ISOTOPE PRODUCTION AND THE FUTURE POTENTIAL OF ACCELERATORS

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Isotope production is carried out by charged particle bombardment (usually by cyclotrons) and by neutron irradiation (inside research reactors), and the medically useful isotopes support a large world-wide commercial market. A summary of this usage and the current trends are given, highlighting the recent technology changes that have been implemented on compact cyclotron systems. Ongoing cyclotron development is likely to produce better and more efficient isotope production systems. However, present day isotope production relies heavily on neutron irradiation in research reactors particularly for the important isotope Mo^{99} and its daughter product Tc^{99m}. As access to research reactors diminishes, other technologies are being considered for the production of these isotopes - including accelerator driven systems, spallation sources etc. A review of the current status of this technology is given as well as some potential developments that could benefit from the research programmes on accelerator driven transmutation and energy production systems.

1 Introduction

During the last sixty years, radioisotopes have been used extensively in industry, in life science experiments and particularly in medicine. Present-day industrial applications include gamma-radiography and industrial sterilisation, smoke detection where longer lived nuclides are used in sealed source form and disposal of the source is an important issue. Radioisotopes also are used as labelled compounds in biological R&D for nucleic acid analysis, protein studies and research into cellular interactions. Although alternative non-radioactive methods are often available, these radioisotopic techniques are still widely practised. However it is in medicine that radioisotope applications play a vital role and will continue to do so as more pharmaceutical grade products are developed.

2 Medical Isotopes

Medical isotopes are used in three areas:-

- In *clinical testing* or radio-immunoasssay, reagents containing small quantities of radioisotope (usually I^{125}) are used to measure thyroid activity, hormone and steroid levels, hepatitis etc. Again non-radioactive methods exist which are often more convenient for automated testing with large batches.
- In *nuclear medicine imaging* , gamma camera detectors generate precise human imaging information on specific organs or the whole body using radioisotopes with half-lives in the range 0.5 - 10 days. Again, other competing modalities exist, such as MRI, CT or ultra-sound, but nuclear medicine imaging provides unique information on metabolism and body function. PET is the advanced form of nuclear imaging providing better spatial resolution and more accurate tracking of metabolic processes using isotopes with very short half-lives of 2 -120 mins.
- In *therapy*, radioisotopes may be used in reloadable sealed medical sources, in surgical implant devices or as injectable radiopharmaceuticals for the treatment of diseases, particularly cancer.

Nuclear medicine is probably the most successful present-day application area for isotopes and is reviewed in this paper from an industrial perspective.

3 Production of Radionuclides

The table of known nuclides includes over 2200 isotopes, 263 are stable naturally occurring and of the others, some 460 have half-lives in the range 1 to 100 days; for medical applications the radiation emission characteristics limit the selection to around 50 suitable radionuclides. For example the features for a good nuclear imaging isotope are:-

- half-life 1- 3 days,
- single gamma emission (100-250 keV),
- decays to a stable daughter product,
- appropriate chemical formulations,
- can be manufactured to GMP standards, and
- has a low cost of production

Neutron-deficient radioisotopes can be produced by charged-particle bombardment , usually with low-energy cyclotrons, and neutron-rich isotopes by irradiation in research reactors. Historically, neutron irradiation has been available at very low cost from the 'parasitic' utilisation of research reactors designed for materials testing etc. For many radioisotopes, the simplest production route is reactor production or (n,γ) such as in $Sr^{88}(n,\gamma)Sr^{89}$ whereas cyclotron production with (p,xn) type reactions is also common commercial practice e.g. $Cd^{112}(p,2n)In^{111}$. However detailed examination of the radionuclide table will reveal that for a given radionuclide, many routes are possible from reactions such as (n,p), (d,xn), (α,xn) etc. Small reaction cross - sections, low particle fluxes or low isotopic abundance of the starting material usually mitigate against the use of these more obscure reactions particularly when alternative low cost thermal neutron (n,γ) alternative routes exist.

4 Production of Tc^{99m}

The most commonly used imaging isotope is Tc^{99m} and is produced as a daughter product from the decay of Mo^{99}, which is itself produced by neutron irradiation and the fission production of 93% enriched uranium. In addition to the intermediate isotopic product Mo^{99}, large amounts of high level radioactive waste are also generated. Nevertheless this complex, equipment intensive process does produce the high specific activity isotope needed by nuclear medicine and at an extremely low price.

In common with all (n,γ) routes, production by Mo^{98} (n,γ) Mo^{99} can generate low cost but low specific activity isotope and special techniques are needed to extract the Tc^{99m}.

A cyclotron-produced route does exist viz- Mo^{100} (p,2n)Tc^{99m} and several laboratories have investigated this route [1,2] . The cross-section is not small but large quantities of activity must be generated to support the delivery of this rapidly decaying, 6-hour half-life isotope. The present-day constraints for producing commercial quantities of Tc^{99m} by this route are:-

- high cost of highly enriched Mo^{100},
- the need for high intensity proton beams i.e. 3000 μA and greater .
- impact of grow-in radionuclidic impurities such as Tc^{96} and Tc^{95},
- the design of extremely high heat-capacity targetry,
- the development of high speed chemical processing,
- the chemistry development for the re-cycling of the Mo^{100} raw material.

Large-scale production of Tc^{99m} by this method is unlikely to be realised commercially until proton intensities of 3000 to 5000 μA can be delivered reliably and at a cost level similar to existing 500 μA beams.

