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SYNTHESIS OF POLYMERIC MICROSPHERES BASED ON 3-CHLORO-2-HYDROXYPROPYL METHACRYLATE

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SUMMARY: In this study polymer microspheres were prepared by precipitation and dispersion polymerizations of CHPMA. The effect of polymerization solvent and type of stabilizer on the particle size, size distribution and yield was investigated. In the polymerization experiments two solvents: benzene and dipropyl ether and three stabilizers: MPEG 750, MPEG 5000, PVAc were used. The possible route to modify the surface of the microspheres to obtain epoxide groups was proposed.

Introduction

Precipitation and dispersion polymerizations have been traditionally used to produce small polymeric spheres of controlled size distribution. In precipitation polymerization, both the monomer and the initiator are soluble in the polymerization mixture whereas the medium is a poor solvent for the resulting polymer, which thus precipitates from initially homogeneous solution. There is no dispersion stabilizer and the beads resulted from precipitation polymerization are thus pure. The particles formed are often polydisperse and their size is between 0.1 and 10 μm[1-4]. The term "dispersion polymerization" refers to a category of precipitation polymerization carried out in the presence of suitable steric stabilizer of precipitating particles. Dispersion stabilizers are polymers or macromonomers soluble in reaction medium. This polymerization generates monodisperse microspheres or those with a narrow size distribution, having diameter within the range of 0,5 – 20 μm[4-8]. Covalently bonded or adsorbed stabilizer usually changes more or less the character of particle surface and for some applications may be considered as undesirable contamination.

There are numerous reports concerning the preparation of monodisperse microspheres with potential biomedical or industrial applications (informatics, microelectronics)[9-12]. In biological applications they can either serve as a carrier for drug delivery systems or for enzyme immobilization. In such applications, functional polymers are preferred. The functional groups can be introduced to the particle surface in two ways: either by employing

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the functional comonomer during polymerization or by modifying the polymer after it is prepared [13)].

The present paper describes the synthesis and characterization of poly(3-chloro-2-hydroxypropyl methacrylate) (PCHPMA) and investigations on the influence of the type of steric stabilizer and solvents on the diameter, size distribution and yield of the microspheres produced in precipitation or dispersion polymerization of 3-chloro-2-hydroxypropyl methacrylate (CHPMA). Possibility of surface modification of PCHPMA microspheres by generating epoxy groups has been proved as well.

Experimental

Materials

3-chloro-2-hydroxypropyl methacrylate (ALDRICH) was distilled under reduced pressure, fraction boiling at 95°C/3 mm Hg was collected; dipropyl ether (MERCK), benzene (POCh Gliwice), poly(vinyl acetate) with MW ~ 45 000 (BDH Chemicals Ltd), polyethylene glycol monomethyl ethers with molecular weight of 750 and 5000 (FLUKA) were used as received; benzoyl peroxide (ARGON, Łódź) was dissolved in chloroform at room temperature and precipitated in methanol.

Preparation of the microspheres

Precipitation polymerization

5% (v/v) solution of 3-chloro-2-hydroxypropyl methacrylate (CHPMA) in dipropyl ether or benzene containing benzoyl peroxide (BPO, 1% w/w in relation to the monomer) was placed in a glass vessel equipped with a magnetic stirrer. The solution was kept at 70°C for 2,5 h under nitrogen atmosphere. After cooling to room temperature, the microspheres formed were separated by filtration, washed with ethyl ether and dried at room temperature under vacuum.

Dispersion polymerization

The polymerization was carried out under nitrogen atmosphere in a glass vessel equipped with a magnetic stirrer. 5% (v/v) solution of CHPMA in benzene containing 1% of BPO (w/w, in relation to the monomer), 5% of poly(vinyl acetate) (PVAc) or 5% polyethylene glycol 750 monomethyl ether (MPEG 750) or polyethylene glycol 5000 monomethyl ether (MPEG 5000) (w/w in relation to monomer) was stirred at 70°C for 2,5 h. After cooling to room temperature, the microspheres formed were separated by filtration, washed with ethyl ether and dried at room temperature under vacuum.

Functionalization of the microspheres

1 g of PCHPMA microspheres ($5{,}6*10^{-3}$ mole of chlorohydrine groups) was treated with 10 cm^3 of 2M KOH for 1,5 h at room temperature. The polymer was filtered off, washed with distilled water and dried at room temperature under reduced pressure.

Characterization of microspheres

The particle size of the polymeric microspheres and to some extend their morphology were examined by use of a scanning electron microscope (SEM, Model TESLA BS 340). The particle size distribution was determined from the micrographs.

