Journal of Applied Polymer Science

Differential Microemulsion Polymerization as a New Root for Entrapment of Drugs

A. B. Moustafa,[1] R. A. Sobh,[1] A. M. Rabie,[2] H. E. Nasr,[1] M. M. H. Ayoub[1]

[1]Polymers & Pigments Department, National Research Center, Dokki, Cairo, Egypt

[2]Faculty of Science, Chemistry Department, Ein Shams University, Cairo, Egypt

This article is a part of PhD Thesis of R. A. Sobh.

Correspondence to: A. B. Moustafa (E-mail: abakr25@yahoo.com)

ABSTRACT: Nanosized particles derived from poly(methyl methacrylate) as well as copolymer of methyl methacrylate (MMA) and 2-hydroxyethyl methacrylate (HEMA) were synthesized by differential microemulsion technique in the presence of ammonium persulfate as water-soluble initiator. The polymerization was stabilized by adding biologically safe emulsifiers namely the sodium dodecyl sulfate (SDS) or polyvinyl pyrrolidone (PVP) either alone or in conjunction with polyethylene glycol. The turbidity measurements, surface tension, ζ potential, and morphological characterizations of the obtained nanosized poly MMA and its copolymer with HEMA in different monomer feed compositions were investigated. It is found that increasing HEMA content leads to increase in the particle size, turbidity measurements but the negatively charged ζ potential decreased. However, when SDS is used, the surface tension of the prepared lattices increased, whereas it is decreased by using PVP. Kinetic studies of (MMA/HEMA) in ratio of 95/5 wt % in the presence of SDS or PVP revealed that the emulsifier concentration has a considerable effect on the rate of polymerization and the power of the emulsifier. The entrapment of drug was investigated using two active molecules different in water solubility (sodium warfarin and ibuprofen). It is noted that entrapment efficiency is independent of HEMA content in the monomer feed composition but dependent on type of drug and the amount of drug introduced. Hence, higher entrapment efficiency was attained for sodium warfarin (more hydrophilic) than that of ibuprofen (more hydrophobic) and they were 95.5 and 85%, respectively. © 2012 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 000: 000–000, 2012

KEYWORDS: differential microemulsion; nanoparticles; methyl methacrylate; 2-hydroxyethyl methacrylate; drug entrapment

Received 7 December 2011; accepted 8 May 2012; published online

DOI: 10.1002/app.38059

INTRODUCTION

Nanosized polymeric materials can be prepared through polymerization using various techniques such as emulsion, miniemulsion, microemulsion, and dispersion techniques. Among them, microemulsion is one of the most versatile methods to prepare polymeric nanoparticles.

Microemulsions are at least ternary mixtures of two immiscible liquids stabilized with an emulsifier or a mixture of surface-active agents. They are isotropic, transparent, and thermodynamically stable. Unique properties of microemulsions such as lower viscosity, greater stability, and transparency owing to uniformly dispersed smaller droplets make them an attractive medium of polymerization.[1] Microemulsion was first reported by Stoffer and Bone.[2] This procedure is effective in producing stable polymer latexes with particles in the nanosize range (<50 nm)[3] and offers the advantage of spontaneous formation, ease of manufacture with little energy input, and optical transparency with low viscosity as well as their stability over a wide temperature range, and improved solubilization of bioactive materials.[4]

Moreover, many microemulsion polymerizations have been kinetically studied by many authors and they characterized the properties of the obtained latex.[5–10] By that time, the obtained latex was characterized by low solid content and high emulsifier concentration ($\sim$ 10% of the total mass). After that, many efforts have been undertaken to obtain nanosized latexes containing higher polymer content at lower emulsifier concentration, which can be subdivided into two different approaches. The first is to find more effective emulsifier systems that are able to solubilize larger amounts of monomer in the conventional microemulsion polymerization.[3] The other approach is to increase the amount of polymer produced for a given amount of emulsifier with certain methods that involve semi-continuous[11–14] and continuous microemulsion[15] polymerization technique. Also, using polymerizable emulsifiers or coemulsifiers can raise the monomer to

emulsifier ratio.[16] The differential continuous[17–20] microemulsion polymerization is an alternative method to overcome this drawback, through adding the monomer continuously through a long period of time. Nanolatexes with such characteristics are desirable for certain applications, such as high-performance nanocoating, encapsulation of dyes,[21] or drug delivery.[22–28]

One of the most important applications for these polymeric nanoparticles is the polymeric drug delivery system[4] which could be prepared as nanospheres or nanocapsules.[29] Nanospheres are matrix systems in which the drug is dispersed within the polymer throughout the particle. However, nanocapsules are vesicular systems, which are formed by a drug-containing liquid core surrounded by a single polymeric membrane. An efficient and versatile drug carrier system has to fulfill the following requirements: (i) particle size in the submicron range, (ii) the possibility of surface modifications, (iii) high drug-loading capacity, (iv) colloidal stability of the latex in biological media, and (v) the lack of toxic side effects induced by the carrier or additives.[30]

In addition, poly(2-hydroxyethyl methacrylate [HEMA]/methyl methacrylate [MMA]) copolymers have recently stimulated an increasing interest and research attention owing to their biocompatibility and water insolubility. Besides, the poly(HEMAMMA) copolymers have also an excellent chemical stability because of their three-dimensional polymeric networks[31] that make poly(HEMA/MMA) microspheres extremely valuable for various applications in therapeutical and biotechnological fields. The effect of copolymerization of MMA with HEMA was studied by Özer et al.[32] in oil-in-water batch microemulsions stabilized by cetyltrimethylammonium bromide with a weight ratio of 9.3% and produced nanoparticles of about 42.2 nm in size but they could not increase the ratio of HEMA above 10% because it caused a significant change in the size distribution and formation of very large particles and even agglomeration in the medium. Among the safe emulsifier used is polyvinyl pyrrolidone, PVP, where it is hydrophilic (nonionic) polymer and approved by the US Food and Drug Administration FDA as a biocompatible and nonantigenic compound and is therefore safe for biological experiments.[33,34]

In this study, nanosized polymeric particles were synthesized using comparatively low concentration of sodium dodecyl sulfate (SDS) and PVP through a differential microemulsion technique as standard and biocompatible emulsifiers, respectively. The produced polymer particles were characterized in terms of their particle size, colloidal aspects (turbidity), surface tension, and ζ potential measurements as a function of changing MMA/HEMA ratio with the selected emulsifier types. Also, transmission electron microscopy (TEM) was used for investigating the shape of the obtained nanoparticles loaded with drugs.

