CHAPTER II

BASIC PRINCIPLE

Technetium 99m

1. General properties

Of the conveniently available radionuclides, technetium has by far the best nuclear properties for imaging with the gamma camera (Bingham and Maisey, 1978; Sampson, 1990). Technetium is an artificial radioactive element with the atomic number 43. It was discovered in 1937 by Perrier and Segre. More than thirty technetium isotopes have been discovered. Of all technetium radionuclides, the metastable ^{99m}Tc is particularly interesting for nuclear medicine because of its advantageous physical properties. The 6-hour half-life and the absence of beta radiation result in a low equilibrium dose constant (Δ = 0.303 g-rad/μCi-hr). The 141-keV gamma emission has satisfactory tissue penetration; 50 % is absorbed in 4.6 cm of tissue.The energy is low enough to be collimated easily and is very convenient for detectors (scintillation counters and cameras). A high counting efficiency has been obtained even when ^{99m}Tc is located in various critical organs with different thickness of the biological tissue. Technetium Tc 99m is produced indirectly either by neutron irradiation of ^{98}Mo or as a fission product of ^{235}U:

$^{98}Mo(n,\gamma)$

$$\searrow \quad \beta- \qquad \gamma \qquad \beta-$$

$$^{99}Mo \longrightarrow {}^{99m}Tc \longrightarrow {}^{99}Tc \longrightarrow {}^{99}Ru(stable)$$

$$\nearrow \quad 66\ hr \qquad 6.08\ hr \qquad 2.1x10^{5}\ yr$$

$^{235}U(n,fission)$

The accumulation of ^{99}Tc, the daughter nuclide, in the critical organ might appear to danger the patient, due to $2.1x10^{5}$ years of the half-life of ^{99}Tc, with an energy of 0.3 Mev. However, this danger is quite low because of the following properties of technetium:

a) the biological half life of ^{99}Tc is identical with that of ^{99m}Tc, about 75 hours, and total elimination occurs in approximately 14 days

b) the elimination of ^{99m}Tc from the organism occurs rapidly , i.e., during the first 24 hours' 88% of ^{99m}Tc is excreted (mainly by urinary excretion when administered intravenously)

c) the amount of ^{99}Tc resulted after administering a ^{99m}Tc dose of 10 mCi, is only $3.3x10^{-6}$ μg

2. Technetium Generator

Generally, radionuclide generator consists of a longer-lived parent that decays to form a shorter-lived daughter. The radionuclide pair is contained in an apparatus that allows separation and removal of the daughter as well as retention of the parent. Within the generator, the short-lived daughter radionuclide is continually formed by decay of the parent. The most successful and widely used generator system

in use today is the $^{99}Mo/^{99m}Tc$ generator.

The $^{99}Mo/^{99m}Tc$ generator system consists of a glass or plastic column filled with Alumina (Al_2O_3). The eluent is normal saline solution. The ^{99}Mo used to load the column is fission-produced allowing for greater specific activity (> 370 TBq/g or 10^4 Ci/g) and corresponding decrease in column bed material (Molinski, 1982). This lessens the chance of ^{99}Mo breakthrough and allows elution with a small volume of saline. ^{99}Mo produced by neutron bombardment contains a high percentage of carrier free ^{98}Mo (specific activity ~370 GBq/g or 10 Ci/g). Thus, more alumina is needed for the column, and consequently, more lead is required for shielding. This results in variable column performance (Theobald, 1989). With fractional elution of ^{99}Mo produced by neutron bombardment, the same high specific concentration of ^{99m}Tc can usually be achieved (Harbert and Da Rocha, 1984). For ^{99m}Tc eluted from either fission or cyclotron produced ^{99}Mo, the major radionuclidic impurity is ^{99}Mo itself.

3. Technetium Chemistry

The coordination chemistry of technetium is complicated by the case with which it can move from one oxidation state to another (Deutsch et al., 1983). Given any new ligand and/or new set of reduction/coordination condition, it is often difficult to predict which oxidation state of technetium will be result. Generally, technetium chemical properties are very similar to those of manganese. Technetium has the valence states +7, (+6), (+5), +4, (+3) (Balaban, 1986). In fact, all oxidation numbers from 0 to +2 have been reported (Deutsch et al.,1983). The (+3), (+6),

(+5) state of technetium are unstable in solution, which tend to form compounds in stable valence states (+7 and +4) (Balaban, 1986).

