Nonionic Nanoparticles by Miniemulsion Polymerization of Vinyl Acetate with Oligocaprolactone Macromonomer or Miglyol as Hydrophobe. Application to the Encapsulation of Indomethacin

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ABSTRACT: To produce nonionic nanoparticles suited for the encapsulation of hydrophobic drugs, miniemulsion polymerization of vinyl acetate has been carried out with nonionic surfactants and AIBN or hydrogen peroxide−ascorbic acid system as initiator. In addition, oligocaprolactone macromonomers, benzyl benzoate, or triglycerides from fatty acids (Miglyol) have been used as the hydrophobe in order to get biocompatible systems. These oligocaprolactones have been obtained by anionic coordinated ring-opening polymerization in the presence of a transfer agent. Molecular weights have been controlled by using transfer agents. Finally, encapsulation of indomethacin has been performed by adding the drug in the miniemulsion recipe.

Introduction

For many applications, microencapsulation and drug delivery technologies need small and stable nanoparticles, the average diameter of which must be around 200 nm and able to incorporate hydrophobic components.[1,2] Besides natural vectors, the importance of synthetic polymer structures is now well recognized in order to control the encapsulation as well as the transport and the drug targeting at the desired organ.[3]

These nanoparticles can be obtained directly from preformed polymers by using physicochemical processes such as coacervation, nanoprecipitation, or emulsification−diffusion[4] of polymer organic solutions. Another attractive approach consists of using polymerization of pertinent monomers in disperse media in order to produce directly the required particles. For instance, poly(alkylcyanoacrylate) particles have been obtained by emulsion polymerization. The use of a nonionic surfactant enables to reduce their size up to 50 nm.[5]

Among all heterogeneous polymerization processes, miniemulsion appears to be the most versatile one for that aim. Indeed, contrary to emulsion polymerization, there is no monomer transport from droplets to polymer particles, and the average size of the polymer particles is expected to remain identical to that of the monomer droplets (provided no renucleation occurs during the polymerization). In these systems, the small droplets are protected against monomer diffusion (in suppressing the Ostwald ripening) by the addition of a hydrophobic compound, such as hexadecane, that ensures a low polydispersity in size. Therefore, according to Landfester, the miniemulsion can be described by using a concept of nanoreactors dispersed in an aqueous continuous phase.[6,7] More interestingly, this hydrophobic compound can advantageously be replaced by another polymer.[8,9] This idea enables to get hybrid latexes, provided the latter polymer can be dissolved in the monomer to be polymerized.[10] For instance, hybrids acrylic latexes containing polyimides have been prepared in our laboratory.[11]

Miniemulsion polymerization of vinyl acetate is well-suited to get nanoparticles for the encapsulation of hydrophobic drugs. The challenge is to adapt the classical recipes for the preparation of miniemulsion in order to answer to the constraints required for possible biomedical applications. For instance, usual hydrophobic components such as hexadecane are of course prohibited as much as the ionic surfactants have to be replaced by nonionic ones such as poly(ethylene glycol) (PEG) derivatives. Interestingly, these PEG are often used to prevent the recognition of the particles by the macrophages of the organism and then to prolong the in vivo circulation.[12] Finally, the initiator itself may contribute to the final ζ potential, so that AIBN or hydrogen peroxide is required. Of course, the use of PEG as surfactants as well as other hydrophobes in miniemulsion has already been reported.[7,13] The problem is to use them together in order to give a possible recipe for biocompatible miniemulsions able to encapsulate hydrophobic drugs. Vinyl acetate was chosen as the monomer, keeping in mind that transfer agents would be necessary in order to decrease the molecular weight and get bioresorbable materials.

This paper reports some results about the effects of these various parameters (hydrophobe, surfactant, initiator) on the vinyl acetate miniemulsion polymerization, the aim being to get nonionic particles, the diameter of which lies around 200 nm. The use of oligocaprolactone macromonomers as hydrophobe is particularly highlighted. Some results concerning encapsulation of a hydrophobe drug, namely indomethacin, are also given.

Experimental Section

Materials. For the synthesis of CL macromonomer, THF and alcohols were dried under molecular sieves 3 Å and kept under argon. ϵ-Caprolactone was distilled on calcium hydride under vacuum and kept under molecular sieves.

