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Radioiodination of Atorvastatin as a Model Radiopharmaceutical for Targeting Liver

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Abstract—Atorvastatin was radioiodinated and formulated using chloramine-T *via* an electrophilic substitution reaction for the development of a potential radiopharmaceutical for targeting liver. The impact of different reaction parameters and conditions that affected the labeling yield such as pH of the reaction, concentration of atorvastatin and reaction time were optimized in order to increase the radioiodination efficiency. The labeling yield was 94.3 ± 1.41 %. *In vitro* analysis demonstrated that the compound was steady for up to 24 h. The liver uptake was 40.35% and the clearance pathways proceed *via* the hepatobiliary and renal clearance.

Keywords: atorvastatin, radioiodination, chloramine-T, biodistribution, liver-targeting agents

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INTRODUCTION

Atorvastatin is a representative of lipid-lowering drug family recognized as statins. It acts selectively in the liver as inhibitor of HMG-CoA reductase and cholesterol synthesis. It is chemically described as (3*R*,5*R*)-7-[2-(4-fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid [1]. The lipophilicity/hydrophilicity of the radiolabeled complexes determines the binding affinity for hepatic transport proteins, the efficiency of their hepatocyte uptake, and the excretion pathways [2, 3].

Atorvastatin is taken up selectively into the liver (hepatocytes) via organic anion-transporting polypeptide 1B1 (OATP1B1) [4, 5], excreted into the biliary system, and stored by the gallbladder [6, 7]. Atorvastatin is a lipophilic statin but is relatively hydrophilic compared to simvastatin and lovastatin, which makes it more hepatoselective and able to cross cellular membrane either by passive diffusion and/or active carrier-mediated process [8, 9]. The liver-selective uptake and the tissue-specific distribution of atorvastatin via organic anion transporters ensure high pharmacological effect. In the liver, the statin drug undergoes Cytochrome P450 mediated metabolism [10–13]. The dominant active metabolites are 2-hydroxy- and 4-hydroxy-atorvastatin acid [14, 15]. Elimination of atorvastatin occurs from the systemic circulation through the liver via the bile into the feces and through the kidneys via the renal-urinary system [16–19]. Most of the hepatobiliary radiopharmaceuticals available for imaging are labeled with ^{99m}Tc. They exhibit identical pharmacokinetic properties in animals. They are efficiently removed from the blood by the liver and excreted into the bile. Moreover, they diagnose diseases of hepatocytic function and the functional status of the cystic duct and the gallbladder [6].

The mechanism of in situ oxidative radioiodination using chloramine-T (CAT), involving the formation of iodine monochloride (ICl), was elucidated [20, 21]. In weakly acidic media, CAT dissociates to $ArSO_2NCl^-$ anion, which may react directly with iodide to form ICl. Subsequently the iodine monochloride (ICl) reacts with any position in the target molecule that can experience electrophilic substitution [20, 22]. Owing to the difference in the electronegativity between iodine and chlorine, ICl is highly polar and acts as a source of iodonium ion (I^+). Therefore, aromatic electrophilic labeling with electropositive radioiodide usually proceeds in high radiochemical yield compared to 50% yield if molecular

iodine is used, because ICl is a stronger iodinating agent than I_2 [23, 24]. The electrophilic iodination method is applied to various types of receptors and ligands as long as those ligands have a site where the substitution can occur and are stable under the oxidizing conditions at pH of the reaction.

Synthetic routes to radioiodinated compounds are usually more difficult compared to other halogen-containing radiopharmaceuticals because iodine is the largest, the least electronegative, and the most polarizable of the halogens and forms the weakest C–X bond [25, 26]. Elemental iodine is weakly reactive, requiring an activator for efficient introduction into organic compounds [27]. On the other hand, iodonium ion (I^+), which acts as an electrophile for the radioiodination process, can be generated in situ in the presence of CAT as a convenient oxidizer, thus enabling the efficient and selective direct iodination of atorvastatin under ambient conditions [28, 29]. This work describes the development of a simple and efficient procedure for the radioiodination of atorvastatin under ambient conditions using CAT and characterization and evaluation of the biological behavior of ^{125}I-atorvastatin as a promising selective radiopharmaceutical for targeting hepatobiliary system for liver imaging.

