Title:	Surface Functionalized Biocompatible lipid Nanocarriers as an Oral Anti-Leishmanial Therapy
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Abstract:	Oral therapy is often one of the most preferred routes of drug administration on account of its low cost, ease of use, and superior patient compliance. Traditionally, oral therapy has been the most popular and dominant controlled drug release, yet it was ascertained that more than 90% of therapeutically active compounds possess bioavailability constraints when administered orally. However, the hostile enzymatic environment of the gastrointestinal tract (GIT) poses a massive challenge for orally administered bioactives. Thusly, the development of enzymatically stable nanocarriers is the immediate priority to enhance the pharmacokinetics and biodistribution kinetics. Additionally, conventional drug therapy is usually characterized by diminutive half-lives and pervasive delivery to non-targeted cells. To mitigate stability issues and drug-associated toxicity, nanotechnology-based drug delivery platforms have entered the targeted therapy arena and rapidly sculpt complex formulations. The advent of nanotechnology has emerged as a powerful ally owing to its size-dependent unique physio-chemical properties. The remarkable potential of nanocarriers has attracted tremendous applications in enhancing the bioavailability and pharmacokinetic profile of the incorporated drug. Additionally, surface functionalization of the nanoparticle drug delivery system has been proposed to enhance their performance in complex biological systems and localize the therapeutic moiety to the desired site of action. Specific biocompatible molecules can be immobilized onto the surface of these nanocarriers to generate membrane-mimetic platforms for drug delivery applications. Among the various drug delivery systems, lipid-basednanocarriers have emerged as one of the most promising versatile vehicles to deliver therapeutic agents effectively. These colloidal drug delivery systems composed of physiologically derived lipids offer ubiquitous advantages of enhanced permeation and higher drug loading of hydrophilic and hydrophobic drugs. Concurrently, their surface engineering proffers enhanced cellular and lymphatic uptake and mucoadhesive properties. In this perspective, surface functionalization with natural biomolecules could impart specialized bio- functions and enhance the biocompatibility of the developed nanoformulations to the desired physiological application. The present thesis focuses on developing biocompatible therapeutic nanoparticles to treat visceral leishmaniasis (VL), a complex derelict infectious disease caused by the trypanosomatid parasite Leishmania donovani. It is a neglected tropical disease that affects millions annually, making it the second most common parasitic killer after malaria. VL is ranked second in mortality and fourth in morbidity among tropical parasitic diseases, blameworthy of over 2 million disability-adjusted life years (DALYs) lost. The World Health Organization classified leishmaniasis as one of the most neglected diseases due to the paucity of financial support for preventing and controlling the disease. First-line therapy previously relied on pentavalent antimonials like sodium stibogluconate (Pentostam) and meglumine antimoniate (Glucantime); however, incessant usage resulted in the development of multidrug resistance and hence the emergence of next-generation chemotherapy involving amphotericin B (AmB). AmB has shown high therapeutic efficiency in kala-azar-infected patients in the Indian subcontinent when administered intravenously. However, parenteral administration has also been linked with stumbling blocks like nephrotoxicity, hypokalaemia, thrombophlebitis, and myocarditis, limiting the dose administrable. Coupled with stipulations like continuous monitoring and prolonged hospitalization, the cost of treatment inevitably increases. Consequently, an ideal treatment for VL in underdeveloped regions would encompass oraladministration, stability at tropical temperatures, minimal side effects, and is economically affordable. Herein, the pragmatically designed nanoparticles were engineered to overcome multiple oral obstacles, including the mucosal and epithelial barriers, to enhance the bioavailability of poorly soluble drugs while obviating their associated systemic toxicities. We developed two different surface-functionalized lipid-based nanocarriers with specific lipid composition, considering the fluidity and stability, which in turn influences their uptake by target cells. First, liposomes composed of specific phospholipids were synthesized and used as drug delivery vehicles due to their exceptional properties like biocompatibility, biodegradability, and controlled release. They were tailored to encapsulate amphotericin B, a class IV biopharmaceutical classification active pharmaceutical drug with poor solubility and permeability, thereby prolonging its bioavailability and ameliorating its toxic side effects. Furthermore, grafting the liposomes with carboxymethyl chitosan proffers additional advantages like targeted delivery, sustained release, and superior therapeutic effects as advocated by in vitro and in vivo antileishmanial studies. However, apart from augmented therapeutic potential, the developed nanoformulations exhibited loftier pharmacokinetic potential with minimal toxic side effects, as advocated by the serum hepatic and renal toxicity markers. Next, we adopted a systematic approach for developing smart solid lipid nanoparticles for biomedical drug delivery vehicles, wherein alerting the surface properties can alter their interactivity with biomacromolecules. Therefore, utilizing the well-characterized intrinsic uptake pathway of vitamin B 12 would make the nanoformulations an excellent candidate for delivering drug moieties into infected cells. Furthermore, we were committed to explicating the bio interaction of the nanoformulation with the mucus layer, cellular uptake, and translocation mechanisms across the gastrointestinal epithelium and target cells. The augmented pharmacokinetic properties and enhanced stability of the nanoformulations subjugate the harsh gastrointestinal acidic conditions and tropicaltemperatures and still be stable enough to stave off any cellular metabolic disturbances, which we surmise to be a potential clinical oral drug delivery system.
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