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**Quality control of commercial
radioiodines**

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Statutory declaration

This study was elaborated at Department of Organic and Nuclear Chemistry under supervision of Doc. RNDr. Ladislav Lešetický Csc.

I hereby declare that I listed all used literature and other information sources.

In Prague, 1th September 2008

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Abbreviations

α	alpha radiation
β^-	beta particle (electron)
β^+	positron
γ	photon
EC	electron capture
IT	isomer transition
RTG	roentgen
λ	wave length
Bq	SI derived unit of radioactivity (Becquerel)
$T_{1/2}$	half-time
EI	Electron ionization (formerly known as electron impact)
ESI	Electrospray ionization
SPECT	single photon emission computed tomography
PET	positron emission tomography
TLC	thin layer chromatography
HPLC	high performance liquid chromatography
R_f	retention factor
MeOH	methanol
EtOAc	ethyl acetate

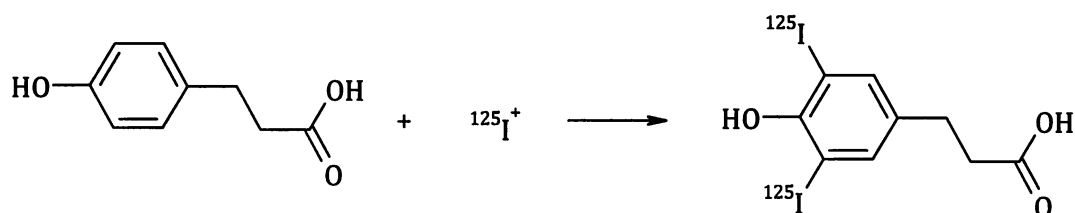
Objective

Commonly used commercially available radioiodine agents declare to be pure, but often they give radioiodination reaction without any oxidizing agent added. Aim of this study is review these solutions and try to explain this behavior.

1. Introduction

Radioactive isotopes of iodine play a major role in nuclear medicine especially in field of radiolabeling. Although many different radionuclides have been used to radiolabel proteins^{1,7} the largest number of labeled protein studies have used radionuclides of iodine, principally ¹²⁵I and ¹³¹I. These radionuclides of iodine have properties that are adequate for a number of different applications, and the radionuclides are relatively easy to use and readily available at a nominal cost from commercial sources. Problems with radioiodination reactions are that there are often irreproducible results that by our opinion are caused by presence of reducing agents in commercial available radioiodides.

Studied radioiodination reaction was:



For our purposes we used 3-(4-hydroxyphenyl)propionic acid because it is supplied in very pure form, is cheap and it's easy to radiolabel. We studied two commonly used commercially available radioiodines ¹²⁵I and ¹³¹I.

2. Physical properties and areas of application

2.1 Properties

Iodine is the lowest in the periodic table of the common halogens, and although it shares common properties with chlorine and bromine, there are differences that lend a distinction to the behavior of iodine. The oxidation potential of the iodide-iodine couple is only -0.54 V compared with -1.4 V for chlorine and -1.1 V for bromine, so that iodide is a reducing agent (is easily oxidized). The electronegativity of iodine is approximately equal to that of carbon, and iodine bonds with other elements tend to have less ionic character, as seen by comparing the H-X bond energies for HCl, HBr, and HI: for HCl and HBr, the bond is much stronger (by 12-22 kcal/mol) than would be predicted from calculated bond energies, whereas the HI bond energy corresponds well. As a result of having similar electronegativities, carbon-iodine bonds have similar polarities to carbon-carbon bonds. The iodine atom occupies a similar volume to that of a methyl or ethyl group and can substitute for an alkyl group in an organic molecule without unduly perturbing the steric or polar configuration. Elemental iodine is a Lewis acid and tends to form complex ions. The stability of the tri-halide ion (I_3^-) is highest for iodine and least for chlorine. Polyvalent compounds of iodine such as iodosobenzene are known^{2,3} and higher complexes of iodine occur, e.g. with 8 and 11 atoms of iodine per molecule^{5,9}. The ^{131}I species⁹ has been inferred from chromatographic data⁴. Such species may explain anomalous chromatographic results observed in aged samples of ^{125}I , as well as progressive decrease of labeling yields as the age of the radioisotope sample increases.

3. Radionuclides

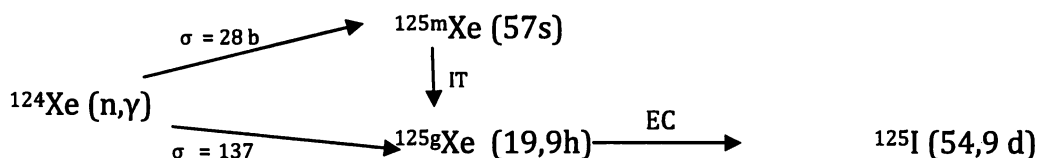
List of some radionuclides with their decay mode and application.

