Stealth nanoparticles for the intracellular curcumin delivery induce cell cycle arrest in mesothelioma cells

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Purpose: Curcumin (CURC), a polyphenol extracted from the rhizome of *Curcuma Longa Linn*, can be potentially used in cancer treatment taking advantage of its ability to block the proliferation of many tumor cells. Unfortunately, the pharmacological potential of CURC is severely restricted by its low water solubility, short half-life and extremely poor bioavailability. To overcome these issues, CURC-loaded nanoparticles (NPs) were produced and the effects of the preparation technique on NP size and cellular uptake investigated.
Methods: Poly(lactic-co-glycolic acid) (PLGA) NPs coated with hydrophilic polyethylene-oxide (PEO) were obtained by blending poloxamers and PLGA at different polymer concentrations in an organic phase, used to produce the NPs, both with nanoemulsion/solvent evaporation and nanoprecipitation techniques [1]. NPs have been characterized in terms of size, morphology, zeta potential, yield and CURC entrapment efficacy. NP stability was evaluated by measuring their size over time both at 4°C in aqueous media and at 37°C in complete cell culture medium. Moreover, *in vitro* drug release studies have been carried out. A mesothelioma cell line MSTO-211H was used to investigate NP cellular uptake and effect on cell proliferation and cell cycle progression.
Results: PEO-coated PLGA NPs had a mean size between 90-200 nm and ZP ~-22 mV, for all formulations. NP size was roughly stable for at least 30 days in water at 4°C and in RPMI-1640 medium at 37°C up to 72 hours. *In vitro* CURC release was found to be mainly driven by drug diffusion and was completed within approximately 4 days. Studies on MSTO-211H cells showed that CURC-loaded NPs can inhibit cell growth and promote a prolonged cell cycle arrest in the G0/G1 phase up to 72 hours, thus overcoming the drug tolerance phenomenon, normally evidenced when free CURC is used. Moreover, CURC-loaded NPs displayed a rapid uptake in the first 48 hours, strongly dependent on the size of the devices.
Conclusions: Taken altogether, the results show that nanodelivery strategies are helpful in overcoming CURC stability issues and that, by properly engineering the devices in terms of meansize and surface properties, the active molecule can be effectively internalized by cancer cells.

[1] Mayol et al. European Journal of Pharmaceutics and Biopharmaceutics, 2015.