NUKLEONIKA 2005;50(Supplement 3):S83–S87

PROCEEDINGS

Radioisotopes for medical and industrial use during the 50-year history of the Institute of Nuclear Research

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Abstract The paper summarises the 50-years long history of the development of research programmes related to the practical applications of radionuclides in various fields of the Polish economy. The changing trends of interest of the potential users are reflected in the research and development activities of the Radioisotope Centre POLATOM. In the 1960's and 1970's the main areas of activity were focused on the sealed sources and radiolabelled compounds for the investigation of industrial processes. The introduction to the routine practice of the RIA and the IRMA kits for hormonal *in vitro* diagnostics in the 70-ties and 80-ties resulted in the general availability of this diagnostic technique in Poland. The number of radioisotopes having the required radiation type, energy and half-life is steadily increasing due to the progress in irradiation facilities and in chemical separation processes. The need for modern radiopharmaceuticals, more specific and providing higher diagnostic and therapeutic potential as an alternative to other medical modalities is reflected in the research programmes carried out and implemented currently at the Radioisotope Centre POLATOM.

Key words radiopharmaceuticals • isotope application • sealed sources • radiotherapy • brachytherapy

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Received: 12 October 2005

Introduction

Practical applications of radiotracers in industry and science had a high priority at the Institute of Nuclear Research from the very beginning of its activity, which started in 1955. The commissioning of the first research nuclear reactor "Ewa" created the possibility to produce radioactive isotopes in the form of radiolabelled compounds and sealed sources.

In 1967, within the structure of the Institute of Nuclear Research an experimental unit called the Centre for Production and Distribution of Isotopes has been established. The main activity of this Centre was to provide radioactive isotopes for the application in medicine and industry. The radioisotopes were produced through irradiation of suitable targets in the reactor.

Many procedures have been developed to convert the radioisotopes into radiolabelled compounds. These compounds have been delivered to the customers working in science, medicine and industry. In connection with the production of these materials it was necessary to develop suitable radioactivity measuring techniques and analytical methods. In the 1990's, the research and production capability of the Centre was significantly enlarged to cover the increasing demands from medicine.

Radiolabelled compounds

At the beginning, a large effort has been invested in the synthesis of organic compounds labelled with the radionuclide ^{14}C. One should mention here the compounds such as ^{14}C-methionine, ^{14}C-tyrosine, ^{14}C-alanine, ^{14}C-α-aminobutyric acid. Application of ^{14}C-labelled compounds as the substrates in chemical reactions allowed to investigate their kinetics or to follow their metabolism in the living organisms. Production of compounds labelled with tritium, ^{3}H, carbon, ^{14}C, and radionuclides of iodine was continued until the late 1990's, compounds being supplied as tracers for various scientific research programmes as well as for experiments in life sciences and agriculture.

Brachytherapy

Brachytherapy belongs to the category of cancer treatment methods of more and more extensive application world-wide. It involves direct irradiation of the affected tissues using sealed radiation sources containing various radionuclides introduced directly in the cancerous spot. The overall size of such sources, including both the core and casing, varies between a fraction of a millimetre to several millimetres. Under such limitations it becomes indispensable to develop a most effective method for absorbing a given radionuclide on the metal surface. The new research area was allocated in the development of ^{125}I sources intended for implantation therapy [5, 6] and brachytherapy in ophtalomology using ^{125}I and ^{106}Ru sources for therapy of intraocular tumours [15]. The technology of production of sealed ^{125}I sources in the form of miniature iodine seeds is a subject of research work currently conducted. The ^{125}I seeds can be applied in nuclear medicine chiefly for brachytherapy of brain, prostate and intraocular tumours.

New types of ophthalmic applicators and their production technology were developed as a result. It was the complicated shape of ^{106}Ru applicators used in therapy of the eyeball melanoma that triggered the search for new techniques of depositing the radionuclide on a metallic base [15, 20]. The Centre has developed a novel method of application of the internal electrolysis for this purpose. The results obtained have provided ample evidence that the internal electrolysis running without an external source of current constitutes a good alternative for galvanic methods and serves as a simple means of binding considerable amounts of an isotope on the metal surface. The same technique was found useful for manufacturing of the active cores of monolithic ophthalmic ^{125}I applicators [24, 25] (Fig. 1).

