Chapter 3

Stannous Chloride in the Preparation of ^{99m}Tc Pharmaceuticals

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3.1 Introduction

^{99m}Tc pharmaceuticals need to be labeled by a simple procedure shortly before use. Because there is no effective chemistry available to attach a pertechnetate ion to an organic moiety, reduction of Tc(VII) in TcO_4^- to a lower oxidation state is a prerequisite for ^{99m}Tc complex formation in high yield and purity. Experience with various ligands has shown that the oxidation state of technetium is affected by the nature of the reducing agent, the chelator, and the reaction conditions. The choice of a suitable reducing agent for one-step labeling at mild pH conditions has been a major research effort.

Requirements of an "ideal" reducing agent for kit preparation:

- Effective reduction at mild pH conditions
- Formation of a single-component complex with distinct oxidation state
- No interference with the complexation process
- Not included in the final complex
- Stable during storage of the kit (long shelf-life)

Mild reaction conditions mean a neutral or weakly acidic pH, exclusion of toxic substances, and labeling at room temperature. Certain ligand systems favor distinct oxidation states; therefore, in kit formulations the nature and amount of reducing agent should be in balance with the ligand to ensure quantitative conversion of pertechnetate for complex formation, without further reduction to lower oxidation states. The reductant should not participate or interfere with the complexation process. Neither the reductant itself nor its oxidized form is part of the tracer molecule.

Several reducing agents with a reduction potential below that of pertechnetate (+0.747 V, Schwochau 2000) are capable of reducing pertechnetate in aqueous solution. In the absence of an appropriate ligand, reduction proceeds to insoluble technetium(IV) oxide $TcO_2 \cdot xH_2O$. In order to avoid colloid formation, reductions are generally carried out in the presence of a ligand that will stabilize a lower valence state of a technetium complex, thus limiting colloid formation (Srivastava and Richards 1983; Fig. 3.1).

Labeling and, in particular pertechnetate reduction, have been the topic of a series of articles (Alvarez 1975; Clarke and Podbielski 1987; Eckelman and Steigman 1991; Noronha 1978; Novotnik 1990; Rhodes 1991; Srivastava et al. 1977; Steigman and Richards 1974).

From the beginning of technetium-99m chemistry, a wide range of reducing agents have been used for pertechnetate, examples are given below (Srivastava and Richards 1983):

- Ferric chloride and ascorbic acid has been used as a reducing mixture to prepare ^{99m}Tc-labeled albumin (Persson and Liden 1969; Stern et al. 1965; Yokoyama et al. 1975). Ascorbate ion itself does not reduce technetium efficiently. However, ferric salt is reduced at acidic pH, generating ferrous ion, which upon elevation of pH can

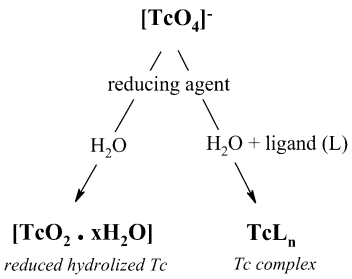

Fig. 3.1. Reduction and complex formation of pertechnetate

reduce pertechnetate; labeling of albumin occurred after adjustment to acidic pH. The reaction required strict control of the reaction conditions, several pH adjustments, and was therefore unsuitable for kit formulation.

- The use of borohydride (Deutsch et al. 1980; Smith et al. 1978) is presently limited to the synthesis of the *fac*-$[^{99m}Tc^{(I)}(H_2O)_3(CO)_3]^+$ as a precursor for technetium(I)-based radiopharmaceuticals (Alberto and Abram 2003). The typical feature of this reagent is production of an inhomogeneous mixture of various Tc species, even under well-controlled reaction conditions, including metallic technetium.
- Certain ligands, preferably those with phosphine (Deutsch et al. 1981; Vanderheyden et al. 1984) and thiol groups (Spies et al. 1978) also act as reductants. Although the reduction rate is low and an excess of ligand is required for quantitative yield, P and S ligands may have some advantages. Thus, water-soluble triphenylphosphine sulfonates suitably reduce disulfide bonds and pertechnetate simultaneously, which might offer advantages for direct labeling of peptides (Greenland et al. 2002).
- Hydrohalic acids (Hal = Cl, Br, I) (Thomas et al. 1979) are effective reducing agents for technetium, but their use requires harsh reaction conditions that lie outside the radiopharmaceutical milieu.
- Metallic reducing agents are convenient and efficient. Their disadvantage lies in the formation of colloids due to hydrolysis in aqueous solution, e.g., tin (II) and iron(II) (Lin et al. 1971), zinc metal (Kremer et al. 1989) or salts of titanium(III) (Kalincak et al. 1982), antimony(III) (Vilcek et al. 1982), molybdenum(III) (Vilcek et al. 1984), or tungsten(III) (Vilcek et al. 1985).
- Electrolytical reduction of ^{99m}Tc-pertechnetate has been investigated (Benjamin 1969, 1970; Dworkin and Gutkowski 1971; Eckelman et al. 1971a; Gil et al. 1976). When using zirconium or tin electrodes, anodic dissolution of metal ions produced in situ reduction of pertechnetate (Steigman et al. 1974). Electrolysis has been used as a reliable method for laboratory production of ^{99m}Tc pharmaceuticals.
- Ferrous salt and tin(II) were identified as active reductants (Lin et al. 1971), producing labeling of human serum albumin (HSA) at pH 2.5. Ferrous salt needed pH elevation to increase its reduction potential (Zolle et al. 1975).

