

Title of the Invention: A Microdroplet Generating Device and Method

Technical Field

[0001] The present invention relates to microdroplet generation technology, in particular a device capable of shearing a fluid into microdroplets of uniform size and dispersing them in another immiscible fluid; the present invention also relates to further curing the generated microdroplets into microspheres. This technology, the microdroplets produced thereby, and the microparticles formed by curing the microdroplets all have a wide range of applications in various technical fields.

Background Art

- [0002] In the prior art, a device for generating microdroplets is known, as shown in FIGS. 1A and 1B. In FIG. 1A, the first phase fluid 90 enters a cavity 91, which has at least one nozzle 92 on one side, and at least one actuator 93 is disposed inside the cavity 91. This actuator 93 may be a heater, which vaporizes a portion of the fluid using the high temperature generated by instantaneous heating to form pulsed bubbles 94 of the second phase (FIG. 1B). Since the second phase fluid 94 (bubbles) is immiscible with the first phase fluid 90, the second phase bubbles block fluid from entering the right side of the cavity 91 (located below the nozzle) and exert strong shear pressure on the first phase fluid 90 below the nozzle. This shear pressure extrudes fluid 90 from the nozzle 92. By the interaction mechanism between shear pressure, fluid, and nozzle shape (creating a complex vortex effect near the nozzle), droplets can be ejected through this interaction process. Repeating the two steps in FIGS. 1A and 1B (deactivate the actuator to allow fluid entry, activate the actuator to generate pulsed bubbles) enables continuous generation of droplets.
- [0003] However, this known technology has the following disadvantages: Its structure is complex, the actuator design is complex, and it requires the integration of relevant circuits and systems to control the actuator. The system (of this device) is complex and costly. Additionally, if large quantities of droplets need to be generated, this method is highly energy-intensive, costly, and completely impractical. Furthermore, the high-temperature actuator is not suitable for all fluids, and the resulting droplets may have different characteristics from the original fluid. These shortcomings need to be overcome and addressed. Therefore, the relevant industry still has a strong demand for microdroplet production devices that are simple in structure, easy to operate, and low in cost.

Summary of the Invention

- [0004] The present invention aims to solve the above problem, thereby providing a column device for producing microdroplets. The device has at least one input end and at least one output end, allowing a disperse system, which consists of a continuous phase and a disperse phase, to be fed through the at least one input end and then discharged through the at least one output end. A three-dimensional periodic cavity structure is disposed in the column device, which may be a three-dimensional ordered microstructure composed of a plurality of packed monodisperse spheres (wherein the voids between the spheres form narrow flow channels that allow the disperse system to pass through), or an inverse structure of the three-dimensional ordered microstructure (wherein a plurality of orderly arranged spherical cavities form a three-dimensional ordered porous microstructure, and the communication holes between these spherical cavities form narrow flow channels that allow the disperse system to pass through). The inventors have found that when the disperse system is fed into the column device of the present invention through the at least one input end, the continuous phase fluid interacts with the three-dimensional periodic cavity structure inside the column device, creating a complex vortex effect at the opening of the narrow flow channels. As a result, the disperse phase is gradually reduced in size from the original macro-droplets under the shear stress of the continuous phase fluid and further sheared into microdroplets. These microdroplets can be separated from the continuous phase fluid after further curing and used independently.
- [0005] Accordingly, a first embodiment of the present invention provides a column device for producing microdroplets, comprising:
- [0006] a hollow tube body having at least one input end and at least one output end disposed opposite the at least one input end; and
- [0007] a three-dimensional periodic cavity structure disposed inside the hollow tube body, which is selected from the group consisting of three-dimensional ordered microstructures formed by a plurality of packed spheres and inverse structures of the three-dimensional ordered microstructures. This structure allows a disperse system to be fed through the at least one input end, pass through the three-dimensional periodic cavity structure, and then be discharged through the at least one output end; the disperse system comprises a continuous phase and a disperse phase immiscible with the continuous phase.
- [0008] A second embodiment of the present invention provides a method for producing microdroplets using a column device, where the column device comprises:
- [0009] A hollow tube body having at least one input end and at least one output end disposed opposite the at least one input end; and
- [0010] A three-dimensional periodic cavity structure disposed in the hollow tube body, which is

selected from the group consisting of three-dimensional ordered microstructures formed by a plurality of packed spheres and inverse structures of the three-dimensional ordered microstructures. This structure allows a disperse system to be fed through the at least one input end, pass through the three-dimensional periodic cavity structure, and then be discharged through the at least one output end; the disperse system comprises a continuous phase and a disperse phase immiscible with the continuous phase;