MATERIALS AND METHODS

Materials

MMA (Across, NJ) was used after purification through basic aluminum oxide column, whereas HEMA (Sigma, Germany) was purified through silica gel column. SDS (Across, NJ), and PVP (M.wt. = 40,000; Bioshop Canada, Burlington, ON) were used as received without further purification. Ammonium persulfate (APS; BDH Laboratory Supplies Poole, BH15 1TD, England) was used as water-soluble initiator. Polyethylene glycol (PEG, M.wt. = 300) is purchased from Hoba Chemie, Mumbai, India. Ethanol is a pure reagent for analysis from El-Nasr Pharmaceutical Chemicals, Egypt. Double-distilled water was used in all experiments. Sodium warfarin (a water-soluble anticoagulant) and ibuprofen (hydrophobic nonsteroidal anti-inflammatory drug) were supplied as a gift from GlaxoSmithKline, Egypt.

Table I. The Relationship Between Emulsifier Concentration and Rate of Polymerization for Batch Microemulsion Copolymerization of (MMA/HEMA) 95/5% Using 0.0228 g mol/L of APS at 65°C

SDS			PVP		
[E] × 10^3 (g mol/L)	R_p × 10^4 (g mol/L s)	D_v (nm)	[E] × 10^3 (g mol/L)	R_p × 10^4 (g mol/L s)	D_v (Nm)
11.5	3.38	48	0.5	2.99	126
17	4.76	29	0.75	3.88	95
23	6.98	27	1	6.34	82
35	8.4	23	1.5	5.98	40
69.3	8.05	-	2	3.38	-
138.7	6.5	-	2.5	2.23	-
208	2.46	-			

Experimental

Microemulsion Polymerization Techniques

A-Batch Technique. Poly(methyl methacrylate-*co*-2-hydroxyethyl methacrylate), Poly(MMA-*co*-HEMA), in a weight ratio MMA : HEMA of (95 : 5) was synthesized by a batch process using monomer concentration 10% in the presence of different emulsifiers namely SDS and PVP. A water-soluble initiator APS (0.0228 g mol L^{-1}) was added into the round-bottomed reaction flask equipped with continuous stirring under reflux. The polymerization process was carried out at 65°C using thermostated water bath under an inert atmosphere of N_2.[32] The recipe used for the preparation is summarized in Table I.

The kinetics of the reaction was studied by withdrawing the aliquots at regular time intervals. The reaction was quenched by adding 40 ppm of hydroquinone.

B-Differential Microemulsion Polymerization. Poly MMA and poly(MMA-*co*-HEMA) with various feed monomer compositions were synthesized by a continuous process in a ternary oil-in-water microemulsion system containing 10% monomer concentration stabilized by SDS or PVP emulsifiers. The initiator concentration was 0.0228 g mol L^{-1} and added in three portions along the experiments. The stirring was kept at ~350 r.p.m. during the whole process.

In a typical procedure, the experiment was carried out as follows[14]: in a 250-mL three-nicked round-bottomed flask, equipped with reflux condenser, the emulsifier dissolved in 30 mL distilled water was mechanically stirred overnight at room temperature. Then, the first portion of the initiator (30%) was added to the reactor and left in water bath at 65°C in the presence of continuous nitrogen gas stream to remove the dissolved oxygen. The desired monomers' concentration as well as the second portion of initiator (60%) was dropwise added through a period of 1 h. The third

Table II. Differential Microemulsion Polymerization at Different Feed Monomer Compositions of MMA/HEMA and Their Average Particle Size D_v Using Different Types of Emulsifiers and Constant Concentration of Initiator (0.0228 g mol/L) at 65°C.

Type of emulsifier															
[SDS] [23 × 10^{-3}] g mol/L				[PVP] [0.75 × 10^{-3}] g mol/L				[PVP] [1.5 × 10^{-3}] g mol/L				[PVP/PEG] [1.5/74] × 10^{-3} g mol/L			
	Compositions wt %				Compositions wt %				Compositions wt %				Compositions wt %		
Code	MMA	HEMA	D_v	Code	MMA	HEMA	D_v	Code	MMA	HEMA	D_v	Code	MMA	HEMA	D_v
A1	100	0	24	B1	100	0	19	C1	100	0	28	D1	100	0	33
A2	95	5	27	B2	95	5	50	C2	95	5	30	D2	95	5	36
A3	92.5	7.5	30	B3	92.5	7.5	65	C3	92.5	7.5	32	D3	92.5	7.5	39
A4	90	10	34	B4	90	10	70	C4	90	10	33	D4	90	10	40.5
				B5	85	15	71	C5	85	15	33.5	D5	85	15	33.5
				B6	80	20	77	C6	80	20	41	D6	80	20	41.0
								C7	75	25	43	D7	75	25	52.0
								C8	70	30	51	D8	70	30	53.5

portion of the initiator (ca. 10%) was added and the reaction content was left for another 2 h to complete the polymerization. The recipes of these experiments are summarized in Table II.

Entrapment of Drugs Through Differential Microemulsion Polymerization. Each of different monomer feed composition of (MMA/HEMA) as 100/0, 90/10, 80/20, and 70/30 is entrapped by both hydrophilic (sodium warfarin) and hydrophobic (ibuprofen) drugs in monomer to drug ratios as 20 : 1, 10 : 1, and 6 : 1.

Entrapment of sodium warfarin.. An appropriate amount of the drug as water-soluble drug[35] was dissolved in the aqueous phase before polymerization, and then the differential microemulsion polymerization was preceded as described previously by adding each of feed monomer composition dropwise using a dropping funnel.

Entrapment of ibuprofen.. The lipophilic drug (ibuprofen) was dissolved in the monomer phase before differential microemulsion polymerization procedure. The crosslinking agent ethylene glycol dimethacrylate has also been included along with monomer for polymerization in a ratio of 2% of the total monomers.[36] The monomer including the drug and the crosslinker was dropped slowly to the emulsifier solution using a dropping funnel as mentioned obviously in the differential microemulsion technique.

Characterization

Critical Micelle Concentration Determination. The critical micelle concentration (CMC) for each used emulsifier was determined by measuring the surface tension of the aqueous solution of emulsifier with various concentrations[37] and the mean value for three measurements was taken.

Kinetic Studies. Batch polymerizations were carried out and samples were withdrawn at several time intervals. Monomer conversion percentage was calculated gravimetrically[9,38] at several times and variation of monomer conversion during the polymerization time is plotted and rate of polymerization was calculated for several concentrations of emulsifier.[38] The power of the emulsifier was calculated from the slope of the curves produced double logarithmic plots of rate of polymerization (R_p) and concentration of emulsifiers [E].

Liquid–Vapor Surface Tension Measurement. The liquid–vapor surface tensions of the resulting nanolatexes were measured at room temperature using a K9 tensiometer (Krüss, Germany) (Optisch-Mechanische werkstätten Humberg39, Germany) based on the Lecomte de Noüuy method using a rigid *O*-platinum ring.[39] For each emulsifier type, the measurements were carried out on the prepared polymer latex. Careful cleaning was performed after each change of polymer latex. After the *O*-ring had been immersed into a sample solution and allowed to stay there, the reading was taken and recorded. The mean value of three measurements for each sample was taken and registered.

