REVIEW

University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, India

Radioactive microspheres in therapeutics

V. R. SINHA, V. GOYEL, A. TREHAN

Received July 28, 2003, accepted November 02, 2003

Dr. V.R. Sinha, University Institute of Pharmaceutical Sciences, Panjab University Chandigarh 160014, India
vr_sinha@yahoo.com

Pharmazie 59: 419–426 (2004)

Microspheres as a drug delivery system hold great promise in reaching the goal of controlled drug delivery as well as site specific delivery. In the last few decades, scientific and technological advancements have been made in the research and development of radiolabeled microspheres. These are used successfully for the treatment of various cancers and tumors. Since response to chemotherapy and external radiotherapy is not so effective and hazardous too, so an alternative to this is internal radiation therapy. These radiolabeled microspheres are very stable and have a proven efficacy in the field of primary as well as metastatic cancers. Radioactive microspheres can be selectively targeted to various tumors without undue radiation to the nontumorous tissues. The radioactive microspheres are injected to halt tumor growth via the blood supply, thereby enabling surgical removal once the tumor size decreases. This review provides an outlook to various aspects of radioactive microspheres and their role in treatment of various tumors and cancers.

1. Introduction

In connection with aim of maximizing the bioavailability of conventional drugs with minimum side effects, new drug delivery systems continue to attract much attention. Such systems include microspheres, liposomes, nanospheres etc. These drug delivery systems lend themselves to parenteral administration and are useful for sustained release of drugs. There is also the possibility of directing the drug to an appropriate organ or target site within the body through these colloidal drug delivery systems. Microspheres form the basis of colloidal drug delivery systems, hence they have received a great impetus. Microspheres are solid, approximately spherical particles ranging from 1 to 1000 μm in size. They are made of polymeric, waxy or other protective materials that include biodegradable synthetic polymers and modified natural products such as starches, proteins, fats and waxes. The natural polymers include albumin and gelatin whereas the synthetic polymers include polylactic acid, polyglycolic acid etc. In the past few decades, microspheres have been extensively exploited for therapeutic purposes, especially for the treatment of various cancers. This approach involves the use of microspheres labeled with suitable radionuclides or isotopes instead of a drug. For therapeutic purposes, radiolabeled microspheres are used for radioembolization therapy of tumors and cancers. Radioactive microspheres have an advantage of delivering high concentration of radioactivity to the target area without causing any damage to the surrounding tissues and organs. Following administration, these microspheres get entrapped in the web of small blood vessels feeding a tumor and thus deliver the required concentration of radioactivity at the target site. The radioactivity is never released from the microspheres and acts from within. The effective treatment range is up to 90 μm for alpha emitters, for beta emitters the range is not more than 12 mm and for gamma emitters the range is up to several centimeters. In chemotherapeutic approach, the drugs have to be withdrawn even before the complete removal of the tumor, which finally leads to revival of tumor tissue. Withdrawal problems are not there in the case of radioactive microspheres and thus the use of radioactive microspheres shows better chances for complete eradication of tumors. Another important advantage of radioactive microspheres is patient compliance since the radioactivity dose persists at a target site for at least four weeks and high concentrations can be achieved at the target site.

2. Selection of radionuclide

The choice of radionuclide is determined by the organ/tissue to be treated. Absorption, distribution, metabolism and excretion of radiopharmaceuticals can be followed by scintigraphy. Depending upon their use, they may be administered orally or by injection. The use of radionuclides for the treatment of various types of cancers have been an effective alternative to other therapies such as chemotherapy and external radiation therapy (Glajch et al. 2002). General requirements for the selection of radionuclides include lack of toxicity, ease of elimination from the body, small size to allow intravenous injection, sufficient radiation spectrum, simple labeling procedures and no leakage of isotope from particles surface. Most routinely used

radiopharmaceuticals are technetium-99m (^{99m}Tc) labeled compounds that are prepared by adding sodium pertechnetate to nonradioactive lyophilized ingredients supplied in a "kit" form suitable for administration. ^{99m}Tc has ideal physical characteristics. It emits only gamma radiation in the range of a gamma camera detector. Its half-life of 6 h limits the radiation dose to the patient. Other important radioisotopes are ^{90}Y (Yttrium), ^{188}Re (Rhenium) and ^{166}Ho (Holmium).

2.1. Yttrium

^{90}Y is the decay product of strontium-90. Also produced by ^{89}Y(n, γ). ^{90}Y is a high energy pure beta emitting isotope with a half life of 64.1 h. The maximum energy of beta particles is 2.27 MeV and the maximum range of emission in tissue is 11 mm. ^{90}Y has two major disadvantages. Firstly, a long neutron activation time (> 2 weeks) is needed to attain therapeutic activities of yttrium. Secondly, biodistribution of ^{90}Y loaded microspheres cannot be directly determined in clinical trials since ^{90}Y is a pure beta emitter and does not produce imageable gamma rays (Hafeli et al. 1999).

2.2. Rhenium

The radioisotopes of rhenium ^{188}Re and ^{186}Re have unique physical properties that make them attractive for radiotherapy. ^{188}Re has a half life of 3.78 days with maximum beta energy of 1.07 MeV whereas ^{186}Re has a shorter half life of 17 h and a maximum beta energy of 2.12 MeV. Both isotopes have imageable gamma rays (Hafeli et al. 1999).

2.3. Holmium

^{166}Ho is produced by neutron capture of ^{165}Ho which has a natural abundance of 100%. ^{166}Ho has a half-life of 26.83 h and decays by emission of 1.855 MeV and 1.776 MeV maximum energy beta particles. Its physical properties are suitable for plenty of medical applications, for example, skin and hepatic malignancies, rheumatoid arthritis etc. (Mumper et al. 1991).

