JAN ŁUKASZCZYK, ANNA CEBULSKA
Department of Physical Chemistry and Technology of Polymers
Silesian University of Technology, Gliwice

Preparation of functional microspheres by polymerization using macromonomers

Summary — Methyl methacrylate (MMA) was transesterified with poly(ethylene glycol) monomethyl esters to yield four poly(ethylene glycol) monomethyl ether methacrylates (MPEGMA). The resulting monomethylacrylate monomers were used as stabilizing agents in dispersion polymerization of allyl methacrylate (AMA) or an AMA—MMA mixture. Functional microspheres were prepared and their preliminary characteristics is given.

Key words: macromonomers, allyl methacrylate, functional microspheres.

Polymer microspheres are used in various fields of science and technology, *e.g.*, in medical diagnostics, packing of haemoperfusion columns [1], drug delivery systems [1, 2], calibration standards, *etc.* [3]. Macrospheres having functional groups on their surfaces, which enable the active agent to be chemically bonded, are indispensable for various applications.

Epoxy groups, which are able to react with numerous compounds even under moderate conditions, belong to such functional groups [4]. Microspheres of this type are usually obtained directly from monomers containing epoxy group (glycidyl methacrylate, *etc.*). In the direct methods including emulsion or suspension polymerization, epoxy groups are in part consumed by side reactions, *e.g.*, hydrolysis. It can be foreseen that microspheres having epoxy groups on the surface could be obtained also in an indirect manner. *i.e.*, by epoxidation of double bonds originating from allyl methacrylate at the surface of microspheres.

Microspheres can be obtained by using chemical methods, *e.g.*, by polymerization carried out so that spherical particles of a polymer are formed, as well as by physical methods, *e.g.*, from the existing polymers [1]. One of the chemical methods is dispersion polymerization, *i.e.*, a solution—precipitation process run in the presence of a dispersion stabilizing agent. During this process, spherical particles precipitate from an initially homogeneous reaction mixture. Polymer particles formed have usually narrow size distribution and their average diameter is within the range of 1—10 μm [3, 5]. Homopolymers, block and graft copolymers, as well as macromonomers soluble in the reaction mixture are used as stabilizing agents. The macromonomers take part in the copolymerization. Their long chains are concentrated on the surface of the polymer particles precipitating from the solution, thus forming a protective layer preventing coagulation [3].

The aim of this study is to investigate the possibility of the synthesis of macromonomers of the methoxypolyethylene glycol methacrylate (MPEGMA) type by transesterification of methyl methacrylate (MMA) with corresponding methoxypolyethylene glycol (MPEG) and the use of these macromonomers as stabilizing agents in preparation of functional microspheres by dispersion polymerization or copolymerization of allyl methacrylate (AMA). The products of the latter may be considered to be precursors of epoxy functional microspheres.

EXPERIMENTAL

Materials

Polyethylene glycol monomethyl ethers of molecular weight 550, 750, 2000, 5000 (FLUKA), methanol (POCh, Gliwice) were used as received; methyl methacrylate (Z.Ch. Oświęcim) and allyl methacylate (ALDRICH) were purified by treating with a solution of NaOH and NaCl and then dried over anhydrous $CaCl_2$; benzoyl peroxide (ARGON, Łódź) was dissolved in chloroform at room temperature and precipitated in methanol; potassium carbonate (POCh, Gliwice) was heated for 7 h at 120°C.

Synthesis of MPEGMA 2000 macromonomer

To a 100-cm^3 round-bottomed flask equipped with a stirrer, column and condenser, 3.6 g (0.036 mol) of MMA, 36 g (0.018 mol) of MPEG 2000, 0.92 g of K_2CO_3 and 0.0003 g of hydroquinone monomethyl ether (an inhibitor) were added. The reaction mixture was heated to boil and the MMA—methanol azeotrope was distilled off. After 1 h, 0.46 g of K_2CO_3 and 0.36 g (0.0036 mol) of MMA were added. Heating was continued until the temperature at the top of the column dropped and simultaneously the temperature in the flask rose; then the mixture was allowed to cool. When cooled to below 60°C the reaction mixture partly solidified. The solid was filtered off from the low amount of the liquid and dried in vacuum to constant weight at room temperature; yield of MPEGMA, 30.4 g (82%).

