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(54) **MICROENCAPSULATION SYSTEM AND METHOD**

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B01J 13/02 (2006.01)

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264/DIG. 37

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264/4.3, 4.32, 4.33, 4.7, 14, 233, 408, 412,
264/DIG. 37; 425/6, 10, 86, 145, 169, 455,
425/457, 458

See application file for complete search history.

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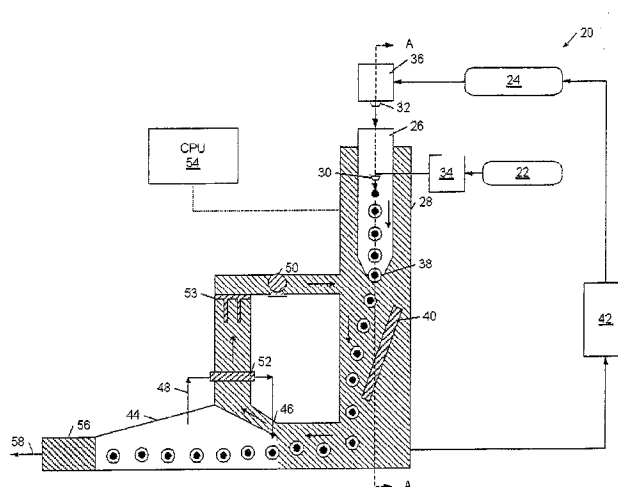
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(57) **ABSTRACT**

A microencapsulation apparatus is provided which is configured to form co-axial multi-lamellar microcapsules from materials discharged from first and second microspheres dispensers of the apparatus. A method of fabricating and processing microcapsules is also provided which includes forming distinct droplets comprising one or more materials and introducing the droplets directly into a solution bath to form a membrane around the droplets such that a plurality of microcapsules are formed. A microencapsulation system is provided which includes a microcapsule production unit, a fluidized passage for washing and harvesting microcapsules dispensed from the microcapsule production unit and a flow sensor for sizing and counting the microcapsules. In some embodiments, the microencapsulation system may further include a controller configured to simultaneously operate the microcapsule production unit, fluidized passage and flow sensor to process the microcapsules in a continuous manner.

5 Claims, 4 Drawing Sheets



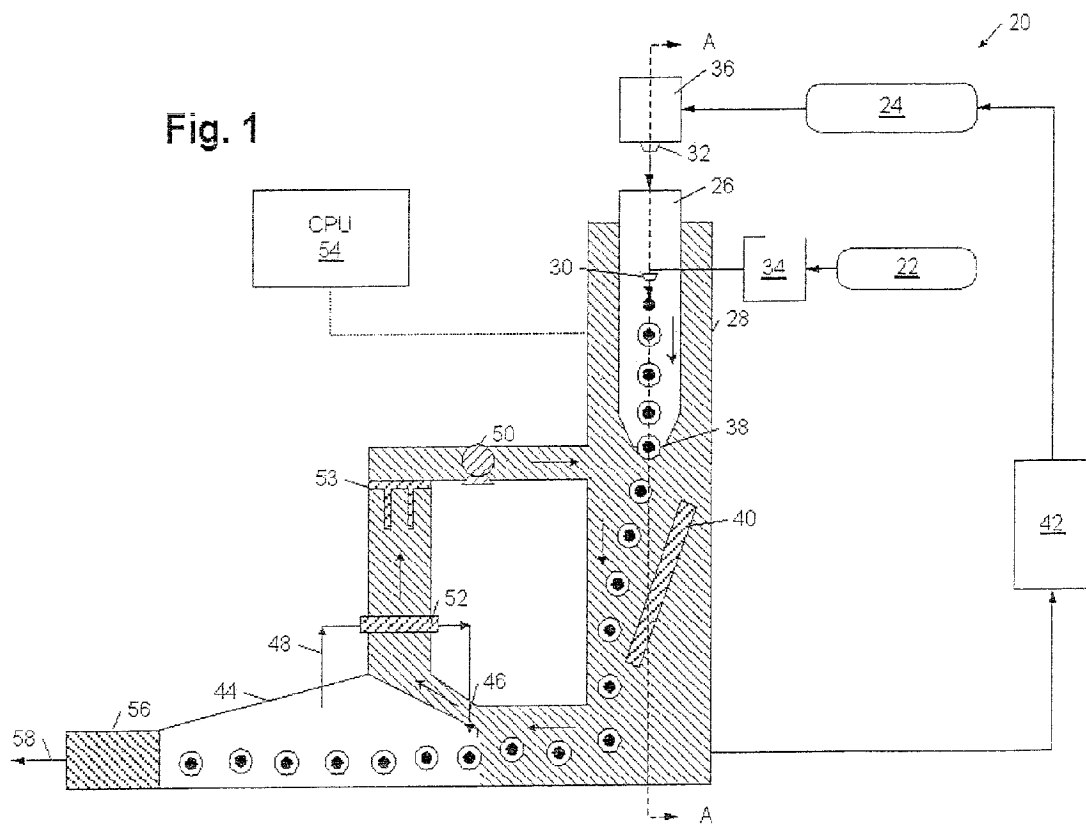


Fig. 2

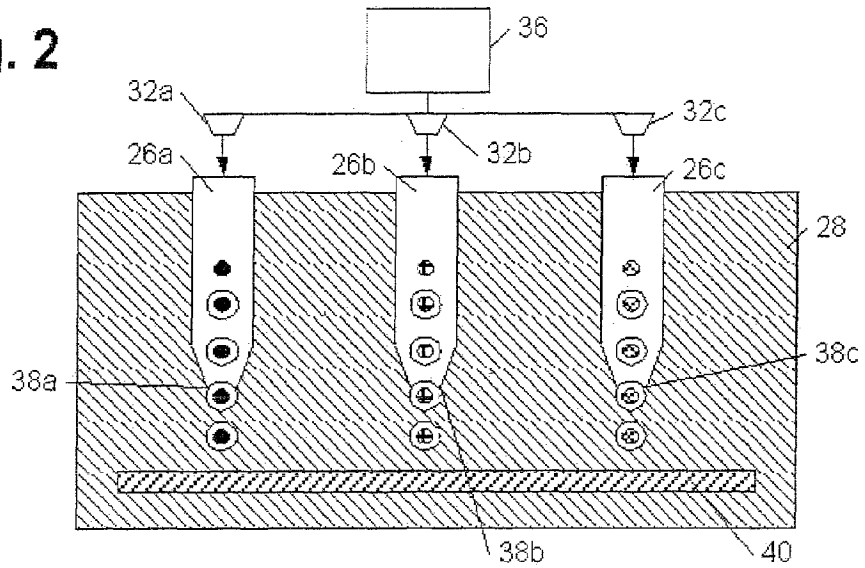
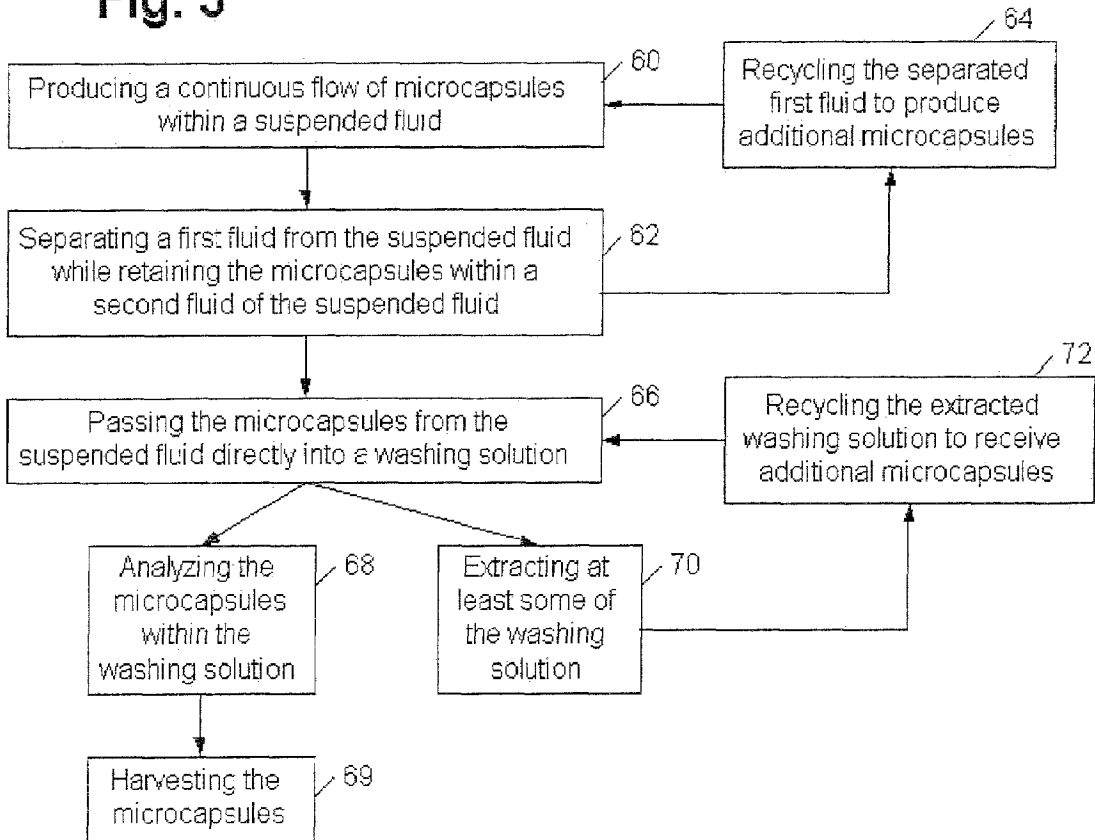


