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PREPARATION AND CHARACTERIZATION OF [68Ga]NODAGAPAMIDRONIC ACID FOR PET BONE CANCER IMAGING

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By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

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PREPARATION AND CHARACTERIZATION OF [^{68}Ga]NODAGA-PAMIDRONIC ACID FOR PET BONE CANCER IMAGING

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Chair: Nor Azah Yusof, PhD
Faculty: Science

Early detection of bone metastases is essential to prevent skeletal-related events. Unlike biopsies, a non-invasive technique to diagnose bone metastases is by utilizing radiopharmaceuticals and detected using a nuclear imaging modality. Hence, this research deems to determine the role of gallium-68 radiolabeled bisphosphonates ([^{68}Ga]NODAGA-Pamidronic acid) for PET bone cancer imaging. This study aims to ascertain the preparation, characterization, and radiolabeling of [^{68}Ga]NODAGA-Pamidronic acid. Lastly, to determine its potential application, the *in vitro* bone binding assay and *in vivo* bone-to-blood ratio is examined. Firstly, NODAGA-Pamidronic acid (NODPAM) was prepared via the NHS ester conjugation method and characterized using tandem mass spectrometry (MS/MS). The RP-HPLC method was then developed to remove the free NODAGA using 0.1% trifluoroacetic acid and water as the mobile phase at a flow rate of 0.5 ml/ min. Based on the MS/MS analysis of NODPAM, the precursor ion and product ion observed were according to the theoretical value (theoretical $[M-H]^-$m/z: 591.14, obtained $[M-H]^-$m/z: 591.14, $[M-H-H_3PO_3]^-$m/z: 509.17). The isotopic abundance M+1 (calculated m/z: 22.02, obtained m/z: 20.99±0.94) confirms the molecular formula $C_{18}H_{34}N_4O_{14}P_2$. The HPLC method developed shows a good separation between peaks with a resolution of 1.613. The freeze-dried NODPAM produces a solid white powder. Next, the radiolabeling of [^{68}Ga]NODPAM was optimized by looking into three parameters; pH, temperature, and amount NODPAM. Finally, the *in vitro* bone binding assay and *in vivo* bone-to-blood ratio was determined using synthetic hydroxyapatite and Sprague Dawley rats, respectively. From the results obtained, the %RCP of radiolabeled [^{68}Ga]NODPAM was above 90% within 15 minutes at pH 4-4.5 and a temperature of above 60ºC. The *in vitro* hydroxyapatite (HA) bone binding assay displayed a significant difference between the [^{68}Ga]NODPAM 82.25%±1.72 and [^{99m}Tc]MDP of 53.21%±0.28 ($p<0.05$). The bone-to-blood ratio of [^{68}Ga]NODPAM 2-hour post-injection was significantly higher ($P<0.05$) compared to ^{68}Ga(III); 27.53 and 0.74, respectively. In conclusion,

[^{68}Ga]NODPAM was prepared and characterized accordingly, and the *in vitro* bone binding assay and *in vivo* bone-to-blood ratio were assessed. The preliminary data suggests that there is a need for a complete pre-clinical study of [^{68}Ga]NODPAM before translating it into clinical research.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

