HYALURONIC ACID-COATED BIODEGRADABLE NANOPARTICLES FOR TARGETED DRUG DELIVERY

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Purpose: Hyaluronic acid (HA), a naturally occurring anionic polysaccharide, has attracted significant research attention for tumor-targeted delivery since it is biocompatible and non-immunogenic , and can specifically bind CD44 and RHAMM receptors, which are overexpressed in many forms of cancer. Here we propose a novel method to promote a spontaneous arrangement of HA on the surface of irinotecan (IRIN)-loaded poly(lactic-co-glycolic acid) (PLGA) nanoparticles (NPs) through a modified single emulsion-solvent evaporation method.

Methods: NPs were prepared and characterized in terms of morphology, size and zeta potential (ZP), differential scanning calorimetry, encapsulation efficiency and *in vitro* drug release. NP suspension stability was evaluated by measuring their size over time. Cellular uptake studies and cytotoxiticy assay were taken on breast cancer cell line, which overexpress CD44 (MCF-7) and healthy adipose mouse cells (L929).

Results: The obtained NPs had a mean size of ~110-420 nm depending on HA/PLGA/poloxamer weight ratio. NP amphiphilicity allowed to obtain a IRIN encapsulation efficiency of 61.2% w/w. IRIN *in vitro* release kinetics were sustained up to 24 days with an initial phase controlled by diffusion and a second slower release governed by degradation. ZP was negative for all formulations, and decreased from approximately -23 to -50 mV when HA was added. Furthermore, the presence of HA in NP formulation promoted device stability for at least 10 days compared to NPs made up of PLGA alone, which immediately aggregate in water. Finally, thermal analysis revealed that in the NP formulations PLGA, poloxamer and HA act as independent entities and not as a polymeric blend. All these data suggested that PLGA constitutes NP bulk while HA is superficially exposed, with amphiphilic poloxamers acting as a bridge between the PLGA and HA. Finally, in cell culture studies, the tumor-targeting ligand HA enhances NP intracellular delivery of IRIN-loaded PLGA NPs in cell lines overexpressing the CD44 receptor.

Conclusion: Here we propose a NP production method easy to scale up, being a single step process. By this method is possible to obtain HA-coated NPs for targeted drug delivery to a number of important types of CD44-overexpressing cancer cells.