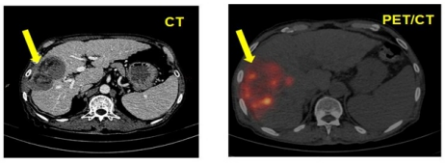
यकृत के घातक रोगों का किफायती उपचार

14

भारत में यकृत रोगों के किफायती उपचार के लिए यिट्रिया [^{90}Y] एल्युमिनो सिलिकेट ग्लॉस माइक्रोस्फियर (भाभास्फियर) का विकास, मूल्यांकन और मानव पर क्लीनिकल ट्रांसलेशन

के. वी. विमलनाथ [1], ए. राजेश्वरी [1], अनुपम दीक्षित [2], शरद पी. लोहार [1], रुबेल चक्रवर्ती [1,3], मधुमिता गोस्वामी [2,3] और सुदीप्त चक्रवर्ती [1,3]*

[1]विकिरणभेषज प्रभाग, भाभा परमाणु अनुसंधान केंद्र, ट्रांबे -400085, भारत
[2]ग्लास एवं प्रगत पदार्थ प्रभाग ,भाभा परमाणु अनुसंधान केंद्र ,ट्रांबे -400085,भारत
[3]होमी भाभा राष्ट्रीय संस्थान, प्रशिक्षण विद्यालय परिसर, अणुशक्तिनगर, मुंबई -४०००९४



90 एम. सी. आई. [^{90}Y] वाई. ए. एस. ग्लास माइक्रोस्फियर के प्रयोग के 24 घंटे बाद दाहिने लोब हेपेटोसेलुलर कार्सिनोमा के साथ एक 56y पुरुष रोगी की पोस्ट-थेरेपी पी. ई. टी./सी. टी. छवि जो जैव वितरण दिखाती है।

सारांश

[^{90}Y] यिट्रिया एल्युमिनो सिलिकेट ([^{90}Y] YAS) ग्लॉस माइक्रोस्फियर (भाभास्फियर) का बेंच टू बेड क्लीनिकल ट्रांसलेशन, यूएस एफडीए द्वारा अप्रमाणित यकृत कैंसर के निदान के लिए अनुमोदित थेरास्फियर® का एक बायोसिमिलर फॉर्मूलेशन, प्राप्त किया गया है। संरचना $40Y_2O_3$-$20Al_2O_3$-$40SiO_2$ (w/w) एवं 20-36 µm के बीच के व्यास के YAS ग्लास माइक्रोस्फियर को न्यूट्रॉन को 7 डी के लिए ~ 1.4×10^{14} n.cm^{-2}.s^{-1} के थर्मल फ्लक्स पर किरणित किया गया ताकि आंतरिक रूप से विकिरणचिह्नित [^{90}Y] YAS ग्लॉस माइक्रोस्फियर का उत्पादन किया जा सके। मानव नैदानिक उपयोग के लिए संरूपण की उपयुक्तता स्थापित करने के लिए व्यापक रेडियोकेमिकल और जैविक अध्ययन किए गए थे। डीएई-आरपीसी से नियामक अनुमोदन प्राप्त करने के बाद, भाभास्फियर (50-180 एम. सी. आई.) की सोलह अनुकूलित मानव नैदानिक खुराकों को दस बैचों में तैयार किया गया और विकिरणभेषज प्रभाग, भापअ केंद्र से नैदानिक उपयोग के लिए आपूर्ति की गई।

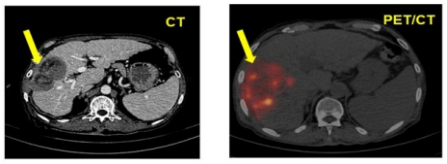
Affordable Treatment of Liver Malignancies

14

Development, Evaluation and Human Clinical Translation of [^{90}Y]Yttria Alumino Silicate Glass Microspheres (BhabhaSphere) for Affordable Treatment of Liver Malignancies in India

K. V. Vimalnath[1], A. Rajeswari[1], Anupam Dixit[2], Sharad P. Lohar[1], Rubel Chakravarty[1,3], Madhumita Goswami[2,3] and Sudipta Chakraborty[1,3]*