The synthesis of MPEGMA 5000 was run in an analogous way (yield, 81%). MPEGMA 550 and 750 did not separate from the reaction mixture; unreacted MMA was distilled off under vacuum (yields, 95 and 82%, respectively).

Dispersion polymerization

Polymerization was carried out in a nitrogen atmosphere in sealed glass ampoules equipped with a magnetic stirrer. The monomers (AMA-MMA 1:1, mol/mol), 5% solution in methanol, 1% of benzoyl peroxide and 1%, 2.5% or 5% of MPEGMA (w/w, in relation to the monomers) were placed in the ampoules. The ampoules were evacuated, refilled with nitrogen and sealed, then stirred at 70°C for 4 h. The precipitate was separated by filtration, washed with methanol, and dried to constant weight at room temperature.

Characterization of polymers and microspheres

^{1}H-NMR spectra of solution of the products in $CDCl_3$ were recorded by using a UNITY/INOVA (VARIAN) 300 MHz spectrometer (pulse delay equal to 1 s). TMS was used as an internal standard.

IR spectra of samples in KBr pellets or films were recorded in BIO-RAD FTS 175 L spectrometer.

Number-average molecular weight M_n(VPO) was determined at 37°C in chloroform on a Knauer & Co GmbH vapor-phase osmometer.

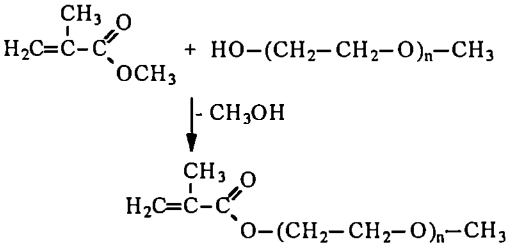
SEM microphotographs of microspheres were obtained by using a TESLA BS 340 scanning electron microscope.

RESULTS AND DISCUSSION

Synthesis of macromonomers

Recently, methacrylates and acrylates of alkyl ethers of poly(ethylene glycol) are arousing an ever increasing interest. They are usually prepared in the reaction of poly(ethylene glycol) derivatives with methacrylic acid chloride [6—10] or, when terminating with methacryloyl chloride, by polymerization of ethylene oxide initiated by alcoholates [6].

In the present study, MPEGMA was obtained by direct transesterification of MMA with MPEG, the method employed recently in the synthesis of di-, tri- and tetraethylene glycol monomethacrylates [11, 12]. There are no reports on the application of this simple method to the synthesis of methacrylate macromonomers, except for a single patent information [13]. Anhydrous K_2CO_3 was used as a catalyst; its preparation seems to be more convenient than that of the catalysts mentioned in [13], *i.e.*, $Ca(OH)_2$ and LiCl.



(1)

The synthesis was carried out by using a commercial grade MPEG with molecular weight of 550, 750, 2000 or 5000. All MPEGs are soluble in water, methyl methacrylate and chloroform; however, MPEG 550 and 750 solutions in chloroform are slightly turbid.

The action of a macromonomer as a stabilizing agent is known to depend on chain length [3]. Therefore, in order to characterize the reactants more precisely, the numbers of oxyethylene units, n, in the starting compounds of $CH_3O(CH_2CH_2O)_nH$ type, were calculated from the nominal molecular weight values given by the manufacturer of MPEG, from M_n(VPO) values, and from the relative intensities of appropriate signals in ^{1}H-NMR spectra ($n_{(NOM)}$, $n_{(VPO)}$ and $n_{(CH_3-O)}$, respectively). For the latter, the length of chain n was calculated on the basis of signal intensities (Fig. 1) of the methoxy group (δ_{CH_3-O} = 3.38 ppm) and chain methylene groups (δ_{CH_2O} = 3.52—3.53 ppm) by using the formula (1):

$$n = \frac{3I_b}{4I_a} \qquad (2)$$

where: I_a, I_b *are the intensities of signals of methyl* CH_3*-O- and methylene* $-OCH_2CH_2-$ *protons in MPEG (Fig. 1).*

The n-values obtained on various ways are practically equal to each other in the case of MPEG 550 and 750. In the case of MPEG 2000 and 5000, the M_n-values determined by the VPO method are higher than the nominal values and $n_{(VPO)}$ values are much higher than those estimated by other methods (Table 1).

