Past, Present and Future Use of Accelerators in the Nuclear Medicine Industry

T. Grey-Morgan
Amersham International plc
White Lion Road
Amersham
England, HP7 9LL

Abstract

A variety of particle accelerators are used in Nuclear Medicine industry supporting a turnover in excess of $1.2billion in 1994. These include isotope separators which enrich the target material and cyclotrons which bombard the target with charged particles. Interest is also growing in the accelerator production of neutrons as an alternative to nuclear reactors. This paper gives an overview of the requirements for such machines and highlights the technical challenges that have been overcome in the past and that are faced in the future.

1. INTRODUCTION

Production of radioactive isotopes by particle bombardment of targets has been possible since the early 1930's. Initially the interest was in accelerating particles to higher energies and in the measurement of the nuclear physics parameters of the target.[1]. In 1947 the isotope separators located at Oak Ridge, Tennessee started enriching isotopes of interest to the scientific community [2]. Over 250 stable isotopes were separated from 50 elements and in 1954 a program of radioactive isotope separation started. A similar facility was built in Russia during the 1950's [3].

Although radioisotopes had been produced on cyclotrons since the 1930's [4] it was not until the 1960's that cyclotrons were used commercially solely for this purpose. In 1966 Amersham International (formerly The Radiochemical Centre) bought a 25MeV cyclotron from Philips and adapted it to irradiate enriched zinc-68 to produce the radiopharmaceutical product gallium-67. This cyclotron will cease operation in 1994 after more than 150000 hours of target irradiations.

Other radiopharmaceuticals are currently produced by neutron irradiation of enriched material in a nuclear reactor. As the number of suitable reactors declines other production routes are being evaluated including the use of spallation sources to create the high neutron fluxes required.

2. ELECTROMAGNETIC ISOTOPE SEPARATORS

To comply with pharmaceutical licences issued by the Federal Drug Administration (FDA)in the US, Ministry of Health & Welfare (MHW) in Japan etc it is a requirement that the isotope which is going to become radioactive is isotopically pure. In most cases the required isotope is enriched to be greater than 95% abundant. In some applications a more stringent purity is required if another isotope of the same element will give rise to a radionuclidic impurity. For instance, in the case of the radiopharmaceutical Metastron™ (Amersham's palliative treatment for prostate cancer) the natural abundance of strontium-88 is specified to be greater than 99.5% whereas the naturally occurring isotope is 82% abundant. This level of enrichment is required to reduce the content of strontium-84 to below 20ppm from a naturally occurring 0.56%. When irradiated the target material undergoes the following reactions.

$$^{88}Sr\ (n,\gamma)\ ^{89}Sr$$
$$^{84}Sr\ (n,\ \gamma)\ ^{85}Sr$$

The strontium-89 decays by beta particle emission. It is this emission that is responsible for the pain palliation. The unwanted Strontium-85 also produced during the reactor irradiation decays by x-ray emission. This plays no role in the treatment and would expose the patient to an unnecessary dose uptake if the strontium-84 has not been substantially removed.

Historically the enrichment process of the elements in the 30-200 amu range has been done using the technique of electromagnetic separation. The isotopic purity of the material is determined by the performance of the separator. Many physical phenomena inside the machine can affect the ultimate purity of the material.

Multimilliamp ion beams are formed in hot filament ion sources. Particular emphasis is given to the optics of the beam extraction to ensure a good object is formed and that the ion beam produced is space-neutralised. Differential pumping is used to minimise the possibility of collision between an ionised atom and a neutral species in the acceleration region where the ions are accelerated by upto 60keV. Ions created just outside the source attain a slightly lower energy and thus appear as a low mass tail at the collector. Typically these separators are pumped by oil diffusion pumps so operating pressures in the 10^{-6}millibar range are usual.

The beam then enters a magnetic sector where the momentum selection of the different isotopes occurs. Aberrations in the magnetic field are corrected by shims and magnetic field clamps. The separated isotope beamlets enter watercooled collectors whose design is customised to each isotope in order to minimise secondary sputtering and cross-contamination. Physically the individual collector pockets will be several millimetres apart so it is imperative that phenomena that give rise to image broadening are well controlled. As well

as a good vacuum, well regulated power supplies are used to minimise the noise of the beam. Sophisticated control systems that were created for ion implanters can also be used to optimise the throughput on isotope separators.

Typical system efficiency is about 10-20% so it in not usually cost effective to repeat the process if a batch of material is not sufficiently pure. Collection rates of usable material are measured in milligrams/ hour making the starting material for the radiopharmaceutical an expensive material. Pharmaceutical grade strontium-88 costs about $1150/gram and thallium-203 about $3500/gram.[5] A number of other particle accelerators have been devised for isotope enrichment although none are being used on a commercial scale at present. These include the Plasma Separation Process [6], Vacuum arc centrifuge [7] and Solitron [8].

