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RADIOCHEMICAL PURITY CONTROL OF ^{99m}Tc-MERTIATIADE (MAG-3) RADIOPHARMACEUTICAL

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Abstract. *Several methods have been recommended in the literature for the radiochemical purity control of ^{99m}Tc-mertiatide (MAG-3, mercaptoacetyltriglycine) radiopharmaceutical. This study aimed to compare these miniaturized chromatographic systems to verify their true usefulness and to determine the best way to quantify the radiochemical purity of this radiopharmaceutical, which is used in nuclear medicine for dynamic renal imaging for purposes of diagnosing the problems in kidneys. Instant Thin Layer Chromatography (ITLC) silica gel and Paper Chromatography using different solvents in different supports are analyzed. The chromatographic systems were: ITLC-SG, Whatman S&S 2589C, Whatman 4 (as support phase) in Acetone, NaCl, MEK, Absolute Alcohol, Ethyl Acetate:MEK 3:2, Acetonitrile 50% (as mobile phase). ITLC-SG was found to be the best support for these miniaturized chromatographic methods because it saves considerable time, fits quite well in the nuclear medicine department's daily routine production, and meets the labelling criteria formulated by the manufacturer.*

Keywords: *radiopharmaceutical, technetium, radiochemical purity, stability test*

1. INTRODUCTION

Each radiopharmaceutical must pass several quality control tests before dispensing for human administration [1]. Regular checks should be made for the sterility, pyrogenicity and radiochemical purity of all labeled products. For each radiopharmaceuticals the European Pharmacopoeia recommends a method for the quality control. However, the methods for the quality control of 99mTc- MAG-3 based on high-pressure liquid chromatography combined with paper chromatography is time-consuming and costly. As a result, it is not widely used in nuclear medicine. Therefore, several alternative methods have been already proposed. Radiochemical purity may be assessed by a variety of analytical techniques such as liquid chromatography, pare chromatography, thin-layer chromatography, and electrophoresis. After or during separation of different components occurring in the radiolabeled products, the distribution of radioactivity on the chromatogram is determined. Different measuring techniques are used depending on the nature of the radiation and the chromatographic technique. The quantity of substance applied to the chromatographic support (paper, plate or column) is often extremely small (because of the high sensitivity of detection of the radioactivity) and particular care has to be taken in interpretation concerning the formation of artifacts.

The radiochemical purity of a radiopharmaceutical is the fraction of the total radioactivity in the desired chemical form in the radiopharmaceutical [2]. Radiochemical impurities arise from decomposition due to the action of solvent, change in temperature or pH, light, presence of oxidizing or reducing agents, and radiolysis. The most frequently radiochemical impurities presented in 99mTc-labeled complexes are free 99mTcO4- and hydrolyzed 99mTc. Examples of radiochemical impurities are free $^{99m}TcO_4^-$ and hydrolyzed ^{99m}Tc in many ^{99m}Tc-labeled complexes.

The presence of radiochemical impurities in a radiopharmaceutical result in poor-quality images due to the high background from the surrounding tissues and the blood and gives unnecessary radiation dose to the patient. The decomposition of the labeled compound by radiolysis depends on the specific activity of the radioactive material, the energy of the emitted radiation, and the half-life of the radionuclide. Absorption of radiations by labeled molecules results in the formation of free radicals with unpaired electrons, which in turn leads to further decomposition of other molecules. The stability of the compound is time-dependent on exposure to light, change in temperature, and radiolysis. The longer a compound is exposed to these conditions, the more it will tend to break down. For this reason, most radiopharmaceuticals are assigned an expiratory date after which they are not guaranteed for this intended use.

^{99m}Tc-mertiatide (MAG-3) radiopharmaceutical is a radioactive diagnostic agent used in renal function determination [3].

