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(54) **Title**: METHOD FOR MAKING DESIGNED PARTICLE SIZE DISTRIBUTIONS BY FLOW MANUFACTURING

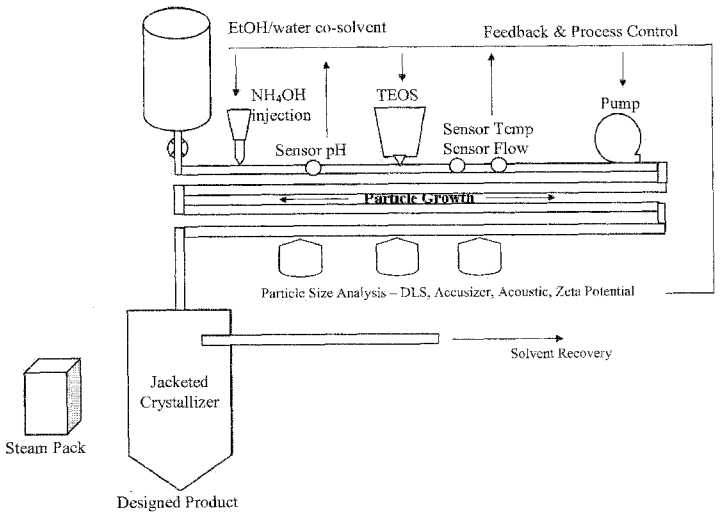

Figure 1

(57) **Abstract**: A continuous flow method for the preparation of micro and nanoparticles involves the introduction of particle precursors in a fluid or suspended state such that the physical variables that define the size and size distribution of resulting particles can be controlled and adjusted in a predetermined manner. By the inventive method, any size within the range accessible for a given composition of precursors, catalyst and solvents as defined by the capabilities of pumps, heaters, chillers, and the pressure limits of the system can be achieved. By including sensors for particle size and concentration coupled to a computer to control the pumps, heaters and chillers, verification of and, as needed, adjustment of the physical variables can be made to correct the size and size distribution of particles or the physical variables can be changed during production to obtain particle mixtures with uncommon size distributions in a predetermined manner. By varying the physical variables, size distributions can be monomodal, bimodal, multimodal, or polymodal, and can be narrow, normal or broad. The method can be applied to the production of particles of metal oxides, metals, alloys, organic polymers, pharmaceuticals and other organic solids.

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DESCRIPTION

METHOD FOR MAKING DESIGNED PARTICLE SIZE DISTRIBUTIONS BY FLOW MANUFACTURING

The subject invention was made with government support under a research project supported by National Science Foundation Grant No. EEC9402989.

CROSS-REFERENCE TO RELATED APPLICATION(S)

The present application claims the benefit of U.S. Provisional Application Serial No. 61/047,290, filed April 23, 2008, which is hereby incorporated by reference herein in its entirety, including any figures, tables, or drawings.

BACKGROUND OF INVENTION

The control of particle size and particle size distribution is important for the optimization of micro and nanoparticulate materials for a variety of applications in the fields of ceramics, chromatography, catalysis, absorbents, pharmaceuticals, emulsions, and abrasive slurries for chemical mechanical polishing (CMP). The formation of these particles can involve synthesis, association, crystallization, precipitation and combinations thereof. Several techniques have been used for the manufacture of microparticles, but these techniques suffer from some inherent limitations, have not been practical for the formation of sub-micron particles, nanoparticles, or are difficult to scale in a manner such that high throughput is readily achieved. Some of the conventional techniques include spray drying, milling, fluid energy grinding, lyophilization, and precipitation. Other techniques have been explored, including the use of supercritical fluid technology to form particles. The more effective supercritical techniques that have been employed include Supercritical Antisolvent (SAS) Precipitation, where supercritical CO_2 acts as a non-solvent, and Rapid Expansion of Supercritical Solutions (RESS), where a nozzle is employed. Again, the supercritical fluid methods have not produced consistent particles less than a micron in size.

