ABSTRACT

**AN EXTENDED DURATION OPERATION FOR
SOLID HOLLOW FIBER COOLING CRYSTALLIZATION METHOD**

by
Chi Jin

As recently demonstrated by Chen et al. [1], the solid hollow fiber cooling crystallization method to achieve continuous polymer coating/encapsulation of submicrometer particles, has advantages of no problem with high pressure, easy scale-up and production of free-flowing coated particles. There is a concern whether this crystallization method can be applied for an extended duration coating process; it was not investigated in the previous study. Therefore, in order to examine this problem, in this work, the duration of the whole crystallization coating process has been greatly extended from 5 min to 60 min and 120 min. For the purpose of being comparable to the experiments of Chen et al. [1], Eudragit RL 100 was chosen as the coating polymer and Cosmo 55 (550nm silica particles) as the host core for the coating process in an acetone solution. The feeding and cooling process were exactly the same as in the previous research. Scanning electron microscopy and thermogravimetric analysis were employed to characterize the coated samples. The results showed that the solid hollow fiber cooling crystallization method had no problem in extended time running operation; the characterization of products indicated a stable product consistent with uniform and fine spherical shape; the thickness of the coating of the samples tended to be essentially identical as the coating process went through.

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by
Chi Jin

A Thesis
Submitted to the Faculty of
New Jersey Institute of Technology
in Partial Fulfillment of the Requirements for the Degree of
Masters of Science in Materials Science and Engineering

Interdisciplinary Program in Materials Science and Engineering

May 2015

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APPROVAL PAGE

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Chi Jin

Dr. Kamalesh K. Sirkar, Thesis Advisor	Date

Distinguished Professor of Chemical, Biological and Pharmaceutical Engineering, NJIT

Dr. N. M. Ravindra, Committee Member	Date

Professor and Director of Materials Science and Engineering Program, NJIT

Dr. Piero M. Armenante, Committee Member	Date

Distinguished Professor of Chemical, Biological and Pharmaceutical Engineering, NJIT

BIOGRAPHICAL SKETCH

Author: Chi Jin

Degree: Masters of Science

Date: May 2015

Undergraduate and Graduate Education:

- Masters of Science in Materials Science and Engineering,
  New Jersey Institute of Technology, Newark, NJ, 2015

- Bachelor of Science in Materials Science and Engineering,
  Shenyang University of Technology, Shenyang, P. R. China, 2013

Major: Materials Science and Engineering

I would like to dedicate my thesis to
my beloved family for the love and support, and
my lovely girlfriend CQF for being by my side all the way!

ACKNOWLEDGMENT

I am using this opportunity to express my gratitude to everyone who supported me all the way throughout this thesis. I am thankful for their aspiring guidance, invaluably constructive criticism and friendly advice during the project work. I am sincerely grateful to them for sharing their truthful and illuminating views on a number of issues related to the thesis.

I express my warm thanks to Prof. Kamalesh K. Sirkar and Mr. Dengyue Chen for their support and guidance during the whole process.

I would also like to thank Prof. N.M. Ravindra from the materials science project and all the people who provided me with the facilities being required and conducive conditions for my thesis project.

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CHAPTER 1

INTRODUCTION

1.1 Objectives

The objective of this thesis is to investigate the extended duration performance of the method of continuous polymer coating of submicrometer and nanometer particles by the solid hollow fiber cooling crystallization technique and find out whether this novel particle coating/encapsulation method is stable and reliable in long duration operation and to indicate whether the process produces a consistent product.

1.2 Background Information

Drug delivery systems are widely researched and developed to improve the delivery of pharmaceutical compounds and molecules. There are many drug delivery systems: (i) microparticle-based depot formulations, (ii) nanoparticle-based cancer drugs, (iii) transdermal systems, (iv) oral drug delivery systems, (v) pulmonary drug delivery, (vi) implants and (vii) antibody－drug conjugates [2]. Nanoparticle-based drug delivery platforms have received considerable attention as they can provide sustained release, cellular targeting, and even intrinsic antimicrobial or adjuvant properties that can improve the potency and efficacy of prophylactic and therapeutic modalities [3].

Nanoparticles based on gelatin, one of the most versatile natural biopolymers, are used for gene delivery system due to its biocompatibility, biodegradability, low cost and numerous available active groups for attaching targeting molecules [4]. With the cargo of

the anticancer drugs, nanoparticle drug delivery system shows conspicuous advantages of higher selectivity, reduced toxicity, longer clearance times, and increased efficacy compared to conventional systemic therapeutic approaches [5]. As for antibiotics delivery application, nanoparticle drug delivery system (1) provides protection to antibiotics against environmental deactivation and alter antibiotic pharmacokinetics and biodistribution, (2) overcomes the tissue and cell barriers and deliver antibiotics into very dense tissues and inaccessible target cells, (3) can be modified to target or respond to particular tissues, cells, and even bacteria, and thereby facilitate the selective concentration or release of the antibiotic at infection sites, respectively [6]. An even more common application is to provide protection of the drug from stomach acids.

Polymeric materials, often biodegradable, are frequently used to provide protection cargo for the drug and control over drug release. Poly (lactic-co-glycolic) acid (PLGA), poly (lactic acid) (PLA) and polyglycolic acid (PGA) are perhaps the most commonly studied polymers due to their versatility in tuning biodegradation time and high biocompatibility arising from their natural by-products, lactic acid and glycolic acid [2]. By appropriate engineering methods, these polymeric materials can be coated on the nanosize drug particles, like a protection shield, to overcome the barriers in the human body environment, allowing sustained drug delivery to specific target to enhance therapeutic effect.

Chong et al. [7] applied a modified supercritical antisolvent (SAS) method to fabricate nanoparticles using carbon dioxide as the supercritical fluid (SCF), in which the fumed silica had been coated and 50 nm diameter of nanoencapsulated acetaminophen had been produced. The main principle of the supercritical antisolvent (SAS) process is

that the mutual diffusion of organic solvent in supercritical CO_2 produces phase separation, in which the solute is able to be precipitated.

Ratcharak et al. [8] applied rapid expansion of supercritical CO_2 solution (RESS) method to encapsulate poly (trifluoroethyl enthacrylate) on substrate to improve hydrophobicity. Rapid expansion of supercritical method was also used by Ovaskainen et al. [9] but combined with electrostatic deposition (RESS-ED). With the help of electrostatic deposition treatment, larger and thinner coatings were produced with a more averaged surface coverage of the created polymer particles compared to spraying without the applied voltage. In the RESS process, both the coating material and the material to be coated are dissolved in supercritical CO_2. When rapid de-pressurization is introduced into the supercritical solution, a very high supersaturation of solute is produced due to the CO_2 experiencing substantial phase transition into gas. As the solvent, the supercritical CO_2 becoming less and less, the coating material and the host particles will precipitate out and combine with each other to finish the coating process.

Besides, other effective approaches, including various emulsion and double emulsion methods, have been studied extensively for the fabrication of microparticles and nanoparticles used for coating or encapsulation and controlled drug release and delivery. By using the double emulsion method, Chen et al. [10] prepared PLGA nanoparticles carrying antibody to enhances anti-tumor cytotoxic T cell responses, in which the samples were shown to have an average diameter of 86 nm with a loading efficiency of 25%. The general emulsion techniques can be considered to consist of following four steps: (1) preparing the solution of polymer in an organic solvent (maybe with some active agent to make the solution biocompatible); (2) dispersing the polymer solution into

the dispersion medium under stirring; (3) stabilizing under certain condition, like temperature, pH, or surfactants or emulsifiers; (4) evaporating the organic solvent, during this process the polymer will precipitate out to finish the coating process.

However, these methods like SAS, RESS and emulsion all have their own limitations. The notorious drawbacks of emulsion technique are residual organic solvent in the final products, volatilization of organic compounds, and heavy downstream processing. Supercritical CO_2-based process requires a very high pressure operating condition (~190MPa); although SAS processes require much lower pressure at ~10 MPa, it is still high [11]. The application of the RESS process is seriously restricted by the solubility of the polymer in supercritical CO_2 at temperature below 80 ^{o}C. As a novel idea for micro/nano meter particles coating process, solid hollow fiber cooling crystallizer (SHFCC), has great advantages of producing free-flowing coated particles without any need for high pressure; it can be easily scaled up and employs a simple experimental setup.

1.3 Solid Hollow Fiber Cooling Crystallizer (SHFCC)

Chen et al. [1] proposed a novel idea, recently, to achieve continuous polymer coating or encapsulation of submirometer particles by using solid hollow fiber cooling crystallization (SHFCC), which practically can be also applied to nanoparticle coating process [12]. Figure 1.1 illustrates the fundamental working process of this novel crystallizer at a single fiber level. The internal diameter of a single solid hollow fiber is 420 μm and the outer diameter is 570 μm. The polymer (coating material) solution with suspended silica particles is fed through the lumen side of the solid hollow fiber, while an appropriate cooling solution is circulated through the shell side of the solid hollow fiber

in a countercurrent mode. In the experiment, a bundle of such solid hollow fibers, normally 20 or 40 according to the amount of the expected production rate, would be assembled together into one device, as shown in Figure 1.2. Therefore, the scale-up problem can be solved easily by adding more hollow fibers and enlarging the diameter of the tubular shell, which is a major strength of SHFCC devices. In such an arrangement, the polymer solution with suspended silica particles, subdivided into numerous fluid packets, travels through each hollow fiber with the same velocity and under the same cooling conditions [13]. As the temperature gets reduced, the polymer will precipitate out from the solution to finish the coating step on the silica particles in each fiber under the same conditions leading to a narrow crystal size distribution (CSD).
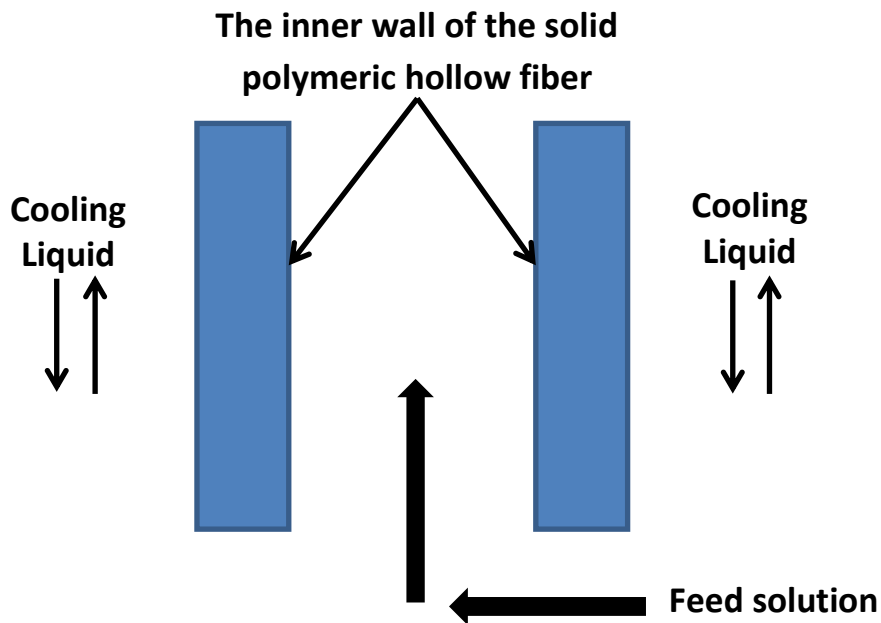

Figure 1.1 Solid hollow fiber cooling crystallization (SHFCC): operating principle.

