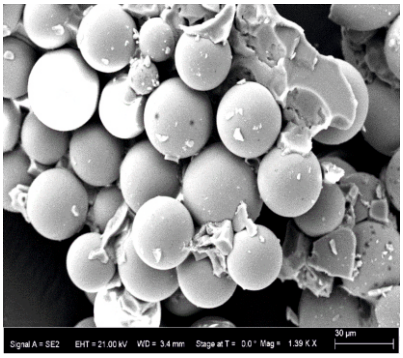
Glass for Affordable Radiotherapy

Development of Yttrium-Alumino-Silicate Glass Microspheres for HCC Radiotherapy Application

Senthil Kumar, R. S. Nair, A. Dixit, M. G. Sawant, P. Mollick, M. Goswami*, Ashok K. Arya

Glass & Advanced Materials Division, Bhabha Atomic Research Centre, Mumbai 400085, INDIA



SEM image of YAS glass microspheres

ABSTRACT

^{90}Y-loaded glass microspheres are one of the potential candidate for selective internal radiotherapy treatment (SIRT) for Hepatocellullar carcinoma (HCC). We report here the indigenous development of the Yttria loaded alumina silicate (YAS) glass microsphere of controlled size for Hepatocellullar carcinoma radiotherapy using Oxy-hydrogen flame (H_2-O_2) spheroidization process. The complete flow chart has been formulated by optimising different process steps for obtaining the YAS glass microsphere of 20-35μm sizes and with 100% sphericity. Initial study for optimisation of base glass composition was carried out for optimum yttria loading and highly leach resistance glass. Efforts were made to set up a complete facility for flame spheroidization process for synthesis of YAS glass microsphere of controlled size. For optimised parameters the maximum conversion efficiency obtained was >99% for Oxy-Hydrogen flame spheroidization process. Additionally to address the issue of H_2 gas dependency in flame spheroidization process, Ar-plasma gun for synthesis of YAS glass was conceptualized, designed and fabricated. The process also shown encouraging results.

KEYWORDS: *YAS glass microsphere, Ytrria loaded glass microsphere, HCC radiotherapy*

Introduction

Currently, Hepatocellular carcinoma (HCC) is one of the most pervasive causes of cancer related deaths worldwide. Selective internal radiation therapy (SIRT) using a suitable b-emitting radionuclide is one of the most promising treatment modality for primary and metastatic hepatic malignancies. Among other treatments, 90Y-labelled glass microsphere is most extensively used radiotherapeutics agent for SIRT. Once administered in the hepatic artery, the microspheres preferentially lodge in the vasculature of the malignant hepatic cells and the dose of ionizing radiation get deposited from ^{90}Y [$T_{½}$ = 64.1h, $E_{β}$(max) = 2.28 MeV] without damaging nearby healthy tissues (maximum penetration length of beta radiation from ^{90}Y is 11mm with mean length 2.5mm). As per reported data, the life expectancy of a Hepato-cellular carcinoma (HCC) patient is normally in the range of 2 months to 2 years, which can be enhanced from one to 5 years by a treatment of 100mg of labelled YAS glass microspheres. Alumino silicate glass matrix was chosen because of its higher yttria loading, glass stability and good chemical resistance. In addition, the constituents of glass matrix are stable under neutron irradiation and do not show any additional. radioactive emission. Commercially, ^{90}Y loaded microspheres are available in two different forms, i.e. ^{90}Y-resin microsphere (SIR-sphere, SIRTEX Australia) and ^{90}Y-Glass microsphere (Therasphere, Nordon, Canada). The loading of ^{90}Y is comparatively higher in case of glass microspheres with additional advantages higher of chemical stability. ^{90}Y-labelled glass microsphere (TheraSphereR) is approved by FDA, USA for the treatment of liver cancer and is available commercially. However, the prohibitively high cost of commercially available ^{90}Y-labelled glass microspheres severely restricts its utility in countries like India. Glass and Advanced Materials Division (G&AMD), MG, BARC, initiated the indigenuous development of Yttria loaded alumina-silicate glass microsphere with required clinical characteristic with an economical price. Synthesized ^{90}Y-glass microsphere showed characteristics equivalent/better compared to imported TherapshereR. The materials has been successfully characterised after neutron irradiation in collaboration with Radio Pharmaceuticals Division, BARC and a limited clinical trial has been taken up in collaboration with Tata Memorial Hospital, Mumbai. Preliminary results were quite satisfactory.

