Microencapsulated Controlled-Release Cisplatin Formulations for Oncology Applications

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ABSTRACT

Drug delivery technologies that enable sustained-release of the anti-cancer drug, Cisplatin, offer the potential for greater efficacy and reduced systemic toxicity. We report on a microencapsulation based formulation of Cisplatin, which enable controllable sustained-release of the active pharmaceutical ingredient (API). Furthermore, the technology has been developed into product concepts for multi-encapsulation of Cisplatin, as well as Radio Frequency Ablation devices combined with drug delivery features.

Microencapsulation of Cisplatin was achieved with 72.5 poly- 

tylox-ylic-glutaric (PLGA) polymer. Microspheres were generated using either a polymeric surfactant (Na- 

tar) with water dilution or by a method involving water evaporation, and were collected in 105-150 μm size range. The microspheres displayed uniform size and morphology, as illustrated by optical microscopy and SEM. Additionally consistent drug loadings for three distinct formulations in the range of 10-30% (w/w) were achieved, as measured by HPLC, NMR, and XRD methods. Furthermore, the combination of Cisplatin and microencapsulated Cisplatin formulations was employed to determine in-vitro release profile kinetics for Cisplatin, covering the range of release over a few hours to that over several weeks.

Our background is the development of polymeric microencapsulation based formulations of Cisplatin, with the specific goal of allowing for the use of the formulation with a variety of promising therapeutic strategies. In addition to the stand-alone use of the polymeric microencapsulation formulation for systemic administration, our goal includes (a) stand-alone local administration (b) local administration with the formulation incorporated into a medical device as a delivery platform as a combination product, and (c) the above strategies in concert with other drug molecules (i.e., combination therapy administered both systemically and locally). The overarching motivation was to create a Cisplatin formulation with relevance to all the above therapeutic strategies.

We have successfully been creating a range of microencapsulated Cisplatin formulations using poly- 


tylox-ylic-glutaric (PLGA) polymers, with the employment of solid in oil in water (W/O) emulsion based solvent evaporation methods. This has resulted in particles that are uniformly spherical and a wide particle size range (from the sub-micron (100 nm) range to 150 μm in diameter). Additionally high drug loading levels were achieved, in the range of 20-30% (w/w), which is at the higher end for loading, compared to what is published in the literature.1,2 Most importantly, we have been successful in achieving a wide range of release profile kinetics for Cisplatin, covering the range of release over a few hours to that over several weeks. The characteristic formulation provides information on the morphology of the microencapsulated particles, the distribution of drug within them, as well as the crystalline state and surface conformation of the drug molecule. These characteristics provide the basis to optimize the release characteristics of the formulation by a combination of strategies such as drug-loading, type of PLGA polymer, weight of encapsulating polymer, as well as process variables such as shear rate, speed of phase addition, and others. Preliminary data generated in cell culture with the A549 lung cancer cell line has established a significantly lower IC50 value for the microencapsulated Cisplatin formulation compared to un- 


capsulated Cisplatin, thus emphasizing the increased potency of our formulation with the promise of better efficacy at lower drug dosage.

In addition, we have been successful in achieving double-encapsulation / multi-encapsulation for Cisplatin, which opens up significant new possibilities, such as (a) co-encapsulation of two or more drugs, including Cisplatin and (b) multiple bursts in the kinetics of Cisplatin release profile. We have also been successful in crystallizing new combination product concepts, such as microencapsulated drug delivery components into RF Ablation devices through which the microencapsulated Cisplatin could be administered locally into the tumor ablation margins. These preliminary results provide an encouraging basis for our ongoing work, namely further characterization and optimization of our formulation, followed by the evaluation of their efficacy in cell culture and preclinical models.

REFERENCES