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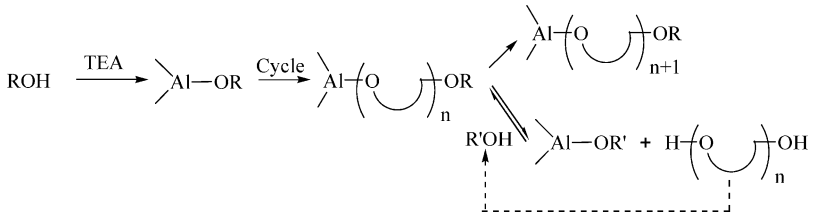
Scheme 1. Ring-Opening Polymerization of Heterocycles: Propagation vs Transfer Reaction



All the miniemulsion polymerizations were carried out using deionized water. Vinyl acetate (Sigma Aldrich) was distilled under vacuum and stored in a refrigerator before use. Miglyol 812N was purchased from Condea.

Macromonomer Synthesis. The CL macromonomer was synthesized by anionic coordinated polymerization in the presence of a transfer agent according to Hamaide et al.[14−16] The initiator used is the aluminum alkoxide obtained by reaction of triethylaluminum (TEA) with the pertinent alcohol (hydroxyethyl methacrylate[14] or 2-allyloxyethanol[17]). The reaction was made in THF under argon in a 250 mL round-bottomed flask. In a first step, TEA and alcohol in excess (1/10 molar ratio) are mixed together in THF at room temperature to form the aluminum alcoholate. ϵ-Caprolactone is then added. The expected degree of polymerization is controlled by the [monomer]/[alcohol] ratio. After complete completion of the monomer, as checked by SEC, the macromonomer is precipitated in cold heptane at −18 °C. The macromonomers are characterized by NMR and Maldi-Tof mass spectrometry.

Miniemulsion Preparation and Polymerization. Miniemulsions were prepared according to the following recipe: the organic phase (20 g composed of vinyl acetate, hydrophobe, indomethacin (IMC), transfer agent, or initiator if organosoluble) and the aqueous phase (180 g composed of water, surfactant, and eventually oxygenated water) were weighted separately. Both phases were purged with nitrogen for 10 min. The miniemulsion was created by dispersing the monomer solution into the water solution and then pouring it into a mixing device (Ultraturrax or Ultrasonic processor Branson; 480W) for 150 s. During this time, the vessel is immersed in a cold water bath to prevent heat-up.

Polymerizations were then carried out under a nitrogen atmosphere in a glass reactor (250 mL) under moderate stirring (250 rpm) at 40−70 °C. Polymerization kinetics and particle size were followed upon sampling at given times. The solid content was usually 10%. Residual monomer can be stripped at 50 °C under vacuum and its elimination checked by gas chromatography.

Monomer droplets and latex particles size distributions were measured by dynamic light scattering (spectrometer LOC Malvern) at a wavelength of 633 nm. The number of particles present in the system is estimated according to the relation $N = [Mp/d_p + M(1 - p)/d_m + M_{hy}/d_{hy}]/(\pi/6)D^3$, where M and M_{hy} are the monomer and hydrophobe charges, respectively, p is the conversion, d is the density (0.94, 1.18, and 0.94 for AcV, PVAc, and Miglyol, respectively), and D is the diameter of the particles.

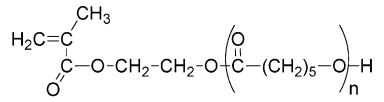
Drug Loading Efficiency. The amount of indomethacin (IMC) loaded inner core of nanoparticles was investigated using a UV spectrophotometer Uvicon 922. A calibration with IMC standard solutions (0−0.007 g/L) was previously carried out.

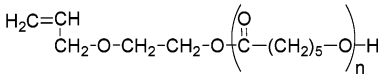
Results and Discussion

1. The Hydrophobic Component. Hexadecane, which is usually utilized as the hydrophobe in a standard recipe, has to be replaced by a biocompatible component. The first idea is to choose an oil such as Miglyol which is employed by chemists to make nanoparticles by emulsification−diffusion procedures.[18,19] In that case, demixtion and phase segregation will occur during polymerization since poly(vinyl acetate) is insoluble in Miglyol. This system would lead to nanoparticles in which small oily domains will be encapsulated in the polymer matrix.

Another step would be to adopt a biocompatible polymer such as polylactide or polycaprolactone since it was found that polymers can be used as the hydrophobic component. Finally, it was thought that a polymerizable function could be grafted on this chain (i.e., using a CL macromonomer) in order to get a branched copolymer. This approach can be compared to that of Chern and Liou,[20] who demonstrated that reactive hydrophobes such as dodecyl methacrylate can be used in order to stabilize the miniemulsions.

