Accelerator-Produced Therapeutic Radionuclides

6

6.1 Introduction

Cyclotrons are generally used for the preparation of neutron-deficient radionuclides, which decay mostly by β^+ emission or electron capture (EC), which are used for diagnostic applications (IAEA 2009). However, these production facilities are also sometimes used for the production of therapeutic α emitting and β —emitting radionuclides. In some instances, Auger- and Conversion electron-emitting (CE) therapeutic radioisotopes are also reactor-produced, but in general, the large majority of radioisotopes used for therapy are reactor-produced. Because of the power requirements, operational costs, and in general focused operations, cyclotron production of radionuclides is generally more expensive compared with those produced by reactor irradiation. With reactors, the general operation is not affected by target insertion and radiation, and usually many different experiments and irradiations are concurrently conducted. However, higher specific activities (SA) are generally available from the accelerator production routes, and no-carrier-added products (NCA) can often be obtained because the atomic number, Z, usually changes (Fig. 6.1).

As summarized in Table 6.1, a variety of accelerator-produced radioisotopes are of current interest for targeted therapy.

6.2 Accelerators for Radionuclide Production

The use of accelerators for production of medical radionuclides requires the delivery of charged particle beams which have two primary characteristics, since they must both have sufficient energy to induce the desired nuclear reaction and sufficient beam current to provide practical product yields. The basic characteristics of a medical cyclotron, for instance, include an ion source for ion production, an acceleration chamber for ion acceleration, a magnet to contain the ions on a circular path, and finally a stripper to "extract" the ions from the accelerator and direct on the target (Fig. 6.2). The extracted beam can be appropriately tuned to focus on a target or a few targets in separated beam stops simultaneously, since the beam can be focused within the accelerator itself or can be focused on a target station which is located exterior to the accelerator. The targets can consist of a solid, liquid, or gas (IAEA 2009).

When an energetic-charged particle passes through any material, there is a definite probability to interact with nucleus of atoms along its path. The particle may be scattered off the nucleus or, if the energy is high enough when collision occurs, may combine to form a compound nucleus which will then decompose through one of the several possible pathways, leading to the formation of the product radionuclide. Another important and often challenging requirement is

© Springer India 2016

F.F. (Russ) Knapp, A. Dash, *Radiopharmaceuticals for Therapy*, DOI 10.1007/978-81-322-2607-9_6

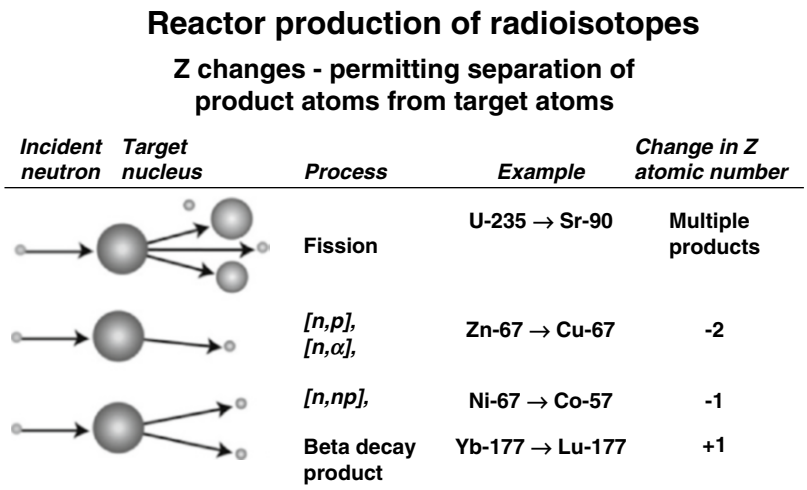

Fig. 6.1 Examples of particle reactions where Z changes and radioisotopic products can be separated from target atoms by traditional methods

Table 6.1 Key examples of accelerator-produced therapeutic radionuclides

Product Nuclide	Principle emission Type	Half-Life	Key examples Production route
Actinium-225	Alpha	10 days	Thorium
Astatine-211	Alpha	7.21 h	
Copper-67	Beta	2.58 days	$^{nat}Zn/^{68}Zn(p,2p)^{67}Cu$ $^{70}Zn(p,\alpha)^{67}Cu$
Gallium-67	Auger	3.26 days	$^{68}Zn(p,2n)^{67}Cu$ $^{64}Zn(d,2n)^{67}Cu$ $^{65}Cu(\alpha,2n)^{67}Cu$
Indium-111	Auger	2.8 days	$^{111}Cd(p,n)^{111}In$ $^{112}Cd(p,2n)^{111}In$
Radium-223	Alpha	11.4 days	Thorium
Rhenium-186	Beta	3.78 days	$^{186}W(p,n)^{186}Re$ $^{186}W(d,2n)^{186}Re$
Tin-117 m	CE	13.6 days	$^{nat}Sb(p,xn)^{117m}Sn$

the availability of efficient chemical methods for separation of the microscopic levels of the radionuclide products from the macroscopic target levels, which in turn must often be recovered for recycling for subsequent irradiation.

6.2.1 Calculation of Production Yield

The rate of radionuclide production is dependent on a number of factors, including the magnitude of the reaction cross section (i.e., probability of capture) as a function of energy; the incident particle energy; the thickness of the target in atoms per cm^2, which will determine the exit particle energy; and the flux of incoming particles. In the simplest case, where the cross section is assumed to be constant, the rate of production is given by the equation:

$$R = n_T I \sigma \tag{6.1}$$

where:

R is the number of nuclei formed per second.
n_T is the target thickness in nuclei/cm^2.
I is the incident particle flux per second and is related to the beam current.
σ is the reaction cross section, or probability of interaction, expressed in cm^2 and is a function of energy.

The cross section is always a function of energy, and hence Eq. (6.1) becomes modified as:

$$R = n_T I \int_{E_i}^{E_f} \frac{\sigma(E)}{dE / dX} dE \tag{6.2}$$

E is the energy of the incident particles.
x is the distance travelled by the particle.
$\int_{E_i}^{E_f}$ is the integral from the initial energy to the final energy of the incident particle along its path.

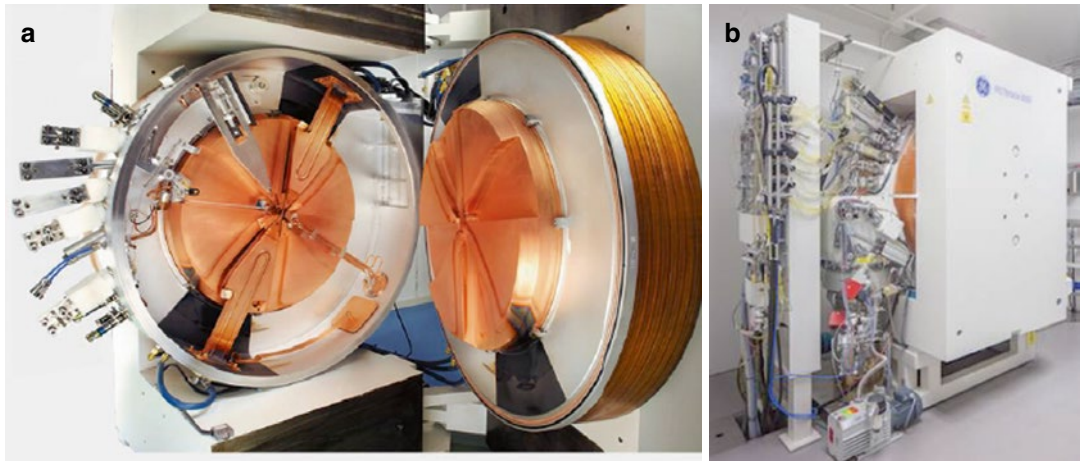

Fig. 6.2 Medical cyclotron, (**a**) internal view. (**b**) Medical cyclotron at RMC, India

As the charged particles passes through the target material, energy is lost due to interactions with the target electrons which is represented in the above equation by the term dE/dx (also called the "stopping power").Returning to the expression for the cross section, it is evident that n_T is given by the following expression:

$$n_T = \frac{\rho x}{A_\Gamma}\zeta \tag{6.3}$$

where:

n_T is the target thickness in nuclei/cm^2.
ρ is the density in g/cm^3.
x is the distance the particle travels through the material.
ζ is Avogadro's number.
A_T is the atomic weight of the target material in grams.