5 Compact Cyclotron Technology

Although negative-ion extraction was implemented onto production cyclotrons in 1982, the early extracted beam intensities were not significantly higher than for internal target cyclotrons; some production target benefits were achieved however. A major step was achieved in 1987 with the construction of the Cyclone-30 by IBA [3] . This 'third generation' machine not only delivered extracted beam intensities of 350 to 400 μA but also provided a technology package customised to the needs of the industrial isotope producer viz.:-

- high reliability operation
- low electrical consumption,
- minimum maintenance requirement,
- automated start-up, control and monitoring,
- low radiological dose to personnel etc.

This cyclotron design has been further exploited to construct a new 18 MeV cyclotron, producing 2000 μA on internal targets - in this case for the production of a new therapeutic isotope by the route Rh^{103}(p,n) Pd^{103} .

Recently, another 'third generation' cyclotron - the EBCO Industries TR30 [4] (operated by TRIUMF/Nordion) has been upgraded for proton extraction up to 1000 μA at 30 MeV [5] . With further improvements to ion source and RF systems the realistic possibility exists that future industrial cyclotrons will be operating with proton beams 'on target' in the range of 1000 to 2000 μA. The benefit to radiopharmaceutical industry will be immense:-

- lower raw material costs,
- economic production of targets
- shorter cyclotron operating schedules,
- smaller number of production batches,
- better management of personnel dose.

However high capacity isotope production targets will still have to be developed; particularly for some metallic nuclides with low melting points such as Tl^{201}, and also for gas targets such as the Xe^{124} system used for the production of I^{123}.

6 Future Trends for Accelerator-Produced Isotopes

6.1 *Isotopes for Imaging*

It is expected that the most common cyclotron-produced isotopes (i.e. Tl^{201}, I^{123} and In^{111}) will remain in demand, with industry having to continually improve manufacturing efficiency and maintain high delivery service standards. The majority of these isotopes will be produced by (p,xn) reactions with 30 MeV compact cyclotrons and these production facilities will continue to be financed and operated by commercial companies.

PET isotope studies have always been considered expensive and beyond the reach of regular clinical nuclear medicine. However, commercial distribution of the very short-lived PET isotope F^{18} has now commenced in some regions but the pharmaceutical registration of the first pharmaceutical FDG, has still not been achieved.

6.2 *Isotopes in Development*

Because of ongoing cost pressures on industry, it is unlikely :-

- to operate the higher energy accelerators,
- to manufacture small infrequent production batches ,
- to produce isotopes for the research phases of clinical development programmes.

Therefore there is a real need for a spectrum of specialised accelerators at research laboratories to continue production of this category of isotopes.

6.3 *Isotopes* for *Therapy*

Long-term success of nuclear medicine will probably rest on the development and licensing of more therapy isotope products to cure or at least to cause remission of disease. Many of these isotopes will be generated by neutron irradiation, but accelerator-produced isotopes do have the necessary characteristics for therapy - high specific activity and no-carrier added formulations. Typical developmental isotopes of this type are:-

- Cu^{67} produced by the routes Zn^{68}(p,2p) and Zn^{70}(p,α) at energies up to 200 Mev [6],
- At^{211} produced by Bi^{209} (α,2n) reaction [7].
- Sn^{117m} produced by the Cd^{114} (α,n) route.

7 Future Trends in Accelerator Technology

After several decades of prolific neutron availability, the large world-wide family of research reactors is now declining rapidly, due to ageing or shortage of operating funds. Medical isotope production only occupies a small proportion of this large reactor capacity; nevertheless several replacement options are already under consideration:-

- A proposal by IBA for the production of Mo^{99} (and Tc^{99m}) by replacing the reactor with a 1500μA, 150 MeV accelerator [8]. Proton beams would strike a spallation target to create one neutron per incident proton; the target would be surrounded by an assembly of U^{235} targets with a moderating medium to create a thermal neutron flux of $2x10^{14}$ $cm^{-2}.sec^{-1}$. Manufacturers would be able to load their production targets into this device prior to the fission processing to extract Mo^{99}.
- The spallation source concept is further exploited in the accelerator-driven technology pursued by many research laboratories. The proposal by Rubbia and his collaborators [9] is to construct a 7000 μA, 1500 MeV accelerator or cyclotron complex to bombard a spallation source positioned in a sub-critical assembly containing a moderator and naturally-occurring thorium as fuel. The resultant waste product liability of this device will be significantly less with this fuel and high net energy will be generated from the thermal neutron field of $1x10^{14}$ $cm^{-2}.sec^{-1}$. This type of device has all the attributes of a prototype large scale isotope production facility.
- Large spallation devices have already been built for neutron physics studies. One of the latest devices (SINQ) [10] at the Paul Scherrer Institute in Switzerland will use the 1500 μA, 590 MeV two-cyclotron system to produce high neutron fluxes. Various target studies have indicated a thermal neutron flux in the range 1 to $3x10^{14}$ $cm^{-2}.sec^{-1}$. Provided that filtering of higher energy projectiles could be achieved this type of target would also be highly suitable for isotope production.

8 Conclusion

Accelerator-produced medical isotopes will continue to be needed for the foreseeable future; industry will continue to develop new radiopharmaceutical products and procedures, whilst their production plants will continue to seek more cost-efficient operations. Improved designs will appear for compact cyclotron systems and for the different types of accelerator-driven neutron sources.

A new age of cyclotron technology is now within reach of industry, but a complete switch away from reactor systems to accelerators will not occur until production-cost parity is achieved for the main isotopes used in nuclear medicine.

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