Applied Radiation and Isotopes 125 (2017) 9–14

Contents lists available at ScienceDirect

Applied Radiation and Isotopes

journal homepage: www.elsevier.com/locate/apradiso

On the use of positron counting for radio-Assay in nuclear pharmaceutical production

D. Maneuski[a,*], F. Giacomelli[b], C. Lemaire[b], S. Pimlott[d], A. Plenevaux[b], J. Owens[c], V. O'Shea[a], A. Luxen[b]

[a] SUPA School of Physics and Astronomy, University of Glasgow, Glasgow G12 8QQ, UK
[b] Cyclotron Research Centre, University of Liege, 4000 Liege, Belgium
[c] PET Radiopharmaceutical Production Unit, Gartnavel General Hospital, Glasgow G12 0YN, UK
[d] School of Medicine, University of Glasgow, Glasgow G12 8QQ, UK

ARTICLE INFO

Keywords:
Timepix
Medipix
F18
FDG
Nuclear detector
Positron
PET
Radiopharmaceutical

ABSTRACT

Current techniques for the measurement of radioactivity at various points during PET radiopharmaceutical production and R & D are based on the detection of the annihilation gamma rays from the radionuclide in the labelled compound. The detection systems to measure these gamma rays are usually variations of NaI or CsF scintillation based systems requiring costly and heavy lead shielding to reduce background noise. These detectors inherently suffer from low detection efficiency, high background noise and very poor linearity. They are also unable to provide any reasonably useful position information.

A novel positron counting technique is proposed for the radioactivity assay during radiopharmaceutical manufacturing that overcomes these limitations. Detection of positrons instead of gammas offers an unprecedented level of position resolution of the radiation source (down to sub-mm) thanks to the nature of the positron interaction with matter. Counting capability instead of charge integration in the detector brings the sensitivity down to the statistical limits at the same time as offering very high dynamic range and linearity from zero to any arbitrarily high activity.

This paper reports on a quantitative comparison between conventional detector systems and the proposed positron counting detector.

1. Introduction

PET radiopharmaceuticals are produced as diagnostic agents for numerous clinical areas in medical imaging. A detailed review of the radiopharmaceutical production process can be found in (Sampson, 1999). In brief, the production process involves incorporating a radionuclide, that can be produced by numerous different methods i.e. on a cyclotron or on a radionuclide generator, into a biological molecule. Automated synthesisers are used to remotely perform the radiolabelling of molecules in lead lined hotcells to reduce operator exposure to radiation. Once the radiolabelling is complete the PET radiopharmaceutical needs to be purified, often using high performance liquid chromatography (HPLC) and formulated into a patient injection. Calibrated ionisation chambers are then used to measure the final radioactive concentration of a final patient vial (single or multi dose vials). Before a radiopharmaceutical can be released for patient use a number of quality control tests need to be conducted to ensure the product quality is acceptable. For example, a gamma spectrometer is used to determine the identity of the radionuclide present and the radionuclide purity. Determination of radiochemical purity is also required using radiodetection and either HPLC or thin layered chromatography (TLC). Typically, a radiopharmaceutical with a radiochemical purity of greater than 95% is considered acceptable for patient injection.

Current techniques for the measurement of radioactive content (RAC) of PET radiopharmaceuticals at various stages through the production process are based on the detection of the annihilation gamma rays from the positrons emitted from the active radionuclide in the radiopharmaceutical (reviewed by (Cherry)). The detectors required to measure these photons with high precision are bulky and provide little or no position resolution due to the elevated energy of the gamma ray 511 keV which requires the detector to be made from high Z materials and have a minimal size in order to maintain a reasonable detection efficiency. For example, high density scintillators such as NaI and CsF with photomultiplier tubes (PMTs) are currently used to measure radiochemical purity but these suffer from poor linearity at

* Corresponding author.
E-mail address: dima.maneuski@glasgow.ac.uk (D. Maneuski).

http://dx.doi.org/10.1016/j.apradiso.2017.03.021
Received 30 June 2016; Received in revised form 9 March 2017; Accepted 22 March 2017
Available online 24 March 2017