The transesterification products are solids (MPEGMA 2000 and 5000) or semi-solids, soluble in water and common organic solvents.

The signals in the ^{1}H-NMR spectrum of MPEGMA (Fig. 2) correspond to the expected reaction products, *i.e.*, $CH_3O(CH_2CH_2O)_{n-1}CH_2CH_2OOCC(CH_3)=CH_2$. As compared with the spectrum of starting MPEG, the spectrum of MPEGMA contains the characteristic signals of methyl (δ_{CH_3-C} = 1.93 ppm) and methylene (δ_{CH_2} = 6.11 and 5.56 ppm) protons of the methacrylate group. The presence of the signal at δ = 4.28 ppm, which can be as-

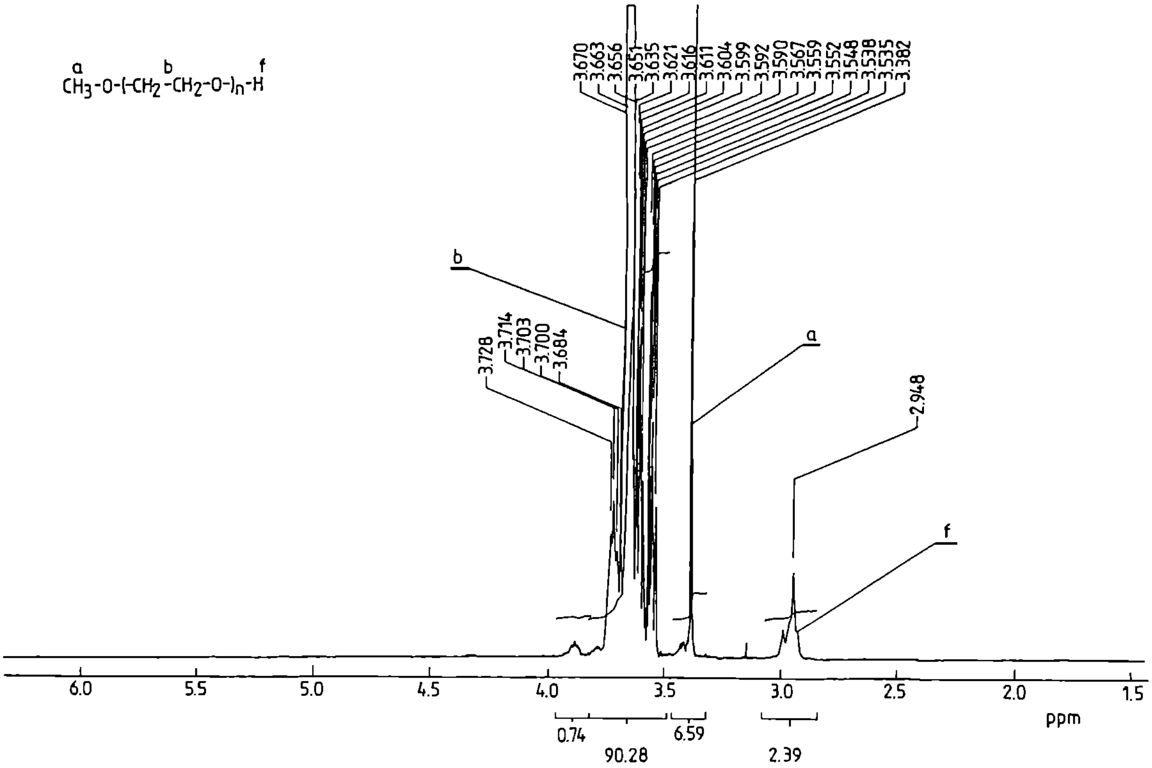


Fig. 1. ^{1}H-NMR spectrum of MPEG 550

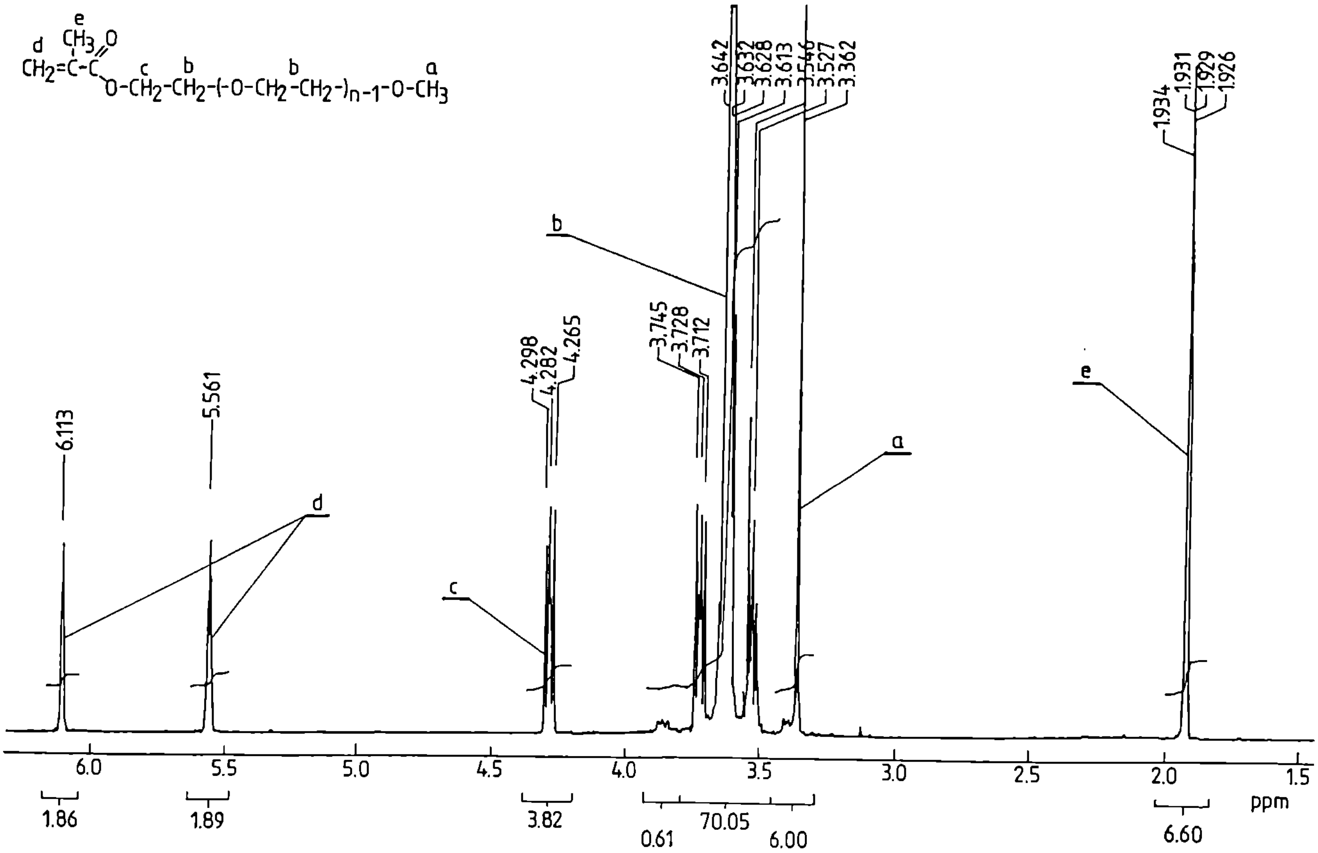


Fig. 2. ^{1}H-NMR spectrum of MPEGMA 55O

T a b l e 1. The number n of oxyethylene units in $CH_3O(CH_2CH_2O)_nH$

Molecular weight of MPEG		Value of n		
nominal	M_n(VPO)	$n_{(NOM)}$	$n_{(VPO)}$	$n_{(CH_3-O)}$
550	430	12	9	12
750	590	16	13	17
2000	2000	45	45	43
5000	4950	113	112	120

$n_{(NOM)}$ — calculated for nominal molecular weight taken from the producer; $n_{(VPO)}$ — calculated for $M_{n(VPO)}$; $n_{(CH_3-O)}$ — calculated from ^{1}H-NMR spectra according to eqn. (1).

