Polyurea Microcapsules from Oil−in−Oil Emulsions via Interfacial Polymerization

ARTICLE *in* MACROMOLECULES · AUGUST 2006

Impact Factor: 5.8 · DOI: 10.1021/ma061455x

2 AUTHORS, INCLUDING:

David Tyler Mcquade
Florida State University
82 PUBLICATIONS **5,463** CITATIONS

SEE PROFILE

Polyurea Microcapsules from Oil-in-Oil Emulsions via Interfacial Polymerization

Muris Kobašlija and D. Tyler McQuade*

Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301

Received June 28, 2006; Revised Manuscript Received July 3, 2006

ABSTRACT: Polyurea microcapsules were obtained via interfacial polymerization at the interface of methanol-in-cyclohexane, formamide-in-cyclohexane, and *N*,*N*-dimethylformamide-in-cyclohexane emulsions. Coumarin-1 was used as a model encapsulant; both dye leaching and encapsulation efficiency were examined. For the methanol-in-cyclohexane system, design of experiments was used to assess the influence of five different variables on capsule size. A model was obtained that accurately predicts the size of capsules resulting from a given formulation.

Introduction

This paper demonstrates the preparation of polyurea microcapsules templated by oil-in-oil emulsions. Microcapsules prepared via interfacial polymerization are used to encapsulate a variety of materials including adhesives, agrochemicals, live cells, enzymes, flavors, fragrances, drugs, and dyes.[1] Microcapsules are traditionally templated by either water-in-oil or oil-in-water emulsions.[2] Microencapsulation of pesticides, for example, is usually accomplished via an interfacial polymerization of oil-in-water emulsions that yields mainly polyurea microcapsules. The composition of the emulsion dictates both the type of material that may be encapsulated and the capsule wall properties.[3] Since most emulsions consist of water and a nonpolar organic solvent, the material to be entrapped must be soluble either in water or in a nonpolar solvent. This strict solubility profile limits the types and/or amounts of materials that can be encapsulated. An alternative protocol that enables the encapsulation of materials that are soluble in polar organics is a desirable advance. We suggest the use of oil-in-oil emulsions as an alternative to classical approaches, as the discovery of novel polymerization methods for making microcapsules is important for both industrial and academic applications.[2] For example, we and others have been using microcapsules as new solid supports for making heterogeneous catalysts.[4] To our knowledge, this is the first paper describing a general polymerization strategy at an oil-in-oil interface.

Although counterintuitive, oil-in-oil emulsions have been reported. Often, emulsion stabilization requires polymeric amphiphiles.[5] Only two examples describe the use of oil-in-oil emulsions for the production of microcapsules via interfacial polymerization.[6] Shukla and Sivaram prepare polyurethane capsules using paraffin oil as the continuous phase and an alcohol macromonomer as the disperse phase. A drawback of this system is the lack of cosolvent in the disperse phase, which limits control over size, shell thickness, and porosity. The approach reported by Zydowicz et al. uses a poly(dimethylsiloxane) (PDMS):THF (1:1) continuous phase and a benzyl benzoate disperse phase to create ortho ester-based microcapsules. Again, the limitations on the disperse phase cosolvent restrict the scope of substrates that can be encapsulated. These initial reports suggest that polymerization at oil-in-oil interfaces is attainable only in very specific systems. In this report, we extend these methods to a more general system using polar protic or aprotic solvent-in-cyclohexane emulsions to template the formation of polyurea microcapsules (Figure 1) and demonstrate control over capsule size.

