet diameter did not vary when changing simultaneously the amounts of oil and polymeric surfactant while keeping constant the weight ratio of both constituents. The difference could be explained by the conformation of adsorbed molecules. In the case of low-modified dextrans, the sticking hydrophobic groups are randomly distributed within polysaccharide chains and give rise to the formation of loops protruding into the (continuous) aqueous phase, thus proving efficient steric repulsions between droplets. These steric

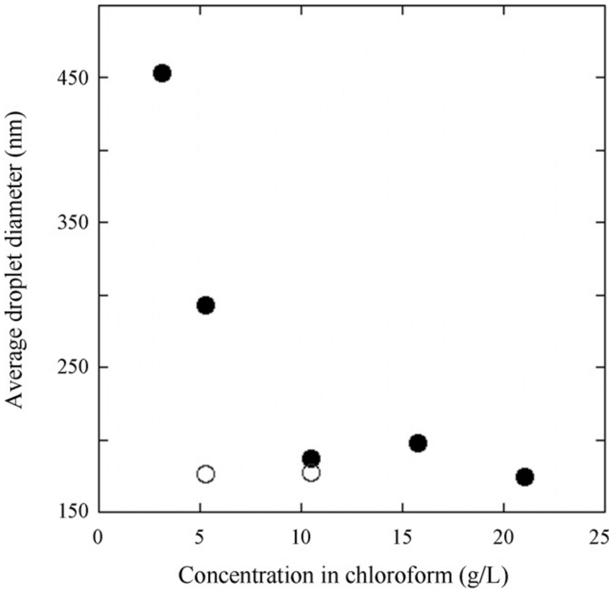

Fig. 3. Average droplet diameter of water-in-chloroform emulsions as a function of DexC10$_{164}$ (bold symbols) or Span 80 (open symbols) concentration in the organic phase. The aqueous phase was a 0.5 M sodium sulfate solution and its volume fraction was 0.05.

repulsions reduce efficiently the occurrence of coalescence events, even when the volume fraction of disperse phase is increased up to 30% or 40%. On the contrary, for DexC10$_{164}$, at least one C10 chain is attached within each glucose ring on average. Thus, at the oil/water interface, the polymer conformation may be rather flat which would reduce the efficiency of steric repulsions. Such effect should be particularly critical when the volume fraction of disperse phase increases. Thus even if the primary droplets produced by sonication have lower diameters, rapid coalescence processes may influence significantly the "initial values" observed. This effect is probably not encountered with oil-in-water emulsions prepared in the presence of low-modified dextran derivatives because of more efficient steric repulsions between droplets, coming from the loops of unmodified dextran chains. More experimental data about polymer layer thickness are required to check the proposed explanation which, at that stage, should only be considered as a reasonable basis.

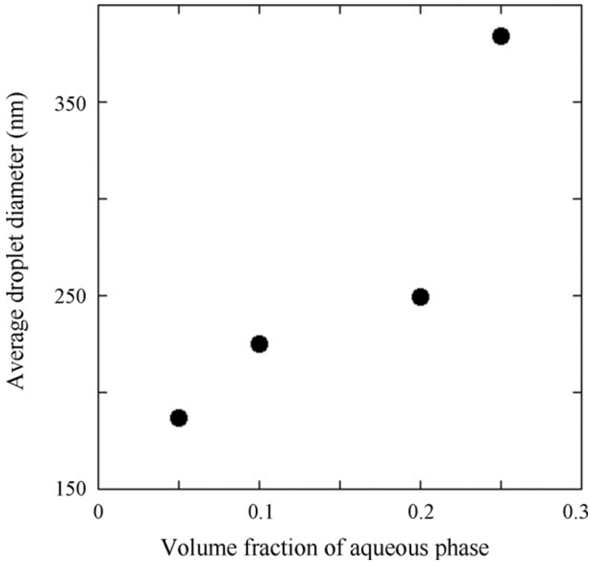

Fig. 4. Average droplet diameter of water-in-chloroform emulsions stabilized by DexC10$_{164}$ as a function of volume fraction of aqueous phase. The weight ratio of DexC10$_{164}$ to aqueous phase was maintained equal to 0.2. The aqueous phase was a 0.5 M sodium sulfate solution.

