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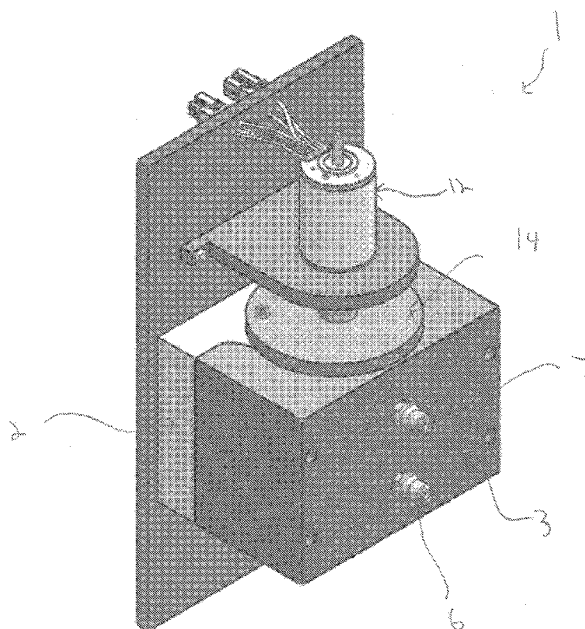


FIGURE 1

(57) Abstract: The present disclosure is directed to cross-flow membrane emulsification devices 1 with an impeller 9. The devices disclosed herein can have a continuous phase housing 2 that houses an impeller, a dispersed phase housing 3, and a membrane 4 between the continuous phase housing and the dispersed phase housing. The impeller can be rotated about a rotational axis such that a continuous phase inside the continuous phase housing imparts a shear force on the membrane. A dispersed phase can be forced through the membrane such that the dispersed phase enters into the continuous phase in a direction that is perpendicular to the rotational axis of the impeller, thereby forming a dispersed phase microspheres.



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MEMBRANE EMULSIFICATION DEVICE WITH IMPELLER FOR MICROSPHERE CREATION

Cross Reference to Related Applications

[0001] This application claims the priority benefit of U.S. Provisional Application Serial No. 62/689,741, filed June 25, 2018, which is hereby incorporated by reference in its entirety.

Field of the Disclosure

[0002] This disclosure relates to membrane emulsification devices. More specifically, this disclosure relates to cross-flow membrane emulsification devices for the creation of microspheres using an impeller.

Background

[0003] Membrane emulsification refers to a technique for creating drops of one liquid (dispersed phase) in another (continuous phase). Specifically, a dispersed phase can be forced through pores in a membrane directly into the continuous phase. Droplets of the dispersed phase can be formed and detached at the end of the pores with a drop-by-drop mechanism.

[0004] On a side of the membrane opposite the dispersed phase, the continuous phase can be applying a shear stress to the droplets in formation. The shear stress can help detach the dispersed-phase droplets from the membrane so that they do not coalesce on the membrane surface and are more uniform in size. However, many membrane emulsification systems only allow batch processing, wherein the composition of the continuous phase changes over time making it difficult for scaling up the process.

Summary

[0005] Provided are cross-flow membrane emulsification devices for the creation of microspheres using an impeller to generate continuous phase shear. Because the membrane emulsification devices include an impeller, the shear applied to the membrane does not necessarily depend on the continuous phase flow through the device itself. For example, the devices disclosed herein can have a slow flow of continuous phase through the device (simply to harvest the microspheres and refresh the content of the device, not to create shear on the membrane) and maintain the high shear required for the formation of microspheres by

adjusting the RPM of the impeller. In addition, the impeller can impart an equal shear force and pressure on all parts of the membrane unlike other membrane emulsification devices. This can provide the advantages of making the device easier to use, reduce the volume of continuous phase required to manufacture microspheres _ especially at large scale _ and improve microspheres homogeneity.

[0006] The devices disclosed herein can provide a plurality of microspheres with a narrow and uniform size distribution. Furthermore, the devices disclosed herein are continuous flow devices that are easily scalable to a large-scale manufacturing process by either increasing the duration of manufacturing, or the size of the membrane while preserving a uniform shear force on all parts of the membrane. The devices disclosed herein can be easily scalable due to the design of the devices. In addition, the devices disclosed herein can be easily cleaned and/or sterilized in place or out of place. The devices disclosed herein can be used for applications that require the device to be used under aseptic manufacturing conditions and in compliance with Good Manufacturing Practices (for example, as defined in CFR Title 21). As such, the devices is designed to have no void spaces, dead ends/loops, or inaccessible spaces that would be difficult to clean, sanitize, or sterilize.

[0007] In some embodiments, a device includes a continuous phase housing including a continuous phase inlet and an impeller; a dispersed phase housing including a dispersed phase inlet; a membrane including a plurality of pores, wherein the membrane is located between the continuous phase housing and the dispersed phase housing, and the dispersed phase inlet is fluidly connected to the plurality of pores in the membrane; an outlet that is fluidly connected to the continuous phase inlet; and a motor for rotating the impeller. In some embodiments, an outer circumference of the impeller is concentric with the membrane. In some embodiments, the outer circumference of the impeller is separated from the membrane by a distance of 0.01-1 mm. In some embodiments, the membrane is in the shape of a portion of an annular cylinder. In some embodiments, the membrane is in the shape of an annular cylinder. In some embodiments, the impeller has a rotational axis that is transverse to a flow of a dispersed phase through the plurality of pores. In some embodiments, the continuous phase housing comprises the outlet. In some embodiments, the dispersed phase housing comprises a bleed valve. In some embodiments, the membrane is removably attached to the continuous phase housing and the dispersed phase housing. In some embodiments, the continuous phase housing is removably attached to the dispersed

phase housing. In some embodiments, the membrane is clamped to the continuous phase housing by the dispersed phase housing. In some embodiments, the device includes gaskets located between the membrane and the continuous phase housing and between the membrane and the dispersed phase housing. In some embodiments, the dispersed phase housing comprises stainless steel. In some embodiments, the continuous phase housing comprises stainless steel. In some embodiments, the membrane comprises stainless steel, tantalum, tungsten, molybdenum, manganese, tin, zinc, or an alloy thereof. In some embodiments, the membrane comprises porous glass or a ceramic. In some embodiments, one or more pores of the plurality of pores has a size less than 50 microns. In some embodiments, one or more pores of the plurality of pores has a size less than or equal to 10 microns. In some embodiments, the plurality of pores is uniformly sized. In some embodiments, the impeller rotates at 100-5,000 RPMs. In some embodiments, the impeller is a paddle wheel impeller. In some embodiments, the device includes a coupler that couples the motor to the impeller. In some embodiments, the device includes a plate that seals the continuous phase housing and allows a portion of the impeller to exit the continuous phase housing for connection to the motor.

[0008] In some embodiments, a method of forming microspheres includes flowing a continuous phase through a continuous phase housing including an impeller; rotating the impeller about a rotational axis such that the continuous phase imparts a shear force on a membrane including a plurality of pores, wherein the membrane is located between the continuous phase housing and a dispersed phase housing; and forcing a dispersed phase through the plurality of pores such that the dispersed phase enters into the continuous phase in a direction that is perpendicular to the rotational axis of the impeller, wherein forcing the dispersed phase through the plurality of pores into the continuous phase forms a plurality of microspheres comprising the dispersed phase. In some embodiments, a median diameter of the plurality of microspheres is between 1-1000 microns. In some embodiments, a median diameter of the plurality of microspheres is between 10-40 microns. In some embodiments, a median diameter of the plurality of microspheres is less than 20 microns. In some embodiments, at least 70% of the plurality of microspheres has a diameter within 10 microns above or below the median diameter. In some embodiments, the coefficient of variation of a size distribution of the plurality of microspheres is less than 30%. In some embodiments, the coefficient of variation of a size distribution of the plurality of microspheres is less than 20%.

In some embodiments, the coefficient of variation of a size distribution of the plurality of microspheres is between 10-20%. In some embodiments, the continuous phase exerts a shear force at a shear rate at the membrane of 1,000-25,000 s⁻¹. In some embodiments, the continuous phase includes an aqueous solvent and the dispersed phase includes an organic solvent. In some embodiments, the continuous phase further includes a surfactant. In some embodiments, the dispersed phase includes a water insoluble polymer. In some embodiments, the dispersed phase includes a therapeutic compound or pharmaceutically acceptable salt thereof. In some embodiments, the dispersed phase includes a polyol. In some embodiments, the impeller rotates at 100-5,000 RPMs.

[0009] Additional advantages will be readily apparent to those skilled in the art from the following detailed description. The examples and descriptions herein are to be regarded as illustrative in nature and not restrictive.

[0010] All publications, including patent documents, scientific articles and databases, referred to in this application are incorporated by reference in their entirety for all purposes to the same extent as if each individual publication were individually incorporated by reference. If a definition set forth herein is contrary to or otherwise inconsistent with a definition set forth in the patents, applications, published applications and other publications that are herein incorporated by reference, the definition set forth herein prevails over the definition that is incorporated herein by reference.

Brief Description of the Drawings

[0011] Exemplary embodiments are described with reference to the accompanying figures, in which:

[0012] Figure 1 illustrates an example of a membrane emulsification device disclosed herein.

[0013] Figure 2 illustrates an example of an exploded view of a membrane emulsification device disclosed herein.

[0014] Figure 3A illustrates an example of a top view of a membrane emulsification device disclosed herein.

[0015] Figure 3B illustrates an example of a side view of a membrane emulsification device disclosed herein.

[0016] Figure 3C illustrates an example of a front view of a membrane emulsification device disclosed herein.

[0017] Figure 4 illustrates an example of a cross section of a membrane emulsification device disclosed herein along line A-A in Figure 3B.

[0018] Figure 5 illustrates an example of a cross section of a membrane emulsification device disclosed herein along line B-B in Figure 3C.

[0019] Figure 6 illustrates an example of a cross section of a membrane emulsification device disclosed herein along line B-B in Figure 3C.

[0020] Figure 7A illustrates an example of a membrane disclosed herein.

[0021] Figure 7B illustrates an example of an impeller disclosed herein.

[0022] Figure 7C illustrates an example of the relationship between a membrane and an impeller disclosed herein.

[0023] Figure 8A illustrates an example of a continuous phase housing disclosed herein.

[0024] Figure 8B illustrates an example of a dispersed phase housing disclosed herein.

[0025] Figure 9 illustrates an example of a membrane emulsification device disclosed herein.

[0026] Figure 10 illustrates an example of an exploded view of a membrane emulsification device disclosed herein.

[0027] Figure 11A illustrates an example of a top view of a membrane emulsification device disclosed herein.

[0028] Figure 11B illustrates an example of a side view of a membrane emulsification device disclosed herein.

[0029] Figure 11C illustrates an example of a front view of a membrane emulsification device disclosed herein.

[0030] Figure 11D illustrates an example of a bottom view of a membrane emulsification device disclosed herein.

[0031] Figure 12 illustrates an example of a cross section of a membrane emulsification device disclosed herein along line B-B in Figure 11A.

[0032] Figure 13 illustrates an example of a membrane disclosed herein.

[0033] Figure 14 illustrates an example of an impeller disclosed herein.

[0034] Figure 15A illustrates an example of a cross section of a membrane emulsification device disclosed herein along line D-D in Figure 11C.

[0035] Figure 15B illustrates a close up of a portion of Figure 15A.

[0036] In the Figures, like reference numbers correspond to like components unless otherwise stated. In addition, the Figures are not drawn to scale.

Detailed Description

[0037] The membrane emulsification devices disclosed herein can create microspheres using an impeller. As such, the devices disclosed herein can have a slow flow of continuous phase (simply to harvest the microspheres and refresh the content of the device, not to create shear on the membrane) and maintain the high shear required for the formation of microspheres by adjusting the RPM of the impeller. In addition, the devices disclosed herein are continuous flow devices that are easily scalable to large scale manufacturing processes and can be easily cleaned and/or sterilized.

[0038] The Figures illustrate examples of membrane emulsification devices and their various components. Membrane emulsification device 1 can include continuous phase housing 2, dispersed phase housing 3, and membrane 4. The continuous phase housing can allow a continuous phase to enter into the device. For example, a user of the device can flow a continuous phase through continuous phase inlet 5 such that the continuous phase enters the device through continuous phase housing 2. In some embodiments, the continuous phase inlet is on an outer surface of the continuous phase housing. The continuous phase inlet does not have to be on an outer surface. Instead, the continuous phase inlet can be on any one of the surfaces of the continuous phase housing such as the top or bottom of the continuous phase housing. The continuous phase housing can be made out of a material that is solvent resistant for the particular microspheres that are being created. In some embodiments, the continuous phase housing can be made out of stainless steel, aluminum, Hastelloy, fluoropolymers (e.g., PVDF), or polyether ether ketone ("PEEK").

[0039] The dispersed phase housing can allow a dispersed phase to enter into the device. For example, a user of the device can flow a dispersed phase through dispersed phase inlet 6 such that the dispersed phase enters the device through dispersed phase housing 3. In some embodiments, the dispersed phase inlet is on an outer surface of the dispersed phase housing. The dispersed phase inlet does not have to be on an outer surface. Instead, the dispersed phase inlet can be on any one of the surfaces of the dispersed phase housing such as the top or bottom of the dispersed phase housing. The dispersed phase housing can be made out of a

material that is solvent resistant for the particular microspheres that are being created. In some embodiments, the dispersed phase housing can be made out of stainless steel, aluminum, Hastelloy, fluoropolymers (e.g., PVDF), or PEEK.

[0040] Figures 1-15 illustrate the membrane emulsification devices as being vertical. However, the membrane emulsification device can be horizontal. In addition, in some embodiments, the continuous phase and/or the dispersed phase can be flowing against gravity.

[0041] In some embodiments, the dispersed phase housing can include a bleed valve 7. The bleed valve can allow the removal of bubbles of air and/or continuous phase that has become trapped on the dispersed phase side of the membrane. Furthermore, the dispersed phase inlet can be connected to a bleed valve. In some embodiments, the bleed valve can be on an outer surface of the dispersed phase housing. The bleed valve can also be on any one of the surfaces of the dispersed phase housing such as the top or bottom. For example, the bleed valve can be situated toward the top of the dispersed phase housing to improve removal of floating air bubbles or residual low-density fluids.

[0042] In some embodiments, the continuous phase housing can be removably attached to the dispersed phase housing. Having the housings be removably attached to one another can allow for quick dismantling of the device for cleaning, maintenance, or any other reason. In addition, removing the continuous phase housing from the dispersed phase housing can allow for access to the membrane for replacement and/or maintenance of the membrane. The continuous phase housing can be secured to the dispersed phase housing. For example, the continuous phase housing can be screwed, nailed, or clamped to the dispersed phase housing. In some embodiments, the continuous phase housing can be attached to the dispersed phase housing using an adhesive. In some embodiments, the continuous phase housing can be attached to the dispersed phase housing using clamps pressing both housings together.

[0043] As shown in Figure 2, membrane 4 having a plurality of pores 4a is located between the continuous phase housing and the dispersed phase housing. The continuous phase housing and/or the dispersed phase housing can have alignment members 8. These alignment members can be used to align the membrane between the continuous phase housing and the dispersed phase housing. In addition, gaskets can be used to seal the membrane to the continuous phase housing and/or dispersed phase housing. These gaskets

can be located where the alignment members are located in the Figures. In some embodiments, the alignment members can be gaskets.