EXPERIMENTAL

Atorvastatin ($C_{33}H_{35}FN_2O_5$, M = 558.64 g/mol) was a kind donation from EIPICO, Egypt. Radioactive iodine (no-carrier-added Na^{125}I, 4 GBq/mL in 0.1 N NaOH) was obtained from the Institute of Isotopes, Budapest, Hungary. Chloramine-T [CAT, $ArSO_2NClNa$ (Ar = $CH_3C_6H_4$)], sodium metabisulfite ($Na_2S_2O_5$), sodium acetate (CH_3COONa), phosphate buffered saline (PBS), and acetonitrile (CH_3CN) were purchased from Alfa Aesar. All solvents and reagents were of analytical grade and were used without additional purification. Deionized water was used in all experiments.

Atorvastatin radioiodination. A freshly prepared solution of atorvastatin in acetonitrile (100 μL) was added to a CAT solution in phosphate buffer. No-carrier-added Na^{125}I (4.5 MBq) was transferred to the reaction vial, and the reaction mixture was agitated at ambient temperature for the preset time. A drop of saturated $Na_2S_2O_5$ solution in H_2O (100 mg/mL) was added to terminate the reaction. The radiochemical yield of the radioiodinated product was determined by TLC and HPLC. The influence of the CAT concentration (3–75 mM), atorvastatin amount (25–200 μg), pH of the reaction mixture (3–11), and the reaction time (5–60 min) on the radiochemical yield was examined. The conditions were optimized in order to enhance the labeling yield.

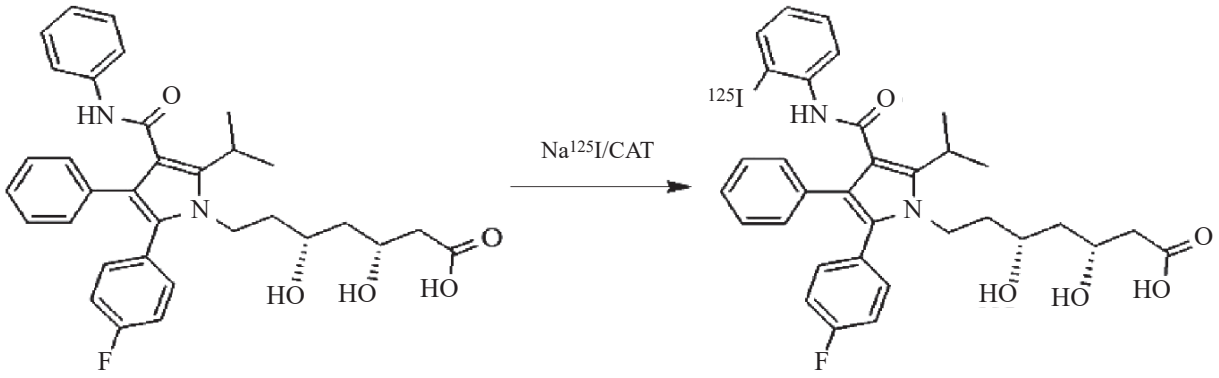
Radiochemical analysis. The radiochemical yield of ^{125}I-atorvastatin was determined by silica gel thin-layer chromatography (SG-TLC). Samples were spotted 2 cm above the lower edge of the strip (1 cm width, 13 cm length). TLCs were developed in a benzene : ethyl acetate mixture (7 : 3 v/v). The radiochemical yield was expressed as the percent ratio of the radioactivity of ^{125}I-atorvastatin to the total radioactivity. The radiochemical yield was the mean value of three experiments. Purification and chromatographic analysis of the radioiodinated complex were performed on Agilent HPLC system coupled to a sodium iodide radiometric detector. A 10-μL aliquot of ^{125}I-atorvastatin solution at the optimum conditions was injected into a reversed-phase C18 column (Waters, 150 × 4.6 mm; 5 μm) kept at 25°C and was eluted with a mobile phase that contained 0.05 M CH_3COONa buffer and CH_3CN (40 : 60, v/v) and was adjusted to pH 4.0. Atorvastatin was detected by UV absorbance at 246 nm. The mobile phase was filtered and degassed before use and was pumped at a flow rate of 1.00 mL/min [30].

