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ORIGINAL CONTRIBUTION

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On the preparation of stable poly(2-hydroxyethyl methacrylate) nanoparticles

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Abstract A comprehensive experimental study of aqueous heterophase homopolymerization of 2-hydroxyetyl methacrylate revealed special conditions that must be fulfilled in order to obtain stable latex particles in the nanometer size range. The results clearly show that the formation and the stability of this kind of hydrophilic latex particle strongly depends on the hydrophobic-hydrophilic properties of both the initiating radicals and the stabilizers. Hydrophobic initiators in combination with sodium alkyl sulfate surfactants of proper chain lengths or ionic surface-active initiators lead to stable latex particles. In the latter case the particles keep their identity and spherical shape even after drying of the aqueous dispersion.

Keywords 2-hydroxyethyl methacrylate · Heterophase polymerization · Latex particles · Hydrophobic initiators · Surface-active initiators

Introduction

Poly(2-hydroxyethyl methacrylate) (P-HEMA) is a polymer used for several medical applications such as soft contact lenses [1], endovascular occlusion of blood vessels [2], and in drug delivery systems [3]. Although the monomer is limitlessly soluble in water, the polymer is not; only highly swellable [4]. The Flory-Huggins interaction coefficients for P-HEMA–water and P-HEMA–HEMA are about 0.8 and 0.57, respectively. Both values increase with increasing polymer volume fraction and so phase separation takes place. In the dry state, P-HEMA is a hard and brittle polymer with a glass transition temperature of about 86 °C [5], but it is soft and flexible in the swollen state. It is swellable in water and aqueous electrolyte solutions by about 40% by weight [6], up to 150% in sodium hydroxide solution [7].

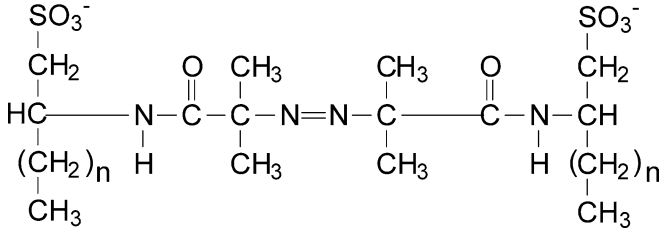
Therefore, the polymerization of 2-hydroxyethyl methacrylate (HEMA) in aqueous media, where HEMA is not only the monomer but also a cosolvent, possesses all of the features of dispersion polymerization; that is, the reaction system is homogenous before the chain growth is initiated, and becomes it heterogeneous as the polymer precipitates with increasing conversion [8]. The size of the polymer particles typically prepared in dispersion polymerizations is in the μm-size range. Suspension polymerization is used for the preparation of monodisperse P-HEMA particles in the size range of a few hundreds of micrometers for biomedical applications [9]. There are a few papers that describe the use of HEMA as a comonomer in emulsion polymerization in order to hydrophilize particle surfaces and to improve latex stability [10–16]. However, only one research group has (recently) described the preparation of P-HEMA particles in the ~100 nm size range using sodium dodecyl sulfate (SDS) and 2,2′-azobisisobutyronitrile (AIBN) as stabilizer and initiator, respectively [17, 18]. According to these results, the experimental conditions in regard to the initiator and emulsifier (type and concentration), as well as the stirring speed are all crucial factors. For instance, the authors described that latex formation was not observed if potassium peroxodisulfate (KPS) was used as water-soluble initiator, or if poly(vinyl alcohol) was

used as sole stabilizer, or if a high monomer content was used [17]. Furthermore, the authors pointed out the crucial role of the stirrer speed as they obtained best results at a stirrer speed of 100 rpm. A recipe published by Chu et al [18] with a medium SDS concentration was the starting point for our own investigations. The aim of our studies was to gain more information about the conditions that govern the homopolymerization of HEMA in aqueous solutions in order to get stable nanoparticles. In particular, various kinds of initiators (hydrophilic, hydrophobic, and surface-active ones) and sodium alkyl sulfate emulsifiers with variable hydrophobic chain lengths have been investigated. The results allow us to gain new insights into the importance of hydrophilic-hydrophobic interactions in aqueous heterophase polymerizations of water-soluble monomers.

