Abstract

Disposable components for a separation and purification system include a flow cell, an end cap for a chromatography column, and a chromatography column useful for medium-pressure liquid chromatography (MPLC).
CHROMATOGRAPHY COMPONENTS

FIELD OF THE INVENTION

[0001] The present invention is directed to the field of chromatographic separation or purification. More specifically, the present invention is directed to chromatography equipment components.

BACKGROUND OF THE INVENTION

[0002] Positron emission tomography works by measuring the spatial distribution of a specific molecular imaging probe, a so called PET-tracer, in the body of the patient. The tracer is injected in trace amounts into the patient and has the ability to specifically bind to tissue or be enriched in certain areas because of their specific involvement in biological processes. PET-tracers are used in cancer diagnosis and therapy control.

[0003] In current PET tracer synthesis protocols, there is a drive towards the use of disposable components. This simplifies the process of maintaining purity, sterility, and process control. One important step without a disposable solution at present is the final purification of the radiopharmaceutical compound. In the general case of PET tracer synthesis, final purification is performed by liquid chromatography, such as high-pressure liquid chromatography (HPLC), in a non-disposable column operating at about 300 bar back-pressure within the column. The purified compound is then detected via an optical flow cell for ultraviolet light absorption and a gamma detector for the activity. The optical flow cell is currently not disposable because of the high costs of metal parts, seals, and quartz windows.

[0004] After each use, the separation system i.e. the HPLC column and flow cell, are then rinsed by solvents in order cleaning the system from chemicals and minimizing the residual activity as much as possible. These systems must also be disinfected at regular intervals. The lack of disposability also requires extensive process validation in order to avoid cross contamination between runs and ensures the acceptable level of sterility and bacterial endotoxins of the system.

[0005] There is therefore a need for a disposable chromatography column, or a column having disposable components which obviates the difficult and costly need for cleaning and disinfecting a column prior to a subsequent use. There is thus a need for a compact separation system that uses all disposable components.

BRIEF DESCRIPTION OF THE DRAWINGS

[0006] FIG. 1 depicts a flow cell of the present invention.
[0007] FIG. 2 depicts the operation of the flow cell of FIG. 1.
[0008] FIG. 3 depicts an alternate flow cell of the present invention.
[0009] FIG. 4 depicts yet another flow cell of the present invention.
[0010] FIG. 5 depicts still another flow cell of the present invention.
[0011] FIG. 6 depicts a disposable UV cell with connectors for fiber optics and fluid path.
[0012] FIG. 7 depicts an end-cap of the present invention for a chromatography column.
[0013] FIG. 8 depicts a cross-sectional view of the end-cap of FIG. 7.

[0014] FIG. 9 depicts a medium-pressure liquid chromatography column employing beads in accordance with the present invention.
[0015] FIG. 10 shows an example of a disposable purification column integrated in a disposable synthesis cassette.
[0016] FIG. 11 shows an end-cap of FIG. 7 modified to incorporate shaped optical guides.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

[0017] A first embodiment of the present invention replaces the current design of a flow cell with a simple, low-cost design suitable for mass fabrication. The flow cell can have applications on microfluidic devices for process control and quality control. The integration of an optical absorbance path into a miniature synthesizer device (such as a FASTLab® synthesizer and FASTLab® cassette sold by GE Healthcare) allows in-synthesis-process monitoring of the transport of fluids through a miniature synthesizer system. The different optical absorbance properties of reagents and precursors can be used as a feedback signal for controlling the overall transport of material through the miniature synthesizer. Depending on the interrogation wavelength, the optical flow cell can utilize windows formed from the miniature synthesizer bulk material e.g. polymer, or can integrate materials such as quartz for use over a broader range of wavelengths. Identification and verification of the product peak after chromatographic purification of synthesized tracers, is often preformed by analyzing the output from the separation media, within a target time window, by a combination of a gamma and ultraviolet absorbance measurements. The ultraviolet absorbance measurements can be performed on a miniature synthesizer by routing the output of the chromatography step into an ultraviolet flow cell, of geometric configurations as previously described, where the flow cell is integrated in the miniature synthesizer bulk material. Moreover, as for product peak identification after purification, an ultraviolet flow cell can also be utilized for quality control or process control after reformulation. For example, a 3-way fraction valve can be controlled to direct purified product to a collection vessel and everything else (the impurities) to a waste bottle. The fraction valve would be opened to the collection vessel just during the time where the “product peak” appears in the chromatogram.

