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Double loading of cyclosporine A in liposomes using cyclodextrin complexes

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Abstract

When liposomes are used as drug delivery systems, it is important that the therapeutic agent is efficiently and adequately encapsulated. In this study, cyclosporine A (CyA) was chosen as a model drug for two reasons. First, liposomes are a potential delivery system for CyA, as it has been shown that CyA has decreased side effects when encapsulated in liposomes. Secondly, if the aqueous solubility of a lipophilic drug can be increased, then it is possible to increase liposomal encapsulation by additionally loading the drug into the liposomes' aqueous compartments. Therefore, we investigated the use cyclodextrins (CDs) for complexing CyA to increase aqueous solubility as a strategy to increase liposomal loading. The effect of CyA loading on the liposomes' characteristics, stability and rigidity of the bilayer, and also the drug release profile were evaluated. Liposomes encapsulating CyA, liposomes containing CyA-CD complexes, and liposomes loaded with both plain drug and complex (double-loaded liposomes) were prepared. For evaluation of the effect of CD on bilayer rigidity and integrity, the permeability of the liposomal membrane in terms of carboxyfluorescein (CF) leakage was studied. Among liposomal formulations containing only CyA, ١, ٢-distearoyl-sn-glycero-٣- phosphocholine (DSPC):cholesterol (CHOL) (١:١) and hydrogenated soybean phosphatidylcholine (HSPC):CHOL (١:١) formulations demonstrated maximum drug entrapments of ٦٥.٩٤ ± ٤,٦٨٪ and ٧٥,٠٣ ± ٤,٨٧٪, respectively. There was no significant difference in encapsulation efficiencies between different liposomal formulations for those containing CyA-CD complexes (P > ٠,٠٥). Measurement of encapsulation efficiency showed that the amount of drug entrapped in the lipid bilayers was identical when prepared in the form of CyA inclusion complexes. Drug entrapment in double-loaded liposomes was increased by approximately ٢-fold. The release profile of all liposomal formulations was biphasic, with an initial rapid phase during the first ٥ h followed by a continuous and slower release thereafter. During the first ٥ h, CyA used as the complex was released to a greater extent than free CyA. Leakage of CF from liposomes was affected by the inclusion of CD. The leakage rate was minimum for CyA liposomes and maximum for double-loaded (CyA and CyA-CD) liposomes. In conclusion, it is possible to encapsulate CyA both in the aqueous and lipidbilayers of liposomes if the aqueous solubility of CyA is increased by complexation with CD. Although entrapment of a higher amount of drug was achieved, the stability of the liposomes was compromised and should therefore be considered. ©PDA, Inc. ٢٠٠٩.

Reaxys Database Information

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Author keywords

Cyclodextrin; Cyclosporine A; Double loading; Liposome

Indexed Keywords

EMTREE drug terms: ٢ distearoyl sn glycero ٣ phosphocholine; carboxyfluorescein; cholesterol; cyclodextrin derivative; cyclosporin A; phosphorylcholine; unclassified drug

EMTREE medical terms: aqueous solution; article; drug formulation; drug release; drug solubility; drug stability; lipid bilayer; lipophilicity; liposomal delivery; membrane permeability; rigidity; slow drug release