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ORIGINAL CONTRIBUTION

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Water-soluble microgels made by radical polymerization in solution

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Abstract The goal of this study was to prepare and characterize water-soluble, high-molecular-weight microgels. *N*-Vinylpyrrolidone (NVP) and vinylacetate (VAc) in combination with cross-linkers diethylene glycol dimethacrylate (DEGDMA) or diethylene glycol divinyl ether (DEGDVE) were copolymerized in solution to high conversion. Polymerization was performed in different solvents or solvent mixtures, with solubility parameters ranging from 16.0 to 47.6 $J^{0.5}cm^{-1.5}$, and at different initial monomer concentrations. In solvent mixtures with solubility parameters of 20–40 $J^{0.5}cm^{-1.5}$, macrogelation did not occur below a critical gelation concentration and microgels were formed. For NVP/VAc/DEGDMA (85.0/10.0/5.0 wt%, 84.8/12.9/2.4 mol%) and NVP/VAc/DEGDVE (85.0/10.0/5.0 wt%, 84.8/12.9/3.5 mol%) the critical gelation curves were determined. The molecular weights of the microgels depend on the solvent systems and the initial monomer concentration. Microgels of high molecular weight but low cross-linking density gave aqueous solutions with high viscosities. Increasing the amount of cross-linker to 20 wt% gave high-molecular-weight microgels with lower solution viscosity. Microgels with a monomer composition NVP/VAc/DEGDVE (65.0/15.0/20.0 wt%, 66.2/19.5/14.3 mol%) were prepared in ethanol at different monomer concentrations (3–20 wt%). The molecular weights were determined by a combination of field-flow fractionation and light scattering. By increasing the initial monomer concentration, the molecular weight and the molecular-weight distribution as well as the intrinsic viscosity increased. The exponent of the Mark–Houwink equation was 0.26.

Key words Microgels · Solution radical polymerization · Size-exclusion chromatography · Field-flow fractionation · Light scattering

Introduction

Water-soluble polymers with low solution viscosities are needed for a range of biomedical applications. Microgels, which are intramolecularly cross-linked macromolecules with a globular structure are known for their low solution and melt viscosity. The molecular-weight exponent in the Mark–Houwink equation is very low (below 0.3) in contrast to linear polymers, for which the exponent is about 0.7 [1].

Two general methods of microgel synthesis are available: emulsion polymerization and solution polymerization. Both require monomers with a functionality greater than 2. For the first process, surfactants are needed to create separate microcontinuous reactors, which contain all the components, i.e. monomers and radicals from the aqueous phase. The second option is very interesting since it does not need addition of surfactants.

Microgels made by solution polymerization were first detected by Staudinger and Husemann [2]. The degree of reaction at the gel point has been predicted by theories proposed initially by Carothers and Flory [3], and developed by many others since [4]. Microgel formation has been propounded as a precursor to many macrogelations. Primary microgel particles are single linear polymer backbones, which have coiled up and cross-linked internally. When polymerization proceeds these microgels combine to covalently linked aggregates, which leads eventually to macrogelation [5]. Therefore, microgels are generally formed in solution only at low concentrations and/or low conversions.

The formation of macroscopic networks and premature gelation may be avoided, even at higher concentrations and higher conversions, by selecting suitable monomer–solvent systems [6]. The solvating power of the solvent strongly influences the onset of macrogelation, and in a good solvent macrogelation is retarded [7]. Graham and coworkers [8–12] have shown that macrogelation can be avoided even at complete conversion and high monomer concentration in the presence of thermodynamically good solvents. Then, macrogelation cannot occur below a critical gelation concentration (CGC). In these circumstances, the chains formed in the initial reaction act as autosteric stabilizers to provide repulsive forces between microparticles in solution to prevent further intermolecular reaction and so form soluble microgels. For radical polymerizations, this hypothesis has been proven only for methyl methacrylate based microgels, which were not soluble in water.

