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Published in:
Nukleonika

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Final author's version (accepted by publisher, after peer review)

Publication date:
2003

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
Paans, AMJ. (2003). Compact cyclotrons for the production of tracers and radiopharmaceuticals. *Nukleonika*, *48*(2), S169-S172.

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NUKLEONIKA 2003;48(Supplement 2):S169–S172

Compact cyclotrons for the production of tracers and radiopharmaceuticals

Anne M. J. Paans

Abstract Positron Emission Tomography (PET) is a method for determining biochemical and physiological processes *in vivo* in a quantitative manner. The most commonly used radionuclides are ^{11}C, ^{13}N, ^{15}O and ^{18}F, with respective half-lives of approximately 20 min, 10 min, 2 min, and 110 min. ^{18}F labeled FDG (fluoro-2-deoxy-D-glucose) is now the most frequently used radiopharmaceutical and finds its application prominently in the field of oncology. Originally, the production of these radionuclides was performed with the existing accelerators, designed for nuclear physics, but with increasing interest in the PET methodology specially designed PET-production cyclotrons became available. The nuclear reactions involved are (p,n), (d,n), (p,α) and (d,α) and the thresholds for the nuclear reactions involved are 5 to 6 MeV. Based on these values and on other parameters, a proton 15 to 20 MeV cyclotron is often chosen. Since the half-life of a radionuclide limits the production time, the maximum beam current is an important parameter, together with the target construction, for the ultimate yield obtainable. In the development of special PET production cyclotrons, attention has also been paid to improve the extraction efficiency and the possibility of multiple extractions by designing negative ion cyclotrons. Commercial cyclotrons can often be acquired as an easy to operate integrated radionuclide production unit including targetry and some units. Regional FDG factories are nowadays being created to fulfil the demand for PET radiopharmaceutics. The possible choices in commercially available cyclotrons for the production of PET radionuclides will be discussed.

Key words Positron Emission Tomography (PET) • cyclotron • radionuclide production • radiochemistry

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Received: 14 October 2002, Accepted: 10 March 2003

Introduction

The idea of *in vivo* measurement of biological and/or biochemical processes was already envisaged in the 1930's when the first artificially produced radionuclides of the biologically important elements carbon, nitrogen and oxygen were discovered with help of the then recently developed cyclotron. These radionuclides decay by pure positron emission and the annihilation of positron and electron results in two 511 keV γ-quanta under a relative angle of about 180°, which are measured in coincidence. This idea of PET could only be realized when the inorganic scintillation detectors for the detection of γ-radiation, electronics for the coincidence measurements and the computer capacity for data acquisition and image reconstruction became available. For this reason the technical development of Positron Emission Tomography [6] as a functional *in vivo* imaging discipline began just over 30 years ago.

PET employs mainly short-lived positron emitting radiopharmaceuticals. The most widely used radionuclides are: ^{11}C ($t_{1/2}$ = 20.38 min), ^{13}N ($t_{1/2}$ = 9.96 min), ^{15}O ($t_{1/2}$ = 2.03 min) and ^{18}F ($t_{1/2}$ = 109.7 min). Carbon, oxygen, nitrogen and hydrogen are the elements of life and the building blocks of nearly every molecule of biological importance. However, hydrogen has no radioactive isotope decaying with the emission of radiation which can be detected outside the human body. For this reason, the

fluorine-18 isotope is often used to replace a hydrogen atom in a molecule. Due to these short half-lives the radionuclides have to be produced in-house, preferably with a small, dedicated cyclotron. Since the chemical form of accelerator produced radionuclides can only be simple, input from organic- and radiochemistry is essential for synthesis of the desired complex molecules [1, 2]. Their final formulation and the evaluation of pharmacokinetic studies lie in the domain of pharmacy. Medical science is applied in the evaluation of the clinical application with respect to the radiopharmaceuticals used.

