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EVALUATION OF $^{68}Ge/^{68}Ga$ GENERATOR PRE-ELUTION EFFICIENCY ON METALLIC IMPURITIES IN THE COMPOSITION OF $^{68}GaPSMA$-11 RADIOPHARMACEUTICAL IN NUCLEAR MEDICINE PET CHEMISTRY

NÜKLEER TIP PET KİMYASINDAKİ $^{68}GAPSMA$-11 RADYOFARMASÖTİK BİLEŞİMİNDEKİ METALİK KİRLİLİKLER ÜZERİNDE $^{68}Ge/^{68}Ga$ JENERATÖRÜNÜN ÖN ELÜSYON ETKİNLİĞİNİN DEĞERLENDİRİLMESİ

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ABSTRACT

Objective: The presence of metallic impurities can pose a serious concern due to their interaction with receptor-specific biomolecules that require the highest possible specific activity, especially in radioactive labeling. There are studies in which Zn and other toxic metal pollution increases if the generator is not used for a long time. In this study the effect of pre-elution on chemical and radiochemical impurities in the synthesis product was investigated.

Material and Methods: In the study, $^{68}GaPSMA$-11 labeling was performed with the generator eluate that was not used for one month (sample 1). A blank elution was taken 24 hours after using the generator (sample 2). In the next 24 hours, the second $^{68}GaPSMA$-11 labeling was performed (sample 3). Six hours after this labeling, another $^{68}GaPSMA$-11 synthesis was performed (sample 4). Eluates were analyzed by Inductively Coupled Plasma Mass Spectrometry (ICP-MS).

Results: Results was reported as a table in µg/ml. ^{68}Ge levels determined at 0.018 ppm, 0.012 ppm and 0.009 ppm levels in the labeled products were determined below the pharmacopoeia limits. Zn(II) impurities were found as 0.625 ppm in the labeling performed without generator pre-elution. In generator pre-eluted labelings; Zn(II) impurities were determined as 0.133 ppm and 0.108 ppm.

Conclusion: Pre-elution of the generator prior to synthesis does not seem to be a chemical requirement other than zinc

ÖZET

Amaç: Metalik safsızlıkların varlığı, özellikle radyoaktif etiketlemede mümkün olan en yüksek spesifik aktiviteyi gerektiren reseptöre özgü biyomoleküllerle etkileşimleri nedeniyle ciddi bir endişe oluşturabilir. Jeneratörün uzun süre kullanılmaması durumunda Zn ve diğer toksik metal kirliliğinin arttığı çalışmalar da bulunmaktadır. Bu çalışmada ön elüsyonun sentez ürünündeki kimyasal ve radyokimyasal safsızlıklar üzerindeki etkisi araştırılmıştır.

Gereç ve Yöntemler: Çalışmada, $^{68}GaPSMA$-11 işaretlemesi, bir ay kullanılmayan jeneratör eluatı (örnek 1) ile yapıldı. Jeneratör kullanıldıktan 24 saat sonra boş bir elüsyon alındı (örnek 2). 24 saat içinde, ikinci $^{68}GaPSMA$-11 işaretlemesi gerçekleştirildi (örnek 3). Bu etiketlemeden 6 saat sonra başka bir $^{68}GaPSMA$-11 sentezi gerçekleştirildi (numune 4). Elüatlar, Endüktif Olarak Birleştirilmiş Plazma Kütle Spektrometresi (ICP-MS) ile analiz edildi.

Bulgular: Sonuçlar µg/ml cinsinden tablo olarak rapor edildi. İşaretli ürünlerde 0,018 ppm, 0,012 ppm ve 0,009 ppm seviyelerinde belirlenen ^{68}Ge seviyeleri farmakope limitlerinin altında belirlendi. Jeneratör ön elüsyonu yapılmadan yapılan işaretlemede Zn(II) kirliliği 0,625 ppm bulundu. Önceden yıkanmış jeneratör eluatı ile işaretlemelerde; Zn(II) kirliliği 0,133 ppm ve 0,108 ppm olarak belirlenmiştir.