Technetium Tc 99m eluted from a generator is pertechnetate ($^{99m}TcO_4^-$), with concentration of 10^{-9} to 10^{-11} M (Balaban, 1986). The incorporation of ^{99m}Tc in organic compounds involves the reduction of technetium from the valence state (+7) to lower valences (+5) and (+4). For this purpose $SnCl_2$ is used as reducing agent in acidic solution according to the reaction ;

$$Tc(VII) + Sn(II) \rightleftharpoons Tc(V) + Sn(IV) \quad (Rapid)$$

Several factors will influence the oxidation state of technetium following reduction of pertechnetate, including the nature of reductant and ligand (the anion of the organic compound to which Tc will be bound),pH and temperature (Balaban,1986; Sampson, 1990). Technetium may be incorporated in the valence form (+5) and in other cases as (+4), the reduction of technetium occurs as a sequence of reactions following the above reaction.

$$Tc(V) + Sn(II) \rightleftharpoons Tc(V) + Sn(III) \quad (Slow)$$
$$Tc(V) + Sn(III) \rightleftharpoons TC(IV) + Sn(IV)$$

In aqueous solution, the reduced species of technetium have a high tendency toward hydrolysis. At higher pH value, the hydrolysis degree increases. The reaction of Tc(IV) at pH = 2 is as follow;

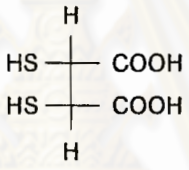
$$TcO^{2-} + H_2O \rightleftharpoons TcO(OH)^+ + H^+$$

Technetium Tc 99m Succimer Injection

1. Succimer

Succimer (*meso-2,3-dimercaptosuccinic acid ; DMSA ; DMS*) is a kind of water soluble chelating agent that has the molecular formula of HOOCCH(SH)CH(SH)COOH, molecular weight of 182.21 (The Merck Index, 1989) The structural formula is shown in figure 1.

Figure 1. The structural formula of Succimer.



Succimer crystalized from aqueous methanol is a white crystal, melting point of 192-194°C. The LD50 (intraperitoneal) in mice is more than 3,000 mg/kg (Friedheim and Corvi, 1975).

2. General Properties of Technetium 99m Succimer Injection

Succimer complexed with technetium 99m has been use as a radioactive imaging agent. Succimer itself has been use as an antidote of heavy metal poisoning (Friedheim et al.,1978).

In 1974 Lin, Khentigan and Winchell labeled Succimer or DMSA with ^{99m}Tc by mixing $^{99m}TcO_4^-$ with an equal part of a solution of 1 mM $SnCl_2$ (0.19 mg/ml) and 3 mM DMSA (0.547 mg/ml) and injected intravenously to the dog. The study in dog

showed that in vivo kinetics mimic that of ^{203}Hg-Chlormerodrin (a kind of radiolabeled diuretic agent useful for imaging of renal cortical morphology). Since then, this complex has been use as a renal imaging agent. Technetium 99m succimer injection is the agent of choice for static renal scintigraphy (Bingham and Maisey.,1978; De Lange et.al.,1989),especially on the study of scarred kidneys (Merrick,Uttley and Wild.,1980; Mackenzie,1990). The most widespread use of ^{99m}Tc DMSA scanning is in the assessment and serial follow up of patients with diseases that are liable to destroy the cortex progressively. These include chronic pyelonephritis, tuberculosis, obstructive nephropathy from any cause. Careful comparison of the total counts over both kidneys provides a good working estimate of the proportion of renal function derived from each kidney (Sutton,1987).

Despite its frequent use, little is known about the mechanism of uptake in the kidney. It has been shown that the tracer is concentrated in the proximal tubular cells of the kidney (Willis et.al.,1977). ^{99m}Tc DMSA could enter the proximal tubular cell either by glomerular filtration and subsequent reabsorption or by direct uptake from the peritubular capillaries. Autoradiography study in rats shows that ^{99m}Tc DMSA concentrates in the renal tubules, proximal and distal with little activity going to the renal medulla, the glomeruli collecting tubules and blood vessels. Studies of subcellular distribution of ^{99m}Tc DMSA show that the complex penetrates the kidney cells. It is bound mostly to soluble cytoplasmic proteins and mitochondria and to a lesser extend to microsomes and nuclides (O'Reilly, Shields and Testa, 1986). Work performed in rats demonstrates that at one hour after injection 54% of the dose is localized in the kidney, 7% in the urinary bladder, 5% in the liver and spleen and

19% in the blood (O'Reilly et.al.,1986).