Nuclide symbol	Half-life	Mode of decay (%)	Application
¹¹⁹ I	19.1 min	β ⁺ (100%)	
¹²⁰ I	81.6 min	β ⁺ (56%) EC (44%)	PET
¹²¹ I	2.12 h	β ⁺ (100%)	
¹²² I	3.63 min	β ⁺ (77%) EC (23%)	PET
¹²³ I	13.2235 h	EC (100%)	SPECT*
¹²⁴ I	4.1760 d	EC (78%) β ⁺ (22%)	PET Therapy control
¹²⁵ I	59.400 d	EC (100%)	RIA Auger therapy
¹²⁶ I	12.93 d	EC (55%) β ⁺ (44%) β ⁻ (1%)	
¹²⁷ I	STABLE	β ⁻ (94%) EC (6%)	
¹²⁸ I	24.99 min	β ⁻ (100%)	
¹²⁹ I	1.57 a	β ⁻ (100%)	
¹³⁰ I	12.36 h	β ⁻ (100%)	
¹³¹ I	8.02070 d	β ⁻ (100%)	Therapy
¹³² I	2.295 h	β ⁻ (100%)	
¹³³ I	20.8 h	β ⁻ (100%)	
¹³⁴ I	52.5 min	β ⁻ (100%)	
¹³⁵ I	6.57 h	β ⁻ (100%)	

4. Source of Radioiodine

4.1 Production of ^{125}I

Iodine - 125 is reactor-produced radionuclide and is available in large quantities. Its production follows reaction:



The irradiation target is natural xenon gas containing 0,0965% ^{124}Xe . It is filled in zircaloy-2 capsule to pressure about 100 bars. On irradiation in a nuclear reactor, several radionuclides of xenon are produced. Fortunately only the decay of ^{125}Xe leads to radioiodine ^{125}I . The other radioxenons decay either to stable xenon or some cesium isotopes. It needs however, to be pointed out that long irradiations are disadvantageous. Iodine-125 itself has a neutron capture cross section of 900 barns, and consequently during a long irradiation, part of the ^{125}I formed will be converted to ^{126}I . In practice, the irradiation time amounts to a few days. Thereafter the irradiated gas is allowed to decay for several days.

For isolating radioiodine, the irradiated capsule is cooled and Xe gas is allowed to escape. The inner walls of the capsule are then rinsed with dilute NaOH solution. In order to eliminate long-lived ^{135}Cs and ^{137}Cs , which may be present in small amounts, the solution is passed through a cation-exchange column. The radioiodine remains in solution.

4.1.1 Availability and purity:

Iodine-125 is commercially available in dilute NaOH solution as [^{125}I]iodide. The radioactive concentration lies at 4 to 11 GBq/ml and the specific radioactivity amounts to $>75\text{GBq}/\mu\text{mol}$. The chemical and radiochemical

purity is high. The radionuclidic purity is also high; only some ^{126}I ($t_{1/2}=13.1\text{d}$) is unavoidable. Its tolerable content lies at about 0.2%.

4.2 Production of ^{131}I

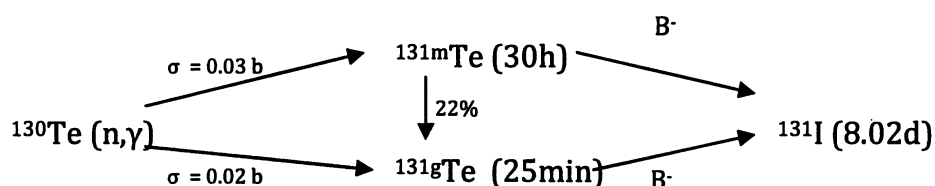
Iodine-131 is also a reactor-produced radionuclide and is commercially available in large quantities^{20,21}. There are two routes for its production:

4.2.1 (a) Fission of ^{235}U

Since the chain yield of mass 131 is fairly high (2.885%) and the radioiodines with mass higher than 131 are short-lived, ^{131}I is easily obtained in a rather pure form. The irradiated $^{235}\text{UAl}_3$ is first stored for 24 hours to allow decay of short-lived products. Thereafter it is treated with NaOH whereby radioactive inert gases (Kr and Xe) are emitted; on filtration, uranium and some fission products are removed. The filtrate is then acidified with HNO_3 . On heating, radioiodine is distilled over and collected in trap. The rest of the reaction mixture is treated further for separation of ^{90}Mo and fission products.