In vitro stability. The in vitro stability of the complex was evaluated by incubating 1 mL of the reaction mixture at 37°C for 24 h. Exact 2–30 μL aliquots were extracted and analyzed at various time intervals using TLC and HPLC to determine the percent content of ^{125}I-atorvastatin.

Lipophilicity (partition coefficient log *P*). The lipophilicity of ^{125}I-atorvastatin was measured experimentally by adding 5 mL of *n*-octanol and PBS (50 : 50) to a centrifuge tube containing a 1 mL aliquot of the radioiodinated compound. The tube was shaken for 5 min at room temperature and centrifuged at 4000 rpm for 15 min. The two phases were separated before aliquots (500 μL) of each phase were removed and counted in a well-type NaI(Tl) γ-counter. The partition coefficient (log *P*) is the ratio of the radioiodinated compound concentrations in the octanol phase and PBS at equilibrium. The extraction was performed in triplicate.

Biodistribution studies of ^{125}I-atorvastatin in normal mice. The animal experiments were performed

Scheme 1. Radioiodination of atorvastatin.



according to the Egyptian Atomic Energy Authority guidelines and were authorized by the Animal Care Committee, Labeled Compound Department. Before the study, normal Albino mice (20–25 g on average) were accommodated in groups of five and supplied with food and water. The mice were injected with 10 μL of the purified labeled complex intravenously through the tail vein. Anesthetized mice were sacrificed by cervical dislocation at 0.5, 1, and 4 h post injection (n = 5). Each animal was weighed and dissected, and the blood was withdrawn from the heart directly after sacrifice. The tissues and organs were washed with saline, collected in plastic containers, and weighed. Then, the background radiation level as well as the radioactivity of each sample were counted in a well-type counter based on a NaI(Tl) crystal coupled to an SR-7 scaler ratemeter. Biodistribution data were expressed as percent injected dose per organ (% ID/organ ± S.D.) in a population of five mice for each time point. Experiments on predosing the mice with nonradioactive atorvastatin 30 min before the injection of ^{125}I-atorvastatin and determining the average liver uptake percent at 1 h post injection (n = 5) were also performed. Student's t test was used to determine the differences in the data. The two-tailed test was used to evaluate the statistical significance of the data; the results for P are represented. All the results are reported as mean ± SEM. The scale of significance was set at $P < 0.05$.

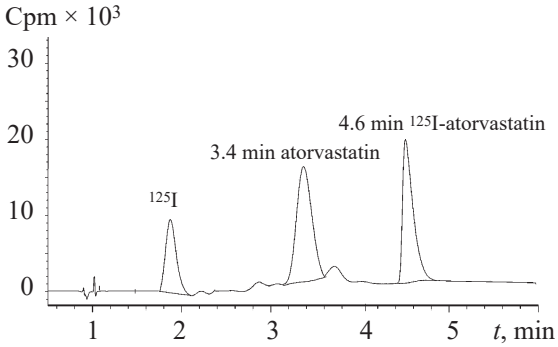


Fig. 1. Overlaid chromatograms of atorvastatin and ^{125}I-atorvastatin.

RESULTS AND DISCUSSION

Synthesis of ^{125}I-Atorvastatin

Synthesis of ^{125}I-atorvastatin was carried out by direct electrophilic substitution with no-carrier-added ^{125}I ($T_{1/2}$ = 60 days) under oxidative conditions in the presence of CAT. The presumable reaction is shown in Scheme 1. The TLC results show that radioiodide stayed near the origin (R_f = 0–0.1), while ^{125}I-atorvastatin proceeded with the solvent front (R_f = 0.8–1). The radiolabeling yield was 94.3 ± 1.4% (n = 5). It was determined by HPLC analysis, where the retention times of free iodide and ^{125}I-atorvastatin were 1.5 and 4.6 min, respectively, as given in the chromatogram (Fig. 1). The HPLC system allowed the separation of the radiolabeled compound from the free radioiodide and the unlabeled atorvastatin as well as the purification and quality control of the radiolabeled compound.

