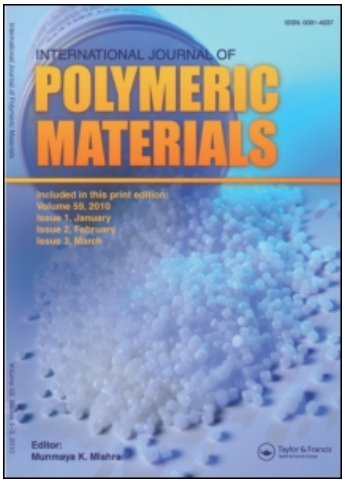

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SYNTHESIS OF NANOPARTICLES BY MICROEMULSION POLYMERIZATION AND THEIR APPLICATION IN A DRUG DELIVERY SYSTEM

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SYNTHESIS OF NANOPARTICLES BY MICROEMULSION POLYMERIZATION AND THEIR APPLICATION IN A DRUG DELIVERY SYSTEM

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Poly (styrene-divinylbenzene-acrylic acid) nanoparticles were synthesized through microemulsion polymerization using a three component oil-in-water microemulsion containing sodium dodecylsulphate. Stable and transparent poly (styrene–DVB-acrylic acid) nanolatexes were produced. The latexes were characterized for particle size and number of particles by dynamic light scattering and TEM. The isolated products were characterized by IR. The particles were further used for the loading of Acryflavin drug. Acryflavin was selected as a model drug to understand the behavior of in-vitro drug release pattern at different pH in nanoparticles.

Keywords: microemulsion, nanoparticles, acryflavin, styrene–acrylic acid, copolymerization

INTRODUCTION

In recent years, considerable attention has been focused on the development of new drug delivery systems because of [1–2].

- Recognition of the possibility of repatenting successful drugs by applying the concepts and techniques of controlled release drug delivery systems, coupled with the increasing expenses involved in developing new drug entities.
- Need for new systems to deliver the new genetically engineered pharmaceuticals to their sites of action without incurring biological inactivation.

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- Treatment of enzyme-deficient diseases and cancer therapies through drug targeting.
- Improvement in efficiency and safety of drugs administered by conventional method through more precise spatial and temporal placement within the body, thereby reducing both the size and number of doses.

Hence, efforts are made on focusing the development of controlled release drug delivery systems to achieve the following objectives:

- To maximize the bioavailibility of the therapeutic agent in a target tissue.
- To minimize the side effects of the therapeutic agent.
- To optimize the onset, rate, and duration of the drug delivery.
- To maintain the steady state plasma drug level within a therapeutic range as long as required for an effective treatment.

A chemical reaction that can be hydrolytic or enzymatic cleavage of a labile bond, which is known as a chemically controlled device, controls the rate of release of active agent from the polymer. The drug release can occur from drug covalently attached to polymer backbone. (where polymer acts as a carrier) or drug contained in a core surrounded by biodegradable rate controlling membrane or drug homogeneously dispersed in polymer matrix.

Due to small size and large surface area, nanoparticles lead to a variety of applications. The aqueous suspension of nanoparticles with smaller size up to 10–25 nm can be obtained by the microemulsion polymerization. Unique properties such as low viscosity and high transparency make microemulsions an attractive medium for the polymerization. The pharmaceutical industry is one of the major areas that required nanoscale-size products. Research in nanoparticles is focused on control of particle size and surface properties for specfic applications, development of core-shell particles, drug delivery system, oligonucleotide delivery, diagnostic application, microencapsulation, formation of reactive particles, development of chromatographic adsorbent, semiconductors, fluorescent particles, and their uses in biomedical applications [3–9]. In the last decade the emphasis was on nanoparticles synthesized through microemulsion polymerization. The primary goal of polymerization in microemulsion is to control the structural properties and the smaller size and narrow distribution of particles [10–15]. Microemulsion polymerization as a successful route for the synthesis of functionalized nanoparticles was reported by Larpent et al. [16]. The synthesis of nanoparticles with desired functionality has some limitations due