The material of the polymeric hollow fiber is polypropylene (PP) which has considerable chemical, pH and solvent resistance. A diversity of other polymers, like

poly(tetrafluoroethylene) (PTFE), polyimide, and so on, can be used to replace PP; the polymer PP in hollow fiber form is particularly fitting due to the smooth and nonsticky surfaces, which will guarantee that the accumulation of the precipitating particles or crystals must not stick to the fiber internal surface as long as the solution is flowing. Even if a few hollow fibers get accidentally stuck by the agglomeration of the silica or polymer precipitation, the influence to the rest of the solid fibers is not much since each hollow fiber acts as an independent crystallizer. Further there are many hollow fibers in the tubular shell to insure the effectiveness of the whole coating process.
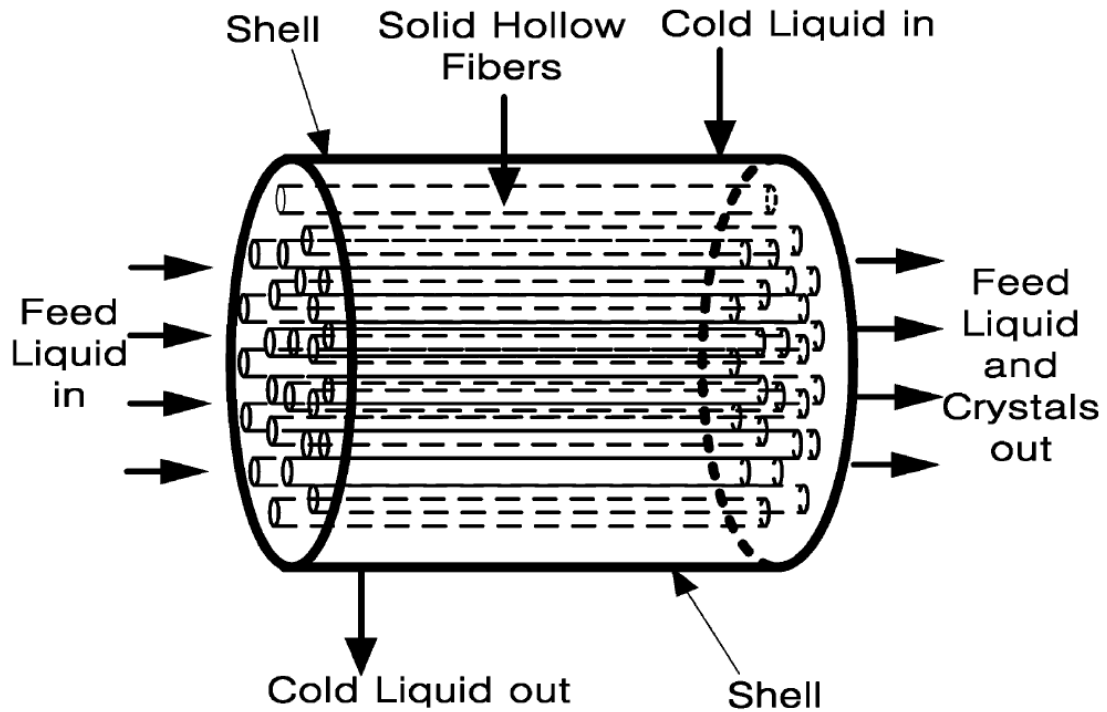

Figure 1.2 Schematic of multiple fiber containing solid hollow fiber crystallizer.

One of the key points of this solid hollow fiber crystallizer is that the change of the polymer solubility follows the change of temperature—the lower the temperature, the lower the polymer solubility in the solution, then the easier the coating operation. In this

case, a highly efficient heat exchanger would be necessary to enhance the precipitation of the polymer to guarantee the efficiency of the coating process. This is exactly what solid hollow fiber cooling crystallizer can offer due to the large surface/volume ratio. This salient feature facilitates accurate control of the temperature difference between the crystallizing solution and the cooling solution. Therefore, it can be used to control the rate at which supersaturation of the polymer solution is generated and to make the coating process much easier and more efficient. Zarkadas and Sirkar [14] experimentally demonstrated this distinguishing feature of the cooling crystallizer device, named as polymeric hollow fiber heat exchanger (PHFHE), which can be fittingly applied to both aqueous and organic solutions. In their experiment, each of KNO_3 and paracetamol [15] was individually crystallized from an aqueous solution, and salicylic acid from ethanol— organic solution. As the result illustrated, CSDs were much narrower, and the average crystal sizes were 3-4 times smaller than those products from conventional crystallizer.

In a previous study, Chen et al. [1] used Eurdragit RL 100 and PLGA poly(D,L-lactide-co-glycolide) as coating materials. Cosmo 55 nanoporous hydrophilic silica particles with the diameter of 550 nm were taken as the surrogate host particles. Acetone, an excellent solvent for both Eurdragit RL 100 and PLGA, was employed as the solvent. Technically, the experimental coating processes were divided into two parts to examine the function and effectiveness of this method: a small module with 23 solid hollow fibers in an 8mm diameter shell tube and a larger module with 46 solid hollow fibers in a 14 mm diameter tubular shell. The results indicated that the silica particles had been successfully coated by the polymer in each case. Especially from the STEM micrographs, a uniform, thin coating was perfectly displayed, covering the silica particles.

Meanwhile the coating characterizations for both of the modules were very similar. The thickness of the coating calculated based on the TGA results was 33.1 nm for the large module and 33.3 nm for the small module, which demonstrated the scale-up process was easy to implement in this technique.

However, one problem that has not been addressed from the former experiments: the running time. The duration of the running operation of coating process for both 550 nm diameter and 12 nm diameter silica particles [12] was between 5-10 min. One wonders whether this technique could be applied for a longer and an even longer operation, like 60 min or even 120 min; if it were indeed suitable for such longer running operation, whether the characterizations of the samples, like the coating thickness, the particle size distribution, are stable, integral and consistent. Therefore, this thesis is going to address these problems and concerns mentioned above. A longer running operation from 60 min to 120 min has been studied to explore the development potential of this novel coating/encapsulation process.

CHAPTER 2

MATERIALS AND METHODS

2.1 Materials

Coating polymers were Eudragit RL 100 (copolymer of ethyl acrylate, methyl methacrylate, and a low content of methacylic acid ester; M_w, 150,000; Evonikdegussa, Parsippany, NJ, USA). Host silica particles were Cosmo 55 nonporous hydrophilic silica particles with diameter of 550 nm, (Presperse, Somerset, NJ, USA). Acetone, an excellent organic solvent for Eudragit RL 100, was obtained from Fisher. Sodium dodecyl sulfate (SDS), used as a surfactant, was purchased from Aldrich. 50% by volume of ethylene glycol was applied as an aqueous cooling solution. All materials were used as received.

2.2 Experimental Preparation

The experiments aimed to figure out whether the SHFCC (solid hollow fiber cooling crystallization) is a stable and reliable coating/encapsulation method in an extended duration operation. So except for extending the amount of experimental materials, there is no difference in the conditions and module with those of the former experiment. A total number of 23 polypropylene solid hollow fibers having length of 30 cm length and fluorinated ethylene propylene (FEP)-based polymer tube were applied to the experiment setup.

The specific contrast for the amount of the material used between the previous research and this thesis is showed as Table 2.1. The samples were collected every 10min

for 60 min process and every 20 min for 120 min process. The 60 min long experiment was operated in a very different manner from the 120 min long experiment. In the third experiment all of the material was mixed in one 1000 ml Erlenmeyer flask, while for the second one, the 280 ml acetone and 56 ml water were divided into three 100 ml Erlenmeyer flask and one 50ml Erlenmeyer flask (showed in Table 2.2 below).

Table 2.1 Materials Used in Experiments

Materials	Acetone	Eudragit RL 100	Silica 550 nm	SDS	Water
Previous	20 ml	2.4 g	0.4 g	0.023 g	4 ml
60 min extension	280 ml	33.6 g	5.6 g	0.322 g	56 ml
120 min extension	500 ml	60 g	10 g	0.575 g	100 ml

Table 2.2 Treatment for 60 min Long Experiment

Materials	Acetone	Eudragit RL 100	Silica 550 nm	SDS	Water
100 ml bottle	80 ml	9.6 g	1.6 g	0.092 g	16 ml
50 ml bottle	40 ml	4.8 g	0.8 g	0.046 g	8 ml

The reason for this treatment is to reduce the influence of acetone volatilization and the uneven distribution of suspended silica particles. In the experiment, the flasks were kept in the 45 $^{\circ}$C water bath and there was no way to seal the bottle perfectly so that the acetone volatilization was unavoidable, which would change the concentration of the

polymer solution and the ratio of silica suspension; impact the thickness of the coating on the particle (this will be specified in Chapter 3).

2.3 Experimental Method

Figure 2.1 indicates a schematic diagram of the experimental setup for SHFCC coating/encapsulation process. A flask containing the polymer solution and suspended silica was kept in the water bath at temperature of 45 ^{o}C. Meanwhile, a magnetic stirrer was set under the water bath to make sure that the suspended silica wouldn't agglomerate or cluster at the bottom of the flask. The experimental setup was not far for that used for the 60 min one. All three 100 ml flasks and one 50 ml flasks were kept in the water bath at the same temperature. The bottles of polymer solution with suspended silica particles would be applied one by one.

