U.K. Radiopharmacy Group

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Radiochemical Purity Testing of Radiopharmaceuticals

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1.1 General description of thin-layer chromatographic (TLC) techniques

Radiochemical purity (RCP) is the proportion of the radioactivity which is present in the desired chemical form. It is sometimes called labelling efficiency. A minimum acceptable RCP is specified for each radiopharmaceutical, in order that the impurities do not interfere with the quality of the image or result in an unacceptably high radiation dose to the patient (eg free iodide going to the thyroid gland).

^{99m}Tc labelled agents constitute the vast majority of the radiopharmaceuticals used in nuclear medicine. The main impurities which can be present are free pertechnetate ($^{99m}TcO_4$) and reduced hydrolysed (RH) ^{99m}Tc colloid. Generally two TLC systems are used, one to quantify each of the main impurities, and the % bound (RCP) is calculated by subtracting the total impurities from 100%.

Radiopharmaceutical TLC is generally performed using paper or fibreglass sheets (stationary phase) which are easily cut using scissors into narrow strips, from 1x6 cm to 2x20 cm. A spotting line is carefully marked in pencil 1-2 cm from the bottom of the strip. A solvent front may be marked near the other end of the strip. A drop of the radiopharmaceutical is placed on the spotting line and the strip is placed in a tank or tube containing the mobile phase (solvent) specified. When the strip is placed in the tank, the spot must remain above the level of the solvent. The solvent is allowed to migrate up the strip until it reaches the top or the premarked solvent front, then the strip is removed and allowed to dry.

There are two approaches to determining the distribution of radioactivity along the strip. One is to image the strip, using a radiochromatogram scanner, phosphor imager (digital autoradiography), or gamma camera. Quantification is then performed by placing regions of interest along the radiochromatogram. If imaging equipment is not available, the alternative is to cup the strip into two or more pieces and determine the activity in each portion using a dose calibrator or gamma counter, depending on the level of activity present. The "cut-and-count" technique has the disadvantage that the cut point(s) is/are based on the assumed chromatographic behaviour of the components which may be present. Although a reasonable profile could be obtained by cutting the strip into 10 or 20 portions, this is not practical for routine use.

For a more complete description of the theory and practice of RCP testing, the reader is referred to "Quality control methods for radiopharmaceuticals" by T Theobald and P Maltby in *Sampson's Textbook of Radiopharmacy* (4th edition, T Theobald, editor, The Pharmaceutical Press, 2010).

1.2 Consumables

Stationary phases	
ITLC-SG	Instant thin-layer chromatography, silica gel SGI0001, Agilent www.agilent.com
ITLC-SA	Instant thin-layer chromatography, silicic acid A120B12, Agilent
3MM	Whatman 3MM chromatography paper
No 1	Whatman No 1 chromatography paper
Silica gel	Silica gel 60, e.g. Merck
Alumina	Aluminium oxide, Bakerflex
Cellulose	Cellulose, e.g. Merck
Mobile phases	
Butanone	2-butanone = methyl ethyl ketone = MEK
1 M Sodium acetate	82 mg/mL anhydrous sodium acetate or 136 mg/mL sodium acetate trihydrate
0.1 M Citrate	21 mg/mL monosodium citrate dihydrate
1 M Ammonium acetate	77 mg/mL ammonium acetate
Mixtures of volatile solvents should be made freshly	

1.3 Thin-layer chromatography of technetium radiopharmaceuticals - Full list

Radiopharm-aceutical	Stationary phase	Mobile phase	Rf RH-Tc	Rf TcO_4	Rf Tc-bound
Polar					
^{99m}Tc-Pertechnetate	ITLC-SG	Acetone or saline	0.0	1.0	-
^{99m}Tc-MDP/HDP	ITLC-SG or 3MM	Acetone	0.0	1.0	0.0
	ITLC-SG	Saline (MDP) or 1 M Sodium acetate	0.0	1.0	1.0
^{99m}Tc-DTPA	ITLC-SG or 3MM	Acetone	0.0	1.0	0.0
	ITLC-SG or 3MM	Saline	0.0	1.0	1.0
^{99m}Tc-DMSA	3MM	Acetone	0.0	1.0	0.0
	ITLC-SA	Butanol acidified with 0.3 M HCl	0.0	0.9	0.5
^{99m}Tc-Pyrophosphate	ITLC-SG or 3MM	Acetone	0.0	1.0	0.0
	ITLC-SG	Water	0.0	1.0	1.0
^{99m}Tc-IDAs	ITLC-SA	20% Sodium chloride	0.0	1.0	0.0
	3MM (Spot must be dry)	Butanone	0.0	0.9	0.0
	ITLC-SG	Water or 50% acetonitrile	0.0	1.0	1.0