4.2.2 (b) (n,γ) reaction

The (n,γ) reaction of nature tellurium leads to the formation of $^{131\text{m}}\text{Te}$ and $^{131\text{g}}\text{Te}$, both of which eventually decay to ^{131}I . The other iodine nuclides produced by this reaction are present in neglectable amounts and thereby can be omitted. The reaction sequence is:



The target material for irradiation is either Te-metal or TeO_2 , depending on whether a wet chemical separation procedure is employed or dry distillation method used. In general, the second method is proffered. The irradiated TeO_2 is allowed to decay for about three days so that a greater part of $^{131\text{m}}\text{Te}$

is transferred into ^{131}I . The distillation of radioiodine is then done in a stream of air at 750 C, i.e. just above the melting point of TeO_2 , and it is collected in the trap. Naturally occurring tellurium consists of eight isotopes; three of them are observed to be radioactive. ^{128}Te has the longest known half-life, 2.2×10^{24} years, among all radioactive isotopes.

The cross sections for the formation of both ground and metastable states of ^{131}Te are rather low, so the expected overall yield of ^{131}I via (n, γ) reaction is much lower than via the fission process.

4.2.3 Availability and purity of ^{131}I

Iodine-131 is commercially available in dilute NaOH solution as [^{131}I]iodide. The radioactive concentration lies at 2 GBq/ml. Although production is done at a reactor, n.c.a. ^{131}I is formed via indirect route and the specific radioactivity amounts to $\sim 100 \text{ GBq}/\mu\text{mol}$. The chemical and radiochemical purity are high. The radionuclidic purity is also high for both processes. Some ^{129}I ($t_{1/2} = 1.57 \times 10^7$ a) may, however, be present at the ppb level. In the case of fission process, the chain yield of mass 131 is four times higher than that of 129, but in the (n, γ) reaction the cross sections of equally abundant ^{128}Te and ^{130}Te are almost equal. The level of ^{129}I in the case of (n, γ) produced ^{131}I may thus be slightly higher.

Na^{131}I of high specific activity in dilute NaOH solution may undergo self-radiolysis and oxidation to iodate and other chemical forms. Addition of a reducing agent (e.g. Na_2SO_3) prevents this and preserves the isotope in the form of iodide. The reducing agent may, however, interfere in the use of ^{131}I for labeling organic compounds, especially with in situ oxidation methods. An excess of reducing agent can be avoided by newer technologies using either hydrazine⁶ or even more elegantly acid-treated platinum¹⁰.

5. Radiochemical purity

The introduction of an iodine atom into molecule is generally realized by nucleophilic or electrophilic substitution on carbon atom. However, all production methods deliver the radioisotopes in the form of iodide. Commercially, Na¹²⁵I solutions are available in 10⁻² M NaOH or in phosphate buffer, while Na¹³¹I and Na¹²³I are available in 10⁻² M NaOH for labeling purposes.

Radiochemical purity is defined as the fraction of radioisotope that is present in the specified chemical form. Depending on the isolation process after nuclide production and on storage, radioiodine can be contaminated by different chemical forms of iodine. Most probable these are oxidized forms ^{*}I₂, ^{*}IO₂, ^{*}IO₃⁻ and ^{*}IO₄⁻, which is due to the low oxidation potential of iodide and radiolytic process^{8,11}. Since the radiochemical purity of the radioiodide hampers the radiochemical yields of nucleophilic and electrophilic labeling method, it has to be controlled by means of thin layer chromatography (TLC) or high-performance liquid chromatography (HPLC).

The HPLC methods for the determination of chemical nature of iodine in ¹³¹I and ¹²⁵I samples proved to be highly sensitive, rapid and reproducible. Not only better resolution was obtained compared to other routine techniques but many new and previously unresolved species could be separated as well¹³.

On the other hand TLC method on silica gel with ethyl acetate/hexane solution (3:1) as mobile phase is more convenient and fast but lacks the resolving power of HPLC.

Recently, a simple process was described to transform the all radioactivity into the form of radioiodide using hydrazine as reducing agent⁶.