Due to its high level of cortical renal fixation it is a very useful agent for imaging the renal parenchyma with no interference from pelvicalyceal activity. Good cortical images are obtained between 1 and 3 hours after injection, with practically no activity in the medulla or pelvicalyceal system (O'Reilly et.al.,1986).

Dosage administration (as recommended by Amersham International)

1. Kidney imaging. The usual adult (70 Kg) dose is 37-74 MBq (1-2 mCi) by intravenous injection. Optimal kidney imaging is obtained between 1 and 3 hour following injection.

2. Assessment of kidney function. For these studies the usual adult intravenous dose is 74 MBq (2 mCi). However, clinical reasons may make greater amounts necessary. Quantitative measurement should be carried out between 6 and 24 hours following administration.

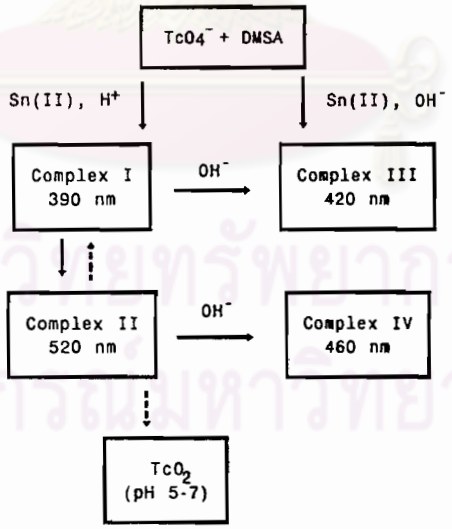
3. Chemistry

Many attempts have been made to determine the chemical state of ^{99m}Tc-DMSA complex used as a radiopharmaceutical. Ikeda et al.(Ikeda,Inoue and Kurata.,1976) proposed that various ^{99m}Tc-DMSA were probably formed and one of these ^{99m}Tc-DMSA complexes concentrated in the kidney. Their experiment using carrier technetium showed that when adding Sn(II)-DMSA (molar ratio 1:3) to the

excess ^{99m}Tc solution, a yellow Tc-DMSA complex with a maximum absorbance at 390 nm was obtained and this complex was stable for at least 24 hours. In case of large excess of Sn(II)-DMSA, a purple complex (complex II) with a maximum absorbance at 520 nm was obtained, and its absorbance increased with time. The diagram showing the formation of possible technetium-DMSA complexes is shown in figure 2.

Further study indicated that complex II showed the highest kidney uptake while the complex I excreted from the kidney rapidly.

Figure 2. Formation of possible Tc-DMSA complexes and maximum absorbances (Ikeda et al.,1976).



Formation of Tc-Succimer complexes -- In the Tc-DMSA complex formation process, two major types of complexes, Sn(II)-DMSA complexes and Tc-DMSA complexes, are involved. From the study of Ikeda et al.(1976), Sn(II)-DMSA existed as a 1:1 complex in the presence of excess amount of DMSA. However, various species of ^{99m}Tc-DMSA complexes were formed in the presence of 1:1 Sn(II) DMSA alone. There was little possibility of the formation of mixed metal complexes Tc-Sn(II)- DMSA. On the other hand, Krejcarek et al.(1976) purposed that DMSA formed two distinct complexes with stannous ion, one at low pH, i.e., 1-4, and another at a neutral or alkaline pH, i.e., pH 7 and above. The complex formed under acidic conditions when labeled with ^{99m}Tc concentrated in the kidneys while the complex formed at alkaline pH was more rapidly excreted in the urine. Stoichiometry of the two DMSA/Sn(II) chelates was also determined. At pH 4 the ratio of DMSA to Sn(II) was 2:1 while at pH 8 it was 1:1. Potentiometric titration of the 2:1 complex indicates that one mercapto group per mole of DMSA was involved in the chelate. The 1:1 complex involved two mercapto groups per mole of DMSA.

