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Production of PET radionuclides

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Over the last two decades the PET method became a powerful tool in life sciences. Primarily nuclear medicine uses the diagnostic approach but more and more PET is exploited for pharmaceutical development. Beside technical improvements such as the PET/CT technique and the optimal reliability of the actual medical accelerator generation it is mainly the growing number and the large variety of radionuclides for different applications which assured the breakthrough of PET.

The production of a radionuclide depends on the cross section of the nuclear reaction and the particle energy. The mostly applied PET radionuclides, i.e. Carbon-11, Oxygen-15 and Fluorine-18 are produced by irradiation with protons via the (p,α)-reaction in case of C-11 and (p,n)-reaction in case of F-18) or by bombardment with deuterons via the (d,n)-reaction for O-15 and as an alternative for F-18. The cross sections are in the energy range of modern accelerators (examples: CTI RDS 112, GE PETtrace, IBA Cyclone 18/9) which allow proton energies between 11-18 MeV and deuteron energies between 8-9 MeV (GE, IBA).

In general, a production route is preferred which uses the advantages of a gaseous state or fluid state target system because automation and transportation into the radiochemical production location is relatively easy. Solid state targets, however, exhibit principal disadvantages since the usually applied manual disconnection of the target gives rise to additional radiation exposure of the operator. A different problem is the following radiochemical processing of the target material in order to get the radionuclide in an appropriate chemical form for the final labelling reaction. The automation of those processes is not always possible but highly desirable because the recent developments in PET radionuclide production (Cu-64, Y-86, I-124) are based on solid state targets. Other problems are the use of highly enriched and, thus, expensive target material and the efficient cooling of the target during irradiation. A good solution to reduce the amount of target material is the use of an irradiation angle of 10° which leads nearly to a surface irradiation. The applications of radionuclides such as Cu-64, Y-86, or I-124 become increasingly interesting but solutions commercially available are still rare.

The most important PET radionuclides are C-11 and F-18. The mainly used production route for C-11 is the 14N(p,α)11C nuclear reaction. The optimum range for this nuclear reaction is between 3-15 MeV. Thus accelerators with lower maximum proton energies than 15 MeV are not able to produce high activities and high specific activities, respectively. The addition of oxygen to the target gas leads to the formation of 11CO and $11CO_2$. The relative amounts of both compounds depend mainly on the beam current, the absorbed dose and on the amount of oxygen. Usually between 2 ppm and 0,5 % O_2 are used in the modern high beam current targets. Two high energy process routes (as result of the recoil after the nuclear reaction; "hot atom chemistry") lead at least to $11CO_2$. The use of a static C-11 target yields more than 90 % of the C-11 in form of $11CO_2$, while the production with a flow-through target leads to a lower amount of $11CO_2$. Higher amounts of O_2 give raise to the formation of undesirable 13N via the 16O(p,α)13N, respectively, the 14N(p,pn)13N nuclear reaction.

In case of C-11 production the specific activity is an important parameter. The use of a high quality target gas mixture ($14N_2$ 6.0 with O_2 in 6.0 purity) is highly recommended as well as the additional purification of the target gas via CO_2/CO adsorbing traps as lithiumhydroxid, ascarite®, molsieve (4 Å, 5 Å) or porapak©. In the following the specific activity depends highly on the following production way of the secondary labeling precursor, which mainly is 11C methyl iodide. The gaseous phase high temperature reaction via 11C methane and iodine is superior over the liquid phase preparation via $LiAlH_4$ and HI or P_2I_4, respectively, or similar reactions.

For the production of F-18 mainly two production ways are applied. The 18O(p,n)18F nuclear reaction on enriched water (H_218O, ≥ 95 %) leads to 18F fluoride in aqueous solution which can be used after drying and activation via phase transfer catalysts (e.g. Kryptofix©) under base support for nucleophilic exchange in labeling reactions. The optimum range for this nuclear reaction is between 3-11 MeV. That gave an impact to the development of smaller accelerators (minitrace, GE) which are able to produce F-18 in satisfactory yields. The second production path for F-18 is the 20Ne(d,α)18F nuclear

reaction under carrier added conditions. An alternative is the production via an $18O_2$ gas target via the 18O(p,n)18F nuclear reaction. In both cases F_2 must be added to the target gas to allow an isotopic exchange with F-19 after the nuclear reaction. Without this procedure it would be impossible to get the F-18 out of the target body for the desired electrophilic reaction path. Disadvantage of this procedure is the clearly limited specific activity and on the other hand the relatively low yields with respect to the nuclear reaction.

Further reading:

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C.B. Sampson (Ed.): Textbook of Radiopharmacy. Theory and Practice. 3rd Ed. Gordon and Breach 1999