Experimental

Surface active initiators (inisurfs) of the 2,2′-azobis (*N*-2′–methylpropanoyl-2-amino-alkyl-1)-sulfonate type (AAS), as depicted in Scheme 1, were prepared via a modified Ritter reaction between the corresponding α-olefin, AIBN, and fuming sulfonic acid as described in [19, 20], and employed as their ammonium salts. The homologous series of alkyl sulfates with different carbon atom numbers (C_C) was prepared as described in [21]. HEMA monomer (Acros) was cleaned by passing it over neutral alumina (Sigma Aldrich). The water was taken from a Seral purification system (PURELAB Plus) with a conductivity of 0.06 μS cm^{-1} and degassed prior to use for the polymerizations. 2,2′-azobisisobutyronitrile (AIBN) from Fluka and benzoyl peroxide (BPO) from Aldrich were both recrystallized from methanol before use.

Symmetrical poly(ethylene glycol)-azo initiators (PEGA), with molecular weights of the poly(ethylene glycol) chains (PEG) as indicated by the subsequent number (PEGA200, PEGA4000), were prepared as described elsewhere [22]. These PEGA initiators may be regarded as non-ionic inisurfs that provide stability to particles due to steric effects, whereas the AAS inisurfs are electrostatic stabilizers.



Scheme 1 Structures of the inisurfs. $n = 2$, 5, 7, 11, 13 (the number of carbon atoms of the α-olefins is $C_C = n + 3$)

Polymerization

All polymerizations were carried out in a 250 ml all-glass reactor. The reactor was equipped with stirrer, reflux condenser, nitrogen inlet and outlet, heating jacket to control the temperature, and a valve on the bottom to remove the latex. Two sets of experiments were carried out. The first study investigated the influence of the chain length of alkyl sulfate emulsifiers with either hydrophilic (KPS), or hydrophobic initiators (2,2′-azobisisobutyronitrile, AIBN, and BPO), and PEGA200 and PEGA4000, with the following recipe at 60 °C: 0.2 g of initiator, except 4 g in the case of PEGA4000 in order to consider the much higher molecular weight, 0.35 g of surfactant (S), 185 g of water (W), and 15 g of HEMA, stirrer speed 100 rpm. In the second study, surface active initiators (see Scheme 1) with various hydrophobic chain lengths were used as combined initiating and stabilizing systems with the following recipe at 90 °C: 0.5 g of inisurf (S), 250 g of water (W), and 3 g of HEMA, stirrer speed 45 rpm.

After the polymerizations, and before any characterization of the latexes was performed, the coagulum was removed by passing the dispersion through a pore 1 or 2 sintered glass frit.

Latex characterization

All latexes were characterized in terms of their solids content with a HR 73 Halogen Moisture Analyzer (Mettler Toledo, Gießen, Germany), and the average particle size was investigated using dynamic light scattering with a NICOMP particle sizer (model 370, NICOMP particle sizing systems, Santa Barbara, California, USA). Using the solids content (*FG* in %), the intensity-weighted average particle size (D_I in nm), and the density of the polymer (ρ_P), the stabilizer efficiency (E in cm^2 g^{-1}, in other words the particle surface per g of stabilizer) could be calculated via Eq. 1 where W is the amount of water and S the amount of surfactant (either sodium alkyl sulfates or surface active initiators). Note, that the efficiency calculated in this way is not a material constant but a good measure for characterizing the performance of the stabilizer during a particular procedure. A value of $\rho_p = 1.289$ g cm^{-3} was used for the calculations, which neglects any influence from the swelling of the particles with water [5].

$$E = \frac{W}{S} \cdot \frac{FG}{100 - FG} \cdot \frac{6}{\rho_P D_I 10^{-7}} \quad (1)$$

Another note is necessary regarding the solids content. A low value of *FG* does not indicate a low conversion, because all of the coagulum was removed by

passing the dispersion through a pore 1 or 2 sintered glass frit. Consequently, *FG* is more a measure of the latex yield and/or the stabilizing ability of the particular recipe. Transmission electron microscopy (TEM) was used to investigate the shapes and morphologies of the P-HEMA particles. TEM was performed with a Zeiss EM 912 Omega microscope operating at 100 kV. For TEM the solids content of the latexes was adjusted to about 0.5% and a suspension preparation technique was employed to deposit the particles on the grid.

