19 Basic Principles of Cyclotron and Production of Positron-Emitting Isotopes

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What is a Cyclotron?

Cyclotron is a type of particle accelerator which accelerates charged particles using a high-frequency, alternating voltage (potential difference). A perpendicular magnetic field of constant magnitude and direction causes the particles to spiral almost in a circle so that they re-encounter the accelerating voltage many times. A cyclotron body consists of electrodes, called "dees" because of their shape, in a vacuum chamber. This vacuum chamber is flat and sits in a narrow gap between poles of a large magnet which creates a perpendicular magnetic field. A stream of charged particles is fed into the center of the chamber and a high-frequency alternating voltage is applied across the electrodes. This voltage alternately attracts and repels the charged particles causing them to accelerate. The magnetic field moves the particles in a circular path and, as they gain more energy from the accelerating voltage, they spiral outwards until they reach the outer edge of the chamber.

Inside the cyclotron, there are two D-shaped regions known as dees. In each dee, there is a magnetic field perpendicular to the plane of the page. In the gap separating the dees, there is a uniform electric field pointing from one dee to the other. When a charge is released from rest in the gap, it is accelerated by the electric field and carried into one of the dees. The magnetic field in the dee causes the charge to follow a half-circle that carries it back to the gap. While the charge is in the dee, the electric field in the gap is reversed, so the charge is once again accelerated across the gap. The cycle continues with the magnetic field in the dees continually bringing the charge back to the gap. Every time the charge crosses the gap, it picks up speed. This causes the half-circles in the dees to increase in radius, and eventually the charge emerges from the cyclotron at high speed (Fig. 19.1).

Historical Developments

The first cyclotron, built in 1930 by Ernest Lawrence and Stanley Livingston, was 4.5" (11 cm) in diameter and capable of accelerating protons to an energy of 80 keV. Lawrence soon went on to construct higher-energy and larger-diameter cyclotrons to provide particle beams for research in nuclear physics. Almost 80 years ago, he and Livingston published a seminal paper in which they described the production of light ions with kinetic energies in excess of 1 MeV using a device with magnetic pole pieces 28 cm across (Lawrence and Livingston 1932). By 1936, John Lawrence, Ernest's brother, had made the first recorded biomedical use of a cyclotron when

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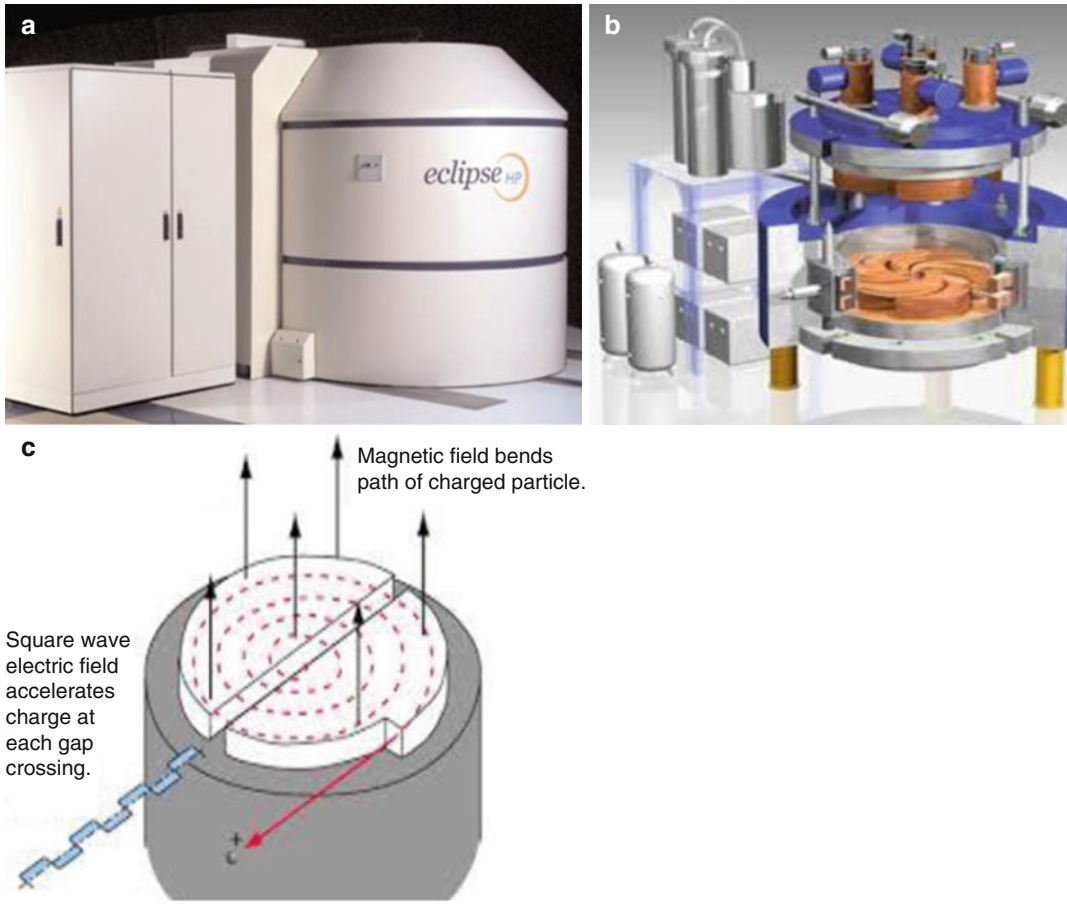