A. CL Macromonomer as Hydrophobe. The required macromonomers were synthesized by anionic ring-opening polymerization of ϵ-caprolactone in the presence of hydroxyethyl methacrylate[14] or allyloxyethanol as transfer agent[17] (Scheme 1). The average degree of polymerization is controlled by the [transfer agent]/[ϵ-caprolactone] ratio and varies from 7 to 30 and checked by SEC, NMR, and Maldi-Tof mass spectroscopy. As an example, Figure 1 displays the ^{1}H NMR spectrum of a oligocaprolactone end-capped with an allyloxy ether group obtained by using allyloxyethanol as transfer agent. An average number polymerization degree of 12.1 can be estimated from the intensities of peaks at 3.6−3.7 and 4.0−4.1 ppm. Figure 2 displays the related Maldi mass spectrum. The peaks are assigned to the $[M-Na]^+$ species and are detected at $m/z = 114.114n + 102.133 + 22.989 \pm 0.05\%$. The expansion clearly shows there is no residual impurity in the samples. An average number polymerization degree of 12.7 can be calculated from the mass spectrum, with a polydispersity index of 1.12. Oligocaprolactone end-capped with methacrylate group have been characterized in the same way.[14]





Miniemulsions have been first prepared with 10% PCL macromonomer dissolved in vinyl acetate. Its molecular weight varies between 1400 and 4600 g/mol. A 50/50 mixture of SDS−Triton X-405 (2 g/L of each component in aqueous phase) was used as surfactant. Some attempts have also been performed in order to investigate the dependence of PCL content on the miniemulsion. Polymerizations were carried out at 60 °C with KPS (1%) as initiator, and conversion was followed by measuring the solid content. Some results are reported in Table 1.

The initial droplet size D_m is always around 200 nm at the beginning of the polymerization, whatever the

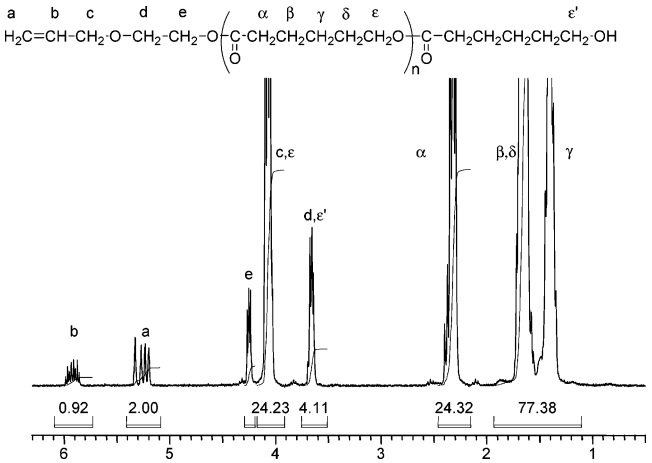


Figure 1. ^{1}H NMR of a functionalized oligocaprolactone obtained from allyloxy ethanol as tranfer agent.

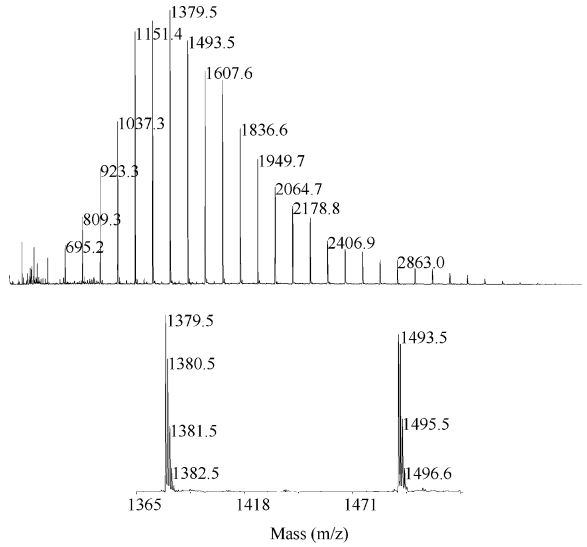


Figure 2. Maldi-Tof mass spectrum of oligocaprolactone end-capped with allyloxy ether group and an expansion. The peaks are assigned to the $[M-Na]^+$ species and are detected at $m/z = 114.114n + 102.133 + 22.989 \pm 0.05\%$.