[0018] Both the column and flow cell designs of the present invention should be made from material that are suitable for sterilization (gamma, Ethylene Oxide or steam), in order to ensure sterility of the purified product. The assembly of the column, cell, tubings and fluid path (cassette) should be handle in appropriate clean room class to ensure bioburden level per system below 200 cfu.

[0019] The flow cell of the present invention may be constructed using, by way of illustration and not of limitation, only rods (made of for example quartz or UV transparent or semitransparent polymers such as polymethylmethacrylate (PMMA) and a polymer body, (made of for example Cyclic Olefin Copolymer (COC), Polyetheretherketone (Pektron™), Polyetherketone (PETK), polyvinylidenefluoride (PVDF), Polytetrafluoroethylene (PTFE), Polysulfone (PES), Polysulfone and other polymers suitable for the purpose). The rods are aligned coaxially and
secured in a polymer block. Their opposing end faces are separated by a short length of empty space inside the polymer block. The end faces of the rods form the internal walls at the ends of a chamber through which the fluid sample flows. By this means UV absorption can be measured across the fluid guided into the chamber between the quartz rods. An inlet and outlet channel are formed in the polymer block for passing fluids into and out of the measuring chamber. Because the flow cell consists of only simple quartz rods and an injection molded piece of polymer, the costs of the cell are low and manufacturing is straightforward, thereby enabling disposability. The quartz rods make it possible to measure absorbance into the UV range where many other materials become highly absorbing. This maintains the useful optical wavelength range of a classical flow cell, but dramatically reduces the cost.

0020] With additional reference to FIG. 1, the present invention provides a disposable flow cell 10. Flow cell 10 includes a cell body 12 which defines an elongate fluid channel 14 therethrough. Cell body 12 is desirably formed from a low-cost disposable material such as a polymer. Cell body 12 includes a first face 15 which defines both a fluid inlet port 16 and a fluid exit port 18 such that fluid channel 14 extends in fluid communication therewith. Cell body 12 defines fluid channel 14 to include a fluid entry segment 20 proximate inlet port 16 and a fluid exit segment 22 proximate fluid exit port 18. Fluid interrogation segment 24 extends in fluid communication between fluid entry segment 20 and fluid exit segment 22.

0021] Cell body 12 also defines an optical channel 26 extending between first optical port 28 and second optical port 30. Optical channel 26 includes a first optical segment 32 in optical-communication with first optical port 28 and a second optical segment 34 in optical-communication with second optical port 30. First optical segment 32 and second optical segment 34 are coaxially-aligned across fluid interrogation segment 24 of fluid channel 14. First optical segment 32 accommodates a transparent first optical guide 36 therein so as to fluidly-seal optical segment 32. Similarly, second optical segment 34 accommodates a transparent second optical guide 38 therein so as to fluidly-seal optical segment 34. First and second optical guides 36 and 38 are desirably formed from optically-transparent guiding rods or fibers. In operation, an interrogation light beam is directed into cell body 12 through first optical guide 36, through interrogation channel 24 of fluid channel 14, and then out cell body 12 through second optical guide 38. Optical guides 36 and 38 provide a polished end face, 36a and 38a, respectively, for free space coupling of light into and out of a detector instrument (not shown) that utilizes flow cell 10.

0022] The orientation of fluid entry and exit segments 20 and 22 with respect to fluid interrogation segment 24 may be selected according to the preferences of the user. For example, in FIGS. 1 and 2, fluid channel 14 takes the shape of a block letter U, whereby the bore of the lower part of the U is extended to the outer edges of the flow cell polymer block so as to provide first optical segment 32, fluid interrogation segment 24 and second optical segment 34. These bores are sealed by two quartz rods press-fitted or inserted into the mold before polymer injection. The light gets guided by the first quartz rod, passes through the liquid, and gets coupled back into the second quartz rod to be captured by the detector’s fiber bundle. Fluid may be directed through fluid channel 14 in the direction of arrow A. Suitable fluid conduit and connections are established at the inlet and exit ports of the present invention to properly direct a fluid into and out of the flow cells of the present invention.

0023] Alternatively, the fluid entry and exit segments may be arranged to each extend in different directions from the fluid interrogation segment. For example, in FIG. 3, a flow cell 40 of the present invention works by generating a flow path within a piece of a suitable polymer, e.g. COC, by means of machining or injection molding as for flow cell 10. Flow cell 40 includes the same components as flow cell 10, except that flow cell 40 includes cell body 42 defining a fluid entry port 44 and a fluid exit port 46 located on opposing faces 45 and 47, respectively, thereof. Cell body 42 thus defines a fluid channel 48 having an entry segment 50, an interrogation segment 52, and an exit segment 54, whereby entry segment 50 and exit segment 54 extend in opposite directions from interrogation segment 52 towards fluid entry port 44 and fluid exit port 46, respectively. Cell body 42 defines first and second optical ports 56 and 58 on opposed surfaces 55 and 59, respectively. Cell body 42 also defines first and second optical segments 60 and 62, fluidly-sealing optical ports 56 and 58 by accommodating optical guides 64 and 66, respectively, therein so as to provide optical coupling to the fiber bundle of a detector (not shown).

