Combinatorial Approach of Curcumin and 5-Fluorouracil Loaded Chitosan Derivatives-Based Nanoparticles towards the Treatment of Carcinoma of Colon

Abstract

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Colorectal cancer being one among the major causes of cancer death worldwide and the first line chemotherapeutic agent used for colorectal cancer is 5-fluorouracil (5-FU). Despite surgical resection and aggressive chemotherapy, almost 50% of patients with colorectal carcinoma develop recurrent disease. Thus the rationale of developing an agent that could improve the current chemotherapeutic regimen would therefore be highly desirable. Earlier reports about the in vitro and in vivo works in colorectal cancer have shown the effectiveness of combined treatment of 5-FU with other regimen in comparison with 5-FU treatment alone. Even these approaches are associated with poor patient compliance results from the unwanted toxic side effects of the chemo drugs. Current thesis work pinpoints about an effective strategy to improve the efficacy of 5-FU assisted chemotherapy against colon cancer. This has been addressed by developing a combinatorial nanomedicine using 5-FU with a phytochemical anticancer drug, curcumin; CRC. The combination of these two drugs poses synergistic anticancer effects in colon cancer cells under in vitro conditions which had been proven earlier. The nanoencapsulation has been employed to improve the limitations of 5-FU (systemic toxicity) and CRC (low bioavailability) and to reduce the dose of 5-FU. Thus we employed combinatorial approach along with nanoencapsulation to improve the chemotherapeutic efficacy of 5-FU against colon cancer. The nanoencapsulation (will protect the drugs against degradation, and it reduces the non selective exposure) has been achieved by biodegradable non-toxic chemically modified chitosans; N, O-carboxymethyl chitosan (N, O-CMC) and
thiolated chitosan (TCS). These are characterized by their ease of solubility in water at neutral pH unlike chitosan and improved functionality, which further improves the drug encapsulation and the properties. Hence we have developed CRC loaded N.O-CMC nanoparticles, 5-FU loaded N.O-CMC nanoparticles (system 1) and CRC loaded TCS nanoparticles and 5-FU loaded TCS nanoparticles (system 2) and characterized. The hemocompatibility of the developed nanoformulation was confirmed by hemolysis and clotting assays which pinpoints the intravenous administration potential of the nanomedicine. The in vitro combinatorial anticancer evaluation of both of the systems by MTT, live dead, mitochondrial membrane potential and cell cycle analysis measurements in colon cancer (HT29) cells proved the enhanced anticancer effects of the combinatorial nanomedicine unlike the individual nanoformulations and individual free drugs. The cellular internalization of nanoformulation was confirmed by confocal laser scanning microscopy. In addition, the pharmacokinetics studies in mouse model confirmed the improved bioavailability of 5-FU and CRC after the administration of individual as well as the combinatorial nanoformulations. Overall, the results showed the enhanced anticancer effects of the combinatorial nanomedicine in colon cancer cells under in vitro and improved the bioavailability of the drugs under in vivo conditions. These in vitro and in vivo results suggest the potential of the combinatorial nanomedicine in colon cancer treatment. Further in future, the study needs to be extended to prove the in vivo efficacy of the combinatorial nanomedicine in colon cancer xenograft model.