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(54) Benævnelse: **RADIOISOTOPGENERATOR**

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Description

The present invention relates to a radioisotope generator for medical application, preferably arranged in a shielded casing, the said casing being preferably made at least in part of a dense material, such as for example tungsten or lead, comprising an eluent reservoir and a chromatography column connected to one another by a first eluent transmission duct, the said chromatography column having a stationary phase charged with a parent radioisotope that spontaneously disintegrates into a daughter radioisotope.

This radioisotope generator is used inter alia in the field of nuclear medicine to produce an eluate of radioisotopes (daughter radioisotopes) from a source (that is to say a chromatography column having a stationary phase charged with parent radioisotopes which spontaneously disintegrate into daughter radioisotopes that are to be eluted by an eluent). These daughter radioisotopes in the eluate are intended to be used as such or to bind to a molecule, such as for example a biocompatible molecule (protein, antibody, etc.), so as to form a radio-labelled molecule, resulting from the combination of the daughter radioisotope with the molecule, which is generally then administered to a patient by injection, typically in the form of a solution or liquid suspension when the molecule is biocompatible. The administration of the radioisotope or radio-labelled molecule in this case allows certain cancers to be diagnosed or treated, depending on the choice of the radioisotope and/or the biocompatible molecule.

There are numerous constraints in the particular context of the preparation of a solution or a suspension comprising a radioisotope or a radio-labelled biocompatible molecule to be administered to a patient.

In fact, first of all it is necessary to ensure that the production and sampling of the eluate containing the daughter radioisotopes, as well as the labelling reaction of the biocompatible molecule by the daughter radioisotope to form the radio-labelled molecule, are carried out under sterile conditions.

Then, so that the labelling reaction is as efficient as possible, it is important to have an eluate in which daughter radioisotopes have a high degree of purity, that is to say an eluate highly concentrated in daughter radioisotopes and in which the presence of contaminants that can interfere with or inhibit the labelling reaction is sufficiently low so as not to compromise this labelling reaction.

Unfortunately, the passage phenomenon of the parent radioisotope through the stationary phase of the column, i.e. breakthrough, is often encountered in the operation of the generator described below and is problematic.

Indeed, this phenomenon corresponds to an undesirable entrainment by the eluent of parent radioisotopes which uncouple from (or do not bind to) the stationary phase and are found in the eluate at the outlet of the chromatography column.

The result in an eluate that comprises a mixture of parent and daughter radioisotopes, and which after the labelling reaction is administered to the patient may be toxic if the parent radioisotope activity in the solution or suspension comprising the radio-labelled biocompatible molecule is too high.

Within the context of the present invention the terms "parent radioisotope" and "parent radioisotopes" mean the radioisotope initially loaded on the stationary phase as well as the intermediate generation radioisotopes which will provide the daughter radio-isotope. In fact, in some cases the decomposition of the parent radioisotope produces a very short half-life compound, which in turn breaks down into the daughter radioisotope of interest. These radioisotopes of the generation before those of the daughter radioisotopes of interest are called "parent radioisotope(s)".

Within the context of the present invention the term "daughter radioisotope(s)" means the radioisotope(s) resulting from the decomposition, which will be the eluted radioactive molecule of interest for uses in nuclear medicine, biomedical research and diagnostics.

One way of reducing this "breakthrough" is to carry out an elution of the stationary phase of the column with a large volume of eluent and then re-concentrate the eluate resulting from such elution using a re-concentrator so as to increase the concentration of daughter radioisotopes and to reduce the activity of parent radioisotopes to a threshold value which cannot be exceeded and for which the toxic effects of this radioisotope cannot be recorded in the an individual receiving the solution or suspension containing the radio-labelled biocompatible molecule from the re-concentrated eluate.

In this process, which takes place before the labelling reaction with a biocompatible molecule, the re-concentrator is placed downstream of the generator and is connected to the generator at the outlet of the chromatography column. During the re-concentration the daughter radioisotopes, circulated by a carrier solution (typically a physiological saline solution), are retained by a stationary phase that has a specific affinity for these radioisotopes, so that only the latter are retained by this stationary phase. This stationary phase is moreover specially chosen so that a small elution volume is sufficient, for example using physiological saline (of the order of 1.5 ml to 5.0 m) and thus allows a re-concentrated eluate of limited volume to be obtained, but in which the activity of daughter radioisotopes is sufficiently high and the activity of patent radioisotopes is sufficiently low so as to be compatible with the aforementioned medical applications.

However, this re-concentration step is costly, since it requires the provision of an additional re-concentration system, and should be sufficiently long so that a significant loss of performance of the daughter radioisotope activity in the re-concentrated eluate can be detected, which constitutes a loss of profitability of the generator and an additional risk of contamination.

Another solution is to carry out using the generator a fractional elution well known to the person skilled in the art, which consists of collecting the eluate in predetermined volume fractions and retaining and combining the fractions in which, on the other hand, the activity of the parent radioisotope is considered sufficiently low and, on the other hand, the activity of the daughter radioisotope is sufficiently high for medical applications.

Unfortunately, like the re-concentration step, fractional elution has the disadvantage of being a fairly long process, since the flow of eluate has be interrupted between each fraction in order to identify the parent radioisotope activity. This results in a significant loss of performance of the daughter radioisotope activity in the eluate thereby obtained, which is a loss of profitability of the generator and again is a risk of contamination. Therefore fractional elution, in order to be effective, requires the use of a maintenance system to determine the proper fractionation and to measure the activities of parent and daughter radioisotopes in each fraction in real time, which is an alternative that is at least as complicated as the re-concentration step.

Then, the implementation of a fractional elution of the stationary phase also causes a problem when it involves producing an eluate charged with daughter radioisotopes under sterile conditions. In this case it has to be ensured with certainty that each container intended to receive an eluate fraction is sterile, and that the step of pooling the fractions comprising the daughter radioisotopes is carried out under sterile conditions, which constitutes a not-insignificant and de facto costly logistics constraint.

There is therefore a need for a generator which makes it possible to reduce this breakthrough phenomenon and to obtain directly after elution, a sterile eluate in which the activity of the parent radioisotope is sufficiently low and the activity of the daughter radioisotope is sufficiently high, so that this eluate can be directly utilised and implemented in the form of a solution of radio-labelled molecules.

The document US 2011/0280770 proposes to meet this need by providing a generator comprising an elution line connecting the chromatography column to the first eluent reservoir (upstream) and to the eluate outlet (downstream). This elution line comprises a first sleeve valve arranged so as to regulate the flow of eluent from the reservoir to the column, and a second sleeve valve arranged on a branch of the elution line. This branch provides a parent radio-isotope charging line (^{62}Zn) concentrated in a liquid phase. In this case, the second sleeve valve thus enables the radioisotope inflow ^{62}Zn into the column to be selectively regulated. A third sleeve valve is located on the elution line, at the eluate outlet, downstream of the chromatography column. This third line is intended to enable the flow at the column outlet to a second eluate reservoir to be regulated.

However, the generator according to document US 2011/0280770 is still complicated in design since its operation requires, during the elution of the stationary phase of the column, continuous control by means of sleeve valves of, on the one hand, at least two flow rates: the charging rate of ^{62}Zn from the branch line to the column and the outlet flow of eluent from the eluent reservoir to the column, and, on the other hand, volumes of solution loaded with parent radioisotopes and eluent.

Other devices are also known from the documents US 2003/0127395 and US 4585941 and describe systems that depend on a pumping system for carrying out the elution process.

