 DOI: 10.1002/masy.200900152

Synthesis of Spherical Core-Shell PVAc-*co*-PMMA/PVA Particles for Use in Vascular Embolization

Luciana S. Peixoto,[1] *Felipe B. Cordeiro,*[2] *Príamo A. Melo,**[1] *Márcio Nele,*[2] *José Carlos Pinto*[1]

Summary: Previous published works described suspension polymerization processes for the production of spherical core-shell poly(vinyl acetate)/poly(vinyl alcohol) (PVAc/PVA) particles with regular morphology for use as embolic agents in vascular embolization procedures. Although the clinical performance of the produced particles was regarded as excellent, the produced PVAc/PVA particles were prone to agglomeration during storage. For this reason, methyl methacrylate is now used as comonomer in order to increase the glass transition temperature of the final product and prevent agglomeration of polymer particles. The final expansion of particles, intended to control the density of the polymer beads, also exerts a beneficial effect on the rate of particle agglomeration. Therefore, a methodology to obtain spherical poly(vinyl acetate)-co-poly(methyl methacrylate)/poly(vinyl alcohol) (PVAc-co-PMMA/PVA) particles with core-shell structure is presented in this work.

Keywords: core-shell particles; embolization; suspension copolymerization

Introduction

Vascular embolization constitutes an important clinical procedure, used to reduce tumor size, to facilitate tumor removal during surgeries and for the definitive treatment of tumoral malformations (without operative procedures). This technique consists of injecting a fine solid powder (dispersed in an aqueous suspension and with the help of a catheter) into the blood vessels that are located next to a tumoral region in order to interrupt the supply of nutrients to the lesioned area.[1] Thus, the tumoral region tends to shrink and eventually die, allowing for the recuperation of the unhealthy tissue after some time.[2]

Different types of materials have been developed for use in embolization procedures.[3–6] Among them, PVA particles are the materials that have been used most frequently due to their inherent advantageous mechanical and physico-chemical properties, such as the biocompatibility and capacity to reassume its original shape after compression, when the PVA foam is put in contact with blood.[7–8] Nevertheless, typical commercial PVA particles show some undesirable characteristics, such as the irregular, flock-like morphology and tendency to form particle aggregates (responsible for the difficult flow of the particle suspension through the catheter, which may cause sometimes the catheter occlusion and the interruption of the operation procedures), the fast biodegradability (responsible for the potential recanalization of the treated vascular vessels) and their comparatively high costs.[9] In order to avoid particle agglomeration during the application and vessel recanalization after the clinical intervention, spherical particles can be employed.[1,4,9–11]

In order to overcome some of the undesirable characteristics of available

[1] Programa de Engenharia Química / COPPE, Universidade Federal do Rio de Janeiro, Cidade Universitária, CP 68502, Rio de Janeiro, 21945-970, Brazil
E-mail: melo@peq.coppe.ufrj.br
[2] Escola de Química, Universidade Federal do Rio de Janeiro, Cidade Universitária, CP 68502, Rio de Janeiro 21945-970, Brazil

embolization products, a suspension polymerization process was developed to allow for production of spherical core-shell PVAc/PVA particles for vascular embolization.[1,12,13] The core-shell structure of the final polymer beads leads to lower rates of water absorption (when compared to particles constituted entirely by PVA), resulting in improved volume stability of the particles. Besides, as the final PVAc/PVA particles have spherical morphology, they are less likely to aggregate and cause catheter obstruction. These particles were used in embolizations performed *in vivo* and led to much better results, when compared to conventional PVA particles.[1] In order to improve the settling time of the final suspensions and make the application of the product easier in the operation room, an additional particle expansion stage was introduced after the end of the reaction. The expansion step aims at removing heptane from the swollen polymer particles as well as the residual monomer and, thus, promote the formation a porous structure and reduce the particle density.[14–15]

Despite the successful clinical performance of the expanded core-shell PVA/PVAc particles in embolizations, the beads are prone to agglomeration during storage due to the low glass transition temperature (Tg) of PVAc (around 40 °C). For this reason, methyl methacrylate (MMA) can be used as a comonomer to increase the Tg of the final polymer material, as PMMA presents much higher glass transition temperatures (around 100 °C) and is biocompatible, being commonly used as a dental and orthopedic material.[16–17]

The main objective of this work is the preparation of poly(vinyl acetate)-co-poly(methyl methacrylate)/poly(vinyl alcohol) (PVAc-co-PMMA/PVA) core-shell particles with controlled density and spherical morphology for use in vascular embolization procedures. In order to produce PVAc-co-PMMA/PVA particles, MMA is used as a comonomer during the suspension polymerization stage. Besides, an organic solvent is added during the polymerization stage in order to reduce the density of the final polymer particles in the expansion stage. As shown here, the expansion stage also exerts a beneficial effect on particle drying, preventing particle aggregation during post-polymerization processing of the polymer beads.

