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EVALUATION OF 99Mo/99mTc GENERATOR COLUMNS AFTER IRRADIATION WITH DIFFERENT ABSORBED DOSES

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ABSTRACT

The $^{99}Mo/^{99m}Tc$ generator is widely used in nuclear medicine and it consists of a glass column containing Teflon® strips and alumina in which ^{99}Mo produced by ^{235}U fission is adsorbed. The $^{99m}TcO_4^-$ eluate shall meet the sterile and pyrogen free conditions for injectable radiopharmaceuticals as determined by the Good Manufacturing Practices. The purpose of this study was to evaluate the feasibility of using gamma radiation in the sterilization of the $^{99}Mo/^{99m}Tc$ generator column and the influence on the elution efficiency. Alumina-containing columns were irradiated with 10, 15, 25 and 50 kGy absorbed doses. Alumina samples and control (non-irradiated) were submitted to X-ray diffraction and the combined use of scanning electron microscopy and elemental analysis. Teflon® samples were evaluated by thermogravimetry (TGA) and differential scanning calorimetry (DSC). X-ray diffractograms and micrographies with elemental analysis showed no significant changes in the crystalline structure of the alumina because it was stable α-Al_2O_3. TGA demonstrated that higher doses showed changes in lower temperatures and times than the control material. For DSC the higher the absorbed dose, the greater the polymer chain breakage and crosslinking in the material. The generator system without radioactivity was set up with the irradiated columns and the eluates demonstrated to be sterile and pyrogen free. The effects of different absorbed doses on the generator column, although some reported changes in the materials, demonstrated that the sterilization of the columns by irradiation with gamma rays as an alternative to wet heat sterilization is feasible from a technical and financial point of view.

1. INTRODUCTION

The growth and extensive application of diagnostic nuclear medicine has been driven primarily by the easy availability of the $^{99}Mo/^{99m}Tc$ generator system. ^{99m}Tc decays by isomeric transition to ^{99}Tc by emitting 140 keV (87.9%) energy photons which are suitable for SPECT imaging. Its physical half-life of 6 h is long enough to obtain the diagnostic information desired in many studies and short enough to cause minimal radiation exposure of the patient and the operator [1,2,3].
Radionuclide generators have been developed for medical applications for convenience in obtaining these radionuclides in clinics and hospitals. In principle, the longest lived parent radionuclide generates a daughter radionuclide of shorter life by radioactive decay. The growth of the daughter radionuclide continues until a maximum is reached, constituting an equilibrium with the parent radionuclide. As long as they are different elements, the daughter radionuclide can be separated by a simple chemical process, generally by liquid elution [2,4,5].
The $^{99}Mo/^{99m}Tc$ generator consists of a glass column containing polytetrafluoroethylene (Teflon®) strips and alumina (Al_2O_3) in which ^{99}Mo produced by ^{235}U fission is adsorbed. The parent nuclide of 66 h physical half-life decays to ^{99m}Tc of 6 h physical half-life. Since the affinity of ^{99m}Tc for alumina is small, it can be easily eluted using sterile saline solution

and vacuum vial. The column is closed at both ends and at one end there is a 0.22 μm filter. The generator is lead-shielded and the entire system is adequately protected to reduce operator exposure to radiation. The $^{99m}TcO_4^-$ eluate obtained in the $^{99}Mo/^{99m}Tc$ generator system should meet the sterile and pyrogen free conditions for injectable radiopharmaceuticals as determined by the current Good Manufacturing Practices (cGMP) and should be prepared under conditions that exclude microbial contamination in the product [1,3,4,6].

Fig. 1 shows a simple scheme of a $^{99}Mo/^{99m}Tc$ generator.

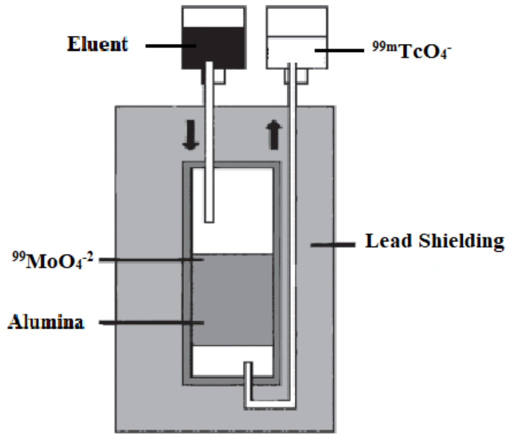


Figure 1: Scheme of a $^{99}Mo/^{99m}Tc$ generator [3].