3. Radioactive microspheres for radiation therapy

An early approach in radiation therapy involved the use of yttrium oxide powder suspended in a viscous media. Yttrium was selected as it emits nearly 100% beta radiation. But the major disadvantage of yttrium oxide powder is its high density (5.01 g/cm^3) and irregular particle size. The high density makes it difficult to suspend the particles in the medium and this accelerates their tendency to settle in the blood stream prior to reaching the tumor as desired. Sharp corners and edges of the particles irritate the surrounding tissues and interfere with uniform distribution (Day et al. 1994). In recent applications, microspheres comprising of glass material, polymer or resin are being used. Depending upon the application it is desirable to link the microspheres with a suitable radionuclide. The stability of these microspheres is such that they do not release a significant amount of radiation emitting material into the surrounding tissues. The suitability of the microspheres for radiation therapy is based upon the properties of targeted delivery of radioactivity, uniform distribution of radioactive material throughout the microsphere material, easy activation by neutron irradiation of microspheres bearing a suitable isotope, low leakage or leaching of radioactive material, suitability for parenteral administration, uniform size distribution and easy labeling. The three major microsphere materials viz glass-based, resin-based and polymer-based are preferably used for microsphere preparation. An overview of radiolabeled microspheres is given in the Table.

3.1. Glass microspheres

The glass microspheres are incredibly small (20–30 μm) in size. Glass has minimum radionuclide impurities and is non-toxic, non-resistant to radiation damage. Glass microspheres can be easily prepared in uniform sizes and easily administered. Each injection contains five to ten million microspheres for delivering radioactive material to the desired target. The manufacturing process was described by Ehrhardt and Day. A beta-emitting radioisotope was chemically dissolved in and distributed uniformly throughout the glass material. The glass based materials used were aluminosilicate, magnesium aluminosilicate, lithium silicate, potassium silicate etc. containing ^{166}Ho, ^{186}Re, ^{90}Y as radioisotopes (Day et al. 2002). Glass has many advantages over nonglass materials: it confers targeted delivery of radioactivity to the tumor site; sufficient dosage of radiation and ease in the preparation of glass microspheres (Glajch et al. 2002). But the major drawback of glass microspheres is

Table: Radiolabeled microspheres in use

Types of material used	Diameter of microsphere (μm)	Radio-isotope used	Purpose
I) Glass a) Aluminosilicate b) Lithium silicate c) Magnesium alumino silicate d) Potassium silicate	20–30	^{32}P ^{186}Re/^{188}Re ^{90}Y ^{166}Ho	For imaging of primary and metastatic tumors
II) Albumin a) Human bovine serum albumin	25	^{90}Y ^{186}Re/^{188}Re ^{99m}Tc	Lung tumours, Radiosynovectomy, Lung scanning
III) Resins a) Aminex A-27 b) Aminex A-5 c) BioRex-70	29–35	^{166}Ho ^{90}Y ^{186}Re/^{188}Re	For liver cancer
IV) Polymers a) Polylactic acid b) Polyglycolic acid	20–50	^{166}Ho ^{186}Re/^{188}Re ^{90}Y	For head and neck cancer

their high density (3.29 g/ml) (Andrew et al. 1994) and nonbiodegradability (Mumper et al. 1991). The high density results in side effects due to premature intravenous settling and falling back into the gastroduodenum (Lau et al. 1998). In radiotherapy, glass microspheres labeled with radionuclide have been used. This eliminates the problem of leaching of radionuclide material. More recently, new yttrium based glass microspheres in which the leaching problem has been eliminated have been developed under the trade name "Theraspheres". Theraspheres with a diameter of 15–30 μm contain a stable ^{89}Y isotope which is activated by neutron bombardment in a nuclear reactor to ^{90}Y.

Houle et al. (1989), used ^{90}Y glass microspheres in the treatment of hepatocellular carcinoma (HCC). The ^{90}Y microspheres were injected via a hepatic artery catheter. No toxicity was observed for doses between 50 and 100 Gy to the liver and up to 320 Gy to the tumor itself. Thus as desired, the large absorbed doses of internal radiation can be safely delivered to hepatic tumors if the presence of extrahepatic shunting is excluded.

Radioactive rhenium glass microspheres are an alternative to yttrium glass microspheres as the production of ^{90}Y is time consuming and include costly neutron activation in a nuclear reactor. Rhenium microspheres are used for the *in vivo* irradiation of diseased organs in the body, for example, malignant tumors and the inflammed synovium of the joints. The radioactive microspheres are directly injected into the synovial sac where they deliver enough radiation (100 Gy) to destroy the inflammed lining of the diseased synovial membrane (Wang et al. 1998a).

