Isotope Production at Brookhaven National Laboratory

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Introduction

The Brookhaven Linac Isotope Producer (BLIP) was the world's first facility to seriously exploit the isotope production capabilities of a high energy proton accelerator. The use of higher energy particles allows the use of relatively thick targets, where the large number of target nuclei can compensate for the generally smaller reaction cross sections compared to low energy nuclear reactions. The BLIP, built in 1972, utilizes the excess beam capacity of the 200 MeV proton Linac that injects into larger synchrotrons (Booster, Alternating Gradient Synchrotron, and the Relativistic Heavy Ion collider) at BNL. After irradiations ranging from minutes to months, dependent on isotope half life and production needs, the targets are transferred to shielded hot cells. The irradiation creates many radioisotopes so that the product of interest must be chemically separated from coproduced impurities as well as the bulk target material. Standard techniques of analytic separation chemistry are used, such as anion and cation chromatography, solvent extraction, distillation, electrolysis, and precipitation. These processing techniques must then be adapted to the unique requirements of radiochemistry – remote handling due to the hazards of radiation exposure and contamination, rapid separation times in order to minimize decay losses, and the separation of essentially massless (called carrier-free) amounts of product from bulk target. These techniques and some of the diagnostic or therapeutic medical applications of the radioisotopes prepared here will be reviewed.

Linac/BLIP Capabilities

The 500 foot Linac is a pulsed accelerator with bunches of H- ions of high current, up to 37mA, lasting 425μs duration, and a repeat rate of 6.67 Hz. This gives a time averaged intensity of 105μA. The beam intensity profile is roughly Gaussian with FWHM of 2.4cm and 1.8cm in horizontal and vertical directions respectively. There are nine accelerating cavities capable of a maximum particle energy of 202 MeV, but lower energies can be delivered by sequentially turning off the accelerating sections. The Linac can control both the energy and intensity pulse by pulse. Indeed, typically low intensity full energy pulses are injected into the Booster and high intensity lower energy pulses are sent to BLIP. In fact most BLIP operation for isotope production now utilizes 118 MeV. Beamline windows strip the two electrons from the H- ions so only protons actually interact in targets.

The BLIP consists of a pulsed bending magnet that diverts pulses not needed by the physics programs into a 100 foot long evacuated transport line that directs the protons to a shielded target area for radioisotope production. The target area is a 30 foot deep 8 foot diameter buried tank that contains radiation shielding and two long shafts. A 16 inch diameter target shaft is water filled and holds the target assembly. This consists of an array of disk shaped target disks with the beam energy degrading as it penetrates from front to back. Since the nuclear reaction cross sections are a function of particle energy, the order of the target disks in the array is chosen to maximize the production of the

desired isotope and minimize impurities. Because significant heat is deposited by the protons (up to 21kW), all targets must be water cooled. The height of the water column also provides neutron shielding in the vertical direction. The target cooling water is delivered individually past the faces of target disks and then simply empties into the bulk shaft. At the top the water is cycled through a filter, heat exchanger and then pumped back to the bottom of the target assembly. There are six mechanically independent target channels, but most recently these have been grouped into two boxes holding four targets each. The boxes are attached to stainless steel bicycle chain and motor driven up and down for insertion/removal. The velocity of the water is approximately 12 gallons per minute in each box. A second shaft plugged with removal concrete cylinders is used for inspection and pump out if a leak occurs in the target shaft. A cross section of the BLIP target area is shown in Figure 1.

