

## Synthesis of single core/shell type bimodal nanoparticles for the development of novel PET-MRI contrast agents

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### 1. Introduction

Bimodal Nano Particle (BNP) with both radioactive and magnetic properties, can be used as a core production technology of PET-MRI contrast agents. This technique has been attracting attention as a third-generation nuclear medicine diagnostic device.

Generally, the research and development of PET-MRI contrast agents have been focused on the synthesis of chemical labeling compounds, which have developed from synthesizing technology of nuclear medicine contrast agents by ligand binding between magnetic superparamagnetic iron oxide (SPIO) and radioactive labeling compounds.[1,2,3]

But, recently the development of a nanoparticle synthesis method with two different elements into a single core particle can be applied to BNP manufacturing technology, which makes different single heteronuclear elements with radioactive and magnetic properties into a single particle. This type of new contrast agent technology is an excellent research area to have the leading role of technology development in the nuclear medicine imaging contrast agent market and securing the source technology through future R&D.

This present study is devoted to the synthesis of single core nanoparticles combining heterogeneous elements by cold model method using stable isotope material for the fabrication of BNP having both radioactive and magnetic properties. In this, the Fe element was used as a magnetic component for MRI (Magnetic Resonance Imaging) imaging, and the stable isotope Cu ion was used as the model for  $^{64}\text{Cu}$ ,  $^{67}\text{Cu}$  radioisotope for PET (Positron Emission Tomography) imaging. The nanoparticles were synthesized via hydrothermal reaction performed at  $200^\circ\text{C}$ . Then the recovered hydrophobic nanoparticles surface was converted to hydrophilic surface using tetraethoxysilane. The BNP obtained by this method was confirmed to have an internal particle size of a 6 nm with hydrophilic silica surface.

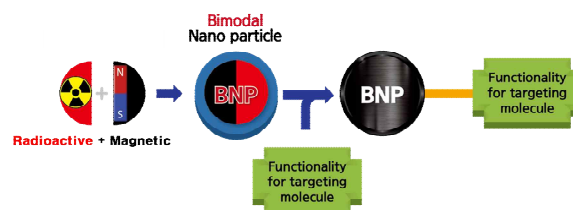


Fig. 1. Synthesis concept scheme of a single core/shell BNP

### 2. Method and Results

#### 2.1 Synthesis process

Copper(II)acetylacetonate(0.261g, 1 mmol), Iron(III)acetylacetonate hydrate (0.352 g, 1 mmol), dodecylamine(0.7ml 3mmol), lauric acid (0.6 g, 3 mmol) and 1,2-hexadecanediol(3.8g, 16mmol) were add in 10 ml diphenyl ether. Then, the mixture was heated up to  $240^\circ\text{C}$  and refluxed for 2 h under Ar atmosphere.

After the reaction, the reactor was cooldown to room temperature and precipitated by adding 5 ml of ethanol

Then, the precipitates were collected, dispersed in 15 ml hexane and centrifugated under 10000 rpm for 10 min to remove residue solvent.

The centrifugation process was repeated thrice and the black color nanoparticles were collected and used for further analysis.

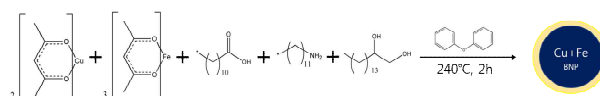


Fig. 2. Synthesis scheme of Cu+Fe nano particle precursor used for the fabrication of core/shell BNP

#### 2.2 Analysis

The particle size of recovered black nanoparticles was analyzed using SEM-image analysis. Figure 3 shows the SEM image of nanoparticles and the particle size was determined using two vertical line highlighted between one particle, where the small bright dot represents a single nanoparticle. From this analysis, the size of nanoparticle was confirmed to be  $\sim 6$  nm.

### 3. Conclusions

The Cu+Fe nanoparticles were synthesized using controlled hydrothermal technique under Ar atmosphere. The elemental and morphological analysis confirmed that the experiment can able to fabricate small Cu+Fe nanoparticles with size of ~ 6 nm and capable for dispersed into small particles.

Thus, this method demonstrates that radioactive Cu and magnetic Fe can be synthesized as a single nanoparticle.