Table 1. Some Results from Vinyl Acetate Miniemulsion Polymerization with Polycaprolactone (PCL) as Hydrophobe and a Mixture of SDS (2 g/L)−Triton X-405 (2 g/L) as Surfactant; KPS Is the Initiator

M_n PCL (g/mol)	PCL content (%)	polymerization yield	D_m[a] (nm)	I_m[a]	D_p[b] (nm)	I_p[b]	N_p/N_m[c]
1400	10	83	203	0.14	134	0.17	2.75
1600	10	82	186	0.14	133	0.17	2.16
2500	10	54	222	0.18	145	0.32	2.84
3760	10	79	217	0.16	147	0.19	2.54
4600	10	80	199	0.18	127	0.27	3.04
1750	35	67	188	0.21	162	0.26	1.23
2430	35	57	flocculation				

[a] Droplets diameter and polydispersity index. [b] Particles diameter. [c] N_p and N_m are the particles number and the droplets number, respectively. The values are determined according to the relation $N = (V/d)/[(\pi/6)D^3]$, where V is the volume phase, d the density, and D the diameter.

molecular weight of the PCL and its content in the formulation may be. This size does not vary in a noticeable way after 1 week storage (without polymerization), which establishes the ability of the CL macromonomer to stabilize the miniemulsion.

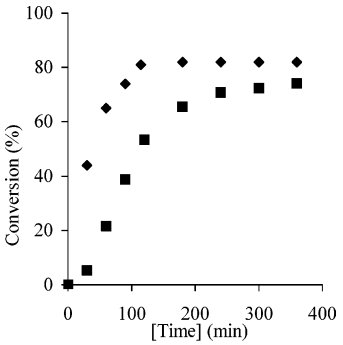


Figure 3. Influence of hydrophobe on the polymerization kinetics: (◆) hexadecane, (■) PCL macromonomer (5%) with Brij (4 g/L) as surfactant.

Table 2. Nonionic Surfactants Investigated in This Study

Surfactant	
Sodium dodecyl sulfate (SDS)	$C_{12}H_{25}-O-\overset{O}{\overset{\|}{S}}(=O)-ONa$
Triton® X-405	$C_8H_{17}-C_6H_4-(O-CH_2-CH_2)_n-OH$, $n \approx 40$
Sorbitan® monolaurate	$HO-(CH_2CH_2O)_w$, $(OCH_2CH_2)_x-OH$, $(OCH_2CH_2)_y-OH$, $(OCH_2CH_2)_z-OC(=O)-C_{11}H_{23}$, $x + y + z + w = 80$
Brij® 700	$C_{18}H_{37}-(O-CH_2-CH_2)_n-OH$

The diameter of the particles is decreasing during the polymerization, and the N_p/N_m ratio increases. The polydispersity index is increasing in the same way. These results are explained by micellar renucleation processes, which occur because of the use of a water-soluble initiator and a concentration of surfactants which is close to their cmc.

Some experiments were monitored by SEC in order to follow the macromonomer consumption. As expected, the methacrylic macromonomer reacts faster than the allylic one. Furthermore, only one SEC trace was noticed for the polymer, which clearly shows we are not faced with a mixture of copolymer and poly(vinyl acetate).

Figure 3 compares the monomer conversion when using hexadecane or CL macromonomer as hydrophobe with Brij 700 (cf. Table 2) as surfactant and hydrogen peroxide/ascorbic acid as initiator. It can be observed that using the PCL macromonomer causes a slight decrease of the polymerization rate.

B. Miglyol as Hydrophobe. Miglyol is frequently used to dissolve hydrophobic drugs and to prepare nanocapsules by the emulsification−diffusion procedures. It is a mixture of triglycerides of caprylic (50−65%) and caproic acids.

