

# Synthesis, stabilization and formulation of [ $^{177}\text{Lu}$ ]Lu-AMBA, a systemic radiotherapeutic agent for Gastrin Releasing Peptide receptor positive tumors

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Received 30 July 2007; received in revised form 30 October 2007; accepted 13 November 2007

## Abstract

A robust formulation was developed for [ $^{177}\text{Lu}$ ]Lu-AMBA ( $^{177}\text{Lu}$ -DO3A-CH<sub>2</sub>CO-G-[4-aminobenzoyl]-QWAVGHLM-NH<sub>2</sub>), a Bombesin-like agonist with high affinity for Gastrin Releasing Peptide (GRP) receptors. During optimization of labeling, the effect of several radiostabilizers was evaluated; a combination of selenomethionine and ascorbic acid showed superiority over other tested radiostabilizers. The resulting two-vial formulation maintains a radiochemical purity (RCP) of >90% for at least 2 days at room temperature. The method of stabilization should be useful for other methionine-containing peptide radiopharmaceuticals in diagnostic and therapeutic applications.

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**Keywords:**  $^{177}\text{Lu}$ -AMBA; Bombesin; Gastrin releasing peptide; Targeted radiotherapy; Radiolysis protection

## 1. Introduction

Interest in using radiolabeled bombesin derivatives as agents for diagnostic imaging and/or systemic radiotherapy of tumors (Smith et al., 2003; Zhang et al., 2004; Lantry et al., 2006 and references therein) has increased considerably because of the observation that Gastrin Releasing Peptide receptors (GRPr) are over-expressed in a variety of human tumor cells. Lantry et al. (2006) recently demonstrated that the [ $^{177}\text{Lu}$ ]Lu-labeled Gastrin Releasing Peptide (GRP) derivative known as [ $^{177}\text{Lu}$ ]Lu-AMBA (AMBA = (DO3A-CH<sub>2</sub>CO-G-(4-aminobenzoyl)-QWAVGHLM-NH<sub>2</sub>)) binds with nanomolar affinity to GRP receptors; preclinical studies with this Lu-labeled compound demonstrated therapeutic efficacy in a GRPr positive PC-3 human prostate tumor-bearing nude mouse model. [ $^{177}\text{Lu}$ ]Lu-AMBA is now in clinical trials for the radiotherapeutic treatment of prostate cancer.

Radiopharmaceuticals for systemic therapeutic applications are designed to deliver a therapeutic dose of radiation to specific disease sites. The ionizing radiation (e.g.,  $\alpha$ - or  $\beta$ -particles) given off from such compounds can either damage cellular components in the target tissue directly, or indirectly via the free radicals (e.g., OH $\cdot$ , H $\cdot$ , O $_2^{\cdot-}$ ) formed by the interaction of ionizing radiation with water in the target tissue (Burton and Lipsky, 1957; Liu and Edwards, 2001; Liu et al., 2003; Pozzi and Zalutsky, 2005). However, the potentially destructive properties of a therapeutic radioisotope's emissions are not limited to their cellular targets. Radiation-induced damage to the radiolabeled compound itself is one of the most challenging aspects in the development of a therapeutic radiopharmaceutical. For peptides and proteins, Garrison (1987) has reported that radiation induced damage may include oxidation, hydroxylation, aggregation and/or bond scission.

Preliminary tests showed that [ $^{177}\text{Lu}$ ]Lu-AMBA was very radiosensitive; in the absence of radiostabilizers, degradation occurred both during and after radiolabeling.

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In particular, the methionine residue of the targeting peptide was found to be readily oxidized to its methionine sulfoxide [Met(O)] form, one of the major radiolytic degradants of [ $^{177}\text{Lu}$ ]Lu-AMBA. Biological studies demonstrated that the targeting capability of [ $^{177}\text{Lu}$ ]Lu-AMBA was totally inactivated by this oxidization. Hence, use of a radiostabilizer or stabilizer combination in the [ $^{177}\text{Lu}$ ]Lu-AMBA formulation was an absolute requirement.

