SEPARATION OF IODINE-131 FROM NEUTRON IRRADIATED TELLURIUM USING HYDROGEN PEROXIDE

T. S. Murthy, V. C. Nair and S. G. Naik
Isotope Division, Bhabha Atomic Research Centre, Trombay, Bombay-85

INTRODUCTION

Iodine-131 is one of the most widely used radiolabels in medicine for diagnostic and therapeutic purposes, either directly as sodium iodide or in the form of iodine-131 labelled compounds. Hence, the production of this isotope assumes top priority in any isotope programme. Iodine-131 is produced during nuclear fission or by the pile irradiation of tellurium and its compounds.

\[
\begin{align*}
\text{Te}^{130}(n,\gamma) & \rightarrow \text{Te}^{131} \\
& \beta^- \rightarrow \text{I}^{131} \\
& 24.8 \text{ m} \\
& (\beta^- , \gamma) \rightarrow \text{Xe}^{131} \text{ stable}
\end{align*}
\]

When the former method is employed for production, enriched uranium irradiated for 2-3 weeks in the nuclear reactor is dissolved in nitric acid and the iodine-131 is distilled and collected. But separation of iodine-131 from pile irradiated tellurium targets is the most commonly used method of production. The methods of separation vary for different targets. With metal tellurium the target is dissolved in a mixture of sulphuric acid and chromic acid and the iodine is distilled off after reduction with oxalic acid. A dry distillation method is generally used when tellurium dioxide is used as the target. The methods of separation take a little more than a day for completion and it was of interest to develop a speedier method. In the Isotope Laboratory at Trombay, we have developed a new method based on the dissolution of neutron irradiated tellurium in hydrogen peroxide and sodium hydroxide followed by acidification and distillation of the iodine-131. The present paper is an extension of this work in line with a method reported by Gleason wherein tellurium is directly dissolved in hydrogen peroxide and sulphuric acid.

EXPERIMENTAL

E. Merck tellurium and all other reagents of analytical grade were used in the experiments. In the dissolution experiments 5 grams of tellurium and 30 ml. of 100 vol. hydrogen peroxide containing the required amount of sulphuric acid diluted to 100 ml. were refluxed in a round bottom flask. In the distillation studies the total volume of the reaction mixture was maintained at 300 ml. The apparatus consisted of a two necked 1 litre distillation flask and a 3 necked 1 litre receiver flask with an iodine trap, connected by a right-angled bridge having a splash head at one end and a water condenser at
the other end. In the modified version the two limbs of the bridge were replaced by two feet long water condensers. The yield of iodine-131 was estimated by counting the initial and final samples in a well type thallium activated sodium iodide scintillation detector at the 0.36 MeV iodine photo-peak and comparing the values after accounting for dilution.

RESULTS AND DISCUSSION

a) Dissolution of Tellurium in Hydrogen Peroxide and Sulphuric Acid

While studying the distillation of iodine-131 from acidified solutions of sodium tellurate prepared by dissolving tellurium in sodium hydroxide and hydrogen peroxide, the effect of adding tellurium was investigated. It was found that tellurium dissolved completely and the yield of iodine-131 remained unaffected so long as there was enough hydrogen peroxide present (5). Hence, the dissolution of tellurium in hydrogen peroxide at various concentrations of sulphuric acid was studied, with a view to developing it as a method of production. Very little tellurium dissolved when the acid concentration was below 7N. Addition of more hydrogen peroxide, prolonged refluxing or increasing the total volume did not have any effect in bringing the tellurium into solution. In the concentration range of 7-13 N the tellurium dissolved completely in about 10-15 minutes. Above 13 N tellurium did not go into solution. This may be due to the formation of a thin film of telluric acid over the tellurium powder.

