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MAGNETICALLY RESPONSIVE NANOPLATFORMS FOR OTOPROTECTION: LIPOSOMAL CORTICOSTEROID DELIVERY AND PROTOCATECHUIC ACID–ENGINEERED IRON OXIDE NANOPARTICLES

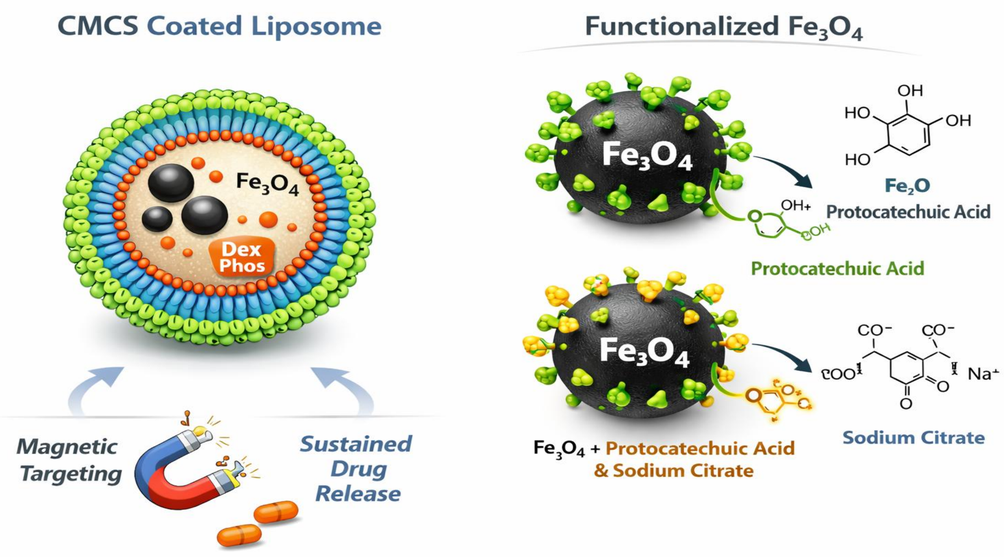
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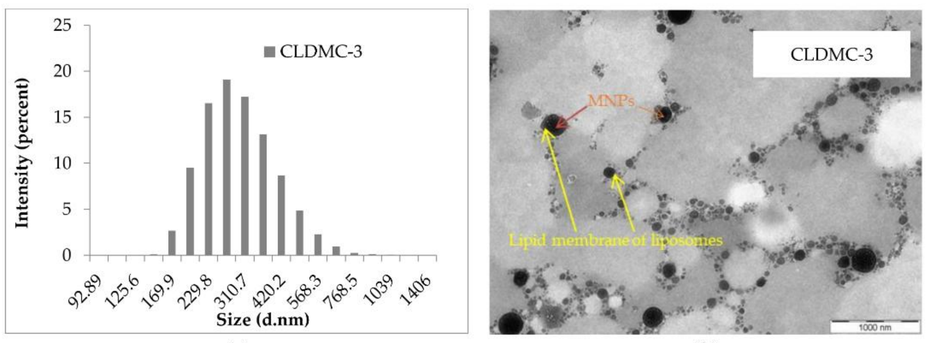
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Abstract

- **Introduction.** Hearing loss caused by platinum-based chemotherapeutics and aminoglycosides remains a major clinical limitation. Poor drug access to the inner ear restricts pharmacological protection of auditory cells. To address this, we develop two magnetically responsive nanoplatforms for targeted drug delivery and cytoprotection.
- **Methods.** Cationic liposomes coated with carboxymethyl chitosan were formulated to encapsulate magnetite nanoparticles (Fe_3O_4) and dexamethasone phosphate, enabling magnetic guidance and sustained corticosteroid release. In parallel, Fe_3O_4 nanoparticles were surface-functionalized with protocatechuic acid (3,4-dihydroxybenzoic acid). With or without sodium citrate, to introduce antioxidant and anti-inflammatory properties. Hei-OC1 auditory cells were challenged with cisplatin or gentamicin and co-treated with the nanomaterials. Cell viability, mitochondrial membrane potential, and senescence-associated β-galactosidase activity were analyzed to assess cytoprotective efficacy.
- **Results.** Both nanoplatforms exhibited excellent biocompatibility (≥85% viability) and significantly attenuated drug-induced mitochondrial depolarization and senescence. Polymer-coated magnetic liposomes ensured corticosteroid delivery while preserving mitochondrial integrity, whereas PCA-functionalized Fe3O4 nanoparticles stabilized redox balance and enhanced cellular resilience.
- **Conclusions.** These findings establish proof-of-concept for multifunctional magnetic nanomaterials integrating magnetic responsiveness, controlled drug release, and intrinsic antioxidant activity. This approach holds promise for magnetically guided delivery to the inner ear and future translational strategies in hearing preservation.