[0011] The method comprises the following steps:

[0012] A) Feeding the disperse system into the at least one input end, wherein the disperse phase in the disperse system consists of one or more macro-droplets dispersed in the continuous phase;

[0013] B) Causing the disperse system to pass through the three-dimensional periodic cavity structure, so as to shear the one or more macro-droplets into a plurality of microdroplets dispersed in the continuous phase; and

[0014] C) Causing the continuous phase and the microdroplets to be discharged from the column device via the at least one output end.

Description of Drawings

[0015] FIGS. 1A and 1B are schematic diagrams showing a conventional microdroplet generating device and its operation mode;

[0016] FIG. 2 is a schematic diagram of a column device according to a specific example of the present invention;

[0017] FIG. 3A is a schematic diagram of a three-dimensional periodic cavity structure according to a specific example of the present invention, showing a three-dimensional ordered microstructure composed of a plurality of packed spheres;

[0018] FIG. 3B is a schematic diagram of a three-dimensional periodic cavity structure according to another specific example of the present invention, showing the structure as a three-dimensional ordered porous microstructure;

[0019] FIG. 4 is a flow diagram for producing microdroplets using the column device of the present invention;

[0020] FIG. 5 illustrates the relationship between flow rate and disperse phase microdroplet size for the column device of a specific example of the present invention, under different packed sphere diameters and packing lengths; FIG. 6 illustrates the relationship between flow rate and the dispersity of the disperse phase microdroplet size for the column device of a specific example of the present invention, under different packed sphere diameters and packing lengths.

[0021] Description of the Symbols:

[0022] Column Device 10

[0023] Hollow Tube Body 12

- [0024] Input End 14
- [0025] Output End 16
- [0026] Three-Dimensional Periodic Cavity Structure 18
- [0027] Sphere 20
- [0028] Gaps 22
- [0029] Spherical Cavity 24
- [0030] Connecting Hole 26
- [0031] Disperse System 30
- [0032] Continuous Phase 32
- [0033] Disperse Phase 34
- [0034] Macro-Droplets 36
- [0035] Microdroplets 38
- [0036] First Phase Fluid 90
- [0037] Cavity 91
- [0038] Nozzles 92
- [0039] Actuators 93
- [0040] Second Phase Fluid 94.

DETAILED DESCRIPTION

- [0041] The present invention provides a column device for producing microdroplets, which is suitable for processing a disperse system, in which macro-droplets dispersed in the continuous phase are sheared into microdroplets of uniform size. Fig. 2 is a schematic diagram of a column device 10 according to a specific example of the present invention, which comprises a hollow tube body 12 having at least one input end 14 and at least one output end 16 disposed opposite the at least one input end 14. In a specific example, the hollow tube body 12 is made of a material selected from the group consisting of stainless steel, titanium, quartz, glass, and hard plastics such as polypropylene, and is formed into a cylindrical, rectangular, or polygonal tube; a three-dimensional periodic cavity structure 18 is disposed inside the hollow tube body 12.
- [0042] According to a specific example of the present invention, the three-dimensional periodic cavity structure 18 may be a three-dimensional ordered microstructure composed of a plurality of packed spheres 20, as shown in FIG. 3A. The three-dimensional ordered microstructure refers to a microstructure composed of spheres 20 arranged in a three-dimensionally ordered manner. As used herein, “orderly” means that the distances between the spheres 20 exhibit a regular periodicity, and preferably the distances between the spheres 20 are approximately equal. The spheres 20 composing such a microstructure typically have uniform particle size, shape, chemical composition, internal structure, or surface properties, so as to facilitate the

arrangement of the spheres 20 into regular lattice-like structures. In a preferred specific example, the spheres 20 have monodispersity, meaning that the spheres 20 have a narrow size distribution and their particle sizes are highly uniform.