The purpose of this study was to establish a robust formulation for [ $^{177}\text{Lu}$ ]Lu-AMBA for use in Phase I clinical trials. The effect of pH, ligand concentration, and reaction time were determined, and several stabilizers were evaluated to identify a formulation yielding and maintaining high radiochemical purity (RCP).

## 2. List of abbreviations

Potential radiostabilizers evaluated included (a) amino acids: glycine (Gly), methionine (Met), cysteine (Cys), cysteine ethyl ester (CEE), tryptophan (Trp), and histidine (His); (b) naturally occurring selenium compounds: selenomethionine (Se-Met) and selenocysteine (Se-Cys); (c) sulfur-containing reducing agents: 2-mercaptoethanol (ME), dithiothreitol (DTT), and 1-pyrrolidinecarbodithioic acid (PDTC). The results were compared to those obtained with the commonly used radical scavengers such as ascorbic acid (AA), gentisic acid (GA), human serum albumin (HSA), and ethanol (EtOH).

## 3. Materials and methods

Glacial acetic acid (Ultrapure) and sodium acetate trihydrate (USP) were purchased from J.T. Baker. L-(+)-Selenomethionine (Se-Met) was obtained from Sabinsa Corp. Amino acids, ammonium sulfate, trifluoroacetic acid (TFA), acetonitrile and methanol were bought from EMD Chemicals, Inc. Bacteriostatic 0.9% Sodium Chloride Injection (USP) was purchased from Abbott Laboratories. ASCOR L500<sup>®</sup> Ascorbic Acid Injection (USP) [containing 500 mg/mL Ascorbic acid and 0.025% (w/v) Edetate disodium] was obtained from McGuff Pharmaceuticals, Inc. [ $^{177}\text{Lu}$ ]LuCl<sub>3</sub> in 0.05 N HCl was purchased from Missouri University Research Reactor (MURR). ITLC SG strips were from Pall Life Sciences. Deionized water was used for all solutions containing water, including HPLC mobile phases.

### 3.1. Peptide synthesis

AMBA [(DO3A-CH<sub>2</sub>CO-G-(4-aminobenzoyl)-QWAVGHLM-NH<sub>2</sub>), DO3A = (1,4,7,10-tetraaza-4,7,10-tris(carboxymethyl)-cyclododecyl)-acetyl] was synthesized using solid phase peptide synthesis chemistry, as described by Lantry et al. (2006). The compound structure was confirmed by LC/MS, amino acid sequence and elemental analysis. The proposed chemical structure of its lutetium complex is shown in Fig. 1. An authentic sample of AMBA-Met(O), a mixture of the two unresolvable methionine oxide epimers of the AMBA ligand was prepared using the appropriate Met(O) containing protected amino acids. This methionine oxidized compound mixture and its Lu complex [Lu-AMBA-Met(O)] were characterized by MS and HPLC.

