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**Review of the doctoral dissertation by Arshiya Anees Ahmed,
entitled "Production of $^{99m}\text{Tc}/^{99}\text{Mo}$ radioisotopes using proton and electron
beams".**

The reviewed doctoral dissertation presents the results of experiments in which ^{99m}Tc and ^{99}Mo radioisotopes were produced with the use of proton and electron beams. ^{99m}Tc is currently one of the basic radioisotopes used in nuclear medicine. It is used in over 80 % of medical procedures mainly related to diagnosis of cancers. It is mainly produced in research nuclear reactors in nuclear fission reaction $^{235}\text{U}(n, f)^{99}\text{Mo}$ using enriched uranium-235, or by the neutron capture reaction $^{98}\text{Mo}(n, \gamma)^{99}\text{Mo}$, and distributed as the radioisotope $^{99m}\text{Tc}/^{99}\text{Mo}$ generator. In the last decade, several independent reactor shutdowns and outage extensions have significantly disrupted global supplies of this precious radioisotope. Therefore, new methods of production of ^{99m}Tc for nuclear medicine applications are required. Arshiya Anees Ahmed's research takes up this challenge and is therefore important and current.

Basically, the dissertation can be divided into two parts. The first part is based on an analysis of specialist literature, while the second one concerns directly conducted experiments. The part based on the literature includes the chapters: Introduction and Theoretical background, in which author presents the basics of nuclear medicine in a wide range of aspects. All the basic concepts used in nuclear medicine were explained. Author discussed the methods of introducing radioisotopes into the patient's body, the imaging method with the use of a gamma camera, as well as the methods of producing radioisotopes, with particular emphasis on the production of technetium-99m. In chapter 2.1 author discusses the basics of knowledge about radioactivity. The decays to which unstable atomic nuclei undergo are listed and the mathematical description of radioactive decay is provided. However, author omitted the internal conversion wherein an excited nucleus interacts electromagnetically with one of the orbital electrons of the atom. This process causes the electron to be emitted from the atom. In chapters 2.2 and 2.3 formulas of practical importance have been derived, binding, among others, activity of the produced

particles with the beam current and cross-section for reactions induced by charged particles and photons (i.e. photonuclear reactions), respectively. It is worth emphasizing that the literature part of the dissertation is an excellent introduction to the experimental one and to the presentation of the obtained results.

The part of the dissertation directly related to the performed experiments begins with chapter 3, which describes the experimental environment, including the cyclotrons (Cyclotron AIC-144 and Synchrotron SOLARIS) and HPGe detectors used in the research. Proton irradiations were carried out using the Cyclotron AIC-144 at the Cyclotron Center Bronowice (CCB) in Cracow. This cyclotron is an isochronous one producing a mono-energetic proton beam with energy of 60 MeV and current of 80 μ A, suitable to achieve the purpose of the research. The production of the radioisotope ^{99}Mo in photonuclear reactions was possible thanks to the use of an electron beam generated in the SOLARIS linac system accelerating electrons up to 550 MeV with a maximum electron bunch charge of 0.2 nC. Three high-resolution HPGe detectors were used in the measurements presented in the dissertation. Technical details of the used detectors are described in chapter 3.3.5.

The performed energy calibration of the HPGe detectors was described in detail in chapter 3.3.2. The standard calibration sources of ^{241}Am , ^{133}Ba , ^{109}Cd , ^{60}Co , ^{137}Cs , ^{152}Eu and ^{22}Na were used, which made it possible to determine the energy calibration curve very accurately, using 31 points. Author describes also the efficiency calibration of the used HPGe detectors (chapters 3.3.3, 3.3.4 and 3.3.5). The equation (3.3) by which the detector efficiency was experimentally determined was discussed. The efficiency calibration curve as a function of photon energy for the used detector was derived by fitting the characteristic function (3.4), which is the sum of logarithms in successive powers up to the 4th power, to the points corresponding to the detector efficiency obtained from the measurements. The dissertation (chapter 3.3.4) also includes a description of the gamma spectroscopy procedure, in which the identification of radioisotopes was based on the comparison of the obtained results with data from three databases: "Nuclear structure and decay data by IAEA", "National Nuclear Data Center, Brookhaven National Laboratory" and "Table of Radioisotopes in Version 2.0". The use of three independent, information-rich databases allowed to identify all peaks visible in the measured spectra.

Natural molybdenum discs were used in the experiments. Natural molybdenum consists of seven stable isotopes, which means that in addition to the expected ^{99}Mo radioisotope, other radioisotopes are also produced in the target.

