Determination of Stannous Ion Content of Radiopharmaceutical Kits Using N-bromosuccinimide

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The two most commonly used means of quantitating stannous ion in radiopharmaceutical kit preparations are the iodimetric titration and stannous ion spot tests. The N-bromosuccinimide technique described herein is a rapid, simple titrimetric method that correlates very well with the more complex iodine titration procedure.

Presently the most quantitative means for assessing stannous tin content is by iodimetric titration. Although this method is very sensitive and quantitative, it is extremely tedious and entails preparation of a primary standard, which is used to standardize a sodium thiosulfate solution, which in turn is used to standardize the iodine solution. This iodine solution is unstable and requires frequent restandardization with sodium thiosulfate. Due to the extensive time required and the complexity of standardizing the iodine solution, this technique is rarely performed in a busy radiopharmacy.

The advantages of the N-bromosuccinimide (NBS) method over the iodine technique are that it is quick, convenient, and quantitative in nature, and can be performed in any moderately equipped laboratory. N-bromosuccinimide is a solid that is accurately weighed and put into solution; no further standardization is required. This NBS solution is then used to titrate stannous tin directly. Another similar method is a potentiometric titration using iodate in 1 N HCl (*1*) but this technique has drawbacks comparable to iodimetric titration. The stannous ion spot test described by Zimmer et al. (*2*) is also convenient, but reportedly is only semiquantitative in nature. We feel that both the NBS method and the Sn(II) ion spot test are ideally suited for routine use in the radiopharmacy and for those few instances requiring strict quantitative measurements, NBS is the method of choice.

Materials and Methods

The only involved and time-consuming portion of this test is the initial purification of the NBS crystals. When NBS (Sigma Chemical Co., St. Louis, MO) is first received from the manufacturer it should be dissolved in a volume of water equivalent to ten times its total weight. Use heat (75–80° C) to completely dissolve the NBS, then allow the solution to cool. If upon cooling the NBS solution does not recrystallize, boil off a little more water and allow to cool again. Once recrystallization is accomplished, harvest the crystals and wash thoroughly with cold water, then wash with ethanol. The washed crystals are then placed on filter paper in a Buchner funnel and dried in vacuo (*3*). A small quantity of purified NBS will last for years under normal use.

The methyl-red indicator solution is also prepared in advance and a stock solution will last for months. To prepare methyl-red indicator solution dissolve 100-mg methyl red in 100 ml of alcohol and filter if necessary (*4*).

N-bromosuccinimide ($C_4H_4BrNO_2$) has a molecular weight of 178.0 and can be prepared in any desired concentration by simple dissolution in water. A 0.01% (w/v) NBS solution is commonly used; to prepare, carefully weigh out exactly 100 mg of purified NBS and transfer to a 1-liter volumetric flask, dilute quantity sufficient to 1 liter with distilled H_2O, shake frequently, and allow to stand at least 5 min. One mole of NBS reacts completely with one mole of stannous; therefore 1 ml of a 0.01% NBS solution is equivalent to 66.7 μg of stannous tin, which is also equivalent to 126.8 μg stannous chloride dihydrate.

A Sn(II) standard of any concentration can be made by accurately weighing out pure granulated tin and dissolving it completely in an exact volume of concentrated HCl (*1*). To determine the Sn(II) content of a kit add 1 ml of 1 N HCl and two drops of methyl-red indicator solution to the freeze-dried material and mix well. Titrate immediately with NBS solution to a colorless endpoint. The NBS may be added with either a burette or micro-

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burette. If a microburette is used a needle may be attached and inserted directly into the vial, thus preventing the introduction of oxygen, which will oxidize stannous to stannic. If the titration is carried out in an open vial it must be done quickly to minimize oxidation. Most researchers advocate use of an inert gas environment, but I don't find this necessary if the titration is done quickly. Methyl red is not an ideal indicator and does not become colorless until there is a slight excess of oxidant; therefore, a titration blank must also be determined. Place 1 ml of 1 N HCl and two drops of methyl red into an empty vial and titrate to a colorless endpoint with NBS.

To calculate μg of Sn(II) in the vial, subtract the volume of NBS used in the titration blank from the volume of NBS used to titrate the kit, and multiply by 66.7 μg (SnII)/ml 0.01% NBS. If not using a 0.01% NBS solution, calculate (SnII) equivalents from Table 1:

$$\mu g\ Sn(II)=(A-B)\ (C);$$

where A=ml of NBS required to reach colorless endpoint; B=ml of NBS required for titration blank; and C=μg Sn(II) equivalents/ml NBS.

TABLE 1. N-bromosuccinimide Solutions

Concentration	Weight of NBS/ 1000 ml H_2O	μg stannous (II)/ml NBS	μg $SnCl_2 \cdot 2H_2O$/ml NBS
0.01%	100 mg	66.70	126.8
0.005%	50 mg	33.35	63.4
0.0025%	25 mg	16.68	31.7

Results

The NBS technique was tested against the iodine titration method using a Sn(II) standard. Titration results of a Sn(II) standard containing 50μg Sn(II) are shown in Table 2, using both the NBS and iodimetric methods. The two methods correlate very well, with the NBS method giving a slightly larger standard deviation. All titration values showed less than 50μg Sn(II); this is due either to a weighing error or slight oxidation of Sn(II) to Sn(IV) during storage or titration.

TABLE 2. Comparison of NBS and Iodimetric Titrations

	Samples					
	1	2	3	4	5	
Method	μg Sn (II)					Mean and s.d.
NBS	48.35	47.55	47.70	48.80	47.90	48.06 ± 0.511
Iodimetric	48.50	48.95	48.76	47.85	48.66	48.54 ± 0.420

Conclusion

The NBS technique was used to test several different radiopharmaceuticals for Sn(II) content. Almost all Sn(II) values correlated very well with the manufacturer's stated amount; the only exception was macroaggregated albumin (MAA). Several MAA kits showed virtually no (SnII) tin when tested with the NBS method. This probably indicates some kind of binding between NBS and proteinaceous material. Aside from albumin-containing kits, the NBS method was found to be a reliable, simple, quantitative, and quick means for assessing (SnII) ion content in radiopharmaceuticals.

References

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