b) Distillation of Iodine-131 from the Dissolution Mixture

In our studies reported earlier (5) the distillation of iodine-131 from sulphuric acid solutions of telluric acid containing hydrogen peroxide the yield was found to be independent of the concentration of sulphuric acid beyond 5N. Considering various factors like smooth dissolution of tellurium, time of distillation and acid carried over, the acid strength was fixed at 9N and a few experiments were carried out doing dissolution of tellurium and distillation of iodine-131 simultaneously. The distilled iodine was absorbed in sodium hydroxide. The yield was found to vary from 40-60% for the same 75 minutes distillation period. In view of the fact that nearly 90% of the iodine distilled under identical conditions in the earlier work (5), this result was a little unexpected. The only probable reason that could be attributed to this low fluctuating yield was the carry-over of iodine-131 along with the decomposed oxygen from hydrogen peroxide. This was confirmed by the unusually high iodine-131 activity recovered from the iodine-131 trap over the receiver flask. To counteract this the limbs of the bridge tube were replaced by two 2 feet long water condensers and the mixture was refluxed for about 25 minutes before distillation to ensure complete dissolution of tellurium and decomposition of bulk of the excess hydrogen peroxide. With this modification, an yield of about 88% was obtained for 75 minutes distillation in a series of experiments at 9 N. The distillate took about 5 ml i N sodium hydroxide for adjusting the pH to about 8. The time of distillation can be reduced with increasing acid concentration. But there will be the disadvantage of increased
acid carry-over in the distillate.

Two experiments at production scale were carried out using 25 grams of tellurium. The total volume of the dissolution mixture was maintained at 500 ml. and acid normality 9 N with the volume of 30% hydrogen peroxide added being 150 ml. Here again the yield over a period of 75 minutes distillation was about 85%, with practically very little iodine distilling in the next 15 minutes.

c) Purity of the Product Solution

Distillate from production scale runs were concentrated to about 20 ml. and were analysed for radiochemical purity as well as the presence of other elements. More than 95% of the iodine-131 was found to be in the form of iodide by paper chromatography(7). Spectrographic analysis showed that the elements Al, As, Ag, Be, Mn, Sn, Te, B, Ca, Cs, Cr, Fe, Ilg, Ni and Pb were all present in less than 2 ppm. Only silicon was found to be of the order 10 ppm. These purity conditions are satisfactory for its use in medicine for oral administration(8).

ACKNOWLEDGEMENT

The authors are thankful to Dr. V. K. Iya, Head, Isotope Division, BARC, for his keen interest in the work and also to Shri N. G. S. Gopal, Head, Quality Control Section, for the analysis of the samples.

REFERENCES

2. V. K. Iya, T. S. Murthy, K. R. Balakrishnan and V. C. Nair; AEET/Radiochem/50 (1964)
3. K. Taugbol and K. Samasahl; JENER/34 (1954)
5. T. S. Murthy and V. C. Nair; Indian J. Chem. 5(7) 337 (1967)
6. G. I. Gleason; U. S. Pat. 3, 107, 155 (to Abbot Labs.) (15th October, 1965)

DISCUSSION

B. M. Patel : What is the purity of your starting chemical Te?

V. C. Nair : Chemically pure tellurium supplied by E. Merck Chemical Company was used for irradiation.
STUDIES ON THE STABILITY AND SHELF-LIFE OF SOME LABELLED RADIOPHARMACEUTICALS

C. N. Desai, R. S. Mani and T. P. Prabhu
Isotopes Division, Bhabha Atomic Research Centre, Trombay, Bombay-85

Radio pharmaceuticals are routinely used in diagnostic nuclear medicine. For this purpose they are required to be of the highest purity and high specific activity. These products, however, undergo decomposition during storage due to self-irradiation and radiolysis. The consequences of this problem are encountered by the radiopharmaceutical manufacturer and also the users. In view of this, stability studies of radiopharmaceuticals are carried out so that the degree of decomposition and preventive measures to minimise the latter are known.

In the case of radioactive pharmaceuticals, in addition to chemical and pharmaceutical stability, one needs to examine their radiation stability also. This is mainly because radiations are sufficiently energetic to degrade the chemical compounds through their ionising and oxidising effects which are known as primary and secondary effects. As a consequence of this, radiopharmaceuticals are usually less stable than their non-radioactive counterparts.