The molecular weights were measured by GPC on a Knauer chromatograph equipped with RI detector and calibrated with polystyrene standards. THF was used as a carrier solvent.

Epoxyfunctional microspheres were characterized by IR and ATR-IR spectroscopy using a BIO-RAD FTS 175 spectrometer. The epoxide content (EC) was determined using hydrochloric acid / dioxan titration methods.

Results and Discussion

In this study polymeric microspheres were prepared by precipitation and dispersion polymerizations of CHPMA.

In the precipitation polymerization the effect of the solvent on particle size has been examined. PCHPMA obtained in solution polymerization in 1,4-dioxane appeared to be insoluble in water, diethyl and dipropyl ethers, benzene and chloroform, while the monomer was soluble in most common solvents except H_2O and aliphatic hydrocarbons. In the polymerization experiments two solvents were used: benzene and dipropyl ether. In both cases polymer particles precipitated from the reaction medium were soluble in THF, methanol, ethanol and acetone. Microspheres prepared in benzene were obtained with the yield of 30% whereas in dipropyl ether with the yield of 60%. The yield of the microspheres was relatively low because a part of the polymer was lost due to agglomeration of particles and sticking to the walls of a reaction vessel. Typical scanning electron micrographs of the microspheres obtained in precipitation polymerization are shown in the Figure 1. All they appeared to be spherical particles.

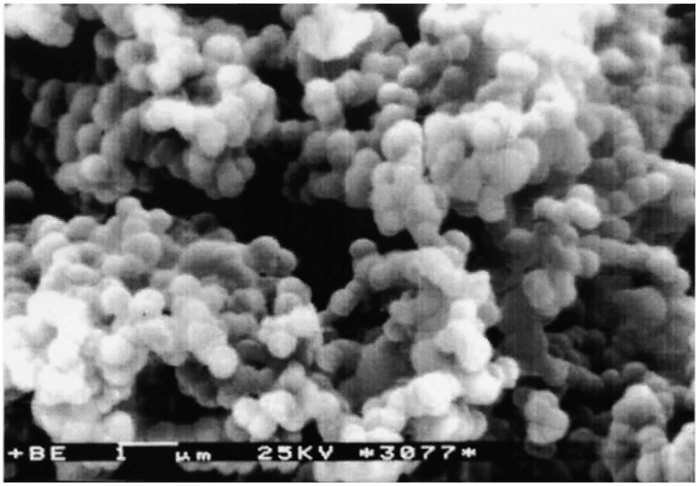


Fig.1a.: SEM micrographs of PCHPMA microspheres prepared by precipitation polymerization in benzene

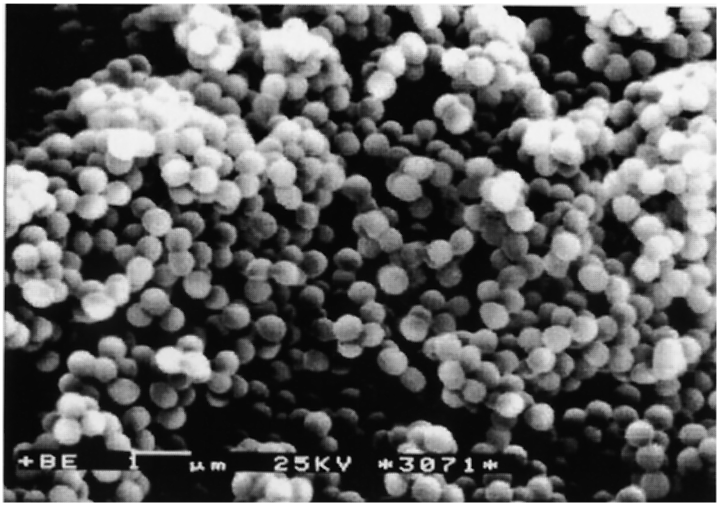


Fig.1b.: SEM micrographs of PCHPMA microspheres prepared by precipitation polymerization in dipropyl ether

The figure 1a presents the microspheres obtained in benzene. Microspheres of $\phi = 0.4\text{-}0.6\ \mu m$ are sticked together to some extent thus forming loose agglomerates.

Precipitation polymerization in dipropyl ether produced well shaped spherical particles of similar size ($\phi = 0{,}48 \pm 0{,}04\ \mu m$) as those from benzene, but with relatively narrow size distribution (fig.1b). Degree of polydispersity calculated according to[14)] as the ratio between volume and number averaged diameter D_V/D_n amounted to 1.029, while 1.047 for those obtained in benzene (tab.1).

