

SMALL-SCALE BIOREACTOR

TECHNICAL FIELD

[0001] The present invention relates to a bioreactor system and methods of operating the same, and more particularly, to a disposable, small-scale bioreactor and its method of use.

BACKGROUND

[0002] A variety of vessels, devices, components and unit operations are known for carrying out biochemical and/or biological processes and/or manipulating liquids and other products of such processes. In order to avoid the time, expense, and difficulties associated with sterilizing the vessels used in biopharmaceutical manufacturing processes, single-use or disposable bioreactors and single-use mixers are used as such vessels. For instance, biological materials (e.g., animal and plant cells) including, for example, mammalian, plant or insect cells and microbial cultures can be processed using disposable or single-use mixers and bioreactors.

[0003] Typically, small-scale bioreactors used during process development are designed such that the impeller, spargers, and probes are inserted into the bioreactor through the top of the bioreactor, such as through a top cap. While this may provide for a simpler bioreactor vessel, it makes scaling of the desired process more difficult. For example, using top-driven impellers at small scale has a negative effect on scalability when the larger-scale bioreactor implements a bottom-driven impeller. This is due, at least in part, to the differences in mixing characteristics of top vs. bottom driven impellers. Further, inserting sparging tubes and probes through the top cap create arbitrary baffling locations which have a negative effect on flow patterns, power number, and overall mixing performance, further deviating from the general geometry of the larger-scale bioreactor.

[0004] However, biopharmaceutical manufactures desire the ability to scale up their process from lab scale to production, without significant changes to their process. This allows the customer to retain the value of their initial development and minimizes additional costs to

ensure that the same performance is achieved at commercial scale. This aids customers in minimizing their cost to bring products to market.

[0005] Thus, there is a need for a small-scale bioreactor that mimics the overall geometry of larger-scale bioreactors, thus making scale up simpler, more efficient and cost effective.

BRIEF DESCRIPTION

[0006] A first aspect of the invention relates to a bioreactor 100, including a cap 101; a sidewall 120 connected to the cap 101; and a base 150 connected to the sidewall 120 via a sealing mechanism 105, wherein the cap (101), sidewall (120) and base (150) define an internal volume (121), the base 105 comprising a bottom surface (154) that defines a fluid containment portion (122) configured retain a cellular culture; an integral impeller shaft (165); and at least one integral sparge line (131, 132) wherein the bioreactor is configured to carry out cell culture at a maximum working volume 2L or less.

[0007] In embodiments, the integrated impeller shaft (165) and at least one sparge line (131, 132) are integrated towards a central portion of the bottom surface (154). The at least one sparge tube (131, 132) and impeller shaft (165) are each unitarily formed with the base (150). The bioreactor 100 further includes a an impeller (164) connected to the impeller shaft (165), the impeller (164) comprising at least one magnet (167), the impeller 164 configured to rotate by application of a magnetic field external to the bioreactor.

[0008] In embodiments, the base (150) further comprises at least one port (102, 103, 107, 151, 158, 162) unitarily formed therein, the at least one port (102, 103, 107, 151, 158, 162) is configured to allow a probe to pass therethrough into the internal volume. The base (150) further comprises a base lip (159) and at least one support leg (158). A magnetic drive (300) is configured to magnetically couple to the impeller (164) when the base lip (159) is in contact with a housing (301) of the magnetic drive (300).

[0009] In embodiments, the base lip (159) includes at least one first attachment mechanism (156, 156', 160, 160') configured to attach to at least one second attachment mechanism 302, 302') on the magnetic drive (300) such that the bioreactor (100) is physically connected to the magnetic drive (300).

[0010] In embodiments, the bioreactor (100) is sterilizable and configured to carry out cell culturing for the production of a therapeutic, and wherein the bioreactor (100) is configured to be disposed of after carrying out cell culturing.

[0011] A second aspect of the invention relates to a method of culturing cells, comprising providing a bioreactor 100, the bioreactor comprising: a cap 101; a sidewall 120 connected to the cap 101; and a base 150 connected to the sidewall 120 via a sealing mechanism 105. The cap 101, sidewall 120, and base 150 define an internal volume 121. The base comprises a bottom surface 154 that defines a fluid containment portion 122 configured retain a cellular culture; an integral impeller shaft 165; and at least one integral sparge line 131, 132, culturing cells within the bioreactor 100, wherein the culturing is taking place with a working volume of between 250ml and 2L.

[0012] In embodiments, the integrated impeller shaft 154 and at least one sparge line 131, 132 are integrated towards a central portion of the bottom surface 154. The at least one sparge tube 131, 132 and impeller shaft 165 are each unitarily formed with the base 150. An impeller 164 is connected to the impeller shaft 165, the impeller 164 comprising at least one magnet 167. The method further includes rotating the impeller 164 by application of a magnetic field external to the bioreactor 100.