Experimental Part

The experimental setup and procedures have been thoroughly described elsewhere and are not presented here to avoid repetition.[1,12–15] The interested reader must refer to the original references for detailed additional information.

VAc monomer with minimum purity of 99.9% and NaOH with minimum purity of 99% were supplied by Spectrum Laboratories Inc. (Ft. Lauderdale, USA). MMA monomer was supplied by Sigma-Aldrich (St. Louis, USA) with minimum purity of 99.9%. The initiator (benzoyl peroxide, BPO) with minimum purity of 99% was supplied by Fluka (Seelze, Germany). The suspending agent [poly(vinyl alcohol), PVA] with weight-average molecular weight of 78000 Da and degree of hydrolysis of 85% and heptane and cyclohexane with minimum purity of 99% were supplied by Vetec Química Fina (Rio de Janeiro, Brazil). Nitrogen was supplied by AGA S/A (Rio de Janeiro, Brazil) with 99.9% purity. Micro filtered and demineralized water was used as the suspending medium in suspension copolymerization reactions and for preparation of 40 wt.% NaOH solutions, used for caustic treatments. All chemicals, except water, were used without further purification.

Reactions were carried out in a 1 L jacketed glass reactor (FGG Equipamentos Científicos Ltda, São Paulo, Brazil) at 90 °C with the total organic load of 30 wt.% under inert nitrogen atmosphere. Initially, the reactor was loaded with micro filtered and demineralized water, containing the specified amount of suspending agent (PVA). When the desired temperature was reached, a solution containing the desired amounts of initiator (BPO), monomers

(VAc and 30 wt.% MMA of the VAc load) and organic solvent (20 wt.% heptane of the organic load) was added into the reactor. The system was kept under isothermal conditions with a constant agitation. Reactions were carried out with agitation of 400 rpm and 500 rpm. After 4 h of reaction, the agitation was set to 500 rpm and the temperature was reduced to 30 °C in order to perform the saponification stage, as discussed in the following paragraphs. The PVAc-co-PMMA particles were maintained inside the reactor vessel.

PVAc-co-PMMA/PVA beads were prepared by partial saponification of PVAc-co-PMMA beads in an aqueous solution of NaOH. The saponification reaction takes place predominantly at the particle surface, producing particles with an outer PVA shell and an inner PVAc-co-PMMA core. (As a matter of fact, hydrolysis leads to formation of a complex copolymer material, containing VAc, MMA, VA and methacrylic acid. VA is formed through hydrolysis of VAc units, while MA is formed through hydrolysis of MMA units. Detailed characterization of the shell is beyond the scope of the present manuscript.) When the desired temperature of 30 °C was reached, the reactor was fed with 40 wt.% NaOH solution and micro filtered and demineralized water, under a constant agitation of 500 rpm. The amounts of 40 wt.% NaOH solution and micro filtered and demineralized water that are added to the system depend on the amount of PVA that must be produced. After 2 h of saponification, the reaction medium was cooled down to ambient temperature and particles were filtered and washed with cold distilled water.

Vacuum expansions were carried out in a 200 mL stainless steel vessel (Brawsitech, Rio de Janeiro, Brazil). After the end of the saponification stage, particles were washed with cold distilled water, quickly filtered and placed inside the expansion vessel. The vessel was closed, the vacuum pump was turned on and the needle valve was opened rapidly in order to attain the highest possible pressure drop and the fastest extraction of solvent and residual monomer. In general, a pronounced pressure drop was observed immediately after the opening of the valve and then the system pressure stabilized between 3–7 mbar after a few seconds. In order to control the temperature during expansion, the expansion vessel was immersed in a mild hot bath (around 30 °C), as reported elsewhere.[14–15]

