PATENT SPECIFICATION (11) 1 582 708

1 582 708

(21) Application No. 16642/77 (22) Filed 21 April 1977
(31) Convention Application No. 687 713 (32) Filed 19 May 1976 in
(33) United States of America (US)
(44) Complete Specification published 14 Jan. 1981
(51) INT. CL.³ G21G 4/08
(52) Index at acceptance
G6R 1A9

(72) Inventors NABIL AZIZ MORCOS
GERALD ANTHONY BRUNO
THOMAS ALBERT HANEY

(19)

(54) MOLYBDENUM-99/TECHNETIUM-99M GENERATORS

(71) We, E. R. SQUIBB & SONS INC., a corporation organised and existing under the laws of the State of Delaware, United States of America, of Lawrenceville-Princeton Road, Princeton, New Jersey, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

The invention relates to molybdenum-99/technetium-99m generators.

Technetium-99 has become widely used in the field of nuclear medicine for the scanning and visualizing of various organs and tissues in the body. When coupled with various substances it has been used, for example, for visualization of the brain, lungs, blood pool, thyroid, liver, spleen, bone and kidney. One of the reasons for the wide-spread acceptance of technetium-99m in the field of nuclear medicine is its relatively short half-life of about 6 hours. While the short half-life of technetium-99m is advantageous in minimizing the physiological risks associated with the use of radioisotopes, it also makes it highly desirable to generate the short lived radionuclide as close to its time of use as possible.

Published patent literature provides many examples of apparatus and methods which can be used for the generation of technetium-99m (referred to in the generator art as the "daughter radionuclide") from molybdenum-99 (referred to in the generator art as the "parent radionuclide"); see, for example, United States Patents 3,369,121 and 3,920,995. The generators currently in use for the generation of technetium-99m from molybdenum-99 comprise a containerized support medium, *e.g.*, chromatographic grade alumina, having adsorbed thereon molybdenum-99. The container is part of a sterile system which further comprises inlet means for introducing an eluant onto the support medium having the molybdenum-99 adsorbed thereon, and outlet means for removing the eluate containing the technetium-99m from the support medium. The operation of this type of generator, as explained by Boyd, "Recent Developments in Generators of 99mTC", Proceedings of a Symposium on Radiopharmaceuticals and Labelled Compounds, Copenhagen, March 26-30, 1973, International Atomic Energy Agency, Vienna (1973), is based on the differences in the distribution-coefficient values of the carrier material for the ions of molybdenum-99 and technetium-99m. The passage of the proper eluant through the support medium will result in the elution of technetium-99m. If physiological saline is utilized as the eluant, the technetium-99m will be eluted in the form of sodium pertechnetate. The pertechnetate ion has a valence of +7, and is technetium's highest and most stable oxidation state in solution.

Commercial generators of the above-described kind, having alumina as the support medium, are delivered to customers for periodic elution. The amount (in millicuries) of technetium-99m obtained in the initial elution will depend on the original potency of the generator. The activity obtained in subsequent elutions will depend on the time interval between elutions. A problem often encountered with the generators is low yield (incomplete removal) of technetium-99m. These yield problems occur most frequently during the early elutions of high activity generators, and are usually the result of a delayed release of technetium-99m from the alumina. It is possible for the generator user to compensate for the low yield by an additional elution of the generator, but such an additional elution is highly undesirable because of the

additional risk of exposure to radiation and because of the inconvenience involved.

Low yield problems have been discussed in the literature (see Boyd, supra. and Vesely et al. "Some Chemical and Analytical Problems Connected with Tc-99m Generators", Radiopharmaceuticals from Genertaor-Produced Radionuclides (Proc. Panel Vienna, 1970) International Atomic Energy Agency, Vienna (1970)) and have been attributed to the effect of ionizing radiation on the valence state of technetium-99m. The reductive nature of the combination of high radiation levels and water may cause technetium to go from its highest valence state of +7 to lower oxidation states, making the technetium difficult, if not impossible, to remove from the generator system with isotonic saline solution.

Previously proposed solutions to the problems of low yields include using an oxidizing agent in the saline eluant or on the alumina column (see, for example, United States patent 3 664 964). The major disadvantage of this technique is that the technetium eluate from the generator is frequently used, as described above, to label substances for localization (and subsequent imaging and visualization) in various organs and tissues. The materials are often in the form of commercial kits which contain, in addition to the substance to be labelled, a reducing agent to facilitate labelling. The presence of an oxidizing agent in the eluate can be detrimental to this process.