Nanocrystals, as well as microcrystals, have been formed using synthesis and precipitation techniques. Most of these syntheses control particle size only in the broadest sense, where the chemical formulation is crafted to yield large or small assemblages of particles with a mean of a specific size. However, apart from some monodisperse systems,

there is often little or no control over the size distribution and the synthesis technique often results in broad uncontrolled size distributions. Whether a broad or narrow size distribution forms depends on such factors as reactant concentration, temperature, mixing, solvent system and many other considerations. For crystallization processes, the size and morphology of crystallized particles can be partially controlled by varying component concentrations and environmental conditions, but it is often difficult to control or eliminate the very fine or very coarse undesirable fractions of particles in these assemblages. Typically, designed bimodal or multimodal size distributions are achieved only by mixing two or more such particle assemblies in various proportions.

Silica has been synthesized and precipitated as monodispersed nanoparticles by the hydrolysis of tetraethoxyorthosilicate (TEOS) in an aqueous ammonia alcohol system as taught in Stober *et al.*, *J. Colloid & Interface Sci.*, 1968, 26, 62, where the proportions of the alcohol solvents, ammonia, TEOS and water yield different sized crystals. However, this system and others that are based upon this system often do not give a predictable or sufficiently narrow size distribution for some applications (e.g. reference materials) and is practically limited to rather small batch reactions. The use of surfactants and emulsions has been employed to improve particle size distribution. More exotic methods have been employed to form small silica particles, such as the laser ablation of silicon in an oxygen helium environment where very small particles are produced with relatively broad particle size distribution. However, the use of silica particles for CMP applications requires smaller and more controlled particle size distributions as the size of features on electronic devices shrink in size.

Metal nanoparticles have been found to be valuable for a variety of applications, such as catalysis, therapeutic, and fuel cells. Again, as these applications achieve greater commercial penetration, current Good Manufacturing Practices (cGMP) will require greater control of their size and size distribution. Concerning pharmaceuticals, the particle size and size distribution can be critical for use of the drugs as large particles can be ineffective for absorption of a drug while very small drug particles can result in unpredictable delivery rates.

In these and many other applications, there is an increasing need for small particles, particularly nanoparticles, of controlled size and size distribution. However, particle size and size distribution variations for a given micro or nanoparticle mixture have remained a significant impediment for manufacture of many particulate products.

BRIEF SUMMARY

The invention is directed to a continuous flow method of preparing particles where at least one fluid particle precursor is introduced to a tube at a controlled concentration, flow rate, pressure, and temperature and collected as a suspension of particles having a predetermined size and size distribution. The method is adaptable to synthetic methods, crystallization methods and precipitation methods to produce particles. Therefore, the fluid particle precursors include as needed: reagents, catalysts solvents, non-solvents, seed particles and dissolved components of the particles. In one synthetic embodiment of the invention, the reagents are TEOS and water, the catalyst is ammonia, and the solvent is ethanol from which the method results in the formation of silica particles. Alternately, in one embodiment of the invention, the reagents can be a metal salt, such as a gold salt, and a reducing agent in water, such as citric acid, tartaric acid, or ascorbic acid, to yield metal micro or nanoparticles. In another embodiment of the invention, the precursors can be a dissolved species where a non-solvent or other reactant can be mixed with the dissolved species such that a controlled crystallization or precipitation of particles occurs in the tube. In yet another embodiment of the invention, the precursors can be vinyl monomers in an emulsion system, where initiation results in an emulsion polymerization of the monomers.

The components can be introduced while varying at least one of the variables for formation of the particles such as the absolute and/or relative concentrations of precursors, flow rate, pressure, and temperature between values where each of the values are attained for at least one period of time. In this embodiment, the size distribution of the particles becomes bimodal where one set of values results in monodispersed particles of one size and the other set of values results in monodispersed particles of another size. Depending on the duration of time at each set of values, the proportion of particles of each size can be varied at will in the collected bimodal distribution of particles. When three or more different sets of values are used, trimodal or other multimodal or polymodal distributions of particle sizes can be prepared with any desired proportions of each size class. With the proper input parameters, a predictable smooth continuous distribution of the desired particle sizes can be produced.