If the target material is a compound rather than a pure element, then the number of nuclei per unit area is given by the following expression:

$$N_G = \frac{F_A C \zeta}{A_A} \tag{6.4}$$

where:
N_G is the number of target nuclei per gram.
F_A is the fractional isotopic abundance.
C is the concentration by weight.
A_A is the atomic mass number of nucleus A.

The above equations illustrate that it is not always possible to eliminate the radionuclidic impurities in the product during radionuclide production using cyclotrons. This occurs even when using the highest isotopic target enrichment and the most precise energy selection, resulting from incident particle energy depletion with initiation of secondary nuclear reactions which is increased with higher-energy incident particles.

6.2.2 Saturation Factor

Radionuclide product decay begins as soon as they have formed, which leads to the following expression, where the overall rate of production becomes:

$$-\frac{dN}{dt} = n_T I \int_{E_f}^{E_o} \frac{\sigma(E)}{dE/dX} dE - \lambda N \tag{6.5}$$

where:
λ is the decay constant and is equal to ln $2/T_{½}$.
t is the irradiation time in seconds.
N is the number of radioactive nuclei in the target.

The term dE/dx in the above expression is often referred to as the total stopping power. At a particular energy E, it can be represented as $S_T(E)$ in units of MeV · cm^2 · g^{-1} and is given by the following expression:

$$S_T(E) = \frac{dE}{dX} \tag{6.6}$$

where:
dE is the differential loss in energy.
dx is the differential distance travelled by the particle.

The loss of energy, dE, in MeV of the particle is then given by:

$$dE = S_T(E)\rho dx \tag{6.7}$$

where ρ is the density of the material in units of g/cm^3, and the thickness of the target? ρdx (in g/cm^2) can be expressed as a function of dE:

$$\rho dx = \frac{dE}{S_T(E)} \tag{6.8}$$

If this equation is integrated to include the stopping power to account for energy loss during the transit of the particle through the target material and assuming that the beam current is the same as the particle flux (which is true only for particles with a charge of +1), then the yield of a nuclear reaction is given by:

$$Y_{EOB} = \frac{N_A I}{A_T}\left(1 - e^{-\lambda t}\right)\int_{E_F}^{E_i} \sigma_T(E)\frac{dE}{S_T(E)} \tag{6.9}$$

The radionuclide production rate is of course affected by the radioactive decay of the resulting radionuclide product. For short-lived nuclides, the competing reaction rates, production, and decay will achieve equilibrium at sufficiently long bombardment times since the rate of decay is proportional to the number of radionuclide present. The $(1 - e^{-\lambda t})$ term is often referred to as the saturation factor and accounts for the competition of the production of nuclei due to the particle reaction and the radioactive decay of the nuclei that have been produced. For an infinitely long irradiation, the saturation factor $(1 - e^{-\lambda t})$ tends to the value 1.

6.3 Key Accelerator-Produced Therapeutic Radionuclides

6.3.1 Actinum-225 and Radium-223

The accelerator production route which involves irradiation of natural ^{232}Th targets with medium-energy protons (Fig. 6.3) appears to be an attractive route in terms of yield and cost-effectiveness.

Actinium-225 is of great interest for therapy as well as a generator parent for the availability of ^{213}Bi (Apostolidis et al 2005; Miederer et al 2008; Scheinberg and McDevitt 2011). The scope of availing ^{225}Ac as well as ^{213}Bi for ^{229}Th is schematically depicted in Fig. 6.4.

Chemical isolation of Ra from irradiated metallic Th was performed by a gas-chemical method (Zhuikov et al. 2011). For ^{225}Ac and ^{223}Ra processing following irradiation of ^{nat}Th targets using 800 MeV protons, solvent extraction with ethyl acetate has been used (Weidner et al. 2012). A method for purification of ^{225}Ac from irradiated ^{226}Ra-targets consisting of a first extraction chromatography for separating ^{225}Ac from ^{226}Ra and other Ra-isotopes and a second extraction chromatography for separating ^{225}Ac from ^{210}Po and ^{210}Pb has been reported. The finally purified ^{225}Ac can be used in the preparation of radiopharmaceuticals (Turlera et al. 2013). This separation scheme is shown in Figs. 6.5 and 6.6.

Radium-223 has recently emerged as a key agent for bone pain palliation in castration-resistant metastatic cancer from prostate cancer and is discussed in detail in Chap. 12. An ^{227}Ac/^{223}Ra extraction generator based on selective extraction of ^{223}Ra from a solution of chlorinated cobalt dicarbollide and polyethylene glycol in a polar diluent from a solution of

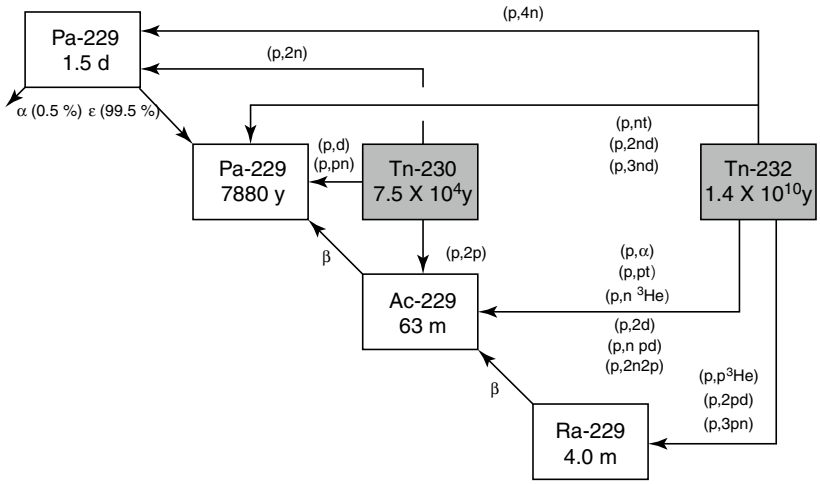

Fig. 6.3 Proton-induced reactions for the production of ^{229}Th

a mineral acid and a complexing agent has been proposed. Radium is stripped to any appropriate aqueous solution on adding TBP into the extractant (Weidner et al. 2012). A number of additional radiochemical separations approaches for the isolation of ^{223}Ra from ^{227}Th have been reported (Henricksen et al. 2001; Horowitz and Bond 2003; Boll et al. 2005; Kirby 1969). While the isolation of high purity ^{223}Ra and ^{227}Th from ^{227}Ac chemically appears to be straightforward, it is mechanically complex due to intense alpha and gamma radiation which produces reactive species (solvated electrons, hydroperoxide ions, atomic hydrogen, and free hydroxyl) that can cause the radiation damage to the ion exchangers and solvents and interfere with radiochemical separations.

