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Radiopharmaceuticals for Nuclear Medicine and Oncology – The Central Role of Chemistry

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Abstract

Research reactors play a key role in providing a variety of radioisotopes with important medical applications, especially from processing of molybdenum-99 and other important products from fission of uranium-235 targets. In addition, the production of medical radioisotopes from the neutron irradiation of targets provides radioisotope products by both “direct” and “indirect” production pathways. The usual “direct” production approach involving radiative neutron capture [i.e. (n,γ) – no change in Z] by target nuclei, however, usually provides products with much lower specific activity then required because of contamination by target atoms which cannot be removed by usual methods. The use of innovative production approaches, however, can provide the desired radioisotopes by beta- or electron capture-decay (i.e. change in Z) of the initial reactor-produced product. These approaches represent attractive strategies, if efficient chemical methods are available for separation of microscopic levels of the desired decay product from macroscopic amounts of the non-activated target material. Key examples of current interest for therapeutic applications in nuclear medicine and oncology include such “indirect” production of high specific activity lutetium-177 (Lu-177), platinum-195*m* (Pt-195*m*) and rhenium-188 (Re-188). The Lu-177 lanthanide ($t_{1/2}$ 6.71 d, 497 keV β^-) can be produced by the Yb-176(n,γ)Yb-177(β^- decay)Lu-177 route. High specific activity Lu-177 is then separated from Yb and other non-Lu impurities by HCl elution of product mixture adsorbed on the Ln HDEHP resin. The Pt-195*m* noble metal ($t_{1/2}$ 4.02 d, Auger electron emitter) can be produced by the Ir-193(2n,γ)Ir-195(*m*)(β^- decay) route and obtained by Dowex HCl chromatography of the thiourea complexes. The Re-188 transition metal ($t_{1/2}$ 16.9 h, 2.12 MeV β^-) is produced by the W-186(2n,γ)W-188(β^- decay)Re-188 route. This n.c.a. high energy beta emitter is obtained from a generator by NaCl elution of the reactor-produced tungsten-188 adsorbed on alumina. This report will briefly discuss these and other methods that are being developed for “indirect” reactor production and processing of radioisotope that are generally produced in low specific activity by traditional reactor production routes. Examples of the important therapeutic applications for cancer therapy, palliation and arthritis therapy of these therapeutic radioisotopes will also be discussed.

Introduction

Radiochemistry and radiopharmaceutical science are not well defined disciplines and thus attract and depend upon the multidisciplinary contributions of investigators from the basic science disciplines. The complementary focus of multiple disciplines is an integral strength of nuclear medicine research and practice, and the development of tissue-specific radiopharmaceuticals requires expertise in the both the chemical and life sciences. Chemistry plays a central role for the development of radiopharmaceutical agents which are used for both diagnostic and therapeutic applications, particularly in nuclear medicine and oncology. The organic synthesis of radiopharmaceutical substrates and the introduction of chelating groups and other functional moieties required for radioisotope binding represent important areas of chemistry in the radiopharmaceutical arena. Inorganic and analytical chemistry play key roles in metal chemistry, radioisotope processing and purification and analysis.

In the area of radioisotope production and processing, the availability of chemical methods for the separation of radioisotopes with sufficient specific activities is an important aspect which is often mandatory for potential clinical use of the radiopharmaceutical agents. Usually, high specific activity radioisotopes are desired for human use, which reduces the administered mass. Low administered mass is required to minimize possible pharmacological effects of the administered radiopharmaceuticals and/or to minimize receptor saturation. Reactor-produced radioisotopes, in particular, are often obtained in lower specific activity then required, especially since the common production pathway involves radiative neutron capture [i.e. (n,γ) – no change in *Z*]. However, the use of innovative production approaches - which can provide the desired radioisotopes by beta- or electron capture-decay (i.e. change in Z) of the initial reactor-produced product - represent attractive strategies, if efficient chemical methods are available for separation of microscopic levels of the desired decay product from macroscopic amounts of the non-activated target material.

This lecture discusses these and other examples of methods that are being developed for “indirect” reactor production and processing of radioisotope that are generally produced in low specific activity by traditional reactor production routes. Examples of the important therapeutic applications for cancer therapy, palliation and arthritis therapy of these therapeutic radioisotopes are also discussed.