### 4. Acknowledgments

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### REFERENCES

- [1] T. Tang, J. Garcia, and A. Y. Louie, PET/SPECT/MRI Multimodal Nanoparticles, Design and applications of Nanoparticles in Biomedical Imaging Springer, p205- 228, 2017.
- [2] Burke BP, Cawthorne C, Archibald SJ. Multimodal nanoparticle imaging agents: design and applications. *Phil.Trans. R. Soc. A* **375**: 20170261.
- [3] E.A. Salvanou, P. Bouziotis, C. Tsoukalas, Radiolabeled Nanoparticles in Nuclear Oncology, advanced Nano Research, Volume 1, Issue 1, pp. 38-55, 2018

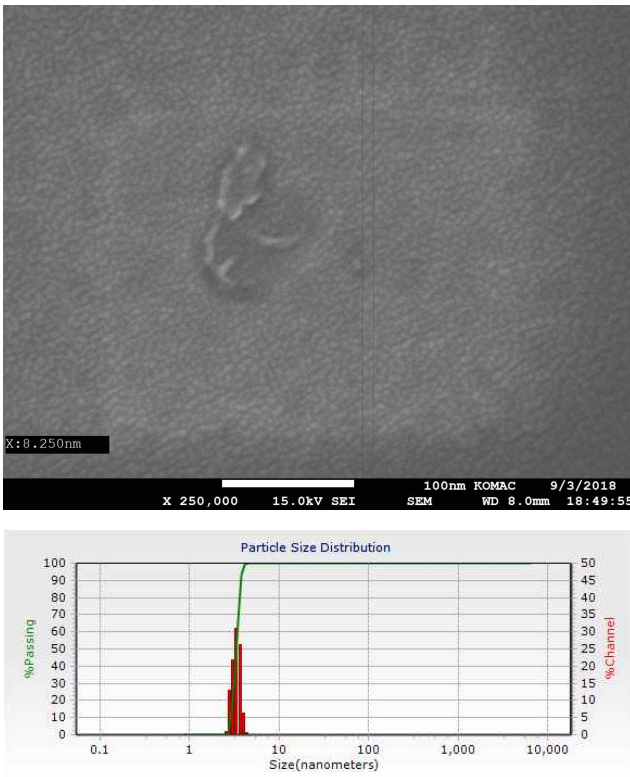
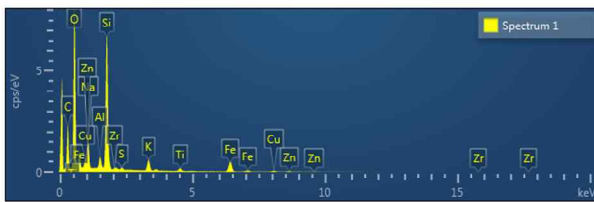


Fig. 3. SEM image and particle distribution ratio analysis of Cu+Fe ion BNP

The presence of various components in the nanoparticles were obtained through EDX analysis. Fig. 4 displays the EDX spectrum of nanoparticles confirming the presence of Cu and Fe element with outer silica surface.



| Element | Line Type | Apparent Concentration | k Ratio | Wt%    | Wt% Sigma | Standard Label | Factory Standard | Standard Calibration Date |
|---------|-----------|------------------------|---------|--------|-----------|----------------|------------------|---------------------------|
| C       | K series  | 0.35                   | 0.00353 | 28.53  | 0.47      | C Vit          | Yes              |                           |
| O       | K series  | 1.82                   | 0.00614 | 39.03  | 0.33      | SiO2           | Yes              |                           |
| Na      | K series  | 0.13                   | 0.00054 | 2.65   | 0.09      | Albite         | Yes              |                           |
| Al      | K series  | 0.04                   | 0.00031 | 0.97   | 0.04      | Al2O3          | Yes              |                           |
| Si      | K series  | 0.59                   | 0.00466 | 12.36  | 0.12      | SiO2           | Yes              |                           |
| S       | K series  | 0.01                   | 0.00011 | 0.28   | 0.03      | FeS2           | Yes              |                           |
| K       | K series  | 0.09                   | 0.00079 | 1.82   | 0.04      | KBr            | Yes              |                           |
| Ti      | K series  | 0.03                   | 0.00034 | 0.82   | 0.04      | Ti             | Yes              |                           |
| Fe      | K series  | 0.29                   | 0.00286 | 6.94   | 0.13      | Fe             | Yes              |                           |
| Cu      | L series  | 0.06                   | 0.00061 | 2.80   | 0.19      | Cu             | Yes              |                           |
| Zn      | L series  | 0.07                   | 0.00071 | 3.26   | 0.21      | Zn             | Yes              |                           |
| Zr      | L series  | 0.02                   | 0.00019 | 0.54   | 0.08      | Zr             | Yes              |                           |
| Total:  |           |                        |         | 100.00 |           |                |                  |                           |

Fig. 4. SEM-EDX image of Cu+Fe ion BNP