[0043] The spheres 20 can be made of any inert material that does not undergo substantial physical or chemical reactions with the disperse system. Non-limiting examples of suitable materials include metallic materials, as well as non-metallic materials such as polymeric materials and inorganic materials. Examples of metallic materials include but are not limited to, gold, silver, copper, platinum, aluminum, zinc, cerium, thallium, barium, yttrium, zirconium, tin, titanium, tungsten, cadmium and iron, as well as alloys thereof such as stainless steel. Polymeric materials are preferably thermoplastic polymers. Examples of such materials include, but are not limited to, polymeric homopolymers such as polystyrene (PS), polymethyl methacrylate (PMMA), polybutyl methacrylate (PBMA), polymethyl acrylate, poly(ethyl acrylate) (PEA), poly(butyl acrylate) (PBA), polybenzyl methacrylate, poly- α -methylstyrene, polyphenyl methacrylate, polydiphenyl methacrylate and polycyclohexyl methacrylate; as well as polymeric copolymers such as styrene-acrylonitrile copolymer, styrene-methyl methacrylate copolymer, styrene-butyl methacrylate copolymer and styrene-butyl acrylate copolymer. Examples of inorganic materials include, but are not limited to, titanium oxide, zinc oxide, cerium oxide, tin oxide, thallium oxide, barium oxide, aluminum oxide, yttrium oxide, zirconium oxide, copper oxide, nickel oxide, silicon oxide, as well as ceramics, glass, quartz and the like.

[0044] Those skilled in the field of geometric structures will appreciate that the properties and arrangements of the three-dimensional periodic cavity structures described herein may include various packing patterns. In a preferred specific example where the spheres 20 have monodispersity, when the spheres 20 are packed into the hollow tube body 12, they tend to stack in a closest-packed configuration to form the three-dimensional periodic cavity structure 18. That is, adjacent microspheres are tangent to each other; the centers of any three microspheres that are tangent to each other pairwise form an equilateral triangle; the coordination number of each microsphere is 12; and a plurality of triangular-like voids are left between adjacent microspheres. Preferably, at least a portion of the spheres 20 in the three-dimensional periodic cavity structure 18 are arranged in a closest-packed configuration. That is, at least 50% of the spheres 20 in the three-dimensional periodic cavity structure 18, more preferably at least 60% of the spheres 20, for example, at least 70% of the spheres 20, are arranged in a closest-packed configuration. Said closest-packed configurations include, but are not limited to, three-dimensional hexagonal closest packing (hcp), three-dimensional face-centered cubic packing (fcc), three-dimensional body-centered cubic packing (bcc), and combinations thereof. However, it is understood by those skilled in the relevant technical field

that due to limitations in manufacturing processes and materials, the spheres 20 cannot achieve an absolutely uniform size, and their configuration is not necessarily limited to perfect spheres, but may also be, for example, ellipsoids. Therefore, the three-dimensional periodic cavity structure 18 composed of the spheres 20 has periodicity in a macroscopic and statistically averaged sense. Inevitably, crystal-like defects such as vacancies, dislocations and stacking faults exist in the structure, but these defects do not impair the core concept or the intended technical effects of the present invention. The pore system of the three-dimensional periodic cavity structure 18 composed of a plurality of spheres 20 is mainly formed by the voids 22 between the spheres 20, thereby defining narrow flow channels for shearing the disperse system.