For use as polymers in many biomedical applications, water solubility is essential. It is, therefore, interesting to know whether it is possible to exploit the CGC concept to form water-soluble microgels. In this study water-soluble microgels were made by copolymerizing *N*-vinylpyrrolidone (NVP), vinylacetate (VAc) and diethylene glycol divinyl ether (DEGDVE) or diethylene glycol dimethacrylate (DEGDMA) in different solvent systems and at different initial monomer concentrations. The CGCs were determined and the microgels were characterized with size-exclusion chromatography (SEC) or field-flow fractionation (FFF) in combination with multiangle light scattering (MALS) and viscometry.

Experimental

Materials

Monomers and crosslinkers

NVP, VAc, DEGDVE and DEGDMA were purchased from Sigma-Aldrich and were used without further purification.

Solvents

2,6-Dimethyl-4-heptanone, heptane, 2-butanone, ethanol, methanol and 2,2′-azobis(isobutyronitrile) (AIBN) (Sigma-Aldrich) were used as obtained without further purification.

Microgel preparation

The solubility parameters of solvent systems are shown in Table 1.

The monomers and the cross-linkers were mixed in the desired ratio. Desired amounts of the mixture being evaluated were weighed into Wheaton bottles of 30 cm^3. The solvent or the solvent mixture was added. As initiator 3 wt% (relative to monomer/cross-linker) AIBN was used. After purging with nitrogen for 5 min, the bottles were then closed with Teflon-faced rubber septa and aluminium caps and were put into an oven at 60 °C for 15 min, after which the bottles were shaken vigorously to dissolve the AIBN. Then, the bottles were put back into the oven for 48 h to let the monomer and cross-linker polymerize.

To determine the conversion preweighed dishes were charged with a weighed volume about 1 cm^3 cold polymerization solution. After evaporation of the solvent at room temperature, the residue was heated in an oven to 140 °C to constant weight. The normalized mass of the residue is the mass of polymer formed from 1 g solution, from which the conversion of monomer to polymer can be calculated as $100 \times$ weight of residue/weight of monomer and cross-linker in the nonpolymerized reaction mixture. Microgels, except those made in water, were precipitated in diethyl ether. Solutions of microgels synthesized in water were evaporated, the microgels were redissolved in methanol and precipitated in diethyl ether.

The following mixtures of monomers were polymerized in a variety of solvents covering a range of concentration and solubility parameter values: 85/10/5 wt% NVP/VAc/DEGDMA, 85/10/5 wt% NVP/VAc/DEGDVE and 65/15/20 wt% NVP/VAc/DEGDVE.

Characterization

M_w and M_n were determined using SEC or thermal FFF coupled with a MALS detector. The refractive index increment (d*n*/d*c*) was determined for all the samples to allow calculation of the molecular weights from the scattered light intensity.

SEC was performed with an MZ Hema-Bio 40,300,1000 column and 50/50 CH_3OH/H_2O with 0.1% LiBr as the mobile phase. FFF was performed with an F1000 column using the same solvent mixture as for the mobile phase.

MALS and refractive index measurements were performed using a Wyatt DAWN light scattering detector and a Wyatt Optilab DSP interferometric refractometer, respectively. Intrinsic viscosities were determined with a Ubbelohde viscometer using water as the solvent.

Table 1 Solubility parameters and compositions of solvent mixtures (in percent by volume)

Solubility parameter δ ($J^{0.5}cm^{-1.5}$)	Polymerization solvent system
16.0	100% 2,6-dimethyl-4-heptanone
17.2	100% heptane
19.0	100% 2-butanone
22.5	50% 2-butanone + 50% ethanol
26.0	100% ethanol
29.7	100% methanol
33.3	80% methanol + 20% water
35.8	67% methanol + 33%water
39.7	45% methanol + 55% water
42.2	31% methanol + 69% water
45.3	14% methanol + 86% water
47.9	100% water

Results and discussion

NVP copolymers were the polymers of choice because of their solubility in water and their biocompatibility. They have been used in contact lenses for many years. NVP was copolymerized with VAc, which can be converted into vinyl alcohol, to introduce hydroxyl functionality.

