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CHITOSAN NANOPARTICLES FOR NOSE-TO-BRAIN TARGETING

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Introduction: Cerebral disorders represent one of the most common causes of death and disability today. Due to the blood brain barrier (BBB) the biodistribution in the central nervous system (CNS) of administered drugs is seriously limited [1], so producing a lack of efficacy of these drugs. To circumvent this problem one approach could be the intranasal administration of drugs, representing the olfactory and trigeminal patways a direct access from external environmental to brain [2].

Aim: In this work chitosan nanoparticles containing cyclodestrins (CH/CyD-NPs) have been prepared and characterized for nose-to-brain targeting of Idebenone (IDE), a strong antioxidant drug [3]. Its very low water solubility, its metabolism after oral administration and its bind to serum proteins are causing a very poor bioavailability at the level of CNS and limiting its clinical application [4].

Materials and Methods: CH/CyD-NPs were prepared by ionic gelation of CH, using aqueous solutions of sulfobuthyl-ether-β-cyclodextrin (SBE-β-CyD) as polyanion. SBE-β-CD complexing IDE can allow the encapsulation of the lipophilic drug within the NPs during the preparation process in aqueous solution. Overloaded systems were prepared adding IDE as an inclusion complex with hydroxypropyl-β-cyclodextrin (HP-β-Cyd). Physico-chemical and technological properties of NPs were investigated and *in vitro* biological assays were performed on U373 cell cultures.

Results and Discussion: SBE-β-CyD and HP-β-CyD strongly complexed with IDE, significantly increasing its water solubility and permitting very good encapsulation within CH-NPs (about 50% encapsulation efficiency). STEM pictures showed spherical NPs with a dense core surrounded by a less dense shell made of CH chains. This morphology guaranteed a positive value of zeta potential (about +30 mV), so ensuring the interaction of NPs with nasal mucosa. Preliminary *in vitro* studies on U373 cells demonstrated IDE loaded-NPs maintained its antioxidant effect.

Conclusions: IDE, in the form of an inclusion complex with CyDs, can be efficiently encapsulated in CH-NPs. Particularly the complexation with HP-β-CD significantly improves technological parameters and physical-chemical properties of the systems and prolonged IDE release over time.

All NPs formulations presented sizes suitable to nasal administration and good antioxidant activity, showing good potentiality as nose-to-brain targeted delivery system for IDE.

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