3.2. Polymer based microspheres

Polymers are used as vehicles for the immobilization and local delivery of radionuclides or radiopharmaceuticals. Radionuclides are either physically adsorbed or chemically linked to a polymeric surface. Polymer based microspheres have many advantages over glass microspheres which include biodegradability, biocompatibility, systemic and controlled release of radionuclide from polymer etc. This provides a way to control local dosage of radiation without the need for physical removal of the implanted radionuclide. The best known biodegradable polymers which are hydrolysed without enzymes and metabolized by the body are polylactic acid, polyglycolic acid and their copolymers poly(lactic-co-glycolic acid). Preferred radioisotopes are those which have a particle range in tissue according to the tissue layer which is to be targeted. For example beta particles emitting radioisotopes like carbon-14, sulphur-35 and phosphorous-33 will be absorbed in the first 70 microns of tissue whereas more energetic beta particles emitting the radioisotope phosphorous-32 have a longer range of about a centimeter and can be used to treat thicker tumors (Leavitt et al. 2002). Polymeric microspheres are prepared by the solvent evaporation technique. The polymer is dissolved in a suitable volatile solvent and dispersed in a continuous medium using a stabilizing agent. Controlled evaporation of solvent results in the formation of solid microspheres. The solvent evaporation method has been used for the preparation of polylactic acid microspheres containing ^{166}Ho, ^{90}Y, ^{186}Re as radioisotopes (Jayakrishan and Latha 1997). Radioactive ^{166}Ho loaded polylactic acid microspheres were prepared by Mumper et al. (1991). Holmium-165-acetylacetonate (HoAcAc) and polylactic acid were dissolved in chloroform and the solution was added to polyvinyl alcohol solution. The final solution was stirred until the evaporation of the solvent. Microspheres were graded and collected according to size. These microspheres were recently tested for the treatment of hepatic malignancies in rabbits. The biodistribution and histological analysis confirmed that radioactive microspheres got heterogeneously distributed over the liver and accumulated preferentially in the tumor area. It was demonstrated that ^{166}Ho polylactic acid microspheres were the promising systems for the liver tumor treatment (Nijsen et al. 2001a). Van et al. (2001a) used ^{166}Ho loaded polylactic acid microspheres for radioembolization of unresectable head and neck cancer in rabbits. Complete tumor remissions were obtained in 79% of rabbits. Over 95% of the microspheres retained in the tumors indicated that polymeric microspheres could be used for the embolization of tumors. Magnetic polylactic acid microspheres loaded with a beta emitting radioisotope like ^{90}Y were made by Hafeli et al. (1994). It was reported that magnetic microspheres could be selectively delivered to the target site after incorporating 10% Fe_3O_4 (magnetite). Magnetic microspheres get slowly hydrolysed into lactic acid after the complete decay of radioactivity. These microspheres were used for intracavital tumor therapy. Experiments showed a twelve fold increase in the activity in tumor with a directional magnet fixed over the tumor.

3.3. Albumin based microspheres

Albumin is a type of globular protein and is present in blood and tissues. When human serum albumin is to be used for organ imaging, it is denatured to produce albumin aggregates and then selectively sieved to obtain desired particle size. When used diagnostically, albumin is combined with a radioisotope such as ^{99}Tc, ^{131}I. Albumin microspheres received considerable attention because of their biodegradability, biocompatibility, non-antigenicity and organ specific targeting properties. Various methods have been reported for the preparation of albumin microspheres. Microspheres of ovalbumin (OVA), prepared by emulsifying an aqueous solution of albumin in soybean oil have been labeled with technetium after reduction by thiosulfate or stannous chloride. Currently ^{99m}Tc microspheres of human serum albumin are widely used for lung scanning (Rhodes et al. 1969). More recently ^{99m}Tc human serum albumin microspheres have been used successfully for the treatment and assessment of the radiation induced gastritis, pneumonitis, lungs shunting etc. The tumor to normal tissue (T/N) ratio determines how safe and effective the treatment is (Ho et al. 1997). This determination of tumor to normal tissue ratio by simulation with ^{99m}Tc albumin microspheres is recommended before internal radiation therapy. Lau et al. in 1994 used ^{99m}Tc macroaggregated albumin (MAA) to assess the vascularity of liver metastasis and to predict the tumor to normal (T/N) tissue ratio in selective internal radiation therapy. It was estimated that if T/N ratio is not less than 2, then selective internal radiation therapy should be followed. This allowed the radioactive dose to be delivered to the tumor while keeping the radiation dose to the nontumorous liver within the tolerance limit. In 2000 Wunderlich et al. reported human serum albumin (HSA) microspheres labeled with ^{188}Re for internal radiotherapy of tumors. These microspheres were uniform in size, with a mean diameter of 25 μm and were biocompatible and biodegradable. Intravenous injection in Wistar rats, using the lungs as a model for a well-perfused tumor, demonstrated sufficient *in vivo* stability. Yttrium was also used with human serum albu-

min for internal radiotherapy of lung tumors. Experiments were carried out in mice using ^{90}Y macroaggregates of human serum albumin for whole lung irradiation. Based on its rapid clearance from the lung, it was suggested for internal radiotherapy.

3.4. Resin based microspheres

Microspheres based on ion exchange resins are favoured for radioembolization due to lower density compared with glass, ease in labeling and their commercial availability. In comparison to polymers and glass, resin microspheres are suspended in physiological saline, thus avoiding any complications whereas ceramic microspheres must be suspended in either viscous or dense solutions (Day et al. 1994).

Zielinksi and Kasprzyk (1983), prepared cation exchange resin microspheres labeled with ^{32}P for radiation therapy of hepatic neoplasms. The maximum energy of the ^{32}P beta particle was 1.71 MeV resulting in tissue penetration of 8 mm thickness. The range was short enough to minimize unwanted irradiation to sensitive adjacent organs. Approximately 15 mCi of ^{32}P labeled microspheres distributed uniformly in a 2100 g liver and delivered a dose of 5000 rads. ^{99}Tc labeled anion exchange resin (AG1-X8) microspheres were also prepared and studied. Microspheres of AG1-X8 (60 μm diameter) were mixed with 5–200 mCi of ^{99}Tc pertechnetate in physiological saline. The labeled microspheres were washed with water, supernatant was removed and placed into an oven for 15 min (270 °C). The ^{99}Tc labeled microspheres were ultrasonically dispersed in saline. ^{99}Tc radiopharmaceuticals are used routinely in nuclear medicine practice.

Turner et al. (1994) prepared microspheres by the addition of ^{166}Ho-chloride to the cation exchange resin Aminex A-5. A reproducible, nonuniform distribution of the ^{166}Ho-microspheres throughout the liver was observed on scintigraphic images, following intrahepatic arterial administration in pigs. This predictable distribution allowed these investigators to determine the radiation absorbed dose and to define the administered activity required to provide a therapeutic dose. Aminex A-27 was labeled with ^{188}Re by adding ^{188}Re-perrhenate and $SnCl_2$ to vacuum dried resin particles by Wang et al. (1998a). These ^{188}Re labeled microspheres were injected by direct intratumoral injection into rats with hepatoma. In the treated group, survival over 60 days was better than in a control group. Campbell et al. 2000 investigated the microscopic distribution of microspheres in human liver following hepatic infusion of 32 μm resin microspheres labeled with ^{90}Y as a treatment for an liver cancer with a diameter of 80 mm. The observed deposition patterns indicated that the vascular tumor periphery received much greater radiation doses from radioactive microspheres than both normal and the avascular tumor centre.