6.3.2 Astatine-211

The radiotherapeutic potential of α-emitting ^{211}As ($T_{1/2}$ = 7.21 h) (see Chap. 3) has been recognized for over 30 years (Smit et al. 1973). Astatine in a halogen and the branched pathway for ^{211}As decay is illustrated in Fig. 6.7. The 7.2 h half-life is sufficient to permit multistep synthetic procedures and is also sufficiently long to accommodate for the pharmacokinetics of a wide variety of potential cell-specific targeting agents. The halogen chemistry of astatine is diverse and permits radiolabeling of a wide range of molecules. It is possible to exploit both its metallic characteristics (Milesz et al. 1989; Yordanov et al. 2000) and its halogen properties for the synthesis of ^{211}At-labeled molecules. Astatine-211 decays either directly by α-decay to ^{207}Bi (42 %), followed by EC decay to stable ^{207}Pb, or by EC decay to ^{211}Po (58 %), followed by α-emission to stable ^{207}Pb. The α particles have a range of only 55–80 μm in biological soft tissue, which represents only a few cell diameters. The high mean LET value of about 100 keV/μm is close to the optimum value for a high RBE to maximize the lethal damage (Zalutsky and Bigner 1996). The ^{211}Po daughter emits 77–92-keV X-rays that provide a valuable means for tissue tracking ^{211}At by SPECT imaging (Johnson et al. 1995). With regard to radiation protection issues, ^{211}As is easy to handle, since α particles represent more than 99 % of the radiation energy (Larsen et al. 1999).

Spallation reactions can be useful for ^{211}At production either directly or indirectly through the decay of ^{211}Rn, but the required high particle energies between 160 and 660 MeV and limited beam intensity, in addition to the extensive required separation procedures, emerged as major impediments for the use of this strategy for routine production required to meet expected clinical demands (Kirby 1985). Currently, the

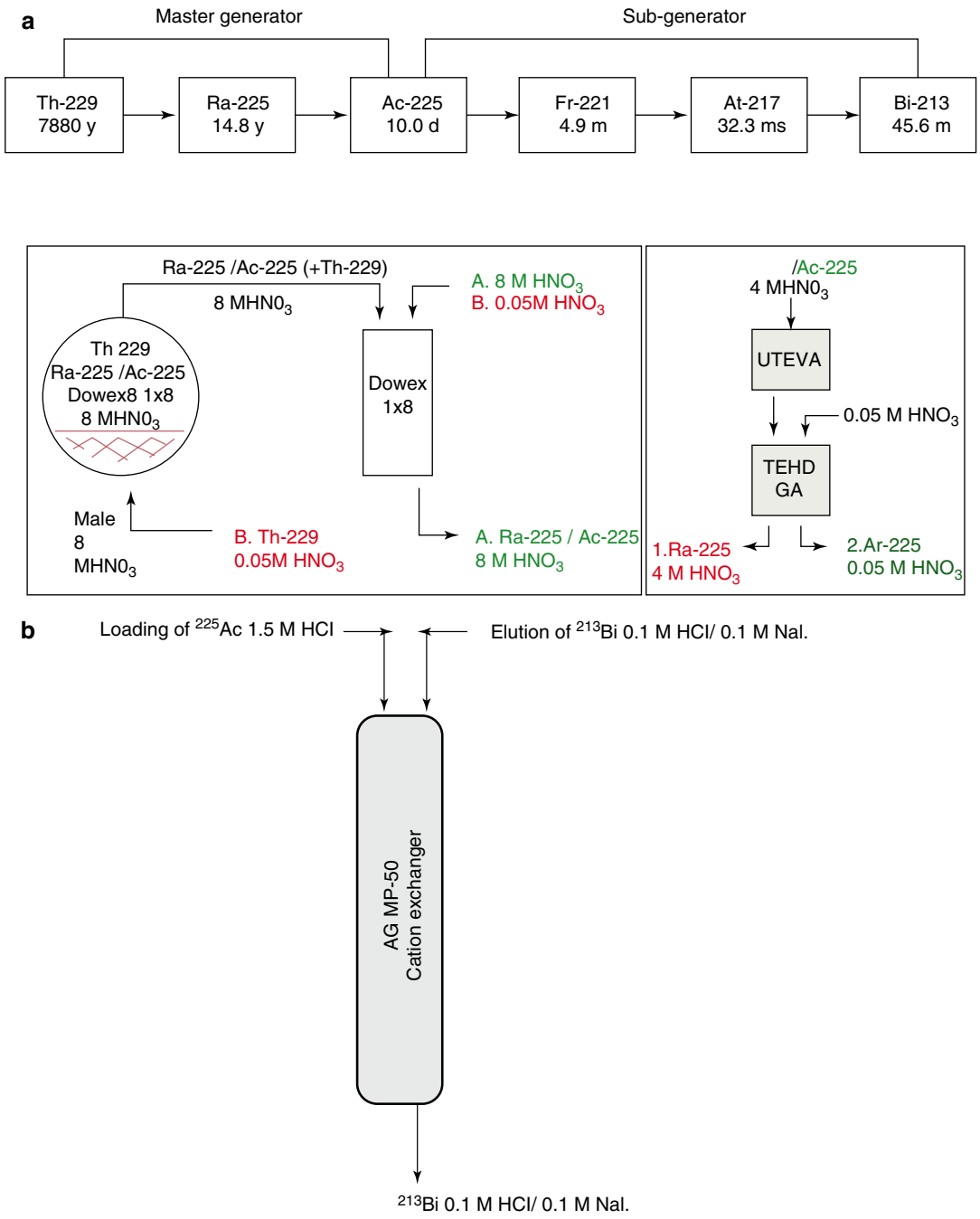

Fig. 6.4 Availability of ^{225}Ac as well as ^{213}Bi from ^{229Th}. (**a**) Master ^{229}Th/^{225}Ac generator, (**b**) sub ^{225}Ac/^{213}Bi generator

most commonly used method for producing ^{211}At is the bombardment of natural bismuth, usually in metallic form, with α particles (Zalutsky and Pruszynski 2011). Although the use of natural bismuth constitutes an ideal target material in terms of cost-effectiveness and precludes the need for chemical recovery for its subsequent use, its poor thermal conductivity (7.97 $W \cdot K^{-1} \cdot m^{-1}$) and low melting point (272 °C) necessitates adequate target cooling at high current production runs.

The purity of ^{211}At required for research and clinical studies is influenced by the radiochemical procedures adapted for the recovery of ^{211}At from the bismuth cyclotron target. Although a variety of methods have been reported for ^{211}At recovery (Eberle 1985), the most common method involves dry distillation or acid treatment of the target followed by solvent extraction. The most commonly utilized approach for separating ^{211}At from bismuth cyclotron targets is dry distillation at a temperature range of 650–800 °C for 30 min using a flow of carrier gas such as nitrogen (Lidegren 2001) or argon (Zalutsky 1996) in a quartz vessel. After volatilization from the cyclotron target, ^{211}At can be trapped using silica columns (Friedman et al. 1977), bubbler traps (Lindgren 2001), and capillary tubing cryotraps (Lambrecht and Mirzadeh 1985). The solvent extraction procedure consists of dissolution of target using concentrated HNO_3 followed by extraction of ^{211}At into either butyl or isopropyl ether (Yordanov et al. 2004). Another approach reported is based on dissolution of the Bi_2O_3 target in concentrated perchloric acid followed by solid–liquid extraction employing thiosemicarbazide incorporated onto Amberlite IRC-50 resin (Roy et al. 2004).