T a b l e 2. The number n of oxyethylene units and ratio of the end groups in $CH_3O(CH_2CH_2O)_nOOCC(CH_3)=CH_2$

Macromonomer	$M_{n(VPO)}$	$n_{(NOM)}$	$n_{(VPO)}$	$n_{(CH_3-O)}$ *)	$n_{(CH_3-C)}$ *)	CH_3-C/ CH_3-O mol/mol
MPEGMA 550	546	12	10	12	11	1.04
MPEGMA 750	756	16	15	16	18	0.90
MPEGMA 2000	4300	45	95	43	54	0.87
MPEGMA 5000	6600	113	148	63	156	0.46

*) $n_{(CH_3-O)}$ and $n_{(CH_3-C)}$ — calculated from relative intensities of respective signals in ^{1}H-NMR spectra according to eqns. (3) and (4).

signed to the methylene protons adjacent to the ester group - CH_2OOC-, indicates the formation of the ester. There are no signals in the MPEGMA spectra attributable to hydroxyl groups. Such signals are present in the spectra of MPEG (Fig. 1).

The IR spectra of the transesterification products exhibit the bands of stretching vibrations of $C=CH_2$ of the methacrylate group ($\nu_{C=C}$ = 1633—1639 cm^{-1}), ester carbonyl group ($\nu_{C=O}$ = 1717—1721 cm^{-1}), and ester C-O of α,β-unsaturated acids (ν_{C-O} = 1281—1297 cm^{-1}).

Similarly as in the case of starting MPEGs, the chain length expressed as n was calculated for macromonomers. By using NMR spectra, chain length was calculated from the signal intensity ratio of the methylene protons in the chain to the methyl protons of the two end groups, methoxyl and methacrylate. By using ^{1}H-NMR spectra, the mole ratio of the two end-groups in MPEGMA, theoretically equal to 1, was calculated.

The value $n_{(CH_3-O)}$ was calculated from the intensity of the methoxy end group signal as:

$$n_{(CH_3-O)} = \frac{3(I_b + I_c)}{4I_a} \tag{3}$$

where : I_a, I_b, I_c *are the intensities of the signals of methyl* CH_3*-O-, methylene -*OCH_2C*- and -C-*CH_2OOC*- protons in MPEGMA.*

The value $n_{(CH_3-C)}$ was calculated from the intensity of the signal of methyl group of methacrylate end group as

$$n_{(CH_3-C)} = \frac{3(I_b + I_c)}{4I_e} \tag{4}$$

where: I_e *denotes the intensity of the signals of methyl protons in methacrylate group at* δ *= 1.93 ppm.*

The above results were compared with the chain length calculated from $M_{n(VPO)}$ and nominal molecular weight (Table 2). In the case of the macromonomers synthesized from MPEGs of lower molecular weight, the values of n obtained in different ways are similar to each other and the ratio of the end groups expected in the product is close to 1. The values of M_n(VPO) and $n_{(VPO)}$ for higher macromonomers are distinctly higher than those obtained by other methods. Discrepancies, however, appear in the case of MPEGMA 500; the n values calculated from signal intensities of the protons of the two end groups, *i.e.*, $n_{(CH_3-O)}$ and $n_{(CH_3-C)}$, are quite different. In this case, the number of methoxy groups deduced from the ^{1}H-NMR is twice as high as that of methacrylate groups. This fact can hardly be ascribed to the inaccuracy of the NMR method for M_n ~ 5000. However, basing on the NMR spectra, the product of the transesterification can be assumed to contain no dimethacrylates, but only some amount of dimethyl ether of PEG.

Dispersion polymerization

AMA and a (1:1, by moles) mixture of AMA:MMA was subjected to dispersion polymerization in the presence of each of the macromonomers obtained. Concentrations of the latter were 1%, 2.5% or 5% (w/w) in relation to the sum of AMA and MMA. The polymerization was carried out for 12—24 h.