Radionuclidic purity is defined as the fraction of total radioactivity that is present as the specified radionuclide. In general, high radionuclidic purity of an ^{131}I -labelled radiopharmaceutical is needed:

- i.) to avoid unnecessary radiation dose to the subject
- ii.) to minimize any degradation of the quality of the image
- iii.) to limit errors on measurement of the biological process

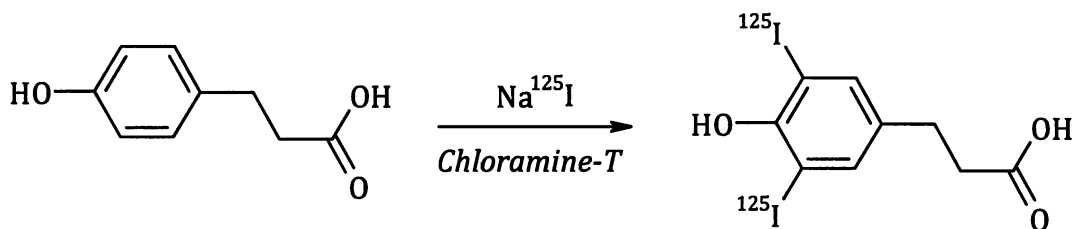
For example the radionuclidic purity of ^{123}I depends essentially on nuclear reaction used and the time of use after the end of radionuclide preparation.

Thus the choice of the production reaction is of crucial importance. For example, in some laboratories ^{123}I is produced by the $^{124}\text{Te}(\text{p},2\text{n})^{123}\text{I}$ nuclear reaction with 23 to 26 MeV protons. When using this pathway, the level of ^{124}I impurity is rather high due to the (p,n) side reaction. Therefore, this reaction route is not allowed in some countries for production of ^{123}I for human use. If applied, it is highly recommended to use ^{123}I within the first day of production, since the percentage of longer-lived radiocontaminant ^{124}I increases due to its longer half-life of 4.2 days.

The levels of radionuclidic impurities are generally determined by gamma ray spectrometry with appropriate detectors (e.g. Ge(Li), or NaI(Tl)). Such measurements are necessary to ensure that radionuclidic contaminants are within the acceptable limits at the time of radiopharmaceutical administration. Typical purity levels are given later for individual isotopes.

6. Radioiodination reaction:

All the tests were carried out on radioiodination reaction of 3-(4-hydroxyphenyl)propionic acid. This reaction is electrophilic substitution on aromatic ring. Oxidizing agent used was Chloramine -T

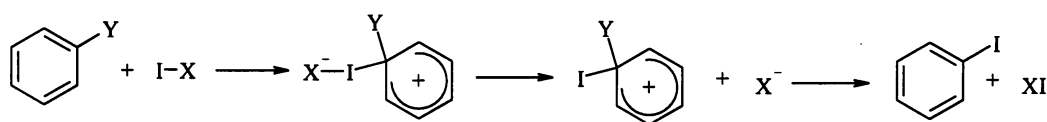


7. Mechanism of reaction

Electrophilic radioiodination is a process in which formally a positively charged iodine (I^+) attacks a system with high electron density such as an aromatic ring. As a result a covalent carbon-iodine bond is formed with loss of a positively charged leaving group. The most important leaving groups are those that can best exist without the pair of electrons necessary to fill the outer shell, i.e. the weakest Lewis acids. The most common leaving group is the proton. In aliphatic systems, the proton can be leaving group, but the reactivity depends on the acidity. Since metallic ions are easily able to bear positive charges, organometallic moieties are especially susceptible to electrophilic substitution.

For electrophilic substitution at least four possible major mechanisms are distinguished, which are called SE_1 , SE_2 , SE_i and the arenium ion mechanism, which is observed with arenes and abbreviated SE_{Ar} ¹². The first three concern substitutions in aliphatic compounds are not discussed in detail. The vast majority of electrophilic radioiodination reactions, however, concerns aromatic substitution.

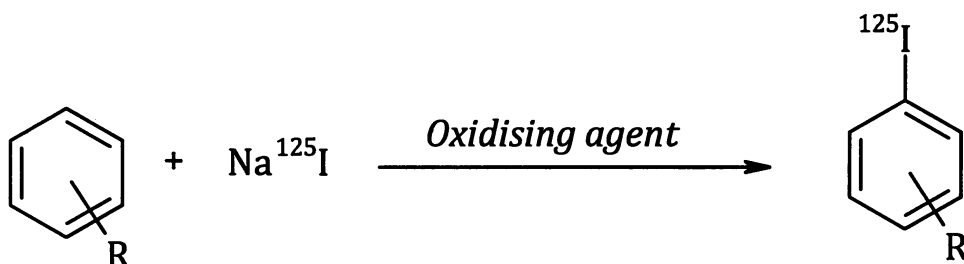
Due to the high energy of formation, iodine cannot exist in the oxidation state +1 in condensed phase. Rather, the attacking species is a dipole ($\delta^-X-I \delta^+$) in which iodine is positively polarized and where X is an electron-withdrawing group or solvent molecule.



The mechanistic features of the electrophilic aromatic substitution have been discussed in details.