to non-availability of monomers. However, well-defined highly functionalized nanoparticles can be prepared by performing surface modification on previously prepared nanoparticles. Cammas and coworkers studied thermo-responsive polymeric nanoparticles with a core-shell micelle structure as site-specific drug carrier [17]. The thermo-responsive polymeric micelles have been prepared from amphiphilic block copolymers composed of N-isopropylacrylamide (a thermo-responsive outer shell) and styrene (hydrophobic inner core) by Akashi et al. [18]. They have synthesized N-vinylacetamide-styrene copolymeric nanoparticles and used them for slow release drug delivery. Sakuma and coworker studied the oral delivery of peptide using nanoparticles [19]. They synthesized nanoparticles composed of graft copolymers having a hydrophobic backbone and hydrophilic branches using dispersion polymerization of polymethacrylic acid macro-monomer with styrene in a polar solvent. The potential of these nanoparticles as carriers for oral peptide delivery was investigated using salmon calcitonin in rats. They observed that the release rate of salmon calcitonin incorporated in nanoparticles was high and was affected by the macro-monomer structure. Charreyre et al. [20] have prepared functionalized latexes using emulsion polymerization and used them in a biomedical diagnostic study. They have functionalized polystyrene nano-particles with liposaccharide monomers. Ciprofloxacin-loaded polyisobutylcyanoacrylate nanoparticles were synthesized by Fawaz and coworkers [21].

The present authors have tried covalent binding of Acryflavin to styrene-divinylbenzene-acrylic acid copolymer nanoparticles. Covalent binding is expected to decrease the rate of release. Thus, duration between the doses can be increased. Details of nano-copolymeric particles and drug loading and release are discussed here.

EXPERIMENTAL

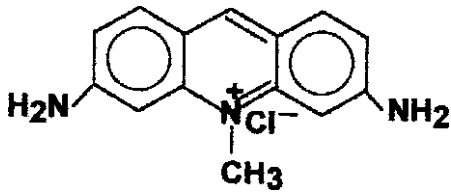
Materials

Acrylic acid (AA) from National Chemicals, Baroda, India was distilled under vacuum and was stored at 2°C until further use. Styrene from National Chemicals, Baroda, India was made free from inhibitor by washing it with 2% w/v sodium hydroxide solution and then drying over anhydrous calcium chloride. It was further purified by passing through alumina column and distilling under vacuum. Potassium persulphate (KPS) from Sisco Chemicals, Mumbai, India was recrystallized from water. Divinyl benzene from Fluka, Switzerland, was

used as a crosslinker, Sodium dodecylsulphate (SDS) from Qualigens, Mumbai, India and 2,8 diamino-10 methyl chloride acrydine monochloride (Acryflavin) from Royal pharmaceuticals, Baroda, India were used as received.

Information of the Drug

Acryflavin, which is used as an Antiseptic, bacteriostatic and deodorant for the use in gonorrhoeal arthritis, cystitis pyletics, and other infections of the genitourinary tract, also in burns, wounds, infection of ear, nose, throat, gums and arthritis, is known as 2,8 diamino-10 methyl chloride acrydine monochloride. Its structure is shown in Scheme 1.



SCHEME 1

Microemulsion Polymerisation

The microemulsion polymerization was carried out in a three-neck reaction kettle equipped with mechanical stirrer, nitrogen inlet, and condenser. Microemulsion comprising 5% w/w of styrene, 12% w/w of SDS, 1.66% w/w of acrylic acid (AA), 4% of monomer divinyl benzene as crosslinker and water was loaded in the reaction kettle. The reaction mass was purged with nitrogen for 30 min. The polymerization was carried out by using KPS as a free radical initiator at 70°C. The polymerization was continued for 2 h and resulted in bluish transparent and stable latexes. The polymerization was terminated using 20 ppm of hydroquinone.