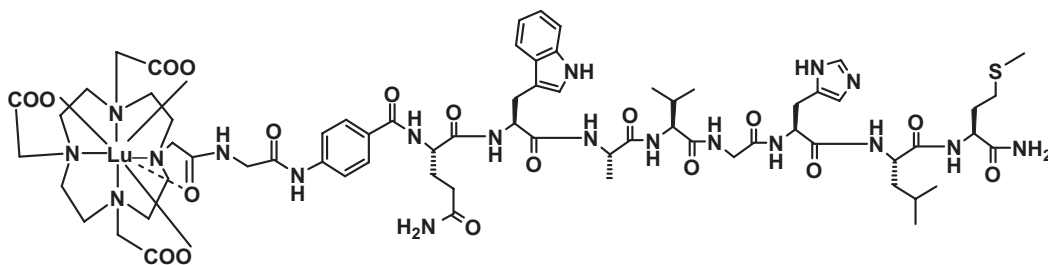
### 3.2. Radiochemistry

#### 3.2.1. Standard procedure for preparation of [ $^{177}\text{Lu}$ ]Lu-AMBA

To a lead-shielded 7-mL vial containing 120  $\mu\text{g}$  of AMBA and 1 mg Se-Met in 1 mL of 0.2 M (pH 4.8) sodium acetate (NaOAc) buffer, was added  $4.07 \pm 0.37$  GBq [ $^{177}\text{Lu}$ ]LuCl<sub>3</sub> in 0.05 N HCl (radioconcentration  $\sim 37$  GBq/mL, specific activity 103.6–151.3 GBq/ $\mu\text{mol}$ ). The mixture was heated at 100 °C in a heating block for 10 min. After cooling to ambient temperature in a water-bath for  $\sim 2$  min, the reaction solution was diluted by adding 4 mL of ascorbate dilution solution [a 9:1 mixture of Bacteriostatic 0.9% Sodium Chloride Injection USP and ASCOR L500<sup>®</sup> Ascorbic Acid Injection USP (final ascorbic acid concentration, 40 mg/mL)] yielding a final radioconcentration of  $\sim 814$  MBq/mL (22 mCi/mL). Any possible non-incorporated  $^{177}\text{Lu}$  remaining in the reaction solution was converted to [ $^{177}\text{Lu}$ ]Lu-EDTA by the EDTA contained in the Ascorbic Acid Injection. The radio-complex was then characterized by HPLC. In some cases, this reaction was performed at a 1/10th or 1/5th scale, maintaining the same concentrations as described above, but using a 2-mL reaction vial.

#### 3.2.2. Effect of buffer pH and ligand concentration

For the effect of buffer pH on [ $^{177}\text{Lu}$ ]Lu-AMBA incorporation, studies were performed at 1/10th of the full scale formulation as described above, but using 0.2 M



NaOAc buffers at pH values from 2.8 to 6.8. To study the effect of ligand concentration, [ $^{177}\text{Lu}$ ]Lu-AMBA was prepared using the standard procedure at 1/10th of the full scale formulation, using 7.5, 10, 12.5, or 15  $\mu\text{g}$  of AMBA instead of 12  $\mu\text{g}$ , thus providing AMBA:Lu ratios from 1.5:1 through 3:1. RCP and radiocolloid were assayed immediately after labeling.

### 3.2.3. Effect of temperature and heating time on Met oxidation

To determine if heating at 100 °C for 10 min causes Met oxidation in the absence of radiation, labeling reactions were performed as described for the standard procedure, but using 30 nmol of  $^{175}\text{Lu}$  ( $\text{Lu}_2\text{O}_3$  dissolved in 5%  $\text{HNO}_3$ ) in the place of  $^{177}\text{Lu}$ . Two such reactions were performed, one containing 1 mg/mL Se-Met, the other containing no stabilizer. These reactions were examined by UV ( $A_{280}$ ) after 10 min at 100 °C to determine the amount of Lu-AMBA Met(O) formed. Studies on the effect of heating time were performed with [ $^{177}\text{Lu}$ ]Lu-AMBA prepared as described in the standard procedure, but reaction mixtures were heated for 8, 9, 10, 12 or 15 min.

## 3.3. Evaluation and comparison of potential stabilizers

### 3.3.1. Post-labeling stabilization of [ $^{177}\text{Lu}$ ]Lu-AMBA

In these studies, the stabilizer was added immediately after radiolabeling; no stabilizer was present during  $^{177}\text{Lu}$  incorporation. Five amino acids were evaluated: Met, Cys, Trp, His, and Gly. For comparison, studies with the commonly used radiolysis protecting agents AA, GA, HSA, and EtOH were also performed. A 10 mg/mL solution of each potential stabilizer was prepared in 0.05 M (pH 5.3) citrate buffer or 10% (v/v) for the EtOH. [ $^{177}\text{Lu}$ ]Lu-AMBA was prepared by treating 36  $\mu\text{g}$  AMBA in 300  $\mu\text{L}$  of 0.2 M (pH 4.8) NaOAc buffer with  $\sim 0.5$  GBq [ $^{177}\text{Lu}$ ]LuCl<sub>3</sub>. Immediately after labeling, 50  $\mu\text{L}$  ( $\sim 83$  MBq) of the [ $^{177}\text{Lu}$ ]Lu-AMBA solution was mixed with the stabilizer solution (100  $\mu\text{L}$ ) to yield a final radioactivity concentration of 0.55 GBq/mL and a final stabilizer concentration of 6.6 mg/mL or 6.6% (v/v) for the EtOH. An aliquot of [ $^{177}\text{Lu}$ ]Lu-AMBA solution mixed with 0.05 M citrate buffer, pH 5.3 (100  $\mu\text{L}$ ) was used as a control. The samples were stored at room temperature (RT), and analyzed by HPLC at 0, 24 and 48 h to determine the RCP and percentage of the Met(O) form of [ $^{177}\text{Lu}$ ]Lu-AMBA.