When the experiment was started, the well-mixed solution was fed into the lumen side of the SHFCC by a pump (Masterflex, model no. 7523-20, Cole-Parmer, Vernon Hills, IL, USA) at a rate of 5 ml/min. At the same time, a chiller (Polystat CR250WS, Cole-Parmer) was introducing the cooling solution to the shell side of the SHFCC. The temperature of the cooling solution—50% by volume of ethylene glycol, was set up and kept at −10 ^{o}C before the operation start. In this case, the feeding solution in the lumen side would be cooling down to around 2-5 ^{o}C to trigger the polymer precipitation out from the acetone solution.

The samples would be collected once every 10 min for 60 min long experiment and every 20 min for 120 min long experiment. Vacuum filtration method was employed to collect samples of coated particles from the polymer solution for both experiments.

When the coated particles and solution came out of the SHFCC devices, the redundant acetone solution could be removed and left the coated silica samples behind on the filter paper by the vacuum filtration treatment (Omnipore membrane; PTFE (Catalog No. JHWP09025); 0.45 µm pore size; 90 mm filter diameter; Millipore, Billerica, MA, USA). After filtration, coated silica samples on the filter paper was then placed into DI water under sonication for about 30s to break up the loose agglomeration or cluster. The liquid containing the dispersed particles was then placed onto aluminum sample pins—sample holders and subjected to vacuum drying.
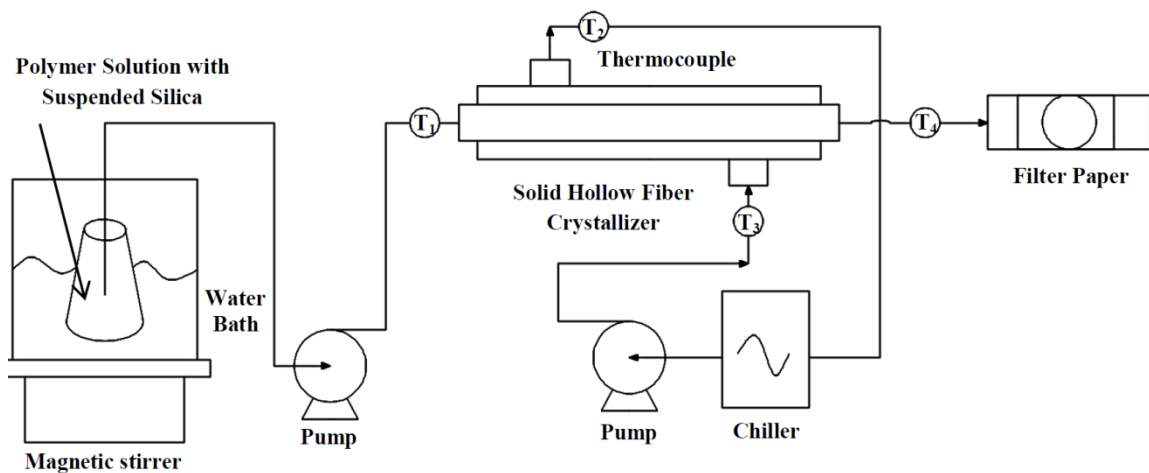

Figure 2.1 A schematic diagram of the experimental setup for SHFCC coating/encapsulation process.

2.4 Cloud Point Determination of Eudragit RL 100

Before the coating experiment operation in the SHFCC, it is necessary to determine a useful concentration level for the polymer solution in acetone. If the solution concentration is too low, it will harm the effectiveness of the coating process. Further it may be that the polymer coating cannot completely cover the whole spherical silica particle. On the other hand, at higher concentrations of the solution, the issue of

agglomeration/cluster development in the sample and redundant polymer in the final sample will appear. Besides, the polymer will precipitate out quickly at high concentrations with very high possibility of blocking the pump tube. Therefore, an appropriate concentration contributes a lot to the success of the experiment.

According to the cloud point experiment of Chen et al. [1], although the UV test of transmissivity decreased for the polymer solution as the temperature was going down, there was no specific cloud point for the Eudragit RL 100. The polymer precipitated out from the acetone continuously as the temperature was going down. It means that the UV spectrometer transmissivity will go down continuously as the temperature of the polymer solution was being reduced. In this thesis, 0.16 g/ml, provided by Chen et al. [1], was taken as a reference cloud point at room temperature and also an estimated concentration for the solution in the experiment. Concentrations of 0.1 g/ml, 0.12 g/ml, 0.14 g/ml, 0.16 g/ml, 0.18g/ml, 0.2 g/ml would be examined in the UV transmissivity test to find out the most fitting one for this experiment. Pure acetone was taken as the baseline to reduce the impact of acetone; then the concentration programs were run to obtain transmissivity vs wavelength plots. The higher the transmissivity percent in the result plot, the clearer the solution. In this case, the polymer solution will have relatively low transmissivity while precipitation proceeded.

A Cary 50 UV spectrophotometer (Agilent, Santa Clara, CA, USA) with a temperature control module was used in the present study. By identifying the transmissivity of the solution in the visible wavelength range (550-800 nm), the cloud point can be easily examined; also the concentration can be obtained accordingly.

2.5 Characterization of Submicrometer Particles

A scanning electron microscope (LEO 1530 Gemini, Zeiss, and Thornwood, NY, USA) was employed for morphological observations of the coated silica particles. To characterize the coating covering the submicrometer silica particles, it is necessary to cover these sample with a very thin layer of carbon to make the sample conductive enough to get a clear surface image. If not, charging would occur on the surface of the specimen with poor electrical conductivity, leading to distortion or noise on the image.

A thermogravimetric analyzer (Pyris I, PerkinElmer, Waltham, MA, USA) was used to determine the amount of coating on the sample particles. According to the weight loss percentage of each sample, one can estimate a uniform coating thickness by calculation. This will be used as a major evidence for the judgement of the continuing reproducibility for this novel coating/encapsulating technique.

CHAPTER 3

RESULTS AND DISCUSSION

The results of concentration determination are discussed first for the ternary (polymer/water/solvent) system. The detailed characterization of the coated particles from different process durations is provided by means of SEM and TGA. Future research directions are discussed at the end.

The binary system of polymer/solvent is not presented in this thesis, since the cloud point at room temperature was already determined in previous study. Besides, due to the limitation of the lowest temperature (about 10 $^{\circ}$C) of the UV equipment, the precipitation of Eudragit RL 100 was not easy to achieve at low concentrations (lower than 0.16 g/ml); an even higher concentration made no sense to the experimental process. In this case, to improve the effectiveness of the polymer precipitation, water (as antisolvent) was added to the polymer solution to improve the cloud point temperature of the solution and facilitate the precipitation of the polymer. Thus the ternary system of polymer/solvent/water was employed to find out an appropriate concentration for further experiment.

3.1 Polymer/Solvent/Water Ternary System for Concentration Determination

A certain amount of water, 10%-20% by volume, was added to the Eudragit RL 100 solution in acetone at concentrations of 0.12 g/ml, 0.16 g/ml, 0.2 g/ml. At the same concentration compared to the polymer solution in pure acetone, if additional water was added, more polymer would precipitate out at same temperature; further the solution

viscosity would be lower to make it easier to flow in the solid hollow fiber and the pump tube. Another importance of this approach is that low viscosity can guarantee that the filtration on the filter paper takes place rapidly.

The results of the UV test for the concentration of 0.12 g/ml and 0.16 g/ml are shown in Figure 3.1 and 3.2, respectively. An amount of water of 20% by volume was added to the 0.12 g/ml solution and 10% of water was added to the 0.16 g/ml solution. The transmissivity went down as the temperature was decreased. The polymer would precipitate out of acetone continuously during the cooling process. When transmissivity fell lower than about 40%, the precipitation of the polymer would become relatively obvious and could be figured out visually. The solution would appear cloudy at about 10 ^{o}C for the solution at concentration of 0.12 g/ml, while for the solution at concentration of 0.16 g/ml, this would show up at about 25 ^{o}C. At even lower temperature of 15 ^{o}C to 10 ^{o}C, the 0.16 g/ml solution would show significant precipitation and become milky. In this case, the transmissivity percentage would fall down to near 10%, as shown in Figure 3.2. Clearly, additional water can facilitate the precipitation process effectively. Even though the polymer precipitation was facilitated apparently, the issue of viscosity still cause problem. Operations were suspended several times for the pump tube blockage in the experiments of the 0.16 g/ml concentration solution.

However, this promotion by antisolvent was not always favorable. For the solution at concentration of 0.2 g/ml, the solution would become cloudy as soon as additional water was added, even at a temperature of 30 ^{o}C. In the experiment process, the feeding solution would be cooling from 40 ^{o}C to −10 ^{o}C. In this case, if such solution had been used as the feeding solution, there was a great chance that the pump tube and

connection between the tube and the experiment device would be clogged by the polymer. Since the inner diameter of the tube and the joint part was just 1.6 mm, the polymer was viscous enough to adhere and clog the connecting part.

At a concentration of 0.12 g/ml with addition 10% of water by volume, the transmissivity percentage was always higher than 80% in the temperature range of $40\,^{\circ}\text{C}$ to $10\,^{\circ}\text{C}$. Therefore, additional 10% of water is not enough to accelerate the precipitation process of the solution at concentration of 0.12 g/ml. For the concentration of 0.2 g/ml polymer solution, redundant polymer was found in the final samples, which is definitely unfavorable for the experiment (as shown in Figure 3.3 (a)). The solution at concentration of 0.16 g/ml with additional 20% had the same issue with the 0.2 g/ml concentration solution, although it was a little bit better. Figure 3.3 (b) shows the SEM image of the final products at concentration of 0.12 g/ml with additional 20% of water, in which silica particles were covered by the polymer with fine spherical shape. Comparing with Figure 3.3 (a), obviously, the condition of the samples in Figure 3.3 (b) is much better on every aspect. Therefore, a concentration of 0.12 g/ml with additional 20% of water (antisolvent) was chosen and applied for further experiment and examination.
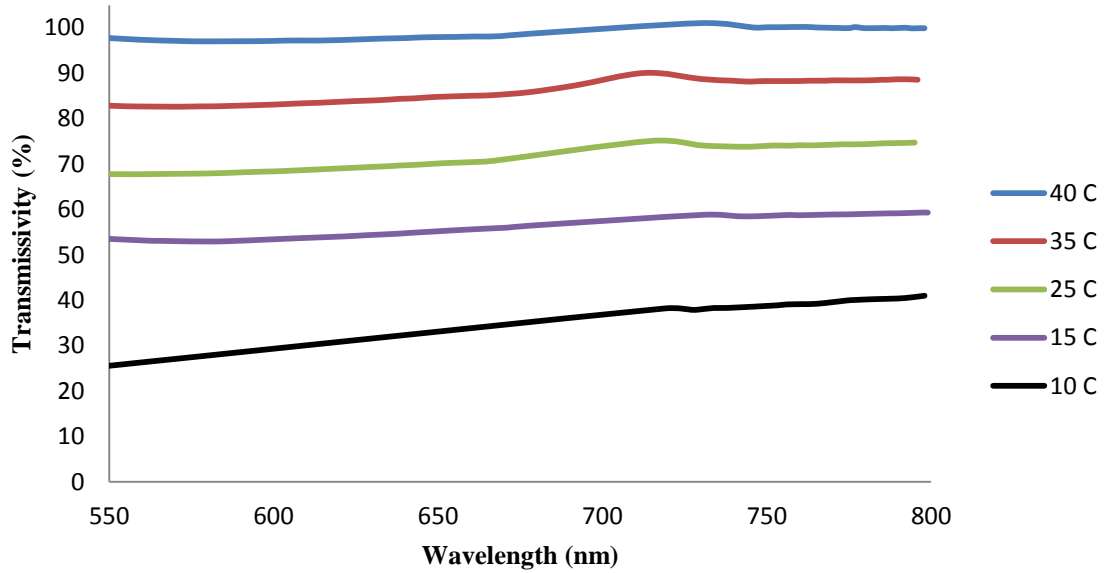
Figure 3.1 Transmissivity percentage of Eudragit RL100 acetone solution with 20% water at 0.12 g/ml.

