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Optimized Formulations of 5-FU-conjugated Iron Oxide Nanoparticles Inhibit the MCM-2 Protein Expression in Colorectal Cancer Cells †

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Abstract: Despite de advances registered in drug delivery nanosystems, the poor loading capacity of nanoparticles and the lack of efficiency of therapeutics that reach the target site remain some of their major limitations for passing clinical trials. Hence, the present study aimed to optimize the 5-fluorouracil (5-FU) loading on iron oxide nanoparticles (IONP) by varying nanoparticles:5-FU ratios and investigating the effects of the resulting nanoformulations (IONP:5-FU) on the drug response in colorectal cancer cells. Maghemite nanoparticles (ɣ-Fe2O3) synthesized by co-precipitation and 5-FU solution were mixed in physiological serum and optimized to obtain the ratios of 0.5:1, 1:1, and 1.5:1 in the final suspensions. Caco-2 cells were then incubated for 24 and 48 h with different concentrations (5-250 µg/mL 5-FU) of the optimized nanoformulations to assess the cell viability and morphology, cell loading with nanoparticles, and antitumor activity (oxidative stress, apoptosis, inhibition of proliferation). Individual components were tested in parallel. The results showed that IONP:5-FU, which has the maximum content of IONP (ratio of 1.5:1), had the highest capacity to decrease cancer cell viability after 48 h (IC50 of 5-FU dropped from 200 to 80 µg/mL when conjugated with IONP). Yet, it was noted that after 48 h, all nanoformulations induced changes in Caco-2 cell morphology, characteristic for cell death initiation, and completely inhibited the expression of MCM-2 protein, a marker of proliferation. The intracellular accumulation of IONP was dependent on IONP:5-FU ratio and was correlated with the production of hydrogen peroxide in colorectal cancer cells. However, the apoptotic effector caspase-3 was not activated, and neither the LDH level from culture media was modified. Our findings indicate that iron ions might play a role in enhancing 5-FU antitumoral activity, thereby setting the premises for a novel approach to improve the 5-FU-based treatment of colorectal cancer.

Keywords: iron oxide nanoparticles; drug delivery; colorectal cancer; 5-FU; MCM-2.

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Conflicts of Interest

The authors declare no conflict of interest.