### 3.3.2. Evaluation of reducing agents as stabilizers

The use of reducing agents as radioprotectants (specifically, to prevent methionine sulfoxide formation) and their efficacy in reducing methionine sulfoxide residues to methionyl residues was evaluated. For radiostabilization studies, 1 mg (5 mg/mL) of Cys, CEE, or PDTC was added into a 1/5th scale formulation in the place of Se-Met. After labeling, 0.8 mL of Bacteriostatic 0.9% Sodium Chloride

Ascorbic Acid Injection, was added to dilute the reaction solution. RCP was determined at 0 and 24 h after the labeling.

Cys, ME, and DTT were tested to determine their ability to reduce the methionine sulfoxide [Met(O)] residue in [ $^{177}\text{Lu}$ ]Lu-AMBA-Met(O), the primary radiodegradant of [ $^{177}\text{Lu}$ ]Lu-AMBA. [ $^{177}\text{Lu}$ ]Lu-AMBA-Met(O) was prepared by heating 12  $\mu\text{g}$  AMBA-Met(O) ligand in 100  $\mu\text{L}$  of 0.2 M (pH 4.8) NaOAc buffer with  $\sim 55.5$  MBq [ $^{177}\text{Lu}$ ]LuCl<sub>3</sub> in the absence of any radiostabilizer. An aliquot (10  $\mu\text{L}$ ) of the [ $^{177}\text{Lu}$ ]Lu-AMBA-Met(O) solution was mixed with the reducing agent (90  $\mu\text{L}$ ) at a final concentration of 10 mg/mL. As controls, Met and Se-Met were used in the place of the reducing agents. The samples were analyzed by HPLC after storage at RT for 1 and 3 days to determine the percentage of [ $^{177}\text{Lu}$ ]Lu-AMBA that formed via reduction of [ $^{177}\text{Lu}$ ]Lu-AMBA-Met(O).

### 3.3.3. Evaluation of selenium compounds

Two naturally occurring organoselenium compounds, Se-Met and Se-Cys were evaluated. The [ $^{177}\text{Lu}$ ]Lu-AMBA solution was prepared in a full scale formulation as described in the standard procedure above, using 1 mg of either Se-Met or Se-Cys as the stabilizer present during labeling. [ $^{177}\text{Lu}$ ]Lu-AMBA formulated using the same conditions without any stabilizer was tested as a control. Immediately after the labeling, the reaction solutions were diluted by addition of 4 mL of ascorbate dilution solution, and characterized by HPLC.

### 3.3.4. Labeling of frozen formulations

In this study, five stabilizers found to have efficacy in preliminary studies (Met, Se-Met, Cys, CEE, and PDTC) were further evaluated to determine their capacity for radiolysis protection after storage at  $-20$  °C in a frozen formulation solution for 1 month. Stabilizer (1 mg/mL) and AMBA (120  $\mu\text{g}/\text{mL}$ ) were dissolved in 0.2 M (pH 4.8) NaOAc buffer under  $\text{N}_2$ , and 1-mL aliquots of the solution dispensed into 7-mL vials. Vials were bubbled with  $\text{N}_2$  gas, crimp-sealed, and stored at  $-20$  °C. After 1 month of storage, the vials were warmed to ambient temperature, and an aliquot (100  $\mu\text{L}$ ) of each solution was used to prepare [ $^{177}\text{Lu}$ ]Lu-AMBA (1/10th of the full scale formulation). After labeling, 0.4 mL of Bacteriostatic saline containing 1 mg/mL EDTA, without ASCOR<sup>®</sup> Ascorbic Acid Injection, was added to dilute the reaction solution to a radioconcentration of 0.814 GBq/mL. RCP was determined at 0 and 24 h after labeling.