The advantages of stannous salts for kit formulation have been demonstrated (Eckelman and Richards 1970, 1972), and the stability of kits was increased by lyophilization (Deutsch and Redmond 1972), suggesting commercial production.

3.2 Stannous Chloride: the Preferred Reducing Agent for Tc Pharmaceuticals

The need for simple labeling methods for ^{99m}Tc pharmaceuticals had been expressed by scientists and physicians as early as 1965. The introduction of stannous ion as a reductant for kit preparation offered new perspectives in the development of ^{99m}Tc radiopharmaceuticals and attracted interest of all parties (Alvarez 1975; Eckelman et al. 1971b).

Kits are a powerful tool in ^{99m}Tc chemistry, offering labeling in isotonic solution at room temperature simply by adding the ^{99m}Tc activity in a suitable volume. Stannous salts are nontoxic, and stable when lyophilized and kept in a nitrogen atmosphere. Stannous salts are a reliable reductant used in all kit formulations.

Redox Chemistry. Tin forms compounds in the oxidation states +II and +IV. Potentials for the sequence $Sn^0 \rightarrow Sn^{II} \rightarrow Sn^{IV}$ in acidic and basic media are shown below (Wardell 1994):

Acidic solution:	Sn^0, 0.136 V	Sn^{II}, −0.15 V	Sn^{IV}
Basic solution:	Sn^0, 0.91 V	$Sn^{II}(OH)_3^-$, 0.93 V	$[Sn^{IV}(OH)_6]^{2-}$

The feature that makes tin(II) so interesting for Tc pharmaceutical preparation is the ease of the stannous ion to be oxidized to tin(IV) according to the reaction

$$Sn^{2+} \rightarrow Sn^{4+} + 2e^-$$

There were many investigations to explain the mechanism of reduction. Since direct chemical measurements are out of question at carrier-free concentrations of ^{99m}Tc (10^{-9} M), carrier technetium (^{99}Tc) in hydrochloric acid was used to determine the oxidation state of technetium in diethylene triamine pentaacetate (DTPA) and in citrate solution. Polarographic and iodometric techniques were used to analyze for unreacted stannous ion and to perform direct potentiometric titrations of pertechnetate-99 with stannous chloride (Münze 1980; Steigman et al. 1975). No quantitative kinetic studies had been made, but qualitative conclusions have been drawn for the reduction mechanism. Most probably, the first step is the reduction to Tc(V). Reduction to Tc(III) proceeds in two successive complementary reactions, both of which should be rapid in the low concentrations at radiopharmaceutical level:

$$Tc(VII) + Sn(II) \rightarrow Tc(V) + Sn(IV) \quad (1)$$

$$Tc(V) + Sn(II) \rightarrow Tc(III) + Sn(IV) \quad (2)$$

Whether the reaction stops at the Tc(V) (reaction a) or Tc (III) (reaction b) oxidation state, or subsequent reactions occur, e.g., to Tc(IV), is dependent primarily on the nature of the ligand applied. Incidentally, the first established case of the existence of a Tc(V) compound in water came from a study of Tc(V) citrate (Steigman et al. 1975).