Fig. 3



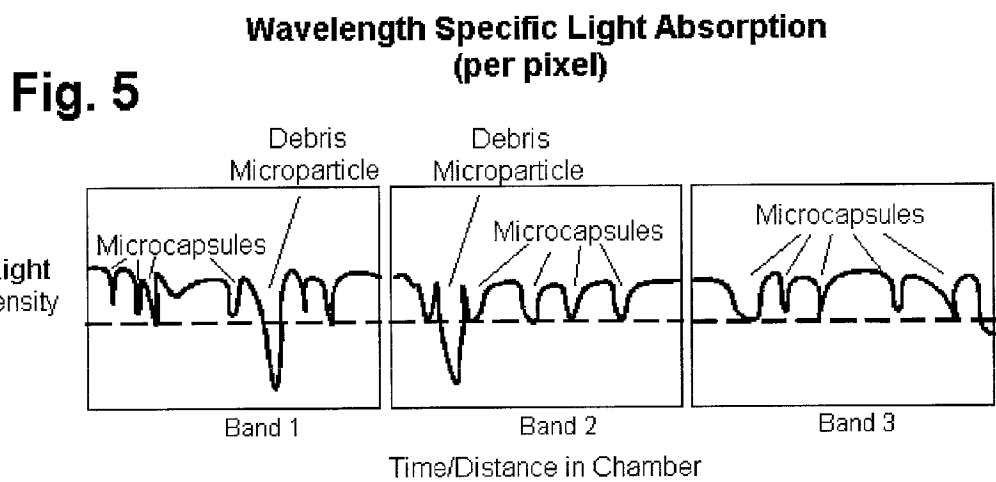
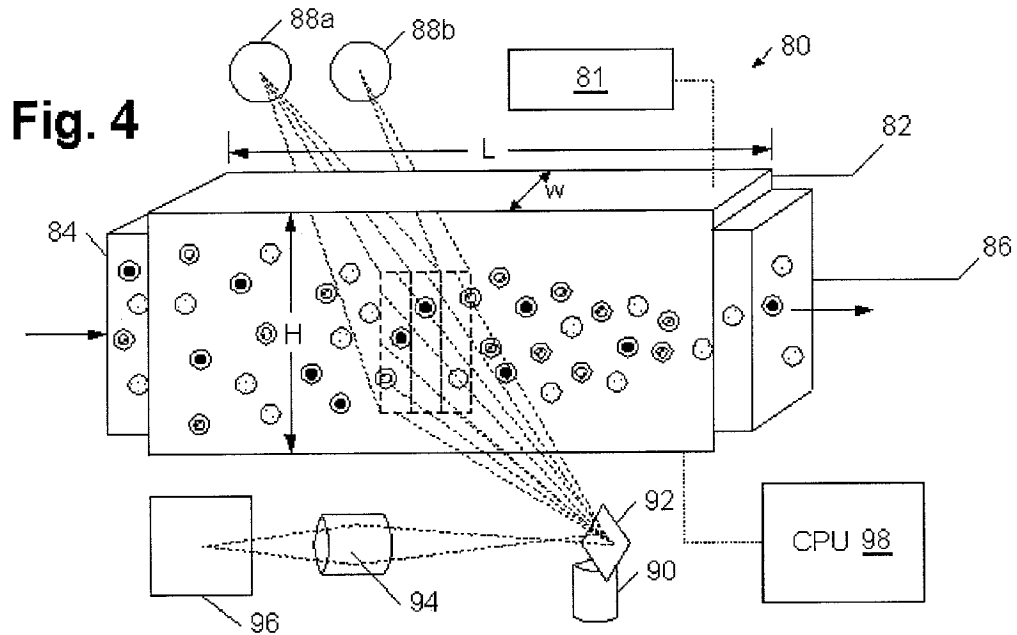
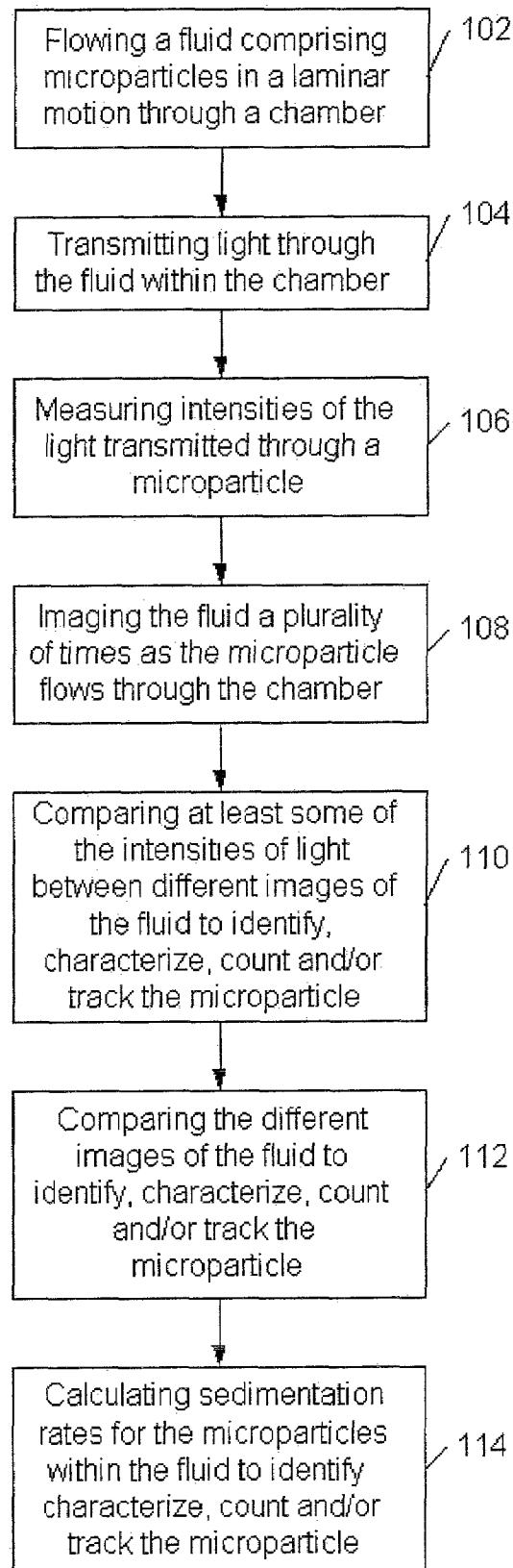


Fig. 6

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MICROENCAPSULATION SYSTEM AND METHOD

CLAIM OF BENEFIT OF PRIORITY OF PRIOR-FILED CO-PENDING NON-PROVISIONAL APPLICATION

This application is a divisional of commonly-owned U.S. patent application Ser. No. 10/734,754, filed Dec. 9, 2003 now issued as U.S. Pat. No. 7,094,045 on Aug. 22, 2006.

CROSS-REFERENCE TO RELATED APPLICATION

This application is also related to U.S. patent application Ser. No. 10/734,753, filed Dec. 9, 2003, entitled "Microparticle Analysis System and Method" now issued as U.S. Pat. No. 7,295,309 on Nov. 13, 2007.

ORIGIN OF THE INVENTION

The invention described herein was made by an employee of the United States Government and may be manufactured and used by or for the Government of the United States of America for governmental purposes without the payment of any royalties thereon or therefor.

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention generally relates to microencapsulation or, more specifically, to methods and systems for producing, processing and/or analyzing microcapsules.

2. Description of the Related Art

The use and/or detection of particles having diameters ranging from submicrons to a few hundred microns can be useful in a variety of industries. For example, the chemical manufacturing industry may utilize microparticles to distinguish different process liquids and/or identify ownership of liquid products. On the other hand, the pharmaceutical industry sometimes encapsulates drugs or biological therapeutics to form liquid microcapsules. Such microcapsules are used to deliver bioactive components to target organs before the drug or enzyme is released. In this manner, the drug or enzyme may be directed primarily into the target tissue. A "microcapsule", as used herein, may generally refer to a droplet of material synthetically encased with an outer protective shell having a diameter ranging from sub-micron dimensions to a few hundred microns. In contrast, a "microparticle", as used herein, may generally refer to a liquid or solid particle having a diameter ranging from sub-micron dimensions to a few hundred microns. Such a definition of a microparticle may include intentionally and unintentionally formed synthetic and naturally occurring particles. Consequently, a microcapsule is a microparticle, however, a microparticle is not necessarily a microcapsule.

In some cases, it may be beneficial to detect, identify, and count microparticles. For example, in cases in which microparticles are synthetically fabricated, it may be advantageous to identify and count the microparticles during their production for quality assurance purposes. In other applications, such as wastewater processing and/or bulk pumping of industrial chemicals, microparticles may be indicative of contamination. As such, in some embodiments, it may be advantageous to detect and count microparticles to determine the concentration of contaminants within the systems. In some cases, dilution of dyes or taggants may be alternatively used

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to measure contamination volumes, however, such techniques typically involve a taking sample to a central laboratory for detailed analyses. In addition, some dyes have adverse environmental problems and/or may be very difficult to assay once spilled or evaporated into the air.

Consequently, systems have been developed which are configured to identify and count microparticles. As noted above, microparticles may be used in a variety of applications which have microparticles suspended in fluids such as, waste water processing, bulk pumping of industrial chemicals, and ownership identification of liquid products. Conventional analysis systems, however, often have difficulty in accurately identifying and counting microcapsules which are suspended within fluids. In particular, conventional measurement systems tend to miss microparticles that are moving behind or in the shadow of other microparticles that are in the foreground. As such, quite often, microcapsules have to be removed and collected from the fluid for analysis. As explained in more detail below, however, such a batch-style production process tends to be time-consuming. Conventional systems also have difficulty in distinguishing between known target microparticles, such as microcapsules, and non-target microparticles, such as debris particles and bubbles. As such, obtaining accurate information from conventional systems is sometimes difficult.

As noted above, microcapsules may be synthetically fabricated for a variety of applications. In general, the production of multi-lamellar, fluid-filled microcapsules involves a plurality of processes. For example, the formation of microcapsules typically involves spraying a fluid through air such that a trajectory of atomized droplets is formed. In addition to forming the microcapsules, the production process may include curing and/or washing the microcapsules as well as counting and/or sizing the microcapsules for production control data. Typically, the processes of forming, curing, washing and analyzing the microcapsules are performed in a batch type production sequence and, therefore, are not processed continuously under sterile conditions. More specifically, most conventional production systems are configured to harvest the microcapsules after each process and collectively move the microcapsules to the next process. In this manner, each process may be closely monitored and optimized to perform its function within specification.

Unfortunately, however, such batch-style production systems tend to be bulky, thereby occupying valuable production space. In addition, batch-style production systems tend to be time consuming resulting in relatively low production throughput. Another drawback affecting production throughput of multi-lamellar microcapsules is that conventional microcapsule production systems are generally limited to fabricating a single type of microcapsule, or more specifically, microcapsules with the same composition and configuration. In other words, conventional systems are not configured to co-encapsulate different particles and liquids or, more specifically, particles and liquids of greatly different densities. As a result, the flexibility of the production system is limited.

As such, it would be beneficial to develop a system configured to simultaneously encapsulate particles and liquids having different viscosities. In addition, it would be advantageous to develop a system and a method in which multiple processes of a microcapsule production process are performed in a continuous manner. Moreover, it would be advan-

tageous to develop a system with which to detect, identify and count microparticles accurately and in an efficient manner.

SUMMARY OF THE INVENTION

The problems outlined above may be in large part addressed by systems and methods for fabricating and processing microcapsules as well as systems and methods for analyzing microparticles within flowing fluids. Consequently, a microencapsulation system is provided which includes a microcapsule production unit. In general, the microcapsule production unit may include a dual-dispenser system configured to form co-axial multi-lamellar microspheres and a bath of solution configured to receive and form a membrane about the co-axial multi-lamellar microspheres to form microcapsules. More specifically, the microcapsule production unit may include one microsphere dispenser arranged in alignment with another microsphere dispenser by a distance configured to form the co-axial multi-lamellar microspheres. In some cases, the flow rates of the materials discharged through the first and second microsphere dispensers may influence the formation of the co-axial multi-lamellar microcapsules as well. In some embodiments, the microcapsule production unit may include one or more pulsatile flow generators coupled to the first and/or second microsphere dispensers to synchronize the frequencies and/or optimize the flow rates at which the materials are discharged from the first and second microsphere dispensers to form the co-axial multi-lamellar microcapsules. In addition or alternatively, each of the first and second microsphere dispensers may, in some embodiments, be configured to dispense a single fluid. In yet other embodiments, however, at least one of the first and second microsphere dispensers may include a plurality of nozzles configured to dispense substantially uniform droplets of materials having substantially different viscosities.

