

INCOMPATIBILITY OF PHOSPHATE BUFFER IN**^{99m}Tc-SULFUR COLLOID CONTAINING ALUMINUM ION**

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The widespread use of ^{99m}Tc-sulfur colloid for RES scanning has been warranted by the excellent physical characteristics of ^{99m}Tc and by the ease and reproducibility in the daily preparation of the radiopharmaceutical. In response to necessity or convenience, there have been some variations or options in the formulation of this product since it was first introduced; for example, (A) choice of hydrogen sulfide or sodium thiosulfate as source of sulfur, (B) availability of several colloid stabilizers for ease in the preparation or as a substitute for ingredients which have caused anaphylactic reactions, and (C) a compensating increase in the amount of sodium thiosulfate for those using ^{99m}Tc generator eluates containing oxidizing agents. Despite these differences in formulation, the sulfur colloid being made with any of these variations can still conform to AEC specifications.

However, recent reports have indicated occasional appearance of a flocculation of the colloid accompanied by increased lung uptake of the radioactivity (1,2). Experimentation has shown that such flocculation accompanies the appearance of aluminum ion in the eluate from ^{99m}Tc generators, with the rate of precipitation a function of the aluminum ion concentration in the eluate (2). Other reports have shown that the amount of aluminum ion which has appeared in eluates was varied and ranged to about 150 µg/ml (3,4).

One effective means of preventing this flocculation requires the addition of a chelating agent like EDTA to sequester the aluminum ion (2). Some commercial manufacturers of kits for making this product include chelating agents in their formulations.

But closer examination of the cause of flocculation indicates that aluminum ion is only part of the problem. The other part stems from the use of phosphate buffers to adjust the final pH. In almost all buffered formulations reported, the buffer has been phosphate.

Even when aluminum ion is present in concentration less than permitted by AEC regulation, the addition of larger amounts of phosphate can cause the solubility product of aluminum phosphate (1.3×10^{-20}) to be exceeded. Coprecipitation of colloid with aluminum phosphate results.

To demonstrate a simpler method for prevention of this precipitation, we prepared several batches of sulfur colloid with deliberate addition of enough aluminum chloride to the eluate of the generator to provide 100 µg of aluminum ion/ml in the final product. Each batch was adjusted with different solutions to the final pH.

Figure 1 shows the appearance of unbuffered and buffered batches of sulfur colloid using sodium hydroxide and phosphate, citrate and acetate buffers for pH adjustment to the range of 5–5.5. Although the photograph was taken 2 hr after the preparation was made, the flocculation was noted within minutes when phosphate ion was added. At this pH, no aluminum hydroxide precipitate was evident when sodium hydroxide was used. With citrate and acetate buffers, there was no significant change in the pictured appearance for more than 24 hr.

In the latter two, microscopic appearance of the colloid and tissue distribution in mice indicated that they were completely satisfactory for RES scanning. On the other hand, the microscopic appearance of the batch buffered with phosphate showed many large agglomerated particles, and such batches would not satisfy AEC criteria for this product. Sodium hydroxide is not as dependable as a buffer system for pH adjustment to the 5–5.5 range.

We have deliberately chosen a level of aluminum ion higher than that usually anticipated to emphasize

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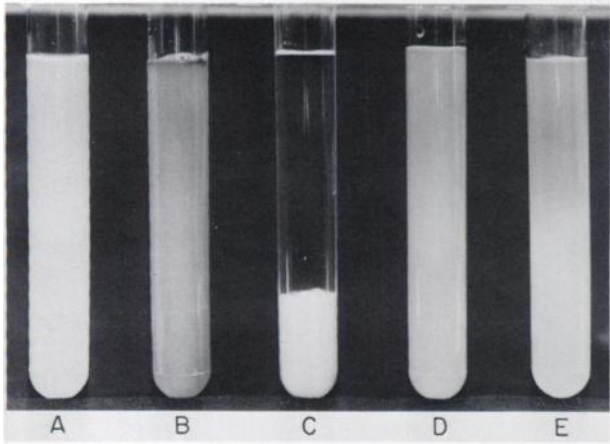


FIG. 1. Sulfur colloid prepared as described as scanning agent for RES, except containing 100 μg of aluminum ion/ml, and in (A), left unbuffered, pH 1.7; others adjusted to pH 5-5.5 using sodium hydroxide solution (B), phosphate buffer (C), citrate buffer (D), and acetate buffer (E).

the stability of the product buffered with citrate or acetate. The minimum amount of aluminum ion at which precipitation can be detected has already been reported by others to be as low as 1 $\mu\text{g}/\text{ml}$ of eluate (2).

Phosphate buffers should be used with caution for the potential incompatibility in connection with the eluate from the $^{99\text{m}}\text{Tc}$ generator. Either citrate or acetate would be a satisfactory substitute, in which case any added chelating agent would be superfluous (4). However, we prefer the citrate system for its additional anticoagulant effect. This minimizes blood-clot formation in the event blood is aspirated into

the syringe and there be some delay in the completion of the injection. Clot formation can alter subsequent distribution of the colloid.

We have been using the following parenteral grade solutions for the daily preparation of $^{99\text{m}}\text{Tc}$ -sulfur colloid:

1. Gelatin USP 2.5% solution	2.0 ml
Hydrochloric acid 1 N	0.5 ml
2. $^{99\text{m}}\text{TcO}_4^-$ eluate, not more than	5.0 ml
3. Sodium thiosulfate 1% solution	0.5 ml
4. Sodium citrate 1 M solution	1.0 ml

The citrate solution is added to the cooled product after formation of the colloid. The final pH is in the range of 5-5.5.

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