Table 3.1. Content of stannous chloride and calculated Sn-to-Tc ratios in selected commercially available cold kits

Technetium kit	$SnCl_2 \times 2H_2O$ (mg)	Sn/Tc ratio [a]
MDP	0.5 [b]	1.2×10^5
HSA microspheres B1	0.4 [b]	9×10^4
DMSA	0.4 [b]	9×10^4
DTPA	0.3 [b]	7×10^4
HIDA	0.2 [b]	5×10^4
EC	0.2 [b]	5×10^4
HSA microspheres B20	0.1 [b]	2×10^4
MIBI (Cardiolite)	0.075	1.7×10^4
MAG_3	0.06 [a]	1.4×10^4
Tetrofosmin (Myoview)	0.03	7×10^3
ECD (Neurolite)	0.008	2×10^3
HMPAO (Ceretec)	0.0076	2×10^3

MDP methylenediphosphonate, *HSA* human serum albumin, *DMSA* dimercaptosuccinic acid, *DTPA* diethylene triamine pentaacetate, *HIDA* hepatoiminodiacetic acid, *EC* ethylene dicysteine, *HSA* human serum albumin, *MIBI* monodentate methoxyisobutyl isocyanide, MAG_3 mercaptoacetyltriglycine, *ECD* ethylene dicysteine dimer, *HMPAO* hexamethylpropylene amine oxime

[a] ^{99m}Tc eluate (370 MBq), ^{99}Tc is not considered

[b] Average of different kit formulations

Tin in the Labeling Process. Although stannous ion has become the reducing agent of choice, some inherent problems have to be considered:

- Complicated solution chemistry of stannous compounds
- Product contains Sn(IV)
- Easily oxidized to Sn(IV)
- Shelf-life

Stannous compounds have a complicated solution chemistry. $SnCl_2 \cdot 2H_2O$ is very difficult to purify; the purest commercially available product contains at least 5% of Sn(IV) (Donaldson and Moser 1960). Stannous ion is readily oxidized by various oxidants, such as the oxygen in air. Oxidation proceeds already on standing, but is more critical in both the freeze-dried kit formulation, and in particular in solution during reconstitution because of the low Sn concentration (Table 3.1). A minimum concentration of stannous ion must be maintained to guarantee reduction during the shelf-life. First, the amount of stannous ion must ensure the Sn(II) capacity required for reduction of both ^{99m}Tc and excess of long-lived ^{99}Tc-pertechnetate present in generator eluates. Second, since the reduction potential of a solution of $SnCl_2$ depends on the ratio of activities of Sn(IV) and Sn(II), the ratio of Sn(II) to Sn(IV) must not be too low. Oxygen and other oxidizing agents have to be carefully excluded from stannous chloride preparations. Due to oxidation on standing and side oxidation reactions, Sn(IV) is an unavoidable, relatively concentrated impurity in radiopharmaceutical preparations.

The amount of stannous chloride is empirically optimized for each individual kit formulation, maintaining the balance between two parameters: A large excess of stannous chloride should be used with respect to the added pertechnetate activity and the amount of stannous chloride kept as low as possible in order to avoid further reduction of pertechnetate to a lower oxidation state. In addition, the level of tin(IV) impurity in the radiopharmaceutical should be kept as low as possible. The calculated optimal content of stannous chloride in a series of commercial kits is shown in Table 3.1, where

the stannous chloride amount per vial covers the range from 0.0076–0.5 mg, corresponding to a ratio of Sn to Tc in the range of 10^3 to 10^5.

The amount of reductant must be strictly controlled, in particular when the ligand used stabilizes technetium in more than one oxidation states.

In direct labeling of proteins, stannous chloride is administered for "pretinning". By incubating the protein with stannous ion, reactive disulfide bonds are reduced in addition to pertechnetate (Eckelman and Steigman 1991; Rhodes 1991).

The reaction kinetics of reduction and complexation are actually affected by the "usable" tin(II) and the ligand/tin ratio, summarized in the subsequent recommendations (Srivastava et al. 1977):

- Stannous solution used for formulation should be prepared with great caution to avoid oxidation and hydrolysis.
- A minimum quantity of Sn(II) and an excess of the complexing ligand (as optimized for a particular kit system) should be used.
- If the kit contains very little usable tin(II), the carrier content of $^{99m}TcO_4^-$ solutions should be evaluated. Total technetium sometimes may exceed the reductive capacity of tin.

Problems Associated with the Use of Stannous Ion. The kits could fail in the way that only a fraction of the original tin may be available in the desired form at reconstitution. Situations may occur that the kit contains very little usable tin(II), and the carrier content of the eluate may exceed the reductive capacity of tin. This is critical with kits containing a very small quantity of Sn(II) (see Table 3.1) (Srivastava et al. 1977).