## 3.4. Effect of heating time and radioconcentration

For the effect of heating time, [ $^{177}\text{Lu}$ ]Lu-AMBA was prepared as described in the standard procedure above, but the heating time was varied from 8 to 15 min. To determine the effect of radioconcentration,  $^{177}\text{Lu}$ -complexation was

instead of 4.07 GBq (110 mCi). RCP was determined after 0 and 48 h at RT.

### 3.5. Analytical methods

#### 3.5.1. Instrumentation

An Agilent Technologies quaternary 1100 Series HPLC equipped with an autosampler and variable wavelength detector was used. The radioactivity was monitored using a Canberra NaI detector (Model 802-2 × 2W) with high voltage power supply (Model 3102D), single channel analyzer (Model 2015A) and either a linear ratemeter (Model 2081) or a linear/logarithmic ratemeter (Model 1481LA). The Model 1481LA ratemeter provided excellent linearity ( $R^2 > 0.99$ ) from  $3.7 \times 10^{-3}$  to  $\sim 4.44$  MBq of injected radioactivity.

#### 3.5.2. HPLC analysis

[ $^{177}\text{Lu}$ ]Lu-AMBA HPLC analysis was performed as follows: column: Zorbax Bonus-RP (5  $\mu\text{m}$ , 80  $\text{\AA}$  pore size, 250 × 4.6 mm, Agilent); column temperature: 37 °C; flow rate: 1.5 mL/min; mobile phases: (A = H<sub>2</sub>O; B = 30 mM ammonium sulfate with 0.1% TFA (v/v); C = methanol; D = acetonitrile). The HPLC gradient started at 30%A/60%B/5%C/5%D, ramped to 14%A/60%B/13%C/13%D over 5 min, and was held at this composition for 32 min. The retention times for unlabeled peptide ligand, [ $^{177}\text{Lu}$ ]Lu-AMBA and its methionine oxide analog [ $^{177}\text{Lu}$ ]Lu-AMBA-Met(O) were  $\sim 24$ ,  $\sim 30$ , and  $\sim 12$  min, respectively. RCP was calculated as the percentage of the area present as [ $^{177}\text{Lu}$ ]Lu-AMBA relative to the total integrated area (all combined radioactive peaks plus any segments of elevated baseline). Percentage  $^{177}\text{Lu}$  incorporation was defined as the percentage of activity in all combined radioactive peaks except that in the void volume of the column, relative to the total integrated area, where the radioactive peak in the void volume of the column (“void peak”) represented [ $^{177}\text{Lu}$ ]Lu-EDTA.

#### 3.5.3. Radiocolloid determination and recovery studies

Radiocolloid was monitored using 2 × 10 cm silica gel (SG) thin layer chromatography (TLC) strips developed with acetone/0.9% saline (1:1). Radiocolloid remained at the origin; [ $^{177}\text{Lu}$ ]Lu-EDTA and [ $^{177}\text{Lu}$ ]Lu-AMBA migrated with the solvent front. The percentage radiocolloid was calculated as the percentage of the total applied radioactivity that remained at the origin. Recovery studies were performed by removing all product from the vial using a glass pipette and counting the radioactivity that could be removed relative to that which remained in the “empty” vial and crimp-seal.