*Author for Correspondence: Madhumita Goswami
E-mail: mgoswami@barc.gov.in

Synthesis of YAS Glass Microsphere

Glass preparation

The glass composition based on Al_2O_3-SiO_2-Y_2O_3 system was chosen from glass forming region of the Al_2O_3-SiO_2-Y_2O_3 phase diagram (Fig.1) with a criteria of maximum Y_2O_3 loading and good thermal and chemical resistance glass. Glasses of optimised composition $40Y_2O_3$-$20Al_2O_3$-$40SiO_2$ (wt.%) were prepared by taking high purity initial chemical constituents in the form of oxides of Al_2O_3 (99.9% purity New Met), SiO_2 (99.5% purity, Leico) and Y_2O_3 (99.9% purity, Otto Kemi). The weighing of each oxide was done with utmost accuracy of ±0.002gm. Precaution were taken to avoid any cross contamination during preparation process. The glass was prepared using standard melt-quench technique. All constituents were mixed and ground thoroughly and kept overnight at 110°C for removal of any moisture absorbed during mixing and grinding process. The batch was heated in a Pt-Rh crucible at 1650°C in an electrically heated Raising-Lowering (R-L) melt furnace. The melt was stirred and held for sufficient time at melting temperature for homogeneous mixing and to remove all air bubbles to obtain a clear melt. Afterwards, the melt was removed from the furnace and quenched with an optimum

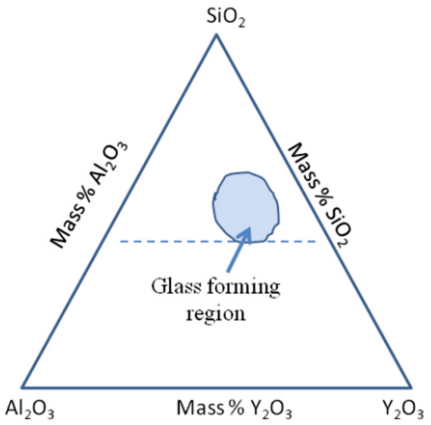


Fig.1: Glass forming region of Y_2O_3-Al_2O_3-SiO_2 (YAS) glass system.

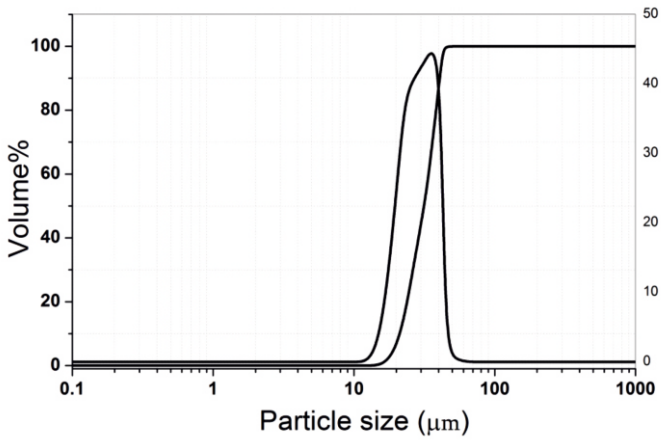


Fig.2: Particle size analysis of glass feed particles using laser scattering method.

condition to obtain cracked small pieces of glasses. The density of the glass was measured using Archimedes principle with distilled water as solvent. The density value obtained is 3.42 g/cm^3.

Feed particle preparation

The glass frits were ground in a planetary ball milling machine followed by a mortar pestle and transferred into a series of sieves with lid and collection pan. The sieving and crushing process are carried out with at most care to avoid generation of very fine particles and reduce the efficiency. Manual sieving were done by gentle tapping from top and side of the sieved frame. Crushing and sieving were done continuously to collect sufficient feed particles in the required range. The collection was done for the glass particles in the range between 20-37μm. To speed up the sieving process, an automated Shieve Shaker unit equipped with 5-6 stacks was used. Final cleaning of dust particles from the sieved particle are done using a airjet sieving machine. The feed particles were pre-heated for sufficient time to remove moisture before flame spheriodization process.

Particle size analysis of feed particles

Size distribution analysis of feed articles was done using particle size analyser (Model: ZEPHYR OcchioSA, Belgium) based on laser scattering technique. About 100-150mg of particles were taken in water and the solution was agitate to make the colloidal solution. The particle size distribution was obtained by diffracting the laser light on these feed particles. Fig.2 shows the size distribution of the particles. Approximately 85% of particles are in the range of 15-40μm.