Results and Discussion

The polar organic solvents chosen were those that could both disperse in cyclohexane and dissolve the polyamine monomer (polyethylenimine, PEI) used to create the polyurea shell. Methanol, *N*,*N*-dimethylformamide (DMF), and formamide met both of these criteria. Images of emulsions formed by dispersing these solvents in cyclohexane are shown in Figure 2. In all of these cases, the polar organic disperse phase contained PEI and the cyclohexane continuous phase contained polyisobutylene as a polymeric stabilizer.[7] These emulsions were short-lived and would break within minutes if left standing but could be captured via interfacial polymerization upon addition of 2,4-tolylene diisocyanate (TDI) to the continuous phase with constant stirring. The obtained polyurea microcapsules had smooth shells and displayed similar coefficients of variation of 20−30% (Figures 3 and 4B). In addition to smooth shells, the capsules show the ability to undergo shrinking and swelling reversibly depending on the osmotic pressure. Figure 3A is an optical micrograph of crenated (shrunken) capsules in hexanes, and Figure 3B shows the same capsules swollen in methanol. This shrinking and swelling behavior is a common trait of flexible walled microcapsules.

One application of this new interfacial polymerization method is the encapsulation of water-insoluble molecules. As a demonstration, we encapsulated coumarin-1 (C-1) dye (Figure 5). C-1 is soluble in methanol, DMF, chloroform, and dimethyl sulfoxide (DMSO) but only sparingly soluble in water and nonpolar solvents such as cyclohexane. Utilization of classical water-in-oil systems would prohibit high loading due to the solubility limitations. Use of an oil-in-water system (chloroform-in-water) or our oil-in-oil system (methanol-in-cyclohexane) provides a solution for high loading needs. The methanol-in-cyclohexane system provides an excellent alternative to chloroform-in-water because chlorinated solvents are problematic due to environmental, cost, and safety concerns.[8] Without optimization, C-1 was encapsulated in a methanol-in-cyclohexane system with 63.0 ± 1.0% encapsulation efficiency and a dye loading of 18.2 ± 0.3% (w/w) after drying the capsules.

* Corresponding author. E-mail: dtm25@cornell.edu.

10.1021/ma061455x CCC: $33.50
Published on Web 08/18/2006

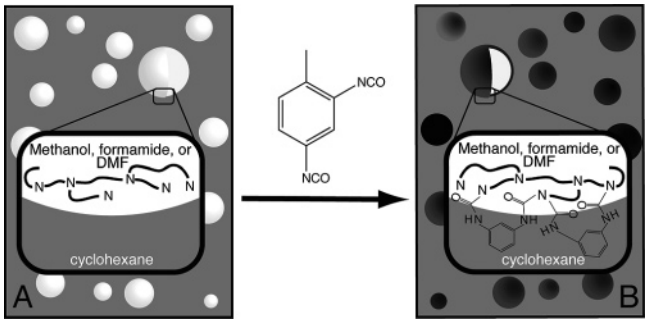

Figure 1. (A) Emulsions are prepared by dispersing a polar phase containing anhydrous PEI into a nonpolar phase. (B) A cross-linked polyurea shell forms upon addition of TDI to the continuous phase.

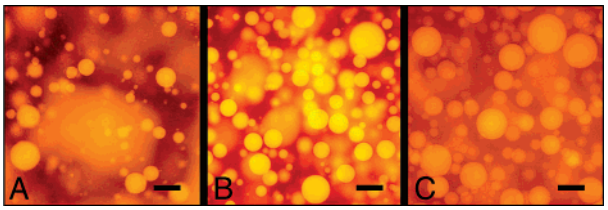

Figure 2. Emulsions formed with rhodamine as an entrapped tracer (scale bar is 10 μm): (A) methanol-in-cyclohexane, (B) DMF-in-cyclohexane, and (C) formamide-in-cyclohexane.

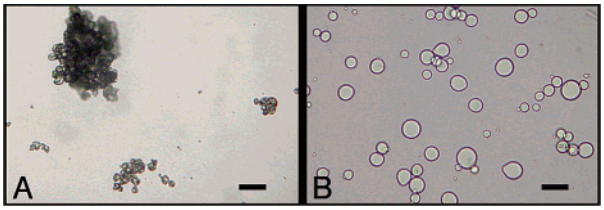

Figure 3. Methanol-in-cyclohexane capsules subjected to a range of conditions (scale bar is 10 μm): (A) crenated in hexanes and (B) swollen in methanol.