Nuclear reactions and specific activity

For the production of the four most essential PET radionuclides low energy cyclotrons (E_p < 20 MeV) are sufficient, as can be seen from Table 1 where the nuclear reaction involved, the Q-values, the target materials and the chemical form of the produced radionuclide are summarized [3, 5]. Sometimes oxygen or fluorine gas is added to the target gas in order to obtain the produced radioactivity in the desired chemical form. By this addition the specific activity, see below, will be lowered.

Nowadays, small dedicated cyclotrons are commercially available. These accelerators are one- or two-particle machines, mostly with fixed energies. Mostly negative-ion machines are being installed because of their relatively simple extraction system and high extraction efficiency. They are installed complete with the targetry for making the four above-mentioned short-lived radionuclides in batches of up to 100 GBq or higher. Also, the chemistry for some simple chemical products is incorporated, e.g. $^{11}CO_2$, ^{11}CO, $C^{15}O$, $C^{15}O_2$, $H_2{}^{15}O$ etc. Sometimes synthesis modules for the preparation of more complex molecules, e.g. ^{18}FDG, ^{18}F-DOPA, $H^{11}CN$, $^{11}CH_4$, $^{11}CH_3I$ or $^{13}NH_3$, are also available from the cyclotron manufacturer or from another specialized company. These products become available via dedicated, automated systems or via a programmable robotic system. Production of other radiopharmaceuticals has to be set-up individually in each PET center.

Due to the nature of the induced nuclear reaction (p,n), (d,n), (p,α) or (d,α) there is a change in element:

$$Z \rightarrow Z + 1 \text{ or } Z \rightarrow Z - 1$$

Table 1. Nuclear reactions and target products for the four important PET radionuclides.

Nuclear reactions	Q-value (MeV)	Target	Product
$^{18}O(p,n)^{18}F$	–2.4	$H_2{}^{18}O$ $^{18}O_2(+F_2)$	$^{18}F^-$ $^{18}F_2$
$^{20}Ne(d,\alpha)^{18}F$	+2.8	$Ne(+F_2)$	$^{18}F_2$
$^{14}N(p,\alpha)^{11}C$	–2.9	$N_2(+O_2)$	$^{11}CO_2$
$^{16}O(p,\alpha)^{13}N$	–5.2	H_2O + EtOH*	$^{13}NO_3$, $^{13}NO_2$,$^{13}NH_3$
$^{14}N(d,n)^{15}O$	+5.1	$N_2(+O_2)$	$^{15}O_2$
$^{15}N(p,n)^{15}O$	–3.5	$^{15}N_2(+O_2)$	$^{15}O_2$

* Direct production of ammonia is possible by adding ethanol to water.

The term "carrier free" is used when no "cold" material of the same chemical composition as the radioactive species is present. This is very difficult to achieve because often natural dilution occurs. Contamination, to the order of a few ppm is very difficult to avoid. Often the term "no carrier added" production is used. This means no "cold" material of the same chemical identity is added on purpose by the investigator during preparation of the radiopharmaceutical.

Specific activity is the amount of radioactivity per gram or mole. The theoretical maximum of the specific activity is related to the number of radionuclides A (Bq) = $N_o\lambda$ with $\lambda = \ln 2/t_{1/2}$ the decay constant. The maximum specific activity for ^{11}C of 340 TBq/μmol *vs.* the specific activity of ^{14}C of 2.3 MBq/mmol is completely explained by the difference in their half-lives, 20.4 min *vs.* 5730 yrs. In reality, the theoretical maxima in specific activity are never reached. Very special precautions have to be taken to keep the dilution factor low; e.g. the target should not be opened, always kept pressurized, target materials should be selected on the basis of their contaminations with ppm amounts of non-desired elements etc. With a carrier free or no carrier added synthesis one expects no toxic effects (e.g. $H^{11}CN$ or $C^{15}O$ are toxic no more) nor any physiological effects (tracer principle). Radiopharmaceuticals with a high specific activity are essential in the case of studies of receptor systems such as, e.g., the dopaminergic system.