In the first series of microgels 85.0 wt% (84.8 mol%) NVP, 10.0 wt% (12.9 mol%) VAc and 5 wt% cross-linker were polymerized in different solvent mixtures at different initial monomer concentrations. As cross-linker 5 wt% DEGDMA (2.4 mol%) or DEGDVE (3.5 mol%), was used. Copolymerized NVP/VAc microgels were formed within the perimeter of the critical gelation curves shown in Fig. 1 for the macrogels cross-linked with DEGDMA and those show in Fig. 2 for the microgels cross-linked with DEGDVE. The degree of conversion was between 97 and 100% for all the polymerizations.

The curves (Figs. 1, 2) reveal that microgels were formed over a very wide range of the solubility parameters, from about 20 to 40 $J^{0.5}cm^{-1.5}$, each showing a maximum at about 20 $J^{0.5}cm^{-1.5}$. Neither curve is symmetrical, which may possibly be attributed to the fact that the solvents of higher solubility, i.e. ethanol, methanol and water, have much stronger hydrogen-bonding ability than the ketones and heptane. It is noteworthy is that NVP/VAc/DEGDVE microgels can be made at concentrations higher than 80% in 2-butanone; this is due to the fact that in 2-butanone only low-molecular-weight microgels are formed.

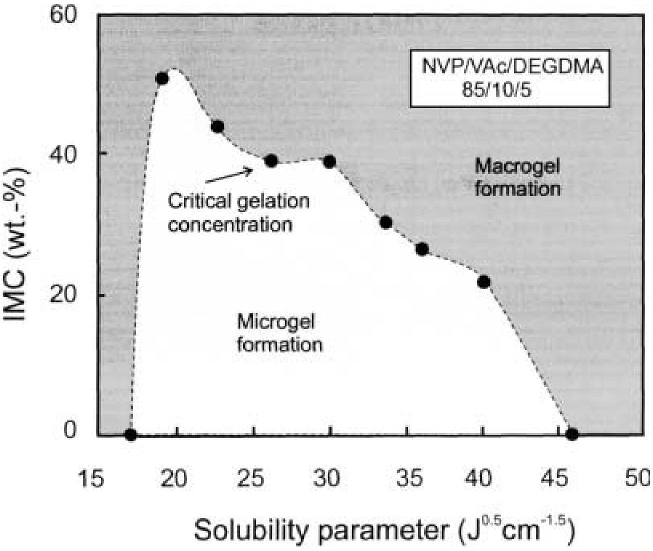

Fig. 1 Plot of critical gelation concentrations (*CGC*) as function of the initial monomer concentration (*IMC*) and solubility parameter of the solvent used for the polymerization of 85/10/5 *N*-vinylpyrrolidone (*NVP*)/vinylacetate (*VAc*)/diethyleneglycol dimethacrylate (*DEGDMA*) at 60 °C. At concentrations below the CGC, microgels are formed and at concentrations above the CGC a macrogel was formed

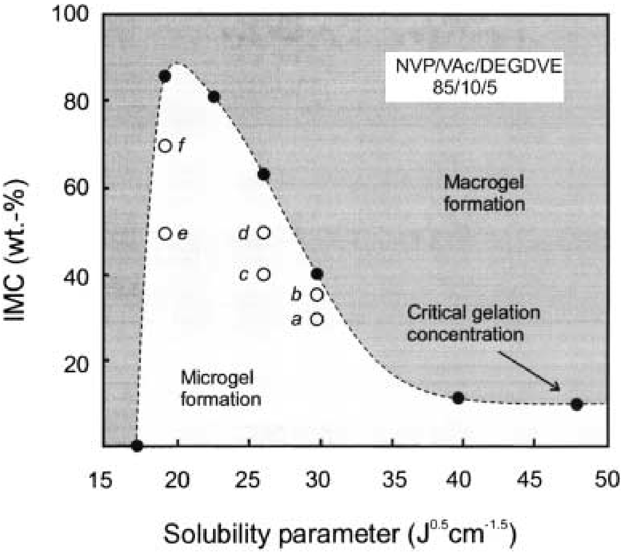

Fig. 2 Plot of CGC as function of IMC against solubility parameter of the solvent used for the polymerization of 85/10/5 NVP/VAc/diethyleneglycol divinylether (*DEGDVE*) polymerizations at 60 °C. Microgels were made at different IMC and in different solvents. *a* 30 wt% in methanol; *b* 35 wt% in methanol; *c* 40 wt% in ethanol; *d* 50 wt% in ethanol; *e* 50 wt% in 2-butanone; *f* 70 wt% in 2-butanone