4. Applications of radioactive microspheres

In the past few decades, radioactive microspheres are being exploited for therapeutic applications. But owing to their ability to deliver high concentrations of radioactivity to the target site without damaging normal surrounding tissues, they are extensively exploited for the treatment of cancer. The limited efficacy of current approaches to the treatment of cancer has reawakened interest in the use of radiolabeled therapy which involves the use of radiolabeled microspheres. Microspheres labeled with a radioactive isotope are injected directly into the diseased areas. External beam radiation requires about ten treatments over a period of 30 days to deliver a dose of 2000 to 2500 rads. In contrast, radioactive microspheres safely deliver an average dose of 15000 rads in a single treatment with minimal damage to healthy surrounding tissues. Currently this novel approach is finding success in fighting different cancers viz. liver cancer, head and neck cancer, spleen cancer etc.

4.1. Applications in oncology

4.1.1. Treatment of liver metastases or secondary cancer

Hepatic tumors derive most of their blood supply from the hepatic artery, whereas the nontumorous part of the liver gets 80% of its blood supply from the portal vein and only 20% from the hepatic artery. So most of the radioactive substances including microspheres injected through the hepatic artery are delivered to the tumor, giving a favourable uptake ratio of tumor to normal tissue (T/N). In early studies Grady (1979) estimated the good objective regression of cancers, improvement of symptoms and prolongation of life in seventeen of the twenty five patients treated by ^{90}Y resin microspheres. Blanchard et al. 1989 carried out a study by injecting ^{90}Y plastic microspheres (15 μm diameter) into the hepatic artery of fifteen patients with liver metastases and one patient with hepatoma. The study revealed that there was reduction in tumor volume by more than 50% while the mean survival rate was 62 weeks. However there was gastric ulceration due to unintended infusion of the radiolabeled microspheres into the gastric circulation. By measuring the radiation doses received by the tumor and the nontumorous liver parenchyma separately, it was found that nontumorous liver could tolerate more than 30 Gy which is currently considered the limit for whole liver irradiation using external beams without any evidence of radiation hepatitis. Based upon the observation that patients who received up to 138.9 Gy to the nontumorous liver did not develop radiation hepatitis, an arbitrary safety limit of 80 Gy to the normal liver delivered by ^{90}Y microspheres was recommended (Gray et al. 1990). Magnesium alumino borate glass microspheres containing radioactive rhenium were prepared and successfully used to treat liver tumors by radioembolization. The microspheres were made radioactive by neutron activation and then injected into the hepatic artery of sprague-dawley rats with one week old hepatoma. The biodistribution studies showed a sevenfold increase of microsphere uptake by hepatoma as compared to healthy liver tissue. Tumor growth in the animals receiving radioactive microspheres was significantly lower than in the animals receiving nonradioactive microspheres. So it was concluded that radioactive rhenium microspheres were effective in slowing down or even diminishing liver tumor growth without altering hepatic enzyme levels (Hafeli et al. 1999). Recently, biodegradable polylactic acid microspheres labeled with ^{166}Ho have been manufactured for internal radiation therapy of hepatic tumors. Nijsen et al. (2001a), investigated the therapeutic effects of ^{166}Ho loaded polylactic acid microspheres in rabbits with liver tumors. Rabbits were divided into three groups as Sham treated rabbits ($n = 3$), "cold" microspheres treated rabbits ($n = 3$) and ^{166}Ho microspheres treated rabbits. Biodistribution and histological analysis confirmed that radioactive microspheres got heterogeneously distributed over the liver and accumulated preferentially in the tumor area. Sham treated and cold microspheres treated rabbits

showed an exponential tumor growth. The study demonstrated that ^{166}Ho polylactic acid microspheres were the promising systems for liver tumor treatment (Nijsen et al. 2001a).

A new approach uses ^{90}Y glass microspheres (Theraspheres®) averaging 21 μm in diameter in hepatic cancer treatment. These particles deliver a much higher dose to the liver than is possible with standard radiotherapy. Tolerance in the patients whose livers are highly susceptible to radiation induced damage is fairly high. In a recent study by Herba and Thirlwell (2002), 37 patients with metastatic liver disease, predominantly from colorectal cancer were treated by intrahepatic arterial embolization of radioactive ^{90}Y glass microspheres. The calculated liver dose was increased in stages from 50 Gy to 150 Gy. Complications were low. No leaching of the radionuclide into the circulation was evident as no hemopoietic depression occurred in any of 37 patients. Only in 15 patients out of 30, post treatment beneficial effects were noted. Hence hepatic radioembolization was considered as primary method of therapy. This method provides a single session technique for treatment of hepatic metastases.