Sonuç: Jeneratörün sentezden önce ön elüsyonu, çinko kirliliği dışında kimyasal bir gereklilik gibi görünmemektedir.

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pollution. ^{68}GaPSMA-11 can be pre-eluted for high labeling efficiency, but it is thought that pre-elution is not significant in terms of chemical and radiochemical contamination.

Keywords: Radiopharmaceutical product, ^{68}GaPSMA-11, metallic impurities, ^{68}Ge/^{68}Ga generator

^{68}GaPSMA-11, yüksek işaretleme etkinliği için önceden ayrıştırılabilir, ancak ön elüsyonun kimyasal ve radyokimyasal kontaminasyon açısından önemli olmadığı düşünülmektedir.

Anahtar Kelimeler: Radyofarmasötik ürün, ^{68}GaPSMA-11, metalik safsızlık, ^{68}Ge/^{68}Ga jeneratör

INTRODUCTION

Germanium is a rare element; it represents 10-11% of the earth's crust. There are four different stable isotopes of germanium; ^{70}Ge (20,55%), ^{72}Ge (27.37%), ^{73}Ge (7,67%), ^{74}Ge (36,74%). ^{68}Ge can be produced with the reactions ^{75}As(d,α2n) ^{68}Ge(79) or ^{69}Ga(p,2n) ^{68}Ge (80). However, recently a way to produce carrier-free germanium by reaction ^{66}Zn (a, 2n) ^{68}Ge has been obtained by liquid-liquid extraction with CCl_4 and Xylene (1).

The use of ^{68}Ge/^{68}Ga generator systems that do not require cyclotron has been a source of motivation for the evolution of ^{68}Ga-radiopharmacy (2-4). Gallium-68 ($^{68}Ga^{3+}$, β^+=89%, Eβ^+ max=1.90 MeV) is usually obtained through the electron capture decay of germanium-68), absorbed on an appropriate solid phase (i.e. generator produced). The half-life and other physical properties of both mother and daughter nuclei make ^{68}Ge/^{68}Ga generators suitable for clinical application in cyclotron-free imaging facilities. The daughter exists in secular equilibrium with the ^{68}Ga (t1/2=68.1 min), the mother ^{68}Ge (t1/2=271 days) (5).

In the ^{68}Ge/^{68}Ga generator system, ^{68}Ge is loaded into column material based on mineral oxides or organic extracts, and ^{68}Ga can be eluted using acidic media that vary depending on the generator material (6). Injection of $^{68}Ga^{3+}$ in the ionic form results in its very rapid association to native transferrin. The well stable binding requires that $^{68}Ga^{3+}$ radiopharmaceutical preparations be free from metallic impurities to ensure that the background blood radioactivity is as low as possible. With the increase in the age of the generator and the increase in the number of elations performed, the ^{68}Ge value may increase in addition to the regular activity. Metal impurities from the generator may not just be radionuclides. Toxic metals coming from the column material are also among the pollutants which can compete with gallium in the complexation reaction. Zn formation occurs with the decay of ^{68}Ga. It is known that the accumulation of Zn(II) in the generator column is constantly increasing. During equilibrium, when the maximum amount of ^{68}Ga accumulates, the amount of Zn(II) exceeds 10 times of ^{68}Ga. This excess is discarded when the generator is eluted and the ^{68}Ga/Zn(II) ratio is still above after ~2 half-life. Therefore, there are studies showing that regular elution before synthesis reduces the Zn(II) concentration 4-5 times (1, 3). The presence of non-radioactive metals such as Pb, As, Ni, which are considered metallic impurities in the ^{68}Ge/^{68}Ga generator eluate, is known. The presence of these metallic impurities could cause serious concern, particularly due to its interaction in radioactive labeling with receptor-specific biomolecules that require the highest possible specific activity (7). Therefore, secondary purification prior to labeling is an important step in radiopharmaceuticals labeled the used ^{68}Ga for clinical applications (8-10). Different methods used for these processes are based on anion exchange chromatography, cation exchange chromatography, or a combination thereof (11). The intended use of the cation exchange resin is to chemically distinguish between ^{68}Ga(III) and ^{68}Ge(IV). The aim is to quantitatively separate ^{68}Ga on the cartridge from ^{68}Ge completely passed through the cation exchange resin.