The differences in the shape of the curves may be due to the different natures of the cross-linkers, although DEGDVE was used in a molar concentration approximately 50% greater than that used for DEGDMA (3.5 and 2.4, respectively). Further, the reactions involving DEGDVE produced homogeneous transparent solutions and/or macrogels in all of the solvent systems, whereas DEGDMA only produces homogeneous transparent solutions and macrogels in methyl ethyl ketone and 67/33 CH_3OH/water. In the other systems opaque or white gels were formed. It was therefore concluded that DEGDVE is the most appropriate cross-linker for this polymer system for preparation of transparent, water-soluble microgel solutions. Recently, we found that VAc is essential for the copolymerization of DEGDVE with NVP. In the absence of VAc, DEGDVE is not incorporated into the NVP polymer [13].

The determination of the molecular weights (M_n and M_w) is the most important characterization for these materials, but it is impossible to obtain even approximately accurate values with conventional SEC. Absolute techniques are required. A combination of SEC and light scattering is particularly useful. The light scattering molecular-weight averages are usually at least 5 times greater then those obtained from SEC using conventional linear polymer calibration standards. M_n and M_w for the DEGDVE cross-linked microgels determined by SEC/MALS are presented in Table 2. The samples

Table 2 Number-average and weight-average molecular weights and molecular-weight distributions for 85/10/5 *N*-vinylpyrrolidone (*NVP*)/vinylacetate (*VAc*)/diethylene glycol divinyl ether (*DEGDVE*) microgels polymerized in different solvent systems at different concentrations

Sample[a]	Solubility parameter δ ($J^{0.5}cm^{-1.5}$)	Initial monomer concentration (wt%)	M_n (10^3 g/mol)[b]	M_w (10^3 g/mol)[b]	D[b]
a	29.7 (methanol)	30	113	346	3.1
b	29.7 (methanol)	35	57.5	280	5.0
c	26.0 (ethanol)	40	32	494	15.4
d	26.0 (ethanol)	50	49	728	15.0
e	19.0 (methyl ethyl ketone)	50	11	27	2.5
f	19.0 (methyl ethyl ketone)	70	13	43	3.3

[a] The initial monomer concentrations and solvent of the samples relative to the get point are presented in Fig. 2

[b] Determined by size-exclusion chromatography and light scattering

correspond with the samples of Fig. 2. The corresponding differential molecular-weight fractions are presented in Fig. 3.

It was very difficult to filter the samples that were made in ethanol and methanol close to the gel point; some polymer remained on the filter. Therefore, one has to be cautious with the interpretation of the corresponding results.

