ALTERNATE WAY TO PRODUCE ^{113m}In-MACRO-IRON HYDROXIDE

Our continuing research on the formation of ^{113m}In-tagged compounds has shown that an alternate procedure for the production of ^{113m}In-macro-iron hydroxide has advantages over the one previously reported (*1,2*). Systematic examination of the variables shows that the rate of particle formation and particle size distribution is influenced by: the *p*H of the "precipitating" solution, the molarity of the titrating NaOH solution, the speed of the NaOH addition, the speed of mixing (agitation), the time of mixing and, most important of all, the temperature of the "precipitating" solution and the purity of each of the solutions—the eluant, the eluate, the ferric chloride solution and the sodium hydroxide titrating solution.

At elevated temperatures, however, the production of the macro-iron hydroxide particles is more rapid, and the other variables mentioned above have an appreciably less apparent influence. For example, we observed that when the solution was heated to between 80°C and 95°C, macro-iron hydroxide particles were formed; this resulted in greater than 95% tagging by ^{113m}In and gave a more uniform particle of 30–50 microns diameter with no particles greater than 75 microns. From these data we were able to develop a simpler formulation for the production of ^{113m}In-tagged iron hydroxide compound for lung scanning. The formulation is as follows:

1. To 5 ml of the acidic eluate, add 100 μg of iron as Fe^{+3} in 0.1*N* HCl (e.g., 0.1 ml of an 0.1*N* HCl solution containing 5 mg of $FeCl_3 \cdot 6H_2O$ per 1 ml of 0.1*N* HCl). The particle size and the particle size distribution is not influenced over the iron concentration range of 5–30 μg/ml of eluate. The macro-particle forms more readily at the higher iron concentration; however, 15 μg/ml was selected because previous data (*2*) indicate that at this concentration about 100,000 particles are formed.

2. Add 0.5*N* and 0.1*N* NaOH until *p*H is between 7.2 and 8.0. (Stir solution while adding NaOH.)

3. Heat solution to 80–95°C for 10 min. (This is simply done by placing test tube in a water bath that is at incipient boiling. Prolonged heating does not appear to have a significant effect on particle size or distribution.)

4. Remove vial from hot water bath and shake vial vigorously. (Vial can be cool or hot when shaking. The shaking disperses the particles for coating with gelatin.)

5. Add 1 ml of 10% gelatin solution (Neutral granulated gelatin—not acid). (The gelatin solution may be added either to the hot or cold solutions. However, the gelatin must be added before the solution is autoclaved. Autoclaving, which is at a higher temperature than the hot water bath, will give rise to larger particles if no gelatin is present.)

6. Our experience indicates that the final product can be sterilized by autoclaving at 250°F and 15 psi for 20 min. (The autoclaving step appears to reduce the particle size distribution by 10–15%; e.g., 40–60-micron particles will be reduced to 30–50-micron particles.)

7. To insure a homogeneous withdrawal from the vial, shake vigorously immediately before using.

The major advantage of this formulation is that it appears to circumvent the problems associated with the room-temperature formulation and gives rise to a more uniform particle size distribution with no particle greater than 75 microns (as observed with a hemacytometer). The data obtained from products produced by the above formulation showed that more than 95% of the tagged activity did not pass through a 14-micron Millipore filter. Animal-uptake experiments showed more than 85% of the dose deposited in the lungs with a lung-to-liver ratio greater than 20. Another advantage is that the formulation is considerably simpler than the one we first developed (*1,2*) because it eliminates the HCl back-titration step (often a rather difficult one) and uses a gelatin solution that does not have to be heated before use.

At room temperature the rate of particle formation and particle size distribution is very dependent on other elements in the eluate. It appears that the purer the solution, the more difficult it is to make macro-iron hydroxide particles, even at very high *p*H (13.5). Consequently, we investigated the effect of zirconium and silicon impurities in the eluate. We looked at zirconium because ^{113m}In generators may have zirconia as the supporting substrate and at silicon primarily because HCl and NaOH solutions stored in glass containers will contain silicon that is

dissolved from the walls of the containers. We observed that silicon concentrations of 0.5–25 ppm (the latter is commonly observed in sodium hydroxide solutions) do not affect the formation of macro-iron hydroxide particles and do not appear to alter their particle size distribution. However, zirconium contents as low as 0.05 ppm appear to catalyze the precipitation reaction but, at this level, do not have any affect on the particle size distribution. At zirconium concentration levels of 4 ppm and higher the particle size distribution is altered—particles greater than 100 microns were observed and were different in appearance. The number of particles greater than 100 microns in diameter increased as the zirconium concentration increased. At 10 ppm a large number of particles were formed with diameters considerably larger than 100 microns.

We recommend that the macro-iron hydroxide particles be submitted to rigid quality control before human use. Our studies indicate that at least two tests should be performed:

1. Large particle size—to insure that no particles greater than 100 microns in diameter are present in the solution. When the eluate is pure, we found that no particles greater than 75 microns were formed by the formulation. However, trace amounts of certain cations will catalyze the formulation of very large particles when one uses the formulation.

The test: Shake the solution vigorously, aliquot several drops, place one drop on a hemacytometer and then cover the drop with a cover glass. Do not place cover glass on hemacytometer before adding the prepared compound because the larger particles will not diffuse into the scribed areas but will remain at the edge of the cover glass. Observe the sizes of the particles on the scribed portion of the hemacytometer. Look at the edges of the cover glass for large particles that may have been squeezed out and away from the scribed area.

2. Small particle size—to ascertain liver and lung uptake.

The test: Filter a small aliquot of the final solution through a 14-micron Millipore filter. The fact that more than 90% of the activity was deposited on the filter indicated (in our animal data) more than 90% lung uptake with less than 5% liver uptake.

REFERENCES

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COMMENT ON QUANTITATIVE COUNTING

The authors of the article on "Quantitative Counting in the Presence of Coincidence-Summing Scintillations" (JNM, July '67, p. 502) should be congratulated on the excellent presentation and timely topic.

The article also demonstrates the problems that can be encountered in quantitative separation of dual isotopes using well crystals.

It might be of interest to mention ^{133}Ba. Because of its long half-life and similarity to ^{131}I, it is often used as a counting standard or calibration source. When it is used in a well crystal, this isotope exhibits a spectrum that resembles that of a beta particle due to coincidence summing. Thus it is difficult to determine the true location of the main photopeak. The situation can be greatly improved by surrounding the source with lead absorber that is thick enough to attenuate low energies. The penalty of course is a lower photopeak counting rate.

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