Particle Size and Morphology Analysis. The particle size of the nanoparticles was measured by TEM. TEM images were obtained by JEM-1230-electron microscopy operated at 60 KV. A drop of well-dispersed diluted sample was deposited on a copper grid (200 mesh and covered with a carbon membrane) and dried at ambient temperature. A drop of phosphotungstic acid (0.4%) as a stain was deposited over the dried sample.[40] Before taking a TEM image, the sample was diluted at least 10 times by water.

Turbidity Measurement. The turbidity of the prepared latexes was measured as a function of the effect of type of the emulsifier and the change in the HEMA ratio in the monomer feed composition. It was evaluated with a HANNA instruments model HI98703 portable turbidimeter.[41] The polymer latex samples were diluted to 5% using distilled water and measured in a cylindrical glass cell. The turbidity[42] of the emulsions was characterized by a turbidity index, $T = -\log(I_0 - I)$, where I_0 is the intensity of the incident light and I is the intensity of the transmitted light. The optical absorbance was measured immediately and recorded.

ζ Potential Measurement. The electrophoretic mobility (μ_e) of the latex particles was measured at various HEMA ratios using the Zeta Sizer from Malvern Instruments (3000-HS model). The ζ potential[43] was calculated from the electrophoretic mobility using the Smoluchowski's equation,

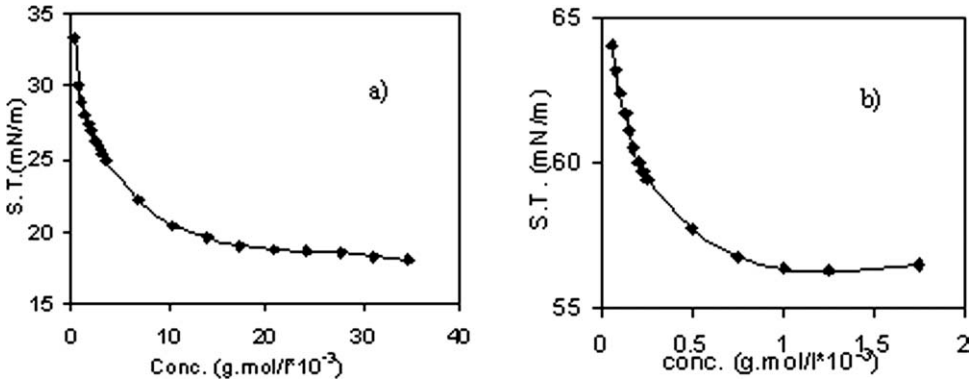


Figure 1. The critical micelle concentration of the surfactants (a) SDS and (b) PVP.

$$\zeta = \eta/\varepsilon\mu_e$$

where η is the viscosity and ε is the permittivity of the medium. For ζ potential measurement, sodium chloride solution of 10^{-3} mol L^{-1} was used.

Drug Entrapment Efficiency. To determine the drug entrapment efficiency (EE), the content of drug loaded in the polymeric nanospheres was determined by an indirect method through the determination of the free drug (unloaded drug). The unloaded drug was collected from the nanoparticles' stable dispersion by dissolving in ethanol and then free drug was determined in the clear supernatant following separation of nanoparticles by a combined ultracentrifugation technique at 50,000 r.p.m. for 30 min, then the drug concentration in the solution was determined by measuring the absorbance at 250 and 270 nm on an Shimadzu Ultraviolet–visible spectrophotometer[30] using a standard calibration curve experimentally obtained with ethanol solutions, respectively. The drug entrapment efficiency was defined as the ratio of the weight of the drug entrapped in the polymeric nanoparticles to the weight of the drug initially used.[44]

RESULTS AND DISCUSSIONS

CMC Determination

The CMC is defined as the lowest concentration of the emulsifier solution to begin micelle formation. CMC for each emulsifier used, SDS and PVP, was determined by measuring the surface tension of the aqueous emulsifier solution at different concentrations. There was a distinctive reduction in surface tension as the concentration increased. A break in the surface tension curve is also shown in Figure 1. It has been reported that the observed change in the slope is related to the value of a CMC at high concentration remains relatively constant or changes with a lower slope.[37] The results are shown in Figure 1 which gives the CMC values as 8.3×10^{-3} and 0.3×10^{-3} g mol L^{-1} for the SDS[45] and PVP,[46] respectively.

Kinetic and Morphological Studies

The kinetics of the MMA/HEMA copolymerization lattices with monomer feed composition 95/5 was studied for different concentrations of both SDS and PVP in two series using batch polymerization technique. Also, the morphology of the obtained copolymer particles was studied via measuring average particle size, D_v.

The monomer conversion was followed gravimetrically by removing aliquots of the reaction content at several time intervals. The variation of monomer conversion during the polymerization with time is plotted at several concentrations of both of the emulsifiers and shown in Figures 2 and 3. Then, the rate of polymerization was calculated in g mol L^{-1} s^{-1} as follows[38]:

$$R_p = d[\mathrm{M}]/dt$$

where $d[\mathrm{M}]$ is the variation in monomer concentration in g mol L^{-1} at a certain time dt and their values are listed in Table I. In addition, double logarithmic plot of rate of polymerization and emulsifier concentration are plotted and shown in Figure 4, and the power of the emulsifier was calculated from the resulted slope.

It is shown that the emulsifier concentration has a great influence on the rate of polymerization behavior from low- to high-emulsifier concentrations. Figures 2 and 3 show that two regions of behavior are formed, where, when increasing the emulsifier concentrations at enormous amount; it results in a transition from emulsion to microemulsion polymerization. As shown in Figures 2 and 3, it is clear that at low-emulsifier

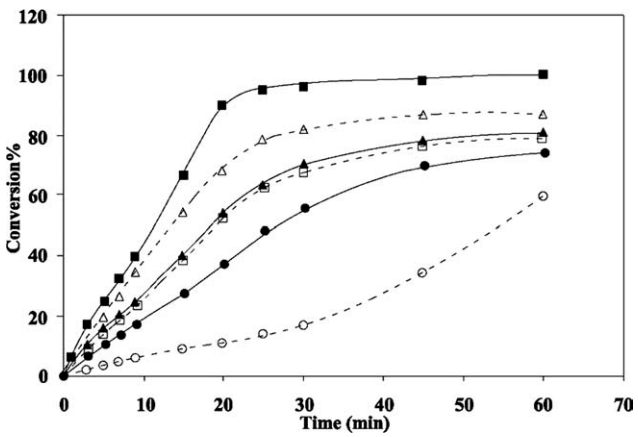


Figure 2. Conversion time curve for microemulsion copolymerization of (MMA/HEMA) 95/5% using different concentrations of poly vinylpyrrolidone: (•]) 0.5×10^{-3}, (▲) 0.75×10^{-3}, (■)1×10^{-3}, (□)1.5×10^{-3}, ([squo])2×10^{-3}, and (○) 2.5×10^{-3} g mol L^{-1}.

