Chapter 17

Brief Introduction to Complete Radioisotope Production Cycle

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In the recent times, radionuclides have gained a lot of importance for its use as nuclear medicine especially in targeted radionuclide therapy. In radionuclide therapy, radiation emitted by a radioisotope during its decay is utilized for the treatment of cancer and tumour. The radioactive radiation emitted by radionuclide in the form of alpha, beta, auger or conversion electrons is used to destroy the DNA of the deceased cell. Apart from therapeutic applications, radioisotopes are also used for diagnostics and imaging of abnormal parts in the body. Imaging of bones as well as soft tissues is possible, which provides a distinct advantage over its counterpart (x-ray imaging). The radionuclide used for medical applications are mostly artificially generated either in the particle accelerators or by irradiation of stable nucleus in the nuclear reactor. The radioisotopes from nuclear reactor are mostly produced by irradiation of neutrons to the specific stable isotopes. This stable isotope is required to be enriched for attaining high specific activity by the radioisotope after neutron irradiation in nuclear reactor. The complete cycle of production of radio medicine involves the following steps.

1. Enrichment of stable isotope;
2. Irradiation of stable enriched isotope to produce radioisotope;
3. Separation of radioisotope from stable isotope and other burn up products;
4. Formation of radio labelled molecule, to attach to targeted tissues in human.

17.1 Enrichment of Stable Isotope

Enrichment of isotope got triggered with the intention of making nuclear weapons. Later it got momentum with requirement of enriched uranium for fuel fabrication of commercial power reactor. However, there are many other applications where enriched isotopes are needed, e.g.,

1. Enriched isotope target are required for irradiation to produce radioisotopes for medical applications;
2. Enriched isotopes required for semiconductors;
3. Low neutron capture isotopes and high neutron capture isotopes for various applications in nuclear reactor;
4. Isotopes for industrial tracer, identification applications.

Many techniques have been tried for isotope enrichment/separation. Some of them include gaseous diffusion, centrifuge, electromagnetic separation, photochemical separation, nozzle separation, laser isotope separation etc. Laser based techniques further divided into atomic and molecular one. Atomic approach is known as atomic vapour laser isotope separation and molecular approach as molecular laser isotope separation. Atomic vapour laser isotope separation (AVLIS) technique is already utilized worldwide for the successful enrichment of uranium. The single stage high enrichment factor and yield make it ahead with many of its counterparts. Low abundant isotopes can also be enriched with desired purity. Even in the presence of many isotopes, desired isotope can be easily enriched by employing precisely tuned lasers with desired laser linewidth/polarization. AVLIS technique has matured enough for successful commercialization to produce enriched isotopes for medical applications. AVLIS is fusion of many branches for science and technology but broadly it can be classified into the following.

(1) Constructing an efficient and selective photoionization scheme;
(2) Development of lasers with required parameters;
(3) Generation of atomic vapor, photon atom interaction and photoion collection.

17.1.1 Constructing an efficient & selective photoionization scheme

Constructing a photoionization scheme is a challenging task as it needs optimization of many atomic parameters for attaining high selectivity and photoionization yield. These atomic parameters include transition wavelengths, autoionization energy levels, photoexcitation/ photoionization cross-sections, isotope shifts, radiative lifetimes, J-values, hyperfine structure etc. The transition wavelengths should be producible by the commercially available laser dyes. A strong autoionization transition reduces the required energy demand for the terminating transition in comparison to continuum. In the same way, strong photoexcitaion cross-sections reduce the energy requirements for the first and second-step transitions. Decent isotope shifts can relax stringent laser linewidth requirement. Overlap of hyperfine components with desired isotope can reduce the selectivity. Energy levels lifetimes should be more than laser pulse width. Proper J-value sequence is also very important especially in polarization-based laser isotope separation. Four-color, three-step photoionization scheme utilizing the ground and metastable state population through common first-step energy state can also be advantageous in some cases so that maximum possible atoms in vapour state can be employed and throughput can be enhanced. Many techniques/methodologies required to be developed for the measurement of these atomic parameters [184–199].

17.1.2 Development of lasers with required parameters

Laser wavelength, pulse energy, linewidth, pulse width, repetition rate, polarization are main laser parameters vital for the AVLIS. Laser linewidth should be less than the isotope shift and it should take care of nearest hyperfine component, if present, to attain high selectivity. All the transitions need to be saturated in order to optimize the photoionization yield. The laser power stability for longer duration helps in maintaining the yield for entire duration

of experiments. Wavelength stability is vital for the photoionization yield as well as selectivity. Laser repetition rate should be high enough so that no atom should pass the laser atom interaction zone un-illuminated. Precise wavelength tuning to acquire the transition wavelengths for realizing selective photoionization needs sophisticated instruments like time-of-flight-mass-spectrometer, wavemeter with required resolution. A lot of instrumentation/ automation is required for the wavelength locking, tuning of dye lasers and conditioning of pump lasers. In short, single mode wavelength and power stabilized precisely tuned dye laser beams are required for AVLIS experiments. A detailed study on every aspect is essential [85, 86, 100, 200–202].

