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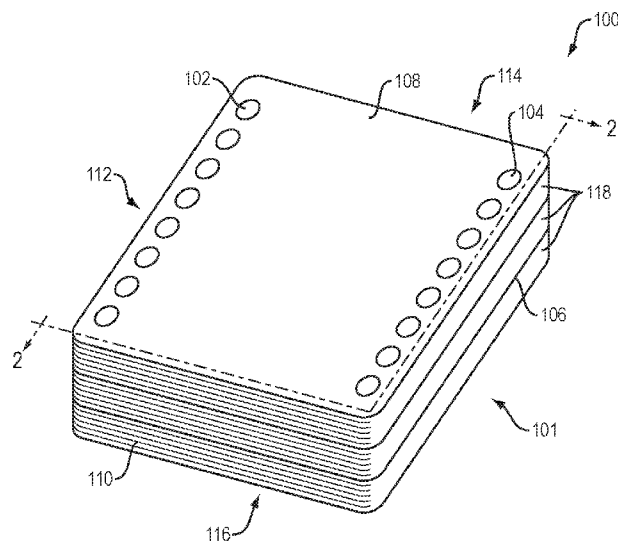


FIG. 1

(57) Abstract: Devices for removing extractables downstream from a filter, including a tangential flow filter, the filter housed within a housing; and an adsorber housed within the frame and downstream of the filter, the adsorber containing media for removing extractables, wherein extractables are removed from a permeate side of the filter without contacting a product of interest, are disclosed.



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TANGENTIAL FLOW FILTERS HAVING EXTRACTABLES ADSORBER

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims the benefit of priority of U.S. Provisional Application No. 62/727,896, filed September 6, 2018, the entire contents of which is incorporated by reference herein in its entirety.

BACKGROUND

FIELD

[0002] This disclosure relates to filtration devices. More specifically, embodiments according to the disclosure relate to tangential flow filters having at least one adsorber housed within the tangential flow filters for removing extractables and/or leachables.

DESCRIPTION OF THE RELATED ART

[0003] Tangential Flow Filtration (TFF), also known as cross-flow filtration, is a method of filtering during which a majority of a fluid flow travels tangentially across a surface of a filter, rather than into and through the filter (dead-end filtration). The principal advantage of this is that the filter cake, which can blind (block) the filter, is substantially washed away during the filtration process, increasing the length of time that a filter unit can be operational. Moreover, TFF can be a continuous process, unlike dead-end filtration, which is a batch process. In crossflow filtration, the fluid flow is passed across the filter membrane (tangentially) at positive pressure relative to the permeate side (i.e., downstream of the filter or membrane). A proportion of the materials/particles, which are smaller than a membrane pore size, passes through the membrane as permeate or filtrate; wherein all else is retained on the feed side of the membrane as retentate (i.e., upstream). With crossflow filtration, the tangential motion of the bulk of the fluid across the membrane causes trapped particles on the filter surface to be rubbed off. This means that a crossflow filter can operate continuously at relatively high solids loads without blinding.

[0004] Tangential flow filtration (TFF) cassettes, including membrane-based cassettes, clarify, concentrate, and/or purify fluid streams containing macromolecules, for example, a macromolecule of therapeutic interest. Macromolecules of therapeutic interest include, for example, antibodies,

antibody drug conjugates (ADCs), proteins, peptides, hormones, monoclonal antibodies, vaccines, antibody drug conjugates, polysaccharides, and like products of interest, etc. In TFF processes, a feed stream, i.e., a fluid containing a macromolecule, is pumped tangentially along the surface of a membrane. The pressure forces at least a portion of the feed stream through the membrane surface to the filtration side. Particles and macromolecules that do not pass through the membrane are therefore retained on the retentate side. [0005] TFF devices are used for ultrafiltration, diafiltration, and buffer exchange of biological macromolecules, which is typically the last operation in the downstream processing of therapeutic macromolecules because it is used to concentrate the drugs for final formulation. TFF devices operate using an ultrafiltration membrane that retains the molecule of interest on the retentate side by size-exclusion, while the unwanted impurities, particles/materials, water, or buffer components pass through the membrane into the permeate side. TFF devices are self-contained, and can embody a flat-sheet or spiral-wound design. TFF devices can be supplied pre-integrity tested and pre-flushed, are wet with water, and pre-sterilized by gamma radiation for single use.

[0006] TFF devices typically consist of several polymeric materials, which contact the fluid stream. Polymeric materials include polyether sulfone (PES), polyethylene (PE), polypropylene (PP), polyethylene terephthalate (PET), polyurethanes (PU), polydivinylidene difluoride (PVDF), cellulose, thermosets/epoxies, and silicones. The materials are specified for combinations of physical mechanical properties, chemical stability, low amounts of extractables, and gamma radiation stability. However, because all materials have some degree of extractables, e.g., organic and inorganic extractables, and because chemical and gamma radiation sterilization are harsh processes that produce extractables, the final product of the fluid stream will have a certain degree of undesirable extractables, which are detected using analytical techniques including total organic carbon (TOC), reverse phase HPLC or gas chromatography, mass spectrometry (GC/MS, LC/MS), and/or inductively coupled plasma mass spectrometry (ICP-MS). Removal of low residual organic or inorganic extractables or leachables, which can be toxic to

products of interest, from fluid streams containing a macromolecule of therapeutic interest is often required.

[0007] A device having a downstream adsorber for removing extractables without contacting the product fluid feed or retentate stream is therefore an advance in the art.

SUMMARY

[0008] Devices for removing extractables downstream from a filter having a tangential flow filter, the filter housed within a frame; an adsorber housed within the frame and downstream of the filter, the adsorber containing media for removing extractables, wherein extractables are removed from a permeate side of the filter without contacting a product of interest, are disclosed. Various benefits, aspects, novel and inventive features of the present disclosure, as well as details of exemplary embodiments thereof, will be more fully understood from the following description and drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0009] FIG. 1 depicts an upper perspective view of a flat-sheet tangential flow filter device, according to some embodiments described in the disclosure;

[0010] FIG. 2 depicts a partial cross-section 2-2 of a filter element of the flat-sheet tangential flow filter device of FIG. 1 and a depiction of feed flow, according to some embodiments of the disclosure;

[0011] FIG. 3 depicts an upper perspective view of a spiral-style tangential flow filter device, according to some embodiments described in the disclosure;

[0012] FIG. 4 depicts a cross section 4-4 of a spiral-wound filter element of the spiral-style tangential flow filter device of FIG. 3 and an adsorber outside the spiral-wound filter element, according to some embodiments described in the disclosure;

[0013] FIG. 5 is a functional diagram of fluid flow within a spiral-wound filter element of a spiral-style tangential flow filter device and an adsorber, according to some embodiments of the disclosure; and

[0014] FIG. 6 depicts a side view of a filter element of a flat-sheet tangential flow filter device, according to some embodiments described in the disclosure.

DETAILED DESCRIPTION

[0015] So the manner in which the features disclosed herein can be understood in detail, more particular descriptions of the embodiments of the disclosure,

briefly summarized above, may be had by reference to the appended drawings. It is to be noted, however, that the appended drawings illustrate only typical embodiments of this disclosure and are therefore not to be considered limiting of its scope, for the described embodiments may admit to other equally effective embodiments. It is also to be understood that elements and features of one embodiment may be found in other embodiments without further recitation and that, where possible, identical reference numerals have been used to indicate comparable elements that are common to the figures. As used herein, the singular forms "a", "an," and "the" include plural referents unless the context clearly dictates otherwise.

[0016] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which these embodiments pertain. Also, the following terms used herein are subject to the following definitions, unless the context indicates otherwise.

[0017] Extractables/leachables are unwanted or undesirable by-products or degradation products resulting from sterilization of the materials used to manufacture the filters, frames, and the like, including small molecules, inorganic molecules, ions, and oligomers that are considered contaminants to the product or macromolecule of therapeutic interest.

[0018] Extractables/leachables adsorbers are chemical adsorbers comprising at least one of hydrophobic entities, lipophilic entities, activated carbon, charged cation or anion entities, fumed silica, glass, controlled pore glass, or other inorganic minerals capable of removing organic or inorganic solutes from a fluid phase.

[0019] Encapsulated extractables/leachables adsorbers are chemical adsorbers enclosed in a physical barrier, mesh screen, polymeric membrane, non-woven fabric, chemical binder, etc.

[0020] Sterilization methods are chemical, thermal, or radiation methods used to eliminate bioburden in filtration devices. Examples of sterilization methods include applying gamma radiation, beta radiation, autoclaving, steaming, caustic treatments, peracetic acid solutions, e.g., MINNCARE®, ethylene oxide (ETO) treatments, ozone treatments, dry heating, and other sterilization methods known to those in the art.