[1]Radiopharmaceuticals Division, Bhabha Atomic Research Centre, Trombay-400085, INDIA
[2]Glass & Advanced Material Division, Bhabha Atomic Research Centre, Trombay-400085, INDIA
[3]Homi Bhabha National Institute, Anushakti Nagar, Mumbai-400094, INDIA



Post-therapy PET/CT image of a 56y male patient with right lobe hepatocellular carcinoma 24 h after administration of 90 mCi [^{90}Y]YAS glass microspheres showing biodistribution

ABSTRACT

Bench to bed clinical translation of [^{90}Y]Yttria Alumino Silicate ([^{90}Y]YAS) glass microsphere (BhabhaSphere), a formulation biosimilar to US FDA approved TheraSphere® for treating unresectable liver cancer, is achieved. YAS glass microspheres of composition $40Y_2O_3$-$20Al_2O_3$-$40SiO_2$ (w/w) and diameter ranging between 20-36 µm was neutron irradiated at a thermal flux of ~1.4×10^{14} n.cm^{-2}.s^{-1} for 7 d to produce intrinsically radiolabeled [^{90}Y]YAS glass microspheres. Extensive radiochemical and biological studies were carried out to establish the suitability of the formulation for human clinical use. Subsequent to obtaining regulatory approval from DAE-RPC, sixteen customised human clinical doses of BhabhaSphere (50-180 mCi) were formulated in ten batches and supplied for clinical use from Radiopharmaceuticals Division, BARC.

KEYWORDS: *SIRT, Yttria Alumino Silicate (YAS) Glass microspheres, ^{90}Y, BhabhaSphere*

**Author for Correspondence: Sudipta Chakraborty*
E-mail: sudipta@barc.gov.in

Introduction

Liver malignancies, either primary or metastatic, are prevalent causes of cancer related deaths worldwide. Hepatocellular carcinoma (HCC), a form of neoplasm of liver cells, is common among the various types of liver malignancies constituting 90% of liver cancer [1-4]. Selective internal radiation therapy (SIRT), which involves intra-hepatic administration of customized doses of β-particle emitting radionuclide in suitable chemical form [Fig.1], is one of the most effective treatment modalities for management of unresectable liver carcinoma [5]. Intrinsically ^{90}Y [$T_{1/2}$ = 64.1h, E_{max} of β-emission = 2.28 MeV] labeled glass microspheres of 20-35 μ particle size range is extensively used radiotherapeutic agent for SIRT [5,6]. The radiotherapeutic agent is approved by US FDA for radioembolization therapy and is commercially available as TheraSphere® with personalized doses as per the therapy requirement. SIRT using TheraSphere® offers a well-tolerated treatment for patients with liver malignancies[7]. In our country, the nuclear medicine hospitals had to rely on import of this product at very high cost (each dose costing around US$ 10000-12000) for treatment of liver cancer patients, severely restricting its wider utility. This gave us the motivation toward indigenous development of ^{90}Y-labeled glass microsphere formulation biosimilar to TheraSphere®, which can be made available at an affordable cost for use in SIRT for treating patients in India suffering from unresectable liver carcinoma.

Yttria alumino silicate (YAS) glass microspheres having particle size in the range of 20-36 μm and chemical composition $40Y_2O_3$-$20Al_2O_3$-$40SiO_2$ (w/w) were synthesized following procedure developed indigenously and characterized to ensure their suitability in SIRT. Intrinsically ^{90}Y-labeled YAS glass microspheres ([^{90}Y]YAS glass microspheres) aka 'BhabhaSphere' were produced by thermal neutron irradiation of cold microspheres in Dhruva research reactor, BARC, such that ^{90}Y becomes an integral constituent of the glass microspheres. BhabhaSphere formulation is delivered to the tumor vasculature through hepatic artery via catheterisation [Fig.1]. The radioactive glass microspheres then penetrate the tumor arteriolar capillaries where they emit lethal beta radiation that is localised to the surrounding tumor tissue. The targeted distribution of microspheres provides high absorbed dose coverage to the tumor while sparing normal tissue.