Radiolabeled PSMAs are the most important targets for imaging diagnosis and targeted radionuclide therapy of PC and its metastases because of their rapid and effective localization in tumors (12, 13). In particular, gallium, as a radionuclide, is used to label PSMAs to obtain suitable imaging ligands for PET/CT imaging. It shows higher tumor uptake and provides more acceptable background clarity. In this context, between ^{68}Ga-PSMA11, ^{68}Ga-PSMA617, and ^{68}Ga-PSMA I&T, ^{68}Ga-PSMA I&T as therapeutic agents are widely used for PET/CT imaging (14-16).

In addition to these disadvantages, studies on the long shelf life of the generator, the radiological stability of the column material, metal cationic impurities, the sterility of the eluate, and the long-life ^{68}Ge waste management are continuing. The development of stable materials addressing the aforementioned issues is an inevitable process that requires continuous improvement efforts by researchers.

In this study; ^{68}GaPSMA-11 synthesis was performed without pre-elution of the generator, which was not used for one month. With the same generator, ^{68}GaPSMA-11 synthesis was carried out by pre-elution at different day and time intervals. A comparison of the metal impurities in the composition of the ^{68}GaPSMA-11 radiopharmaceuticals was made at the present work.

MATERIALS AND METHOD

Chemicals

All reagents to be used for synthesis and quality control were purchased from Merck in high purity pharmaceutical grade. Kit equipment for the synthesis of ^{68}Ga peptides using cationic purification were obtained from ABX D-01454 Radeberg (Germany). The kit contains chemicals, hardware, and the cassette required for radiosynthesis of ^{68}Ga peptides the Scintomics GRP synthesizer using cationic purification. The kit components are cassette, PSH$^+$ cartridge, 5 M sodium chloride solution, ethanol, ethanol/water(1/1), phosphate buffered saline, 1.5 M HEPES buffer solution, and water for injections. The cassette exhibits are disposable and therefore made for single use. Reference PSMA-11 peptide was purchased from ABX D-01454 Radeberg (Germany) and stored at -20°C. Dilutions of PSMA11 were prepared with Farmako brand sterile water (1:1). Hydrochloric acid (0.1 N ultra-pure HCl) and 1.5 M HEPES (2-[4-(2-hydroxyethyl) piperazin-1-yl] ethane sulfonic acid) buffer solutions were obtained from ABX D-01454 Radeberg (Germany).

Instruments

$GaCl_3$ eluates were obtained from PARS Isotope-GalluGEN (Iran) ^{68}Ge/^{68}Ga generator with HCl solution in Scintomics GmbH GRP module 4V synthesis module.

^{68}Ge/68Ga Generator Certificate Properties; Column material SnO_2, TiO_2; HCl eluate concentration 0,1 N; Elution volume 7 ml; Generator age 6 month old, 120th elution; Chemical Impurity Zn<10 µg/GBq, Fe<10 µg/GBq.

Labelling of PSMA 11 with $^{68}GaCl_3$ elution in automated synthesis module

Cation exchange cartridge (PSH$^+$, no-preconditioned) was used to remove trace metals in $GaCl_3$ solution eluted from ^{68}Ge/^{68}Ga generator. $GaCl_3$ eluted from the PSH$^+$ cartridge with 5.0 M NaCl was added to the reaction vial containing 25 µg peptide dissolved in HEPES buffer. The mixture was then heated for 15 minutes at 90°C for labeling of the peptide with ^{68}Ga(III). Solution of ^{68}GaPSMA-11 in the reaction vial was passed through the C18 ion exchange cartridge to remove the unbound free ^{68}Ga ions. The retained ^{68}GaPSMA-11 was eluted from the C18 ion exchange cartridge with 2.0 ml ethanol/water (1/1). The product was passed through the 0.22 µm filter syringe and collected in the final vial.