[0021] Some tangential flow filters are spiral wound filtration devices, which are filtration devices made by wrapping alternate layers of membranes and plastic separator screens around a hollow core, wherein product, such as a fluid stream, enters one end of the cartridge under pressure, flowing tangentially through an axis of the device. A spiral-wound filter element may be contained within a housing. Ultrafiltrate, e.g., salts, water, and other species not rejected by the membrane(s), flows through the membranes into permeate channels and spirals to the central core, from which it is removed. Retentate flows out a retentate channel and/or opening.

[0022] Ultrafiltration is a separation process using pressure and/or concentration gradients, wherein a fluid stream leads to a separation through a semipermeable membrane. This separation process is used in industry and research for purifying and concentrating macromolecular (10^3 - 10^6 Dalton) solutions, e.g., protein solutions. Ultrafiltration separates high molecular weight solutes from fluids and low molecular weight solutes based on size exclusion or particle capture. Ultrafiltration is fundamentally different from membrane gas separation, which separate based on different amounts of absorption and different rates of diffusion. Ultrafiltration membranes are defined by the molecular weight cut-off (MWCO) of the membrane used. The terms ultrafiltration membrane and UF membrane are generally defined as membranes having pore sizes in the range of between approximately one nanometer to approximately 100 nanometers or, alternatively, defined by the molecular weight cut-off of the membranes, expressed in units of Daltons (Da), and abbreviated as MWCO. In various embodiments, the embodiments according to the present disclosure utilizes ultrafiltration membranes having MWCO ratings in the range from about 1,000 Daltons to a 1,000,000 Daltons.

[0023] Some tangential flow filters are flat sheet filtration devices, which are filtration devices made by layering membranes, feed screens, permeate screens, and non-wovens or films in a stack assembled device where product, e.g., fluid stream, can be directed in one end of the device under pressure, flowing tangentially down the upstream side of the membrane. Ultrafiltrate, e.g., salts, water, species not rejected by the membranes, flows through the membrane(s) into permeate channels and out the permeate openings. Retentate flows out a retentate channel and/or opening. Suspended

solids and solutes of high molecular weight are retained in a retentate, while water and low molecular weight solutes pass through the membrane, downstream of the semipermeable membrane, into the permeate (filtrate).

[0024] The terms microfiltration membranes and MF membranes are used herein to refer to membranes that have pore sizes in the range between about 0.1 micrometers to about 10 micrometers.

[0025] Cross flow is the flow rate between inlet and outlet of the feed channel in a filter or a series of filters. Unless otherwise stated, "cross flow" refers to an average cross flow.

[0026] The terms feed, feed sample, and feed stream refer to the solution being introduced into a filtration module, e.g., any of the **spiral wound filtration devices** or the flat sheet filtration devices described herein, for separation.

[0027] The term separation generally refers to the act of separating the feed sample into two streams, a permeate stream and a retentate stream.

[0028] The terms permeate and permeate stream refer to that portion of the feed sample that has permeated through a membrane.

[0029] Feed channel refers to a conduit in a filtration assembly, module or element in which a feed sample or feed stream traverses.

[0030] Permeate channel refers to a conduit in a filtration assembly, module, or element in which a permeate, e.g., filtrate, traverses.

[0031] Diafiltration is a dilution and/or re-concentration process during which fresh solvent may be delivered to a feed stream, replacing a permeate volume.

[0032] The terms diafiltrate, diafiltration buffer, and diafiltrate stream refer to the solution being used to wash permeate solutes out of the feed stream during a diafiltration process.

[0033] The term retentate, e.g., concentrate, refers to the portion of the feed that has been retained by the membrane. When referring to a system, filter element, or filter module, retentate or retentate stream refers to the retentate exiting the system, filter element, or filter module.

[0034] The term flow path refers to a channel comprising a filtration membrane (e.g., ultrafiltration membrane, microfiltration membrane) through which the solution being filtered passes (e.g., in a tangential flow mode). A flow path can have any topology which supports tangential flow (e.g., straight, coiled, arranged in zigzag fashion). A flow path can be open, as in an example of

channels formed by hollow fiber membranes, or have one or more flow obstructions, as in the case, for example, of rectangular channels formed by flat-sheet membranes spaced apart by woven or non-woven spacers.

[0035] TFF assembly, TFF system, and TFF apparatus are used interchangeably herein to refer to a tangential flow filtration system that is configured for operation in a single-pass mode and/or a recirculation mode (e.g., full or partial recirculation).

[0036] Filtration membrane refers to a selectively permeable membrane capable of use in a filtration system, such as a TFF system.

[0037] The terms “fluidly connected” and “in fluid communication” refer to a plurality of filter elements that are connected to one another by one or more conduits for a liquid, such as, a feed channel, retentate channel and/or permeate channel or in which a liquid can flow.

[0038] Product or product of interest refers to a target species or compound that is to be recovered by processing. Examples of products include macromolecules of interest, fusion proteins, polysaccharides, antibodies and antibody fragments, monoclonal antibodies, antibody-drug conjugates, albumin, hemoglobin, intravenous immunoglobulin (IVIG), clotting factors, growth factors, vaccines, hormones, enzymes, and antigens.

[0039] Embodiments of the disclosure comprise filtration devices, such as a spiral-flow or flat-sheet TFF devices, further comprising an extractables/leachables adsorber(s). Some embodiments of the disclosure comprise sterilized, wet filtration devices. The adsorber is disposed at a permeate side of a tangential flow filtration device. In some embodiments, the adsorber is located on the downstream side of an ultrafiltration membrane. Accordingly, in some embodiments, the adsorber does not contact the feed flow or the product of interest, and is, optionally, a permanent component of the device. The adsorber is stable to sterilization methods, such as gamma radiation and beta radiation. The adsorber may be stable to caustic treatments and/or other sterile treatment methods. Accordingly, the adsorber can remove or adsorb extractables/leachables generated by the sterilization method and/or released from the materials of construction over time. Also, in some embodiments, because the adsorber is on the permeate side, it will not contact the molecule product of interest and adsorbs small extractables over long term

storage and during use, and is inert to chemical and gamma radiation sterilization. The adsorber may comprise activated carbon, carbon blacks, molecular sieves, ion-exchange or hydrophobic resins or membranes. In some embodiments, the adsorber is a carbon pad comprising a non-woven polyester impregnated with ground, activated carbon. In some exemplary embodiments, the adsorber is a carbon pad is a SUREFIT™ carbon pad manufactured by Air Filters, Inc. Some embodiments of the adsorber described herein may comprise activated carbon enclosed within a hydrophilic or hydrophobic membrane or screen pouch. In some embodiments, the adsorber is encapsulated into part(s) of the permeate materials. The adsorber can “soak up” or adsorb any small molecule extractables over time, on storage, because the extractables will cross-over the membrane into the permeate side where the adsorber is located and does not contact the biological molecule or product of interest on the feed or retentate side of the ultrafiltration membrane. In some embodiments, an adsorber is disposed on both the permeate side and the retentate side of the membrane. For example, an adsorber may be inert to the feed stream and therefore does not adsorb a product of interest. In some embodiments, a feed screen having activated carbon dispersed therein would not adsorb a monoclonal antibody but would adsorb extractables, improving the efficiency by adsorbing extractables on both sides of the membrane without having to cross through the membrane.

[0040] In spiral-wound devices, the adsorber comprising activated carbon can be enclosed in a hydrophilic or hydrophobic membrane pouch and inserted into the permeate core of the spiral wound device. The adsorber(s) can be free floating or attached in the permeate core. Restrictions on residual extractables, such as total organic carbon, devices for final TFF, especially following aggressive sterilization methods such as gamma radiation, make requirements harder to meet. Therefore, a built in extractables/leachables adsorber that does not contact the product of interest and can remove extractables/leachables after sterilization and during storage can help meet these increasingly tougher regulations. Also, because the materials of construction are polymeric they can have leachables from manufacturing can introduce extractables produced as degradation or reaction products from the sterilization methods.

[0041] For flat-sheet devices, the adsorber can be enclosed in a pouch or encapsulated into the materials commonly used in the permeate channel, such as polymeric mesh screens, non-woven fiber mats, or encapsulated into porous sheets of such as activated carbon in porous polymers with binders.

[0042] TFF systems may be configured for a single pass or multiple passes of the feed through the filter. Any of the embodiments described herein may be configured for single pass or multi-pass filtration. In multi-pass filtration, some permeate and/or a buffer may be added to the retentate and recirculated within the feed stream. The extractables adsorbers described below can adsorb extractables from the liquid, i.e., feed stream containing recirculated retentate over the time the feed stream is recirculated.