0024] Yet another embodiment of the flow cell of the present invention is shown in FIG. 4, whereby flow cell 70 includes the same components as flow cell 10, except that the fluid entry port and first optical port are defined on the same surface of the flow cell, as are the fluid exit port and second optical port on a second opposing surface of the flow cell. Flow cell 70 includes cell body 72 defining a fluid entry port 74 and a fluid exit port 76 located on opposing faces 75 and 77, respectively, thereof. Cell body 72 defines a fluid channel 78 having an entry segment 80, an interrogation segment 82, and an exit segment 84. Cell body 72 defines first and second optical ports 86 and 88 on opposed surfaces 75 and 77, respectively. Cell body 72 also defines first and second optical segments 90 and 92, fluidly-sealing optical ports 86 and 88 by accommodating optical guides 94 and 96, respectively, in linearly-alignment therein so as to provide optical coupling to the fiber bundle of a detector (not shown).

0025] Yet another embodiment of the flow cell of the present invention is shown in FIG. 5, whereby flow cell 110 includes the same components as flow cell 10, except that the fluid entry port and fluid exit port are defined on transversely-oriented surfaces of the flow cell, while the first and second optical ports are defined by opposing surfaces of the flow cell. Flow cell 110 includes cell body 112 defining a fluid entry port 114 and a fluid exit port 116 located on transverse faces 115 and 117, respectively, thereof. Cell body 112 defines a fluid channel 118 having an entry segment 120, an interrogation segment 122, and an exit segment 124. Cell body 112 defines first and second optical ports 126 and 128 on opposed surfaces 119 and 121, respectively. Cell body 112 also defines first and second optical segments 130 and 132, fluidly-sealing optical ports 126 and 128 by accommodating optical guides 134 and 136, respectively, in linearly-alignment therein so as to provide optical coupling to the fiber bundle of a detector (not shown).

0026] Yet another embodiment of the flow cell of the present invention is shown in FIG. 6, whereby flow cell 350 includes the same components as flow cell 40, except that the fluid entry port 351 and fluid exit port 352 are coaxially-aligned and on oppositely oriented surfaces of the flow cell.
Connections to the fluid path 353 and 357 and to the fiber optics 356 and 354 have been added also compared to the flow cell 40. Flow cell 350 includes cell body 358 defining a fluid entry port 351 and a fluid exit port 352 located on opposite faces 359 and 360, respectively, thereof. Cell body 358 defines a fluid channel 361 having an entry segment 362, an interrogation segment 363, and an exit segment 364. Entry segment 362 and exit segment 363 are linearly-aligned across fluid channel 361. Cell body 358 defines first and second optical ports 354 and 356 on opposed surfaces 365 and 366, respectively. Cell body 358 also defines first and second optical segments 367 and 368, fluidically-sealed by O-rings 369 and 370 when fiber optic bundles 371 and 372 are compressed or screwed inside cavity 356 and 357, respectively, in linearly-alignment therein so as to provide optical coupling to the fiber optics. Fiber optic bundles 371 and 372 may be disconnected from cell body 358 prior to disposing of flow cell 350.

[0027] Similarly still, the present invention contemplates that the flow cell may be formed such that either one of the fluid entry and exit ports is co-defined by a single surface of the flow cell with one of the optical ports while the other of the fluid entry and exit ports and the other optical port are each defined by different surfaces of the flow cell. The fluid entry and exit segments need not extend in a co-planar manner within the cell body.

[0028] In each such embodiment, the present invention provides a flow cell that is formed by low-cost, simple to manufacture, and all FDA approved materials. The geometry of the cell allows for different “interaction” lengths and volumes of the fluid channel allowing the simple adaptation of the design towards different radiotracer separations. The optical guides simplify the coupling of the UV light into and out of the flow cell, thereby obviating the need for complex optics. For example, the flow cell may be formed with quartz rods for the optical guides which seal the optical ports by means of a press fit, over-molding, or other low-cost manufacturing or assembly technique.