Fig. 19.1 Outward view of a cyclotron (**a**), inside view (**b**), and schematic diagram of functioning (**c**)

he used the 36" (91 cm) machine at Berkeley to produce ^{32}P for the treatment of leukemia. Since then, the physics design of the cyclotron has improved rapidly, with the introduction of alternating-gradient sector focusing, edge focusing, external ion-source injection, electron cyclotron-resonance sources, negative-ion acceleration, separated-sector technology, and the use of superconducting magnets.

However, other accelerator designs were evolving even faster, with the construction of the synchrocyclotron, the invention of the synchrotron, of linear accelerators and of particle colliders that were capable of generating the extremely high energies needed by the particle-physics community. The usefulness of the cyclotron appeared to diminish. But, in 1972, the TRIUMF laboratory in Canada turned on the world's largest cyclotron, at 2,000 tonnes with a beam-orbit diameter of 18 m and negative-ion acceleration. Two years later, in Switzerland, PSI brought into commission a large separated sector, 590 MeV proton cyclotron. Both of these machines have contributed to isotope-production programs. But the value of the cyclotron as a method for producing medical isotopes had come under further pressure due to the availability of numerous nuclear research reactors that had high neutron fluxes, large-volume irradiation positions, and considerable flexibility for isotope production. These attributes allowed the production of important radioisotopes such as ^{99}Mo, ^{131}I, ^{35}S, and even ^{32}P more easily and more cost-effectively.

How the Cyclotron Works

A cyclotron consists of two D-shaped regions known as dees. In each dee, there is a magnetic field perpendicular to the plane of the page. In the gap separating the dees, there is a uniform electric field pointing from one dee to the other. When a charge is released from rest in the gap it is accelerated by the electric field and carried into one of the dees. The magnetic field in the dee causes the charge to follow a half-circle that carries it back to the gap.

While the charge is in the dee the electric field in the gap is reversed, so the charge is once again accelerated across the gap. The cycle continues with the magnetic field in the dees continually bringing the charge back to the gap. Every time the charge crosses the gap it picks up speed. This causes the half-circles in the dees to increase in radius, and eventually the charge emerges from the cyclotron at high speed.

The electrodes would be in the vacuum chamber, which is flat, in a narrow gap between the two poles of a large magnet. In the cyclotron, a high-frequency alternating voltage applied across the "D" electrodes (also called "dees") alternately attracts and repels charged particles. The particles, injected near the center of the magnetic field, increase in speed (and therefore energy) only when passing through the gap between the electrodes. The perpendicular magnetic field (passing vertically through the "D" electrodes), combined with the increasing energy of the particles, forces the particles to travel in a spiral path. With no change in energy, the charged particles in a magnetic field will follow a circular path. In the cyclotron, energy is applied to the particles as they cross the gap between the dees and so they are accelerated (at the typical sub-relativistic speeds used) and will increase in mass as they approach the speed of light. Either of these effects (increased velocity or increased mass) will increase the radius of the circle and so the path will be a spiral. (The particles move in a spiral, because a current of electrons or ions, flowing perpendicular to a magnetic field, experiences a force perpendicular to its direction of motion. The charged particles move freely in a vacuum, so the particles follow a spiral path) (Fig. 19.2). The radius will increase until the particles hit a target at the perimeter of the vacuum chamber. Various materials may be used for the target, and the collisions will create secondary particles which may be guided outside of the cyclotron and into instruments for analysis. The results will enable the calculation of various properties, such as the mean spacing between atoms and the creation of various collision products. Subsequent chemical and particle analysis of the target material may give insight into nuclear transmutation of the elements used in the target.