Sample analysis

In the study, ^{68}GaPSMA-11 labeling was performed with the generator eluate that was not used for two months (sample 1). A blank elution was taken 24 hours after using the generator (sample 2). In the next 24 hours, the second ^{68}GaPSMA-11 labeling was done (sample 3). Six hours after this labeling, another ^{68}GaPSMA-11 synthesis was performed (sample 4).

Qualitative and quantitative analyzes of metal contents in ^{68}GaPSMA-11 eluate was made at the µg/ml(ppm) level and reported with the ICP-MS device located in the Advanced Technology Application and Research Center of the university. Some parameters of the device used are shown in Tables 1. With the ICP-MS analysis method; Germanium (Ge), Manganese (Mn), Zinc (Zn), Tin (Sn), Cobalt (Co), Nickel (Ni), Lead (Pb), Aluminum (Al) metal presence was examined. ICP-MS standard solutions were obtained from Perkin Elmer. Certified levels of standard solutions Ge: 999 µg.ml^{-1}±5 µg/mL. Mn: 1002 µg.ml^{-1}±5 µg/mL, Zn: 998 µg.ml^{-1}±5 µg/mL, Sn: 1002 µg.ml^{-1}±5 µg/mL, Co: 999 µg.ml^{-1}±5 µg/mL, Pb: 999 µg.ml^{-1}±5 µg/mL, Al: 1002 µg.ml^{-1}±5 µg/mL and Ge, Mn, Zn, Sn, Co, Pb and Al were used as internal standards for ICP-MS analysis. Analyzed metals; during extraction of nat-Ga to ^{68}Ge in cyclotron; column matrices in the ^{68}Ge/^{68}Ga generator and environmental factors have been selected for consideration. The results were recorded in the table format of the device and reported in excel format in the order of µg/ml.

Table 1: The operating conditions of the ICP-MS device

The operating conditions	
Rf Powers	1300 W
Gas flow rate	1.5 ml/min
Plasma gas flow	15 ml/min
Auxiliary gas flow	0.2 ml/min
Nebulizer gas flow	0.65 ml/min
Sample flow rate	1.5 ml/min
Flush time	20 sec
Read time	3 s

RESULTS

The purification method of ^{68}Ga eluate from the generator has been standardized using an automated system. The Ga^{3+} form of Ga is easily converted into other forms for use as a radiopharmaceutical. ^{68}Ga-gallate in HEPES medium was complexed by heating to convert to ^{68}GaPSMA-11. Therefore, no additional quality control was required for method validation. The automated synthesis was performed within 32 min. The pH of the final products was determined to be in between 6 and 7. The radiochemical yield of ^{68}GaPSMA-11 was > 99% by RP-HPLC. All samples were analyzed for metallic contamination by ICP-MS. The results are shown in Table 2.

Non-radioactive metal ions such as Zn(II) (produced by the decay of ^{68}Ga), Sn(IV) (produced from the SnO_2 column-based ^{68}Ge/^{68}Ga generator) and Mn, Fe(III) general

Table 2: ICP-MS analysis of ^{68}GaPSMA-11 radiopharmaceuticals and generator eluate

Metal pollution	^{68}GaPSMA-11 labeling (without pre-eluted, µg/ml)	Pre-elute of the generator (µg/ml)	^{68}GaPSMA-11 labeling (pre-eluted, µg/ml)	^{68}GaPSMA-11 labeling (After 6 hours, µg/ml)
Ge	0.018	0.325	0.012	0.009
Co	ND	0.001	ND	ND
Zn	0.625	1.382	0.133	0.108
Al	0.012	0.708	0.015	0.010
Pb	<0.001	0.008	<0.001	<0.001
Sn	0.004	0.003	0.001	0.001
Mn	<0.001	<0.001	<0.001	<0.001

Ge: Germanium; Co: Cobalt; Zn: Zinc; Al: Aluminum; Pb: Lead; Sn: Tin; Mn: Manganese

chemical impurity for labeling of radiopharmaceutical precursors it represents the metal ions that can compete with Ga^{3+}. Other chemical non-radioactive impurities arise in the production of ^{68}Ga; Nb, Ni or Cu.

