

Holmium-Loaded PLLA Nanoparticles for Intratumoral Radiotherapy Via the TMT Technique: Preparation, Characterization, and Stability Evaluation after Neutron Irradiation

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This article describes the preparation of biocompatible radioactive holmium-loaded particles with appropriate nanoscale size for radionuclide intratumoral administration by the targeted multitherapy (TMT) technique. For this objective, holmium acetylacetonate has been encapsulated in poly-L-lactide (PLLA)-based nanoparticles (NP) by oil-in-water emulsion-solvent evaporation method. NP sizes ranged between 100 and 1,100 nm being suitable for the TMT administration method. Elemental holmium loading was found to be around 18% wt/wt and the holmium acetylacetonate trihydrate (HoAcAc) encapsulation efficacy was about 90%. Different experiments demonstrated an amorphous state of HoAcAc after incorporation in NPs. The NPs were irradiated in a nuclear reactor with a neutron flux of 1.1×10^{13} n/cm²/s for 1 h, which yielded a specific activity of about 27.4 GBq/g of NPs being sufficient for our desired application. Microscopic analysis of irradiated NPs showed some alteration after neutron irradiation as some NPs looked partially coagglomerated and a few pores appeared at their surface because of the locally released heat in the irradiation vials. Furthermore, differential scanning calorimetry (DSC) results indicated a clear decrease in PLLA melting point and melting enthalpy reflecting a decrease in polymer crystallinity. This was accompanied by a clear decrease in polymer molecular weights, which can be ascribed to a radiation-induced chain scission mechanism. However, interestingly, other experiments confirmed the chemical identity retention of both HoAcAc and PLLA in irradiated NPs despite this detected decrease in the polymer crystallinity and molecular weight. Although neutron irradiation has induced some NPs damage,

these NPs kept out their overall chemical composition, and their size distribution remained suitable for the TMT administration technique. Coupled with the TMT technique, these NPs may represent a novel potential radiopharmaceutical agent for intratumoral radiotherapy.

Keywords holmium; nanoparticles; PLLA; radionuclide; tumor; irradiation; TMT technique

INTRODUCTION

Despite the great progress achieved in the technologies used to investigate better treatment modalities, cancer will remain a major social and health concern for the next few years, with more than 11 million new cases diagnosed annually (Buono et al., 2007).

In oncology, nuclear medicine is playing an important role as a diagnostic and therapeutic tool. In the challenge against cancer, major advancement has been made toward its treatment with medical radioisotopes. Some researchers predict that over 80% of cancer types should be treatable with radioisotopes (Scenter, 2007). In current nuclear medicine, two general types of radiotherapy can be carried out to treat tumors: (a) external radiotherapy applying high-energy radiations and unfortunately inducing radionecrosis of normal adjacent tissues and resulting in several side effects and considerable complications (Kaylie et al., 2000) and (b) radionuclide-based therapies including arterial embolization (Kobeiter et al., 2007; Nijsen et al., 2002), metabolic radiotherapy (Alevizaki et al., 2006; Borbath et al., 2005), immunoradiotherapy (Andratschke et al., 2007; Garkavij et al.,

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