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(54) **MICROFLUIDIC RADIOSYNTHESIS OF A RADIOLABELED COMPOUND USING ELECTROCHEMICAL TRAPPING AND RELEASE**

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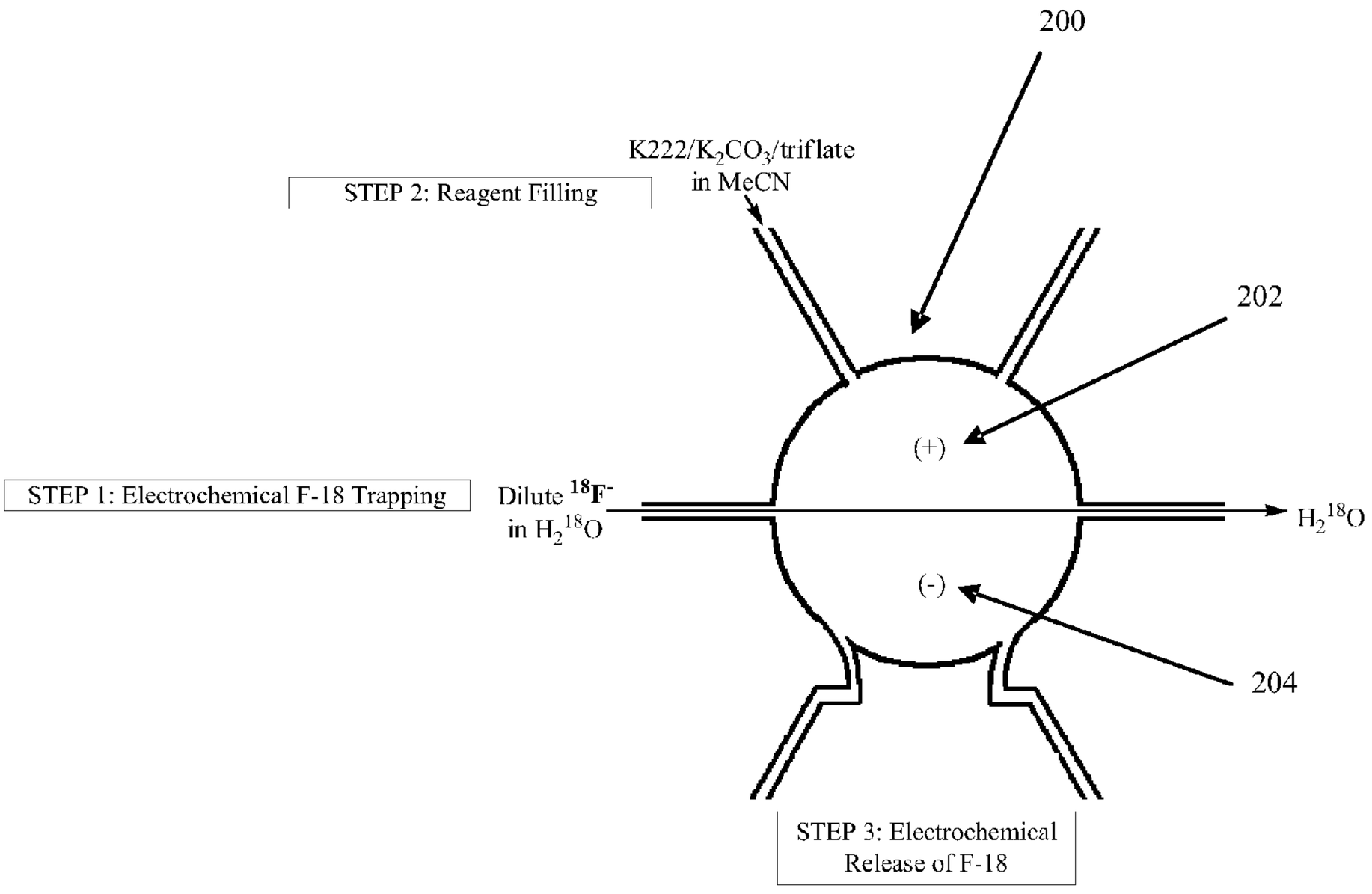
(57) **ABSTRACT**

Methods and apparatus enable radiosynthesis of radiolabeled compounds using electrochemical trapping and release. The trapping and release of radioactive isotopes all occur inside a microreactor, a vial or similar device, thus eliminating the need for azeotropic drying and several dead-end filling steps, as well as the necessity to move concentrated radioisotopes from one compartment of the chip to another. These and other features allow radioisotope enrichment to be carried out internally within a radiochemical synthesis chip, providing faster and more robust operation, as well as producing very high radiochemical labeling yields.



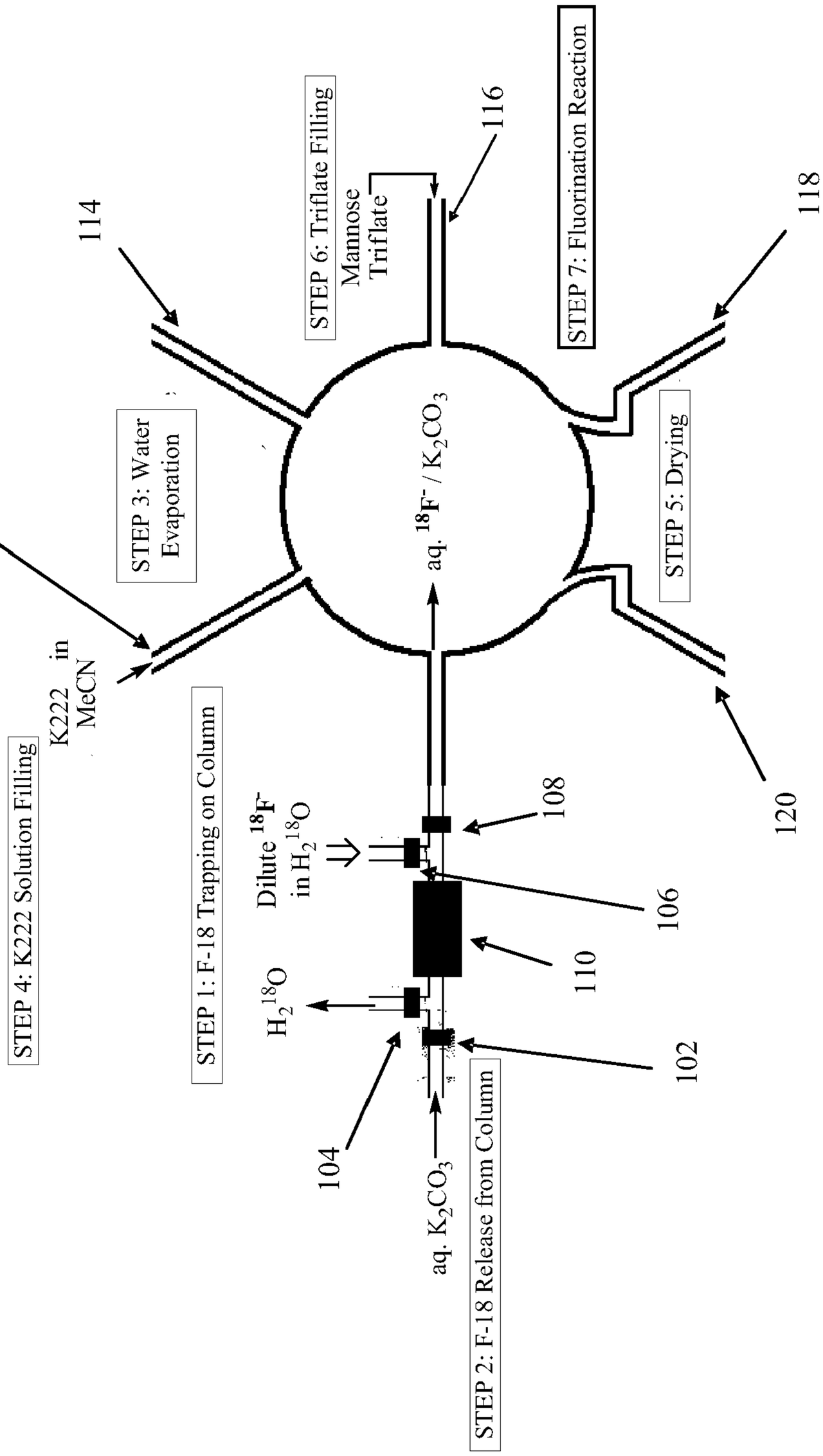

STEP 4: K222 Solution Filling
K222 in MeCN
112
STEP 1: F-18 Trapping on Column
Dilute $^{18}F^-$ in $H_2{}^{18}O$
$H_2{}^{18}O$
104
aq. K_2CO_3
STEP 2: F-18 Release from Column
STEP 3: Water Evaporation
aq. $^{18}F^-$ / K_2CO_3
108
106
110
102
STEP 5: Drying
120
STEP 6: Triflate Filling
Mannose Triflate
116
STEP 7: Fluorination Reaction
114
118