Purification of Microlatex

Separation and purification of nanoparticles was carried out by cooling the latexes below *Kraft* temperature for the precipitation of surfactant. This process removed most of the surfactant from the latex. Using

four-fold quantity of methanol the remaining surfactant along with copolymer was precipitated. The traces of surfactant were removed by washing the precipitate several times with hot water. The nanoparticles were isolated by ultra-centrifuging at 6000 rpm.

Immobilization of Acryflavin on Styrene–DVB–Acrylic Acid Nanoparticles

In a three-neck flask equipped with stirrer, calcium chloride guard tube, claisen head, addition funnel, and condenser, 1 g styrene–DVB–acrylic acid copolymer in the form of nanoparticles was dispersed in 50 ml of dimethyl formamide solution and 2 ml of triethylamine. 5 ml of thionyl chloride was added dropwise into the reaction mass, which was heated at 50°C in a water bath for 2 h. 0.1 g of Acryflavin was dissolved in dimethyl formamide and added dropwise to the reaction flask with constant stirring, and kept in a water bath maintaining the temperature at 80°C for 24 h. The product was precipitated out in a large volume of water and filtered, dried, and was examined for drug delivery at different pH using phosphate buffer.

Characterization of Copolymers

The IR spectrum of drug-loaded nanoparticles and nanoparticles without drug were recorded on a Perkin-Elmer 16 PC-FTIR Spectrophotometer using KBr pellet. The concentration of released drug was determined using a 240 Graficord UV-240 Shimadzu UV spectrophotometer and measuring the absorbance at 460 nm and using calibration plot. Polymer latexes were characterized for the size of the latex particles by TEM and DLS. Particle size was determined using a Brook-haven BI-90 dynamic light scattering (DLS) analyzer at 25°C and JEOL-100CX transmission electron microscope (TEM) operated at 100 kV. The polymerized latex was diluted 100 times with deionized distilled water and one drop of the diluted dispersion was placed on a 200-mesh carbon-coated copper grid. Adequate staining was obtained by placing the latex-coated grid in a drop of 10% aqueous solution of uranyl acetate. Excess of staining reagent was removed and sample was used for TEM analysis. For light scattering measurements latexes were diluted with deionized water to get count rate within the optimal range of the spectrometer. The dilute solutions were purified by filtering them through a Millipore 0.2 μm filter.

RESULTS AND DISCUSSION

Styrene–acrylic acid crosslinked with divinyl benzene copolymer latex was observed to be optically transparent and no phase separation was detected before as well as after polymerization. The microlatex remained stable with respect to coagulation for more than six months.

Figure 1 shows the comparison of IR spectra of nanoparticles with and without attached drug. Copolymerization of styrene and acrylic acid was confirmed by the appearance of bands at 3025 cm^{-1} for C=C stretching from aromatic ring; at 2921 cm^{-1} for C–H stretching from alkane backbone; at 3450 cm^{-1} for -OH stretching and band at 1706 cm^{-1} for carbonyl stretching from acrylic acid units; band at 1602 cm^{-1} due to C–C stretching from aromatic ring and at 697 and 756 cm^{-1} due to C–H bending from mono-substituted benzene in the IR spectrum of nanoparticles (Figure 1). Qualitatively, the intensity of carbonyl peak was observed to decrease in case of nanoparticles loaded with drug.

The microlatex was characterized for the particle size using dynamic light scattering. Figure 2 shows the histogram of particle size distribution. Average particle size was observed to be 24 nm. TEM shows that particles were small and polydisperse (Figure 3).

In-Vitro Drug Release Studies

The drug release was studied by following the release into phosphate buffer of pH 7.2, 7.4, 7.6, and 7.8 spectrophotometrically. In a typical experiment 100-mg of polymer-bound acryflavin samples were equilibrated with 10 ml of the buffer. The release of drug was estimated from the supernatant buffer solution and measuring the abosorbance at 460 nm.

