

Heparin-Anthranoid Conjugates Associated with Nanomagnetite Particles and Their Cytotoxic Effect on Cancer Cells

Anamaria Durdureanu-Angheluta¹, Cristina M. Uritu¹, Adina Coroaba¹, Bogdan Minea¹, Florica Doroftei¹, Manuela Calin^{1,2}, Stelian Sergiu Maier³, Mariana Pinteala^{1,*}, Maya Simionescu², and Bogdan C. Simionescu^{1,4}

¹Centre of Advanced Research in Bionanoconjugates and Biopolymers, "Petru Poni" Institute of Macromolecular Chemistry of Romanian Academy, 41A Grigore Ghica Voda Alley, 700487 Iasi, Romania

²"Nicolae Simionescu" Institute of Cellular Biology and Pathology of Romanian Academy, Bucharest, Romania

³Department of Textiles and Leather Engineering, "Gheorghe Asachi" Technical University of Iași, 700050 Iasi, Romania

⁴Department of Natural and Synthetic Polymers, "Gheorghe Asachi" Technical University of Iasi, 700050 Iasi, Romania

The paper describes a methodology for preparing monodisperse, water-soluble magnetite nanoparticles, coated with heparin and loaded with 4,5-dihydroxy-9,10-dioxoanthracene-2-carboxylic acid (Rhein), able to be used as a drug delivery system for cancer chemotherapy. Upon preparation, nanoparticles structure and morphology were investigated. The surface charge and the equivalent dimensions of the nanoparticles dispersed in water were measured, as a function of the suspension pH. The concentration of the drug into the nanoparticles shell, and the drug release profile was determined. The functionality of Rhein-loaded heparin-coated magnetic nanoparticles was assessed by monitoring their cytotoxic effect on cultured human tumor hepatocyte cell line, HepG2, using MTT assay. We found that upon exposure of HepG2 cells to Rhein-loaded heparin-coated nanoparticles, the cell viability was drastically reduced (to approximately 10%) as compared to that of the cells exposed to the free drug, indicating the potential of these magnetite nanoparticles to be used in cancer therapy.

KEYWORDS: Anthranoids, Heparin, Magnetic Particles, Drug Delivery, Chemotherapy.

INTRODUCTION

Magnetite nanoparticles coated with various surface active chemical species, either low- or high-molecular compounds, can be guided and accumulated in tissues by using a strong local magnetic field. Such complex entities are already applied as magnetic resonance imaging agents,^{1,2} as heat-inducing vectors for the treatment of solid cancerous tumors by intracellular hyperthermia, or as drug delivery carriers after their loading with different bioactive agents.^{3–6} To improve their efficiency, factors such as:⁷ the chemical nature of the particle shell, the physico-chemical behavior and the reactivity of the carried drug, the dimensions and the magnetic properties of the inorganic core

(especially when the particulate entities must be introduced in relatively large amount into tumor cells) etc. should be assessed.

The aim of this paper was to design, to prepare and to characterize a complex carrier of nanoparticulate type, which consists of a magnetite core coated with heparin, able to be loaded with Rhein, an antitumor drug. The resulted carrier may possibly be able to concomitantly function as a drug delivery system, and as a heat-inducing vector suitable for hyperthermia. As a prerequisite for its therapeutic applicability, testing of the carrier cytotoxicity was also envisaged.

Rhein (4,5-dihydroxy-9,10-dioxoanthracene-2-carboxylic acid) (RH) is an anthranoid compound^{8,9} whose antitumor activity was recently certified by *in vitro* studies and *in vivo* trials. Its efficiency as a drug was also observed in combination with different biomolecules

* Author to whom correspondence should be addressed.

Email: pinteala@icmpp.ro

Received: 12 November 2012

Accepted: 9 April 2013