^{68}Ge radioactive impurity was detected 0.325 ppm in the generator elution. It separated ^{68}Ge of the PSH^{+} cartridge and the liquid were sent to waste. ^{68}Ge levels determined at 0.018 ppm, 0.012 ppm, and 0.009 ppm levels in the labeled products were determined below the pharmacopoeia limits. And there was no significant difference between labeled products with elutions of pre-eluted generator and non-pre-eluted generator. Cobalt impurity occurs during the extraction of 68Ge from the cyclotron. Contamination detected during generator elution is within limits and there is no detection in marked products. Since Zn (II) is a metal that competes with ^{68}Ga, it is known that it can cause the reaction efficiency to decrease. Zn (II) contamination was found as 0.625 ppm in the labeling performed without generator pre-elution. In generator pre-eluted labeling; it was determined as 0.133 ppm and 0.108 ppm. No significant difference was found between the Zn impurities detected in the labeling product. Aluminum impurity occurs at column material in ^{68}Ge/^{68}Ga generator and during ^{68}Ge extraction from cyclotron. Aluminum impurity occurs at column material in ^{68}Ge/^{68}Ga generator and during ^{68}Ge extraction from cyclotron. It appears that the PSH^{+} cartridge does not purify this contamination. When the study data were examined, lead impurity was determined that although it was in generator elution, it did not switch to radiopharmaceutical. Tin metal pollution caused by the column material of the generator was detected at very low values. Manganese pollution was determined at values less than <0.001 ppm.

DISSUCUSION

Fifty percent of the 68Ga activity in the generator column is produced within a half-life. The generator can be decomposed every 3.5 hours to provide almost full (90%) radioactivity. Thus, the generator perfectly allows three separate elutions per day.

In this study, three different labeling processes were successfully performed in the automatic synthesis module with 99% efficiency. The chemical and radiochemical impurities examined that may pass into product compositions were compared with the limit values of European Pharmacopoeia monograph and IAEA Safety Standards. Chemical separations with PSH+ cartridge have been reported to reduce the amount of impurities to ppm levels.

The limit value of ^{68}Ge fraction in a ^{68}Ga solution used in radiopharmaceuticals labeling is stated as 0.001% in the European Pharmacopoeia monograph (4). Zn(II) (2 ppm), Nb (<7 ppm) and Cu, Pb, Co, Cr, Cd, Ni, Fe, Mn and Al (all <1 ppm) (4). According to the European Pharmacopoeia, the total radionuclide impurity limit in the [^{68}Ga] GaCl3 solution for radiolabeling cannot exceed 0.1% [17]. Lead is in the heavy metals class and is a highly toxic metal [18]. In terms of human health, this metal should not be in the radiopharmaceutical composition. The van der Waals radius of the Ga^{3+} (62 pm) ion is very similar to Mn^{+3} (64 pm), so they compete with ^{68}Ga in labeling, reducing the labeling efficiency of the generator.

It is thought that pre-elution of the generator before labeling increases the labeling efficiency when labeling PSMA-11 with ^{68}Ga. However, when the analysis results of the labeled products were examined, no significant difference was observed in chemical and radiochemical impurities between the product labeled with pre-elution generator elution and the labeled product with non-elution generator elution.

CONCLUSION

The stability and robustness of generator performance is important for product quality, patient safety, and to process traceability. There are known methods for obtaining the final product (labeled radiopharmaceutical) with the

least possible metal contamination. All of these methods cannot completely prevent the presence of metal cation impurities and ^{68}Ge radioactive impurity. In radiopharmaceutical production, these sources of contamination are considered a GMP issue controlled by process validation.

In the reported study, it was examined whether these metal impurities were contaminated in the product profile. In addition, whether generator pre-elution is important for contamination was evaluated. Pre-elution of the generator prior to synthesis does not seem to be a chemical requirement other than zinc pollution. Pre-elution can be made for ^{68}GaPSMA-11 in high yield, but no difference was observed in pre-elution in chemical and radiochemical terms.

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