[0043] In some embodiments, where the ultrafiltration membrane contains glycerin as a humectant, the adsorber can be enclosed or encapsulated in a hydrophobic membrane. In such embodiments, the device can be wet-out, rinsed free of glycerin, integrity tested, and the extractables/leachables adsorber be wet out in the permeate channel with alcohol and re-flushed with water, before sending for gamma radiation sterilization (or other sterilization processes), removing glycerin from the adsorber. In some embodiments, the adsorber can be sized to exceed the glycerin to be rinsed out of the membrane to continue to have enough capacity for the extractables/leachables, for e.g., from a feed stream. The adsorber will remove extractables/leachables over time during storage and will help reduce device flush-out volume and time before use.

[0044] Embodiments of the disclosure comprise an encapsulated adsorber(s) having sufficient capacity to adsorb all or substantially all extractables and leachables for e.g., after the device is wet out for integrity testing.

Furthermore, glycerin in the membrane is washed out before testing, sterilization treatments, and end use. Embodiments of the disclosure comprise an adsorber(s) that can be encapsulated in a hydrophobic membrane/screen that can be wet with alcohol after an initial water flushing and integrity testing. In some embodiments, additional flushing to remove the alcohol is employed, followed by sterilization, e.g., gamma sterilization.

[0045] Turning now to the figures, FIG. 1 depicts an upper perspective view of a flat-sheet tangential flow filter device 100, according to some embodiments

described in the disclosure. The flat-sheet tangential flow filter device 100 also comprises ultrafiltration membranes (not shown) as described below. The flat-sheet tangential flow filter 100 comprises a frame 101. The frame 101 comprises six sides, having a front side 110 and a back side 114 opposite the front side 110, a first lateral side 106 that is opposite a second lateral side 112, and a top side 108 that is opposite a bottom side 116. The housing 110 comprises three cartridges 118. The flat-sheet tangential flow filter 100 comprises frit holes 102. As shown, the frit holes 102 are disposed along the second lateral side 112. The flat-sheet tangential flow filter 100 further comprises distribution holes 104. As shown, the distribution holes 104 are disposed along the first lateral side 106. As depicted, there are eight frit holes 102 and eight distribution holes 104, although any suitable amount may be employed.

[0046] FIG. 2 depicts a partial cross-section 2-2 of a filter element 150 of the flat-sheet tangential flow filter device 100 of FIG. 1 and a depiction of feed flow 160 (shown as dark arrows), according to some embodiments of the disclosure. The feed flow 160 traverses tangentially across a first ultrafiltration membrane 166 and tangentially across a second ultrafiltration membrane 168. The first ultrafiltration membrane 166 is opposite the second ultrafiltration membrane 168, wherein an extractables adsorber 172 is disposed therebetween. Permeate flow 170 (shown as light arrows) permeates from the feed flow 160, through the first UF membrane 166 and the second UF membrane 168. The permeate flow 170 then contacts the extractables adsorber(s) 172 within permeate channels 174. The permeate flow 170 contains extractables, such as low molecular weight volatiles. The feed flow 160 does not contact the extractables adsorber(s) 172. The extractables adsorber(s) 172 can be of any shape, i.e., rectangular, square, conical, etc. In some embodiments, the extractables adsorber(s) 172 may be permanently attached to the first ultrafiltration membrane 166 and/or the second ultrafiltration membrane 168. In some embodiments, the extractables adsorber(s) 172 may be free-floating within the permeate channel(s) 174.

[0047] Spiral-wound filter elements are generally known in the art and may be produced in both single-leaf and multi-leaf formats. FIG. 3 depicts an upper perspective view 200 of a spiral-style tangential flow filter 202, according to

some embodiments described in the disclosure. As shown, the spiral-style tangential flow filter 202 is a capsule. The spiral-style tangential flow filter 202 comprises a canister 206 for housing a filter element (shown below). The spiral-style tangential flow filter 202 further comprises a first end cap 204 having an outlet 208, and a second end cap 212 having an inlet 210. The first end cap 204 is adjacent a first end 207, which is opposite the second end cap 212 adjacent a second end 209. The canister 206 is disposed between the first end cap 204 and the second end cap 212.

[0048] FIG. 4 depicts a cross section 4-4 of a spiral-wound filter element 300 of the spiral-style tangential flow filter 202 of FIG. 3 and an extractables adsorber 400 outside the spiral-style tangential flow filter 202, according to some embodiments described in the disclosure. The spiral-wound filter element 300 includes at least one membrane layer 304, at least one feed channel spacer 302, and at least one permeate collection material 306 (e.g., permeate spacer) wound about a perforated central tube 310. The perforated central tube 310 comprises a hollow core having holes, which houses the extractables adsorber 400. The extractables adsorber 400 may be permanently attached to the perforated central tube 310 or be free-floating therewithin. As shown, the spiral-wound filter element 300 further comprises additional filter layers 312, e.g., membrane layer(s) 304, feed channel spacers 302 and permeate collection materials 306. The membrane layer(s) 304 are in planar contact with outer surfaces of the feed channel spacer 302. The feed channel spacer(s) 302 serves as both a mechanical stabilizer for channel geometry and a turbulence promoter for reducing polarization phenomena near a surface of the membrane layer(s) 304. The permeate collection material 306 acts as a spacer. In some embodiments, the permeate collection material 306 provides support for the membrane layer(s) 304 and maintains a flow channel for the discharge of permeate. An optional outer wrap 308 wraps the spiral-wound filter element 300. As shown, the spiral-style tangential flow filter 202 includes an inlet 210, a first end 209, a second end 207, and a canister 206 as discussed above. The spiral-style tangential flow filter 202 further optionally includes a gasket 320. The feed solution or stream enters the spiral-style tangential flow filter 202 at inlet 210. A permeate of the feed solution passes through the membrane layer(s) 304, spiraling inward to the perforated central tube 310. The permeate

contains extractables, such as low molecular weight volatiles. The feed solution does not contact the extractables adsorber(s) 400.

[0049] FIG. 5 is a functional diagram 500 of feed flow within a **spiral-wound filter element** of a spiral-style tangential flow filter and an adsorber 400, according to some embodiments of the disclosure. In some embodiments, the spiral-wound filter is, e.g., spiral-wound filter 300, as described above. The functional diagram 500 shows that the extractables adsorber 400 is placed within the perforated central tube 310. As the feed is delivered into the device, a portion of the feed traverses through the membrane(s) 304, spiraling toward the perforated central tube 310, becoming the permeate. The permeate then enters the perforated central tube 310, where the e.g., hydrophobic entities, lipophilic entities, activated carbon, charged cation or anion entities, fumed silica, glass, controlled pore glass, or other inorganic minerals capable of removing organic or inorganic solutes, within the extractables adsorber 400, remove the organic or inorganic solutes, e.g., contaminants, from the feed and/or permeate.

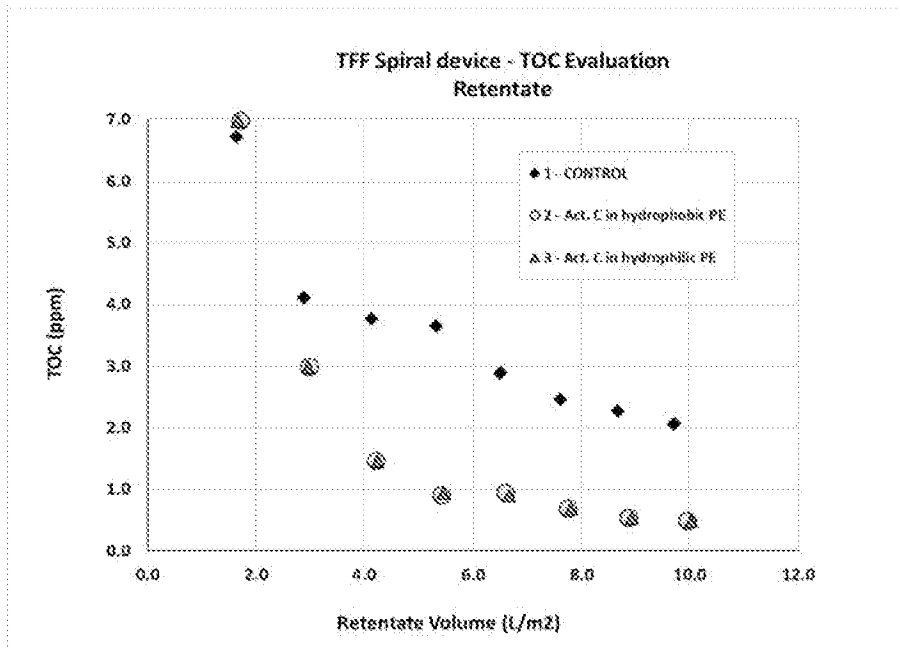
[0050] FIG. 6 depicts a side view 600 of a filter element of a flat-sheet tangential flow filter, according to some embodiments described in the disclosure. In some embodiments, the flat-sheet tangential flow filter is the tangential flow filter 100, as is described in FIGS. 1-2. The feed flow 160 flows into the tangential flow filter 100 and flows tangentially across a membrane(s), such as the first ultrafiltration membrane 166 and tangentially across the second ultrafiltration membrane 168. The first ultrafiltration membrane 166 is opposite the second ultrafiltration membrane 168, wherein a feed screen 186 is disposed therebetween. The permeate flow 170 then traverses through a non-woven 182, a permeate screen 184, a second non-woven 182 and the extractables adsorber(s) 172. The permeate flow 170 contains extractables, such as low molecular weight volatiles. The feed flow 160 does not contact the extractables adsorber(s) 172. In some embodiments, the extractables adsorber(s) 172 may be permanently attached to the first ultrafiltration membrane 166 and/or the second ultrafiltration membrane 168. In some embodiments, the extractables adsorber(s) 172 may be free-floating within the permeate channel(s) 174.

