Pixelated scintillator-based compact radio thin layer chromatography scanner for radiopharmaceuticals quality control

S.J. Jeon, K.M. Kim, I. Lim, K. Song and J.G. Kim

Korea Institute of Radiological and Medical Sciences, Seoul 01812, Republic of Korea

E-mail: jgkim@kim.re.kr

ABSTRACT: We evaluated a compact and cost-effective radio thin-layer chromatography (radio-TLC) scanner for the quality control (QC) of radiopharmaceuticals. We adapted a scintillation detector, which is a Gd$_3$Al$_2$Ga$_3$O$_{12}$ (GAGG:Ce) scintillation crystal array coupled with a photodiode array. The performance of the scintillator array-based radio-TLC was compared with that of a commercial device. We scanned 1 µCi/µL of Tc-99m and F-18 with each device. The difference between the ROI count ratios of the developed and commercial scanners was less than 1.2%. Our scanner is sensitive enough to take measurements for a radiochemical purity test.

KEYWORDS: Gamma detectors (scintillators, CZT, HPG, HgI etc); Detector design and construction technologies and materials; Pixelated detectors and associated VLSI electronics; Models and simulations
1 Introduction

Radiopharmaceuticals are a group of pharmaceutical drugs that emit radiation for diagnosis and therapy. It is very important for radiopharmaceuticals to undergo strict quality control (QC) procedures. One of these procedures involves testing the radiochemical purity. Radio-thin layer chromatography (radio-TLC) is an accurate, simple, and user-friendly method for analyzing the purity [1, 2]. The radio-TLC method consists of three steps: spotting, development, and visualization. Spotting consists of placing a small amount of radiopharmaceutical on one end of a thin film. Development consists of placing the bottom of the thin film into a solvent that is drawn up the thin film by capillary action. Different components in the radiopharmaceutical move different distances from the original location and show up as separate spots. During the visualization step, a radio-TLC scanner is used.

The radio-TLC scanner generally shows a graph of the gamma radioactivity count with position information emitting by radiopharmaceutical components, including a specific radioisotope. The purity is analyzed according to the ratio of the distance from the original spot and radioactivity. Figure 1 is an example of the radiochemical purity determination of a 99mTc-labeled compound by radio-TLC method using two different solvents, saline and acetone. The most common impurities in radiopharmaceuticals remain at the origin or migrate with the solvent front (SF). This method guarantees the quantitative accuracy and reproducibility for chemical stability and changes to a target radiopharmaceutical [2–4].

At present, the most common radio-TLC scanners are made from a gas-filled proportional counter and operate with a continuous supply of counting gas. These gas-based radiation detectors need continuous maintenance and periodic calibration.

In this study, we developed a new type of radio-TLC scanner with a solid detector that consists of a scintillation crystal and photodiode. The solid detector is compact in size, has no maintenance costs, and requires no periodic calibration.
2 Methods

The design objective of the proposed radio-TLC scanner was to reduce the size and cost while realizing a sufficient level of performance with a photodiode and scintillation crystal array. Figure 1 shows the design concept of the detector. The minimum sensitivity with an F-18 source was set to about 37 kBq/µL, and the detection area was set to 20 mm (D) × 100 mm (W).

Figure 2. Concept diagram of radiation detector for Radio-TLC.

For this design, we used a silicon photodiode array (Hamamatsu S11866-128-02) with a peak wavelength response of 720 nm and a 128-pixel structure with a pixel area of 0.8 mm (W) × 0.8 mm (H) and gap of 0.2 mm between pixels. The overall width of the photodiode array was 102.4 mm, which was sufficient for the target size of the detection area. Spectral matching between the scintillator emission spectrum and spectral response range of the photodetector is the most frequently used characteristic to ensure high sensitivity of the scintillation detector. In order to choose the appropriate scintillation crystal, we analyzed four kinds of scintillator coupled photodiodes through calculations and measurements with 37 kBq/µL of F-18. The crystals were GAGG:Ce, LYSO:Ce, BGO, and CsI:Tl); the properties are presented in table 1 and figure 3 [5–13]. They had equal dimensions of 3 mm (W) × 3 mm (D) × 20 mm (H), as shown in figure 4.
Figure 3. Emission spectra of the scintillation crystals and spectral response of S11866-128 photodiode array.