Figures 4 (a),(b),(c), and (d) illustrate the cumulative percentage of released drug as a function of time. It was seen that the rate and order of release pattern of drug is very much dependent on pH. It was observed that drug release follows almost zero order at pH 7.2 and first order at pH 7.8. However, in between at pH 7.4 and 7.6 mixed trend was observed. This pharmacokinetic study should be followed by a pharmacodynamic study for the monitoring of the drug dose.

CONCLUSION

A microemulsion polymerization is a successful route for the synthesis of nanoparticles and can be utilized as a drug delivery system. A different pattern was observed for the release of Acryflavin drug in different

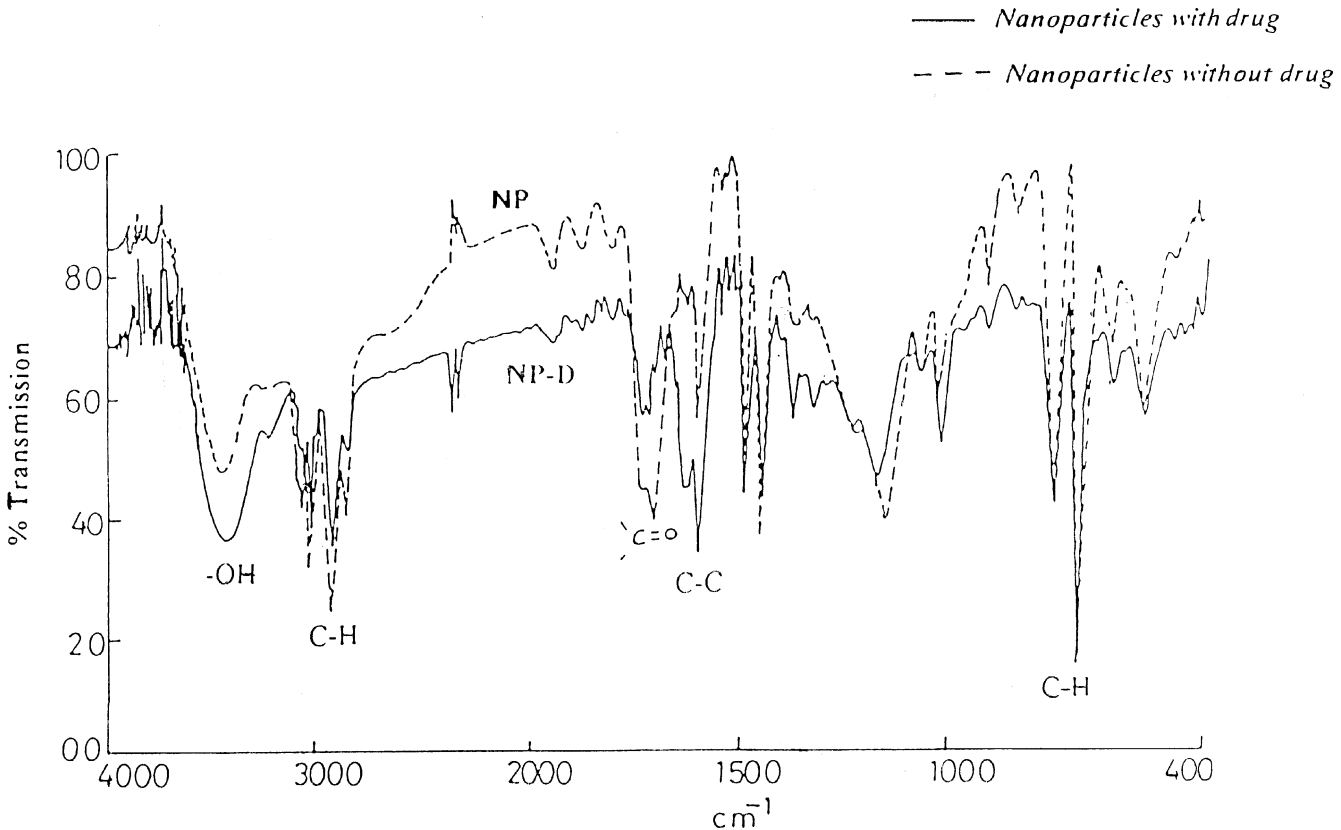


FIGURE 1 Comparison of IR spectra of nanoparticles attached with drug and without drug.

