

Stable amphiphilic nanoparticles for the targeted and sustained release of silibinin

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Purpose: Silibinin (SLB) is a polyphenolic flavonoid derived from the seeds of the milk thistle plant, *Silybum marianum*. SLB is active against several carcinomas such as breast, lung, colon, brain, and also against prostate cancer. SLB also possesses significant anti-proliferative activity through the regulation of cell cycle, apoptosis induction, chemosensitization, growth inhibition, anti-inflammation, reversal of multi-drug resistance along with the inhibition of angiogenesis, tumor invasion and metastasis. Unfortunately, the pharmacological activity of SLB is severely restricted by its poor water solubility and oral bioavailability. Therefore, SLB encapsulation in nanoparticles (NPs) is a promising strategy for its improved delivery. The NPs were made up of an amphiphilic blend of poloxamers and poly(lactic-co-glycolic acid) (PLGA) so as to endow them with an hydrophilic surface to take advantage of the enhanced permeability and retention (EPR) effect.

Methods: NPs were produced by nano-precipitation/solvent evaporation method and characterized in terms of size, zeta potential (ZP) and morphology. *In vitro* drug release studies were carried out by placing NPs in dialysis membranes in phosphate buffer solutions and quantifying the drug by spectrophotometric assay. NP stability was evaluated by measuring their size over time both in aqueous suspension at 4°C and cell culture medium at 37°C. To investigate on the drug-polymer interactions, thermal analyses were performed on SLB-loaded NPs by differential scanning calorimetry (DSC).

Results: The obtained NPs were spherical, with a mean size of approximately 110 nm and, for all formulations, ZP ranged between -20 and -27 mV. Morphological, ZP and size analyses confirmed an effective, hydrophilic PEO coating on NP surface. SLB was effectively loaded into the produced NPs and *in vitro* release studies demonstrated NP ability to sustain the release of the drug. Results of thermal analyses evidenced the lack of chemical interaction between SLB and the polymers constituting the devices, thus indicating that SLB was only physically encapsulated. This indicates that the pharmacological potential of the drug is not affected both by the preparation technique and the loading in the nanodevices.

Conclusion: Based on these promising results, we believe that the use of delivery strategies based on nanoparticles could promote the use of SLB in therapy.