The object of the present invention is to provide a radioisotope generator of simplified design and which is therefore easier to use, under sterile conditions, than the generator described in document US 2011/0280770, while being free from the problem of "breakthrough".

According to the present invention this object is achieved by providing a generator as described in the introduction, characterised in that it comprises a second duct and a valve arranged between an upstream portion of the first eluent duct and a downstream portion of the first eluent duct, and connecting the said second duct to the said upstream portion of the first eluent duct and to the downstream portion of the first eluent duct, the said valve having a first position in which the second duct is in fluid communication with the said first upstream portion of the first eluent duct and a second position in which the second duct is in fluid communication with the said downstream portion of the first eluent duct, the said second duct having a branch section with a predetermined volume of eluent, the said section being located directly between the said valve and a section end extremity, the said predetermined volume of eluent being a volume sufficient to obtain, when the said sufficient volume passes through the chromatography column under the action of a driving force of the eluent, an eluate comprising an activity of parent radioisotope in a range of values ranging from 0.0 % to 30.0 % with respect to an activity of daughter radioisotope of the said eluate.

The presence of the second duct in fluid communication, via the valve, with the first duct connecting the eluent reservoir to the chromatography column enables a generator to be provided that is completely sterile when the reservoir, the first and second ducts and also the valve are previously sterilised before being interconnected to form a closed elution line and connected to the chromatography column of the generator. Alternatively, the various aforementioned elements are interconnected and the resulting elution line is then sterilised as a whole.

In addition, the generator according to the invention requires only the control of a valve in order to generate an eluate that can be used directly for medical applications, the sampled volume being predetermined by the predetermined length and diameter of the branch section.

In fact, when the user wishes to carry out an elution, the user first sets the valve to its first position, which is a position in which the second duct is in fluid communication with the said

upstream portion of the first eluent duct, so as to charge the branch section with a predetermined and sufficient volume of eluent.

Then, when the branch section is filled with eluent, the user sets the valve to its second position, in which the second duct is in fluid communication with the said downstream portion of the first eluent duct, and the eluent is discharged from the branch section to the chromatography column.

Once the elution is complete, the daughter radioisotope, which continues to be generated in the column from the parent radioisotope loaded on the column, sees its activity increase to reach a threshold value of activity which cannot to be exceeded, and which is governed by an equilibrium between the parent radioisotope and the daughter radioisotope. A cycle is thus formed, and it is the frequency between the successive elutions that determines the respective activities of parent and daughter radioisotopes in the eluate obtained for each of these successive elutions.

The predetermined volume corresponds here to the sufficient and optimal volume to elute overwhelmingly the daughter radioisotope resulting from the decay but only a minimum fraction of parent radioisotope, thereby reducing the "*breakthrough*" phenomenon.

In fact, the predetermined volume makes it possible to obtain, after elution of the column, an eluate in which a daughter radioisotope activity is measured in a range of values ranging from 60.0 % to 100.0 %, preferably from 70.0 % to 100.0 %, more particularly greater than 80.0 % with respect to the daughter radioisotope activity present on the column at the time of the elution, whereas the parent radioisotope activity itself in the eluate is in the range from 0.0 % to 30.0 % with respect to the daughter radioisotope activity of the said eluate.

The generator according to the present invention thus makes it possible, for each elution with a sufficient predetermined eluent volume, to obtain a completely unexpected elution profile of the daughter radioisotope. Indeed, as explained above, in the existing wet generator systems, that is to say systems in which the elution is carried out continuously, the elution profile of the daughter radioisotope normally has a first fraction comprising mainly the parent radioisotope followed by a second fraction comprising mainly the daughter radioisotope.

In contrast, in the context of the present invention it has surprisingly been observed that the activity of the parent radioisotope of the eluate is sufficiently reduced so that this eluate can be used directly in the aforementioned medical applications.

Thus, with the generator according to the present invention, for an elution with the sufficient predetermined volume of eluent it is ensured, and what is more under sterile conditions, that not only can the parent radioisotopes activity in the eluate be controlled, but also a sufficient daughter radioisotope activity is obtained, so as to provide an eluate that can be used directly in the context of medical applications.

In fact, the eluate obtained by the passage of the predetermined volume of eluent through the chromatography column of the generator according to the invention exhibits a narrow peak elution of the daughter radioisotope that is substantially free of parent radioisotopes by optimising the synchronisation between the elution and the complete generation of daughter radioisotopes on the stationary phase according to the normal cycle of disintegration of the parent radioisotopes.

During the life of the generator, the solutions of daughter isotope of interest are recovered by an alternating succession of loading and unloading of the section, until the eluent contained in the reservoir is exhausted: it is therefore a discontinuous elution consisting of a succession of elutions with the sufficient volume of eluent.

In this context, each elution is associated with the collection of an eluate volume intended for an appropriate medical use.

Between each elution the user will ensure that the column is dried, for example by pumping sterilised ambient air from the section end extremity or from a free end of the second duct to the eluate outlet.

The drying enables a residual volume of excess eluent present in the column to be evacuated, and thereby minimises the risk of the parent radioisotope migrating towards the eluate outlet of the column between two successive elutions.

The choice of sufficient predetermined volume is determined by the elution profile of the radioisotopes and therefore: (i) by the physicochemical properties of the chromatography

column and the eluent; (ii) as well as by the pair of parent and daughter radioisotopes that is employed.

The generator according to the invention thus constitutes a simpler alternative design and use compared to the solutions proposed in the prior art, and in particular to the solution provided by conventional dry generators, in which it is necessary systematically to manually load the column by injecting a predetermined volume of eluent, wherein this type of generator by definition does not include an eluent reservoir.

Indeed, the difficulty inherent in the use of this type of generator lies in the fact that a sterile connection for each injection of eluent into the column must be ensured in order to prevent the risk of contamination.

Preferably, the said reservoir is situated above the said chromatography column, the said section end extremity, which may be a free end of the second duct, being arranged at a sufficient height, measured from an apical end of the chromatography column, so that the gravitational force has sufficient intensity to allow a flow of the eluent through the sampling section.

Advantageously, at least one branch section portion connected to the said valve is inclined with respect to a horizontal plane at an angle α defined between the said horizontal plane and a straight line intersecting the said horizontal plane, the said angle α having a predetermined value of so that its sine value is greater than 0 and less than or equal to 1 and its cosine value is between -1 and 1.

In this way the intensity of the gravitational force acting on the eluent withdrawn close to the sampling section is first of all determined by the drop height, measured from the apical end of the chromatography column, from the branch section to the chromatography column, and additionally, by the angle α whose value determines the inclination of the portion of section connected to the said valve.

The inclination thus allows a gravitational flow of the predetermined sufficient volume of eluent.

Optionally, the generator according to the invention comprises a means for blocking the eluent in fluid communication with the said branch section, so as to block the passage of the said eluent volume beyond the said section end extremity.

The presence of the blocking means makes it possible on the one hand to determine accurately the sampled volume and, on the other hand to possibly avoid the overflow of the said eluent volume from the said free extremity of the second duct.

Advantageously, the said free extremity is connected to a second sterile filter of reverse polarity to that of the said eluent.

The said section end extremity may also be directly connected to a first sterile filter of reverse polarity to that of the said eluent, the said first sterile filter being the said means for blocking the eluent.

In this way the air entering the interior of the second duct and the branch section is sterilised, which has the advantage that a sterile generator is provided in which the directly obtained eluate is suitable for medical use.