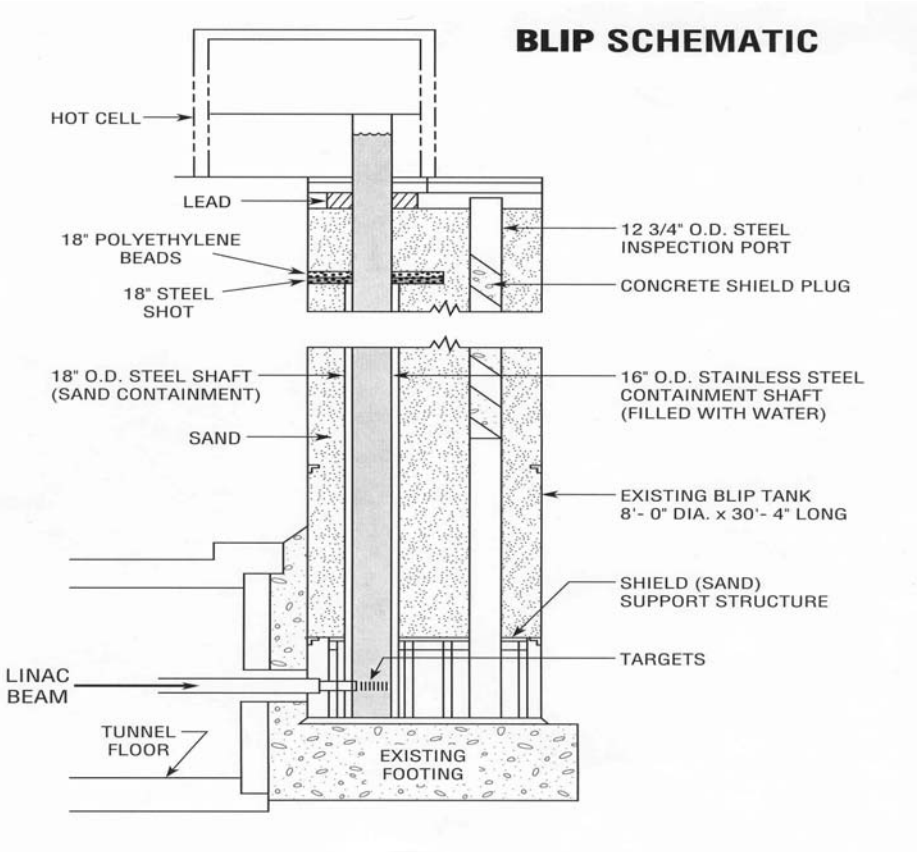

Figure 1. Drawing of BLIP target area.

The BLIP generally operates in a secondary, parasitic mode, sharing pulses with the driver nuclear physics programs. The schedule and duration of Linac operation is largely determined by the plans and funding of the nuclear physics experiments, not isotope production needs. The BLIP share and cost depend on the details of the downstream physics programs. The average BLIP intensity in parasitic mode is about 20% less than full Linac output, but the cost is 75% less than the full cost. In recent years substantial operation at full cost was necessary because of declining funding for the proton nuclear physics programs at BNL, but total BLIP annual running has been no more than half the

year. Production coordination with the Isotope Production Facility at Los Alamos National Laboratory, iThemba in South Africa, and Institute of Nuclear Research in Russia, has allowed year round availability of longer lived, high value isotopes, such as Sr-82 and Ge-68.

Chemical Processing

Except for low energy neutron induced nuclear reactions that leave the product in the same elemental form as the target, most produced radionuclides require chemical separation from the bulk target material and from induced radioactive byproducts. Generally one or more of conventional techniques, such as chromatography, solvent extraction, distillation and precipitation are used. Other techniques include electrolysis and electro-deposition, and separations based on sublimation. These processing techniques are adapted to the unique requirements of radiochemistry - the hazards of radiation exposure and contamination, rapid separation times in order to minimize decay losses, and the separation of essentially massless (carrier-free) amounts of product from bulk target. A great deal of effort has gone into developing processes suitable for each application.

Solvent extraction: This technique involves the selective partitioning of particular chemical complexes between two immiscible solvent phases. Usually an aqueous solution of acid, base or salt and an organic solvent such as ketone, ether, amine or carbon tetrachloride are used. Its use in radiochemistry is partly due to the fact that partition coefficients are approximately independent of concentration down to tracer levels. It is also relatively simple and rapid to perform, can be extremely selective, and can be adapted to remote or automated operation. Extraction of a complex containing the radionuclide into the organic phase is often followed by evaporation or a back extraction into an appropriate aqueous phase. The variables to be controlled are pH, relative phase volumes, salt concentration and mixing time. For example we use solvent extraction regularly to purify Ge-68 from irradiated gallium targets (1). This process involves extraction of Ge-68 (and some Zn-65) in 4N HCl with 30% hydrogen peroxide from the liquid gallium target. In order to further remove Zn-65 and traces of gallium, the solution is made 10N HCl and Ge-68 is extracted into toluene and back extracted with water.

Chromatography: This method is one of the most powerful and widely used for radiochemical separations, especially ion exchange. It is related to solvent extraction in that it depends upon the differential distribution of a species between two phases, except that in chromatography the phases move relative to one another. In ion exchange the distribution of an element between a solution (mobile phase) and stationary resin (usually packed in a column) depends on the ionic form, the solute concentration, and the functional group on the resin. Cation exchangers such as Dowex 50 have sulfonic acid groups, while in anion exchangers such as Dowex 1 the functional group is quaternary amine groups. Once a resin type is chosen, the variables to be controlled are ionic concentration, column volume and diameter, flow rate, and eluant. With proper choice of conditions, ion exchange is very useful for separating carrier-free radionuclides from bulk target (mass ratio $>10^8$) having significantly lower affinity toward the resin. This method has been particularly successful in separating transition metals from each other and from the rare earth elements. A relevant example is the separation of ^{55}Co from iron target (2). Ion exhange

can be combined with solvent extraction for better separation factors, as was demonstrated in the case of ^{67}Cu (3). It is also readily adaptable to remote or automated operation and represents the most often used radiochemical separation in use here.