FIG. 1

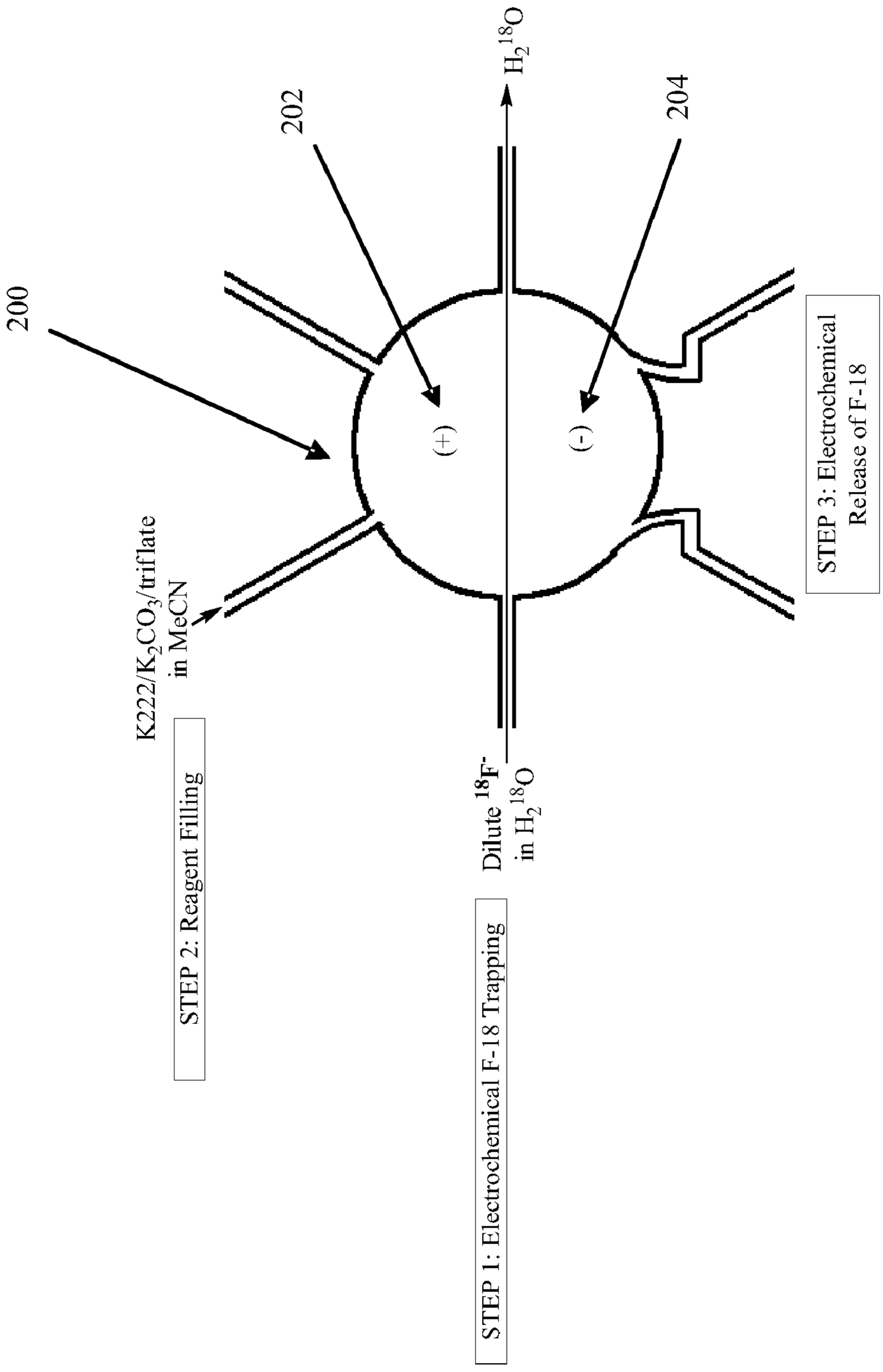
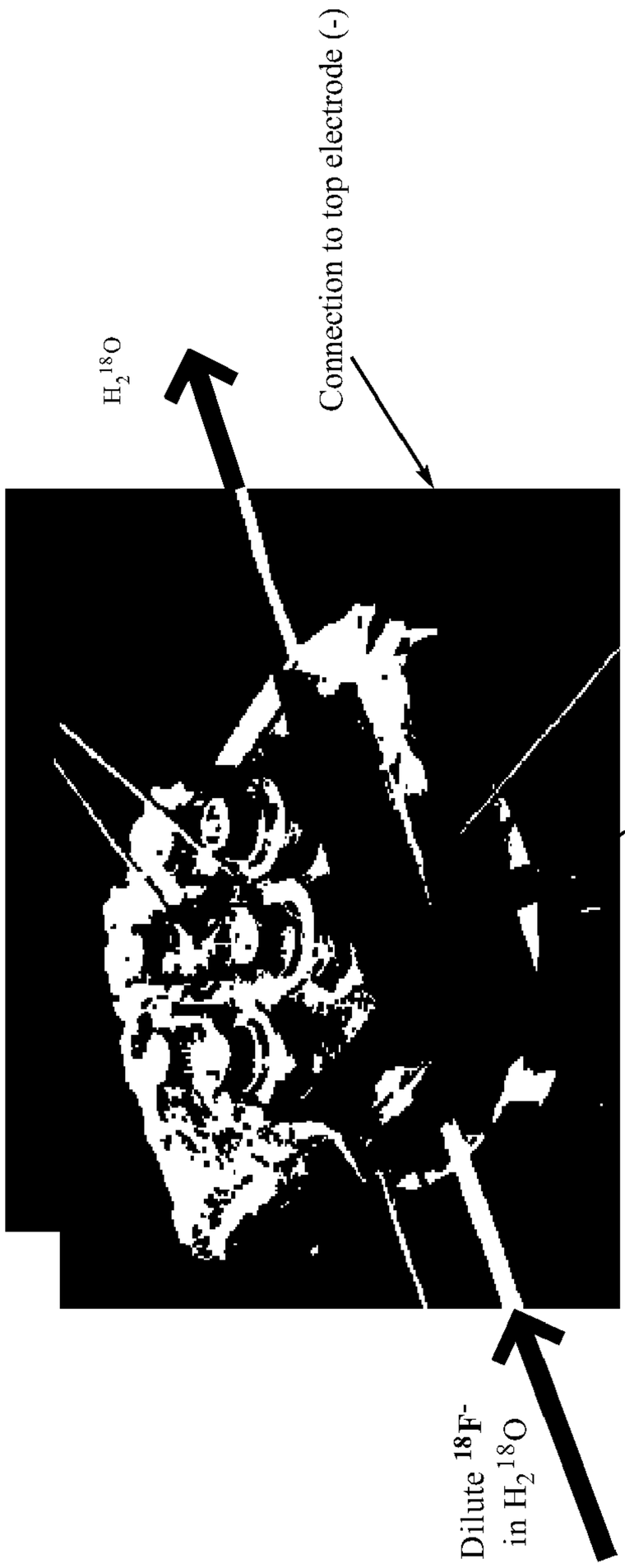

200
202
$H_2{}^{18}O$
204
K222/K_2CO_3/triflate in MeCN
(+)
(-)
Dilute $^{18}F^-$ in $H_2{}^{18}O$
STEP 2: Reagent Filling
STEP 3: Electrochemical Release of F-18
STEP 1: Electrochemical F-18 Trapping

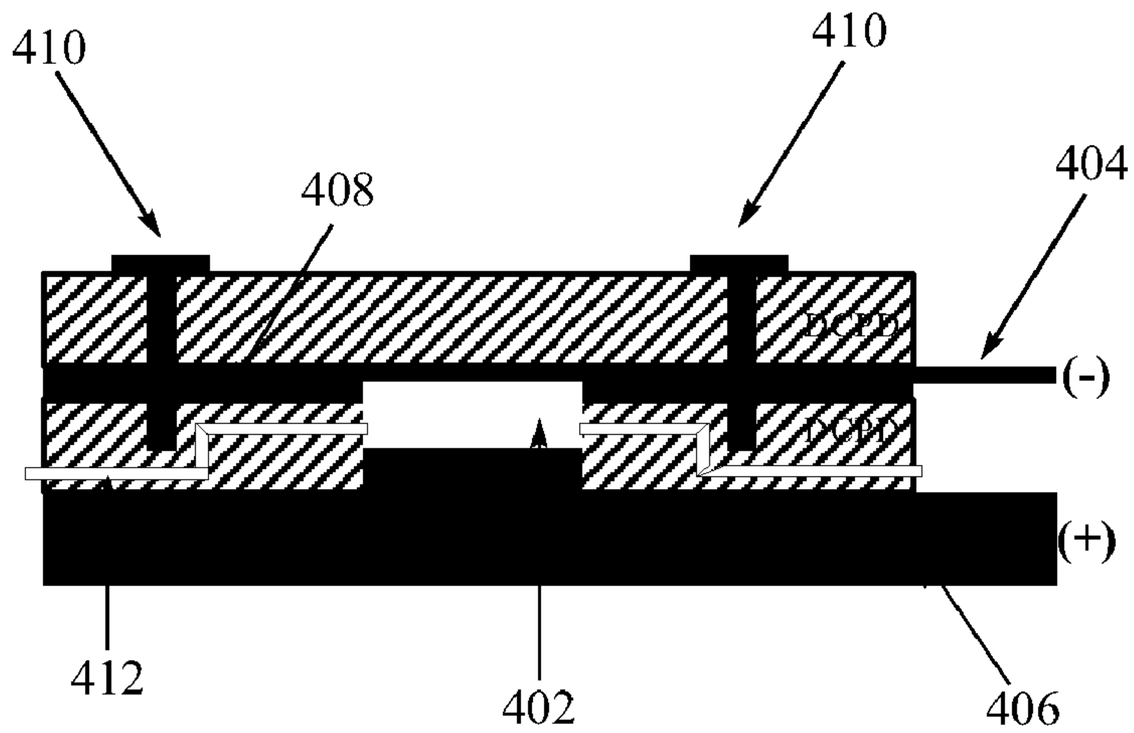
FIG. 2


$H_2{}^{18}O$
Connection to top electrode (-)
Connection to bottom electrode (+)
Dilute $^{18}F^-$ in $H_2{}^{18}O$

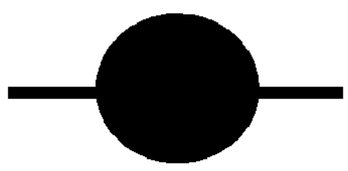
(B)

(A)

FIG. 3



(A)



(B)

(C)