The in vitro stability of the radiolabeled compound was considered in order to estimate the appropriate time for injection to exclude the formation of unacceptable products resulting from the radiolysis of ^{125}I-atorvastatin. These products might be accumulated in non-target organs. As we found, ^{125}I-atorvastatin was stable for up to 24 h.

The lipophilicity was determined by measuring the distribution of ^{125}I-atorvastatin between n-octanol and

water. The experimental log *P* of the labeled molecule (5.9 ± 0.3) was found to be higher than that of atorvastatin (5.4), which may be due to the attachment of iodine. Therefore, atorvastatin is eluted before radioiodinated atorvastatin on reversed-phase HPLC chromatogram (Fig. 1). The lipophilic characteristics of ^{125}I-atorvastatin are important for predicting the uptake and excretion pathways, as hydrophobic radiopharmaceuticals are generally extracted via the hepatobiliary pathway (efficiently taken up from the blood by the liver, excreted into the bile, and stored by the gallbladder) and slightly via the renal route as it was demonstrated from the in vivo biodistribution studies. The structural and physicochemical link between the hydrophilic and lipophilic functional groups in ^{125}I-atorvastatin is involved in the assessment of the binding affinity for hepatic transport proteins, the efficacy of their hepatocyte uptake, and the elimination rate.

Effect of Reaction Conditions on the Radiochemical Yield

Effect of atorvastatin concentration. The radiochemical yield as a function of atorvastatin concentration is plotted in Fig. 2. With an increase in the amount of atorvastatin from 25 to 50 μg (0.45–0.9 mM), the radiochemical yield increased from 85 to 94.3 ± 1.4%. Further increase in the amount of atorvastatin beyond 50 μg had no effect on the labeling yield; i.e., the amount of 50 μg is sufficient to capture all the produced iodonium ions.

Effect of CAT concentration. The effect of CAT concentration on the radiochemical yield of ^{125}I-atorvastatin is shown in Fig. 3. High radiochemical yield (94.3 ± 1.4%) was attained with an increase in the CAT concentration from 3 to 13 mM at pH 5 and 30 min reaction time. Further increase in the oxidizing agent concentration over 13 mM decreases the radioiodination yield due to the production of undesirable oxidation by-products as a result of denaturation and chlorination of atorvastatin exposed to high concentration of CAT for a relatively long time.

Effect of reaction time. Chloramine-T is a powerful oxidant, and it may cause oxidative damage of sensitive biological substrates or targets if overexposed. Therefore, the radiochemical reaction should be quenched by adding a reductant such as sodium metabisulfite. It reduces hypochlorous acid and hypochlorite ion, thus

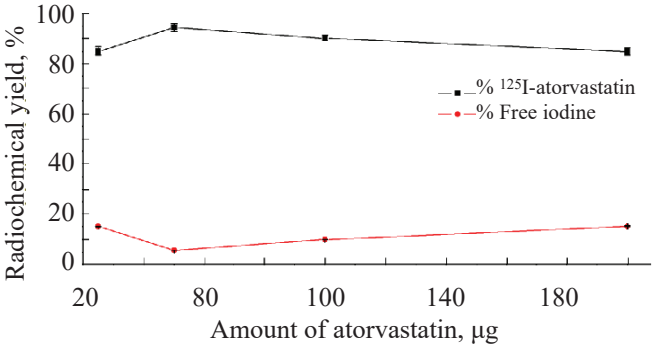


Fig. 2. (Color online) Radiochemical yield of ^{125}I-atorvastatin as a function of atorvastatin amount.

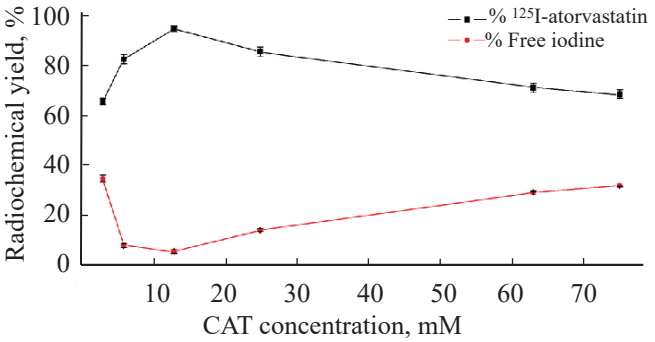


Fig. 3. (Color online) Radiochemical yield of ^{125}I-atorvastatin as a function of oxidant concentration.