In any case, the microcapsule production unit may further include a module configured to direct spherical droplets formed from the materials discharged from the first and second microsphere dispensers to a chamber within the microencapsulation system. The chamber may include the aforementioned bath of solution and, therefore, may be adapted to suspend the spherical droplets within the solution to form a membrane around the spherical droplets to form the co-axial multi-lamellar microcapsules. In some cases, the microencapsulation system may include a separation baffle system arranged down stream from the microcapsule production unit to separate residual amounts of one or more of the materials used to form spherical droplets from the solution used to form the membrane about the spherical droplets. In such an embodiment, the microencapsulation system may further include a recirculation conduit configured to recycle the one or more fluids back to the dual-dispenser system. Moreover, the microencapsulation system may include a recirculation conduit configured to recycle the solution back to the bath.

In addition to a microcapsule production unit, the microencapsulation system may further include a fluidized passage for washing and harvesting microcapsules dispensed from the microcapsule production unit as well as a flow sensor for sizing and counting the microcapsules. In some cases, the flow sensor may include an imaging system configured to acquire images of the microcapsules and a photometer configured to measure intensity of light transmitted through the microcapsules as described in more detail below. In general, however, the flow sensor may include any system which is adapted to analyze microcapsules, including but not limited to the flow sensor described below. In some embodiments, the microencapsulation system may include a controller config-

ured to simultaneously operate the microcapsule production unit, fluidized passage and flow sensor to process the microcapsules in a continuous manner. In some cases, the controller may be configured to provide feedback control for the microcapsule production unit, fluidized passage and flow sensor.

A method of fabricating and processing microcapsules is contemplated herein which includes forming distinct droplets comprising one or more materials and introducing the droplets directly into a solution bath to form a membrane around the droplets such that a plurality of microcapsules are formed. In general, the step of forming the distinct droplets may include dispensing substantially uniform droplets of a first fluid and coating the substantially uniform droplets with an immiscible solution. In some cases, at least one of the steps of dispensing and coating the substantially uniform droplets may include discharging multiple fluids having substantially different viscosities. In any case, the steps of forming the distinct droplets and introducing the droplets directly into a solution bath may produce a continuous flow of the microcapsules within the solution bath. In addition, the method may include passing the continuous flow of microcapsules from the solution bath directly into a washing solution and analyzing the microcapsules as the microcapsules flow through the washing solution.

As noted above, systems and methods for analyzing microparticles within flowing fluids is also provided herein. In particular, a device for analyzing microparticles is provided which includes a chamber comprising an inlet and an outlet for respectively introducing and dispensing a flowing fluid comprising microparticles. Such a chamber may be adapted to induce a laminar flow of the fluid such that the microparticles flow abreast with the chamber walls. In addition, the device may include one or more light sources adapted to provide incident light through the chamber and a photometer configured to measure the intensity of light transmitted through individual microparticles. In this manner, the chamber may include two opposing view ports through which the incident light may be transmitted. In cases in which the device includes more than one light source, the device may be configured to provide incident light through the chamber at different wavelengths. In addition to the light sources and photometer, the device may include an imaging system configured to acquire images of the flowing fluid within the chamber. In some cases, the device may include a moveable mirror system configured to reflect the light transmitted through the chamber to the imaging system. In addition or alternatively, the imaging system may include a magnification lens configured to enlarge the appearance of individual microparticles within the flowing fluid to be equal to or slightly larger than a pixel size of the images produced by the imaging system. In any case, the device may be component of a larger system, such as a microencapsulation apparatus, or may be an independent unit.

In some cases, the microparticle analytical device may further include a microprocessor controller with a storage medium having program instructions executable using a processor for analyzing the measured light intensities and acquiring images of the flowing fluid. In particular, the storage medium may include program instructions for identifying microparticles within the fluid and determining a quantity of the microparticles. For example, in some embodiments, the storage medium may include program instructions for distinguishing different types of microcapsules contained within the fluid. In addition, the storage medium may include program instructions for distinguishing the microcapsules from debris microparticles. In yet other embodiments, the storage medium may additionally or alternatively include program

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instructions for determining a shape and size of the microparticles (i.e., characterizing the microparticles) and/or tracking the trajectory of the microparticles within the fluid. In any case, the program instructions used to accomplish such tasks may include instructions for comparing measured intensities of light transmitted through the microparticles at different locations within the chamber. In addition or alternatively, the program instructions may include commands for matching the measured light intensities with spectral characteristics of known microparticles.

A method for identifying, counting, characterizing and tracking microparticles in motion is also contemplated herein. In particular, the method may include flowing a fluid comprising microparticles in laminar motion through a chamber and transmitting light through the fluid within the chamber and measuring the intensities of the light transmitted through a microparticle. In some embodiments, the step of transmitting light may include transmitting a spectrum of light through the fluid. In any case, the method may further include imaging the fluid a plurality of times as the microparticle flows through the chamber and comparing at least some of the intensities of light between different images of the fluid. In general, the step of comparing the intensities of light may be used to identify and count the microparticles within the fluid. In some embodiments, the step of comparing the intensities of light may be specifically used to calculate a time of flight of individual microparticles and determine trajectories for the individual microparticles.

There may be several advantages to using the systems and methods provided herein. For example, a method and a system for forming multi-lamellar co-axial microcapsules is provided which may be particularly advantageous in embodiments in which two materials are needed for a microcapsule application. For instance, multi-lamellar co-axial microcapsules comprising an aqueous drug and contrast agent medium may be beneficial for delivering drugs to a particular location within a body. More specifically, the contrast agent medium may allow the microcapsule to be imaged with a CT scan, for example, as well as administer drug delivery. A microparticle analysis system is also provided herein which is configured to analyze microparticles within a flowing fluid. More specifically, the microparticle analysis system offers a manner in which to accurately identify and count microparticles within a flowing fluid. In some embodiments, the microparticle analysis device may be portable and, therefore, may be used in a variety of applications, including those in remote regions without power sources. In other embodiments, the analysis system may be included within a microencapsulation system such that the production and processing of microcapsules may be continuous. Such a continuous process averts the disadvantages of down-time and increased production costs associated with batch processing.

BRIEF DESCRIPTION OF THE DRAWINGS

Other objects and advantages of the invention will become apparent upon reading the following detailed description and upon reference to the accompanying drawings in which:

FIG. 1 depicts a schematic diagram of a microencapsulation system;

FIG. 2 depicts a partial cross-sectional view of the microencapsulation system depicted in FIG. 1;

FIG. 3 depicts a flowchart of a method for producing and processing microcapsules;

FIG. 4 depicts a schematic diagram of a system configured to analyze microparticles within a flowing fluid;

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FIG. 5 depicts exemplary graphical data which may be obtained from the microparticle analysis system depicted in FIG. 4; and

FIG. 6 depicts a flowchart of a method for analyzing microparticles within a flowing fluid.

While the invention is susceptible to various modifications and alternative forms, specific embodiments thereof are shown by way of example in the drawings and will herein be described in detail. It should be understood, however, that the drawings and detailed description thereto are not intended to limit the invention to the particular form disclosed, but on the contrary, the intention is to cover all modifications, equivalents and alternatives falling within the spirit and scope of the present invention as defined by the appended claims.

DETAILED DESCRIPTION OF THE INVENTION

Turning now to the drawings, exemplary embodiments of a system and a method for encapsulating microparticles are shown in FIGS. 1-3. In particular, FIG. 1 illustrates a schematic view of microencapsulation system 20 and FIG. 3 illustrates a flowchart outlining a method for producing microcapsules using such a system. FIG. 2 illustrates a partial cross-sectional view of microencapsulation system 20 taken along line AA of FIG. 1. In general, microencapsulation system 20 may be adapted to encapsulate liquid and/or solid particles and process the microcapsules in a single continuous system. More specifically, microencapsulation system 20 may be adapted to produce, cure, wash and analyze a continuous flow of microcapsules without disrupting the production flow of the microcapsules. In some embodiments, microencapsulation system 20 may include additional mechanisms with which to process microcapsules. Such mechanisms may be those known for use in the industry of microencapsulation and incorporated within microencapsulation system 20 in a manner accommodating a knowledgeable sequence of process steps. As described in more detail below, the fabrication and processing of microcapsules employs a variety of fluids. In an effort to simplify the drawings, however, the illustrations of microencapsulation system 20 in FIGS. 1 and 2 do not depict the presence of such fluids within the system with exception to the formation of the microcapsules. Instead, the different components of microencapsulation system 20 are distinguished by reference numbers and, in some cases, accompanying cross-hatch patterns.

As shown in FIG. 1, microencapsulation system 20 may include reservoirs 22 and 24, inner chamber 26, chamber 28 and microsphere dispensers 30 and 32, all of which may constitute a "microcapsule production unit" of microencapsulation system 20. In particular, reservoirs 22 and 24, inner chamber 26, chamber 28 and microsphere dispensers 30 and 32 may be collectively adapted to form microcapsules having one or more encapsulated particles and/or fluids. In some embodiments, microencapsulation system 20 may include pulsatile flow generators 34 and 36 respectively coupled to reservoirs 22 and 24 as shown in FIG. 1. In such embodiments, pulsatile flow generators 34 and 36 may constitute a part of the microcapsule production unit of microencapsulation system 20. As discussed in more detail below, however, pulsatile flow generators 34 and 36 are not necessarily needed for the generation of microcapsules in some embodiments. Consequently, one or both of pulsatile flow generators 34 and 36 may be omitted from microencapsulation system 20 in some embodiments. As noted above, a "microcapsule", as used herein, may generally refer to a droplet of material synthetically encased with an outer protective shell having a diameter ranging from sub-micron dimensions to a few hun-

dred microns. Such a term may generally be synonymous with any spherical microscopic vesicle including microspheres, micelles, inverted micelles, bilayer vesicles and liposomes.

The microcapsules described herein and fabricated using microencapsulation system **20** are generally directed at microspheres having a dual-material inner core encapsulated by a polymer membrane. In particular, the processing of microcapsules described in more detail below is generally directed toward microcapsules having an inner core of one material surrounded by an intermediate shell of an immiscible material, which is in turn surrounded by an outer polymer shell. The system and method described herein, however, are not restricted to fabricating microcapsules with such structure. In particular, the system and method described herein may be used to form and process microcapsules having any number and arrangement of materials encapsulated by an outer membrane, including microcapsules with a single inner material and others with more than two inner materials encapsulated by an outer membrane.