When the process was carried out in the (65:35 v/v) methanol/benzene system, only non spherical particles or agglomerates were obtained. The polymer yield calculated in relation to the monomer and macromonomer weights after 12 h was 69—85%, whereas that of the AMA/MMA copolymer after 24 h did not exceed 21%.

The polymerization carried out in methanol yielded spherical particles in a much shorter time, since polymer precipitation started after as few as 80 min. Therefore, the polymerization time was shortened to 4 h. SEM photomicrographs (Fig. 3) illustrate the influence of the macromonomer concentration and of the length of its chain on the microsphere size and size distribution. At the same macromonomer concentration, the diameter of the microspheres obtained decreases with the rise in the molecular weight of MPEGMA, *i.e.*, as the length of its hydrophilic chains is increased. Average diameters of the microspheres, calculated from SEM microphotographs, were within the range 0.5—1.5 μm; standard deviations were *ca.* 25% of mean values.

Poly-AMA and AMA-MMA copolymer microspheres did not dissolve in organic solvents, perhaps because of crosslinking on account of the reaction of part of the AMA allyl groups in the polymerization process.

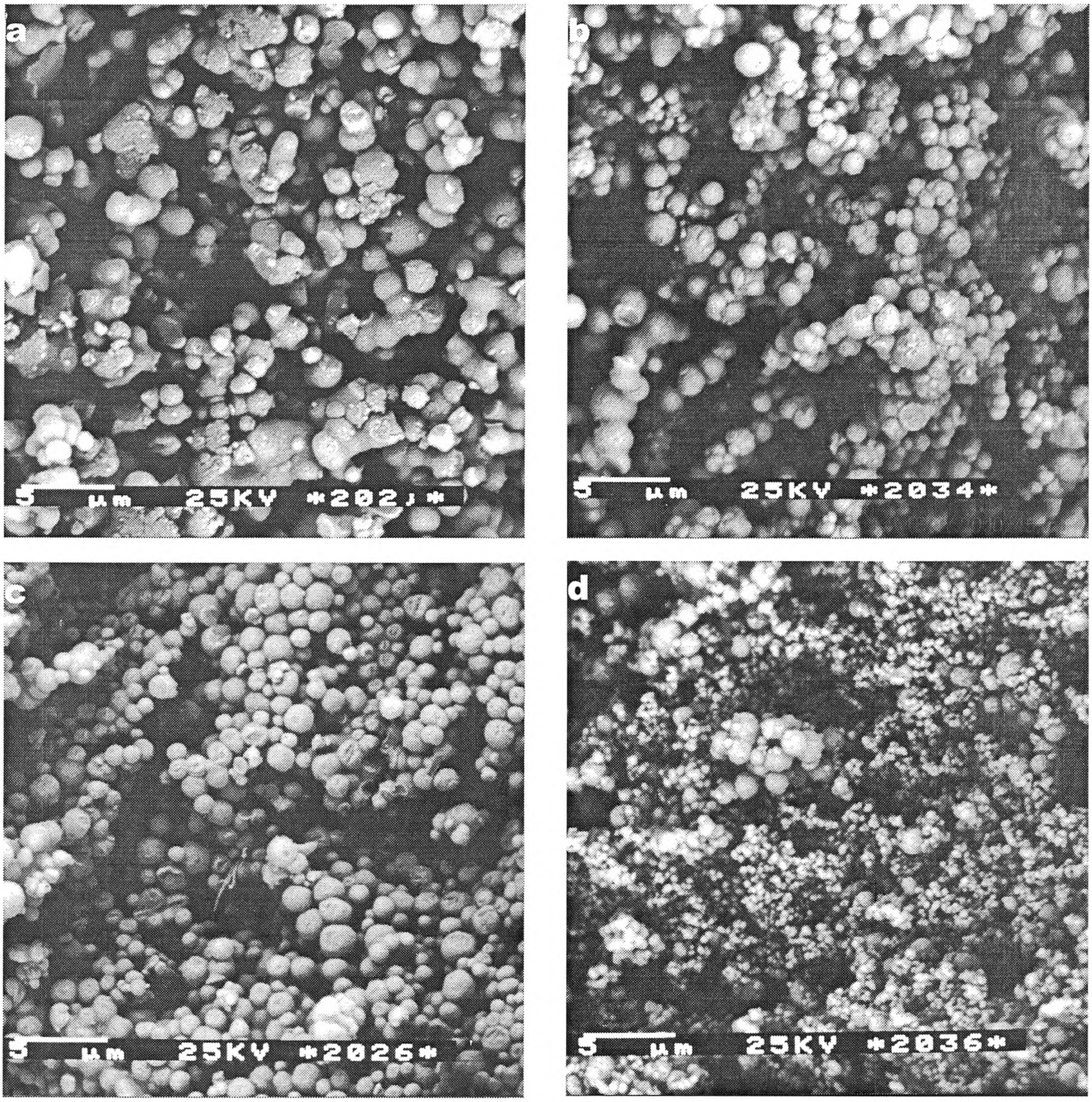


Fig. 3. SEM photomicrographs (4000×) of poly(AMA/MMA) microspheres obtained by dispersion polymerization in methanol in the presence of 5% of MPEGMA: (a) MPEGMA 550, (b) MPEGMA 750, (c) MPEGMA 2000, (d) MPEGMA 5000

CONCLUSIONS

Transesterification of methyl methacrylate with monomethyl ether of poly(ethylene glycol) is a convenient method of preparing MPEGMA macromonomers.

The best solvent for use in dispersion polymerization of AMA or the AMA/MMA mixture is methanol and optionally methanol/water mixture. The presence of benzene in the solvent mixture results in sticking of the precipitating copolymer particles, in spite of using the stabilizing agent of MPEGMA type.