4.1.2. Treatment of hepatocellular carcinoma

Encouraged by the results achieved in the case of liver metastases, the therapy was extended to patients with hepatocellular carcinoma. In the late 1960's and early 1970's, ^{90}Y labeled inert ceramic or resin microspheres were injected into hepatic arteries of patients at an estimated dose ranging from 50 to 200 Gy. Inspite of striking response and survival rates, complications arised due to unexpected leaching of yttrium from the surface of microspheres and due to subsequent uptake of free yttrium by the bone marrow which led to lethal myelosuppression and radiation hepatitis. Largely as a result of these complications interest in this approach declined until the late 1980's. The recently developed 22 μm glass microspheres (Theraspheres®) incorporate ^{89}Y oxide into a glass matrix from which yttrium is unable to leach out. Wollner et al. (1988) found that injection of cold theraspheres to be well tolerated. Moreover microspheres did not appear in the bone-marrow causing no myelosuppression. Burton et al. (1989) demonstrated that pretreatment with angiotensin II increased the microspheres uptake by the tumor by threefold in rabbits with VX_2 hepatoma and Walker carcinoma in rats. Accessibility of the microspheres to the central portion of the tumors had also increased. Earlier there were no reports on the effect of ^{90}Y glass microspheres in the treatment of liver cancer via the portal vein. In 1993 Yan et al. studied the administration of ^{90}Y glass microspheres via the portal vein. It was concluded that ^{90}Y glass microspheres were effective in the treatment of liver cancer. In the study, conducted by Wang et al. (1998a), ^{188}Re was used to label microspheres. The authors analysed the biodistribution and survival times after the intratumoral injection of ^{188}Re microspheres into rats suffering from hepatoma. The biodistribution studies revealed that radioactivity in the tumor was very high while in all other organs it was quite low. In addition, it was concluded that direct injection of ^{188}Re microspheres was extremely attractive as a therapeutic alternative in hepatoma patients. Hepatocellular carcinoma constitutes a difficult health challenge because of its poor prognosis and limited treatment options. UPCI (2002) reported a new treatment for inoperable primary liver cancer with Theraspheres® which appeared to be safe and effective for liver cancer patients. Recently a new attractive approach was suggested to selectively deliver therapeutic doses of radiation to hepatic tumors. In a recent study by Georgiades et al. (2002) ^{90}Y microspheres were administered via the hepatic artery to patients with liver malignancies. This procedure provided a way of delivering radiation doses in excess of 100 Gy to the tumors by sparing the normal tissue. Carr et al. (2002) used ^{90}Y glass microspheres for the treatment of unresectable and transplantable advanced stage hepatocellular carcinoma. These ^{90}Y labeled glass microspheres were delivered via the hepatic artery in 43 patients. It was observed that 27 out of 43 patients were evaluable for the response and 12 patients had stable disease. From the study, it was estimated that Theraspheres® appeared to be a promising, nontoxic and effective treatment for unresectable hepatocellular carcinoma. More recently in 2003, Sarfaraz *et al*., administered ^{90}Y microspheres via the hepatic artery to selectively deliver therapeutic doses of radiation to liver malignancies. This procedure allowed to deliver radiation absorbed doses in excess of 100 Gy to the tumors without significant liver toxicity. Microspheres were administered via a catheter placed into the hepatic artery. The actual radiation absorbed doses to tumors and normal liver tissue was calculated based on the ^{99m}Tc macroaggregated albumin study and computed tomography scans. As expected, the activity uptake within the liver was found to be highly nonuniform and a multifold increase of uptake in tumor compared to nontumor tissue was observed. The radiation absorbed dose for tumor and liver were 402 Gy and 118 Gy, respectively.

4.1.3. Bone tumor

A traditional and definite method for bone tumor diagnosis is bone biopsy but this procedure has many risks and also increases the rate and extent of tumor cell metastases. An alternative to this traditional approach is the use of radioactive microspheres. In 1985, Robertson *et al*. used radioactive microspheres of 15 μm (diameter) to explore the spread of tumor cells from the distal femur into the lymphatic system, venous drainage and local tissue. Radioactive microspheres have been used for the study of bone microcirculation in aseptic osteonecrosis of the femoral head. With the injection of radioactive microspheres it was possible to show that aseptic necrosis begins with global ischaemia and is followed by incomplete revascularisation leaving a necrotic area. On the border between the two areas hypervascularity produced a zone of fragility where microfractures developed with detachment of a sequestrum (Steib et al. 1987).

4.1.4. Head and neck cancer

The role of intra-arterial radioisotope therapy in the treatment of head and neck cancer was studied. From an experimental study in rabbits, it was found that ^{166}Ho loaded polylactic acid microspheres are promising candidates for studies on radioembolization of unresectable head and neck cancer. The effects on tumor growth, retaining efficiency of microspheres in primary tumor and the excretion of free ^{166}Ho were analysed by embolizing the radioactive Ho-labeled PLA microspheres into rabbits with VX_2 squamous cell carcinoma. Complete tumor remission was obtained in 79% of the rabbits following embolization with radioactive microspheres. Over 95% of the microspheres were retained in the tumor (Van et al. 2001). Dextran hydrogel microspheres for chemoembolization and holmium-

polylactic acid microspheres for radioembolization proved to be promising candidates for the embolization of head and neck cancer. Particles with a mean diameter of at least 40 μm and volume weight mean size up to 70 μm are preferably used for the embolization of head and neck cancer (Van et al. 2001a).

4.1.5. Spleen tumors

Spleen imaging illustrates anatomic changes in the spleen and radiocolloids have been successfully used for the this purpose. Radiocolloids get concentrated in splenic tissues by phagocytosis. Therefore by spleen scanning we can depict the size, shape and position of the splenic tissue. Conventional splenic embolization with radiolabeled microspheres was introduced as an alternative to splenectomy. Hypersplenism is characterized by inappropriate sequestration and destruction of blood elements and results in a diminished number of circulating thrombocytes or RBCs, WBCs. Hypersplenism may occur in patients with a variety of haematologic, inflammatory, metabolic and neoplastic disorders. Many patients with hypersplenism have an increased risk at surgery. Partial embolization of the spleen serves as an alternative to surgery. In 1995 Becker et al. successfully used ^{90}Y labeled microspheres (diameter 45–75 μm) in radioembolization of the spleen. In patients with severe thrombocytopenia attributable to congestive hypersplensim the necessary therapeutic dose was estimated to be 100 Gy and a computer tomography (CT) study was performed after radioembolization. It was found that the splenic volume decreased from 1400 to 470 cm^3 and the platelet count increased to almost normal levels. The treatment showed no evidence of any complications so intraarterial radioembolization with ^{90}Y resin microspheres was clinically effective and well tolerated in hypersplenism.