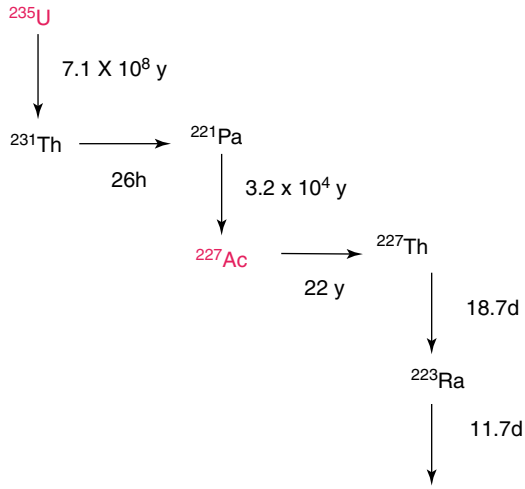

Fig. 6.5 Decay scheme for ^{223}Ra

6.3.3 Copper-67

The production yields of ^{67}Cu in a nuclear reactor by the ^{67}Zn(p,n)^{67}Cu reaction (*vide ante*) are low because of a low neutron capture cross section, even when high-energy neutrons are available. Accelerator production is the preferred approach to obtain both the high specific activity and high activity levels of ^{67}Cu which are required for

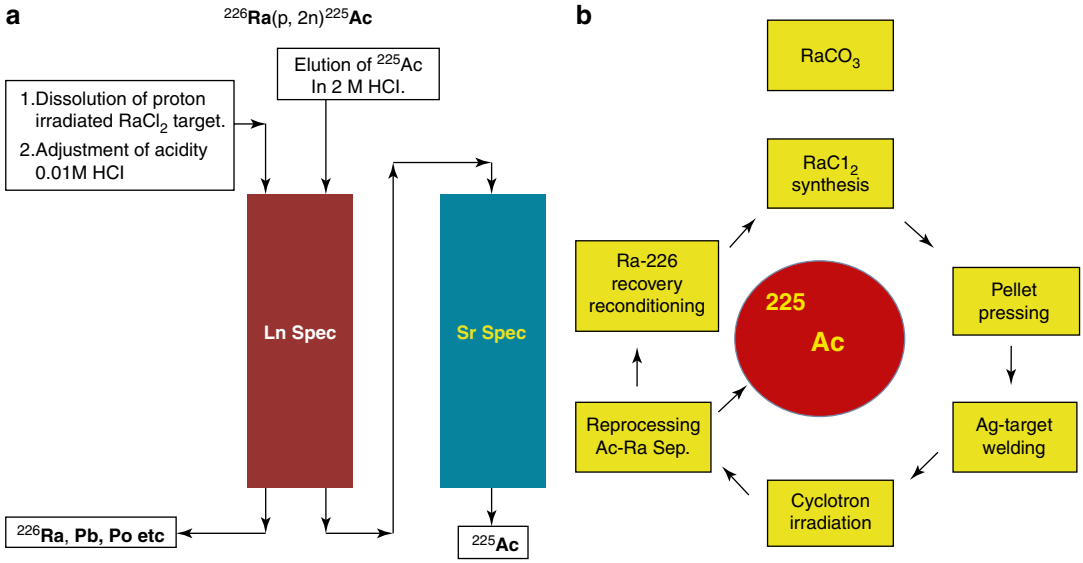

Fig. 6.6 Production and separation of ^{225}Ac by proton irradiation of ^{226}Ra target

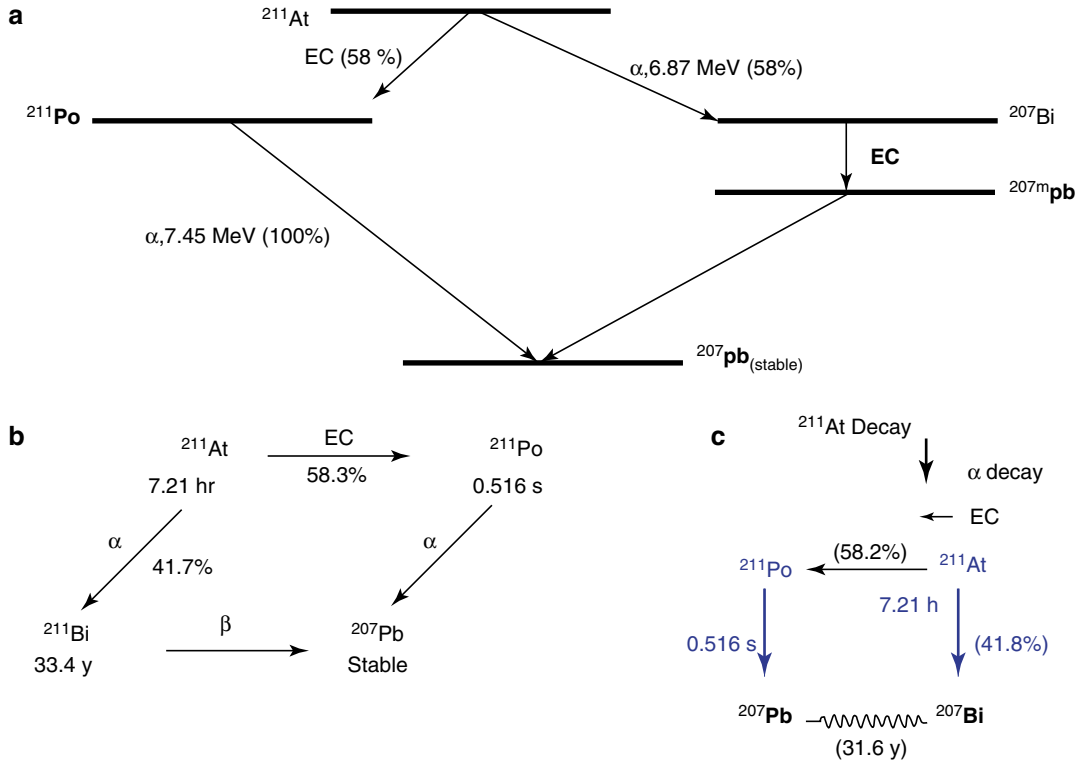

Fig. 6.7 Simplified decay scheme of ^{211}At

Table 6.2 Principal nuclear reactions for ^{67}Cu production

Particle	Nuclear reaction	Cross section (σ) in mb
p	^{68}Zn(p,2p)^{67}Cu	*6* (E_p=30…85 MeV) *24.8* (E_p=130…425 MeV)
	^{70}Zn(p,α)^{67}Cu	*15* (E_p=16 MeV)
α	^{64}Ni(α,p)^{67}Cu	*34* ($E_α$=22 MeV)
n	^{67}Zn(n,p)^{67}Cu	*1.07*
e→γ (photonuclear reaction)	^{68}Zn(γ,p)^{67}Cu	*11* ($E_γ$=22 MeV)

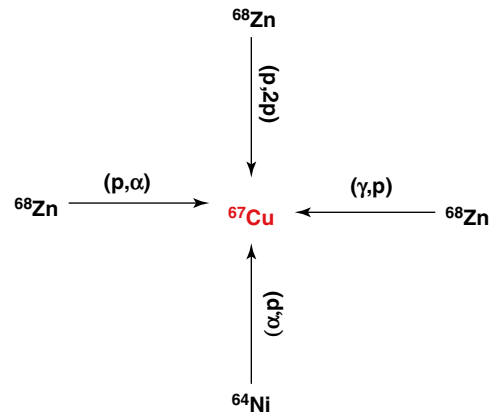

Fig. 6.8 Summary of key cyclotron production routes for ^{67}Cu

clinical applications, and several particle reactions have been evaluated (Table. 6.2) as shown in Fig. 6.3. Because of broad interest in the availability of ^{67}Cu, a wide variety of production and processing methods have been evaluated as described in the following sections. However, in spite of this effort, very few ^{67}Cu-labeled radiopharmaceuticals have been developed and evaluated in clinical trials (Fig. 6.8).

Cyclotron production of ^{67}Cu is performed by irradiating ^{nat}Zn or enriched ^{68}Zn with protons or α particles, and the most typical production route of

^{67}Cu has been the high-energy proton irradiation of natural zinc targets particles (Schwarzbach et al. 1995; Dasgupta et al. 1991; Mirzadeh et al. 1986). Copper-67 has been produced in the United States with high-energy accelerators at the Brookhaven (BNL) and Los Alamos (LANL) National Laboratories. Since 1994, the Center for Radiopharmaceutical Science at the Paul Scherrer Institute (PSI) in Switzerland has undertaken the production of ^{67}Cu with a 72-MeV accelerator to meet their own requirement (Knogler et al. 2007). The ^{68}Zn(p,2p)^{67}Cu nuclear reaction produces ^{67}Cu of low yields and requires an efficient separation procedures to remove radioactive contaminants, which include ^{62}Zn, ^{67}Ga, ^{65}Zn, ^{55}Co, ^{58}Co, and ^{57}Ni.