Table 1. Scintillator properties.

| Properties               | GAGG | LYSO | BGO  | CsI:TI |
|--------------------------|------|------|------|--------|
| Density (g/cm$^3$)       | 6.63 | 5.4  | 7.13 | 4.51   |
| Peak emission (nm)       | 520  | 420  | 480  | 550    |
| Decay time (ns)          | 90   | 40   | 300  | 1000   |
| Luminosity (photons/MeV) | 57,000 | 34,000 | 8,000 | 52,000 |
| Hygroscopic              | No   | No   | No   | Slightly |

Figure 4. Structure of scintillation detector.

The performance of the scintillation detector is determined by spectral matching of the scintillation crystal and photodiode. The spectral matches were compared according to the photocurrent of each scintillation detector. The photocurrent $I_{ph}$ is given by

$$I_{ph} = W \times S$$  \hspace{1cm} (2.1)

Where $S$ is the spectral response of the photodiode (figure 2) and $W$ is the work of emission optical
photons expressed in watts [14]. $W$ is calculated as

$$W = E_{ab} \times L \times \lambda \times C \times h$$

(2.2)

Here, $E_{ab}$ is the absorbed gamma-ray energy in the scintillation crystal expressed in electronvolts and calculated by using the MCNPX Monte-Carlo simulation code. $L$ is the luminosity of the crystal (table 1), and $\lambda$ is the wavelength of the optical photons emitted from each scintillation crystal (figure 2). $C$ and $h$ are the speed of the photon and Planck’s constant, respectively.

We calculated the photocurrent of each scintillation detector with 37 kBq of F-18 by using eqs. (2.1) and (2.2). To measure the performances of the four types of scintillation detectors, we developed a photodiode array-based detection system, which includes a detector driver circuit, signal processing, and a data acquisition (DAQ) board (figure 5).

![Figure 5. Block diagram of detection system.](image)

The photodiode driver circuit has two input pulses and two output pulses. The input pulses are a clock and reset pulse for operation timing. The clock pulse determines the signal charge integration time for operation in the order of each pixel, and the reset pulse determines when the operation starts and ends. The two outputs are the charge integrated signal of each pixel and a trigger signal [15, 16]. We used 16-bit 250 kS/s signal processing and a DAQ board with Lab View software. We set up an operating cycle of 128 pixels per second. Every second, the data of 128 channels were processed and transferred to a PC. We measured the four types of scintillation detectors for 1 min with 37 kBq/µL of F-18.

3 Results

3.1 Pixelated detector design

The calculated photocurrents and the measured count rates allow us comparing the performance of each scintillation detector. Figure 6 shows the photocurrent with the spectral response, and table 2 presents the calculated and measured values. The GAGG:Ce coupled photodiode showed the best photocurrent and count rate. Although the BGO and the LYSO:Ce showed the highest gamma ray absorption, the low luminosity and spherical response matching with the photodiode
Figure 6. Calculated photocurrent of scintillator coupled photodiode.

Table 2. Calculated and measured data of scintillator coupled photodiode with 37 kBq of F-18.

| Crystal    | Calculation | Measurement |
|------------|-------------|-------------|
|            | Absorption energy (MeV/µCi) | Photon emission (# of photons) | Photocurrent @PD (pA) | ADC count (count/s) |
| GAGG:Ce    | 1808.0      | 103,058,394 | 3.8 | 746 |
| LYSO       | 2362.1      | 80,310,720  | 2.1 | 0  |
| BGO        | 2808.8      | 22,470,544  | 0.7 | 0  |
| CsI:Tl     | 1196.4      | 62,214,464  | 2.2 | 0  |

produced a poor photocurrent. Based on these results, we decided on the GAGG:Ce crystal for the radio-TLC detector.