[0051] In Example 1, according to embodiments of the disclosure, three TFF spiral devices were made, each having approximately 0.1 m² of ultrafiltration

membrane area. Devices were made with similar construction to Figures 3-5, as described herein, using the aforementioned materials of construction. A 30 kilodalton ultrafiltration membrane comprising regenerated cellulose on a polyethylene membrane substrate was employed. Device 1 is a control as a spiral TFF device. Device 2 is a spiral TFF device containing granular activated carbon in a hydrophobic polyethylene porous membrane located in the permeate core. Device 3 is a spiral TFF device containing granular activated carbon in a hydrophilic polyethylene porous membrane located in the permeate core. Devices 1-3 were wet out using water flowing at approximately 6 L/min.m² to 20 L.m² (Liters per minute of square meters) with the retentate and permeate sent to drain to remove the glycerin. Devices passed flux and air integrity testing and devices 1 and 3 were capped and bagged in polyethylene. Device 2 was drained free of water in the permeate core and isopropanol was pipetted in to wet out the hydrophobic PE membrane, followed by additional flushing with water.

[0052] All three devices were gamma irradiated at 25 kilogray (kGy) and accelerated aged at 45°C to a room temperature equivalent of 12 months. The three devices were then flushed-out to 10 L/m² with water and samples take to analyze for total organic carbon content in the retentate. Devices 2 and 3 had lower Total Organic Carbon (TOC) in parts-per-million (ppm) in the retentate flush-out under the same conditions than the Device 1 control, which did not contain activated carbon as a leachables/extractables adsorber. Comparison results are shown in Graph 1.

[0053] Graph 1: TFF Spiral Device – TOC Evaluation



[0054] In Example 2, a TFF device was made with approximately 0.1 m² of Ultrafiltration membrane area. The device was made with a 30 kilodalton regenerated cellulose on a polyethylene membrane substrate. The UF membrane contained glycerin as a humectant to prevent membrane collapse during storage and to enable dry device manufacturing. The device was wet out, flushed with a water volume of 20 L/m², integrity tested, sanitized, flushed with water, vacuum bagged, gamma irradiated at 25 kGy, and accelerated aged to a room temperature equivalent of 6 months. After accelerated aging, the hold-up water was gravity drained and 40 mL of water collected.

[0055] The water was diluted to 80 mL (2x) and 40 mL was retained as the control. The other 40 mL was soaked for 24 hours over 1.25 grams of granulated activated carbon in two sequential steps, with filtering between soaks to remove the granular carbon. Table 1 shows the TOC in parts-per-million (ppm) for the three samples. The control contains higher total TOC from glycerin and other organic molecules resulting from gamma degradation or reactions of extractables from other device components. The three samples have relatively similar glycerin (ppm) by HPLC assay and TOC (ppm) from glycerin, while the remaining TOC from unidentifiable species/not from glycerin is lower for the two samples soaked over activated carbon. The data in Table 1 shows that TOC not from glycerin can be reduced by 69.0% and

84.4% with activated carbon if it were in the device. Samples after the activated carbon soak were also noticeably free of the organic odor present in the control. Without intending to be bound by theory, this explains why TOC flushes out faster and to lower levels in the other examples.

[0056] Table 1

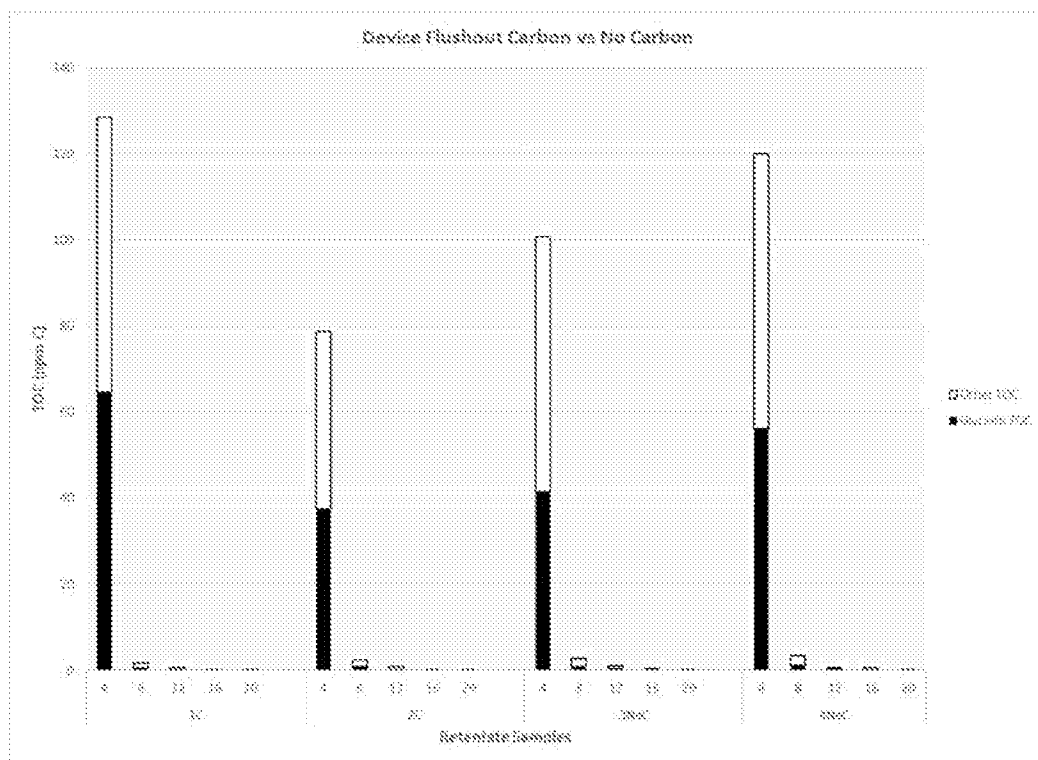
Sample	TOC (ppm)	Glycerin (ppm)	TOC from glycerin (ppm)	TOC not from glycerin (ppm)	Final TOC from glycerin (ppm)	Final TOC not from glycerin (ppm)	% TOC reduction not from glycerin (ppm)
Control	2481	3836	1501	980	3002	1960	
After activated Carbon (1.25g/40ml*24hrs)	1730	3644	1426	304	2852	608	69.0
After activated Carbon (additional 1.25g/40ml*24hrs)	1383	3144	1230	153	2460	306	84.4

[0057] In Example 3, four TFF devices were made similar to Examples 1 and 2, having approximately 0.1 m² of regenerated cellulose ultrafiltration membrane area. Devices 1C and 2C in Graphs 2-4 contained approximately five grams of granular activated carbon sealed in polyethylene mesh located in the permeate core. Devices 3NoC and 4NoC were controls without activated carbon in the permeate core. The devices were wet out, flushed with a water volume of 20 L/m², integrity tested, sanitized, flushed with water, vacuum bagged, gamma irradiated at 25-40 kGy, and accelerated aged to a room temperature equivalent of 6 months. After accelerating aging, each of the four devices were independently flushed with Milli-Q grade water at 5 Liters/min.m² to 20 L/m² total and fractions collected at 4, 8, 12, 16, 20 L/m². Samples were analyzed for total organic carbon (TOC) and glycerin by HPLC. Glycerin was converted to TOC and the total TOC was attributed to TOC (other) and TOC (from glycerin) in Graphs 2, 3, and 4.