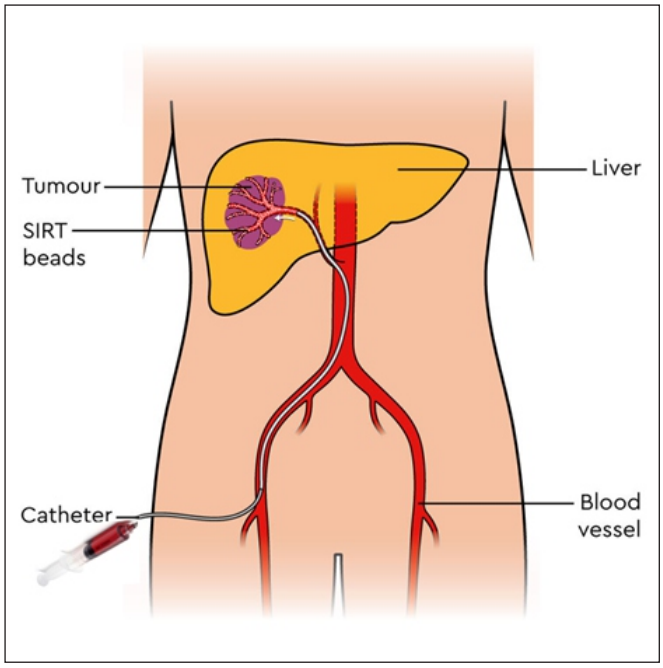


Fig.1: Schematic representation of Selective Internal Radiation Therapy (SIRT) process.

Materials and Methods

Yttria Alumino Silicate (YAS) glass having composition $40Y_2O_3$-$20Al_2O_3$-$40SiO_2$ (wt.%) was prepared by melt-quench process. The glass frits are slowly ground and glass particles of 20-36 mm size range were segregated by sieving. These feed glass particles were converted to glass microspheres by flame spheroidization using H_2-O_2 torch. Subsequently, the microspheres were screened to remove the particles with defects, cleaned with acetone and further heated in a furnace to remove organic impurities. YAS glass microspheres prepared were analyzed under SEM to check for sphericity, size and visible defects. XRD and SAXS are recorded before and after neutron irradiation to observe the glassy nature of the microspheres and evaluate post irradiation surface changes. Analysis of chemical composition of all batches of YAS glass microspheres were carried out by EDXRF and ICP-OES techniques.

Typically, 80-100 mg YAS glass microspheres were taken in a quartz ampoule [5 mm (ϕ) × 12 mm (h)], sealed and irradiated at thermal neutron flux of ~1.4×10^{14} n.cm^{-2}.s^{-1} for 7 days after placing inside a standard Al irradiation container. Post irradiation, quartz ampoule is opened inside a glove box and the irradiated glass microspheres [^{90}Y]YAS transferred into a sterile bottom tapered quartz container. Radioactive glass microspheres were washed twice using sterile water for injection. Finally, 0.6 mL sterile water for injection was added to [^{90}Y]YAS glass microspheres, sealed and autoclaved.

Radioactivity content of ^{90}Y in [^{90}Y]YAS glass microsphere formulation was measured in a pre-calibrated isotope dose calibrator. Radionuclidic purity (RNP) was determined by recording γ-ray spectra of an aliquot withdrawn from [^{90}Y]YAS glass microsphere formulation using an HPGe detector coupled to a 4K MCA system. For determination of radiochemical purity (RCP), the radioactive glass microspheres were allowed to settle and ^{90}Y activity of a measured aliquot from the supernatant was determined. Specific activity was calculated as ^{90}Y activity (mCi) produced per mg YAS irradiated. Sterility of the [^{90}Y]YAS glass microsphere formulation was tested by Direct Inoculation method and pyrogenicity by Gel Clot-BET assay method as per approved Indian Pharmacopeia (IP) procedures.

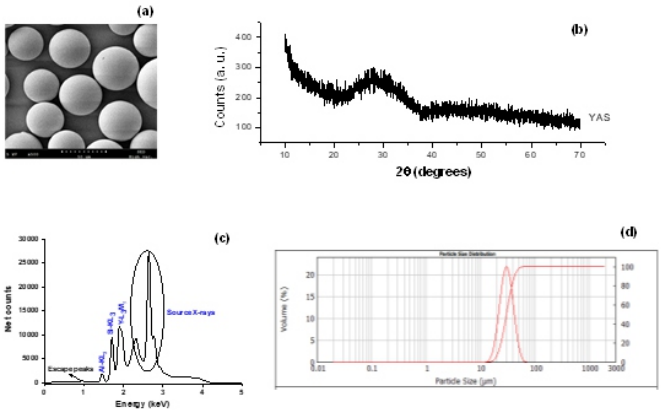


Fig.2: Characterization of YAS microspheres: (a) SEM image (b) XRD pattern (c) EDXRF spectrum (d) particle size distribution.