Preferably, the generator according to the invention comprises a pumping means arranged to be hermetically connected to an eluate outlet and designed to pump, when the said valve is in its second position and after elution of the stationary phase of the chromatography column by the said sufficient volume of eluent, a fluid from the section end extremity or from the free extremity of the second duct to the eluate outlet, the said fluid being a remaining fraction of the said sufficient volume of eluent present in the column or ambient air pumped from the said free extremity or from the said section extremity of the said second duct.

By way of example, the pumping means may be a vacuum vessel or an actuator comprising a piston installed in a cylinder, which cylinder has a first end communicating with the said eluate outlet of the chromatography column, the said piston being extended by an arm extending beyond the said cylinder through an orifice arranged on a second cylinder end opposite the first cylinder end, which piston has a first rest position and a fluid pumping position, and the said piston when set in motion between the said first rest position and the said pumping position generates a pumping force of the fluid.

The pumping means allows the excess eluent present in the column to be evacuated and enables the latter to be optionally dried, so as to obtain a column which is dried or slightly impregnated with eluent.

By enabling this fraction of excess eluent present in the column to be evacuated, this minimises the risk of the parent radioisotope migrating towards the eluate outlet of the column between two successive elutions.

Other embodiments of the generator according to the invention are given in the appended claims.

The present invention furthermore relates to a method for eluting a chromatography column of a radioisotope generator comprising an eluent reservoir and connected to a chromatography column by a first eluent duct, the said chromatography column having a stationary phase impregnated with eluent and charged with a parent radioisotope that spontaneously disintegrates into a daughter radioisotope, wherein the said method comprises the following steps:

- removal of a predetermined volume in a sampling section of a second eluent duct connected to an upstream part of the first eluent duct and to a downstream part of the first eluent duct by a valve, wherein the said sampling section is located directly between the valve and a section end extremity, the sampling being carried out when the valve is in a first position in which the second duct is in fluid communication with the said upstream portion of the first eluent duct; and

- an elution, under the action of a force driving the eluent of the said predetermined volume of eluent from the said sampling section to the said chromatography column when the valve is in a second position in which the second duct is in fluidic communication with the said downstream portion of the first eluent duct, a step of drying the column by pumping sterilised ambient air from the section end extremity or from a free end of the second duct to the eluate outlet,

The said predetermined volume of eluent being a volume sufficient to obtain, when the said sufficient volume passes through the chromatography column, an eluate having a parent

radioisotope activity in a range of values from 0.0 % to 30.0 % with respect to a daughter radioisotope activity of the said eluate.

Preferably, the method comprises a step of blocking the eluent, following the said injection step, so as to block the passage of the said eluent volume beyond the said section end extremity.

The method may further comprise a purge step, performed before the drying step, when the valve is in its second position and after elution of the stationary phase of the chromatography column by the sufficient volume of eluent, which consists in pumping a remaining fraction of the sufficient volume of eluent present in the column.

Alternatively, the parent radioisotope activity is in a range of values ranging from 0.0 % to 20 %, advantageously from 0.0 % to 10 %, more preferably from 0.0 % to 5.0 %, still more preferably 0.0 % to 2.0 %, more advantageously 0.0 % to 1.0 %, with respect to the daughter radioisotope activity of the said eluate. Advantageously, the parent radioisotope activity is equal to 0.0 mCi.

Other embodiments of the method according to the invention are given in the appended claims.

Other features and advantages of the invention will become apparent from the description given hereinafter, by way of non-limiting example and with reference to the examples described below.

Fig. 1 schematically illustrates a first embodiment of the generator according to the invention.

Figs. 2a and 2b schematically illustrate two possible variants of a second embodiment of the generator according to the invention.

Fig. 3 schematically illustrates a third embodiment of the generator according to the invention.

In these figures, similar elements have the same reference numerals.

The radioisotope generator 1 according to the invention and shown in Fig. 1 comprises an eluent reservoir 2 and a chromatography column 3 interconnected by a first eluent transmission duct 4, so that the eluent contained in the reservoir 2 is in fluid communication with the chromatography column 3.

The chromatography column 3 comprises a stationary phase impregnated with eluent and charged with a parent radioisotope that spontaneously disintegrates into a daughter radioisotope.

The first eluent transmission duct 4 connects an eluent inlet 5 disposed upstream of the stationary phase to an eluent outlet 6 of the reservoir 2.

The radioisotope generator 1 also comprises a second duct 7 and a valve 8 connecting an upstream portion 4' of the first eluent duct and a downstream portion 4" of the first eluent duct. The upstream portion 4’ connects the eluent outlet 6 of the reservoir 2 to a first inlet 8' of the valve 8, while the downstream part 4" connects a second inlet 8" of the valve 8 to the eluent inlet 5 of the chromatography column 3.

The valve 8 furthermore connects a linked portion end 7' of the second duct 7 to the upstream portion 4' and downstream portion 4"of the first eluent duct 4.

The second duct 7 is in fluid connection with the valve 8 via a connection between the linked portion end 7’ of the second duct 7 and a third inlet 8"' of the valve 8.

In this context, the valve 8 has a first position in which the second duct 7 is in fluid communication with the upstream portion 4' of the first eluent duct 4 and a second position in which the second duct 7 is in fluid communication with the downstream portion 4" of the first eluent line 4.

The second duct 7 furthermore has a branch section 9 of a predetermined volume v of eluent. This section 9 is located directly between the valve 8 and a section end extremity 9'.

Typically, the predetermined volume v of eluent is defined by a branch section length and a branch section diameter.

In the first embodiment as described in Fig. 1, the section 9 is located between the linked portion end 7 of the second duct 7 and the section end extremity 9'.

The section end extremity is connected to a means 17 for blocking the eluent in fluid communication with the branch section 9, so as to block the passage of the eluent volume beyond the section end extremity 9'.

The blocking means 17 is a sterile filter of reverse polarity to that of the eluent, whose function is to allow ambient air to pass through the branch section 9 and block the passage of the eluent in a defined direction from the end 7'of the linked portion of the second duct 7 to the section end extremity 9'.

Preferably, the generator 1 is arranged in a shielded casing C for example made at least in part of a dense material, such as for example tungsten or lead. The casing C comprises a first access opening 10 to the reservoir 2 and an outlet opening 11 disposed downstream of an eluate outlet 12 of the chromatography column 3 and arranged to be traversed by a third eluate outlet duct 12' arranged to connect the eluate outlet 12 of the column 3 to an eluate receptacle 13 arranged so as to be housed in a chamber 14 provided in the casing and located downstream of the outlet opening 11. Preferably, the eluate receptacle 13 and/or the chamber 14 comprises a shielding of a dense material, such as for example tungsten or lead.

In the first embodiment as illustrated in Fig. 1, the reservoir 1 is arranged above the chromatography column 3.

The end extremity 9' of the branch section 9, which may for example be a free end 15 of the second duct 7, is arranged at a predetermined height H, measured from an apical end 16 of the chromatography column 3.

Optionally, at least one branch section part 9 connected to the valve 8 is inclined with respect to a horizontal plane h by an angle α defined between the horizontal plane h and a straight line d intersecting the horizontal plane h.

Advantageously the angle α has a predetermined value so that its sine value is greater than 0 and less than or equal to 1 and its cosine value is between -1 and 1.

During the operation of the first embodiment of the generator (Fig. 1), the valve 8 is initially in its first position. The eluent flows from the reservoir 2 through the upstream portion 4' of the first duct 4 to the second duct 7.