In general, reservoirs **22** and **24** may be adapted to store materials with which to form the interior of a microcapsule. In some medical or pharmaceutical applications, reservoir **22** may be specifically configured to store a contrast agent medium for imaging CT scans, while reservoir **24** may be configured to store an aqueous drug solution, such as antibiotics, enzymes and/or immune stimulants. In other cases, reservoir **22** may be adapted to store live cells for transplantation purposes and reservoir **24** may be adapted to store an immunosuppressant medium. In such an embodiment, the fluid stored within reservoir **22** may be configured to serve as a drug carrier within the interior of a microcapsule. Other mediums used in the medical or pharmaceutical industry may also or alternatively be stored within reservoirs **22** and **24**. In yet other embodiments, materials which are used to form microcapsules for applications other than for the pharmaceutical and medical industries may be stored within reservoirs **22** and **24**. In particular, reservoirs **22** and **24** may be used to store mediums which are known to be used for the production of microcapsules in applications for waste water processing, bulk pumping of industrial chemicals and/or ownership identification of liquid products.

In any case, reservoirs **22** and **24** are preferably used to store materials which are immiscible to each other such that the materials do not become a homogeneous mixture upon formation of the microcapsule. For example, in some embodiments, reservoirs **22** and **24** may be used to store materials with which to respectively form an inner core and an intermediate shell of a microcapsule as described above. The term "immiscible", as used herein, may generally refer the solubility of multiple materials having no more than 10 gm/100 ml in an adjoining material and that the adjoining materials form an interface resembling a meniscus. In other embodiments, however, materials which form a homogenous mixture may be respectively stored within reservoirs **22** and **24**.

As noted above, microencapsulation system **20** may, in some embodiments, be configured to encapsulate more than two materials. For example, in some cases, reservoirs **22** and/or **24** may be adapted to store more than one material such that the inner core and/or the intermediate shell of a microcapsule may each include more than one medium. More specifically, reservoirs **22** and/or **24** may include a plurality of reservoirs and/or may be configured to have different compartments such that a variety of materials may be stored within the reservoirs. Consequently, reservoirs **22** and **24**, as used herein, may respectively represent a single reservoir or multiple reservoirs. In some embodiments, microencapsula-

tion system **20** may be configured to encapsulate a single material. As such, in some embodiments, one of reservoirs **22** and **24** may be omitted from microencapsulation system **20**. In yet other embodiments, however, microencapsulation system **20** may be adapted to separately encapsulate the materials stored within reservoirs **22** and **24**. In this manner, microencapsulation system **20** may be adapted to form different types of microcapsules, each with a different single-material interior. In some cases, microencapsulation system **20** may be additionally or alternatively adapted to form different types of microcapsules with multi-material interiors.

In any case, microencapsulation system **20** may be configured to allow a variety of different microcapsules, particularly microcapsules having different viscosities, to be formed within a single system. An exemplary embodiment of microencapsulation system **20** including an adaptation to form a variety of different microcapsules is illustrated in FIG. **2** and described in more detail below. It is noted that the variety of microcapsules which may be formed from a microencapsulation system having such an adaptation may differ not only by composition, but also or alternatively by the number of materials within the microcapsule and/or the structure of the microcapsule. In general, the "structure" of a microcapsule, as used herein, may generally refer to the arrangement of materials within the microcapsule. For example, one structure of a microcapsule may include an inner core of one material surrounded by an intermediate shell of an immiscible material, which is in turn surrounded by an outer polymer shell. An alternative microcapsule structure may include two immiscible materials forming two halves of a spherical droplet which is in turn surrounded by an outer polymer shell. Other microcapsule structures may be formed as well using the system and method described herein, depending on the design specifications of the system and microcapsule to be formed.

As shown in FIG. **1**, microencapsulation system **20** may, in some embodiments, be adapted to introduce the materials stored within reservoirs **22** and **24** into inner chamber **26** of chamber **28**. More specifically, microencapsulation system **20** may include microsphere dispensers **30** and **32**, which are adapted to respectively discharge material stored within reservoirs **22** and **24** into inner chamber **26**. In general, the volume ratio of materials respectively discharged from reservoirs **22** and **24** to form the interior of a microcapsule may be between approximately 1:2 and approximately 1:10 or, more specifically, between approximately 1:5 and approximately 1:10. In embodiments in which reservoir **24** stores an aqueous drug solution, it may be particularly advantageous to employ volume ratios between approximately 1:5 and approximately 1:10 to maximize the drug payload of the microcapsule. In some embodiments, particulate matter may be combined with the materials from reservoirs **22** and **24** to form the interior of a microcapsule. In such an embodiment, the volume ratio of the particulate matter may be less than approximately 1% of the total volume of the microcapsule interior.

In some embodiments, the ratio of materials used to form the interior of a microcapsule may be characterized with regard to the density of the materials rather than the volume of materials. In particular, the density of materials respectively discharged from reservoirs **22** and **24** to form the interior of a microcapsule may be between approximately 1:2 and approximately 1:10 or, more specifically, between approximately 1:5 and approximately 1:10. In any case, the volume and density ratios of materials forming an interior of a microcapsule may vary, depending on the design specifications and intended application of the microcapsules. Consequently,

smaller or larger volume and/or density ratios than the ones recited above may be appropriate.

As noted above, microencapsulation system 20 may, in some embodiments, be configured to form microcapsules having an inner core of one material surrounded by an intermediate shell of an immiscible material, which is in turn surrounded by an outer polymer shell. As such, in some cases, microencapsulation system 20 may be configured to dispense materials from microsphere dispensers 30 and 32 such that the material discharged from reservoir 24 may coat the material discharged from reservoir 22. In particular, microsphere dispenser 32 may, in some embodiments, be configured to fill inner chamber 26 such that droplets of the material from reservoir 22 may be dispensed into a bath of the material from reservoir 24. In other embodiments, microsphere dispenser 32 may be configured to dispense just enough material into inner chamber 26 to envelop a single droplet of material dispensed from microsphere 30 for the formation of each microcapsule.

In either case, microsphere dispensers 30 and 32 may be arranged in alignment with each other. "Arranged in alignment", as used herein, may generally refer to the placement of microsphere dispensers 30 and 32 relative to each other to dispense materials from reservoirs 22 and 24 such that spherical droplets comprising the two materials may be formed. In other words, microsphere dispensers 30 and 32 may be arranged such that the material from reservoir 24 encases a droplet of material from reservoir 22. In some embodiments, microsphere dispenser 32 may be arranged above microsphere dispenser 30 as shown in FIG. 1. In other embodiments, microsphere dispenser 32 may be arranged in the vicinity of microsphere dispenser 30 or, more specifically, at approximately the same location as microsphere dispenser 30. In yet other cases, microsphere dispensers 30 and 32 may be positioned near opening 38 of inner chamber 26. In general, opening 38 may serve as an orifice or nozzle by which to pass spherical droplets formed of the materials from reservoirs 22 and 24 into chamber 28. In this manner, the spherical droplets, in some embodiments, may be formed upon passing through opening 38.

In general, the viscosity and surface properties of the materials used to form the spherical droplets may influence the distance at which to position microsphere dispensers 30 and 32 as well as the frequency and flow rate at which to discharge materials from reservoirs 22 and 24 such that the spherical interiors of the microcapsules may be formed. As such, microsphere dispensers 30 and 32 may be spaced farther or closer together than depicted in FIG. 1. An exemplary distance between microsphere dispensers 30 and 32 may generally be less than 1 inch, however, the dispensers may be spaced apart by larger distances in some cases. In some embodiments, microsphere dispenser 32 may be arranged within inner chamber 26, such as near microsphere dispenser 30 and/or opening 38 as noted above. In any case, microsphere dispensers 30 and 32 may be configured to move within microencapsulation system 20 in some embodiments.

In view of the alignment configurations of microsphere dispensers 30 and 32 and opening 38 discussed above, microencapsulation system 20 may be configured to produce a vertical flow of spherical droplets formed from the materials stored within reservoirs 22 and 24. For example, a vertical flow of spherical droplets may, in some embodiments, be formed within inner chamber 26 as shown in FIG. 1. In other cases, a vertical flow of spherical droplets may be formed upon passing through opening 38. In either case, the spherical droplets may be gravity lead through microencapsulation system 20 in addition to or alternative to being lead via a fluid

through the system. In other embodiments, however, microencapsulation system 20 may be configured to produce a production flow of spherical droplets other than a vertical production flow. For example, in some cases, microencapsulation system 20 may be configured to produce a production flow spherical droplets which traverse nearly horizontal through the system. In particular, inner chamber 26 and/or chamber 28 may be arranged on its side relative to the illustration shown in FIG. 1. In such a case, microsphere dispensers 30 and 32 may, in some embodiments, be arranged at substantially the same level within microencapsulation system 20. In yet other embodiments, however, microsphere dispensers 30 and 32 may be arranged in vertical alignment with each other. In either case, microsphere dispensers 30 and 32 may be arranged such that the material discharged from reservoir 22 may be encapsulated by the material discharged from reservoir 24.

As noted above, microencapsulation system 20 may be configured to dispense distinct droplets of material from microsphere dispensers 30 and/or 32 in some embodiments. In some cases, microencapsulation system 20 may include pulsatile flow generators 34 and 36 respectively coupled between reservoirs 22 and 24 and microsphere dispensers 30 and 32. Such pulsatile flow generators may be configured to supply materials from reservoirs 22 and 24 at any flow rate and frequency suitable for the generation of microcapsules having a diameter ranging from sub-micron dimensions to hundreds of microns, or more specifically between approximately 1 micron and approximately 800 microns and even more specifically between approximately 1 micron and approximately 300 microns. The nozzles included within microsphere dispensers 30 and 32 and/or opening 38 may be adapted to form microcapsules of such size as well. More specifically, microsphere dispensers 30 and 32 and/or opening 38 and, in some embodiments, pulsatile flow generators 34 and 36 may be configured to dispense the materials from reservoirs 22 and 24 in a synchronous manner to form microcapsules with co-axial interiors. In this manner, spherical droplets having an inner core of material from reservoir 22 and an intermediate shell of material from reservoir 24 may be formed. In some embodiments, pulsatile flow generators 34 and/or 36 and the nozzles within microsphere dispensers 30 and 32 and opening 38 may be configured to generate a flow of materials at an ultrasonic frequency. Microencapsulation system 20 may be configured to deliver materials at lower or higher frequencies, however, depending on the design specifications of the system.

As noted above, one or both of pulsatile flow generators 34 and 36 may be omitted from microencapsulation system 20 in some embodiments. Consequently, the generation of microcapsules within microencapsulation system 20 may not be dependent on the inclusion of such flow generators. In particular, microencapsulation system 20 may be configured to generate microcapsules with the aforementioned diameters using other means, such as the inclusion of one or more pulsatile pumps coupled to microsphere dispensers 30 and 32 and/or opening 38. In yet other embodiments, microsphere dispensers 30 and 32 and/or opening 38 may be spaced apart by a distance sufficient to form microcapsules without the use of pulsatile mechanisms coupled to both dispensers, as described in more detail below.