Results and discussion

The data summarized in Table 1 prove the strong influence that the initiator type has on the polymerization of HEMA with SDS as emulsifier. KPS, which is the standard initiator for aqueous heterophase polymerizations, leads to almost complete coagulation (latex yield about 8%) and an average hydrodynamic particle diameter of about 250 nm. On the other hand, the hydrophobic initiators AIBN and BPO lead to stable latexes (conversions with regard to latex yield, X_L, of 97 and 100%, respectively) with hydrodynamic diameters below 100 nm. Moreover, the efficiency of SDS is about 1.5 orders of magnitude higher for the nonionic initiators than for KPS. These results highlight the role that the nature of the end groups of the growing chains plays in the particle nucleation process, since hydrophobic end groups such as 2-cyano propyl, or phenyl end groups from AIBN and BPO, respectively, favor the formation of small P-HEMA particles as we will discuss below.

We wish to emphasize that these results are completely different to those for hydrophobic monomers such as styrene, where the latex yields from hydrophilic and hydrophobic initiators are similar [23], and even the kinetics of the polymerizations are not that different [24].

The strong influence of the hydrophobicity of the primary radicals led to the conclusion that the hydrophilic-hydrophobic balance of the stabilizer might also strongly influence the polymerization. The hydrophilic-hydrophobic balance of the initiator emulsifier system (IES) was varied by employing either sodium alkyl sulfates of different C_C ($C_C = 6, 8, 10, 12, 14, 16, 18$) with a given hydrophobic initiator (AIBN), or by using surface-active initiators prepared with α-olefins of different C_C ($C_C = 5, 8, 10, 14, 16$). The results for latex yield, average particle size, and stabilizer efficiency, as shown in Figs. 1, 2, and 3, respectively, confirm the strong influence of the hydrophobicity of the stabilizing system on the homopolymerization of HEMA in aqueous solution. The only common feature for both IES is that the values under consideration strongly depend on C_C, which is a direct measure of the hydrophobicity. For the alkyl sulfates and the inisurfs, latex formation ($X_L > 0$) starts at $C_C = 12$ and $C_C = 8$, respectively, and the maximum

Table 1 Influence of the initiator hydrophobicity on the aqueous heterophase polymerization of HEMA

Initiator	FG (%)	X_L (%)	D_I (nm)	E (cm^2 g^{-1})
AIBN	7.53	97.01	88.80	2.26×10^7
BPO	7.86	100.00	94.30	2.22×10^7
KPS	0.87	8.03	248.20	8.7×10^5