[0029] In another aspect of the present invention, an end cap is provided which incorporates a flow cell of the present invention. That is, the function of an optical flow-cell and an end cap for a chromatography column, ion exchange column, solid phase extraction column, or similar, are combined in the end-cap for the column. Identification and verification of the product peak after chromatographic purification of synthesized tracers, is often performed by analyzing the output from the separation media, within a target time window, by a combination of a gamma and ultraviolet absorbance measurements. The ultraviolet absorbance measurements can be performed on a miniature synthesizer by routing the output of the chromatography step into an ultraviolet flow cell, of geometric configurations as previously described, where the flow cell is integrated in the miniature synthesizer bulk material.

[0030] The disposable flow cell function is added to the end-cap by creating a fluid channel in the low-cost disposable end-cap material such as a polymer. Light is guided into and out of a fluidic path through light guiding rods or fibers. These seal the flow cell fluidically, guide the light optically, and provide a polished end face for free space coupling of light into and out of the detector instrument that utilizes the flow cell.

[0031] This aspect of the invention replaces the current design of a stand-alone flow cell and, e.g., a stand-alone chromatography column, with a single integrated flow-cell and column. This is achieved by integrating the flow-cell into the end-cap of the column. The end-caps of disposable columns are often made of polymeric materials by low-cost processes such as molding. By using the end cap body for the flow cell body, the function of endcap and flow cell can be combined. This remains a simple, low-cost design suitable for mass fabrication and simplifies the handling for the user since two components (column and flow cell) are now replaced with one component. The only two materials used in the disposable cell are quartz rods and a polymer, e.g. COC. The quartz rods are aligned coaxially and secured in a polymer block. Their opposing end faces are separated by a short length of empty space, the interrogation passageway, inside the polymer block. The end faces of the rods form the internal walls at the ends of a chamber through which the fluid sample flows. By this means UV absorption can be measured across the fluid guided into the chamber between the quartz rods. An inlet and outlet channel are formed in the polymer block for passing fluids into and out of the measuring chamber. Because the flow cell consists of only simple quartz rods or fibers and an injection molded piece of polymer, the costs of the cell are low and manufacturing is straightforward, thereby enabling disposability. The quartz rods make it possible to measure absorbance into the UV range where many other materials become highly absorbing. This maintains the useful optical wavelength range of a classical flow cell, but dramatically reduces the cost.

[0032] Referring now to FIGS. 7, 8, and 11, a disposable end-cap 210 is provided for use at the dispense end of a column. End-cap 210 is desirably formed from a polymeric body 212 having first and second co-axially aligned optical guides 214 and 216 sealingly engaging first and second optical ports 218 and 220, respectively. Body 212 defines an elongate interrogation channel segment 224 extending between optical guides 214 and 216. Body 212 further includes a first major surface 226 which defines a fluid inlet port 228 to be placed in fluid communication with the interior of a separations column (not shown). Body 212 also defines an inlet channel segment 230 extending in fluid communication between inlet port 228 and a first end of interrogation channel segment 224 proximate to first optical guide 214. Similarly, body 212 further includes a second major surface 232 which defines a fluid exit port 234. Body 212 defines an exit channel segment 236 extending in fluid communication between exit port 234 and a second end of interrogation channel segment 224 proximate to second optical guide 216. The main conceptual difference between end-cap 210 and the flow cells of the present invention is the location of exit port 234, in that the entry and exit ports are not placed in such proximity that both still open within a column, i.e., exit port 234 is located so as to conduct fluid from the column interior to outside of the column. Body 212 includes an upstanding perimetrical wall 238 defining a cylindrical cavity 240 for being placed in sealed fluid communication with the cavity of a chromatography column wall so that inlet port 228 is placed in fluid communication with the column interior cavity.

[0033] The manner of attaching an end-cap of the present invention to a column will be understood to those familiar with the art. The end-cap may attach to the column by mating engagement between opposed threaded surfaces, interference fit between the two, or by application of a suitable adhesive that maintains the two components to each other without deleteriously affecting the reaction materials within the column.
[0034] Inlet channel segment 230, interrogation channel segment 224, and exit channel segment 232 form an elongate fluid channel 242 through body 212. End-cap 210 is formed within a piece of a suitable polymer, e.g., COC, by means of machining or injection molding. The polymer substrate is the path for the fluid and is also shaped to function as the end-cap for a column such as a chromatography column. In this way fluid leaving the column passes through the end-cap and optical flow cell region before leaving the end-cap. Within the end-cap, the fluid flows between the two co-axially aligned quartz rods or fibers, 214 and 216, such that light is directed from one rod, through the fluid sample, and into the second rod. The quartz rods form the light path that allows transmission into the ultraviolet range, and together with the polymer substrate, form the walls that define the channel for the fluid. The light out from the second quartz rod can be guided to the optical absorbance detector by known methods.