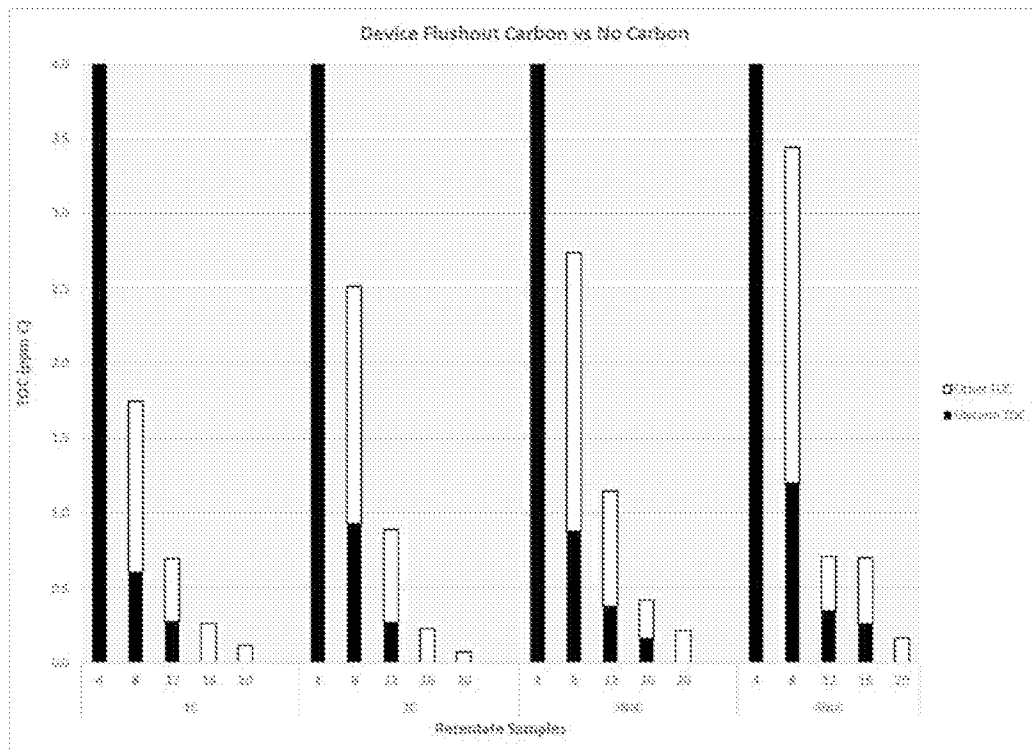
[0058] Graphs 2-3 show that retentate flushout from devices 1C and 2C with carbon had less TOC (other) and TOC (glycerin) than in devices 3NoC and 4 NoC at the 8-20 L/m² flushout, indicating activated carbon could reduce the flushout volumes on the retentate side to achieve specified TOC levels. Samples 1C and 2C were noticeably less yellow in color and had no organic odor compared with flushout samples from 3NoC and 4 NoC. Graph 4 shows flushout on the permeate side had less TOC (other) and TOC (glycerin) for devices 1C and 2C with carbon than in devices 3NoC and 4 NoC. Permeate flushout from Samples 1C and 2C were also noticeably less yellow in color and had no organic odor compared with flushout samples from 3NoC and 4 NoC. Based on data in Graph 4 for the permeate side, one would expect the

difference to be even greater on the retentate flushout if activated carbon were, optionally, designed into the retentate side. Examples 1-3 indicate that if activated carbon is sized properly to TOC generated within a device a potential no flush device could be achieved.

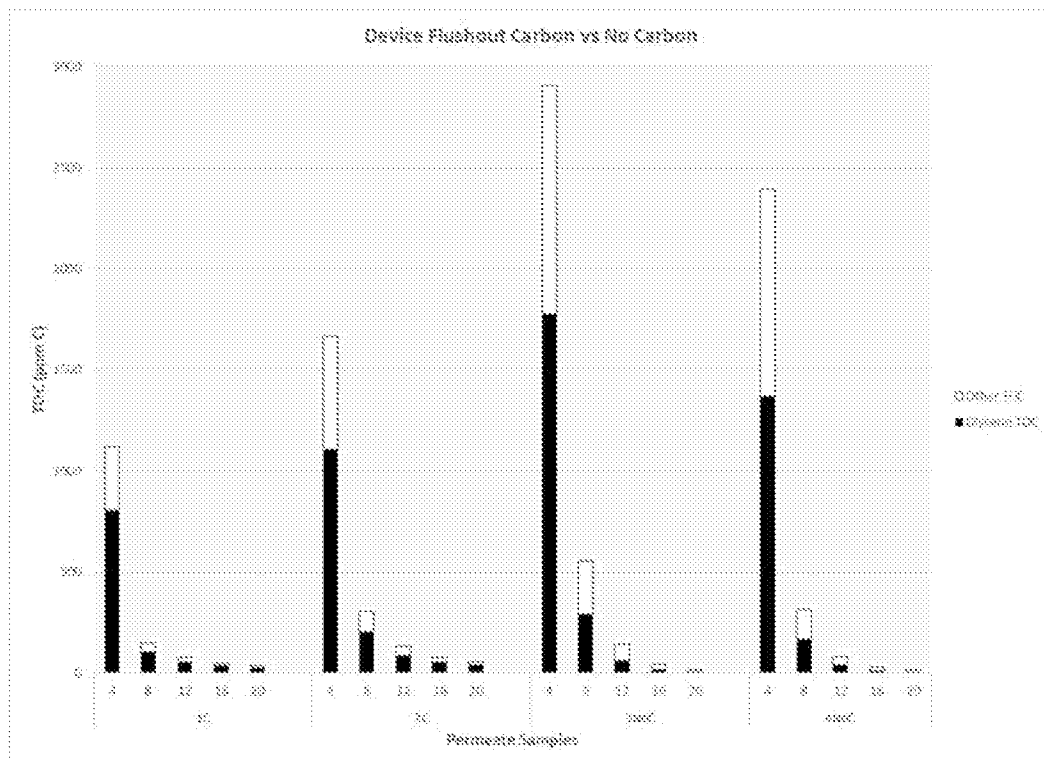
[0059] Graph 2 – Retentate flushout (L/m²) with water analyzed for TOC (other) and TOC (from Glycerin).



[0060] Graph 3 – zoom in of Graph 2 Retentate flushout (L/m²) with water analyzed for TOC (other) and TOC (from Glycerin)



[0061] Graph 4 – Permeate flushout (L/m²) with water analyzed for TOC (other) and TOC (from Glycerin)



[0062] Any of the embodiments disclosed herein can include any TFF filtration device, as is disclosed in PCT/US2017/034709, which is incorporated by reference in entirety. For example, an extractables adsorber can be incorporated within a TFF filtration device having hollow fiber, tubular, flat plate, and spiral wound formats. Spiral TFF devices containing one or more rectangular permeate membrane envelopes, with the open end originating at the perforated permeate discharge tube, and the free end wound continuously around it to form the nearly circular spiral wound element, are contemplated herein. Filter elements of the present disclosure further include a TFF filtration device having a radial discharge path, which provides for shortened permeate channel lengths as compared to conventional, spiral-wound filter elements. In some embodiments, the radial discharge path filter elements include a closed membrane structure wrapped about a core in reciprocating clockwise and counterclockwise directions, forming semicircular folds of membrane about the core. The semicircular folds of membrane have oppositely situated apical ends separated by a gap, the gap defining a radial permeate discharge path. The closed membrane structure has an interior portion defining at least one feed channel and an exterior portion defining at least one permeate channel.

[0063] Filtration membranes can comprise, for example, regenerated cellulose, polyarylsulphones, polyvinylidene fluoride (PVDF), polypropylene, polyester, polyethersulfone (PES), polyethylene, polyethersulfone, polysulfone, polyacrylonitrile, nylon, polyimide, polyamide, ethylene chlorotrifluoroethylene, fluoroethylenepropylene, perfluoroalkoxy, polytetrafluorethylene, polyetheretherketone, polysynidilenesulfide, and polycarbonate.

[0064] Filtration membranes that can be used in the radial-path filter elements described herein are known in the art and include, for example, ultrafiltration membranes, microfiltration membranes, reverse-osmosis membranes, and nanofiltration membranes. Such membranes generally have a non-woven backing material or microporous membrane support.

[0065] In some embodiments, radial-path filter elements of the present disclosure include an ultrafiltration membrane. Ultrafiltration membranes can have pore sizes in the range of about 1 nanometer to about 100 nanometers. Examples of ultrafiltration membranes include BIOMAX®-30 membranes and ULTRACEL®-30 membranes, marketed by the EMD Millipore Corporation.