[0045] According to another specific example of the present invention, the three-dimensional periodic cavity structure 18 may be the inverse structure of the aforementioned three-dimensional ordered microstructure, which is structurally a three-dimensional ordered porous microstructure. As shown in FIG. 3B, the three-dimensional ordered porous microstructure has a plurality of orderly arranged spherical cavities 24 and a plurality of connecting holes 26 connecting the spherical cavities 24. The term “ordered” as used herein means that the distances between the spherical cavities 24 exhibit regular periodicity, and preferably the distances between the spherical cavities 24 are approximately equal. The pore system of the three-dimensional ordered porous microstructure is composed of the spherical cavities 24 and the connecting holes 26. As described hereinafter, these connecting holes 26 constitute narrow flow channels for shearing the disperse system. In a preferred specific example, at least a portion of the spherical cavities 24 in the three-dimensional periodic cavity structure 18 are arranged in a closest-packed configuration. That is, at least 50% of the spherical cavities 24 in the three-dimensional periodic cavity structure 18, more preferably at least 60% of the spherical cavities 24, for example, at least 75% of the spherical cavities 24, are arranged in a closest-packed configuration. Said closest-packed configurations include, but are not limited to, three-dimensional hexagonal closest packing (hcp), three-dimensional face-centered cubic packing (fcc), three-dimensional body-centered cubic packing (bcc), and combinations thereof. However, those skilled in the relevant technical field will understand that due to limitations in manufacturing processes and materials, the spherical cavities 24 cannot achieve an absolutely uniform size, and their configuration is not necessarily limited to perfect spherical cavities, but may also be, for example, elliptical cavities. Therefore, the three-dimensional periodic cavity structure 18 formed by the combination of the spherical cavities 24 and the connecting holes 26 has periodicity in a macroscopic and statistically averaged sense. Inevitably, crystal-like defects such as vacancies, dislocations and stacking faults exist in the structure, but these defects will not impair the core concept or the intended technical effects of the present

invention.

- [0046] The method for manufacturing a three-dimensional ordered porous microstructure may comprise the following steps: First, a plurality of spheres 20 are stacked to form the aforementioned three-dimensional ordered microstructure. Then, the three-dimensional ordered microstructure is used as a template, and an inverse structure material is infiltrated into the voids of the template to form an inverse structure. Finally, the template is removed by means of calcination, extraction or other methods to produce a three-dimensional ordered porous microstructure. Inverse structure materials include, but are not limited to: Metals such as gold, silver, copper, nickel, platinum, nickel-tungsten alloy and the like; oxides such as zinc oxide, silica, cuprous oxide and the like; and polymeric materials such as polystyrene, polyacrylates, polymethacrylates, acrylamides, polypyrrole, polyethylene, polypropylene, polyvinyl chloride, silica gel and the like. The filling of the inverse structure material can be carried out by centrifugation, vacuum extraction, pressure extrusion, sputtering, electroplating, chemical vapor deposition, atomic layer deposition and other methods. In the specific case where the inverse structure material is a polymeric material, the monomers or precursors of the polymeric material may be filled into the voids prior to curing and shaping.
- [0047] The term “disperse system” as used herein means a system consisting of a continuous phase and a disperse phase that is immiscible with the continuous phase. As used herein, “continuous phase” refers to a mutually connected phase composed of the same substance, in which some isolated heterogeneous substances can be accommodated. A “disperse phase” is a phase consisting of mutually isolated substances dispersed in the aforementioned continuous phase, each of which isolated units is surrounded by the continuous phase. In a specific example, the continuous phase and the disperse phase are immiscible fluids (which can be liquids or gases), and the disperse system is in the form of a water-in-oil emulsion or an oil-in-water emulsion. In another specific example, the continuous phase is an aqueous liquid or an oily liquid, while the disperse phase is a gas. In certain specific examples, the individual dispersed units in the disperse phase may themselves comprise two immiscible phases, i.e., the dispersed units themselves may be oil-in-water emulsions or water-in-oil emulsions.
- [0048] FIG. 4 is a flowchart of a method for producing microdroplets using the column device of the present invention, the method comprising Step A: feeding the disperse system into the column device via an input end; Step B: passing the disperse system through the three-dimensional periodic cavity structure inside the column device to shear one or more macro-droplets in the disperse system into microdroplets; and Step C: discharging the continuous phase and microdroplets from the column device via the output end.
- [0049] Referring to FIGS. 2 and 4 concurrently, the disperse system 30 includes a continuous phase 32 and a disperse phase 34 that is immiscible with the continuous phase 32, and the disperse

phase 34 is composed of one or more dispersed units dispersed within the continuous phase 32. Due to surface tension, these dispersed units are dispersed within the continuous phase 32 in the form of macro-droplets 36. The disperse system 30 may be fed into the column device 10 via the input end 14. As previously described, a three-dimensional periodic cavity structure 18 is provided in the column device. As the disperse system 30 enters and flows within the three-dimensional periodic cavity structure 18, the fluid of the continuous phase 32 will exert shear stress (shear force) on the macro-droplets 36 during the flow. When the shear stress is large enough, the macro-droplets 36 will be sheared into smaller microdroplets 38. Subsequently, the continuous phase 32, along with the microdroplets 38, is discharged from the column device 10 via the output end 16. Notably, the geometric size of the microdroplets 38 depends on the structural geometry of the column device 10 as well as parameters such as fluid properties and the flow rate of the continuous phase 32 fluid. These parameters are discussed in further detail hereinafter.