The density of the final polymer particles was determined by pycnometry, using 50 mL glass pycnometers (Roni Alzi Vidros Científicos Ltda, Rio de Janeiro, Brazil) and cyclohexane as diluent. Cyclohexane is not a solvent for the polymer and was used to reduce the experimental noise, as densities of the final polymer particles may be very close to the water density.[14] The morphology of the polymer particles was determined by optical microscopy, using a Nikon SMZ 800 stereomicroscope (Nikon, USA). Particle morphology was also determined through Scanning Electron Microscopy (SEM). The images were recorded with a Quanta 200 (FEI Company, USA) operating at accelerating voltages of 20 keV. Glass transition temperatures of polymer samples were determined by DSC measurements in a DSC-7 calorimeter (Perkin Elmer, Torrance, California, USA) at heating rates of 10 °C/min. The chemical composition of the polymer particles was determined by ^{13}C-NMR. The ^{13}C-NMR spectra were recorded using a Varian UNIT-Plus (Varian Analytical Instruments, USA) spectrometer operating at 100 MHz, using deuterated chloroform ($CDCl_3$-d_1) as solvent.

Results and Discussion

Suspension copolymerizations using low MMA contents (20 wt.% or less) were

Table 1.
Tg of the PVAc/PVA and PVAc-co-PMMA/PVA particles.

Polymer	Tg (°C)
PVAc/PVA	40.5
PVAc/PVA	39.7
PVAc-co-PMMA/PVA	56.6
PVAc-co-PMMA/PVA	60.1

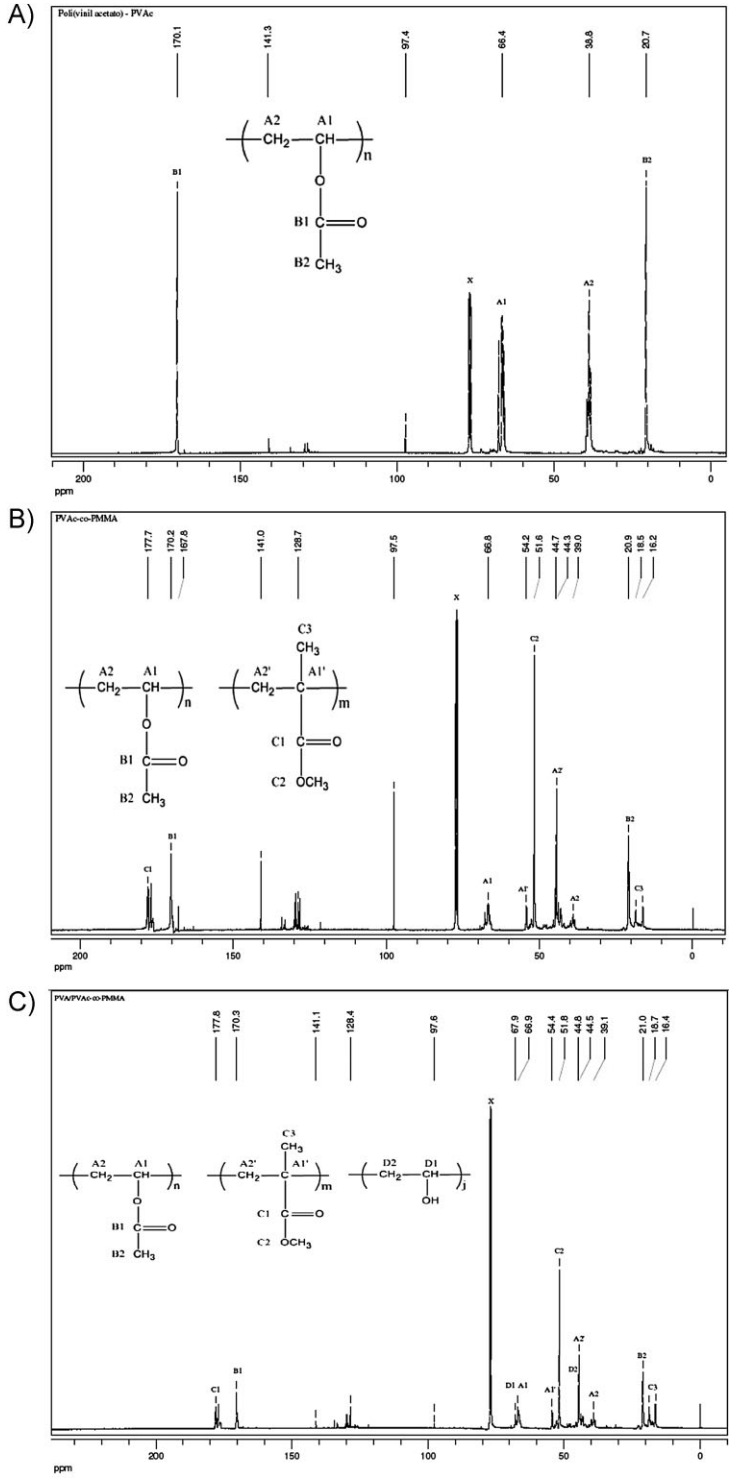

Figure 1.
^{13}C-NMR spectra of (A) PVAc, (B) PVA-co-PMMA and (C) PVAc-co-PMMA/PVA beads.