[0044] The dispersed phase housing can be fluidly connected to the dispersed phase inlet and the membrane (i.e., the plurality of pores of the membrane). As such, the dispersed phase can enter the device through the dispersed phase inlet and flow through the dispersed phase housing. The dispersed phase can then be forced through the pores of the membrane into the continuous phase housing.

[0045] The continuous phase can enter the device through the continuous phase inlet and flow through the continuous phase housing to outlet 10. As such, the continuous phase housing can be fluidly connected to the continuous phase inlet and the outlet. Inside the continuous phase housing is impeller 9. In some embodiments, the impeller can be a paddle wheel impeller. In some embodiments, the impeller may have a pitch (e.g., the vanes that can be partial helices). If the impeller has a pitch, the impeller can act as a pump for the continuous phase. As such, an external pump for the continuous phase might not be necessary if the impeller has a pitch. The impeller can be rotated by a motor 12 about a rotational axis. This rotation of the impeller can set the continuous phase inside the continuous phase housing in motion and make it exert a shear force on the membrane. The rotational axis of the impeller can be transverse to the flow of the dispersed phase through the plurality of pores such that the dispersed phase enters into the continuous phase in a direction that is perpendicular to the rotational axis of the impeller.

[0046] The continuous phase housing can also include plate 14. The plate can seal the continuous phase housing. In addition, the plate can have a bearing for a portion of the impeller such as the impeller axle. The device can also include coupler 15. The coupler can couple the motor to the impeller. For example, it can couple the motor to the impeller drive shaft. In some embodiments, the coupler can be mechanical. However, coupler can also be a magnetic coupler. If a magnetic coupler is used, the axle does not have to penetrate the continuous phase housing. As such, the device can provide improved sterility assurance.

[0047] During membrane emulsification disclosed herein, a dispersed phase can be forced through the pores of a membrane, while the continuous phase flows along the membrane surface by the rotation of the impeller. Droplets of the dispersed phase can grow at pore outlets until they reach a certain size and detach. The shear force of continuous phase flow can essentially wash these droplets off the membrane and carry them to the outlet. By

washing these droplets off of the membrane, the size of these droplets can be controlled by controlling the dispersed phase flow rate through the pores and the rotational rate of the impeller (i.e., the shear rate).

[0048] The size of the droplets (i.e., microspheres) can be determined by a variety of factors. For example, these factors include, but are not limited to, the shear force on the droplet from the flowing continuous phase due to impeller rotation, differential surface tension between the continuous phase and dispersed phase, density of the two phases, viscoelastic properties of the liquids, the rate of extrusion of the dispersed phase through the membrane, presence of surfactants, and the pore size. The droplets at the pores tend to a form short filaments or cylinders with a rounded top that detach from the membrane surface and then form spheres to minimize surface area after detachment. The filaments pinch off/detach due to the force of the continuous phase stream and Rayleigh instability. As such, once these droplets detach from the membrane, they can be considered to be microspheres of the dispersed phase. The final size of these microspheres and the size distribution of these microspheres are not only determined by the flowrate of dispersed and continuous phase, pore size and size distribution of the pores, but can also be affected by the degree of coalescence of the droplets, properties of the two phases, and presence of surfactants, both at the membrane surface and in the bulk solution.

[0049] As discussed above, the membrane can include a plurality of pores. In some embodiments, the membrane has the most holes per unit area while still obtaining good uniform particle size distribution. This plurality of pores can be within at least one region of the membrane. For example, Figure 7A illustrates at least one region 13 with plurality of pores 4a. In some embodiments in which there are more than one region of the membrane, the regions of the membrane can have the same dimensions. In other embodiments, the regions can all have different dimensions or some of the regions can have the same dimensions. If there is more than one region, the regions can be separated by a gap. In addition, the gap(s) may not have any pores. The membrane may also have a gap(s) between at least one region and the edge of the membrane. This gap(s) can be used to clamp down the membrane between the continuous phase housing and the dispersed phase housing. In other words, a portion of the continuous phase housing can be in contact with the gap(s) to help compress the membrane between the dispersed phase housing and the continuous phase housing. In addition, the continuous phase housing and the dispersed phase housing (with the

membrane) can be compressed such that the membrane does not move or has minimal movement/deflection when the device is in operation.

[0050] As shown in Figure 5, the outer circumference of the impeller can be concentric with the membrane. As such, the shape of the membrane can be such that it is concentric with the outer circumference of the impeller. In some embodiments, a flat membrane can be used that is bent to conform to the shape of a portion of an annular cylinder by securing it between the continuous phase housing and the dispersed phase housing. In addition, impeller 9 in Figure 5 is slightly offset (downward in Figure 5) such that the outer circumference of the impeller is concentric with membrane 4 that is in the shape of a portion of an annular cylinder. Figures 7A and 13 illustrate membrane 4. As shown in Figure 7A, the membrane can be in the shape of a portion of an annular cylinder. In contrast to Figure 7A, Figure 13 illustrates a membrane in the shape of an annular cylinder. The advantages of a membrane that is the shape of a portion of an annular cylinder rather than an annular cylinder can include flat fabrication of the membrane (i.e., no need to form a cylinder out of a flimsy membrane) and the ability to conform the membrane to tight cylindrical tolerances by clamping between the continuous phase housing and the dispersed phase housing. This tight tolerance can enable a very narrow gap between the impeller and the membrane and correspondingly high fluid shear rates. For example, the outer circumference of the impeller can be separated from the membrane by a distance of about 0.01-5 mm, about 0.01-2 mm, about 0.01-1 mm, about 0.05-0.5 mm, or about 0.1 mm.

[0051] In some embodiments, the pores can be less than or equal to about 50 microns, about 20 microns, about 10 microns, about 5 microns, or about 1 micron. In some embodiments, the pores of the membrane can have a size of about 0.1-100 microns, about 1-75 microns, about 5-50 microns, about 10-50 microns, about 10-40, about 10-35 microns, about 10-20 microns, or about 15-25 microns. In some embodiments, the plurality of pores is uniformly sized. In some embodiments, the membrane can have at least about 1,000 pores, about 3,000 pores, about 5,000 pores, about 10,000 pores, about 12,500 pores, about 15,000 pores, about 20,000 pores, about 50,000 pores, about 75,000 pores, about 100,000 pores, or about 200,000 pores. In addition, the membrane can have about 1,000-500,000 pores, about 3,000-20,000 pores about 5,000-15,000 pores, about 10,000-15,000 pores, or about 12,500 pores. In some embodiments, these pores can be laser drilled in the membrane.

[0052] The regions of the membrane that include the pores are the active membrane. In some embodiments, these regions of the active membrane can have a pore density of at most about 1 pore per 225 square microns, about 1 pore per 250 square microns, about 1 pore per 275 square microns, about 1 pore per 300 square microns, about 1 pore per 350 square microns, about 1 pore per 400 square microns, about 1 pore per 450 square microns, about 1 pore per 500 square microns, about 1 pore per 550 square microns, about 1 pore per 600 square microns, about 1 pore per 650 square microns, about 1 pore per 700 square microns, about 1 pore per 750 square microns, about 1 pore per 800 square microns, about 1 pore per 850 square microns, about 1 pore per 900 square microns, about 1 pore per 950 square microns, about 1 pore per 1000 square microns, about 1 pore per 2000 square microns, about 1 pore per 5000 square microns, about 1 pore per 10000 square microns, about 1 pore per 15000 square microns, about 1 pore per 20000 square microns, about 1 pore per 25000 square microns, about 1 pore per 30000 square microns, about 1 pore per 35000 square microns, or about 1 pore per 40000 square microns.

[0053] The membrane can be made out of stainless steel, tantalum, tungsten, molybdenum, manganese, tin, zinc, or an alloy thereof. In addition, the membrane can be made out of porous glass (e.g., Shirazu porous glass) or a ceramic material. In a cylindrical membrane, it can be hard to form a thin metal membrane into a cylinder or a portion of a cylinder with sufficient structural strength. A porous glass cylinder or portion of a cylinder, by contrast, can be easy to make and is strong. The porous glass cylinder can be cast and does not have to be thin, whereas a metal membrane may need to be thin to facilitate laser drilling. In some embodiments, the membrane can include fused silica capillaries. In some embodiments, the membrane is a hydrophilic membrane or is treated to increase hydrophilicity of the membrane material. In some embodiments, the membrane can be made out of a rigid material.

[0054] As explained above, forcing the dispersed phase through the plurality of pores into the continuous phase can form a plurality of dispersed phase microspheres. The device disclosed herein is capable of producing microspheres with a narrow size distribution. Specifically, the median diameter of the plurality of microspheres can be about 5-100 microns, about 10-50 microns, or about 20-40 microns. In some embodiments, the median diameter of the plurality of microspheres can be even smaller. For example, the median diameter of the plurality of microspheres can be about 10nm to 5 microns, about 25 nm to 2

microns, or about 50 nm to 1 micron. In some embodiments, at least about 50%, about 60%, about 70%, about 80%, about 85%, about 90%, about 95%, or about 98% of the plurality of microspheres can have a diameter within 5, 10, 15, or 20 microns above or below the median diameter. In some embodiments, the microspheres have a bimodal distribution wherein a first mode occurs at a diameter of less than about 5, 10, 15, or 20 microns and the second mode occurs at a diameter of 5, 10, 15, 20, 25, 30, 35, or 40 microns or greater where at least about 50%, about 60%, about 70%, about 80%, about 85%, about 90%, about 95%, or about 98% of the plurality of microspheres can have a diameter within 5, 10, 15, or 20 microns above or below the median diameter.

[0055] In some embodiments, the coefficient of variation of a size distribution of the plurality of microspheres can be less than about 40%, about 30%, about 25%, about 20%, about 15%, or about 10%. In some embodiments, the coefficient of variation of a size distribution of the plurality of microspheres can be about 1-30%, about 5-25%, or about 10-20%. The coefficient of variation of a size distribution can be calculated by performing image recognition on light microscopy pictures (Cell Profiler for image analysis). The coefficient of variation can be calculated using the standard error of the population (diameter) divided by the average diameter and multiply by 100.

[0056] As the dispersed phase is forced through the pores of the membrane, the continuous phase can exert a shear force at a shear rate at the membrane. The average shear rate at the membrane can be at most about 25,000 s⁻¹, about 19,000 s⁻¹, about 15,000 s⁻¹, about 10,000 s⁻¹, about 9,000 s⁻¹, or about 5,000 s⁻¹. In some embodiments, the average shear rate at the membrane can be about 1,000-20,000 s⁻¹, 2,000-20,000 s⁻¹, about 5,000-19,000 s⁻¹, about 5,000-15,000 s⁻¹, or about 5,000-10,000 s⁻¹. In some embodiments, the average shear rate at the membrane can be about 1,000-10,000 s⁻¹, about 2,000-8,000 s⁻¹, about 3,000-6,000 s⁻¹, or about 4,000-5,000 s⁻¹. The average shear rate at the membrane can be calculated by using simple shear defined by the gradient of velocity defined as the average flow divided by the distance. As explained above, the impeller moves the continuous phase such that it exerts the shear force on the membrane. The rotations per minute (RPM) of the impeller can depend on the impeller diameter since the speed of the impeller across the pores, and thereby the shear is proportional to both the RPM and the diameter and inversely proportional to the gap between the impeller and the membrane. As such, the impeller can rotate at about 100-5,000 RPMs

[0057] After the microspheres are washed from the membrane by the continuous phase flow, the continuous phase and the microspheres carried by the continuous phase can flow to the outlet. In some embodiments, the device may only have one outlet. In other embodiments, the device may have at least two outlets. In some embodiments, the outlet is on an outer surface of the continuous phase housing. The outlet does not have to be on an outer surface. Instead, the outlet can be on any one of the surfaces of the continuous phase housing. In some embodiments, the outlet can be a separate structural part attached to the continuous phase housing that is fluidly connected with the continuous phase housing.

[0058] As stated above, the membrane can be in the shape of an annular cylinder. Figure 9 depicts a membrane emulsification device 1 with a membrane in the shape of an annular cylinder. As shown in Figure 10, the dispersed phase housing 3 surrounds the continuous phase housing 2 comprising impeller 9 and surrounds membrane 4. In the embodiments disclosed in Figures 9-15, the continuous phase can be pumped or flowed through continuous phase inlet 5 into the continuous phase housing 2 where it can surround the impeller. The dispersed phase can be pumped or flowed into the dispersed phase housing 3 through dispersed phase inlet 6. As such, the continuous phase and the dispersed phase are on opposite sides of the membrane in the device. The dispersed phase can be then forced through the plurality of pores 4a of membrane 4. The extruded dispersed phase can be swept away by the shear force generated by the rotating impeller 9. The resulting microspheres and surrounding continuous phase can then exit the device through outlet 10.

[0059] Figures 15A-B illustrate an example of a cross section of a membrane emulsification device disclosed herein along line D-D in Figure 11C. Figure 15B illustrates dispersed phase volume 21 on one side of membrane 4 and outer impeller radius 20 on the other side of membrane 4. In addition, inner circumference of the dispersed phase housing 22 is depicted. The dispersed phase can flow from outer dispersed phase volume 21 through membrane 4 into the continuous phase housing where the extruded dispersed phase particles come into contact with the continuous phase.

Dispersed Phase and Continuous Phase Flows

[0060] The continuous phase can include an aqueous solvent and the dispersed phase can include an organic solvent. The continuous phase can also include a surfactant. A variety of surfactants are known in the art and can be selected by one of skill in the art. In some

embodiments, the surfactant is selected from polysorbate 20 or polysorbate 80 (*e.g.*, of the TWEEN® series), poloxamer (*e.g.*, of the PLURONIC® series; BASF), and polyvinyl alcohol (PVA). In some embodiments, the concentration of surfactant in the continuous phase is from 0.05% to 2% (w/w). In some embodiments, the concentration of surfactant in the continuous phase is at least about any of the following concentrations (in percentage, w/w): 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2. In some embodiments, the concentration of surfactant in the continuous phase is less than about any of the following concentrations (in percentage, w/w): 2, 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1. That is, the concentration of surfactant in the continuous phase can be any concentration in a range having an upper limit of about 2, 1.9, 1.8, 1.7, 1.6, 1.5, 1.4, 1.3, 1.2, 1.1, 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1% (w/w), and an independently selected lower limit of about 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2% (w/w), wherein the upper limit is greater than the lower limit. In some embodiments, the concentration of surfactant in the continuous phase is about 0.5-1.5% (w/w). In some embodiments, the concentration of surfactant in the continuous phase is about 0.5-1% (w/w). In some embodiments, the aqueous solvent comprises water.

[0061] The dispersed phase can also include a water insoluble polymer. The water insoluble polymer can dissolve in the organic solvent. Examples of water insoluble polymers include, but are not limited to, poly(lactic-*co*-glycolic acid) (PLGA) including PLGA that is ester capped, polylactic acid (PLA), polyglycolide, poly(glycolide-*co*-lactide) (PLG), polyhydroxybutyrate, poly(sebacic acid), polyphosphazene, poly[(lactide-*co*-ethylene glycol)-*co*-ethyloxyphosphate], PLA-polyethyleneglycol (PEG)-PLA triblock copolymer, or PLG-PEG-PLG triblock copolymer, or combinations thereof. In some embodiments, the organic solvent comprises ethanol, methanol, propanol, dichloromethane, chloroform, ethyl acetate, butyl acetate, methyl ethyl ketone, or mixtures thereof.