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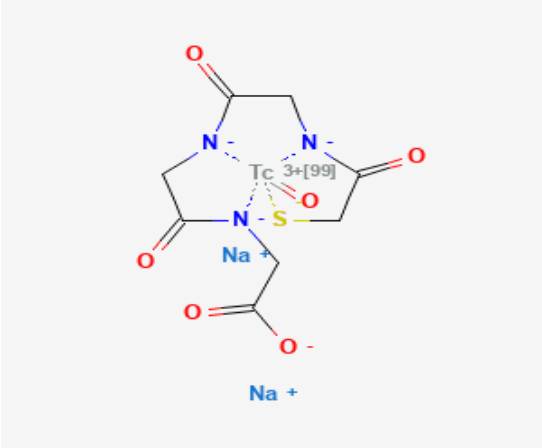

Figure 1. Structural formula of ^{99m}Tc-mertiatiade (MAG-3) radiopharmaceutical

2. Materials and Methods

The radiochemical purity of prepared ^{99m}Tc-MAG 3 was tested using the standard method [4].

2.1. MAG 3 Radiopharmaceutical Preparation

The Tc-MAG 3 radiopharmaceutical is prepared by adding 5 ml of eluate containing 750MBq pertechnetate, to the vial kit. After agitation, the vial was incubated at room temperature for 15 min before performing the radiochemical purity test.

2.2. Chromatographic Systems

The stationary phases were silica gel-impregnated glass fibred sheets (Gelman Sciences) for ITLC-SG and paper Whatman S&S 2589C, Whatman 4, and Whatman 1Chr. All supports were divided into 1x100mm strips. The chromatographic solvents used were Acetone, NaCl, MEK, Absolute Alcohol Ethyl Acetate: MEK 3: 2, acetonitrile 50%. Glass tubes with a glass stopper were used as chromatographic chambers.

2.3. Chromatographic Tests

The tests performed using the above systems included ascending chromatography placing an aliquot of the prepared MAG 3 radiopharmaceutical (3 µl) at the origin of the strip and leaving the solvent front to reach the height of 9-10 cm.

The time required for this migration was also measured in all systems.

The development strips were dried in air at room temperature.

The chromatographic patterns were determined using a TLC Scanner.

2.4. Stability of ^{99m}Tc-MAG-3

Radiochemical purity is performed by standard and the best system (MEK: Ethyl acetate=2: 3 or 40%: 60%/ITLC-SG and 50% acetonitrile/ITLC-SG) up to 4 hours after preparation and in different volumes/concentrations.

3. Results and Discussion

Instant Thin Layer Chromatography (ITLC) silica gel and Paper Chromatography using different solvents in different supports are analyzed. The chromatographic systems were: ITLC-SG, Whatman S&S 2589C, Whatman 4 (as support phase) in Acetone, NaCl, MEK, Absolute Alcohol, Ethyl Acetate: MEK 3: 2, Acetonitrile 50% (as mobile phase). Below are the chromatographic radiograms for all systems used.

3.1. Instant Thin Layer Chromatography Method

ITLC-SG strips Gelman Sciences in different eluents are used to determine impurities of the prepared/labelled Mag-3 radiopharmaceutical [5]. Some of the radiochromatograms obtained using TLC Scanner are presented in Fig. 2-4.