These C-1 loaded capsules did not show evidence of "burst" kinetics (initial rapid release of the active molecule) when exposed to water (Figure 5). "Burst" kinetics hamper controlled release systems, especially in cases where the encapsulant is a polar hydrophobic molecule.[9] Successful and efficient encapsulation of C-1 suggests that the oil-in-oil approach is very effective relative to classical systems.

Next, we examined the solubility of methanol, DMF, and formamide in cyclohexane as capsule formation is strongly dependent on the partition coefficient of the disperse and continuous phase. ^{1}H NMR spectra of the cyclohexane layer after a 2 min emulsification revealed that methanol and DMF were present in 11% and 8%, respectively ($\pm$1% based on ^{13}C satellites), in cyclohexane (Figure 6). Formamide and water were below the spectrometer detection limit of 1%. These observations may explain why methanol- and DMF-in-cyclohexane templated microcapsules exhibit thicker shells compared to formamide-in-cyclohexane. We are currently exploring the hypothesis that the partial solubility of methanol and DMF in cyclohexane contributes to a thicker polymerization boundary, thus yielding thicker shells.[10]

The formation of capsules (hollow microspheres), as evident from confocal (Figure 4A,D,E) and SEM images (Figure 4B,C), supports our hypothesis that the polymerization takes place only at the interface of the emulsion droplets. We had considered a mechanism in which diisocyanate diffused fully into the PEI-rich region, rendering the reaction a solution polymerization in one phase. We dismissed this scenario for multiple reasons. Capsules, apparent from microscopy images, would not form

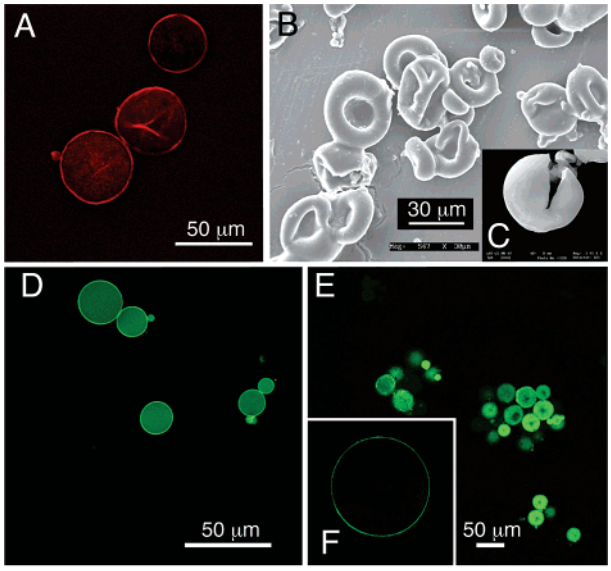

Figure 4. (A−C) Capsules prepared from methanol-in-oil emulsions: (A) confocal micrograph of capsules with lissamine rhodamine labeled shells, (B) SEM image of capsules, and (C) close-up SEM image of a broken capsule. Confocal micrographs of capsules with fluorescein labeled shells: (D) formamide-in-oil, (E) DMF-in-oil, and (F) close-up of a DMF-in-oil templated capsule.

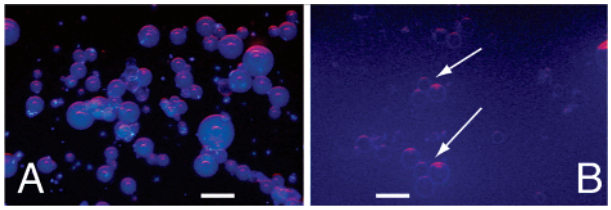

Figure 5. Fluorescence microscope images of microcapsules containing coumarin-1 (scale bar is 10 μm) formed using methanol-in-oil templated encapsulation. Capsules suspended in (A) water (coumarin-1 does not leach rapidly) and (B) methanol (arrows indicate hard-to-see capsules due to the haze that coumarin-1 creates as it leaches rapidly).