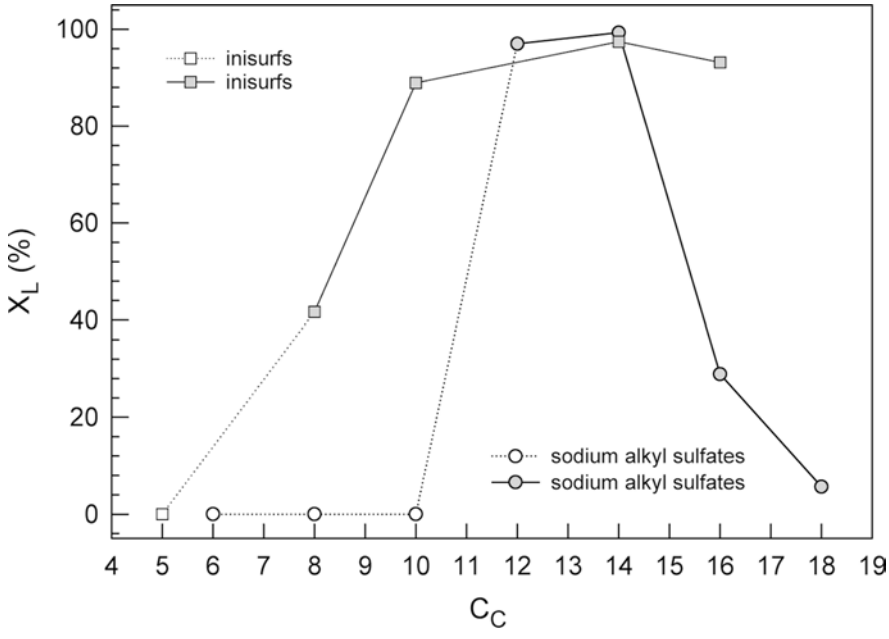


Fig. 1 Dependence of latex yield (X_L) on C_C for both initiator-emulsifier systems. Empty symbols indicate polymerizations where complete coagulation occurred

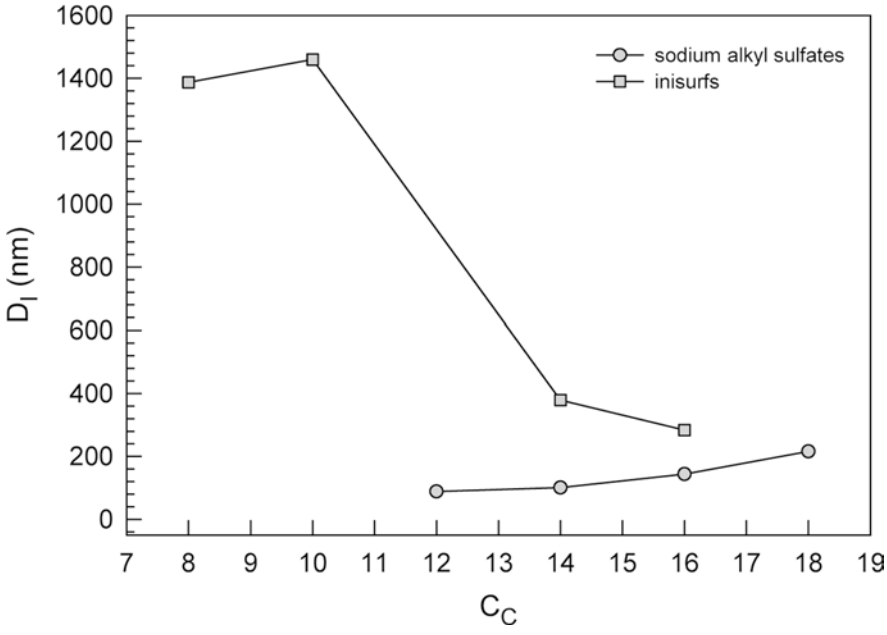


Fig. 2 Dependence of average particle diameters of P-HEMA latexes on C_C for both initiator-emulsifier systems

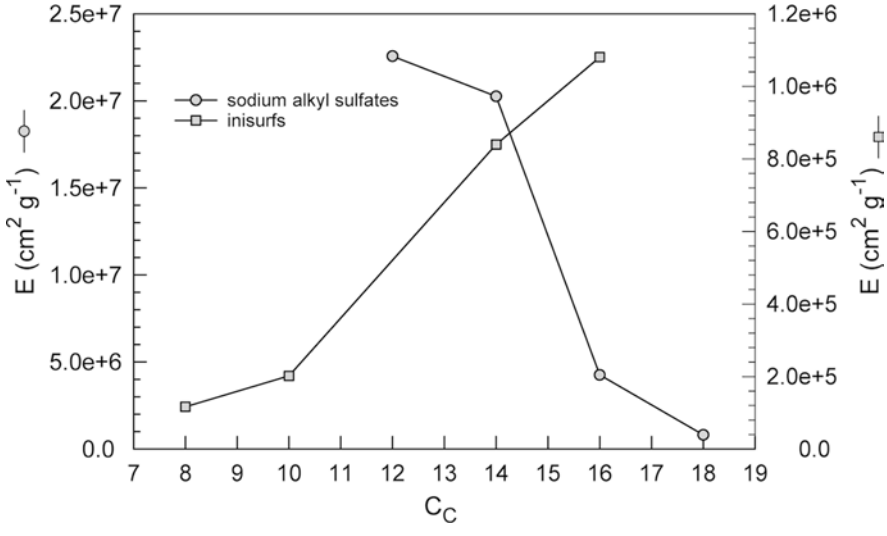


Fig. 3 Dependence of the stabilizer efficiency (E) on C_C for both initiator-emulsifier systems

latex yield is reached at $C_C = 14$ in both cases (see Fig. 1).