[0050] As an example, the three-dimensional periodic cavity structure 18 formed by the packing of a plurality of spheres 20 shown in FIG. 3A, according to an academic paper by Barth et al. (see H. G. Barth & F. J. Carlin Jr., *Journal of Liquid Chromatography*, (1984) 7: 9, 1717-1738), the shear stress produced in the three-dimensional periodic cavity structure 18 can be described by the following equation:

[0051] The relationship between shear stress (τ), fluid viscosity (η), and shear rate ($\dot{\gamma}$) is as follows:

[0052]
$$\tau = \eta \dot{\gamma} \dots (1)$$

[0053] And the relationship between shear rate ($\dot{\gamma}$), fluid flow rate (Q) within the column device 10, cross-sectional area of the hollow tube (A), equivalent radius of the flow path (R_h), and porosity (ε) of the column device 10 can be expressed as follows:

[0054]
$$\dot{\gamma} = 4Q / \varepsilon A R_h \dots (2)$$

[0055] The relationship between the equivalent radius of the flow path (R_h), the diameter of the packed spheres 20 (D_p), and the porosity (ε) of the column device 10 is as follows:

[0056]
$$R_h = D_p \varepsilon / 3 (1 - \varepsilon) \dots (3)$$

[0057] Within the fluid channel, velocity gradients generated by the contraction or expansion of the flow path during fluid flow induce shear stress, causing the disperse phase 34 to be stretched and broken when the shear rate is sufficiently high. In general, the magnitude of shear stress acting on a solute or dispersed droplet is positively correlated with its size. According to the study by Bird et al. (Bird, R. Byron et al., *Dynamics of Polymeric Liquids*, (1977): 593), there is no quantitative theory or method for evaluating the stability of disperse phases or solutes under such shear stress, and the relationships between various parameters can only be determined experimentally under strictly defined conditions.

[0058] Therefore, the relationship between flow rate (Q) and shear stress (τ) can be derived as

Formula (4):

[0059] $\tau = 4\eta Q / \varepsilon AR_h \dots (4).$

[0060] That is, when the disperse system 30 flows through the three-dimensional periodic cavity structure 18, the macro-droplets 36 within the disperse phase 34 will be subjected to the shear stress (τ) applied by the fluid of the continuous phase 32, and this shear stress (τ) is directly proportional to the flow rate (Q) of the disperse system 30.

[0061] The inventors further conducted actual tests in which the sizes (diameters) of the silicon oxide spheres 20 in the three-dimensional periodic cavity structure 18 were varied, and the disperse system 30 was passed through the three-dimensional periodic cavity structure 18 at different flow rates under the condition of the same tube diameter, thereby obtaining microdroplets 38 in the disperse phase 34. Subsequently, the microdroplets 38 were solidified and separated from the continuous phase 32, thereby observing the relationship between the particle size (D_{v50}) of the microdroplets 38 generated after the disperse system 30 was sheared by the column device 10, and the diameters of the silicon oxide spheres 20 in the three-dimensional periodic cavity structure 18 as well as the flow rate. The results are shown in FIG. 5. The dotted lines shown in FIG. 5 represent the relationship between the flow rate and the particle size (D_{v50}) of the microdroplets 38 for column devices with different packing lengths under the condition of the same sphere diameter (e.g., 273 μm , 385 μm , or 500 μm). It was found that this mathematical relationship conforms to the following Formula (5):

[0062] $D_{v50} = A \ln(\text{flow rate}) + B \dots (5)$

[0063] where D_{v50} is the median value of the particle size distribution of the solidified microdroplets 18 (unit: μm); the flow rate refers to the flow rate of the disperse system 30 passing through the three-dimensional periodic cavity structure 18; A is the slope (unit: $\mu\text{m}/\ln(\text{mL}/\text{min})$); and B is the intercept.