The molecular weight of PCHPMA particles obtained in dipropyl ether was determined by GPC. The number average molecular weight (Mn) was equal to 89,5 kDa, while the weight average one (Mw) was 1069 kDa, thus the molecular weight distribution (Mw/Mn) was 11,95.

In next stage the influence of the additives, intended to be dispersion stabilizers, on the yield, diameter and size distribution of the microspheres obtained by the polymerization in benzene has been investigated. PCHPMA microspheres were obtained in the polymerization carried out in the presence of 5% of MPEG 750, MPEG 5000 or PVAc. Table 1 lists the results of dispersion polymerization and for comparison also of precipitation one.

Table 1. Results of dispersion polymerization of CHPMA in benzene[a)]

Expt. No.	Type of stabilizer	D_n [μm]	D_V/D_n[b)]	Yield of particles [%]
1	-	0,49 ± 0,05	1,047	30
2	MPEG 750	0,49 ± 0,11	1,146	71
3	MPEG5000	0,74± 0,09	1,062	75
4	PVAc	0,44± 0,02	1,011	70

[a)] 5% (v/v) monomer solution, 1% of BPO and 5% of the stabilizer (w/w, in relation to the monomer), 70°C, 2,5h,

[b)] $D_n = \Sigma D_i n_i / \Sigma n_i$, $D_v = \Sigma D_i^4 n_i / \Sigma D_i^3 n_i$

The yield of the microspheres produced by the dispersion polymerization is much higher than that obtained in the precipitation one. The use of MPEG 750 and PVAc had practically no effect on the size of particles (fig. 2, tab.1), while bigger microspheres were obtained in the presence of MPEG 5000. Both MPEGs, especially that with lower MW, increased to some extent polydispersity of the microspheres, while PVAc decreased it. The microspheres obtained in benzene in the presence of the latter polymer are practically monodisperse and their averaged diameter is 0.44±0.02 µm (fig.2c). Probably higher MW of a stabilizer is advisable for the preparation of monosized PCHPMA microspheres.

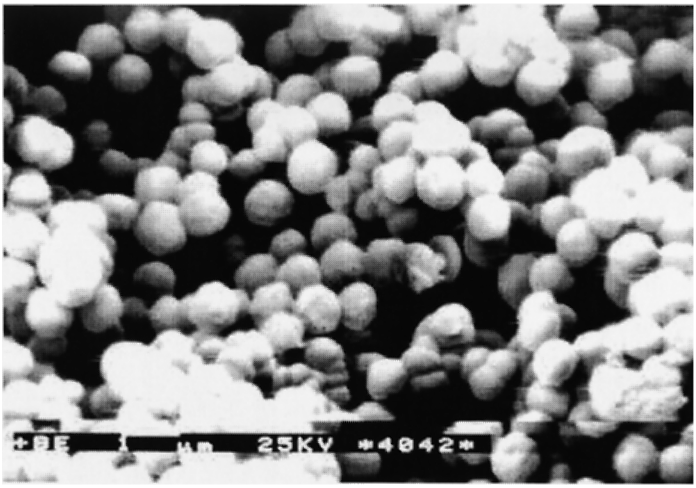


Fig. 2a.: SEM micrograph of PCHPMA microspheres prepared by dispersion polymerization in the presence of MPEG 5000 as stabilizer

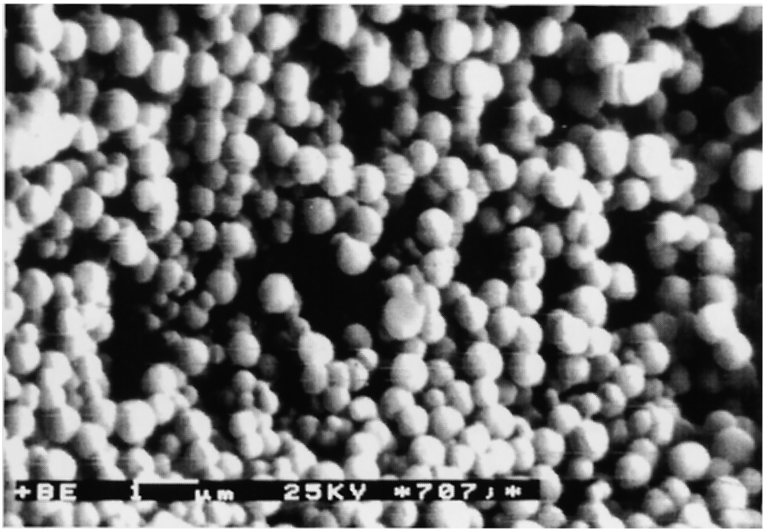


Fig. 2b.: SEM micrograph of PCHPMA microspheres prepared by dispersion polymerization in the presence of MPEG 750 as stabilizer