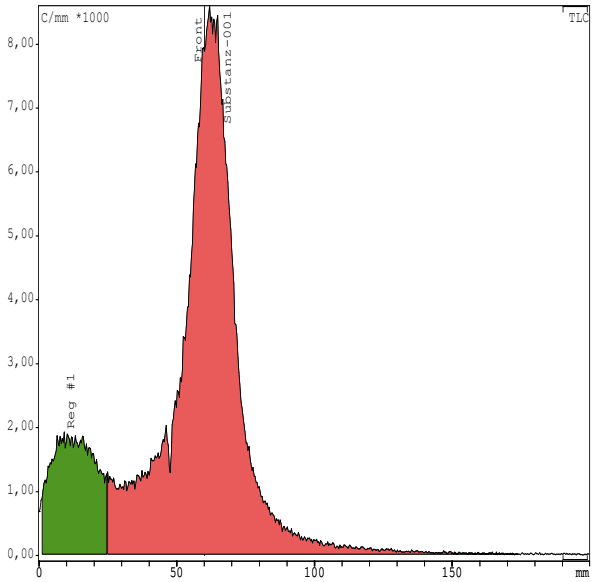

Figure 2. Radiochromatograms: ITLC-SG/Acetone

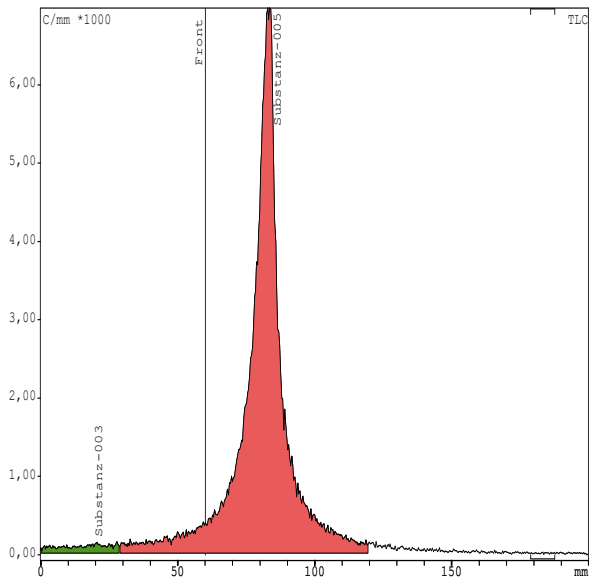

Figure 3. Radiochromatograms: ITLC-SG/NaCl

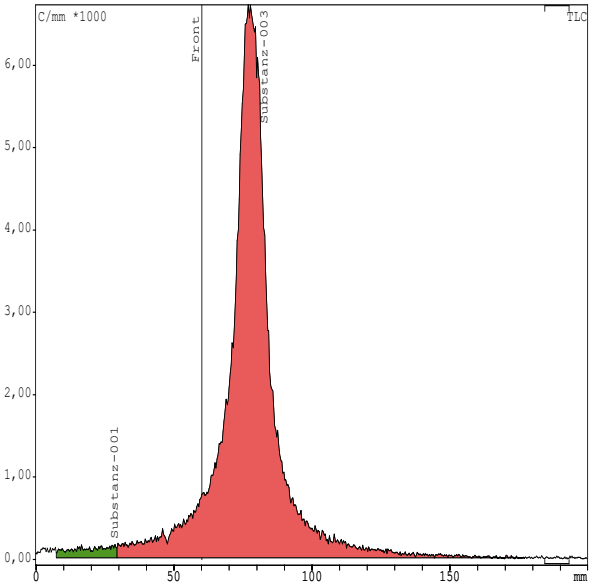

Figure 4. Radiochromatograms: ITLC-SG/Alcohol absolute

3.2. Paper Chromatography Method

Whatman S&S 2589C papers are used to determine radiochemical purity of the prepared/labelled mag-3 radiophamaceuticals. These strips are developed in different eluents and some of the radiochromatograms are presented in Fig. 5-7.