[0062] In some embodiments, the dispersed phase can include a therapeutic compound or a pharmaceutically acceptable salt thereof. In some embodiments, the dispersed phase can also include a polyol.

[0063] In some embodiments, the dispersed phase comprises one or more polymers at a concentration of at least about 75 mg/mL, at least about 100 mg/mL, at least about 125 mg/mL, at least about 150mg/mL, at least about 160mg/mL, at least about 170mg/mL, at

least about 180mg/mL, at least about 190mg/mL, at least about 200mg/mL, at least about 225mg/mL, at least about 250mg/mL, at least about 275mg/mL, or at least about 300mg/mL. In some embodiments, the dispersed phase comprises a therapeutic compound or salt at a concentration of at least about 5mg/mL, at least about 10mg/mL, at least about 20mg/mL, at least about 30mg/mL, or at least about 40mg/mL. In some embodiments, the dispersed phase comprises the one or more polymers at a concentration of at least about 200mg/mL and the therapeutic compound or salt at a concentration of at least about 20mg/mL.

[0064] In some embodiments, a polymer of the present disclosure comprises at least one anionic terminus. In some embodiments, a polymer of the present disclosure comprises at least one acid terminus. In certain embodiments, a polymer of the present disclosure comprises at least one carboxylic acid terminus. Exemplary polymers include, without limitation, those comprising poly(lactic-*co*-glycolic acid) (PLGA), polylactic acid (PLA), polyglycolide, poly(glycolide-*co*-lactide) (PLG), polyhydroxybutyrate, poly(sebacic acid), polyphosphazene, poly[(lactide-*co*-ethylene glycol)-*co*-ethyloxyphosphate], PLA-polyethyleneglycol (PEG)-PLA triblock copolymer, or PLG-PEG-PLG triblock copolymer.

[0065] Exemplary polymers can also include those prepared from biocompatible and biodegradable polymers, such as linear polyesters, branched polyesters which are linear chains radiating from a polyol moiety, e.g. glucose. Other esters are those of polylactic acid, polyglycolic acid, polyhydroxybutyric acid, polycaprolactone, polyalkylene oxalate, polyalkylene glycol esters of acids of the Kreb's cycle, e.g. citric acid cycle and the like and copolymers thereof. The linear polyesters may be prepared from the alphahydroxy carboxylic acids, e.g. lactic acid. and glycolic acid, by the condensation of the lactone dimers, see for example U.S. Pat. No. 3,773,919.

[0066] The branched polyesters may be prepared using polyhydroxy compounds e.g. polyol e.g. glucose or mannitol as the initiator. These esters of a polyol are known and described in GB 2,145,422 B. The polyol contains at least 3 hydroxy groups and has a molecular weight of up to 20kD, with at least 1, at least 2, e.g. as a mean 3 of the hydroxy groups of the polyol being in the form of ester groups, which contain poly-lactide or co-poly-lactide chains. Typically 0.2% glucose is used to initiate polymerization. The structure of the branched polyesters may be star shaped. The polyester chains in the linear and star polymer compounds optionally used according to the present disclosure are copolymers of the alpha carboxylic acid moieties, lactic acid and glycolic acid, or of the lactone dimers. The molar

ratios of lactide: glycolide is from about 5:25 to 25:75, e.g. 60:40 to 40:60, with from 55:45 to 45:55, e.g. 55:45 to 50:50. The star polymers may be prepared by reacting a polyol with a lactide and optionally also a glycolide at an elevated temperature in the presence of a catalyst, which makes a ring opening polymerization feasible. Alternatively, the star polymers may be prepared by reacting a polycarboxylic acid (e.g., maleic acid) with hydroxyl-containing monomers in a polymerization reaction.

[0067] In some embodiments, a polymer of the present disclosure comprises a molecular weight less than or equal to 17kD. In some embodiments, a molecular weight refers to the average molecular weight of a polymer species. In some embodiments, a molecular weight refers to the minimum or maximum molecular weight of a polymer species. For example, RESOMER® RG 502H (Evonik Industries) has a molecular weight of 7kD-17kD, and RESOMER® RG 503H (Evonik Industries) has a molecular weight of 24kD-38kD. In some embodiments, a polymer of the present disclosure comprises a maximum molecular weight less than or equal to 17kD. In some embodiments, a polymer of the present disclosure comprises a minimum molecular weight less than or equal to 7kD. In some embodiments, a polymer of the present disclosure comprises a maximum molecular weight less than or equal to 38kD. In some embodiments, a polymer of the present disclosure comprises a minimum molecular weight less than or equal to 24kD.

[0068] In some embodiments, a microsphere of the present disclosure comprises (or is made with a dispersed phase comprising) more than one polymer, e.g., 2, 3, 4, 5, or more polymers. In some embodiments, at least one of the polymers has a pI at least 1.5 units lower than the pI of the therapeutic compound or salt. In some embodiments, at least one of the polymers comprises one or more anionic termini. In some embodiments, a first of the multiple polymers has a lower molecular weight than a second of the multiple polymers. In some embodiments, a first of the multiple polymers has a lower molecular weight (e.g., average, minimum, or maximum molecular weight) by at least 10kD than a second of the multiple polymers. In some embodiments, the molecular weight (e.g., average, minimum, or maximum molecular weight) of the first polymer is less than or equal to 17kD. In some embodiments, the molecular weight (e.g., average, minimum, or maximum molecular weight) of the first polymer is less than or equal to 17kD, and the molecular weight (e.g., average, minimum, or maximum molecular weight) of the second polymer is at least 24kD. In some

embodiments, the first polymer has one or more anionic termini, and the second polymer does not.

[0069] In some embodiments, the first polymer comprises poly(lactic-*co*-glycolic acid) (PLGA), polylactic acid (PLA), polyglycolide, poly(glycolide-*co*-lactide) (PLG), polyhydroxybutyrate, poly(sebacic acid), polyphosphazene, poly[(lactide-*co*-ethylene glycol)-*co*-ethyloxyphosphate], PLA-polyethyleneglycol (PEG)-PLA triblock copolymer, or PLG-PEG-PLG triblock copolymer; and the second polymer comprises a polymer independently selected from poly(lactic-*co*-glycolic acid) (PLGA), polylactic acid (PLA), polyglycolide, poly(glycolide-*co*-lactide) (PLG), polyhydroxybutyrate, poly(sebacic acid), polyphosphazene, poly[(lactide-*co*-ethylene glycol)-*co*-ethyloxyphosphate], PLA-polyethyleneglycol (PEG)-PLA triblock copolymer, or PLG-PEG-PLG triblock copolymer. In some embodiments, the first polymer comprises poly(lactic-*co*-glycolic acid) (PLGA), polylactic acid (PLA), polyglycolide, poly(glycolide-*co*-lactide) (PLG), polyhydroxybutyrate, poly(sebacic acid), polyphosphazene, poly[(lactide-*co*-ethylene glycol)-*co*-ethyloxyphosphate], PLA-polyethyleneglycol (PEG)-PLA triblock copolymer, or PLG-PEG-PLG triblock copolymer; and the second polymer comprises the same polymer (but a species thereof having a different molecular weight than the first polymer) of poly(lactic-*co*-glycolic acid) (PLGA), polylactic acid (PLA), polyglycolide, poly(glycolide-*co*-lactide) (PLG), polyhydroxybutyrate, poly(sebacic acid), polyphosphazene, poly[(lactide-*co*-ethylene glycol)-*co*-ethyloxyphosphate], PLA-polyethyleneglycol (PEG)-PLA triblock copolymer, or PLG-PEG-PLG triblock copolymer. In some embodiments, the first and second polymers represent different species of PLGA. In some embodiments, the first and second polymers represent different species of PLGA that both comprise a carboxylic acid terminus. In some embodiments, the first and second polymers are PLGA species having a difference in minimum molecular weight of at least about 7kD, at least about 10kD, at least about 17kD, or at least about 20kD. In some embodiments, the first and second polymers are PLGA species having a difference in maximum molecular weight of at least about 7kD, at least about 10kD, at least about 17kD, or at least about 20kD. In some embodiments, the first and the second polymers both comprise PLGA, and the molecular weight (*e.g.*, average, minimum, or maximum molecular weight) of the first polymer is at least 10kD lower than the molecular weight of the second polymer. In some embodiments, a microsphere of the present disclosure

comprises (or is made with a dispersed phase comprising) PLGA having a molecular weight of 7kD-17kD, and PLGA having a molecular weight of 24kD-38kD.

[0070] In some embodiments, a microsphere of the present disclosure comprises (or is made with a dispersed phase comprising) the first and the second polymer at a ratio of between about 20:80 and about 80:20 (first polymer:second polymer). In some embodiments, a microsphere of the present disclosure comprises (or is made with a dispersed phase comprising) the first and the second polymer at a ratio of greater than 20:80, 25:75, 30:70, 35:65, 40:60, 45:55, 50:50, 55:45, 60:40, 65:35, 70:30, or 75:25 (first polymer:second polymer). In some embodiments, a microsphere of the present disclosure comprises (or is made with a dispersed phase comprising) the first and the second polymer at a ratio of less than 80:20, 75:25, 70:30, 65:35, 60:40, 55:45, 50:50, 45:55, 40:60, 35:65, 30:70, or 25:75 (first polymer:second polymer). That is, a microsphere of the present disclosure comprises (or is made with a dispersed phase comprising) the first and the second polymer at a ratio having an upper limit of 80:20, 75:25, 70:30, 65:35, 60:40, 55:45, 50:50, 45:55, 40:60, 35:65, 30:70, or 25:75 and an independently selected lower limit of 20:80, 25:75, 30:70, 35:65, 40:60, 45:55, 50:50, 55:45, 60:40, 65:35, 70:30, or 75:25 (first polymer:second polymer), wherein the upper limit is greater than the lower limit. In some embodiments, a microsphere of the present disclosure comprises (or is made with a dispersed phase comprising) the first and the second polymer at a ratio of 20:80, 25:75, 30:70, 35:65, 40:60, 45:55, 50:50, 55:45, 60:40, 65:35, 70:30, 75:25, or 80:20 (first polymer:second polymer). In certain embodiments, a microsphere of the present disclosure comprises (or is made with a dispersed phase comprising) the first and the second polymer at a ratio of about 75:25 (first polymer:second polymer).

[0071] In some embodiments, the dispersed phase comprises a ratio of between 150:30 to 300:10, between 200:30 and 200:20, and between 5:1 and 10:3 (first polymer:therapeutic compound or salt) by weight. In some embodiments, the dispersed phase comprises a ratio of greater than any of 5:1, 6:1, 7:1, 8:1, 9:1, or 10:1 (first polymer:therapeutic compound or salt) by weight. In some embodiments, the dispersed phase comprises a ratio of less than any of 10:3, 10:2, 10:1, 9:1, 8:1, 7:1, or 6:1 (first polymer:therapeutic compound or salt) by weight. That is, the dispersed phase can comprise any ratio in a range of ratios having an upper limit of 10:3, 10:2, 10:1, 9:1, 8:1, 7:1, or 6:1 (first polymer:therapeutic compound or salt) and an independently selected lower limit of 5:1, 6:1, 7:1, 8:1, 9:1, or 10:1 (first polymer:therapeutic

compound or salt), wherein the upper limit is greater than the lower limit. In some embodiments, the dispersed phase comprises a ratio of between 10:1 and 10:3 (first polymer:therapeutic compound or salt) by weight, *e.g.*, a ratio of 10:1, 10:2, or 10:3 (first polymer:therapeutic compound or salt) by weight.

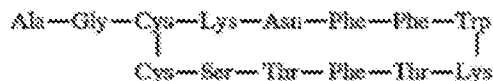
[0072] In some embodiments, the dispersed phase comprises a therapeutic compound or salt of the present disclosure at a concentration of about 10-60mg/mL by weight. In some embodiments, the dispersed phase comprises a therapeutic compound or salt of the present disclosure at a concentration of about 20-40mg/mL by weight.

[0073] In some embodiments, a therapeutic compound or salt of the present disclosure comprises at least one cationic moiety.

[0074] In some embodiments, a therapeutic compound or salt of the present disclosure comprises a therapeutic peptide. In some embodiments, the therapeutic peptide comprises at least two amino-containing amino acid side chains. In some embodiments, the therapeutic peptide has a length from 6 to 40 amino acids, *e.g.*, a length of 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, or 40 amino acids. In certain embodiments, the therapeutic peptide has a length of 8 amino acids. In some embodiments, the therapeutic peptide is cyclic. In some embodiments, the therapeutic peptide is selected from veldoreotide, somatostatin (SST-28), SST-14, lanreotide, octreotide, vapreotide, pasireotide, and pharmaceutically acceptable salts of any of the foregoing. In some embodiments, the therapeutic peptide is human growth hormone or a pharmaceutically acceptable salt thereof. In some embodiments, the therapeutic peptide is octreotide or a pharmaceutically acceptable salt thereof.

[0075] In some embodiments, the therapeutic peptide is a somatostatin analog or a pharmaceutically acceptable salt thereof. Naturally occurring somatostatin is produced by the hypothalamus as well as other organs, *e.g.* the gastrointestinal tract, and mediates, together with growth-hormone releasing factor (GRF), the neuroregulation of pituitary growth hormone release. In addition to inhibition of growth hormone (GH) release by the pituitary, somatostatin is a potent inhibitor of a number of systems, including central and peripheral neural, gastrointestinal and vascular smooth muscle. It also inhibits the release of insulin and glucagon. Analogs (*e.g.*, agonist analogs) of somatostatin are thus useful in replacing natural somatostatin in its effect on regulation of physiologic functions. For exemplary descriptions

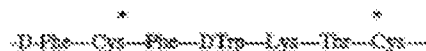
of somatostatin analogs, *see, e.g.*, U.S. Pat. No. 5,639,480. Naturally occurring somatostatin is a tetradecapeptide having the structure:



[0076] As used herein, the term "somatostatin" includes its analogues or derivatives thereof. By derivatives and analogues is understood straight-chain, bridged or cyclic polypeptides wherein one or more amino acid units have been omitted and/or replaced by one or more other amino radical(s) of and/or wherein one or more functional groups have been replaced by one or more other functional groups and/or one or more groups have been replaced by one or several other isosteric groups. In general, the term covers all modified derivatives of a biologically active peptide which exhibit a qualitatively similar effect to that of the unmodified somatostatin peptide.

[0077] The term derivative includes also the corresponding derivatives bearing a sugar residue. When somatostatins bear a sugar residue, this can be coupled to an N-terminal amino group and/or to at least one amino group present in a peptide side chain, such as to a N-terminal amino group. Such compounds and their preparation are disclosed, *e.g.* in WO 88/02756. Exemplary derivatives are N.sup.α-[α-glucosyl-(1-4-deoxyfructosyl)]-DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol and N.sup.α-[β-deoxyfructosyl]-DPhe-Cys-Phe-DTrp-Lys-Thr-Cys-Thr-ol, each having a bridge between the -Cys- moieties, optionally in acetate salt form and described in Examples 2 and 1 respectively of the above mentioned application.