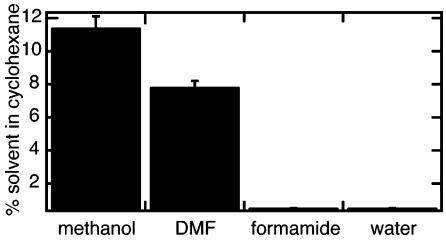

Figure 6. Presence of polar solvents in cyclohexane detected by ^{1}H NMR upon 2 min of emulsification.

in a solution polymerization in one phase; rather, solid spheres would form. The fact that these particles crenate and swell in polar solvent suggests that interfacial polymerization takes place, yielding thin-shelled capsules. Even though TDI can be mixed with methanol for a short time (1 min) before they visibly react to form urethane, the reaction of PEI with TDI is very fast (less than a second). Thus, TDI cannot reach inside of the polyamine-rich emulsion droplet before it reacts with PEI on the periphery of the droplet. These interfacialy formed polyurea cross-links would slow the inward diffusion of TDI further. In addition, we tested this hypothesis further by performing a homogeneous TDI/PEI polymerization in chloroform/methanol mixture under the same stirring conditions as those when cyclohexane is present. When the TDI was added to a stirred PEI solution in chloroform/methanol, we found that a solid mass of polymer instantly formed. Because of the fact that the homogeneous case

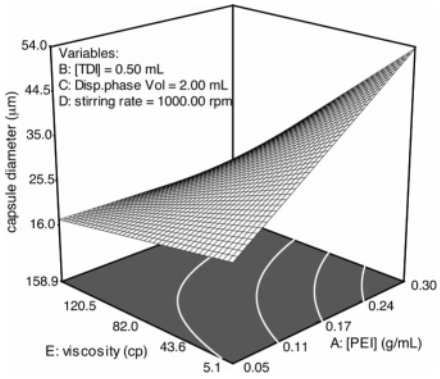

Figure 7. Response surface graph indicating capsule diameter as a function of the two interacting variables (viscosity of the continuous phase and concentration of PEI) when the remaining three variables are held constant.

provides no capsules and that we can observe an emulsion prior to polymerization in the case of the cyclohexane/methanol system, we feel that the best explanation for the formation of capsules is an interfacial polymerization taking place at the cyclohexane−methanol interface.

Surprisingly, the size of the capsules in the DMF or methanol-in-cyclohexane emulsions could not be controlled by stirring speed alone, as is the case in classical emulsions and in the formamide-in-cyclohexane system. To ascertain the factors that influence the size of microcapsules, we studied the methanol-in-cyclohexane system in more detail.

On the basis of previous interfacial polymerization work, we postulated that factors such as stirring speed, concentration of PEI and TDI monomers, viscosity of the phases, and the volume ratio of the phases would influence capsule size.[11] To get a more comprehensive understanding of how these factors influence the capsule diameter, we decided to use the engineering method known as design of experiments (DOE).[12]

DOE is a systematic optimization technique in which changes of an observable property, such as capsule size, are monitored as a function of the input variables, such as monomer concentration or stirring rate. This statistical technique enables understanding of how the input variables affect the system in a minimum number of experiments. This technique is powerful because both the effect of each individual variable and the interactions between the variables are extracted by changing multiple variables during each experiment. This way, optimization of the property of interest can be achieved. "Changing one variable at a time" is not a good method of investigation because the parameters are rarely independent of each other.[13] A five-variable (2-level $2^{(5-1)}$) fractional factorial DOE was selected (see Supporting Information for a more detailed description), and a total of 16 experimental runs were designed with Design-Expert,[14] a DOE program, to examine the influence of the selected variables on the capsule diameter.

From the DOE analysis a response surface model was developed that relates capsule diameter to the tested variables (Figure 7). All of the variables chosen were important for controlling capsule size except for the concentration of diisocyanate monomer. It is interesting to note that the concentration of polyamine monomer has a significant effect. We hypothesize that PEI acts as an emulsifier.