^{99m}Tc(V)-DMSA	ITLC-SG	Butanone	0.0	1.0	0.0
	ITLC-SG	Saline	0.0	1.0	1.0
	Silica gel	Butanol-acetic acid-water (3:2:3)	0.0	0.8	0.5
Particulate					
^{99m}Tc-MAA	ITLC-SG or 3MM	Acetone or saline	0.0	1.0	0.0
^{99m}Tc-Colloid (tin colloid, nanocolloid)	ITLC-SG or 3MM	Acetone or saline	0.0	1.0	0.0
Non-polar					
^{99m}Tc-Sestamibi	Alumina (Pre-spot with ethanol; do not allow spot to dry)	Ethanol	0.0	0.0	1.0
^{99m}Tc-Tetrofosmin	ITLC-SG (Spot must be dry)	Acetone-dichloromethane (35:65)	0.0	1.0	0.5
^{99m}Tc-MAG3	ITLC-SG	Ethyl acetate-butanone (3:2)	0.0	1.0	0.0
	No 1	Chloroform-acetone-THF (1:1:2)	0.0	1.0	0.0
	ITLC-SG	50% Acetonitrile	0.0	1.0	1.0
^{99m}Tc-Exametazime (HMPAO)	ITLC-SG	Butanone	0.0	1.0	1.0
	ITLC-SG	Saline	0.0	1.0	0.0
	No 1	50% Acetonitrile	0.0	1.0	1.0
Protein					
^{99m}Tc-HSA	ITLC-SG or 3MM	Acetone	0.0	1.0	0.0
	ITLC-SG (Strip is pre-saturated with human serum albumin and dried)	Ethanol-ammonia-water (2:1:5)	0.0	1.0	1.0
^{99m}Tc-Sulesomab (Leukoscan)	ITLC-SG or 3MM	Acetone, saline, or 0.1 M citrate	0.0	1.0	0.0
^{99m}Tc-Besilesomab (Scintimun)	ITLC-SG	Butanone	0.0	1.0	0.0

Substitutions:

- In most cases, 2-butanone (methyl ethyl ketone, MEK) can be substituted for acetone
- In most cases, water can be substituted for saline
- In most cases, Whatman No 1 can be substituted for Whatman 3MM paper
- In most cases, ITLC-SA can be substituted for ITLC-SG (not for MDP)
- ACD can be substituted for 0.1 M citrate

1.4 Thin-layer chromatography of technetium radiopharmaceuticals: Simplified strategy

System A-1	
Impurity	Free pertechnetate
Radiopharmaceuticals	MDP/HDP, DTPA, MAA, DMSA, DMSA(V), Nanocolloid, Tin colloid, Sulesomab, Besilesomab, HSA, Pertechnetate
Stationary phase	ITLC-SG
Mobile phase	2-Butanone (MEK)
Interpretation	Origin – bound Front – free pertechnetate
System A-2	
Impurity	Reduced hydrolysed technetium
Radiopharmaceuticals	MDP/HDP, DTPA
Stationary phase	ITLC-SG
Mobile phase	Saline (MDP, DTPA) or 1 M sodium acetate (HDP)
Interpretation	Origin – reduced hydrolysed Front – bound
System B	
Radiopharmaceuticals	Sestamibi
Stationary phase	Aluminium oxide (Bakerflex)
Mobile phase	Ethanol (95% or greater)
Precautions	Prespot with ethanol. Spot sample while still wet. Then allow to dry before developing
Interpretation	Origin – impurities Front – bound
System C	
Radiopharmaceuticals	Tetrofosmin
Stationary phase	ITLC-SG
Mobile phase	Acetone-dichloromethane (35:65)
Precautions	Spot must be allowed to dry before developing
Interpretation	Origin – reduced hydrolysed Middle - bound Front – free pertechnetate
System D-1	
Impurity	Free pertechnetate
Radiopharmaceutical	MAG3
Stationary phase	Whatman No 1 paper
Mobile phase	Chloroform-acetone-THF (1:1:2)
Interpretation	Origin – bound Front – free pertechnetate
System D-2	
Impurity	Reduced hydrolysed technetium
Radiopharmaceutical	MAG3, Mebrofenin
Stationary phase	ITLC-SG
Mobile phase	50% Acetonitrile
Interpretation	Origin – reduced hydrolysed Front – bound