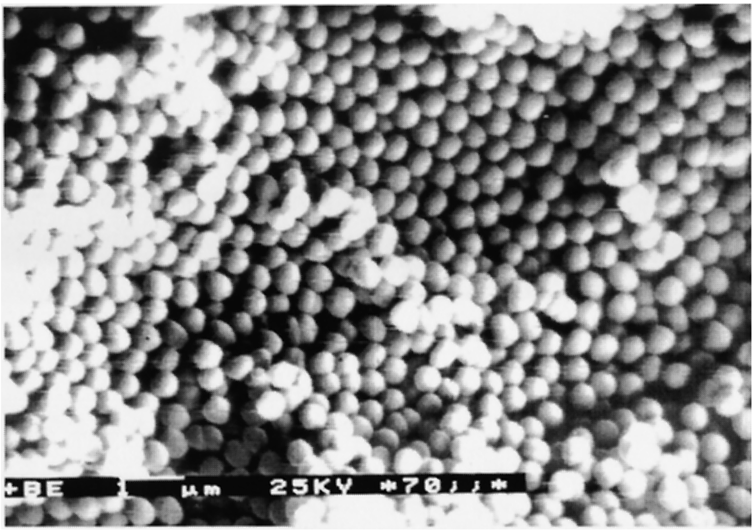
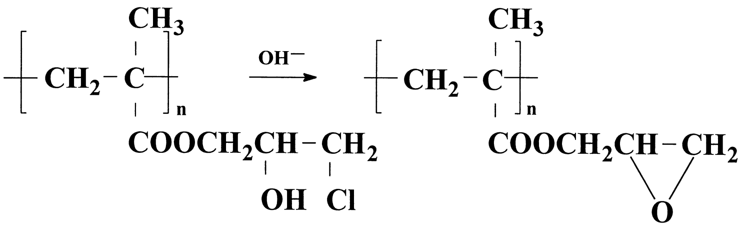


Fig.2c.: SEM micrograph of PCHPMA microspheres prepared by dispersion polymerization in the presence of PVAc as stabilizer

It might be assumed that epoxyfunctional microspheres could be obtained from PCHPMA ones by simple dehydrochlorination. Thus, in order to convert chlorohydrine groups of PCHPMA into the oxirane ones, the microspheres obtained were treated with aqueous KOH at room temperature.



The dehydrochlorination reaction was carried out in heterogeneous systems, so it might be expected to occur mainly at the surface of PCHMA microspheres or in thin outer layer.

The products of dehydrochlorination were characterized by IR and ATR-IR spectroscopy. Figure 3 shows the ATR-IR spectra of starting PCHPMA microspheres and that of dehydrochlorinated ones. In the spectra of the latter, the bands of epoxy group at 849 and

902 cm^{-1} were observed, thus confirming the transformation of surface chlorohydrine groups into oxirane ones.

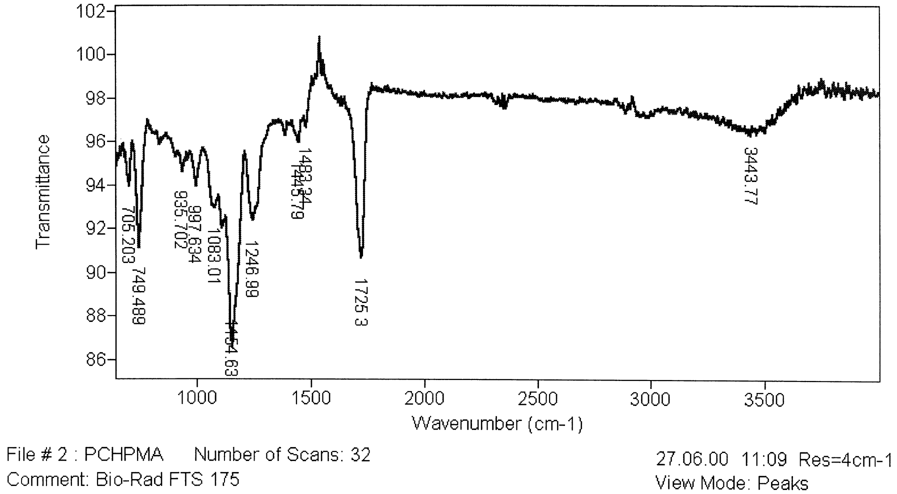


Fig. 3a.: ATR-IR spectrum of starting poly(3-chloro-2-hydroxypropyl methacrylate)

