Design and synthesis of angiopep-conjugated chitosan-coated Mg0.5Co0.5Fe2O4 nanoparticles for brain-targeted delivery

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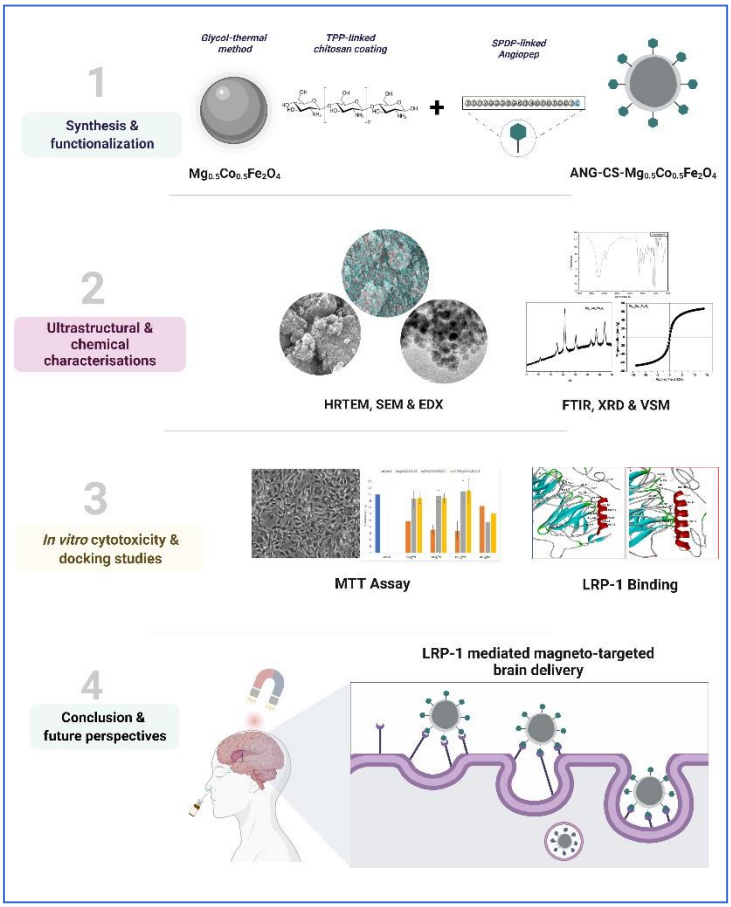

Figure 1.: Design and synthesis of angiopep-conjugated chitosan-coated $Mg_{0.5}Co_{0.5}Fe_2O_4$ nanoparticles for brain-targeted delivery

Introduction: Nanotherapeutics intended for brain delivery are currently limited due to the taut nature of the blood brain barrier (BBB). To overcome this, researchers often modify the surface of nanoparticles (NPs) to exploit receptor-mediated traversing of molecules across the BBB. Ferrite nanoparticles (NPs) have recently emerged as attractive nanocarriers owing to their facile synthesis and surface functionalization.

Methodology: In this study, we report on the synthesis of ferrite nanoparticles targeted for brain delivery using the glycol-thermal route. The *as*-prepared NPs *viz*. magnesium-doped cobalt ferrites were coated with chitosan (CS) using sodium tripolyphosphate (TPP) as a crosslinker and conjugated with angiopep-2 (ANG), a blood brain barrier targeting peptide to yield ANG-CS-$Mg_{0.5}Co_{0.5}Fe_2O_4$. The physical, chemical, and magnetic properties were characterised by X-ray diffraction (XRD), high resolution transmission electron microscopy (HR-TEM), scanning electron microscopy (SEM), vibrating sample magnetometer (VSM), Fourier transform infrared spectroscopy (FTIR) and nanoparticle tracking analysis (NTA).

Results and Discussion: XRD and VSM results revealed spinel crystalline ferrite core NPs exhibiting superparamagnetic behavior. TEM data confirmed particle core sizes of up to 9.8 nm. The peak shifts in the FTIR spectra were noted upon CS-coating and functionalization with angiopep-2. Hydrodynamic sizes of 123.1 nm were reported for the ANG-CS-$Mg_{0.5}Co_{0.5}Fe_2O_4$ using the NTA. Furthermore, NP colloidal stability was measured with zeta potential of up to +20.7 mV for the CS-coated $Mg_{0.5}Co_{0.5}Fe_2O_4$. *In vitro* MTT studies demonstrated improved biocompatibility of NPs with > 70% viability in the glioblastoma (U87mg) cell line at concentrations of up to 200 µg/ml. Furthermore, *in silico* investigation of binding energies demonstrated comparable binding affinity for the ANG-conjugated NPs to to the free Angiopep-2.

Conclusion: Overall, these CS-coated magnesium-cobalt ferrites exhibit great promise for targeted brain delivery. Further, the ANG-CS-$Mg_{0.5}Co_{0.5}Fe_2O_4$ NPs can be explored for *in vitro* and *in vivo* LRP-1 mediated magneto-targeted gene and drug delivery studies.

Keywords: ferrites, chitosan, angiopep-2, brain delivery, magnetic, nanoparticles, CNS