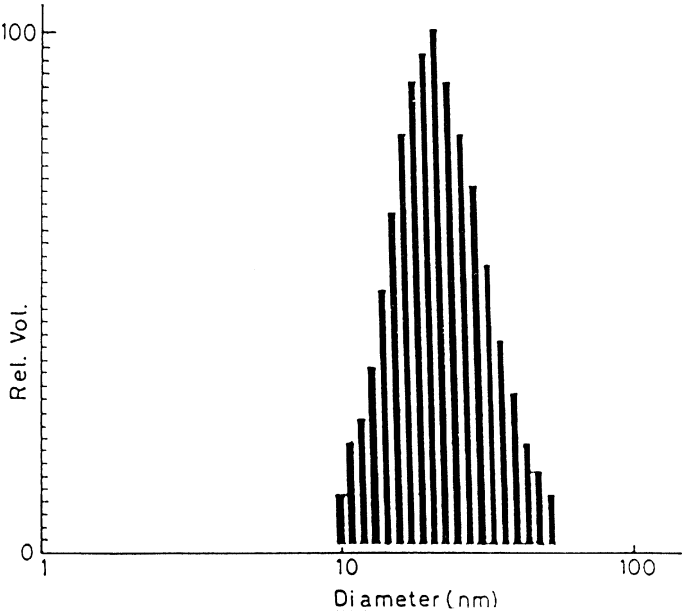


FIGURE 2 Histogram of particle size distribution of styrene-DVB-acrylic acid (3:1 w/w) microlatex.

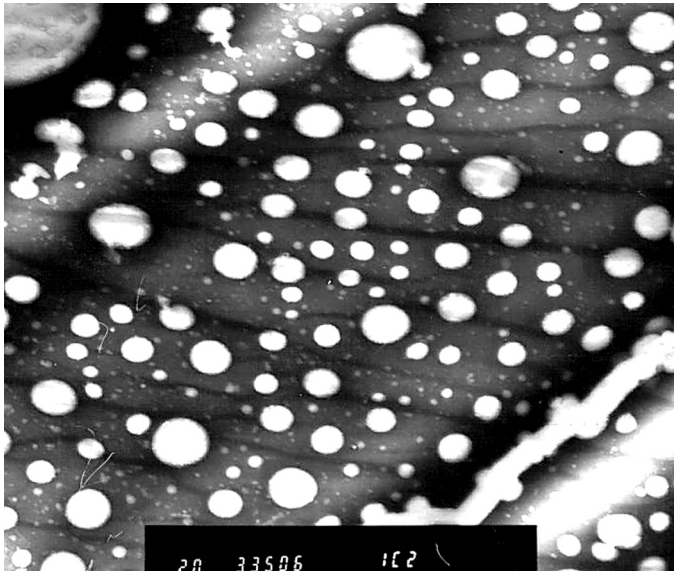


FIGURE 3 Transmission electron micrograph of styrene-DVB-acrylic acid (3:1 w/w) microlatex synthesized at 70°C using KPS (0.37 mM) as initiator.

