**ABSTRACT**

Nanosponges are new class of material, made of sub-microscopic particles with cavities a few nanometers wide, characterized by the capacity to incorporate a large variety of substances. Cyclodextrin nanosponges (CDNS) are cross-linked lyophilized polymeric materials used for solubility enhancement of poorly soluble drugs. CDNS also provide controlled release of a drug by modifying the cross-linker ratio. Cilostazol (CLZ) is an antplatelet drug used for the treatment of intermittent claudication. It is a BCS class II drug showing dissolution rate-limited absorption. The clinical applications of CLZ are limited by its low aqueous solubility. It shows dose dependent side effects such as headache, diarrhoea and palpitations.

Nanospponge formulations of CLZ, considerably enhanced its solubility, and also provided controlled release of CLZ for 24 hours. This increase in solubility may result in reduction of dose. Moreover, the controlled release profile may reduce bio-variability associated with plain CLZ.

**INTRODUCTION**

Many of the advantages of plain CDs are limited by the fact that individual CDs and their derivatives dissociate from the drug on dilution. CDNS are known to form stable, inclusion and non-inclusion complexes with different drugs. They have been used in recent years as drug delivery vehicles to improve the therapeutic efficacy and bioavailability of poorly-water soluble and biovariable drugs. Experiments on drug inclusion and subsequent release have provided amazing results, particularly in case of anticancer drugs. Cilostazol with low aqueous solubility and bioavailability lends itself for formulation of an extended release dosage form using CDNS.

**OBJECTIVES**

Solubility enhancement of CLZ

Controlled release of CLZ

**EXPERIMENTAL WORK**

**Synthesis of CDNS**

\[
\text{Dibenzylicarbonate} \quad \text{+} \quad \beta-\text{Cyclodextrin} \quad \text{+} \quad \beta-\text{Cyclodextrin based Nanosponge} \quad \text{90°C} \quad \text{5 hrs} \quad \text{Water} \quad \text{Methanol} \quad \text{Unreacted CD} \quad \text{Unreacted DPC}
\]

**RESULTS AND DISCUSSION**

**Drug Loading in CDNS**

- CDNS were dispersed in water and sonicated for 1 hr.
- CLZ was added to solution/suspension of CDNS and allowed to stir for 24 hours
- The dispersion was centrifuged at 3000 rpm for 10 mins.
- The supernatant was collected and lyophilized to obtain CLZ-CDNS

**Molecular modeling studies**

Computational studies were performed on high performance computing cluster with Intel Xeon hexacore processors backed with Rocks Cluster Suite 6.1. The structures were prepared for docking in Schrödinger Suite 2013.2, defining the atom types and partial charges using OPLS 2005. The free energy of binding for the CLZ-CDNS was calculated as follows:

\[
\Delta G = k_B T \times \ln \left[ \sum_{m,n} \exp \left( \frac{-E}{k_B T} \right) \right]
\]

**Summary**

The reaction for the preparation of CDNS was monitored using TLC and UV spectroscopy. There was a gradual reduction in the DPC concentration, where after 5 hours it did not show any absorbance. Maximum percent drug loading (30%) was obtained in 1:4 (CLZ-CDNS) ratio. FTIR spectroscopy showed a characteristic peak of carbonyl compound at 1690 cm\(^{-1}\). DSC thermograph did not show any peak for DPC at 80\(^\circ\)C. The reaction was further confirmed using HSM. XRD confirmed the presence of crystalline nanosponges. The saturation solubility for CLZ increased from 5 to 96 mcg/ml. CDNS in 1:4 ratio could prolong the release of CLZ for 24 hours. Molecular modeling studies showed that CLZ loaded CDNS in the ratio 1:4 were quite stable with free energy of ~3.1 Kcal/mol.

**CONCLUSION**

Complexation of CLZ with CDNS increased its solubility by more than 18%. Optimizing the BCD to cross-linker ratio at 1:4 could give desired release profile up to 24 hours. CLZ-CDNS was found to be non-hemolytic up to 10 mg/ml, thereby negating the chances of hemolysis on oral administration. CDNS provide a good carrier system for controlled release of cilostazol. This is a promising strategy for parenteral, ophthalmic and oral drug delivery systems.

**REFERENCES**


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