[0078] In some embodiments, the therapeutic peptide is selected from somatostatin (SST-28), SST-14, lanreotide, octreotide, vapreotide, pasireotide, and pharmaceutically acceptable salts of any of the foregoing. Octreotide derivatives are also contemplated for use and include, without limitation, those comprising the moiety:



having a bridge between Cys residues.

[0079] The somatostatins may exist *e.g.* in free form, salt form or in the form of complexes thereof. Acid addition salts may be formed with *e.g.* organic acids, polymeric acids and inorganic acids. Acid addition salts include *e.g.* the hydrochloride and acetates. Complexes are *e.g.* formed from somatostatins on addition of inorganic substances, *e.g.*

inorganic salts or hydroxides such as Ca- and Zn-salts and/or an addition of polymeric organic substances.

[0080] The acetate salt is an exemplary salt for such formulations, especially for microspheres leading to a reduced initial drug burst. The present disclosure also provides the pamoate salt, which is useful, particularly for implants and the process for its preparation. The pamoate may be obtained in conventional manner, e.g. by reacting embonic acid (pamoic acid) with octreotide e.g. in free base form. The reaction may be effected in a polar solvent, e.g. at or below room temperature.

[0081] In some embodiments, a therapeutic compound or salt of the present disclosure comprises a small molecule drug or compound.

[0082] In some embodiments, the therapeutic compound or salt comprises an mTOR inhibitor. The term “mTOR inhibitor” broadly encompasses multiple classes of molecules, including molecules that bind FKBP12 (*e.g.*, first-generation mTOR inhibitors such as rapamycin and rapalogs that inhibit mTORC1), molecules that inhibit the kinase activity of mTOR (*e.g.*, second-generation, ATP-competitive mTOR inhibitors that inhibit mTORC1 and mTORC2), molecules that bind FKBP12 and inhibit the kinase activity of mTOR (*e.g.*, third-generation mTOR inhibitors such as RapaLinks), and dual PI3K/mTOR inhibitors (*e.g.*, BEZ235 or LY3023414). In some embodiments, an mTOR inhibitor inhibits mTORC1, mTORC2, or both. Examples of specific mTOR inhibitors include, without limitation, tacrolimus (also known as FK506, fujimycin, PROGRAF®, PROTOPIC®, ADVAGRAF®, ENVARSUS®, and ASTAGRAF®), temsirolimus (also known as CCI-779 and TORISEL®), everolimus (also known as RAD001, ZORTRESS®, AFINITOR®, CERTICAN®, VOTUBIA®, and Evertor), rapamycin (also known as sirolimus and RAPAMUNE®), ridaforolimus (also known as AP23573, MK-8669, and deforolimus), AZD8055, Ku-0063794, PP242, PP30, Torin1, WYE-354, PI-103, BEZ235 (also known as NVP-BEZ235 and dactolisib), PKI-179 (also known as PKI-587), LY3023414, omipalisib (also known as GSK2126458 and GSK458), sapanisertib (also known as MLN0128 and INK128), OSI-027, RapaLink-1 and voxalisib (also known as XL765 and SAR245409).

[0083] In some embodiments, the therapeutic compound or salt comprises a glucocorticoid, *e.g.*, a compound that binds the glucocorticoid receptor. Examples of specific glucocorticoids include, without limitation, triamcinolone (*e.g.*, triamcinolone acetonide),

beclomethasone, betamethasone, budesonide, cortisone, hydrocortisone, methylprednisolone, prednisolone, prednisone, and dexamethasone.

[0084] In some embodiments, the therapeutic compound or salt comprises a Janus kinase (JAK) inhibitor. The term “JAK inhibitor” broadly encompasses molecules that inhibit the function of one or more JAK family kinases, such as JAK1, JAK2, JAK3, and TYK2. For example, in some embodiments, a JAK inhibitor inhibits one or more activities of JAK1; JAK2; JAK3; JAK1 and JAK2; JAK1 and JAK3; JAK3 and JAK2; TYK2 and JAK1; TYK2 and JAK2; TYK2 and JAK3; JAK1, JAK2, and JAK3; or JAK1, JAK2, TYK2, and JAK3. Examples of specific JAK inhibitors include, without limitation, ruxolitinib (also known as JAKAFI®, JAKAVI®, and INCB018424, including the phosphate and sulfate salts and S enantiomer), tofacitinib (also known as tasocitinib, CP-690550, XELJANZ® and JAKVINUS®, including (3R,4S), (3S,4R), and (3S,4S) enantiomers and the citrate salt), oclacitinib (also known as APOQUEL®, including the maleate salt), baricitinib (also known as LY3009104, INCB-28050, and OLUMIANT®, including the phosphate salt), filgotinib (also known as G-146034 and GLPG-0634), gandotinib (also known as LY-2784544), lestaurtinib (also known as CEP-701), momelotinib (also known as GS-0387 and CYT-387, including mesylate and sulfate salts), pacritinib (also known as SB1518), PF-04965842, upadacitinib (also known as ABT-494), peficitinib (also known as ASP015K and JNJ-54781532), fedratinib (also known as SAR302503 and TG101348), cucurbitacin I (also known as JSI-124), decernotinib (also known as VX-509 and VRT-831509), INCB018424, AC430, BMS-0911543, GSK2586184, VX-509, R348, AZD1480, CHZ868, PF-956980, AG490, WP-1034, JAK3 inhibitor IV (also known as ZM-39923, including the hydrochloride salt), atiprimod (including the dihydrochloride salt), FM-381, SAR20347, AZD4205, ARN4079, NIBR-3049, PRN371, PF-06651600 (including the malonate salt), JAK3i, JAK3 inhibitor 31, PF-06700841 (including the tosylate salt), NC1153, EP009, Gingerenone A, JANEX-1 (also known as WHI-P131), cercosporamide, JAK3-IN-2, PF-956980, Tyk2-IN-30, Tyk2-IN-2, JAK3-IN1, WHI-P97, TG-101209, AZ960, NVP-BSK805 (including the dihydrochloride salt), NSC 42834 (also known as Z3), FLLL32, SD 1029, WHI-P154, WHI-P154, TCS21311, JAK3-IN-1, JAK3-IN-6, JAK3-IN-7, XL019, MS-1020, AZD1418, WP1066, CEP33779, ZM 449829, SHR0302, JAK1-IN-31, WYE-151650, EXEL-8232, solcitinib (also known as GSK-2586184 and GLPG-0778), itacitinib (also known as INCB039110, including the adipate salt), cerdulatinib (also known as PRT062070 and

PRT2070), PF-06263276, delgatinib (also known as JTE-052), AS2553627, JAK-IN-35, ASN-002, AT9283, diosgenin, JAK inhibitor 1 (*see* US20170121327, compound example 283), JAK-IN-1, LFM-A13, NS-018 (including hydrochloride and maleate salts), RGB-286638, SB1317 (also known as TG02), curcumol, Go6976, JAK2 inhibitor G5-7, myricetin (also known as NSC 407290 and cannabiscetin), and pyridine 6 (also known as CMP6). For more description and chemical structures of exemplary JAK inhibitors, *see, e.g.*, U.S. Pat. Nos. 9,198,911; 9,763,866; 9,737,469; 9,730,877; 9,895,301; 9,249,149; 9,518,027; 9,776,973; 9,549,367; and 9,931,343.

[0085] In some embodiments, a microsphere of the present disclosure comprises more than one therapeutic compound or pharmaceutically acceptable salt thereof. For example, a microsphere of the present disclosure can comprise multiple somatostatins, *e.g.*, to target a particular somatostatin receptor profile in order to attain an altered pharmacodynamics effect.

[0086] In some embodiments, the dispersed phase comprises a polyol. Any of the polyols described herein may be used. In certain embodiments, the polyol comprises glycerol. In some embodiments, the polyol is present in the dispersed phase. In some embodiments, the polyol is solubilized in the dispersed phase.

[0087] In some embodiments, a microsphere of the present disclosure further comprises (or is made with a dispersed phase further comprising) a polyol. In some embodiments, the polyol comprises a (C₃₋₆) carbon chain containing alcohol having 2 to 6 hydroxyl groups and a mono- or di-saccharide, an esterified polyol having at least 3 polylactide-co-glycolide chains, glycols (*e.g.*, propylene glycol with the number of OH reduced to 2), glucose, mannitol, or glycerol. In certain embodiments, the polyol is glycerol.

[0088] In some embodiments, the dispersed phase comprises the polyol at a concentration of between about 0.3mg/mL and about 1.2mg/mL. In some embodiments, the dispersed phase comprises the polyol at a concentration of between about 0.6mg/mL and about 0.9mg/mL. In some embodiments, the dispersed phase comprises the polyol at a concentration of about 0.9mg/mL.

[0089] In some embodiments, a microsphere of the present disclosure is prepared according to a formulation described in Table A.

Table A. Microsphere formulations

Formulation name	#73	#121	#131	#137	#139	#154	#17 5	#17 3
Actual loading (%)	4.6	9.7	3.6	9.0	5.9	3.8	9.0	8.4
PLGA 502h (%)	0	100	0	75	50	0	75	65
PLGA 503h (%)	100	0	100	25	50	100	25	35
PLGA concentration (mg/ml)*	200	200	200	200	200	200	200	200
Octreotide acetate (mg/ml)*	20	40	20	30	20	0	30	30
Octreotide benzoate (mg/ml)*	0	0	0	0	0	20	0	0
Glycerol (mg/ml)*	0	0	0.9	0	0	0	0.9	0
Continuous phase	100% DCM sat. 150 mM NaCl, 0.5%PV A, 200mM Gly, pH 8.5	100% DCM sat., 0.5%PV A, 200mM Gly pH 9.0	100% DCM sat. 150 mM NaCl, 0.5%PV A, 50mM Gly pH 8.5	100% DCM sat., 0.5%PV A, 200mM Gly pH 9.0	100% DCM sat., 0.5%PV A, 200mM Gly pH 9.0	100% DCM sat. 150 mM NaCl, 0.5%PVA, 50mM Gly, pH 8.5	100% DC M sat., 0.5 %PV A, 200 mM Gly pH 9.0	100% DC M sat., 0.5 %PV A, 200 mM Gly pH 9.0
Membrane pore size (μm)	15	20	15	20	20	15	20	20

*Final concentration in dispersed phase.

[0090] In some embodiments, the methods of the present disclosure further include adjusting the pH of the aqueous continuous phase. In some embodiments, the pH of the aqueous continuous phase is adjusted to the pI of the therapeutic compound or salt minus 0.5 or greater. In some embodiments, the pH of the aqueous continuous phase is adjusted to

about 8 to about 9.5, *e.g.*, to about 8, to about 8.5, to about 9, or to about 9.5. In some embodiments, the pH of the aqueous continuous phase is adjusted to about 7.5 to about 8.5, *e.g.*, to about 7.5, to about 8, or to about 8.5. In some embodiments, the pH of the aqueous continuous phase is adjusted with a buffer solution. A variety of buffer solutions are known in the art and may be selected by one of skill in the art; exemplary buffers include, without limitation, glycine, glycyglycine, tricine, HEPES, MOPS, sulfonate, ammonia, potassium phosphate, CHES, borate, TAPS, Tris, bicine, TAPSO, TES, and Tris buffer solutions. In some embodiments, the buffer is glycyglycine, bicine, or tricine. In some embodiments, the buffer is not Tris buffer. In some embodiments, the pH of the aqueous continuous phase is adjusted to about 8.0 in glycyglycine, bicine, or tricine buffer. In some embodiments, the pH of the aqueous continuous phase is adjusted to about 8.0 in glycyglycine buffer.

[0091] In some embodiments, the continuous phase comprises ethanol, propanol, or methanol. In some embodiments, the continuous phase comprises dichloromethane, chloroform, or ethyl acetate.

[0092] In some embodiments, a continuous phase of the present disclosure comprises a surfactant. A variety of surfactants are known in the art and can be selected by one of skill in the art. In some embodiments, the surfactant is selected from polysorbate 20 or polysorbate 80 (*e.g.*, of the TWEEN® series), poloxamer (*e.g.*, of the PLURONIC® series; BASF), and polyvinyl alcohol (PVA). In some embodiments, the concentration of surfactant in the continuous phase is from 0.05% to 1% (w/w). In some embodiments, the concentration of surfactant in the continuous phase is at least about any of the following concentrations (in percentage, w/w): 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, or 0.9. In some embodiments, the concentration of surfactant in the continuous phase is less than about any of the following concentrations (in percentage, w/w): 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1. That is, the concentration of surfactant in the continuous phase can be any concentration in a range having an upper limit of about 2, 1.5, 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, or 0.1% (w/w), and an independently selected lower limit of about 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, or 0.9% (w/w), wherein the upper limit is greater than the lower limit. In some embodiments, the concentration of surfactant in the continuous phase is about 0.5% (w/w).

[0093] The flowrates of the dispersed phase and continuous phase can vary depending on the application. The continuous phase flow rate can be adjusted such that the continuous phase volume is replenished frequently enough to keep the microparticle concentration low

enough to prevent frequent collisions or aggregation, in particular in the apparatus. The continuous phase flow rate can increase with increases in dispersed flow rate to maintain a microparticle density within the continuous phase housing that is sufficiently low. The flow through the continuous phase housing can be determined experimentally and can depend also on the polymer used surfactants. As examples, the continuous phase volume might be turned over once every two minutes to five times per minute. If the available volume of the continuous phase space were 500mL, for example, then that would correspond to flow rates of 0.25 liters per minute to 2.5 liters per minute. Importantly, these flow rates depend on the scale of the device, namely, the rate of turnover of the volume would stay the same with scale but the absolute volumetric flow rate would scale one-to-one with the volume of the device. In some embodiments, the flow rate of the continuous phase is at least about 0.01 liters/min, about 0.05 liters/min, about 0.1 liters/min, about 0.3 liters/min, about 0.5 liters/min, about 0.925 liters/min, about 1 liter/min, or about 5 liters/min. In some embodiments, the flow rate of the continuous phase can be about 0.01-5 liters/min, about 0.05-3 liters/min, about 0.1-2 liters/min, or about 0.5-1 liters/min.

[0094] In some embodiments, the flow rate of the dispersed phase per pore can be at least about 0.1 mL/min, about 0.5 mL/min, about 0.75 mL/min, about 1 mL/min, about 1.25 mL/min, about 1.4 mL/min, about 2 mL/min, about 5mL/min, or about 10 mL/min. In some embodiments, the flow rate of the dispersed phase per pore can be about 0.1-10 mL/min, about 0.5-5 mL/min, about 1-2 mL/min, or about 1.4 mL/min. In some embodiments, a ratio of the flow of continuous phase to dispersed phase can be about 50:1 to about 5000:1, about 500:1 to about 3000:1, or about 750:1 to about 1000:1.

[0095] In some embodiments, the flow rate of the continuous phase is about 1.5L/min to about 3.5L/min or about 1.7L/min to about 3.4L/min. In some embodiments, the flow rate of the continuous phase is about 1.7L/min, about 2.0L/min, about 2.5L/min, about 3.0L/min, or about 3.4L/min. In certain embodiments, the flow rate of the continuous phase is about 3.4L/min.