The branch section 9 is filled, under the effect of the gravitational force acting on a volume V of eluent contained in the reservoir 2, with the predetermined volume v of eluent at a branch flow rate having a value determined by the length and the diameter of the branch section 9.

The air contained in the section is expelled to the sterile filter 17 by the eluent. The flow of the eluent from the reservoir to the free end 15 is stopped by the presence of the sterile filter 17.

The height H and the value of the angle α enable a sufficient intensity value to be determined for the gravitational force acting on the sufficient volume v_s of eluent removed so as to permit the flow of the sufficient volume of eluent through the section 9.

Once the predetermined volume v of eluent has been taken from the reservoir, the valve is then in its second position.

The eluent flows from the sampling section 9 through the chromatography column 3 at an elution rate determined by the pressure drop of the chromatography column 3.

The predetermined volume v of eluent is a volume V_s that is sufficient to obtain, when the sufficient volume passes through under the action of a driving force of the eluent, which may for example be a withdrawal force of the eluent generated by a pump system connected to the output of the chromatography column 3 at the fixed elution rate, an eluate having a parent radioisotope activity in a range of values ranging from 0.0 % to 30.0 % with respect to a daughter radioisotope activity of the said eluate.

The parent radioisotope activity in the eluate is preferably in a range of values ranging from 0.0 % to 20.0 %, more preferably from 0.0 % to 10.0 %, with respect to the daughter radioisotope activity of the said eluate.

More preferably, the parent radioisotope activity is in a range of values ranging from 0.0 % to 5.0 % with respect to the daughter radioisotope activity of the said eluate.

Even more preferably, the parent radioisotope activity is in a range of values ranging from 0.0 % to 2.0 % with respect to the daughter radioisotope activity of the said eluate.

More advantageously, the parent radioisotope activity is in a range of values ranging from 0.0 % to 1.0 % with respect to the daughter radioisotope activity of the said eluate.

Most advantageously, the parent radioisotope activity is preferably 0.0 mCi.

Figs. 2a and 2b illustrate a portion of two particular variants of a second embodiment of the generator 1 according to the invention.

The second embodiment incorporates the characteristic features of the first embodiment and, in addition, a pumping means M_P arranged to be connected hermetically to the eluate outlet 12. The pumping means M_P may for example be a vessel under a vacuum.

Alternatively, the pumping means M_P can be an actuator 18 comprising a piston 19 installed in a cylinder 20 (Fig. 2a).

The cylinder 20 has a first end 21 communicating with the eluate outlet 12 of the chromatography column 3.

The piston 19 is extended by an arm 22 which extends from the cylinder 20 through an orifice 23 present on a second cylinder end 24, opposite the first cylinder end 21.

The piston has a first rest position R and a pumping position P (see the equivalent Fig. 2b).

In operation, after a first elution and before a subsequent second elution, the first valve 8 is maintained in its second elution position and the pumping means M_P is connected hermetically to the eluate outlet 12 while ensuring that the valve 8 is maintained in its second position.

Preferably, the eluate outlet is extended by a needle which is connected to a vacuum capsule by piercing a liquid-tight wall covering a fluid inlet orifice located on the capsule.

As soon as the needle penetrates the capsule a residual volume of the said sufficient volume of eluent that is free, that is to say which is not retained by the stationary phase of the column, and which is immobile in the column, is aspirated automatically into the capsule.

By enabling this residual volume of excess eluent present in the column to be evacuated, this therefore minimises the risk of the parent radioisotope migrating towards the eluate outlet of the column between two successive elutions.

Once this free eluent is aspirated, ambient air is then pumped from the free end 15 or the end 9' of the section 9 of the second duct 7 so as to dry the excess eluent fraction.

The aspiration of the free eluent and the passage of air into the column thus enables the latter to be purged and dried so as to obtain, between two elution, a column that is dried or slightly impregnated with eluent.

Once the purging and drying of the column has been carried out, the capsule is disconnected from the eluate outlet 12 and the eluate container 13 is reconnected to the column. Similarly to the vacuum capsule, the container comprises a liquid-tight wall intended to be pierced by the needle arranged in the extension of the eluate outlet 12 of the column 3.

A new elution is then carried out by firstly positioning the first valve 8 in its first position so as to charge the branch section 9 with eluent and then adjusting the first valve 8 to its second elution position. This new elution is then followed by a new purging and drying step.

Thus, once a first elution has finished the daughter radioisotope, which is still being generated in the column from the parent radioisotope loaded on the column, increases in activity to reach a threshold activity level which cannot be exceeded and which is governed by a secular equilibrium between the parent radioisotope and the daughter radioisotope. A cycle is thus established, and it is the frequency between each successive elution (second, third, etc. elution) after the first elution that determines the respective activities of parent and daughter radioisotopes in the eluate obtained for each of these successive elutions.

In addition, the actuator 18 may be hermetically connected by a second valve 25 to the eluate outlet 12 (Fig. 2b).

The second valve 25 has an elution position in which the third duct 12' is in fluid communication with the eluate container 13 via a fourth duct 12" connecting the eluate container 13 to the valve, and a purge position in which the third duct 12' is in fluid communication with the pumping means.

In operation, after a first elution and before a second following elution, the second valve 25, which is initially in its elution position, is adjusted to its purge position, while the first valve 8 is maintained in its second elution position. The piston is then moved between its first rest position R and its second pumping position P, which generates a pumping force on the remaining fraction of the sufficient volume of eluent.

The remaining fraction of the sufficient volume of eluent is therefore conveyed from the chromatography column 3 to the cylinder 20 of the actuator 18, which fills with eluent.

If the piston is kept in motion and when the free eluent is aspirated from the column, ambient air is then pumped from the free end 15 or the end 9' of the section 9 of the second duct 7 in order to dry the excess eluent fraction so as to obtain a column which is at most impregnated with eluent.

After the purging and drying of the column has been carried out, the second valve 25 is adjusted to its first position and a new elution is carried out by first positioning the first valve 8 to its first position so as to load the branch section 9 with eluent and then positioning the first valve 8 in its second elution position.

This new elution will then be followed by a new purge and drying step.

The generator according to a third embodiment (Fig. 3) includes in addition a pressure switch 15' connected to the free end 15 of the second duct or to the end extremity 9' of the section 9.

In this third embodiment of the generator according to the invention the pressure switch 15' enables the elution rate of the sufficient volume of eluent to be monitored, like a purge flow rate, that is to say a pumping rate of the eluent, and a drying rate, that is to say a rate of pumping air through the column, and enables any operating anomalies of the generator to be determined.

For each of the embodiments of the generator described above, the choice of the sufficient predetermined volume is determined by the elution profile of the radioisotopes and therefore: (i) by the physicochemical properties of the chromatography column and of the eluent; (ii) as well as by the pair of parent and daughter radioisotopes that is used.

With reference to Figs. 1 and 2, the present invention also relates to a method for eluting a chromatography column 3 of a radioisotope generator 1 comprising an eluent reservoir 2 and connected to a chromatography column 3 by a first eluent duct 4, wherein the said chromatography column 3 has a stationary phase impregnated with eluent and loaded with a parent radioisotope that spontaneously disintegrates to a daughter radioisotope.

The method according to the invention comprises the following steps:

- a sampling of a predetermined volume in a sampling section 9 of a second eluent duct 7 connected to an upstream part 4' of the first eluent duct 4 and to a downstream part 4" of the first eluent duct 4 by a valve 8, which sampling section 9 is located directly between the valve 8 and an end extremity of the section 9'. The sampling is carried out when the valve 8 is in a first position in which the second duct 7 is in fluid communication with the upstream portion 4' of the first eluent duct; and

- an elution step, under the action of a driving force of the eluent, of the predetermined volume of eluent from the sampling section 9 to the chromatography column 3 when the valve 8 is in a second position in which the second duct 7 is in fluid communication with the said downstream portion 4" of the first eluent duct 4.