Accelerators for PET radionuclide production

In the proton energy range from 10–20 MeV all four basic radionuclides: ^{11}C, ^{13}N, ^{15}O and ^{18}F, can be produced. A deuteron beam of 5–10 MeV is prefered for the production of ^{15}O and sometimes ^{18}F in the molecular form. In general, the device of choice is a cyclotron, not a linear accelerator, because in this energy range the cyclotron is a more versatile and economic solution. Although at higher energies a larger part of the excitation function can be exploited resulting in a higher yield, some companies have purposely designed cyclotrons of proton energy range of 10–11 MeV, for economic reasons. In Table 2 an overview is given of the commercially available cyclotrons with 10 MeV < E_p < 20 MeV. The requirements imposed on a radionuclide production machine differ from those imposed on machines designed for experimental nuclear physics. For radionuclide production beam quality parameters such as momentum resolution or beam emittance are less important. On the other hand, a high beam current distributed over a larger (cm^2 instead of mm^2) beam spot is essential for achieving a high radionuclide production rate. Technical descriptions of these cyclotrons are available from the respective manufacturers. All these cyclotrons are negative ion machines. The operation of this class of cyclotrons is most often done by the radiochemists, and no special operator group is required. For daily operation and maintenance, obviously, the required knowledge has to be available.

The target systems are mostly installed just at the beam exit of the cyclotron. Sometimes a short beam line is installed to focus the beam on the target. The big advantage of negative ions is that after passing through a carbon stripper foil, all electrons are removed and the beam is automatically bended out of the machine. Extraction

Table 2. Commercially available cyclotrons with 10 MeV < E_p < 20 MeV.

Company	Type	Particle	E_p/E_d (MeV)	I_p (μA)	I_d (μA)
CTI	RDS111	H^-	11/na	2 × 40	na
	Eclipse	H^-	11/na	2 × 60	na
EBCO	TR14(19*)	H^-	14/na	>100	na
	TR19	H^-	11–19/9****	>200	>100
GE	MINItrace	H^-	10/na	yield**	na
	PETtrace	H^-,D^-	16.5/8.4	>75	>60
IBA	10/5	H^-,D^-	10/5	>60	35
	18/9	H^-,D^-	18/9	>80	>35
Sumitomo***	HM-12	H^-,D^-	12/6	80	30
	HM-18	H^-,D^-	18/10	>70	>50
	MINItrace	H^-	10/na	yield**	na

The companies involved are CTI Inc., Knoxville (TN), USA; EBCO Technologies Inc., Richmond (BC) Canada; GE, Milwaukee (WI), USA; IBA, Louvain-la-Neuve, Belgium and Sumimoto Heavy Industries Ltd, Tokyo, Japan.

* The EBCO TR14 is upgradable to a TR19.

** Instead of current the yield is specified.

*** The Sumimoto cyclotrons are not marketed in Europe.

**** The 9 MeV deuteron beam is optional.

na – not applicable.

efficiency of 100% is possible and by positioning the stripper foil partially intercepting the beam, also multiple (at least 2) extracted beams are available. With short-lived radionuclides the maximum beam current a target can withstand under irradiation conditions is the crucial parameter for the yield obtainable. An irradiation time of two half-lives produces 75% of the saturation value (the saturation yield is defined as the yield (GBq/μA) at infinite irradiation time). So, increasing the beam current or increasing the beam energy are the only two possibilities to increase the yield. Increasing the beam current gives a linear increase in yield as long as the target can withstand the heat dissipation. Increasing the beam energy will increase the yield but this depends on the actual values of the excitation function of the nuclear reaction used. For production of ^{18}F by the proton induced reaction on ^{18}O, a factor of nearly 2 can be gained in yield, the saturation yield increasing from about 4 GBq/μA at E_p = 10 MeV to roughly 7.5 GBq/μA at E_p = 20 MeV. Hence, the lower the energy, the higher is the required beam current for the same yield and the more critical is the target construction. Since also the energy losses in the respective foils will be higher at lower energies, the target construction will become even more critical. Sometimes, simultaneous irradiation of two targets is possible in negative ion cyclotrons. Targets for the production of the four essential radionuclides are also commercially available and often the installation of a cyclotron is a turn-key project comprising of the targets, transport of the radionuclides and some radiochemistry units for the production of radiopharmaceuticals.