[0096] In some embodiments, the flow rate of the dispersed phase is about 8mL/min to about 13 mL/min or about 9mL/min to about 12mL/min. In some embodiments, the flow rate of the dispersed phase is about 9mL/min, about 10mL/min, about 11mL/min, or about 12mL/min. In certain embodiments, the flow rate of the dispersed phase is about 10mL/min.

In certain embodiments, the flow rate of the dispersed phase is about 10mL/min, and the flow rate of the continuous phase is about 3.4L/min.

[0097] In some embodiments, the droplet is allowed to harden for at least about 60 minutes, at least about 90 minutes, or at least about 120 minutes.

[0098] In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres are 22-36 μ m in diameter. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 90-95% of the microspheres are 22-36 μ m in diameter. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres are 26-34 μ m in diameter. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 60-70% of the microspheres are 26-34 μ m in diameter. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres are 20-40 μ m in diameter. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres are 28-32 μ m in diameter. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres are 22-34 μ m in diameter. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres are 26-36 μ m in diameter.

[0099] In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) 7 μ m of a mean diameter of 29 μ m. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%,

at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) $7\mu\text{m}$ of a mean diameter of $30\mu\text{m}$. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) $4\mu\text{m}$ of a mean diameter of $30\mu\text{m}$. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) $4\mu\text{m}$ of a mean diameter of $29\mu\text{m}$. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) $10\mu\text{m}$ of a mean diameter of $30\mu\text{m}$. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) $2\mu\text{m}$ of a mean diameter of $30\mu\text{m}$.

[0100] In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) 7% of the mean diameter of the plurality of microspheres. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) 7% of the median diameter of the plurality of microspheres. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) 6% of the mean diameter of the plurality of microspheres. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the

plurality have a diameter within (e.g., plus or minus) 6% of the median diameter of the plurality of microspheres. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) 5% of the mean diameter of the plurality of microspheres. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) 5% of the median diameter of the plurality of microspheres. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) 7% of the mean diameter of the plurality of microspheres. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) 7% of the median diameter of the plurality of microspheres. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) 4% of the mean diameter of the plurality of microspheres. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) 4% of the median diameter of the plurality of microspheres. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) 10% of the mean diameter of the plurality of microspheres. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the

plurality have a diameter within (e.g., plus or minus) 10% of the median diameter of the plurality of microspheres. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) 15% of the mean diameter of the plurality of microspheres. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) 15% of the median diameter of the plurality of microspheres. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) 20% of the mean diameter of the plurality of microspheres. In some embodiments, the present disclosure provides a plurality of microspheres, where at least 50%, at least 55%, at least 60%, at least 65%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95% of the microspheres of the plurality have a diameter within (e.g., plus or minus) 20% of the median diameter of the plurality of microspheres.

Definitions

[0101] Unless defined otherwise, all terms of art, notations and other technical and scientific terms or terminology used herein are intended to have the same meaning as is commonly understood by one of ordinary skill in the art to which the claimed subject matter pertains. In some cases, terms with commonly understood meanings are defined herein for clarity and/or for ready reference, and the inclusion of such definitions herein should not necessarily be construed to represent a substantial difference over what is generally understood in the art.

[0102] Reference to “about” a value or parameter herein includes (and describes) variations that are directed to that value or parameter per se. For example, description referring to “about X” includes description of “X”. In addition, reference to phrases “less than”, “greater than”, “at most”, “at least”, “less than or equal to”, “greater than or equal to”, or other similar phrases followed by a string of values or parameters is meant to apply the

phrase to each value or parameter in the string of values or parameters. For example, a statement that the membrane has at least about 1,000 pores, about 5,000 pores, or about 10,000 pores is meant to mean that the membrane has at least about can be less 1,000 pores, at least about 5,000 pores, or at least about 10,000 pores.

[0103] As used herein, the singular forms “a,” “an,” and “the” are intended to include the plural forms as well, unless the context clearly indicates otherwise. It is also to be understood that the term “and/or” as used herein refers to and encompasses any and all possible combinations of one or more of the associated listed items. It is further to be understood that the terms “includes,” “including,” “comprises,” and/or “comprising,” when used herein, specify the presence of stated features, integers, steps, operations, elements, components, and/or units but do not preclude the presence or addition of one or more other features, integers, steps, operations, elements, components, units, and/or groups thereof.

[0104] This application discloses several numerical ranges in the text and figures. The numerical ranges disclosed inherently support any range or value within the disclosed numerical ranges, including the endpoints, even though a precise range limitation is not stated verbatim in the specification because this disclosure can be practiced throughout the disclosed numerical ranges.

[0105] The above description is presented to enable a person skilled in the art to make and use the disclosure, and is provided in the context of a particular application and its requirements. Various modifications to the preferred embodiments will be readily apparent to those skilled in the art, and the generic principles defined herein may be applied to other embodiments and applications without departing from the spirit and scope of the disclosure. Thus, this disclosure is not intended to be limited to the embodiments shown, but is to be accorded the widest scope consistent with the principles and features disclosed herein.

Claims

1. A device, comprising:
a continuous phase housing comprising a continuous phase inlet and an impeller;
a dispersed phase housing comprising a dispersed phase inlet;
a membrane comprising a plurality of pores, wherein the membrane is located between the continuous phase housing and the dispersed phase housing, and the dispersed phase inlet is fluidly connected to the plurality of pores in the membrane;
an outlet that is fluidly connected to the continuous phase inlet; and
a motor for rotating the impeller.
2. The device of claim 1, wherein an outer circumference of the impeller is concentric with the membrane.
3. The device of claim 2, wherein the outer circumference of the impeller is separated from the membrane by a distance of 0.01-1 mm.
4. The device of any of claims 1-3, wherein the membrane is in the shape of a portion of an annular cylinder.
5. The device of any of claims 1-4, wherein the membrane is in the shape of an annular cylinder.
6. The device of any of claims 1-5, wherein the impeller has a rotational axis that is transverse to a flow of a dispersed phase through the plurality of pores.
7. The device of any of claims 1-6, wherein the continuous phase housing comprises the outlet.
8. The device of any of claims 1-7, wherein the dispersed phase housing comprises a bleed valve.
9. The device of any of claims 1-8, wherein the membrane is removably attached to the continuous phase housing and the dispersed phase housing.

10. The device of any of claims 1-9, wherein the continuous phase housing is removably attached to the dispersed phase housing.
11. The device of any of claims 1-10, wherein the membrane is clamped to the continuous phase housing by the dispersed phase housing.
12. The device of any of claims 1-11, further comprising gaskets located between the membrane and the continuous phase housing and between the membrane and the dispersed phase housing.
13. The device of any of claims 1-12, wherein the dispersed phase housing comprises stainless steel.
14. The device of any of claims 1-13, wherein the continuous phase housing comprises stainless steel.
15. The device of any of claims 1-14, wherein the membrane comprises stainless steel, tantalum, tungsten, molybdenum, manganese, tin, zinc, or an alloy thereof.
16. The device of any of claims 1-15, wherein the membrane comprises porous glass or a ceramic.
17. The device of any of claims 1-16, wherein one or more pores of the plurality of pores has a size less than 50 microns.
18. The device of claim 17, wherein one or more pores of the plurality of pores has a size less than or equal to 10 microns.
19. The device of any of claims 1-18, wherein the plurality of pores is uniformly sized.
20. The device of any of claims 1-19, wherein the impeller rotates at 100-5,000 RPMs.
21. The device of any of claims 1-20, wherein the impeller is a paddle wheel impeller.

22. The device of any of claims 1-21, further comprising a coupler that couples the motor to the impeller.

23. The device of any of claims 1-22, further comprising a plate that seals the continuous phase housing and allows a portion of the impeller to exit the continuous phase housing for connection to the motor.

24. A method of forming microspheres, comprising:
flowing a continuous phase through a continuous phase housing comprising an impeller;

rotating the impeller about a rotational axis such that the continuous phase imparts a shear force on a membrane comprising a plurality of pores, wherein the membrane is located between the continuous phase housing and a dispersed phase housing; and

forcing a dispersed phase through the plurality of pores such that the dispersed phase enters into the continuous phase in a direction that is perpendicular to the rotational axis of the impeller,

wherein forcing the dispersed phase through the plurality of pores into the continuous phase forms a plurality of microspheres comprising the dispersed phase.

25. The method of claim 24, wherein a median diameter of the plurality of microspheres is between 1-1000 microns.

26. The method of claim 24, wherein a median diameter of the plurality of microspheres is between 10-40 microns.

27. The method of claim 24, wherein a median diameter of the plurality of microspheres is less than 20 microns.

28. The method of any of claims 24-27, wherein at least 70% of the plurality of microspheres has a diameter within 10 microns above or below the median diameter.

29. The method of any of claims 24-28, wherein the coefficient of variation of a size distribution of the plurality of microspheres is less than 30%.

30. The method of claim 29, wherein the coefficient of variation of a size distribution of the plurality of microspheres is less than 20%.
31. The method of any of claims 24-30, wherein the coefficient of variation of a size distribution of the plurality of microspheres is between 10-20%.
32. The method of any of claims 24-31, wherein the continuous phase exerts a shear force at a shear rate at the membrane of 1,000-25,000 s⁻¹.
33. The method of any of claims 24-32, wherein the continuous phase comprises an aqueous solvent and the dispersed phase comprises an organic solvent.
34. The method of claim 33, wherein the continuous phase further comprises a surfactant.
35. The method of claim 34, wherein the dispersed phase further comprises a water insoluble polymer.
36. The method of any of claims 34-35, wherein the dispersed phase comprises a therapeutic compound or pharmaceutically acceptable salt thereof
37. The method of any of claims 34-36, wherein the dispersed phase comprises a polyol.
38. The method of any of claims 24-37, wherein the impeller rotates at 100-5,000 RPMs.