The decomposition of labelled compounds depends on the amount of radiation energy absorbed by the compound itself or its environs during its useful life. The percentage decomposition can be correlated with the "G(-M)" values - defined as the molecules permanently altered or decomposed per 100 ev (energy) of ionizing radiation absorbed. "G(-M)" value of some of the labelled compounds has been determined. Generally, high "G(-M)" values indicate less stability.

In addition to radiation, factors such as oxidation, hydrolysis influence chemical decomposition of the labelled compounds, since the latter are often used in very dilute solution. It is also essential to guard against photochemical, microbiological decomposition and also the decomposition caused by inactive impurities. Several of the iodo-organic compounds (Rose Bengal, Hippuran, Hypaque, cholangiographyn etc.) are sensitive to light, and their labelled preparations should be stored in amber-glass containers to prevent photochemical decomposition.

This paper reports the stability studies carried out on radioiodine labelled radiopharmaceuticals such as Tetrachloro-(P)-tetra-iodo-(R)-fluorescein (Rose Bengal), sodium orthoiodo hippurate (Hippuran), Glyceryl-trioleate (Triolein), oleic acid, Human serum albumin (HSA), L-Trilodothyronine (TIT), Thyroxine (T\textsubscript{4}) and sulfobromophthalein (BSP). Table I
illust"rates the specifications and diagnostic use of some of the radio-
pharmaceuticals supplied by the Isotope Division, Bhabha Atomic Research
Centre, Trombay(6).

EXPERIMENTAL

Several lots of the individual radiopharmaceuticals were stored under
different conditions of temperature, pH, specific activity and radioactive concentration and examined over a regular interval of time for several weeks.

In a few cases, trace concentration of (i) known metallic impurities
and (ii) oxidising agents were added and their effect on radiochemical purity
was studied e.g. Rose Bengal, Hippuran, Cholographyn and BSP.

It has been observed that metallic impurities such as silver, copper
and cadmium as well as oxidising agents such as H2O2 have deteriorating
effects when their concentrations exceed the optimum value(7).

The samples of radioactive pharmaceuticals were checked for free
iodide by paper electrophoresis using veronal buffer pH 8.6 for 1 hour at
200 volts. The free iodide migrates 10-12 cms from the point of spotting
whereas the labelled compounds remain very near the point of spotting. The
percentage free iodide was calculated by counting and/or scanning the electrophoretograms.

The integrity of labelling defined by the radiochemical purity was
ascertained by ascending paper chromatography using Whatman No. 3 paper,
e.g., Rose Bengal I\textsuperscript{131} on paper chromatographic analysis in ethanol: ammonia:
water moves with $R_f = 0.42$ while the lower halogenated fluoresceins have
different $R_f$ values(8).

Hippuran-I\textsuperscript{131} has the $R_f = 0.5$ while the probable impurity O-ido-
benzoic acid and free iodide have the $R_f$ values 0.8 and 0.1 respectively in

The absorption spectra of the labelled compounds and the molar
absorbance values were determined over a period of storage. This gave
some indication of radiation induced decomposition in a few cases e.g. Rose
Bengal ($\lambda_{max} 550 \text{ m} \mu$) and BSP ($\lambda_{max} 585 \text{ m} \mu$).

In the case of labelled iodo-thyronines their radiochemical purity was
also determined by thin layer chromatography using silica gel(10) in addition
to the paper chromatographic analysis(11). These techniques reveal the
presence of the possible contaminating impurities such as MIT, DIT etc.

Triolein-I\textsuperscript{131}, oleic acid-I\textsuperscript{131} were chromatographed on a standard-
ized silicic acid column and their elution patterns were compared(12).
Radio-iodinated human serum albumin was examined for degraded labelled polypeptides using DEAE sephadex A-50 and DEAE-cellulose columns (13).

In a few specific instances, electivity tests and other suitable biological tests were also carried out to evaluate the presence of biologically unacceptable trace impurities produced by radiolysis e.g., denatured protein in RIHSA and labelled hormones (14).