The method further comprises a step of drying the column by pumping ambient air from the end extremity 9'of the section 9 or from a free end 15 of the second duct 17 to the eluate outlet 12, and the method furthermore comprises an eluent blocking step following the injection step, so as to block the passage of the said eluent beyond the said end extremity of the section 9’.

The ambient air is sterilised on passing through the sterile filter 17 present on the second duct 7.

A purge step can be carried out before the drying step. This purge step is performed when the valve 8 is in its second position and after elution of the stationary phase of the chromatography column 3 by the sufficient volume of eluent, which consists of pumping a remaining fraction of the sufficient volume of eluent present in the column 3.

In this method, the predetermined volume of eluent is a volume sufficient to obtain, when the sufficient volume passes through the chromatography column 3, an eluate comprising a parent radioisotope activity in a range of values ranging from 0.0 % to 30.0 % with respect to a daughter radioisotope activity of the eluate.

Preferably, the method comprises a step of blocking the eluent, following the said injection step, so as to block the passage of the said eluent volume beyond the end extremity of the section 9'.

The blocking step is ensured by the presence of a sterile filter 17 of reverse polarity to that of the eluent, whose function is to allow air to enter the branch section 9 and to block the passage of the eluent in a defined direction from the connected portion extremity 7' of the second duct 7 to the end extremity 9' of the section.

The method according to the invention enables a parent radioisotope activity to be preferably obtained in a range of values ranging from 0.0 % to 20 % with respect to the daughter radioisotope activity of the said eluate.

Advantageously, the parent radioisotope activity is in a range of values ranging from 0.0 % to 10 % with respect to the daughter radioisotope activity of the said eluate.

More preferably, the parent radioisotope activity is in a range of values ranging from 0.0 % to 5.0 % with respect to the daughter radioisotope activity of the said eluate.

Even more preferably, the parent radioisotope activity is in a range of values ranging from 0.0 % to 2.0 % with respect to the daughter radioisotope activity of the said eluate.

More advantageously, the parent radioisotope activity is in a range of values ranging from 0.0 % to 1.0 % with respect to the daughter radioisotope activity of the said eluate.

Advantageously, the parent radioisotope activity is equal to 0.0 mCi.

The results relating to the operation of the generator according to the present invention are described below for purposes of illustration and are in no way to be considered as limiting.

These results relate to loading and elution tests of the generator according to the invention for different pairs of parent/daughter radioisotopes and different stationary phases.

Operating mode

Charging of the generator

Test 1 relates to the pair $^{99}Mo/^{99m}Tc$ (parent/daughter) on a first titanium-based stationary phase of a first generator according to the invention carried out in aqueous phase at an acidic pH. The activity loaded on the stationary phase was 27.9 mCi at the charging time T_0.

Test 2 relates to the pair $^{99}Mo/^{99m}Tc$ on a second aluminium-based stationary phase of a second generator according to the invention carried out in aqueous phase at an acidic pH. The activity loaded on the stationary phase was 57.8 mCi at the charging time T_0.

Elution test

For the tests 1 and 2, the reservoir consists of a pouch of saline solution (NaCl) at a concentration of 0.9 % by volume.

The two generators were eluted daily for a given period in order to follow the elution yields and salting-out rates ^{99}Mo in each of the eluates sampled daily (" breakthrough ").

Results

The elution yield Y (in %) is understood in the context of the present invention as the ratio of the activity of ^{99m}Tc [$A(^{99m}Tc)^{ei}$ in mCi] in the eluate and the activity of the ^{99m}Tc [$A(^{99m}Tc)^{-col}$ in mCi] which is present on the column at the time of the elution, and is calculated according to the following formula:

$$Y(\text{in } \%) = 100 \text{ X } [A(-^{99m}Tc)^{el} / A(^{99m}Tc)^{col}]$$

The salting-out rates of ^{99}Mo are given in % and correspond to the following ratio:

R = 100 X [A (^{99}Mo)^{el} / A (^{99m}Tc)^{el}], where A (^{99}Mo)^{ei} represents the ^{99}Mo activity in the eluate.

The results for Tests 1 and 2 are shown in Tables 1 and 2 below:

Table 1.- Pair ^{99}Mo / ^{99}m Tc on TiO_2 - Test 1

Time T	Y (in %)	R (%)*
T_0	99	$< 1.4\ 10^{-5}$
T_0 + 1 day	91	$< 1.6\ 10^{-6}$
T_0 + 2 days	93	$< 2.0\ 10^{-6}$
T_0 + 8 days	95	$< 1.9\ 10^{-6}$
T_0 + 9 days	95	$< 3.2\ 10^{-7}$
T_0 + 10 days	95	$< 1.4\ 10^{-6}$
T_0 + 11 days	97	$< 1.6\ 10^{-6}$
T_0 + 13 days	94	$< 6.4\ 10^{-6}$
T_0 + 14 days	96	$< 6.9\ 10^{-6}$
T_0 + 15 days	98	$< 6.8\ 10^{-6}$
T_0 + 16 days	98	$< 7.1\ 10^{-6}$
T_0 + 17 days	95	$< 9.0\ 10^{-6}$
T_0 + 21 days	94	$< 3.0\ 10^{-6}$
T_0 + 22 days	94	$< 2.1\ 10^{-6}$

ate (^{99m}Tc) monographs for injection produced by fission “Eur.Phar 0124” and sodium pertechnetate (^{99}m Tc) monographs for injection not produced by fission “Eur Phar 0283") specify a threshold value that should not exceed the order of 0.1 %.

Table 2.- Pair $^{99}Mo/^{99m}Tc$ torque on Al_2O_3 - Test 2

Time T	Y (in %)	R (in %)*
T_0	92	$< 4.4\ 10^{-4}$
T_0 + 1 day	100	$< 3.1\ 10^{-4}$
T_0 + 2 days	100	$< 2.3\ 10^{-4}$
T_0 + 3 days	100	$< 1.2\ 10^{-4}$
T_0 + 6 days	100	$< 3.3\ 10^{-4}$
T_0 + 7 days	101	$< 4.5\ 10^{-5}$
T_0 + 9 days	99	$< 2.8\ 10^{-4}$
T_0 + 10 days	101	$< 6.3\ 10^{-5}$
T_0 + 13 days	99	$< 5.0\ 10^{-5}$
T_0 + 14 days	99	$< 2.7\ 10^{-5}$

* The specifications of the European Pharmacopoeia (Sodium pertechnetate (^{99m}Tc) monographs for injection produced by fission “Eur.Phar 0124”and sodium pertechnetate (^{99m}Tc) monographs for injection not produced by fission “Eur Phar 0283") specify a threshold value that should not exceed the order of 0.1 %.

On the basis of Tests 1 and 2 and a reference test, the values shown in Table 3 are adopted:

Table 3.-

Couple // stationary phase	Y (in %)	R (in %)*
$^{68}Ge/\ ^{68}Ga//\ TiO_2$ §	> 70 %§§§	10^{-4} - 10^{-6} §§§§
$^{99}Mo/^{99m}Tc\ //\ TiO_2$ §§	~95 %	~10^{-8} - 10^{-7}
$^{99}Mo/^{99m}Tc\ //\ Al_2O_3$ §§	~100 %	10^{-4} - 10^{-5}

§: Values measured at time T = T_0

§§: Average values

§§§: Y (in%) = 100 X [$A(^{68}Ga)^{el}$ / $A(^{68}Ge)^{col}$]

§§§§: R = 100 X [$A^{68}Ge)^{el}$ / $A(^{68}Ga)$, where $A(^{68}Ge)^{el}$ represents the ^{68}Ge activity in the eluate.