Sensors to detect physical variable of the suspension of particles can be used to transmit a signal to a computer where the signal can be processed to determine the state of the particles of the suspension. The computer can then send an electronic signal to pumps or

other means of controlling concentrations and flow rates, such as valves, to a heater or chiller to control the temperature, and/or to a pressure controller to control the pressure in a predetermined fashion. In this manner, conditions can be corrected or varied to yield a desired particle size and size distribution that can be mono-, bi-, multi- or polydispersed with narrow, normal or broad dispersivities. The sensing of physical variables can be carried out by use of differential light scattering detector, a single particle optical sensing analyzer, a turbidity meter, a spectrometer, an acoustic sensor, or any combination of such sensors.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 shows a schematic of a flow system with sensors and feedback control.

Figure 2 is a graph of particle size for multiple batches of a Stober synthesis of silica nanoparticles (a) as normally performed, (b) as performed with extraordinary manual control of variables, and (c) as performed continuously according to an embodiment of the invention.

Figure 3 shows a plot of nanoparticle formation upon variation of the conditions in the continuous process to achieve a bimodal distribution of particle sizes and the repeatability of the system according to an embodiment of the invention.

DETAILED DISCLOSURE

Embodiments of the invention is directed to the use of a continuous flow manufacturing method to produce custom designed particle size and size distributions for synthesized, polymerized, precipitated or crystallized particulate systems. This continuous method overcomes the control problems encountered using traditional batch modes where various steps such as mixing, super saturation and nucleation are not easily and often not well controlled. Additionally, the continuous method allows for continuous analysis of the product and automatic adjustment of compositions and parameters to correct any departure from a desired size and size distribution, or to easily achieve uncommon size distributions of particles.

Precursors are continuously mixed in small volumes using fluid pumps and particles are nucleated and grown during continuous flow inside a specific length of tubing. Furthermore, the tubing can include a dialysis sector where concentration or solvent exchange can take place to assure a product of the desired size distribution, concentration, and dispersion properties in a desired solvent. Embodiments of this method allow precise

control over the particle size distribution of synthesized, precipitated, or crystallized systems for the manufacture of particulate systems such as (but not limited to) precipitated metals, inorganic materials, polymers, emulsions, and pharmaceuticals. For example, the inventive method allows the controlled formation of precipitated or crystallized pharmaceutical powders, stable emulsions for consumer products and foodstuffs, and abrasive slurries for the microelectronics industries.

Continuous methods for particle manufacture according to embodiments of the invention enable producers to create particulate systems or slurries on-site for their inclusion into a product formulation in a very precisely controlled fashion with a high throughput such that large quantities of consistent nanoparticles can be produced. The system can be used for on-demand manufacturing where it has the potential to save costs related to transportation, inventory, and shelf-life and can provides great flexibility in slurry particle size selection that can be modified without down time related to procurement of new particles. For example, precipitated nanometer sized silica is used in a wide variety of commercial and consumer products including the microelectronics industry, where large quantities (1000's of tons) of nanometer size silica slurries are used for chemical mechanical planarization in the manufacture of computer and/or memory chips. Control over the size and dispersion of these slurries is paramount. The inventive method allows significantly better control over particle size distribution for silica particles than that of currently employed batch methods, such as the acidification of sodium silicate in large tank reactors. This process can be used on location to create CMP slurries on demand at the CMP tool with precisely controlled size distribution, dispersion and other vital properties.