4.2. Treatment of rheumatoid arthritis

Radioisotope synovectomy (Synoviorthesis) is a noninvasive therapy used for the treatment of rheumatoid arthritis. Radioisotope synovectomy constitutes an effective alternative to operative therapy. Advantages of radioisotope synovectomy include a simple technique, decreased or no hospitalization, lower costs, early and easier mobilization of the patients, reliable results and free of side effects. Radioisotope synovectomy involves the intraarticular injection of a radionuclide to alter or ablate the inflammed synovium. The treatment controls the synovial inflammation and maintains joint function. Upon administration, microspheres get uniformly distributed along the synovial membrane and emit beta radiation to fully irradiate the membrane while sparing the more distant joint structures (Day et al. 1989). Mumper et al. 1992 investigated poly-L-lactic acid (PLA) microspheres containing neutron activated ^{166}Ho as potential agents for radionuclide synovectomy. *In vivo* retention studies were conducted by administering irradiated ^{166}Ho polylactic acid microspheres into the joint space of normal rabbits ($n = 6$). Biodistribution data for ^{166}Ho was acquired by killing the rabbits 44 h ($n = 1$) or 120 h ($n = 5$) after administration of polylactic acid microspheres. It appeared that the majority of ^{166}Ho leaching occurred from the joint in the first 44 h after administration. However no ^{166}Ho activity was observed in the feces or lymph nodes after 120 h. The maximum soft tissue penetration of a beta particle emitted from ^{166}Ho is 8.4 mm. This appears ideal for the treatment of an inflamed knee synovium, which may become 1–7 mm thick depending on the severity of the disease. Thus the potential use of ^{166}Ho in rheumatoid arthritis is very promising. In 1998, Wang et al. administered ^{188}Re microspheres via intra-articular injection in rabbits with antigen induced arthritis (Wang et al. 1998b). A biodistribution study was carried out. The study revealed that leakage of the radiotracer from the knee was negligible. Ultimately ^{188}Re microspheres proved to be effective radiopharmaceuticals for radiation synovectomy. Recently Wang et al. (2001) conducted the histologic study to assess the effect of radiation synovectomy on synovium and articular cartilage. ^{188}Re microspheres were administered into the knee joints of rabbits via intra-articular injection. This resulted in mild reactive inflammation and thrombotic occlusion of vessels which subsided rapidly. After 12 weeks of injection, sclerosis of the subsynovium was studied. There was no significant difference in the articular pattern after injection of 0.3 or 0.6 mCi ^{188}Re microspheres. It was reported that a treatment dose of ^{188}Re microspheres caused transient inflammation of the synovium without causing any detectable damage to the articular cartilage of knee joint.

The selection of the radioisotope depends upon the size of the joint. Usually ^{90}Y and ^{188}Re are used for knee and shoulder, ^{186}Re for finger or elbow etc. The traditionally used radiation colloids were not ideal since their large size distribution led to radiation leakage from the joint leading to toxicity problems. The agents for potential use in radiation synovectomy are ^{90}Y glass microspheres, ^{166}Ho polylactic acid microspheres, ^{188}Re human skin albumin microspheres.

5. Selective internal radiation therapy (SIRT)

A new approach regarding the use of radioactive microspheres in the treatment of liver tumors and cancer is selective internal radiation therapy (SIRT). SIRT is another means of attack in the battle against liver cancer. SIRT is a treatment for both hepatocellular carcinoma and colorectal liver metastasis. It involves the delivery of millions of microscopic radioactive microspheres containing ^{90}Y directly to the liver tumor. The targeted nature of SIRT enables the delivery of up to 40 times more radiation than would be possible using conventional radiotherapy. In Australia, approximately 200 patients have been treated in various phase I and phase II trials with SIRT. A phase III trial in Perth compared the treatment with fluorodeoxyuridine (FUDR) hepatic artery chemotherapy as the control group against the same chemotherapy plus SIRT. The patients who received SIRT had a better outcome than those treated with chemotherapy alone. Patients treated with SIRT showed an increase of 2 years in survival time from 26% to 39% and an increase of 3 years in survival time from 6% to 17% (Yan and Morris 2002). SIRT targets a very high radiation dose to tissue in close contact with microspheres, but this diminishes rapidly with distance away from the microspheres. Thus the area close to the microspheres is highly effected while areas distant from the microspheres are spared. This is in contrast to the delivery of radiation to a tumor by external beam therapy where the prescribed dose is delivered evenly to every element of the target tissue. Thus SIRT causes harm only to the tumorous cells and is sparing the healthy hepatic cells (Burton et al. 1989). By selective internal radiation therapy, established liver cancer can be effectively treated by the use of intrahepatic articular injection of ^{90}Y resin microspheres. 25 out of 25 patients treated by Grady in 1979 showed good

results thus leading to the prolongation of their life. For adjuvant therapy of colon cancer internal radiation therapy of the liver was done with phosphorous-32 colloid. 4 patients with colon cancer were selected. Out of 4 patients 3 did well without significant side effects and no evidence of liver cancer was found after 2 years. The fourth one died of brain metastases but having reduced liver cancer. Side effects of SIRT include post procedural fever, abdominal pain, radiation hepatitis and peptic ulcer. Recently in 2001, Stubbs et al. treated 50 patients with advanced, nonresectable colorectal liver metastases and a median age of 61.5 years with SIRT. A titrated single dose of 2.0–3.0 of ^{90}Y microspheres was injected into the hepatic artery. This was followed by regional chemotherapy with 5-fluorouracil at four weekly intervals for four days by continuous infusion. Responses to SIRT were assessed by falling tumour markers CEA (Carcinoembryonic antigen) and by CT (computer tomography) scans. Tumour marker data suggested that there was a destruction of liver tumour in 90% of the patients by a single treatment with SIRT. Thus it was concluded that selective internal radiation therapy was well tolerated though accompanied by liver pain and nausea. There was no treatment related mortality in the patients.