Spheroidization of glass particles

The feed particles were converted into glass microsphere by two process (i) Flame spheroidization (ii) Plasma gun spheroidization. Details of both these processes are discussed below.

Flame spheriodization using oxy-hydrogen torch (H_2-O_2 Torch): The schematic of a Flame spheroidization unit is seen in Fig.3. In this process, the glassy feed particles are converted into glass microsphere by introducing them into an oxy-hydrogen (O_2-H_2) flame. Before passing through the flame glass powder was heated to remove any moisture and agglomeration and make them free flowing through the feeder. The vertically placed glass feeder was mounted with two layer of mesh of size 40-50μm to control the flow of particles and directed into the flame. The flame was conditioned by passing H_2:O_2 ratio 2:1. The glass particles exposed to the flame melts and spherodizes due to surface tension and cooled rapidly to maintain the sphericity. The flame is directed into a quartz chamber of approximately one meter long and 100mm dia, which collects the glass microspheres after expelled from the flame. Conversion of feed particle into microsphere is >99% and sphericity is almost 100%. Fig.4(a) shows the optical image of the feed particles used in spheroidization and glass microsphere in Fig.4(b) obtained from flame spheroidization process using the optical microscope (BX60MF5,60M model, Olympus). The sphericity of the particles is confirmed from particle size analyser (Model: ZEPHYR OcchioSA, Belgium) and optical microscope.

Plasma spherodization using argon-plasma spray gun:

To reduce the dependency of O_2-H_2 flame which has lots of safety issue because of handling of hydrogen gases, spheroidization using plasma gun has been conceptualized, designed, fabricated and commissioned. Argon plasma was generated using microwave power source with a rated capacity of 2kW. The maximum temperature of the said plasma flame could achieve 2200 °C. The design criteria for the temperature of the plasma and its flame length has been obtained using Finite Element Method (FEM) simulation using COMSOL Multiphysics software (Version 5.6, Year 2000). Simulation was performed to process the glass particle of cubic shape to convert it to spherical shape when falling through the plasma flame under gravity. Based on the simulation results, it takes about 300 milliseconds to travel through the plasma flame up to an about 100μm to get it spherodized, if the temperature of the plasma flame is 2200 °C.

The unit has a unique design of gas outlet nozzle through which argon is passed to develop plasma flame at the tip of the nozzle. A fluidized bed system attached with this facility fluidizes non-spherical glass particles which is further being sucked through an ejector to enter into the plasma flame along

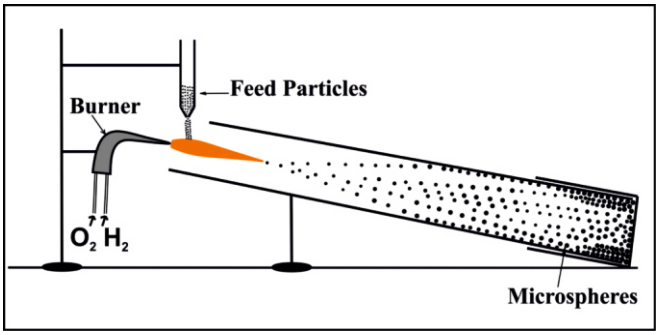


Fig.3: Schematic of flame spheroidization process.