An embodiment of the continuous method involves the inclusion of at least one pump for introduction of components such as solvents, non-solvents, catalysts, surfactants, adjuvants, reagents, and/or dissolved products (dissolved particles) into a fluid flow system where rapid mixing of precise quantities of reagents can be done at a controlled temperature and pressure for a predetermined period of time based on a flow rate and length of a tube reactor. Static or active mixers can be included in the system. The components can be introduced to the system as pure liquids, solutions, or suspensions. The system can also include sensors for analysis of the size and size distribution of the produced particles, as well sensors to determine the concentrations of components and conditions of the reactor, for example, the temperature or pressure. The sensor for size and size distribution can be a

differential light scattering detector, single particle optical sensing analyzer, turbidity meter, spectrometer, acoustic sensor, or other means to determine a property of the suspension in the system that can be related to the size, size distribution, shape, dispersion, surface property and composition of the nanoparticles. These sensors can provide feedback to computer controlled reactant pumps or other components to maintain or automatically change reactant concentrations, temperatures, pressures or other conditions according to predetermined profiles designed to achieve the desired particle size and size distributions and can be programmed into the computer and stored in a memory storage device coupled to the computer. The system can also include heat exchangers, heaters and/or chillers to achieve and maintain a desired temperature or temperature gradient. The system can also contain chambers for precipitation and collection of nanoparticles and components for the isolation of the nanoparticles from the liquid components, including centrifuges, filters, and evaporators.

Examples of particles that can be formed using the continuous flow system via a reaction process include, but are not limited to, gold, silver, copper and other metal colloids through a chemical reduction process, silica, alumina, titania and other metal oxides through precipitation processes (for example the acidification precipitation of sodium silicate for colloidal silicas), emulsion polymerization for the synthesis of various polymer powders, and crystallization processes with tightly controlled dissolved particle precursor concentrations and supersaturation levels.

The continuous flow system is illustrated by the following embodiments directed to the synthesis of silica particles. In these embodiments, the continuous flow system produces monodispersed silica particles with a size difference of less than 2%. The continuous flow system is shown to be reproducibile for different size parameters. In various embodiments either monodisperse or polydisperse silica powders can be prepared using a Stober silica process in a controlled manner by computer control of the reactant introduction rates.

A system for the preparation of silica particles by a continuous Stober synthesis is shown in Figure 1. As illustrated, an ethanol or other alcohol/water solution is introduced to a reaction tube, with ammonium hydroxide solution injected into the flow in the tube with a pH sensor imbedded in the tube to display, record, and/or provide input to a processor for controlling the pH of the system. This basic alcohol solution is then combined with TEOS or other alkoxysilanes with a flow sensor and temperature sensor to display, record and/or supply an input to control the temperature and flow in the system. A pressure sensor can also

be included to sense, fix, and/or adjust the pressure in the system. The length of the tube and/or flow rate can be adjusted to achieve a desired residence time within the tube such that a suspension can be discharged into a crystallizer where the solvent and any by-product or unreacted reagent can be removed to yield the desired nanoparticles.

Figure 2 shows typical variation in the particle size for Stober synthesis batches while trying to repeat the monodisperse size of the product. Figure 2(a) is typical of the variation experienced in size and size distribution for room temperature batch syntheses with a formulation of 200 ml Ethanol, 30 ml water, 12 ml concentrated ammonium hydroxide, and 20 ml TEOS. Figure 2(b) is a series of batch syntheses where great care was taken to precisely duplicate reaction conditions. As indicated in figure 2, the mean particle size was 400 nm with a standard deviation of 63 nm (16%) for the typical batch reaction 2(a) but yielded a mean size of 467 nm with a standard deviation of 13.4 nm (3%) for the tightly controlled synthesis 2(b). Although the only difference between the two syntheses was the extraordinary attention to details of mixing, concentrations and mode of addition in 2(b), there was a difference of 14% in the size of the particles. In contrast Figure 2(c) depicts the variation over time in a flow synthesis with formulation of 0.15 ml/minute additions of a 50/50 mixture of Ethanol and ammonium hydroxide (Reactant A), a 50/50 mixture of Ethanol and water (Reactant B) and a 50/50 mixture of Ethanol and TEOS (Reactant C) to yield silica particles with a size of 188nm and a standard deviation of 2.2 nm (1%).

