block specific Silica Actinide Resin having P,P' di-octyl methane bisphosponic acid binding groups on a silica support. This provided relatively high purity, of less than $4x10^{-3}\%$ ^{227}Ac in comparison with ^{223}Ra, but required a large number of manual handling steps and was poorly suited for scaling-up or automation. Furthermore, because the resin irreversibly sorbed the mother and grandmother nuclei, the issue of radioactive damage to the resin becomes significant if such a resin is to be used for the commercial lifetime of an ^{227}Ac source (tens of years). This is especially the case on a commercial scale, where concentrations of isotopes need to be kept as high as possible to maximise batch sizes and minimise handling volumes.

No previously known method for the generation of ^{223}Ra addresses issues such as yield of ^{223}Ra, speed of the purification process, automation, minimising of wasted isotopes and corresponding production or radioactive waste or any similar issues associated with commercial-scale production. Furthermore, all methods known to produce ^{223}Ra of viable pharmaceutical purity use specialist resins which cannot be guaranteed to be available and are potentially more difficult to validate as reliable. Guseva *et al.* (Radiochemistry **46**, 58-62 (2004)) proposed a basic generator system for ^{223}Ra using an anion exchange method developed for extracting radium from environmental samples. This, however, was on a very small scale and never intended or indicated as providing material of pharmaceutical purity.

In view of the above, there is a considerable need for an improved method by which ^{223}Ra may be generated and purified for pharmaceutical use at a purity appropriate for direct injection into human subjects. It would be a considerable advantage if the method were to provide a high yield of ^{223}Ra, a low loss of ^{227}Ac and/or ^{227}Th parent isotopes and/or utilise widely available separation media. It would be further advantageous if the method was rapid, was viable for relatively large (commercial scale) radioactive samples, included only a minimum number of manual handling steps, and/or was suitable for automation.

~~Brief Description of the Invention~~Summary

The present inventors have now established that by separation of a $^{227}Ac/^{227}Th/^{223}Ra$ generator using a strong base anion exchange resin, followed by separation utilising a strong acid cation exchange resin, a ^{223}Ra solution of very high radiochemical purity may be produced while providing a number of desirable advantages in the method.

In a first aspect, the present invention refers to ^{223}Ra comprising no more than 0.05 Bq ^{227}Ac per 1MBq ^{223}Ra. In another aspect, the present invention refers to a pharmaceutical composition comprising the ^{223}Ra and optionally at least one pharmaceutically acceptable diluent, wherein said radium comprises less than 45 Bq ^{227}Ac per 1MBq ^{223}Ra.

~~In a first aspect, the present invention therefore provides~~Also disclosed herein is a method for the generation of ^{223}Ra of pharmaceutically tolerable purity comprising

i) forming a generator mixture comprising ^{227}Ac, ^{227}Th and ^{223}Ra;
ii) loading said generator mixture onto a strong base anion exchange resin;
iii) eluting said ^{223}Ra from said strong base anion exchange resin using a first mineral acid in an alcoholic aqueous solution to give a first eluted ^{223}Ra solution;
iv) loading the ^{223}Ra of the first eluted ^{223}Ra solution onto a strong acid cation exchange resin; and
v) eluting the ^{223}Ra from said strong acid cation exchange resin using a second mineral acid in aqueous solution to provide a second eluted solution.

The process will optionally and preferably also include either one or both of the steps of:

x) eluting said ^{227}Ac and ^{227}Th from said strong base anion exchange resin using a third mineral acid in aqueous solution, whereby to recover a mixture of ^{227}Ac and ^{227}Th; and
y) storing said mixture of ^{227}Ac and ^{227}Th for a period sufficient to allow ingrowth of ^{223}Ra by radioactive decay, whereby to re-form a generator mixture comprising ^{227}Ac, ^{227}Th and ^{223}Ra.

Step x) may be carried out at any point following step iii) of the above-described process. Step y) will begin immediately following elution step iii) and may occur primarily on the anion resin (i.e. before or without step x)) and/or after recovery of the ^{227}Ac and ^{227}Th mixture from the resin (i.e. after step x)).

After ingrowth step y), the generator mixture may be re-used to generate a further batch of ^{223}Ra, and a single ^{227}Ac sample will preferably be used repeatedly (e.g. more than 10 times, such as 50 to 500 times). If the ^{227}Ac and ^{227}Th mixture is not eluted from the strong base anion exchange resin then the process may be repeated from step iii). Preferably, however, step x) will be carried out and the ^{227}Ac and ^{227}Th mixture eluted from the strong base anion exchange resin. In this case the process will be repeated from step i) or step ii).