BIOMAX®-30 membranes are modified polyethersulfone membranes on non-woven polyolefin backings with nominal molecular weight cutoff of 30 kilodaltons. ULTRACEL®-30 membranes are regenerated cellulose membranes on high density polyethylene 0.6 µm micro-porous substrates having a nominal molecular weight cutoff of 30 kilodaltons. In some embodiments, radial-path filter elements include a microfiltration membrane. Microfiltration membranes can have pore sizes in the range of about 0.1 micrometers to about 10 micrometers. Particular examples of microfiltration membranes include those made from polyvinylidene fluoride (PVDF), such as, for example, EMD Millipore 0.22 µm DURAPORE® membrane in PELLICON® TFF cassettes P2GVPPV01 or 0.65 µm DURAPORE® membranes in a ProstaK TFF device PSDVAG021, and those made from polyethersulfone (PES), such as, for example, EMD Millipore MILLIPORE EXPRESS® membranes in dead end PELF cartridge filter CPGE75TP3.

[0066] In some embodiments, the feed channel spacer(s) 302 can comprise a variety of materials, for e.g., polyethylene, polypropylene, and polyester, and can embody a variety of geometries, for e.g., extruded bi-planar and woven monofilament mesh polypropylene in square weave or twill.

[0067] In some embodiments, the permeate collection materials 306 comprise a variety of materials, for e.g., polyethylene, polypropylene, and polyester. In some embodiments, the permeate collection materials 306 comprise a variety of geometries, for e.g., extruded bi-planar and woven monofilament mesh polypropylene in square weave or twill. In some embodiments, feed channel spacer(s) and/or permeate collection materials comprise, for example, a-screens, b-screens, and c-screens (PROPYLTEX® screens, Sefar, QC, Canada). An a-screen is a woven, approximately, 200 micron (µm) monofilament polypropylene diameter fiber screen employing a square twill 2-over-1 right hand weave at 51 strands per inch, having a total nominal weave thickness of 420 µm and open area of about 36%. A b-screen is a woven 150 µm (approximate) monofilament polypropylene fiber screen employing a square twill 2-over-1 right hand weave at 70 strands per inch and having total nominal weave thickness of 320µm and open area of about 34%. A c-screen is a woven 250 µm (approximate) monofilament polypropylene diameter fiber screen

employing a square twill 2-over-1 right hand weave at 42 strands per inch and having total nominal weave thickness of 525 μm and open area of about 34%. [0068] Some embodiments of the present disclosure comprise a radial-path filter element disposed within a housing e.g., a re-usable housing, disposable housing, a sleeve, or a liner. Radial-path filter elements can be placed in housings in such a way as to enable connection to a filtration system (e.g., a TFF system), contain pressure, and keep feed, retentate, and permeate streams separated. Housings can be stainless steel, plastic, or other suitable material based on considerations such as strength, chemical compatibility, and safety of extractable materials for the intended application. In some embodiments, several individual modules can be networked within a manifold. Manifolds can comprise parallel, series, or mixed flow of feed, retentate, and permeate through the module network.

[0069] In some embodiments, radial-path filter elements described herein can be single-use filter elements, such that they are intended to be disposed of following their initial use. Single-use filters are particularly suitable for applications in the biotechnology industry because single-use filters attenuate the need for cleaning, cleaning validation, and validation of the performance of the re-used filter. Furthermore, single-use radial-path filter elements and modules eliminate cross-contamination, which is favorable for biotechnology industry processing.

[0070] Radial-path filter elements are distinguishable from single-leaf and multi-leaf spiral-wound filters, particularly in applications requiring larger filter elements. For example, radial-path filter elements comprise shorter permeate discharge paths compared with single-leaf spiral-wound filter elements. The shorter permeate discharge paths of radial-path filter elements reduce the pressure level(s) required in constant flux applications, which is practical for use in such applications. Radial-path filter elements described herein also provide higher productivity for small molecule processing, where pressure affects flux, and smaller, more cost-effective filters may be used in such applications. Filter elements of the present disclosure can alleviate bottlenecks that often occur with spiral-wound filter elements that incorporate single membrane leaves of longer lengths. Filter elements of the present disclosure can also be simpler to assemble than multi-leaf filter elements.

[0071] As compared to conventional multi-leaf spiral-wound filters, radial-path filter elements of the present disclosure do not require the preparation of multiple membrane leaves, thereby resulting in less labor and higher yield due to less complexity during manufacturing processes. Additionally, as radial-path filter elements can include a single feed screen, there is less exposure of the membrane sheet to cut ends of feed screen, thereby minimizing potential damage to the membrane. Radial-path filter elements can also provide increased membrane utilization as less membrane area is lost during sealing.

[0072] Radial-path filter elements may also be more durable than spiral-wound filter elements, even when including long membrane leaves, as the amount of slip between adjacent layers is minimized by the reciprocating clockwise-counterclockwise winding of the membrane leaf about the core. Radial-path filter elements also offer flexibility to wind to different diameters and manufacturing may be more fully automated as rollstock materials may be directly used.

[0073] Radial-path filter elements of the present disclosure can offer similar performance to pleated spiral-wound filter elements, with similar permeate discharge path lengths and similar slip distances between adjacent layers for similar reduced risk of wrinkle formations. Moreover, radial-path filter elements may be more robust as pleated spiral-wound filters include multiple feed screen insertion points, which can lead to membrane damage.

[0074] Any of the embodiments described herein may be further used within a system. For example, the system may comprise a feed tank, a filtration module, and a feed pump that pumps a feed to the filtration module, wherein the feed tank, filtration module, and feed pump are in fluid communication. The system may further comprise a pressure gauge, disposed between the feed pump and the filtration module, to measure and provide feedback regarding the measured pressure to the pump for control purposes. The system may further comprise a conduit having a sensor to measure a retentate pressure, wherein the conduit comprises a valve and is in fluid communication with the feed tank.

[0075] Embodiments of the disclosure comprise methods for removing extractables. For example, some methods for removing extractables, include flowing a fluid stream into a tangential flow filter; filtering proteins and/or particulates from the fluid stream; and removing extractables and/or organic

compounds (TOCs) downstream of the tangential flow filter using an adsorber, the adsorber containing media for removing extractables, wherein extractables are removed from a permeate side of the filter without contacting a macromolecule of therapeutic interest.

[0076] Some embodiments of the method include, wherein the tangential flow filter further comprises an ultrafiltration membrane. Some embodiments of the method include wherein the tangential flow filter is a flat-sheet filter or a spiral-style filter.

[0077] All ranges for formulations recited herein include ranges therebetween, and can be inclusive or exclusive of the endpoints. Optional included ranges are from integer values therebetween (or inclusive of one original endpoint), at the order of magnitude recited or the next smaller order of magnitude. For example, if the lower range value is 0.2, optional included endpoints can be 0.3, 0.4, . . . 1.1, 1.2, and the like, as well as 1, 2, 3 and the like; if the higher range is 8, optional included endpoints can be 7, 6, and the like, as well as 7.9, 7.8, and the like. One-sided boundaries, such as 3 or more, similarly include consistent boundaries (or ranges) starting at integer values at the recited order of magnitude or one lower. For example, 3 or more includes 4, or 3.1 or more.

[0078] Reference throughout this specification to “one embodiment,” “certain embodiments,” “one or more embodiments,” “some embodiments,” or “an embodiment” indicates that a feature, structure, material, or characteristic described in connection with the embodiment is included in at least one embodiment of the disclosure. Therefore, the appearances of the phrases such as “in one or more embodiments,” “in certain embodiments,” “in one embodiment,” “some embodiments,” or “in an embodiment” throughout this specification are not necessarily referring to the same embodiment.

[0079] Although some embodiments have been discussed above, other implementations and applications are also within the scope of the following claims. Although the specification describes, with reference to particular embodiments, it is to be understood that these embodiments are merely illustrative of the principles and applications of the present disclosure. It is therefore to be further understood that numerous modifications may be made to the illustrative embodiments and that other arrangements and patterns may be devised without departing from the spirit and scope of the embodiments

according to the disclosure. Furthermore, particular features, structures, materials, or characteristics may be combined in any suitable manner in any one or more of the embodiments.

[0080] Publications of patent applications and patents and other non-patent references, cited in this specification are herein incorporated by reference in their entirety in the entire portion cited as if each individual publication or reference were specifically and individually indicated to be incorporated by reference herein as being fully set forth. Any patent application to which this application claims priority is also incorporated by reference herein in the manner described above for publications and references.