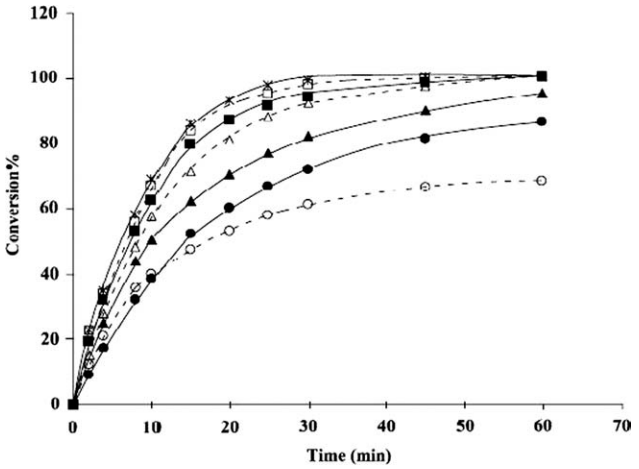


Figure 3. Conversion time curve for microemulsion copolymerization of (MMA/HEMA) 95/5% using different concentrations of SDS (●)35 × 10^{-3}, (▲)23 × 10^{-3}, (■) 17 × 10^{-3}, (*) 11.5 × 10^{-3}, (□) 69 × 10^{-3}, (△) 138.7 × 10^{-3}, and (○) 208 × 10^{-3} g mol L^{-1}.

concentration [11.5–35] × 10^{-3} and [0.5–1] × 10^{-3} g mol L^{-1} for SDS and PVP, respectively, there is an increase in the initial rate of polymerization with increasing of the emulsifier concentration that increased from $R_p = 3.38 \times 10^{-4}$ to 8.4×10^{-4} g mol L^{-1} s^{-1} and from $R_p = 2.99 \times 10^{-4}$ to 6.34×10^{-4} g mol L^{-1} s^{-1} for SDS and PVP, respectively.

In addition, the emulsifying power of the emulsifier was calculated from the resulted slope of Figure 4 with respect to the rate of polymerization, where the emulsifying power of emulsifier measures its ability to help the formation of an emulsion that results in the stability of emulsion. The emulsifying power was found to be 0.7 and 0.8 for SDS and PVP, respectively, and these results are slightly different from that obtained by Smith and Ewart.[47] It can be deduced that the ability of PVP to form stable emulsion is higher than the ability of SDS. These results elucidate that the polymeric emulsifiers such as PVP provide good chemical and mechanical stability different from the conventional emulsifier such as SDS.[48]

However, at higher concentrations of the emulsifiers [35–208] × 10^{-3} and [1–2.5] × 10^{-3} g mol L^{-1}, for SDS and PVP, respectively, we observed unusual kinetic and colloidal behaviors; where with extreme increase in the emulsifier concentrations, the overall rate of polymerization decreases accompanied by an increase of the incubation time of the polymerization.

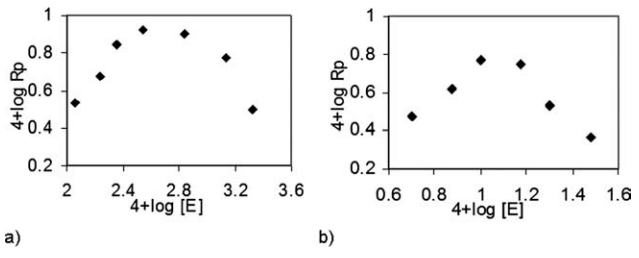


Figure 4. Double logarithmic plots of rate of polymerization (R_p) and concentration of emulsifiers [E] (a) SDS and (b) PVP.

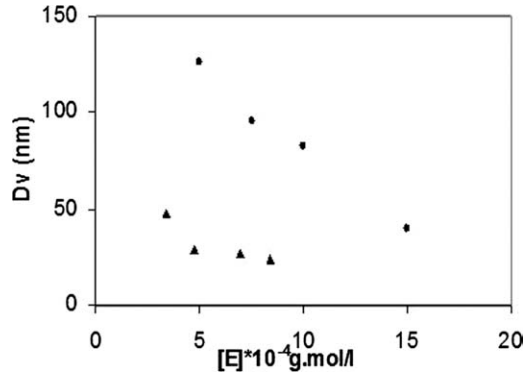


Figure 5. The relationship between the emulsifier concentration and the volume average particle diameter D_v where (●) PVP and (▲) SDS.

The rate of polymerization decreased from $R_p = 8.4 \times 10^{-4}$ to 2.46×10^{-4} g mol L^{-1} s^{-1} and from $R_p = 6.34 \times 10^{-4}$ to 2.23×10^{-4} g mol L^{-1} s^{-1} for SDS and PVP, respectively, and these results are approved by many authors[38,49] when they studied the effect of emulsifier concentration on the microemulsion polymerization of vinyl acetate and butyl acrylate. This may be attributed to the shell structure formed by adsorption of the emulsifier on the microemulsion droplets that may slightly retard the entry of oligomeric radicals and lead to a lower radical capture efficiency. The powers of emulsifier with respect to the rate of polymerization at this region were found to be −0.72 and −0.88 for SDS and PVP, respectively.

The average particle size of some obtained MMA/HEMA latex particles was measured using the TEM and shown in Figure 5 which gives the relationship between the average particle size D_v and the concentration of both of SDS and PVP. As shown in Figure 5, it is clear that the average particle size decreases with increasing of the emulsifier concentration where the values of D_v decreased from 48 to 23 nm for SDS and from 126 to 40 nm with respect to PVP.

Characterization of Polymeric Nanoparticles Produced by Differential Microemulsion Polymerization Technique

A series of differential microemulsion polymerization of MMA and HEMA are carried out with different monomer feed compositions as summarized in Table II using APS as an initiator in the presence of SDS as well as PVP alone or in conjunction with PEG as biologically safe emulsifier. The obtained microemulsion was bluish nanolatex with nanosized particles, almost uniform in size and enables to increase HEMA in the monomer feed composition without any aggregation by using the differential microemulsion polymerization technique. This result of microemulsion lattices is more advanced than that obtained by Özer et al.[32] who found that increasing HEMA content over 10% in the feed monomer composition through batch microemulsion polymerization caused a significant change in the size distribution and formation of very large particles and even agglomeration in the medium took place. However, the properties of the nanolatex are influenced by the content of HEMA in the monomer feed composition, and this effect was characterized in terms of the liquid–vapor surface tension measurements, the particle size of the particles, the colloidal aspects or the

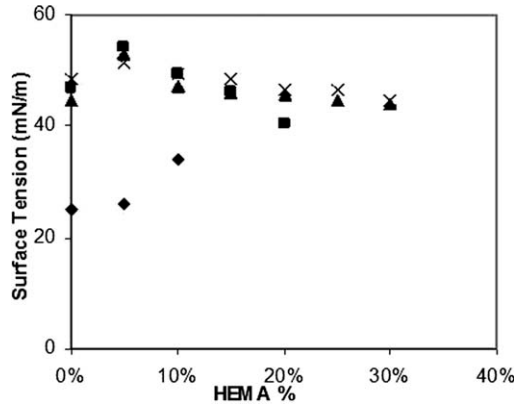


Figure 6. The surface tension of the latex as a function of feed monomer composition MMA/HEMA (◆) 23 × 10^{-3} g mol L^{-1} SDS, (■) 0.75 × 10^{-3} g mol L^{-1} PVP, (▲) 1.5 × 10^{-3} g mol L^{-1} PVP, and (×) 1.5 × 10^{-3} g mol L^{-1} PVP + 1 mL PEG.