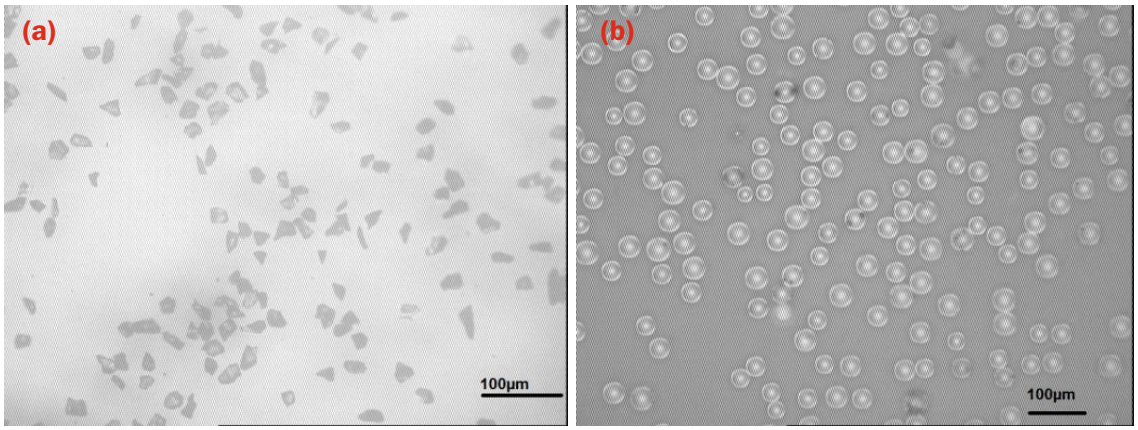


Fig.4: Optical images of (a) feed particles and (b) glass microsphere synthesised by flame spheriodization process.

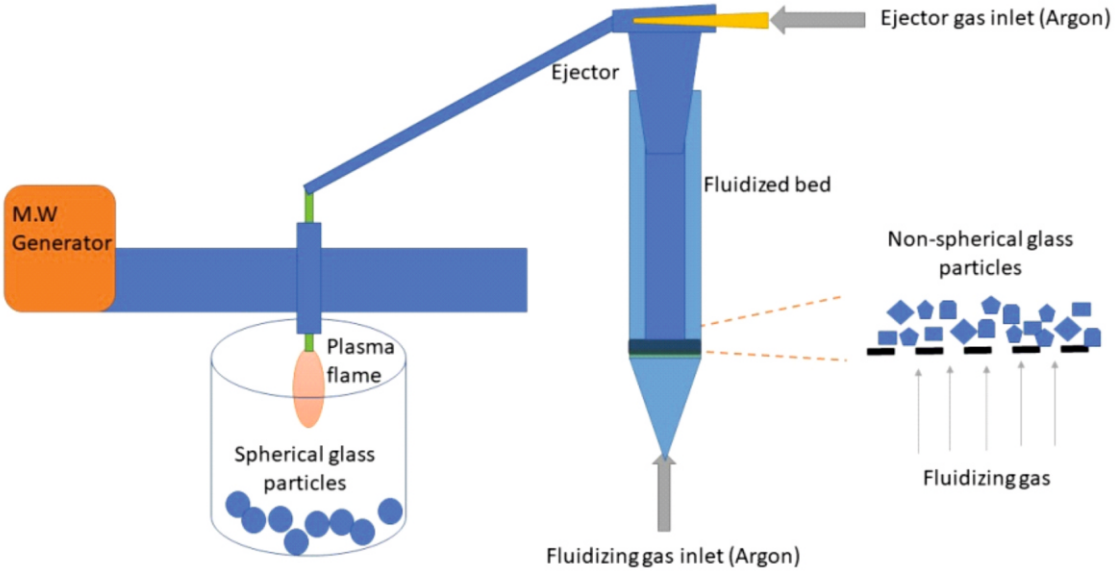


Fig.5: A simplified schematic of the plasma processing facility attached with fluidized bed and ejector.

with the argon gas as shown in schematic Fig.5. As a result, the non-spherical glass particles of typical size 20 to 35µm gets spheroidized upon melting (melting point ~1650°C) followed by droplet formation due to surface tension. Once the particle leaves the plasma flame after a travel length of 30mm, it starts cooling and thus solidified and collected as spherical glass microspheres. Fig.6 shows a photograph of the commissioned plasma processing facility in G&AMD.

After several trials experiments, the facility has been optimized for maximum conversion of feed particle to glass microsphere. With present facility, conversion efficiency achieved has been >90% and sphericity >99%. Further modification are in the process to increase the conversion efficiency of the process. Fig.6 shows Scanning Electron Microscopy (SEM) image of the YAS feed particles and the plasma spherodized YAS particles captured using SEM instrument, Model Table Top Mini SEM, Korea.

Post synthesis treatment

After spherodization, the glass microspheres were collected from the quartz chamber and seen under microsphere for checking any unmelted micropsheres. Then the microspheres were sorted by sieving to obtain desired size range of microspheres. Further, the microspheres are screened using sedimentation technique with a suitable solvent to remove microspheres with air bubbles/defects. The glass microspheres are then heated in a furnace to remove organic impurities and then cleaned with acetone and dried. In final stage, microspheres were cleaned in a cold plasma furnace. Microspheres sphere was observed under SEM and optical microscope to check for sphericity, size and visible defects. Size distribution measurement was carried out using optical image analysis process.