It has been described previously that excess amounts of Sn(II) are necessary for the formation of ^{99m}Tc-DMSA complex used as a renal scanning agent. However, even though the concentration of Sn(II) ($10^{-3}$to 10^{-4}M) is a large excess over Tc(VII)(TcO_4^-) when a trace amount of TcO_4^- is used for preparation, the formation of this complex does not always proceed continuously. Ikeda et al.,(1976) have compared the change of reduction yield of Tc(VII) with percentage ^{99m}Tc remaining at the origin by paper chromatography and kidney uptake in mice. The result showed that the reduction yield remained constant even though the molar ratio of

Sn(II)/Sn(IV) = 0.1, which was indicated that the Tc(VII) was almost completely reduced to lower valence states. Both Rf = 0 fraction on paper chromatography (part of renal scanning complex bound to the paper)and the kidney uptake were increased with increased molar ratio of Sn(II)/Sn(IV). This indicated that the formation of renal scanning complex depended not only on the amount of Sn(II) but also the molar ratio of Sn(II)/Sn(IV).

It can be assumed that many oxidation states are involved in the formation of Tc-99m succimer complex. The commercially available kit is formulates at a slightly acidic pH level. The study of Ohata et al (1988) indicated that when the pH of the complex formation was raised, a complex was form with much reduced in renal activity, but demonstrated soft tumor uptake. Westera et.al.(1985) pointed out that Tc(IV)-DMSA was formed at low pH and Tc(V)-DMSA was formed at high pH. On the other hand, Millar(1989) stated that at pH 3 the kidney imaging ^{99m}Tc(III)-DMSA was obtained.

Factors affecting the formulation of Succimer cold kit.

1. Reductant

Technetium in aqueous solution can be reduced to lower oxidation state easily, therefore it can form complexes with many substances. Wide ranges of reductants that can facilitate the complex formation are available. The list includes sodium borohydride, sodium dithionite, sodium bisulphite, formamide, sulphonic acid and hydrazine (Sampson, 1990). The nature of reductant employed in the formation

of technetium complex can cause a significant effect on biodistribution of the resultant complex (Baldas et al.,1982). The choice of reductant can influence the oxidation state of technetium and the proportion of each form of radioactive components of the mixture in case a mixture of complexes is formed. For practical reasons, the properties of the reductant such as water solubility, stability, low toxicity, and effectiveness at room temperature should be considered (Salehi, N. 1987). From these aspects stannous salts are the preferred reductants for kit formulations, and without exception , all current commercially available cold kits contain a stannous salt as a reductant.

The importance of an optimal amount of stannous ion (Sn^{2+}) as a reducing agent in the preparation of ^{99m}Tc-labeled radiopharmaceuticals is widely recognized. Too small amount of Sn^{2+} will limit reducing capacity , which causes the decrease of labeling efficiency and the increase of free ^{99m}Tc-pertechnetate impurity; too large quantity of Sn^{2+} may result in the formation of ^{99m}Tc-labeled colloidal impurities and/or decrease labeling efficiency (Hladik III et al,. 1987). At neutral pH, Sn^{2+} reacts with water to form colloids or large particles. These colloids and large particles coprecipitate with reduced technetium as unwanted impurities (Harbert and Da Rocha, 1984).

Solutions containing Sn^{2+} are good reducing agents, in fact, oxygen of the air oxidizes solution of Sn^{2+} to Sn^{4+} unless some metallic Sn is presented.

Sn metal can be dissolved in 1 M solution of non oxidizing acids. In practice, however, a hot concentrated solution of HCl is necessary to dissolve Sn metal. The solution thus formed contains Sn(II), not as the $Sn^{2+}_{(aq)}$ ion but as the

chloro-complexes $[SnCl_4]^{2-}$ or $[SnCl_3]^-$. With oxidizing acids such as concentrate nitric acid, Sn reacts slowly to form the insoluble dioxide, SnO_2.