The DOE analysis also revealed that two sets of variables depend on each other: (1) the viscosity of the continuous phase and concentration of PEI and (2) the stirring speed and disperse-phase volume (Figure 8). A one variable at a time approach

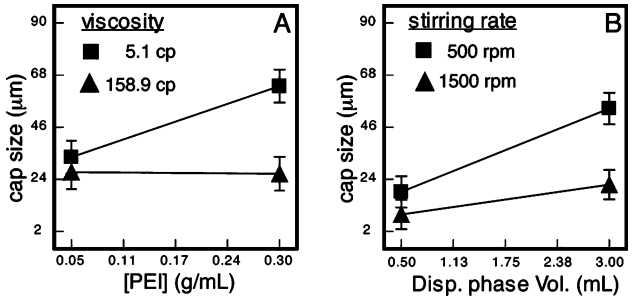

Figure 8. Interaction plots depicting the dependence of (A) viscosity of the continuous phase and concentration of PEI monomer and (B) stirring rate and volume of the disperse phase.

Table 1. Comparison of Capsule Size Predicted by the DOE Model with the Actual Size of Three Different Formulations

formulation[a]	predicted size (μm)	actual size[b] (μm)
1	6.7	4.7 ± 1.4
2	35.1	28.2 ± 5.7
3	46.0	55.6 ± 14.1

[a] Detailed description of the three formulations can be found within the Supporting Information. [b] Confocal images were used to determine average capsule diameter. See the Supporting Information for more details.

would not have revealed to us that these variables are coupled to each other. We hypothesize that the viscosity of continuous phase and PEI concentration are coupled because the shear forces responsible for droplet breakup are dependent on the ratio of continuous phase viscosity to disperse phase viscosity.[15] In this case PEI concentration is proportional to disperse phase viscosity. Stirring speed/disperse phase volume interaction can be explained through shear field argument.[16] As the volume increases, a low-shear region far away from the stir bar increases and droplets overall feel a smaller shear field. It is clear that the DOE approach is powerful not only because it provides new information that a one variable at a time approach cannot obtain but also because it allows one to map out the conditions to achieve a desired capsule size.

Figure 7 shows a response surface that correlates capsule size with the two interacting variables (viscosity of the continuous phase and concentration of PEI) when the other variables are held constant. To validate the ability of the model to predict capsule diameter, we picked three different conditions that were not run in the DOE trials. The capsule sizes observed experimentally compared well to the capsule sizes predicted by the model (Table 1). These results suggest that the DOE model is a reliable indicator of capsule size dependence on the tested variables.

In conclusion, we have shown that oil-in-oil emulsions serve as effective templates for creating polyurea microcapsules. While neither the concept of interfacial polymerization nor oil-in-oil emulsions are novel in themselves, the combination of the two in a general method that broadens the field of microencapsulation is new and will be broadly useful. We demonstrated that this encapsulation procedure is excellent for encapsulating materials that are not compatible with classical water-in-oil or oil-in-water emulsions.

In addition to presenting a model for interfacial polymerization of oil-in-oil emulsions, we have also demonstrated that a simple DOE provides conditions for controlling capsule size and provides valuable information regarding the variables that effect capsule size. By understanding the variables responsible for controlling the polymerization of the capsules, we were able to develop a mechanistic model for shell formation. In this case, the DOE was used to model capsule size, but the DOE analysis

could be extended to include factors such as wall thickness, porosity, or release characteristics.

From a practical standpoint, encapsulation of various compounds used in the adhesive, agrochemical, flavor, fragrance, drug, and dye industries will benefit from this new approach helping to solve problems in cases where the classical systems are hampered. Equally as import, we feel that these results impact polymer science broadly because we clearly demonstrate that oil-in-oil emulsions are another powerful tool available to polymer chemists for making well-defined polymeric structures.

Materials and Methods

Materials. Unless otherwise specified, materials were obtained from commercial suppliers and used without further purification. DMF was purified using a standard procedure.[17] Coumarin-1 dye was a generous gift from Prof. Alan Taylor, New York State Agricultural Experimental Station, Cornell University. Use of Span 85 as an emulsifier was based purely on empirical data after many other emulsifiers were tried. Possible interference from "surface active impurities", as reported by Eastoe,[18] was considered. However, upon making capsules from materials obtained from several different suppliers and not seeing any change in capsule morphology, it was hypothesized that any surface active impurity influence, if present, would be masked by the Span 85 emulsifier.