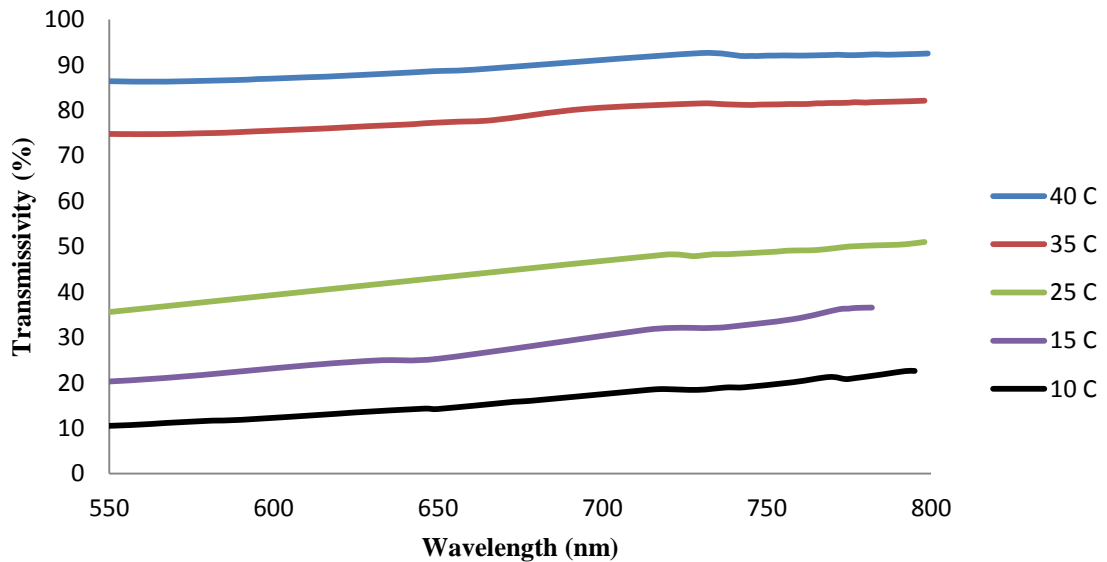**Figure 3.2** Transmissivity percentage of Eudragit RL100 acetone solution with 10% water at 0.16 g/ml.

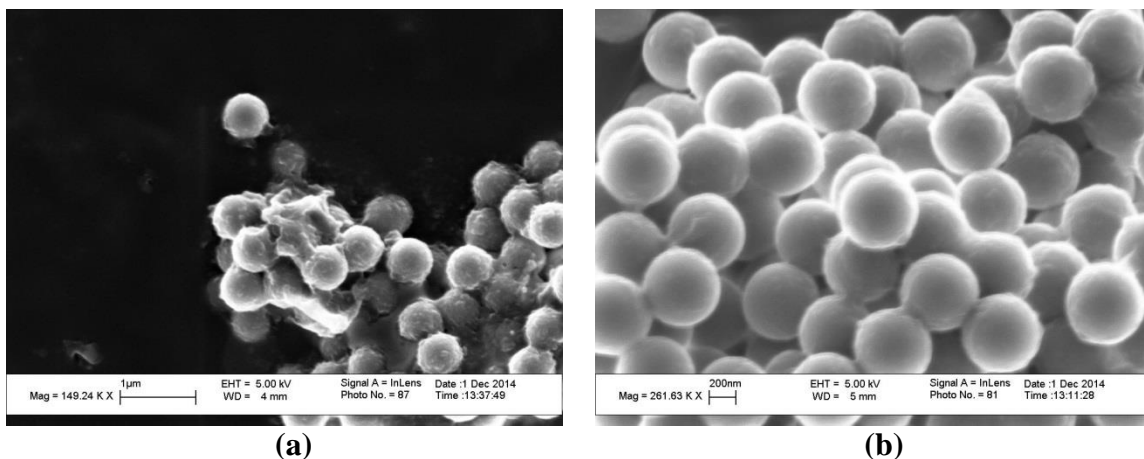**(a)**   **(b)**

Figure 3.3 (a) SEM photographs of solution at concentration 0.2 g/ml with 10% of water and **(b)** solution at concentration 0.12 g/ml with 20% of water.

3.2 Thermogravimetric Analysis of the Particles

Thermogravimetric analysis (TGA) is a method of thermal analysis in which the change in mass of the sample is measured as a function of continuously increasing temperature. Dry coated and uncoated cosmo 55 silica particles were both analyzed by TGA. The temperature of TGA test was increased at a rate of 10 ^{o}C/min until it reached 550 ^{o}C and kept for 5 min. During this period, as a result of heating, the polymer coating would decompose while the uncoated silica remained unaffected. In this way, the amount of the coating by mass percentage of the samples will be obtained from TGA and the thickness of the coating on the sample from various processing duration can be estimated by equation. If products, produced by this technique, can have consistency in the coating thickness, then it would be fair to conclude that SHFCC is a stable and reliable process for microparticles coating/encapsulation.

Figure 3.4 illustrates the weight percent change of coated silica samples from the initial 80 min of the 120 min process. For the first 20 min, the amount of coating was stable at 10% by mass of the samples. However, as the procedure proceeded to 80 min,

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the amount of the coating would increase to 12%. This 2% increment was the result of the influence of the volatilization of acetone, which would increase the concentration of the polymer solution and suspension ratio of the silica. Since the boiling point of acetone is just 56 $^{\circ}$C and it would be rather easy for acetone to be lost from the solution by evaporation when it was kept in the water bath of 40 $^{\circ}$C; besides the magnetic stirrer was mixing the solution, which will make the volatilization issue more severe. Therefore, after another 20 min processing, the amount of the coating on the sample would increase to 15% due to the much higher polymer concentration (shown in Figure 3.5 the yellow line). The suspended silica would be greatly consumed in the previous processing (from 80 min to 120 min) and at the end of the experiment (after 120 min operation), as a result of lack of host particles, the amount of coating was reduced to 11% as shown in Figure 3.5 the black line.

To estimate the thickness deviation of the coating on samples from a variety of process durations, an assumption that the spherical silica particles of radius r were integrated and uniformly coated by the polymer was employed. Then the relation between the mass of the polymer and the mass of the particles is

$$\frac{m_{silica}}{m_{polymer}} = \frac{\frac{4}{3}\pi r^3 \rho_{silica}}{\frac{4}{3}\pi[(r+h)^3 - r^3]\rho_{polymer}} \tag{1}$$

The coating thickness h can be calculated as

$$h = r\left(1 + \frac{\rho_{silica} m_{polymer}}{\rho_{polymer} m_{silica}}\right)^{1/3} - r \tag{2}$$

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where m_{silica} and $m_{polymer}$ are the masses of the particles and polymer, and ρ_{silica} (2.65 g/ml) and $\rho_{polymer}$ (1.1 g/ml) are the respective densities. According to the result of TGA, the coating thickness for the final products under assumed conditions is showed in Table 3.1:

Table 3.1 The Coating Thickness of Samples from 120 min Process

Process time	6 min	20 min	40 min	60min	80 min	100 min	120 min
$m_{polymer}/m_{silica}$	0.109	0.114	0.141	0.150	0.139	0.177	0.127
Thickness (h)	22.2 nm	23.2 nm	28.2 nm	29.8 nm	27.8 nm	34.6 nm	25.6 nm
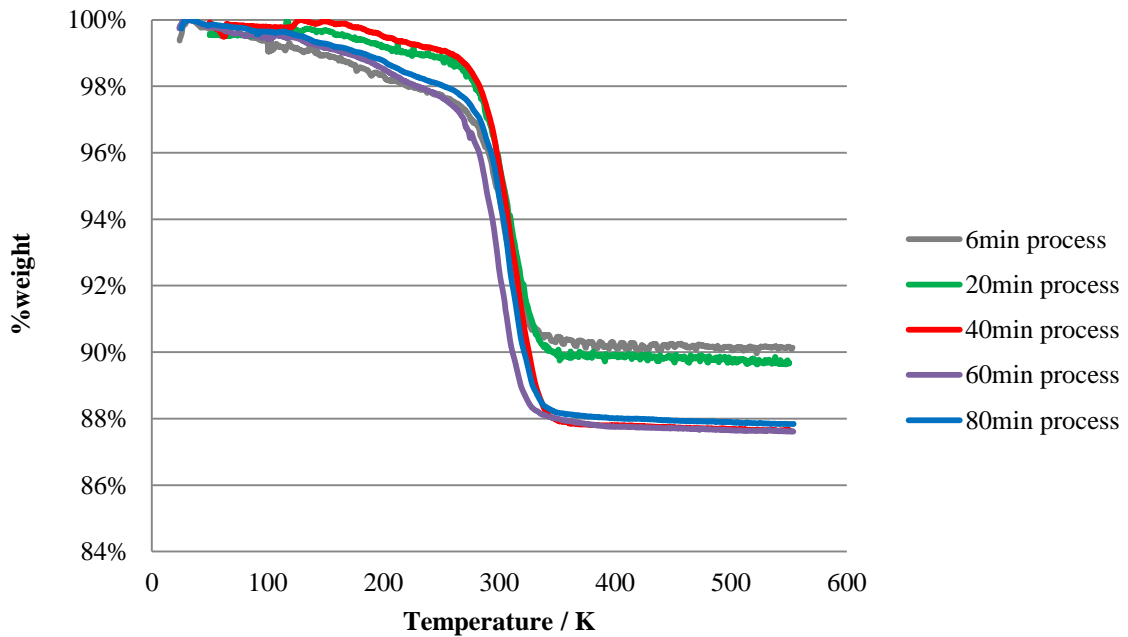
Figure 3.4 The percent weight change of coated silica samples for the first 80 min of a 120 min duration process.
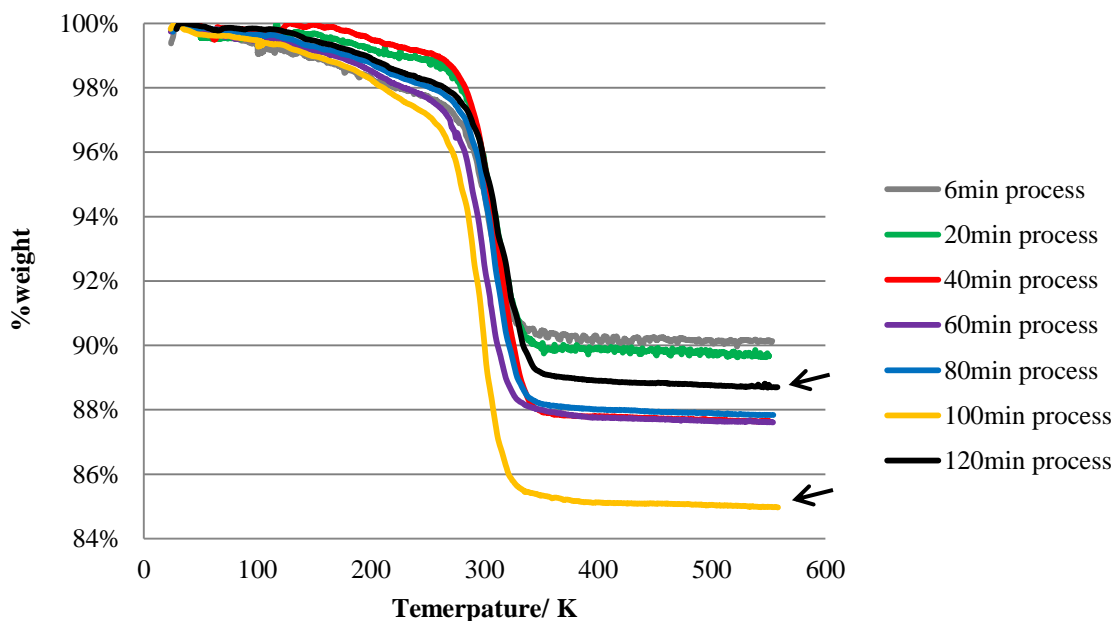
Figure 3.5 The percent weight change of coated silica samples for 120 min process.

From the calculation, the coating thickness ranges from 22.2 nm to 34.6 nm. Volatilization of the acetone is one of the reasons for this inconsistency. Another reason is the 1000 ml bottle used in the experiment, which would significantly influence the distribution of the suspended silica particles. The dimension of 1000 ml flask is divided into three parts: A, B, C, as shown in the Figure 3.6. Although, the polymer solution was under stirring, the silica particles were not evenly distributed in the bottle. Further, because the stirring would accelerate the volatilization of the acetone, the stirring rate was kept at a low level, which would make the uneven distribution of suspended silica worse. The amount of silica particles in part C is the highest and part B had more particles than part A. Thus, when the experiment came to the last 40 min (80 min to 120 min), much more silica particles would participate in the coating process. According to the former research, at the same polymer concentration, the more host particles were added, the thinner the coating. As the result, there would be less coating percentage in the

TGA results. However, at the same time due to volatilization of the acetone, the concentration of the polymer solution would be much higher than the previous duration. Therefore, more polymers would be precipitated out and cover these additional silica particles, which would increase the polymer percentage as shown in the TGA results. This would be another main reason for the products inconsistency.

In order to minimize the negative influences, another 60 min experiment was established with different preparation method. The total 340 ml polymer solution with suspended silica particles was divided into 4 bottles: three 100 ml bottles (11.5 cm in height and 6.4 cm bottom diameter) and one 50 ml bottle (8.3 cm in height and 5.1 cm bottom diameter). The three parts in the Figure 3.6 would be reduced in a small bottle, and because the bottle was much smaller, the magnetic stir could work well to mix the silica suspension even at a low stir rate. In this case, the issue of the uneven distribution of silica particles would be greatly relieved. Moreover, because of the small volume of the bottle, the volatilization of the acetone would be relatively suppressed. At last, the solution of each bottle would not be totally consumed in the experiment to avoid the high concentration of polymer and silica suspension in the bottom of the bottle (part C) at the end of the experiment.

As shown in the Figure 3.7, although the mass percentage of the coating still decreased as the experiment progressed, it would be relatively stable at around 14%; according to the coating thickness calculation in Table 3.2, the coating thickness is maintained at around 31.5 nm. Not exactly the same with each other, but much better than the results in the 120 min experiment. Therefore, using several small bottles instead

of a large one could relatively mitigate the issues of the acetone volatilization and the uneven distribution of suspended silica particles.

For both 120 min and 60 min experiments, at the initial stage of the experiments, the mass percentages of the samples from TGA results are relatively high: 90% for 120 min and 88% for 60 min. This could be the result of inadequate heating. Before the experiment started, the bottle would be kept in the water bath for 5 min, but apparently, the water bath is not efficient enough to heat 800 ml polymer solution in such short time. Beside, due to the volatilization of the acetone, it was not appropriate to keep the bottle in the water bath for an even long duration. In such situation, the polymer precipitation—coating process, was not as effective as the later the process. Thus, the coating thickness was relatively thin at the initial stages of the experiment.
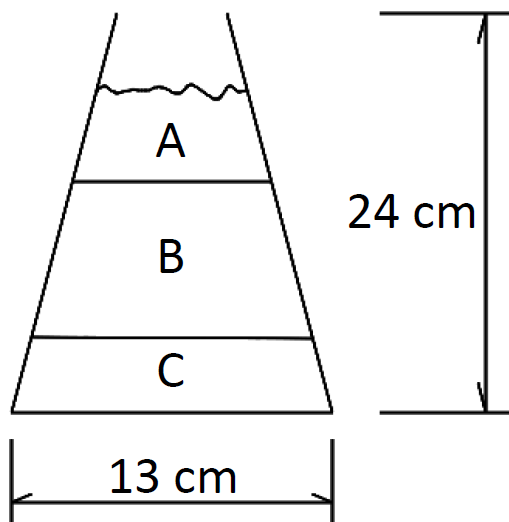
Figure 3.6 The dimension of 1000 ml flask.

Table 3.2 The Coating Thickness of Samples from 60 min Process

Process time	3 min	14 min	28 min	39 min	55 min
$m_{polymer}/m_{silica}$	0.138	0.158	0.161	0.166	0.162
Thickness (h)	27.6 nm	31.2 nm	31.7 nm	32.6 nm	31.9 nm
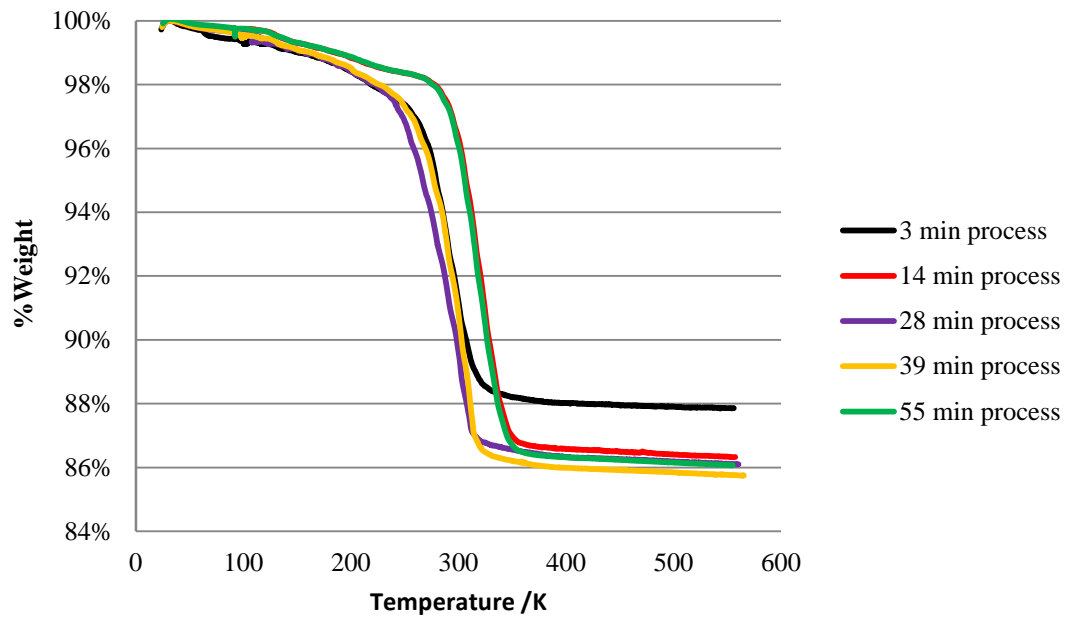
Figure 3.7 The percent weight change of coated silica samples for 60 min process.