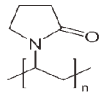
turbidity of the latex, and ζ potential via the electrophoretic mobility (μ_e) of the latex particles.

Liquid–Vapor Surface Tension Measurement. The effect of monomer feed composition MMA/HEMA on the physical properties of the latex was studied by measuring the liquid–vapor surface tension of the final latex at different HEMA contents in the monomer feed composition. The surface tension is measured using a rigid *O*-platinum ring technique and provides the values shown in Figure 6. It is noted that using PVP as a polymeric emulsifier resulted in latex solution with high surface tensions, different from the use of the standard emulsifier with low molecular weight as SDS (M.wt. = 288). In addition, the presence of HEMA that is considered as a polymerizable coemulsifier also causes the raise of surface tension of the latex, and hence the surface tension in the beginning presence of HEMA is higher than those in the presence of MMA alone.[50] Further, the surface tension of the nanolatex decreased with increase of HEMA content in the monomer feed composition when PVP is used as an emulsifier. This can be attributed to the presence of excess of HEMA as a polymerizable coemulsifier and hydrophilic comonomer tends to air–water interface saturation by its polymer molecules.[51]

In addition, the surface tensions of the latex with PVP emulsifier, that is in the presence of the polymer, are in the range of 40.5–54.1 mN/m which are lower than that of the aqueous PVP emulsifier solution alone of the same concentration that are 56.75 and 56.4 mN/m at PVP concentration as 0.75 × 10^{-3} and 1.5 × 10^{-3} g mol L^{-1}, respectively (above the CMC) measured previously through the critical micelle concentration determination, which may indicate air–water interface saturation by polymer molecules.[51]

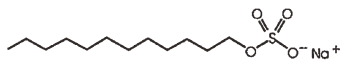
On the contrary, when SDS is used as an emulsifier, it is found that the surface tension of the nanolatex increases with an increase of HEMA content in the monomer feed composition by the effect of the polymerizable coemulsifier that causes rise in the surface tension.[50] Also, by comparing the surface tension of the aqueous emulsifier SDS solution in the presence and absence of the polymer, it is noted that the surface tensions in the presence of the polymer are in the range of 25–34 mN/m which are higher than that of the corresponding aqueous SDS solution with the same concentration that is 18.6 mN/m at SDS concentration as 23 × 10^{-3} g mol L^{-1} (above the CMC). These values of the surface tension prove first, almost complete conversion of the monomer and second, the complete coverage of the particle water interfaces with emulsifier.[38]

These different behaviors of both emulsifiers may be attributed to the difference in the structure of both PVP and SDS, where the former emulsifier is a high molecular weight (40,000), hydrophilic and nonionic polymeric emulsifier that permits the resulted polymer molecules to saturate the air–water interface.



Structure of Poly (N-vinyl pyrrolidone)

SDS, with anionic structure and low-molecular-weight emulsifier, prevents the polymer molecules from saturation of the air–water interface and causes the surface tension to increase.



Structure of Sodium dodecyl sulfate SDS

Particle Size and Turbidity Measurement. The average particle sizes of the obtained nanoparticles with different monomer feed compositions are listed in Table II. It is noted, for all cases, that the presence of HEMA causes an increase in the average particle sizes which increase with increasing HEMA content in the monomer feed composition, concerning that the total monomer concentration is constant in the all recipe. By using SDS as an emulsifier, the average particle size for PMMA was 24 nm and increase with increasing HEMA content to 34 nm. On the other hand, in the case of using PVP with low concentration (0.75 × 10^{-3} g mol L^{-1}), the average particle size of PMMA was 19 nm and HEMA content in the monomer feed composition could be raised to 20% without any coagulation with average particle size as 77 nm but increasing of HEMA content above 20% caused coagulation formation. However, with higher PVP concentration, HEMA content in the monomer feed composition could be increased till 30% without any observed coagulation with average particle size 51 nm and this was the same in the presence of PEG, where the average particle size raised to 53.5 nm without any observed coagulation at 30% HEMA.

Generally, the average particle size showed a noticeable increase with increasing HEMA content in the monomer feed composition and these results agree with the former results showed by Özer[32] and Bhawal[36] and this behavior is a direct result of the difference in the monomer partitioning of MMA and HEMA in the different phases involved in the particle formation and the subsequent stabilization of the particles by the available emulsifier. MMA, being less soluble in water than HEMA, partitions mainly in the micelles, whereas HEMA partitions between the

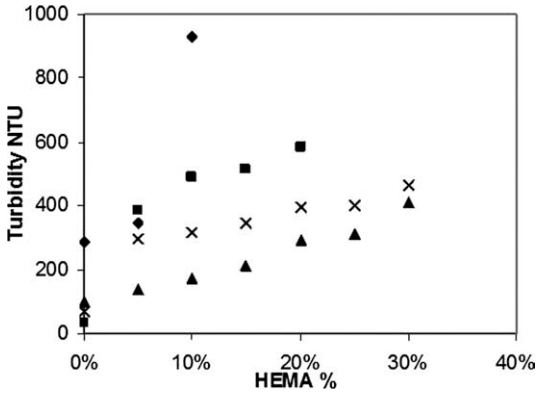


Figure 7. Turbidity measurements of the latex as a function of feed monomer compositions MMA/HEMA (◆) 23 × 10^{-3} g mol L^{-1} SDS, (■) 0.75 × 10^{-3} g mol L^{-1} PVP, (▲) 1.5 × 10^{-3} g mol L^{-1} PVP, and (×) 1.5 × 10^{-3} g mol L^{-1} PVP + 1 mL PEG.

aqueous phase and the micelle–water interface and the water-soluble initiator generates free radicals in the aqueous phase. Hence, HEMA grows at the interface, leading to growth in the particle size with increasing in HEMA ratio.[36]

In addition, the turbidity of the prepared latexes was measured as a function of the effect of the change in HEMA content in the monomer feed composition to elucidate the stability over the addition of HEMA. The polymer latex samples were diluted to 5% using distilled water and measured in a cylindrical glass cell. The polymer formed during the polymerization decreases the ordering in the microemulsion system and this is reflected in an increased scattering intensity (or turbidity). This behavior can simply be explained by the increased attraction between droplets (particles) (Figure 7).[52] As expected, in all cases the turbidity increased with increasing HEMA content, where it is known that the turbidity is a function of particle size and concentration,[53] concerning that the total monomer concentration is constant in all recipes but the variation occurs only in the particle sizes that increases as a result of increasing of HEMA content. Increase in HEMA content leads to a shift in particle formation, mainly through a coagulative nucleation mechanism,[36] resulting in greater particle size and higher turbidity.