The dissertation contains a detailed description of the system used to irradiate the targets. The methods called by author as "single target activation" and "stack-foil activation" were used for irradiation with a proton beam. In this first method, the 60 MeV proton beam produced in the cyclotron was degraded to an energy of 26 MeV by means of an aluminum layer with a thickness of 11.7 mm. In such a degraded beam, a molybdenum disc was placed and irradiated for 5 h, and then cooled for 18 h. In the method of stack-foil activation a

thicker degrader with a thickness of 13.22 mm was used, and the target consisted of 6 0.01 mm thick discs of natural molybdenum sandwiched between copper 0.01 mm thick foils monitoring the beam current. Such target was irradiated for 5 h and then cooled for 8 h. It is worth noting that author also used computational techniques. The gamma-ray attenuation, the spatial distribution of the beam and the energy of the protons after passing through the degrader and the target were estimated using the SRIM and GEANT4 software.

The experiment related to the use of the photonuclear reaction was performed by means of electron beams with energies of 60 MeV, 100 MeV and 200 MeV, and the size of the beam spot of 3 mm. The electron beam was converted to X-rays on a 6 mm thick tungsten brick placed 26 mm from the linac exit window. The thickness of the brick was optimized to obtain the highest photon flux, using the Geant4 simulations.

Spectroscopic measurements (chapter 4.3) were performed at 20-minute, 2 and 5-hour intervals for various distances between the detector window and the targets. This distance was selected in such a way as to reduce the pile-up effect. The results of the spectroscopic measurements were professionally presented in figures (4.4, 4.5) and in tables (4.5, 4.6). A total of 8 radioisotopes were produced in the proton reactions, while 7 radioisotopes were produced in the photonuclear reactions.

In chapter 5 data analysis methods are presented. Author based the procedure of identification of the radioisotope on the estimated life-time and the identified gamma-ray energy from decay of this radioisotope. Activity changes as a function of measurement time used to determine the half-lives for selected radioisotopes are shown in Figure 5.3 and 5.6. In chapter 5.1.2 the formulas for determination of cross-section and yield are described. In chapter 5.1.3 author describes a method of the determination of the beam current by means of a monitoring reaction. As monitoring reactions, those with a known cross-section within the studied energy range for the used type of projectile were chosen, i.e. the $^{nat}\text{Mo}(p,x)m+g^{96}\text{Tc}$ reaction for the single target activation and proton reactions with ^{nat}Cu for the stack-foil activation. Author took care of all the details of the experiment, including that the surface of the monitoring target and the production target were identical. Detailed information on monitoring targets is included in Table 5.1. Monitoring foils were also used for verification of the beam energy in the stack foil activation experiment. For the single target activation, the energy distribution in the target was determined using the SRIM and GEANT4 simulation (Figure 5.4) with no monitoring foils. Author notes that there are no data available for photon-induced monitoring reactions in the energy range of interest. Therefore, Geant4 Monte-Carlo simulations were performed for the determination of the photon flux as a function of energy (Figure 5.7) whereas the TALYS software was used for the calculation of the production cross-section of ^{99}Mo through the photonuclear reaction on a ^{nat}Mo target.

In chapter 6 author presents and discusses the obtained results. The determined cross-sections of $^{nat}\text{Mo}(p,x)$ reactions are presented in Figure 6.1 whereas in Figure 6.2 and

6.3 the cross-sections of the $^{100}\text{Mo}(p,x)^{99}\text{Mo}$ reaction and the $^{100}\text{Mo}(p,x)^{99m}\text{Mo}$ one are shown, respectively. They are compared with those obtained by others. The cross-section at 22.5 MeV comes from the single activation experiment. The stack-foil experiment made it possible to determine the cross-section for even six energies up to 17 MeV. The obtained results turn to be in a good agreement with the literature data. Experimentally determined target yield of production of all detected radioisotopes in proton reactions in a $^{\text{nat}}\text{Mo}$ target are included in Table 6.1 and presented in Figures 6.4 and 6.5. They were compared with the literature experimental data by Cervenak and Lebeda (2016) and by Takacs et al. (2015) and with TALYS predictions derived using TALYS cross-section data and not the TALYS produced yield data. The measured yield data are in agreement with the mentioned experimental data within the error limitations understood as the energy range in the target, not the energy uncertainty. The exception in this agreement is ^{93}Tc . The TALYS yield data is generally somewhat less consistent. In chapter 6.2 the results of the experiment with the photon-induced reactions are presented and discussed. In this experiment long-lived radio-impurities were produced along with the radioisotope of interest - ^{99}Mo (Table 6.3), because natural molybdenum targets were used. Therefore the knowledge of the amount of impurities was needed to find the optimal beam conditions for the production of ^{99}Mo and to choose suitable separation method. The GEANT4 simulations with the cross-section of the $^{\text{nat}}\text{Mo}(\gamma,n)^{99}\text{Mo}$ reaction calculated by TALYS were used for estimation of the production yield of the long-lived radio-impurities. Author discusses different methods of Mo^{99} separation from the activated target. She claims that the best way of the separation is to choose the appropriate photon energy of 100 MeV for which the ratio of ^{99}Mo to ^{90}Mo has the highest value.