[0035] The combination of an optical flow-cell and column end-cap according to the present invention simplifies the overall separation procedure by combining two components (the column and the flow cell) into one component. The end-cap of the present invention provides easier handling for the user since only one component is involved. The advantage to the producer is a lower cost of production. In general the concept described also embodies all the advantages described for the flow cell of the present invention, i.e., low cost, ease of manufacture, and using all FDA approved materials. The geometry of the cells allows for different “interaction” lengths and volumes allowing the simple adaptation of the design towards different radiotracer separations. The optical guides simplify the coupling of the UV light into and out of the flow cell while obviating the need for complex optics.

[0036] The present invention further contemplates that either optical guide could incorporate or be in the form of a lens to better focus an interrogation signal. For example, an optical guide could be shaped as a partial conical or could provide a concave or convex surface at one or both ends to account for signal diffraction entering or exiting the medium. FIG. 11 depicts a cross sectional view of end-cap 210, modified to incorporate first and second conical optical guides 250 and 256. First guide 250 includes an outer convex surface 252 at one end and an opposed concave surface 254 facing flow interrogation channel segment 224. Second guide 256 includes a convex surface 258 in facing opposition to surface 254 of first guide 250. Second guide 256 also includes an outer concave surface 260. An interrogation beam, represented by arrow C, may thus be more focused on the fluid passing through the interrogation channel, and/or a sensor in facing opposition to surface 260 of second guide 256. The present invention further contemplates that only one of the optical guides may be provided with such a focusing shape.

[0037] In yet another aspect of the present invention, a disposables separation column is provided which incorporates the end-cap of the present invention to a polymeric column body. The column, e.g., a chromatography column suitable for MPLC, uses separation particles of a size range of 15-30 micrometers (spherical or broken material shape). This way the column is substantially cheaper than an HPLC column using 1-5 micron particles while maintaining sufficient separation power for the purification of many PET-tracers.

[0038] Referring now to FIG. 9, disposable column 310 includes an elongate polymeric cylindrical body wall 312, a first polymeric end cap 314, and a second polymeric end cap 316. Column 310 defines an elongate cylindrical interior column cavity 318 extending between end caps 314 and 316. End cap 314 includes an end cap body 320 defining an input port 322 and input passage 324 extending in fluid communication between port 322 and cavity 318. End cap 316 includes an end cap body 326 defining an outlet port 328 and outlet passage 330 extending in fluid communication between outlet port 328 and cavity 318.

[0039] It is contemplated by the present invention that second end cap 316 may be in the form of end cap 210 of the present invention. Additionally, the present invention further contemplates that end caps 314 and 316 are joinable to body wall 312 by conventional means, i.e., by mating threads and/or a suitable (for purpose) adhesive. Moreover, the present invention contemplates that either end cap 314 or 316 is formed as a unitary structure with body wall 312. Alternatively, it is contemplated that both end caps 314 and 316 are formed with mating portions of body wall 312 which may be joined to form column cavity 318 therebetween.

[0040] Column 310 also incorporates a separations media comprising particles of 15 to 30 micrometer diameter particles. Column 310 is ideally suited for MPLC for operation at lower pressures, desirably in the range of 1 to 20 bars.

[0041] The disposable chromatography column of the present invention includes 15 to 30 micrometer diameter particles, a polymeric column body and end-caps (made of for example quartz or UV transparent or semitransparent polymers such as polymethyl methacrylate (PMMA) and a polymeric body, (made of for example Cyclic Olefin Copolymer (COC), Polyetheramide (also called as Ultem®), Polypropylene (PP), Polystyrene (PS), Polycarbonate (PC), fluoropolymer (PF), or other materials suitable for the purpose. Because of the particle size, the backpressure of the column at typical flowrates is much lower, between 1 to 20 bars at 1 to 10 ml/min flow rate as compared to an HPLC column (which operates at up to 300 bars). At this particle size range, chromatographic performance is still acceptable for many PET-tracers using reverse polarity phase such as for example Poly(styrene/Divinyl Benzene based or silica based such as C2, C4, C8, C18, tC18 or C30, or other particle types). Because the particles provide for better separation, the small particles also require higher backpressure to force a fluid therapeutically. Because of the high price and the expense of an HPLC column, a one-size-fits-all column has to be used leading to an over specification in many cases.