The ability of the method to rapidly adjust reagents feeds and change the particle size and the good repeatability is illustrated in Figure 3 for silica particles prepared by the Stober method. The formulation was alternated from the formulation indicated above with equal 0.15 ml/minute proportions of the different Reactant mixtures with a formulation of 0.22 ml/minute of Reactant A, 0.26 ml/minute of Reactant B and 0.22 ml/minute of Reactant C. The latter unequal formulation resulted in a silica particle size distribution of 320 nm with a standard deviation of 2.5 nm (0.1%). By continuously varying the Reactant proportions, any combination of particle sizes (within the upper and lower size limits of the synthesis) can be created and collected at the end of the flow reactor system to create a the desired final particle size distribution. In this manner, the size distribution of the nanoparticles can be narrow, normal or broad and can be monomodal, bimodal, multimodal or polymodal depending on the proportions of reagents, catalyst concentrations and other conditions that can be preprogrammed into the system.

All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all figures and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application.

CLAIMS

We claim:

1. A continuous flow method of preparing particles comprising the steps of:

providing at least one fluid particle precursor;

introducing said at least one precursor to a tube at a controlled concentration, flow rate, pressure, and temperature; and

collecting a suspension of said particles, wherein said particles have a predetermined size and size distribution.

2. The method of claim 1, wherein said fluid particle precursors comprise reagents, catalysts and solvents for the reagents.

3. The method of claim 2, wherein said reagents comprise TEOS and water, said catalyst comprises ammonia, and said solvent comprises ethanol, and wherein said particles are silica particles.

4. The method of claim 2, wherein said reagents comprise a metal salt and a reducing agent, wherein said solvent is water, and wherein said particles comprise metal particles.

5. The method of claim 4, wherein said metal salt comprises a gold salt and said metal particles comprise gold particles.

6. The method of claim 1, wherein at least one of said precursors comprises a dissolved solute, wherein varying said concentration, flow rate, pressure, and/or temperature promotes formation of said particles in said tube.

7. The method of claim 1, wherein said precursors comprise vinyl monomers, and said particles are formed by emulsion polymerization of said monomers.

8. The method of claim 1, wherein said step of introduction comprises varying at least one of said controlled concentration, flow rate, pressure, and temperature between two values, each of said values for at least one period of time, wherein said size distribution of said particles is bimodal.

9. The method of claim 1, wherein said step of introduction comprises varying at least one of said controlled concentration, flow rate, pressure, and temperature between multiple values, each of said values for at least one period of time wherein said size distribution of said particles is multimodal.

10. The method of claim 1, wherein said step of introducing comprises varying one or more of said controlled concentration, flow rate, pressure, and temperature between multiple values in a smooth manner, wherein said size distribution of said particles is smooth and has a predetermined shape.

11. The method of claim 1, wherein said step of introducing said precursor at a controlled concentration, flow rate, pressure, and temperature comprises:

sensing a physical variable of said suspension of said particles using a sensor;

transmitting a signal from said sensor to a computer wherein said signal is processed to determine the state of said particles of said suspension; and

transmitting a second signal from said computer to a pump or other means of controlling said concentration and flow rate, a heater or a chiller to control said temperature, or a pressure controller to control said pressure in a predetermined fashion.

12. The method of claim 11, wherein said physical variable is sensed by a differential light scattering detector, a single particle optical sensing analyzer, a turbidity meter, a spectrometer, an acoustic sensor, or any combination thereof.