*The European Pharmacopoeia Specifications (sodium pertechnetate (^{99m}Tc) monographs for injection produced by fission "Eur.Phar.O124"; sodium pertechnetate (^{99m}Tc) monographs for injection not produced by fission "Eur Phar 0283” and monographs for "gallium solution (^{68}Ga)

(chloride) for radiolabelling" "Eur Phar 2464") specify a threshold value that should not to be exceeded the order of 0.1 %.

As the results given above show, the activity of parent radioistopes detected in the eluate is on average less by a factor of $10^{-6} – 10^{-8}$ with respect to the activity daughter radioisotopes in the same eluate, which means a parent radioisotope activity of less than 1.0 % with respect to the daughter radioisotope activity of the eluate, which is quite remarkable.

It is understood of course that the present invention is in no way limited to the embodiments described above and that modifications can be made without departing from the scope of the appended claims.

For example, the generator according to the present invention can be used in applications other than those that fall within the scope of a use for pharmaceutical or medical purposes.

Furthermore, although the description discloses a generator comprising a valve, it is understood that the present invention is not limited to a generator that comprises only one valve, but also covers other embodiments in which several valves fluidically connect the collection section to the reservoir and to the column.

By way of illustration, a fourth embodiment in which the generator comprises a first valve connecting the sampling section to the reservoir and a second valve connecting the same section to the chromatography column can perfectly well be envisaged as an equivalent implementation of the generator according to the invention.

Patentkrav

1. Radioisotopgenerator (1) omfattende et elueringsmiddelreservoir (2) og en kromatografisk søjle (3) forbundet til hinanden med en første elueringsmiddelledning (4), hvilken kromatografiske søjle (3) har en stationær fase ladet med en moderradioisotop, som opløses spontant til en datterradioisotop, hvor nævnte generator omfatter en anden ledning (7) og en ventil (8) huset mellem en opstrømsdel (4') af den første elueringsmiddelledning (4) og en nedstrømsdel (4") af den første elueringsmiddelledning (4), og forbinder nævnte anden ledning (7) til nævnte opstrømsdel (4') af den første elueringsmiddelledning og nedstrømsdelen (4") af den første elueringsmiddelledning, hvor nævnte ventil (8) har en første position, hvor den anden ledning (7) er i fluidforbindelse med nævnte opstrømsdel (4') af den første elueringsmiddelledning (4) og en anden position, hvor den anden ledning (7) er i fluidforbindelse med nævnte nedstrømsdel (4") af den første elueringsmiddelledning (4), hvilken anden ledning (7) har et udledningsafsnit (9) af en forudbestemt elueringsmiddelvolumen, hvor nævnte afsnit (9) er defineret direkte mellem nævnte ventil (8) og et afsnitsslutpunkt (9'), hvor nævnte forudbestemte elueringsmiddelvolumen er en tilstrækkelig volumen til at opnå, når nævnte tilstrækkelige volumen krydser den kromatografiske søjle (3) under virkningen af en drivkraft af elueringsmidlet, et elueringsmiddel omfattende en moderradioisotop-aktivitet omfattet inden for et område af værdier fra 0,0 % til 30,0 % i forhold til en datterradioisotop-aktivitet af nævnte elueringsmiddel, **kendetegnet ved, at** nævnte afsnits- (9) slutpunkt (9') er direkte forbundet til et første sterilt filter (17) af modsat polaritet til det af nævnte elueringsmiddel, som danner et blokeringsorgan til elueringsmidlet (17) i fluidforbindelse med nævnte udledningsafsnit (9), for således at blokere passagen af nævnte elueringsmiddelvolumen længere end nævnte afsnits- (9) slutpunkt (9').

2. Generator ifølge krav 1, hvor nævnte reservoir (2) er situeret over nævnte kromatografiske søjle (3), hvor nævnte afsnits- (9) slutpunkt (9') er anbragt ved en tilstrækkelig højde (H), målt fra en apikal ende (16) af den kromatografiske søjle (3), således at tyngdekraften har en tilstrækkelig intensitet til at tillade en strømning fra nævnte elueringsmiddelvolumen igennem afsnittet (9).

3. Generator ifølge krav 2, hvor mindst en del af udledningsafsnittet (9) forbundet til nævnte ventil (8) er skrående i forhold til et horisontalt plan (h) fra en vinkel α defineret mellem nævnte horisontale plan og en skæringslinje (d) på nævnte horisontale plan, hvor nævnte vinkel α har en forudbestemt værdi således at sinusværdien deraf er større end 0 og mindre end eller lig med 1, og cosinusværdien deraf er mellem -1 og 1.

4. Generator ifølge et hvilket som helst af de foregående krav, hvor nævnte afsnitsslutpunkt (9') svarer til en fri ende (15) af den anden ledning (7).

5. Generator ifølge et hvilket som helst af de foregående krav, hvor nævnte frie ende (15) er forbundet til et andet sterilt filter (17) af modsat polaritet til det af nævnte elueringsmiddel.

6. Generator ifølge krav 4 eller 5, omfattende et pumpeorgan (M_P) indrettet til at blive forbundet hermetisk til et eluatudløb (12) og beregnet til at pumpe, når nævnte ventil (8) er i den anden position deraf og efter eluering af den stationære fase af den kromatografiske søjle (3) af nævnte tilstrækkelige elueringsmiddelvolumen, en fluid fra afsnits- (9) slutpunktet (9’) eller fra den frie ende (15) af den anden ledning (17) mod eluatudløbet, hvor nævnte fluid er en resterende fraktion af elueringsmiddel til stede i søjlen eller den omgivende luft pumpet fra nævnte frie ende (15) eller nævnte afsnits- (9) slutpunkt (9') af nævnte anden ledning (7).

7. Generator ifølge krav 6, hvor nævnte pumpeorgan (M_P) er en vakuumeret beholder.

8. Generator ifølge krav 7, hvor pumpeorganet (M_P) er en aktuator (18) omfattende et stempel (19) monteret i en cylinder (20), hvilken cylinder har en første ende (21) i forbindelse med nævnte eluatudløb (12) af den kromatografiske søjle, hvor nævnte stempel (19) forlænges af en arm (22), der strækker sig uden for nævnte cylinder igennem en åbning (23) til stede på en anden cylinderende (24), modstående den første cylinderende (21), hvilket stempel har en første

hvileposition (R) og en fluidpumpeposition (P), hvilket stempel (19), når det er bevæget mellem nævnte første hvileposition (R) og nævnte pumpeposition (P), genererer en fluidpumpekraft.

9. Generator ifølge et hvilket som helst af de foregående krav, anbragt i en afskærmet beklædning C, hvor nævnte beklædning er fortrinsvis fremstillet af mindst delvist et tæt materiale, såsom eksempelvis wolfram eller bly.

10. Generator ifølge et hvilket som helst af de foregående krav, hvor moderradioisotop-aktiviteten er inden for et område af værdier fra 0,0 % til 20 %, fordelagtigt fra 0,0 % til 10 %, fortrinsvis fra 0,0 % til 5,0 %, endnu mere fortrinsvis fra 0,0 % til 2,0 %, mere fordelagtigt fra 0,0 % til 1,0 %, i forhold til datterradioisotop-aktiviteten af nævnte eluat.