Equipment, **Characterization**, **and Methods. A.** Viscosities were measured with a Gilmont dropping ball viscometer.

B. Scaning electron microscopy images were obtained on a Leica 440 SEM at the Cornell Center for Materials Research. Capsules were characterized at 25 kV after sputter-coating with palladium−gold.

C. Confocal microscopy was performed on a Leica TCS SP2 spectral confocal microscope system at Cornell's Microscopy, Imaging & Fluorimetry Facility. Capsules prepared with fluorescently labeled PEI were swelled and dispersed in methanol and then in water. Water dispersion was applied to the microscope slide, and the capsules were analyzed using provided Leica software.

D. For nonconfocal images, inverted Leica DMIL was used with a mounted Sony DSC-F717 digital camera and ebq100 UV source. An emulsion of polar solvent-in-cyclohexane with rhodamine as an encapsulant was placed onto the microscope slide. For coumarin-1 burst kinetics assay dry capsules were placed onto the microscope slide and incubated with either water or methanol. The capsules were then examined for burst kinetics.

E. Electronic absorption (UV) spectra were recorded on a Cary 50 Bio UV/vis spectrometer. Capsules loaded with coumarin-1 dye were swollen in methanol for 5 min. The methanol supernatant was then examined for coumarin-1 concentration. Absolute loading of dye per gram of dry capsules was then back calculated. Loading efficiency was calculated as the actual loading over theoretical loading in percent.

F. DOE analysis was done using Design-Expert 7 software by Stat-Ease. Average capsule size obtained via confocal microscopy was used as the input, and the variables were examined for significance and interaction. The software built a model for capsule size dependence on five tested variables. This model was used to predict capsule size of three different formulations tested.

G. ImageJ software (NIH, http://rsb.info.nih.gov/ij/) was used to measure perimeters (px) of capsules produced in three tested formulations. Using Microsoft Excel, perimeters were converted to diameters (μm), and the mean size and standard deviation were calculated.

Preparation of PEI Labeled with FITC. Polyethylenimine (PEI, 99%, MW 10 000, PDI = 2.5, 53.0 g) was stirred with fluorescein isothiocyanate isomer I (FITC, 0.132 g, 0.3 mmol) in methanol (400 mL) overnight at room temperature. Methanol was evaporated in vacuo, and the residue was dissolved in a minimal amount of water (about 10 mL). The solution was dialyzed against deionized water for 2 days while contained within a SnakeSkin dialysis bag (Pierce, 34 mm dry flat width, 3.7 mL/cm, MWCO 3500) or until no more color leached out. The remaining residue was lyophilized overnight and used as is.

Preparation of PEI Labeled with Lissamine Rhodamine. Polyethylenimine (PEI, 99%, MW 10 000, PDI = 2.5, 53.0 g) was stirred with lissamine rhodamine B sulfonyl chloride (0.185 g, 0.3 mmol) in methanol (400 mL) overnight at room temperature. Methanol was evaporated in vacuo, and the residue dissolved in a minimal amount of water (about 10 mL). The solution was dialyzed against deionized water for 2 days while contained within a SnakeSkin dialysis bag (Pierce, 34 mm dry flat width, 3.7 mL/cm, MWCO 3500) or until no more color leached out. The remaining residue was lyophilized overnight and used as is.

Preparation of Viscous Cyclohexane Solution. Polyisobutylene (52.74 g, MW 400 000) was added to cyclohexane (850 mL) and stirred overnight to dissolve. The obtained solution had 158.9 cP viscosity. A 5-fold dilution resulted in solution with 5.1 cP viscosity.

General Procedure for Microcapsule Preparation from Oil-in-Oil Emulsions. To cyclohexane (15 mL, viscosity modified with polyisobutylene) and Span 85 mixture (2% v/v) stirred with a magnetic stirrer, the disperse phase was added at once. After 2 min of stirring, 2,4-tolylene diisocyanate (TDI, in cyclohexane) was added at once and the stirring was reduced to 500 rpm. After 10 min, polymerization was stopped by the addition of cyclohexane (30 mL). The resulting capsules were left to settle, further washed with hexanes, and finally vacuum-dried.

