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HYBRID LIPOPOLYSACCHARIDE-BASED NANOSYSTEM FOR THE DELIVERY OF ANTI-TUBERCULOSIS THERAPEUTICS

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ABSTRACT

Tuberculosis (TB) is reported as one of the leading causes of morbidity and mortality globally, accounting for about 10 million new cases and 1.5 million deaths annually with the poorest and socially excluded groups bearing the largest burden of the disease. The conventional treatment approach for susceptible cases involves a daily oral dose of four first-line drugs, such as rifampicin, isoniazid, pyrazinamide and ethambutol (RIPE), which are scheduled into an initial intensive phase of two months with RIPE regimen and a continuous phase of four months with rifampicin/isoniazid regimen. Currently, the treatment of tuberculosis still remains a global challenge due to inconsistent drug bioavailability, dose-related side effects, systemic drug toxicity and poor patient compliance, which could be attributed to poor delivery of conventional anti-TB therapeutics. Therefore, the issue of drug resistance, non-targeted delivery, sub-optimal dosage at disease sites and side effects on healthy cells have rendered conventional treatment approach inefficient and ineffective in combating the disease even after combination chemotherapy. This research aimed to address the shortfalls associated with oral delivery of anti-TB therapeutics by employing nanotechnological approach to design a novel nano-enabled surface-functionalized drug delivery system (DDS) that will specifically target the infection site of *Mycobacterium tuberculosis* (Mtb) following oral administration. Alveolar macrophages, the reservoir for Mtb, displays special surface receptors, such as mannosyl, galactosyl, and lectin, which can be explored in the design of a smart and intelligent nanodelivery system to improve the preferential accumulation of anti-TB drugs within the alveolar macrophages, thereby reducing systemic side-effects and enhancing therapeutic activity. Based on this concept, we have designed, optimized and characterized a smart ligand-functionalized nano-construct – referred to herein as a 'mannosylated hybrid lipopolysaccharide-based (MHLP) nanosystem' – with encapsulated rifampicin and isoniazid for targeted and controlled delivery to Mtb infection site following oral administration.

The physicochemical parameters that characterized the design of a smart nano-construct in TB therapeutics including satisfactory size, shape and surface properties, good gastrointestinal permeability, cellular uptake and internalization by RAW 264.7 macrophages, as well as low cellular toxicity to healthy cells informed the fabrication of the MHLP nanosystem. In this study, an optimized CT-SL nano-conjugate was developed and surface-functionalized with mannose as targeting moiety. Fourier Transform Infrared (FTIR) spectroscopy, Differential Scanning Calorimetry (DSC), Thermogravimetric analysis (TGA) and Phenol-Sulphuric acid assay confirmed the successful grafting and functionalization of the nano-conjugates while Dynamic Light Scattering (DLS) analyses confirmed the synthesis of MHLP nanoparticles with an average size less than 300 nm and surface charge of +20 to +30 mV. Scanning Electron Microscopy (SEM) results confirmed the morphology of the MHLP nanosystem to be spherical with uneven surfaces and a spongy appearance due to the attachments of the functionalized moiety. Optical scattering analysis confirmed the stability profile of the nanosystem in suspension while the *in vitro* dissolution study showed a sustained release of rifampicin and isoniazid at the simulated physiological pH, indicating a positive influence of lipopolysaccharide architecture on drug release kinetics. Additionally, *ex vivo* permeability studies demonstrated a 2-fold increase in gastrointestinal rifampicin permeability within 8-hour study period in comparison with the free drug solution. Interestingly, MHLP nanoparticle uptake and intracellular drug accumulation studies showed an enhanced rifampicin/isoniazid delivery to RAW 264.7 macrophages when compared with the unmodified nanosystem and the free drug solution. Cytotoxicity assay demonstrated a good biocompatibility with greater than 80% cell viability achieved at nanoparticle concentrations 120 µg/mL during 24-hour treatment time.

Overall, detailed *in vitro* and *ex vivo* experimental results validated the fabricated MHLP nanoparticulate systems as efficient cargo system for rifampicin and isoniazid delivery to alveolar macrophages for enhanced anti-TB therapeutics. While rifampicin and isoniazid were selected as the model drugs in this study due to their established anti-mycobacterial activities and limitations, the novel MHLP nanosystem can also be employed to incorporate other anti-TB chemotherapeutics for enhanced on-site delivery of the bioactives.