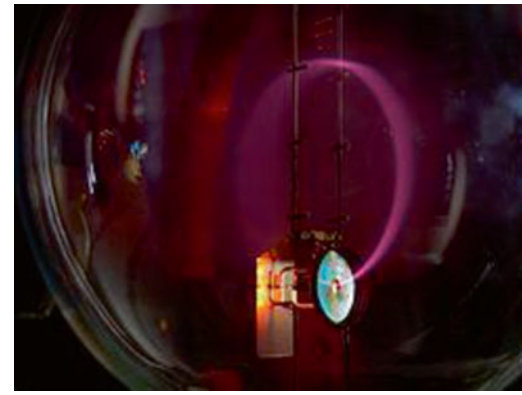

Fig. 19.2 Beam of electrons moving in a circle. Lighting is caused by excitation of gas atoms in a bulb

Production of Positron-Emitting Radiopharmaceuticals

Positron-emitting radioisotopes used in medicine are produced in cyclotrons. The cyclotron is an accelerator of subatomic particles. It produces a large quantity of protons (heavy particles with an electrical positive charge) and gets them moving at an accelerated rate along a circular orbit, inside a chamber controlled by powerful alternating electromagnetic fields. Thus, the particles gain energy and are smashed against a target at nearly the speed of light. The atoms of a substance placed in this target are transformed by this bombardment into radioactive, unstable isotopes, by means of a nuclear reaction.

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their shape, in a vacuum chamber. This vacuum chamber is flat and sits in a narrow gap between poles of a large magnet which creates a perpendicular magnetic field. A stream of charged particles is fed into the center of the chamber and a high-frequency alternating voltage is applied across the electrodes. This voltage alternately attracts and repels the charged particles causing them to accelerate. The magnetic field moves the particles in a circular path and, as they gain more energy from the accelerating voltage, they spiral outwards until they reach the outer edge of the chamber.

Modern cyclotrons accelerate negative ions created in a plasma. When these negative ions reach the outer edge of the chamber, the excess electrons are stripped off the ions forming positive particles such as a proton or deuteron, which can then be extracted from the cyclotron as a beam. The size of the vacuum chamber determines the length of the spiral path and hence the amount of energy attained by the particle.

Medical Cyclotrons

Medical cyclotrons produce proton beams, which are used to manufacture radioisotopes used in medical diagnosis. Radioisotopes produced in a cyclotron decay by either positron emission or electron capture. Positron emission tomography (PET) and single photon emission computed tomography (SPECT), which utilizes the gamma rays associated with electron capture, are two imaging techniques that rely on cyclotron-produced radioisotopes.

Radionuclides used in PET scanning are typically isotopes with short half-lives such as

Carbon-11 (~20 min),
Nitrogen-13 (~10 min),
Oxygen-15 (~2 min),
Fluorine-18 (~110 min)., or
Rubidium-82 (~1.27 min).

These radionuclides are incorporated either into compounds normally used by the body such as glucose (or glucose analogues), water, or ammonia, or into molecules that bind to receptors or other sites of drug action. PET technology can be used to trace the biologic pathway of any compound in living humans (and many other species as well), provided it can be radiolabeled with a PET isotope. Thus, the specific processes that can be probed with PET are virtually limitless, At present, however, by far the most commonly used radiotracer in clinical PET scanning is fluorodeoxyglucose (also called FDG), an analogue of glucose that is labeled with Fluorine-18. This radiotracer is used in essentially all scans for oncology and most scans in neurology, and thus makes up the large majority of all of the radiotracer (>95 %) used in PET and PET-CT scanning.