After deciding the crystal material, we designed the optimal geometry of the crystal array for good spatial resolution and detection efficiency by using a MCNPX simulation with 37 kBq of F-18 as the radiation source. The MCNPX code was used to investigate the optical photons created from various sizes of GAGG crystal arrays. The simulated photon emissions were converted to incident optical photons into the photodiode pixel detector.

GAGG:Ce crystal arrays (0.6 mm (W) × 20 mm (H) × 1–5 mm (D) × 128 crystals, 1.4 mm (W) × 20 mm (H) × 1–5 mm (D) × 64 crystals) were modeled in the simulation. Each crystal was polished and separated by 0.2 mm thick white reflectors. The depth was fixed according to the size of the chromatogram film, and the width was determined from the photodiode pixel size. The value of 0.6 mm (W) is the width of one photodiode pixel, and the value of 1.4 mm (W) is two pixels and the gap between them.

Figure 7 shows the incident optical photons on a photodiode pixel that were emitted from GAGG crystal arrays of several sizes. To determine the crystal geometry, we set the data of the 3 mm (W) × 20 mm (H) × 3 mm (D) × 33 crystals array (black line in the figure) to the minimum value of the incident optical photons. As described in section 2, the calculated photocurrent and experimental data indicated that the target sensitivity was satisfied. The green and red points represent the simulated data of the 0.6 mm (W) × 20 mm (H) × 1–5 mm (D) × 128 crystals array and
Figure 7. Simulated data of incident optical photons on a photodiode surface.

Figure 8. Simulated spatial resolution data of the GAGG crystal arrays.

1.4 mm (W) × 20 mm (H) × 1–5 mm (D) × 64 crystals array. All of the points at 0.6 mm (W) had lower incident optical photons than 3 mm (W). Over a depth of 3 mm with 1.4 mm (W) × 20 mm (H), the optical photons showed sufficient intensity.

Figure 8 shows the spatial resolution simulation data of the crystal arrays. The 1.4 mm (W) × 20 mm (D) × 3 mm (H) scintillator array had the best full width at half maximum (FWHM) among the 3–5 mm (H) scintillator arrays. We decided upon a 1.4 mm (W) × 20 mm (D) × 3 mm (H) × 64 pixels array for the GAGG crystal, as shown in figure 9.

We developed and designed a GAGG crystal-based scintillation detector and used electronic boards. The fabricated compact radio-TLC device was designated as RT-102. RT-102 has the compact size of 166 mm (W) × 142 mm (D) × 71 (H) mm. Figure 10 shows a photo comparing the size of RT-102 with the commonly used radio-TLC scanner (Bioscan AR-2000).
3.2 Radio-TLC performance test

In order to test the performance of RT-102, we used 1 µCi/µL of Tc-99m and F-18 solutions. Spots of radioisotope (RI) solutions were placed on 10 mm × 100 mm pieces of paper made from pressed cellulose fibers. Volumes of 1 µL RI solution were placed at three spots at equal distances from each other.

We scanned each sample by using RT-102 and AR-2000 and compared the ROI count ratio and position data. To compare the peak position, we calculated the distance ratio of each peaks. Figures 11 and 12 show the chromatogram scanning data of the Tc-99m and F-18 spots. The spatial
Figure 11. Chromatogram scanning data of Tc-99m.

Figure 12. Chromatogram scanning data of F-18.

Table 3. ROI count analysis data from figures 10 and 11.

| Isotope | Device | 1st % ROI (FWTM) | 2nd % ROI (FWTM) | 3rd % ROI (FWTM) |
|---------|--------|-----------------|-----------------|-----------------|
| Tc-99m  | AR-2000| 32.1            | 35.0            | 32.9            |
|         | RT-102 | 31.3            | 36.2            | 32.5            |
| F-18    | AR-2000| 32.2            | 30.4            | 37.5            |
|         | RT-102 | 31.1            | 31.8            | 38.1            |

resolution of RT-102 was poor compared to AR-2000 but showed good results regarding the ROI count ratio and position of each peak.