In a first set of experiments, nanoparticles have been prepared with 10−60% of Miglyol 812N (and then 90−40% of vinyl acetate) in the organic phase without adding any other hydrophobe. Brij 700 was used as

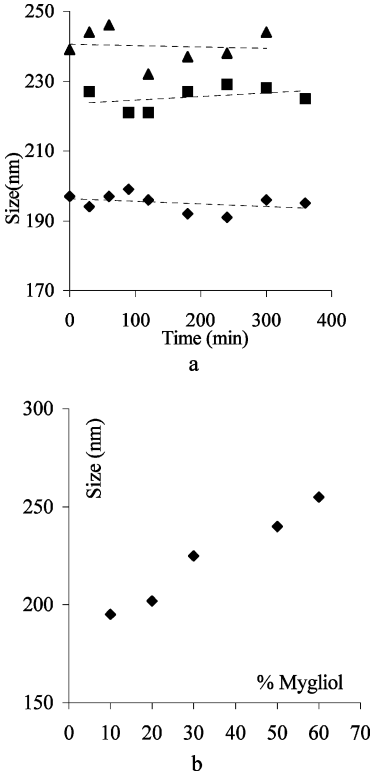


Figure 4. Influence of the amount of Miglyol on the particle size. (a) During polymerization: (◆) 10% Miglyol; (■) 30%; (▲) 50%. (b) At the end of the reaction.

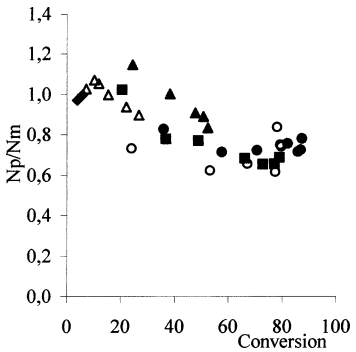


Figure 5. Variation of the N_P/N_M ratio during polymerization for various Miglyol contents in the organic phase: (◆) 10% Miglyol; (●) 20%; (■) 30%; (○) 40%; (▲) 50%; (△) 60%.

surfactant and ascorbic acid/oxygenated water as the initiator. As shown in Figure 4, the diameter of the droplets depends on the Miglyol content and varies from 190 and 260 nm but does not vary significantly during the polymerization. Finally, the N_p/N_m ratio decreases gently during the polymerization with values usually slightly below the unity, meaning that some coalescence may occur (Figure 5). Nevertheless, it seems that Miglyol can efficiently be used as a hydrophobe.

In another set, with a mixture of Triton and SDS (2 g/L each) as surfactant and KPS as initiator, it was observed that the addition of 4% PCL macromonomer to 40% Miglyol allowed a better stabilization of the polymer particles. The diameter of particles latex decreases from 307 to 270 nm while the N_p/N_m ratio goes from 2.33 to 1.49. This feature shows that PCL macromonomer is more effective than Miglyol in that case.

2. The Surfactants. As discussed in the introductory part, one of the main goals is to replace as much as possible the anionic surfactant, usually SDS, by a nonionic one (Table 2). A systematic study was then undertaken with hexadecane as hydrophobe and hydrogen peroxide/ascorbic acid as initiator (Figure 6). Contrary to the electrostatic stabilization provided by SDS, nonionic surfactants give rise to steric repulsion between particles, insensitive to any change of the ionic strength of the aqueous solution. For instance, styrene miniemulsion polymerization with nonylphenol PEG with around 40 EO units (NP-40) as surfactant was reported.[20]

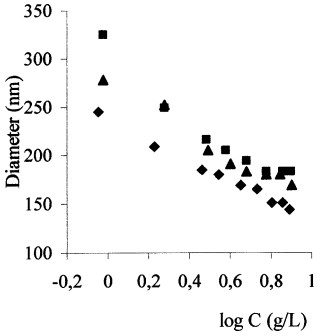


Figure 6. Dependence of droplet size on surfactant concentration with hexadecane as hydrophobe: (◆) Triton, (■) Sorbitan, (▲) Brij.

Table 3. Influence of the Triton X-405 Concentration on VAC Miniemulsion Polymerization with 10% PCL Macromonomer ($M_n \approx 1000$ g/mol) as Hydrophobe and KPS as Initiator[a]

Triton (g)	D_m (nm)	N_m	yield (%)	D_p	N_p	N_p/N_m
0.60	224	3.58×10^{15}	95	320	1.01×10^{15}	0.281
0.70	155	1.08×10^{16}	95	225	2.90×10^{15}	0.268
0.76	159	1.00×10^{16}	94	205	3.84×10^{15}	0.383

Triton (g)	A_m	A_p	A_T	A_T/A_m	A_T/A_p
0.60	5.65×10^{20}	3.24×10^{20}	5.52×10^{20}	0.98	1.70
0.70	8.16×10^{20}	4.61×10^{20}	6.44×10^{20}	0.79	1.40
0.76	7.96×10^{20}	5.07×10^{20}	6.97×10^{20}	0.87	1.38

[a] The volume of the miniemulsion is 200 mL.