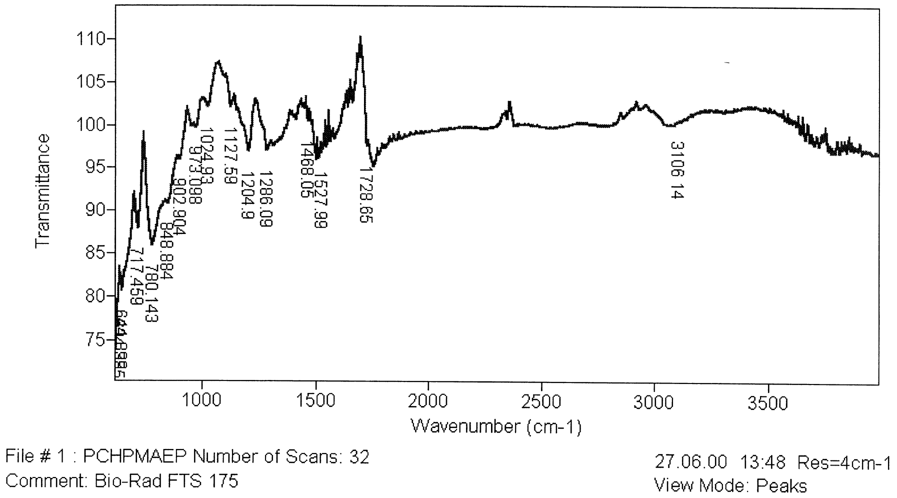


Fig. 3b.: ATR-IR spectrum of epoxidized poly(3-chloro-2-hydroxypropyl methacrylate)

IR spectra of dehydrochlorinated microspheres (fig.4) displayed only a weak signal of epoxide groups, while intensive, broad one of hydroxyl ones at 3500 cm^{-1}. A weak signal at 748 cm^{-1} can be assigned to C-Cl stretching vibration. It may be concluded that according to our expectation epoxide groups have been formed at the surface, while inner part of PCHPMA microspheres remained unchanged. The products of dehydrochlorination were characterized also by determination of epoxide content (EC). The product of the reaction, which should be formed at least at the surface of the particles, should correspond to poly(glycidyl methacrylate), for which theoretical EC is equal to 0,7 mole/100g. The EC of the products amounted to 0,39 mole/100g for microspheres obtained by precipitation polymerization and 0,40 mole/100g for microspheres prepared by dispersion polymerization. This indicates that epoxide groups were formed not only at the surface but also in outer layer of PCHPMA microspheres.

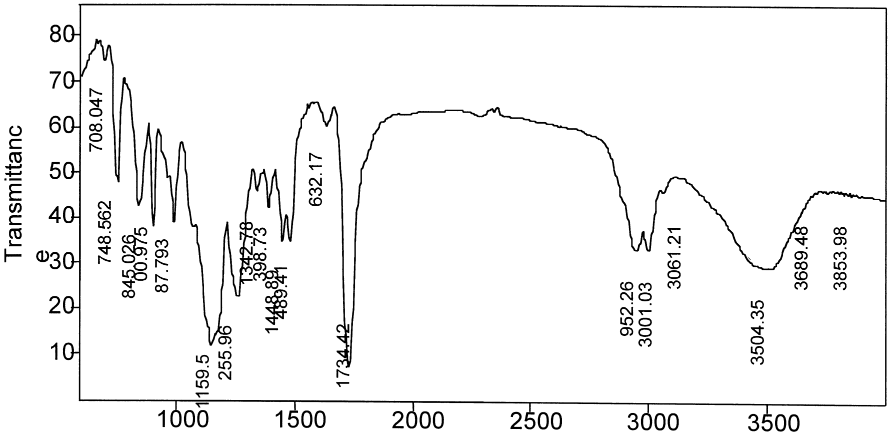


Fig. 4. IR spectrum of dehydrochlorinated poly(3-chloro-2-hydroxypropyl methacrylate)

Conclusions

The experimental results presented above indicate that for production of well shaped PCHPMA microspheres with narrow size distribution in precipitation polymerization, dipropyl ether is a better dispersion medium than benzene.

In the case of the polymerization carried out in benzene use of low or medium molecular weight additives results in much higher yield of microspheres.

PVAc was found to be the best dispersion stabilizer among those used for the preparation of monodisperse PCHPMA microspheres by the polymerization in benzene. Use of PVAc results in very narrow particle size distribution of the microspheres obtained.

Epoxyfunctional microspheres can be easily obtained from preformed poly(3-chloro-2-hydroxypropyl methacrylate) microspheres by treatment with aqueous alkalia.

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