REMARKS

1. Even under ideal conditions of storage, the labelled radiopharmaceutical formulations show contamination of small percentages of labelled impurities, essentially of an organic nature. However, these are yet to be characterized in detail. Quantitatively speaking the main impurity is free iodide. The latter could be controlled to less than 5% by storing the compounds (i) at 0-2°C (ii) by keeping the pH 6-8 (iii) maintaining the radioactive concentration upto 3.0 mCi/ml (iv) having the sp. activity exceeding in many cases 1 c/m M during the storage period of 4 weeks for (I-131) and 12 weeks for (I-125) labelled compounds.

2. Stability studies help us (i) to select suitable labelling radio-nuclide for specific biological studies, (ii) to supply and use better radiopharmaceuticals with high purity suitable as genuine tracers, (iii) to assign acceptable shelf-life for the radiopharmaceuticals. However, it must be noted that due to the limited sensitivity of analytical methods and lack of complete knowledge of radiation chemistry of these labelled compounds, the exact nature of the breakdown products becomes difficult to be predicted.

3. The shelf-life of iodine labelled radiopharmaceuticals can be prolonged by (i) adding protective agents (e.g., inactive human serum albumin in I\(^{131}\) and I\(^{125}\) labelled RIHSA (ii) sequestering free iodide using silver salt impregnated silver saddles e.g., I\(^{131}\) radio hippuran (iii) continuous removal of free iodide using sterile ion exchange resins enclosed in dialysis membrane (15).

4. Insufficient purification procedures decrease the stability and hence the shelf-life of radioactive pharmaceuticals.

5. I\(^{125}\) labelled compounds are more stable than the corresponding I\(^{131}\) labelled compounds mainly because of absence of \(\beta\)-emission which indicates that \(\beta\)-rays accelerate the radiation decomposition of labelled compounds.

ACKNOWLEDGEMENTS

The authors wish to thank Dr. V.K. Iya for the keen interest taken by him in this work.
REFERENCES

1. R. J. Bayly and E. A. Evans; J. Labelled Compounds 2, 1 (1966)
3. B. M. Tolbert; Advances in Tracer Methodology (Third Symposium) p. 64 (1959)
5. V. K. Iya, R. S. Mani and C. N. Desai; Synthesis of Labelled Molecules (to be published)
9. R. S. Mani; (Unpublished observations)
14. K. N. Jeejeebhoy; (personal communication)
15. W. H. Blahd; Nuclear Medicine, McGraw Hill, N. Y. p. 149 (1965)
J. P. Mittal : (1) What do you think is the mechanism of free iodide production in the system (i.e., I\textsuperscript{−})?

(2) Do you think I\textsuperscript{−} is produced via a free radical or ionic mechanism? I am asking this question because, if we know the mechanism by which I\textsuperscript{−} is produced, it may be easier for you to develop or find better so-called 'preservatives'.

(3) If it is due to dissociative electron capture by iodo gp i.e., RI + e\textsuperscript{−} → R + I\textsuperscript{−}, then various electron scavengers can be tried as potential 'protectors'.

C. N. Desai : (1) & (2). It is not possible to say exactly whether it is a free radical or ionic mechanism in the cases we have studied since the radiation chemistry of these compounds has not been adequately studied. But it is quite probable that free radical and/or ionic mechanism must be involved in all the cases.

(3) I agree with you.

Manohar Lal : What is the purpose of using cysteine HCl in your studies?

C. N. Desai : It serves as a preservative, probably by acting as a reducing agent and/or by sequestering the free radicals.