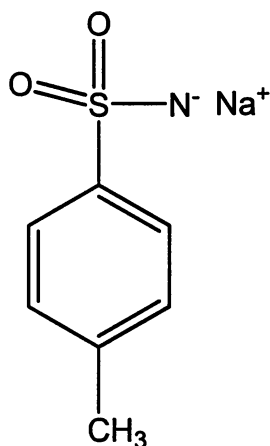
For the development of radioiodinated tracers, it is important to take into account that aromatic and vinylic iodo compounds possess the highest chemical and often in vivo stability. In vinyl iodides the strength of the C-I bond is at least as high as that of the corresponding aryl iodides and identical labeling methods can be applied for the synthesis of both types of iodo compounds.

Aliphatic radioiodinated tracers, which are almost exclusively labeled via nucleophilic substitutions, play only a minor role. Thus, nearly all the electrophilic labeling methods developed up to now have focused on radioiodoarenes. Molecular radioiodine (*I_2) is not a suitable labeling reagent at the n.c.a. level, because it is highly volatile, rather unreactive and of course a carrier-added reagent. However, the low oxidizing potential of iodide ($I^- \leftrightarrow 1/2I_2 + e^- \quad \epsilon_0=0.5355$) allows for the direct formation of an electrophilic species in which iodine is formally oxidized to "I⁺". Mainly two methods, i.e. direct iodo-deprotonation and iodo-demetalation, both based on in situ oxidation of iodide, are suitable for radioiodination on the n.c.a level and have gained importance.



8. Chloramine-T

Chloramine-T or *N*-chloro-4-methylbenzenesulfonamide sodium salt (CAT) in aqueous solution is believed to slowly release hypochlorite (OCl^-), which oxidizes iodine under formation of a hydrated iodonium ion (H_2OI^+). However, in strongly acidic aqueous medium, interhalogen species are probably formed from the sodium salts, whereas under neutral or slightly basic conditions, the corresponding radioiodoanalogs of the *N*-chloroamides are postulated. In organic solvent dichloroamine-T (DCT) is sometimes used for in situ oxidation.



8.1 Chloramine T

The relatively strong oxidizing conditions and possible chlorination side reactions often lead to by-product formation. It is recommended to work at low temperatures and to keep reagent concentration as low as possible.

9. Experimental

9.0.1 Chemicals and materials

Sodium [¹²⁵I]iodide : purchased from Institute of Isotopes Co., Ltd. Budapest ,
370MBq, Act. Date: 17.1.2008, volume 0.1cm³,

Sodium [¹³¹I]iodide: purchased from ÚJV Řež a.s., 400MBq/ml, Act. Date
20.6.2008, volume 0.1cm³

3-(4-hydroxyphenyl)propionic acid, ethyl acetate, n-hexane, water, silica gel
TLC plates (Merck), sodium iodate, sodium periodate

9.0.2 Preparations

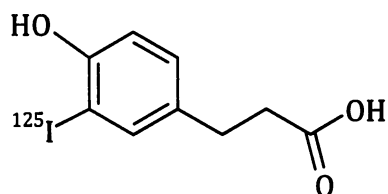
- Iodine sample volume 2μl was diluted in various volumes of distilled water to obtain solution with specific activity of about 10MBq/ml. These stock solutions were used for TLC analysis.
- Sodium periodate: 12.7g pulverized elemental iodine was dissolved in 54ml of 10% NaOH solution. Afterwards elemental chlorine gas was introduced into the solution (chlorine was prepared by reaction $16\text{HCl} + 2\text{KMnO}_4 \rightarrow 5\text{Cl}_2 + 2\text{MnCl}_2 + 2\text{KCl} + 8\text{H}_2\text{O}$). Periodate was filtered from solution and rinsed with cold water.

9.1 Radioiodination of 3-(4-hydroxyphenyl)propionic acid

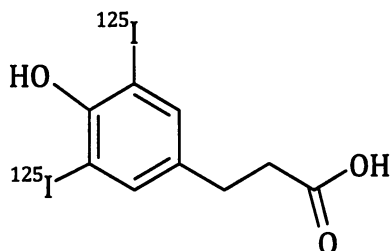
100μg of 3-(4-hydroxyphenyl)propionic acid was dissolved in 1ml of water. Also 100μg of NaI was dissolved in 1 ml of water and was used as stock solution of carrier iodine. Iodine-125 solution was prepared as written above.

Reaction was carried out in neutral conditions without the need of heating. We used carrier iodine to achieve uniform conditions for all reactions (with/without CAT and for reaction with different iodine radionuclides).