Whereas for the inisurfs X_L remains above 90% for $C_C > 8$, it decreases steeply for the alkyl sulfate stabilizers for $C_C > 14$. The average particle sizes (see Fig. 2) increase for the alkyl sulfates but decrease for the inisurfs with increasing C_C.

On the other hand, the efficiencies for the inisurfs increase as C_C increases, whereas they decrease for the alkyl sulfates (see Fig. 3). It is important for the subsequent discussion to emphasize that the concentrations of both the alkyl sulfates and the inisurfs are above the critical micelle concentration (CMC) at C_C values between 12–14. Although this is an estimate based on CMC data for 25 °C [25, 26], it should also be applicable at polymerization temperatures, since the CMC of ionic surfactants generally increases only slightly with increasing temperature [27] and the dependence of the CMC on the alkyl chain length is much steeper than that of the concentration.

The experimental data in Figs. 1, 2, 3 reveal differences in the mechanisms for both types of IES, which are illustrated by the schematic drawings in Figs. 4a, b. The common feature in both cases is that aggregation of oligomers takes place due to the interactions of hydrophobic initiator end groups. As aggregation starts when a proper hydrophilic-hydrophobic balance of the oligomers is reached, the initial HEMA chain length strongly depends on the hydrophobicity of the initiating radicals.

