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Hydrophobically Modified Glycol Chitosan Nanoparticles as a Carrier for Etoposide

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Abstract : Development of efficient delivery system for hydrophobic drugs remains a major concern in chemotherapy. The objective of the current study was to develop polymeric drug-delivery system for etoposide from amphiphilic derivatives of glycol chitosan, capable to improve the pharmacokinetics and to reduce the adverse effects of etoposide due to various organic solvents used in commercial formulations for solubilisation of etoposide. As a promising carrier, amphiphilic derivatives of glycol chitosan were synthesized by chemical grafting of palmitic acid N-hydroxy succinimide and quaternisation to glycol chitosan backbone. To this end a 7.9 kDa glycol chitosan was modified by palmitoylation and quaternisation into 13 kDa. Nano sized micelles prepared from this amphiphilic polymer had the capability to encapsulate up to 3 mg/ml etoposide. The pharmacokinetic results indicated that GCPQ based etoposide formulation transformed the biodistribution pattern. AUC 0.5-24 hr showed statistically significant difference in ETP-GCPQ vs. commercial preparation in liver (25 vs 70, $p<0.001$), spleen (27 vs. 36, $P<0.05$), lungs (42 vs. 136, $p<0.001$), kidneys (25 vs. 30, $p<0.05$) and brain (19 vs. 9,$p<0.001$). Using the hydrophobic fluorescent dye Nile red, we showed that micelles efficiently delivered their payload to MCF7 and A2780 cancer cells in-vitro and to A431 xenograft tumor in-vivo, suggesting these systems could deliver hydrophobic anti- cancer drugs such as etoposide to tumors. The pharmacokinetic results indicated that the GCPQ micelles transformed the biodistribution pattern and increased etoposide concentration in the brain significantly compared to free drug after intravenous administration. GCPQ based formulations not only reduced side effects associated with current available formulations but also increased their transport through the biological barriers, thus making it a good delivery system.

Keywords : glycol chitosan, Nile red, micelles, etoposide, A431 xenografts
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