EXPERIMENTAL





(a) (b)

Figure 1: (a) The intensity-weighted size distribution and (b) TEM image of CLDMC-3 sample (CMCS-coated magnetic liposomes) obtained at an accelerating voltage of 100 kV with a magnification of 19,000.

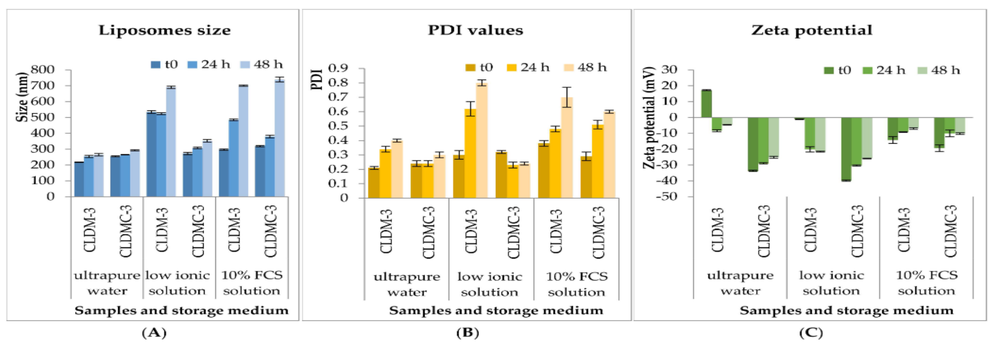
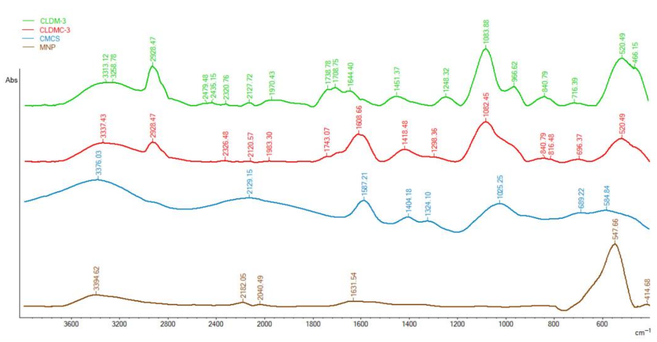


Figure 2. CLDM-3 and CLDMC-3 liposomes' size (A), PDI value (B), and zeta potential (C) evaluated at 37 ◦C



The successful coating of magnetic liposomes is revealed by the appearance or the shift of characteristic peaks in the FT-IR spectrum of the magnetic liposomes coated with CMCS (CLDMC-3) (Figure 2), as follows:

(i) Appearance in the spectrum of CLDMC-3 sample of peaks at 2928 cm−1, 1082 cm−1,and 840 cm−1 characteristic of the uncoated magnetic liposomes sample;
(ii) The shift of the peaks from 3376 cm−1 to 3337 cm−1, from 1587 cm−1 to 1608 cm−1, and from 1404 cm−1 to 1418 cm−1 in the spectrum of CMCS to the spectrum of CLDMC-3;
(iii) The presence of the characteristic CMCS peak at 1025 cm−1 in the broad peak of the coated magnetic liposomes.

Figure 3: FT-IR spectra of the CMCS, MNPs, magnetic liposomes (CLDM-3), and coated magnetic liposomes (CLDMC-3).