FIG. 4

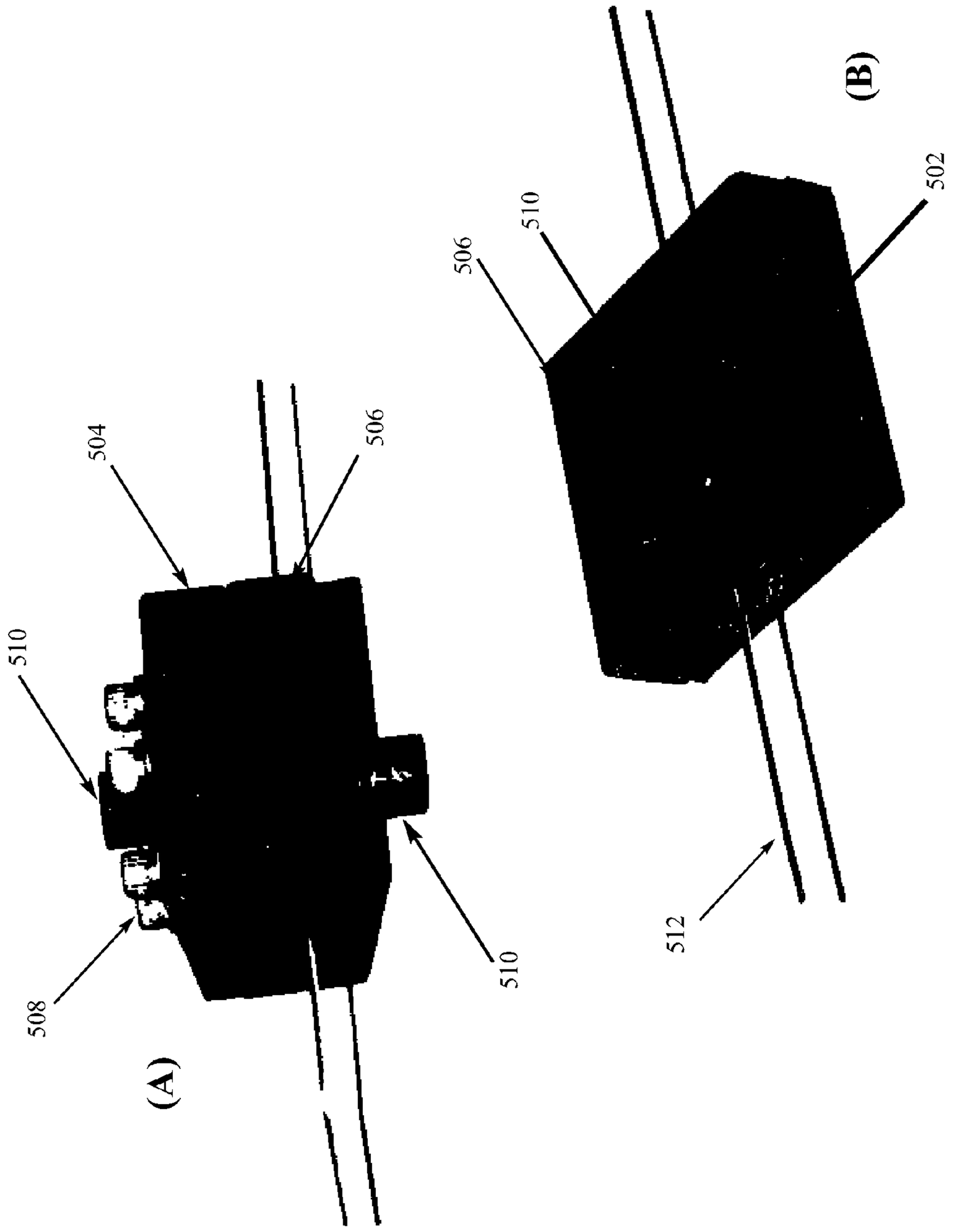
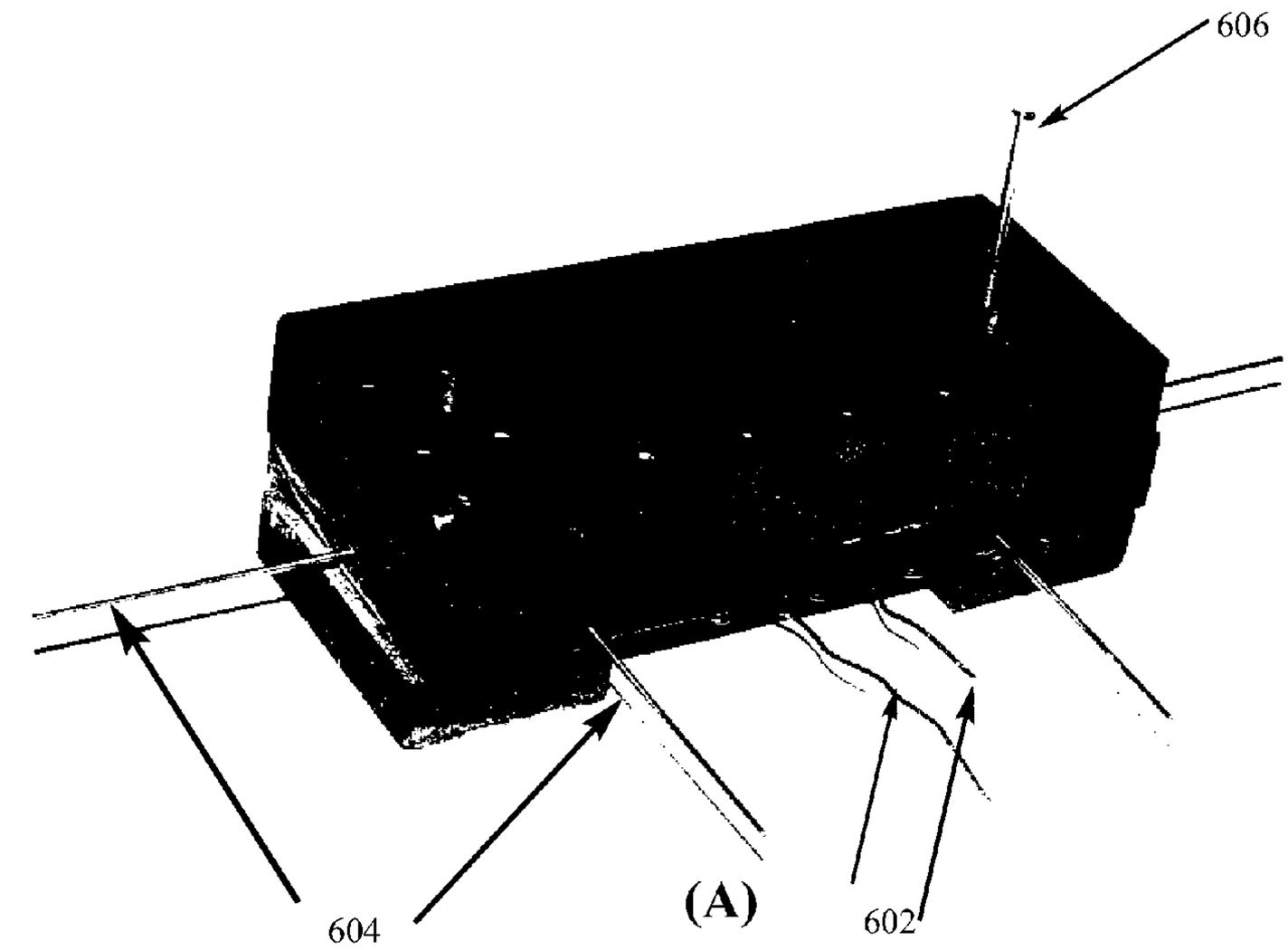
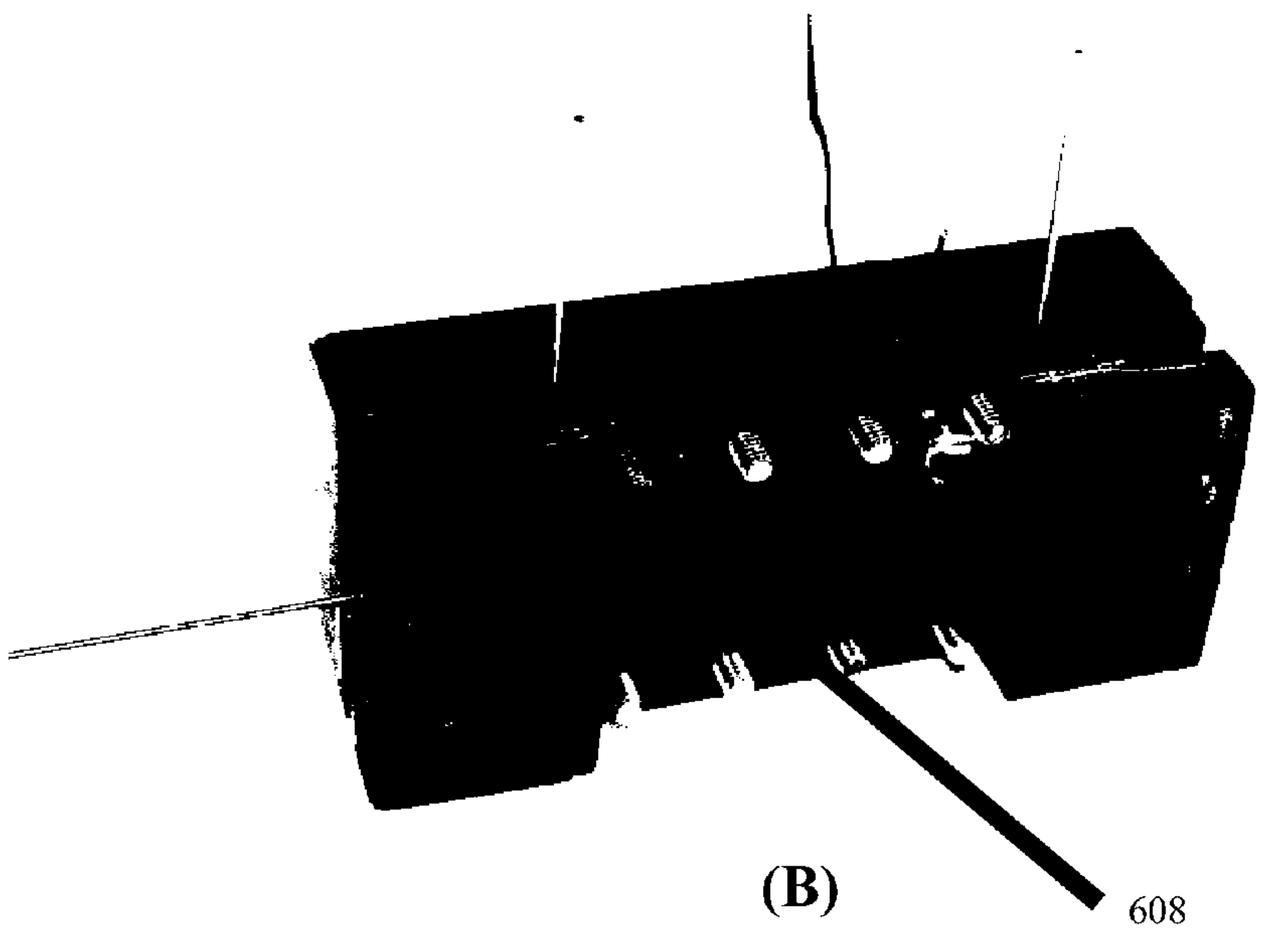


FIG. 5



(A)



(B)