As shown above, the first studies carried out with a mixture of anionic/nonionic surfactants gave always renucleation, but as expected, it was found that stable miniemulsions could be obtained without using any anionic surfactant, although particles size are always lower than those obtained with a nonionic surfactant (60 nm with SDS at 4 g/L instead of around 170−200 nm with a nonionic surfactant at the same concentration).

Using only Triton X-405, with surfactant concentrations ranging from 3 to around 3.8 g/L, gives particles, the diameter of which is higher than that of droplets, suggesting a coalescence process, maybe due to a lack of surfactant (Table 3). The ratio A_T/A_P of the total surface area that Triton can recover to that of the particles is always around the unity. (The saturated particle surface area for Triton is 0.9×10^{21} nm^2/g (300×10^{-16} cm^2/molecule).) The actual value for this ratio must be lower since there is always a small amount of free surfactant in aqueous phase. The polydispersity is smaller than that observed with a SDS/Triton mixture, around 0.07 at 3.85 g/L. The yield of polymerization lies between 80 and 90%.

High solid content particles can be directly obtained with Triton and Miglyol (Table 4). This process was found to be more efficient than trying to concentrate the

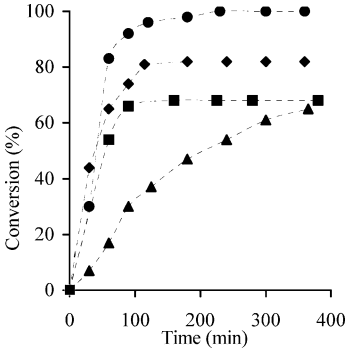


Figure 7. Influence of various surfactants on the polymerization kinetics: (◆) Brij, 4 g/L; (■) PVA, 8 g/L; (▲) sorbitan monolaurate, 8 g/L; (●) Triton, 4 g/L; hexadecane as hydrophobe and hydrogen peroxide (5 g/L)/ascorbic acid as initiator.

Table 4. High Solid Content Latex

% organic phase	droplet diameter; polydispersity	particle diameter; polydispersity	polymerization yield (%)
10	225; 0.17	300; 0.19	
20	285; 0.17	270; 0.16	97
37	320; 0.21	290; 0.18	92
50	292; 0.10	310; 0.13	99

lattices by stripping water at 55 °C under vacuum. In that latter case, some flocculation appeared rapidly.

Sorbitan monolaurate and Brij were also used with PCL macromonomer as hydrophobe. Polymerization were carried out with hydrogen peroxide/ascorbic acid as initiator and PCL macromonomer as hydrophobic agent. A concentration of 4 g/L leads to particles with a diameter around 200 nm. Particle sizes of 180 nm were obtained when doubling the surfactant concentration. Brij 700 gives particles with the same size, but the rate of polymerization is faster than with Sorbitan monolaurate (Figure 7). Finally, poly(vinyl alcohol) did not give more satisfactory results. Particle size increases from 170 to 210 nm during the reaction, and this tendency to coalescence leads to some flocculation after 1 week storage.

As a conclusion, although Triton appears to be the best surfactant, its further use could become questionable due to the potential toxicity brought by the phenolic group. Brij could be a good candidate since the polymerization kinetics is faster than with the sorbitan monolaurate.[21]

3. The Initiators. Surface charges are brought by both the initiator and the ionic surfactant. In our conditions, measurements of ζ potential give a value of −45 mV when using simultaneously KPS and SDS and −38 mV when using only KPS with Triton as nonionic surfactant. Therefore, most of the charges are due to the initiator. To overcome this drawback, we used the ascorbic acid−hydrogen peroxide redox system. Ascorbic acid in solution (1.25 g/50 mL) was poured continuously in the miniemulsion containing 5 g/L hydrogen peroxide with a flow equal to 1.2 mL/h to get the same radical flux as that obtained from KPS at 70 °C. 100% conversion can be obtained, and the particles size is around 180 nm.

Hydrophobic initiators such as AIBN, benzoyl peroxide, or lauroyl peroxide were also used and gave interesting results. These hydrophobic initiators generate radical inside the particles and must impede eventual secondary nucleation processes. Table 5 reports some results about the influence of these initiators on the droplets diameter and particles size. In this first approach, hexadecane was used as hydrophobe. Further studies with polycaprolactone confirmed these observed trends. The N_p/N_m ratio decreases that means some coalescence processes occur. As expected, this ratio increases again when adding some water-soluble initiator.