[0042] The exact dimensions and therefore separation power can be adapted to each type of separation required as the columns become disposable. The cost is low due to the almost exclusive use of polymeric materials. The larger particles are also lower in price as is the manufacturing method. As each column is only used once, the elution time of the product is known in advance and therefore product collection can be automated, leading to a reduction in qualification requirements for the operator.

[0043] Additionally, the column of the present invention provides adaptability to specific separation problems by selection of particle size and surface chemistry (C4, C18, NH2, etc.), and the column diameter and length. For example, the column length may be made to be from 25 mm to 500 mm, or even shorter as a particular application may necessitate.
The column may be custom tailored to specific PET tracer separation and thus saves time and reduces volumes for reformulation as compared to using a standard HPLC column. The column allows for sterility to be established at the factory during fabrication, so that GMP and QC may be provided by the column producer, thereby sparing the operator from these tasks. Thus, column 310 may be assembled and sterilized at the factory, then sealed within a protective package for delivery to the end-user. The end-user may remove column 310 from the package within a environmentally-controlled operating space for direct incorporation into a manufacturing or production line. It is further contemplated that the inlet port 322 and outlet port 328 may be shipped with removable seals thereon so as to maintain the sterility of the interior surfaces, the seals being removed within the clean space of the production facility for direct incorporation into the process.

[0044] While described as being formed from suitable polymers, the column of the present invention may alternatively be formed using suitable metals for the end caps and column wall. Whereas forming the column from polymers provides a low-cost disposable chromatography column, forming the column from metals provides a column which may be a freestanding device which may be cleaned, sterilized, and configured for multiple uses.

[0045] In yet another aspect of the present invention, the disposable column of the present invention, together with the flow cell of the present invention, is integrated in the fluid path of a disposable synthesis cassette. The disposable synthesis cassette, allows managing of the fluid transfer i.e. selecting the solvent for purification, loading of the crude mixture to be purified on the column and finally collecting the final product. Depending on the injectability of the purification eluent, the disposable synthesis cassette fluid path might be used to reformulate, in an injectable form, the purified tracer.

[0046] The interface between the disposable column and flow cell of the present invention with a disposable synthesis cassette includes tubings and connectors which are pressure-resistant in the range of 1 to 20 bars. The tubings and connectors are desirably made of material chemically resistant against necessary organic solvents or chemicals present in the mobile phase, including by way of illustration and not of limitation, ethanol, methanol, acetonitrile, DMSO, THF or triethylamine.

[0047] Reference is now made to FIG. 10, which depicts a disposable synthesis cassette 400 and its components which are used to synthesize radiotracers when operated by a synthesis unit such as a FASTLab® synthesizer, sold by GE Healthcare, a division of General Electric Company (Liege, BE). Cassette 400 is a variant of a pre-assembled cartridge designed to be adaptable for synthesizing clinical batches of different radiopharmaceuticals with minimal customer installation and connections. Cassette 400 includes reaction vessel, reagent vials, cartridges, filters, syringes, tubings, and connectors for synthesizing a radiotracer according to the present invention. Connections are desirably automatically made to the reagent vials by driving the septums thereof onto penetrating spikes to allow the synthesizer access to use the reagents.

[0048] Cassette 400 includes a manifold 412 including twenty-five 3 way/3 position stopcocks valves 501-525, respectively. Manifold valves 501-525 are also referred to as their manifold positions 1-25 respectively. Manifold valves 501, 504-505, 507-510, 517-523, and 525 have female luer connectors projecting up therefrom. Manifold valves 502, and 512-516 have an elongate open vial housing upstanding therefrom and support an upstanding cannula therein for piercing a reagent vial inserted in the respective vial housing. Manifold valve 506 receives an input plunger which delivers a radioisotope to manifold 412 for processing. Movement of the reagent vial to be pierced by the respective cannula is performed under actuation by the synthesizer device. Valves 503, 511, and 524 support an elongate open syringes upstanding therefrom. Each of valves 501-525 include three open ports opening to adjacent manifold valves and to their respective luer connectors, cannulas, and syringe barrels. Each valve includes a rotatable stopcock which puts any two of the three associated ports in fluid communication with each other while fluidically isolating the third port. Manifold 412 further includes, at opposing ends thereof, first and second socket connectors 521 and 523, each defining ports for connection to the synthesis device through which either nitrogen gas is delivered or a vacuum is applied to assist in driving fluid through cassette 400. Manifold 412 and the stopcocks of valves 501-525 are desirably formed from a polymeric material, e.g., PP, PE, Polysulfone, Ultem, or Peek.