Due to the short half-lives of most positron-emitting radioisotopes, the radiotracers have traditionally been produced using a cyclotron in close proximity to the PET imaging facility. The half-life of fluorine-18 is long enough that radiotracers labeled with fluorine-18 can be manufactured commercially at offsite locations and shipped to imaging centers. Rubidium-82 generators have also become commercially available. These contain strontium-82, which decays by electron capture to produce positron-emitting rubidium-82.

Limitations to the widespread use of PET arise from the high costs of cyclotrons needed to produce the short-lived radionuclides for PET scanning and the need for specially adapted on-site chemical synthesis apparatus to produce the radiopharmaceuticals after radioisotope preparation. Organic radiotracer molecules that will contain a positron-emitting radioisotope cannot be synthesized first and then the radioisotope prepared within them, because bombardment with a cyclotron to prepare the radioisotope destroys any organic carrier for it. Instead, the isotope must be prepared first, then afterward the chemistry to prepare any organic radiotracer (such as FDG) accomplished very quickly in the short time before the isotope decays. Few hospitals and universities are capable of maintaining such systems, and most clinical PET is supported by third-party suppliers of radiotracers that can supply many sites simultaneously. This limitation restricts clinical PET primarily to the use of tracers labeled with fluorine-18, which has a half-life of 110 min and can be transported a reasonable distance before use, or to rubidium-82 (used as rubidium-82 chloride)

with a half-life of 1.27 min, which is created in a portable generator and is used for myocardial perfusion studies. In recent years, cyclotrons with integrated shielding and "hot labs" (automated chemistry labs that are able to work with radioisotopes) are available to accompany PET units to remote hospitals (Fig. 19.3 and 19.4).

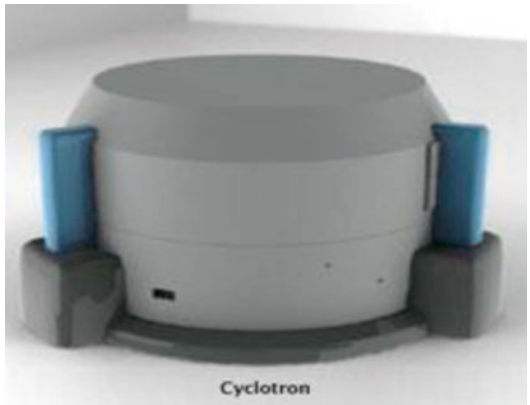

Fig. 19.3 View of a cyclotron used in many nuclear medicine centers to produce positron-emitting radioisotopes to be used locally

Because the half-life of fluorine-18 is about 2 h, the prepared dose of a radiopharmaceutical bearing this radionuclide will undergo multiple half-lives of decay during the working day. This necessitates frequent recalibration of the remaining dose (determination of activity per unit volume) and careful planning with respect to patient scheduling.

PET radiopharmaceuticals are formed by reactions of the organic compounds with radionuclides or positron emission isotopes. They are also called the labeled compounds. So-called tracers, required for the production of the radiopharmaceuticals, are usually produced by an accelerator of the elements, a cyclotron, possibly by a nuclear reactor. 11C, 13N, 15O, and 18F are the most used in positron emission tomography (next only PET) – scanning technology based on a detection of the gamma radiation, appeared because of the annihilation of the positrons emitted by the radioisotopes, made by PET scanners.

An advantage of the positron emission radionuclides is their short half-life time. For

