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Efficient production of therapeutic doses of [^{131}I]-metaiodobenzylguanidine for clinical use

G. Prabhakar, Anupam Mathur, G. Shunmugam, Y.D. Teje, S.S. Sachdev, N. Sivaprasad *

Radiopharmaceuticals Program, Board of Radiation and Isotope Technology (BRIT), Sec. 20, Vashi, Navi Mumbai 400705, India

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ABSTRACT

[^{131}I]-metaiodobenzylguanidine (mIBG) is a known radiopharmaceutical used for the treatment of neuroendocrine tumors. The development of therapeutic [^{131}I]-mIBG doses at production level is highly challenging due to rapid product degradation and high radiation exposures to the production plant personnel. In the present work, a working module for the production of 10 doses (100 mCi each) in a single operation was developed following copper (I) assisted isotope exchange. The labeled product complies with the pharmaceutical specifications suitable for in-vivo patient use.

1. Introduction

[^{131}I]-Metaiodobenzylguanidine (mIBG) is used worldwide for the diagnosis and therapy of neuroendocrine tumors, in particular, adrenal medullae tumors. These tumors store and secrete large amount of catecholamines, which is of high risk to the patients (Wieland, 1986). [^{131}I]-mIBG due to its structural similarity with norepinephrine, enters the cell of neuroendocrine tumors by active type I amine uptake mechanism (McEwan et al., 1985) and gets localized, making it highly sensitive and specific tool for the detection and treatment of tumors.

[^{131}I]-mIBG is mainly produced by isotope exchange of the cold mIBG ligand for clinical use (Vaidyanathan, 2008). Several exchange labeling methods, involving use of ammonium sulphate (Mangner et al., 1982) and copper (I and II) salts as catalyst (Neves et al., 1992; Stanko et al., 1984; van Doremalen and Janssen, 1985), have been used for improving the labeling yield of the reaction and the specific activity of the product. The in-situ copper (I) catalyzed reaction has yielded the product with best radiolabeled specifications (Wafelman et al., 1994). In an attempt to increase the tumor efficacy of the labeled [^{131}I]-mIBG and eliminate the possibilities of pharmacological effects associated with unlabeled mIBG, a number of methods for the preparation of no carrier added (NCA) [^{131}I]-mIBG were attempted (Vaidyanathan, 2008). The preparation of NCA [^{131}I]-mIBG from silyl (Vaidyanathan and Zalutsky, 1993) or stannyl derivatives (Samnick et al., 1999; Vaidyanathan et al., 2007) or polymer supported tin precursor (Hunter and Zhu, 1999) is of immense interest and has shown considerable promise in vitro and is presently under clinical trial.

The diagnostic doses of [^{131}I]-mIBG vary from 0.5 to 1 mCi per patient (McEwan et al., 1985), however, single therapeutic dose ranges from 100 to 300 mCi with a mean cumulative dosage of 3.3 doses per year (Chrisoulidou et al., 2007). The total therapeutic dosage to the patient, however, is variable, with the limiting factor being the total radiation dose to the patient bone marrow. Some of the therapeutic protocols recommend an initial single therapeutic dosage of 300–800 mCi for favorable therapeutic response (Chrisoulidou et al., 2007). To meet the increasing demands, a working protocol for the large scale production of therapeutic doses of [^{131}I]-mIBG is essential. However, the development of therapeutic doses of [^{131}I]-mIBG in bulk level is very challenging as it involves handling of high levels of ^{131}I radioactivity thereby increasing the radiation risk to the production personnel. Also, high radioactive concentrations of the therapeutic product formulations lead to poor product stability thereby limiting its clinical utility over short period and supply to Nuclear Medicine Centres in close proximity.

In the present work, the authors have presented a working module for the preparation of therapeutic doses of [^{131}I]-mIBG, for the regular production of 10 doses of 100 mCi each in a single production batch, with increased product shelf-life and reduced radiation burden to the plant operating personnel. The authors present here the production results of 25 batches of therapeutic doses supplied to various Nuclear Medicine Centres.

* Corresponding author. Tel.: +91 22 27887200; +91 22 27887218.
E-mail address: drnsivaprasad@rediffmail.com (N. Sivaprasad).

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2. Experimental

2.1. Materials and method

The radiolabeling was carried in a 2 inch lead shielded glove box plant, fitted with charcoal and HEPA filters, having a negative pressure of 3 cm water gauge and equipped with UV-tube, dry heat bath, de-capping tool, crimping tool, moving trolley with a provision of keeping sterile vials, pantograph with a pipette and vacuum line. mIBG was obtained from M/s ABX Chemicals, Germany. Copper sulphate, sodium metabisulphite, glacial acetic acid, sodium acetate, benzyl alcohol and Dowex 1×8 resin were procured from Merck, India. All the reagents used were of analytical grade. [^{131}I]-sodium iodide was obtained from Dhruva Reactor, Bhabha Atomic Research Centre (BARC), India. Fission produced [^{131}I] sodium iodide was procured from NTP Radioisotopes Private Limited, South Africa. Whatman no.1 chromatography paper was used for the paper chromatography (PC) and paper electrophoresis. Sterile 0.22 μm membrane syringe filter was procured from Millipore, India. The radioactivity profile of PC and paper electrophoresis strips were determined using GINA-Star TLC evaluation system, Germany. Dry heat bath was procured from M/s Neo Lab Instruments, India.