According to one aspect of the invention there is provided apparatus for the generation of technetium-99m from molybdenum-99 comprising an alumina support medium for absorption of the molybdenum-99, means for containing the alumina support medium, inlet means for introducing eluant, and outlet means for removing eluate, wherein the alumina support medium comprises at least two beds of alumina, a first bed having a pH above 6 and a further bed having a pH below 6, the difference in the pH of the two beds being at least 0.5, and no bed having a pH higher than a bed which precedes it.

Preferably, the pH of the alumina in the first bed will be from 7 to 10 and the pH of the alumina in the further bed will be between 3.5 and 5.5 and most preferably 4.1.

According to another aspect of the invention there is provided a process for generating technetium-99m from molybdenum-99 comprising pasisng an eluant through an alumina support medium having molybdenum-99 adsorbed thereon and collecting the eluate containing technetium-99m, wherein an alumina support medium is employed comprising at least two beds of alumina, a first bed having a pH above 6, and a further bed having a pH below 6, the difference in the pH of the two beds being at least 0.5, and no bed having a pH higher than a bed which precedes it.

By the apparatus and method of the invention, low yield problems in molybdenum-99/technetium-99m generators can be mitigated without the aid of an oxidizing agent.

Spreading of the molybdenum-99 on the alumina support medium depends upon the relationship between alumina pH and the affinity of molybdenum-99 for the alumina.

Maximum absorption of molybdenum-99 (in aqueous solution) occurs at a pH between 2 and 6.

Thus a molybdenum-99/technetium-99m generator of apparatus according to the invention has an alumina support medium comprising multiple beds of controlled pH preferably loaded into a column. The expression "first bed" refers to the alumina which first receives the molybdenum-99 during column loading and the expression "further bed" refers to the alumina which receives the molybdenum-99 after it has passed through the first bed. Since the first alumina bed has a pH of above 6, the molybdenum-99 loaded onto the column will diffuse through the first bed and reach the further bed. The further bed is needed to prevent the leakage of molybdenum-99 (known in the art as "moly leakage") from the column.

The alumina support medium can have additional beds of alumina between the first and further beds or after the further bed. The critical limitation is that the pH of the various alumina beds does not increase (*i.e.*, the alumina does not become more basic) from the first bed sequentially through the subsequent beds. Thus the alumina support medium is made up of alumina having a decreasing pH gradient from the alumina first contacted with molybdenum-99 to the alumina furthest from the first contacted alumina.

The design of a multiple pH alumina support medium for use in a generator necessitates the optimization of the alumina bed heights. The first bed should be of sufficient height to allow the molybdenum-99 to spread into the alumina to a degree that will result in substantially no low yield problems. The further bed should be of sufficient height to prevent any significant molybdenum-99 leakage. Optimum bed heights will of course vary with the pH of the aluminas utilized. It is preferred, however, that the first bed contain about 15 to 25 weight percent of the total alumina and the further bed contain about 75 to 85 weight percent of the total alumina in a two bed column.

The invention is diagrammatically

illustrated by way of example in the accompanying drawing, in which:—

Figure 1 is a perspective view of a generator of apparatus according to the invention partially cut away to reveal internal details; and

Figure 2 is a fragmentary side elevational view of a column of the generator of Figure 1 shown in cross-section to illustrate the multiple pH alumina support medium.

A more complete description of a generator of the kind shown in Figure 1 can be found in United States patent 3 920 995. The generator 10 has a housing 12 which is sealed at its top 14 and bottom 16 by respective stoppers 17 which can be pierced my hypodermic needles for the purpose of loading molybdenum-99 onto alumina beds, comprising a first bed 42, and a further bed 44, which rest on a perforated disc 46. Eluant may be introduced into the generator 10 via a conduit 18 and eluate removed via a conduit 20. The conduits 18, 20 are shown as separate tubes encapsulated within respective projections 22, 24 which are unitary with the housing 12. The conduits 18. 20 may, of course, be unitary with the housing 12, the entire unit being formed of a moulded plastics material. Covers 26, 28 which seal the conduits 18, 20 respectively, each comprise a moulded cup 30 having a stem 32, which stem encapsulates the upper terminus of the respective conduit 18, 20. The open ends of the conduits 18, 20, however, are not blocked by the cups 30, but are open to the chamber formed by the respective cup. A pierceable closure 34 is sealingly received in each cup 30, and is held in place by means of a flexible metallic ring 33 which is crimped about the cup 30 and the closure 34.

