Atlas of Science
another view on science
https://atlasofscience.org

Toward more accessible PET imaging: Miniaturizing the last step of radiotracer preparation

Positron emission tomography (PET) is a 3D body imaging method for visualizing dynamic biochemical processes in living subjects with unparalleled specificity and sensitivity. PET scans, often performed together with CT or MRI imaging, are used clinically to diagnose disease, as well as to predict and monitor response to therapy. PET is also an indispensable research tool for uncovering mechanisms of various diseases and for developing new drugs or treatment approaches. Prior to a PET scan, a tiny amount of a short-lived compound known as a 'radiotracer' is injected into the patient that circulates through the bloodstream. The tracer is designed to home in on a certain biological target (receptor or enzyme), which allows the target distribution in the body to be observed with a PET scanner.

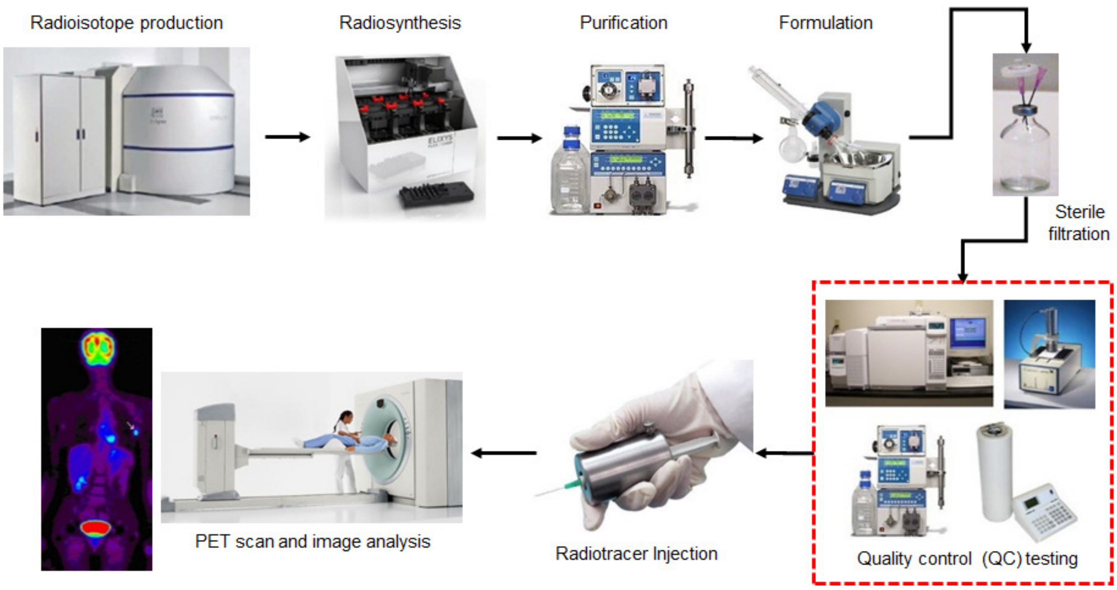

Fig. 1. Production of radiotracers for clinical PET imaging.

Production of radiotracers is a multi-step process, involving radiolabeling, purification to remove unwanted side-products, formulation into an injectable solution, and stringent quality control (QC) testing to ensure patient safety as required by regulatory agencies (Fig. 1). Unlike ordinary pharmaceuticals, the short lifetime of radiotracers requires them to be produced in relatively small batches close to the geographical location where the patient is scanned, and, for every batch, a whole set of QC tests must be rapidly performed. Recently, there has been interest to use microfluidic technology to transform the practice of radiotracer production to make tracers much more affordable through reductions in instrument cost, consumption of expensive reagents, lab space requirements, and operation time. While many steps of tracer production have been miniaturized, there has been relatively little development of microscale systems for the critical QC testing step, including assessment of the chemical and radiochemical purity and identity of the tracer. These are among the most complex of the required QC tests, as they differ for each tracer; they also require bulky and expensive high-performance liquid chromatography (HPLC) equipment since high-resolution separation and high-sensitivity detection are needed to ensure the levels of multiple impurities (some that are chemically similar to the radiotracer) can be measured.

