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Evaluation of alternative rapid thin layer chromatography systems for quality control of technetium-99m radiopharmaceuticals

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HIGHLIGHTS

- Whatman 3MM™ paper and Tec-Control™ systems validated as ITLC-SG alternatives.
- Full solvent migration in Tec-Control™ was not reproduced for 99mTc-tetrofosmin.
- Systems are comparable to ITLC-SG, Tec-Control™ is more conservative for 99mTc-sestamibi.
- Tec-Control™ (~1 min) and Whatman 3MM™ (7–9 min) are faster than ITLC-SG (10–15 min).
- Overall, Tec-Control™ is preferred but Whatman 3MM™ recommended for 99mTc-tetrofosmin.

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ABSTRACT

Whatman 3MM™ and Tec-Control™ systems were evaluated as ITLC-SG alternatives for 99mTc-radiopharmaceuticals. They compare well in accuracy and reproducibility, and are faster and more convenient than ITLC-SG. Tec-Control™ radiochemical purity values for 99mTc-sestamibi were more conservative than ITLC-SG. Full solvent migration was not reproduced for 99mTc-tetrofosmin in Tec-Control™, and for this Whatman 3MM™ is preferred. Developing times were 10–15 min, 7–9 min and ~1 min for ITLC-SG, Whatman 3MM™ and Tec-Control™, respectively. Overall, Tec-Control™ strips are preferred due to speed and ease of use.

1. Introduction

Silica gel-impregnated instant thin layer chromatography (ITLC-SG) strips have been in widespread use in the quality control of radiopharmaceuticals for over three decades (Saha, 2010). The major advantages of a validated ITLC analytical process have been the speed of the test and its relative simplicity and inexpense. The primary vendor of ITLC-SG strips (Pall Life Sciences, Ann Arbor, MI) discontinued supply in 2008, with severe implications for everyday radiopharmacy practice, eased later by availability of the product from a different vendor (Agilent, product SGI0001). This discontinuation followed that of polysilicic acid-impregnated ITLC strips in 2004/5, which were widely used for the quality control of 99mTc-dimercaptosuccinic acid and other 99mTc-iminodiacetic acid (IDA) complexes. Subsequently, an alternative solid extraction procedure for the 99mTc-mebrofenin was developed and validated, applicable to other 99mTc-IDAs (Billinghurst et al., 2004). A number of groups have also reported on alternative quality control systems to replace ITLC-SG systems, although most of the literature is applicable to single radiopharmaceutical products (Amin et al., 2011; Eggert et al., 2010; Ponto, 2011; Zlata et al., 2010).

The central radiopharmacy at Winnipeg Health Sciences Centre supplies and provides services to five hospitals affiliated to the Winnipeg Regional Health Authority and prepares a variety of radiopharmaceuticals. QC operations would therefore have been severely impacted by the discontinuation of the commercial ITLC-SG strips and there was strong motivation to identify and validate QC tests alternative to the routine ITLC-SG systems (Table 1),

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Table 1
Routine chromatography systems used at the radiopharmacy.

Product	Media	Manufacturer and model	Solvent
99mTc-DTPA	ITLC-SG[a,b]	Pall Corp. 61886	Methylethyl ketone 0.9% Saline
99mTc-MDP	ITLC-SG[a,b]	Pall Corp. 61886	Methylethyl ketone 0.9% Saline
99mTc-SbS colloid	ITLC-SG[a]	Pall Corp. 61886	0.9% Saline
99mTc-Sestamibi	Aluminum Oxide IB-F[c]	J.T. Baker 4467-02	Ethanol
99mTc-DMSA	ITLC-SG[a]	Pall Corp. 61886	Methylethyl ketone
99mTc-Sulfur colloid	ITLC-SG[a]	Pall Corp. 61886	Methylethyl ketone
99mTc-Tetrofosmin	ITLC-SG[a]	Pall Corp. 61886	Ethyl Acetate

[a] Developed in a 22 × 6 cm glass cylindrical tank.
[b] Developed in a 30 × 30 cm rectangular chamber.
[c] Developed in a 18 × 12 cm rectangular chamber.

Table 2
ITLC chromatography systems based on Tec-Control™ miniaturized strips.