Characterisation of Glass Microsphere

X-Ray Diffractometer study of YAS glass microsphere

Fig.8(a) shows the X-ray diffraction pattern of synthesised glass microspheres measured using powder X-ray diffractometric (XRD) technique (Model Bruker 8 tools) with Cu Kα as radiation source the XRD pattern of synthesised glass microspheres. Lack of sharp reflection peaks confirm typical glassy nature of prepared glass microspheres samples. The characterisation has been repeated for 6 batches to see the reproducibility of the synthesis process. Fig.8(b) shows the DTA(Differential thermal Analysis) plot of the glass microsphere measured using TG/DTA Labsys 1600 instrument, M/s. Setaram. The endothermic shift at 876°C conform the glass transition temperature and glassy nature of glass microspheres.

Chemical analysis

To see the intact of glass composition before and after microsphere synthesis, chemical analysis of six different bathes of YAS glass microspheres are carried out and results

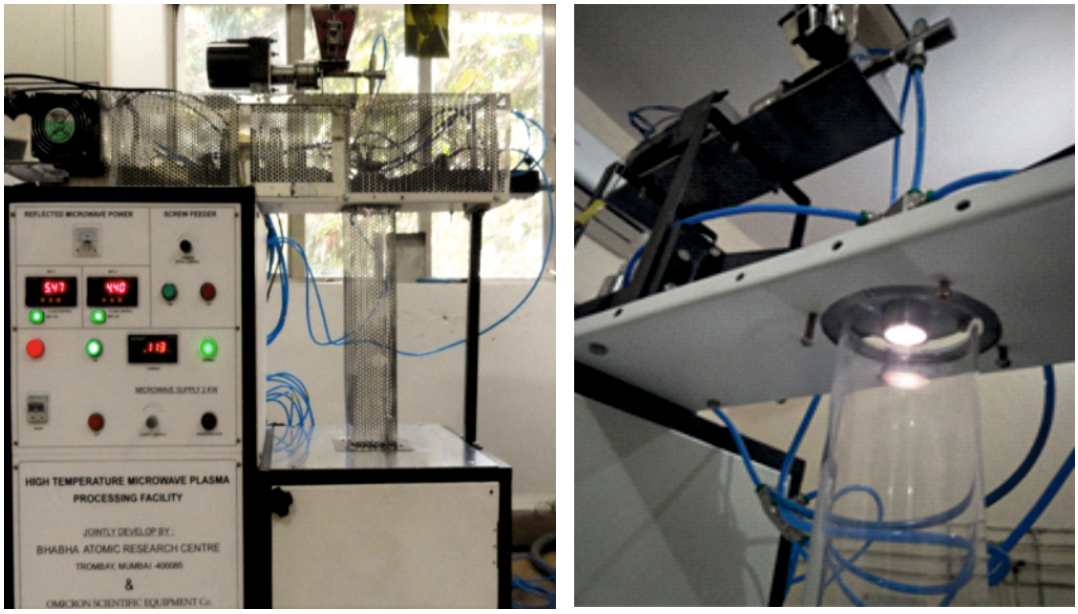


Fig.6: Plasma processing setup facility in BARC.