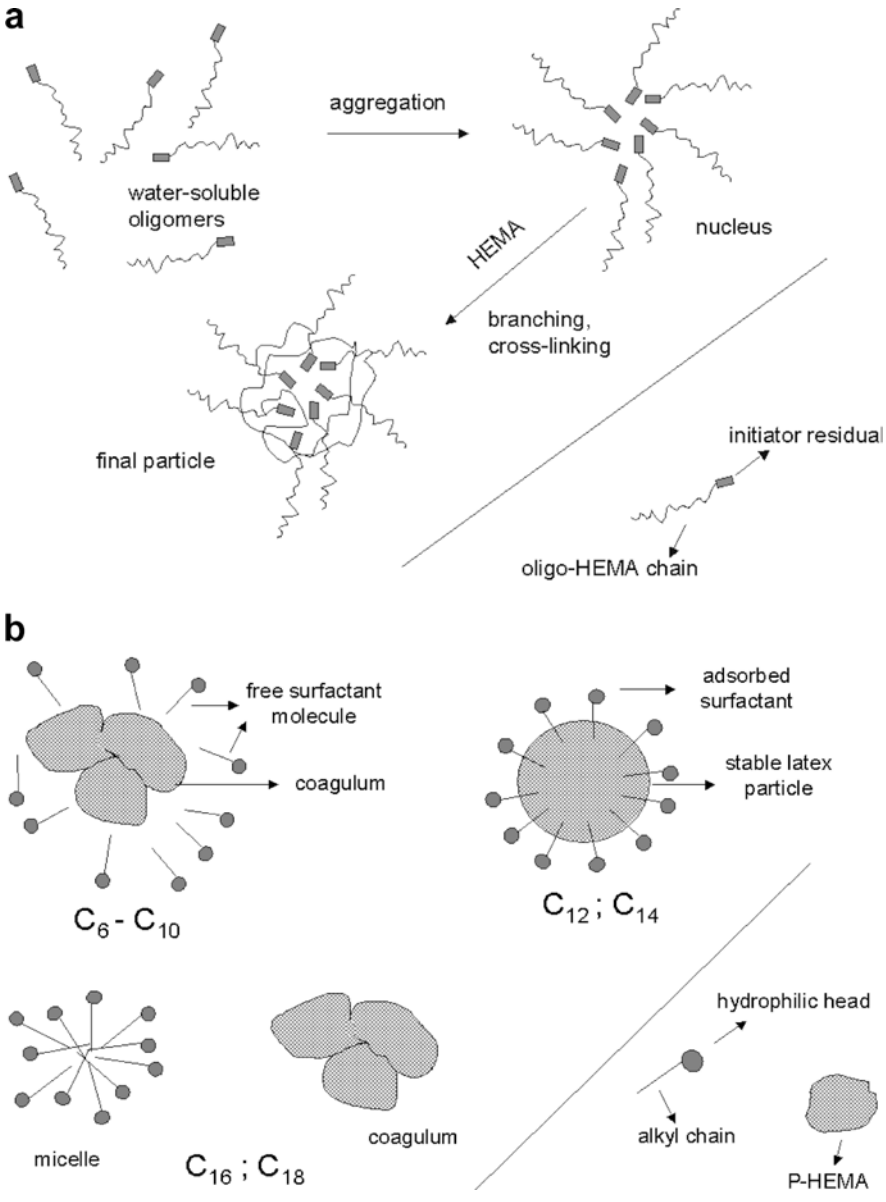


Fig. 4 **a** Sketch of the particle formation mechanism during HEMA polymerization in the aqueous phase due to oligomer aggregation caused by aggregation of hydrophobic initiator end groups (not to scale). **b** Sketch of various states of surfactant distribution for P-HEMA dispersions, and their dependence on C_C, for sodium alkyl sulfate surfactants (not to scale)

The particles might also remain stable if chain growth continues after aggregation. Reasons that this may occur include:

- The longer the P-HEMA chain length, the less hydrophilic the molecule.
- Cross-linking and branching takes place via either impurities, mainly ethylene dimethacrylate, or the so-called dismutation reaction (the coupling of two HEMA units during formation of an ethylene dimethacrylate junction between two P-HEMA chains and the release of glycol [28]).

This controlled or induced (by the initiator end groups) aggregation at an early stage of the polymerization is obviously a necessary prerequisite for the formation of well-defined, nanosized P-HEMA particles. If the aggregation is only caused by the increasing hydrophobicity of the growing P-HEMA chains, the resulting particles do not contain regions of much higher hydrophobicity due to the initiator residuals. The experimental results with the different initiators, either the common types such as KPS, AIBN, and BPO at a given SDS concentration, or the inisurfs, where undecomposed molecules act as surfactant molecules, lead to the conclusion that the presence of hydrophobic domains inside the particles is absolutely necessary for surfactant adsorption, causing stability of the nanosized particles and hindrance of coagulation.

Whether or not surfactant molecules with a given C_C or hydrophobic-hydrophilic balance will adsorb and

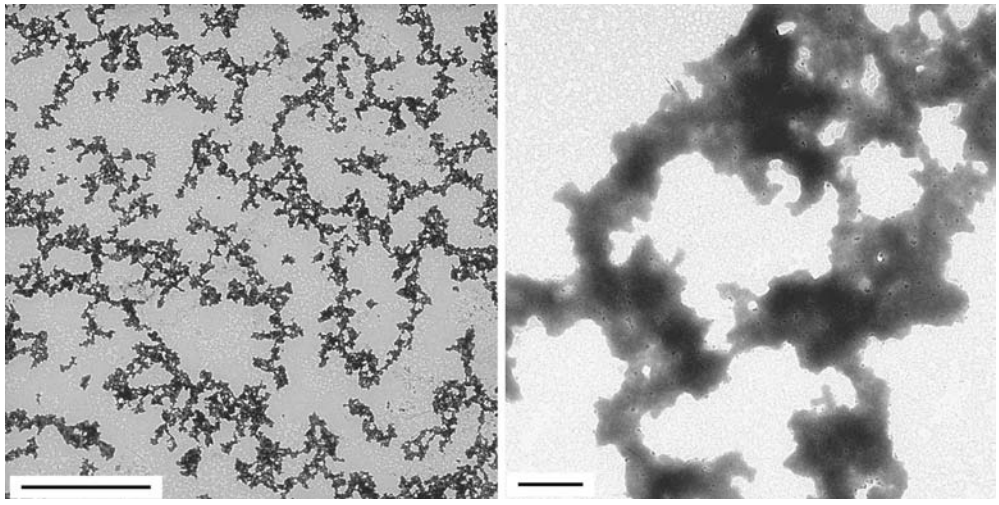


Fig. 5 TEM pictures of dried P-HEMA latex prepared with sodium tetradecyl sulfate as stabilizer at two different magnifications; the bars left and right indicate 10 μm and 500 nm, respectively