11. Generator ifølge krav 10, hvor moderradioisotop-aktiviteten er lig med 0,0 mCi.

12. Fremgangsmåde til at eluere en kromatografisk søjle af en radioisotopgenerator (1) omfattende et elueringsmiddelreservoir (2) og forbundet til en kromatografisk søjle (3) af en første elueringsmiddelledning (4), hvilken kromatografisk søjle (3) har en stationær fase og er ladet med en moderradioisotop, som opløses spontant til en datterradioisotop, hvilken fremgangsmåde omfatter de følgende trin:

- at udtage en forudbestemt volumen i et udtagelsesafsnit (9) af en anden elueringsmiddelledning (7) forbundet til en opstrømsdel (4') af den første elueringsmiddelledning (4) og til en nedstrømsdel (4") af den første elueringsmiddelledning (4) af en ventil (8), hvilket udtagelsesafsnit (9) er defineret direkte mellem ventilen (8) og et afsnitsslutpunkt (9'), hvor udtagelsen er gjort, når ventilen (8) er i en første position, hvor den anden ledning er i fluidforbindelse med nævnte opstrømsdel af den første elueringsmiddelledning; og

- at eluere, under virkningen af en drivkraft af elueringsmidlet, nævnte forudbestemte elueringsmiddelvolumen fra nævnte udtagelsesafsnit (9)

mod nævnte kromatografiske søjle (3), når ventilen (8) er i en anden position, hvor den anden ledning (7) er i fluidforbindelse med nævnte nedstrømsdel (4") af den første elueringsmiddelledning, og en tørring af søjlen ved at pumpe steriliseret omgivende luft fra afsnits- (9) slutpunktet (9') eller fra en fri ende (15) af den anden ledning (17) mod eluatudløbet (12),

kendetegnet ved, at fremgangsmåden omfatter et trin at blokere elueringsmidlet, forud for nævnte injektionstrin, for således at blokere passagen af nævnte elueringsmiddelvolumen længere end nævnte afsnits- (9) slutpunkt (9'), hvor nævnte forudbestemte elueringsmiddelvolumen er en tilstrækkelig volumen til at opnå, når nævnte tilstrækkelige volumen krydser den kromatografiske søjle, et eluat omfattende en moderradioisotop-aktivitet inden for et område af værdier fra 0,0 % til 30,0 % i forhold til en datterradioisotop-aktivitet af nævnte eluat.

13. Fremgangsmåde ifølge krav 12, omfattende et ekspurgeringstrin, forud for tørringstrinnet, når nævnte ventil (8) er i den anden position deraf og efter eluering af den stationære fase af den kromatografiske søjle (3) af nævnte tilstrækkelige elueringsmiddelvolumen, bestående af en pumpning af en resterende fraktion af nævnte tilstrækkelige elueringsmiddelvolumen til stede i søjlen mod en ekspurgeringsbeholder tidligere forbundet til et søjle- (3) udløb (12).

14. Fremgangsmåde ifølge krav 12 eller krav 13, hvor moderradioisotop-aktiviteten er inden for et område af værdier fra 0,0 % til 20 %, fordelagtigt fra 0,0 % til 10 %, fortrinsvis fra 0,0 % til 5,0 %, endnu fortrinsvis fra 0,0 % til 2,0 %, mere fordelagtigt fra 0,0 % til 1,0 %, i forhold til datterradioisotop-aktiviteten af nævnte eluat.