[0013] In embodiments, the base 150 further comprises at least one port 102, 103, 107, 151, 158, 162 unitarily formed therein, the method further including passing a probe

through at least one port 102, 103, 107, 151, 158, 162 in the bioreactor, such that the probe is at least partially within the internal volume 121.

[0014] In embodiments, base 150 further comprises a base lip 159 and at least one support leg 158. A magnetic drive 300 is configured to magnetically couple to the impeller 164 when the base lip 159 is in contact with a housing 301 of the magnetic drive 300. The base lip 159 includes at least one first attachment mechanism 156, 156', 160, 160' configured to attach to at least one second attachment mechanism 302, 302' on the magnetic drive 300 such that the bioreactor 100 is physically connected to the magnetic drive 300.

[0015] In embodiments, the method further includes sterilizing the bioreactor 100 prior to the step of culturing the cells, and disposing of the bioreactor 100 after the culturing step is completed, wherein the cell culture is for producing a therapeutic.

DRAWINGS

[0016] The present invention will be better understood from reading the following description of non-limiting embodiments, with reference to the attached drawings, wherein below:

[0017] Figure 1 is a perspective view of a small-scale bioreactor, according to embodiments of the invention.

[0018] Figure 2 is a cross-sectional view of the small-scale bioreactor of Figure 1, attached to a base, according to embodiments of the invention.

[0019] Figure 3 is a perspective view of a base portion of the bioreactor shown in Figures 1 and 2, , according to embodiments of the invention.

[0020] Figure 4 is a cross-sectional view of a portion of the base of Figure 3, according to embodiments of the invention.

[0021] Figure 5 shows the base of the bioreactor shown in Figures 1 and 2, according to embodiments of the invention.

[0022] Figure 6 shows a bioreactor according to a further embodiment of the invention.

DETAILED DESCRIPTION

[0023] Reference will be made below in detail to exemplary embodiments of the invention, examples of which are illustrated in the accompanying drawings. Wherever possible, the same reference characters used throughout the drawings refer to the same or like parts.

[0024] As used herein, an element or step recited in the singular and proceeded with the word "a" or "an" should be understood as not excluding plural of said elements or steps, unless such exclusion is explicitly stated. Furthermore, references to "one embodiment" are not intended to be interpreted as excluding the existence of additional embodiments that also incorporate the recited features. Moreover, unless explicitly stated to the contrary, embodiments "comprising" or "having" an element or a plurality of elements having a particular property may include additional such elements not having that property

[0025] It should be noted that the arrangement of components (e.g., the number, types, placement, or the like) of the illustrated embodiments may be modified in various alternate embodiments. For example, in various embodiments, different numbers of probe ports, tube barbs, as well as the volume of the space intended for mixing, can be modified, and is within the scope of the invention.

[0026] As used herein, a structure, limitation, or element that is "configured to" perform a task or operation may be particularly structurally formed, constructed, or adapted in a manner corresponding to the task or operation. For purposes of clarity and the avoidance of doubt, an object that is merely capable of being modified to perform the task or operation is not "configured to" perform the task or operation as used herein. Instead, the use of "configured to" as used herein denotes structural adaptations or characteristics, and denotes

structural requirements of any structure, limitation, or element that is described as being “configured to” perform the task or operation.

[0027] Embodiments of the invention provide bioprocessing systems 10, and in particular, small-scale bioreactor systems 10. In an embodiment, a bioprocessing system 10 includes a bioreactor 100 defining an internal volume 121, the vessel 100 generally comprising three parts: a cap 101, a side wall 120, and a base 150. When fastened to each other the cap 101, side wall 120, and base 150 define the internal volume 121, which is suitable for carrying out a bioprocess (e.g., cell culturing, cell expansion, and mixing).

[0028] With reference to Figures 1 and 2, bioreactor 100 includes a side wall 120 that is sealed to a cap 101 at one end and a base 150 at an opposing end via a sealing mechanism 105, such that a fluid and gas tight seal is created between the cap 101 and the sidewall 120 and the base 150 and the sidewall 120. Sealing mechanism 105 can include a tongue and groove connection sealed by an O ring or gasket. Alternatively, sealing mechanism 105 may include snap fit components, threaded engagements, and magnets or chemical adhesives. Still further, sealing mechanism 105 can be created by welding cap 101 and base 150 to the side wall 120, via, for example, heat sealing, ultrasonic welding, or the like.. This connection between cap 101 and sidewall 120 and the base 150 and sidewall 120 creates an internal volume 121 that is sealed from external air and contamination. Optionally running down the length of the sidewall 120 in the direction of the base 150 are one or more baffles 123.