In chapter entitled "Summary and outlook" author, among others, notes that the use of an enriched molybdenum target would avoid the production of many radio-impurities, however, the price of such material is currently around \$30000 per gram, whereas the price of $^{\text{nat}}\text{Mo}$ ranges from \$0.25 to \$0.80 per gram. Author emphasizes that impurity formation can be reduced by using protons with the energy from 9 to 26 MeV. Moreover, author provides very important observations. Namely, the beam lifetime in the ring of synchrotrons is of the order of several hours, and linac injectors are only used for a small part of that period. Thus at those facilities, ^{99}Mo could be produced in parallel with other ongoing experiments, which would lead to a more efficient use of the existing infrastructure while meeting the local demand for ^{99}Mo , thereby eliminating losses that are unavoidable in transportation. The proposal to use a synchrotron for the production of ^{99}Mo seems all the more justified as more than 50 electron linac facilities, similar to SOLARIS, exist in research institutes all over the world, delivering beams of energy more than 100 MeV.

The dissertation ends with a bibliography of 62 references. 3 of these references are articles with the results of the dissertation.

Comments for discussion

The points on the efficiency calibration curve do not deviate from the fitted curve (Figure 3.6). This indicates that coincidence summing corrections was applied. However, there is no information in the dissertation on how this correction was done.

In chapter 4.4.1 author writes that an aluminum foil of 11.7 mm thickness was used as a proton energy degrader. In chapter 4.1.2 the name "foil" is used for a 13.2 mm thick aluminum layer. A layer of aluminum or any other material more than 1 cm thick should not be called a foil. Foils are usually materials with thicknesses of a fraction of a millimeter or thinner.

Author fits photo-peak using a Gaussian function and a linear background, and also determines the half-life by means of fitting with an exponential function. However, nothing is mentioned about the fit method and the used software. The reviewer guesses that the fitting was done using the least squares method.

Author writes that "To estimate the production yield of the long-lived radio-impurities listed in Table. 4.6, we used the Geant4-simulated photon flux convolved with the TALYS package generated cross section of the $^{nat}\text{Mo}(\gamma, n)^{99}\text{Mo}$ reaction as shown in Fig. 5.7." There is confusion in the context of this statement. Were the values of activity and yield of the produced radio-impurities at the end of bombardment, presented in Table 6.3 determined by the experiment or using the simulations?

In the discussion of the results, there is no correlation between the ^{99m}Tc activity that can be achieved and the number of diagnostic tests that can be performed.

Evaluation of the research and the author of the work

In the presented dissertation, its author has demonstrated advanced knowledge in the field of nuclear physics. It should be emphasized that Arshiya Anees Ahmed used both experimental and computational methods. The dissertation contains a detailed description of the conducted experiments and is supported by comprehensive theoretical knowledge. The results included in the dissertation were published in 3 articles, in which author of the dissertation is the first author. The dissertation was accompanied by an authorship statement with the precise determined authorship contribution of Arshiya Anees Ahmed. Her contribution includes, among others, conception and design of study, data acquisition, analysis and interpretation of data, drafting the manuscripts, revision the manuscripts critically for important intellectual content and approval of the versions of manuscripts to be published.

The dissertation is written professionally in scientific language. The structure of the chapters is clear and typical of doctoral dissertations. The selection of the cited literature is correct and justified. It is worth noting that the cross-section data from the proton experiments have been added to the International Atomic Energy Agency database EXFOR.

Summarizing, I state that the candidate meets the criteria for candidates in the Act on academic degrees and academic title as well as on degrees and title in the field of art (Dz.U. z 2016 r. poz. 882).

I am in favor of awarding the reviewed doctoral dissertation distinction, due to the very important application of the research and innovative nature. With the ^{99m}Tc reactor crisis in view, advanced research into new methods of producing this precious radioisotope could contribute to the continuity of technetium-99m-based diagnostics, which is the basis for successful treatment of many types of cancer. Innovation of the research is related to the application of beams of high-energy photons with the energy of 100 MeV and 200 MeV produced by a linac injector of a synchrotron for the production of ^{99}Mo .

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