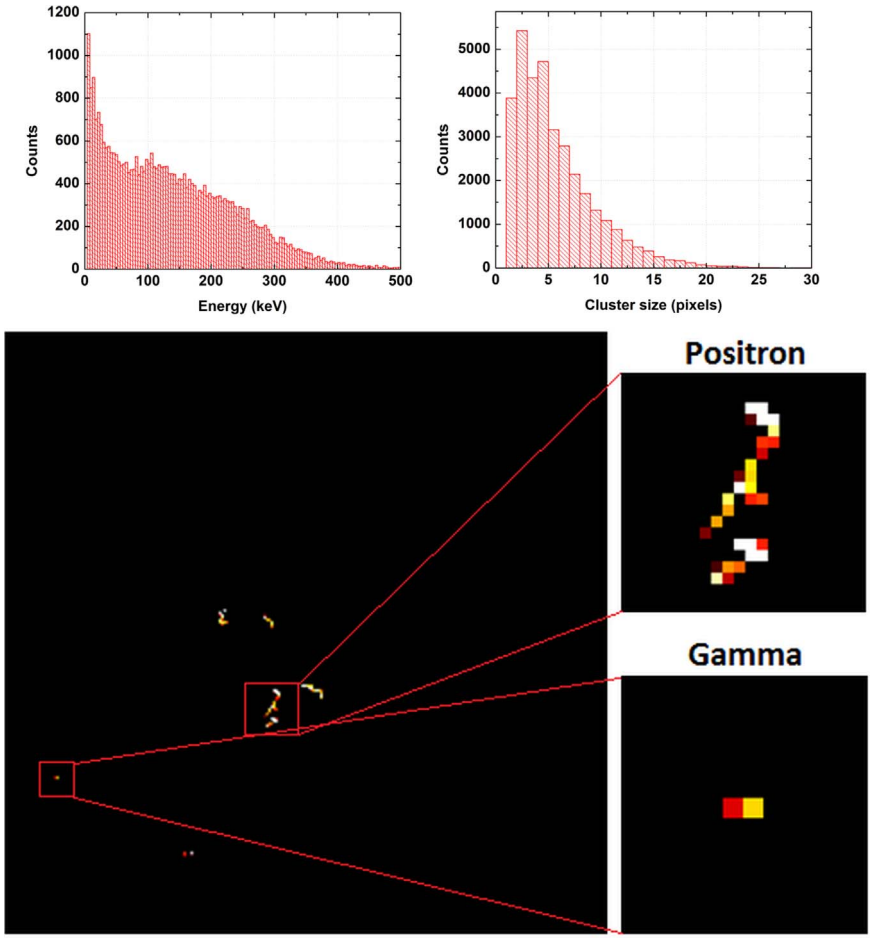

Fig. 1. Distribution of positron energy incident on the Timepix detector operated in ToT mode is shown in the top left graph. Note that the spectrum is modified by the loss of energy as the positrons pass through the Teflon tube. The graph on the top right shows the average number of pixels hit per positron for this measurement. The panel below depicts single positron and gamma interaction in the detector operating in ToT mode.

high levels of radio activity and poor energy resolution. Furthermore, the configuration of these detectors does not provide any measurement of sample radioactivity as a function of the position of the sample.

The use of a suitably configured silicon pixel detector to measure the positron output directly from a radioactive sample will dramatically improve both the linearity of the measurement and provide relatively precise information about the location of the positrons in applications such as novel micro-fluidic production platforms. The silicon detector measures the charge created by the loss of kinetic energy of the positron as it passes through the silicon. In the case of ^{18}F the positron is emitted from a proton in ^{18}F decaying to a neutron and releasing a positron and a neutrino. The positron energy has a continuous spectrum with an end point of 634 keV and a mean positron energy of 250 keV. This energy is dissipated along the path of the positron according to Braggs Law or until the positron annihilates. For each 3.6 eV deposited in the silicon an electron hole pair is created and so the passage of the positron may be detected by measuring this charge. The spatial resolution of this measurement is only limited by the spatial resolution of the pixel detector used and does not depend on measuring the total path of the positron in the silicon (although this can also be improved by measuring the energy deposition per pixel and fitting to a Bragg curve). Monte Carlo simulations show that 87% of incident positrons each with a kinetic energy of 635 keV will pass through 300 μm of silicon leaving about 60 keV of energy in the detector material. As the energy of the incident positron decreases, the specific energy loss (outside the Bragg peak) in the detector increases. The detection of 60 keV energy loss in the silicon is easily registered in an optimized pixel detector where each pixel is sensitive to energy losses of a few keV deposited in the pixel volume.

The use of positron counting offers several advantages in the field of radiopharmaceutical production as the actual positrons are very easily absorbed by a little material (unlike the gamma rays they produce) and so may be very effectively shielded. This enables the use of very compact (e.g. micro-fluidic) devices for the production that could have several assay points measured on a single detector - each being very well isolated from the other through judicious design of the production device layout. Such a concept has been demonstrated in (Thonon, 2013), but its usability is limited to radio-HPLC application only.

The purpose of this article is to demonstrate the potential of this type of measurements for the effective assay of RAC in radiopharmaceutical R & D and routine production. The principle difficulty is to find an appropriate method to present the positrons to the detector as any intervening material can easily absorb the positrons leaving the detector to count only the gamma induced background. Silicon is largely insensitive to photons with an energy above 20 keV and so the detector counts primarily scattered photons when the positrons are absent. As these are created all about the active sample there is no spatial distribution across the surface of the detector. This is not the case when a source of positrons that can impinge on the detector is near its sensitive volume.

2. Materials and methods

2.1. Positron counting detector

The detection system used for these measurements was a 300 μm