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Design and *in vitro* evaluation of self-assembled indometacin prodrug nanoparticles for sustained/controlled release and reduced normal cell toxicity

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Highlights

- For its intrinsic amphiphilic property, the IND prodrug self-assembled into NPs in aqueous solution and served two roles-as an anti-inflammatory prodrug and a drug carrier. The constructed IND-PEG-IND NPs had naoscaled particle size of approximately 80 nm, negative surface, spherical shape, and good water-dispersity. IND-PEG-IND NPs demonstrated sustained and cathepsin B-controlled drug release behavior. More importantly, IND-PEG-IND NPs significantly reduced the acute tototoxicity against normal osteoblast cells compared to the free IND.

Abstract: Despite the great efficacy of indomethacin (IND) as an anti-inflammatory agent, its clinical translation has been obstructed by the water insolubility, severe side effects, and exceedingly low bioavailability. Indomethacin prodrug-based nanoparticles (NPs) combining the strengths of both nanotechnology and prodrugs that might overcome this crucial problem are presented. Here, using the carbodiimide-mediated couple reaction, IND was conjugated to clinically approved poly(ethylene glycol) (PEG) polymer via peptide linkage that was cleaved in the presence of cathepsin B, which was significantly induced after inflammatory. The synthesized IND-PEG-IND conjugate was characterized by UV-vis, FTIR, ¹H NMR, XRD, and MALDI-TOF-MS analyses. For its intrinsic amphiphilic property, the IND prodrug self-assembled into NPs in aqueous solution and served two roles-as an anti-inflammatory prodrug and a drug carrier. The constructed IND-PEG-IND NPs had naoscaled particle size of approximately 80 nm, negative surface, spherical shape, good water-dispersity, and high and fixed drug-loading content of 20.1 wt%. In addition, IND-PEG-IND NPs demonstrated sustained and cathepsin B-controlled drug release behavior. More importantly, IND-PEG-IND NPs significantly reduced the acute tototoxicity against normal osteoblast cells and displayed the

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