The ^{70}Zn(p,α)^{67}Cu reaction using 30-MeV alpha particles is promising owing to the production of minimal impurity levels and the accessibility of this reaction. Of the several options tabulated, the photonuclear reaction cross section is by an order of magnitude higher than the corresponding value for the (n,p) path. The photonuclear ^{68}Zn(n,p)^{67}Cu method is also attractive in view of a relatively low cost of electron accelerators and their low running expenses in comparison with heavy particle accelerators. In this method, linear accelerators generating 30–60 MeV electrons were allowed to focus on a convertor plate such as tungsten or tantalum to produce photons with a similar energy range (Starovoitova et al. 2014). One of the major hurdles of this method of production using natural zinc target is the coproduction of ^{63}Zn and ^{65}Zn which decay to stable copper, thereby reducing the ^{67}Cu-specific activity. The ^{66}Zn(γ,d)^{64}Cu side reaction is also problematic and leads to production of the ^{64}Cu ($T_{1/2}$ 1 = 12.7 h) radionuclide impurity, which can be reduced by allowing sufficient cooling time. The use of enriched targets is preferred in most of the production schemes summarized in Table 6.2 in order to achieve higher levels radionuclidic purity.

Because of methods which are well established for copper chemistry, several separation processes described below have been evaluated for purification of cyclotron-produced ^{67}Cu, which are based on differences in the physical and chemical properties of Zn and Cu. These strategies involve initial removal of the bulk zinc matrix followed by a secondary ion-exchange step as a final cleanup procedure.

6.3.3.1 Ion Exchange

A number multistep sequential ion-exchange chromatographic techniques using a variety of ion-exchange resins such as dithizone-impregnated resin, Bio-Rad AG-1 MP-1, Dowex-1, Bio-Rad AG-5OW, and Chelex-100 have been used to separate ^{64}Cu from irradiated Zn (Mausner et al. 1998; Dolley et al. 2006; Jamriska et al. 1995; Mushtaq et al. 1990; Shikata 1964; Yagi and Kondo 1978; Katabuchi et al. 2008; Polak et al. 1986; Schwarzbach et al. 1995). The method used at BNL for the production, chemical separation, and purification of ^{67}Cu obtained by the (n,p) path uses zinc oxide targets (Mausner et al. 1998). The target used for reactor irradiation consists of a 40-g pressed pellet of ZnO as well as enriched ^{67}ZnO powder in a quartz ampoule. After irradiation, the target is cooled, dissolved in concentrated HCl, evaporated to dryness, and reconstituted with 0.5-M sodium acetate buffer maintained at pH 3.27. The solution is then passed through a chromatographic column containing Chelex-100 (100–200 mesh), where the ^{67}Cu remains adsorbed and the bulk of the Zn passes through the column. After washing the column with 0.001 N HC1, Cu is eluted with 12 N HCl. Gallium and Fe are separated from Cu by passing this solution through a chromatographic column containing a cation exchange resin (Bio-Rad AG50W-X8, 100–200 mesh), where the impurities are adsorbed. The column is then washed with 10 N HCI. For final purification, the washing and the effluents are collected, and the combined fractions are loaded onto a chromatographic column containing an anion exchange column (Bio-Rad AGI-X8, 100–200 mesh). A 4.5 N HC1 rinse removes any Co isotopes which are collected and discarded as radioactive waste, and the ^{67}Cu is finally eluted with 3 N HCl. In order to perform radiolabeling, the ^{67}Cu solution is evaporated to dryness and reconstituted with 0.1 N HCl (Mausner et al. 1998).

6.3.3.2 Electrodeposition

The use of an electrolytic technique is another strategy for processing and recovery of ^{67}Cu (Mirzadeh et al. 1986). After irradiation, the target is dissolved in 10 mL of a 10:1 mixture of conc. HCI and conc. HNO_3. Following evaporation to near dryness the residue dissolved in 1 M H_2SO_4. The volume of solution is adjusted with1 M H_2SO_4 to maintain an ~ 2 M concentration of Zn^{2+}. The solution is then transferred to the electrolysis cell provided with a rotating Pt electrode. Under a constant potential of 2.1 V for 2 h, Cu is electroplated on the rotating (~1500 rpm) Pt electrode. The original electrolyte is removed and replaced with a second electrolyte (20 mL of 0.1 M ZnSO, and 1 M H_2SO_4,) without disconnecting the circuit. The polarities of the circuit are reversed and electrolysis is carried out for 5–10 min to dissolve the Cu from the Pt electrode. The electrolysis is repeated to electrodeposit Cu back onto the Pt cathode for an additional 2 h. Finally, the Pt cathode is removed and immersed in 2 mL of 3-M HNO_3 to recover the ^{67}Cu. For final purification, the solution containing ^{67}Cu is evaporated to near dryness, reconstituted with 1 mL of 1.8-M HCI and passed through an anion exchange column (MP-I, 100–200 mesh, 3×40 mm, prewashed with 1.8 M HCI) wherein all anionic impurities get trapped. The column is then washed with an additional 4 mL of 1.8 M HCI. The eluates are combined, and the total volume is adjusted to 5 mL with the addition of water (Mirzadeh et al. 1986),

6.3.3.3 Liquid–Liquid Extraction

The most commonly used procedure for recovery of ^{67}Cu by liquid–liquid extraction (Dasgupta et al. 1991; Stoll et al. 2002) consists of a primary extraction using 0.01 % dithizone in CCI_4 contacting a 0.5 M HCI layer containing the dissolved target. This solvent extraction is repeated four times to obtain the ^{67}Cu of desired purity. The ^{67}Cu is then back extracted from the organic fraction with 7.2 M HCI and H_2O_2. The aqueous back extracted layers are combined and contacted with isopropyl ether to remove Ga. Finally, the solution is passed through an anion exchange column to remove Ni, Mn, Cr, and Co isotopes.

6.3.3.4 Sublimation

This method exploits the low sublimation temperature and pressure of Zn compared to Cu (Mausner et al. 1998). Typically, the irradiated zinc target is placed in a sublimation assembly and heated at a temperature of ~800 °C in which zinc sublimes leaving the copper behind. Final purification is performed using ion-exchange chromatographic technique.

6.3.4 Gallium-67

Gallium-67 ($T_{1/2}$ = 3.26 d) decays by 100 % by electron capture and emits γ radiation with energies of 93.3 keV (37 %), 184.6 keV(20.4 %), and 300.2 keV(16.6 %). In addition to its use for diagnostic applications, interest in the effectiveness of Auger emissions from ^{67}Ga for some specific therapeutic applications has also been reported. Gallium-67 can be reactor-produced (Chap. 5), and the most common ^{67}Ga cyclotron production methods include (Fig. 6.9) proton irradiation of isotopically enriched ^{68}Zn targets by the ^{68}Zn(p,2n)^{67}Ga nuclear reaction (Little and Lagunas-Solar 1983). Deuteron irradiation has also been reported on isotopically enriched ^{67}Zn targets by the ^{67}Zn(d,2n)^{67}Ga nuclear reaction (Gul 2001) and α-particle irradiation by the ^{64}Zn(α,n)^{67}Ga or ^{65}Cu(α,2n)^{67}Ga reaction has been reported (Naidoo and Van der Walt 2001; Martin and Osso 2013).