Biodistribution studies of [^{90}Y]YAS glass microsphere were performed in a group of healthy male Wistar rats each weighing 200-250 g. Appropriately diluted aliquots of [^{90}Y]YAS glass microsphere formulations (0.1 mL, ~135 mCi radioactivity) were injected through portal vein of each animal. Uptake of [^{90}Y]YAS glass microsphere in different organs and tissues are calculated and expressed as percentage injected activity (dose, % ID) per organ. Animal experiments were performed in compliance with national laws for conducting animal experimentations in India with prior approval of Institutional Animal Ethics Committee of Bhabha Atomic Research Centre (BARC).

A proposal comprising comprehensive experimental data for six independent batches was submitted to Radiopharmaceutical Committee of Department of Atomic Energy (DAE-RPC) seeking approval for formulation and deployment of 'BhabhaSphere' for human clinical use. Subsequent to DAE-RPC approval, first clinical investigation of [^{90}Y]YAS glass microsphere formulation was carried out in a male patient (56 y) with right lobe hepatocellular carcinoma. Customized dose of 90 mCi of [^{90}Y]YAS glass microsphere formulation was administered through right hepatic artery. PET/CT images were recorded at 24 h post administration. Subsequently, 15 more customised human clinical doses of BhabhaSphere (50-160 mCi) were formulated in 10 batches and supplied for clinical use.

Results and Discussion

YAS glass microspheres were synthesized using flame spheroidization process with conversion efficiency of almost 100% and sphericity >99%. SEM images (Fig.2(a)) confirmed high degree of sphericity and uniformity. XRD pattern (Fig.2(b)) confirmed its glassy nature. EDXRF spectrum is shown in Fig.2(c) confirmed chemical purity. Particle size distribution (Fig.2(d)) showed >90% of particles were within the range of 20-36 m.

Intrinsically [^{90}Y]Y-labeled glass microspheres were produced with specific activity of 3.9 ± 0.3 μCi ^{90}Y/mg of microspheres that corresponds to ~0.183 μCi (~6800 Bq) ^{90}Y per microsphere. RNP and RCP of formulations were >99.9% and >99.0% respectively, desirable for human clinical applications. Sterility and bacterial endotoxin tests (BET) revealed that all batches of [^{90}Y]YAS glass microsphere formulations were sterile and with <175 EU bacterial endotoxin content.

[^{90}Y]YAS glass microspheres exhibited excellent in vitro stability with regard to release of ^{90}Y activity from the formulation when stored at 37^{0}C in physiological saline and in human serum. Biodistribution pattern of [^{90}Y]YAS glass microspheres revealed excellent retention of administered microparticles in liver (97.62 ± 0.68 %ID at 24 h and 94.23 ± 0.57 %ID at 144 h p.i.). First human clinical investigation was carried out at Tata Memorial Hospital, Parel, where a customized dose of 90 mCi of [^{90}Y]YAS glass microspheres was administered in a 56 year male patient with right lobe hepatocellular carcinoma. Figures. 3a and 3b present the trans-axial CT and PET/CT images of liver of the patient 24 h post administration. Target specific localization and near-complete retention of the formulation in the cancerous site is evident from images. Therapeutic dose of the [^{90}Y]YAS glass microsphere formulation, injected into the patient was well tolerated by the patient, as no adverse side effects of the therapeutic procedure were reported. Total 16 human clinical doses of BhabhaSphere (50-160 mCi) were formulated in 11 batches and supplied for human clinical use from Radiopharmaceuticals Division, BARC. In-house developed BhabhaSphere formulation is envisaged to be made commercially available at cost of ~ Rs. 80,000 (US$ 1000) per patient dose as against US$ 10000-12000 per patient dose of imported TheraSphere®

Conclusion

Preparation of ready to use therapeutic doses of [^{90}Y]YAS glass microsphere aka 'BhabhaSphere' suitable for clinical use in the treatment of unresectable liver cancer in patients in India is achieved. YAS glass microspheres were prepared by flame spheroidization process and [^{90}Y]YAS doses were formulated with radionuclidic and radiochemical purity suitable for clinical use. Human clinical evaluation in patient with hepatocellular carcinoma showed near-quantitative retention of the formulation in the injected lobe by post-therapy ^{90}Y-PET scans. Indigenous development of ^{90}Y-labeled glass microsphere (BhabhaSphere) is a significant achievement that will be utilized in the management of inoperable liver cancer in India at affordable cost.