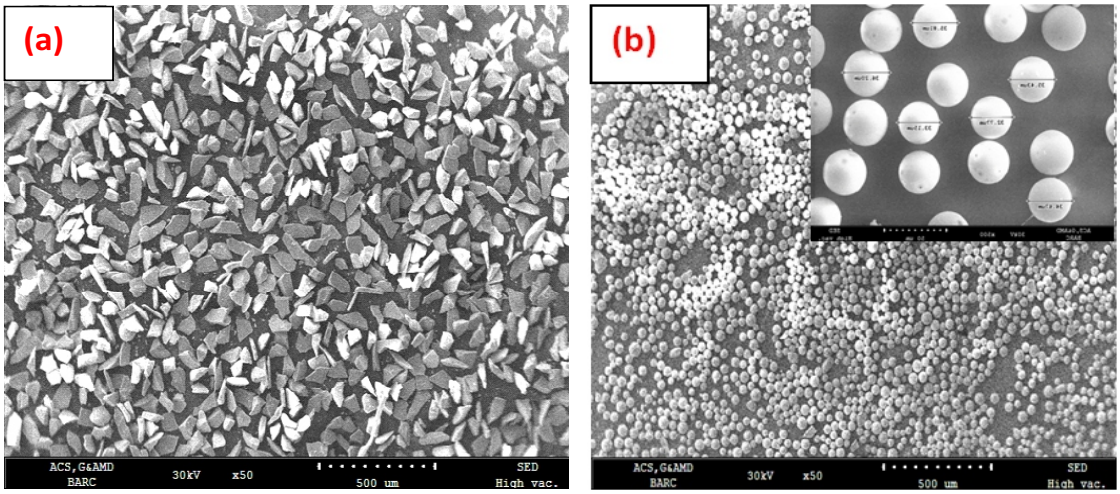


Fig.7: SEM image of (a) feed YAS particles and (b) plasma spherodized YAS particles (inset with higher magnification).

are summarized in Table 1. Analysis was done by ED-XRF technique (EDXRF spectrometer EX 3600 M, Xenemetrix Israel), having Rh-anode X-ray tube and in-built acquisition and analysis software. Results showed no significant changes in composition of the glass microsphere compared to the base glass.

Table 1: Compositional analysis of $40Y_2O_3$-$20Al_2O_3$-$40SiO_2$ glass microspheres (wt .%)

	Y_2O_3	Al_2O_3	SiO_2
Batch I	40.1 ± 2.6	19.4 ± 1.3	40.4 ± 1.1
Batch II	43.2 ± 3.0	18.0 ± 1.6	39.3 ± 1.4
Batch III	38.1 ± 2	20.54 ± 1.3	40.77 ± 1.5
Batch IV	40.3 ± 1.6	21.5 ± 1.3	41 ± 1.6
Batch V	42.1 ± 2	19.1 ± 1.2	40.5 ± 2.3
Batch VI	38.5 ± 1.5	19.5 ± 1.2	39.7 ± 2.3

Size analysis of glass microsphere

As laser scattering process required higher amount (>0.1gm) of sample to see the particle size distribution, size distribution of sorted glass microsphere was carried out using optical image analysis process. Optical images were taken on six different batches of glass microspheres and images were processed suitably to get maximum number of well separated particle (Fig.9). Image J analysis software (v1.3.0.x, 2006) was used for determination of particle size distribution. Statistics of particle size distributions were shown in Fig.10. More than 96% of glass microspheres are within the range of 20-35mm with mean diameter of 32.43µm.

Chemical stability study of YAS glass microsphere

The chemical stability/leaching study of sorted glass microspheres was carried out in aqueous (distilled water) as well as saline medium at RT per the ASTM standard method. These medium were chosen as the glass microsphere will be stored in distilled water and delivered along with saline water. The ratio of the weight of leachant (distilled/ saline water) and glass microsphere was fixed at 100:1. The experiments were carried out in a closed vessel to avoid any loss of water. At regular intervals, the weight of exposed glass microspheres

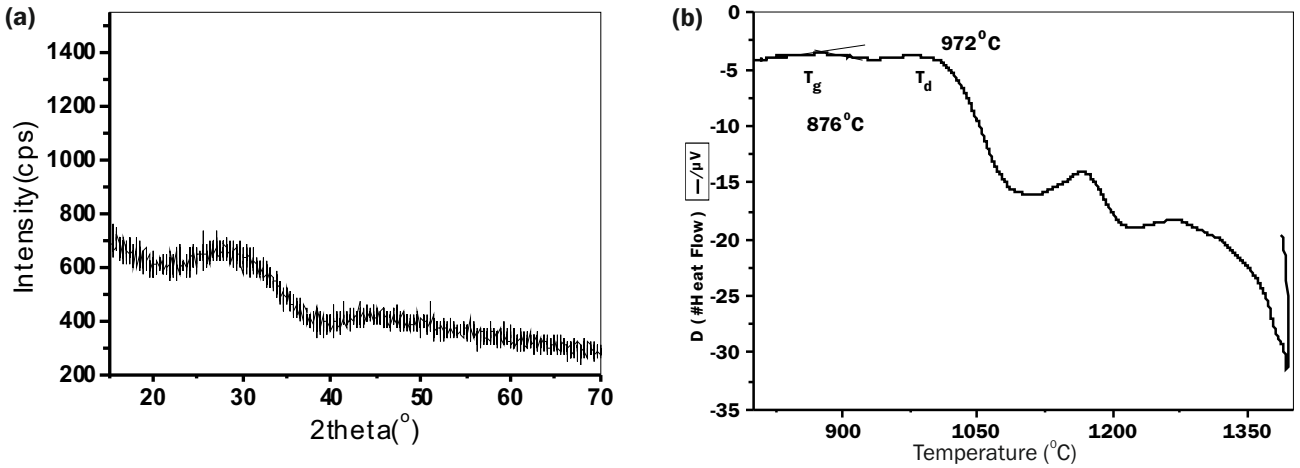


Fig.8: (a) XRD pattern of glass microspheres. (b) DTA plot of glass microspheres.

