Airtight Miniaturized Chromatography: A Safer Method for Radiopharmaceutical Quality Control

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Miniaturized chromatography is widely used for quality control of radiopharmaceuticals. Recently, published chromatography procedures have illustrated or described chromatography chambers open to the air in use, suggesting that volatile toxic mobile phases are harmless to people in the vicinity. We describe the results of our search for an inexpensive closed chromatography chamber that can be used to derive safely the benefits from conventional miniaturized chromatography.

For routine nuclear medicine imaging studies, it is essential to perform chromatography on radiopharmaceuticals to verify their high radiochemical purity. Such chromatography is often performed daily or several times daily in diverse clinical settings. Some of the mobile phases used in chromatography (e.g., acetone, methyl ethyl ketone (MEK), methanol, and chloroform) are volatile and potentially toxic when inhaled. Recently, a popular handbook of miniaturized chromatographic procedures (*1*) has illustrated open chromatography chambers in use with chromatogram strips protruding out and above the neck of the vial. In addition, other published procedures do not caution the chromatographer to use closed chambers when toxic mobile phases are employed (*2–3*).

We are concerned that chromatographers, other nuclear medicine personnel, and even patients may be exposed to acetone, MEK, methanol, and/or chloroform in air from improperly performed chromatography. Recognizing the potential hazard, we sought an airtight, inexpensive, readily-available closed chromatography chamber.

This report describes our partial experience over two years with commercially-available blood-collection tubes as chromatography chambers for radiopharmaceutical quality control.

MATERIAL AND METHODS

Standard 10-ml blood-collection tubes* containing no additive (such as heparin or acid citrate dextrose) are employed as closed chambers for chromatography of ^{99m}Tc and ^{123}I radiopharmaceuticals. The tubes are received with an uncoated (6441) or silicone-coated (6430) interior. The paper label on the exterior of each tube is scraped off by scalpel prior to use.

For chromatography, the necessary tubes are supported in a test tube rack. The volume of mobile phase added to each tube is 0.5 ml, reduced from the 1.0 ml recommended for miniaturized chromatography (*1,3–5*). The reduced volume results from the narrower base of the blood-collection tube when compared with the base of a typical serum vial used in miniaturized chromatography. During chromatographic development (Fig. 1), the snug-fitting rubber stopper seals vapors of mobile phase within the tube. Upon removal of the developed strip, the tube is immediately re-stoppered and disposed of intact. The silicone coating retards wetting of the inside walls of the tube, thereby permitting disposal of the tubes as nonradioactive trash. Each tube is used only once. All other details of our reduced-scale miniaturized chromatography are as described elsewhere (*3–4*).

RESULTS

As a representative soluble radiopharmaceutical, ^{99m}Tc-oxidronate (^{99m}Tc-HMDP) preparations were assayed at 1.5 hr after formulation by our technique incorporating predrying of the silica gel strip (*1*) for measuring hydrolyzed reduced ^{99m}Tc (colloidal ^{99m}Tc). Predrying is necessary only when assaying ^{99m}Tc-HMDP to avoid streaking on the solid

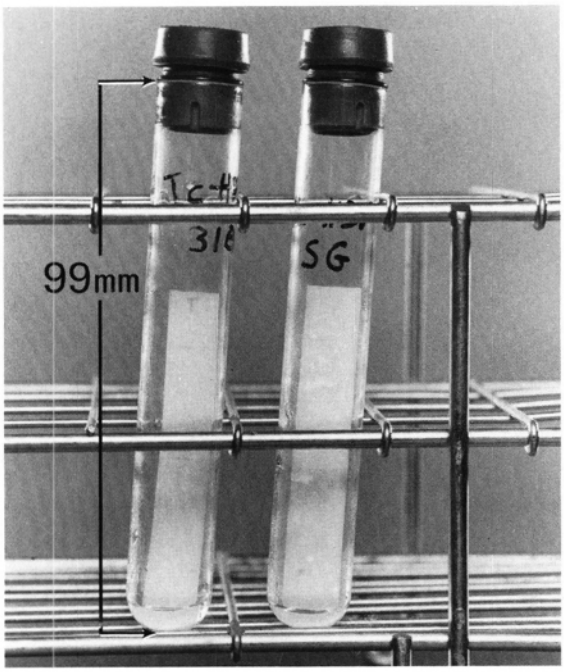

FIG. 1. Standard blood collection tubes being used as closed chromatography chambers.