Fig. 1. Seed-less radioactive core and stainless steel capsule of ^{125}I ophthalmic applicator.

Other sealed radiation sources

To cover the needs arising from industrial, medical and scientific activities, it was necessary to develop technologies and initiate the production of different types of sources containing α, β and γ-emitters at levels ranging from 3.7×10^4 to a number of 3.7×10^{10} Bq.

Many ^{60}Co sources of about 50 TBq of total activity have been produced and mounted in installations for radiation treatment and for research in radiation chemistry. The ^{192}Ir sources, each of several tens of GBq of activity are being supplied regularly to industrial companies dealing with welding for routine control of their products and constructions. Small sources of ^{109}Cd and ^{147}Pr to be used in analytical and testing instruments are also produced according to the customers specifications. Extensive research and development effort was invested in the production technology of ceramic sources containing long-lived α-emitters such as ^{239}Pu and ^{241}Am [12–14]. Thousands of such sources are used in smoke detectors in Poland and many thousands were exported.

Radioimmunology

Radioimmunoassy (RIA) techniques became a new field of research during the 1970's. As a result of the projects oriented towards the development of new radioimmunoassay kits several new, own technologies have been developed, based on the application of polyclonal antibodies (first and second generation of our own produced antibodies). A success was the obtaining for the first time antibody coated test-tubes (a hCG assay kit – Gravidest). Kits for *in vitro* diagnostics of thyroid disorders, T3 and T4, contributed significantly to the total production volume of the Centre at that time. Other kits for the assay of insulin, growth hormone, and tumour markers (AFP, CEA, hCG) have also been elaborated.

At the end of 1980's, the Centre launched a research programme aimed at modernisation and broadening the range of RIA kits by implementation of technology of solid phase based products (glass microspheres and test-tubes coated with polyclonal antibodies). Attempts to separate the hormones TSH, LH, FSH and prolactine from human pituitary glands were made followed by the development of methods for their labelling with ^{125}I. Based on the in-house produced tracers and polyclonal antibodies, new groups of RIA kits have been developed [1, 3, 4].

A significant leap in quality and product range of the radioimmunodiagnostic kits manufactured in the Radioimmunology Department took place after 1990, when a co-operation with foreign companies was initiated. It resulted in the implementation of production technologies of radiotracers for 11 various RIA and IRMA (ImmunoRadioMetricAssay) kits, including one of paramount importance, namely a state-of-the-art technology for the production of indirectly labelled steroid hormones (estradiol, progesterone, testosterone, cortisol) and consequent manufacturing of high quality IRMA kits.

Radiopharmaceuticals

Progress in nuclear medicine caused a growing demand for locally produced preparations of ^{131}I and the Polish-made $^{113}Sn/^{113m}In$ and $^{99}Mo/^{99m}Tc$ generators. At the beginning of 1970's, a technology of manufacturing gelatine capsules containing the ^{131}I isotope, applied in therapy and diagnostics of thyroid diseases was developed, followed by launching the production of ^{99m}Tc generator using the reactor-irradiated ^{99}Mo as mother nuclide. The simultaneously conducted research programmes ended up with the implementation of production technology of a second radionuclidic generator using ^{113}Sn as a source of ^{113m}In. The possibility of obtaining short-lived radionuclides from suitable generators prompted the works on the development of a series of kits for labelling with these radionuclides, intended for *in vivo* diagnostics of kidneys, liver, lungs and osseous system diseases. A method for labelling albumin microspheres used in scintigraphy of lungs with ^{131}I, ^{99m}Tc and ^{113m}In isotopes has been developed. Polish medical clinics were steadily showing an increasing demand for new preparations for isotope-based diagnostics and therapy. That demand was closely reflected in the research programmes implemented within the late 1980's and at the beginning of 1990's. It was then, when a new type of $^{99}Mo/^{99m}Tc$ generator using ^{99}Mo obtained from ^{235}U fission products was developed and reached the production phase. A schematic diagram of the new generator is shown in Fig. 2. This new design helped to significantly reduce the size of the generator's chromatographic column thus yielding considerably higher radioactive concentrations of the ^{99m}Tc eluate than those obtained with the previously used technology. This, in turn, significantly increased the diagnostic capabilities of hospitals using it.

