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**PRODUCTION OF HIGH PURITY RADIOACTIVE
TECHNETIUM-99m****Hirofumi Arino, Suffern, N.Y., assignor to Union Carbide
Corporation, a corporation of New York****No Drawing. Filed June 16, 1967, Ser. No. 646,453****Int. Cl. C09k 3/00****U.S. Cl. 252—301.1****11 Claims****ABSTRACT OF THE DISCLOSURE**

Pure technetium-99m is obtained by a process which comprises selectively extracting technetium-99m from a slurry of its radioactive parent, molybdenum-99, deposited on oxidized, hydrous zirconium oxide.

This invention relates to a novel process for the production of radioactive technetium-99m. In one aspect, this invention relates to a novel process for the production of radioactive technetium-99m in high yields. A further aspect of this invention is directed to a novel process for the production of radioactive technetium-99m which can be obtained in a high degree of purity.

Recent medical investigation has shown that technetium-99m is an extremely useful tool for diagnosis. High purity technetium-99m is used primarily as a radioisotope in a variety of medical research and diagnosis. It is well suited for liver, lung, blood pool and tumor scanning, and is preferred over other radioactive isotopes because of its short half-life which results in reduced exposure of the organs to radiation. In addition to medical uses, technetium-99m can also be employed in industrial applications, such as in the measurement of flow rates, process control, radiometric chemistry, and the like. Since the radioisotope sought to be used has such a short half-life, it is common practice to ship the users of the isotope the parent element; in this case radioactive molybdenum-99. The user then extracts the technetium from the molybdenum-99 as his needs require.

In the past, radioactive technetium-99m has been produced by a variety of methods. For example, M. S. Faddeeva et al., Zhur. Neorg. Khim., 3, 165-166 (1958), has disclosed a process for extracting technetium-99m from 6 N aqueous K_2CO_3 solutions containing dissolved molybdenum-99 containing material, using methyl ethyl ketone as the extracting medium, followed by washing the ketone solutions with K_2CO_3 aqueous solution. The technetium-99m recovered by this process, however, was not pure, since the product contained detectable K_2CO_3 and would therefore not be useable for many purposes, such as for medical purposes.

More recently, a process was perfected for the separation of technetium-99m from molybdenum-99. Separation was effected by contacting the molybdenum-99 (in the form of molybdate ions) with alumina, followed by selective removal of technetium-99m (in the form of TeO_4^- ion) from the bonded alumina. Although, to date, the alumina column generally is acceptable, the chemical purity of the eluant barely meets minimum medical requirements and the column itself is at times unstable, producing an eluant unfit for medical purposes.

Finally, J. J. Pinajian, International J. Applied Radioactive Isotopes, 17, 664 (1966) reported a method which used hydrous zirconium oxide as the absorbing media for the chromatographic selective adsorption of molybdenum and eluded technetium-99m with acid methyl ethyl ketone (5 vol. percent 0.01 M HCl). The methyl ethyl ketone eluant must then be processed to produce a physiologically acceptable solution for parental injection because of its extreme toxicity.

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It is therefore an object of this invention to provide a more efficient method for producing radioactive technetium-99m. Another object of this invention is to provide a process for preparing radioactive technetium-99m in a high degree of purity and by an extremely reproducible process. A further object of this invention is to provide a process which avoids the need for separating radioactive products and other impurities. These and other objects will readily become apparent to those skilled in the art in the light of the teachings herein set forth.

It has now been discovered that the aforementioned objects can be achieved by a process which comprises the steps of (a) producing radioactive molybdenum-99, (b) dissolving the radioactive compound, (c) adjusting the pH of the radioactive solution, (d) contacting the radioactive solution with oxidized hydrous zirconium oxide, and (e) selectively extracting technetium-99m from the oxidized substrate.

Operating in the aforesaid manner provides a selective separation of technetium-99m from all other elements in the dissolved radioactive molybdenum-99 compound with very high efficiency, i.e., over 80 percent.

In addition the process of this invention is readily reproducible and simple to operate.

