FORMULATION, CHARACTERIZATION AND CYTOTOXICITY OF CISPLATIN-PLGA NANO- AND MICROPARTICLES.

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Cisplatin is a chemotherapeutic agent widely used in the treatment of solid tumors. Chronic and/or high doses administration result in cellular drug accumulation inducing resistance mechanisms and systemic toxicity. To reduce some of these side effects (nephrotoxicity, ototoxicity, gastrointestinal problems and visual abnormality) and to increase its therapeutic activity many approaches have evolved [1,2].
The purpose of this work was to develop cisplatin micro- and nanoparticles to study the differences among them in the in-vitro cytotoxic effect in tumor cells.

Cisplatin loaded poly(lactic-co-glycolic) acid particles were prepared by a solvent evaporation method. The A/O/A method was selected for optimizing these preparations [2]. Three main protocols were developed, in two of them the emulsions were prepared by sonication and the last one by sonication followed by ultraturrax system. In order to increase the drug loading, in all protocols a saturation with cisplatin of the external aqueous phase in the second emulsion step was tested. The physicochemical characteristics of these particles were studied. To quantify cisplatin loading a sensible and reproducible HPLC method was developed [3]. In addition, to characterize the cytotoxic effect of the cisplatin released from the different particles, an in-vitro study in culture cells was carried out. The cell viability was measured by the neutral red assay [4].

The experimental results showed that the sonication process lead to a reduction in the size of the particles (200-300 nm) in relation to the ultraturrax system (10 μm). To increase the content of cisplatin in all formulations, a saturation of 5 mg/mL of the external aqueous phase of the second emulsion, was an essential requirement.
The encapsulation of cisplatin, calculated from in-vitro release studies, was a 20 % higher ($P < 0.01$) in microparticles than in nanoparticles. The smaller nanoparticles (200 nm) showed a significant initial burts effect, releasing a 25 % of cisplatin in the first 3 h. This initial burts effect was lower than 10 % for the other two formulations.

In in-vitro studies, all formulations displayed a lower cytotoxicity than free cisplatin. This cytotoxic effect, characterized by the reduction of cell viability, was tested for different concentrations of free cisplatin and encapsulated. A significant ($P < 0.01$) increase in the value of IC_{50} [the concentration of cisplatin that is able to inhibit the 50 % of cellular viability] for all formulations in relation to the free cisplatin (100 μM *vs* 18 μM, respectively) was observed.

In conclusion, the A/O/A method allowed the development of particles with different size that were able to decrease the cytotoxic effect of cisplatin tested in in-vitro studies.

References:

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