Solution containing Sn(II) salts of strong acid are acidic because of the hydrolysis of the hydrates Sn^{2+} ions. A 0.1 M solution of Sn^{2+} hydrolyzed to form insoluble basic salt.

$$Sn^{2+}_{(aq)} + 2Cl^- + H_2O \rightleftharpoons Sn(OH)Cl_{(s)} + H^+_{(aq)} + Cl^-_{(aq)}$$

The addition of H^+ ions prevents the hydrolysis, whereas the addition of a strong base causes the hydrolysis reaction to proceed further to the right-forming a white hydroxide precipitate, which is usually represented simply as $Sn(OH)_2$

$$SnOH^+_{(aq)} + OH^-_{(aq)} \rightarrow Sn(OH)_{2(s)}$$

If excess OH^- ions are added, the precipitate $Sn(OH)_2$ redissolves to form a complex hydroxo-anion of Sn(II), usually written as $[Sn(OH)_4]^{=}_{(aq)}$. The hydroxide $Sn(OH)_2$ also dissolves in acid to yield the corresponding salts of the Sn^{2+} ion, thus, $Sn(OH)_2$ is amphoteric (Qualiano and Vallarino, 1969)

Most ^{99m}Tc "Kits" start with sufficient and usually excess amount of Sn(II). This reducing capacity may be drastically decreased by a variety of factors including loss of Sn^{2+} during manufacture, deterioration and/or oxidation during storage, and oxidation during kit preparation.

2. Oxidation

As has been mentioned previously, to bind to most chelating reagents ^{99m}Tc must be reduced from the +7 valence state of pertechnetate to a lower valence state.

This reduction is usually accomplished by the stannous ion in the reagent kit. Stannous is readily oxidized by atmospheric oxygen to stannic ion, which is no longer capable of reducing pertechnetate.

Radiolytic decomposition is one of the important factors that affect the stability of radiopharmaceuticals. Radiolytic decomposition is a function of total radioactivity content. The significance radiolytic decomposition effects in radiopharmaceutical solution are the indirect radiation effects resulting from the ionization of water that produce the strong oxidants, hydrogen peroxide and, in the present of dissolved oxygen, hydroperoxy radicals (Thornton, Molinski and Spencer, 1979).

Therefore, the stability of radiopharmaceutical can be prolonged by a number of tactic that inhibit oxidation and/or radiolytic decomposition. Since atmospheric oxygen reduces stannous ion and dissolved oxygen promotes formation of hydroperoxy radicals, then minimizing the exposure of a radiopharmaceutical to the atmosphere, limiting introduction of air into the vial, and purge the solution or lyophilized kit with nitrogen help minimize oxidation and/or decomposition (Owunwanne et al.,1977; Mcbride, Shaw and Kessler,1979; Hladik III et al.,1987).

Antioxidant -- The stability of pertechnetate ion is a common problem which limits the post reconstitution shelf life of technetium cold kit, the irreversible oxidation of complexed technetium to pertechnetate. There are two sources of this problem. The introduction of oxygen into the vial (previously containing nitrogen as the only gaseous component) during labeling will start to consume the stannous

reductant, such that any reoxidation to pertechnetate cannot be reversed. A similar effect is achieved when patient dose are subdispensed, or held in the syringes, for a significant period of time prior to patient administration. Stannous reductant may also be consumed by oxidant formed through self radiolysis within the vial (Sampsom, 1990).In case where the technetium complex is kinetically stable, loss of reductant will not cause any practical problem in use of the radiopharmaceutical. However, kinetically labile complexes need to be stabilized to preserve radiopharmaceutical purity. While the employment of greater quantities of stannous salts might be one solution.

In such cases, antioxidants have been used to provide radiopharmaceuticals with greater stability. These materials are believed to compete with stannous salts in react with oxygen or oxidant, so conserving the reductant. Antioxidants which have been used in conjunction with technetium complexes include ascorbic acid (Smal, 1984), gentisic acid (Tofe et al.,1980) and p-aminobenzoic acid.

Ascorbic acid is very soluble in water and is relatively insoluble in ether. The solubility is 300 mg/ml in water,10 mg/ml in glycerol (Handbook of pharmaceutical excipients, 1986). Thus, this agent is typically used as reducing agent in aqueous or partially aqueous formulations. The concentration range used in pharmaceutical formulations is 0.05-3.0 % (Swarbric and Boylan, 1988). Ascorbic acid is easily oxidized and preferentially undergo autoxidation, thus consuming oxygen and protecting the drug or excipient. Because autoxidation of ascorbic acid consumes oxygen, it is sometimes referred to as oxygen scavenger. Thus it is particularly useful in closes system where the oxygen cannot be replaced once it is

consumed.

