SYSTEM FOR RADIATION DELIVERY APPLIED TO BRACHYTHERAPY USING CMC AS POLYMERIC VEHICLE

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Abstract. *This work describes a system for radiation delivery applied to brachytherapy using radioactive macroaggregate produced by sol-gel route incorporating Samarium-153 loaded in a polymeric vehicle. The polymer carboxymethyl cellulose, CMC, was selected as vehicle. It presents high biocompatibility and is suitable for low temperature handling. The CMC is a cellulose subproduct, a water-insoluble natural polymer, that becomes soluble by introducing anionic carboxymethyl group ($CH2OCH2COO\text{-}Na^+$) in the unit of repetition of the polymer. The developed polymeric delivery system is presented as flexible flat surface with a load of macroaggregate in the form of micro seeds or dispersed dust. Such device fits in various brachytherapy applications, especially in interstitial or intracavitary implants and intraoperative radiation therapy. These systems provide mechanical sustentation for the radioactive macroaggregates in well defined spatial distribution improving the conformation of the absorbed dose in the organ or tumor and it can be set up during surgery quickly and safely, reducing the radiation exposition of the medical crew. The degradation time in physiological solution are presented.*

Keywords*: Radiation delivery, brachytherapy, polymer device, carboxymethyl cellulose.*

1. INTRODUCTION

Brachytherapy is a medical treatment that applies radiation in situ, called ionizing radiation, to kill cancer cells on tumors. In recent years, this type of radiation therapy has experienced remarkable grown achieving useful applications for treating various types of tumors.

Unlike external beam therapy (EBT), in which high-energy x-ray beams are generated by a linear accelerator and are point toward the tumor, brachytherapy involves the placement of a radioactive sealed source, at the shape of needles, seeds, wires, inside the body, in fact, into or near a tumor.

Therefore, brachytherapy is a highly conformal radiotherapy, so that high radiation doses may be delivered to the tumor while limits the dose to adjacent normal tissue, therefore reducing the radiation injury rates on the health tissues.

To do so, once the oncologist decides to use brachytherapy, a treatment planning is devised which shows the desired seeds location within tumor area. In most of cases, the accuracy of seed positioning into the implant is not an easy question. Besides that, during the temporary seed implantation, the staff is exposed to a non-neglect ionizing radiation that's increases with time procedure on the surgery's room.

Nowadays, a number of new radioisotopes have being used in several brachytherapy applications.

A very promising radionuclide among those is Samarium-153.

Samarium is a lanthanide element presenting a number of isotopes natural or artificial, stables or not.

Produced by neutron capture on Samarium-152, ^{153}Sm is a radionuclide with very interesting features for brachytherapy, having maximum beta energy of 0,634 MeV (34%), 0,702 MeV (44%) and 0,805 MeV (22%), and 103 keV of gamma radiation, among others. It comes from Europium-153, resulted by ^{153}Sm β-decay. ^{153}Sm has a half life of 46.3 hours (1,9 days). The method used for incorporating Samarium-153 in macroaggregate seeds produced by sol-gel route was developed on recent research at NRI/PCTN (Roberto, Pereira, Campos, 2001, 2002). Actually, the development of a bioglass composite with ^{153}Sm mixed on polymeric matrix is subject of research on NRI. Herein, Carboxymethyl cellulose, or CMC will be addressed as a vehicle for the seeds in the implant procedure.

Carboxymethyl cellulose, or CMC, is a cellulose derivative with carboxymethyl groups ($-CH_2-COOH$) bound to some of the hydroxyl groups of the glucopyranose monomers that make up the cellulose backbone. It is synthesized by the alkali-catalyzed reaction of cellulose with chloroacetic acid. The introduction of polar (anionic) carboxyl groups, in case of Sodium Carboxymethyl cellulose ($CH_2OCH_2COO\text{-}Na^+$), in the polymer's backbone renders the cellulose solubility and chemically reactive (Pereira, 2002).

The functional properties of CMC depend on the degree of substitution of the cellulose structure (i.e., how many of the hydroxyl groups have taken part in the substitution reaction), and also on the chain length of the cellulose backbone. Different preparations may have different degrees of substitution, but it is generally in the range 0.6 - 0.95 derivatives per monomer unit.