System E	
Impurity	Free pertechnetate
Radiopharmaceutical	Mebrofenin (HIDA)
Stationary phase	ITLC-SA
Mobile phase	20% Sodium chloride
Interpretation	Origin – bound Front – free pertechnetate
System F-1	
Impurity	Free pertechnetate
Radiopharmaceutical	HMPAO
Stationary phase	ITLC-SG
Mobile phase	Saline
Interpretation	Origin – bound Front – free pertechnetate
System F-2	
Impurities	Reduced hydrolysed technetium + secondary complex
Radiopharmaceutical	HMPAO
Stationary phase	ITLC-SG
Mobile phase	2-Butanone (MEK)
Interpretation	Origin – reduced hydrolysed and secondary complex Front – bound and free pertechnetate
System F-3	
Impurity	Reduced hydrolysed
Radiopharmaceutical	HMPAO
Stationary phase	Whatman No 1 paper
Mobile phase	50% Acetonitrile
Interpretation	Origin – colloid Front – bound, free pertechnetate and secondary complex
System G	
Radiopharmaceutical	Tc(V)-DMSA (pentavalent)
Stationary phase	Silica gel (not ITLC)
Mobile phase	Butanol-acetic acid-water (3:2:3)
Interpretation	Origin – reduced hydrolysed; Tc(III)-DMSA Middle – Tc(V)-DMSA Front – free pertechnetate
System H-1	
Impurity	Free ^{111}In, ^{90}Y, ^{177}Lu, ^{68}Ga
Radiopharmaceutical	Octreotide, DOTATATE
Stationary phase	ITLC-SG
Mobile phase	0.1 M citrate
Interpretation	Origin – bound Front - free
System H-2	
Impurity	Colloidal ^{111}In, ^{90}Y, ^{177}Lu, ^{68}Ga
Radiopharmaceutical	Octreotide, DOTATATE
Stationary phase	ITLC-SG
Mobile phase	1 M ammonium acetate-methanol (1:1)
Interpretation	Origin – colloid Front - bound

System J	
Impurity	Free fluoride
Radiopharmaceutical	FDG
Stationary phase	Silica gel
Mobile phase	Acetonitrile-water (95:5)
Interpretation	Origin – free fluoride Middle - bound

1.5 Thin-layer chromatography of other radiopharmaceuticals

Radiopharm-aceutical	**Stationary phase**	**Mobile phase**	**Rf free**	**Rf bound**
$^{123/131}$I-MIBG	Silica gel	Ethyl acetate-ethanol (1:1)	0.6	0.0
^{111}In-DTPA	ITLC-SG	10% Ammonium acetate-methanol (1:1)	0.1	1.0
^{111}In-Octreotide ^{90}Y/^{177}Lu/^{68}Ga-DOTATATE	ITLC-SG	0.1 M Citrate buffer pH 5	1.0	0.0
	ITLC-SG	1 M Ammonium acetate-methanol (1:1)	0.0 (colloid)	1.0
^{18}F-FDG	Silica gel	Acetonitrile-water (95:5)	0.0	0.6
^{18}F-Fluoroethylcholine	Silica gel	Acetonitrile-saline (1:1)	0.0	0.6
^{123}I-Ioflupane (Datscan)	ITLC-SG (Spot must be dry)	Chloroform-methanol (9:1)	0.0	1.0
^{123}I-Iomazenil	Silica gel	Ethyl acetate-ammonium hydroxide (200:1)	0.0	0.7
	Silica gel	Chloroform-acetic acid-water (65:35:5)	0.0	0.3
^{131}I-Iodocholesterol	Silica gel	Chloroform-ethanol (1:1)	0.0	0.7

1.6 Solid-phase extraction cartridge methods

1.6.1 Consumables

Solid phase extraction cartridges are available from various suppliers. The original brand was Sep-Pak by Waters Associates. Cartridges can be re-used several times after decay of radioactivity.

1.6.2 General procedure:

1. Pre-wet ("activate") cartridge with 2-5 mL ethanol or methanol.

2. Prepare cartridge with 2-10 mL of preparation solvent.

3. Place a drop of the radiopharmaceutical in the inlet of the cartridge.

4. Elute sequentially with 2-10 mL quantities of eluates A, B, C and collect each in a separate tube; after the last eluate, force air through the cartridge to dry it.