15. Fremgangsmåde ifølge krav 14, hvor moderradioisotop-aktiviteten er lig med 0,0 mCi.

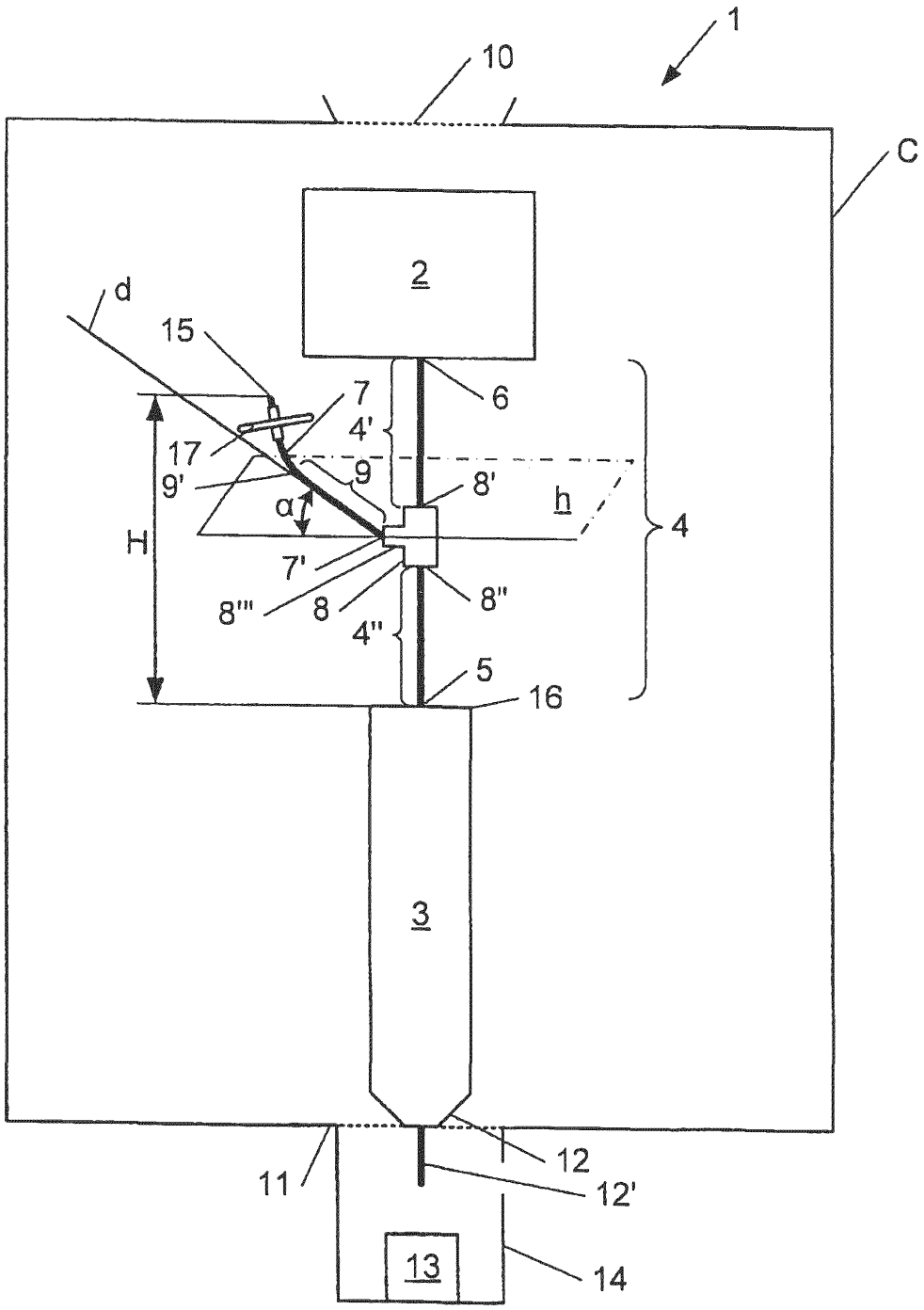


Fig. 1

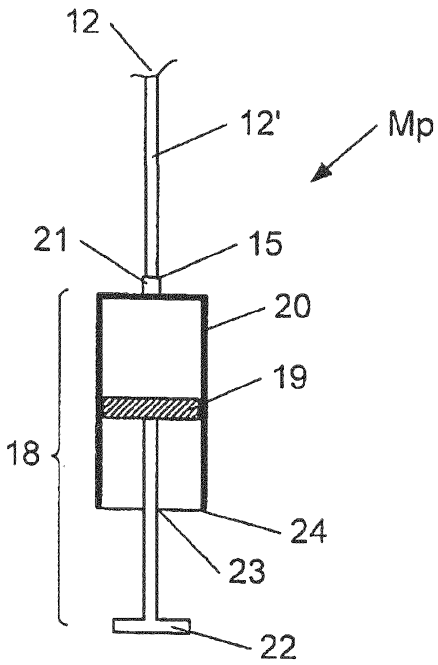

12
12'
Mp
21
15
20
19
18
24
23
22

Fig. 2a

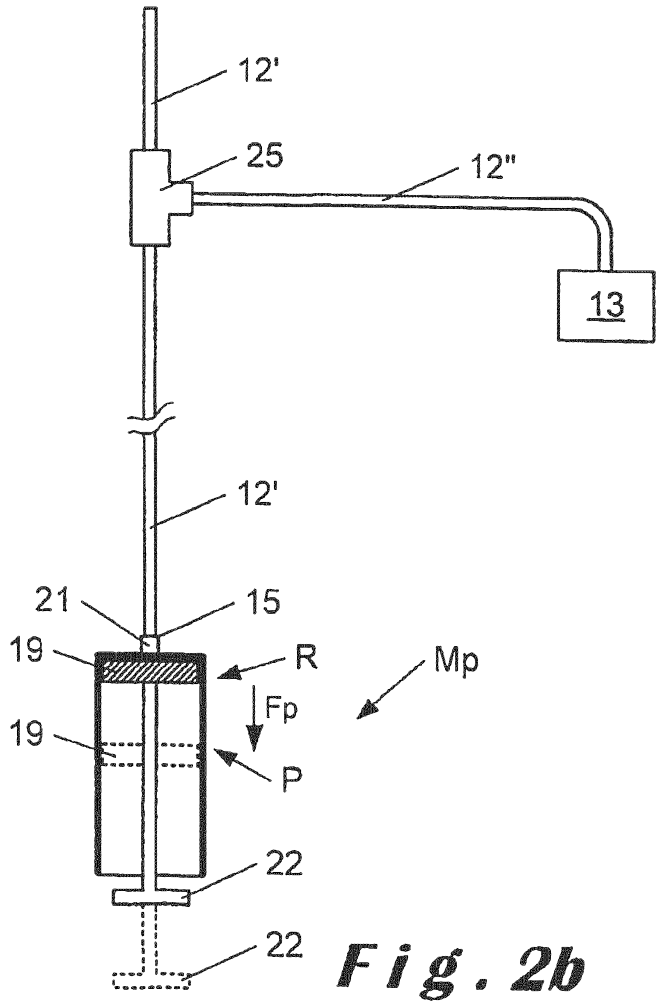

12'
25
12"
13
12'
21
15
19
R
Mp
Fp
19
P
22
22

Fig. 2b

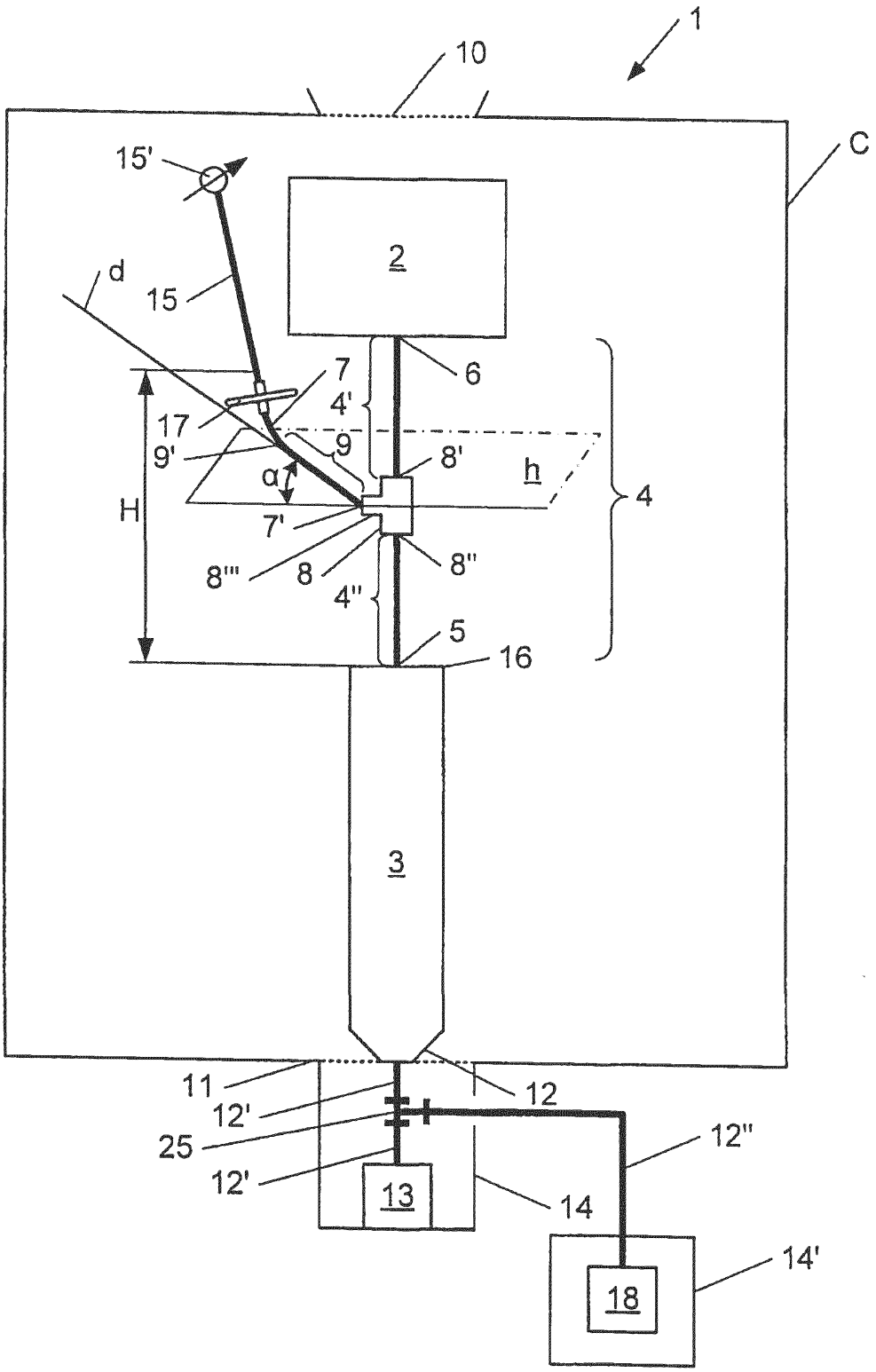

1
10
C
15'
2
d
15
7
4'
6
17
9
9'
8'
h
α
4
H
7'
8'''
8
8''
4''
5
16
3
11
12
12'
25
12''
12'
13
14
14'
18

Fig. 3