This polymer presents high biocompatibility, good stickiness, emulsification, diffusibility, enzyme resistance, thermal stability and low temperature adequate handling.

The present study was carried out to evaluate the possibility of using CMC to develop biocompatible devices to fix seeds in geometric adequate array in order to decreasing the time duration of implantation procedures as well as making sure the accuracy of seed position implant on brachytherapy.

2. MATERIALS AND METHODS

Sodium Carboxymethylcellulose by Reagen Quimibras Ind quimica S.A., Calcium Nitrate, TEOS, Samarium nitrate, HNO_3 solution 2 N, deionized distillated water.

2.1. Preparation of Samarium Macroaggregate

The processing of the macroaggregates and the cylindrical seeds was done as described on literature (Roberto, Pereira, Campos, 2001, 2002). Cold, meaning non radioactive, which means non activated, samarium seeds was prepared for application on this experiment.

Sol-gel route is performed. A solution was prepared by mixing correct proportions of samarium nitrate, TEOS, HNO_3 solution, deionized distillated water and Calcium Nitrate. This solution was castled in an adequate shape and left standing for gelation processing. Then the gel was submitted to thermal treatment in oven in which temperature was slowly increased from room until 60ºC. Then the temperature was increased again until 90ºC, and later to 110ºC. After cooled to room temperature the seeds are putted off on crucible and led to a high temperature for calcinations. The seeds present cylindrical shape with 0.5 mm diameter and 2.6 mm length. These are white, cloudy and resistant.

The powder used on this experiment was prepared early, as described by Mendes and Campos (2003). It represents the macroaggreagate of hydroxyapatita incorporating ^{152}Sm.

2.2. Preparation of Sodium Carboxymethyl Cellulose Membranes

Commercial CMC is supplied as powder amorphous substance. Solving the powder on water at desired proportion starts polymerization reaction.

At first, solutions were prepared with three different weight concentrations of CMC / distilled water, 10%, 20% and 30%. The experimental procedure for polymerization is described as follows. CMC was added slowly to water kept under agitation. The temperature of the reaction mixture was maintained close to 90ºC until complete homogenization, thereafter, the mixture was naturally cooled to room temperature.

The solution with better handling and viscosity was which 20% CMC concentration. Then this CMC solution was leaked in a Petri's dish with 5 cm of diameter in which some seeds was displaced following a geometrical array. Alternatively, a portion of powder, taken form triturate seeds with 90-150 µm, was mixed to the CMC solution and displaced onto Petri's dish.

This set was left on oven for drying at ~ 50 ºC, then, producing itself a membrane for long time period.

2.2. Degradation Tests

A membrane, prepared as described early, was immersed in a recipient filled with 50 ml de physiological serum and kept on observation by 72 hours.

After first half hour the membrane presents high level of water absorption, characterized for volume increase and loss of resistance, and became almost liquid after 24 hours past.

Thereupon, a new membrane was made with the higher concentration of CMC, and other one with 40% CMC concentration. Both of them were presented the same degradability behavior on water.

3. RESULTS

The membranes are transparent and present good mechanical strength when dried and these are flexible (Fig. 1 and 2).

Figure 3a was obtained trough an optical microscope 40X magnification and shows air bubbles formed on contact surface between seeds and membrane. In the powder-membrane, an irregular and random distribution of powder macro aggregate all over the membrane was observed due to the random way of depositing it over the Petri's dish. It could be seen on Fig. 3b.