Microcapsule Preparation from DMF-in-Oil Emulsion. To cyclohexane (15 mL, η = 9.5 cP) and Span 85 mixture (2% v/v) stirred at 1500 rpm with a magnetic stirrer, the disperse phase (0.3 g/mL PEI in 3 mL of DMF) was added at once. After 2 min of stirring, 2,4-tolylene diisocyanate (TDI, 0.1 mL, in 2.9 mL of cyclohexane) was added at once and the stirring was reduced to 500 rpm. After 10 min, polymerization was stopped by the addition of cyclohexane (30 mL). The resulting capsules were left to settle, further washed with hexanes, and finally vacuum-dried.

Microcapsule Preparation from Formamide-in-Oil Emulsion. To cyclohexane (15 mL, η = 9.5 cP) and Span 85 mixture (2% v/v) stirred at 1500 rpm with a magnetic stirrer, the disperse phase (0.3 g/mL PEI in 3 mL of formamide) was added at once. After 2 min of stirring, 2,4-tolylene diisocyanate (TDI, 0.1 mL, in 2.9 mL of cyclohexane) was added at once and the stirring was reduced to 500 rpm. After 10 min, polymerization was stopped by the addition of cyclohexane (30 mL). The resulting capsules were left to settle, further washed with hexanes, and finally vacuum-dried.

Solution Polymerization of Polyethylenimine with 2,4-Tolylene Diisocyanate. To chloroform (15 mL, viscosity modified with polyisobutylene (20% w/v, MW 80 000)) and Span 85 mixture (2% w/v) stirred at 1500 rpm with a magnetic stirrer, the disperse phase (0.167 g/mL PEI in 3 mL of methanol) was added at once. After 2 min of stirring, 2,4-tolylene diisocyanate (TDI, 1.0 mL, in 2.0 mL of chloroform) was added at once and the stirring was reduced to 500 rpm. Polymerization took place instantly, and a big lump of polymer that formed stopped stirring. Obtained polymer was washed with chloroform and analyzed.

Microcapsule Preparation from Methanol-in-Oil Emulsion for DOE Studies.[19] To cyclohexane (15 mL, viscosity at low [−1] level or high [+1] level) and Span 85 mixture (2% v/v) stirred (at low [−1] level or high [+1] level) with a magnetic stirrer, the disperse phase (at low [−1] level or high [+1] level for PEI concentration, at low [−1] level or high [+1] level for volume of the disperse phase) was added at once. After 2 min of stirring, 2,4-tolylene diisocyanate (at low [−1] level or high [+1] level for TDI concentration in cyclohexane−total volume 3 mL) was added at once and the stirring was reduced to 500 rpm. After 10 min, polymerization was stopped by the addition of cyclohexane (30 mL). The resulting capsules were left to settle, further washed with hexanes, and finally vacuum-dried.

Acknowledgment. We thank Dreyfus and Beckman Foundation, NSF (Sensors), NSF-MRSEC (CCMR), ARO MAP-MURI, NYSTAR, and 3M for support.

Supporting Information Available: DOE parameter levels, DOE statistical analysis, values of variables for tested formulations, and relevant equations used. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Thies, C. In *Drugs and the Pharmaceutical Sciences*; Benita, S., Ed.; Marcel Dekker: New York, 1996; Vol. 73, pp 1−19.

(2) (a) Bakhshaee, M.; Pethrick, R. A.; Rashid, H.; Sherrington, D. C. *Polym. Commun.* **1985**, *26*, 185−192. (b) Green, B. K.; Schleicher, L. U.S. Patent 2800457, 1957; *Chem. Abstr.* **1957**, *51*, 87338. (c) Scher, H. B.; Rodson, M.; Lee, K.-S. *Pest. Sci.* **1998**, *54*, 394−400. (d) Chang, T. M. S. *Artificial Cells*; Charles C. Thomas: Springfield, 1972. (e) Tsuji, K. In *Microspheres Microcapsules & Liposomes*; Arshady, R., Ed.; Citus Books: London, 1999; Vol. 1, pp 349−371.