ζ Potential. The effect of surface functionality resulting from HEMA content in the monomer feed composition on the particle charges of the final latex and stability is investigated through ζ potential measurements and these are summarized in Table III. The data showed that microemulsion lattices resulting from using SDS as emulsifier have high negative ζ potential that may be attributed to the ionic of sulfate functionalities in the SDS that showed a much higher degree of particle charging.

Although lattices prepared using PVP as emulsifier have very low negative ζ potential compared with that prepared using SDS samples, and in the same time, the increasing of PVP concentration causes further decrease in the negative charge. Especially, samples resulted from using PVP/PEG as emulsifier are with lower negative charge.

Generally, the less negative values are noted for more HEMA content. These data agree with Owen's results[22] which showed that the more hydrophilic anions had the least negative ζ potential SDS samples. In addition, the observed low ζ potential can be attributed to the screening effect of PVP, which shifts the shearing plan position far from the charged surface of the particles.

From the previous information, it was noted that the polymer resulted from using PVP/PEG as emulsifier is predicted to be the most suitable condition for pharmaceutical applications and in the loading of drugs, because of the biocompatibility components of both PVP and PEG. Besides, the use of poly(MMA/HEMA) copolymers as drug delivery system is because of its biocompatibility, water insolubility, and processibility[54] and also have excellent chemical stability because of their three-dimensional polymeric networks.[30]

Drug Entrapment. The main advantage of poly(HEMA/MMA) copolymers is that both the hydrophilic and the hydrophobic

Table III. Effect of HEMA Ratio on the Particle Size and ζ Potential.

Feed monomer composition MMA/HEMA	[E] (g.mol/l)	Zeta Potential (mV)	Feed monomer composition MMA/HEMA	[E] (g.mol/l)	Zeta Potential (mV)
100/0	SDS 23*10^{-3}	−71.1	100/0	PVP/ PEG [1.5/74]*10^{-3}	−2.02
95/5		−52.7	95/5		−2.62
90/10		−48.9	90/10		−1.95
100/0	PVP 1.5*10^{-3}	−2.02	85/15		−1.03
95/5		−1.95	80/20		−3.51
90/10		−1.35	75/25		−2.666
85/15		−6.176	70/30		−4.662
80/20		−7.192	100/0	PVP 0.75*10^{-3}	–
75/25		−1.648	95/5		−10.8
70/30		−4.024	90/10		−10.616
			85/15		−12.76
			80/20		−9.528

Table IV. The Relationship Between the Entrapment Efficiency EE and Each of Monomer Feed Composition and Drug Content (Monomer to Drug Ratio) for Both Sodium Warfarin and Ibuprofen.

Monomer composition MMA/HEMA	Entrapment Efficiency (EE)					
	Sodium warfarin Monomer : drug			Ibuprofen Monomer : drug		
	20:01	10:01	6:01	20:01	10:01	6:01
100/0	85	93	95.7	79.5	91	96.5
90/10	95.3	96.7	98	84	91.5	96.7
80/20	95.5	96.7	98	84.6	91.6	96.8
70/30	95.5	96.7	98	85	91.7	96.9

drugs can be incorporated. Both the hydrophilic drug sodium warfarin (an anticoagulant drug) and the hydrophobic drug ibuprofen (nonsteroidal anti-inflammatory drug) were entrapped through differential microemulsion polymerization technique, producing PMMA and poly(MMA/HEMA) copolymeric nanospheres with various monomer feed compositions in the presence of biocompatible emulsifiers (PVP and PEG). Each of different monomer feed composition of (MMA/HEMA) as 100/0, 90/10, 80/20, and 70/30 is entrapped by both hydrophilic (sodium warfarin) and hydrophobic (ibuprofen) drugs as monomer to drug ratios of 20 : 1, 10 : 1, and 6 : 1.

It is found that differential microemulsion polymerization technique has a vital role in improving the drug entrapment efficiency of the produced polymeric nanospheres.

The entrapped amount of each drug was quantified using Ultraviolet–visible spectrophotometer measurements in an indirect method as described in the Experimental section. The loading efficiency or EE was studied as a function of drug type, monomer composition, and monomer to drug ratio. The EE values and their relationship with both of the monomer feed composition and the monomer to drug ratio are summarized in Table IV in which the EE was calculated as follows[55]:

$$\text{Entrapment Efficiency} = \frac{\text{actual weight of the drug in sample}}{\text{the oretical weight of the drug}} \times 100$$

It was known that absorption of drugs from a microemulsion formulation is influenced by several factors as particle size and the partition coefficient of the drug between the two immiscible phases.[4] From EE values presented in Table IV, it is shown that drug loading and the entrapment efficiency in the copolymer (MMA/HEMA) nanoparticles appeared to be governed by the partition coefficient of the drug between the organic phase and the continuous aqueous phase employed in nanoparticle preparation in the microemulsion.[56] Where, the partition- (P) or distribution coefficient (D) is the ratio of concentrations of a compound in the two phases of a mixture of two immiscible solvents at equilibrium.[57] Ibuprofen (more hydrophobic, with partition coefficient value as (logP = 2.12–2.48),[58,59] exhibits lower loading in the polymeric nanoparticles than sodium warfarin (more hydrophilic, with lower partition coefficient value as (logP = 0.38–1.6)[60,61] due to the presence of Na+ ion (the most hydrated one) that causes increasing warfarin hydration and significant changes of the distribution coefficient that results in decreasing of the partition coefficient values).

The partition coefficient value of ibuprofen (more hydrophobic) as (log P =2.12–2.48),[58,59] whereas sodium warfarin (more hydrophilic) showed much lower partition coefficient value as (log P = 0.38–1.6)[60,61] owing to the presence of Na^+ ion (the most hydrated one) that causes increasing warfarin hydration and significant changes of the distribution coefficient that results in decreasing of the partition coefficient values.

Generally, it was noted that at low drug content (monomer: drug, 20 : 1) the presence of HEMA causes increase of the entrapment efficiency value EE over that of PMMA where EE increased from 85 to 95.3 and from 79.5 to 85 when HEMA is introduced in the monomer feed for sodium warfarin and ibuprofen, respectively.

But, at the higher drug content, the composition of the copolymer (molar ratio, MMA/HEMA) did not appear to affect the entrapment efficiency strongly and depend only on the drug content, where an increase of the drug proportion in the feed led to increasing drug loading and EE values.