13. The method of claim 1, wherein said particles are microparticles or nanoparticles.

14. The method of claim 1, wherein said particles are monodispersed with a size varience of less than two percent.

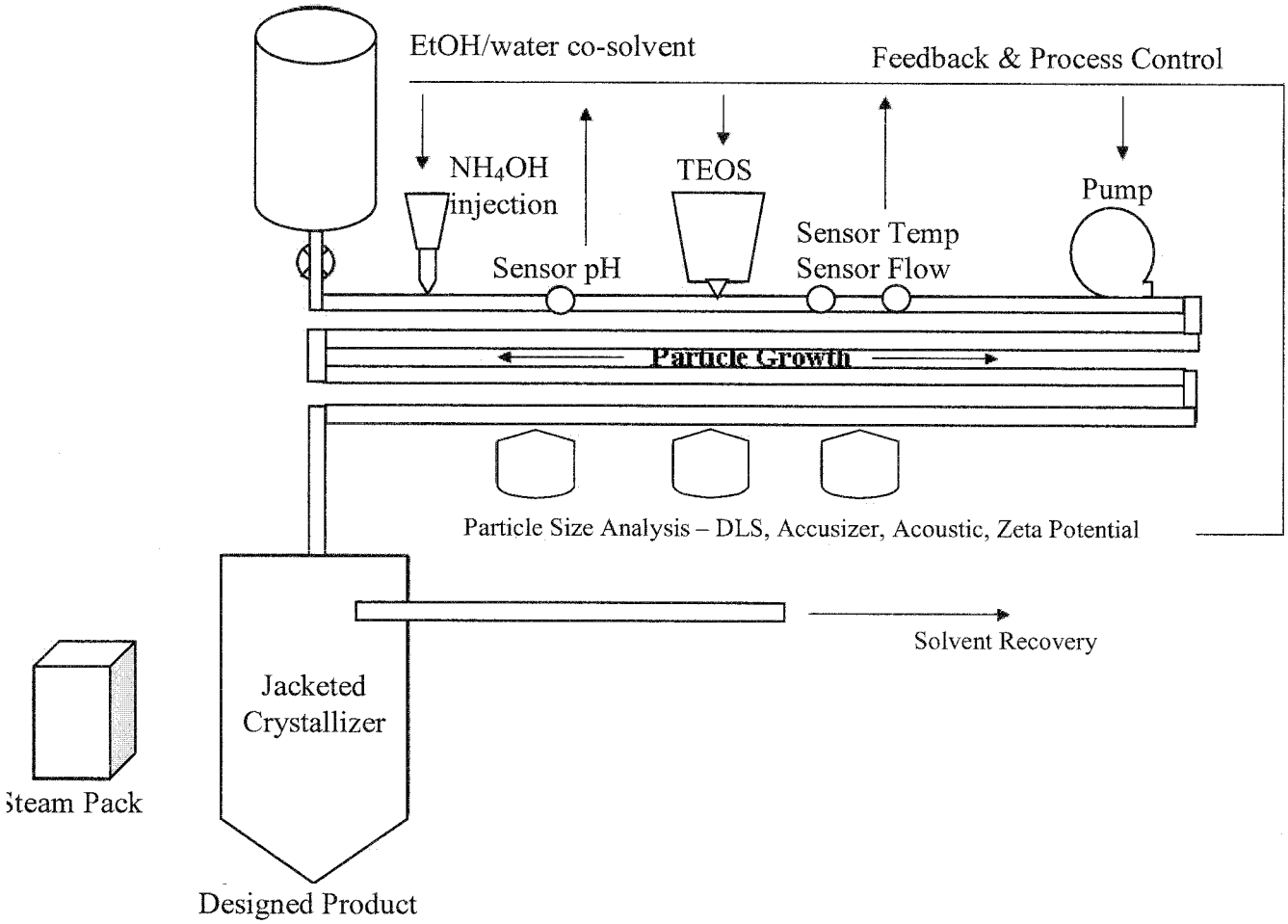
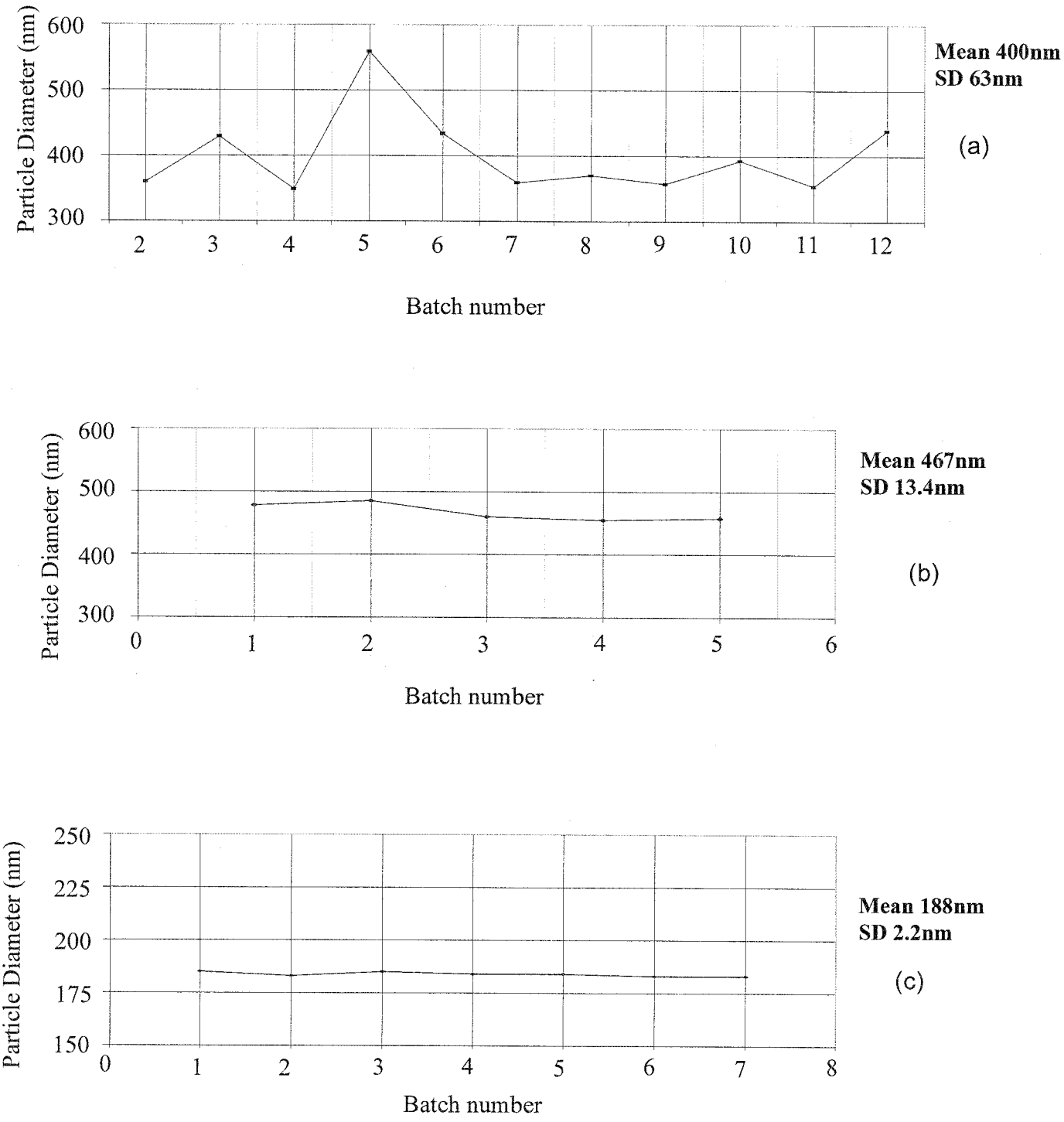