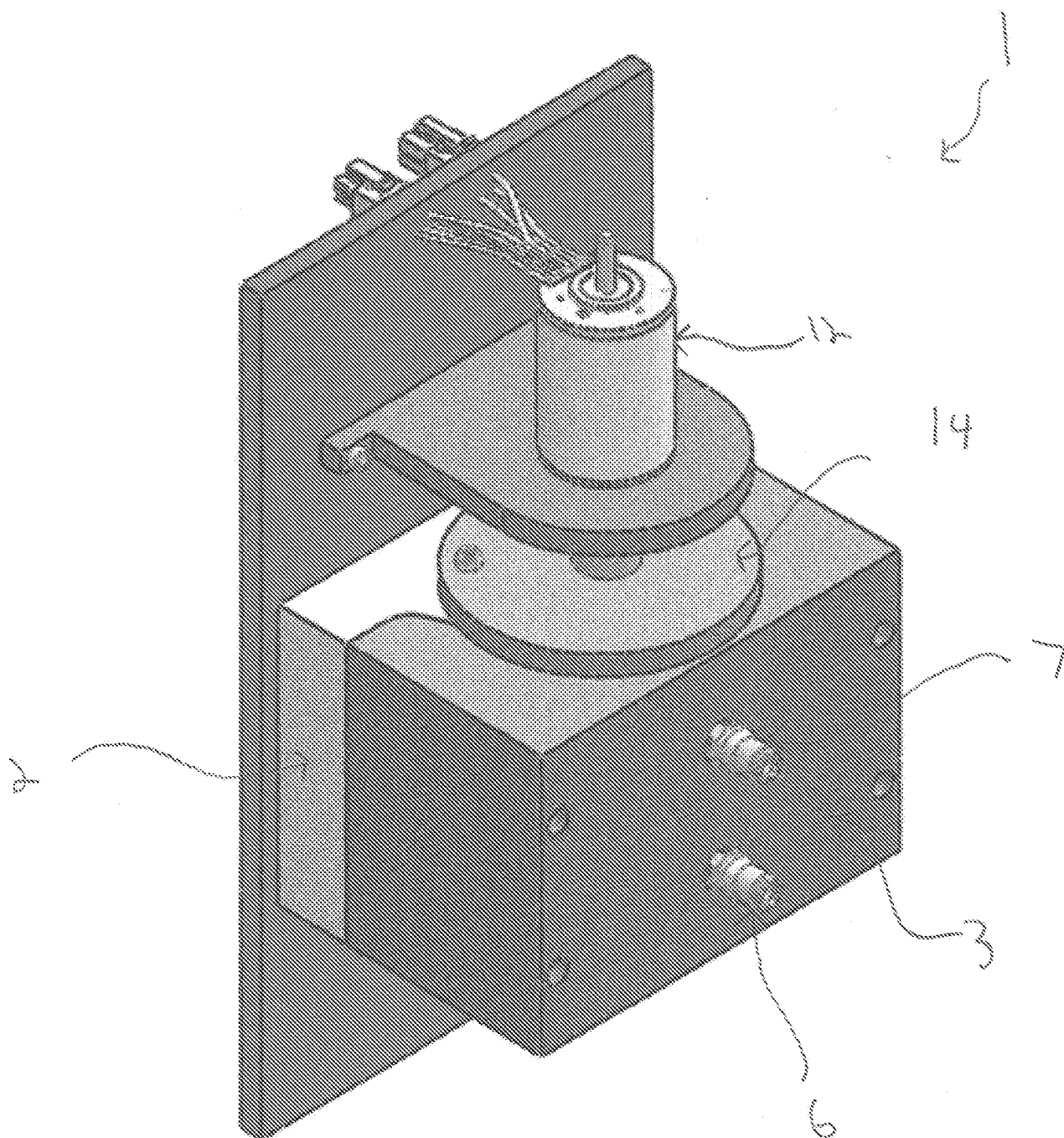
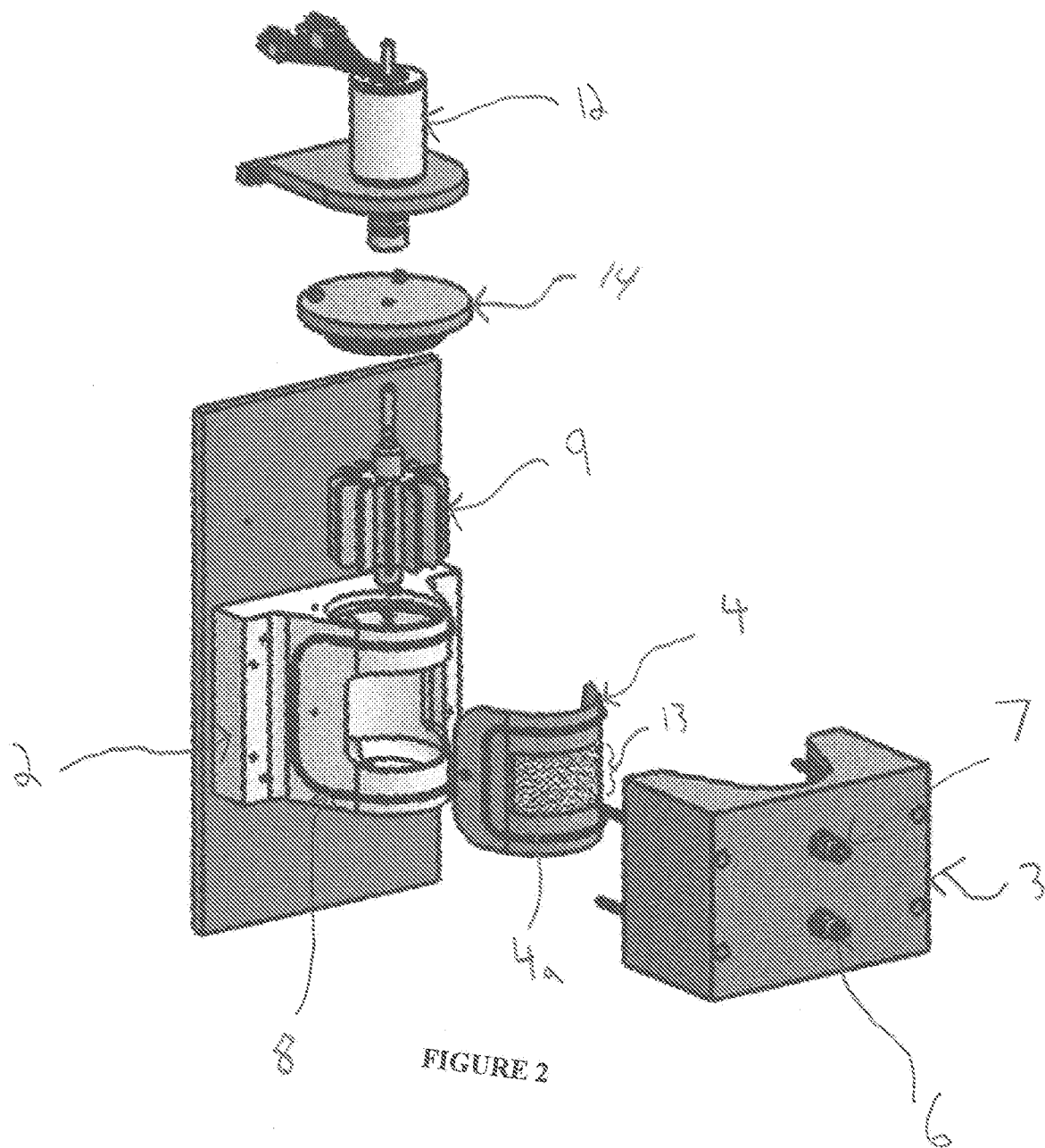
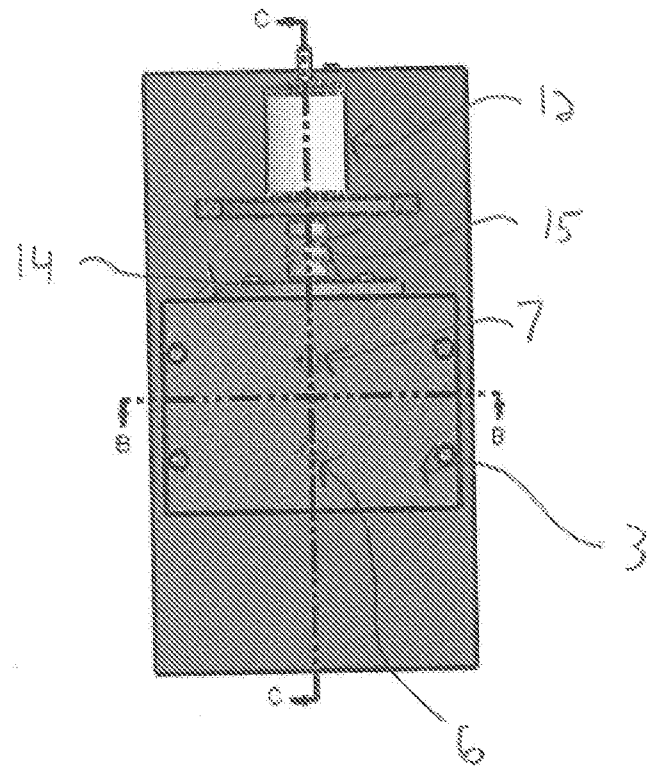
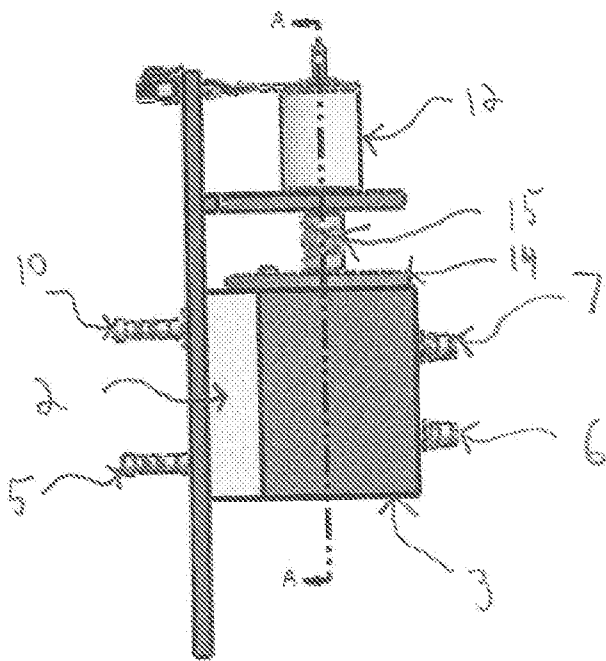
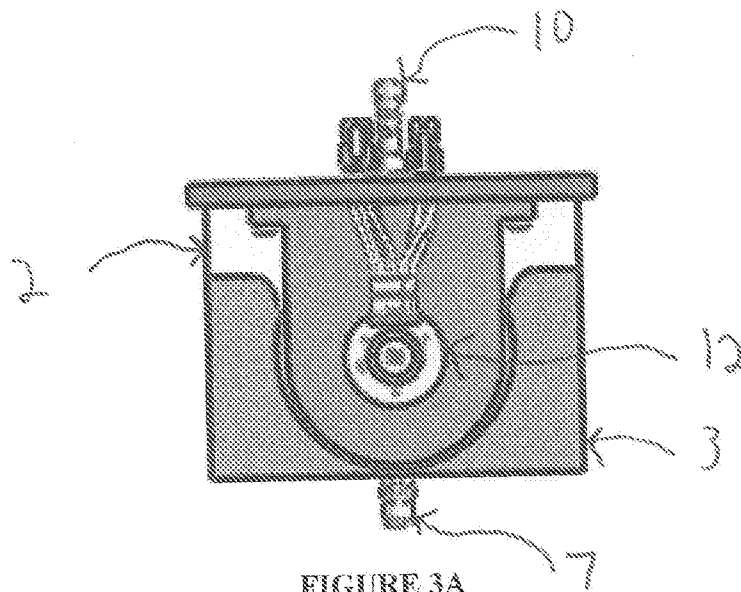
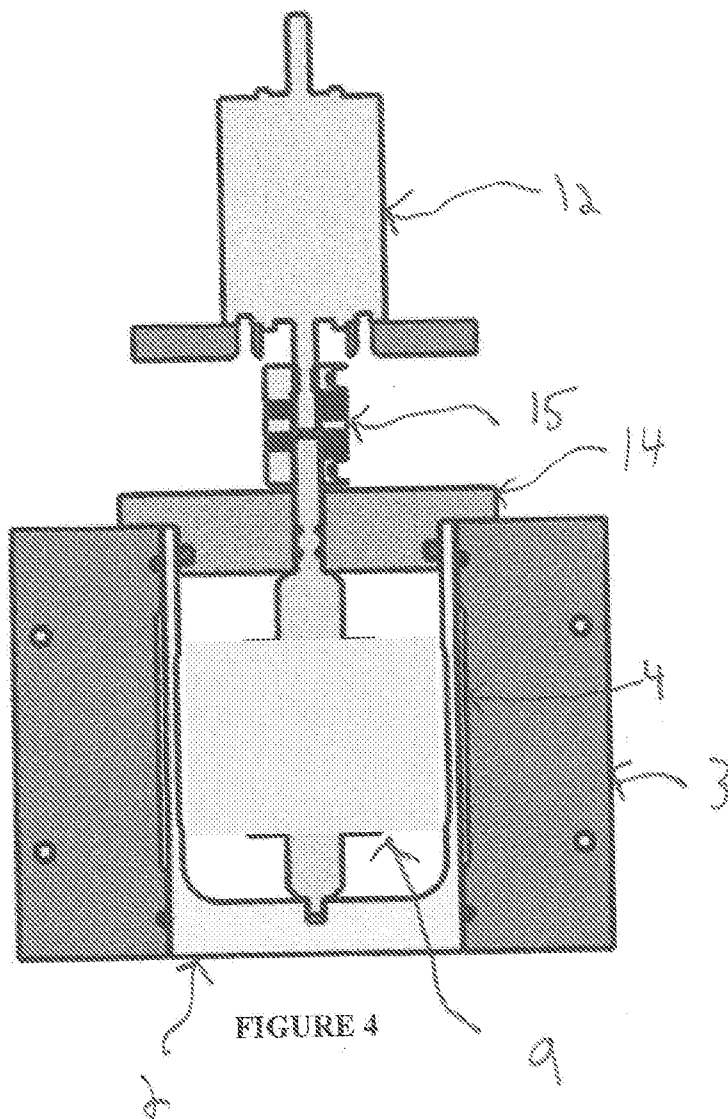