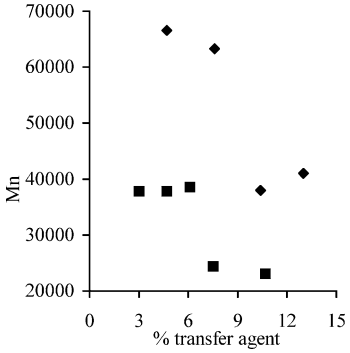


Figure 8. Influence of the concentration of the transfer agent on number-average molecular weight: chloroform (■), dodecanethiol (◆).

Table 5. Influence of the Initiator on the Droplets Diameter and Particles Size with Hexadecane as Hydrophobe

initiator	surfactant (4 g/L)	yield (%)	D_m (nm)	I_m	D_p (nm)	I_p	N_p/N_m
AIBN	Triton	83	164	0.22	163	0.10	0.806
POB	Triton	54	162	0.26	210	0.25	0.363
KPS	SDS + Triton	84	224	0.15	182	0.15	1.476
POB + KPS	Triton	88	205	0.32	171	0.10	1.364

In all the cases, measurements of ζ potential, now around 0 mV, show there is no longer charges on the surface of the particle. Therefore, it is possible to get stable nonionic poly(vinyl acetate) particles, the size of which is around 200 nm, by using both nonionic surfactants and initiators such as AIBN or hydrogen peroxide−ascorbic acid.

4. Control of the Average Molar Mass. It is known that PVAc chains are efficient radical transfer agents, so that high molecular weight branched polymers are obtained. These polymers cannot be analyzed by SEC because they cannot be entirely dissolved in THF. These too high molecular weight makes these polymers unsuitable for biomedical purposes: bioresorbability requires molecular weights below around 20 000 g/mol, so that transfer agents are needed to decrease the chain length. To demonstrate the feasibility of transfer in our conditions, we added two transfer agents in the recipes, namely dodecanethiol and chloroform.

Dodecanethiol ($C_{tr} \approx 50 \times 10^{-4}$) was added in the organic phase in concentration between 3 and 13% (Figure 8). Polymerizations were carried out at 60 °C with ammonium persulfate as the initiator. Concentrations of transfer agent below 5% do not lead to soluble PVAC. A drastic decrease of the molecular weight is observed when using 10% dodecanethiol, but values remain always above 40 000 g/mol. The polydispersity index decreases from 2.9 to 2.1. The particles size are around 150 nm with 10% dodecanethiol (Table 6).

The transfer constant of chloroform is higher than that of dodecanethiol ($C_{tr} \approx 150 \times 10^{-4}$). But polymerizations had to be carried out at lower temperature (45 °C) because of its low boiling point (bp = 55 °C). The hydrogen peroxide−ascorbic acid system was used as initiator. As expected. chloroform is more efficient, and a decrease of molecular weights up to 20 000 g/mol can

Table 6. VAc Miniemulsion Polymerization with Dodecanethiol as Transfer Agent and PCL as Hydrophobe

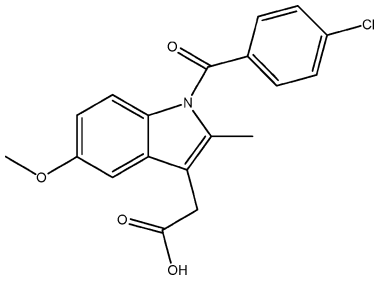
M_n PCL (g/mol)	PCL (%)	Triton/Miglyol (50/50 w/w)	AcV (%)	$C_{12}SH$ (%)	yield (%)	D_m (nm)	D_p (nm)	N_p/N_m
1400	9.7	4	87.4	2.9	90	232	140	3.79
1400	9.5	4	85.7	4.8	86	225	133	4.09
1400	9.25	4	83.3	7.4	89	226	148	3.01
1040	9	4	78.0	13	71	250	130	6.30
1040	8.9	4	80.5	10.6	88	212	120	4.70

Table 7. VAc Miniemulsion Polymerization with Chloroform as Transfer Agent and PCL as Hydrophobe

M_n PCL (g/mol)	PCL (%)	Triton (g/L)	AcV (%)	$CHCl_3$ (%)	yield (%)	D_m (nm)	D_p (nm)	N_p/N_m
1310	9.3	3.75	83.3	7.4	91	163	189	0.53
1310	15[a]	3.75	45.0	7.4	63	281	288	0.83
1475	9.5	3.75	85.7	4.8	68	155	187	0.50
1475	9.7	3.75	87.4	2.9	82	158	227	0.28
1475	9.4	3.75	84.5	6.1	80	176	220	0.44

[a] 5% PCL + 10% Miglyol.