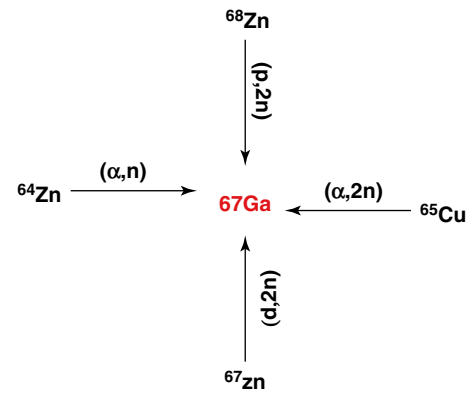

Fig. 6.9 Cyclotron methods for production of ^{67}Ga

Separation of pure gallium radioisotopes produced by cyclotrons—and also produced in nuclear reactors—from the target material and target holder (Zn and Cu, respectively) can be achieved by ion exchange (Aardaneh and Shirazi 2005; El-Azony et al. 2003; Massaoud et al. 2008). Recovery of gallium from aqueous solutions is commonly achieved by chemical precipitation (Sadeghi and Mokhtari 2010), complexation (Dumortier et al. 2005) and ion exchange (Massaoud et al. 2008). Each of these separation techniques of course has its merits and limitations for practical application. The radiochemical processing followed for the separation of ^{67}Ga available from the ^{68}Zn(p,2n)^{67}Ga reaction involves dissolution of the irradiated target in 10 M HCl with subsequent passage of the solution through a cation exchange resin (AG 50 W,H^+ form, mesh 200–400) which is preconditioned with 9 M HCl (Jalilian et al. 2009). The column is washed with 9 M HCl and ^{67}Ga eluted with 6 M HCl solution. The ^{67}Ga obtained from this column is purified by passing through an anion exchange column (AG1X8 Clform,100–200 mesh) pretreated with 6 M HCl where in ^{67}Ga is adsorbed. The ^{67}Ga is then eluted as $^{67}GaCl_3$ using 2 M HCl.

6.3.5 Indium-111

Indium-111 ($T_{1/2}$ = 2.8 d) decays by electron capture (EC 100 %) with emission of γ rays of 173 and 247 keV (89 % and 95 % abundance, respectively). As discussed earlier, these gamma emissions are accompanied by total internal conversions of about 10 % and 6 % (see Chap. 4), respectively. Therapeutic interest in ^{111}In has resulted from the use of ^{111}In-labeled peptides for targeted therapy, utilizing the Auger electrons (see Chap. 9). Commercial production involves irradiation of natural cadmium targets with energetic protons according to the ^{111}Cd(p,n)^{111}In or ^{112}Cd(p,2n)^{111}In reactions, and both remain the most widely used ^{111}In production methods (Zaitseva et al. 1990). When production of ^{111}In is carried out by bombarding Cd targets with protons, the ^{111}In activity at the end of bombardment (EOB) contains radionuclidic contaminates which include ^{109}In ($t_{½}$ = 4.3 h), ^{110m}In($t_{½}$ = 4.9 h), and ^{114m}In ($t_{½}$ = 4.9d). The first two radionuclides of indium have relatively short half-lives and hence cooling for 24 h after EOB is required to significantly reduce the levels of these contaminates (Lahiri et al. 2013).

Radiochemical separation of ^{111}In from the irradiated target can be performed using a wide variety of techniques such as coprecipitation with $Fe(OH)_3$ (Neirincks 1971), ion exchange (Das et al. 1996; Das et al. 1997), extraction chromatography (Levin et al. 1974; Sharma and Smith 1981; Horwitz et al. 1997), thermochromatography (Novgorodov et al. 1984; Schomakher et al. 1988), use of cation exchange resin (Das et al. 1997; Brown and Beets 1972; Nelson and Michelson 1966; Chattopadhyay et al. 1997), coprecipitation with $La(OH)_3$ (Filoosofov et al. 2001), liquid–liquid extraction using Cyanex923 (Guptna et al. 2004), liquid–liquid distribution of ion associates of tetrabromoindate (III) with quaternary ammonium counter ions (Yamamoto and Matsumoto 1977), using organophosphorus compounds as extractants (Rajeh and Subramanian 1994), extraction chromatography using liquid anion exchanger (Horwitz et al. 1995), and solid phase extraction (Horwitz and Dietz 1990; Horwitz et al. 1991; Inoue et al. 1994). Each of these techniques has its own advantages and disadvantages. Liquid–liquid extraction (LLE) (Zheng et al. 1993; Paiva 2001; Horwitz et al. 1993) and ion-exchange chromatography (IEC) are widely used for radiochemical separation of ^{111}In (Das et al. 1997; Rajeh and Subramainan 1994; Horwitz et al. 1995; 1991; Horwitz et al. 1997; Ham 1995).

6.3.6 Rhenium-186

Although ^{186}Re is often reactor-produced, when HSA is required, accelerator production is arising as the preferred production route because of the unique capability of NCA production. High activity levels of NCA ^{186}Re can be produced using cyclotrons (Shigeat et al. 1996; Zhang et al. 1999) by the ^{186}W(p,n)^{186}Re and ^{186}W(d,2n)^{186}Re nuclear reactions. However, because of the low

cross section for the $^{186}W(p,n)^{186}Re$ reaction, production of high activity levels of ^{186}Re using low-energy cyclotrons is a difficult proposition. On the other hand, the $^{186}W(d,2n)^{186}Re$ reaction is more favorable due to the larger cross section (Zhang et al. 2001). The measurement of ^{186}Re production yields by this approach has shown that it is more effective to use a deuteron beam (12.8 MeV) rather than the proton beam (16.5 MeV) for production. In this method the ^{186}W metal target was used dissolved in 30 % H_2O_2 and 1 M NaOH after irradiation with heating. After concentration to near dryness, it was reconstituted with a HCl solution, the pH of which was adjusted to 3–4 and loaded on an acid alumina column. The ^{186}Re was then eluted from the column with saline.

6.4 Tin-117 m

In addition to the expected benefits of AE for therapy, the benefits of conversion electrons (CE) have also been widely recognized and ^{117m}Sn represents one key example. The production of NCA ^{117m}Sn can be carried out in an accelerator using a number of possible nuclear reactions (Ermolaev et al. 2009). Using the $^{115m}In(\alpha,pn)^{117m}Sn$ reaction over the energy range of 45–20 MeV, a relatively pure product can be obtained, however, in very small yields. Natural antimony can be used to produce ^{117m}Sn following the $^{nat}Sb(p,xn)^{117m}Sn$ reaction over the energy range of 38–60 MeV (Mausner et al. 1998). This process, with a cross section of 5 mb, was found enough to produce therapeutic quantities of ^{117m}Sn with high specific activity. Subsequently, the method was upgraded to undertake larger-scale production of NCA ^{117m}Sn with high purity and high specific activity, using targets based on natural or enriched Sb. The thick targets of Sb or Sb–Ti intermetallic compounds are used for irradiation. Chemical recovery of ^{117m}Sn was carried out by solvent extraction with dibutyl ether followed by chromatographic purification on silica gel column. Using these methods, the production of ^{117m}Sn with specific activity of about ~1000 Ci/g with high radionuclidic purity is reported (Ermolaev et al. 2009).

6.5 Summary

Particle accelerators, and in particular cyclotrons, continue to play an integral role for the production of a variety of neutron-deficient therapeutic radioisotopes. The prominent role played by the cyclotrons for the production of therapeutic radionuclides dictates that a holistic consideration should be given to all governing factors while selecting a method. Coalescing the target preparation, cyclotron irradiation of target, and radiochemical separation science is the art of radionuclide production. Persistent efforts are on to uncover new ways to improve the production yields and minimize radioactive contaminants. While the use of enriched target material constitutes a successful paradigm to obtain high-specific-activity radionuclide of interest and good radiopurity, it is necessary to recycle the expensive enriched target material to defray the target cost over many production runs. The interest and availability of alpha-emitting radioisotopes is rapidly increasing, and it is also expected that a variety of other accelerator-produced therapeutic radioisotopes will continue to be evaluated for their potential role for therapy.