Product	Media	Strips color-codes	Solvent	Developing vial (mL)
99mTc-DTPA	Whatman 31 ET	Red	Acetone	10
	ITLC-SG	Black	Distilled water	
99mTc-MDP	Whatman 31ET	Red	Acetone	10
	ITLC-SG	Black	Distilled water	
99mTc-SbS colloid	ITLC-SG	Dark green	0.9% Saline	10
99mTc-Sestamibi	Whatman 31ET	Pink	Ethyl acetate	5
99mTc-DMSA	Whatman 31ET	Yellow	Acetone	10
99mTc-Sulfur colloid	Whatman 31ET	Red	Acetone	10
99mTc-Tetrofosmin	Whatman 1	Teal	Ethyl acetate	5

Table 3
Chromatography systems based on Whatman 3MM™ strips.

Product	Solvent
99mTc-MDP	Methylethyl ketone 0.9% Saline
99mTc-SbS colloid	Methylethyl ketone
99mTc-Sulfur colloid	0.9% Saline
99mTc-Tetrofosmin	Ethyl Acetate
	Acetone: Dichloromethane

including the commercial options Tec-Control™ chromatography (Biodex, Shirley, NY; Table 2) (Barnes et al., 1996; Zimmer, 2004) and Whatman 3MM™ paper system (Table 3). Tec-Control systems are available in color-coded strips for specific radiopharmaceuticals. These systems were compared with the standard ITLC-SG procedures routinely applied at our radiopharmacy.

2. Materials and methods

99mTc-sodium pertechnetate was eluted from Tecknekow™ generators (Mallinckrodt, St. Louis, MO).

2.1. Preparation of 99mTc-radiopharmaceuticals

Commercial kits of diethylene triaminopentaacetic acid (DTPA, DraxImage), methylene phosphonate (MDP, DraxImage), sestamibi (Covidien and Cardiolite, Lantheus Medical), dimercaptosuccinic acid (DMSA, GE Healthcare) and sulfur colloid (GE Healthcare) were reconstituted according to manufacturer product inserts to make 99mTc-radiopharmaceuticals. Procedures for preparation of 99mTc-tetrofosmin (Myoview, GE Healthcare) were adopted from the manufacturer's product insert, but higher activities (up to 25 GBq 99mTc-pertechnetate) were used in reconstitution. 99mTc-antimony sulphide (99mTc-SbS) colloid was prepared using in-house kit formulations and following established procedures (Billinghurst and Jette, 1979). For all preparations, the pass limits for radiochemical purity is 90%, calculated as the net percentage technetium radiolabelled complex after subtraction of tested radiochemical impurities (free pertechnetate, reduced hydrolyzed technetium).

Preparation and evaluation of the effect of vial size and shape on RCP following the Tec-Control procedures was determined using two vial sizes, 5 mL (Biodex, Shirley, NY) and 10 mL (Greer Laboratories, Lenoir, NC).

2.2. Quality control procedures

All spotting of product samples onto the strips were performed using 28 G, 1 cm^3 insulin syringes (Vanishpoint™, Retractable Inc., Little Elm, Texas). Various operators were involved in conducting the QC tests, but in all cases the same person performed each comparative test set. For detection of radiochemical species, the chromatography strips were run on an in-house TLC scanner equipped with a 5 cm NaI(Tl) detector and connected to an Eagle Plus MCA system and a Genie-200 Basic software (Canberra, Concord, Ontario). The comparative time delay to full development of the spotted strips by the relevant solvent in the chamber was determined for the two alternative strip systems and compared to the development times of the routine ITLC-SG systems.

(a) *Routine ITLC-SG and thin layer chromatography (TLC)*
Table 1 summarizes the routine ITLC-SG chromatography systems for each product. The strips (1.5 × 20 cm) were cut from 20 × 20 cm impregnated glass fiber sheets (Pall Life Sciences, Ann Arbor, MI). Product was spotted 2.5 cm from the bottom and developed in a closed 22 × 6 cm glass cylindrical tank or a closed 30 × 30 cm developing chamber, which contained the appropriate developing solvent. When solvent migrated to a mark 2.5 cm from the top, the strips were immediately removed, left to dry (except where solvent was saline), and then wrapped in plastic film and analyzed on the TLC counter.
99mTc-sestamibi analysis requires use of aluminum oxide IB-F chromatography strips (J.T. Baker, Phillipsburg, NJ, USA). The pre-cut 2.5 × 7.5 cm strips were solvated with a drop of