[0049] Cassette 400 is attachable to a synthesis device, such as FASTLab, which cooperatively engages the cassette so as to be able to actuate each of the stopcocks and syringes to drive a source fluid with a radioisotope through the cassette for performance of a chemical synthesis process. Additionally, the synthesis device can provide heat to the reaction vessel of cassette 400 as required for chemical reactions. The synthesizer is programmed to operate pumps, syringes, valves, heating element, and controls the provision of nitrogen and application of vacuum to the cassette so as to direct the source fluid into mixing with the reagents, performing the chemical reactions, through the appropriate purification cartridges, and selectively pumping the output tracer and waste fluids into appropriate vial receptacles outside the cassette. The fluid collected in the output vial is typically input into another system for either purification and/or dispensement. After product dispensement, the internal components of cassette 400 are typically flushed to remove latent radioactivity from the cassette, although some activity will remain. Cassette 400 thus can be operated to perform a two-step radio-synthesis process. By incorporating an MPLC column of the present invention on cassette 400, cassette 400 is further able to provide simple purification so as to obviate the need for HPLC.

[0050] Cassette 400 is mated to an automated synthesizer having rotatable arms which engage each of the stopcocks of valves 501-525. The synthesizer also includes a pair of spigots, one of each of which insert into the ports of connectors 121 and 123 in fluid-tight connection. The two spigots can thus provide a source of nitrogen and a vacuum to manifold 412 so as to assist in fluid transfer therethrough and to operate cassette 400 in accordance with the present invention. The free ends of the syringe plungers are engaged by cooperating members from the synthesizer, which will then apply the reciprocating motion thereto within the syringes. A bottle containing water is fitted to the synthesizer then pressed onto spike 470 to provide access to a fluid for driving compounds under operation of the various-included syringes. The reaction vessel will be emplaced within the reaction well of the synthesizer and the product collection vial, waste vial, and source reservoir are connected. Prior to beginning the synthesis process, arms from the synthesizer will press the reagent vials onto the cannulas of manifold 412. The synthesis process may then commence.
MPLC column 410 and flow cell 420, of similar design and operation as the columns and flow cells described hereinafore, has been successfully tested with a FASTLab cassette to produce, by way of illustration and not of limitation, FLT, FMISO, MPFF, and Fallypride. Other radiotracers are contemplated to be synthesized using the MPLC column and flow cell of the present invention. The present invention also contemplates that by directly supported on a disposable cassette 400 so that the purification of the tracer may be performed on the cassette itself on the synthesizer. Cassette 400 and the synthesizer device can also direct the product to a separate MPLC system of the present invention for purification. The present invention further contemplates that the purified compound from column 410 may be analyzed by flow cell 420 and may then be directly dispensed from cassette 400 or rerouted through cassette 400 for reformulation of the product. Cassette 400 includes the hardware and chemical components to be operated to perform reformulation for the product.

Additionally, the present invention contemplates that flow cell 410 includes an aperture for positioning a cable terminating at a radiation sensor 405 which can detect the radiation signature of the product flowing through flow cell 420. Alternatively, radiation sensor may be separately housed on cassette 400 to analyze the eluate flowing from flow cell 420. An eluate conduit 414 extends from column 410 to the inlet port 416 of flow cell 420. First and second fiber optic cables 422 and 424 are disconnectable connectable to flow cell 420 to interrogate the product fluid flowing therethrough. When product is finished dispensed from cassette 400, the radiation detector and fiber optic cables are disconnected from flow cell 420 to allow their re-use with subsequent cassettes 400. Product exits flow cell 420 through outlet port 418 and then flows through conduit 430, through valve 435 which is set to direct the product fluid through either a simple/waste conduit 445 or a product dispensement conduit 455.

While the particular embodiment of the present invention has been shown and described, it will be obvious to those skilled in the art that changes and modifications may be made without departing from the teachings of the invention. The matter set forth in the foregoing description and accompanying drawings is offered by way of illustration only and not as a limitation. The actual scope of the invention is intended to be defined in the following claims when viewed in their proper perspective based on the prior art.

What is claimed is:

1. An optical UV flow cell chromatographical purification of PET tracers comprising:
   a flow cell body defining for conducting a PET tracer therethrough,
   first and second aligned UV transparent optical guides; and
   an interrogation passageway extending between said first and second optical guides.