Table 3 presents the calculated ROI count ratio of each peak. The difference between the ROI count ratios of RT-102 and AR-2000 was less than 1.2%. Table 4 present each peak position and the calculated distance ratios. All of the peak distance ratios were approximately equal to 1:1 (0.96:1–1:1).
Table 4. Peak position analysis data from figures 10 and 11.

| Isotope | Device | Peak position (mm) | (2\textsuperscript{nd}–1\textsuperscript{st}):/(3\textsuperscript{rd}–2\textsuperscript{nd}) |
|---------|--------|-------------------|----------------------------------|
|         |        | 1\textsuperscript{st} | 2\textsuperscript{nd} | 3\textsuperscript{rd}       |
| Tc-99m  | AR-2000| 15.99             | 52.98             | 91.50             | 0.96:1            |
|        | RT-102 | 20.80             | 54.40             | 88.00             | 1:1               |
| F-18    | AR-2000| 17.49             | 53.49             | 85.99             | 1.1:1             |
|        | RT-102 | 16.00             | 52.80             | 86.40             | 1.1:1             |

4 Conclusions

We developed the RT-102 radio-TLC based on a GAGG crystal array. Compared with AR-2000, RT-102 showed poor spatial resolution but a nearly equal ROI count ratio and peak distance ratio. The purity of radiopharmaceuticals is analyzed according to the ROI ratio and peak distance ratio from chromatogram measurements. Therefore, RT-102 provides sufficient performance to measure the radiochemical purity and has several advantages compared with commercial radio-TLC scanners, such as a compact size, no gas usage, and lower cost.

Acknowledgments

This study was supported by a grant of the Korea Institute of Radiological and Medical Sciences (KIRAMS), funded by Ministry of Science and ICT (MSIT), Republic of Korea (1711045543;1711045540/50462-2017).

References

[1] P.F. Sharp, H.G. Gemmell and A.D. Murray, *Practical nuclear medicine*, 3\textsuperscript{rd} edition, Springer, Berlin Germany (2005).
[2] G.B. Saha, *Fundamentals of nuclear pharmacy*, Springer, Berlin Germany 2003
[3] I. Zolle, *Technetium-99m pharmaceuticals*, Springer, Berlin Germany (2007)
[4] V.S. Loveless, *Quality control of compounded radiopharmaceuticals*, University of New Mexico Health Science Center, U.S.A. (2009).
[5] P. Lecoq et al., *Inorganic scintillators for detector system*, Springer, Berlin Germany (2006).
[6] K.S. Shoji, *Czochralski growth of Gd3(Al5−xGax)O12(GAGG) single crystals and their scintillation properties*, *J. Cryst. Growth* 393 (2014) 134.
[7] J. Jiang et al., *A prototype of aerial radiation monitoring system using an unmanned helicopter mounting a GAGG scintillator Compton camera*, *J. Nucl. Sci. Technol.* 53 (2016) 1069.
[8] J. Bok et al., *GAGG:Ce single crystal line films: new perspective scintillators for electron detection in SEM*, *Ultramicroscopy* 163 (2016) 1.
[9] M. Nikl, *Scintillation detectors for X-rays*, *Meas. Sci. Technol.* 17 (2006) R37.
[10] A. Yoshikawa, V. Chani and M. Nikl, *Czochralski growth and properties of scintillating crystals*, *Acta Phys. Pol. A* 124 (2013) 250.
[11] T. Yanagida et al., *Positive hysteresis of Ce-doped GAGG scintillator*, Opt. Mater. **36** (2014) 2016.

[12] H.L. Kim et al., *Scintillation properties of the Gd₃Al₂Ga₃O₁₂:Ce crystal*, J. Ceram. Process. Res. **16** (2015) 124.

[13] Y. El-Mohri et al., *Optimization of the performance of segmented scintillators for radiotherapy imaging through novel binning techniques*, Phys. Med. Biol. **59** (2014) 797.

[14] Hamamatsu Photonics K.K., *Photomultiplier tubes. Basics and applications*, Iwata City 438-0193, Shizuoka Japan (2006).

[15] Hamamatsu Photonics, *Driver circuit for photodiode array with amplifier C9118 series*, datasheet, February (2005).

[16] F. Carrió et al., *Evaluation of a commercial photodiode array for radiation detectors readout*, Open Opt. J. **5** (2011) 62.