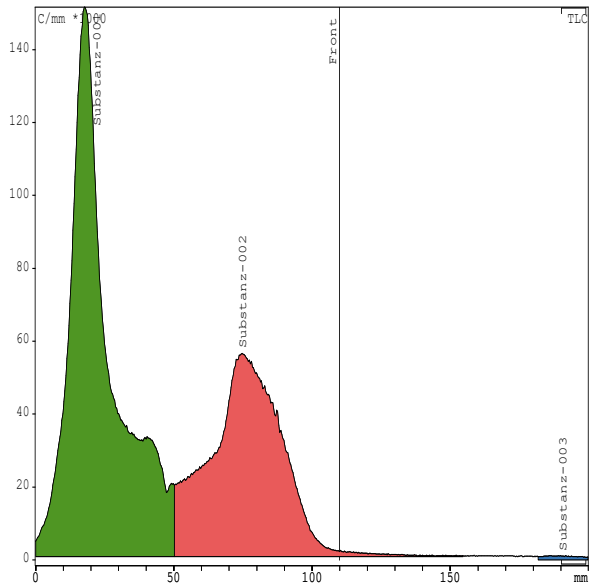

Figure 5. Radiochromatogram-PC Method/Whatman S&S2598 C/Ethyl Acetate: MEK3:2

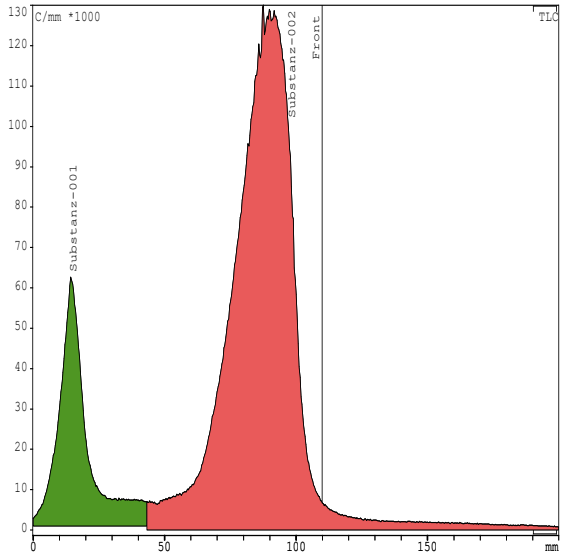

Figure 6. Radiochromatogram-PC Method/Whatman S&S 2598C/ Acetone

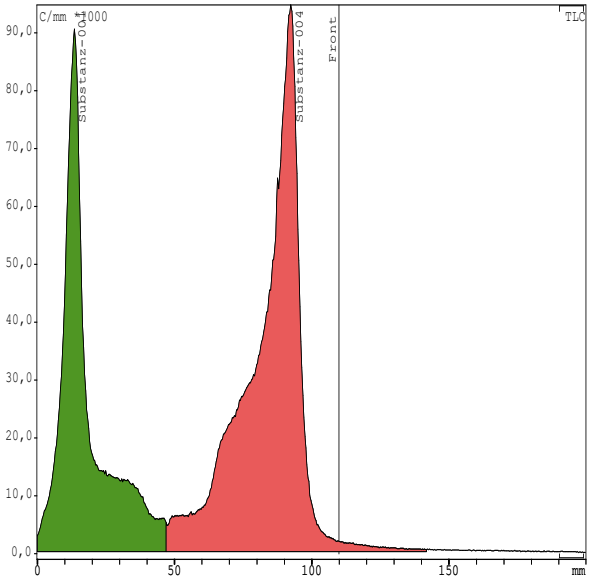

Figure 7. Radiochromatogram-PC Method/Whatman S&S 2589C/ MEK

Whatman 4 papers are also developed in different eluents, the strips are scanned and some of radiochromatograms are presented in Fig. 8-10.