We have been exploring the use of capillary electrophoresis (CE) as an alternative technique to HPLC, due to the potential for drastic miniaturization using microchip electrophoresis (MCE) and the possibility to significantly reduce the size, cost, and complexity of automated QC testing systems and their operation. Previously we showed for a model system (the tracer [^{18}F]FLT and its impurities) that analysis by CE could achieve separation performance and sensitivity similar to HPLC. In our recent paper, we have developed a miniaturized, fully-automated MCE-based system for radiotracer analysis, comprising a sample injection chip, a separation capillary, and an optical detection chip (Fig. 2). The novel injection chip operates analogously to an HPLC injection valve to solve the well-known problems with MCE injection methods that would otherwise prevent the use of MCE for testing of radiotracers for clinical use. On the detection side, an “extended optical path” design was implemented to increase the interaction of the UV light with the sample to increase the absorbance signal. Using the same model compounds as our earlier study, we demonstrated that the ultra-compact MCE system is capable of similar separation and sensitivity performance as HPLC and has repeatability (1%) that is suitable for clinical use (<2% required). Due to the flexibility of CE, this microfluidic approach can test a wide range of radiopharmaceuticals.

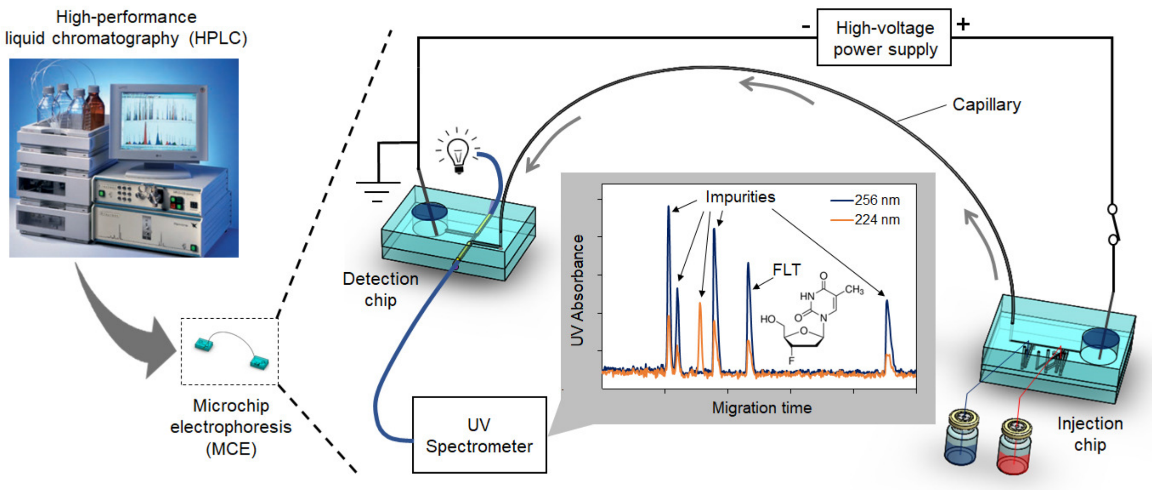

Fig. 2. Miniaturization of QC testing instrument using microfluidics technology instead of HPLC. The prototype MCE system enables rapid separation and detection of impurities in PET radiotracer preparations (e.g. FLT) with high repeatability and minimal sample consumption.

Addition of a miniaturized radiation detector in addition to the UV detector would enable analysis of radiochemical identity and purity in the same device. Furthermore, with integration of other QC testing devices it will become possible for a single compact device to perform the complete set of QC tests to assess the safety of batches of radiotracers. Combined with miniaturized technologies for the radiotracer synthesis, purification, and formulation, these technologies could potentially reduce the overall PET tracer production cost and minimize radiation exposure to radiochemists.

***Noel S. Ha** [1,2], **R. Michael van Dam** [1]*
[1]Crump Institute for Molecular Imaging, David Geffen School of Medicine, University of California Los Angeles (UCLA), Los Angeles, CA, USA
[2]Biological systems and Engineering, Lawrence Berkeley National Laboratory, 1 Cyclotron Road, Berkeley, California, USA

Publications

Toward miniaturized analysis of chemical identity and purity of radiopharmaceuticals via microchip electrophoresis.
Ly J, Ha NS, Cheung S, van Dam RM
Anal Bioanal Chem. 2018 Mar

Novel volumetric method for highly repeatable injection in microchip electrophoresis.
Ha NS, Ly J, Jones J, Cheung S, van Dam RM
Anal Chim Acta. 2017 Sep 8