FIG. 6

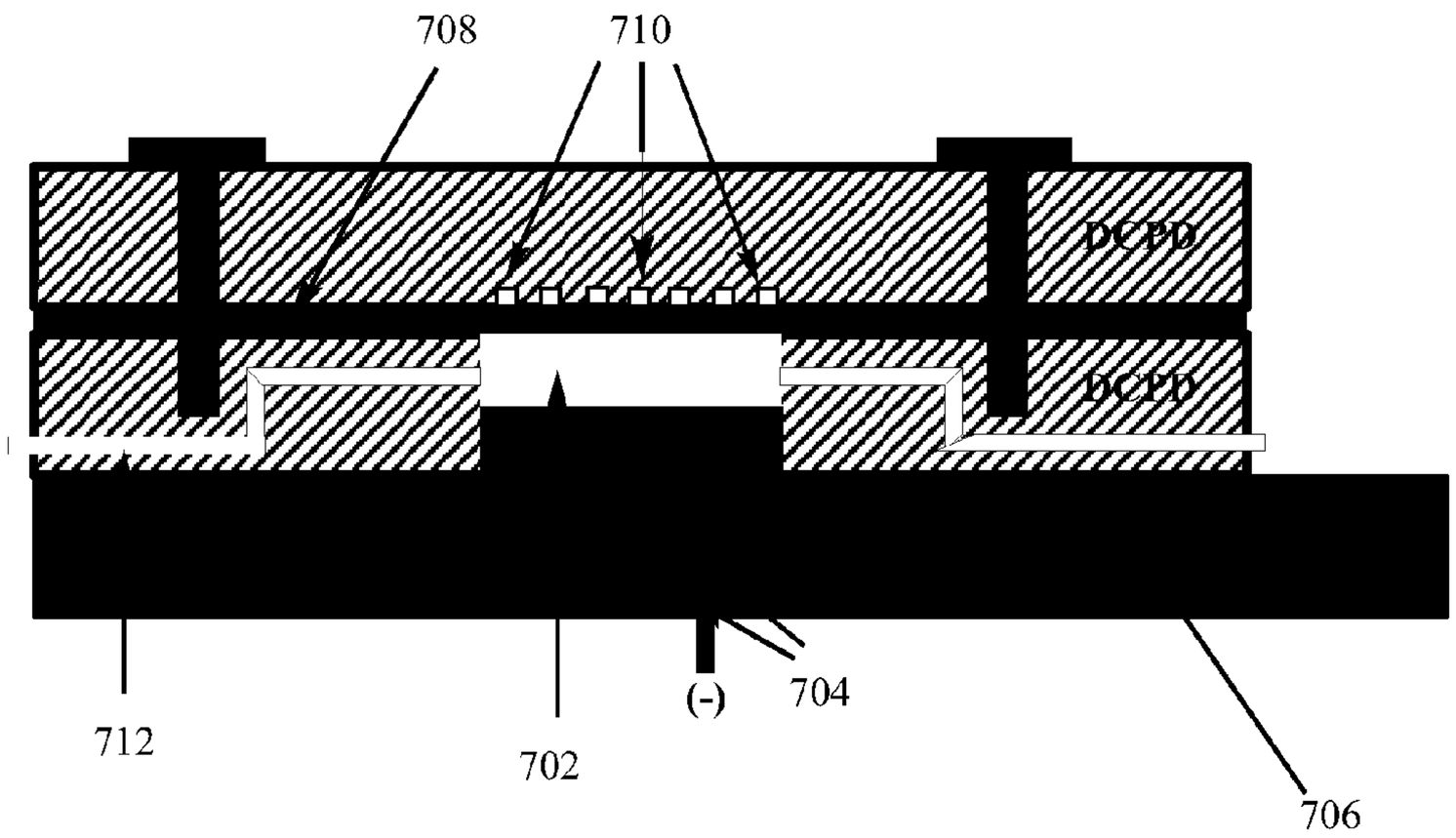
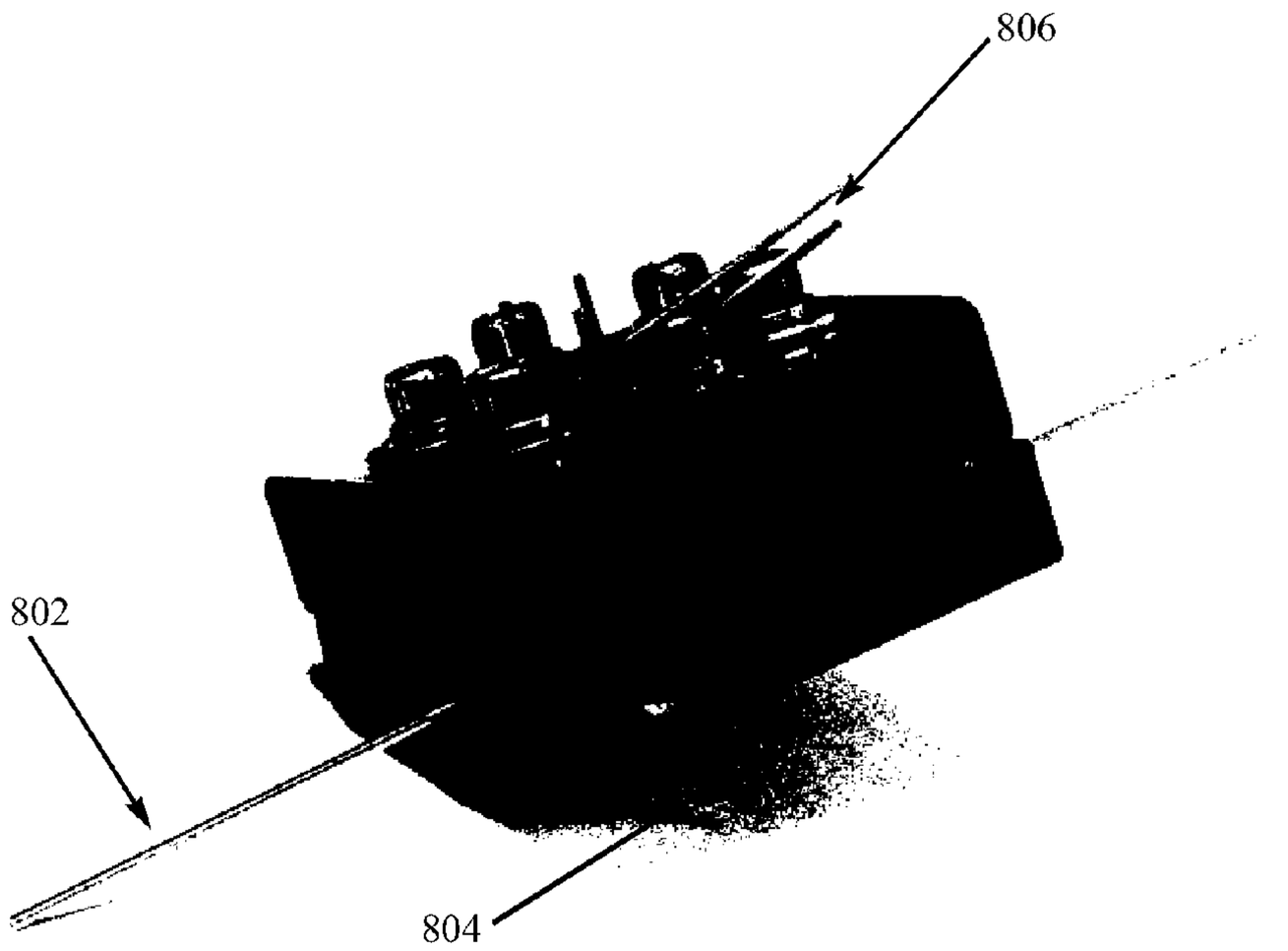
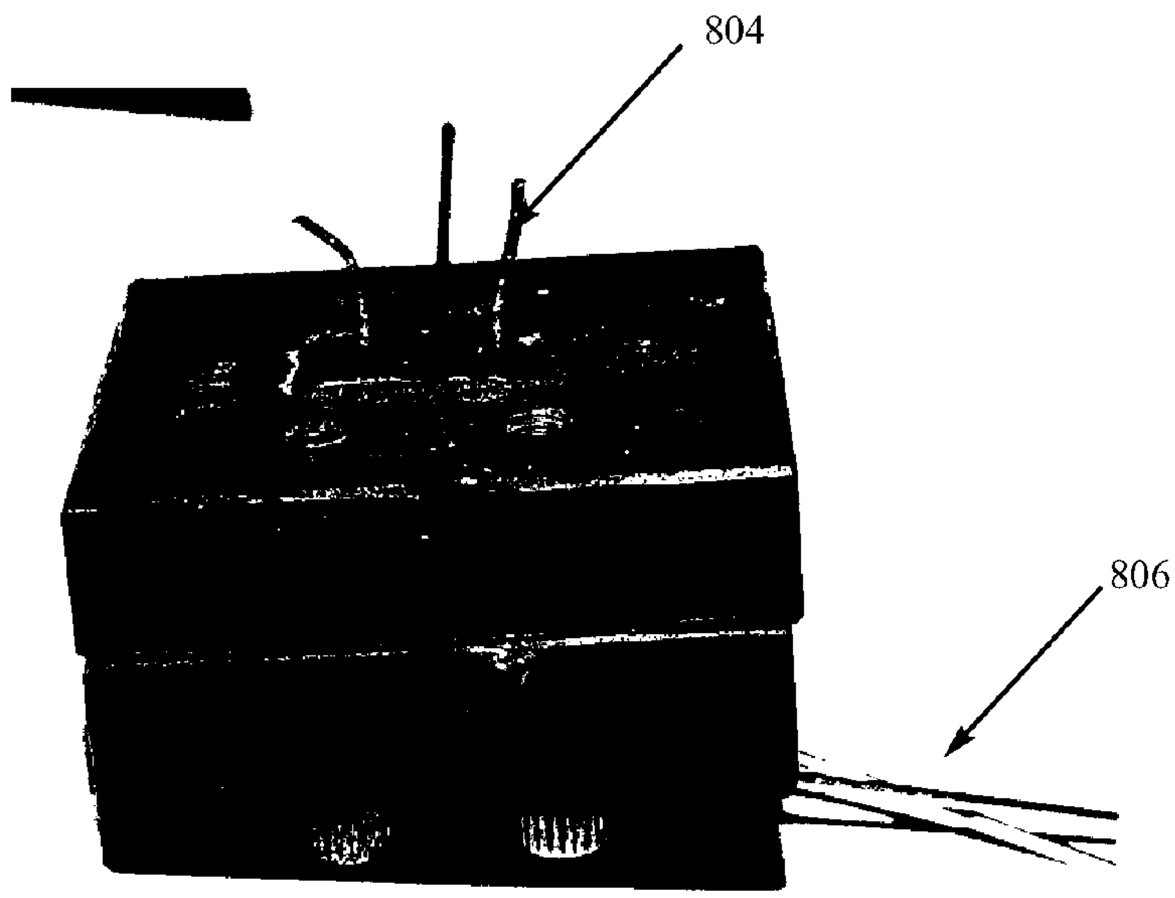


FIG. 7



(A)



(B)

FIG. 8

MICROFLUIDIC RADIOSYNTHESIS OF A RADIOLABELED COMPOUND USING ELECTROCHEMICAL TRAPPING AND RELEASE

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 60/950,976 filed Jul. 20, 2007, the contents of which is hereby incorporated in its entirety by reference.

FIELD OF THE INVENTION

[0002] The present invention relates generally to microfluidic devices and related technologies. More specifically, the invention relates to methods and devices for microfluidic radiosynthesis of radiolabeled compounds.

BACKGROUND OF THE INVENTION

[0003] This section is intended to provide a background or context to the invention that is recited in the claims. The description herein may include concepts that could be pursued, but are not necessarily ones that have been previously conceived or pursued. Therefore, unless otherwise indicated herein, what is described in this section is not prior art to the description and claims in this application and is not admitted to be prior art by inclusion in this section.