3. Lyophilization

Many products of pharmaceutical interest lose their viability in the liquid state and readily deteriorate if dried in air at normal atmospheric pressures. In case of radiopharmaceuticals, oxidation and hydrolysis are the most important factors affecting the stability of the formulations. In order to be stabilized, they must be dehydrates to a solid state. The material to be dried is first frozen and then subjected under a high vacuum to heat so that the frozen liquid sublimes leaving only the solid,dried components of the original liquid. This process is called **lyophilization, freeze drying, gelsication or drying by sublimation**. The dried product can be readily redissolved or resuspended by the addition of water prior to use, a procedure referred to as reconstitution (Lachman, Lieberman and Kanig, 1986).

Suspending medium -- Suspending medium generally means all substances present in the materials other than the active, vital or therapeutic agent. The purpose of using suspending medium in freeze drying process are to facilitate freeze drying,to enhance solubility of the dry product, to confer pharmaceutical elegance and to improve stability.

The suspending medium is sometimes referred to as the menstruum or the support material. By implication it is something added to the material which is used in the course if preparing the material or to stabilize it while held in the liquid state before freeze drying. More often it is a deliberately formulated substance designed

to promote successful freeze drying and a stable shelf life. A typical suspending medium consists of a protective colloid e.g. 5% dextran, 5% sucrose. The 5% inositol has been used instead of sugar but it does not bind a product together well, and fragments tend to break off and to be carried away in the stream of water vapor (Rowe and Snowman, 1976).

Inositol (i-inositol, meso-inositol, myo-inositol) is a sugar alcohol which has molecular formula of $C_6H_{12}O_6$, molecular weight of 180.16.

Radiopharmaceutical Quality Control

1. Radioactivity

Radioactivity is defined in the BP 1990 and USPXXII as the number of nuclear transformations per unit time in a given amount of the radioactive preparation. Radioactivity is measured in unit of the becquerel (Bq), equivalent to an average transformation rate of one per second. The becquerel is an inconveniently small unit for radiopharmaceutical work and the multiple kBq (10^3 Bq), MBq (10^6 Bq), and GBq (10^9 Bq) are used in practice . The older units of the Curie (Ci, equivalent to 37 GBq) and its submultiple mCi (37 MBq) and μCi (37 kBq) are still used in the USA and in many other countries.

Fundamental Decay Law (USPXXII) -- The decay of a radioactive source is described by the equation:

$$N_t = N_0 e^{-\lambda t}$$

in which N_t is the number of atom of a radioactive substance at elapsed time t, N_0 is the number of those atoms when t = 0, and λ is the transformation or decay constant, which has a characteristic value for each radionuclide. The half-life, $T_{1/2}$, is the time interval required for a given activity of a radionuclide to decay to one-half of its initial value, and is related to the decay constant by the equation:

$$T_{1/2} = \frac{0.69315}{\lambda}$$

Since the process of radioactive decay is a random phenomenon, the events being counted form a random sequence in time. Therefore, counting for any finite time can yield only an estimate of the true counting rate. The precision of this estimate, being subject to statistical fluctuations, is depend upon the number of counts accumulated in a given measurement and can be expressed in terms of the standard deviation σ. An estimate for σ is $\sqrt{n}$, where n is the number of counts accumulates in a given measurement.

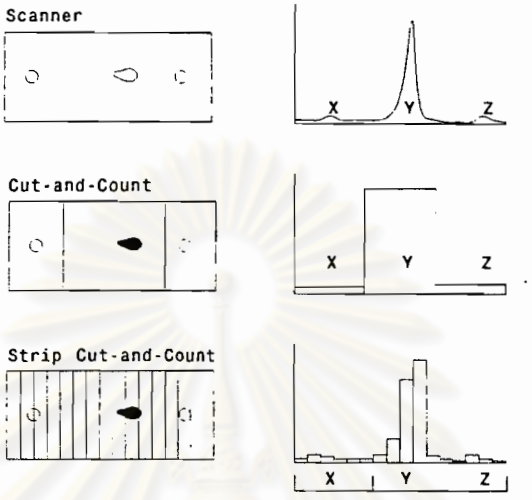
2. Radiochemical Purity

In USP XXII, Radiochemical purity of a radiopharmaceutical preparation refers to the stated radionuclide present in the stated chemical form. BP. 1990 defines this term as the Ratio, expressed as a percentage, of the radioactivity of the radionuclide concerned that is present in the source in the chemical form declared to the total radioactivity of that radionuclide present in the source.