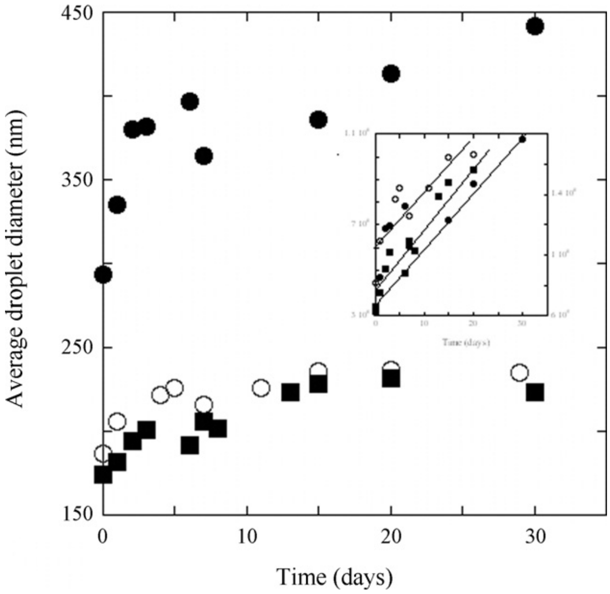

Fig. 5. Average droplet diameter of water-in-chloroform emulsions stabilized by DexC10$_{164}$ as a function of ageing time at 4 °C. The aqueous phase was a 0.5 M sodium sulfate solution with a volume fraction equal to 0.05. The concentration of DexC10$_{164}$ in chloroform was: 5.3 g/L (●), 10.5 g/L (○) and 21.1 g/L (■). Inset: Cube of the average droplet radius as a function of ageing time. Lines are guide for the eye.

3.3.2. *Variation of average droplet diameter with time*

For submicronic emulsion undergoing Ostwald ripening ageing process, it has been established previously that the number-average droplet radius was expected to vary according to Lifshitz and Slyozov (1961):

$$R_d^3(t) = R_d^3(0) + \omega t \tag{1}$$

$$\omega = k(\phi)\frac{8\gamma_i D V_m^2 C_\infty}{9RT} \tag{2}$$

In Eqs. (1) and (2) R_d is the number-average droplet radius, ω (m^3/s) is known as the "ageing rate", γ_i is the interfacial tension (N/m), D is the diffusion coefficient of the disperse phase into the continuous phase (m^2/s), V_m is the molar volume of the disperse liquid (m^3/mol), C_∞ is the solubility of the disperse phase in the continuous phase (mol/m^3), R is the gas constant (8.314 J/mol K), T is the absolute temperature (K) and $k(\phi)$ is a correcting factor taking into account the influence of volume fraction, ϕ. A complete discussion of $k(\phi)$ would be far above the scope of the present study. The theoretical calculations of Enomoto et al. will be used as a convenient basis for discussion (Enomoto, Tokuyama, & Kawasaki, 1986).

Emulsion ageing was followed during storage at a temperature of 4 °C. This low temperature was chosen for limiting solvent evaporation and the resulting non-controlled sample evolution. At a given water volume fraction of 5%, increasing DexC10$_{164}$ concentration in chloroform allowed decreasing the rate of emulsion ageing such that very limited variation of the average droplet diameter was observed over 20 days (Fig. 5). On the contrary, increasing the volume fraction at a constant weight ratio of DexC10$_{164}$ to aqueous phase led to a significant increase of ageing rate (Fig. 6).

By plotting the cube of the average radius as a function of time, a rather linear variation was evidenced which could be interpreted as an indication that molecular diffusion of water between droplets (Ostwald ripening) is the mechanism at the origin of emulsion age-

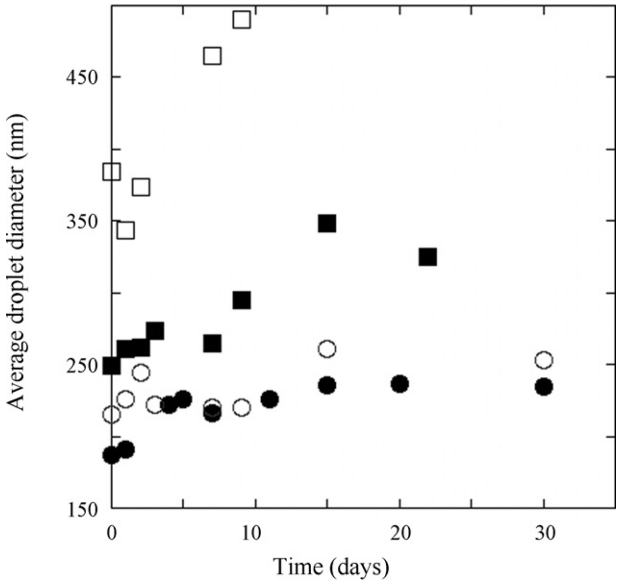

Fig. 6. Average droplet diameter of water-in-chloroform emulsions stabilized by DexC10_{164} as a function of ageing time at 4 °C. The aqueous phase was a 0.5 M sodium sulfate solution. The weight ratio of DexC10_{164} to aqueous phase was equal to 0.2. The volume fraction of aqueous phase was: 0.05 (●), 0.1 (○), 0.2 (■) and 0.25 (□).