P. N. Moorthy : What is meant by free iodide? Free iodine or inorganic iodide ion?

C. N. Desai : Of course, inorganic iodide.
**TABLE I**

<table>
<thead>
<tr>
<th>S No.</th>
<th>Product</th>
<th>Chemical &amp; Pharmaceutical form</th>
<th>Sp. Act mCi/mg</th>
<th>Radioactive concn mCi/ml</th>
<th>Diagnostic use and Dose in uCi</th>
<th>Recommended shelf-life**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Rose Bengal* [131]</td>
<td>Rose Bengal injection</td>
<td>Upto 5.0</td>
<td>Upto 0.0</td>
<td>Liver function (10-25)</td>
<td>4 weeks at 0-2°C</td>
</tr>
<tr>
<td>2.</td>
<td>Hippuran* [131]</td>
<td>Hippuran injection</td>
<td>Upto 2.0</td>
<td>Upto 2.5</td>
<td>Kidney function (10-50)</td>
<td>4 weeks at 0-2°C</td>
</tr>
<tr>
<td>3.</td>
<td>Radioiodinated Human serum albumin</td>
<td>RISA* [131] injection</td>
<td>Upto 5-15 atoms of iodine/molecule of protein</td>
<td>Upto 1.0</td>
<td>1. Plasma &amp; blood volume (3-20); 2. Cardiac output (10-100); 3. Detection &amp; localization of brain tumors (100-500)</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>RISA-[125]</td>
<td>RISA* [125] injection</td>
<td>-do-</td>
<td>Upto 0.5</td>
<td>-do-</td>
<td>12 weeks at 0-2°C</td>
</tr>
<tr>
<td>5.</td>
<td>Triolein-[131]</td>
<td>Triolein [131] in olive oil (non-injectable)</td>
<td>Upto 50% saturation</td>
<td>Upto 0.0</td>
<td>Fat absorption studies (25-50); -do-</td>
<td>4 weeks at 0-2°C</td>
</tr>
<tr>
<td>7.</td>
<td>Triolein-[125]</td>
<td>Triolein [125] in olive oil (non-injectable)</td>
<td>-do-</td>
<td>Upto 2.5</td>
<td>-do-</td>
<td>12 weeks at 0-2°C</td>
</tr>
<tr>
<td>8.</td>
<td>Oleic acid-[125]</td>
<td>Oleic acid [125] in oleic acid (non-injectable)</td>
<td>-do-</td>
<td>Upto 2.5</td>
<td>-do-</td>
<td>12 weeks at 0-2°C</td>
</tr>
<tr>
<td>9.</td>
<td>L-TIT-[131]</td>
<td>L-TIT-[131] in 50% aqueous propylene glycol (pH 6-7)</td>
<td>Upto 20</td>
<td>Upto 5.0</td>
<td>Thyroid function studies (less than 1 uCi)</td>
<td>4 weeks at 0-2°C</td>
</tr>
<tr>
<td>10.</td>
<td>L-T4-[131]</td>
<td>L-T4-[131]</td>
<td>Upto 20</td>
<td>Upto 5.0</td>
<td>do- (20-150)</td>
<td>-do-</td>
</tr>
<tr>
<td>11.</td>
<td>L-TIT-[125]</td>
<td>L-TIT-[125] in 50% aqueous propylene glycol (pH 6-7)</td>
<td>Upto 10</td>
<td>Upto 2.0</td>
<td>Thyroid function studies (less than 1 uCi)</td>
<td>12 weeks at 0-2°C</td>
</tr>
<tr>
<td>12.</td>
<td>L-T4-[125]</td>
<td>L-T4-[125] in 50% aqueous propylene glycol (pH 6-7)</td>
<td>-do-</td>
<td>-do-</td>
<td>Thyroid function studies (20-150)</td>
<td>12 weeks at 0-2°C</td>
</tr>
<tr>
<td>13.</td>
<td>**BSP-[131]</td>
<td>BSP*-[131]</td>
<td>Upto 2.5</td>
<td>Upto 1.0</td>
<td>Liver function (10-50)</td>
<td>4 weeks at 0-2°C</td>
</tr>
</tbody>
</table>

**From the date of analysis**
**Supplied in sterile, pyrogen-free aqueous solution at pH 6-7 on special request**
**Supplied in sterile, pyrogen-free aqueous solution at pH 6-7**

* Supplied in sterile, pyrogen-free aqueous solution at pH 6-7.