6. Future prospects

For radioactive microspheres more exhaustive search is required for the materials which are more biocompatible and biodegradable after the delivery of radioisotopes. The labeling methods are to be improved so that highly stable radiolabeled microspheres can be produced in a single, short step using a simple radiolabeling kit. There is a need for the preparation of more homogenous, monosized microspheres that will allow for better and more reliable biodistribution results. The advances in molecular biology and engineering is required for the design of very selective and site specific therapeutic microspheres. Direct intratumoral injection of radiolabeled microspheres is a sound technique in terms of localization of the radiation dose, but the technique still needs further evaluation, particularly in terms of the safety of both the patient and the operating staff. Internal radiation therapy is likely to play a substantial role in the control of hepatic cancer in the near future.

7. Conclusions

Internal radionuclide therapy using radioactive microspheres plays a substantial role in the control of hepatic and other types of cancers. Radioactive microspheres are very stable and have a proven efficacy in the field of treatment of diseases especially cancer. Radioactive microspheres are an ideal tool for the treatment of diseases like rheumatoid arthritis, spleen tumors etc. Radioactive microspheres are able to deliver high concentrations of radioactivity to the target area without damaging normal surrounding tissue. Improvements in radiolabeling techniques have resulted in increasingly stable microspheres with a leakage of less than 0.1% of the activity. This is the major reason of their gaining popularity in therapeutic applications. These radiolabeled microspheres serve as one of the future materials in the battle against cancer and tumors.

Acknowledgements: We are grateful to University Grants Commission for providing us financial assistance.

References

Andrews JC, Walker SC, Ackermann RJ, Cotton LA, Ensminger WD, Shapiro, B (1994) Hepatic radioembolization with yttrium-90 containing glass microspheres: preliminary results and clinical followup. J Nucl Med 35: 1637–1644.

Becker CD, Rosler H, Biasiutti FD, Baer, HU (1995) Congestive hypersplenism: treatment by means of radioembolization of the spleen with Y-90. Radiology 195: 183–186.

Blanchard RJ, Morrow IM, Sutherland, JB (1989) Treatment of liver tumors with yttrium-90 microspheres alone. Can Assoc Radiol J 40: 206–210.

Burton MA, Gray BN, Klemp PF, Kelleher DK, Hardy, N (1989) Selective internal radiation therapy: distribution of radiation in the liver. Eur J Cancer Clin Oncol 25: 1487–1491.

Campbell AM, Bailey IH, Burton, MA (2000) Analysis of the distribution of intraarterial microspheres in human liver following hepatic yttrium-90 microsphere therapy. Phys Med Biol 45: 1023–1033.

Carr BI, Sheetz M, Brown M, Torok F, McCook B, Zajko A, Collins L, Geschwind JF, Abrams, R (2002) Hepatic arterial ^{90}yttrium-labeled glass microspheres (Therasphere) as treatment for unresectable HCC in forty three patients. Radiation Biology: Abstract No.: 553

Day, Delbert E, Ehrhardt, Gary, J (1989) Composition and method for radiation synovectomy of arthritic joints. US patent 4, 889, 707.

Day, Delbert E, Ehrhardt, Gary, J (1994) Microspheres for radiation therapy. US patent 5,302,369.

Day, Delbert E, White, James, E (2002) Biodegradable glass compositions and methods for radiation therapy. US patent 6,379,648.

Georgiades CS, Ramsey DE, Solomon S, Geschwind, JFH (2002) New nonsurgical therapies in the treatment of hepatocellular carcinoma. Am J Cardiol 21: 32L–35L.

Glajch, JL, Singh P (2002) Inorganic materials for radioactive drug delivery. US patent 6, 455, 024.

Grady ED (1979) Internal radiation therapy of hepatic Cancer. Dis Colon Rectum 22: 371–376.

Gray BN, Burton MA, Kelleher D, Klemp P, Matz, L (1990) Tolerance of the liver to the effects of yttrium-90 radiation. Int J Radiat Oncol Biol Phys 18: 619–623.

Hafeli UO, Sweeney SM, Beresford BA, Sim EH, Macklis, RM (1994) Magnetically directed poly (lactic acid) 90Y-microspheres: novel agents for targeted intracavitary radiotherapy. J Biomed Mater Res 28: 901–908.

Hafeli UO, Casillas S, Dietz DW, Pauer GJ, Rybicki LA, Conzone SD, Day, DE (1999) Hepatic tumor radioembolization in a rat model using radioactive rhenium (186Re/188Re) glass microspheres. Int J Radiat Oncol Biol Phys 44: 189–199.

Herba MJ, Thirlwell, MP (2002) Radioembolization for hepatic metastases. Semin Oncol 29: 152–159.

Ho S, Lau WY, Leung TWT, Chan M, Chan KW, Lee WY, Johnson PJ, Li, AKC (1997) Tumor-to-normal uptake ratio of Y-90 microspheres in hepatic cancer assessed with Tc 99m macroaggregated albumin. Brit. Radiol. 70: 823–828.

Houle S, Yip TCK, Shepherd FA, Rotstein LE, Sniderman KW, Theis E, Cawthorn RH, Cox, KR (1989) Hepatocellular carcinoma:pilot trial of treatment with Y-90 microspheres. Radiology 172: 857–860.

Jayakrishnan A, Latha MS (1997) Biodegradable polymeric microspheres as drug carriers. In: Jain NK(ed.) Controlled and novel drug delivery, 1st ed., New Delhi, p. 238.

Lau WY, Leung WT, Ho S, Leung NW, Chan M, Lin J, Metreweli C, Johnson P, Li, AK (1994) Treatment of inoperable hepatocellular carcinoma with intrahepatic arterial yttrium-90 microspheres: a phase I and II study. Br J Cancer 70: 994–999.

Lau WY, Ho S, Leung TWT, Chan M, Ho R, Johnson PJ, Li AKC (1998) Selective internal radiation therapy for nonresectable hepatocellular carcinoma with intraarterial infusion of 90 yttrium microspheres. Int J Radiation Oncology Biol Phys 40: 583–592.