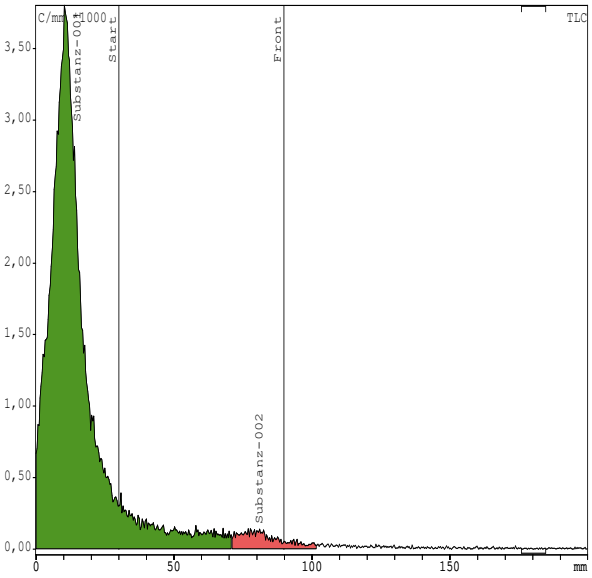

Figure 8. Radiochromatograms-PC Method/Whatman 4/ Acetone

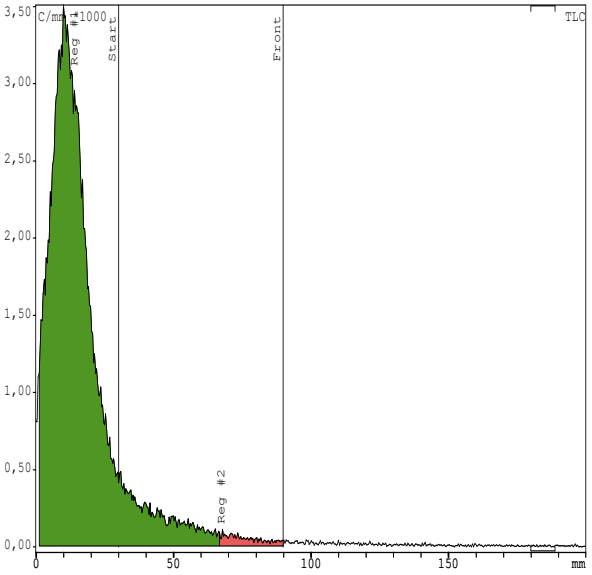

Figure 9. Radiochromatograms-PC Method/Whatman 4/ Alcohol Absolute

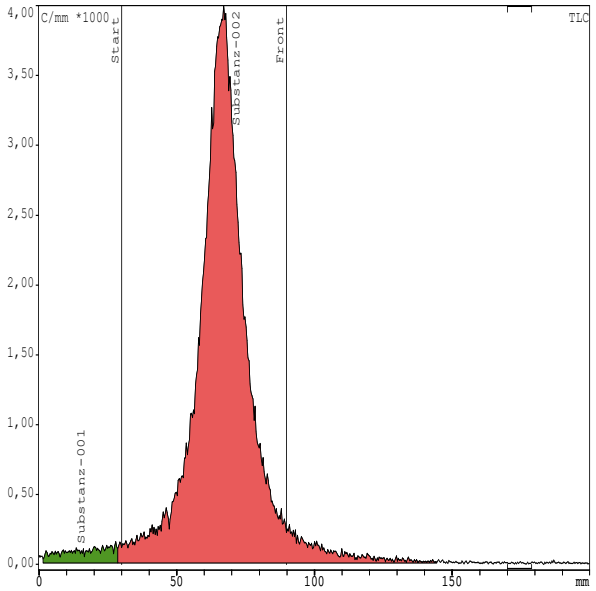

Figure 10. Radiochromatograms-PC Method/Whatman 4/ Acetonitrile

Whatman 1Chr papers are developed in the same eluents, dried and scanned. In Fig. 11-13 some of radiochromatograms obtained after scanning in TLC Scanner, are presented.