Research Reactor Production and the Processing of Medical Radioisotopes

This lecture will focus on the use of innovative radioisotope production methods in research reactors and the use of various chemical methods for the separation of high specific activity products formed by decay of the reactor-produced parents. An important aspect for the development of radiopharmaceuticals is the availability of radioisotopes with the desired specific activity values which are produced with particle accelerators

and research reactors. The interaction of positively charged particles with target atoms usually results in change of the atomic number Z (**Figure 1**) when the product nucleus is formed (i.e [p,n], [d,n], etc., reactions). If adequate methods are available for the efficient separation of the usual microscopic levels of the radioactive product atoms produced from the macroscopic levels of the target material, then high specific activity products can be obtained.

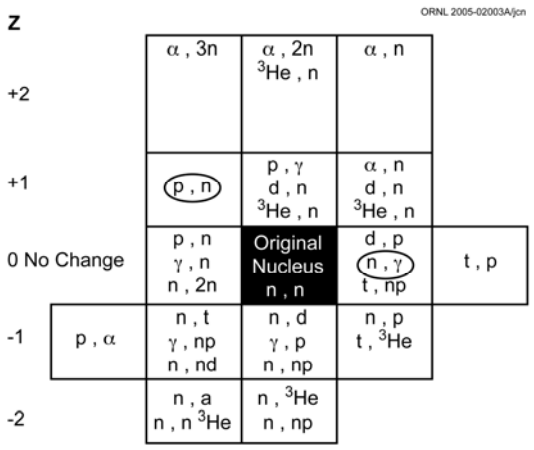

Figure 1. Examples of changes in Z during the accelerator and reactor production of radioisotopes

In contrast to the usual accelerator production routes, the common radiative neutron capture and inelastic routes (**Figure 2**) result in no change of Z, and unless the neutron capture cross sections are very high with low product burn-up, the product specific activities are much lower then theoretical.

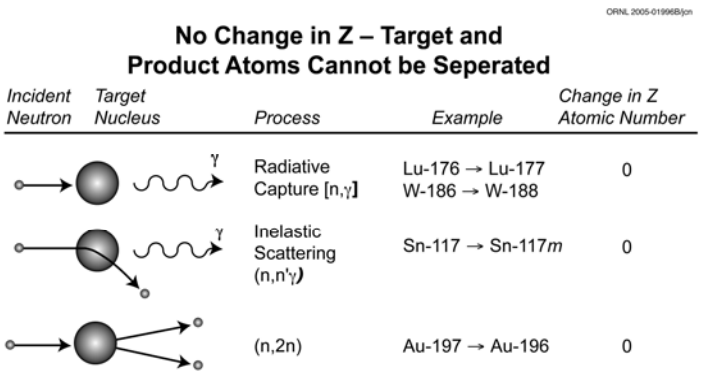

Figure 2 . Examples of nuclear transformations during reactor production of radioisotopes when there is no change in the atomic number Z

Although radioisotopes can be produced in research reactors by the (n,p) reaction, for instance (**Figure 3**), the low production cross sections usually make this approach impractical. As an alternative, when the initial product decays by beta- or electron capture-decay, this approach offers an opportunity to obtain the decay product, if efficient chemical separation methods are available.

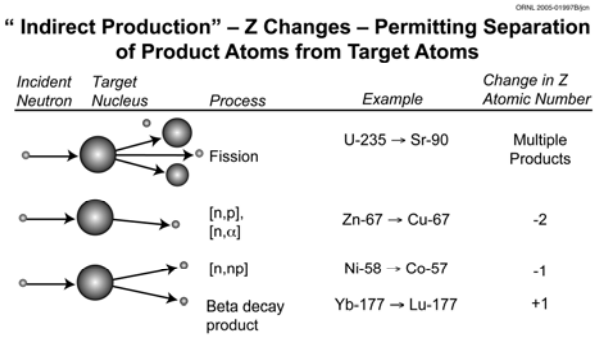

Figure 3 . Examples of nuclear transformations during reactor production of radioisotopes which result in changes in the atomic number Z

Key examples of radioisotopes of current interest which are obtained by beta- or electron capture decay of reactor-produced parents are summarized in **Table 1.** Iodine-131 is a classic example still widely produced on an international scale *via* decay of reactor-produced tellurium-131, and is obtained by either dry- or wet-distillation methods. Prior to the availability of the appropriate radiation generating devices, gadolinium-153 was the radioisotope of choice for dual photon densitometry, for the clinical non-invasive measurement of bone calcium levels. Although gold-199 has been of traditional interest, it has not entered the main stream for therapeutic applications. More recently, cesium-131 has entered the arena as a competitor of palladium-103 and iodine-125 for the radioactive seed treatment of prostate cancer.