2. The optical UV flow cell of claim 1, wherein said flow cell body further defines:
   A first optical port and a second optical port, wherein said first optical guide seals said first optical port and said second optical guide seals said second optical port;
   A fluid inlet port and a fluid entry segment extending in fluid communication between said fluid inlet port and said interrogation passageway; and
   A fluid exit port and a fluid exit segment extending in fluid communication between said fluid exit port and said interrogation passageway, wherein such the PET tracer flows in the interrogation passageway in a direction from the first optical guide towards said second optical guide.

3. The optical UV flow cell of claim 2, wherein said fluid inlet port and said fluid exit port are defined by the same surface of said flow cell body.

4. The optical UV flow cell of claim 2, wherein said fluid inlet port and said fluid exit port are defined by opposing surfaces of said flow cell body.

5. The optical UV flow cell of claim 2, wherein said fluid inlet port and said fluid exit port are defined by non-coplanar surfaces of said flow cell body.

6. The optical UV flow cell of claim 2, wherein said first optical port and said second optical port are defined by the same surface of said flow cell body.

7. The optical UV flow cell of claim 2, wherein said first optical port and said second optical port are defined by opposing surfaces of said flow cell body.

8. The optical UV flow cell of claim 2, wherein said first optical port and said second optical port are defined by non-coplanar surfaces of said flow cell body.

9. The optical UV flow cell of claim 1, wherein said first and second optical guides are formed of quartz.

10. The optical UV flow cell of claim 1, wherein said flow cell body is formed of a polymeric material.

11. An end cap for a chromatography column comprising:
   a cap body further comprising:
   first and second aligned UV transparent optical guides; and
   an interrogation passageway extending between said first and second optical guides.

12. The end cap of claim 11, wherein said flow cell body further defines:
   A first optical port and a second optical port, wherein said first optical guide seals said first optical port and said second optical guide seals said second optical port;
   A fluid inlet port and a fluid entry segment extending in fluid communication between said fluid inlet port and said interrogation passageway; and
   A fluid exit port and a fluid exit segment extending in fluid communication between said fluid exit port and said interrogation passageway.

13. The end cap of claim 12, wherein said fluid inlet port and said fluid exit port are defined by the same surface of said flow cell body.

14. The end cap of claim 12, wherein said fluid inlet port and said fluid exit port are defined by opposing surfaces of said flow cell body.

15. The end cap of claim 12, wherein said fluid inlet port and said fluid exit port are defined by non-coplanar surfaces of said flow cell body.

16. The end cap of claim 12, wherein said first optical port and said second optical port are defined by the same surface of said flow cell body.

17. The end cap of claim 12, wherein said first optical port and said second optical port are defined by opposing surfaces of said flow cell body.

18. The end cap of claim 12, wherein said first optical port and said second optical port are defined by non-coplanar surfaces of said flow cell body.

19. The end cap of claim 11, wherein said first and second optical guides are formed of quartz.

20. The end cap of claim 11, wherein said flow cell body is formed of a polymeric material.
21. The end cap of claim 11, wherein such a PET tracer flows in a direction from the first optical guide towards said second optical guide in the interrogation passageway.

22. A chromatography column comprising:
   An elongate cylindrical wall defining an elongate cavity;
   A first end cap defining an entry port and an elongate entry passageway in fluid communication with said cavity;
   A second end cap defining an outlet port and an elongate outlet passageway in fluid communication with said cavity;
   A separation media comprising particles having a diameter of 15-30 micrometers.

23. A chromatography column of claim 22, wherein said first and second end caps and said cylindrical wall are formed of a polymeric material.

24. A chromatography column of claim 22, wherein said second end cap is an end cap of claim 11.

25. A chromatography column of claim 22, wherein said cylindrical wall has a length between 25 and 500 millimeters.

26. A chromatography column of claim 22, further comprising a sealed package containing said chromatography column.

27. A chromatography column of claim 26, wherein said column is provided in a sterilized condition, and said sealed package maintains the column sterile.

28. A chromatography column of claim 27, wherein said column is provided at a bioburden level below 200 cfu.

29. A chromatography column of claim 27, wherein one of a said end caps are formed as a unitary structure with said cylindrical wall.

30. A method of operating a chromatography column of 22, comprising the step of:
   flowing an eluent through said inlet port and through said cavity and an eluate through said outlet port at a back-pressure within said cavity within the range of 1-20 bar.

31. A cassette device for performing labeling and purification of a product comprising a chromatography column of claim 22.

32. A method of operating the cassette device of claim 30 to perform reformulation of a product.

33. A purification system for PET tracers comprising a chromatographic column operated at low pressure (p<20 bar)

34. A purification system of claim 32, further comprising a gamma radiation detector and a fraction valve.

35. A purification system of claim 32, further comprising a disposable flow cell of claim 1.

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