carried out, but the results were not successful. MMA exerts a strong inhibitory effect in the VAc polymerization due to the large cross-termination constant (ψ_{12}), which leads to significant decrease of the reaction rates and average molecular weights of the final material.[18] In order to avoid these inconveniences and not change reaction conditions drastically, all copolymerizations were conducted with initial loads of 30 wt.% MMA.

The glass transition temperatures of the PVAc/PVA and PVAc-co-PMMA/PVA samples are presented in Table 1. Table 1 shows that PVAc-co-PMMA/PVA particles present higher Tg (around 60 °C) than PVAc/PVA particles (around 40 °C). This result indicates the incorporation of MMA in the polymer chains during the copolymerization process. The increase of the Tg is important because the agglomeration of polymer particles in the storage flasks can be prevented (as observed experimentally after 6 months). In order to confirm the incorporation of MMA in the molecular structure, ^{13}C-NMR analyses were carried out to determine the polymer composition. Figure 1 shows the ^{13}C-NMR spectra of PVAc, PVAc-co-PMMA and PVAc-co-PMMA/PVA particles and can be interpreted with the help of published data.[19] In all cases, the incorporation of MMA is confirmed, indicating that the final copolymer composition is similar to the feed composition, due to the high monomer conversions. Figure 1C also confirms the formation of VA units, due to the saponification of the beads. It should be emphasized that, although PVA was used as the suspending agent, its bulk composition was always smaller than 1 wt.% when saponification is neglected. As VA compositions obtained from NMR spectra were always much higher than 1 wt.%, it can be concluded that saponification was achieved. The degree of saponification was found to be around 10% (although saponification is believed to occur mainly in the particle surface, due to the dense nature of the beads).[1,12–15] The degree of saponification was estimated using the Fox equation, as presented in our previous works.[1,14–15] MA peaks were not detected, which indicates that hydrolysis of MMA units are less likely to occur.

Figure 2 shows optical micrographs of the PVAc/PVA and PVAc-co-PMMA/PVA beads obtained after expansion. It can be observed that the spherical morphology is not affected by the addition of MMA and that PVAc/PVA and PVAc-co-PMMA/PVA particles present a wrinkled surface, due to the addition of solvent into the reaction medium.[14,15] It is possible to notice that PVA/PVAc particles tend to form agglomerates, while PVAc-co-PMMA/PVA particles do not form agglomerates. The expansion stage exerts a beneficial effect on particle drying,[14,15] preventing particle aggregation during post-polymerization processing of the polymer beads. This is explained by the fact that the expansion allows for an efficient removal of the residual monomer, which

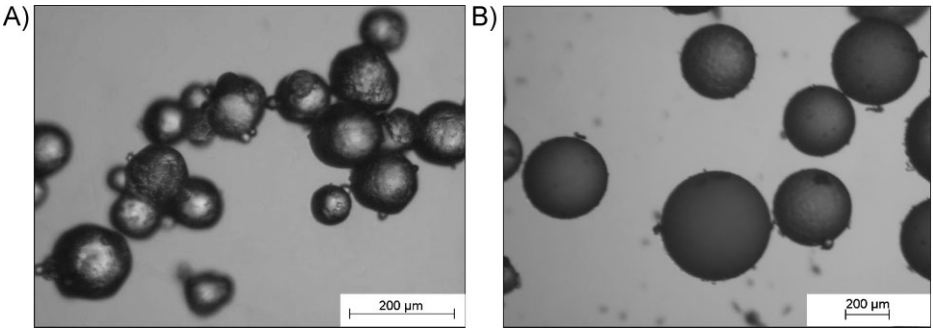

Figure 2.
Optical micrographs of (A) PVAc/PVA beads and (B) PVAc-co-PMMA/PVA beads.

is responsible for particle aggregation. This occurs because the particle surface becomes more rigid (and less sticky) when the residual monomer content is low[14]. Furthermore, the addition of MMA reduces agglomeration dramatically, indicating that addition of MMA can be fundamental to prevent agglomeration in the storage vessels.