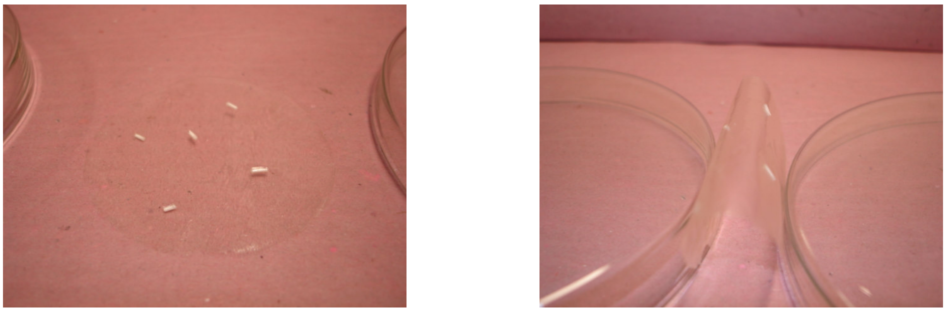

Figura 1 - CMC Membrane loaded with Samarium seeds

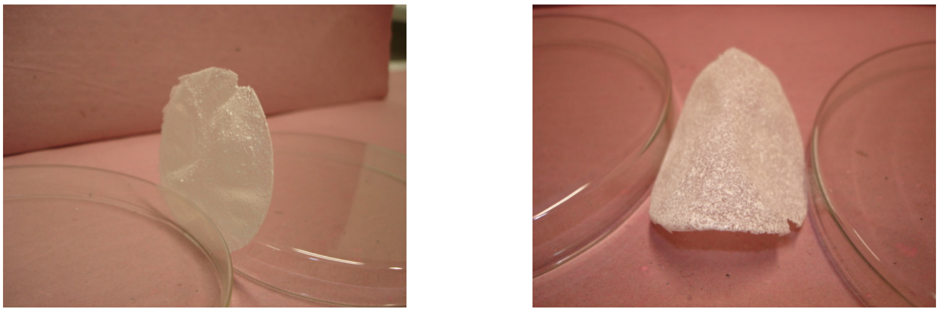

Figura 2 - CMC Membrane loaded with powder of Samarium seeds

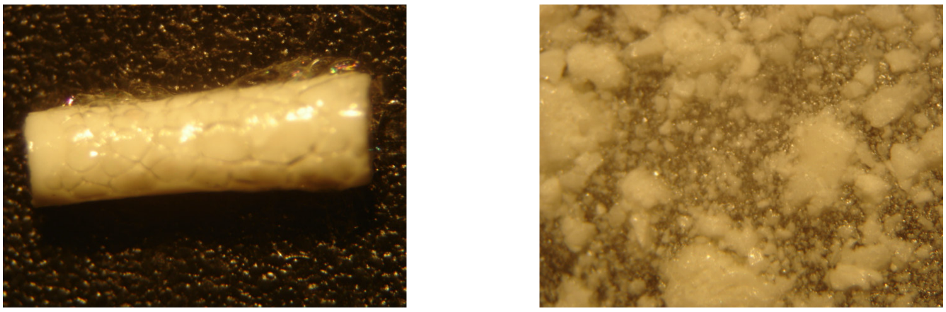

Figura 3 – CMC membrane (a) bubble of air at contact seed's surface (b) membrane with powder on detail

4. DISCUSSION

Degradation time of CMC membranes is found too small compared with ^{153}Sm half life time ($T_{1/2}$ = 1,9 d). The research proposal requires a polymeric membrane with degradation time not smaller than 3 or 4 times ^{153}Sm $T_{1/2}$, in order to guarantee that the seed or powder do not moves into the implant region before to complete its radioactive decay. On the ongoing research, new types of polymers, especially polyvinyl alcohol (PVA), have been tested on NRI with suitable results, not shown here. The formation of air bubbles on contact surfaces between seeds and membrane perhaps could be eliminated by using a vacuum chamber when the seeds are displaced on solution. On the other hand, the irregular distribution of the powder all over the membrane could be reduced by further homogenization on mixture before leaked it in plate of Petri.

5. CONCLUSION

The CMC material shows itself adequate to produce composite material incorporating micro seeds or macro aggregate powder that after drying presented suitable flexibility, stability and resistance. However, on the degradation test on physiological serum, the CMC membrane degrades faster than the proposal research request. The ongoing research are testing new polymers in order to find one that produce suitable implant 'in vivo', supporting a system of dose absorbed delivery for permanent brachytherapy. The absorbed doses will be calculated for this membrane on water using MCNP-5 program. The improvements argued in the previous section will be intended with the new polymer.

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8. RESPONSIBILITY NOTICE