[0029] The cap 101 includes a top wall 104 and a side surface 107. At least one hose barb 102, 103, 106 is connected to other otherwise integrally formed with the cap 101, as illustrated by Figures 1 and 2. In the embodiment shown in Figure 1, at least one hose barb 102, 103 is located on the top wall 104, while at least one hose barb 106 is located on the side surface 107. These hose barbs 102, 103, 106 can be of any diameter or length, and will be dual sided, protruding into the internal volume 121 and away from the cap 101. The number

of hose barbs 102, 103, 106 and their respective locations on the cap 101 can be varied and are within the scope of the invention. The hose barbs 102, 103, 106 can be implemented for various purposes, such as for liquid addition, liquid removal, exhaust, connection of probes, etc..

[0030] The cap 101 generally has a circular/cylindrical shape as illustrated best in Figure 1, the length of the side surface 107 equaling the overall height of the cap 101. While not explicitly illustrated, the cap 101 can take other shapes, for example, square, hexagon, parallelogram, etc..

[0031] In preferred embodiments, the cap 101 is of a unitary construction and can be manufactured through known methods (e.g., injection molding, 3D printing, etc.). By making the part unity, manufacturing complexity is reduced. Moreover, the cap 101 can be made from a polymer, and more specifically, and sterilizable plastic, such that the cap 101 is configured for single use and can be discarded after use. In alternative embodiments, the cap 101 can be manufactured from a plurality of components.

[0032] Like cap 101, side wall 120 has a generally cylindrical shape, the top portion thereof being configured to fit within the cap 101, as illustrated by Figures 1 and 2. As discussed in detail above, sidewall 120 is sealed to the side surface 107 of cap 101, creating a fluid-tight seal. Sidewall 120 can also be made from the same or a similar material as cap 101. Also like cap 101, sidewall 120 can take other shapes, for example, square, hexagon, parallelogram, etc., so long as its shape is complementary to cap 101.

[0033] Base 150 connects or otherwise seals to side wall 120 to confine an internal volume of 121 opposite the cap 101, as discussed above. The base 150 is sealed to the sidewall 120 in the same or a similar way that cap 101 is sealed to the side wall 120 (i.e., implementing sealing mechanism 105), the text of which will be omitted here for brevity. Base 150 includes a sloped bottom surface 154 (e.g., concave surface) in order to create a

fluid containment portion 122, which is the lower portion of internal volume 121 and which houses an impeller shaft 165, an impeller 164, and sparge discs 133, 134, the details of which will be described in greater detail below. In alternative embodiments, the bottom surface 154 need not be sloped (e.g., can have a sidewall and bottom surface that meet to form a right angle).

[0034] With reference to Figures 3 and 4, components of base 150 are illustrated. According to embodiments, sparge lines 131, 132 are integrally formed into base 150 and terminate at the bottom surface 154. These sparge lines 131, 132 provide fluidic access to the fluid containment portion 122 and internal volume 121 such that gases can be introduced into the internal volume 121 during a bioprocess operation (e.g., cell culture). Sparge discs 133, 134 are located at the termination of the sparge lines 131, 132 and are also integrated into the bottom surface 154 of base 150, as best seen in Figure 4. In preferred embodiments, the sparge discs 133, 134 are porous discs that ensure that gases that are introduced into the internal volume 121 form bubbles as they come in contact with liquid (e.g., cell culture media). In a preferred embodiment, the sparge lines 131, 132 are circular at their distal end, having a first internal diameter, and have an increasing internal diameter as they terminate at bottom surface 154 (e.g., take a conical shape), however, other shapes and geometries are within the scope of the invention. At their opposite end, sparge lines 131, 132 terminate in connections 135, 136 (e.g., hose barbs) that can be attached to a source of atmospheric air or other gas that is intended to be introduced into the internal volume 121.

[0035] An impeller 164 and an impeller shaft 165 are located generally at the center of the bottom surface 154 of the base 150. In preferred embodiments, the drive shaft 165 is integrally formed with the base 150, as best shown in Figure 4. The impeller 164 is configured to spin around the impeller shaft 165 in order to agitate a fluid located within the internal volume 121. In one embodiment, agitation occurs through magnetic coupling of

magnets 167 located within the impeller 164 and magnets in the magnetic drive 300. The sparge lines 131, 132 and sparge discs 133, 134, are configured to be located underneath the impeller 164 (e.g., towards the center of the base 150), such that when gases are introduced into the internal volume 121 the impeller 164 disperses the gases into the liquid within the internal volume 121.