Average particle sizes and particle size distributions must also be taken into account when polymer particles are used as embolic agents.[20] As observed experimentally, though, the addition of MMA does not affect the particle size distributions of the final product very significantly. For this reason, obtained results are very similar to the ones already reported in previously published materials.[1,12–15] As a consequence, the agitation speed can be used to tune the average sizes of the final polymer beads, as reported previously.

Table 2.
Densities of PVAc/PVA and PVAc-co-PMMA/PVA beads before and after the expansion stage.

Polymer	Expansion	Density (g/cm^3)
PVAc/PVA	Not expanded	1.16 ± 0.03
PVAc/PVA	Expanded	1.11 ± 0.03
PVAc/PVA	Expanded	1.06 ± 0.03
PVAc-co-PMMA/PVA	Not expanded	1.19 ± 0.03
PVAc-co-PMMA/PVA	Expanded	1.09 ± 0.03
PVAc-co-PMMA/PVA	Expanded	1.08 ± 0.03

Table 2 presents densities of samples of the PVAc/PVA and PVAc-co-PMMA/PVA particles, obtained with and without expansion. According to Table 2, densities

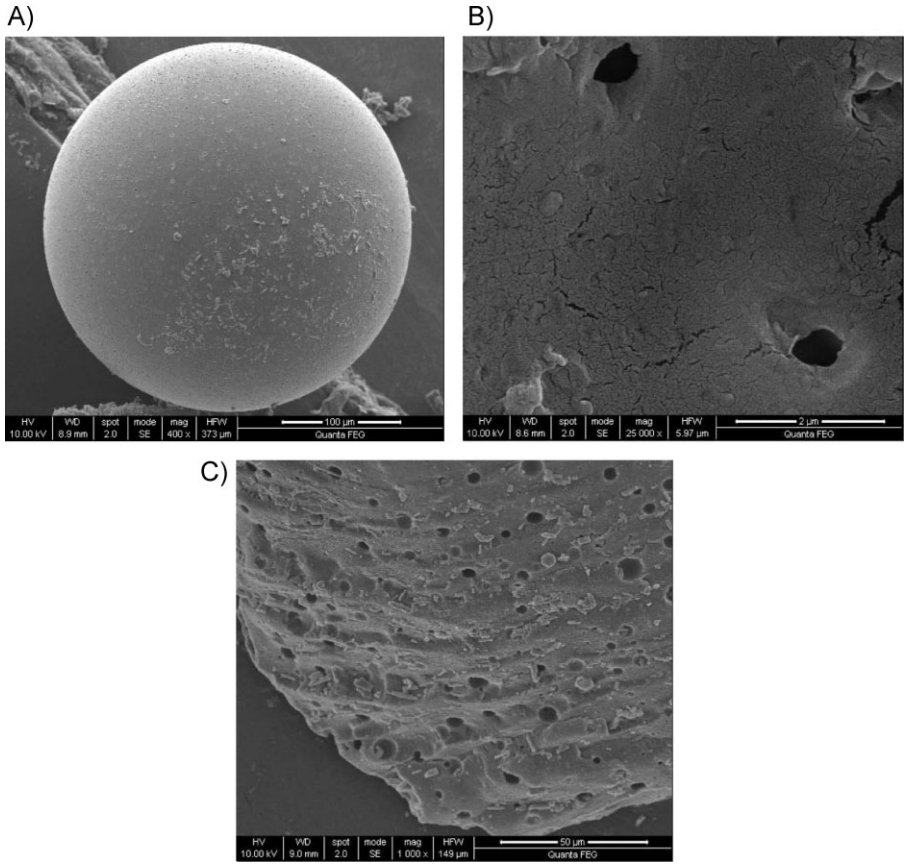

Figure 3.
SEM micrographs of PVAc-co-PMMA/PVA particles obtained after expansion stage. (A) Particle; (B); particle surface and (C) particle core.

decrease after the expansion stage, indicating that the solvent removal exerts a significant effect on the densities of the final polymer beads and that expansion can also be used to control the final bead densities when reaction is performed in presence of MMA. It can also be noted that PVAc-co-PMMA/PVA densities are very similar to PVAc/PVA densities, leading to similar settling responses in the operation room.