ing, at least within the first 30 days following preparation (Fig. 5, inset). The rate of Ostwald ripening was estimated by a linear fitting of the curves giving the cube of the average radius vs. ageing time. In order to take into account the fact that the experimental size values are intensity averaged while Eq. (2) contains a number-averaged radius, the results of curves fitting were divided by 1.48 (Table 1) (Taylor, 1998). These values are one order of magnitude lower than those reported previously for water-in-chloroform emulsions stabilized by a phenoxy-substituted dextran (Durand & Dellacherie, 2006). Nevertheless in that previous work, sodium chloride was used for slowing down Ostwald ripening. In another work, we showed that sodium sulfate was more efficient than sodium chloride as co-stabilizer for glycerol triacetate-in-water inverse emulsions (Raynaud et al., 2008). Thus, the difference in co-stabilizer may explain the observed differences in ageing rates and cannot be attributed to polymer structure. Estimating theoretically these ageing rates would require the knowledge of sodium sulfate solubility in chloroform. As far as we are aware, no values are available for the solubility of electrolytes in chloroform. Thus, it was not possible to compare the values of ageing rates reported in Table 1 to any rough estimation. Nevertheless, using tabulated values of physical properties of water and chloroform, the ageing rate of a dilute emulsion of pure water in chloroform was estimated to 10^{-24} m^3/s (Eq. (2)). The ageing rates of dilute emulsions stabilized by DexC10_{164} are about 3 orders of magnitude lower. This seems reasonable taking into account the surface active effect of the polymer and the osmotic effect of sodium sulfate. Inverse emulsions prepared using a commercial molecular surfactant (Span 80®, Table 1) led to ageing rates lower than those prepared with DexC10_{164}.

Table 1
Ageing rates at 4 °C for water-in-chloroform emulsions stabilized by DexC10_{164} and Span 80® with various volume fractions of aqueous phase and stabilizer concentrations in chloroform. The aqueous phase was a 0.5 M sodium sulfate solution. The values were calculated from average droplet size measurements using Eq. (1) (see text).

Stabilizer	ϕ	C (g/L)	ω (m^3/s)
DexC10_{164}	0.05	5.3	2.1×10^{-27}
		10.5	4.0×10^{-28}
		15.8	3.5×10^{-28}
		21.1	5.1×10^{-28}
	0.2	22.2	1.5×10^{-27}
	0.25	66.7	1.2×10^{-26}
Span 80®	0.05	5.3	0.7×10^{-28}
		10.5	0.9×10^{-28}

When considering the variation of ageing rate with the volume fraction of aqueous phase, it is obvious that its increase above 10% volume fraction is much too sharp to be consistent with that mechanism. Indeed, according to usual theories (Enomoto et al., 1986), increasing volume fraction from 0.05 to 0.25 should give rise to an increase of ageing rate by a factor 1.4 which is one order of magnitude lower than the experimental values. Consequently, we may infer that for volume fractions exceeding 10%, a combination of Ostwald ripening and coalescence processes are involved in overall emulsion ageing. This interpretation is consistent with the one proposed for initial droplet diameter variation with volume fraction (see above). Once again, such variation of ageing rate with volume fraction of disperse phase was not observed with dodecane-in-water emulsions stabilized by water-soluble hydrophobically modified dextrans (Rotureau et al., 2006b). At this stage, we should underline that the variation of volume fraction of aqueous phase was accompanied by a variation of the initial droplet size (Fig. 4). It has been shown that upon increasing droplet size, the mechanism controlling emulsion ageing may change from Ostwald ripening (at low droplet diameters) to coalescence (at higher droplet diameters) (Georgieva, Schmitt, Leal-Calderon, & Langevin, 2009; Schmitt, Cattelet, & Leal-Calderon, 2004). Thus, this increase of initial droplet may also induce a transition of dominant ageing mechanism. With the present data it is not possible to distinguish those two contributions. Further investigations are required for deeper insight into ageing mechanism.

Although emulsion ageing was detected over weeks, it should be noted that, because of the presence of sodium sulfate in the aqueous droplets, the variation of size during the first day was limited, which is an important characteristic for future applications in the preparation of nanoparticles. Indeed, many processes used for preparing nanoparticles involve reaction (polymerization) or physico-chemical steps (evaporation) which require emulsion stability over a couple of hours. The kinetic stability of inverse emulsions with dextran derivatives is thus relevant for the preparation of drug delivery systems by usual processes.

4. Conclusion

Hydrophobically modified dextrans are versatile amphiphilic polymers for which the emulsifying properties can be varied by changing the extent of modification and the nature of attached hydrocarbon groups. In that work, a highly modified dextran carrying hydroxy-2 n-dodecyl groups (more than one per repeat unit on average) was synthesized.

Interfacial tension measurements evidenced the surface active properties of the modified dextran. Submicronic inverse emulsions were prepared using that polymer as the sole surfactant. These emulsions underwent ageing phenomena through Ostwald ripening and coalescence processes. The occurrence of coalescence was attributed to a rather flat conformation of the polymer at interfaces. Nevertheless, since the variation of droplet diameter was limited during the first hours following preparation, these emulsions could be used as intermediates in the formation of nanoparticles for drug delivery applications. The design of such processes is ongoing. In addition, on the basis of these results, new polysaccharide-based polymeric surfactants will be prepared so as to limit coalescence processes and increase emulsion stability even at significant volume fractions of disperse phase. Such results could be obtained by adapting the chemical structure of the polymers to increase steric repulsions either by changing the nature of the hydrophobic tails or by designing graft copolymers.

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