3. CYCLOTRONS

Cyclotrons are now designed specifically for the production of radiopharmaceuticals Small self-shielded machines are operated in hospitals for the production of short-lived (a few minutes) isotopes for positron emission tomography (PET) studies. Higher energy machines operating at about 25-30MeV are used for the commercial production of bulk radiopharmaceuticals. These have half-lives in the range of 4.8 hours (^{81}Kr) to 73 hours (^{67}Ga). Table 1 lists the major cyclotron produced isotopes and their uses.

Reaction	Uses
^{203}Tl (p,3n) ^{201}Pb $\rightarrow$ ^{201}Tl	Myocardial scintigraphy
^{112}Cd (p,2n) ^{111}In	Monoclonal antibody labels
^{68}Zn (p,2n) ^{67}Ga	Tumour location
^{124}Te (p,2n) ^{123}I	Thyroid studies
^{124}Xe (p,2n) ^{123}Cs $\rightarrow$ ^{123}Xe $\rightarrow$ ^{123}I	Thyroid studies
^{127}I (p,5n) ^{123}Xe $\rightarrow$ ^{123}I	Thyroid studies
^{82}Kr (p,2n) ^{81}Rb $\rightarrow$ ^{81m}Kr	Lung studies
^{18}O (p,n) ^{18}F	PET studies

Table 1. Typical cyclotron produced isotopes and their uses.

These machines have been engineered to combine ease of maintenance with high performance and reliability. The use of low activation materials and the placement of the target station remote from the cyclotron enable intensive operation without compromising the radiation dose uptake of the operators [9].

On the larger cyclotrons external ion sources inject H^- into the cyclotron. This significantly reduces the gas load in the cyclotron and thus the amount of beam losses through collision induced charge-stripping. After acceleration the H^- is doubly charge-stripped to produce a proton which is directed into a minivault containing the target. Typical beam energies are 30MeV with simultaneous dual beam extraction of 400μA of protons [10]. Sophisticated monitoring and control systems are essential to optimise the cyclotron performance and ensure that predictive maintenance is possible in the periods between intensive production. Even minor variations in operational parameters can result in product failure. For instance, in the case of thallium-201 production it is important to control the energy of the incident proton beam. Lead-200 can be created by the (p,4n) reaction pathway and this can generate unacceptably high levels of this isotope in the product as a radionuclidic impurity.

With beam powers at the 12kW level the design and longevity of the stripper foil, beamline vacuum foils and target integrity are the major technical challenges. These issues will become more acute as future nuclear medicine proposals include 100MeV, 1mA cyclotrons or proton linacs to produce the required isotopes [11].

4. NEUTRON SOURCES

Conventional neutron activation for radiopharmaceutical production has been done using materials testing reactors with a thermal neutron flux of approximately $2x10^{14}$ neutrons/second. Many of these reactors are now approaching the end of their useful life. With the advent of increasingly powerful particle accelerators it may be possible to produce radiopharmaceutical isotopes with machines such as spallation neutron sources. Several spallation neutron sources have been built for experimental purposes [12] and recently a concept commercial application has been proposed for an energy amplifier [13] and also for atomic waste transmutation. There are significant challenges in the target technology that need to be addressed before these machines could be considered as production tools for radiopharmaceutical production.

In concept the design of such an accelerator is simple compared to the existing spallation sources. High quality pulses are not required which should reduce the sophistication of the RF system. Significant parts of the monitoring and data capture electronics will not be required; on the contrary the machine will be viewed by the operators as a black-box delivering a fixed particle flux to the target. To ensure continuity of radio-isotope supply it is essential that the machine runs for more than 7000 hours per year.

From a user perspective the sophistication of such a machine lies in the target area which must be customised for each application. The target must be capable of dissipating in excess of 1MW of power for long periods in an intense neutron field. The target must be designed to optimise the intensity and distribution of the neutron flux compensating for flux depression. Optimisation of the beam energy and hence current required to generate the required flux is a key consideration. As the beam energy increases the number of neutrons per incident proton increases faster than linearly but so does the hardness of the spectrum. High average beam currents (greater than 1 milliamp) are not yet established commercial systems but the engineering required is understood. It is likely that several isotope production tubes will be located around the target. Positions to the sides and in front of the target will be used to minimise the fast neutron flux component and maximise the evaporation neutron spectrum. The generation of isotopes by the fast neutron component behind the target needs to be considered as it is likely that