#### 3.5.4. Statistical analysis

Statistical analysis was performed using the Student's *t*-

## 4. Results

### 4.1. HPLC analysis

#### 4.1.1. Radiochromatogram of [ $^{177}\text{Lu}$ ]Lu-AMBA

Preliminary labeling studies showed that [ $^{177}\text{Lu}$ ]Lu-AMBA prepared in acetate buffer at a radioconcentration of 814 MBq/mL (22 mCi/mL) in the absence of any radiostabilizers underwent significant radiolysis. Figs. 2a and b show typical radiotracers of unstabilized [ $^{177}\text{Lu}$ ]Lu-AMBA at 0 and 12 h post-formulation, respectively, when stored at RT. [ $^{177}\text{Lu}$ ]Lu-AMBA-Met(O), formed by oxidation of the methionyl residue of [ $^{177}\text{Lu}$ ]Lu-AMBA, was a significant degradant immediately after labeling (Fig. 2a), and RCP fell to <10% within 12 h. It was clear from these results that radiostabilization was needed.

After significant study, an optimized “standard procedure” for radiolabeling was identified, wherein radiolabeling was performed in the presence of Se-Met to prevent radiolysis during  $^{177}\text{Lu}$  incorporation, followed by addition of ascorbic acid and bacteriostatic saline to provide good long-term post-labeling stability. A typical HPLC radiochromatogram of [ $^{177}\text{Lu}$ ]Lu-AMBA prepared using the standard procedure is shown in Fig. 2c.

### 4.2. [ $^{177}\text{Lu}$ ]Lu-AMBA formulation and radiolysis protection

#### 4.2.1. Effect of buffer pH and ligand concentration

The effect of buffer pH is shown in Table 1. The percentage of  $^{177}\text{Lu}$  incorporation did not change significantly between pH 3.8 and 5.8, but at pH values of 2.8 and 6.8, a decrease in the percentage of  $^{177}\text{Lu}$  incorporation was seen. Furthermore, the amount of radiocolloid was significantly increased when the reaction pH reached 6.8. Based on these results, 0.2 M NaOAc buffer at pH 4.8 was selected for all subsequent [ $^{177}\text{Lu}$ ]Lu-AMBA labeling, unless otherwise indicated.

Studies on the effect of ligand concentration (ligand-to-metal ratios) showed that  $^{177}\text{Lu}$  incorporation was incomplete with an AMBA to Lu molar ratio of 1.5, showing a 5% void peak in the radiochromatogram. However, it was close to 100% at all higher molar ratios tested.

#### 4.2.2. Evaluation and comparison of potential stabilizers

Three groups of potential stabilizers were tested by adding them before and/or after [ $^{177}\text{Lu}$ ]Lu-AMBA complexation.

4.2.2.1. Amino acids. The RCP results obtained when amino acids and commonly used radical scavengers (AA, GA, HSA, and EtOH) were added (6.6 mg/mL) to [ $^{177}\text{Lu}$ ]Lu-AMBA (0.55 GBq/mL) after Lu incorporation are shown in Table 2. The percentage of the Met(O) form