The length of MPEGMA type macromonomer chain influences the size of microspheres obtained in the dispersion copolymerization of AMA—MMA in methanol; this relationship can be used to control the size of the resulting microspheres.

REFERENCES

1. Kowalczyk D., Słomkowski S.: *Polimery* 1992, **37**, 442.

2. Davies S., Illum L.: *Biomaterials* 1989, 9, 111.
3. Horak D.: *Acta Polymerica* 1996, **47**, 20.
4. Prokopov P., Gritskova I.: *Usp. Khim.* 1996, **65**, 184.
5. Arshady R.: *Polym. Prepr.* 1997, **38**, 636.
6. Bo G., Wesslen B., Wesslen K.: *J. Polym. Sci., Part A: Polym. Chem. Ed.* 1992, **30**, 1799.
7. Ito K., Tonaka K., Tonaka H., Imai G., Kawaguchi S., Itsuno S.: *Macromolecules* 1991, **24**, 2348.
8. Ito K., Hashimura K., Itsuno S.: *Macromolecules* 1991, **24**, 3977.
9. Ito K., Yokoyama S., Arakawa F., Yukawa Y., Iwashita T., Yamasaki Y.: *Polym. Bull.* 1986, **16**, 337.
10. Gramain P., Frere Y.: *Polym. Commun.* 1986, **27**, 16.
11. Gibas M.: *Zeszyty Nauk. Pol. Śl.* 1996, **134**, 9.
12. Barszczewska-Rybarek I., Gibas M.: *Polymer* 2000, **41**, 3129.
13. Knebel J., Spalt W.: PCT Int. Appl., WO 97 26 293 (1997).

Received 20 VIII 1999.

KALENDARZ IMPREZ

4—9 marca 2001 r. Ventura, Kalifornia, USA. Conference of CAE in Polymer Processing.

Organizator: University of Illinois, Urbana, Illinois, USA + Industrial Materials Institute, Boucherville, Quebec, Kanada.

Informacje: Prof. Charles Tucker, University of Illinois, Dept. of. Mech. and Ind. Engineering, 140 Mechanical Engineering Building, MC-244, 1206 West Green Street, Urbana, IL 61801. Tel.: 217-333-2692, fax: 217-244-6534 + Dr. Andrés Garcia-Rejón, National Research Council Canada, 75 boul. de Mortagne, Boucherville, Qc, J4B 6Y4, Canada. Tel.: (450) 641-5067, fax: (450) 641-5105.