Radioiodination with CAT was confirmed by MS analysis revealed that main product were 3-(4-hydroxy-3,5-di-iodophenyl)propionic acid and 3-(4-hydroxy-3-iodophenyl)propionic acid. Di-iodo product was however present in more than 95%.



1.1 3-(4-hydroxy-3-iodo)propionic acid



1.2 3-(4-hydroxy-3,5-di-iodo)propionic acid

9.2 TLC analysis

A number of TLC setups were examined and evaluated. Most suitable setup was Silica gel plate 60 F₂₅₄, 0.2mm thick as stationary phase and ethyl acetate/water solution (3:1 ratio) as mobile phase. Plates were evaluated visual under UV lamp and activity was measured on Instant Imager Packard instrument.

9.2.1 Analysis of iodine samples

As can be seen from images 1.1 and 1.2 both ¹²⁵I and ¹³¹I samples contain at least three other radioactive iodine species. One of them has been positively identified as iodate.



2.1 ¹²⁵I (silica gel, pure EtOAc)



2.2 ¹²⁵I (silica gel, EtOAc:hexane / 3:1)

9.2.2 Analysis of products of radioiodination reaction

Radio analysis shown that commercial radioiodine agent undergoes in small scale radioiodination reaction even without CAT as oxidizing agent. This proves presence of other iodine species in initial iodine solution (as also seen in earlier TLC analysis).



Reaction products with CAT



Reaction products without CAT

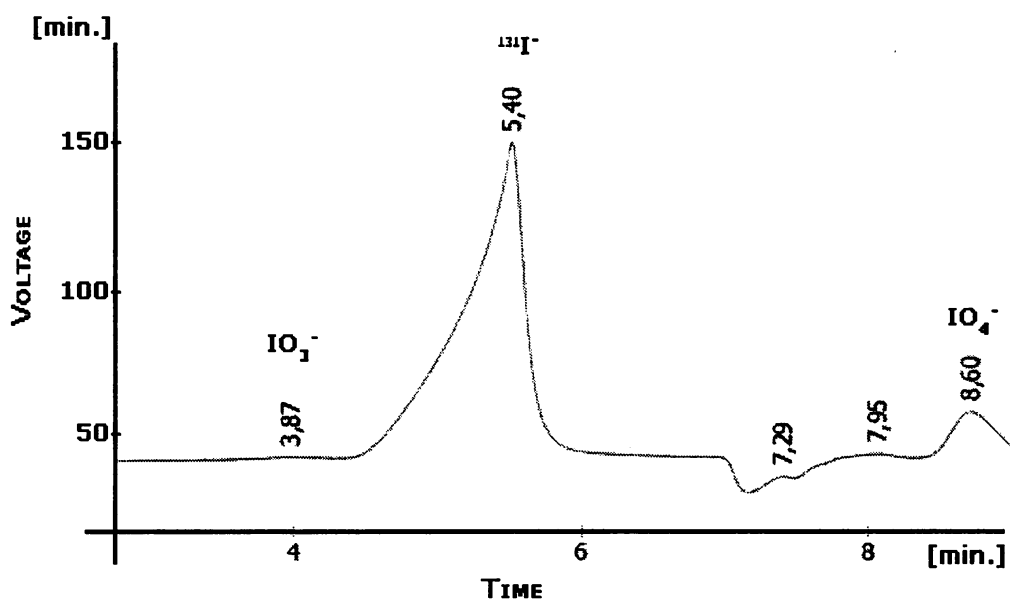
3.1 Activity image of products of radioiodination reaction with/without CAT