Eluant is introduced into the generator 10 through the inlet conduit by being passed through the closure 34 into the respective cup 30, and from there passing into inlet conduit 18. By providing a reduced pressure in the cover 28, the eluant is pulled through the generator 10, pasisng sequentially through the alumina beds 42, 44 where it picks up the technetium-99m and carries it into a lower terminus 40 of the outlet conduit 20. Preferably, an evacuated container is used to provide the reduced pressure in the cover 28, and draw the fluid out of the cup 30 of the cover 28.

Many procedures for loading a generator of the kind described above with the alumina support medium will be apparent to a practitioner of the invention. It has been found, however, that particularly satisfactory results are achieved when the column is first filled with alumina for the further bed, alumina from the further bed is removed from the top of the column to the desired depth of the first bed and alumina for the first bed is then added to the column.

WHAT WE CLAIM IS:—

1. Apparatus for the generation of technetium-99m from molybdenum-99 comprising an alumina support medium for adsorption of the molybdenum-99, means for containing the alumina support medium, inlet means for introducing eluant, and outlet means for removing eluate, wherein the alumina support medium comprises at least two beds of alumina, a first bed having a pH above 6 and a further bed having a pH below 6, the difference in the pH of the two beds being at least 0.5, and no bed having a pH higher than a bed which precedes it.

2. Apparatus according to claim 1, having two beds of alumina.

3. Apparatus according to claim 1 or claim 2, wherein the first alumina bed has a pH of 7 to 10.

4. Apparatus according to any one of claims 1 to 3, wherein the further alumina bed has a pH of 3.5 to 5.5.

5. A process for generating technetium-99m from molybdenum-99 comprising passing an eluant through an alumina support medium having molybdenum-99 adsorbed thereon and collecting the eluate containing technetium-99m, wherein an alumina support medium is employed comprising at least two beds of alumina, a first bed having a pH above 6, and a further bed having a pH below 6, the difference in the pH of the two beds being at least 0.5, and no bed having a pH higher than a bed which precedes it.

6. A process in accordance with claim 5, wherein the alumina support medium has two beds of alumina.

7. A process according to claim 5 or claim 6, wherein the first alumina bed has a pH of 7 to 10.

8. A process according to any one of claims 5 to 7, wherein the further alumina bed has a pH of 3.5 to 5.5.

9. Apparatus for the generation of technetium-99m from molybdenum-99 substantially as hereinbefore described and illustrated with reference to the accompanying drawing.

10. A process for generating technetium-99m from molybdenum-99 as claimed in claim 5 and substantially as hereinbefore described.

For the Applicants,
D. YOUNG & CO.,
Chartered Patent Agents,
10 Staple Inn,
London WC1V 7RD.

Printed for Her Majesty's Stationery Office by The Tweeddale Press Ltd., Berwick-upon-Tweed, 1980.
Published at the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.

1582708 COMPLETE SPECIFICATION

1 SHEET *This drawing is a reproduction of the Original on a reduced scale*

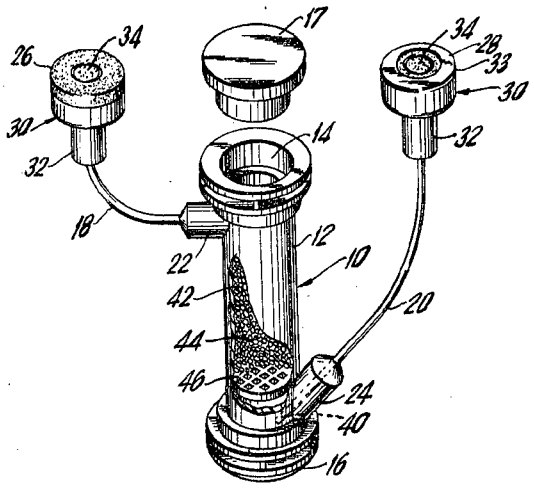

FIG.1

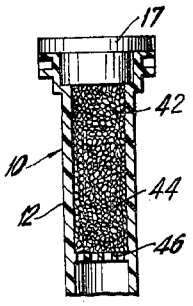

FIG.2