Although a variety of compounds are suitable for use in the process of this invention the preferred target is molybdenum trioxide. In the event that other compounds are employed, it is often necessary to isolate the molybdenum component after irradiation. Illustrative compounds which can be employed as the source of molybdenum-99 include, among others, molybdenum metal, molybdenum nitrate, molybdenum sulfate, organic molybdenum compounds such as molybdenum acetylacetonates, and fissionable materials such as uranium-235, uranium-238, plutonium-239, and the like.

Irradiation of compounds to produce molybdenum-99 is a well known technique and can be effected by placing the proper compound in the irradiation zone of a nuclear reactor, particle generator, or neutron isotopic source.

Thereafter, the irradiated compound is dissolved in a suitable solvent. In the case of molybdenum trioxide it may be necessary to employ a basic solvent such as sodium hydroxide, ammonium hydroxide, and the like, the techniques to dissolve and isolate a pure molybdenum-99 solution are well known in the art.

In contrast to the work disclosed by Pinajian, wherein hydrous zirconium oxide was employed, it has now been unexpectedly and surprisingly found that when a zirconium salt, such as hydrous zirconium oxide, is contacted with an oxidizing agent it produces chemical reactive sites that selectively adsorb molybdenum but does not appear to adsorb technetium. It is also surprising that

- (a) the loading capacity of the system exceeds all other known systems which yield equivalent amounts of technetium when using physiological saline,
- (b) that the saline containing the technetium product has unexpectedly lower elemental impurities due to the molybdenum absorbing substrate, and
- (c) that the saline contains appreciably more technetium and less molybdenum than comparable systems heretofore known.

In accordance with the process of the present invention molybdenum solution, such as aqueous ammonium molybdate is contacted with oxidized zirconium salts. The oxidized zirconium salts are prepared by contacting a compound, such as hydrous zirconium oxide, with an oxidizing agent, in the presence of an acid. Suitable oxidizing agents which can be employed include, among others, bromine water, chlorine water, iodide water, permanganate salts, such as potassium permanganate, chlorate

salts, such as potassium chlorate, hydrogen peroxide, or organic peroxides, such as benzoyl peroxide and the like.

Thereafter, the pH of the contacted solution is adjusted to a range between 2 to 7 and more preferably between 3.5 and 6.0. Normally, it is preferable to heat the solution during pH adjustment and control and to maintain this heat for a duration of approximately twenty minutes to insure adsorption of the molybdenum on the zirconium substrate. Temperature is not necessarily critical and need only be sufficient to insure complete reaction of the molybdenum and the oxidized zirconium salt. In practice, temperatures greater than 70° C., have been found satisfactory, with the preferred temperature being the boiling point of the slurry.

The zirconium substrate containing the molybdenum is then transferred to an appropriate elution system such as a column, or vessel, preferably glass, or other inert material. The supernatant liquid is allowed to drain or removed by filtration or decantation and the substrate washed with isotonic saline.

The technetium-99m in the column or vessel which contains 99Mo-99mTc activity can subsequently be isolated, e.g., milked, filtered, centrifuged or the like for technetium-99m as it is formed with an acidic, neutral or basic solution. Preferably, it has been observed that best results are obtained when the system is eluted with 20 milliliter portions of isotonic saline solutions. This is done by contacting the substrate with the desired volume of saline and collecting the liquid portion.

Numerous variations of the preferred embodiment described above may be practiced, as will be apparent to those skilled in the art, without departing from the basic concepts of the present invention.

As previously indicated, the process of the present invention provides a simple method for the preparation of technetium-99m in a high degree of efficiency. By this process recovery of technetium-99m can be effected with isotonic saline in efficiencies as high as 95% and higher, over a pH range of about 4.0 to about 7.0 without appreciable dissolution of the zirconium substrate or removal of any molybdenum from the zirconium substrate.

A further advantage characteristic of the process of this invention, is that the substrate and/or the entire elution system can be sterilized, i.e., by autoclaving at the normally prescribed temperatures and pressures.

In contrast, the previously known hydrous zirconium oxide, which are loaded with an acid solution containing molybdenum can not be efficiently eluted for technetium with isotonic saline.