PENYEDIAAN DAN PENCIRIAN [^{68}Ga]NODAGA-PAMIDRONIC ASID UNTUK PENGIMEJAN PET KANSER TULANG

Oleh

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Pengesanan awal metastasis tulang adalah penting untuk mengelakkan dari penyakit yang berkaitan dengan tulang. Tidak seperti biopsi, cara tanpa invasif untuk mendiagnosis metastasis tulang adalah dengan menggunakan radiofarmaseutikal dan diimbas menggunakan modaliti pengimejan nuklear. Oleh itu, kajian ini bertujuan untuk menentukan peranan gallium-68 berlabel bisfosfonat ([^{68}Ga]NODAGA-Pamidronic acid) dalam pengimejan tomografi pancaran positron (PET) kanser tulang. Kajian ini menjurus kepada penyediaan, pencirian, dan pelabelan radio, [^{68}Ga]NODAGA-Pamidronic asid. Akhir sekali, untuk menentukan potensi radiofarmaseutikal ini, ujian *in vitro* ikatan tulang dan ujian *in vivo* nisbah tulang-ke-darah dikaji. Prekursor NODAGA-Pamidronic asid (NODPAM) disediakan melalui kaedah konjugasi N-Hydroxysuccinimide (NHS) ester dan dicirikan menggunakan spektrometri jisim tandem (MS/MS). Kemudian, kaedah fasa terbalik kromatografi cecair (RP-HPLC) dibangunkan untuk mengasingkan NODAGA menggunakan 0.1% asid trifluoroacetic dan air sebagai fasa bergerak pada kadar aliran 0.5 ml/min. Berdasarkan analisis MS/MS NODPAM, nilai ion prekursor dan ion produk yang diperhatikan adalah mengikut nilai teori (teori $[M-H]^-$ m/z: 591.14, diperolehi $[M-H]^-$ m/z: 591.14, $[M-H-H_3PO_3]^-$ m/z: 509.17). Kemudian, kelimpahan isotop M+1 (dikira m/z: 22.02, diperolehi m/z: 20.99±0.94) mengesahkan formula molekul $C_{18}H_{34}N_4O_{14}P_2$. Kaedah RP-HPLC yang dibangunkan menunjukkan pemisahan yang baik antara puncak dengan resolusi 1.613. Prekursor NODPAM yang telah dibeku kering menghasilkan serbuk putih pepejal. Seterusnya, pelabelan radio [^{68}Ga]NODPAM dioptimumkan dengan melihat tiga parameter; pH, suhu, dan jumlah NODPAM. Akhirnya, ujian *in vitro* ikatan tulang dan *in vivo* nisbah tulang-ke-darah ditentukan dengan menggunakan hidroksiapatit sintetik dan tikus Sprague Dawley. Dari hasil yang diperoleh, % RCP pelabelan radio [^{68}Ga]NODPAM berada di atas 90% dalam masa 15 minit pada pH 4-4.5 dan suhu di atas 60ºC. Peratusan *in vitro* ujian hydroxyapatite (HA) ikatan tulang menunjukkan perbezaan signifikan antara [^{68}Ga]NODPAM 82.25%±1.72 dan

[^{99m}Tc]MDP daripada 53.21%±0.28 ($p<0.05$). Nisbah tulang-ke-darah [^{68}Ga] NODPAM pasca suntikan 2 jam jauh lebih tinggi ($P <0.05$) berbanding dengan ^{68}Ga (III); 27.53 dan 0.74. Sebagai kesimpulan, [^{68}Ga]NODPAM telah disediakan dan dicirikan dengan sewajarnya, dan ujian *in vitro* ikatan tulang dan *in vivo* nisbah tulang-ke-darah telah dinilai. Data awal menunjukkan bahawa terdapat keperluan supaya kajian pra-klinikal yang lengkap dilakukan [^{68}Ga]NODPAM sebelum diterjemahkan ke kajian penyelidikan klinikal.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities, as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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LIST OF ABBREVIATIONS

^{68}Ga	Gallium-68
^{68}Ge	Germanium-68
^{99m}Tc	Technetium-99m
BFC	Bifunctional Chelator
BPs	Bisphosphonates
Bq	Becquerel
C18	Octadecyl carbon chain
Ci	Curie
CPM	Counts Per Minute
CT	Computed Tomography
DOTA	1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid
EE	Even Electron ion
ESI	Electrospray Ionization
HA	Hydroxyapatite
HSC	Hematopoietic Stem Cell
k’	Capacity Factor
MDP	Medronic acid
MRI	Magnetic Resonance Imaging
MS	Mass spectrometer
N	Theoretical Plate
NaOAc	Sodium Acetate
NHS	N-hydroxysuccinimide
NODAGA	1,4,7-triazacyclononane,1-gluteric acid-4,7-acetic acid
NODPAM	NODAGA-Pamidronic acid
ºC	Degree Celcius
OE	Odd Electron ion
PET	Positron Emission Tomography
pH	A measure of the hydrogen ion concentration of a solution

ppm	Parts per million
Q	Quadrupole
RA	Relative abundance
RCP	Radiochemical Purity
RDBE	Ring plus double bond equivalent
Ret. time	Retention time
RP-HPLC	Reverse Phase High-Performance Liquid Chromatography
Rs	Resolution
RSD	Relative standard deviation
S	The slope of the calibration curve
SG	Silica Gel
SPECT	Single Photon Emission Computed Tomography
T	Tailing factor
TACN	1,4,7-Triazacyclononane
TLC	Thin Layer Chromatography
TOF	Time-of-flight
UV	Ultraviolet
Vis	Visible