References

Aardaneh K, Shirazi B. Rapid separation of radiogallium from Zn and Cu targets using anion exchange technique. J Radioanal Nucl Chem. 2005;265:4.

Apostolidis C, Molinet R, Rasmussen G, Morgenstern A. Production of Ac-225 from Th-229 for targeted alpha therapy. Anal Chem. 2005;77:6288–91.

Boll RA, Malkemus D, Mirzadeh S. Production of actinium- 225 for alpha particle mediated radioimmunotherapy. Appl Radiat Isot. 2005;62:667–79.

Brown LC, Beets AL. Cyclotron production of carrier free indium-111. Int J Appl Radiat Isot. 1972;23:57–63.

Chattopadhyay S, Das MK, Sarkar BR, Ramamoorty N. Radiochemical separation of high purity ^{111}In from cadmium, copper, aluminium and traces of iron: use of a cation exchange resin with hydrobromic acid and hydrobromic acid. Appl Radiat Isot. 1997;48(8):1063–7.

Das SK, Guin R, Saha SK. Carrier-free separation of ^{111}In from a silver matrix. Appl Radiat Isot. 1996;47(3):293–6.

Das MK, Chattopadhayay S, Sarkar BR, Ramamoorthy N. A cation exchange method for separation of ^{111}In from inactive silver, copper, traces of iron and radioactive gallium and zinc isotopes. Appl Radiat Isot. 1997;48(1):11–4.

Dasgupta AK, Mausner LF, Srivastava SC. A new separation procedure for 67Cu from proton irradiated Zn. Appl Radiat Isot. 1991;42:371–6.

Dolley SG, Walt TN, Steyn GFE, Szelecseny F, Kovacs Z. The production and isolation of Cu-64 and Cu-67 from zinc target material and other radionuclides. Czech J Phys. 2006;56:D539–44.

Dumortier R, Weber ME, Vera JH. Removal and recovery of gallium from aqueous solutions by complexation with sodium di-(n-octyl) phosphinate. Hydrometallurgy. 2005;76:207–15.

Eberle SH. Gmelin handbook of inorganic chemistry – astatine. 8th ed. Berlin: Springer; 1985. p. 183–209.

El-Azony KM, Ferieg K, Saleh ZA. Direct separation of ^{67}Ga citrate from zinc and copper target materials by anion exchange. Appl Radiat Isot. 2003;59:329.

Ermolaev SV, Zhuikov BL, Kokhanyuk V, Srivastava SC. Production of carrier-added Tin-117m from proton irradiated antimony. J Radioanal Chem. 2009;280: 319–24.

Filoosofov DV, Lebedev NA, Novogrodov A, et al. Production, concentration and deep purification of ^{111}In radiochemicals. J Appl Radiat Isot. 2001;55:293–329.

Friedman AM, Zalutsky MR, Wung W, et al. Preparation of a biologically stable and immunogenically competent astatinated protein. Int J Nucl Med Biol. 1977;4:219–24.

Gul K. Calculations for the excitation functions of 3–26 MeV proton reactions on ^{66}Zn, ^{67}Zn and ^{68}Zn. Appl Radiat Isot. 2001;54:311–8.

Guptna B, Deep A, Malik P. Liquid-Liquid extraction and recovery of Indium using Cyanex 923. Anal Chim Acta. 2004;513:463–71.

Ham GJ. Determination of actinides in environmental materials using extraction chromatography. Scien Tot Environ. 1995;173/174:19–22.

Henricksen G, Hoff P, Alstad J, Larsen RH. ^{223}Ra for endoradiotherapeutic applications prepared from an immobilized ^{227}Ac/^{227}Th source. Radiochim Acta. 2001;89:661–6.

Horowitz EE, Bond AH. Purification of radionuclides for nuclear medicine: the multicolumn selectivity inversion generator concept. Czech J Phys. 2003;53:A713–6.

Horwitz EP, Dietz ML. Concentration and separation of actinides from urine using a supported bifunctinal organophosphorus extractant. Anal Chim Acta. 1990;238:263–71.

Horwitz EP, Dietz ML, Fisher DE. Separation and pre concentration of strontium from biological, environmental, and nuclear waste samples by extraction chromatography using a crown ether. Anal Chem. 1991;63(5):522–5.

Horwitz EP, Chiarizia R, Dietz ML, et al. Separation and preconcentration of actinides from acidic media by extraction chromatography. Anal Chim Acta. 1993;281:361–72.

Horwitz EP, Dietz ML, Chiarizia R, et al. Separation and preconcentration of actinides by extraction chromatography using a supported liquid anion exchanger. Application to the characterization of high-level nuclear waste solutions. Anal Chim Acta. 1995;310:63–78.

Horwitz EP, Chiarizia R, Dietz ML, et al. DIPEX: a new extraction chromatographic material for the separation and Pre-concentration of actinides from aqueous solution. React Func Polym. 1997;33:25–36.

Inoue K, Yoshizuka K, Yamguchi S. Solvent extraction of indium 8 trialkylphosphine oxide from sulphuric acid solutions containing chloride. J Chem Engin Japan. 1994;27(6):737–40.

International Atomic Energy Agency (IAEA) Publication Technical Reports Series No. Cyclotron produced radionuclides: physical characteristics and production, 468. Vienna; 2009.

Jalilian AR, Yousefnia H, Garousi J, et al. The development of radiogallium-acetylacetonate bis(thiosemicarbazone) complex for tumour imaging. Nucl Med Rev. 2009;12(2):65–71.

Jamriska DJ, Taylor WA, Ott MA, et al. Activation rates and chemical recovery of ^{67}Cu produced with low energy proton irradiation of enriched Zn targets. J RadioanaLl ucL Chem. 1995;195:263–70.

Johnson EL, Turkington TG, Jaszczak RJ, et al. Quantitation of ^{211}At in small volumes for evaluation of targeted radiotherapy in animal models. Nucl Med Biol. 1995;22:45–54.

Katabuchi T, Watanabe S, Ishioka N, et al. Production of Cu-67 via the Zn-68(p,2p)Cu-67 reaction and recovery of Zn-68 target. J Radioanal Nucl Chem. 2008;277:467–70.

Kirby HW. Residue adsorption – III: mutual separation of ^{227}Ac, ^{227}Th and ^{223}Ra. J Inorg Nucl Chem. 1969;31:3375–85.

Kirby HK. Gmelin handbook of inorganic chemistry – astatine. 8th ed. Berlin: Springer; 1985. p. 95–106.

Knogler K, Grünberg J, Zimmermann K, et al. Copper-67 radioimmunotherapy and growth inhibition by anti L1-cell adhesion molecule monoclonal antibodies in a therapy model of ovarian cancer metastasis. Clin Cancer Res. 2007;13:603–11.

Lahiri S, Maiti M, Ghosh K. Production and separation of ^{111}In: an important radionuclide in life sciences: a mini review. J Radioanal Nucl Chem. 2013;297: 309–18.

Lambrecht RM, Mirzadeh S. Cyclotron isotopes and radiopharmaceuticals – XXXV. Astatine-211. Int J Appl Radiat Isotop. 1985;36:443–50.

Larsen RH, Murud KM, Akabani G, et al. ^{211}At- and ^{131}I-labeled bisphosphonates with high *in vivo* stability and bone accumulation. J Nucl Med. 1999;40:1197–203.

Levin VI, Kozlova MD, Malinin AB, et al. The production of carrier-free indium. Int J Appl Radiat Isot. 1974; 25:286–8.

Lindegren S, Back T, Jensen H. Dry-distillation of astatine-211 from irradiated bismuth targets: a time-saving procedure with high recovery yields. Appl Radiat Isot. 2001;55:157–60.