[0036] By integrally forming the sparge lines 133, 134 and impeller shaft 165 into the base 150, manufacturing of the bioreactor 100 is simplified. Moreover, the unitary construction of the components of the base allows for modifications to the design of the impeller and spargers to be easily accomplished. For example, such a unitary configuration allows for the base 150 to be 3D printed, such that changes to the diameter of the sparge lines 131, 132, number of sparge lines 131, 132, and/or size of the impeller 164 to be easily modified without having to significantly change the manufacturing process (e.g., new molds do not have to be created).

[0037] It should be noted, however, that the invention is not explicitly limited to integrally formed sparge lines 133, 134 and impeller shaft 165. Rather, sparge lines 133, 134 and impeller shaft 165 can be attached or otherwise welded into the base 150. Even without integrally forming these components into the base, the present bioreactor is still more easily manufacturable (e.g., compared to top driven systems).

[0038] As further illustrated in Figure 3, protruding from the base 150 and away from the internal volume 121 are one or more hose barbs 151, 157, 162. The hose barbs 151, 157, 162 provide fluidic access to the internal volume 121 and fluid containment portion 122. In embodiments, hose barbs 151 and 162 are sized such that measurement probes can be attached and passed therethrough for taking measurements of the cell culture. Examples of such measurements include pH, DO, and temperature. In embodiments, hose barbs 158 are sized for other purposes, such as for sampling, feeding, perfusion, harvesting/draining, etc..

[0039] In embodiments, support legs 158 extend from the sides of base 150. The support legs 158 may be spaced concentrically around the base 150 and separated by spaces 161, which facilitate access to the underside of base 150, allowing for maneuvering of connections to the sparge lines 131, 132 and providing space for the base 150 to mate with the magnetic drive 300 illustrated by Figures 2 and 5.

[0040] Support legs 158 terminate at base lip 159. The base lip 159 is the bottom surface of base 150 and is larger in circumference than the remaining portions of base 150 such that base lip 159 provides structural support for the bioreactor 100. The base lip 159 pairs with a housing 301 of magnetic drive 300 as illustrated in Figures 2 and 5. In embodiments, this pairing is accomplished via complementary fastening mechanism 156, 160, 302 on the base 150 and housing 301. In one example shown in Figures 2 and 5, housing 301 includes at least one dowel 302 that is configured to fit within at least one slot 156, 160 on base lip 159. Alternative embodiments for pairing the base 150 and magnetic drive 300 include, but are not limited to, a snap fit, press pin, chemical or magnetic adhesion, or clamps. When paired, a drive head 304 of the magnetic drive 300 is magnetically coupled to the magnets 167 located within the impeller 164. In alternative embodiments, the impeller shaft penetrates the base 150 and can be driven through use of a motor shaft.

[0041] The embodiments shown in Figures 1-4 illustrate a bioreactor having a first maximum working volume (e.g., 2 liters). According to further embodiments, the bioreactor can have a smaller (or larger) working volume. For example, Figure 6 illustrates a bioreactor 200 having a second maximum working volume that is smaller than the first working volume (e.g., 250ml). Bioreactor 200 includes the same features as that of bioreactor 100, but at smaller scale, and the description of said features will be omitted for sake of repetition. Magnetic drive 300 includes a second set of dowels 302' that are located on housing 301 closer to the central drive head 304. Dowels 302' are configured to mate with at least one

corresponding slot 156', 160' on base lip 159'. In this way, one magnetic drive 300 can support bioreactors 100, 200 of varying sizes.

[0042] As described above, bioreactor 100, 200 is comprised of three main components, a cap, a sidewall, and a base, each of which can be generally manufactured as a unitary components. The bioreactor 100, 200 is sterilizable and configured to carry out a bioprocess (e.g., cell culturing) for the production of a therapeutic, and configured to be disposed of after use.

[0043] In this way, a small-scale, single-use, bioreactor 100, 200 that is bottom driven (i.e., impeller located at the bottom of the internal volume and driven by a bottom mounted motor) can be easily and robustly manufactured. Such bottom driven bioreactor scales more easily with larger scale bottom driven bioreactors, as the overall geometry and mixing characteristics are the same.

[0044] Moreover, as mentioned above, the bioreactor components can be manufactured via 3D printing, which allows for easy and robust customization without requiring complex manufacturing changes (e.g., new molds do not need to be created). Said another way, by unitarily forming the sparge lines, sparge discs, impeller shaft, and/or hose barbs into the other components (i.e., cap and base), design changes can be made easily without costly changes to molding designs. In this way, the present bioreactor is highly flexible, scales well with larger bottom-driven bioreactors, and is easily manufactured.