From the results of Sivakumar and Rao,[30] it is observed that they prepared PMMA core and poly(MMA/HEMA) copolymeric core–shell hydrogel microspheres loaded with ibuprofen by adsorption method with percentage loading as 35.6 ± 1.62 and 48.7 ± 0.94% only for PMMA core and poly(MMA/HEMA) core–shell hydrogel microspheres, respectively. Also, Thompson et al.[62] incorporated ibuprofen drug in microspheres by the emulsion solvent evaporation method using new linear random copolyesters, giving entrapment efficiency (%) from 58.75 (±1.48) to 67.65 (±3.88) depending on the polymer : ibuprofen ratio and the internal phase volume. Overall, the results of the entrapment efficiency showed high values for both drugs used, suggesting the high efficiency of the copolymer (MMA/HEMA) nanoparticles through differential microemulsion polymerization technique for loading of different types of drugs.

Figure 8 shows micrographs of the polymeric nanospheres composed of MMA/HEMA ratio as 70/30 produced by using PVP/PEG as an emulsifier. Transmission electron micrographs of dried nanospheres showed spherical particles with almost

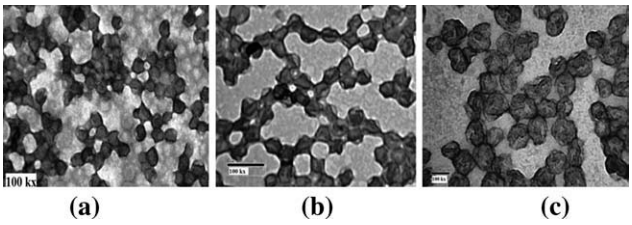


Figure 8. Typical TEM micrographs of nanoparticles produced from (a) free polymer, (b) polymer entrapped with warfarin sodium, and (c) polymer entrapped with ibuprofen at magnification of 100 KX.

similar size (narrowly size distributed) and showed both smooth and ridged surfaces.

By comparing morphologies of the polymer before and after incorporation of the drug, TEM micrographs observation suggested that the entrapment of drugs, including sodium warfarin and ibuprofen, can trigger a significant morphological transformation and owing to Zhang et al.'s[63] suggestion, occurrence of morphology transformation means higher drug loading, and *vice versa*. In addition, the small particle size of the polymeric nanoparticles may also have made the matrix more susceptible to drug percolation.[49] Moreover, particle size increased from 36 nm for the free polymeric nanoparticles to 70 and 81 nm after incorporation of sodium warfarin and ibuprofen, respectively, which also confirms high entrapment of drugs.

CONCLUSIONS

Differential microemulsion polymerization of different monomer feed compositions (MMA/HEMA) using biological safe emulsifiers PVP in conjunction with PEG succeeded in producing quite spherical nanopolymeric particles almost uniform in size, with no aggregates using the least amount of emulsifier. In addition, the differential technique played a vital role in improving the properties of the latex in the presence of HEMA. Increasing HEMA content in the monomer feed composition leads to a shift in particle formation, mainly through a coagulative nucleation mechanism, resulting in greater particle size and higher turbidity. Furthermore, the surface tension of the latex was, also, sensitive to HEMA ratio; it decreases with increasing HEMA ratio when using PVP as emulsifier, whereas in cases of SDS the surface tension increases. Via this study, we pointed out the possibility of entrapment of active drugs in polymeric nanoparticles as a new process to elaborate not only nanocarrier but also elaboration of well-defined active nanoparticles. In fact, during the nucleation step, the formed polymer matrix acts as a sponge of nonwater-soluble active molecules and consequently leads to local entrapment of hydrophobic molecules as well as the hydrophilic drug using the differential microemulsion polymerization.

As a general tendency, it is noted that the entrapment efficiency is independent of HEMA content in the monomer feed composition but depends on the partition coefficient of the drug and its introduced amount. Hence, higher entrapment efficiency is found for sodium warfarin (more hydrophilic) than that of ibuprofen (more hydrophobic) and they were 95.5 and 85%, respectively.

REFERENCES

1. Yildiza, U.; Capek, I. *Polymer* **2003,** *44*, 2193.
2. Stoffer, J. O.; Bone, T. J. *Polym. Sci. A Polym. Chem.***1980,** *8*, 2641.
3. Chen, J.; Zhang, Z. J. *Radiat. Phys. Chem.* **2007,** *76*, 852.
4. Spernath, A.; Aserin, A. *Adv. Colloid Interface Sci.* **2006,** *130*, 47.
5. Shi, Y.; Wu, Y.; Hao, J.; Li, G. *Colloid Surf. A Physicochem. Eng. Aspects* **2005,** *262*, 191.
6. Pérez-Carrillo, L. A.; Puca, M.; Rabelero, M.; Meza, K. E.; Puig, J. E.; Mendizábal, E.; López-Serrano, F.; López, R. G. *Polymer* **2007,** *48*, 1212.
7. Lade, O.; Co, C. C.; Cotts, P.; Strey, R.; Kaler, E. W. *Colloid Polym. Sci.* **2005,** *283*, 905.
8. Bhawal, S.; Sanghvi, P. G.; Devi, S. *Eur. Polym. J.* **2003,** *39*, 389.
9. Puig, J. E.; Mendizábal, E.; Delgado, S.; Arellano, J.; López-Serrano, F. *Comptes Rendus Chim.* **2003,** *6*, 1267.
10. Badran, A. S.; Nasr, H. E.; Ali, A. E. M.; El Enany, G. M.; Abd El-Hakim, A. A. *J. Appl. Polym. Sci.* **2000,** *77*, 1240.
11. Rabelero, M.; López-Cuenca, S.; Puca, M.; Mendizábal, E.; Esquena, J.; Solans, C.; López, R. G.; Puig, J. E. *Polymer* **2005,** *46*, 6182.
12. Xu, P.; Zhong, W.; Wang, H.; Tong, R.; Du, Q. J. *Colloid Polym. Sci.* **2004,** *282*, 1409.
13. T. Wan, Hu, Z. W.; Ma, X. L.; Yao, J.; Lu, K. *Prog. Org. Coat.* **2008,** *62*, 219.
14. Koukiotis, C.; Sideridou, I. *Prog. Org. Coat.* **2008,** *63*, 116.
15. He, G. W.; Pan, Q. M.; Rempel, G. L. *J. Macromol. Rapid Commun.* **2003,** *24*, 585.
16. Yildiz, U.; Capek, I. J. *Prog. Colloid Polym. Sci.* **2004,** *124*, 14.
17. He, G. W.; Pan, Q. M. *J. Macromol. Rapid Commun.* **2004,** *25*, 1545.
18. Norakankorn, C.; Pan, Q.; Rempel, G. L.; Kiatkamjonwong, S. *Eur. Polym. J.* **2009,** *45*, 2977.
19. Chuayjuljit, S.; Boonmahitthisud, A. *Appl. Surf. Sci.* **2010,** *256*, 7211.
20. Wang, H.; Pan, Q.; Rempel, G. L. *Eur. Polym. J.* **2011,** *47*, 973.
21. Donescu, D.; Serban, S.; Petcu, C.; Nistor, C. L.; Ghiurea, M.; Corobea, M. C. *J. Colloid. Polym. Sci.* **2007,** *285*, 1455.
22. Owen, H.; Carter, P. W.; Graham, S.; Werling, J. O. *Int. J. Pharm.* **2009,** *368*, 154.
23. Yin, W.; Dong, Z.; Chen, X.; Finn, N.; Yates, M. Z. *J. Supercrit. Fluids* **2007,** *41*, 293.
24. Graf, A.; Jack, K. S.; Whittaker, A. K.; Hook, S. M.; Rades, T. *Eur. J. Pharm. Sci.* **2008,** *33*, 434.
25. Narang, A. S.; Delmarre, D.; Gaoc, D. *Int. J. Pharm.* **2007,** *345*, 9.
26. Otto, D. P.; Vosloo, H. C. M.; Liebenberg, W.; de Villiers, M. M. *Eur. J. Pharm. Biopharm.* **2008,** *69*, 1121.