[0064] Accordingly, in a preferred specific embodiment of the present invention, the column device of the present invention conforms to Formula (5) above, wherein the slope A is between -10 and -30 $\mu\text{m}/\ln(\text{mL}/\text{min})$, more preferably between -12 and -25 $\mu\text{m}/\ln(\text{mL}/\text{min})$. In addition, the length of the region in the column device packed with spheres 20—i.e., the length of the three-dimensional periodic cavity structure 18 along the flow direction of the disperse system 30—is greater than or equal to 1 cm in one embodiment, greater than or equal to 2 cm in another embodiment, and greater than or equal to 3 cm in yet another embodiment.

[0065] An application example of the present invention can be found in U.S. Patent Application Publication No. 2024/0033713, assigned to the applicant of the present invention, entitled “A Porous Microsphere, a Stationary Phase Medium, and an Adsorption Chromatography Column Comprising the Porous Microsphere”. In the adsorption chromatography column disclosed in this U.S. publication, the packed porous microspheres can be produced using the column

device of the present invention. In detail, this U.S. publication involves first preparing a first emulsion, then dispersing the first emulsion in a third-phase fluid to obtain a macro-emulsion containing macro-droplets. Said macro-emulsion is preferably a water-in-oil-in-water (W/O/W) emulsion, where water serves as the continuous phase described in FIGS. 2 and 4, and the water-in-oil (W/O) emulsion corresponds to the macro-droplets described in FIGS. 2 and 4. Subsequently, said macro-emulsion is fed into the column device of the present invention as the disperse system referred to in the present invention, such that the macro-droplets dispersed in the macro-emulsion are sheared into microdroplets by the three-dimensional periodic cavity structure inside the column device. Finally, these microdroplets are cured to obtain porous microspheres that can be used as a stationary phase medium for chromatography. In this application example, to maintain the convective transport characteristics of the porous microspheres in adsorption chromatography column applications, the particle size of the porous microspheres is preferably less than 500 μm , more preferably less than 300 μm , and even less than 200 μm . In this U.S. publication, porous microspheres with a median particle size of approximately 50 μm were further fabricated, and experimental data demonstrated that the adsorption chromatography column packed with such porous microspheres exhibits excellent convective transport adsorption performance. Based on this characteristic, taking a flow rate of 40 mL/min as an example, if it is desired to obtain microdroplets smaller than 500 μm using the column device of the present invention, the diameter of the packed spheres used must be less than 1.3 mm, and the packing length of the spheres must be greater than 1 cm. Of course, the above application examples do not imply that the column device of the present invention is only suitable for such applications. As long as the process involves mixing at least two fluid phases and intends to form tiny droplets from at least one of the fluid phases, it can be accomplished using the column device of the present invention. Furthermore, the microdroplets produced by the column device of the present invention can be cured for applications such as adsorption chromatography, microcarriers, biological scaffolds, and the purification of various biological, medical and chemical preparations.

[0066] The inventors further packed the column device of the present invention with spheres of different diameters (i.e., 253.5, 335 and 500 μm). After the disperse system 30 was passed through the column devices with different packing lengths (i.e., the length of the three-dimensional periodic cavity structure 18 along the flow direction of the disperse system 30) at different flow rates, the microdroplets 38 flowing out of the column device were cured into microspheres and separated from the continuous phase 32. This experiment was conducted to observe the relationship between the dispersity of the microspheres (Span/D_{v50} , where $\text{Span} = D_{v90} - D_{v10}$) and the diameter of the packed spheres, packing length, and flow rate of the

disperse system in the column device of the present invention. The results are shown in FIG. 6. It can be observed from FIG. 6 that the dispersity of microspheres (Span/Dv50) increases with an increase in the flow rate of the disperse system, indicating that the particle size distribution of the resulting microspheres becomes broader as the flow rate increases; on the contrary, the particle size distribution tends to be more uniform as the flow rate decreases, and this relationship exhibits an approximately linear correlation:

[0067] $Y = aX + b$ (6)

[0068] where Y is the dispersity of microspheres, X is the flow rate of the disperse system (mL/min), a is the slope, and b is the intercept.