The alumina can be visualized by scanning electron microscopy (SEM) that is a useful technique for the characterization of different materials and is based on irradiation of a thin electron beam on a sample. The interaction between the beam and the sample surface results in the emission of a series of radiation that may be secondary electrons, Auger electrons, photons, characteristic X-rays, etc. The detection of the secondary electrons is responsible for the high resolution image of the surface topography of the analyzed sample. The image increase can reach 300,000 times and scales between nanometers and hundreds of micrometers are used [7].

At the top of the $^{99}Mo/^{99m}Tc$ generator column Teflon® strips are placed to promote homogeneous distribution of the $^{99}MoO_4^{-2}$ solution in the alumina.

Teflon® is the commercially used term for polytetrafluoroethylene (PTFE), a polymer with applications in many areas, because it is chemically inert and presents a low coefficient of friction [8].

Among the thermal analysis techniques that can be used to evaluate Teflon® are thermogravimetry analysis (TGA) and differential scanning calorimetry (DSC). In TGA, the sample mass change (loss or gain) is determined as a function of temperature and/or time, while the sample is subjected to a controlled temperature program. TGA allows the evaluation of chemical phenomena (chemosorption, desolvation, decomposition, oxidative degradation, reductive degradation and solid-state reactions) and physicochemical phenomena (dehydration, vaporization, sublimation, adsorption, desorption and absorption). DSC measures the difference in the energy supplied to the substance and to a thermally inert reference material as a function of temperature, while both are subjected to a controlled temperature program. DSC gives quantitative data on the physical or chemical changes of the sample, e.g., changes in the physical state, phase transitions, dehydration or decomposition reactions, etc [7,9,10].

The purpose of this study was to verify the feasibility of using gamma radiation in the sterilization of the ^{99}Mo/^{99m}Tc generator column and to evaluate the influence on the elution efficiency.

2. EXPERIMENTAL

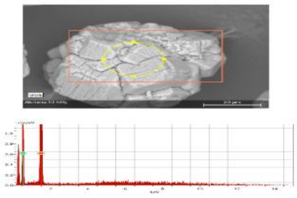
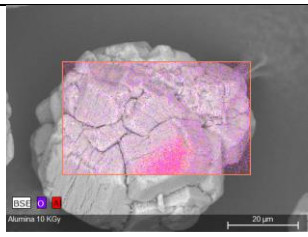
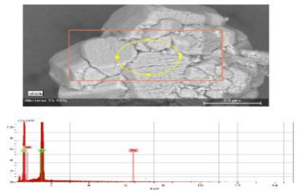
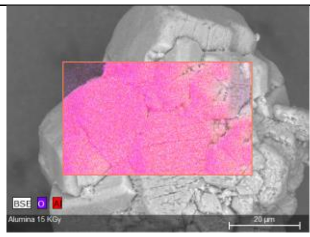
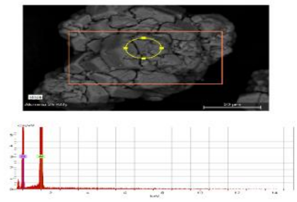
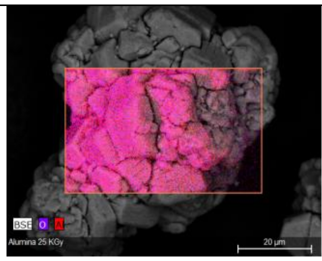
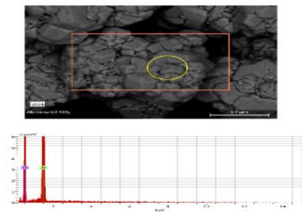
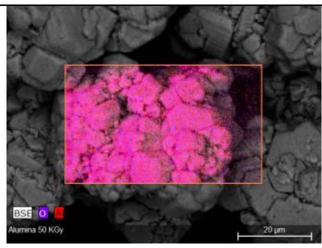
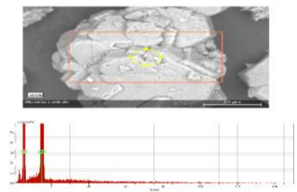
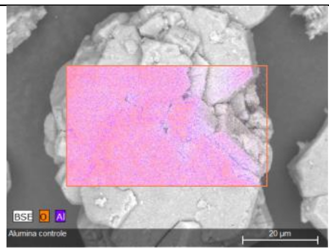
10, 15, 25 and 50 kGy absorbed doses were applied to Teflon® and alumina-containing glass columns and the changes due to the action of gamma radiation on the crystalline structure of the alumina were assessed by scanning electron microscopy (SEM) and elemental analysis (EDS) (Tabletop Microscope, TM-3000 model, Hitachi - Japan) and also by X-ray diffraction (Multiflex, Rigaku -Japan). Teflon® was evaluated by TGA (Thermogravimetric Analyzer, TGA-50 model, Shimadzu -Japan) and DSC (DSC 6000 Differential Scanning Calorimeter, SDT Q600 model, Perkin Elmer - USA) after irradiation with different absorbed doses (IPEN ^{60}Co Multi-Purpose Irradiator). Non-irradiated materials were used as control samples.