FIGURE 1







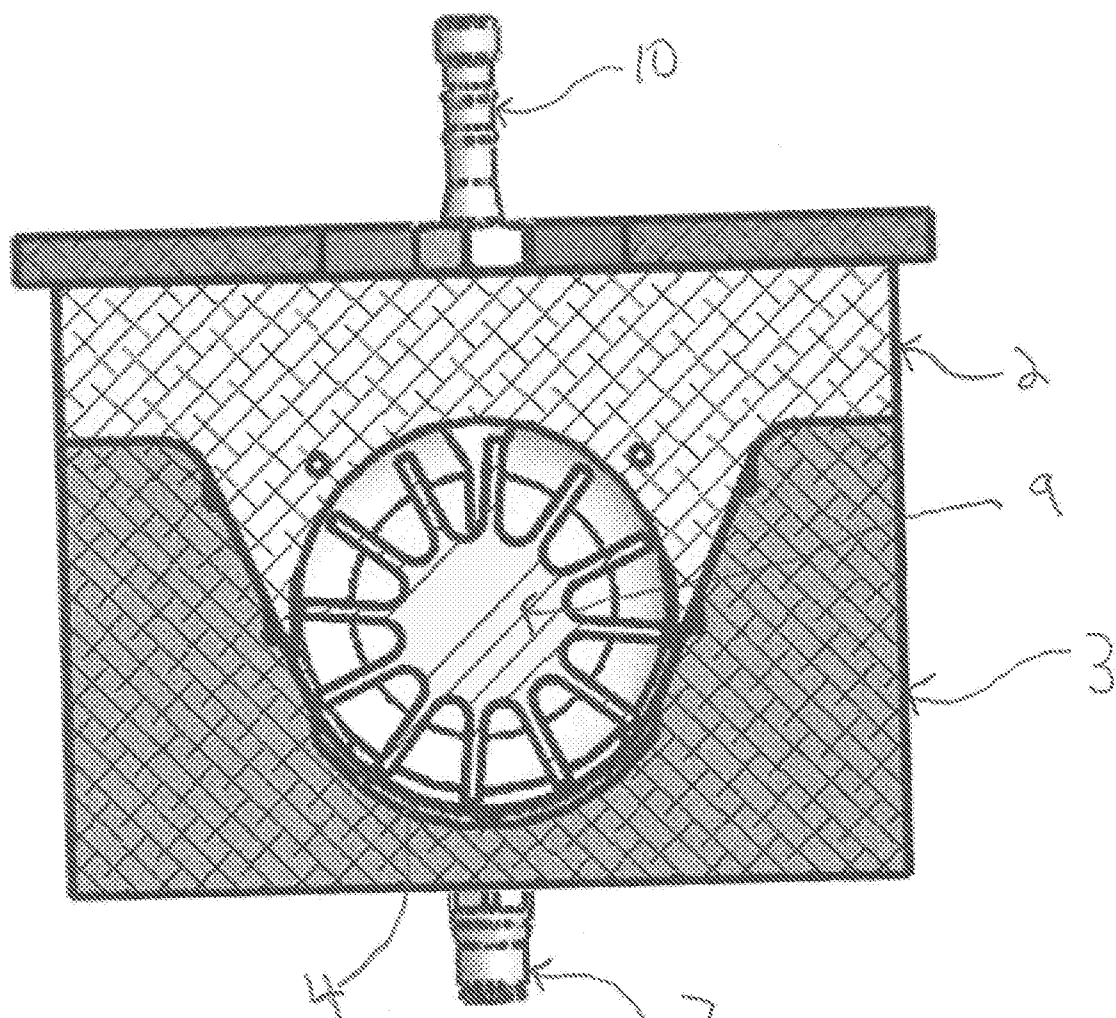


FIGURE 5

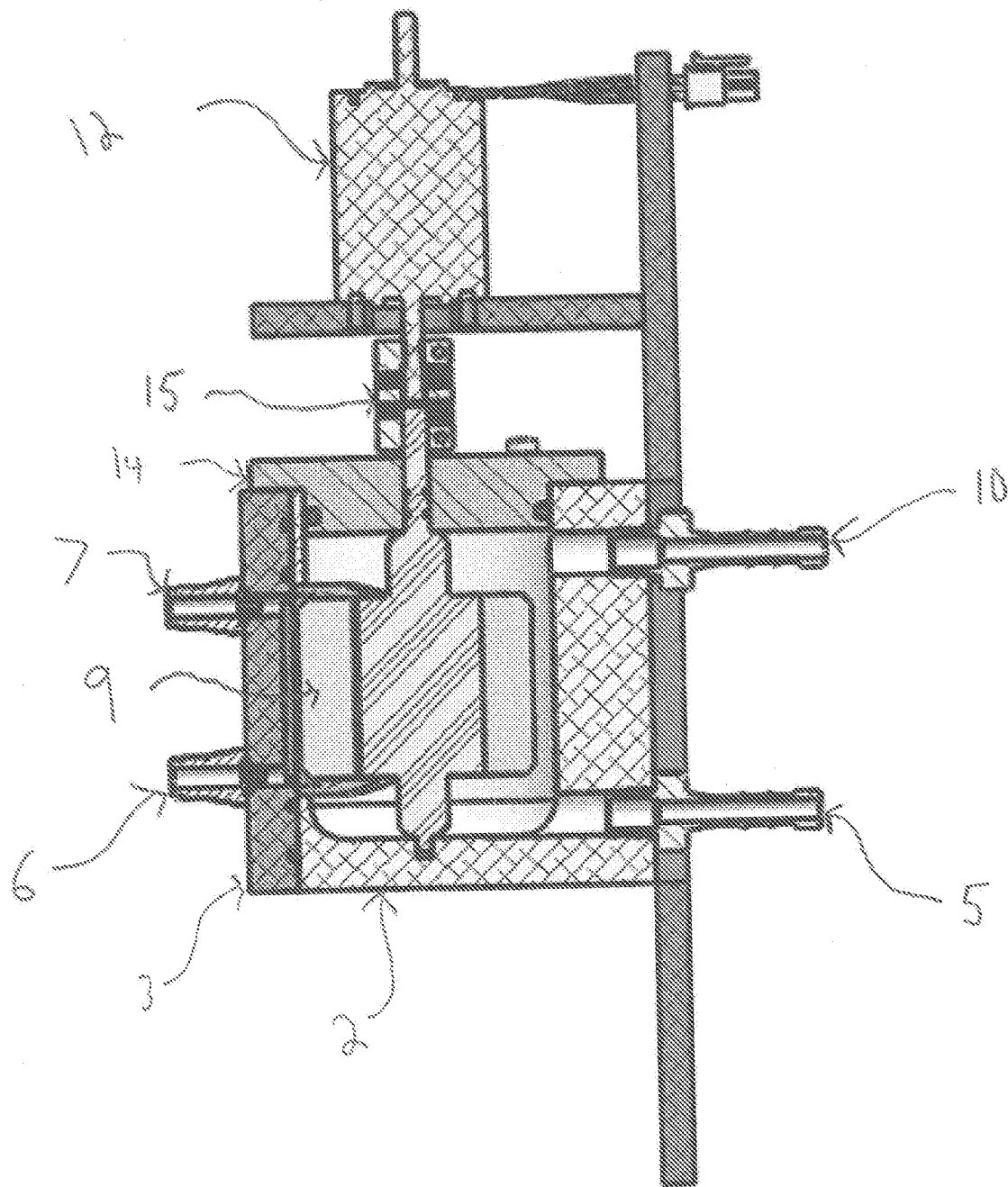


FIGURE 6

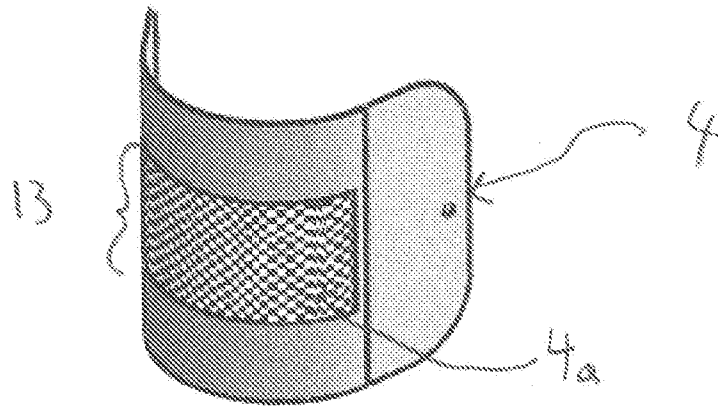


FIGURE 7A

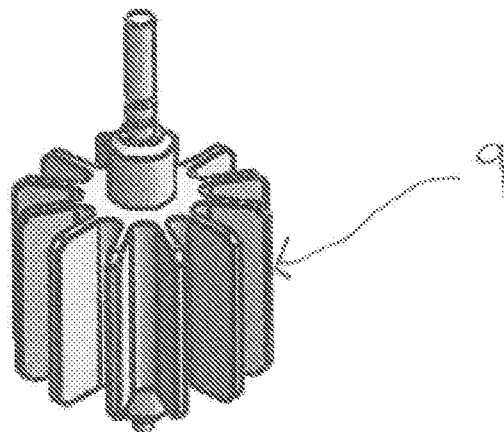


FIGURE 7B

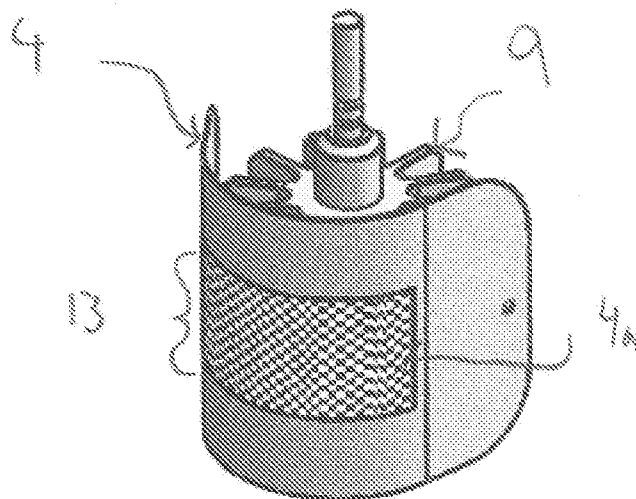


FIGURE 7C

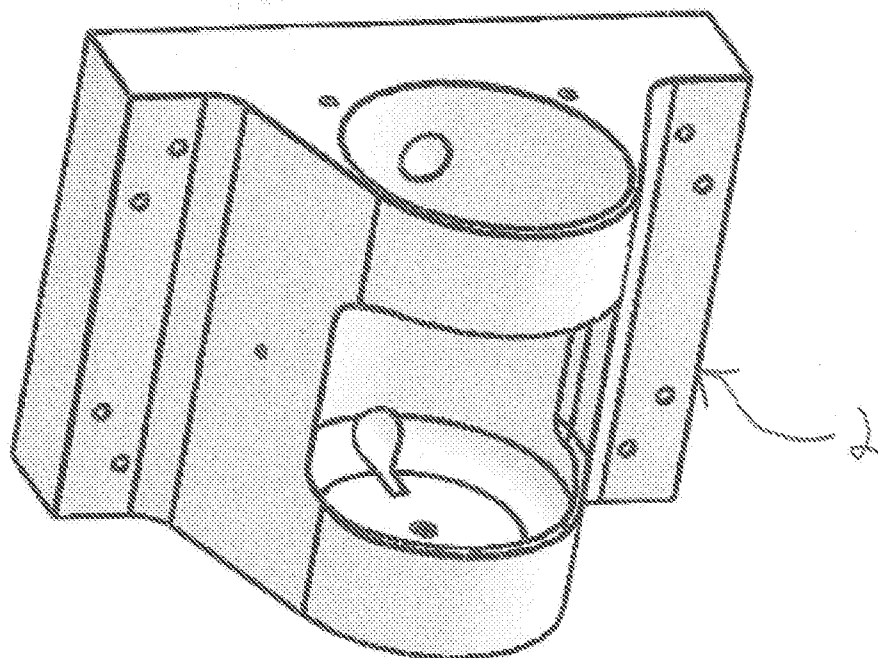


FIGURE 8A

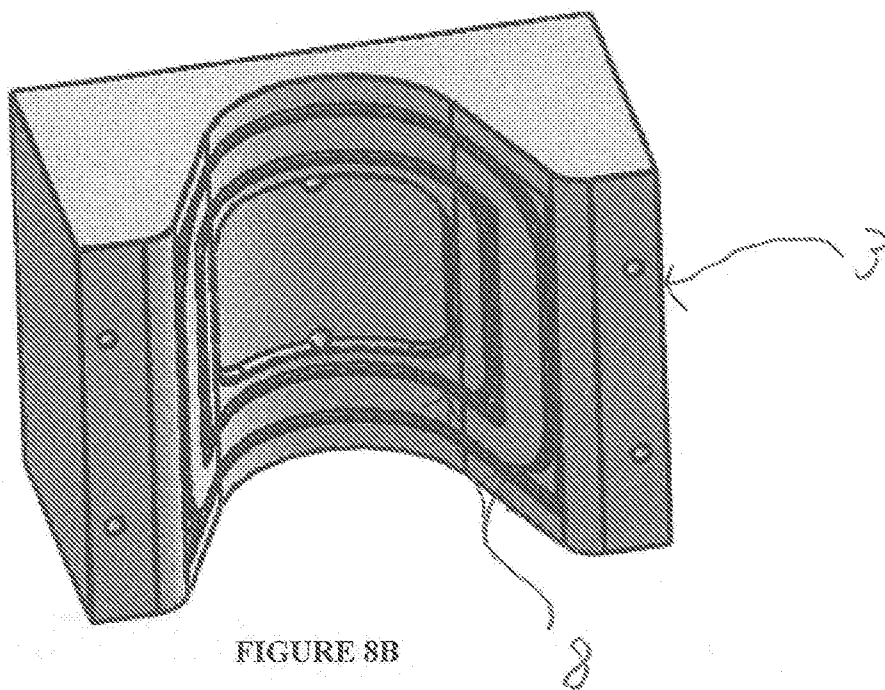


FIGURE 8B

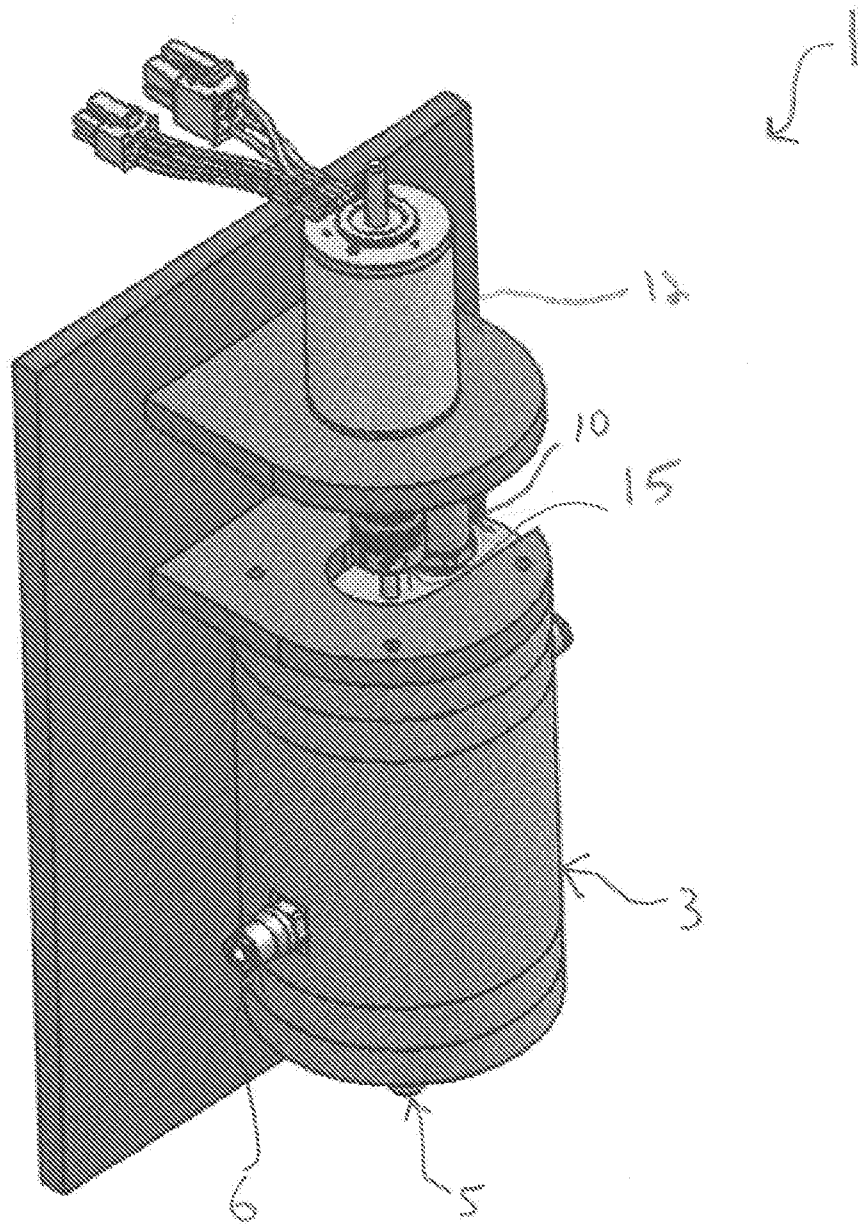
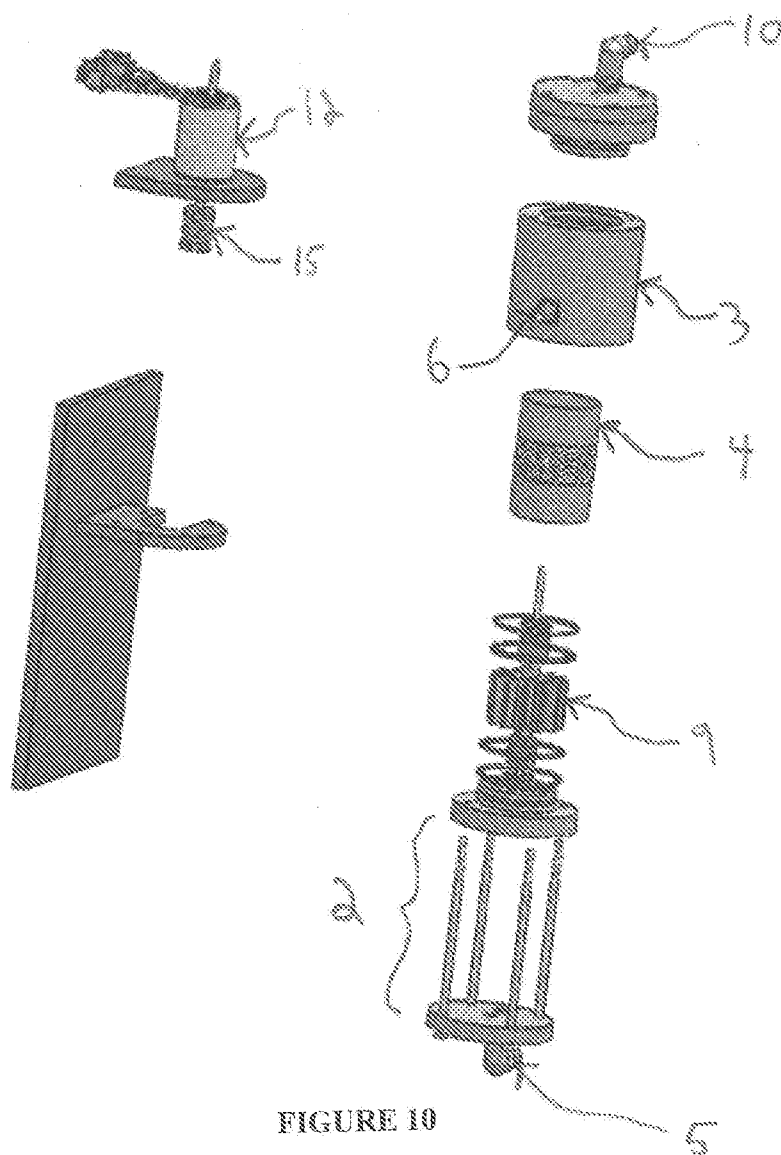