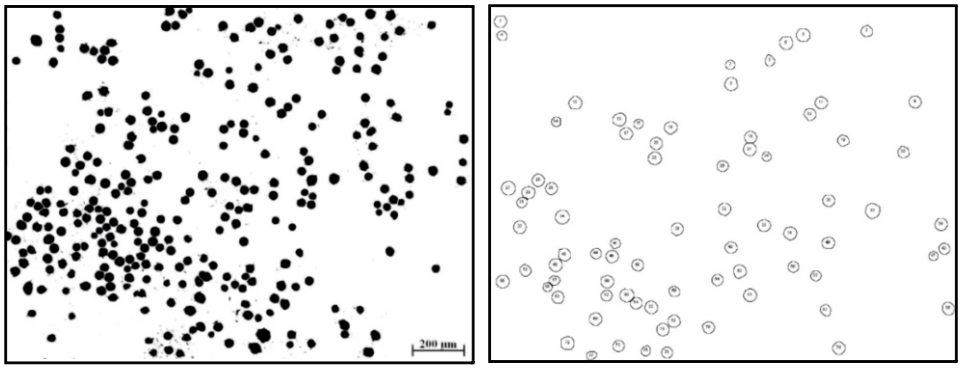


Fig.9: Images processed using analysis software for particle size analysis.

were recorded and weight change was calculated. Small amount of glass microspheres and leaching solution were taken out from the vessels after each interval for different characterizations. The experiments in aqueous medium were carried out for a maximum of 30 days (> 10 $t_{1/2}$ of yttrium) and in saline water for a maximum of 7 days.

There was very minimal or no loss in weight was observed from the glass microspheres after the leaching experiments

Table 2: Weight loss (gm, ±0.002) of YAS glass microsphere with time in aqueous medium.

Sample	Initial weight	Final weight	Weight loss
Batch 1 (24hr)	0.502	0.501	0.001
Batch 2 (3 days)	0.455	0.452	0.003
Batch 3 (7days)	0.416	0.411	0.005
Batch 4 (3 days)	0.385	0.373	0.012
Batch 5 (7days)	0.350	0.335	0.015

Table 3: Weight loss (gm, ±0.002) of YAS glass microsphere with time in saline medium.

Sample	Initial weight	Final weight	Weight loss
Batch 1 (24hr)	0.105	0.103	0.002
Batch 2 (3 days)	0.742	0.730	0.012
Batch 3 (7days)	0.053	0.035	0.018

carried out in both aqueous and saline medium. To see any changes in the surface morphology of the glass microsphere such as formation pores and their size distribution if any, SAXS study was carried out on these microsphere. SAXS experiments was performed using a laboratory based SAXS instrument (x-ray wavelength λ=0.154nm). The sample to detector distance was ~ 1m. Radial averaged scattered intensities, I(q) from each of the samples were recorded as a function of q (wave vector transfer $q=4\pi\sin\theta/\lambda$, where 2θ represents the scattering angle).

SAXS result showed scattering from the surface in nanometric scale, and no internal scattering from the samples, indicates no pores on the surface of the sample. Fig.11(a) shows no changes in SAXS pattern. This indicates both the sample have smooth surface with almost no pores/defects even after leaching study was done on these samples for 30 days. SEM images of glass microsphere after leaching study is shown in Fig.11(b). No changes in surface of the spheres also confirm the chemical stability of the glass microspheres after leaching study in aqueous medium.

The irradiation study of the glass microspheres were carried in Druva reactor in collaboration with RPhD, BARC. The glass microsphere showed required radionuclide purity, specific activity and chemical stability. The in-vivo study carried out in wistar showed complete emobilization of activity in the liver cell. Trial clinical runs were carried out by doctors (Tata Memorial Centre, Mumbai), confirm efficacy of the material for HCC radiotherapy.