~~In a further aspect, the present invention provides~~Also disclosed herein is a solution of ^{223}Ra comprising less than 45 Bq ^{227}Ac per 1MBq ^{223}Ra, preferably a solution of ^{223}Ra comprising less than 10 Bq ^{227}Ac per 1MBq

Claims

1) ^{223}Ra comprising no more than 0.05 Bq ^{227}Ac per 1MBq ^{223}Ra.

2) ^{223}Ra as claimed in claim 1 formed or formable by a method comprising

   i) preparing a generator mixture comprising ^{227}Ac, ^{227}Th and ^{223}Ra;
   ii) loading said generator mixture onto a strong base anion exchange resin;
   iii) eluting said ^{223}Ra from said strong base anion exchange resin using a first mineral acid in an alcoholic aqueous solution to give a first eluted ^{223}Ra solution;
   iv) loading the ^{223}Ra of the first eluted ^{223}Ra solution onto a strong acid cation exchange resin; and
   v) eluting the ^{223}Ra from said strong acid cation exchange resin using a second mineral acid in aqueous solution to provide a second eluted solution.

3) ^{223}Ra as claimed in claim 2, wherein said method additionally comprises the step of:

   x) eluting said ^{227}Ac and ^{227}Th from said strong base anion exchange resin using a third mineral acid in aqueous solution, whereby to provide a mixture of ^{227}Ac and ^{227}Th, wherein step occurs at any time following step ii).

4) ^{223}Ra as claimed in claim 3 wherein at least 99.9% of the ^{227}Ac and/or at least 98% of the ^{227}Th loaded onto the resin in step ii) is recovered in step x).

5) ^{223}Ra as claimed in any of claims 2 to 4, wherein said method additionally comprises the step of:

   y) storing said mixture of ^{227}Ac and ^{227}Th for a period sufficient to allow ingrowth of ^{223}Ra by radioactive decay, whereby to regenerate a generator mixture comprising ^{227}Ac, ^{227}Th and ^{223}Ra.

6) ^{223}Ra as claimed in any of claims 2 to 5 wherein the method purifies sufficient ^{223}Ra for more than 10 typical doses.

7) ^{223}Ra as claimed in any of claims 2 to 6 wherein a ^{227}Ac radioactivity of at least 500 MBq is employed in step i).

8) ^{223}Ra as claimed in any of claims 2 to 7 wherein the strong base anion exchange resin is a polystyrene/divinyl benzene copolymer based resin, preferably containing 1-95 % DVB and/or is an R-$N^{+}Me_3$ type (type I) resin or an R-$N^{+}Me_2CH_2CH_2OH$ (Type II) resin.

9) ^{223}Ra as claimed in any of claims 2 to 8 wherein the first mineral acid is an acid selected from H_2SO_4 and HNO_3, preferably HNO_3 and/or is used at a concentration of 0.01 to 5 M.

10) ^{223}Ra as claimed in any of claims 2 to 9 wherein the alcoholic aqueous solution comprises at least one alcohol selected from methanol, ethanol and isopropanol, preferably methanol.

11) ^{223}Ra as claimed in any of claims 2 to 10 wherein the alcoholic aqueous solution may comprises 20 to 99% methanol.

12) ^{223}Ra as claimed in of claims 2 to 11 wherein the first eluted solution has a contamination level of no more than 100 Bq ^{227}Ac per 1MBq ^{223}Ra.

13) ^{223}Ra as claimed in any of claims 2 to 12 wherein the steps of loading the generator mixture onto the base anion exchange resin and eluting the first eluted ^{223}Ra solution provide a separation ratio of ^{223}Ra to ^{227}Ac of at least 10,000:1.

14) ^{223}Ra as claimed in any of claims 2 to 13 wherein the strong acid cation exchange resin is a polystyrene/divinyl benzene copolymer based resin, preferably containing 1-95 % DVB and/or is of SO_3H type.

15) ^{223}Ra as claimed in any of claims 2 to 14 wherein the second mineral acid is an acid selected from H_2SO_4, HNO_3 and HCl, preferably HNO_3 and/or is used at a concentration of 0.5 to 5 M.

16) ^{223}Ra as claimed in any of claims 2 to 15 wherein the aqueous solution does not comprise any significant amount of any alcohol selected from methanol, ethanol and isopropanol, preferably wherein the aqueous solution is substantially free of methanol.

17) A pharmaceutical composition comprising the ^{223}Ra and optionally at least one pharmaceutically acceptable diluent, wherein said radium comprises less than 45 Bq ^{227}Ac per 1MBq ^{223}Ra.