Furthermore, an undesirable side reaction between tin and technetium may occur. As outlined above, there is a high excess of tin – as Sn(II) and Sn(IV) – over technetium and this fact leads to the idea that mixed-metal complexes may be formed in radiopharmaceutical preparations. Interest in the question, whether stannous or stannic tin could be involved in the radiopharmaceutical was further stimulated by the formation of a tin-capped ^{99}Tc-dimethylglyoxime complex, $^{99}Tc(oxime)_3(\mu\text{-}OH)SnCl_3$ (Deutsch et al. 1976). However, this compound was prepared under the condition of carrier-added technetium; its ready conversion to uncapped species gives no evidence for the existence of mixed-metal type compounds.

The behavior of stannous ion in kit preparations has been studied in a limited number of compounds, and the conclusion reached so far indicates that, apparently, tin ions only reduce TcO_4^- and indeed, apart from some tin-essential preparations such as stannous oxide colloid labeled with ^{99m}Tc (Subramanian and McAfee 1970), mixed Tc–Sn complexes have not been observed in low-molecular-weight radiopharmaceutical preparations.

Another aspect is hydrolysis and colloid formation. During the reduction of pertechnetate with stannous salts, tin is oxidized and hydrolyzed to form highly polydispersed colloidal particles. In some cases, mainly when weak or unsuitable ligands are used in the ^{99m}Tc labeling, interference of colloidal tin oxides on the biodistribution of ^{99m}Tc-radiolabeled tracers may occur. Such effects and the biodistribution of ^{99m}Tc-Sn colloid in dependence of the preparation conditions were subject of detailed studies.

Some authors hope to prevent complications related to the use of stannous chloride by using other stannous salts such as stannous fluoride, oxalate, tartrate, citrate, and phosphates.

Some efforts were made to use stannous ion fixed to a carrier to improve the labeling procedure. Albumin was labeled using stannous ion adsorbed to an ion-exchange

resin in the presence of albumin and pertechnetate (Dreyer and Münze 1969); an insoluble macromolecular Sn(II) complex (R-Sn) was proposed in order to avoid the disadvantages of stannous chloride being hydrolized and oxidized (Nakayama et al. 1995).

Reduced, hydrolized ^{99m}Tc is a colloidal impurity in kit preparations. Depending on the amount present, it may distort the biodistribution pattern and limit the diagnostic value of the ^{99m}Tc pharmaceutical. The biodistribution of ^{99m}Tc-Sn colloid itself was studied separately (Syhre et al. 1976). The authors observed that the liver-to-kidney ratio is highly dependent on the pH of the preparation, reflecting the hydrolytic properties of tin hydroxide.

Furthermore, it has been shown that tin participates in the chemical binding process between technetium and tetracycline and similarly, it might very well explain how some other complexes are produced (Alvarez 1975).

A more recent example is the biodistribution of ^{99m}Tc-radiolabeled chitosan nanoparticles, using two different methods for reduction, namely, stannous chloride or sodium borohydride. The authors reported a considerable dependence on the method used. They concluded that nanoparticles are adsorbed on the surface of colloidal tin oxide particles that are generated during the labeling process (Banerjee et al. 2005).

Tin as a Foreign Element in the Body. The toxicity of tin compounds is related to the chemical form. The LD_{50} of stannous chloride in dogs (intravenous) is 20–50 mg/kg. The toxicology of colloidal tin oxide was thoroughly investigated (Fisher 1957). Data indicated that four doses as high as 350 mg/kg of tin produced no toxicity. Because of the low doses of tin applied in ^{99m}Tc pharmaceuticals, no toxic effects are expected.

Determination of Sn(II) (Quality Control). Determination of the Sn(II) content in radiopharmaceutical kits is an important aspect of quality control for commercial producers and registration authorities (Rakias and Zolle 1997). Classical methods for the determination of Sn(II) involve titrimetric, electrochemical, spectrophotometric, and chromatographic methods (Lejeune et al. 1996).

Titrimetric methods that are selective for Sn(II) are generally less sensitive. Disadvantages that may occur are related to so-called matrix effects, that is, the reaction of milieu, including the presence of ligands or stabilizers, low sensitivity, or slow formation of colored complex. Thus, iodometric titration as well as spectrophotometry by means of Dithiol-Reagent R are used to determine Sn(II) in, e.g., stock solution, but are not suitable to determine Sn(II) in kits. Methods that allow specification of Sn(II) and Sn(IV) are few. There is, as an example, a colorimetric determination of the Sn(II) concentration in Tc-mercaptoacetyltriglycine (MAG_3) kits based on a molybdate–thiocyanate complex formed in the presence of Sn(II) (Hoffmann et al. 1990). Pulse polarography has offered considerable advantages over the classical methods for the determination of the Sn(II) content, in particular an increase of sensitivity that allows suitable measurements of microgram amounts of tin(II) (Lejeune et al. 1996; Rakias and Zolle 1997).

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