Scheme 2. Chemical Structure of Indomethacin



be obtained. A plateau is observed at low concentration around 40 000 g/mol, followed by an important decrease of the values. The polydispersity index is around 2.2−2.3 and does not change noticeably even after the decrease of the molecular weights. Finally, polymerization yield lies between 70 and 90%, and particles size is noted at 210 nm (Table 7). These results show the effectiveness of transfer agents in our recipes. More biocompatible efficient transfer agents are now to be found for our applications.

5. Incorporation of Indomethacin. Indomethacin (IMC, Scheme 2) can be incorporated in nanoparticles, using PCL macromonomer or a mixture of benzyl benzoate−PCL macromonomer as the hydrophobe. Miglyol cannot be used as hydrophobe, owing to the very low solubility of the drug in the oil. Stable nanoparticles are obtained in all the cases. For instance, particles, the size of which is around 145 nm, are obtained. In addition, UV spectra of indomethacin do not display changes after polymerization, which shows the chemical stability of the drug.

The IMC content in particles was measured by UV spectrometry at 244 nm. For the first time, the total amount of IMC in the latex was measured after disrupting of the nanoparticles with THF. The latex was then centrifuged at 21 000 rpm for 30 min, and the IMC content was measured in the supernatant and the residue. The drug loading efficiency was determined according to the weight of IMC in supernatant/total weight of IMC ratio.

With PCL macromonomer as hydrophobe, IMC is expected to be homogeneously distributed inside the matrix. We found a drug loading efficiency of 92% ± 2%, which is in a good agreement with previous studies.

Indomethacin can also be dissolved in benzyl benzoate. Using this solution as hydrophobe might lead to nanodomains scattered in the PVAc matrix. The first attempts to prepare nanocapsules with 20% benzyl benzoate as the only hydrophobe failed. It was found that adding 0.5% of the PCL macromonomer enabled to get nanoparticles, the size of which is around 160 nm. In that case, the IMC measurement is more or less disturbed by the UV absorbance of the benzyl benzoate in the same wavelengths range (maximum at 252 nm). Nevertheless, it seems that 90% of indomethacin has been encapsulated.

Conclusion

It was demonstrated that it is possible to develop a synthetic way to get stable nonionic nanoparticles for controlled drug release by using the vinyl acetate miniemulsion polymerization process. Brij 700 appears to be the best suitable nonionic surfactant. Further investigations have shown that Pluronic F-68 (poloxamer 188) can also be used to get nanoparticles with a diameter around 200 nm. In addition, initiation of the polymerization by the hydrogen peroxide−ascorbic acid redox system or the AIBN allows to make zero the ζ potential of the nanoparticles. PCL macromonomers or Miglyol can be used as biocompatible hydrophobe to get nanospheres or nanocapsules, respectively, with a diameter ca. 200 nm. Up to 60% Miglyol can be incorporated in the nanoparticles.

Another question to investigate is the actual structure of these nanoparticles. While PCL macromonomer probably leads to homogeneous nanoparticles, Miglyol will give rather heterogeneous particles where Miglyol nanodomains would be scattered inside a PVAc matrix since it is insoluble in poly(vinyl acetate): demixtion would occur all along the VAc polymerization in the particles filled with Miglyol, as is observed for suspension polymerization in the presence of a "nonsolvent" porogenic agent.[22,23] This expectation would be in agreement with the nanoreactor concept postulated for miniemulsion polymerization.[6] Of course, TEM pictures of external surfaces do not reveal clear indications about the morphology inside the particles. TEM pictures of cross sections are to be made but need cryofractures which will be discussed later.

Indomethacin can be incorporated in these nanoparticles. Stable minimemulsions can be obtained by using either CL macromonomer alone or benzyl benzoate containing 0.5% of this macromonomer. The next step would be to use PEG macromonomers in order to get an "all-macromonomer" recipe and polymer carrying sugar derivatives as surfactants. These ways are now under investigation.

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