Generator systems without radioactivity were assembled with the irradiated columns in order to evaluate the elution performance and the eluates were analyzed for sterility by incubation in casein-soybean (TSB) and thioglycollate culture media. The eluates were tested for the presence of bacterial endotoxins by the LAL (Limulus Amebocyte Lysate) test. The elution specifications were: elution time from 30 to 50 seconds and eluted volume from 5.5 to 6.5 mL.

3. RESULTS AND DISCUSSION

Table 1 refers to alumina irradiated with the same absorbed doses of 10, 15, 25 and 50 kGy and control, respectively, and presents SEM images and elemental analysis by EDS. For each experiment, the elemental distribution spectrum was obtained. The colored dots highlight the O (oxygen) and Al (aluminum) elements that were determined in the elemental analysis.

Table 1: Al_2O_3 Micrograph, Spectrum of elements and Micrograph highlighting the elements by color.

Absorbed dose	Al_2O_3 Micrograph and Spectrum of elements	Al_2O_3 Micrograph highlighting the elements by color
10 kGy		
15 kGy		
25 kGy		
50 kGy		
Control		

MEV images showed that Al_2O_3 was more fragmented at higher absorbed doses especially at 25 and 50 kGy. All spectra presented the predominance of aluminum and oxygen elements as expected. Only the 15 kGy absorbed dose spectrum indicated the iron element as a possible contaminant that could be interference from the equipment or the material used to perform the analysis.

The X-ray diffraction spectra are shown in Fig. 2 with the emission intensities (y) of each sample in the range of 10 to 70 θ, where θ is the angle between the incident X-rays and the alumina crystal surface planes [11].

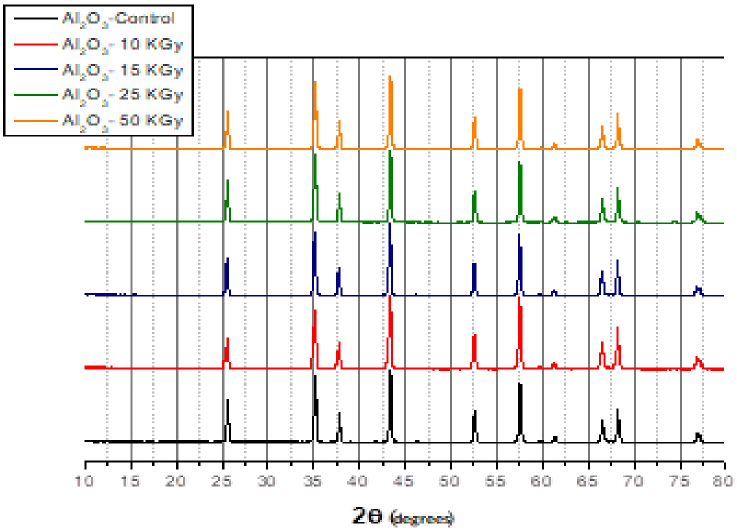


Figure 2: X-ray diffraction spectra for the Al_2O_3 samples irradiated with 10, 15, 25 and 50 kGy absorbed doses and control.

Elemental analysis spectra (EDS) and X-ray diffractograms showed that there was no significant change in the crystalline structure of the alumina submitted to the different irradiation doses, because it is the stable alpha form (α-Al_2O_3) [8].

