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## Chitosan Derivatives for Anticancer Drug Delivery

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**Introduction:** Gossypol (GS) is an effective anticancer agent that can induce apoptosis of cancer cells by inhibiting anti-apoptotic proteins like BCL-2, BCL-XL, and MCL-1, disrupt metabolism, and generate ROS, but has high toxicity and limited solubility in aqueous media.<sup>1</sup> Therefore, its combination with natural polysaccharides, such as chitosan (CS), is a promising solution for providing biocompatible polymeric GS carriers that can potentially reduce its toxicity, allow targeted delivery, and increase solubility.

**Aims:** To produce polymeric GS carriers in the form of CS derivatives and investigate the efficiency of the CS modification with different amounts of two forms: GS and GS-acetic acid (GSAA) by physicochemical characterization.

**Methods:** Chitosan (highly viscous, origin - crab shells, acetylation degree - 17.7%) was derivatized with different loads of GS and GSAA (1, 2.5, 5, 7.5, 10, and 12.5 wt.% relative to CS) via free-radical grafting. The presence of GS and GSAA in the CS derivatives was confirmed by NMR, UV-Vis, and Raman spectroscopy. The comparative analysis of modification efficiency for both series with GS and GSAA was done via elemental composition (C, H, and N), 2,2-diphenyl-1-picrylhydrazyl (DPPH) and Folic-Ciocalteu (F-C) assays.

**Results:** CS derivatives changed color from white to yellow with increasing drug concentration, which was also confirmed by UV-Vis analysis; corresponding signals of GS and GSAA appeared during NMR analysis and Raman spectroscopy documenting the presence of molecules in the derivatives. The total phenolic content evaluated by the F-C assay as gallic acid equivalent was at the maximum of 67.9 mg/g for the GS derivative and 91.3 mg/g for the GSAA derivative with the highest drug load (12.5 wt.%), demonstrating the effective grafting in both series. In the evaluation of radical scavenging activity by DPPH assay, the maximal DPPH inhibition was reached in the case of the highest drug loading (12.5 wt.%) at a low concentration of the analyzed samples (0.025 mg/mL), while for pure CS, even increasing the concentration to 0.375 mg/mL only allowed to reach 30-40 % of inhibition. The elemental composition of derivatives also confirmed that CS grafting with GSAA was 7 % more efficient based on the obtained values of substitution degree (based on the C/N ratio).

**Conclusion:** CS derivatives containing anticancer GS were prepared by free-radical grafting. The effect of increasing drug load on phenolic content, radical scavenging activity, and elemental composition using two forms of GS was investigated. The NMR, Raman and UV-Vis spectroscopy analyses confirmed the efficacy of modification and revealed that CS grafted with GSAA had a higher phenolic content and a better radical scavenging activity than one with GS and is advised to be used for reaching better efficiency of grafting. This convenient design of polymeric GS carriers shows great potential for further surface modification of magnetic nanoparticles with CS derivatives for designing new drug delivery systems for cancer treatment.

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**Reference:** 1. O. Renner, M. Mayer, C. Leischner, et al., Systematic review of gossypol/AT-101 in cancer clinical trials. *Pharmaceuticals (Basel)* 2 (2022):144, doi: 10.3390/ph15020144