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phase. In 10 clinical ^{99m}Tc-HMDP preparations, free pertechnetate measured 0.12 ± 0.34% (SD) (range 0–1.08%) while colloidal ^{99m}Tc measured 0.56 ± 0.30% (range 0.32–1.12%). Majewski et al. (*5*) report free pertechnetate of 0.15 ± 0.07% and colloidal ^{99m}Tc of 0.70 ± 0.42% (their Table 3) in the like radiopharmaceutical at the same time of post-formulation by conventional miniaturized chromatography. As a representative particulate radiopharmaceutical, ^{99m}Tc-macroaggregated albumin (^{99m}Tc-MAA) was assayed by our modification. In 14 clinical preparations of ^{99m}Tc-MAA, free pertechnetate amounted to 0.11 ± 0.07% (range 0%–0.28%) indicating high radiochemical purity.

Kung et al. (*6*) report their ^{123}I HIPDM to contain less than 5% free iodide in preparations tested. Using multidose kits supplied by Kung, we have found ^{123}I HIPDM to contain 2.96 ± 0.83% free iodide (14 preparations) by airtight miniaturized chromatography.

DISCUSSION

Conventional full-scale thin-layer or paper chromatography is performed in closed chambers (frequently with chromatography paper lining the inner walls) to saturate the atmosphere with solvent within the chamber. This is necessary to achieve desired separation of individual chemical moieties on the solid phase. Unfortunately, such separation requires up to several hours to take effect. To remedy the time impediment, several investigators have reduced the size of the solid phase and of the chromatography chamber along with the volume of mobile phase, yielding miniaturized chromatography for radiopharmaceutical quality control.

The reduced scale dramatically shortens the time required to achieve separation of radiochemical species. In such miniaturized chromatography, assay for the free pertechentate contaminant in ^{99m}Tc radiopharmaceuticals usually employs acetone (dimethyl ketone) as the mobile phase, but some investigators (*7–9*) have preferred MEK, partly because it is less hygroscopic than acetone. Assay for hydrolyzed reduced ^{99m}Tc contaminant employs either distilled water, 0.9% NaCl in water, or methanol as the mobile phase, depending on which radiopharmaceutical is used. Assay for free iodide in ^{123}I HIPDM employs chloroform as one component of a mobile phase mixture of three components (*6*).

The speed with which the mobile phase rises on the solid phase (<1 min) requires that the chromatographer remain close to the chromatography chamber in order to stop development by removal of the strip. However, such proximity to an open chromatography chamber favors inhalation of any volatile toxic solvent.

Since acetone, MEK, methanol, and chloroform each has a relatively high vapor pressure at room temperature, and hence is quite volatile, exposure by inhalation in the workplace is likely to occur (*10–11*). While DeVincenzo et al. report that breathing air containing 100 or 500 parts acetone per million parts air (ppm) was without toxic effect, approximately 75% of the inhaled acetone was absorbed into the bloodstream, and half-life for its elimination in expired air was ~ 3 hr (*12*). The threshold for toxic effects in man from acetone in air appears to be ~ 1000 ppm. MEK vapor is irritating to human mucous membranes and conjunctivae at 200 ppm after 15 min of exposure (*13*). Prolonged exposure to high air concentrations of either acetone or MEK can cause central nervous system depression and narcosis (*10*). Workplace exposures to methanol are not very hazardous if concentrations in air do not exceed 200 ppm (*11*). Chloroform is teratogenic, highly embryotoxic, and possibly carcinogenic in animals (*14*). Workers exposed to 2–20 ppm chloroform in air experience headache, nausea, loss of appetite, and a high incidence of enlargement of liver and spleen (*14*). Accordingly, the Occupational Safety and Health Administration (OSHA) limits concentration of acetone in workplace air to 1000 ppm, MEK to 200 ppm, methanol to 200 ppm, and chloroform to 50 ppm (*15*).

The blood-collection tubes described herein are 9.9 cm long with an inner diameter of 13.5 mm. The narrower diameter of those tubes (in comparison to broad-based vials and bottles used in conventional miniaturized chromatography) aids saturation of mobile phase vapor around the chromatogram strip, permitting consistent separation of radiochemical species. The blood collection tubes cost $0.083 each and are readily available from the manufacturer.

In summary, we have successfully employed standard blood-collection tubes as closed chromatography chambers for radiopharmaceutical quality control. Our modification of standard miniaturized chromatography is inexpensive, convenient, and safer for all people present in the vicinity of the chromatography. In addition, the results achieved are accurate and comparable to those from conventional miniaturized chromatography.

NOTE

*Vacutainer 6430 or 6441, Becton-Dickinson Co., Rutherford, NJ.

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