5. Place the cartridge in another tube for measurement of residual activity.

6. Measure the activity in each tube in an ionisation chamber.

7. Calculate radiochemical purity as per table.

1.6.3 Preparation of regents

Reagent	Preparation
1 mM HCl (0.001 M HCl)	1 mL conc HCl per litre of distilled water
PB for MAG3	0.01 M (10 mM) sodium phosphate buffer pH 6 Prepare 100 mL 0.01 M monosodium phosphate solution (NaH_2PO_4). Prepare 20 mL 0.01 M disodium phosphate solution (Na_2HPO_4). Add 10 mL disodium phosephate solution to 100 mL monosodium phosphate solution. pH should still be below 6. Add disodium phosphate solution dropwise until pH of 6 is obtained.
PB for MIBG	0.1 M (100 mM) monosodium phosphate (NaH_2PO_4)
THF	tetrahydrofuran
10 mM NaOH (0.01 M NaOH)	0.4 g dissolved in 1 litre of distilled water or dilute 1 mL 1 M NaOH with 99 mL distilled water

1.6.4 Table of systems

Radiopharma-ceutical	Type of cartridge	Prepar-ation solvent	A	B	C	D	Purity
^{99m}Tc-sestamibi	Alumina N	0.5 mL ethanol	10 mL ethanol	cartridge residue			A/total
	C-18	2 mL saline	2 mL saline	5 mL ethanol	cartridge residue		B/total
^{99m}Tc-tetrofosmin	C-18	2 mL saline	2 mL saline	5 mL ethanol	cartridge residue		B/total
	Silica	5 mL saline then 1 mL air	10 mL methanol-water (70:30) over 2 minutes	cartridge residue			B/total
	Silica	5 mL saline then 1 mL air	10 mL methanol-water (70:30) over 2 minutes	10 mL methanol-saline (80:20)	cartridge residue		B/total
^{99m}Tc-MAG3	C-18	10 mL 1 mM HCl	10 mL 1 mM HCl	10 mL 50% ethanol	cartridge residue		B/total
	C-18	10 mL 1 mM HCl	5 mL 1 mM HCl	5 mL 0.5% ethanol in PB	10 mL 7% ethanol in PB	cartridge residue	C/total
^{99m}Tc-exametazime	C-18	5 mL saline	5 mL saline	cartridge residue			B/total
	C-18	5 mL saline	5 mL saline	5 mL ethanol	cartridge residue		B/total
^{99m}Tc-IDAs	C-18	10 mL 1 mM HCl	10 mL 1 mM HCl	10 mL 95% ethanol	cartridge residue		B/total
^{111}In-octreotide	C-18	10 mL water	5 mL water	5 mL methanol	cartridge residue		B/total
^{90}Y/^{177}Lu-DOTATATE	C-18	20 mL 0.3 M ascorbic acid	3 mL 0.3 M ascorbic acid	5 mL ethanol	cartridge residue		B/total
^{123}I-ioflupane	C-18	5 mL water	5 mL water	5 mL ethanol	cartridge residue		B/total
$^{123/131}$I-MIBG	C-18	5 mL water	5 mL water	10 mL PB-THF (3:1)	cartridge residue		B/total
	C-18	5 mL water	5 mL 10 mM NaOH	cartridge residue			B/total

1.7 ^{99m}Tc-Exametazime extraction method

1. Prepare a 10 mL test tube containing 3 mL of ethyl acetate and 3 mL of saline
2. Add several drops of ^{99m}Tc-exametazime (immediately after reconstitution)
3. Cap the tube and mix on a vortex mixer for 1 min
4. Let the tube stand for 1 min to allow the two phases to separate
5. Remove the top layer using a pipette into another test tube
6. Measure the activities in each layer in an ionization chamber
7. Calculate the % lipophilic complex as follows:

   $$\%\ \text{primary complex} = \frac{\text{activity in ethyl acetate layer}}{\text{total activity in both layers}} \times 100$$

8. Minimum acceptable value: 80%

Reference: Ballinger JR, Reid RH, Gulenchyn KY. Radiochemical purity of [^{99m}Tc]HM-PAO. *J Nucl Med* 1988; 29: 572-573.

1.8 High-pressure liquid chromatography (HPLC)

1.8.1 General procedure

RCP testing of SPECT and PET radiopharmaceuticals can be carried out using high-pressure liquid chromatography (HPLC) on systems equipped with a radio-detector and UV detector, though there are exceptions such as ^{18}F-fluorodeoxyglucose (FDG) where UV detection is not possible and a pulsed amperometric detector is used.