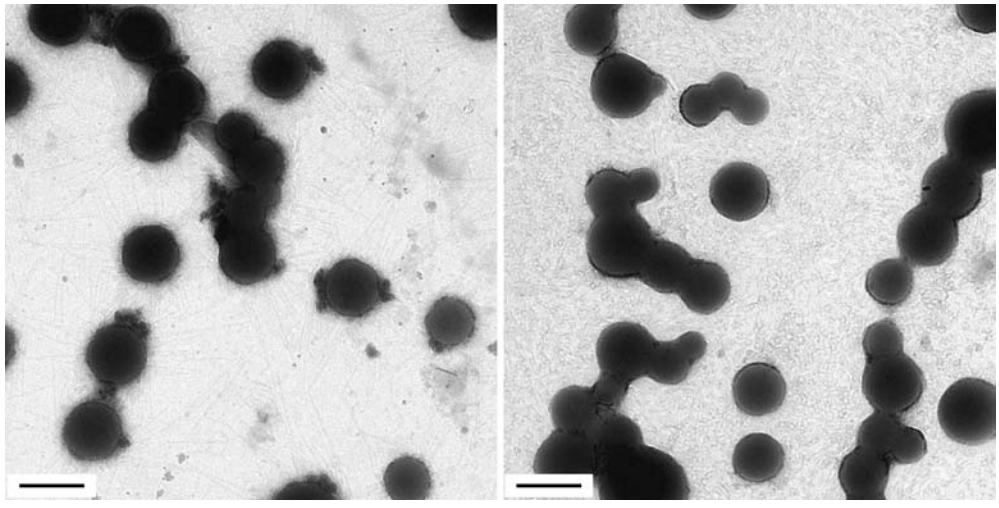


Fig. 6 TEM pictures of dried P-HEMA latexes prepared with inisurfs with two different C_C values. Left: $C_C = 14$, right: $C_C = 16$; the bar indicates 500 nm in both cases

prevent coagulation depends on the energy that the systems can gain, as illustrated in Fig. 4b. Various possible phases compete in dispersions of surfactant molecules: the continuous phase where the surfactants are dissolved, the interface where the surfactants are adsorbed, and the micellar phase where the surfactants are self-assembled. Which of these states will be favored depends on the hydrophobic-hydrophilic balance of the particular surfactant molecules, or C_C for a given class of surfactants. Figure 4b summarizes the experimental data for the aqueous phase polymerization of HEMA with AIBN as initiator and sodium alkyl sulfate surfactants. If C_C is below 10, the surfactants favor the continuous phase, whereas for C_C-values above 14 self-assembly is dominating. The increasing tendency to self-assembly also finds its expression in a decreased critical micelle concentration for surfactants with an extended hydrophobic chain length, where the hydrophobic carbon chains don't like to interact with HEMA or P-HEMA, only with themselves. The optimum C_C-values for dispersion stability are obviously 12 and 14, meaning that the alkyl sulfates are mainly adsorbed at the particle water interface.

For the inisurfs the situation is slightly different, as they affect both the nucleation and the stabilization of the particles. Changing C_C causes a change in the hydrophobicity of the P-HEMA end groups, which directly influences the primary aggregation process. Increasing C_C should lead to the formation of more smaller particles, as verified by the experimental results (see Fig. 2). Moreover, each new polymer chain con-

tributes to the stability since it contains a stabilizing (surface active) end group. On the other hand, the adsorption is influenced as described above. Additionally, adsorption might be favored compared to the other IES as the hydrophobic domain and the adsorbing moiety are chemically identical and have the same C_C. This behavior is indeed observed experimentally, as proven by the efficiency data in Fig. 3 where the IES show opposite behavior.