As noted above, an exemplary embodiment of microencapsulation system 20 configured to form a variety of different microcapsules is shown in FIG. 2. Such an illustration is a cross-sectional view of microencapsulation system 20 taken along line AA of FIG. 1. As shown in FIG. 2, microencapsulation system 20 or, more specifically, inner chamber 26 may,

in some embodiments, include a plurality of inner chambers 26a-26c. It is noted that although FIG. 2 illustrates the inclusion of three inner chambers within microencapsulation system 20, microencapsulation system 20 may include any number of inner chambers. In some cases, microencapsulation system 20 may include an array of inner chambers within chamber 28. In any case, although inner chambers 26a-26c are shown uniformly spaced within chamber 28 and include substantially similar dimensions, inner chambers 26a-26c may alternatively be spaced non-uniformly within chamber 28 and/or having different dimensions than each other. In some cases, microencapsulation system 20 may be configured to dispense a different material within each of inner chambers 26a-26c, as illustrated in FIG. 2 by the different cross-hatch patterned droplets. In other embodiments, however, microencapsulation system 20 may be configured to dispense the same material within each of inner chambers 26a-26c. In either case, the materials dispensed into inner chambers 26a-26c may be from reservoirs 22 and 24 as described above in reference to FIG. 1 and, therefore, may be used to form the inner cores of the microcapsules in some embodiments.

FIG. 2 illustrates pulsatile flow generator 36 arranged above inner chambers 26a-26c. As noted above, pulsatile flow generator 36 may be configured to regulate the flow of material from reservoir 24 through microsphere dispenser 32 or, more specifically, through microsphere dispensers 32a-32c as shown in FIG. 2. In yet other embodiments, microencapsulation system 20 may not include pulsatile flow generator 36. In some embodiments, reservoir 24 may include a single type of material and microsphere dispensers 32a-32c, openings 38a-38c and/or pulsatile flow generator 36 may be configured to discharge the material such that the material coats the droplets of material discharged from reservoir 22. In this manner, microencapsulation system 20 may be configured to form microcapsules having inner cores of different materials surrounded by intermediate shells of the same material.

Alternatively, microencapsulation system 20 may, in some embodiments, be configured to form microcapsules having inner cores of the same material surrounded by intermediate shells of different materials. More specifically, microencapsulation system 20 may be configured to discharge the same material from reservoir 22 and different materials from reservoir 24. In yet other embodiments, microencapsulation system 20 may be configured to form microcapsules having a variety of different inner core materials and different intermediate shell materials. In any case, the material within reservoir 22 may be discharged through one or more microsphere dispensers and, in some embodiments, by one or more pulsatile flow generators similar to the manner described in reference to microsphere dispenser 30 and pulsatile flow generator 34 in FIG. 1. Such microsphere dispensers and pulsatile flow generators, however, are not shown in FIG. 2 due to the cross-sectional view of the drawing.

As noted above, microencapsulation system 20 may, in some embodiments, be configured to form microcapsules having structures other than the one described above having an inner core and intermediate shell surrounding such an inner core. Consequently, it is noted that microencapsulation system 20 may be adaptively configured to accommodate different types of microcapsule structures. In addition, although the droplets in FIG. 2 are shown to be substantially uniform in size, microencapsulation system 20 may be adapted to dispense and form droplets of varying sizes. In particular, microencapsulation system 20 may be adapted to dispense and form droplets of different sizes within each of inner chambers 26a-26c. In some embodiments, however, it

may be advantageous to form the microcapsules to be substantially uniform in size. For instance, the packing density of the microcapsules may be maximized when they are substantially uniform in size. In other embodiments, it may be advantageous to form the microcapsules to be substantially uniform in size and volume ratio such that amount of fluid within the microcapsules may be substantially uniform. Such a condition may be particularly advantageous in embodiments in which the microcapsules are used for the delivery of drugs.

Returning to FIG. 1, inner chamber 26 is shown nested within an upper portion of chamber 28 and includes opening 38 at the bottom thereof. Consequently, inner chamber 26 may serve as a module to direct spherical droplets into chamber 28 via opening 38. In general, chamber 28 may contain a polymer/solvent solution with which to coat the spherical droplets dispensed from inner chamber 26. As such, the spherical droplets formed within inner chamber 26 may be dispensed directly into the polymer/solvent solution. In general, the polymer/solvent solution forms an immiscible outer membrane around the spherical droplet to form a microcapsule. The formation of the outer membrane is achieved in such a way that minimal mixing occurs between the outer membrane and spherical droplet. More specifically, the two phases are brought together such that the fluid shear properties are controlled to levels not exceeding 150 dynes/cm² and the adsorptive surface properties at the immiscible interface are not significantly altered. In some embodiments, the fluid shear properties may be controlled to levels below 80 dynes/cm² or, more specifically, below 12 dynes/cm². Larger or smaller fluid shear levels may be appropriate, however, depending on the design specifications of microencapsulation system 20.

As noted above, a "microcapsule", as used herein, may generally refer to a droplet of material synthetically encased with an outer protective shell having a diameter ranging from sub-micron dimensions to a few hundred microns. In some embodiments, the polymer/solvent solution may include particles which can be activated by external magnetic or ultrasonic fields, such as one or more ceramic-ferromagnetic particles. Such an inclusion of particles may be particularly advantageous in industry applications in which the microcapsules are later exposed to magnetic or ultrasonic fields. For example, in embodiments in which the microcapsules include aqueous drug solutions or dyes, the trigger particles may be used to time the release of the drug or dye within the microcapsules. More specifically, a microcapsule coated with trigger particles may be configured to remain intact until exposed to magnetic or ultrasonic fields. In this manner, microcapsules may be ingested and travel within a body to a target location before the drug therein is released, allowing more efficient use of the drug. Alternatively, trigger particles may be used to release dyes within a fluid for identification purposes. In yet other embodiments, trigger particles may be used to enhance the identification of the microcapsules within a fluid as described in more detail below.

In addition to coating the spherical droplet formed within inner chamber 26, the polymer/solvent solution may further serve to guide the microcapsules through chamber 28. More specifically, the polymer/solvent solution may serve to suspend the microcapsules such that the rate the microcapsules descend through chamber 28 may be controlled. In a preferred embodiment, the microcapsules may be heavier than the polymer/solvent solution and, therefore, may be transferred through the solution by gravity in some cases. As shown in FIG. 1, the microcapsules moving through chamber 28 may be directed toward separation baffle system 40. Such a separation baffle system may be used to recover the residual

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materials carried from inner chamber 26 which were not used to form the spherical droplets. In some cases, separation baffle system 40 may also be used to recover the materials from microcapsules which break during the production process. In any case, separation baffle system 40 may be more specifically used to recover materials which are not soluble with the polymer/solvent solution. Such materials may include materials dispensed from reservoirs 22 and/or 24.

As shown in FIG. 1, the recovered material may be routed from chamber 28 to phase separation recovery unit 42. In general, phase separation recovery unit 42 may be used to separate the materials recovered from separation baffle system 40. In embodiments in which the material originally stored within reservoir 24 is separated from the recovered solution, the material may be recycled back to reservoir 24 as shown in FIG. 1. Such an embodiment may be particularly advantageous in embodiments in which an aqueous drug solution is stored within reservoir 24. In particular, the recycle process may reduce consumption of the drug solution within microencapsulation system 20, thereby lowering processing costs, particularly since drug solutions tend to be relatively costly. In other embodiments, the material originally stored within reservoir 22 may additionally or alternatively be separated from the recovered solution and may, in turn, be recycled back to reservoir 22. In yet other embodiments, the materials removed from chamber 28 may be disposed.

In any case, subsequent to passing through separation baffle system 40, the microcapsules are carried through chamber 28 to washing compartment 44. As shown in FIG. 1, a portion of chamber 28 may extend above washing compartment 44. Such a portion of chamber 28 may serve as a side conduit to recover and recycle the polymer/solvent solution used to suspend the microcapsules prior to, during, and subsequent to traversing through separation baffle system 40. More specifically, pump 50 may be used to draw the polymer/solvent solution from the bottom of chamber 28 such that only a small amount of the solution is transported into washing compartment 44. The recovered polymer/solvent solution may be returned to the main compartment of chamber 28 to encapsulate and suspend the spherical droplets produced from inner chamber 26. In some cases, phase separator 53 may be included in the side conduit of chamber 28. In general, phase separator 53 may be used to separate and dispose of residual materials included within the polymer/solvent solution such that the polymer/solvent solution may return to the main compartment of chamber 28 unpolluted. Such residual materials may include but are not limited to the materials used to form the spherical droplets within inner chamber 26 and which were not recovered in separation baffle system 40.

In general, washing compartment 44 may include a fluidized passage for washing and harvesting microcapsules dispensed from the microcapsule production unit of microencapsulation system 20 or, more specifically, from separation baffle system 40. In particular, washing compartment 44 may include a washing solution with which to remove residual polymer/solvent solution from microcapsules transported from chamber 28. In some cases, the washing solution may be used to cure the microcapsules. In particular, the washing solution may include a component by which to strengthen the outer membrane of the microcapsules. As shown in FIG. 1, the washing solution may be introduced into washing compartment 44 through dispenser 46. It is noted that the washing solution may be introduced into washing compartment 44 in other manners as well or alternatively, depending on the design specifications of microencapsulation system 20. In some cases, washing compartment 44 may be configured to suspend the microcapsules within a flowing stream of the

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washing solution. In this manner, the microcapsules may be transported through washing compartment 44 and subsequently harvested at or subsequent to exit 58.

As shown in FIG. 1, microencapsulation system 20 may include recirculation line 48 routed from washing compartment 44 to pass the washing solution through phase separator 52 back to dispenser 46. In some embodiments, recirculation line 48 may be one of a plurality of recirculation lines routed from washing compartment 44, each used to withdraw a different density fluid from the compartment. In general, phase separator 52 may be used to separate the polymer/solvent solution rinsed from the microcapsules in washing compartment 44 from the washing solution. In this manner, the washing solution may be returned to washing compartment 44 through dispenser 46 and the polymer/solvent solution may be routed to the side conduit of chamber 28. In some embodiments, phase separator 52 may be also used to separate any other materials recycled from washing compartment 44. For example, residual amounts of the materials used to form the spherical droplets within inner chamber 26 and which were not recovered in separation baffle system 40 may be removed from the recycled stream.

In any case, it may be advantageous, in some embodiments, to have washing compartment 44 configured to allow the polymer/solvent solution and other residual materials to separate from the washing fluid prior to recirculating the fluid back through recirculation line 48. In particular, washing compartment may, in some embodiments, be configured to be long enough such that the different density fluids can separate from each other. In such embodiments, recirculation line 48 and any other recirculation lines coupled to washing compartment 44 may be positioned near the end of the washing compartment. In other embodiments, however, microencapsulation system 20 may not include recirculation lines. Instead, the washing solution used to rinse the microcapsules may be disposed upon harvesting the microcapsules.