Little FE, Lagunas-Solar MC. Cyclotron production of ^{67}Ga. Cross sections and thick-target yields for the ^{67}Zn (p, n) and ^{68}Zn (p,2n) reactions. Int J Appl Radiat Isot. 1983;34(3):631–7.

Martins ADA, Osso Jr JA. Thermal diffusion of ^{67}Ga from irradiated Zn targets. Appl Radiat Isot. 2013;82:279–82.

Massaoud AA, Hanafi HA, Siyam T, Saleh ZA, Ali FA. Separation of Ga(III) from Cu(II), Ni(II) and Zn(II) in aqueous solution using synthetic polymeric resins. Cent Eur J Chem. 2008;6(1):39–45.

Mausner LF, Kolsk KL, Joshi V, Srivastava SC. Radionuclide development at BNL for nuclear medicine therapy. Appl Radiat Isot. 1998;49:285–94.

Miederer M, Scheinberg DA, McDevitt MR. Realizing the potential of the Actinium-225 radionuclide generator in targeted alpha particle therapy applications. Adv Drug Deliv Rev. 2008;60: 1371–82.

Milesz S, Norseev YV, Szücs Z, Vasáros L. Characterization of DTPA complexes and conjugated antibodies of astatine. J Radioanal Nucl Chem Lett. 1989;137:365–72.

Mirzadeh S, Mausner LF, Srivastava SC. Production of no carrier-added Cu-67. Appl Radiat Isot. 1986; 37:29–36.

Mushtaq A, Karim H, Khan M. Production of no-carrier-added ^{64}Cu and ^{67}Cu in a reactor. J. RadioanaL Nucl Chem. 1990;141:261–9.

Naidoo C, Van der Walt TN. Cyclotron production of ^{67}Ga (III) with a tandem ^{nat}Ge–^{nat}Zn target. Appl Radiat Isot. 2001;54:915–9.

Neirincks RD. The separation of cyclotron-produced ^{111}In from a silver matrix, radio. Chem Radioanal Lett. 1971;4(2):153–5.

Nelson F, Michelson DC. Ion-exchange procedures ix Cation exchange in HBr solutions. J Chromatogr. 1966;25:414.

Novgorodov AF, Beyer GJ, Zelinski A, et al. Simple method for high temperature release of ^{111}In from silver. J I N R (Dubna). 1984;6(84):609.

Paiva AP. Recovery of indium from aqueous solutions by solvent extraction. Sep Sci Technol. 2001;36(7): 1395–419.

Polak P, Geradts J, Van der Vlist R, Lindner L. Photonuclear production of ^{67}Cu from ZnO Targets. Radiochim Acta. 1986;40:169–74.

Rajeh N, Subramainan MS. Extractive separation and determination of thallium and indium by liquid scintillation counting. Analyst. 1994;119:2071–4.

Roy K, Basu S, Ramaswami A, Nayak D, Lahiri S. Incorporation of thiosemicarbazide in Amberlite IRC-50 for separation of astatine from α-irradiated bismuth oxide. Appl Radiat Isotop. 2004;60: 793–9.

Sadeghi M, Mokhtari L. Rapid separation of ^{67,68}Ga from ^{68}Zn target using precipitation technique. J Radioanal Nucl Chem. 2010;284:471–3.

Scheinberg DA, McDevitt MR. Actinium-225 in targeted alpha-particle therapeutic applications. Curr Radiopharm. 2011;4:306–20.

Schomakher K, Schwratzbach R, Beyer G-J, Novogorodov AF. A further simplified method for the separation of ^{111}In from Silver targets by thermo chromatography. Appl Radiat Isot. 1988;39(6):483–5.

Schwarzbach R, Zimmermann K, Blaeuenstein P, et al. Development of a simple and selective separation of ^{67}Cu from irradiated zinc for use in antibody labelling: a comparison of methods. Appl Radiat Iso. 1995;46:329–36.

Sharma HL, Smith A. The short-lived radioisotope production program at Manchester. J Radioanal Chem. 1981;64(1, 2):249–55.

Shigeta N, Matsuoka H, Osa A, Koizumi M, Izumo M, Kobayashi K, Hashimoto K, Sekine T, Lambrecht RM. Production method of no-carrier-added ^{186}Re, J Radioanal Nucl Chem. 1996;205:85–92.

Shikata E. Research of radioisotope production with fast neutrons. vi. preparation of Cu-67. J Nucl Sci Technol (Tokyo, Jpn). 1964;1:177–80.

Smit JA, Myburgh JA, Neirinckx RD. Specific inactivation of sensitized lymphocytes *in vitro* using antigens labelled with astatine-211. Clin Exp Immunol. 1973;14:107–16.

Starovoitova VN, Tchelidze L, Wells DP. Production of medical radioisotopes with linear accelerators. Appl Radiat Isot. 2014;85:39–44.

Stoll T, Kastleiner S, Shubin YN, Coenen HH, Qaim SM. Excitation functions of proton induced reactions on 68Zn from threshold up to 71 MeV, with specific reference to the production of 67Cu. Radiochim Acta. 2002;90:309–13.

Turlera A, Huenges E, Henkelmann R, et al. Method for purification of ^{225}Ac from irradiated ^{226}Ra-targets. United States Patent No. US 2013/0266475 A1, 10 Oct 2013.

Weidner JW, Mashnik SG, John KD, et al. ^{225}Ac and ^{223}Ra production via 800 MeV proton irradiation of natural thorium targets. Appl Radiat Isot. 2012;70:2590–5.

Yagi M, Kondo K. Preparation of carrier-free 67Cu by the 68Zn(g, p) reaction. Int J Appl Radiat Isot. 1978; 29:757–9.

Yamamoto K, Matsumoto A. Liquid-Liquid distribution of ion associates of tetrabromoindate (III) with quaternarymoniun counter ions. Talanta. 1977;44: 2145–50.

Yordanov AT, Deal K, Garmestani K, Kobayashi H, et al. Synthesis and biodistribution study of a new ^{211}At-calix[4]arene complex. J Label Compd Radiopharm. 2000;43:1219–25.

Yordanov AT, Pozzi O, Carlin S, et al. Wet harvesting of no-carrier-added 211At from an irradiated 209Bi target for radiopharmaceutical applications. J Radioanalyt Nucl Chem. 2004;262:593–9.

Zaitseva NG, Knotek O, Kowalew A, et al. Excitation functions and yields for 111In production using. 113,114, natCd(p, xn)111In reaction with 65 MeV protons. Appl Radiat Isot. 1990;41:177–83.

Zalutsky MR, Bigner DD. Radioimmunotherapy with alpha-particle emitting radioimmunoconjugates. Acta Oncol. 1996;35:373–9.

Zalutsky MR, Pruszynski M. Astatine-211 – production and availability. Curr Radiopharm. 2011;4(3):177–85.

Zhang X, Lp W, Fang K, He W, Sheng R, Ying D, Hu W. Excitation functions for $^{nat}W(p, xn)^{181-186}Re$ reactions and production of no-carrier-added. ^{186}Re via $^{186}W(p, n)^{186}Re$ reaction. Radiochim Acta. 1999;86: 11–6.

Zhang X, Li Q, Li W, Sheng R, Shen S. Production of no-carrier-added ^{186}Re via deuteron induced reactions on isotopically enriched ^{186}W. Appl Radiat Isot. 2001;54: 89–92.

Zheng WI, Sipes IG, Carter DE. Determination of parts-per-billion concentrations of indium in biological materials by electrothermal atomic absorption spectrometry following Ion pair extraction. Anal Chem. 1993;65:2174–6.

Zhuikov BL, Kalmykov SN, Ermolaev SV, et al. Production of ^{225}Ac and ^{223}Ra by irradiation of Th with accelerated protons. Radiochem. 2011;53(1): 73–80.