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NEW OIL CORE SELF-ORGANIZED NANOPARTICLES PREPARED WITH CHITOSAN AND LECITHIN: DEVELOPMENT, CHARACTERIZATION AND PHARMACOKINETIC EVALUATION USING CLOZAPINE AS DRUG MODEL

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Introduction: Chitosan is a cationic polysaccharide, biodegradable, biocompatible, low toxicity, mucoadhesive that has demonstrated to improve the absorption and biodistribution of drugs[1]. In this context, we propose the development of innovative oily core self-organized nanoparticle prepared by the interaction between chitosan and lecithin, to allow the encapsulation of different drugs. Clozapine (CZP) has low bioavailability[2] and was used as a drug model.
Objectives: The aims of this work were: a) to develop and physico-chemically evaluate the influence of isopropyl myristate, chitosan and lecithin on the properties of the self-organized nanoparticles; and b) to develop, physico-chemically evaluate the self-organized chitosan nanoparticles loaded with CZP, and to investigate the drug pharmacokinetics (PK) in rodents.
Materials and Methods: Nanoparticles suspensions were obtained by injecting through a funnel 4 ml of a Lipoid S45 in ethanol and isopropyl myristate solution into 46 ml of a chitosan aqueous solution mechanically stirred through Ultraturrax (3). A 3^3 factorial design was applied varying chitosan viscosity (30, 60 and 90 cP), percentage of isopropyl myristate (1, 2 and 4%) and concentration of Lipoid S45 in the ethanolic solution (25, 50 and 100 mg/mL). The obtained systems were characterized by particle size (laser diffractometry, Mastersizer 2000, Malvern Instruments, London, UK), zeta potential (electrophoresis, Nanosizer®), pH and viscosity (using Brookfield® rheometer). The characterization was conducted right after the preparation. The results were analyzed using Stat graphics ® Plus v. 5.1. CZP (2 mg/mL) was incorporated in the system consisting of 100 mg/mL of Lipoid S45®, 1% of isopropyl myristate and chitosan aqueous solution (30 cP). Physico-chemical evaluation was carried out by determining particle size, polydispersity index (PDI) and zeta potential. Stability evaluation of nanosystems was performed by optical analyzer Turbiscan® *Lab* (25 ºC, 1 h, scan every 5 min). Transmission electron microscopy (TEM) was evaluated after nanosuspensions fixation with uranyl acetate. PK investigation was conducted in Wistar rats (300-350 g) after 10 mg/kg oral dosing of free and nanoencapsulated CZP (n = 6/group). Blood samples were withdrawn from the lateral tail vein at pre-determined time points and plasma samples were analyzed by LC-MS/MS using a previously validated method.
Results and Discussion: Content of chitosan influences the pH values, which ranged from 3.5 to 4.2, using 0.4 % and 0.8 % of the cationic polymer, respectively. Viscosity showed values between 39 and 127 cP. Zeta potential was strongly positive (+41 to +52 mV), and lower values were obtained with 25 mg/mL of Lipoid S45 concentration. Simultaneous increase of surfactant and isopropyl myristate increased the zeta potential. Besides that, it was observed single peaks of zeta potential for each formulation, indicating the absence of other type of particle, only nanocapsules. Nanocapsules presented a wide range of particles size (0.422 to 3.755 µm). The increase of isopropyl myristate increased this parameter, while the concentration of Lipoid S45 was important for the reduction of nanocapsules size. The formulation with 100 mg/mL of Lipoid S45®, 1% of isopropyl myristate and chitosan aqueous solution (30 cP) showed the smallest diameter and PDI and it was chosen for the incorporation of clozapine. CPZ-loaded and blank nanocapsules presented mean diameter of 181 ± 3 and 470 ± 2, nm, acid pH values (3.67 ± 0.01 and 3.75 ± 0.03), positive zeta potentials (+42 ± 1 and + 48 ± 2 mV) and IPD bellow 0.2 and 0.3, respectively. Backscattering analyses demonstrated slight alteration of diameter for CZP-loaded nanocapsule. The TEM evaluation revealed the presence of nanometric, spherical and oval nanoparticles in both suspensions. After Wistar rats oral dosing, an increased AUC was observed encapsulated CZP indicating an increased drug bioavailability.
Conclusions: The results demonstrated the biological applicability of this new self-organized chitosan nanoparticle for improving drugs oral bioavailability.

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