2.2. Radiolabeling

[^{131}I]-mIBG was prepared by copper (I) assisted nucleophilic isotope exchange reaction (Neves et al., 1992). The schematic representation for the synthesis set-up for the production of Therapeutic [^{131}I]-mIBG is shown in Fig. 1. In a typical procedure, 2–4 mg of cold mIBG, 5–6 mg sodium metabisulphite, 68 μg

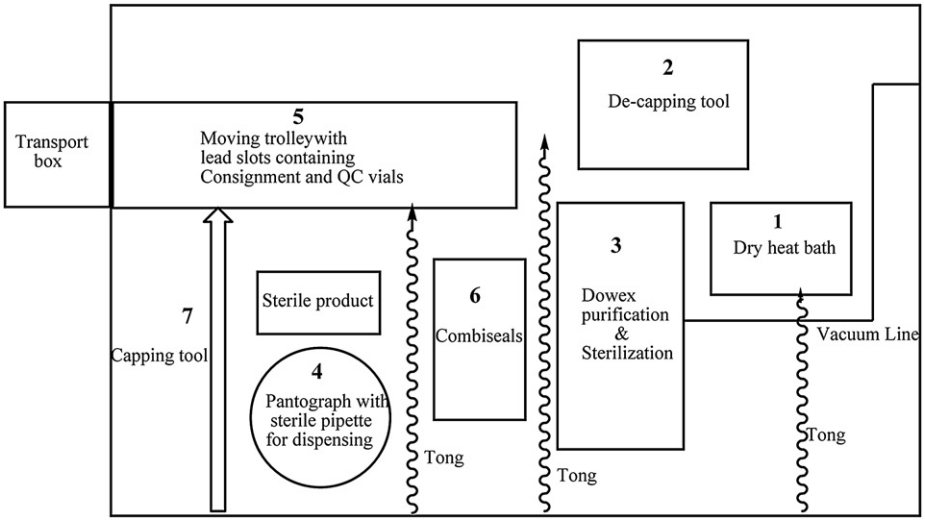

Fig. 1. Schematic representation of the synthesis set-up for the production of [^{131}I]-mIBG therapeutic doses.

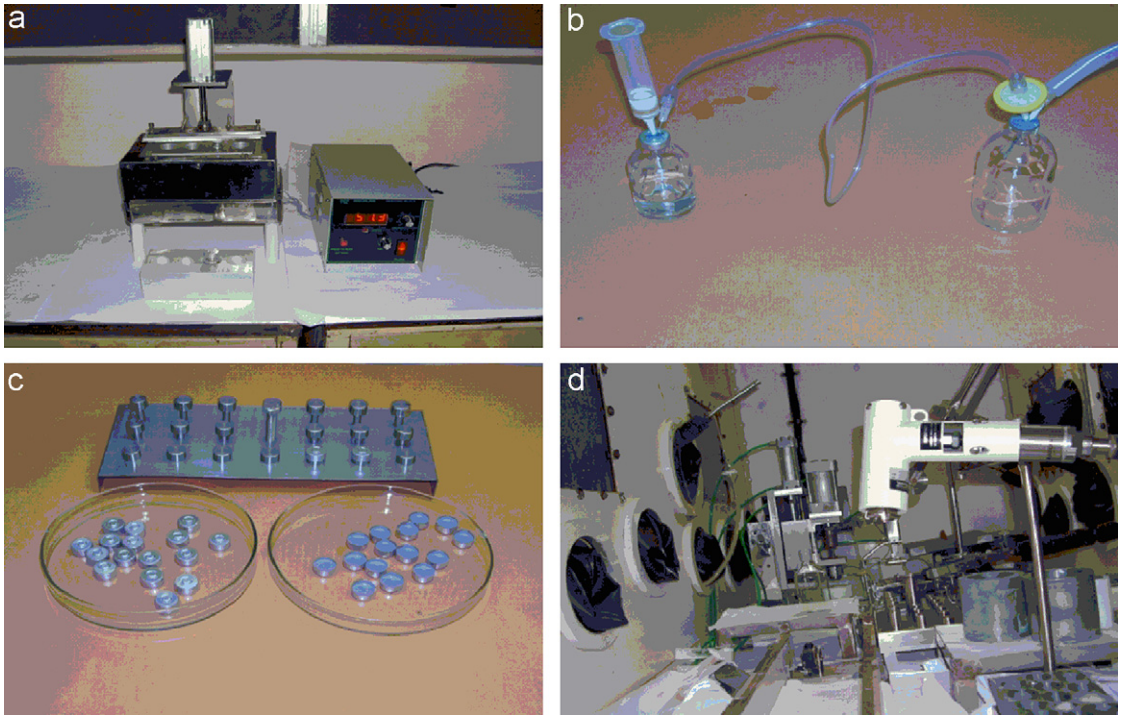

Fig. 2. (a) Dry heat bath (b) Syringe Dowex column along with sterilization assembly under vacuum (c) Combiseals along with its holding base (d) Crimping tool.