SEM micrographs of PVAc-co-PMMA/PVA particles are shown in Figure 3. It can be observed that the particle contains very small pores both on the surface and the core of the beads, formed by solvent removal in the expansion stage. The pore formation is responsible for the reduction of PVAc-co-PMMA/PVA densities, as presented in Table 2. It is important to note that the pores are isolated from each other, which is essential for the application of the particles as embolic agents, since percolation of body fluids through the particle is not possible.

Conclusion

The results presented here show that it is possible to incorporate MMA during batch VAc/MMA suspension polymerizations successfully to obtain core-shell PVAc-co-PMMA/PVA particles for use as embolic agents. It was shown that the final PVAc-co-PMMA/PVA particles present spherical morphology and densities that are similar to the ones of core-shell PVAc/PVA particles. However, PVAc-co-PMMA/PVA particles do not form agglomerates in the reaction and processing stages because of the higher glass transition temperatures and do not agglomerate in the storage flasks, leading to more stable storing performance.

Acknowledgements: The authors thank the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) for providing scholarships and supporting our work.

[1] L. S. Peixoto, F. M. Silva, M. A. L. Niemeyer, G. Espinosa, P. A. Melo, M. Nele, J. C. Pinto, *Macromol. Symp.*, **2006**, *243*, 190.
[2] S. J. Smith, *Am. Fam. Physician*, **2000**, *61*, 3601.
[3] L. E. Latchaw, L. H. A. Gold, *Radiology*, **1979**, *131*, 669.
[4] J. E. Dion, R. N. Rankin, F. Viñuela, A. J. Fox, A. C. Wallace, M. Mervart, *Radiology*, **1986**, *160*, 717.
[5] A. Berenstein, E. Russell, *Radiology*, **1981**, *141*, 105.
[6] M. Herrera, J. Rysavy, F. Kotula, B. Rusnak, W. R. Castaneda-Zuniga, K. Amplatz, *Radiology*, **1982**, *144*, 638.
[7] F. L. Marten, "*Encyclopedia of Polymer Science and Engineering*", 2nd ed., J. Wiley & Sons, New York, 1989, *17*, 167.
[8] S. M. Tadavarthy, J. H. Moller, K. Amplatz, *Am. J. Roentgenol.*, **1975**, *125*, 609.
[9] W. D. S. Mendes, V. L. A. Chagas, J. C. Pinto, J. G. Caldas, G. Espinosa, *Rev. Col. Bras. Cir.*, **2005**, *32*, 120 (in Portuguese).
[10] G. P. Siskin, K. Dowling, R. Virmani, R. Jones, D. Todd, *J. Vasc. Interv. Radiol.*, **2003**, *14*, 89.
[11] M. Bendszus, R. Klein, R. Burger, M. Warmuth-Metz, E. Hofmann, L. Solymosi, *Am. J. Neuroradiol.*, **2000**, *21*, 255.
[12] PI 0404994-2 (2004) invs.: J.C. Pinto, G.E. Lopez, M.A.L. Niemeyer, F.M. Silva, P.A. Melo, M. Nele.
[13] PCT/WO2006/050591 A2 (2006) invs.: J.C. Pinto, G.E. Lopez, M.A.L. Niemeyer, F.M. Silva, P.A. Melo, M. Nele.
[14] L. S. Peixoto, P. A. Melo, M. Nele, J. C. Pinto, *Macromol. Mater. Eng.* **2009**, *294*, 463.
[15] L. S. Peixoto, M. Sc. Thesis, Universidade Federal do Rio de Janeiro, 2007 (in Portuguese).
[16] S. Ramakrishna, J. Mayer, E. Wintermantel, K. W. Leong, *Compos. Sci. Tech.*, **2001**, *61*, 1189.
[17] J. G. F. Santos, Jr., L. S. Peixoto, M. Nele, P. A. Melo, J. C. Pinto, *Macromol. Symp.*, **2006**, *243*, 1.
[18] J. C. Pinto, W. H. Ray, *Chem. Engng Sci*, **1995**, *50*, 715.
[19] A. J. Brandolini, D. D. Hills, "*NMR Spectra of Polymers and Polymer Additives*", Marcel Dekker, New York, 2000.
[20] C. P. Derdeyn, C. J. Moran, D. T. Cross, H. H. Dietrich, R. G. Dacey, *Am. J. Neuroradiol.*, **1995**, *16*, 1335.