[0004] Microfluidic devices have been used for the preparation of a number of radiopharmaceutical compounds. These compounds may be used in medical imaging applications, such as Positron Emission Tomography (PET) systems, that create images based on the distribution of positron-emitting isotopes in the tissue of a patient. The isotopes are typically administered to a patient by injection of probe molecules that comprise a positron-emitting isotope, such as fluorine-18, covalently attached to a molecule that is readily metabolized or localized in the body or that chemically binds to receptor sites within the body. Microfluidic devices offer a variety of advantages over macroscopic reactors, such as reduced reagent consumption, high concentration of reagents, high surface-to-volume ratios, and improved control over mass and heat transfer. These devices are capable of processing small quantities of molecular probes, as well as expediting chemical processing that reduces the overall processing or cycle times, simplifies the chemical processing procedures, and at the same time, provides the flexibility to produce a wide range of probes, biomarkers and labeled drugs or drug analogs, inexpensively.

[0005] All known microfluidic reactors used for radiosynthesis reported to date have relied on ion exchange columns as their source of concentrated F-18. Release of F-18 from such columns requires aqueous solutions of K_2CO_3. With substitution reactions requiring anhydrous conditions, a solvent exchange procedure is necessary between the fluoride release and substitution steps. Most of the known microreactors, being of the flow-through type, perform the solvent exchange externally. Recently reported batch microreactors are capable of performing solvent exchanges. See, for example, C.-C. Lee, G. Sui, A. Elizarov, C. J. Shu, Y.-S. Shin, A. N. Dooley, J. Huang, A. Daridon, P. Wyatt, D. Stout, O. N. Witte, H. C. Kolb, N. Satyamurthy, J. R. Heath, M. E. Phelps, S. R. Quake and H.-R. Tseng, Science, 310, 1793, 2005. However, these processes have certain limitations because of the low permeability of the membranes to water vapor.

[0006] Recent developments have resulted in devices that are completely compatible with radiosynthesis in all regards except for the need to perform water evaporations across a membrane. Alternatively, the solvents can be evaporated without a membrane but with the risk of fluoride loss and with requirements of additional time and high temperatures, both of which have a negative effect on radiosynthesis. Electrochemical trapping of F-18 from cyclotron target water has been reported followed by release into an organic solution. See, for example, Hamacher, K.; Hirschfelder, T.; Coenen, H. H. Appl. Radiat. Isot. 2002, 56, 519. However, these techniques are not suitable for use in microfluidic devices since, for example, they are only applicable to standing solutions, which cannot be reduced to microliter volume, and suffer from long trapping times.

SUMMARY OF THE INVENTION

[0007] The present invention relates generally to microfluidic devices and related technologies. More specifically, embodiments of the present invention relate to trapping and release of radioactive isotopes inside a microreactor, a vial, a channel, or similar device, thus eliminating the need for azeotropic drying and several dead-end filling steps, as well as the necessity to move concentrated radioisotopes from one compartment of the device to another. In accordance with example embodiments of the present invention, radioisotope enrichment is carried out internally within a radiochemical synthesis chip, allowing faster and more robust operation. The disclosed methods and apparatus do not require an ion exchange column to trap the radioisotope, produce high radiochemical labeling yields, while providing significant increase in the device operational speed and reducing material stress, which results in prolonged device life. Non-exclusive examples of the radiolabeled compounds that may be prepared according to the process described herein include compounds selected from the group consisting of 2-deoxy-2-[^{18}F] fluoro-D-glucose ([^{18}F]FDG), 6-[^{18}F] fluoro-L-3,4-dihydroxyphenylalanine ([^{18}F]FDOPA), 6-[^{18}F] fluoro-L-meta-tyrosine ([^{18}F] FMT), 9-[4-[^{18}F] fluoro-3-(hydroxymethyl)butyl] guanine ([^{18}F]FHBG), 9-[(3-[^{18}F] fluoro-1-hydroxy-2-propoxy)methyl] guanine ([^{18}F]FHPG), 3-(2'-[^{18}F] fluoroethyl)spiperone ([^{18}F]FESP), 3'-deoxy-3-[^{18}F] fluorothymidine ([^{18}F]FLT), 4-[^{18}F] fluoro-N-[2-[1-(2-methoxyphenyl)-1-piperazinyl] ethyl]-N-2-pyridinyl-benzamide ([^{18}F]p-MPPF), 2-(1-{6-[(2-[^{18}F] fluoroethyl)(methyl)amino]-2-naphthyl}ethylidine)malononitrile ([^{18}F]FDDNP), 2-[^{18}F] fluoro-α-methyltyrosine, [^{18}F] fluoromisonidazole ([^{18}F] FMISO) and 5-[^{18}F] fluoro-2'-deoxyuridine ([^{18}F]FdUrd).

[0008] One embodiment of the present invention relates to a method for the synthesis of a radiolabeled compound comprising a radioactive isotope using a microfluidic device, the method comprising: introducing a composition comprising a radioactive isotope to the microfluidic device, electrochemically trapping the radioactive isotope using an electrode, adding a composition comprising a reactant to the reactor, electrochemically releasing the radioactive isotope from the electrode, and contacting the reactant with the radioactive isotope to form the radiolabeled compound. While the various aspects of the present application are applicable to any radioactive (or non-radioactive) material with dilute charged ions, in one aspect, the radioactive isotope is F-18. In a different aspect, the reactant comprises mannose triflate. In a particular variation, the composition comprising the reactant is mannose triflate/K_2CO_3/K222; and MeCN is used as a solvent. In

a different aspect, the reactant is N-dimethoxytrityl-5'-O-dimethoxytrityl-3'-O-nosyl-thymidine (also known as "BOC-BOC-Nosyl") and the radiolabeled compound is FLT.

[0009] According to another aspect of present application, a step of blowing an inert gas and a heating of the reactor is performed to dry the trapped F-18 before adding the composition comprising the reactant to the reactor. In one particular variation, the inert gas is nitrogen or argon. In a different aspect, the reactor is a coin-shaped reactor in a radio-synthesis chip. In yet another aspect, the trapping and releasing is carried out by one or more electrodes. In one exemplary aspect, the electrodes are located in or on at least one of a floor, a ceiling, and a side of the reactor or combinations thereof. In different aspect, the electrodes are located in a channel in fluid communication with the reactor. According to another aspect, the electrodes are non-metal electrodes. In one exemplary aspect, the electrodes are made of a material selected from the group consisting of a graphite, a composite graphite, and silicon and combinations thereof. In a different aspect, the electrodes are graphite polymer electrodes. In yet another aspect, the polymer is selected from the group consisting of a DCPD, a polyethylene, and a glass. In one aspect, the electrodes are metal electrodes while in a different aspect, the electrodes are covered with a protective coating.

[0010] According to another aspect of the present application, at least one of the electrochemical trapping and the releasing is carried out in accordance with an on-chip feature. This feature is part of the microfluidic chip but is located outside of the reaction chamber. In a different aspect, at least one of the electrochemical trapping and the releasing is carried out in accordance with an in-reactor feature. This feature is located inside of the reaction chamber. According to yet another aspect, the trapping, the releasing and the radiolabeled compound formation are carried out within the same microreactor. In another aspect, a radiochemical labeling yield of at least 55% is produced. In one aspect, the yield is 55%, 65%, 75%, 85%, 95% or 99%. In a different aspect, the radioactive isotope is released into a non-aqueous solution. In yet another aspect, the non-aqueous solution is an organic solution. In one variation, the organic solution comprises at least one of acetonitrile, THF, dichloromethane, DMF, acetone, alcohols such as ethanol, methanol and t-amyl alcohol, DMSO, fluorous solvents, and mixtures thereof. In another aspect, the reaction to form the radiolabeled compound is a substitution reaction. In a different aspect, the releasing is carried out simultaneously or concurrent with the substitution reaction. In yet another aspect, the reactant is in a solvent. According to another aspect, the electrochemical trapping is carried out in one or more passes, and in another aspect, the electrochemical releasing is carried out in accordance with one or more reversals of a voltage bias.

[0011] Another embodiment of the present application relates to a method for the synthesis of a radiolabeled compound using a microfluidic trap-release device, the method comprising introducing a composition comprising a radioactive isotope to the device, electrochemically trapping of the radioactive isotope, adding a composition comprising a reactant to the device, and electrochemically releasing the radioactive isotope into the trap-release device. In one aspect, the trap-release device is a radiochemical microreactor.

[0012] Another embodiment of the present application relates to a microfluidic radiosynthesis apparatus, comprising a first electrode configured to electrochemically trap a radioactive isotope, a chamber, and a second electrode configured to electrochemically release the radioactive isotope into the chamber. In one aspect, the apparatus is further configured for preparing a radiolabeled compound by performing a reaction of a reactant with the radioactive isotope. In a different aspect, the radioactive isotope is F-18. In yet another aspect, the chamber is filled with a composition comprising a reactant. In one aspect, the reactant comprises mannose triflate. According to a different aspect, the reactant is N-dimethoxytrityl-5'-O-dimethoxytrityl-3'-O-nosyl-thymidine and the radiolabeled compound is FLT. In another aspect, the apparatus is further configured to blow an inert gas and heat the chamber before adding the composition comprising the reactant. In yet another aspect, the chamber is part of a coin-shaped reactor in a radio-synthesis chip. In a different aspect, the electrodes are located in or on at least one of a floor, a ceiling, and a side of the chamber or combinations thereof, while in another aspect, the electrodes are located in a channel in fluid communication with the chamber.

[0013] In another aspect of the apparatus, the electrodes are non-metal electrodes. In a different aspect, the electrodes are made of a material selected from the group consisting of graphite, a composite graphite, and silicon and combinations thereof. In yet another aspect, the electrodes are graphite polymer electrodes. According to another aspect, the polymer is selected from the group consisting of a DCPD, a polyethylene, and a glass, and in yet a different aspect, the electrodes are metal electrodes. In another aspect, the electrodes are covered with a protective coating, and according to a different aspect, at least one of the first and the second electrodes is configured as an on-chip feature or as an in-reactor feature. In one aspect, the electrochemical trapping is carried out in one or more passes, while in a different aspect, the electrochemical releasing is carried out in accordance with one or more reversals of a voltage bias.

[0014] In one aspect of the apparatus, the trapping, the releasing and the radiolabeled compound formation are carried out within the same microreactor. In another aspect of the apparatus, the radiochemical labeling yield of at least 55% is produced. In certain variations, the yield is 55%, 65%, 75%, 85%, 95% or 99%. In another variation, the radioactive isotope is released into a non-aqueous solution. In another variation, the non-aqueous solution is an organic solution, and the reaction to form the radiolabeled compound is a substitution reaction. In a particular variation, the releasing is carried out simultaneously with the substitution reaction. In one variation, the reactant is in a solvent.

