New Biocompatible Microgels

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Summary: Microgel particles have received an increasing interest in the biomedical field. Temperature-sensitive microgels gained particular interest due to their potential use as controlled drug delivery systems. With the objective to produce new thermoresponsive biocompatible microgels, the synthesis and characterization of two families of microgel particles obtained by using *N*-vinylcaprolactam (VCL) as main monomer and *N,N′*-methylenbisacrylamide (BA) or poly(ethylene glycol) diacrylate (PEGDA) as crosslinkers are described. Evidence of hydrolysis VCL during polymerization is also presented.

Keywords: emulsion polymerization; microgels; stimuli-sensitive polymers

Introduction

Among the broad research fields in nanotechnology, microgel particles have received considerable attention in polymer science and biomedicine.[1,2] Microgels rank among the large family of crosslinked polymeric nanoparticles; their distinct property is the ability to swell in a suitable solvent. In 1986 R. H. Pelton and P. Chibante[3] prepared the first reported temperature-sensitive aqueous microgel. Since then, the microgels have been studied composed of hydrophilic polymers capable of undergoing reversible volume-phase transitions in response to environmental stimuli.[4] Among them, temperature-sensitive microgels have been investigated in detail. An example of thermoresponsive polymer is poly(vinylcaprolactam) (PVCL).[5–8] PVCL is biocompatible and its phase transition proceeds in the region of physiological temperature (31–38 °C).[9]

For biomedical applications of these nanomaterials, such as drug delivery systems, their surfaces should be highly hydrophilic in order to increase the service time and stability of nanocarriers in the circulation systems, and, for example, to prevent protein adsorption. This problem can be addressed by synthesizing poly(ethylene glycol)-containing nanoparticles.

In the synthesis of the poly(VCL)-based microgel particles, one of the widely used initiators is potassium persulfate (KPS). It is well known that the persulfate decomposition produced acid ions. In the literature, however, it is not mentioned anything about the effect that these acid ions might have on the side reactions of VCL. The reactions should be avoided when the final microgels are used in biomedical applications.

This work aims to review some conclusions derived from the analysis of the results obtained in the production of microgel particles based on VCL and *N,N′*-methylenbisacrylamide (BA),[10] carried out in batch and semicontinous reactors, and of those based on VCL and poly(ethylene glycol) diacrylate (PEGDA), synthesized in a batch reactor.[11] In addition, the side reactions of the monomer during polymerization[12] are considered.

Microgel Particles Based on poly(VCL-*co*-BA)

To synthesize microgel particles based on poly(VCL-*co*-BA) emulsion polymerizations of VCL and BA, using SDS as

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Table 1.
Recipes used in preparation of crosslinked poly(VCL-*co*-BA) microgel particles in a batch reactor.

Reaction	VCL (wt %)	BA (wt % M)	$K_2S_2O_8$ (wt % M)	SDS (wt % M)
CLX	1	variable	1	4
IX	1	4	variable	4
SX	1	4	1	variable
TX	1	4	1	4
VCLX	variable	4	1	4

Reaction conditions: 400 rpm; T = 70 °C; reaction time 5 h.
Variables: concentration of VCL, BA, KPS and SDS.

stabilizer were carried out in batch (Table 1) and semicontinuous (Table 2) reactors.

Colloidal characteristics, such as the temperature sensitivity of PVCL microgels in water, changes in the volume phase transition temperature (VPTT) as a function of crosslinker, initiator, surfactant, and VCL concentrations, were analyzed by means of photon correlation spectroscopy (PCS). The results for the reactions carried out in a batch reactor showed that almost all the microgel particles swell by decreasing temperature and shrunk at temperature above the VPTT.

An increase in concentration of crosslinker results in a broadening of the temperature over which deswelling occurs. The VPTT is independent of crosslinker concentration for the values lower than about 5 wt % (relative to VCL), but increasing at higher concentrations. When varying the initiator concentration in the recipe, the particles swell more when higher amounts of KPS are used. In such a case, the particles were less crosslinked and as the temperature decreased, they swell more. Regarding the surfactant concentration effect, it was observed that when a higher surfactant amount was added to the reaction medium, the microgel particles swell more at temperatures below the VPTT. Moreover, the addition of SDS shifts VPTT higher. When the effect of VCL concentration was analyzed, nearly the same swelling-deswelling behavior and almost the same VPPT were observed, indicating that the crosslinker is equally distributed in the microgel particles.

The average particle size evolution and temperature sensitivity measurements of microgels synthesized in a semicontinuous reactor showed that different swelling-deswelling behaviors were obtained by feeding the crosslinker, initiator, monomer, and surfactant. The final microgel particles

Table 2.
Recipes used in preparation of poly(VCL-*co*-BA) crosslinked microgel particles in a semicontinuous reactor.

Reaction	VCL (wt %)	BA (wt % M)	$K_2S_2O_8$ (wt % M)	SDS (wt % M)
SBCL	1	4 (1.9 wt %, 0.07 g/min, 150 min)	1	4
SBI	1	4	1(0.6 wt %, 0.13 g/min, 60 min)	4
SBVCL	1(6.7 wt %, 0.83 g/min, 90 min)	4	1	4
SBS	1	4	1	4 (0.4 wt %, 0.83 g/min, 60 min)

Reaction conditions: T = 70 °C; rpm = 400; reaction time = 6 h.
Variable: reagent fed during the polymerization (VCL, BA, KPS, and SDS).