FIGURE 9



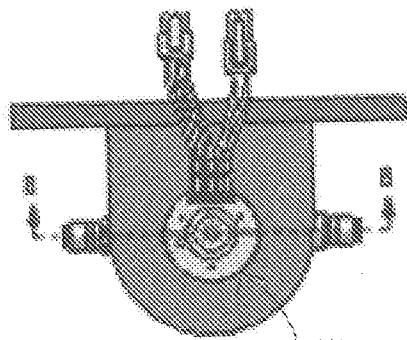


FIGURE 11A

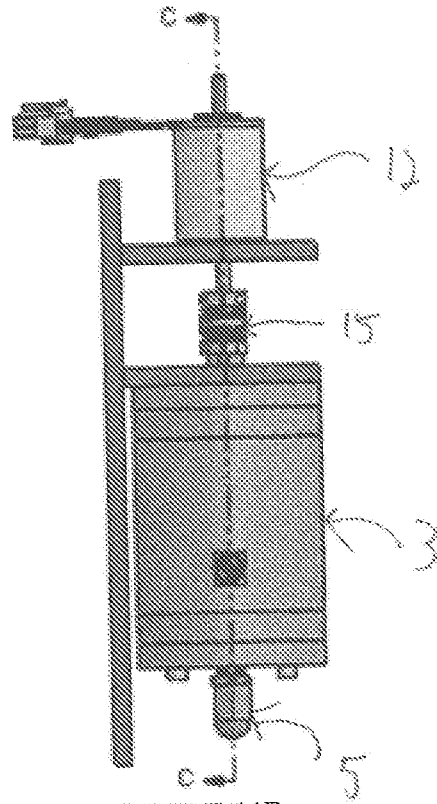


FIGURE 11B

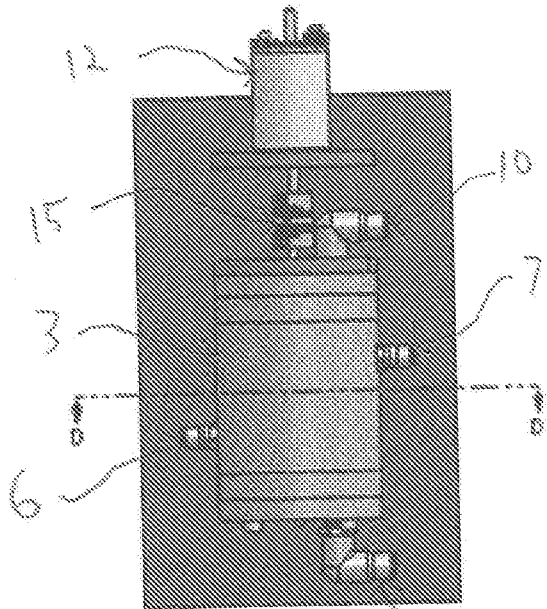


FIGURE 11C

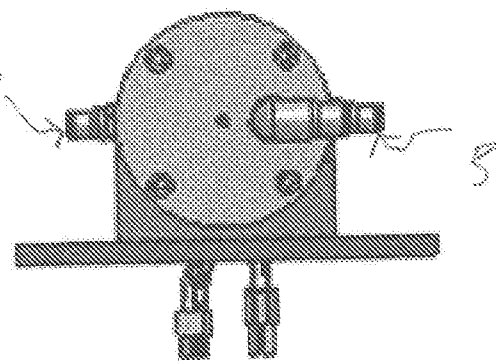


FIGURE 11D

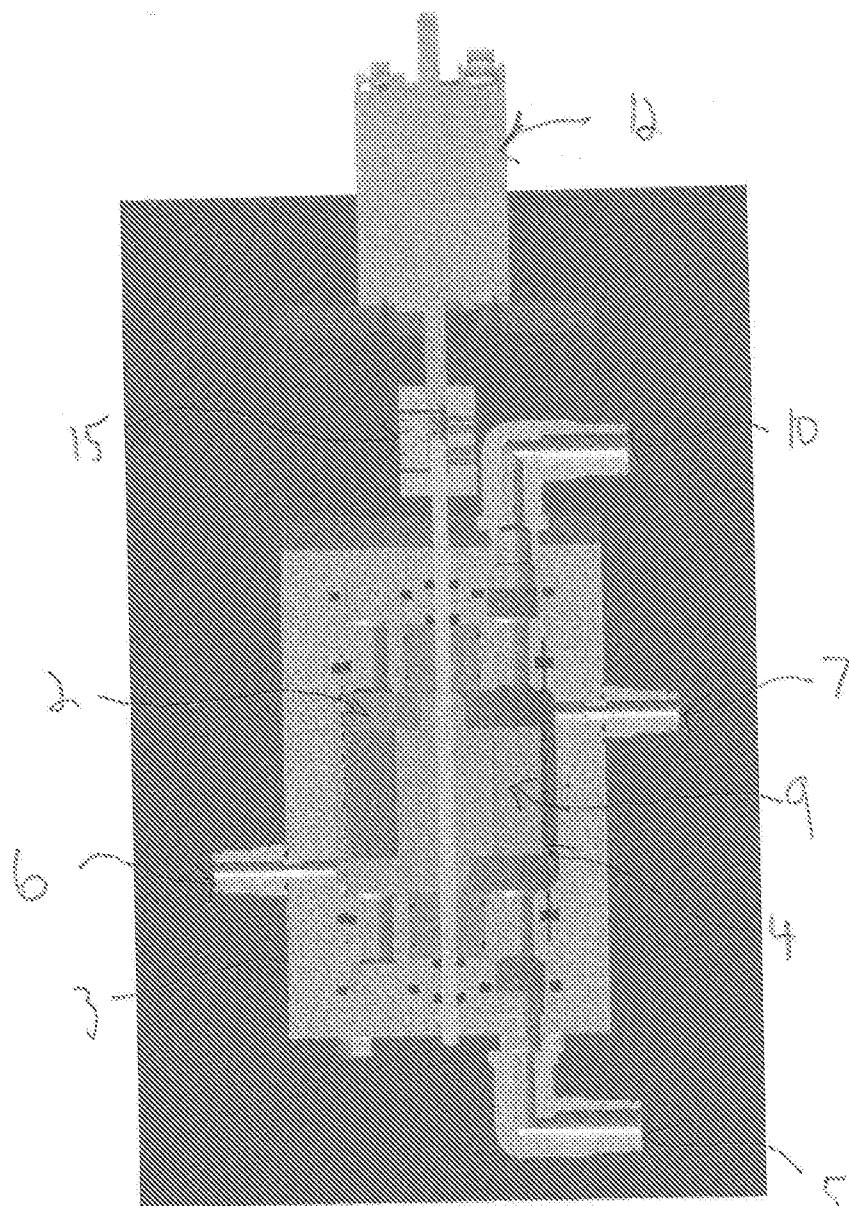


FIGURE 12

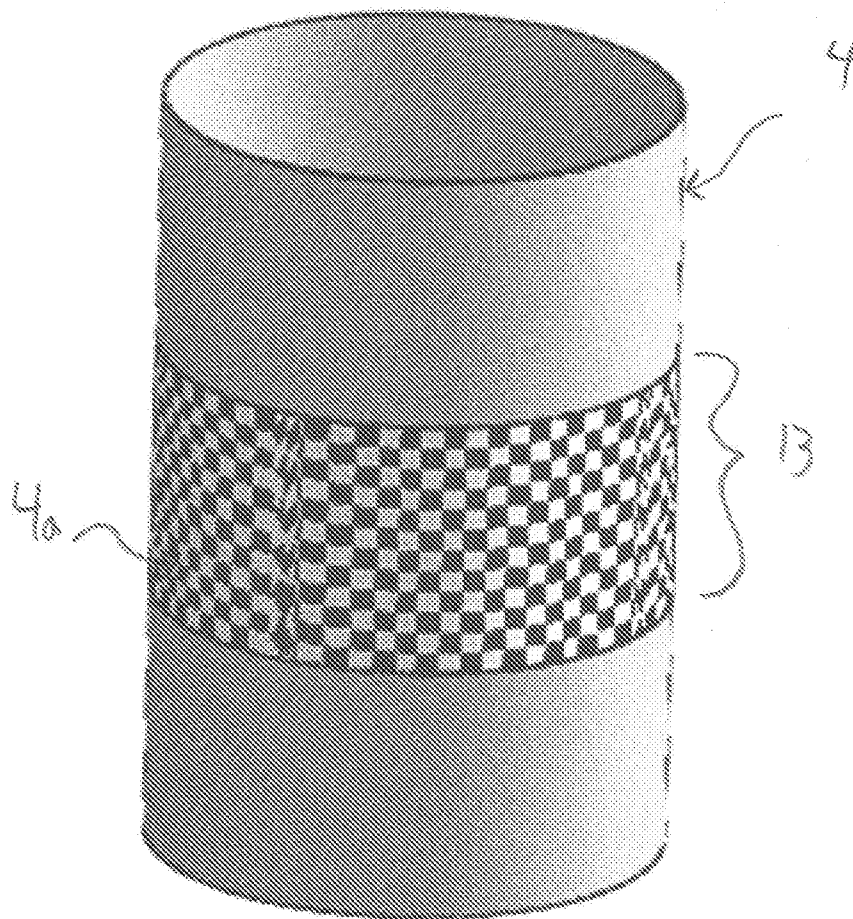


FIGURE 13

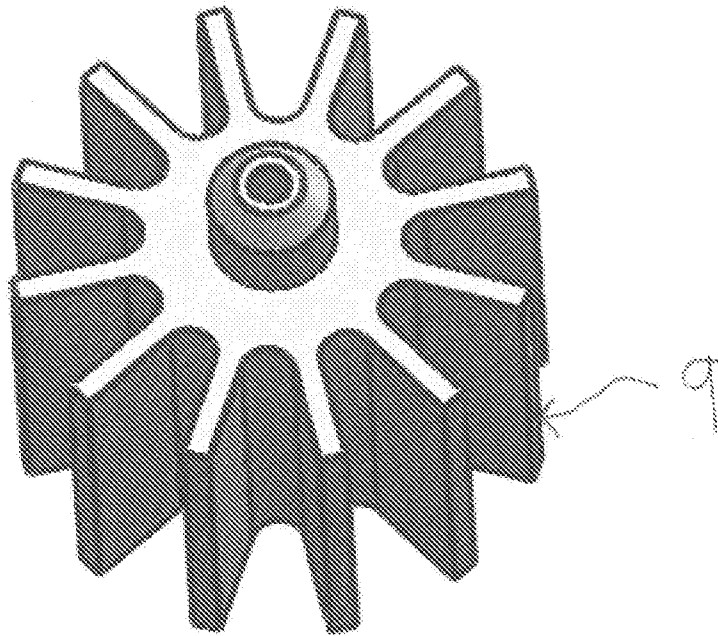
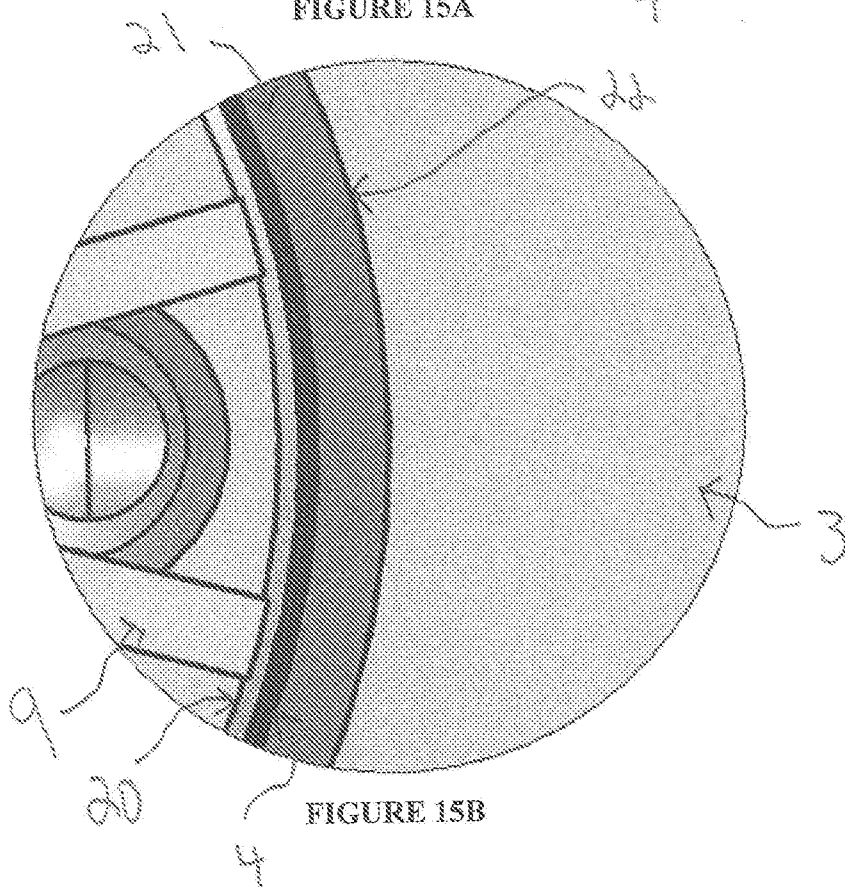
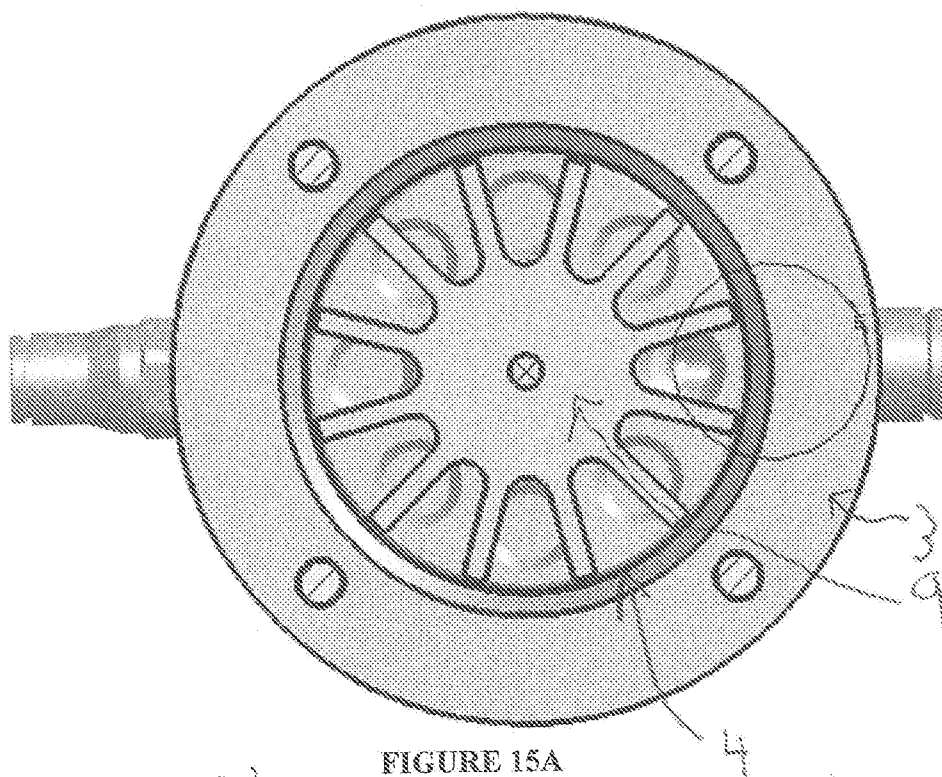


FIGURE 14



INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/038750

A. CLASSIFICATION OF SUBJECT MATTER
INV. B01F3/08 B01F5/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
B01F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2015/352506 A1 (RAMALINGAM SANTHOSH K [US] ET AL) 10 December 2015 (2015-12-10)	1-3,5-7, 9,10, 13-38
A	abstract figures 1-4B paragraphs [0011] - [0018] -----	4,8,11, 12
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A	abstract figure 6 paragraphs [0065], [0080] -----	2-6,8, 11,12, 21,24-38
	-/-	



Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

16 September 2019

Date of mailing of the international search report

24/09/2019

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Krasenbrink, B

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2019/038750

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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