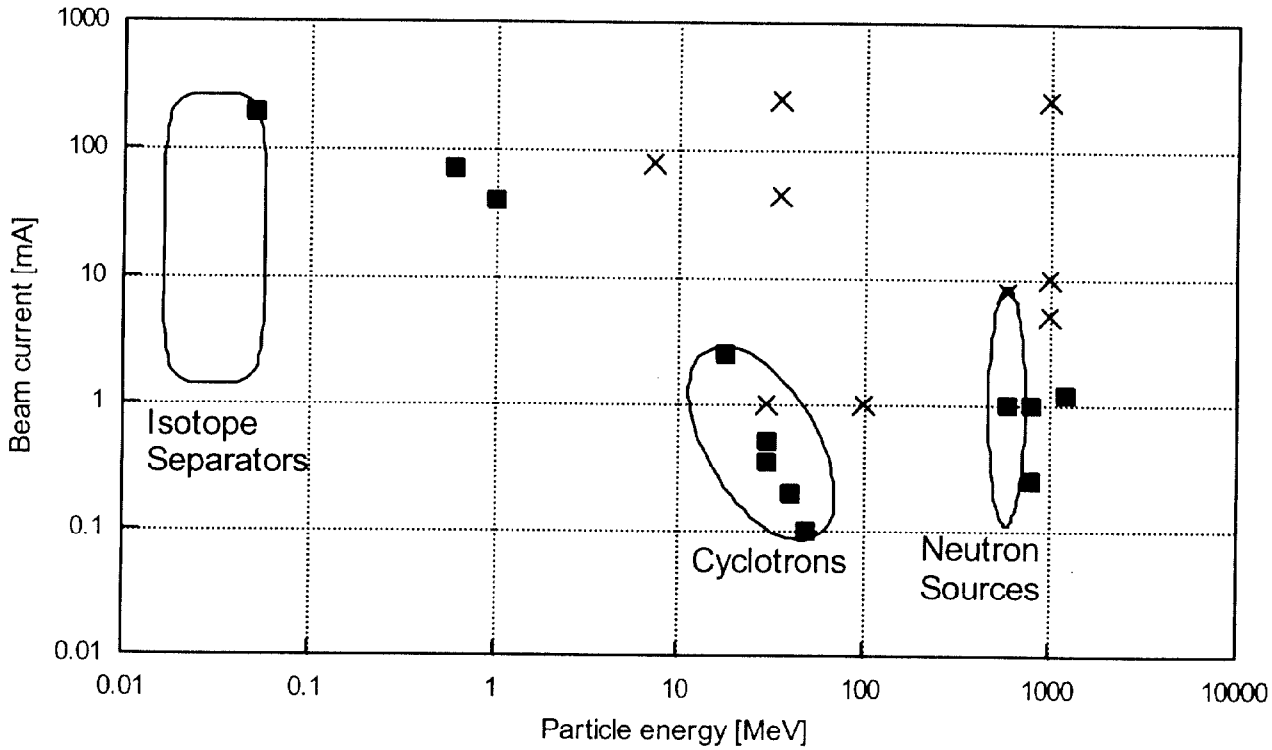

Figure 1 A plot of the beam energy versus beam current for existing (■) and proposed (x) accelerators.

novel routes will be discovered changing the requirements of the enriched stable precursors required.

5. CONCLUSIONS

Accelerators play an important role in the radiopharmaceutical industry. Figure 1 shows the range of accelerator energies and beam currents that exist or are proposed. Those that lie in the highlighted area are used or have potential for use in the nuclear medicine industry.

Often it is pure academic research interests that drive the technology which is exploited later by small specialist accelerator manufacturers. As the size and cost of accelerators increases consortia of accelerator builders and users will be formed to share the burden.

Each year many hundreds of thousands of people benefit from the diagnostic and therapeutic products created by particle accelerators demonstrating that the technology is already of immense benefit to mankind. It is likely that future developments could increase the opportunity for technology transfer into this very rewarding field of application.

6. REFERENCES

[1] M.S.Livingston, "Particle accelerators: A brief History", Cambridge, Massachusetts, Harvard University Press, 1969.

[2] L.O.Love, "Electromagnetic Separation of Isotopes at Oak Ridge", Science,Vol 182, Number 4110 pp.343-352 Oct 1973.

[3] N.A.Kaschejev, L.A.Polyakov & V.V.Tunin, Nuclear Instruments and Methods in Physics Research A334 (1993)pp.27-32.

[4] H.J.Wagner, Editor "Nuclear Medicine" New York: HP Publishing Co, 1975.

[5] EM Separated Stable Isotope Price List, Oak Ridge National Laboratory, 10 January 1993.

[6] J.G.Tracy, Nuclear Instruments and Methods in Physics Research A282 (1989) pp261-266.

[7] R.R.Prasad, M Krishnan, Nuclear Instruments and Methods in Physics Research B26 (1987) pp65-71.

[8] "A Method for Discriminative Particle Selection", R.F.Post Patent#5140158 issued Aug. 18,1992.

[9] "The design of a radioisotope production facility", D.M.Lewis, CERN Accelerator School, La Hulpe, Belgium, 1994.

[10] Y.Jongen et al. Proc. 11th Conference on Cyclotrons and their Applications, Ionics, Tokyo 1987.

[11] K.L. Kliewer & M.A. Green, Editors, " Proceedings of the Purdue National Biomedical Tracer Facility Workshop", Purdue University, Indiana April 28-30, 1992.

[12] F. Atchison, Meeting on targets for neutron beam spallation sources, Julich, June 1979.

[13] F. Carminati et al, CERN-AT-93-47 (ET), Nov 1993.