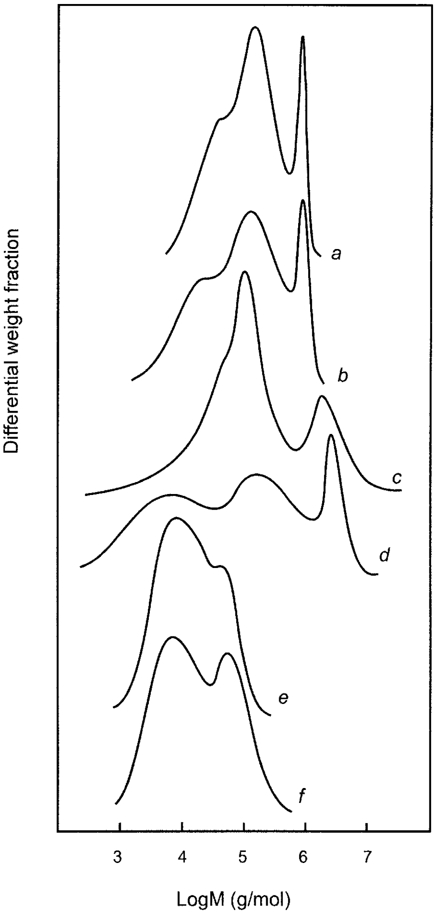

Fig. 3 Differential molecular-weight-distribution plots, determined by light scattering of 85/10/5 NVP/VAc/DEGDVE in different solvents and at different IMC. The initial monomer concentrations and solvents are indicated in Fig. 2: *a* 30 wt% in methanol; *b* 35 wt% in methanol; *c* 40 wt% in ethanol; *d* 50 wt% in ethanol; *e* 50 wt% in 2-butanone; *f* 70 wt% in 2-butanone

In general, the molecular weight of the microgels depends upon the solvent and the position relative to the gel point. At low concentrations, far from the gel point, small separate microgels are formed. The higher the initial monomer concentration the greater the chance that multiple microgel aggregates are formed until the gel point is reached and the molecular weight becomes infinite. The solvents determine the molecular weight because they can give rise to chain transfer. For instance, polymerization in 2-butanone ($\delta = 19.0\ J^{0.5}cm^{-1.5}$) resulted in low-molecular-weight microgels. This is probably due to chain transfer, since it has a higher chain transfer constant with respect to VAc than ethanol and methanol [14], which also probably accounts for the higher concentrations before gelation observed in this solvent.

As can be seen in Fig. 3 the low-molecular-weight microgels show a bimodal distribution and the highest-molecular-weight microgels show a trimodal distribution. A slight change in the slope in the elution profile was observed for the samples, indicating some form of nonideality in the separation. This change in slope occurred at approximately the same position as the valley separating the modes in the distribution of the polymers. This suggested there is a conformational change at a critical point in the growth of the molar mass of the polymers, i.e. intrachain interaction restricting the increase in the root-mean-square radius with respect to the molar mass. It is likely that polymers with different molecular masses correspond to primary microgels and secondary aggregates. They show a distinct pattern of increasing molecular weight and broadening with increasing monomer concentration in each solvent system. As the level of the initial monomer concentration increases, a point is reached at which significantly higher-molecular-weight microgels are produced. The percentage of higher-molecular-weight polymer increases as the initial monomer concentration increases. All the samples a, b, c and d, but not e and f, exhibit a very high molecular weight prepeak. This quite small fraction appears to be of quite narrow molecular-weight distribution. It is thought to comprise very large microgel particles. At present we do not have an explanation for this and for a better understanding more experiments have to be performed in the future.

The gel points for polymerization of 65/15/20 NVP/VAc/DEGDVE in ethanol (δ = 26.0 $J^{0.5}cm^{-1.5}$) and methanol ($\delta = 29.7$ $J^{0.5}cm^{-1.5}$) are 22 and 16 wt%, respectively.

Increasing the amount of cross-linker from 5 to 20 wt% (3.5 to 14.6 mol%), reduces the initial monomer concentration at which macrogelation takes place. Since in ethanol ($\delta = 26.0$ $J^{0.5}cm^{-1.5}$) microgels can be made at higher concentration, a series of microgels at different initial monomer concentration in ethanol were made. The molecular weights were determined by a combination of FFF and light scattering. An advantage of FFF over SEC is the fact that the samples do not have to be filtered. In addition, the SEC column itself can be regarded as a filter. Especially when polymerized close to the gel point, high-molecular-weight microgels are expected to be formed, which will be filtered out in the case of SEC and, therefore, will not be detected.

The intrinsic viscosities and the molecular weights of NVP/VAC/DEGDVE microgels polymerized at different concentrations in ethanol are shown in Table 3. At low concentration, low-molecular-weight microgels are formed. As the concentration is increased, the molecular weight as well as the molecular-weight distribution increase. Even at high molecular weights, the intrinic viscosity remains low.

The differential weight fraction plots of 65/15/20 NVP/VAC/DEGDVE microgels made in methanol at different initial monomer concentrations determined by FFFand light scattering are shown in Fig. 4. The respective molecular weights and intrinsic viscosities are shown in Table 1.