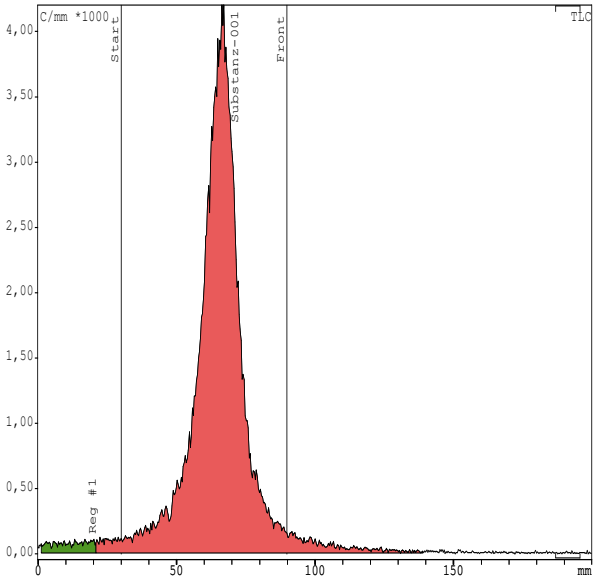

Figure 11. Radiochromatograms-PC Method/Whatman 1Chr/NaCl

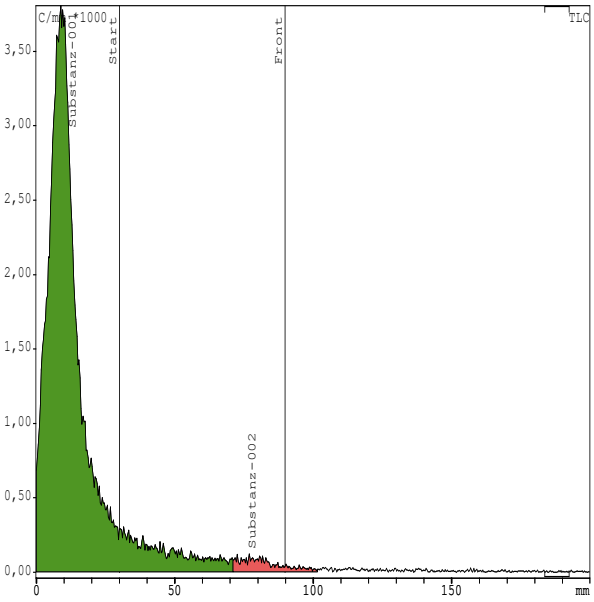

Figure 12. Radiochromatograms-PC Method/Whatman 1Chr/ MEK

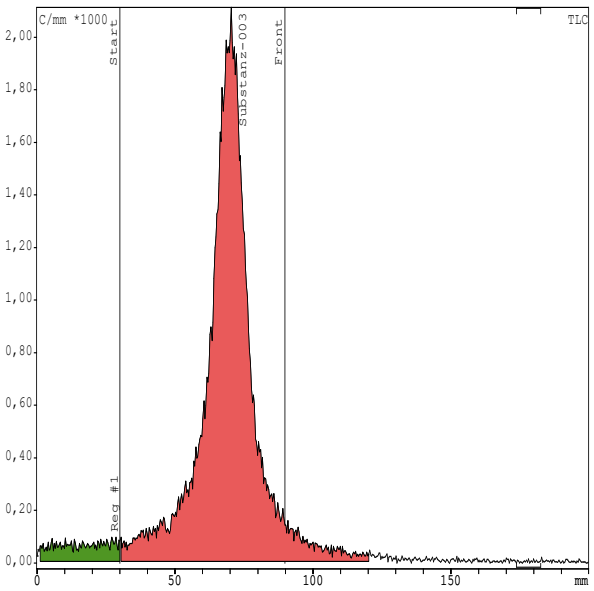

Figure 13. Radiochromatograms-PC Method/Whatman 1Chr/ Acetonitrile 50%

According to our results, the different systems assayed were not equivalent, some being more suitable than others to get clear picks and good separation of the patterns. Despite the relative difficulty of handling the silica gel sheets, which are brittle and need to be stored in a desiccator this stationary phase is the best chromatographic support, considering spot diameter, ascending velocity, and lack of artifacts [6].

4. Conclusion

In summary, our results show that the best chromatography systems were ITLC-SG/MEK: Ethylacetate = 2:3 and ITLC-SG / Acetonitrile 50%.

We recommend these two chromatographic systems for routine radiochemical purity control of ^{99m}Tc-MAG 3 Radiopharmaceutical in Radiopharmacy Departments.

The result shows a stability of 4 hours at room temperature to a final volume of 10ml for 99m Tc- MAG 3 Radiopharmaceutical. More concentrated preparations (4-5ml) may be used for only 1 hour. Storage at 4°C for 99m Tc- MAG 3 Radiopharmaceutical is recommended for multiple administrations to the patients.

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