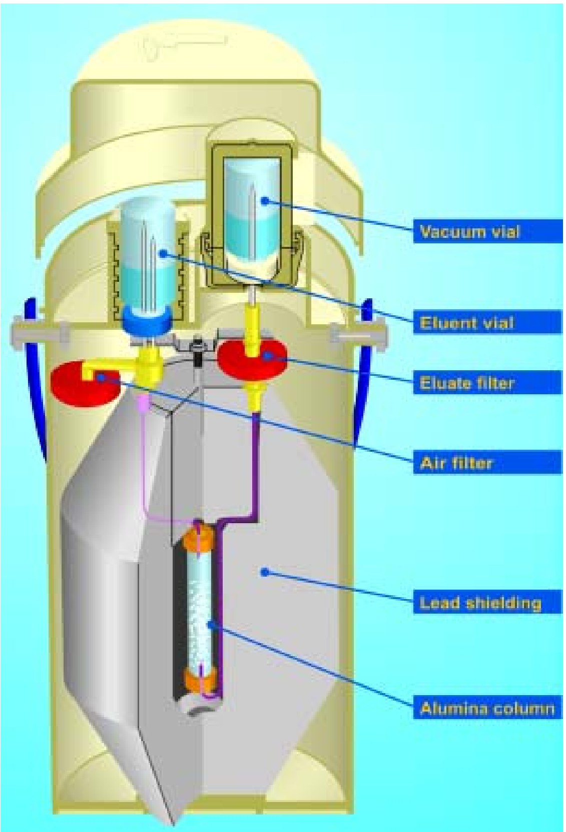

Fig. 2. Schematic view of the $^{99}Mo/^{99m}Tc$ generator.

One of the most significant achievements of that time was launching the production of a diagnostic agent, the ^{99m}Tc-MIBI (sestamibi) kit, used for perfusion scintigraphy of the heart, in the diagnosis of parathyroid and breast tumours. Another offered product was the ^{99m}Tc-MBrIDA (mebrofenine) kit used for scintigraphic examination of the liver, useful in differentiation of hepatitis types, especially at high billirubine levels. The Centre's own research programme led to implementation of the ^{99m}Tc-tin colloid, used in the static scintigraphy of the liver.

Radiopharmaceutical technologies noted another step in the development of scintigraphic kits with a new brain diagnostics agent, ^{99m}Tc-HmPAO. A real breakthrough was the registration and a subsequent start of production of strontium chloride $^{89}SrCl_2$ [7, 8], the first domestic radiopharmaceutical used as pain palliation agent in patients suffering from multiple cancer metastases to the osseous system, mainly originating from the prostate and the breast cancer. The product offered turned out to be preferable over the imported preparations, both in terms of quality and price and contributed significantly to extensive application of that therapy method in Poland.

At the same time, research work was initiated to develop a metaiodobenzoylguanidine (iobenguane, MIBG) production technology, with MIBG being labelled with either ^{123}I (for diagnosis) or ^{131}I (for diagnosis and therapy), both radiopharmaceuticals localising in malignant pheochromocytoma and its metastases and in neuroblastoma. Thanks to the advantageous physical characteristics of ^{123}I, the ^{123}I-MIBG is recommended for diagnosis of these tumours in children, since it yields a better image resolution at lower radiation exposure than ^{131}I-MIBG. Moreover, the former, as a noradrenaline derivative can be applied to diagnostics of the adrenergic system of the heart. Both labelled compounds were introduced to the production in 1999 and a growing interest in their application has been observed since then. It should be emphasised that the application of therapeutic doses of ^{131}I-MIBG became one of the most important treatments in oncology.

New trends in radiopharmaceuticals

Already at the end of 1990's, at the Radioisotope Centre POLATOM the basis for its further development was created, which allowed entering the XXI century with research programmes comprising current trends in isotope technologies. Thanks to the actions taken by the Centre, modern methods for labelling biologically active substances, such as peptides, hormones, monoclonal antibodies and their isolated fragments, with radioactive nuclides have been implemented and found their practical applications in clinics [2, 11, 16, 18, 19, 26]. Pending is the registration process and implementation of production technology of radiopharmaceuticals