In addition to having a microcapsule production unit, separation baffle system 40 and washing compartment 44, microencapsulation system 20 may further include means 56 for analyzing microcapsules. As shown in FIG. 1, means 56 for analyzing microcapsules may be arranged at the end of washing compartment 44. Alternatively, means 56 for analyzing microcapsules may be arranged in another region of washing compartment 44 or down stream from washing compartment 44. In addition, means 56 may be configured to analyze the entire stream of microcapsules generated from microencapsulation system 20 in some embodiments. In other embodiments, means 56 may be configured to take a sample of the production flow of microcapsules. In any case, means 56 for analyzing microcapsules may generally be used to track, count, characterize and/or identify microcapsules. In some embodiments, the characterization of microcapsules may include determining the size, shape and/or content of microcapsules within the production stream. In addition or alternatively, the identification of microcapsules may include distinguishing different types of microcapsules and/or distinguishing microcapsules from debris or bubbles within the production stream. In this manner, means 56 may further be used to determine a concentration of different types microcapsules produced and processed within microencapsulation system 20. In general, the information obtained about the microcapsules (e.g., the size, shape, content and number) may be used for feedback control purposes to optimize the production of microcapsules from microencapsulation system 20.

As described in more detail below, one exemplary system that may be used to identify, count, characterize and/or track

microcapsules may be a system which includes adaptations to acquire images of a flowing fluid comprising the microcapsules as well as adaptations to measure the intensity of light transmitted through the microcapsules. An exemplary embodiment of such a device as well as a method for using the device are described in more detail below in reference to FIGS. 4-6. It is noted, however, that microencapsulation system 20 is not restricted to the inclusion of such a device. In particular, microencapsulation system 20 may include any device or system configured to track, count, characterize and/or identify microcapsules.

In some cases, microencapsulation system 20 may further include central processing unit (CPU) 54 to control the operation of microencapsulation system 20. In particular, microencapsulation system 20 may include a dedicated microprocessor-based controller or a general-purpose computer configured to automate the operations of microencapsulation system 20 such that microcapsules may be fabricated and processed in a single continuous process. Consequently, the method described in reference to FIG. 3 below may, in some embodiments, be a computer-implemented method. As described below, CPU 54 may be used to control a variety of components within microencapsulation system 20 and, accordingly, may be coupled to the components of microencapsulation system 20 which it is configured to control. Such individual connections to the components, however, are not illustrated in FIG. 1 to simplify the illustration of microencapsulation system 20. Instead, CPU 54 is shown coupled to microencapsulation system 20 by a dotted line to show a general connection to the components included within the microencapsulation system.

In some cases, CPU 54 may be configured to control the operation of microsphere dispensers 30 and 32 and/or pulsatile flow generators 34 and 36 to control the production of spherical droplets within inner chamber 26. In particular, CPU 54 may be configured to send program instructions with which to regulate the flow from microsphere dispensers 30 and 32, opening 38 and/or pulsatile flow generators 34 and 36 in order to produce microcapsules at a particular rate and size. In some cases, CPU 54 may be used to control the rate the washing solution is introduced into washing compartment 44 as well as the amount of washing solution that is recycled from washing compartment 44. In addition, CPU 54 may be configured to control the operation of means 56 for analyzing the microcapsules. Consequently, CPU 54 may, in some embodiments, be configured to simultaneously operate the microcapsule production unit of microencapsulation system 20, washing compartment 44 and means 56 to process the microcapsules in a continuous manner. In some cases, CPU 54 may be configured to change the flow rate of materials through dispensers 30, 32, and/or 46 based upon the analysis performed by means 56. In particular, CPU 54 may be adapted to provide a feedback control loop between the microcapsule production unit of microencapsulation system 20, washing compartment 44 and means 56 for analyzing the microcapsules. In this manner, the fabrication and processing of microcapsules may be automatically altered to produce microcapsules within design specifications of the product.

It is noted that although microencapsulation system 20 is adapted to produce, cure, wash and analyze a continuous flow of microcapsules, the system is not necessarily restricted to processing microcapsules through each of the four process steps. In particular, microencapsulation system 20 may be used for fewer process steps than for which the system has adaptations. In some embodiments, microencapsulation system 20 may be adapted to route microcapsules through bypasses such that one or more process steps may be averted.

In other embodiments, microencapsulation system 20 may be adapted such that the microcapsules pass through the entire chamber, but are not processed with all adaptations of the system. In addition, microencapsulation system 20 may, in some embodiments, be configured to process microcapsules under sterile conditions. As noted above, microencapsulation system 20 may be used to form microcapsules for the medical and/or pharmaceutical industry. As such, special precautions may need to be taken to insure that the production of microcapsules is performed under sterile conditions in such applications. For example, components and/or subsystems may be included within microencapsulation system 20 to insure a continuous supply of steam is available for Steam-In-Place (SIP) sterilization of the system.

As noted above, FIG. 3 illustrates a flowchart of a method for processing microcapsules in a single continuous process. It is noted that the method described in reference to FIG. 3 may be conducted using any microencapsulation system configured to produce, cure, wash and analyze microcapsules in a single continuous flow and therefore, may be conducted using microencapsulation system 20 or a similar system thereof. As shown in FIG. 3, the method may include step 60 in which a continuous flow of microcapsules are produced within a suspended fluid. Such a step may include forming microcapsules with any number of materials and any structure, including but not limited to a microcapsule including an inner core and an intermediate shell, which is encapsulated by an outer membrane. The formation of the microcapsules may be conducted, for example, using the microcapsule production unit described above in reference to FIG. 1. In some embodiments, step 60 may specifically include dispensing substantially uniform droplets of fluids of substantially different viscosities, coating the substantially uniform droplets with an immiscible solution and forming an outer polymer shell around the coated fluid droplets. Such sequence of process steps may be particularly advantageous for systems which are adapted to form different types of microcapsules while also maximizing the packing density. It is noted, however, that the aforementioned sequence of process steps merely incorporates an exemplary embodiment of step 60 and, therefore, does not restrict the method described herein to such a process.

As shown in FIG. 3, the method may continue to step 62 in which a first fluid is separated from the suspended fluid while retaining the microcapsules within a second fluid of the suspended fluid. In reference to microencapsulation system 20, step 62 may be conducted as the fluid within chamber 28 traverses through separation baffle system 40. As noted above in reference to FIG. 1, the fluid may be used to suspend the microcapsules. In such an embodiment, the residual materials from inner chamber 26 or, more specifically from reservoirs 22 and/or 24 may be separated from the fluid while the microcapsules remain suspended within the polymer/solvent solution. As noted above, the separated materials may, in some embodiments, be recycled back through the system to form additional microcapsules. Consequently, the method depicted in FIG. 3 includes step 64 outlining such a recycling process. In some embodiments, however, step 64 may be omitted from the method. In such a case, the separated materials may be disposed.

FIG. 3 illustrates the continuation of the method to step 66 in which the microcapsules are passed from the suspended fluid directly into a washing solution. More specifically, step 66 may include removing the retained microcapsules from the suspended fluid and immediately rinsing the removed microcapsules with the washing solution. Such a process is described above in reference to transferring the microcap-

sules from the microcapsule production unit of microencapsulation system **20** into washing compartment **44**. In some embodiments, the method may further include extracting at least some of the washing solution from the washing compartment as noted in step **70** of FIG. **3**. Such an extraction process may, in some embodiments, continue onto step **72** in which the extracted washing solution is recycled in order to rinse other microcapsules. In such an embodiment, the method may include separating the residual fluid rinsed from the microcapsules from the washing solution as described in reference to phase separator **52** in FIG. **1**. In yet other embodiments, the extracted washing solution may not be recycled back through the system. In such a case, step **72** may be omitted from the method described in reference to FIG. **3**. In other embodiments, the washing solution may not be extracted from the washing compartment at all. Consequently, in some cases, step **70** may also be omitted from the method depicted in FIG. **3**.

In either case, the method may further include analyzing the microcapsules as noted in step **68** of FIG. **3**. Such a process is described above in reference to means **56** for analyzing microcapsules in microencapsulation system **20**. In general, step **68** may include tracking, counting, characterizing and/or identifying microcapsules. In some embodiments, the characterization of microcapsules may include determining the size and/or shape of microcapsules within the production stream. In addition, the identification of microcapsules may include distinguishing different types of microcapsules and/or distinguishing microcapsules from debris or bubbles within the production stream. In this manner, step **68** may further include determining a concentration of different types of microcapsules produced and processed within microencapsulation system **20**. In any case, the microcapsules may, in some embodiments, be analyzed while suspended in a flowing fluid. As such, in some cases, step **68** may be conducted while the microcapsules are within the washing compartment of the microencapsulation system. In other embodiments, step **68** may be conducted when the microcapsules are in a different region of the system. In yet other cases, the microcapsules may be analyzed in a stagnant bath or in a region void of fluids. In any case, the method may further include step **69** for harvesting the microcapsules. Such a process may include collecting, sorting and/or packaging the microcapsules for further use.

As noted above, an exemplary embodiment of a system configured to analyze microcapsules is shown and described in reference to FIGS. **4-6**. In particular, FIG. **4** illustrates system **80** configured to track, count, characterize and/or identify microparticles in a flowing fluid. FIG. **5** illustrates exemplary graphical data which may be obtained from system **80** and FIG. **6** depicts a flowchart outlining a method for identifying, counting, characterizing and tracking microparticles in motion. It is noted that although system **80** in FIG. **4**, the graphical data in FIG. **5** and the flowchart in FIG. **6** are described in reference to systems and methods for analyzing microcapsules, such as those fabricated and processed within microencapsulation system **20** of FIG. **1**, system **80** and the method depicted in FIG. **6** is not restricted to such an application. In particular, the system and method described in reference to FIGS. **4-6** may be used in a variety of applications in which it may be desirable to track, count, characterize and/or identify microparticles, such as in pharmaceutical and medical applications, waste water processing, bulk pumping of industrial chemicals and ownership identification of liquid products.

In addition, the system and method described in reference to FIGS. **4-6** is not restricted to tracking, counting, character-

izing and/or identifying microcapsules, but rather may be more broadly used for tracking, counting, characterizing and/or identifying microparticles. As noted above, a "microparticle", as used herein, may include intentionally and unintentionally formed synthetic and naturally occurring particles. In contrast, however, a "microcapsule" may solely refer to synthetically fabricated microspheres. Consequently, the term "microparticle" may encompass a broader range of microspheres. In general, system **80** may be configured to analyze discrete samples of a stream or an entirety of the stream. In either case, system **80** may be configured to make real-time measurements of microparticles flowing in a pipeline or other flowing liquid system. Consequently, chamber **82** may, in some embodiments, be a segment of a chamber or a pipe. In other embodiments, however, chamber **82** may be a distinct component for sampling a fluid from a different chamber.

Although FIG. **4** illustrates chamber **82** arranged to induce a horizontal flow of fluid, chamber **82** may alternatively be configured to induce a vertical flow of fluid or any flow other than a horizontal flow. In addition, the system described in reference to FIG. **4** may, in some embodiments, be a portable unit. More specifically, system **80** may be configured such that it can be moved to different locations. In some cases, system **80** may be configured to operate upon battery power. Consequently, in such an embodiment, system **80** may be used in areas in which alternating current (AC) power is not available. Furthermore, system **80** may, in some embodiments, include means **81** configured to flush out chamber **82** such that residual particles may be removed and the chamber can be cleaned. In general, means **81** may be coupled to chamber **82** in a variety of manners. To simplify the illustration of system **80**, however, means **81** is shown coupled to system **80** by a dotted line to show a general connection to chamber **82**.