Claims

1) A method for the generation of ^{223}Ra of pharmaceutically tolerable purity comprising

   i) preparing a generator mixture comprising ^{227}Ac, ^{227}Th and ^{223}Ra;
   ii) loading said generator mixture onto a strong base anion exchange resin;
   iii) eluting said ^{223}Ra from said strong base anion exchange resin using a first mineral acid in an alcoholic aqueous solution to give a first eluted ^{223}Ra solution;
   iv) loading the ^{223}Ra of the first eluted ^{223}Ra solution onto a strong acid cation exchange resin; and
   v) eluting the ^{223}Ra from said strong acid cation exchange resin using a second mineral acid in aqueous solution to provide a second eluted solution.

2) The method of claim 1 additionally comprising the step of:

   x) eluting said ^{227}Ac and ^{227}Th from said strong base anion exchange resin using a third mineral acid in aqueous solution, whereby to provide a mixture of ^{227}Ac and ^{227}Th, wherein step occurs at any time following step ii).

3) The method as claimed in claim 2 wherein at least 99.9% of the ^{227}Ac loaded onto the resin in step ii) is recovered in step x).

4) The method as claimed in claim 2 or claim 3 wherein at least 98% of the ^{227}Th loaded onto the resin in step ii) is recovered in step x).

5) The method of any of claims 1 to 4 additionally comprising the step of:

   y) storing said mixture of ^{227}Ac and ^{227}Th for a period sufficient to allow ingrowth of ^{223}Ra by radioactive decay, whereby to regenerate a generator mixture comprising ^{227}Ac, ^{227}Th and ^{223}Ra.

6) The method of any of claims 1 to 5 wherein the method purifies sufficient ^{223}Ra for more than 10 typical doses.

7) The method of any of claims 1 to 6 wherein a ^{227}Ac radioactivity of at least 500 MBq is employed in step i)

8) The method of any of claims 1 to 7 wherein the strong base anion exchange resin is a polystyrene/divinyl benzene copolymer based resin, preferably containing1- 95 % DVB.

9) The method of any of claims 1 to 8 wherein the strong base anion exchange resin is an R-$N^{+}Me_3$ type (type I) resin or an R-$N^{+}Me_2CH_2CH_2OH$ (Type II) resin.

10) The method of any of claims 1 to 9 wherein the first mineral acid is an acid selected from H_2SO_4 and HNO_3, preferably HNO_3.

11) The method of any of claims 1 to 10 wherein the first mineral acid is used at a concentration of 0.01 to 5 M.

12) The method of any of claims 1 to 11 wherein the alcoholic aqueous solution comprises at least one alcohol selected from methanol, ethanol and isopropanol , preferably methanol.

13) The method of any of claims 1 to 12 wherein the alcoholic aqueous solution may comprises 20 to 99% methanol.

14) The method of any of claims 1 to 13 wherein the first eluted solution has a contamination level of no more than 100 Bq ^{227}Ac per 1MBq ^{223}Ra.

15) The method of any of claims 1 to 14 wherein the steps of loading the generator mixture onto the base anion exchange resin and eluting the first eluted ^{223}Ra solution provide a separation ratio of ^{223}Ra to ^{227}Ac of at least 10,000:1.

16) The method of any of claims 1 to 14 wherein the strong acid cation exchange resin is a polystyrene/divinyl benzene copolymer based resin, preferably containing 1- 95 % DVB.

17) The method of any of claims 1 to 14 wherein the strong acid cation exchange resin is of SO_3H type.

18) The method of any of claims 1 to 14 wherein the second mineral acid is an acid selected from H_2SO_4, HNO_3 and HCl, preferably HNO_3.

19) The method of any of claims 1 to 14 wherein the second mineral acid is used at a concentration of 0.5 to 5 M.

20) The method of any of claims 1 to 14 wherein the aqueous solution preferably does not comprise any significant amount of any alcohol selected from methanol, ethanol and isopropanol. Preferably the aqueous solution is substantially free of methanol;

21) The method of any of claims 1 to 14 wherein the second eluted solution has a contamination level of no more than 45 Bq ^{227}Ac per 1MBq ^{223}Ra.

22) ^{223}Ra comprising less than 45 Bq ^{227}Ac per 1MBq ^{223}Ra.

23) ^{223}Ra as claimed in claim 22 formed or formable by a method as claimed in any of claims 1 to 21.

24) A pharmaceutical composition comprising the ^{223}Ra as claimed in any of claims 22 to 23 and optionally at least one pharmaceutically acceptable diluent.