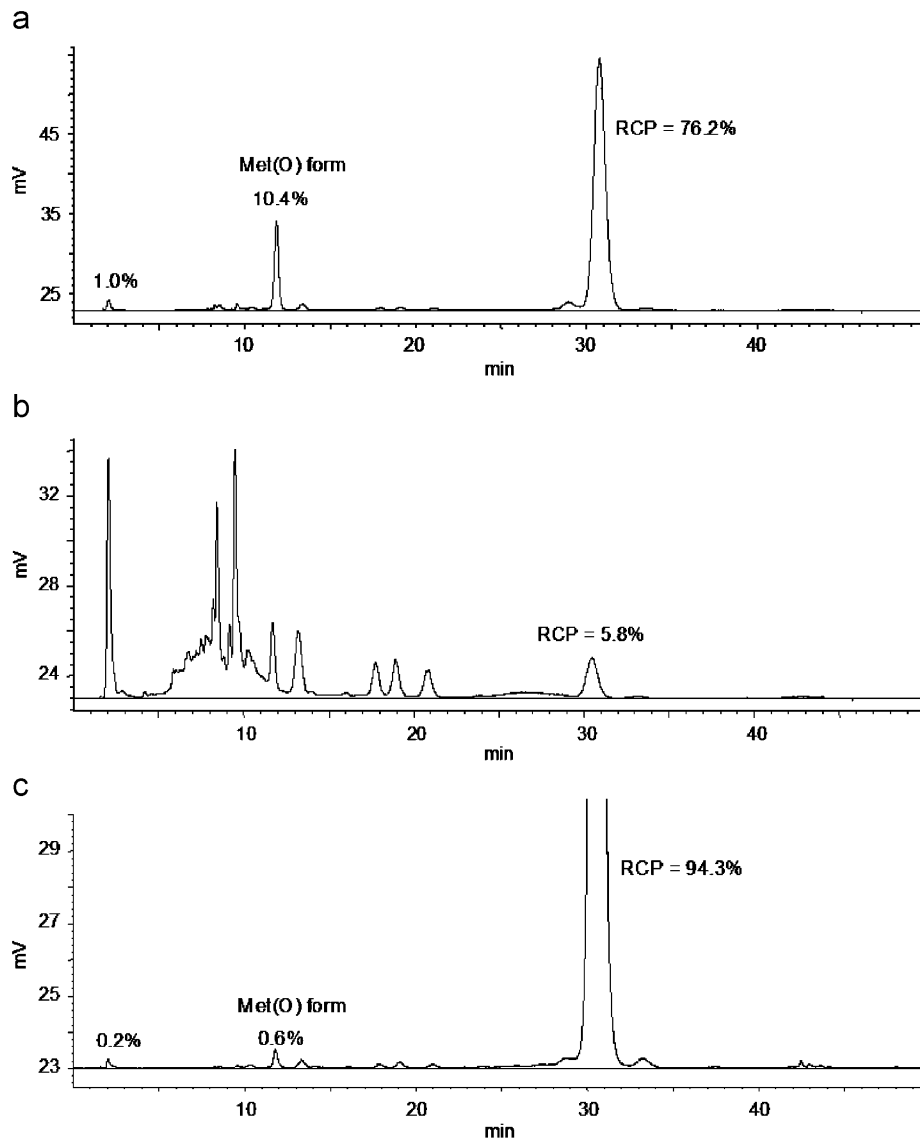


Fig. 2. HPLC radiochromatograms of unstabilized [ $^{177}\text{Lu}$ ]Lu-AMBA at 0 (a) and 12 h (b) post-formulation; and (c) stabilized [ $^{177}\text{Lu}$ ]Lu-AMBA, expanded scale, at 12 h post-formulation. Four microliters of the [ $^{177}\text{Lu}$ ]Lu-AMBA formulation solution ( $\sim 3.26$  MBq) were injected.

Table 1  
Effect of buffer pH on [ $^{177}\text{Lu}$ ]Lu-AMBA incorporation and radiocolloid

pH	Incorporation (%)	Radiocolloid (%)
2.8	97.4	0.30
3.8	99.6	0.32
4.8	99.7	0.31
5.8	99.6	0.34
6.8	96.7	1.20

Ascor solution was added, so the relative effect of each stabilizer could be tested.

Of the amino acids tested in this study, Met was one of the most effective radioprotectants for prevention of the oxidation of the methionine residue in [ $^{177}\text{Lu}$ ]Lu-AMBA. Significant radioprotection was observed for both Cvs and

prevented all damage except the oxidation of the Met residue; almost no other degradants except [ $^{177}\text{Lu}$ ]Lu-AMBA-Met(O) were observed during 2 days of storage at RT.

AA and GA had significant stabilizing effects, but at the concentrations tested, none of the commonly used radioprotection agents evaluated (AA, GA, or HSA) supplied enough protection to inhibit all radiolysis of [ $^{177}\text{Lu}$ ]Lu-AMBA. It was found that EtOH could stabilize the radiocomplex, and sometimes benefited RCP and recovery when a trace amount of ligand was used.

4.2.2.2. *Organic selenium and sulfur containing compounds.* Table 3 lists the initial ( $t = 0$ ) RCP values obtained for [ $^{177}\text{Lu}$ ]Lu-AMBA radiolabeled in the presence or absence of Se-Met, Se-Cvs, Cvs, CEE and PDTTC. At the

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