17.1.3 Generation of atomic vapor, photon atom interaction & ion collection

Generation of atomic vapor with required number density, interaction length, Doppler width is essential. Vapours can be generated using resistive heating, electron beam heating or resistive heating in combination with electron bombardment. Type of heating depends on operating temperature required to generate appropriate number density. The neutral atom scattering should be as minimum as possible in order to attain the high enrichment. Increase in number density enhances the yield as well as neutral atom scattering, which decreases the enrichment. So, it is a trade-off between yield and enrichment. In high number density collisional processes may dominate, allowing charge transfer and momentum exchange, which adversely affect desired isotopic yield/enrichment. Photon atom interaction zone should provide maximum overlap between laser photons and atoms to maximize photoionization yield. Neither photon nor atom should remain unutilized as it is very important for economy point of view. A suitable laser multi-pass is essential to fulfil this requirement. High reflectivity mirrors and antireflection coated windows are required to minimize laser power loss in multi-pass. Keeping reflection optics inside chamber reduces multiple power losses in windows. Ion collection is very important aspect of AVLIS. Design of proper ion collection geometry is essential in order to collect maximum number of ions generated and to minimize neutral atom scattering towards product collector. At higher ion densities, plasma effects start dominating which demands higher electric field. Sputtering by the ions can also hamper the net product collection. Optimization of voltages at different locations is essential to optimize the photoion collection. Detailed studies on atomic vapour generation, plasma parameters, collection voltages and other relevant parameters are vital [203–214].

17.2 Stable Enriched Isotope to Radioisotope

The enriched isotope is then irradiated in nuclear reactor. Irradiation yield can be evaluated by the following Eqs. (17.1) and (17.2).

$$\frac{dN_R}{dt} = \frac{dN_R}{dt}\ Growth - \frac{dN_R}{dt}\ Decay - \frac{dN_R}{dt}\ Product\ burn\ up \tag{17.1}$$

$$\frac{dN_R}{dt} = N_T\ \sigma_T\ \phi - N_R\ \lambda_R - N_R\ \sigma_R\ \phi \tag{17.2}$$

Where
N_R - Number of radioactive atoms such as N_{Sm-153};
N_T - Number of target atoms such as N_{Sm-152};
σ_T - Neutron capture cross section of target atom such as N_{Sm-152} (cm^2);
σ_R - Neutron capture cross section of radioactive atom such as N_{Sm-153} (cm^2);
λ_R - Decay constant of radioactive atom such as N_{Sm-153} (s^{-1});

ϕ - Neutron flux (cm^{-2} s^{-1}).

The irradiation yield reaches its maximum value after that it starts decreasing due to the burn up of radioactive atom. So, duration of irradiation for optimum yield depends on neutron capture cross-sections of target and radioactive atoms, neutron flux and decay constant (half life) of radioactive atom [213, 214].

17.3 Separation of Radioisotope from Stable Isotope & Burn up

In the irradiated yield one gets target isotope (macro constituent, e.g. Yb-176), radioisotope (micro constituent, e.g. Lu-177) and burn up isotopes (micro constituent, e.g. Hf-177). The radioisotope needs to be separated from the macro constituent. It also needs to be separated from burn up isotopes, if possible in order to attain high specific activity. Chemical separation techniques are used for purification of radionuclides in nuclear medicine [213]. It is possible to separate micro amounts of no carrier added (nca) radionuclides from macro amounts of the target material after irradiation at nuclear reactors or cyclotrons.

17.4 Formation of Radio Labeled Molecule to Attach Targeted Tissues in Human

A typical metal-radio-pharmaceutical consists of the following components:

(i) The radionuclide, responsible for providing the therapeutic effect and visualization;

(ii) A dual functional chelator;

(iii) A linker/spacer, which is mostly used as a pharmaco-kinetic-modifier (PKM) depending on the requirements for the radiopharmaceutical;

(iv) A targeting bio-molecule e.g. a peptide an antibody responsible for delivering the attached radionuclide to the target cells.

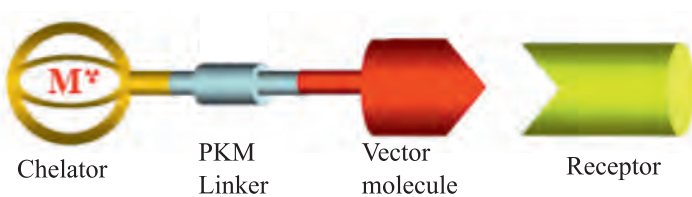

Figure 17.1: The components of receptor mediated metal-radio-pharmaceutical.

The above Fig. 17.1 shows the components of receptor mediated metal-radio-pharmaceutical. The radio-metal is bound to the vector molecule using dual functional chelator.

17.5 Conclusion

Sufficient in-house expertise is available on every aspect of radioisotope production for medical applications [184–199, 203–214]. Lab scale production of some of the medical isotopes is already in progress. Some other radioisotopes can be explored in future as per requirement. The process also needs to be scaled up for economic point of view.