Leavitt, Richard D, Avila, Luis, Z (2002) Polymeric delivery of radionuclides and radiopharmaceuticals. US patent 6,352,682.

Mumper RJ, Ryo UY, Jay, M (1991) Neutron activated holmium166-poly(L-lactic acid) microspheres: a potential agent for the internal radiation therapy of hepatic tumors. J Nucl Med 32: 2139–2143.

Mumper RJ, Mills BJA, Ryo UY, Jay, M (1992) Polymeric microspheres for radionuclide synovectomy containing neutron-activated holmium-166. J Nucl Med 33: 398–402.

Nijsen F, Rook D, Brandt C, Meijer R, Dullens H, Zonnenberg B, deKlerk J, Van Rijk P, Hennink W, Vanhet Schip, F (2001a) Targeting of liver tumour in rats by selective delivery of holmium-166 loaded microspheres: a biodistribution study. Eur J Nucl Med 28: 743–749.

Nijsen JFW et al. (2001b). Radioactive holmium loaded poly(L-lactic acid) microspheres for treatment of hepatic malignancies : efficacy in rabbits. In Radioactive holmium loaded poly(L-lactic acid) microspheres for treatment of liver malignancies. Nijsen (ed.), chapter 7, p110–122. http://www.library.uu.nl/digiarchief/dip/diss/1953758/C7.pdf (12/12/2003)

Rhodes BA, Zolle I, Buchanan JW, Wagner, HN (1969) Radioactive albumin microspheres for studies of the pulmonary circulation. Radiology 92: 1453–1460.

Robertson WW, Janssen HF, Walker, RN (1985) Passive movement of radioactive microspheres from bone and soft tissue in an extremity. J Orthop Res 3: 405–411.

Sarfaraz M, Kennedy AS, Cao ZJ, Sackett GD, Yu CX, Lodge MA, Murthy R, Line BR, Van Echo, DA (2003) Physical aspects of yttrium-90 microsphere therapy for nonresectable hepatic tumors. Med Phys 30: 199–203.

Steib JP, Moyses B, Wenger JJ, Leculee F, Mitteau M, Kehr P, Lang, G (1987) Study by radioactive microspheres of bone microcirculation in aseptic osteonecrosis of the femoral head. Rev Chir Orthop Reparatric Appar Mot 73: 601–608.

Stubbs RS, Cannan RJ, Mitchell, AW (2001) Selective internal radiation therapy with 90 yttrium microspheres for extensive colorectal liver metastases. J Gastrointest Surg 5: 294–302.

Turner JH, Claringbold PG, Klemp PF, Cameron PJ, Martindale AA, Glancy RJ, Norman PE, Hetherington EL, Najdovski L, Lambrecht, RM (1994) 166 Ho-microsphere liver radiotherapy: a preclinical SPECT dosimetry study in the pig. Nucl Med Commun 15: 545–553.

UPCI (2002) Treatment with radioactive glass beads reduces liver tumors and improves quality of life for cancer patients with advanced disease (press release) http://www.upci.upmc.edu/internet/news/upci_news/2002/05172liver_ glassbeads.html

Van Es RJ, Nijsen JF, Vanhet Schip AD, Dullens HF, Slootweg PJ, Koole, R (2001) Intra-arterial embolization of head and neck cancer with radioactive holmium-166 poly(L-lactic acid) microspheres an experimental study in rabbits. Int J Oral Maxillofac Surg 30: 407–413.

Van Es RJ, Nijsen JF, Dullens HF, Kicken M, VanderBilt A, Hennink W, Koole R, Slootweg, PJ (2001a) Tumour embolization of the VX2 rabbit head and neck cancer model with Dextran hydrogel and Holmium-poly (L-lactic acid) microspheres: a radionuclide and histological pilot study. J Craniomaxillifac Surg 29: 289–97.

Wang SJ, Lin WY, Chen MN, Chi CS, Chen JT, Ho WL, Hsieh BT, Shen LH, Tsai ZT, Ting G, Mirzadeh S, Knapp, FF (1998a) Intratumoral injection of rhenium-188 microsphere into an animal model of hepatoma. J Nucl Med 39: 1752–1757.

Wang SJ, Lin WY, Chen MN, Hsieh BT, Shen LH, Tsai ZT, Chen JT, Ho WL, Mirzadeh S, Knapp FF (1998b) Rhenium-188 microspheres: a new radiation synovectomy agent. Nucl Med Commun 19: 427–433.

Wang SJ, Lin WY, Chen MN, Chen JT, Ho WL, Hsieh BT, Huang H, Shen LH, Ting G, Knapp, FF (2001) Histologic study of effects of radiation synovectomy with Rhenium-188 microsphere. Nucl Med Biol 28: 727–732.

Wollner I, Knutsen C, Smith P, Prieskorn D, Chrisp C, Andrews J, Juni J, Warber S, Klevering J, Crudup J, Ensminger, W (1988) Effects of hepatic arterial yttrium 90 glass microspheres in dogs. Cancer 61: 1336–1344.

Wunderlich G, Pinkert J, Andreeff M, Stintz M, Knapp FF Jr, Kropp J, Franke, WG (2000) Preparation and biodistribution of rhenium-188 labeled albumin microspheres B20: a promising new agent for radiotherapy. Appl Radiat Isot 52: 63–68.

Yan ZP, Lin G, Ahazo HY, Dong, YH (1993) An experimental study and clinical pilot trials on yttrium-90 glass microspheres through the hepatic artery for treatment of primary liver cancer. Cancer 72: 3210–3215.

Yan, Morris (2002) Hepatic cryotherapy for liver metastases from colorectal carcinoma. ANZ Journal of Surgery. SRS 39th Annual Scientific Meeting, Brisbane.

Zielinski FW, Kasprzyk, M (1983) Synthesis and quality control testing of ^{32}P labeled ion exchange resin microspheres for radiation therapy of hepatic neoplasms. Int J Radiat Isot 34: 1343–1350.