[0015] These and other advantages and features of various embodiments of the present invention, together with the organization and manner of operation thereof, will become apparent from the following detailed description when taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] Embodiments of the invention are described by referring to the attached drawings, in which:

[0017] FIG. **1** illustrates exemplary steps for synthesis of a radioactive isotope using an ion exchange column;

[0018] FIG. **2** illustrates exemplary steps for synthesis of a radioactive isotope in accordance with an embodiment of the present application;

[0019] FIG. **3**(A) illustrates an exemplary apparatus used for electrochemical trapping and release in a vial in accordance with an embodiment of the present application;

[0020] FIG. **3**(B) illustrates an exemplary apparatus used for on-chip electrochemical trapping and release in accordance with an embodiment of the present application;

[0021] FIG. **4**(A) illustrates a cross-sectional view of an exemplary trap-release chip in accordance with an embodiment of the present application;

[0022] FIG. **4**(B) illustrates a top view of an exemplary coin-chamber apparatus in accordance with an embodiment of the present application;

[0023] FIG. **4**(C) illustrates a top view of an exemplary channel-based apparatus in accordance with an embodiment of the present application;

[0024] FIG. **5**(A) illustrates an exemplary coin-shaped microreactor apparatus in accordance with an embodiment of the present application;

[0025] FIG. **5**(B) illustrates a top view of the bottom section of the exemplary apparatus of FIG. **5**(A) in accordance with an embodiment of the present application;

[0026] FIG. **6**(A) illustrates a top view of an exemplary electrochemical trap-release channel apparatus in accordance with an embodiment of the present application;

[0027] FIG. **6**(B) illustrates a bottom view of the exemplary apparatus of FIG. **6**(A) in accordance with an embodiment of the present application;

[0028] FIG. **7** illustrates a cross-sectional view of an exemplary trap-release chip in accordance with an embodiment of the present application;

[0029] FIG. **8**(A) illustrates a top and side view of an exemplary electrochemical trap-release chip apparatus in accordance with an embodiment of the present application; and

[0030] FIG. **8**(B) illustrates a bottom and side view of the exemplary apparatus of FIG. **8**(A) in accordance with an embodiment of the present application.

DETAILED DESCRIPTION OF THE CERTAIN EMBODIMENTS

[0031] In the following description, for purposes of explanation and not limitation, details and descriptions are set forth in order to provide a thorough understanding of the present invention. However, it will be apparent to those skilled in the art that the present invention may be practiced in other embodiments that depart from these details and descriptions.

[0032] A "microfluidic device" or "microfluidic chip" or "synthesis chip" or "chip" is a unit or device that permits the manipulation and transfer of small amounts of liquid (e.g., microliters or nanoliters) into a substrate comprising micro-channels and micro-compartments. The device may be configured to allow the manipulation of liquids, including reagents and solvents, to be transferred or conveyed within the micro channels and reaction chamber using mechanical or non-mechanical pumps. The device may be constructed using micro-electromechanical fabrication methods as known in the art. Alternatively, the devices can be machined using computer numerical control (CNC) techniques. Examples of substrates for forming the device include glass, quartz, silicon, ceramics or polymer. Such polymers may include PMMA (polymethylmethacrylate), PC (polycarbonate), PDMS (polydimethylsiloxane), DCPD (polydicyclopentadiene), PEEK and the like. Such device may comprise columns, pumps, mixers, valves and the like. Generally, the microfluidic channels or tubes (sometimes referred to as micro-channels or capillaries) have at least one cross-sectional dimension (e.g., height, width, depth, diameter), which by the way of example, and not by limitation, may range from 1,000 μm to 10 μm. The micro-channels make it possible to manipulate extremely small volumes of liquid, for example on the order of nL to μL. The micro reactors may also comprise one or more reservoirs in fluid communication with one or more of the micro-channels, each reservoir having, for example, a volume of about 5 to about 1,000 μL.

[0033] The term "radioactive isotope" refers to isotopes exhibiting radioactive decay (e.g., emitting positrons). Such isotopes are also referred to in the art as radioisotopes or radionuclides. Radioactive isotopes or the correspond ions, such as the fluoride ion, are named herein using various commonly used combinations of the name or symbol of the element and its mass number and are used interchangeably (e.g., ^{18}F, 18F, [F-18], fluorine-18). Exemplary radioactive isotopes include I-124, F-18, C-11, N-13, and O-15, which have half-lives of 4.2 days, 110 minutes, 20 minutes, 10 minutes, and 2 minutes, respectively. In one variation, the term FLT precursor may be used to refer to "N-dimethoxytrityl-5'-O-dimethoxytrityl-3'-O-nosyl-thymidine" (also known as "BOC-BOC-Nosyl").

[0034] "Column" means a device that may be used to separate, purify or concentrate reactants or products. Such columns are well known in the art, and include, but are not limited to, ion exchange and affinity chromatography columns. A "flow channel" or "channel" means a microfluidic channel through which a fluid, solution, or gas may flow. It is also a channel through which vacuum can be applied. By the way of example, and not by limitation, such channels may have a cross section of about 0.1 mm to about 1 mm. By way of example, and not by limitation, the flow channels of embodiments of the present application may also have a cross section dimension in the range of about 0.05 microns to about 1,000 microns. The particular shape and size of the flow channels depend on the particular application required for the reaction process, including the desired throughput, and may be configured and sized according to the desired application.

[0035] The term "electrochemical trapping" refers to of the process of separating charged ions from a solution by applying a voltage across a pair of electrodes that are in contact with the solution, thereby causing some, or substantially all, of the charged ions to be deposited onto, accumulated on, or collected in the vicinity of one of the electrodes. The term "electrochemical releasing" refers to the process of releasing the trapped ions that have been deposited onto, accumulated on, or collected in the vicinity of one of the electrodes, by applying a voltage across the pair of electrodes that are in contact with a solution. The voltage applied to carry out the electrochemical releasing, may, for example, be in the opposite direction of the voltage applied to effect the electrochemical trapping.

[0036] FIG. **1** outlines a series of exemplary steps involved in the synthesis of F-18 using a microfluidic device, from taking F-18 from cyclotron target water to fluorination reaction in a coin-shaped reactor chip using an ion exchange column. In Step **1**, with valves **102** and **108** closed and valves **104** and **106** open, target water is passed through the ion exchange cartridge **110** to trap the F-18 out of a dilute solution. In Step **2**, with valves **104** and **106** closed and valves **102** and **108** open, K_2CO_3 is released into a concentrated solution that enters the reactor. After that delivery has taken place, the valve **108** controlling the F-18 inlet closes, and in Step **3** water evaporation takes place. This drying step requires a significant amount of processing time because of the need to move water vapor across a membrane. In Step **4**, K222/MeCN

solution is delivered from channel **112**. This procedure also requires a significant amount of processing time because of dead end filing. In Step **5** drying, solvents are evaporated, leaving behind a residue containing [F-18]KF/K222 complex. This drying step also consumes a significant amount of processing time because of the need to move solvent vapors across a membrane, and the need for complete dryness. In Step **6**, the precursor or reactant (such as mannose triflate) is delivered to the reactor through channel **116**. This step is also time consuming because of dead end filling. Finally, in Step **7**, the fluorination reaction takes place.

[0037] Even under the best performance conditions, the number of required steps (i.e., seven steps) result in a slow or lengthy process, and further creates many points of potential failure. Furthermore, all steps are slow since they involve flow resistance induced by either the need to pass the solutions through one or more columns, or dead end filling of the reactor displacing gases across the membrane. In particular, the operation illustrated in FIG. **1** also involves two evaporation steps, both of which are slow since the vapor has to be transported across the membrane. In the case of water evaporation, most membranes are readily saturated by water vapors that blocks further gas passage, making it difficult to complete the evaporation within any reasonable period of time. This is the major single obstacle to efficient operation of chips that utilize membranes. Chips without membranes have been designed and tested. However, they face the risk of losing valuable materials into exhaust lines. Even if such risk is mitigated, it is still critically important to remove even minimal traces of water in order to assure efficient radio fluorinations. In addition, both types of devices require heating during evaporation steps, which may easily cause degradation of phase transfer reagents, such as Kryptofix2.2.2.

[0038] In a particular aspect, water evaporation can be avoided altogether if F-18 can be trapped out of target water and released into dry MeCN solution in a concentrated manner. Such operation can be made possible by electrochemical trapping and release. As reported by Hamacher et. al., F-18 can be extracted from a reservoir of target water onto a graphite positive electrode, where Platinum is used as the negative electrode. It can be released into ion-rich organic solution by reversing the bias. However, these systems cannot be adapted for use with a batch microfluidic device for a variety of reasons. For example, the volume incompatibilities (e.g., 2.5 mL versus 50 uL) prevent the use of conventional trapping and/or release techniques in microfluidic devices. Furthermore, since such techniques only work with standing solutions and cannot be used to trap F-18 out of a moving solution, it is not possible to simply reduce the size of such devices. On the other hand, a microfluidics approach, in accordance with the various embodiments of the present application, allows the distance between the electrodes to be made very small both on the absolute scale (e.g., tens to hundreds of microns) and on relative scale (i.e., compared to path length of the fluid). These features allow very efficient trapping of F-18 out of a rapidly moving solution. For instance, the trapping from a moving solution, in accordance with exemplary techniques and devices of the present invention, may be carried out in less than one minute, as opposed to a five-minute trapping time that is typical for the conventional systems. Additionally, the various embodiments of the present invention allow reactions to take place in much more concentrated solutions, resulting in higher yields and shorter reaction times. According to other features of the various methods and apparatus of the present invention, any F-18 that was not initially trapped, may be passed through the microfluidic device one or more times in order to allow trapping of additional F-18. This multiple-pass and/or recirculation capability enables 100% trapping of F-18. Additionally, example embodiments of the microfluidic methods, systems and apparatus of the present application, enable a precise temperature control over a wide range of temperatures, which is crucial for most radiosynthesis reactions. An example device constructed in accordance with the embodiments of the present application has demonstrated the capability for trapping high percentages of F-18 out of various volumes of target water (e.g., 100 μL, 500 μL, 1 mL, 2 mL, 5 mL, 10 mL) in several seconds. These results are already faster than the ion exchange cartridge trapping approach.

[0039] FIG. **2** illustrates a series of exemplary steps for electrochemical trapping and release of F-18 in a fully operational synthesis chip in accordance with an embodiment of the present application. As illustrated in FIG. **2**, both a positive electrode **202** and a negative electrode **204** are placed within a reactor **200**. In Step **1**, electrochemical trapping of F-18 on the inner surface or floor of the reactor **200** takes place. Step **1** may be carried out as a fast unobstructed flow-through of dilute $^{18}F^-$ in $H_2{}^{18}O$, followed by blowing N_2 while heating to dry the trapped fluoride. As the dilute solution of F-18 flows through the reactor, F-18 gets trapped efficiently on the high surface area of the positive electrode **202**. Upon passage of target water, the reactor **200** can be flushed with N_2 for drying purposes. If the dryness is not achieved to a desired level, the reactor **200** can be flushed or rinsed, for example, by MeCN, to remove the residual moisture, thus expediting the completion of this step and avoiding heating altogether when necessary. In Step **2**, the reactor **200** is filled with the solution. In Step **3**, electrochemical release of F-18 takes place.