CHAPTER 1

INTRODUCTION

1.1 Research Background

As cancer is one of the leading causes of death worldwide, efforts in providing an accurate diagnosis, especially in cancer staging, are essential for optimizing patient management. There were 18.1 million new cancer cases reported in 2018 (Bray et al., 2018), and it is expected to increase to 22.1 million by 2030 just by growth and ageing of the population. Recently, personalized medicine has played an essential part in preventive and therapeutic care for cancer patients (Verma, 2012). Developments in nuclear medicine have contributed to personalized medicine through new technologies and novel radiopharmaceuticals focusing on targeted therapy as well as therapeutic response assessment (Kraeber-Bodere & Barbet, 2014).

Early detection of bone metastases is important to prevent skeletal-related events. Several imaging modalities, in particular for bone imaging, have been investigated and compared in terms of their sensitivity and specificity (Costelloe, Chuang, & Madewell, 2010). The European guidelines suggest cost-effective single-photon emission computed tomography (SPECT) imaging using [^{99m}Tc]MDP (Figure 1.1) in diagnosing bone metastases. However, SPECT imaging possesses some weaknesses, especially in quantifying treatment response (Azad & Cook, 2016). In addition, the direct-chelation [^{99m}Tc]MDP complex may have contributed to the slow distribution and excretion. Besides, the usage of [^{99m}Tc]MDP in Malaysia was found to be the highest amongst other SPECT radiopharmaceutical (Ahmad Fadzil, Abdul Hamid, Mohd Janib, Kasbollah, & S M Ghazi, 2017; Ibrahim, Zakaria, & Bohari, 2013).

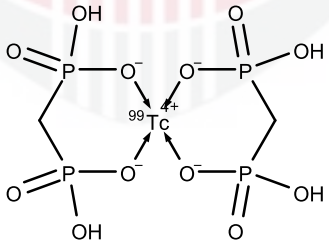

Figure 1.1: Chemical structure of [^{99m}Tc]MDP for SPECT bone imaging

Nevertheless, Positron Emitting Tomography (PET) imaging has emerged as a powerful imaging tool for the detection of various cancers providing accurate patient diagnosis, staging, and restaging (Almuhaideb, Papathanasiou N Fau - Bomanji, & Bomanji, 2011). Besides, the role of a gallium-68 radionuclide has

contributed to personalized medicine through the discovery of lutetium-177 twin for therapy. In which, development of novel gallium-68/ lutetium-177 radiopharmaceuticals has improved therapy selection, predicts adverse effects, and also monitors therapy response (Yordanova et al., 2017).

A recent development in gallium-68 radiolabeled bisphosphonates has been studied potentially for PET bone metastases imaging (Holub, Meckel, Kubíček, Rösch, & Hermann, 2015; Meckel, Bergmann, Miederer, & Roesch, 2017; Passah et al., 2017). Still, it has not been translated into a routine clinical radiopharmaceutical for bone imaging due to a lack of pre-clinical and clinical studies. Nevertheless, there is a need for improving the development of PET bone imaging radiopharmaceutical to meet the current demand in bone imaging, especially in Malaysia.

1.2 Problem Statement

Indeed, the role of PET imaging has undeniably improved cancer patient management and treatment selection. The sensitivity and specificity of PET imaging compared to other imaging modalities have invoked novel radiopharmaceuticals for various indications. Nevertheless, metal-based gallium-68 radiopharmaceuticals have played a vital role in the development of PET imaging. Mainly due to its feasibility, convenience to prepare, and cost-effectiveness. Besides, the gallium-68 radionuclide was found to have a therapeutic pair, which is lutetium-177 and yttrium-90 (Werner, Bluemel, Allen-Auerbach, Higuchi, & Herrmann, 2015).