Table 1. Traditional examples of high specific activity radioisotopes obtained by separation after beta- or electron capture-decay of reactor-produced products

Target	Product	Decay Product	Comment
Desired radioisotope from by beta-decay of reactor-produced product			
Tellurium-130	Tellurium-131	***Iodine-131***	Thyroid Therapy
Europium-151	Europium-152	***Gadolinium-153***	Bone Densitometry
Platinum-198	Platinum-199	***Gold-199***	Therapy
Desired radioisotope from electron capture-decay of reactor-produced product			
Barium-130	Barium-131	***Cesium-131***	Prostate Therapy "Brachytherapy"

For the production of radioisotopes using research reactors, radioactive products are often formed by the radiative capture of neutrons by the targets atoms, in which case Z is not changed and the specific activity of the product is much lower then theoretical,

since the target and product atoms cannot be separated by the usual methods. Several examples are summarized in **Table 2**. With the exception of lutetium-177 - which is produced in high specific activity because of the very high production cross section and subsequent low burn-up cross section - the other examples are produced with specific activities which are far below the theoretical values.

Table 2. Examples of specific activities of radioisotopes of current interest *****

Radioisotope	Specific Activity, Curies/mg		Theoretical/ Experimental	Application(s)
	Theoretical – Max.	(n,γ)		
Rhenium-188 *Transition Metal*	980	12	> 80	Cancer Therapy
Lutetium-177 *Lanthanide*	109	70	1.5	Cancer Therapy
Platinum-195m *Noble Metal*	166	< 0.001	166,000	Cancer Therapy
Promethium-147 *Lanthanide*	925	(Fission)	Not determined	Beta Batteries

*****Examples of production yields in the ORNL High Flux Research Reactor (HFIR) at a thermal flux of 2.5 x 10^{15} neutrons/cm^2/sec, thermal/epithermal = 25/1

Examples of "indirect" production strategies which are currently being developed and which can provide these and other examples by decay of reactor-produced products are shown in **Table 3**.

Table 3. Examples of high specific activity radioisotopes which can be obtained by separation after beta- or electron capture-decay of reactor-produced products

Target	Product	Decay Product	Separation Method
Desired radioisotopes from by beta-decay of reactor-produced product			
Tungsten-186	Tungsten-188	***Rhenium-188***	Alumina Chrom.
Ytterbium-176	Ytterbium-177	***Lutetium-177***	Ln HEDHP Chrom.
Iridium-193	Iridium195(*m*)	***Platinum-195m***	Dowex - Complex
Neodymium-146	Neodymium-147	***Promethium-147***	Not published
Barium-130	Barium-131	***Cesium-131***	Ion Exchange

The chemical separation of the desired radioisotopes from the reactor-produced primary products presents a challenge to radiopharmaceutical scientists and the development and implementation of effective separation methods is required to make these radioisotopes available at the desired specific activity. The use of radionuclide generator systems - such as alumina column separation of n.c.a rhenium-188 from low specific activity reactor-produced tungsten-188 - offers a convenient in-house production system

with a long useful shelf-life to provide an important therapeutic radionuclide with a variety of important therapeutic applications.

Extraction chromatography using the Eichrome Ln resin [HEDHP = di(2-ethylhexyl)orthophosphoric acid] has been found to be an effective method for separation of high specific activity lutetium-177 form irradiated enriched ytterbium-176 targets. Recent studies in progress have also demonstrated the availability platinum-195*m* from decay of reactor-produced iridium1-95(195*m*), with much higher specific activity then available from the radiative Pt-194(n,γ)Pt-195*m* and inelastic Pt-195(nn'γ)Pt-195*m* routes.

Summary

Although many important high specific activity radioisotopes are available from chemical separation of irradiated uranium-235 targets or *via* processing of reactor fuel, the irradiation of enriched and/or high purity targets will continue to be major method to produce medical radioisotopes using research reactors. Although specific activity values can be much lower then required using simple activation approaches, the chemical separation of products formed by beta- or electron capture-decay of initial reactor-produced products is an important strategy to obtain high specific radioisotopes usually not available by neutron capture reactions.

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