(a)

(b)

(c)

(d)

(e)

(f)
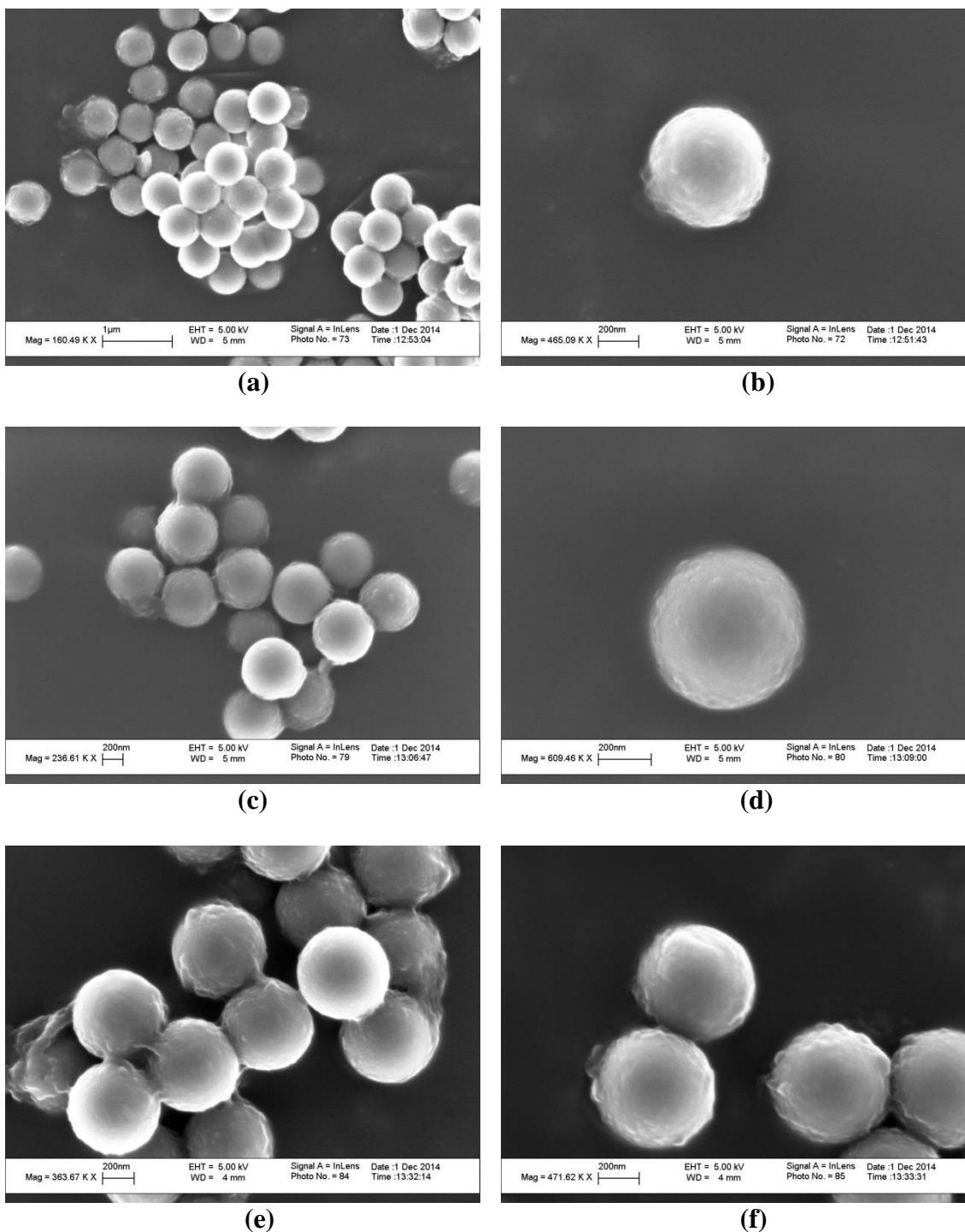
Figure 3.8 SEM images of the coated samples of 120 min operation: (a), (b) 40 min samples; (c), (d) 60 min samples; (e), (f) 80 min samples.

The SEM images of the coated silica samples from 120 min experiments are displayed in Figure 3.8: (a), (b) for samples of 40 min; (c), (d) for samples of 60 min; (e), (f) for samples of 80 min. Compared with the uncoated silica particles (Figure 3.9), the coated particles are all in fine spherical shape but with fuzzy surface shown on coated samples—polymer coating. There is no distinguishing difference between these samples from various duration of operation in the images and the issue of redundant polymer as shown in Figure 3.3 (a) is not found in all of the SEM results for both experiments. No difference could be found out from the SEM image between the 120 min and 60 min experiments, even though their coating thickness is not the same with each other. So the rest of SEM images of coated samples from 60 min and 120 min experiments would be presented in the appendix.
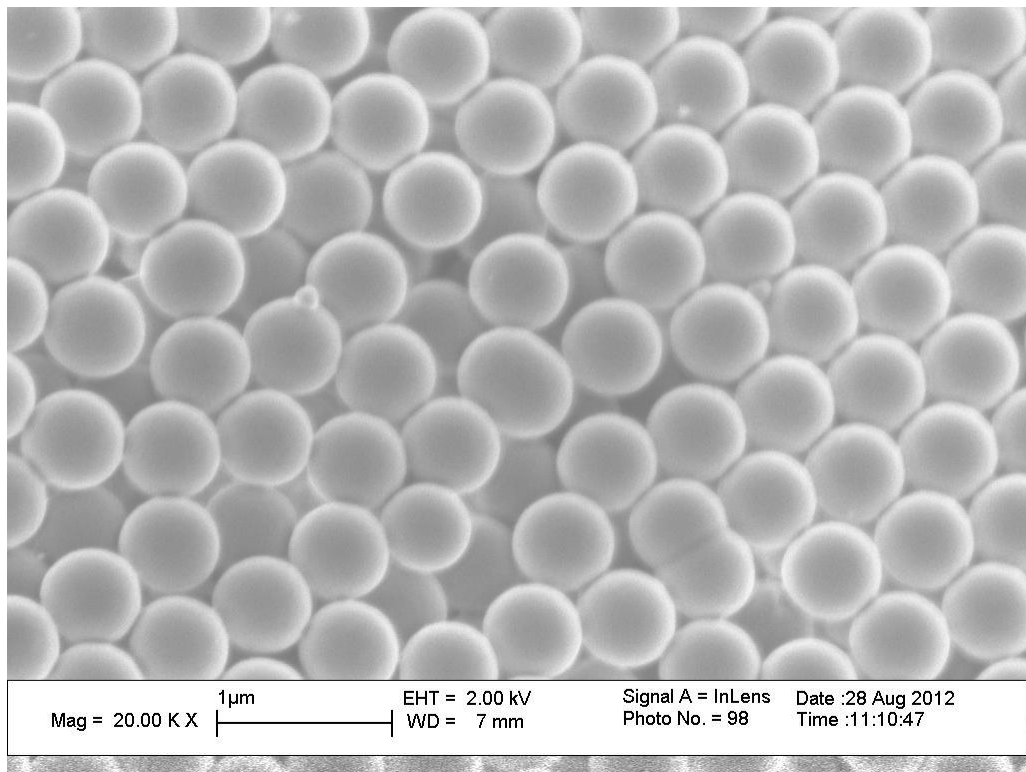

Figure 3.9 SEM image of uncoated silica particles.

CHAPTER 4

CONCLUSION

Extended duration experiments were set up for a novel coating/encapsulation method, solid hollow fiber cooling crystallization, to examine whether this technique can be applied to an extended duration coating process and to determine whether the process produces consistent products. The useful range of concentration of the polymer in the solution was determined based on the results of UV spectrophotometry from the polymer/acetone/water ternary system. A concentration of 0.12 g/ml with 20% water by volume was chosen for the further experiments and examinations. Water, as antisolvent, was added to accelerate the precipitation of the polymer, which would promote the effectiveness of the coating process. Moreover, with additional water, the viscosity of the polymer solution would be reduced and relatively low viscosity would guarantee smooth flowing of the solution.

Thermogravimetric analysis was used to examine the consistency of the final products. Based on the TGA results and calculation, the volatilization of the acetone and the uneven distribution of the suspended silica would cause significant deviation in the coating thickness. However, these issues can be essentially resolved by using smaller bottles to contain the solution separately. In this way, the deviation of the coating thickness would be reduced to 1.4 nm according to the calculation. Thus, if the two issues above can totally solved, the coating thickness should be exactly identical, since the silica particles are coated under the same condition. From Scanning Electron Microscopy results, the samples are displayed as uniform and fine spherical shape with fuzzy polymer

coatings. The issue of redundant polymer is not found in the image. Therefore, solid hollow fiber cooling crystallization, as a novel coating/encapsulation technique, is stable and reliable in the extended duration of coating process and produces consistent and integral coated products.

APPENDIX

SEM IMAGES FOR 120 MIN AND 60 MIN OPERATIONS

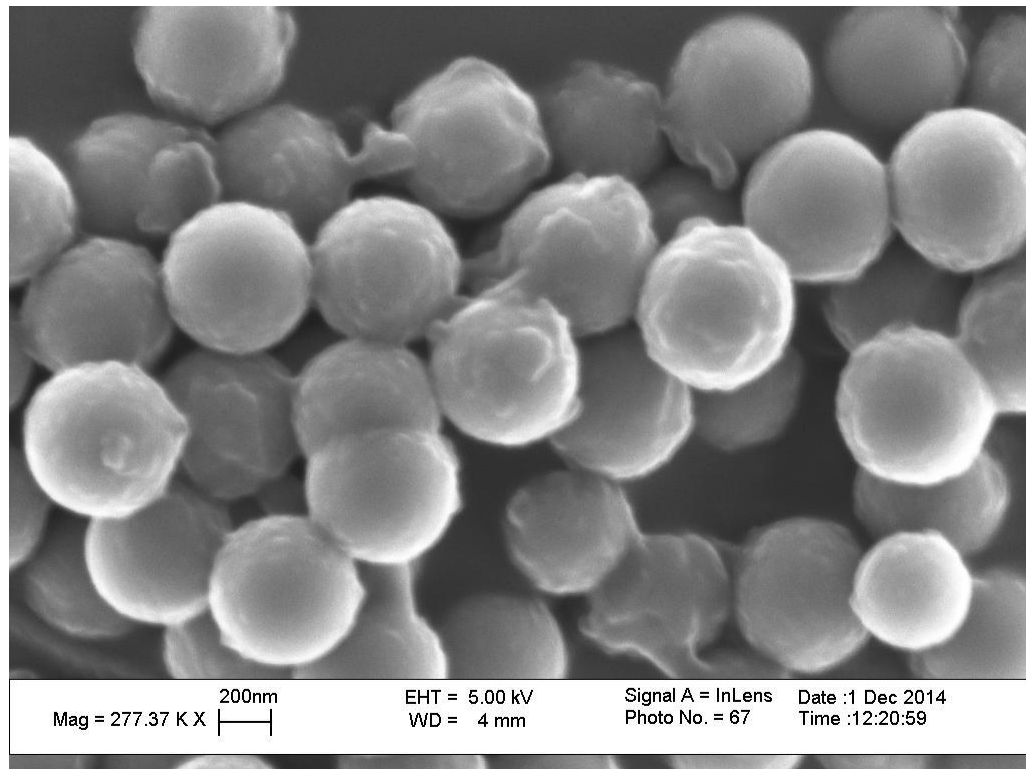Figures A.1 to A.4 illustrate SEM images of the samples for the 120 min operation.