CLAIMS

WE CLAIM:

1. A device for removing extractables downstream from a filter, comprising:
a tangential flow filter, the filter housed within a housing; and
an adsorber housed within the frame and downstream of the filter, the adsorber containing media for removing extractables, wherein extractables are removed from a permeate side of the filter without contacting a macromolecule of therapeutic interest.
2. The device of claim 1, wherein the tangential flow filter further comprises an ultrafiltration membrane.
3. The device of any of claims 1-2, wherein the tangential flow filter is a flat-sheet filter or a spiral-style filter.
4. The device of any of claims 2-3, wherein the adsorber is housed distal to the inlet of the downstream-most ultrafiltration membrane.
5. The device of claim 3, wherein the adsorber is housed within a perforated core of the spiral-wound filter membrane.
6. The device of claim 5, wherein the adsorber is housed within a perforated core of a radial path filter membrane.
7. The device of claim 1, wherein the housing is a plurality of flat cartridges, each cartridge having a UF membrane.
8. The device of claim 1, wherein the housing is a cylindrical capsule.
9. The device of any of claims 1-8, wherein the extractables comprise at least one of residual organic compounds and/or inorganic compounds and/or leachable compounds.
10. The device of claim 9, wherein the organic compounds, inorganic compounds, and/or leachable compounds are at least one material chosen from the group of PES, PE, PP, PET, PU, PVDF, cellulose, glues, adhesives, thermosets, thermoplastic elastomers, epoxies, and silicones, which are remnants of materials of which the frame is comprised.
11. The device of any of claims 1-10, wherein the adsorber comprises at least one of a hydrophobic membrane, a hydrophilic membrane, a screen pouch, or an encapsulant within permeate materials.

12. The device of any of claims 1-11, wherein the media comprises at least one of activated carbon, carbon black, molecular sieves, cation-exchange, and/or anionic exchange materials.
13. The device of any of claims 1-12, wherein the adsorber is stable to sterilization methods.
14. The device of claim 13, wherein the sterilization methods include caustic, beta- and/or gamma-radiation methods.
15. The device of any of claims 1-14, wherein the product of interest is at least one of monoclonal antibodies, proteins, antibody drug conjugates, peptides, and vaccines.
16. The device of any of claims 1-15, wherein the device is sold pre-wetted with water.
17. The device of any of claims 1-16, wherein the macromolecules of therapeutic interest include antibodies, antibody drug conjugates, monoclonal antibodies, vaccines, polysaccharides, proteins, peptides, and hormones.
18. A method for removing extractables, comprising:
 - flowing a fluid stream into a tangential flow filter;
 - filtering proteins and/or particulates from the fluid stream; and
 - removing extractables and/or organic compounds (TOCs) downstream of the tangential flow filter using an adsorber, the adsorber containing media for removing extractables, wherein extractables are removed from a permeate side of the filter without contacting a macromolecule of therapeutic interest.
19. The method of claim 18, wherein the tangential flow filter further comprises an ultrafiltration membrane.
20. The method of either of claims 18-19, wherein the tangential flow filter is a flat-sheet filter or a spiral-style filter.

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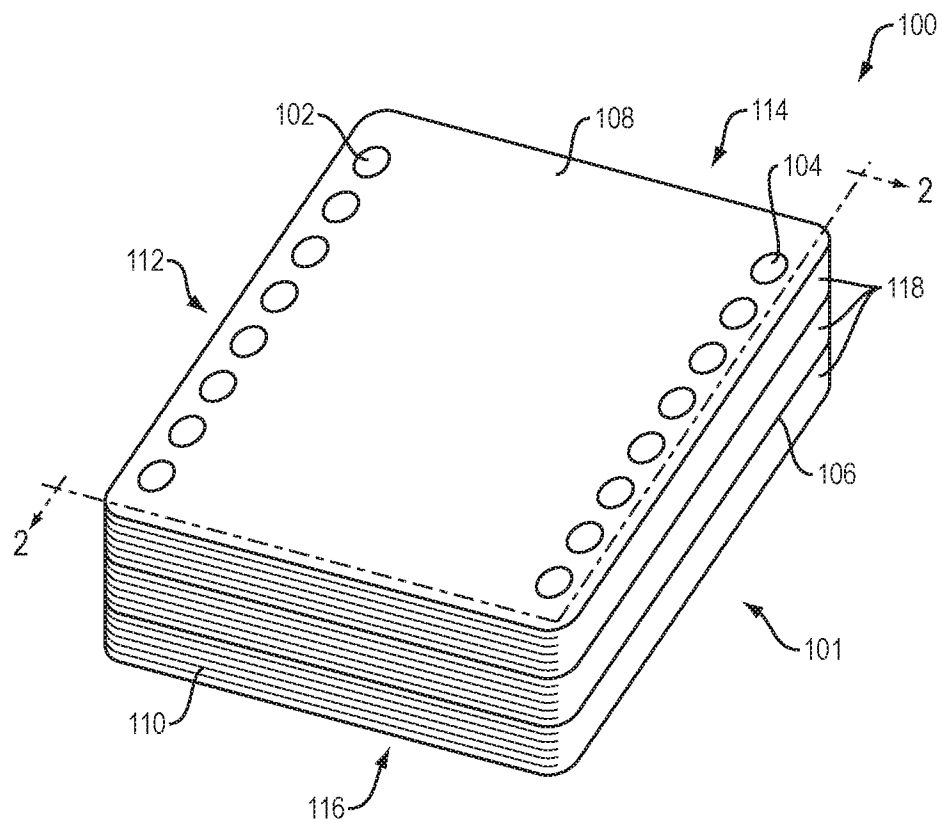