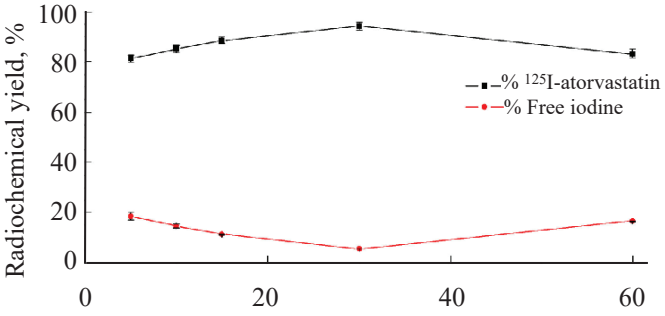


Fig. 4. (Color online) Radiochemical yield of ^{125}I-atorvastatin as a function of reaction time.

suppressing the formation of electropositive iodine. Figure 4 shows how the ^{125}I-atorvastatin yield depends on the reaction time in the range from 1 to 60 min. The labeling yield increased with time, reaching 94.3% in 30 min. An increase in the reaction time beyond 30 min led to a small decrease in the radiochemical yield due to side oxidative reactions, whereas shorter reaction time is apparently insufficient for CAT to fully react with iodide ions and generate the iodonium ions.

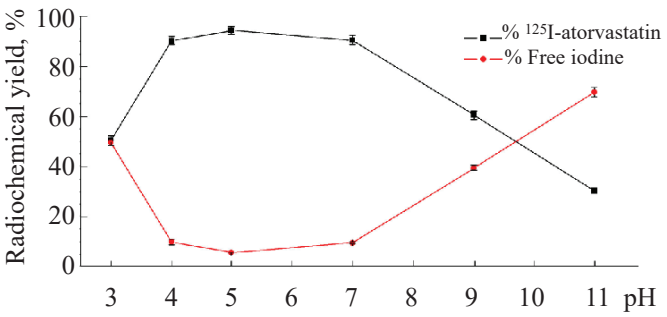


Fig. 5. (Color online) Radiochemical yield of ^{125}I-atorvastatin as a function of pH.

Effect of pH. The effect of pH on the radiochemical yield of ^{125}I-atorvastatin is shown in Fig. 5. The pH of the medium and the reaction conditions determine the nature of active oxidizing species produced. In acidic medium, chloramine-T undergoes hydrolysis to form hypochlorous acid, which, in turn, unergoes protonation to H_2OCl^+. Both HOCl and H_2OCl^+ are considered as the potential oxidizing species in acidified CAT solutions [20]. Both species can oxidize iodine under acidic conditions to iodonium (I^+), which rapidly reacts with any sites within atorvastatin that can undergo electrophilic substitution reactions. In alkaline medium, CAT generates hypochlorite ion; it converts iodide to hypoiodite and iodiate ions, which are unfavorable species for the radioiodination [20].

With atorvastation, the yield was maximal at pH 5 (94.3 ± 1.4%). The iodonium ion attacks the site that is the most reactive in electrophilic substitution. At pH 4, the yield decreased to 90%. In alkaline medium, the yield was relatively low: 60.5% at pH 9 and 30.3% at pH 11.