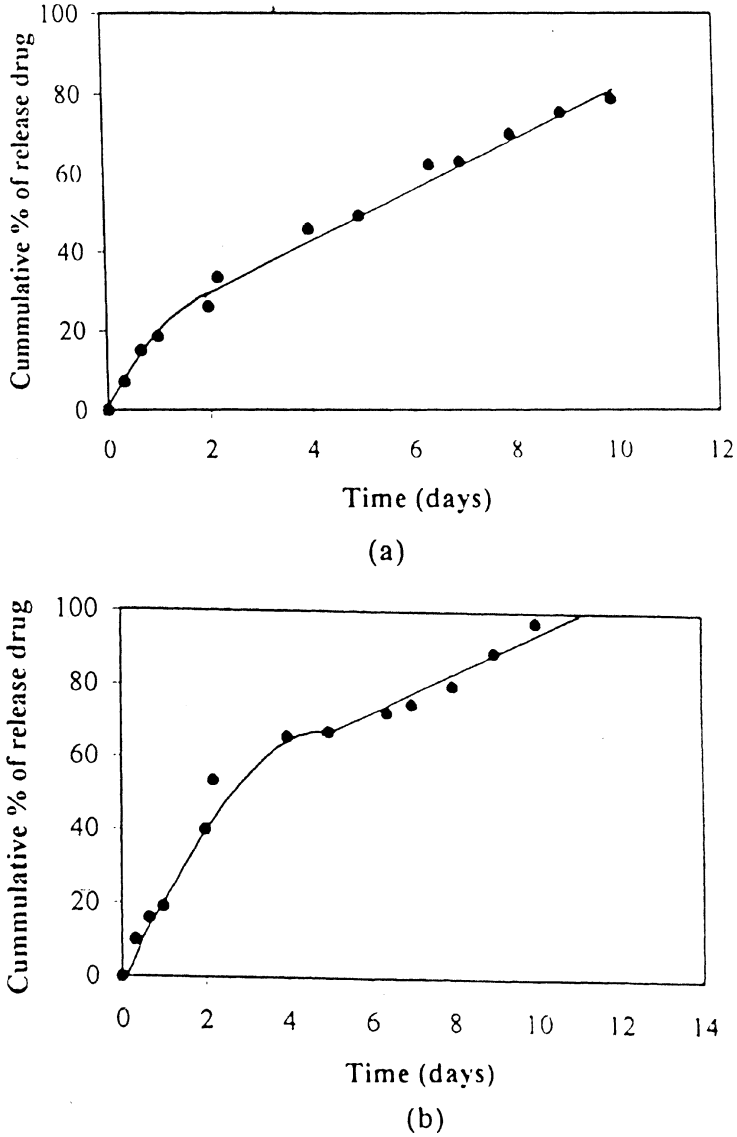
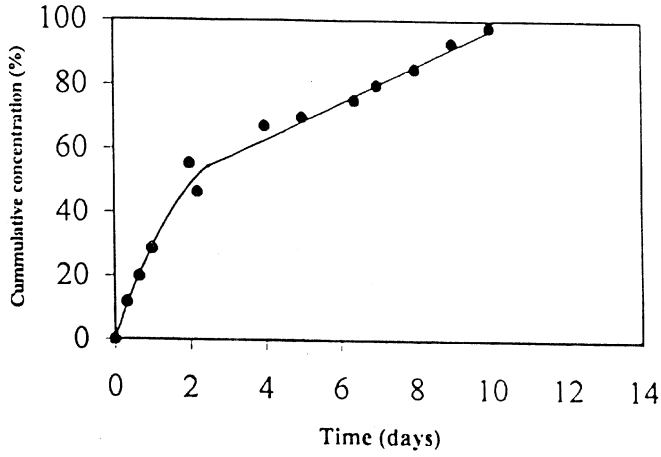
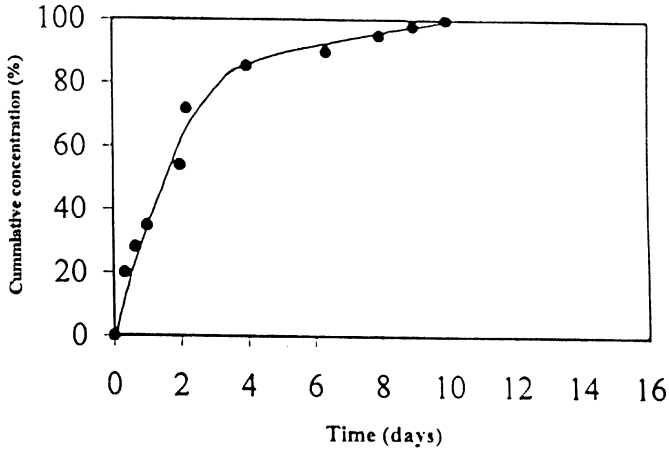