FIG. 1

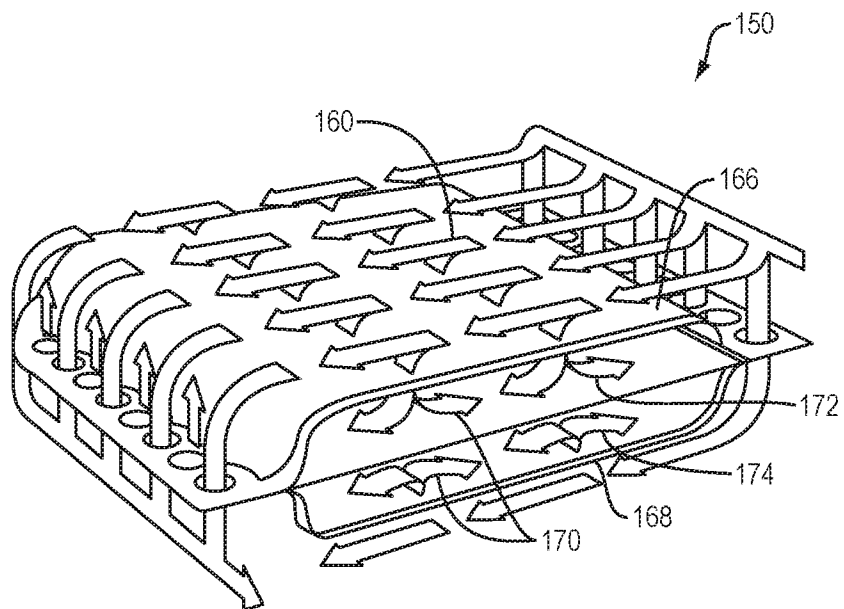


FIG. 2

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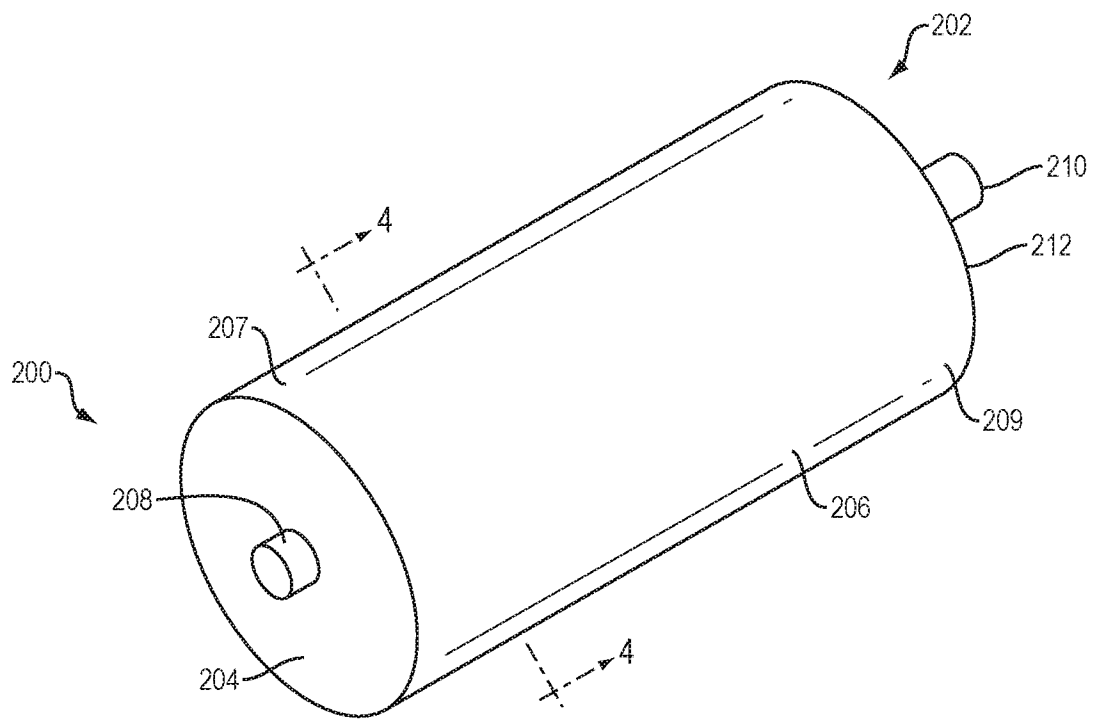
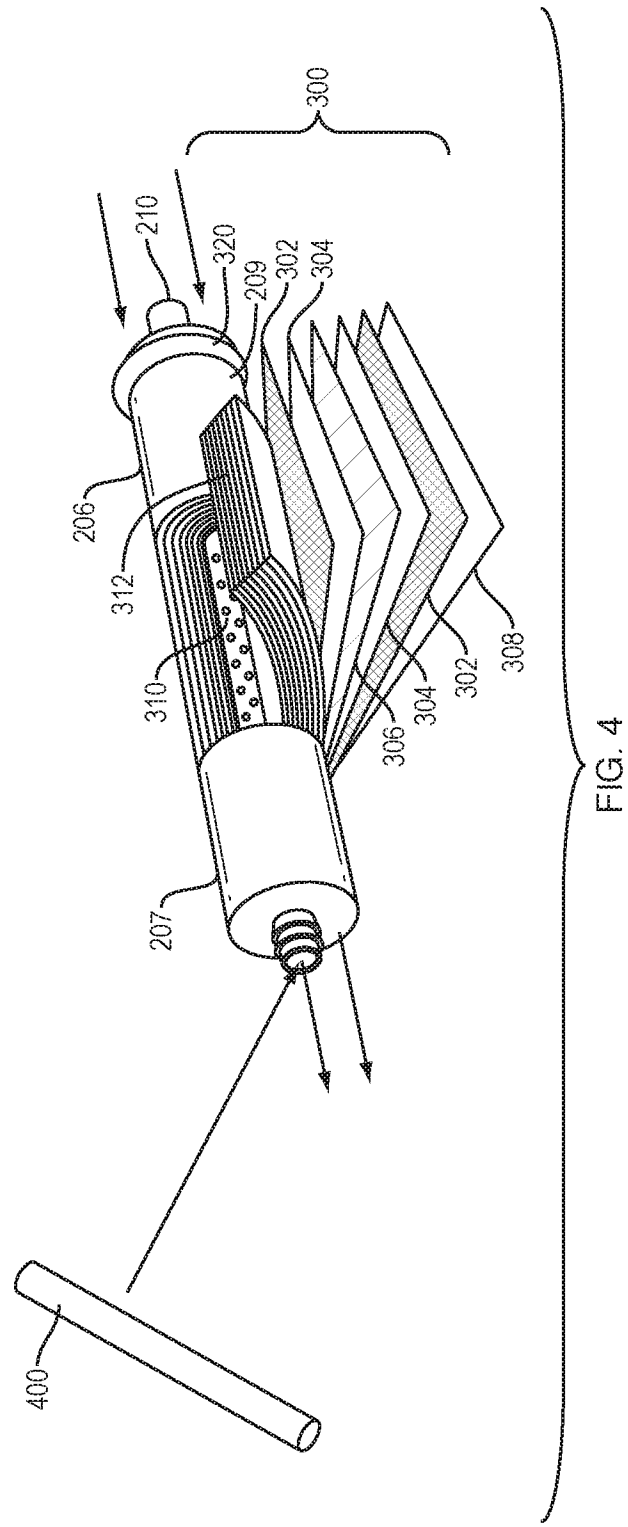
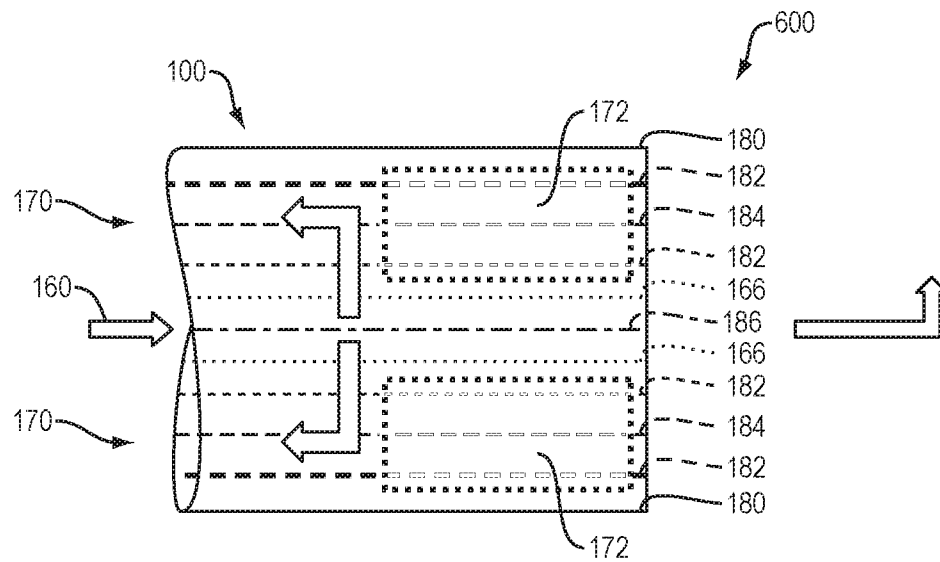
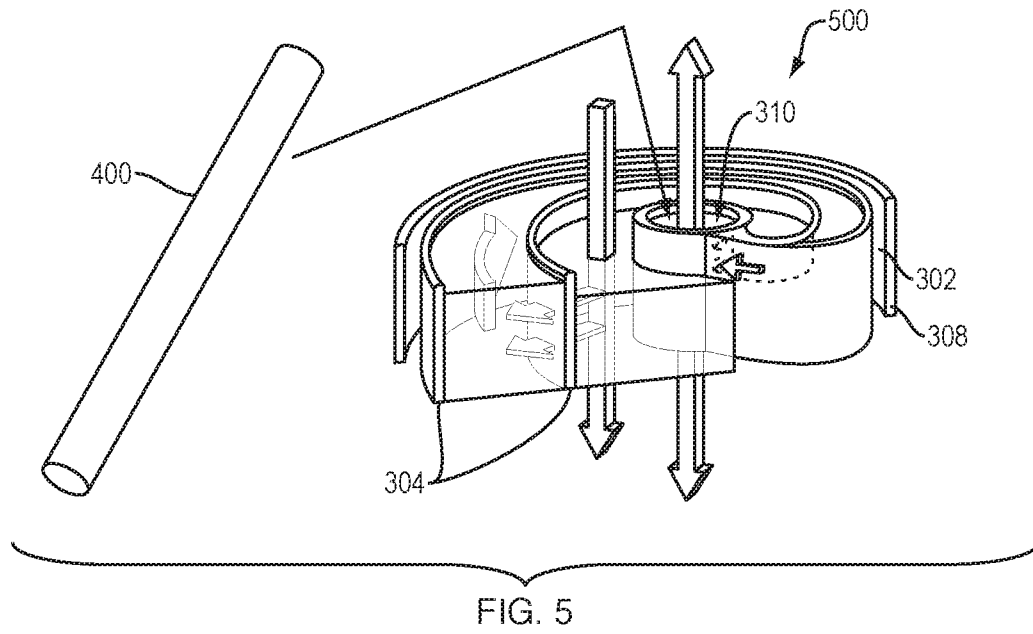


FIG. 3



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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2019/049540

A. CLASSIFICATION OF SUBJECT MATTER
INV. B01D61/14 B01D61/24 B01D63/08 B01D63/10 B01D63/14
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)
B01D

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, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KR 101 810 814 B1 (LEE HEE NAM [KR]) 25 January 2018 (2018-01-25) claim 1 paragraph [0033] -----	1,2,4, 9-15, 17-20
X	GB 2 257 375 A (DOMNICK HUNTER LTD [GB]) 13 January 1993 (1993-01-13) page 3 claim 1 -----	1-4, 8-15, 17-20
X	EP 2 276 556 A1 (WOONGJINCOWAY CO LTD [KR]) 26 January 2011 (2011-01-26) claim 1 ----- -/-	1-4, 8-15, 17-20



Further documents are listed in the continuation of Box C.



See patent family annex.

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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Date of the actual completion of the international search

6 February 2020

Date of mailing of the international search report

18/02/2020

Name and mailing address of the ISA/

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Hoyer, Michael

INTERNATIONAL SEARCH REPORT

International application No

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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