Biodistribution of ^{125}I-Atorvastatin

Table 1 summarizes the biodistribution data. The labeled atorvastatin showed immediate and dynamic clearance from the blood as the radioactivity detected in the blood was 5.51 ± 0.24 and 2.11 ± 0.08% at 0.5 and 4 h post injection, respectively. As expected from the lipophilicity of ^{125}I-atorvastatin, the amount of radioactivity taken up by the liver was relatively high: 40.35 ± 0.59% at 1 h and 10.63 ± 0.36% ID/organ at 4 h p.i. The uptake in the intestines was 19.63 ± 0.76% at 0.5 h and increased to 25.21 ± 0.36% at 4 h p.i., suggesting the clearance via the hepatobiliary excretion pathway through the intestines. The radioiodinated compound showed low accumulation and retention in the kidneys (6.25 ± 0.32% at 0.5 h and 1.54% at 4 h p.i.). The collected activity in the urine was 12.31 ± 0.41% at 4 h post injection, suggesting a second clearance route via renal-urinary excretion system. Thus, ^{125}I-atorvastatin cleared effectively via the hepatobiliary (liver + intestines) excretion pathway and to a lesser extent through the renal-urinary system.

Table 1. Biodistribution (% ID/organ ± S.D., n = 5) of ^{125}I-atorvastatin in normal Albino mice at different time intervals post injection

Organs and body fluids	0.5 h	1 h	4 h
Urine	5.72 ± 0.13	7.33 ± 0.19	12.31 ± 0.41
Blood	5.51 ± 0.24	4.41 ± 0.28	2.110 ± 0.081
Brain	0.510 ± 0.052	0.021 ± 0.006	0.013 ± 0.021
Heart	4.360 ± 0.10	2.310 ± 0.135	1.524 ± 0.032
Lung	1.425 ± 0.032	1.115 ± 0.035	0.025 ± 0.013
Liver	40.35 ± 0.54	33.52 ± 0.32	10.63 ± 0.36
Kidneys	6.250 ± 0.33	3.731 ± 0.010	1.541 ± 0.021
Stomach	4.360 ± 0.15	7.060 ± 0.013	5.231 ± 0.011
Thyroid	1.731 ± 0.003	2.270 ± 0.12	6.140 ± 0.29
Intestines	19.64 ± 0.76	24.52 ± 0.40	25.22 ± 0.36
Spleen	1.001 ± 0.006	0.751 ± 0.056	0.530 ± 0.16
Bone	1.215 ± 0.031	1.520 ± 0.12	0.980 ± 0.32
Muscle	3.440 ± 0.31	3.100 ± 0.020	2.910 ± 0.11

The uptake in the lungs was small (1.42 ± 0.03%). The activity in the majority of organs decreased in the period between 0.5 and 4 h p.i., except for stomach and thyroid, where it increased with time. The increase in the thyroid radioactivity from 1.73 ± 0.03% at 0.5 h and 6.1 ± 0.3% at 4 h p.i. suggests the presence of free radioiodide, presumably due to the metabolism of the compound. The stomach and thyroid uptake shows that only a limited amount of radioiodine was released from the ^{125}I-atorvastatin in vivo, confirming satisfactory in vivo stability and insignificant biological decomposition due to metabolism. The in vivo stability complies with the high in vitro stability in human plasma.

Predosing the mice with nonradioactive atorvastatin 0.5 h prior to the injection of labeled compound decreased the liver uptake to 19.25 ± 0.52% ID/organ. This result suggests that ^{125}I-atorvastatin binds selectively to the liver and that the uptake was specific.

Similar radioiodinated compounds targeting liver such as *m*-iodobenzylguanidine labeled with ^{131}I (^{131}I-MIBG) show the uptake of 1.65% ID/g after 2 h [31]. Growth factor-β1 (TGF-β1) labeled with ^{125}I (^{125}I-TGF-β1), targeting the liver, showed 2.4% ID/g [32].

CONCLUSIONS

An efficient procedure was developed for selective radioiodination of atorvastatin via direct electrophilic substitution at ambient temperature in the presence of an appropriate oxidant, chloramine-T. The product showed good radiochemical stability and metabolic stability in vivo. The biodistribution studies carried out in mice expressed the affinity of ^{125}I-atorvastatin for hepatic cells. ^{125}I-labeled atorvastatin behaves as a lipophilic compound, is extracted by liver on hepatocytes, and is excreted into the bile duct and finally into the intestine. The maximum liver uptake occurs approximately within 30 min after the injection. ^{125}I-atorvastatin clears predominantly by the hepatobiliary pathway.

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CONFLICT OF INTEREST

The authors state that they have no conflict of interest.

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