The following example is illustrative:

EXAMPLE 1

To 100 grams of Bio-Rad hydrous zirconium oxide (100-200 mesh) was added 100 milliliters of 0.1 M HCl and 10 milliliters of saturated bromine water. The mixture was stirred and allowed to stand for 10 minutes. Thereafter 15 milliliters of 1 M NaOH was added to the slurry. A sufficient volume of this slurry was transferred into a 150 milliliter beaker to provide 1 milliliter of slurry per 57 milligrams of molybdenum. Thereafter the slurry was washed three times with water and four drops of saturated bromine water added. To the slurry was added a solution containing 1 gram of irradiated molybdenum material as the molybdate in 20 milliliters of 20 percent ammonium hydroxide. The mixture was heated with stirring and 6 M HNO₃ was slowly added until pH was between 4 to 6. Additional HNO₃ was added to maintain this pH until the chemical reaction was complete. Thereafter, the slurry was heated for 20 minutes and cooled. The slurry was then transferred into a column and washed with isotonic saline solution. After the technetium-99m had built up in the generator it was eluted with isotonic saline solution.

The column was tested for molybdenum break-through

by radiometric analysis and no molybdenum-99 was observed. Chemical purity was tested by emission spectroscopy for the major elements of the column substrate, i.e., zirconium, and none was detectable.

EXAMPLE 2

A comparison of adsorption-elution characteristics of the column of Example 1 and one prepared in accordance with a recent method, wherein an alumina column is employed the data obtained is set forth in Table I below:

TABLE I.—COMPARISON OF ADSORPTION-ELUTION CHARACTERISTICS OF ZIRCONIA AND ALUMINA SYSTEMS

	Alumina	Zirconia
Mo loading (mg. Mo/ml. adsorber).....	<42	>57
99mTc recovery (percent) in isotonic saline solution (ml.):		
Sterile.....	60-80/30	>90/30
Non-sterile.....	80/20	>80/20
Metal impurity (p.p.m.):		
Sterile.....	>1	<1
Non-sterile.....	>50	<1
Stability.....	Fair	Excellent

As previously indicated radiometric analysis of the eluted technetium-99m indicates that it contains up to 95 percent of the available technetium-99m and the radionuclidic purity is greater than 99.99 percent. The total metal element impurity is less than 1 part per million as determined by emission spectroscopy techniques.

The substrate and/or the entire elution system can be sterilized by acceptable autoclave techniques with no reduction in radionuclidic impurity, no increase in the metal element impurities and no reduction in the amount of technetium-99m recoverable.

Although the invention has been illustrated by the preceding example, it is not to be construed as being limited to the materials employed therein, but rather, the invention encompasses the generic area as hereinbefore disclosed. Various modifications and embodiments of this invention can be made without departing from the spirit and scope thereof.

What is claimed is:

1. A process for producing radioactive technetium-99m which is formed by the decay of its radioactive parent, molybdenum-99, which comprises the steps of:

(a) contacting an oxidized zirconium salt with a solution containing radioactive molybdenum-99; to produce a slurry;

(b) adjusting and maintaining the pH of said slurry to within the range of from 2 to 7;

(c) heating said slurry above 40° C. until static conditions of pH are observed,

(d) selectively extracting said slurry with a solvent capable of separating technetium-99m from its radioactive parent molybdenum-99 that is deposited on the slurry.

2. The process of claim 1 wherein said oxidized zirconium salt is oxidized hydrous zirconium oxide.

3. The process of claim 2 wherein said oxidized hydrous zirconium oxide is obtained by contacting hydrous zirconium oxide with an oxidizing agent.

4. The process of claim 3 wherein said oxidizing agent is selected from the group consisting of bromine water, chlorine water, iodine water, potassium permanganate, potassium chlorate, hydrogen peroxide, and benzoylperoxide.

5. The process of claim 3 wherein said oxidizing agent is bromine water.

6. The process of claim 1 wherein technetium-99m is selectively extracted with isotonic saline.

7. The process of claim 1 wherein said slurry is sterilized.

8. The process of claim 7 wherein said sterile slurry is extracted with sterile isotonic saline to provide a sterile solution containing technetium-99m.

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9. The process of claim 1 wherein technetium-99m is selectively extracted with methyl ethyl ketone.

10. The process of claim 1 wherein technetium-99m is selectively extracted with an aqueous solution of an inorganic acid.

11. A sterile, isotonic saline solution consisting of technetium-99m and having a radionuclidic purity greater than 99.99 percent and a total metal element impurity of less than 1 part per million.

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