2—6 kwietnia 2001 r. Birmingham, Wielka Brytania. Targi i wystawa przemysłów opakowaniowych — PAKEX 2001.

Organizator: Reed Exhibition Companies Ltd, Richmond, Surrey, Wielka Brytania + Institute of Packaging, Anglia.

Informacje: Paul Byrom, Reed Exhibition Companies Ltd, Oriel House, 26 The Quadrant, Richmond, Surrey TW9 1DL, UK. Tel.: +44(0) 208 910-7818, fax: +44(0) 208 910-7848; e-mail: paul.byrom@reedexpo.co.uk.

22—25 kwietnia 2001 r. Oostende, Belgia. III Międzynarodowe Sympozjum "Reaction kinetics and the development and operation of catalytic processes".

Organizator: Technological Institute, Oostende, Belgia.

Informacje: Rita Pays c/o Technologisch Instituut vzw, Ingenieurshuis, Desguinlei 214, B-2018 Antwerpen, Belgium. Tel.: +32 3 216 09 96, fax: +32 3 216 06 89; e-mail: kine@conferences.ti.kviv.be *lub* rita.pays@ti.kviv.be; internet: http://www.ti.kviv.be/conf/kinetocs.htm.

21—24 maja 2001 r. Montreal, Kanada. Seventeenth PPS Annual Meeting — PPS-2001.

Organizator: The Polymer Processing Society — Canadian Rheology Group.

Informacje: Prof. André Fortin. Tel.: + 1 514 340-4711 ext. 4410 lub S. Tremblay, tel.: +1 514 340-4711 ext. 4047, fax: +1 514 340-4463; e-mail: pps17@gch.polymtl.ca; internet: http://www.gch.polymtl.ca/pps17.

18—20 czerwca 2001 r. Warszawa, Polska. XII Światowa Konferencja IAPRI '2001.

Organizator: IAPRI — Międzynarodowe Stowarzyszenie Instytutów Badawczych Opakowań + COBRO — Centralny Ośrodek Badawczo-Rozwojowy Opakowań + Krajowa Izba Opakowań.

Informacje: COBRO, ul. Konstancińska 11, 02-942 Warszawa. Tel.: (48-22) 842-20-11, fax: (48-22) 842-23-02; e-mail: info@cobro.org.pl; internet: http://www.cobro.org.pl.

26—28 czerwca 2001 r. Frankfurt nad Menem, Niemcy. Doroczny kongres DECHEMA "3rd European Congress on Chemical Engineering".

Organizator: DECHEMA — Gesellschaft fuer Chemische Technik und Biotechnologie e.V.

Informacje: *a) dla prasy:* Dr. Christina Hirche. Tel.: +49 0 69/7564 2 77, fax: +49 0 69/7564 2 72; e-mail: presse@dechema.de; internet: http://www.dechema.de; *b) dla uczestników:* Ruediger Briel, VDI-GVC; fax: +49 211-6214 162; e-mail: ECCE@vdi.de; *c) dla pozostałych zarejestrowanych gości:* Christiana Hess, DECHEMA e.V., Congress Office; fax: +49 69-7564 441; e-mail: ECCE@dechema.de; internet: http://www.dechema.de.

14—16 września 2001 r. Barcelona, Hiszpania. "Fourth International Congress on Peerview in Biomedical Publication".

Organizatorzy: JAMA Peer Review in Biomedical Publication, Chicago, USA + BMJ Publishing Group, Londyn, Anglia.

Informacje: Annette Flanagin, Peer Review Congress, JAMA, 515 N, State Street, Chicago, IL 60610, USA. Tel.: 001-312-464-2432, fax: 001-312-464-5824; e-mail: jama.peer@ama.assn.org *lub* Jane Smith, BMJ Publishing Group, BMA House, Tavistock Square, London, WC1H 9JR, UK. Tel.: 44-171-383-6109, fax: 44-171-383-6418; e-mail: jsmith@bmj.com.

c.d. na str. 686