The transport of irradiated material can be very easy in the case of a gas target. Just a normal flow can carry the radioactivity over 50–100 m, but a distance of 500 m is possible in a well tuned pipeline [4]. In the case of a fluid target, a flow of helium through thin tubing can move the irradiated material into the desired position. With solid targets an exchange system or train system can transport the target or target material. The local situation will dictate which particular solution is most appropriate.

Targetry

For reliable operation not only a reliable cyclotron but also reliable targets are needed. The targets often need to be adapted to the specific beam size and beam energy used. On the front side often a double foil technique is used. The first foil separates the target from vacuum, helium is circulated between the two foils to cool the foils, and the second foil separates the target material from the helium cooling. The beam size is adapted to the size of the target or vice versa, but the beam size should not be too small because too high a power dissipation (W/cm^2) will cause foil rupture. The foil material is often stainless steel or Havar, of thickness between 10 and 25 μm. In these target foils, longer living radionuclides such as e.g. ^{57}Co will be produced. Under normal conditions the lifetime of a foil is typically around 2000 μAh. The target body itself is often made of aluminium. Practically no long-lived radionuclides can be produced in aluminium, and is easy to machine. Chemistry can dictate other target materials, such as titanium or niobium. On the back-side of the target water cooling is supplied. If enriched materials are used, e.g. $H_2{}^{18}O$, the volume will be minimized while the yield or beam current has to be maximized. These requirements determine the target design. Most cyclotron manufacturers will supply their own target designs but targets can also be purchased from specialized companies. The cyclotron and the target have to form a reliable combination and, as already stated before, by lowering the beam energy the production yield can only be maintained by increasing the beam current onto the target.

Shielding

Normally a cyclotron is placed in a vault made of standard concrete (density 2.35 g/cm^3). The thickness is determined by the estimated flux of neutron and gamma radiation and is in accordance with the local radiation safety regulations, but generally the thickness will be around 1.5 m [7, 8]. Some

Table 3. Shielding for commercial cyclotrons with $E_p < 20$ MeV.

Cyclotron		Vault	Local shielding
CTI	RDS111	optional	standard
	Eclipse	optional	standard
EBCO	TR14/TR19	yes	optional
GE	PETtrace	yes	no
	MINItrace		standard
IBA	10/5-18/9	yes	optional
Sumimoto	HM-18	yes	no
	HM-12	yes	optional
	MINItrace		standard

companies also offer a local shielding by placing concrete and lead as a jacket around the cyclotron, see Table 3. Cyclotrons with this type of local shielding are sometimes advertised as "self-shielded" cyclotrons. The main advantage is that the total weight will be lower than that of a vault. The choice between the two options will depend on the local situation.

Conclusions

The decisive parameters in acquiring a cyclotron for the four most used PET radionuclides i.e. ^{11}C, ^{13}N, ^{15}O and ^{18}F are:

- H^- or H^-/D^- cyclotron;
- Beam energy, $E_p = 10$ MeV and $E_p = 20$ MeV are the extreme values;
- Target technology: what is the yield in combination with the cyclotron, is the transport of product to a radiochemical laboratory included?
- What is the type of shielding, do the authorities approve, what licenses are required?
- Are radiopharmaceutical units included, do the authorities approve of the production procedures, what licenses are required?
- Service contract, what is necessary in the individual case?
- Estimated cost of the whole package;
- Reliability, how reliable is the total production chain delicered? (at least >90% is recommended).

If a more versatile radionuclide production cyclotron is desired, a 30 MeV proton cyclotron has to be considered.

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