[0069] Accordingly, in another preferred specific example of the present invention, the cured microspheres conform to Formula (6) above, and the slope a (unit: min/mL) is between 0.005 to 0.009 min/mL, more preferably between 0.006 to 0.008 min/mL. In addition, the packing length of the spheres 20 in the column device—that is, the length of the three-dimensional periodic cavity structure 18 along the flow direction of the disperse system 30—is greater than or equal to 1 cm in one embodiment, greater than or equal to 2 cm in another embodiment, and greater than or equal to 3 cm in yet another embodiment.

[0070] The above specific examples also demonstrate that the present invention is suitable for producing a large number of monodisperse microdroplets, and the size of the microdroplets can be adjusted by selecting the diameter and packing length of the spheres in the column device.

[0071] According to the present invention, in the method for producing microdroplets, Step C may be followed by an additional step of curing the microdroplets. Here, “curing” refers to the process of converting microdroplets into microspheres with a stable free-standing configuration. For example, in specific examples where the microdroplets contain polymerizable monomers, the curing step may include heating the microdroplets and/or irradiation with light of an appropriate wavelength, or further adding an accelerator to enable the polymerizable monomers to undergo polymerization to form polymers, thereby achieving curing into a solid form.

[0072] A separation step may also be included after the curing step to separate the cured microspheres from the continuous phase fluid. Suitable separation processes may include all conventional solid-liquid separation processes. In a preferred specific example, the microspheres may be separated by filtration methods, such as filtration using a sieve, membrane, vacuum suction, wet filtration, or sieve shaker. The separated microspheres may be washed several times with water (e.g., deionized water, pure water) and/or alcohol-based solvents (e.g., ethanol, isopropanol) to remove residual continuous phase fluid.

Claims

- [Claim 1] A column device for producing microdroplets, characterized by comprising: a hollow tube having at least one input end and at least one output end opposite to the at least one input end; and a three-dimensional periodic cavity structure disposed inside the hollow tube, which is selected from the group consisting of three-dimensional ordered microstructures formed by packing a plurality of spheres and inverse structures of the three-dimensional ordered microstructures; the column device is configured to allow a disperse system to be fed through the at least one input end, pass through the three-dimensional periodic cavity structure, and then be discharged through the at least one output end; the disperse system includes a continuous phase and a disperse phase that is immiscible with the continuous phase and composed of one or more macro-droplets, such that when the disperse system enters and flows inside the three-dimensional periodic cavity structure, the continuous phase will exert shear stress on the one or more macro-droplets, thereby shearing them into a plurality of microdroplets dispersed in the continuous phase; the cured microdroplets satisfy the following Formula (5):
- $$D_{v50} = A \ln(\text{flow rate}) + B \dots (5)$$
- where D_{v50} is the median value of the particle size distribution of the cured microdroplets; the flow rate refers to the flow rate of the disperse system passing through the three-dimensional periodic cavity structure; the slope A of D_{v50} relative to the flow rate is between -10 and -30 $\mu\text{m}/\ln(\text{mL}/\text{min})$, and B is the intercept; and the length of the three-dimensional periodic cavity structure along the flow direction of the disperse system is greater than or equal to 1 cm.
- [Claim 2] The column device according to Claim 1, characterized in that the slope A is between -12 to -25 $\mu\text{m}/\ln(\text{mL}/\text{min})$.
- [Claim 3] The column device according to Claim 1, characterized in that the length of the three-dimensional periodic cavity structure along the flow direction of the disperse system is greater than or equal to 2 cm.
- [Claim 4] The column device according to Claim 3, wherein the length of the three-dimensional periodic cavity structure along the flow direction of the disperse system is greater than or equal to 3 cm.
- [Claim 5] The column device according to Claim 1, wherein the three-dimensional periodic cavity structure is a three-dimensional ordered microstructure formed by packing a plurality of spheres, and at least 50% of the spheres in the three-

dimensional periodic cavity structure are arranged in a closest-packed arrangement.

[Claim 6] The column device according to Claim 5, wherein the three-dimensional periodic cavity structure is a three-dimensional ordered microstructure formed by packing a plurality of spheres, and at least 60% of the spheres in the three-dimensional periodic cavity structure are arranged in a closest-packed arrangement.

[Claim 7] The column device according to Claim 6, wherein the three-dimensional periodic cavity structure is a three-dimensional ordered microstructure formed by packing a plurality of spheres, and at least 70% of the spheres in the three-dimensional periodic cavity structure are arranged in a closest-packed arrangement.