RESULTS

Biological Characterisation

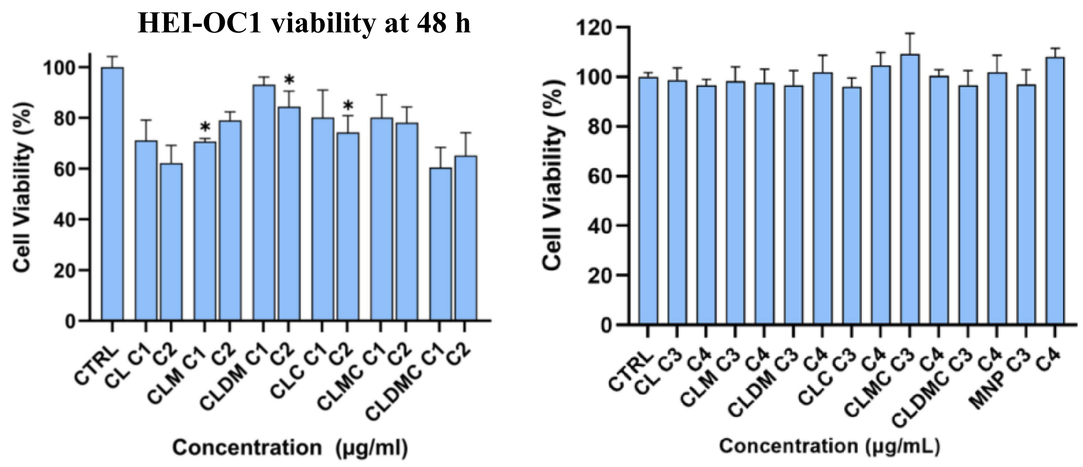


Figure 4: Cell viability of HEI-OC1 after 48 h in the presence of liposomal formulations: (a) C1 = 12.5 µg/mL and C2 = 25 µg/mL; (b) C3 = 6.25 µg/mL and C4 = 12 µg/mL. Data are represented as mean and SD,n = 3; * $p < 0.05$, compared with the control group

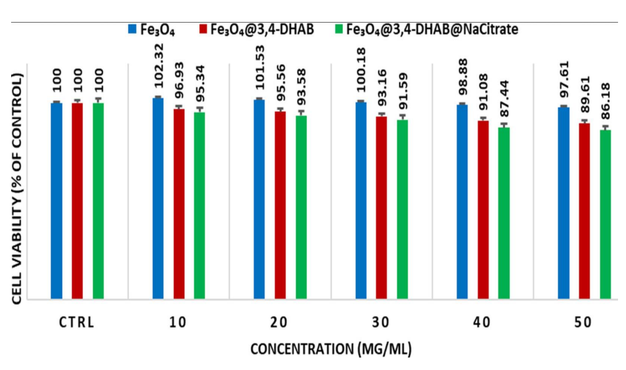


Figure 5: Cell viability of HEI-OC1 cells after exposure to Fe_3O_4, Fe_3O_4@3,4-DHAB, and Fe_3O_4@3,4-DHAB@NaCitrate at various concentrations (10–50 mg/mL.

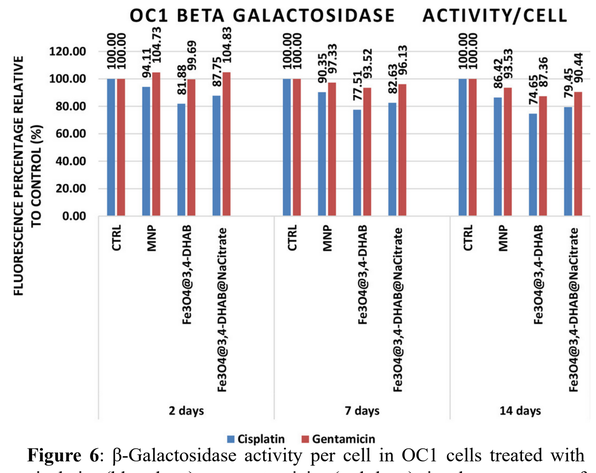


Figure 6: β-Galactosidase activity per cell in OC1 cells treated with cisplatin (blue bars) or gentamicin (red bars) in the presence of uncoated MNPs (Fe_3O_4), Fe_3O_4@3,4-DHAB, or Fe_3O_4@3,4-DHAB@NaCitrate over 2, 7, and 14 days.