What is Claimed

1. A bioreactor (100), comprising:
 - a cap (101);
 - a sidewall (120) connected to the cap (101); and
 - a base (150) connected to the sidewall (120) via a sealing mechanism (105),wherein the cap (101), sidewall (120) and base (150) define an internal volume (121),
and
wherein the base (150) comprises:
 - a bottom surface (154) that defines a fluid containment portion (122) configured retain a cellular culture;
 - an integral impeller shaft (165); and
 - at least one integral sparge line (131, 132)wherein the bioreactor is configured to carry out cell culture at a maximum working volume 2L or less.
2. The bioreactor of claim 1, wherein the integrated impeller shaft (165) and at least one sparge line (131, 132) are integrated towards a central portion of the bottom surface (154).
3. The bioreactor of claim 2, wherein the at least one sparge tube (131, 132) and impeller shaft (165) are each unitarily formed with the base (150).
4. The bioreactor of claim 1, further comprising an impeller (164) connected to the impeller shaft (165), the impeller (164) comprising at least one magnet (167).
5. The bioreactor of claim 4, wherein the impeller (164) is configured to rotate by application of a magnetic field external to the bioreactor (100).

6. The bioreactor of claim 1, wherein the base (150) further comprises at least one port (102, 103, 106, 151, 157, 162) unitarily formed therein.
7. The bioreactor of claim 6, wherein the at least one port (102, 103, 106, 151, 157, 162) is configured to allow a probe to pass therethrough into the internal volume.
8. The bioreactor of claim 1, wherein the base (150) further comprises a base lip (159) and at least one support leg (158).
9. The bioreactor of claim 8, wherein a magnetic drive (300) is configured to magnetically couple to the impeller (164) when the base lip (159) is in contact with a housing (301) of the magnetic drive (300).
10. The bioreactor of claim 9, wherein the base lip (159) includes at least one first attachment mechanism (156, 156', 160, 160') configured to attach to at least one second attachment mechanism (302, 302') on the magnetic drive (300) such that the bioreactor (100) is physically connected to the magnetic drive (300).
11. The bioreactor of claim 1, wherein the bioreactor (100) is sterilizable and configured to carry out cell culturing for the production of a therapeutic, and wherein the bioreactor (100) is configured to be disposed of after carrying out cell culturing.
12. A method of culturing cells, comprising:
providing a bioreactor (100), the bioreactor comprising:
a cap (101);
a sidewall (120) connected to the cap (101); and

a base (150) connected to the sidewall (120) via a sealing mechanism (105),
wherein the cap (101), sidewall (120) and base (150) define an internal
volume (121), and

wherein the base comprises:

a bottom surface (154) that defines a fluid containment portion (122)
configured retain a cellular culture;

an integral impeller shaft (165); and

at least one integral sparge line (131, 132),

culturing cells within the bioreactor (100), wherein the culturing is taking place with a
working volume of between 250ml and 2L.

13. The method of claim 12, wherein the integrated impeller shaft (165) and at least one
sparge line (131, 132) are integrated towards a central portion of the bottom surface (154).

14. The method of claim 13, wherein the at least one sparge tube (131, 132) and impeller
shaft (165) are each unitarily formed with the base (150).

15. The method of claim 12, wherein an impeller (164) is connected to the impeller shaft
(165), the impeller (164) comprising at least one magnet (167).

16. The method of claim 12, rotating the impeller (164) by application of a magnetic field
external to the bioreactor (100).

17. The method of claim 12, wherein the base (150) further comprises at least one port
(102, 103, 107, 151, 158, 162) unitarily formed therein .

18. The method of claim 17, passing a probe through at least one port (102, 103, 107, 151, 158, 162) in the bioreactor, such that the probe is at least partially within the internal volume (121).
19. The method of claim 12, wherein the base (150) further comprises a base lip (159) and at least one support leg (158).
20. The method of claim 12, wherein a magnetic drive (300) is configured to magnetically couple to the impeller (164) when the base lip (159) is in contact with a housing (301) of the magnetic drive (300).
21. The method of claim 20, wherein the base lip (159) includes at least one first attachment mechanism (156, 156', 160, 160') configured to attach to at least one second attachment mechanism (302, 302') on the magnetic drive (300) such that the bioreactor (100) is physically connected to the magnetic drive (300).
22. The method of claim 20, further comprising,
sterilizing the bioreactor (100) prior to the step of culturing the cells, and
disposing of the bioreactor (100) after the culturing step is completed,
wherein the cell culture is for producing a therapeutic.