The generator produced gallium-68 radionuclide has opened a new passage for PET bone imaging. There are two main parameters measured in predicting the potential of a radiopharmaceutical for PET bone imaging; 1) *in vitro* bone binding assay and 2) *in vivo* bone-to-blood ratio. The present [^{99m}Tc]MDP radiopharmaceutical was found to have slow distribution and excretion, which may be due to its direct complexation. Thus indirect chelation in particular for gallium-68 bone radiopharmaceuticals via bifunctional chelator was studied.

Recent findings showed mixed outcomes concerning the discussed field. Radiolabeled [^{68}Ga]DOTA-Alendronic acid did not appear to have an excellent bone-to-blood ratio (Fakhari, Jalilian, Johari-Daha, Shafiee-Ardestani, & Khalaj, 2016). Instead, there was very high kidney retention, which could be due to the presence of unreacted DOTA in the preparation. This may be closely related to the hydrolysis of the DOTA-NHS ester during conjugation.

Further development proves a better outcome with the use of Zoledronic acid and Pamidronic acid as a targeting vector. Both Zoledronic acid and Pamidronic acid has a very excellent bone binding assay (Jahnke & Henry, 2010). The radiolabeled [^{68}Ga]DOTA-Pamidronic acid was found to have a bone binding

assay and an *in vivo* bone-to-blood ratio of > 80%, and >7, respectively (Meckel et al., 2017). Nevertheless, there is still room for improvement by substituting DOTA (Figure 1.2 B), to a more stable bifunctional chelator, such as NODAGA. Not only is it more stable, NODAGA (Figure 1.2 A) radiolabels gallium-68 at a milder condition compared to DOTA. Also, the radiolabeled NODAGA may improve the overall image quality (Ghosh et al., 2015). Hence, in this work, the use of NODAGA bifunctional chelator conjugated to Pamidronic acid would empirically improve previous work for PET bone imaging.

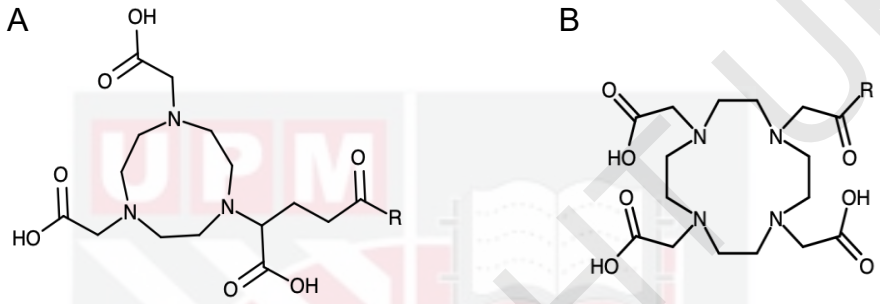

Figure 1.2: Chemical structures of NODAGA (A) and DOTA bifunctional chelator (B)

In order to mitigate issues related to the preparation mentioned earlier, this research aims to develop the RP-HPLC method for separation. In addition, the use of an aprotic organic solvent during conjugation may reduce the NHS Ester hydrolysis. For improvements to current findings, this research deems to investigate the potential of [^{68}Ga]NODAGA-Pamidronic acid for PET bone imaging. It is expected that the indirect chelation of gallium-68 and pamidronic acid via NODAGA chelator improves the in-vitro bone binding assay. Besides, the stability of NODAGA chelator may increase the bone-to-blood ratio, which ultimately enhances image quality.

1.3 Objective

1.3.1 General Objective

The present study aims to determine the potential application of [^{68}Ga]NODAGA-Pamidronic ([^{68}Ga]NODPAM) for PET bone cancer imaging. The [^{68}Ga]NODPAM is proposed based on its high bone binding affinity.

Hence, the objective of this study is to prepare, characterize, radiolabel, and finally perform the *in vitro* and *in vivo* study. To achieve the objective, the following specific objectives are outlined:

1.3.2 Specific Objective

1. To prepare NODAGA-Pamidronic and characterize acid using mass spectrometry technique.
2. To develop the Reversed-Phase-High-Performance Liquid Chromatography method for separation of free NODAGA.
3. To optimize [^{68}Ga]NODAGA-Pamidronic acid radiolabeling condition by looking into the effect of pH, temperature, time, and the amount of NODPAM.
4. To determine the *in vitro* hydroxyapatite bone binding assay and *in vivo* bone-to-blood ratio on Sprague Dawley rats.

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