9.3 HPLC

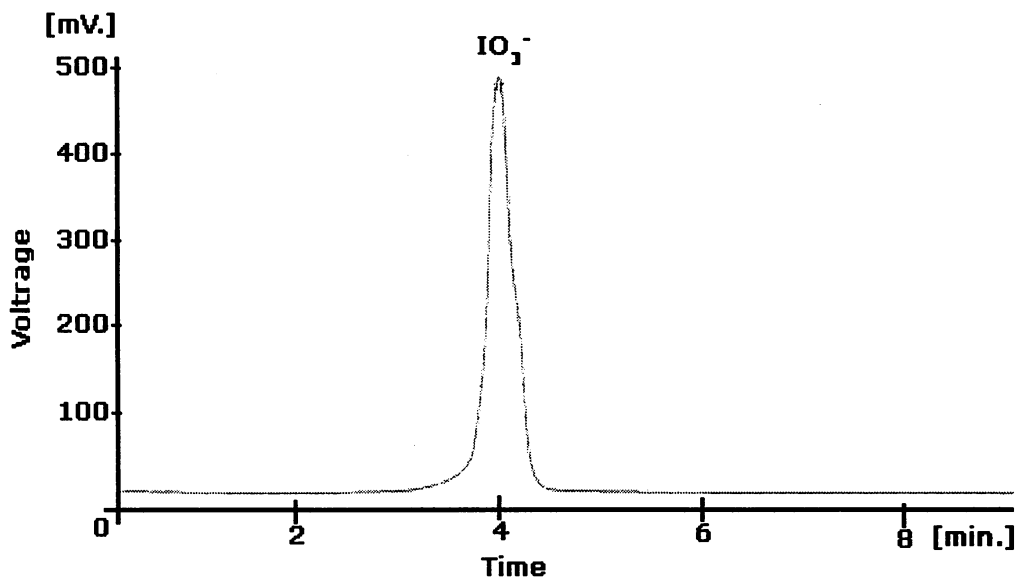
A number of reverse-phase columns and solvent mixtures were evaluated for optimal separation efficiency. A DeltaChrom SDA 150 liquid chromatograph was used. An on-line absorbance detector set to 225nm was utilized to monitor the carrier iodine content of the various separated fractions. A flow scintillation analyzer was used to measure the radioactivity of fractions during elution. The eluting buffers (pH = 7.0) contained 0.05M phosphate and varying concentrations of methanol. After series of runs we determined best separation efficiency with ratio 1:4 for water in methanol. The flow rate was 0.5ml/min and all studies were carried out at room temperature about 23°C using Reprisil 100 C18, 5µm column. The ¹²³I samples were also subjected to cycles of oxidation using Chloramine T and peroxide.

10. Results and Discussion

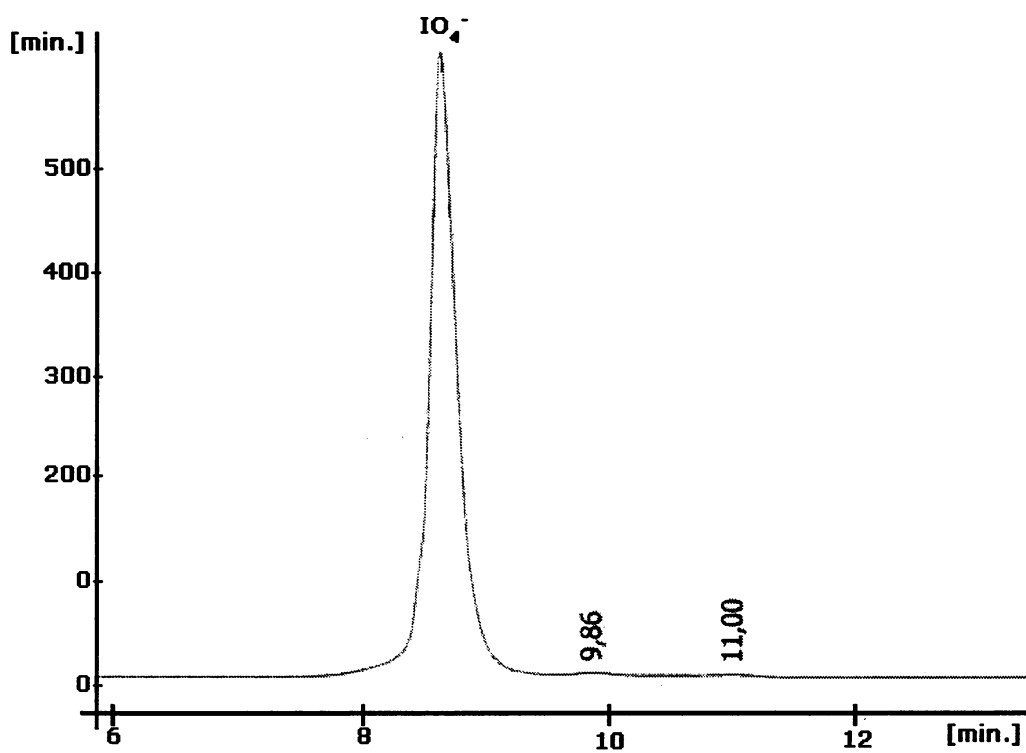
HPLC method has proven to be the best method for evaluating iodine content of various commercial radioiodine samples. With use of this method we studied ^{131}I and ^{125}I samples, both fresh and older (after their half-times). As we assumed, all samples contained more or less amount of other iodine species. We positively identified periodate and iodate in both ^{131}I and ^{125}I samples. See comparison of both graphs under text. Periodate has $R_F = 8.6\text{min}$ and iodate has $R_F = 3.87\text{min}$. Radiolysis resulting from $^{131}\text{I}^-$ may be considered as an initiator of the oxidation. Indeed, it has been shown that γ -ray irradiation of carrier-free $^{131}\text{I}^-$ solutions results in oxidation (mostly IO_3^- and not I_2).