[0040] As the reactor **200** is filled with, for example, K_2CO_3/K222/mannose triflate/MeCN solution, it has sufficient ionic strength for the release of F-18 upon reversing the bias. Since F-18 gets released into the triflate solution it engages in reaction immediately. The release procedure, however, does not have to be immediate. The release can be controlled to be completed within the time period allowed for the fluorination, thus maximizing its yield. On the other hand, the overall process is expedited since the fluorination reaction is not postponed until the end of release and [F-18] fluoride transfer. As evident from the comparison of FIGS. **1** and **2** in the presently described process, five relatively slow steps may be replaced by one fast flow-through step, which involves only one dead-end filling process. Placing both electrodes (i.e., the positive electrode **202** and the negative electrode **204**) inside the reactor **200** generates two more advantages: (a) it eliminates the process for moving the concentrated F-18 from one compartment to another, and (b) it eliminates extra valves necessary for column operation. Note that the procedures involving F-18 transport are associated with noticeable radioactivity losses when very small volumes are involved. This loss is partly due to competing side reactions with system components that are exposed to F-18 before contacting with the triflate. In addition, varying percentages of F-18 may be inevitably lost in transit between the trap/release device and the synthesis vessel or device, if these entities are separate. With the speed of operation being one of the most critical issues in radiosynthesis, reducing the number of steps from seven to three, and eliminating several inefficient or high risk

steps, leads to a dramatic improvement in reducing the process cycle time, radiochemical yield of the desired product and robustness of the chip operation. Experimental results have confirmed yields of at least 55%. Some exemplary yields obtained from the experimental results include 10%, 40%, 55%, 65%, 75%, 85%, 95% and 99%.

[0041] In an alternative embodiment, an electrochemical trapping and release device may be coupled with the reactor but not as part of the reaction chamber itself. Although this arrangement involves the conveyance or transfer of F-18 to the reaction chamber, the advantage of release into an organic solution still remains viable, and the electrodes are not subject to heating that takes place during the reaction stages inside the reaction chamber. Meanwhile, the distance between the trap/release unit and the reactor placed within the same chip is minimal and therefore losses of F-18 in transit or during a transfer process is also minimized.

[0042] FIG. **3**(A) illustrates an example vial containing target water that is used for evaluation of electrodes made from different materials for the trapping/release applications in accordance with various embodiments of the present application. FIG. **3**(B) illustrates an example microfluidic chip that is implemented with trapping and release capabilities in accordance with various embodiments of the present application. Both the vial and the chip of FIGS. **3**(A) and **3**(B) are example embodiments of trap-release devices that may be implemented in accordance with the various embodiments of the present application. The following provides an exemplary set of test results for two different sets of electrodes:

[0043] Copper electrodes may provide up to 75% trapping (500V, and 5 min), up to 79% release into 0.5M $KHCO_3$ solution (500V, and reverse bias pulsing). Some F-18 may be released into pure water, and significant copper contamination of solution may occur.

[0044] Graphite and graphite/DCPD composite electrodes may provide up to 97% trapping, up to 96% release into 0.5M $KHCO_3$ solution. No solution contamination may occur. Graphite/DCPD can be molded/machined into very complex and precise shapes.

[0045] Experimental results indicate that copper fluorides are significantly less reactive and are difficult to solubilize in organic solvents using Kryptofix2.2.2. Graphite is inert in this regard but is fragile, which makes machining and molding of the electrodes difficult. Furthermore, it may not be suitable for exposure to high pressures. In accordance with an example embodiment of the present application, these deficiencies may be overcome by using a composite material comprised of graphite and a polymer, such as polydicyclopentadiene (DCPD), as electrode material. For example, a composite graphite and DCPD material exhibits conductivity that is comparable to that of pure graphite. When the electrodes are fabricated using such composite material, they produce trapping and release efficiencies that are comparable to those of pure graphite electrodes of the same size and shape. Other exemplary material which may be used in construction of composite electrodes include, but are not limited to, graphite blends with glass, quartz or other polymer material such as PMMA (polymethylmethacrylate), PC (polycarbonate), PDMS (polydimethylsiloxane), PEEK and the like. Accordingly, the electrodes of the various embodiments of the present application, may be advantageously fabricated using such composite material since they can be easily machined and molded, are thermally and chemically resistant, and are very tough. See, for example, U.S. Pat. No. 7,339,006, the disclosure of which is incorporated herein by reference in its entirety.

[0046] Two different trapping processes may be used to effect the trapping and release of F-18. In one embodiment, bare electrodes may drive a current through the solution. This approach relies on $^{18}F^-$ being attracted to the positive electrode, where it gets attached to the electrode forming ionic bonds. Using this method, and given enough time, substantially all fluoride may be taken out of the solution since there is no equilibrium to maintain and no repulsion. When the bias is reversed, adsorbed [F-18]F^- is released into the solution. Again, given sufficient amount of time, substantially all F-18 may be released. Experimental results have confirmed proper release of suitable F-18, and its reactivity towards mannose triflate. For example, vial experiments have demonstrated trap and release of F-18, and successful reaction with acetylated mannose triflate, producing, for example, up to 60% yields of acetylated 2-deoxy-2-fluoroglucose. In these experiments, Graphite/DCPD composite electrodes were used to trap F-18 from target water, followed by drying and immersion into mannose triflate/K_2CO_3/K222/MeCN solution and heating (in a vial), resulting in 55-60% fluorination yield (based on released fluoride). This approach has been further confirmed experimentally using on-chip implementations.

[0047] In another exemplified embodiment of the present application, the trapping and release of F-18 may be carried out using insulated electrodes so that F-18 is attracted to the positive electrode by the electric field alone. This approach is advantageously designed to assure that F-18 does not undergo any transformations and/or reactions between the trapping and the release stages, and that it does not pick up any counter ions (such as Cu^{2+}) (or to minimize any such transformations or reactions) that may hinder fluorination reactions. Using insulated electrodes and the electric field, $^{18}F^-$ is attracted towards the positive electrode and is held on its surface electrostatically until the bias is reversed. This method involves high concentration aggregation of $^{18}F^-$ on the positive electrode surface. Concentration of negative charges may start to repel further fluoride adsorption at a certain point when equilibrium is reached since the attraction is much weaker than with bare electrodes. The adsorption of F-18, however, may be improved by increasing the surface area of the positive electrode. This approach has been demonstrated experimentally using both test vials and on-chip implementations.

[0048] FIG. **4**(A) illustrates a cross-sectional view of an example microfluidic chip for implementing a trap/release procedure in accordance with an embodiment of the present application. The example chip of FIG. **4**(A) is specially designed to allow evaluation of the trapping efficiency separately from other variables, without performing subsequent reactions. In addition, it allows a wide range and variations of shape and volume of the trapping feature to be studied. As illustrated in FIG. **4**(A), the positive electrode **406** is positioned in the floor of trapping chamber/channel **402** and the negative electrode **404** is positioned in the ceiling of the trapping chamber/channel **402**. FIG. **4**(A) also illustrates the loading channel **412**, the insulating/sealing gasket **408** that is used to ensure proper sealing between the top and bottom sections of the chip, and the screws **410** that are used to firmly hold the top and bottom sections of the chip together. Once on-chip trapping is optimized, the feasibility of an in-reactor trap integration may be evaluated. The exemplary trap chip

design that is presented in FIG. **4**(A) maximizes the exposure of electrodes to the solution while keeping them insulated from one another. In addition, the chip is sufficiently sealed to prevent leaks. This design has been implemented in a chip, such as the exemplary device that is illustrated in FIG. **3**(B). In one exemplary embodiment, both electrodes are constructed using aluminum, with the bottom electrode being a machined block and the top electrode being foil pressed between DCPD and the soft gasket. The same architecture may be implemented to make devices with coin-shaped chambers, as well as long channel trap devices. FIG. **4**(B) illustrates a top view of a coin-chamber based device, and FIG. **4**(C) illustrates a top view of a channel based device.

[0049] In another example embodiment, both electrodes may be constructed using a graphite-DCPD blend. FIGS. **5**(A) and **5**(B) illustrate one such exemplary chip with a coin-shaped reactor **502** that has been successfully fabricated and tested. This configuration is comprised of two sections: a top section **504** and a bottom section **506** that are firmly held together using a plurality of screws **508** and a thin gasket around the reactor. A coin-shaped reactor **502** is located within the center of the chip assembly, and graphite-DCPD electrodes **510** are placed in the floor and ceiling of the reactor. As depicted in FIG. **5**(A), the two electrodes **510** protrude from the top and the bottom sections of the assembled chip. In FIG. **5**(B), the bottom section of the chip **506** is illustrated, along with liquid ports **512**, a reaction chamber **502** (e.g., 250 μm deep), and the electrode **510** that is connected to the floor of the reaction chamber **502**. The same architecture may be implemented to make devices with a long channel trap, such as the one illustrated in FIGS. **6**(A) and **6**(B). FIG. **6**(A) illustrates the top view of an electrochemical trap with a 4-cm channel, with liquid ports **604**, electrode leads **602** and a valve actuator **606** clearly visible. In FIG. **6**(B), the bottom view of the same device is depicted, with the embedded graphite electrodes **608** clearly visible.

[0050] As compared to coin-shaped trap chips, the chips with long channel trap configurations, such as the ones illustrated in FIGS. **4**(C), **6**(A) and **6**(B), have the advantage of having a larger surface-area-to-volume ratios, which allow the solution to remain in contact with the electrodes for a longer period of time, thus leading to trapping efficiencies that are far superior to those of coin chambers. On the other hand, coin-shaped chips have the following advantages: (a) their evaluation allows easy transformation to in-reactor trapping, (b) such test devices can be easily fabricated using existing parts, and (c) they do not involve transferring of concentrated F-18 solutions. Additionally, if single-pass trapping is not efficient enough, the F-18 solution can be passed through the trap multiple times until all F-18 has been extracted. Similarly, the efficiency of release may be improved by reversing the bias several times in order to release all F-18, even that portion that is adsorbed onto the new positive electrode (i.e., the negative electrode during trapping). As noted earlier, in both the long channel trap and coin-shaped designs metal electrodes may be replaced by a composite material such as graphite/DCPD.

[0051] In accordance with another example embodiment, in certain configurations where the coin-reactor does not demonstrate the desired efficiency, the trapping device may be separated from the radio-synthesis micro-reactor or the entire chip. The advantage of such an arrangement is that the reactor operation is not jeopardized by the integration of electrodes, and that of the trap is not jeopardized by high temperatures and various reagents used in the reaction chamber. However, in this configuration, F-18 may have to be released with extremely high efficiency to make its transport from one place to the next feasible. In another embodiment, in order to increase the trapping efficiency in a coin reactor or a channel, multiple passes of the same F-18 solution may be performed. This technique may further minimize the path length and allow easier integration of electrodes. In yet another embodiment, electrochemical trapping and release may be carried out from one solution into another, where the two solutions form a laminar flow in a microchannel.