Radiochemical impurities may arise during preparation and storage of radiophamaceutical and will frequently modify organ distribution and specificity (Kronn and Jansholt, 1977), Radiochemical purity (or labelling yield) determination are carried out in all radiopharmacies, either to check the quality of a standard formulation or kit, or to establish standard for an in-house preparation. Some form of physicochemical separation technique must be used in order to separate the various radioactive species in the sample prior to measurement of their radioactivities and subsequent calculation of their proportion in the sample (Theobald,1989; Sampson, 1990).

Chromatographic separation methods are almost universally employed in radiochemical purity determination (Harbert and Da Rocha,1984; Sampson,1990). Planar method and electrophoresis being the most popular. Their main advantage over column and other elution methods is that all the applied radioactivity remains on the developed chromatoplate or electrophoretogram, which can then be examined and quantitated by a number of techniques ,e.g. scanned, autoradiographed, cut into regions or strips and radioactivity associated with each area measured under identical conditions, as shown in figure 3.

Figure 3. Simple system for paper chromatography (reproduced from Sampson, 1990).



Whatever separation technique is used the method of calculation is identical. The radioactivity in each spot, sample or other sector is measured, corrected for background and the percentage activity in each piece is calculated from the formula

$$\% \ Component = \frac{100(Count \ for \ component)}{(Total \ count)}$$

Thin layer chromatography -- Thin layer chromatography (TLC) is the most popular planar chromatographic method. The technique is simple and acceptable results are easily obtained. For radiopharmaceutical work TLC is probably useful method, although development time of several hours can be disadvantage with radiopharmaceuticals containing short lived radionuclides.

Thin layer chromatoplate may be prepared "in house" using glass plates and spreading equipment, but these do not always give reproducible chromatograms. Commercial TLC materials are preferable for radiochemical quality control applications. The normal thickness of the layer is 0.25 mm. Glass backed plates are traditional, but are not easily cut or segmented. plastic- and metal foil-backed plated are most versatile. They can be cut with scissors or a sharp scalpel to any required size. Similarly, after development these chromatoplated can be cut into suitable segments for counting and quantitation. A typical procedure for a plate on which the solvent has been allowed to migrate 10 cm would be cut into 5 mm transverse strips and measure the count rate for each strip in a scintillation detector (Theobald, 1989). Some plates have a tendency to flake or crumble when being cut, leading to loss of radioactivity. This can be overcome by covering the layer with sellotape before cutting (Sampson, 1990).

The Gelmen Company produce several Instant Thin Layer Chromatography (ITLC) materials. They consist of a glass fibre web impregnated with the modified silica stationary phases, silica gel and silicic acid. The ITLC materials are very popular among radiopharmacist for routine radiochemical purity determinations. ITLC support/stationary phase are fast running variants of conventional TLC systems. The mobile phase migration speed is increased by the fine random mesh construction of the material, but the resolution is poorer than conventional TLC supports. ITLC chromatographic system for various radiopharmaceuticals, including DMSA, has been developed by Zimmer and Pavel (Zimmer and Pavel, 1977).

3. Radionuclidic Purity

The term radionuclidic purity is defined in the USPXXII as the proportion of radioactivity due to the desired radionuclide in the total radioactivity measured. BP 1990 defines this term as the ratio, expressed as a percentage, of the radioactivity of the radionuclide concerned to the total radioactivity of the source. Radionuclidic purity is important in the estimation of the radiation dose received by the patient when the preparation is administered. Radionuclidic impurities may arise from impurities in the target materials, differences in the value of various competing production cross sections, and excitation functions at the energy or energies of the bombarding particles during production.

4. Biodistribution

The majority of radiopharmaceuticals are diagnostic agents and, in general, they do not produce any pharmacological effects. Intravenous injection is the most widely used method of administration.The efficiency of a diagnosis (or therapeutic) radiopharmaceutical is dependant upon the physical characteristics of the radionuclide (type of emission, energy, half life) but more important, the biological characteristics. These include preferential uptake into, passage through, retention in or exclusion from the biological system to be investigated. Diagnostic information is derived from the observed rate or extend of one or more of these processes.