Alumina can present several transition forms which are differentiated by Greek letters, being the alpha form (α-Al_2O_3) the most stable. According to Brockmann and Schodder (1941), alumina is classified in five types (I to V) and its activity is related to the amount of water adsorbed. Alumina with grade I activity is the most active because it has the highest adsorption capacity and is the most used in column chromatography, and grade V is the least active and contains a greater amount of water (15%) [12-14]. Alumina is a crystalline substance because it has a defined geometric structure. Each crystalline material diffracts the X-rays in different directions and intensities, which makes possible the identification of its crystalline structure [11]. In X-ray diffraction, the diffraction pattern presents a series of reflections which are identified in the diffractogram by the angle (2θ) or the interplanar distance (d) against its intensity. This pattern is related to the chemical composition and the crystal order of the molecules in the crystal [12].

Fig. 3 shows the TGA spectra obtained from Teflon® strips of the irradiated columns.

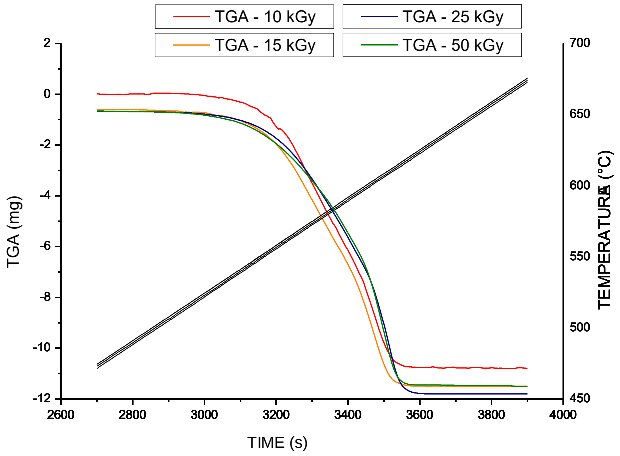


Figure 3: TGA spectra obtained from the Teflon® samples submitted to 10, 15, 25 and 50 kGy absorbed doses.

It was observed that the regions where there are no mass changes are the horizontal portions of the curve (plateau). The materials irradiated at higher doses showed changes in lower temperatures and times than the control (not shown).

The DSC spectrum in Fig. 4 showed that the higher the absorbed dose, the greater the change (polymer chain breakage and crosslinking) of the material. Oxidation (exothermic reaction) of the polymer occurred at about 400 °C.

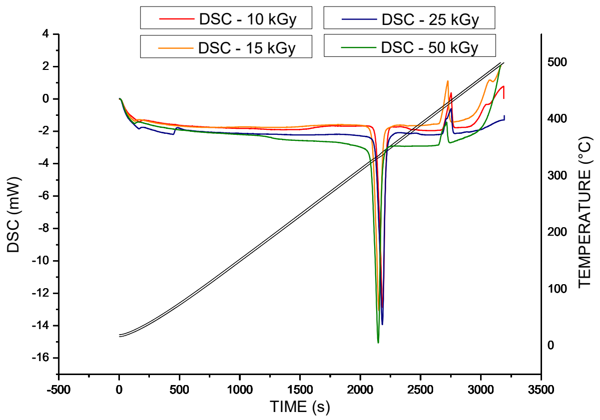


Figure 4: DSC spectra obtained from the Teflon® samples submitted to 10, 15, 25 and 50 kGy absorbed doses.

Polymer irradiation causes degradation (physical and chemical changes) at both microscopic and macroscopic levels, depending on the dose rate and the total dose applied.

Nonradioactive eluates evaluated for sterility by the direct inoculation method in TSB and thioglycollate culture media had no microbial growth after 14 days of incubation. The bacterial endotoxin assays by the LAL method of gel formation presented all results within the specified range. The elution time ranged from 37 to 48 seconds with an elution volume of 5.5 to 6.5 mL, within the specifications.

4. CONCLUSIONS

The effects of the 10, 15, 25 and 50 kGy radiation doses on the generator column, although some reported changes in the structure, were not critical to the proposed objective, demonstrating that the sterilization of the generator columns by irradiation with gamma rays (^{60}Co) as an alternative to wet heat sterilization is feasible from a technical and financial point of view.

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