The relationship between $[\eta]$ and M_w is shown for 65/15/20 NVP/VAC/DEGDVE microgels obtained at different initial monomer concentrations in methanol is shown in Fig. 5. The exponent (a) of the Mark–Houwink equation, calculated from the regression plot using all the points, is 0.26. This value of the exponent is close to the value of 0.25 reported by Zimm et al. [15] for 1,4-divinylbenzene and styrene copolymers and agrees well with other results for the extent of internal cross-linking and thus the formation of microgels [1].

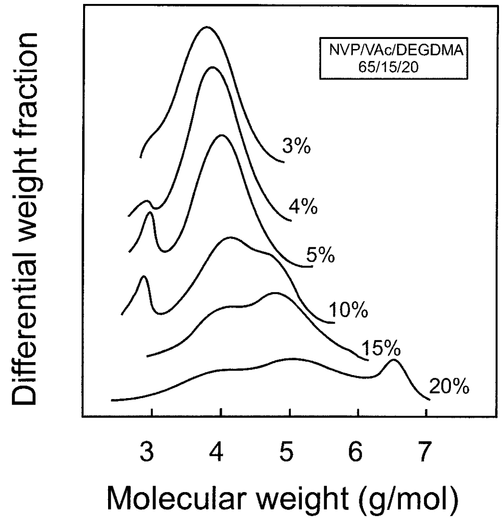

Fig. 4 Differential molecular-weight-distribution plots, determined by light scattering of 65/15/20 NVP/VAc/DEGDVE in ethanol at different IMC

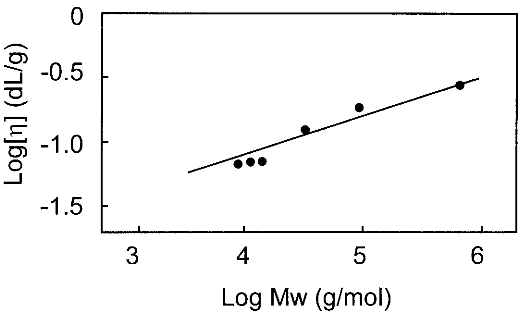

Fig. 5 Relationship between $[\eta]$ and M_w of 65/15/20 NVP/VAc/DEGDVE microgels synthesized at different IMC in ethanol

Conclusions

Solution polymerization appears to be a very simple and useful method to prepare high-molecular-weight, internally cross-linked polymers, microgels with a low

Table 3 Number-average and weight-average molecular weights and molecular-weight distribution for 65/15/20 NVP/VAc/DEGDVE microgels polymerized at different concentrations in ethanol

Solubility parameter δ ($J^{0.5}cm^{-1.5}$)	Initial monomer concentration (wt%)	$[\eta]$ (dl/g)	M_n (10^3 g/mol)[a]	M_w (10^3 g/mol)[a]	D[a]
26.0	3	0.068	3.6	8.0	2.2
26.0	4	0.070	4.0	11	2.8
26.0	5	0.074	3.9	14	3.6
26.0	10	0.124	3.9	30	7.7
26.0	15	0.19	12.2	90	7.4
26.0	20	0.28	125	880	7.0

[a] Determined with field-flow fractionation and light scattering

solution viscosity. In solvent systems covering a wide range of solubility parameters, macrogelation is prevented and microgels were formed at complete conversion. In this study water-soluble microgels were made by copolymerizing NVP with VAc in the presence of a cross-linker DEGDMA or DEGDVE in different solvent systems. DEGDVE resulted in homogeneous clear solutions. The molecular weight and the molecular-weight distribution increase when the initial monomer concentration increases. Microgels made with 20 wt% (14.6 mol%) of the cross-linker DEGDVE, 65 wt% (66.2 mol%) of NVP and 15 wt% (19.5 mol%) of VAc show low viscosity, even at high molecular weights. The exponent in the Mark–Houwink equation was found to be 0.26, which is evidence of a globular conformation of the polymers. Aqueous solutions of the microgels with a concentration of 50 wt% are completely transparent.

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