(3) Arshady, R. In *Microspheres Microcapsules & Liposomes*; Arshady, R., Ed.; Citus Books: London, 1999; Vol. 1, pp 93−96.

(4) (a) Ley, S. V.; Ramarao, C.; Gordon, R. S.; Holmes, A. B.; Morrison, A. J.; McConvey, I. F.; Shirley, I. M.; Smith, S. C.; Smith, M. D. *Chem. Commun.* **2002**, 1134−1135. (b) Broadwater, S. J.; Roth, S. L.; Price, K. E.; Kobašlija, M.; McQuade, D. T. *Org. Biomol. Chem.* **2005**, *3*, 2899−2906. (c) Kobašlija, M.; Poe, S. L.; McQuade, D. T. The Sum is Greater Than the Parts: Controlling Product Outcome Using a Multi-Catalyst System. *Angew. Chem., Int. Ed.*, submitted for publication.

(5) (a) Cameron, N. R.; Sherrington, D. C. *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 1543−1547. (b) Imhof, A.; Pine, D. J. *J. Colloid Interface Sci.* **1997**, *192*, 368−374. (c) Jaitely, V.; Sakthivel, T.; Magee, G.; Florence, A. T. *J. Drug Del. Sci. Technol.* **2004**, *14*, 113−117.

(6) (a) Shukla, P. G.; Sivaram, S. *J. Microencap.* **1999**, *16*, 517−521. (b) Bouchemal, K.; Briancon, S.; Chaumont, P.; Fessi, H.; Zydowicz, N. *J. Microencap.* **2003**, *20*, 637−651.

(7) Kamogawa, K.; Kuwayama, N.; Katagiri, T.; Akatsuka, H.; Sakai, T.; Sakai, H.; Abe, M. *Langmuir* **2003**, *19*, 4063−4069.

(8) Sah, H. *J. Controlled Release* **1997**, *47*, 233−245.

(9) Hyon, S.-H. *Yonsei Med. J.* **2000**, *41*, 720−734.

(10) Ji, J.; Childs, R. F.; Mehta, M. *J. Membr. Sci.* **2001**, *192*, 55−70.

(11) (a) Arshady, R. *Colloid Polym. Sci.* **1992**, *270*, 717−732. (b) El-Aasser, M. S.; Sudol, E. D. In *Emulsion Polymerization and Emulsion Polymers*; Lovell, P. A., El-Aasser, M. S., Eds.; Wiley: New York, 1997; pp 38−42.

(12) (a) Singh, B.; Kumar, R.; Ahuja, N. *Crit. Rev. Ther. Drug Carrier Syst.* **2005**, *22*, 27−105. (b) Singh, B.; Dahiya, M.; Saharan, P.; Ahuja, N. *Crit. Rev. Ther. Drug Carrier Syst.* **2005**, *22*, 215−293.

(13) Laird, T. *Org. Proc. Res. Dev.* **2002**, *6*, 337. For a comprehensive description on DOE use in optimization and model building in organic chemistry, see: Carlson, R.; Carlson, J. E. In *Design and Optimization in Organic Synthesis*; Elsevier: New York, 2005.

(14) Design-Expert Version 7, Stat-Ease, Inc., www.stat-ease.com.

(15) (a) Calabrese, R. V.; Chang, T. P. K.; Dang, P. T. *AIChE J.* **1986**, *32*, 657−666. (b) Stone, H. A. *Annu. Rev. Fluid Mech.* **1994**, *26*, 65−102.

(16) Taylor, G. I. *Proc. R. Soc. London A* **1934**, *146*, 501−523.

(17) Pangborn, A. B.; Giardella, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518−1520.

(18) Eastoe, J.; Nave, S.; Downer, A.; Paul, A.; Rankin, A.; Tribe, K. *Langmuir* **2000**, *16*, 4511−4518.

(19) See the Supporting Information for values of low [−1] and high [+1] levels.

MA061455X