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Inclusion complexation and liposomal encapsulation of an isoniazid hydrazone derivative in cyclodextrin for pH-dependent controlled release

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ABSTRACT

Tuberculosis, a predominantly pulmonary pathology, is currently the deadliest infection worldwide. Its treatment is based on combination therapy involving selected antimicrobials including Isoniazid. However, physicochemical properties of isoniazid negatively affect the clinical performance of current tuberculosis regimens, causing drug resistance development and increasing mortality rates. Liposomal encapsulation improves antituberculosis drug delivery; however, nano-formulation of isoniazid remains challenging due to its small molecular size and high hydrophilicity. Therefore, this study aimed to derivatize isoniazid and formulate a controlled delivery system using the concept of drug-in-cyclodextrins-in-liposomes to enhance drug biopharmaceutical properties. A prodrug of isoniazid was synthesized and screened for its ability to form stable complexes with α, β, and γ cyclodextrins. A selected inclusion complex with β-cyclodextrin was encapsulated in liposomes and assessed for controlled release of isoniazid. Successful formation of a 1:1 complex was established and characterized, followed by molecular modeling studies to demonstrate strength of the interactions within the complex and predicted complex structure. The inclusion complex was successfully encapsulated in liposomes using the thin film hydration method and the ethanol injection ultrasonic dispersion, with the latter giving the best results. These findings demonstrate the potential of combined molecular derivatization and cyclodextrin complexation for improved nanoengineering of drugs.

Abbreviations: TB, Tuberculosis; INH, Isoniazid; HB, 4-hydroxybenzaldehyde; INH-HB, *N*'[(4-hydroxyphenyl) methylidene] pyridine-4-carbohydrazide; CD, cyclodextrin; INH-HB@CD, cyclodextrin inclusion of *N*'[(4-hydroxyphenyl) methylidene] pyridine-4-carbohydrazide; TFH, Thin film hydration; EIUD, Ethanol injection ultrasonic dispersion; DCL, Drug-in-cyclodextrins-in-liposomes; PDI, polydispersity index; ZP, zeta potential; DMSO, dimethylsulphoxide; CE, complexation efficiency; EE, encapsulation efficiency; ZPE, zero-point energy; BSSE, basis set superposition error.

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