As shown in FIG. **4**, system **80** may include chamber **82** comprising inlet **84** and outlet **86** with which to respectively introduce and dispense a flowing fluid comprising microparticles. In general, chamber **82** may be configured such that the fluid carries each suspended microparticle abreast with the chamber walls such that each microparticle within the fluid may be detected and tracked individually. In this manner, chamber **82** may be configured to induce a parabolic flow from inlet **82** to outlet **84**. In other words, chamber **82** may be configured to induce a drag force within the chamber such that fluid near the center flows at a faster rate than the fluid along the sidewalls of the chamber. In this manner, microparticles within the fluid may change their positions relative to each other as they pass through chamber **82**. Consequently, all microparticles within chamber **82** may be accounted for when sequential images of the fluid are taken. The process of obtaining and analyzing the sequential images to identify, track and count microparticles within a fluid is described in more detail below in reference to detector **96**.

In a preferred embodiment, system **80** may be configured to induce a laminar flow of fluid through chamber **82**. For example, system **80** may be configured to control the flow rate of fluid through chamber **82** (i.e., from inlet **84** to outlet **86**) to induce a laminar flow. Although laminar motion of a fluid is dependent on a number of variables, as described below, an exemplary range for system **80** to be adapted to control the flow rate of a fluid may be between approximately 0.10 ml/min and approximately 1.00 ml/min or, more specifically, between approximately 0.10 ml/min and approximately 0.50 ml/min. In some cases, system **80** may be configured to control a flow rate of the fluid through chamber **82** to be between approximately 0.10 ml/min and approximately 0.30 ml/min. Larger or smaller fluid flow rates may be appropriate, how-

ever, depending on the design specifications of the system and the fluid in which the microcapsules are immersed. In addition to controlling the flow rate of the fluid to generate a laminar flow, chamber **82** may be configured to generate a laminar flow of fluid in other manners. For example, chamber **82** may be configured to induce a drag force along the chamber walls of chamber **82** which generates a laminar flow of fluid. In addition or alternatively, inlet **84** and/or outlet **86** may be configured to generate a laminar flow of fluid through chamber **82**. In particular, inlet **84** and/or outlet **86** may be configured with an opening having dimensions that are substantially similar to height H and width W of chamber **82**.

In some cases, the dimensions (i.e., height H, length L and/or width W) of chamber **82** may be configured to generate a laminar flow. Although specific dimensions for height H, length L and width W may be dependent on the design specifications for system **80** and the fluid for which it is configured to allow flow therethrough, an exemplary range for height H may be between approximately 10 microns and approximately 2000 microns, or more specifically between approximately 50 microns and approximately 1000 microns. In addition, an exemplary range for length L may be between approximately 100 microns and approximately 10,000 microns, or more specifically between approximately 100 microns and approximately 5000 microns. Furthermore, an exemplary range for width W may be between approximately 10 microns and approximately 1200 microns or, more specifically, between approximately 10 microns and approximately 100 microns and, in some cases, approximately 20 microns. Larger and/or smaller chamber heights, lengths, and widths of chamber **82**, however, may be appropriate. For example, in some embodiments, chamber **82** may be configured to have a width which is approximately 30% to approximately 100% larger than the diameter of the largest micro-particle likely to flow through the chamber.

In addition to inducing the fluid in a laminar flow, system **80** may be configured to induce a low shear force within the fluid such that the microparticles are not torn apart. In particular, system **80** may be configured to induce a fluid shear force of less than approximately 100 dynes/cm² or, more specifically less than approximately 20.5 dynes/cm². In some cases, it may be advantageous to induce a fluid shear force less than approximately 12 dynes/cm². In any case, the adaptation of system **80** to control the flow rate and motion of the fluid through chamber **82** may be through the inclusion of flow rate generators or solenoid valves on inlet **84** and/or outlet **86**. As described in more detail below, system **80** may, in some embodiments, include CPU **98** with which to operate the flow rate generators and/or solenoid valves.

FIG. 4 further illustrates system **80** having light sources **88a** and **88b** which are adapted to provide incident light to chamber **82**. As shown in FIG. 4, the light from light sources **88a** and **88b** may, in some embodiments, be transmitted through chamber **82** via the sidewalls of the chamber. Accordingly, the back and front sidewalls of chamber **82**, as depicted in FIG. 4, may be translucent. In other cases, light from light sources **88a** and **88b** may be additionally or alternatively transmitted through chamber **82** via the upper and lower walls of the chamber. In such embodiments, the upper and lower walls of chamber **82** may be translucent. In any case, system **80** provides opposing optical view ports with which to allow incident light from light sources **88a** and **88b** to transfer through chamber **82**.

In some cases, it may be advantageous to transmit light through a relatively small dimension of chamber **82** such that system **80** is allowed to accurately track, count, characterize and identify microparticles within the fluid passing there

through. In particular, transmitting light through a relatively narrow dimension of chamber **82** may allow relatively small amounts of the fluid and suspended particles to be analyzed. As a result, a relatively small number of microparticles may exist at a particular section of chamber **82** at a given point in time. More specifically, the density of microparticles in chamber **82** may be such that a substantial number of microparticles are not traversing in the shadow of other microparticles hindering the tracking, counting, characterization and identification of individual microparticles. It is noted that the dimensions of chamber **82** do not necessarily restrict microparticles from traversing in the shadow of each other entirely, but merely serves to minimize the overlap of the number of microparticles in the fluid. As noted above, width W (i.e., the distance between the opposing view ports within the back and front sidewalls of chamber **82**) may, in some embodiments, be configured to be the smallest dimension of chamber **82**. In particular, chamber **82** may have a width between approximately 10 microns and approximately 200 microns or, more specifically, between approximately 50 microns and approximately 100 microns. In yet other embodiments, height H may be configured to be the smallest dimension of chamber **82**, particularly when light sources **88a** and **88b** are configured to transmit light through the upper and lower walls of the chamber.

In some cases, light sources **88a** and **88b** may be configured to provide light of different wavelengths. In this manner, intensity measurements of transmitted light, as described in more detail below, may be obtained for a plurality of wavelengths, providing additional data with which to track, count, characterize and identify microparticles. In other words, system **80** may serve as a spectrophotometer by measuring the amount of wavelength-specific, transmitted or reflected light from each microparticle. In some embodiments, one or both of light sources **88a** and **88b** may be individually configured to provide different wavelengths of light. In such a case, CPU **98** may, in some embodiments, be used to control the selection of wavelengths transmitted from the light sources as described in more detail below. In yet other embodiments, light sources **88a** and/or **88b** may be configured to provide a single wavelength of light. In any case, system **80** may have any number of light sources, including a single light source or more than two light sources and, therefore, is not restricted to the embodiment depicted in FIG. 4. In cases in which multiple wavelengths of light are transmitted through chamber **82**, system **80** may, in some embodiments, include bandpass filters for simultaneous acquisition of the images produced from the transmitted light. Such bandpass filters may be incorporated within detector **96** and/or magnification lens(es) **94**, which are described in more detail below. In other embodiments, the band filters may be distinct components from detector **96** and magnification lens(es) **94**.

In general, system **80** may be adapted to track, count, characterize and/or identify individual microparticles by obtaining multiple images of the fluid as it traverses through chamber **82** and measuring the intensities of light transmitted through the microparticles as they correspond to the respective images. As such, system **80** may include a photometer configured to measure the intensity of light transmitted through individual microparticles from light sources **88a** and **88b**. In addition, system **80** may include an imaging system configured to acquire images of the flowing fluid within chamber **82**, such as a charge-coupled device (CCD) imaging system. Such a photometer and imaging system are collectively illustrated in FIG. 4 as detector **96**. In general, detector **96** may either represent the photometer and imaging system of system **80** as separate components or as integrated com-

ponents of the same device, depending on the design specifications of the system. A more detailed description of how system **80** is adapted to track, count, characterize and/or identify individual microparticles through the use of detector **96** is described in more detail below in reference to FIG. **5**.

As shown in FIG. **4**, system **80** may sometimes include moveable mirror **92** to reflect the light transmitted through chamber **82** to detector **96**. In general, moveable mirror **92** may be powered by motor **90**. In some embodiments, however, moveable mirror **92** may be omitted from system **80**. In such an embodiment, detector **96** and light sources **88a** and **88b** are preferably positioned in alignment with each other. In some cases, detector **96** and light sources **88a** and **88b** may be configured to move along the length of chamber **82**, regardless of whether moveable mirror **92** is included within system **80**. In any embodiment, the aforementioned adaptations of system **80** may allow detector **96** to capture sequential images of the fluid as it traverses through chamber **82**. In cases in which different wavelengths of light are transmitted through chamber **82**, system **80** may be adapted to allow detector **96** to capture images of the same microparticles at each of the multiple wavelengths. Consequently, a multi-spectral absorption data may be obtained for individual microparticles.

An exemplary illustration of wavelength-specific light absorption data depicting microparticles measured in sequential images captured by an imaging system is illustrated in FIG. **5**. In particular, FIG. **5** illustrates the intensity of light transmitted through a region of a chamber in which microparticles exist. A narrow range of light transmissions at specific wavelengths may be used to characterize the content of microparticles and, therefore, may be used to identify specific microparticles (i.e., distinguish microcapsules from debris particles and bubbles). As shown in FIG. **5**, relatively low transmissions (i.e., high absorptions) of light may be indicative of debris microparticles or bubbles, while relatively high transmissions (i.e., low absorptions) of light may be indicative of microcapsules. In some cases, debris microparticles and/or bubbles may additionally or alternatively exhibit higher transmissions of light than the microcapsules. In any case, the reflection and/or transmission of light from microcapsules may be distinguishable from the reflective and/or transmission of light from debris microparticles and/or bubbles and, therefore, may offer a characteristic with which to track, count, characterize and/or identify microparticles within a fluid as discussed in more detail below. In some embodiments, the reflection of light from the microparticles may be plotted versus time and/or distance within the chamber to further enhance the ability to track, count, characterize and/or identify microparticles within a fluid.

As shown in FIG. **4**, system **80** may, in some embodiments, include magnification lens(es) **94** with which to magnify the image acquired by the imaging system of detector **96**. In particular, magnification lens(es) **94** may be interposed between detector **96** and mirror **92**. In yet other embodiments, however, the imaging system of detector **96** may have a magnification lens(es) incorporated therein. In such an embodiment, magnification lens(es) **94** may be omitted from system **80**. In either case, magnification lens(es) **94** may, in some embodiments, include a plurality of lenses arranged in series. In other cases, magnification lens(es) **94** may include a plurality of lenses arranged parallel to one another. In such an embodiment, the image reflected from mirror **92** may shine through a plurality of different lenses such that different magnifications of the image may be obtained and analyzed. In yet other embodiments, magnification lens(es) **94** may include a single magnification lens.