Distillation: Some radiochemical separations can be affected by exploiting differences in volatility. For example, ^{131}I can be separated from Te targets by dry distillation at high temperature (4) or from a dissolved target (5). One can also distill the target away from the product, as was done to separate ^{32}P from an elemental sulfur target (6).

Precipitation: In radiochemistry, precipitation plays less of a role than other separation applications. This is because of the carrier-free nature of the radionuclides - there is simply not enough mass to precipitate. Reversing the process, that is, precipitating the bulk target away from the product is sometimes used, but may still cause problems by carrying down the desired product by mass effects. Though occasionally useful for a first bulk separation or for low specific activity radionuclides, precipitation rarely has the desired selectivity for nuclear medicine requirements. Adsorption on walls of glassware and filter paper can be troublesome, and handling precipitates under remote conditions may be difficult.

Shielded facilities: The handling and processing of reactor produced radionuclides has to be carried out in specially designed radiochemistry laboratories with controlled ventilation and air conditioning, shielded remote handling facilities, and radioactive waste collection and storage tanks (7). In most cases involving processing of reactor or cyclotron targets, radiation shielding for the chemist is required. This may be as simple as some stacked lead bricks inside a standard chemical fume hood. For pure beta emitters, small lucite disks mounted on tongs to shield the hands are all that is necessary. At higher levels of gamma radiation, a completely enclosed hot box or hot cell will be required. Hot cells usually have 4-8 inches of lead in the walls or several feet of concrete, lead glass windows, and master slave manipulators. At BNL most of the hotcells for radioisotope chemistry have 6 inches of lead clad in 0.5 inch steel plate.

Current Requirements and Challenges: Specific activity is an important parameter since in many cases the availability of very high specific activity or carrier-free radioisotopes is required for biological applications. Specific activity is defined as the relative abundance of a radioactive isotope to the stable isotopes of the same element in a homogeneously mixed sample. Specific activity is usually expressed in terms of the disintegration rate per unit mass of the element (e.g. mCi/mg). One example of the importance of high specific activity is the radiolabeling of tumor-specific antibodies or peptides for both diagnostic and therapeutic applications where only very small amounts of the radiolabeled antibodies are administered to insure maximal uptake at the limited tumor cell surface antigen sites. Another example is the use of receptor mediated radiopharmaceuticals that are potentially very important for the clinical evaluation of neurological diseases. Since the population of neurotransmitter sites is very limited, high specific activity agents are required to evaluate site-specific uptake.

Since the specific activity of a radioisotope produced by particle induced reactions is a direct function of the incident particle flux, an increase in the incident particle flux results in an absolute increase in the specific activity of the product. This relationship is linear for simple reactions and non-linear for complex reactions. It is important to note that the half-lives, production and destruction cross-sections, and irradiation time are equally important. Table 1 summarizes the radioisotopes developed at BLIP, their half lives, decay mode, target and typical application. Most of these are still made available to researchers and industry.

Table 1. Radioisotopes developed at BLIP

Radioisotope	Half life	Decay Mode	Target	Application
Be-7	53.2d	EC	water	Gamma ray source
Mg-28	20.9h	β-	KCl	Mg tracer
Sc-47	3.3d	β-	Ti metal	Immunotherapy
Fe-52	8.3h	EC, β+	Ni metal	Fe metabolism
Co-55	17.5h	EC, β+	Fe-56	PET label
Zn-65	244.1d	EC,	Ga metal	Zn tracer
Cu-67	2.6d	β-	ZnO	Immunotherapy
Ge-68/Ga-68	270.8d/1.13h	EC β+	Ga metal	PET calibration, generator parent
As-73	80.3d	EC	Ge metal	As tracer
Rb-81/Kr-81m	4.6h/13.1s	EC	Kr gas	Lung ventilation
Sr-82/Rb-82	25.6d/1.27m	EC/ β+	RbCl	Cardiac studies
Y-86	14.7h	EC, β+	SrCl2	Cancer imaging
Y-88	106.6d	EC, β+	Nb metal	Gamma ray source
Tc-95m	61d	EC	Rh metal	Tc-99m stand in
Ru-97	2.9d	EC	Rh metal	Gastric studies
Cd-109	461.4d	EC	Ag metal	Gamma ray source
Sn-117m	13.8d	IT	Sb metal	Bone pain palliation
I-123	13.3h	EC	NaI	Thyroid & other imaging studies
Xe-127	36.4d	EC	CsCl	Lung ventilation
Pb-203	51.9h	EC	Bi metal	Immunotherapy

EC=electron capture, IT=isomeric transition, β- = beta decay, β+ = positron decay

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