In general, the adsorption behavior in a given dispersion medium for a given class of surfactants at constant temperature and in the absence of specific interactions is largely governed by the alkyl chain length and the polarity of the interface. When water is the continuous phase, the energy gain due to adsorption per CH_2-group, or the adsorption strength, is lower the higher the polarity of the interface. As the P-HEMA interface is extremely polar, the surfactant adsorption is only weak and so they may easily desorb if conditions such as temperature or particle concentration change. Phase separation takes place (''syneresis'', water expulsion out of the cross-linked material) during the polymerization of HEMA in an aqueous medium [4, 28]. Weakly adsorbed surfactants can easily desorb under such conditions. The consequence of surfactant desorption is coagulation or coalescence of the naked P-HEMA particles. Such conditions occur, for example, during fortification of P-HEMA dispersions, which takes place during electron microscopy sample preparation (so-called suspension preparation). The TEM pictures in Fig. 5 of the P-HEMA latex prepared with sodium tetradecyl sulfate ($C_C = 14$) as stabilizer and AIBN as hydrophobic initiator illustrate this behavior clearly, as no single particles are visible, only typical coagulation structures, and dynamic light scattering gave an intensity weighted diameter of about 101 nm.

In contrast to common surfactants, inisurfs cannot desorb completely since a corresponding portion of them is covalently attached to the polymer. Consequently, TEM pictures of P-HEMA latexes prepared with inisurfs do not show the extended coagulation structure but single particles and multiplets, as is shown for two different inisurfs in Fig. 6. Particles that are deposited in close contact on the TEM grid can partly fuse together due to the influence of the electron beam. Such behavior is typical and also frequently observed for polystyrene particles. This statement only holds for ionic inisurfs, not for nonionic ones. At this point we briefly mention results obtained using PEGA200 and PEGA4000 as nonionic inisurfs that serve as examples in this context. P-HEMA latexes were only obtained if sodium dodecyl sulfate was employed as electrostatic stabilizer as well. In terms of their hydrophobic-hydrophilic properties, PEGA initiators are situated somewhere between the hydrophilic and hydrophobic initiators investigated so far. PEG is soluble in water but also in many organic solvents. It possesses a lower critical solution temperature, which is inversely proportional to the molecular weight, and becomes more and more hydrophobic with increasing temperature [29]. These properties of PEG are clearly reflected in the following polymerization results. PEGA200 resulted in a latex yield of about 70%, and P-HEMA particles had an average hydrodynamic diameter of about 131 nm. In contrast, at elevated temperatures the more hydrophobic PEGA4000 leads to a 100% latex yield and particles with an average hydrodynamic diameter of about 230 nm. Surfactant-free polymerization with both PEGAs resulted in zero latex yields – in other words complete coagulation occurred.

The particles are also unable to preserve their forms during drying, and so typical coagulation structures are observed in this case (TEM picture not shown here).

Conclusions

The preparation of P-HEMA latexes containing particles with sizes below 500 nm in diameter requires very careful selection of the polymerization recipe, especially in terms of the hydrophobic-hydrophilic balance of the initiator-emulsifier system. Hydrophilic initiators such as KPS are not useful, as they lead to complete coagulum formation even in the presence of surfactants. In contrast, hydrophobic initiators such as AIBN, BPO, and PEGA lead to latex yields up to 100%, provided the chain length of the alkyl sulfate stabilizers is in the optimum range (between 12–14). Alternatively, ionic inisurfs such as 2,2′-azobis(*N*-2′-methylpropanoyl-2-amino-alkyl-1)-sulfonates can be successfully used if the alkyl chain length is above 10.

P-HEMA particles prepared with ionic inisurf do not form coagulation structures during drying, almost completely maintaining their forms, so that for the first time TEM pictures of spherical homo P-HEMA particles in the nanometer size range have been obtained. Particles prepared with combinations of common initiators and stabilizers lose their form during drying; due to the syneresis with increasing polymer concentration, not only the water but also the stabilizer molecules are expelled and subsequently coagulation takes place.

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