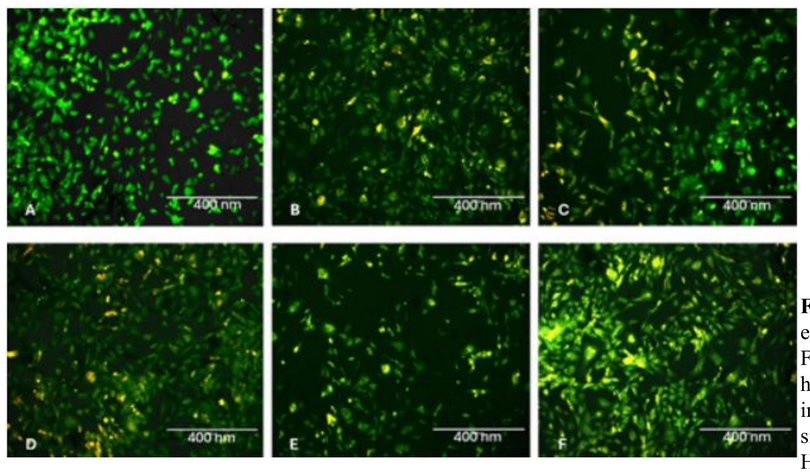


Figure 7: MMP after gentamicin and cisplatin exposure concomitant with Fe_3O_4@3,4-DHAB or Fe_3O_4@3,4-DHAB@NaCitrate. Relative fluorescence intensity stack fluorescent images overlaying JC-1 red and green fluorescence. (A) Cisplatin-treated HEI-OC1; (B) HEI-OC1 cells treated with cisplatin and Fe_3O_4@3,4-DHAB; (C) HEI-OC1 cells treated with cisplatin and Fe_3O_4@3,4-DHAB@NaCitrate; (D) HEI-OC1 cells treated with gentamicin only; (E) HEI-OC1 cells treated with Fe_3O_4@3,4-DHAB and gentamicin; and (F) HEI-OC1 cells Fe_3O_4@3,4-DHAB@NaCitrate and gentamicin.

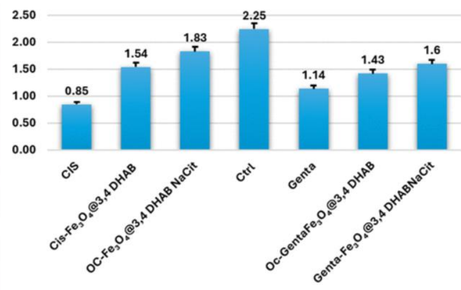


Figure 8: MPP after gentamicin and cisplatin exposure, concomitant with Fe_3O_4@3,4-DHAB or Fe_3O_4@3,4-DHAB@NaCitrate: HEI-OCI cells 24 h after ototoxic drug exposure were able to increase the relative membrane potential, significantly for the case of CIS exposure. CIS = HEI-OC1 cells treated with cisplatin only; Genta = HEI-OC1 cells treated with gentamicin only; Cis-Fe_3O_4@3,4-DHAB = HEI-OC1 cells treated with Fe_3O_4@3,4-DHAB and cisplatin; Cis-Fe_3O_4@3,4-DHAB@NaCitrate = HEI-OC1 cells treated with Fe_3O_4@3,4-DHAB@NaCitrate and cisplatin; Genta-Fe_3O_4@3,4-DHAB@ = HEI-OC1 cells treated with Fe_3O_4@3,4-DHAB@ and genta; Genta-Fe_3O_4@3,4-DHAB@NaCitrate = HEI-OC1 cells treated with Fe_3O_4@3,4-DHAB@NaCitrate and Genta; Ctrl-HEI-OC1

CONCLUSIONS

- **Surface-engineered MNPs functionalized with PCA (Fe_3O_4@3,4-DHAB and Fe_3O_4@3,4-DHAB@NaCitrate) provide significant cytoprotective effects against cisplatin- and gentamicin-induced ototoxicity in auditory HEI-OC1 cells.**
- **These effects are mediated, at least in part, by the preservation of HEI-OC1 metabolic functionality and mitochondrial membrane potential and reduction in senescence-associated enzymes, probably involving the modulation of oxidative stress pathways, such as SIRT1/Nrf2 and NF-κB. Magnetic nanoformulation showed good biocompatibility at therapeutically relevant concentrations in vitro. Further in vivo studies are needed to confirm their utility as preventive and otoprotective agents.**

References

1. Surface HEI-OC1-Engineered Magnetic Nanoparticles with Antioxidant Coatings Mitigate Ototoxic Stress in HEI-OC1 Auditory Cells Adeline Josephine Cumpata, et al, *ACS Omega* 2026 *11* (3), 4500-4509 , DOI: 10.1021/acsomega.5c10593
2. Magnetic Cationic Liposomes-Based Delivery System Reduces Drug-Induced Cytotoxicity in an In Vitro Model of Hearing Loss, Iftode, L., et al., Nanomaterials 2025, 15, 1529. https://doi.org/10.3390/nano15191529

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