Conclusion

Composition and glass synthesis process of Yttria loaded alumino silicate (YAS) glass microsphere has been optimized

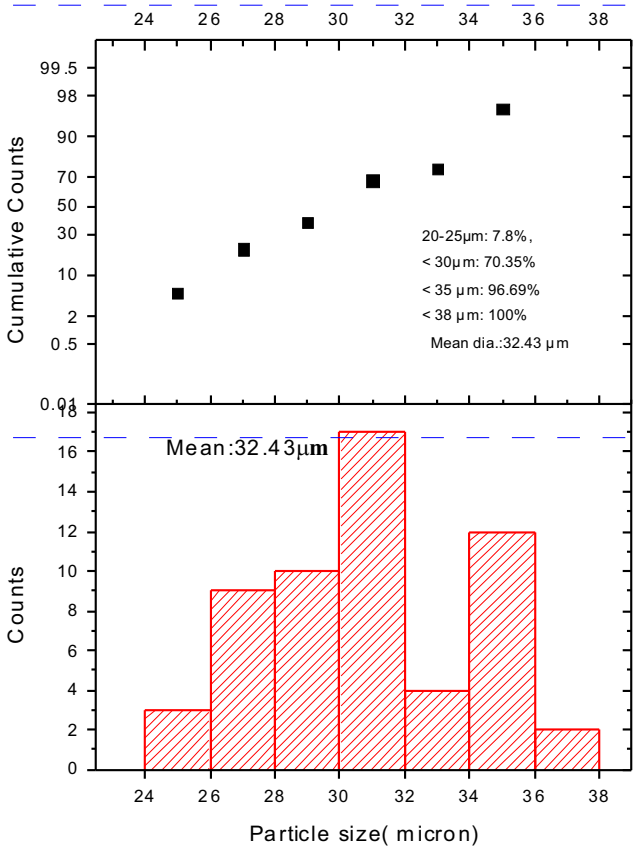


Fig.10: Statistics of particle size distribution obtained from image analysis process.

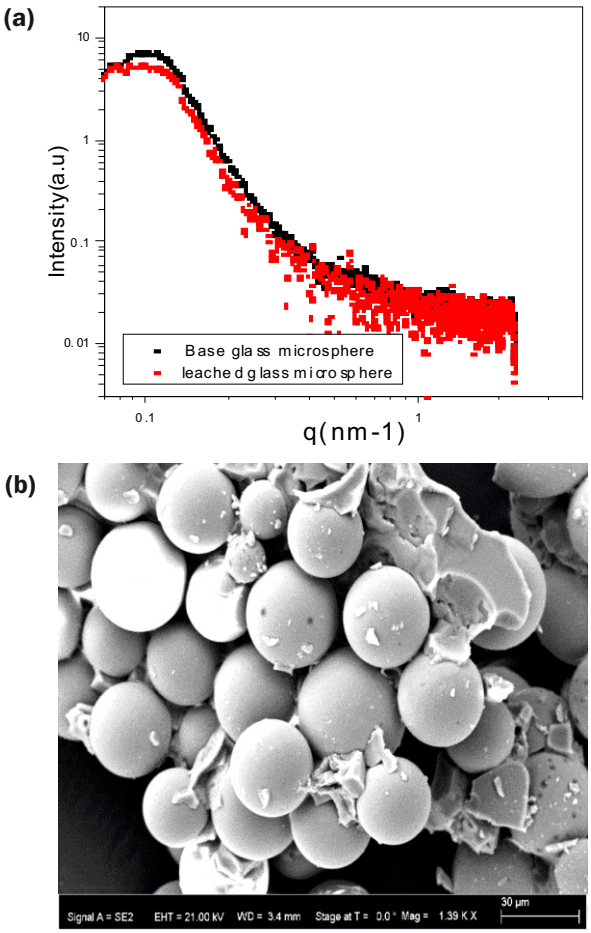


Fig.11: (a) SAXS plots for glass microspheres before & after leaching study. (b) SEM image of glass microspheres after leaching study (intact in size and shape).

with a maximum Yttria loading and optimum chemical stability. The spheroidization process was fine tuned for 100% conversion of feed particle to glass microspheres and sphericity. Glass microsphere of size 20-35µm were sorted with successive sieving. Glassy phase and chemical stability was found intact after spheroidization. The materials shows equivalent physical and chemical characteristic as imported Therasphere material. Irradiation study showed acceptable clinical characteristics and initial clinical trials carried out by Doctors showed encouraging result.

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