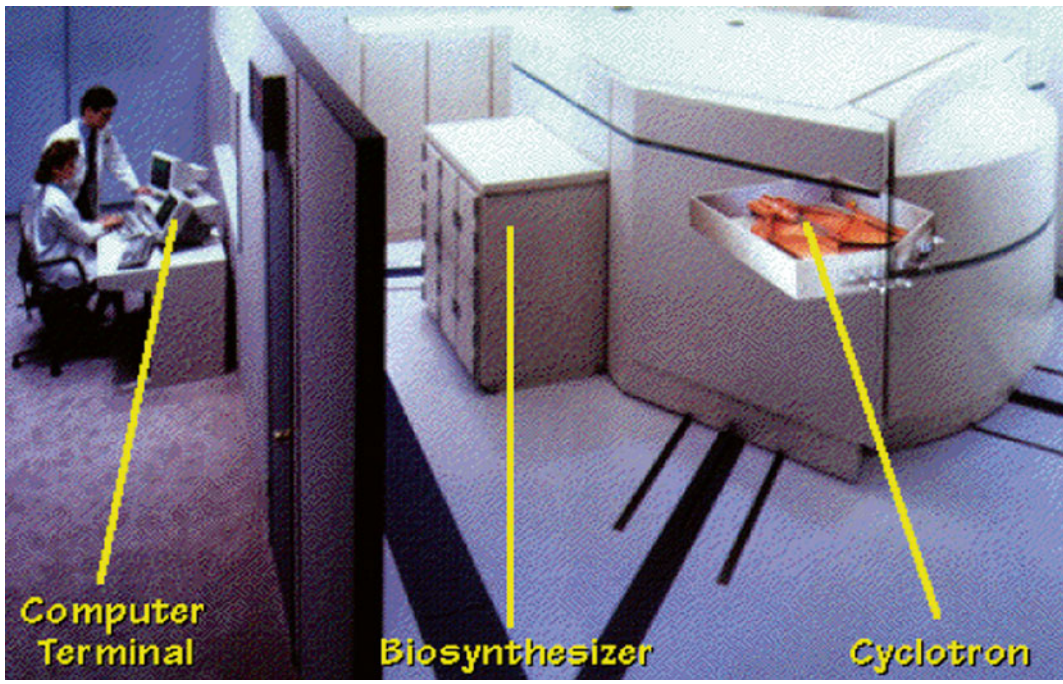

Fig. 19.4 Essential components of a cyclotron facility

that reason, a patient gets much smaller radiation dose then during the other similar medical examinations.

The targets for the preparation of the radiopharmaceuticals can be gases, liquids, and solid materials. The preparation of needed radionuclides precedes the radiopharmaceuticals synthesis. For the preparation of the artificial radionuclides in required amount for a study of chemical and biological processes is necessary to have a high intensity of the bombarding particles flow with the adequate energy.

The cyclotron produce from 1,014 to 1,015 accelerated particles per second. It can be protons, deuterons, hellions, and heavy nuclei. The targets mentioned previously are irradiating with a bunch of the accelerated particles.

Preparation of the [18F] FDG and the [18F] MISO

Irradiated water [18O] H_2O is evaporated in the presence of a cryptand (aminopolyether potassium carbonate complex – Kryptofix 222), which affect as a catalyst of stereospecific S_N2 substitution reaction. Dry evaporated mixture with developed 18F- is dissolved in waterless acetonitrile and leaves at 90 °C to react with prepared precursor, an analog of the mannose 1,3,4,6-tetra-O-acetyl-2-triflate-â-D-mannopyranose, so-called the triflate of mannose.

Formed 1,3,4,6-tetra-*O*-acetyl-2-[18F] fluoro-D-glucopyranose hydrolyzes at 110 °C with dilute hydrochloric acid (14 min) and a product [18F] FDG is clarified with ion exchange chromatography. The synthesis lasts for 30 min and radiochemical yield is 65 %. The product has got the molar activity higher than 400 GBqÅ”ìmol-1 [4]. Same procedure is used for the preparation of fluoromisonidazole ([18F] MISO). However, a precursor is used as ananalog of misonidazole. Radiochemical yield is 20 % and it is lower than in [18F] FDG preparation. The activity of a product [18F] MISO is 3.7 GBq (100 mCi).

For Further Reading

1. Lawrence EO. The Evolution of the cyclotron. Noblel Lecture. 1951.
2. Chao AW, Mess KH, Tigner M, Zimmermann F, editors. Handbook of accelerator physics and engineering. 2nd edn. World Scientific Publishing Company. 2013.
3. Pillai MRA. Cyclotron produced radionuclides: physical characteristics and production methods, IAEA technical report no. 468. Vienna: 2009.
4. Hichwa RD, et al. Design of target systems for production of PET nuclides. Nucl Instrum Methods Phys Res. 1989;B40/41:1110–3.
5. Jacobson MS, Hung JC, Mays TL, Mullan BP. The planning and design of a new PET radiochemistry facility. Mol Imaging Biol. 2002;4:119–27.
6. Ruth TJ, et al. Radionuclide production for the biosciences. Nucl Med Biol. 1989;16(4):323–36.