Figure A.1 The SEM image of 40 min samples from 120 min operation.
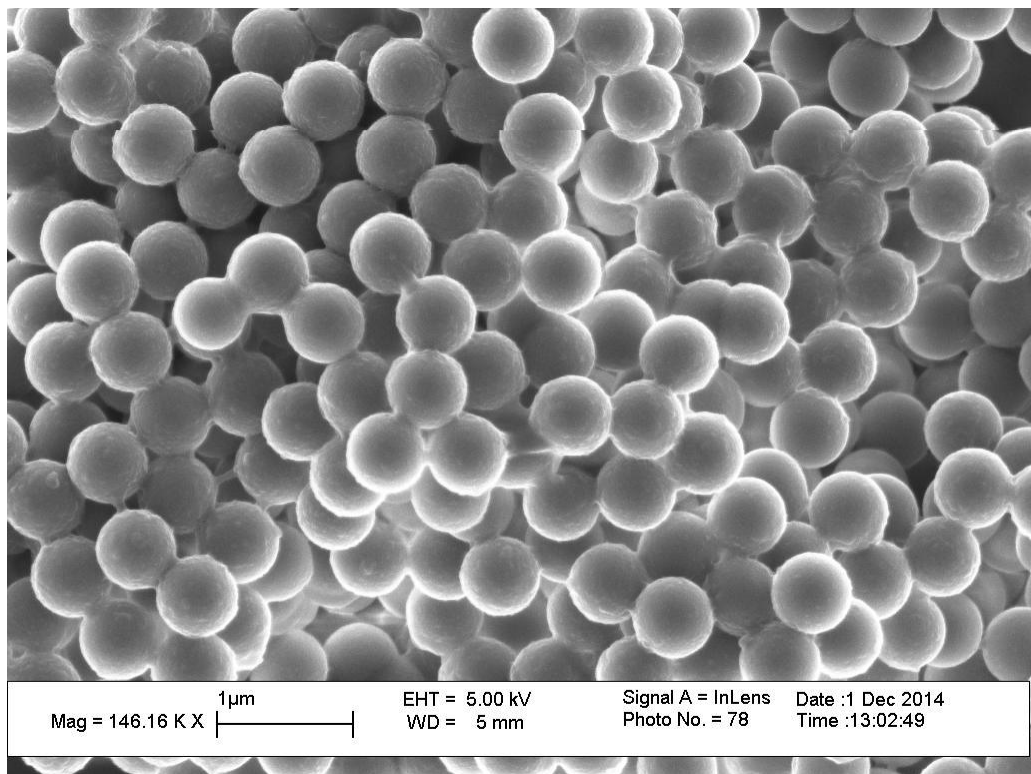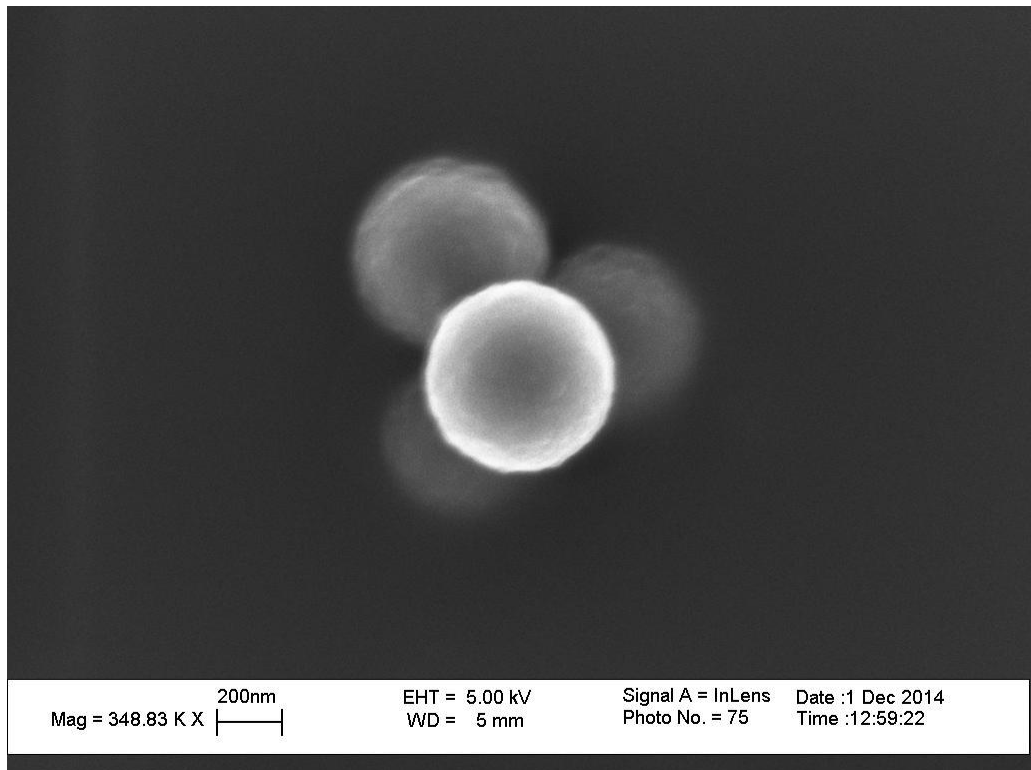
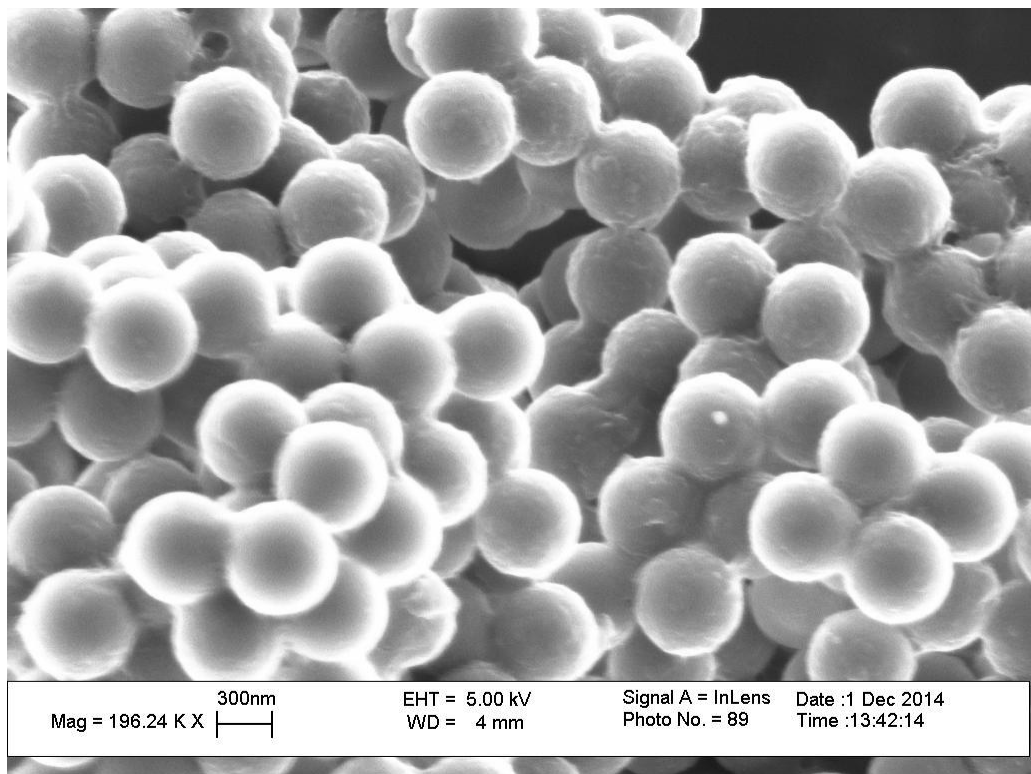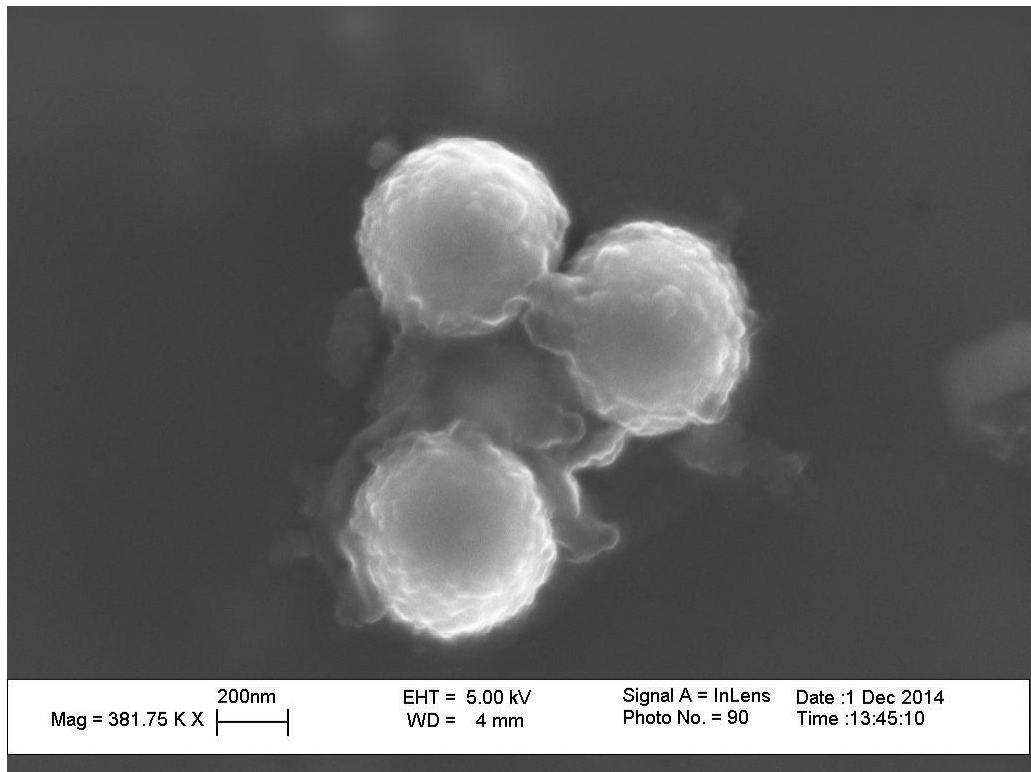**Figure A.2** The SEM image of 20 min samples from 120 min operation.