Table 3.
Recipes used in preparation of poly(VCL-*co*-PEGDA) crosslinked microgel particles.

Reaction	Crosslinker (mol % M)
PEGX	1.8;3.6;5.4;7.2;9

Reaction conditions: 400 rpm; reaction time 5 h; reaction temperature 70 °C.
The concentrations of initiator, buffer, and emulsifier were 1 wt % relative to VCL.
Variable: concentration of PEGDA.

obtained in reactions feeding the initiator and the surfactant were temperature-sensitive. However, the size of the final particles synthesized by feeding the crosslinker and the main monomer did not vary with temperature.

Microgel Particles Based on Poly(VCL-*co*-PEGDA)

The microgel family containing the same main monomer (VCL) but a different crosslinker (PEG-based crosslinker, PEGDA) was synthesized via emulsion polymerization in a batch reactor (Table 3).

The swelling capacity of poly(VCL-*co*-PEGDA)-based microgels did not vary by increasing the crosslinker concentration in the range from 1.8 to 9 mol % (relative to VCL). The reactivity of the crosslinker was higher than that of the main monomer and, consequently, PEGDA was mainly located in the core of the microgel particles. This led to a large shell with a low and almost the same crosslinker density for all the different crosslinker concentrations used.

When the thermal behavior of the microgel particles synthesized with the same amount of reagents but different type of crosslinker was analyzed, it was observed that the swelling ability of the microgels containing BA was much higher than that of the particles containing PEGDA (Figure 1). PEGDA is more hydrophilic than BA and, as a result, when PEGDA was used, a high amount of particles was formed initially. If the concentration of particles is higher than that in the reaction using BA, a lower amount of VCL was incorporated per particle. Moreover, the incorporation of a more hydrophilic crosslinker into microgel particles altered their deswelling thermodynamics increasing the VPTT.

Evidence of Hydrolysis of VCL

In order to analyze the hydrolysis process observed in the emulsion polymerizations carried out to synthesize new VCL-based microgels, the effect produced by the amount of initiator (KPS) used in the recipe was the target. Microgel particles

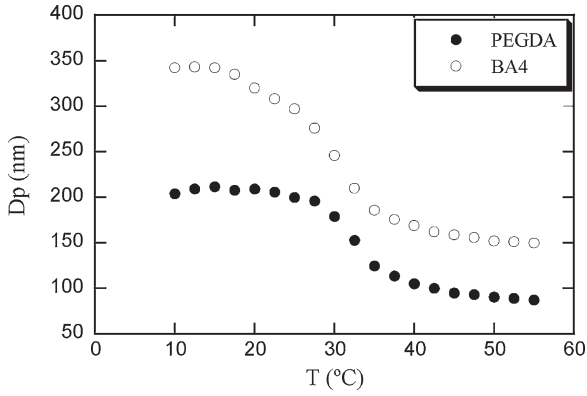

Figure 1.
Final average hydrodynamic diameters as a function of temperature for the reactions carried out by using BA and PEGDA as crosslinker.

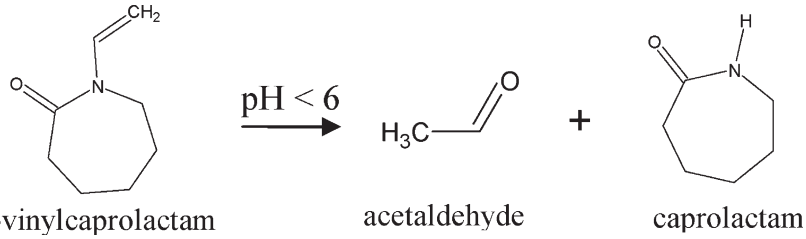

Figure 2.
Hydrolysis of VCL under acid conditions.

were prepared in a batch reactor using 0.3, 0.5, and 1 wt % of KPS (relative to VCL) and in a semicontinuous reactor by feeding the initiator during the polymerization. The samples withdrawn at different reaction times were analyzed by ^{1}H NMR.[12]

By comparing the spectra of all reactions and analyzing the reaction conditions it was demonstrated that the use of KPS under uncontrolled pH conditions had direct influence on the formation of new species, that is, in the hydrolysis of VCL. KPS decomposes thermally to give two sulfate radical-ions. These radicals can react in water to form HSO_4^- and hydroxyl radicals, accompanied by lowering pH. The rate of hydrolysis increased when a higher amount of initiator was added to the reaction medium, but disappeared when using a buffer. As can be seen in Figure 2, the products formed by hydrolysis are acetaldehyde and caprolactam.

Conclusion

The size and the swelling/deswelling behavior of different microgels prepared by batch polymrization can be tuned by modulating the reaction variables (concentration of crosslinker, initiator, surfactant, and main monomer). In semibatch polymerization, carried out by feeding the crosslinker, initiator, monomer, and surfactant, different swelling behaviors were obtained.

The incorporation of PEGDA crosslinker increases the hydrophilicity of the particles, alters the deswelling behavior and decreases the particle sizes.

When *N*-vinylcaprolactam (VCL) is polymerized by emulsion polymerization and the initiator used is KPS, it is extremely important to maintain neutral pH of the reaction medium in order to avoid the VCL hydrolysis.

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