FIGURE 4 Effect of pH on drug release as a function of time; (a) 7.2 pH; (b) 7.4 pH; (c) 7.6 pH; (d) 7.8 pH.



(c)



(d)

FIGURE 4 (Continued).

pH of phosphate buffer. It might be interesting for the pharmaceutical industry.

REFERENCES

[1] Majeti, N. V. and Kumar, R., *J. Pharm. Pharmaceut. Sci.* **3**, 234 (2000).
[2] Pirker, S., Kruse, J., Noe, C. R., Langer, K., Zimmer, K., and Kreuter, J., *Int. J. Pharm.*, 189 (1996).

[3] Talor, J. R., Fang, M. M., and Nie, S., *Anal. Chem.* **72**, 1979 (2000).
[4] Chechik, V. and Crooks, R. M., *J. Am. Chem. Soc.* **122**, 1243 (2000).
[5] Lewis, K. J., Irwin, W. J., and Akhtar, S., *J. Controlled Release* **37**, 173 (1995).
[6] Fawas, F., Guyot, M., Laguency, A. M., and Devissaguet, J. Ph., *Inter. J. Pharmaceutics* **154**, 191 (1997).
[7] Cleek, R. L., Rege, A. A., Denner, L. A., Eskin, S. G., and Mikos, A. G., *J. Biomedical Mater. Research* **35**, 525 (1997).
[8] Nath, N. and Chilkoti, A., *Anal. Chem.* **74**, 504 (2002).
[9] Lamprecht, A., Saulnier, P., Boury, F., Passirani, C., Proust, J. E., and Benoit, J. P., *Anal. Chem.* **74**, 3416 (2002).
[10] Sanghvi, P. G., Pokhriyal, N. K., Hassan, P. A., and Surekha Devi, *Polymer International* **49**, 1417 (2000).
[11] Sanghvi, P. G., Pokhriyal, N. K., and Devi, S., *Polymer International* **51**, 721 (2002).
[12] Antonietti, M., Basten, R., and Lohman, S., *Macromol. Chem. Phys.* **16**, 283 (1995).
[13] Yildiz, U. and Capek, I. *Polymer* **44**, 2193 (2003).
[14] Full, A. P., Kaler, E. W., and Arellano, J. *Macromolecules* **29**, 2764 (1996).
[15] Mendizabal, F., Flores, J., Puig, J. E., Lopez, S. F., and Alvarez, J., *Eur. Polym. J.* **34**, 411 (1998).
[16] Larpent, C., Bernard, E., Ricjhard, J., and Vaslin, S., *Macromolecules* **30**, 354 (1997).
[17] Cammas, S., Suzuki, K., Sone, C., Sakurai, Y., Kataoka, K., and Okano, T., *J. Controlled Release* **48**, 157 (1997).
[18] Akashi, M., Kishida, A., Sakuma, N., Kikuchi, H., Japanese Patent 08268916 A2 (15 Oct. 1996).
[19] Sakuma S., Suzuki, N., Kikuchi, H., Hiwatari, K., Arikawa, K., Kishida, A., and Akashi, M., *Int. J. Pharm.* **149**, 93 (1997).
[20] Charreyre, M. T., Reville, J., Elaissari A., Picot, C., and Gallot, B., *J. Bioact. Compat. Polym.* **14**, 64 (1999).
[21] Fawaz, F., Guyot, M., Lagueny, A. M., and Devissaguet, J. P., *Int. J. Pharm.* **154**, 191 (1997).