[0052] FIG. **7** illustrates an alternative design for an in-reactor trapping process in accordance with an example embodiment of the present application. As illustrated in FIG. **7**, one electrode, for example the positive electrode **706**, as well as the other electrode, for example, the negative electrode **704**, are positioned in the floor of the trapping chamber/reactor **702**, with the positive electrode **706** having a significantly larger surface area than the negative electrode **704**. FIG. **7** also illustrates the loading channel **712** and the insulating/sealing gasket **708** to ensure proper sealing between the top and bottom sections of the chip. The positive electrode **706** may be a block similar to the configuration shown in FIG. **4**(A), but the negative electrode **704** may be constructed by drilling a hole in the positive electrode block **706** that is filled with, for example, a DCPD-insulated negative electrode wire. This configuration allows the current to be still driven through the solution while clearing the top surface of the reactor for implementation of functional vents **710**. In a membrane-free arrangement, this configuration is still advantageous since it allows the vents to be located in the ceiling, where they do not touch the liquid within the reaction chamber. In addition, the transparent reactor ceiling allows monitoring of the reaction chamber and progress tracking. In an in-reactor trapping process, this design allows F-18 to react immediately upon release, and allows residual F-18 to be released after the reaction has started. FIG. **8** illustrates an exemplary trap with a 5-mm channel that has been successfully fabricated and tested in accordance with design principles that are depicted in FIG. **7**. FIG. **8**(A) illustrates a top and side view of the chip with a liquid port **802**, electrode leads **804** and vent ports **806** clearly visible. FIG. **8**(B) illustrates a bottom-and-side view of the same chip with electrode leads **804** and vent ports **806** clearly visible. It should be noted that while FIG. **4** and FIG. **7** illustrate two exemplary electrode configurations, other electrode geometries may be implemented in accordance with various embodiments of the present application. For example, both or either electrodes may be placed within any one of the following elements: floor, ceiling, and sides of the reactor, as well as the channels leading up to the reactor.

[0053] Table 1 illustrates the various exemplary results obtained from evaluating F-18 trapping and release using vial experiments.

TABLE 1

Exemplary Trapping and Release Results Using Vial Experiments

Electrode Material	Test Conditions	Results
Insulate Copper	In-solution; No voltage applied	0.2% trapping by absorption
	Applied 100 Volts for 5 min	1.2% trapping
	Applied 500 Volts for 5 min	1.1% trapping

TABLE 1-continued

Exemplary Trapping and Release Results Using Vial Experiments

Electrode Material	Test Conditions	Results
Bare Copper	Applied 100 Volts for 5 min	10% trapping
	Applied 500 Volts for 5 min	75% trapping
	Reverse bias to release into MeCN K222 solution, 500 Volts for 5 min	1.7% release
	Pulsing voltage to release into $KHCO_3$ solution	79% release
Insulated Graphite	Applied 500 Volts for 5 min	2.3% trapping
Bare Graphite	Applied 500 Volts for 5 min	54% trapping
	Reverse bias to release into K_2CO_3 aqueous solution	No release; too conductive, power shuts off
	Reverse bias to release into pure water with 500 Volts	51% release
	Pulsing voltage; release into 0.5M $KHCO_3$ solution	96% release
Insulated Graphite/DCPD	Applied 500 Volts for 5 min	1.06% trapping
Bare Graphite/DCPD	Applied 500 Volts for 5 min	97% trapping

[0054] Chemistry validation was conducted as follows: trapping was carried out using 100V for 5 min using Graphite/DCPD electrode, followed by drying with hot air and MeCN, followed by release into K222/K_2CO_3/MeCN solution, and followed by addition of acetylated mannose triflate (upon removal of electrodes). The results indicate 55-60% radiochemical yield of acetylated 2-deoxy-2-fluoroglucose as calculated from released fluoride.

[0055] Table 2 illustrates the various exemplary results obtained from evaluating F-18 trapping and release using chip experiments.

TABLE 2

Exemplary Trapping and Release Results Using Chip Experiments

Electrode Material	Test Conditions	Results
Insulated Electrodes	30 μm gasket covering the top electrode; 2-Volt operation	0-0.2% trapping
Bare graphite	100 V trapping, single pass	20%
Bare Aluminum	10 μL/sec flowing solution with 200-Volt operation	92% trapping

[0056] In addition, graphite electrodes with (a) 5 mm channel, (b) 4 cm channel, and (c) coin-reactor with full top and bottom surfaces have been successfully fabricated and tested.

[0057] All references cited herein are incorporated by reference as if each had been individually incorporated by reference in its entirety. In describing embodiments of the present invention, specific terminology is employed for the sake of clarity. However, the invention is not intended to be limited to the specific terminology so selected. Nothing in this specification should be considered as limiting the scope of the present invention. All examples presented are representative and non-limiting. For instance, while one exemplary radioactive isotope may have been described in connection with the various embodiments of the present application, it is understood that other radioactive isotopes, as well as non-radioactive material, may be used in connection with the various embodiments of the present application without departing from the scope of the present application. The above-described embodiments may be modified or varied, without departing from the invention, as appreciated by those skilled in the art in light of the above teachings. It is therefore to be understood that, within the scope of the claims and their equivalents, the invention may be practiced otherwise than as specifically described.

What is claimed is:

1. A method for the synthesis of a radiolabeled compound comprising a radioactive isotope using a microfluidic device, the method comprising:

introducing a composition comprising a radioactive isotope to the microfluidic device;

electrochemically trapping the radioactive isotope using an electrode;

adding a composition comprising a reactant to the reactor;

electrochemically releasing the radioactive isotope from the electrode; and

contacting the reactant with the radioactive isotope to form the radiolabeled compound.

2. The method of claim **1**, wherein the radioactive isotope is F-18.

3. The method of claim **1**, wherein the reactant comprises mannose triflate.

4. The method of claim **3**, wherein the reactant is N-dimethoxytrityl-5'-O-dimethoxytrityl-3'-O-nosyl-thymidine and the radiolabeled compound is FLT.

5. The method of claim **2**, wherein a step of blowing an inert gas and a heating of the reactor is performed to dry the trapped F-18 before adding the composition comprising the reactant to the reactor.

6. The method of claim **1**, wherein the reactor is a coin-shaped reactor in a radio-synthesis chip.

7. The method of claim **1**, wherein the trapping and releasing is carried out by one or more electrodes.

8. The method of claim **7**, wherein the electrodes are located in or on at least one of a floor, a ceiling, and a side of the reactor or combinations thereof.

9. The method of claim **7**, wherein the electrodes are located in a channel in fluid communication with the reactor.

10. The method of claim **7**, wherein the electrodes are non-metal electrodes.

11. The method of claim **7**, wherein the electrodes are made of a material selected from the group consisting of a graphite, a composite graphite, and silicon and combinations thereof.

12. The method of claim **11**, wherein the electrodes are graphite polymer electrodes.

13. The method of claim **12**, wherein the polymer is selected from the group consisting of a DCPD, a polyethylene, and a glass.

14. The method of claim **7**, where the electrodes are metal electrodes.

15. The method of claim **14**, wherein the electrodes are covered with a protective coating.

16. The method of claim **1**, wherein at least one of the electrochemical trapping and the releasing is carried out in accordance with an on-chip feature.

17. The method of claim **1**, wherein at least one of the electrochemical trapping and the releasing is carried out in accordance with an in-reactor feature.

18. The method of claim **1**, wherein the trapping, the releasing and the radiolabeled compound formation are carried out within the same microreactor.

19. The method of claim **1**, wherein a radiochemical labeling yield of at least 55% is produced.

20. The method of claim **19**, wherein the yield is 55%, 65%, 75%, 85%, 95% or 99%.

21. The method of claim **1**, wherein the radioactive isotope is released into a non-aqueous solution.

22. The method of claim **21**, wherein the non-aqueous solution is an organic solution.

23. The method of claim **1**, wherein the reaction to form the radiolabeled compound is a substitution reaction.

24. The method of claim **23**, wherein the releasing is carried out simultaneously with the substitution reaction.

25. The method of claim **1**, wherein the reactant is in a solvent.

26. The method of claim **1**, wherein the electrochemical trapping is carried out in one or more passes.

27. The method of claim **1**, wherein the electrochemical releasing is carried out in accordance with one or more reversals of a voltage bias.

28. A method for the synthesis of a radiolabeled compound using a microfluidic trap-release device, the method comprising:

introducing a composition comprising a radioactive isotope to the device;

electrochemically trapping of the radioactive isotope;

adding a composition comprising a reactant to the device; and

electrochemically releasing the radioactive isotope into the trap-release device.

29. The method of claim **28**, wherein the trap-release device is a radiochemical microreactor.

30. A microfluidic radiosynthesis apparatus, comprising:

a first electrode configured to electrochemically trap a radioactive isotope;

a chamber; and

a second electrode configured to electrochemically release the radioactive isotope into the chamber.

31. The apparatus of claim **30**, wherein the apparatus is further configured for preparing a radiolabeled compound by performing a reaction of a reactant with the radioactive isotope.

32. The apparatus of claim **30**, wherein the radioactive isotope is F-18.

33. The apparatus of claim **30**, wherein the chamber is filled with a composition comprising a reactant.

34. The apparatus of claim **33**, wherein the reactant comprises mannose triflate.

35. The apparatus of claim **34**, wherein the reactant is N-dimethoxytrityl-5'-O-dimethoxytrityl-3'-O-nosyl-thymidine and the radiolabeled compound is FLT.

36. The apparatus of claim **33**, further configured to blow an inert gas and heat the chamber before adding the composition comprising the reactant.

37. The apparatus of claim **30**, wherein the chamber is part of a coin-shaped reactor in a radio-synthesis chip.

38. The apparatus of claim **30**, wherein the electrodes are located in or on at least one of a floor, a ceiling, and a side of the chamber or combinations thereof.

39. The apparatus of claim **30**, wherein the electrodes are located in a channel in fluid communication with the chamber.

40. The apparatus of claim **30**, wherein the electrodes are non-metal electrodes.

41. The apparatus of claim **30**, wherein the electrodes are made of a material selected from the group consisting of graphite, a composite graphite, and silicon and combinations thereof.

42. The apparatus of claim **41**, wherein the electrodes are graphite polymer electrodes.

43. The apparatus of claim **42**, wherein the polymer is selected from the group consisting of a DCPD, a polyethylene and a glass.

44. The apparatus of claim **30**, where the electrodes are metal electrodes.

45. The apparatus of claim **44**, wherein the electrodes are covered with a protective coating.

46. The apparatus of claim **30**, wherein at least one of the first and the second electrodes is configured as an on-chip feature or as an in-reactor feature.

47. The apparatus of claim **30**, wherein the electrochemical trapping is carried out in one or more passes.

48. The apparatus of claim **30**, wherein the electrochemical releasing is carried out in accordance with one or more reversals of a voltage bias.

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