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Doctoral Thesis

"Radiosynthesis of selected tracers for oncology diagnosis using PET technique and adaptation of their production to different types of dispensers."

Abstract

Radiopharmaceuticals are biologically active substances containing a selected radioactive isotope in their structure. They are composed of the three basic elements of a radionuclide, a ligand that has the affinity to accumulate in pathologically changed tissues, and a linker whose function is to permanently bind the first and second components.

A diagnostic method using radiopharmaceuticals is positron emission tomography (PET). This method is an emission method, and unlike absorption methods, the image is generated on the basis of information sent from the object, which requires the source of this information to be located in the object. The information carrier in PET is a gamma-ray quantum, while the source of the emitted radiation is a radiopharmaceutical stored in the body. PET technology is based on the use of isotopes that decay β^+ and emit positrons. The positron collides with the electrons, the next one annihilates, converting its mass into energy emitted in the form of two gamma quanta of 511 keV each in opposite directions. Annihilation is the basis on which PET technology is based.

The preparation and use of radiopharmaceuticals in Poland is regulated by the Regulation of the Minister of Health of 9 November 2015 (Announcement of the Minister of Health of 28 April 2022 on the announcement of the consolidated text of the Regulation of the Minister of Health on the requirements of Good Manufacturing Practice) Annex 3 Manufacture of radiopharmaceutical products and Annex 1 Manufacture of Sterile Medicinal Products. Test methods and quality requirements for radiopharmaceutical products are defined by the Polish Pharmacopoeia, which has been translated from the European Pharmacopoeia.

Specialised equipment is used for the preparation of radiopharmaceuticals, the operation of which must comply with the requirements imposed by the aforementioned legislation and its design must ensure adequate protection against ionising radiation.

Radiopharmaceuticals are medical preparations containing in their structure radioactive isotopes that give the molecules a special character of "decay of the drug in time", and additionally make them dangerous to work with due to the ionising radiation they emit.

The research problem, is the provisions in the mentioned legislation and the design of the equipment do not fully take into account the special characteristics of radiopharmaceuticals such as:

- Short half-life of the isotope used for labelling, not longer than 25 minutes;
- Low synthesis yields typical of niche tracers that have no commercial potential;
- Preparation of radiopharmaceuticals on a small scale (<30 patients), which is typical of radiopharmaceutical production in a hospital setting,
- Emission of ionising radiation regulated by the Atomic Law of 29 November 2000.

The main objective was to investigate the impact of the time required for the preparation of selected tracers for oncology diagnosis using the PET technique taking into consideration the mentioned guidelines and the design of the dispensing equipment on the final yield that can be allocated to patient doses.

Due to the number of experiments to be performed, the main objective was divided into specific objectives:

- Optimisation of the synthesis of selected radiolabels, in order to obtain the highest yield and radiochemical purity;
- Adjustment of batch dispensing for selected tracers on different types of dispensers comparing the time required for their preparation;
- Carry out quality control of selected radiopharmaceuticals while maintaining the required acceptance criteria, in accordance with the guidelines of the Polish Pharmacopoeia and European Pharmacopoeia, taking into account the time needed to perform the necessary tests;

- Calculation of the final yield and number of PET tests possible after the whole manufacturing process, taking into account the decrease in activity and the total time during the preparation of the selected radiopharmaceuticals.

The work carried out on optimising the synthesis of selected radiopharmaceuticals will contribute to achieving higher yields and radiochemical purity. This will allow for the synthesis of selected radiopharmaceuticals in amounts that make it possible to carry out all the necessary steps required by the Regulation of the Minister of Health on the requirements of Good Manufacturing Practice and the Polish and European Pharmacopoeia and European Pharmacopoeias. Optimisations in the form of improved radiochemical purity contribute to improved safety of use, as well as to improved images obtained from PET diagnostic studies by eliminating radioactive compounds showing non-specific binding. In addition, the modifications carried out at the level of the synthesis modules indicate that it is technically possible to improve the equipment in order to improve the radiosynthesis of selected radiopharmaceuticals.

The dispensing, quality control, completion of documentation and release of radiopharmaceuticals are time-consuming activities. The time required to perform these activities in accordance with all regulatory requirements and with highly specialised dispensing equipment, results in a reduction of the final activity for diagnostic testing. For niche markers with low yields and short half-lives, passing these steps is disadvantageous and, in some cases, impossible. Tracers of this type although diagnostically beneficial will not have commercial potential.

Over the past 10 years, the demand for personalised and precision medicine has increased, and the use of radiopharmaceuticals in this field appears to be a promising solution from the point of view of individualised patient treatment, especially in oncology. Technological advances related to molecular imaging using PET technology and the use of isotopic preparations, offer a wide range of possibilities in this field.

The results obtained indicate that, in order to provide opportunities for the development of tracers that are potentially non-commercial and prepared on a small scale, it would be necessary to consider the preparation of such products in hospital units on an 'in-house', using fast and precise equipment adapted to small-scale production.

In addition to technical improvements, the work points to the potential for improved regulation for possible 'in House' manufacturing. The current requirements of the law are difficult to meet for hospital-based nuclear medicine facilities that are state budget units. Therefore, with the support of national pharmaceutical and nuclear regulators for radiopharmaceutical production, new homogeneous standards for hospital radiopharmacy should be developed, providing safety but also flexibility for the preparation of potentially non-commercial and small-scale radiopharmaceuticals with high diagnostic potential on an 'in House' basis.

Keywords: Radiopharmaceuticals, Radiosynthesis, PET diagnostics, Diagnostic isotopes, Dispensers, Synthesis modules

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