In any case, the magnification lens(es) used to enlarge the imaged area of the fluid may include any magnification power which is able to provide an image in which microparticles are clearly visible. For example, the magnification lens(es) may, in some embodiments, include a magnification power which is able to enlarge the appearance of an individual microparticle to be at least the size of one pixel of an image produced by the imaging system of detector **96**. Accordingly, the magnification power of the magnification lens(es) used to enlarge the imaged area of the fluid may generally depend on the size of the microparticles, the area of the fluid to be imaged as well as the design specifications of system **80**. Exemplary magnification powers, however, may generally range from approximately 2× to approximately 100× or, more specifically, between approximately 6× and 75×. In some embodiments, a magnification power of approximately 45× has been found to provide sufficient magnification such that the microcapsules may be easily visualized on a computer monitor.

As noted above, system **80** may be configured to compare light intensity measurements of consecutive images of the fluid such that individual microparticles may be tracked, counted, characterized and/or identified. More specifically, system **80** may be configured to coordinate the images from the imaging system of detector **96** with the light intensities measured by the photometer of detector **96** such that the size, shape, and/or types of microparticles within the fluid may be identified, characterized and counted. In general, debris microparticles and bubbles may vary in size and shape and, therefore, may have similar shapes and sizes as microcapsules in some embodiments. As noted above, however, debris microparticles and bubbles do not absorb the same amount of light as microcapsules. As such, based upon the measured light intensities of the particles, system **80** may be used to identify and characterize microparticles. In particular, the coordinated images may aid in distinguishing different types of microcapsules as well as distinguishing microcapsules from other microparticles (e.g., debris or bubbles) within the fluid since microcapsules will be characterized by particular sizes and the amount of light they will absorb or reflect. In this manner, a concentration of the microparticles within the fluid may also be determined using detector **96**. In general, the identification of a target microparticle is accomplished by comparing the transmitted light received on an adjacent pixel and then subtracting the light level recorded for the target microparticle as it passes from pixel to pixel.

In addition to determining the shape, size and type of microparticles within the fluid, the density of individual microparticles may be determined from the images acquired from the imaging system of detector **96**. In particular, the intensity of the transmitted or reflected light from each microparticle may be measured, then select values above a threshold may be recorded according to the pixel location in the captured image array. Time of flight of individual microparticles may be calculated between the images and, consequently, trajectories of the individual microparticles may be determined according to a pre-determined algorithm. The density of the individual microparticles may, in turn, be calculated from the trajectory of the microparticles. In addition, system **80** may be able to distinguish microcapsules from buoyant or sedimenting non-microcapsules by tracking the trajectory of the microparticles. In any case, the adaptation of system **80** to synchronize images from the imaging system with the light intensities measured by the photometer may be incorporated into detector **96** or may be controlled through CPU **98** as discussed in more detail below.

As shown in FIG. **4**, system **80** may include central processing unit (CPU) **98** to control operation of system **80**. In

particular, system **80** may include a dedicated microprocessor-based controller or a general-purpose computer configured to automate the operations of system **80** such that microparticles may be tracked, counted, characterized and/or identified. Consequently, the method described in reference to FIG. **6** below may, in some embodiments, be a computer-implemented method. As described below, CPU **98** may be used to control a variety of components within system **80** and, accordingly, may be coupled to the components of system **80** which it is configured to control. Such individual connections to the components, however, are not illustrated in FIG. **4** to simplify the illustration of system **80**. Instead, CPU **98** is shown coupled to system **80** by a dotted line to show a general connection to the components included within system **80**.

In some cases, CPU **98** may be configured to control the operation of light sources **88a** and **88b** such that the angle, position and/or wavelength of light transmitted to chamber **82** may be regulated. In addition, CPU **98** may be configured control the movement of moveable mirror **92** in order to capture sequential images of the fluid passing through chamber **82**. In some cases, CPU **98** may be used to control the flow rate of the fluid through chamber **82**. In addition, CPU **98** may be configured to control detector **96** for capturing images of the fluid within chamber **82** as well as measuring the intensities of light transmitted through the microcapsules. Such operational control adaptations of CPU **98** may be incorporated within a storage medium of CPU **98** having program instructions with which to regulate the operation of system **80** such that microparticles may be tracked, counted, characterized and/or identified in a flowing fluid. In particular, CPU **98** may include program instructions with which to control the operation of light sources **88a** and **88b**, moveable mirror **92**, detector **96** and/or the flow rate of fluid through chamber **82** as described above.

In addition, CPU **98** may include program instructions with which to analyze the measured light intensities from the photometer within detector **96** as well as the images captured from the imaging system within detector **96**. More specifically, CPU **98** may include program instructions for identifying microparticles that include comparing measured intensities of light transmitted through the microparticles at different locations within the chamber. In addition, CPU **98** may include program instructions that include matching measured light intensities with spectral characteristics of known microparticles. In this manner, CPU **98** may include program instruction with which to identify, characterize and count microparticles within a flowing fluid as well as track a trajectory of the microparticles through the chamber. More specifically, CPU **98** may include program instructions with which to distinguish different types of microparticles contained within the fluid, such as different types of microcapsules and/or debris microparticles within the fluid. In addition, CPU **98** may include program instructions with which to determine the shape, size and density of microparticles within the fluid. In some embodiments, CPU **98** may be adapted to identify, characterize, track and count more than 1000 microparticles at a time. In addition, CPU **98** may be adapted to identify, characterize and track a microcapsule in approximately 5 seconds or less.

FIG. **6** illustrates a flowchart of a method for analyzing microparticles within a flowing fluid. As shown respectively in steps **102** and **104** of FIG. **6**, the method may include flowing a fluid comprising microparticles in a laminar motion through a chamber and transmitting light through the fluid within the chamber. An exemplary explanation of such process steps are described above in reference to FIG. **4** in which a fluid is respectively introduced and dispensed from inlet **84**

and outlet **86** and light sources **88a** and **88b** are used to transmit light through chamber **82**. In particular, the step of flowing the fluid in a laminar motion may involve controlling the flow rate of the fluid through chamber **82** and/or configuring chamber **82** to generate a laminar flow of fluid. In particular, chamber **82** may be configured such that the drag force along the sidewalls of the chamber to generate a laminar flow of fluid. In addition or alternatively, inlet **84**, outlet **86** and/or chamber **82** as a whole may be configured with dimensions to generate a laminar flow of fluid. In any case, the step of transmitting the light through the fluid may involve transmitting a single wavelength of light or a spectrum of light through the fluid.

As noted in step **106**, the method may further include measuring the intensities of the light transmitted through a microparticle. Such light intensity measurements may be conducted by a photometer of the system as described in more detail above in reference to detector **96**. As shown in FIG. **6**, the method may further include step **108** in which the fluid is imaged a plurality of times as the microparticle flows through the chamber. Such an imaging process is described above in reference to detector **96** as well. Step **110** notes that at least some of the measured intensities of light between the different images of the fluid may be compared. In addition, step **112** outlines that the different images may be compared. Although step **110** is shown prior to the step of **112**, step **112** may alternatively be conducted prior to or at substantially the same time as step **110**.

In any case, the comparisons may generally be used to identify, characterize and/or count the microparticles within the fluid as described above in reference to system **80** in FIG. **4**. In addition or alternatively, the comparisons may be used to track the microparticles within the fluid. For example, in some embodiments, the comparisons of the different images may be used to calculate a time of flight and trajectories of individual microparticles. In some cases, the density of the individual microparticles may be calculated from the trajectories. In yet other cases, the density of the individual microparticles may be determined by terminating the flow of the fluid within the chamber and calculating buoyancy and/or sedimentation rates for the microparticles within the fluid. In other embodiments, the flow of the fluid may not need to be terminated in order to calculate the buoyancy and/or sedimentation rates of the microparticles. In either case, the calculation of trajectories or, more specifically, buoyancy and/or sedimentation rates of the microparticles may also be used to identify and distinguish different types of microparticles within the fluid as noted in step **114**. For example, step **114** may be used to distinguish microcapsules from debris microparticles or bubbles. Such a distinction, however, may also or alternatively be determined by comparing the measured light intensities and/or images of the fluid as described in reference to steps **110** and **112**.

It will be appreciated to those skilled in the art having the benefit of this disclosure that this invention is believed to provide a system and method for fabricating and processing microcapsules in a single continuous process as well as a system and method for analyzing microparticles in a flowing fluid. Further modifications and alternative embodiments of various aspects of the invention will be apparent to those skilled in the art in view of this description. For example, although embodiments of the microencapsulation system described herein are described as including a system which is configured to identify, count, characterize and/or track microparticles using a transmission of multi-wavelength light, a photometer and an imaging system, the microencapsulation system is not restricted to the inclusion of an analytical device

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with such a configuration. Similarly, the system described herein which is configured to analyze microparticles is not restricted to being used in applications in which microcapsules necessarily exist, much less in microencapsulation systems.

Accordingly, this description is to be construed as illustrative only and is for the purpose of teaching those skilled in the art the general manner of carrying out the invention. It is to be understood that the forms of the invention shown and described herein are to be taken as the presently preferred embodiments. Elements and materials may be substituted for those illustrated and described herein, parts and processes may be reversed, and certain features of the invention may be utilized independently, all as would be apparent to one skilled in the art after having the benefit of this description of the invention. Changes may be made in the elements described herein without departing from the spirit and scope of the invention as described in the following claims.

What is claimed is:

1. A method of fabricating and processing at least one microcapsule, comprising:
 dispensing at least one microparticle-sized droplet comprising a material;
 introducing the at least one droplet directly into a bath of solution;
 forming an immiscible outer membrane around the at least one droplet such that at least one microcapsule is formed;
 producing a continuous flow of the microcapsules within the bath of solution;
 passing the continuous flow of microcapsules from the bath directly into a washing solution;

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analyzing the microcapsules with a flow sensor, said step of analyzing the microcapsules comprising the act of transmitting light through the microcapsules, the act of measuring the intensity of light transmitted through the microcapsules, and the act of acquiring sequential images of the microcapsules as the microcapsules move in the washing solution so as to provide information about the microcapsules after the microcapsules have been formed; and

using the information obtained by said step of analyzing the microcapsules as feedback for simultaneously controlling the steps of dispensing the at least one droplet and of passing the continuous flow of microcapsules into a washing solution so as to process the microcapsules in a continuous manner.

2. The method of claim 1, further comprising the step of dispensing at least one microparticle-sized droplet of a second material immiscible with the at least one droplet of first material so as to coat each at least one droplet of first material before introducing each coated droplet into the bath of solution.

3. The method of claim 2, wherein the droplets of first and second material form co-axial multi-lamellar microspheres.

4. The method of claim 2, wherein the droplets of first and second material comprise fluids having substantially different viscosities.

5. The method of claim 2, wherein the droplets of first and second material comprise fluids having substantially different densities.

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