EtOH/water co-solvent
Feedback & Process Control
NH4OH injection
TEOS
Pump
Sensor pH
Sensor Temp
Sensor Flow
Particle Growth
Particle Size Analysis – DLS, Accusizer, Acoustic, Zeta Potential
Solvent Recovery
Jacketed Crystallizer
Steam Pack
Designed Product

Figure 1


Particle Diameter (nm)
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500
400
300
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Batch number
Mean 400nm
SD 63nm
(a)
Particle Diameter (nm)
600
500
400
300
0 1 2 3 4 5 6
Batch number
Mean 467nm
SD 13.4nm
(b)
Particle Diameter (nm)
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225
200
175
150
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Batch number
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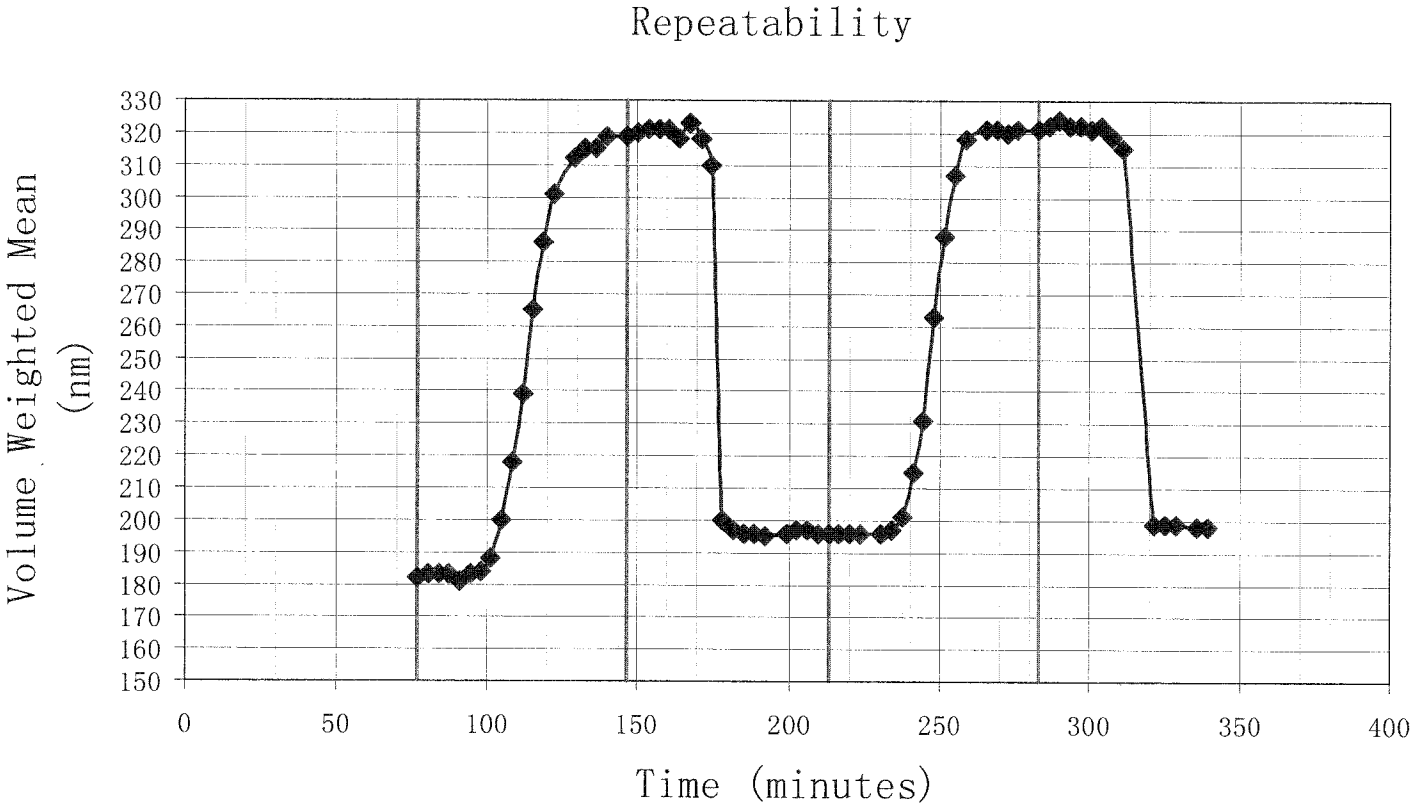
SD 2.2nm
(c)

Figure 2



Mean (nm)	Mean (nm)	SD	Count	Duration (min)
182.71		0.95	7	21.00
	319.09	2.51	11	35.00
196.21		0.58	14	52.50
	320.64	2.17	14	52.50
198.60		0.55	5	17.50

Figure 3