CO-DELIVERY OF DNA-ALKYLATING DRUGS BY CHITOSAN-FOLIC ACID NANOCOMPLEXES FOR MULTIDRUG CANCER THERAPY

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Cancer remains one of the most devastating diseases threatening public health, causing high mortality worldwide every year. For decades, chemotherapy has served, in combination with surgery, as the preferred treatment. [1,2]. However, conventional chemotherapeutics lack selectivity and inevitably damage healthy cells and tissues with evident toxicity. Delivering adequate doses of the pharmaceutical agent to specific sites in the body promotes a drug action where required, which results in a significant decrease of side effects. Targeted delivery has the potential to revolutionise current anticancer treatments and improve the clinical outcomes [3,4]. Active targeting of therapeutics to cancer tissue normally involves linking or load the therapeutic agent to a carrier, such as nanoparticles, with a targeting small molecule or ligand that can be recognised and interact with receptors expressed on the target tissue. Several targeting moieties have been investigated, including antibodies or specific ligands, as transferrin, glycyrrhetinic acid, aptamers, galactose, mannose and peptides (Arg-Gly-Asp) [5]. Among all, a folic acid conjugation is a popular approach facilitating the entry of the therapeutic into tumour cells by receptor-mediated endocytosis.

In the presented work, chitosan (CS) has been conjugated with folic acid (FA) and complexed with alginate (ALG) to develop nanocomplexes able to load simultaneously two model DNA-alkylating agents; temozolomide (TMZ) and doxorubicin (DOX); control their release and improve their therapeutic efficacy and selectivity towards cancer cells. The use of FA as a targeting moiety has the potential to achieve targeted delivery and improve the efficiency of carrier internalization, whilst bypassing cancer cell multidrug-efflux pumps.

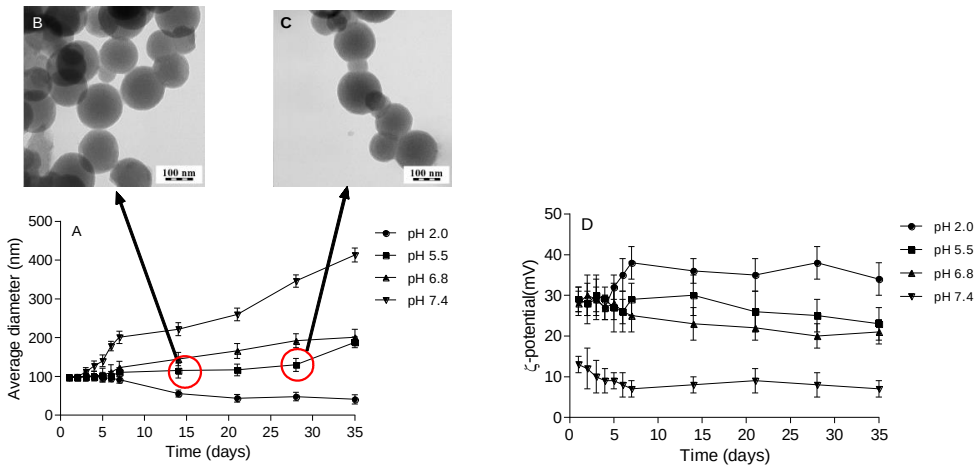

Fig. 1. Evaluation of nanocomplexes dimension over time at different pH. A) Average dimension trend; TEM micrograph of nanocomplexes in solution pH 5.5 after B) 14 days and C) 28 days

The CS-FA-ALG system shown dimension and ζ-potential in the range 70–120 nm, and 30-35mV, respectively, with high stability in physiological condition. Up to 800 g per mg of carrier of drugs were loaded with a weight ratio close to 1. In vitro release patterns demonstrate a two phases controlled release with a pH dependent trend. The possibility to modulate the intensity of the initial burst and the release rate by changing the pH represents an advantage rather than confirm the high versatility of the system. The absence of interference between DOX and TMZ in all phases, from loading to release stand out as important findings. In vitro cytotoxicity studies confirmed the increase of the drugs cytotoxicity and their synergic effect when administered using the carrier compared to the free formulation. Comparing the cell viability results between

FR overexpressing cells and not a significate reduction was observed in the first when CS-FA nanocomplexes were used confirming the importance of labelling. The serum stability studies prove that the prepared formulations were stable and the hemolysis analysis discloses the blood compatibility of the formulations.

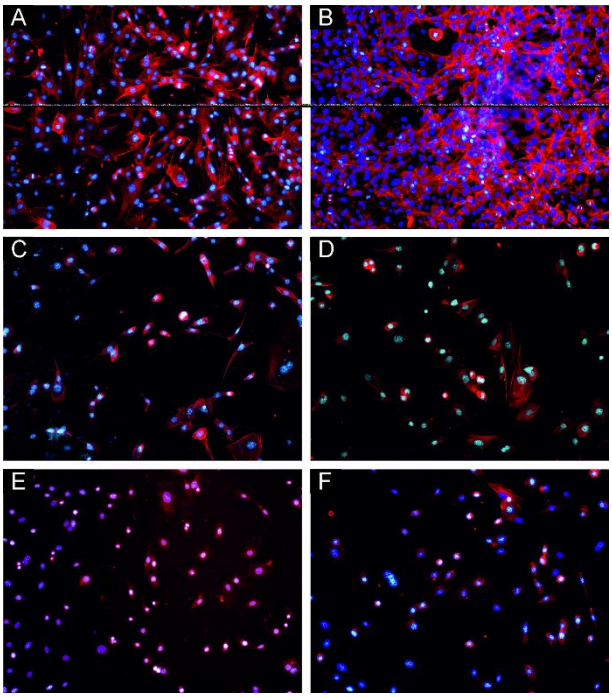

Fig. 2. Inverted fluorescent microscopy of NIH/3T3 cells after 24 h of incubation with A) CS, B) CS-FA, C)CS+DOX, D) CS-FA +DOX, E)CS+ (DOX+TMZ) and F) CS-FA + (DOX+5FU)

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