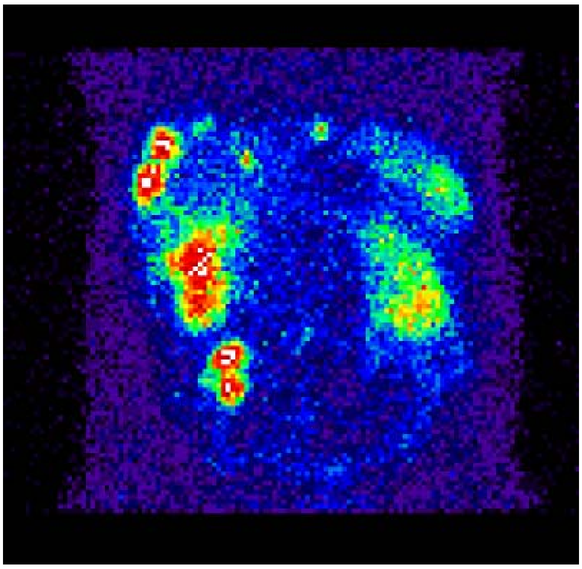

Fig. 3. Scintigraphic visualisation of metastatic tumour obtained after intravenous administration of ^{99m}Tc-HYNIC-TATE.

based on peptides, such as somatostatine derivatives (^{99m}Tc-HYNIC-TOC and ^{99m}Tc-HYNIC-TATE) [10, 22, 23], recommended for localisation, staging and therapy follow-up of tumours of neuroendocrine origin (see Fig. 3).

The growing interest in radiotherapy has led to commencing the research programme aimed at new techniques for nuclear reactor production of β and β/γ radioisotopes, such as ^{186}Re, ^{153}Sm or isotopes obtained by radioactive decay of their mother nuclides (radionuclide generator approach), e.g. carrier-free ^{90}Y, ^{177}Lu or ^{188}Re [17, 21].

Based upon a stationary ^{188}W/^{188}Re generator, a technological line for the production of ^{188}Re has been implemented. This product is sought by cardiologists. It can be used for irradiation of the walls of the coronary vessels, preventing their repeated clogging. ^{188}Re in the form of perrhenate also proves useful for labelling of phosphonates and can be applied to palliative therapy of malignant metastases to the osseous system. After forming stable complexes with other chelates, showing receptor affinity to cancerous tissues, this radioisotope can also be used in radiotherapy. Currently, the Centre is performing research with the aim of full utilisation of the therapeutic potential of ^{188}Re.

As complementary to the scope of work concerning isotopic radiotherapy, the Centre has started its own method for the production of carrier-free ^{90}Y. This, in turn, facilitates fulfilment of a research programme aimed at the application of that isotope to internal radiotherapy of cancers of neuroendocrine origin. A particular achievement of this technology is the application of carrier-free ^{90}Y for labelling of the DOTA-TATE peptide leading to the formation of a radiopharmaceutical featuring therapeutic level of activity. Such a product was applied to the actual treatment of non-surgical metastasised neuroendocrine tumours in 2004, for the first time in Poland.

At its final stage is the research work to initiate the production of radiopharmaceuticals ^{123}I-α-methylotyrosine and ^{131}I-α-methylotyrosine, which are proved to be clinically useful in diagnosis of brain tumours, in particular, for differentiation between the tumour recurrence and a post-surgery scar. Combined with the NMR imaging technique, patient examination using ^{131}I-α-metylotyrosine is helpful in planning the brain tumour surgery [9].

Fig. 4. Production line of ^{131}I.

Summary

What best summarises the Centre's activity in the field of radioisotope application in medicine and industry, is not only the number of the new technologies developed (exceeding 300), but also its record in the scientific degrees awarded and the number of publications in international journals.

Directing the research work conducted by the Centre towards applications in nuclear medicine and oncology has forced the compliance with the requirements of Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) with respect to the technologies and manufacturing methods in use. Modernisation of technology and its adjustment to the European standards' requirements has become a natural process at the Centre. A large-scale new technological process line for the production of ^{131}I for medical applications is one of the examples of that trend (Fig. 4). The application of advanced technologies and procedures, automation of production and measurement processes allowed to decrease the exposure of production and medical personnel to ionising radiation and the risk of internal contamination.

Today, the Radioisotope Centre POLATOM possesses GMP and ISO 9001/2001 certificates and belongs to the group of world's major manufacturers of radioisotopes and radioactive preparations.

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