Acknowledgment

Authors gratefully acknowledge contributions of Reactor Operation Division and Radiation Biology and Health Sciences Division, BARC; and Tata Memorial Hospital, Parel. Authors sincerely express their gratitude to Associate Director, Radiochemistry and Isotope Group; Director, Materials Group; Head, Radiopharmaceuticals Division and Head, Glass and Advanced Materials Division, BARC for their keen interest and support to the program.

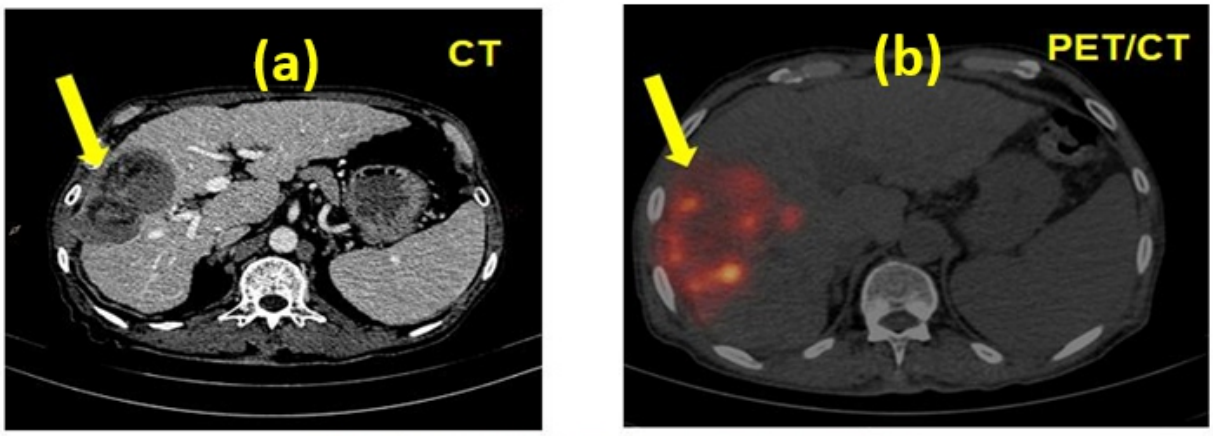


Fig.3: Post-therapy PET/CT image of a 56y male patient with right lobe hepatocellular carcinoma 24 h after administration of 90 mCi [^{90}Y]YAS glass microspheres showing biodistribution (a) trans axial CT of liver and (b) trans axial PET/CT of liver. (Image courtesy: Tata Memorial Hospital, Parel)

References

[1] Llovet J. M., Zucman-Rossi J., Pikarsky E., et al., Hepatocellular carcinoma, Nat. Rev. Dis. Prim., 2016, 2, 16018.

[2] Foerster F., Gairing S. J., Ilyas S. I., Galle P. R., Emerging immunotherapy for HCC: A guide for hepatologists, Hepatology, 2022, 75, 1604.

[3] European Association for the Study of the Liver, European Organisation for Research and Treatment of Cancer, EASL-EORTC clinical practice guidelines: Management of hepatocellular carcinoma, J. Hepatol., 2012, 56, 908.

[4] Shetty V. V., Kellarai A., Comprehensive review of hepatocellular carcinoma in India: Current challenges and future directions, JCO Global Oncol., 2022, 2200118.

[5] Ehrhardt G. J., Day D. E., Therapeutic use of 90Y microspheres, Int J Rad Appl Instrum B., 1987, 14, 233.

[6] Salem R., Fordon A. C., Mouli S., et al., Y-90 Radioembolization significantly prolongs time to progression compared with chemoembolization in patients with hepatocellular carcinoma, Gastroenterology, 2016, 151, 1155.

[7] Goin J. E., Salem R., Carr B. I., et al., Treatment of unresectable hepatocellular carcinoma with intrahepatic yttrium 90 microspheres: Factors associated with liver toxicities, J Vasc Interv Radiol., 2005, 16, 205.