3.1 HPLC Chromatograph of $\text{Na } ^{131}\text{I}$

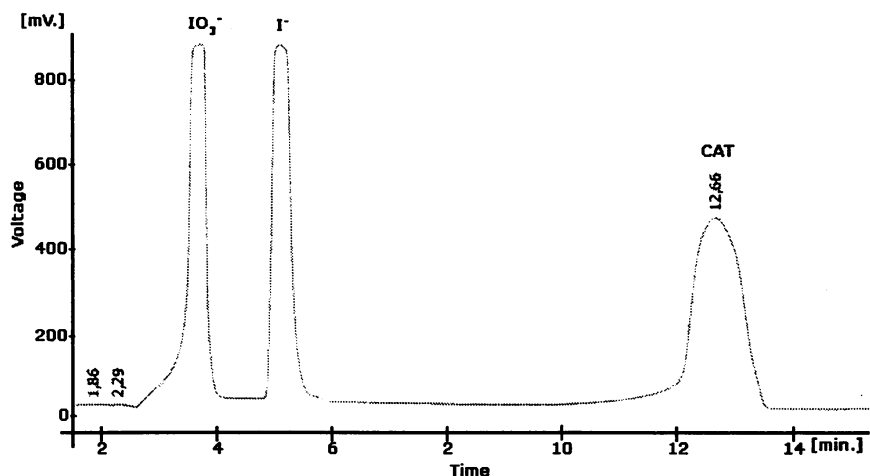


3.2 HPLC Chromatograph of $\text{Na}^{125}\text{IO}_3$

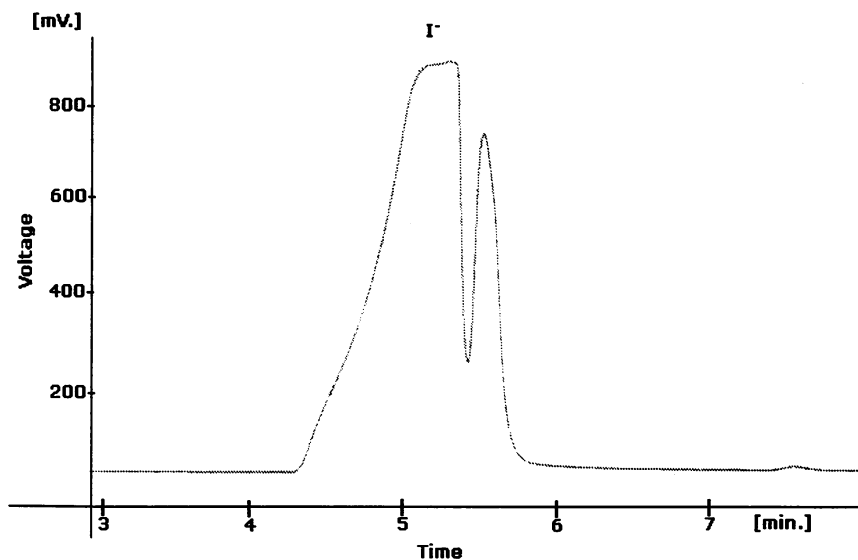


3.3 HPLC Chromatograph of $\text{Na}^{125}\text{IO}_4$

Iodine samples were subjected to cycles of oxidation using CAT and peroxide. Formation of a number of different iodine species was demonstrable. In addition to known species (IO_4^- , IO_3^- , I^- etc.) at least two other unknown species in varying amounts were documented. In case of CAT, IO_4^- was major product of oxidation. With peroxide we weren't able to identify product because of insufficient number of standards.



3.4 HPLC Chromatograph of NaI oxidized with CAT



3.5 HPLC Chromatograph of NaI oxidized with peroxide

11. Conclusion

In a study of radioiodine reaction and consequent TLC and HPLC analysis we proved presence of various iodine compounds. We positively identified some of them. These unknown compounds are species of radioiodine in higher oxidation states rather than radioiodine containing organic compounds and are responsible for positive radioiodination reaction even without use of CAT and thus resulting in irreproducible results.

To avoid this rather unwanted situation Sartor and Guhlke ⁶ developed simple and efficient method for purification and reduction of radioiodine with is achieved by treating the radioiodide solution with hydrazine in acidic solution.

Results from these studies demonstrate the effectiveness of HPLC in allowing a fast and reliable separation not only of various chemical forms of iodine but of a number iodinated radiopharmaceuticals as well. This method provides excellent resolution and appear superior to the commonly used TLC method.

12. References

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