[Claim 8] The column device according to Claim 1, characterized in that the cured microdroplets further satisfy the following Formula (6):

$$Y = aX + b \dots (6)$$

where Y is the dispersity of the particle size distribution of the microdroplets, X is the flow rate of the disperse system, the slope a of Y relative to X is between 0.005 to 0.009 min/mL, and b is the intercept.

[Claim 9] The column device according to Claim 8, characterized in that the slope a is between 0.006 to 0.008 min/mL.

[Claim 10] A method for producing microdroplets using a column device, characterized in that the column device comprises:

a hollow tube having at least one input end and at least one output end opposite to the at least one input end; and a three-dimensional periodic cavity structure disposed inside the hollow tube, selected from the group consisting of three-dimensional ordered microstructures formed by packing a plurality of spheres and inverse structures of the three-dimensional ordered microstructures; the column device is configured to allow a disperse system to be fed through the at least one input end; and the length of the three-dimensional periodic cavity structure along the flow direction of the disperse system is greater than or equal to 1 cm;

The method comprises the following steps:

A) feeding the disperse system to the at least one input end, wherein the disperse system comprises a continuous phase and a disperse phase that is immiscible with the continuous phase and composed of one or more macrodroplets;

B) passing the disperse system through the three-dimensional periodic cavity structure; when the disperse system enters and flows inside the three-dimensional periodic cavity structure, the continuous phase will exert shear stress on the one or more macro-droplets, thereby shearing them into a plurality of microdroplets dispersed in the continuous phase; the cured microdroplets satisfy the following Formula (5):

$$D_{v50} = A \ln(\text{flow rate}) + B \dots (5)$$

wherein D_{v50} is the median value of the particle size distribution of the cured microdroplets, the flow rate refers to the flow rate of the disperse system passing through the three-dimensional periodic cavity structure, the slope A of D_{v50} relative to the flow rate is between -10 and -30 $\mu\text{m}/\ln(\text{mL}/\text{min})$, and B is the intercept; and

C) discharging the continuous phase and the microdroplets from the column device via the at least one output end.

[Claim 11] The method according to Claim 10, characterized in that Step C is followed by a step of curing the microdroplets into microspheres.

[Claim 12] The method according to Claim 10, characterized in that the disperse system is selected from the group consisting of water-in-oil emulsions and oil-in-water emulsions.

[Claim 13] The method according to Claim 10, characterized in that the slope A is between -12 and -25 $\mu\text{m}/\ln(\text{mL}/\text{min})$.

[Claim 14] The method according to Claim 10, characterized in that the three-dimensional periodic cavity structure has a length of greater than or equal to 2 cm along the flow direction of the disperse system.

[Claim 15] The method according to Claim 14, characterized in that the three-dimensional periodic cavity structure has a length of greater than or equal to 3 cm along the flow direction of the disperse system.

[Claim 16] The method according to Claim 10, characterized in that the three-dimensional periodic cavity structure is a three-dimensional ordered microstructure formed by packing a plurality of spheres, and at least 50% of the spheres in the three-dimensional periodic cavity structure are arranged in a closest-packed arrangement.

[Claim 17] The method according to Claim 16, characterized in that the three-dimensional periodic cavity structure is a three-dimensional ordered microstructure formed by packing a plurality of spheres, and at least 60% of the spheres in the three-dimensional periodic cavity structure are arranged in a closest-packed

arrangement.

[Claim 18]

The method according to Claim 17, characterized in that the three-dimensional periodic cavity structure is a three-dimensional ordered microstructure formed by packing a plurality of spheres, and at least 70% of the spheres in the three-dimensional periodic cavity structure are arranged in a closest-packed arrangement.

[Claim 19]

The method according to Claim 10, characterized in that the cured microdroplets further satisfy the following Formula (6):

$$Y = aX + b \dots (6)$$

where Y is the dispersity of the particle size distribution of the microdroplets, X is the flow rate of the disperse system, the slope a of Y relative to X is between 0.005 to 0.009 min/mL, and b is the intercept.

[Claim 20]

The method according to Claim 19, characterized in that the slope a is between 0.006 and 0.008 min/mL.