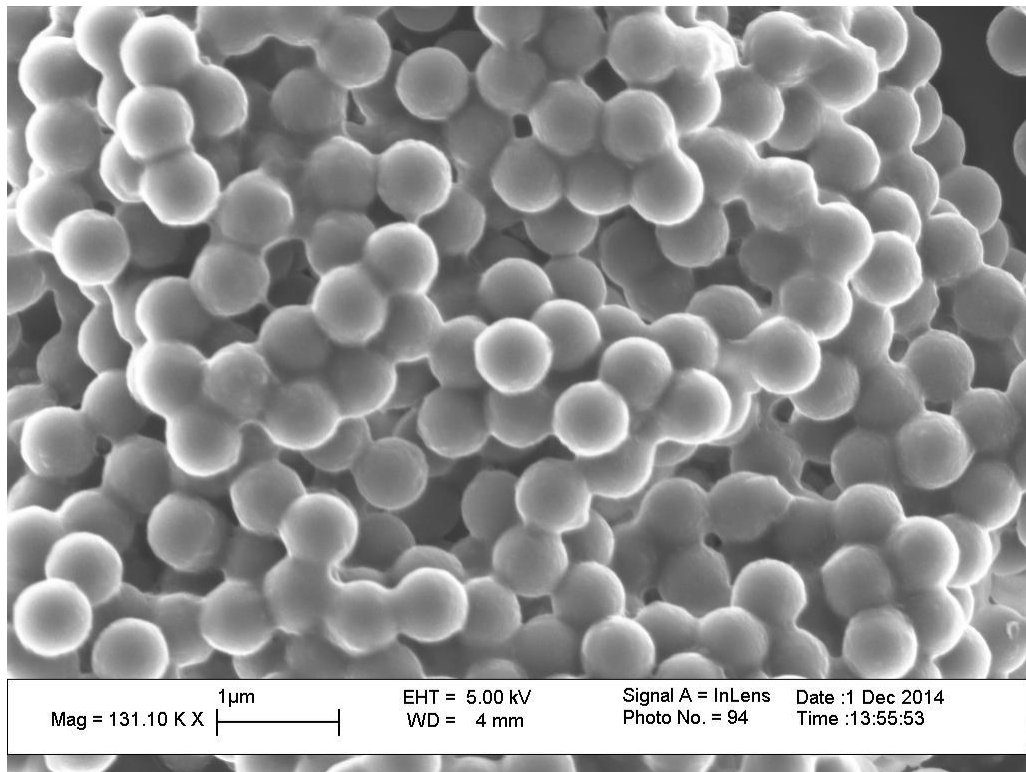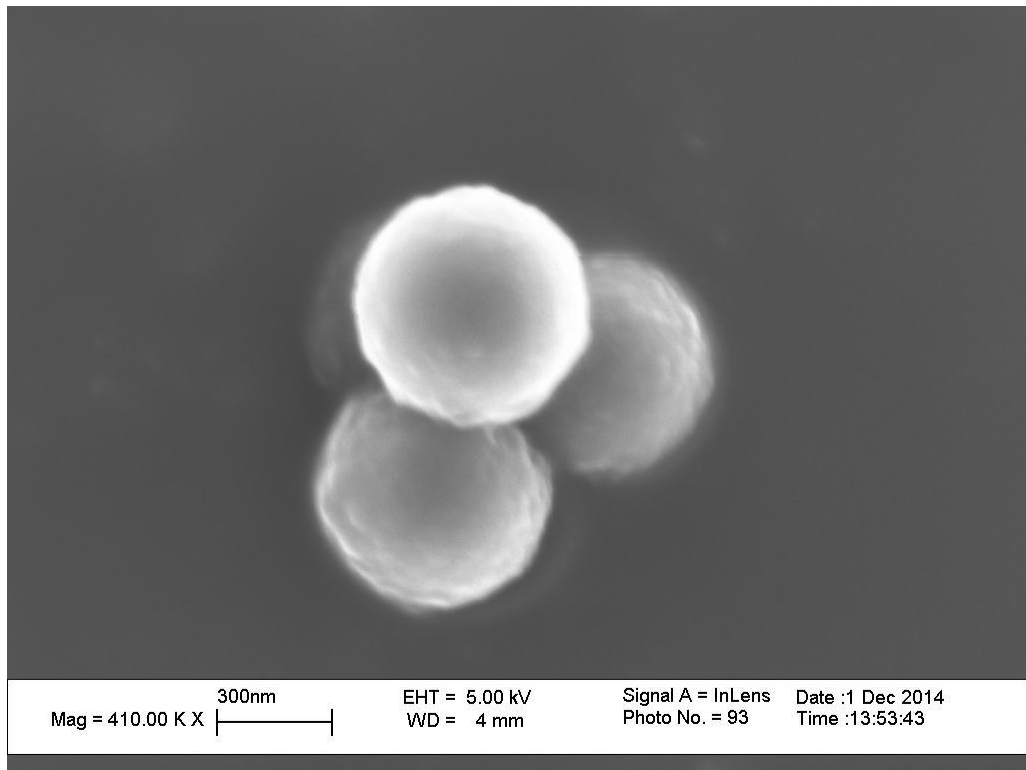**Figure A.3** The SEM image of 100 min samples from 120 min operation.

Figure A.4 The SEM image of 120 min samples from 120 min operation.

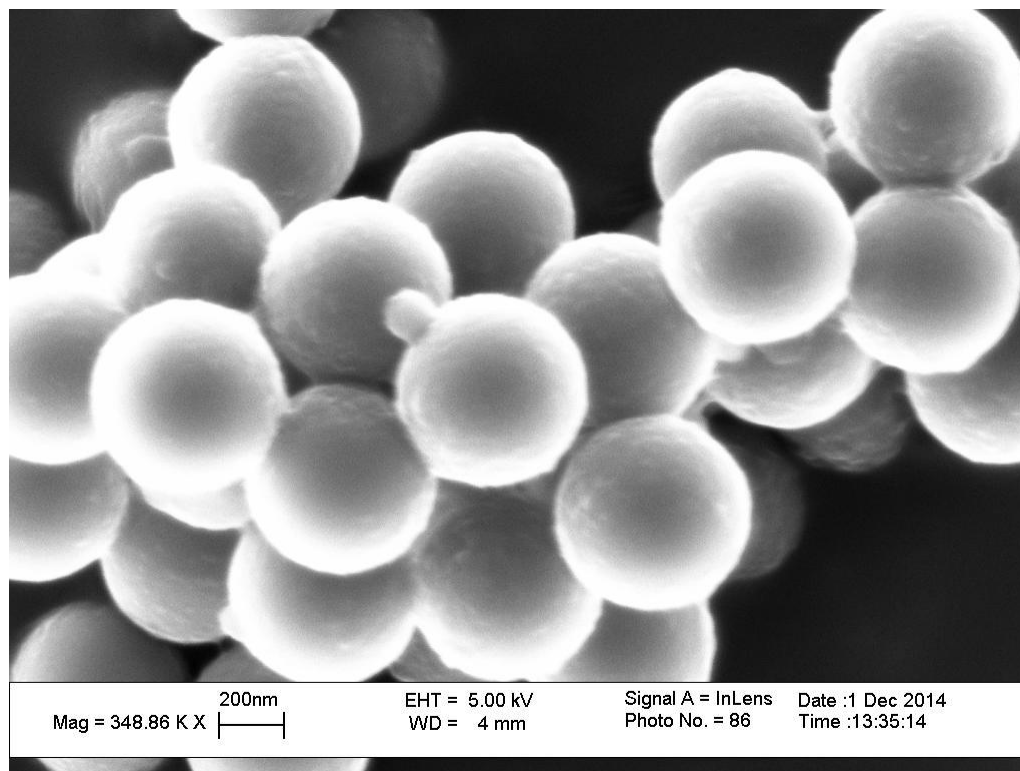Figures A.5 and A.6 illustrate SEM images of the 28 min and 39 min samples for the 60 min operation.

Figure A.5 The SEM image of 28 min samples from 60 min operation.
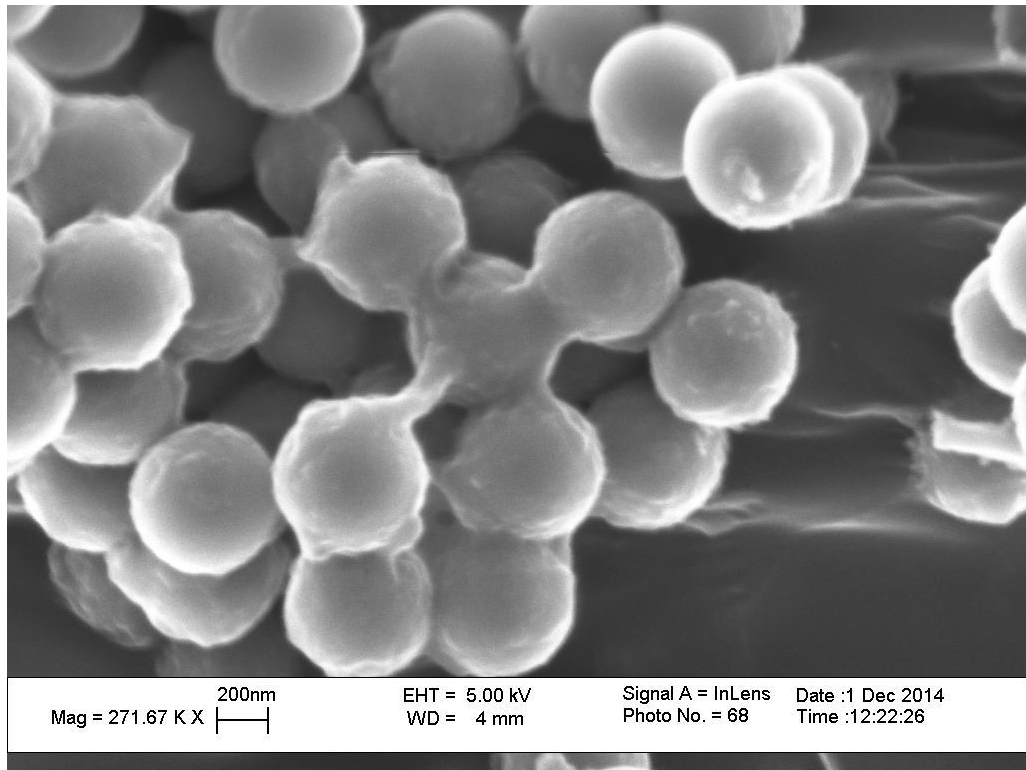
Figure A.6 The SEM image of 39 min samples from 60 min operation.

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