One of the limitations of HPLC is that only compounds which elute from the column are measured. Measurement of recovery of injected activity should be performed for all new compounds and on an occasional basis to check that negligible quantities are being lost, for example due to retention on the guard column.

1.8.2 HPLC systems for SPECT radiopharmaceuticals

Radiopharma-ceutical	Column	Isocratic or gradient	Solvent(s)	Reference
^{99m}Tc-sestamibi	C-8	gradient	A: 50 mM ammonium sulphate B: methanol 0%B to 95%B over 5 minutes	Carvalho 1992 [1]
	C-18	isocratic	A: methanol B: 50 mM ammonium sulphate C: acetonitrile A:B:C 45:35:20	Hung 1991 [2]
^{99m}Tc-tetrofosmin	PRP-1	gradient	A: 10 mM phosphate buffer pH 7.5 B: tetrahydrofuran 0%B to 100%B over 17 minutes	Kelly 1993 [3]
	PRP-1	isocratic	A: acetonitrile B: 10 mM ammonium carbonate A:B 70:30	Millar 1999 [15]
	PRP-1	isocratic	A: 5 mM monopotassium phosphate B: acetonitrile A:B 50:50	Cagnolini 1998 [16]
^{99m}Tc-MAG3	C-18	isocratic with wash	A: ethanol B: 10 mM phosphate buffer pH 6 A:B 5:95 after peak, wash with methanol-water 90:10	Millar 1990 [4]
	C-18	gradient	A: 10 mM potassium phosphate with 1% triethylamine pH 5 B: tetrahydrofuran 0%B to 8%B over 30 minutes	Shattuck 1994 [5]
^{99m}Tc-exametazime	PRP-1	gradient	A: 20 mM phosphate buffer pH 7.4 B: tetrahydrofuran 0%B to 25%B over 6 minutes	Neirinckx 1987 [6]
	PRP-1	gradient	A: 10 mM potassium phosphate pH 7 or water containing 1% methanol B: acetonitrile 0%B to 50%B over 5 minutes	Hung 1988 [7]
	PRP-1	gradient	A: 50 mM sodium acetate pH 5.6 B: tetrahydrofuran 0%B to 100%B over 17 minutes	Weisner 1993 [8]

$^{123/131}$I-MIBG	C-18	isocratic	A: 100 mM sodium phosphate B: tetrahydrofuran A:B 88:12	Wieland 1980 [10]
^{123}I-ioflupane	C-18	isocratic	A: methanol B water C: triethylamine A:B:C 85:15:0.2	Baldwin 1995 [11]
^{123}I-iomazenil	C-18	isocratic	A: methanol B: water A:B 55:45	Zoghbi 1992 [12]
^{125}I-albumin	C-4	gradient	A: 0.1% TFA in water B: 0.1% TFA in acetonitrile 35%B to 90%B in 10 minutes	Liverpool
^{111}In-octreotide	C-18	gradient	A: saline B: methanol 40%B to 80%B in 20 minutes	Krenning 1992 [13]
^{111}In/^{90}Y/^{177}Lu/ ^{68}Ga-DOTATATE	C-18	gradient	A: 0.1% TFA in water B: 0.1% TFA in acetonitrile 0-2 min 100%A, 2-20 min 100%A to 100%B	Wehrmann 2007 [17]
^{18}F-FDG	amino	isocratic	A: acetonitrile B: water A:B 95:5	Hamacher 1986 [14]

1.8.3 HPLC systems for PET radiopharmaceuticals

Radiopharma-ceutical	**Column**	**Isocratic or gradient**	**Solvent(s)**	**Reference**
^{18}F-FDG	Anion exchange	Isocratic	0.1 M aqueous NaOH	EP monograph 1325
	Amino	Isocratic	Acetonitrile / water (70/30)	
^{18}F-NaF	Anion exchange	Isocratic	0.1 M aqueous NaOH	EP monograph 2100
^{11}C-Acetate	Anion exchange	Isocratic	0.1 M aqueous NaOH	EP monograph 1920
^{11}C-Methionine	C-18	Isocratic	10mM aqueous sodium phosphate	EP monograph 1617
^{18}F-FLT	C-18	Gradient	Acetonitrile / water (10/90)	EP monograph 2460
^{18}F-FMISO	C-18	Gradient	Acetonitrile / water (10/90)	EP monograph 2459

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