27. Okur, N. Ü.; Apaydın, Ş.; Yavaşoğlu, N. Ü. K.; Yavaşoğlu, A.; Karasulu, H. Y. *Int. J. Pharm.* **2011,** *416*, 136.
28. Sintov, A. C.; Levy, H. V.; Botner, S. J. *Control. Release* **2010,** *148*, 168.
29. Stubbe, B. G.; De Smedt, S. C.; Demeester, J. J. *Pharm. Res.* **2004,** *21*, 1732.
30. Sivakumar, M.; Rao, K. P. *J. Appl. Polym. Sci.* **2002,** *83*, 3045.
31. Uchegbu, I. F.; Schatzlein, A. G. Polymers in Drug Delivery; Taylor & Francis Group: LLC, **2006.**
32. Özer, F.; Pişkin, E.; Beşkardeş, M. O.; Zareie, H. J. *Appl. Polym. Sci.* **2001,** *82*, 237.
33. Nair, B. *Int. J. Toxicol.* **1998,** *17*, 95.
34. Hamidi, M.; Azadi, A.; Rafiei, P. *Adv. Drug Deliv. Rev.* **2008,** *60*, 1638.
35. Zacchigna, M.; Di Luca, G.; Cateni, F.; Maurich, V. *Eur. J. Pharm. Sci.* **2004,** *23*, 379.
36. Bhawal, S.; Reddy, L. H.; Murthy, R. S. R.; Devi, S. J. *Appl. Polym. Sci.* **2004,** *92*, 402.
37. Tolosa, L. I.; Rodríguez-Malaver, A. J.; González, A. M.; Rojas, O. J. *J. Colloid Interface Sci.* **2006,** *294*, 182.
38. Tauer, K.; Ramírez, A. G.; López, R. G. *Comptes Rendus Chim.* **2003,** *6*, 1245.
39. Sadtler, V. M.; Imbert, P.; Dellacherie, J. E. *J. Colloid Interface* **2002,** *254*, 355.
40. Xiao, X.; Wang, Y. *Colloids Surf. A Physicochem. Eng. Aspects* **2009,** *348*, 151.
41. Hussain, A. I.; Nasr, H. E.; El-Saadany, S. S.; El-Hamouly, S. H. *J. Disper. Sci. Technol.* **2010,** *31*, 1278.
42. Porcel, R.; Jodar, A. B.; Cabrerizo, M. A.; Hidalgo-Alvarez, R.; Rodrıguez, A. M. *J. Colloid Interface Sci.* **2001,** *239*, 568.
43. Santosa, A. M.; Elaïssari, A.; Martinhoa, J. M. *G.; Pichot, C. Polymer* **2005,** *46*, 1181.
44. Chu, H.; Liu, N.; Wang, X.; Jiao, Z.; Chen, Z. *Int. J. Pharm.* **2009,** *371*, 190.
45. Domínguez, A.; Fernández, A.; González, N.; Iglesias, E.; Montenegro, L. J. *Chem. Edu.* **1997,** *74*, 1227.
46. Xia, Y.; Wei, M.; Lua, Y. *Synth. Metals* **2009,** *159*, 372.
47. Smith, W. V.; Ewart, R. H. *J. Chem. Phys.* **1948,** *16*, 592.
48. Chang, Y. H.; Lee, Y. D.; Karlsson, O. J.; Sundberg, D. C. *Polymer* **2000,** *41*, 6741.
49. López, R. G.; Cisneros, M. G.; Trevinõ, M. E.; Peralta, R. D.; Rabelero, M.; Mendizábal, E.; Puig, J. E.; Cesteros, C. *Polymer* **2005,** *46*, 2900.
50. Cochin, D.; Laschewsky, A.; Nallet, F. *Macromolecules* **1997,** *30*, 2278.
51. Braconnot, S.; Hoang, C.; Fessi, H.; Elaissari, A. J. *Mater. Sci. Eng. C* **2009,** *29*, 624.
52. Capek, I. *Adv. Colloid Interface Sci.* **2001,** *92*, 195.
53. Reddy, S. R.; Fogler, H. S. *J. Colloid Interface Sci.* **1981,** *79*, 101.
54. Hwang, J. R.; Sefton, M. V. *J. Control. Release* **1997,** *49*, 217.
55. Valot, P.; Baba, M.; Nedelec, J.-M.; Sintes-Zydowicz, N. *Int. J. Pharm.* **2009,** *369*, 53.
56. Katsikogianni, G.; Avgoustakis, K. J. *Nanosci. Nanotechnol.* **2006,** *6*, 3080.
57. Leo, A.; Hansch, C.; Elkins, D. *Chem. Rev.* **1971,** *71*, 525.
58. Shawahna, R.; Rahman, N. U. *DARU* **2011,** *19*, 83.
59. Scheytt, T.; Mersmann, P.; Lindstaädt, R.; Heberer, T. *Water Air Soil Pollut.* **2005,** *165*, 3.
60. Ingram, T.; Richter, U.; Mehling, T.; Smirnova, I. *Fluid Phase Equilibr.* **2011,** *305*, 197.
61. Directive 98/8/EC concerning the placing of biocidal products on the market, Assessment Report (essay), Sodium warfarin, September (2009), Annex I—Ireland.
62. Thompson, C. J.; Hansford, D.; Higgins, S.; Rostron, C.; Hutcheon, G. A.; Munday, D. L. *Int. J. Pharm.* **2007,** *329*, 53.
63. Zhang, J. X.; Li, S. H.; Li, X. D.; Li, X. H.; Zhu, K. J. *Polymer* **2009,** *50*, 1778.