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DEVELOPMENT OF OLANZAPINE-LOADED BIODEGRADABLE NANOPARTICLES IN THERMO-SENSITIVE HYDROGEL

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Introduction: Administration of drug *in situ* assisted by injectable thermo-sensitive hydrogel, such as Pluronic F127 which exhibit reversible thermal gelation in aqueous solution at concentrations > 15% (w/v), have been an interesting route of administration. Unfortunately, when hydrophobic drugs are considered to be locally delivered by thermo-sensitive hydrogels, their poor solubility make it not well dispersible in the aqueous solution. To overcome the water-soluble problem of hydrophobic drug, biodegradable polymeric nanocapsules were widely studied as drug delivery system. They are a useful tool to encapsulate drug in polymeric nanocapsules to obtain well-dispersed drug to improve its aqueous solubility. Olanzapine, atypical antipsychotic, is a drug used for treatment of schizophrenia and acute manic episodes associated with bipolar disorder.
Objective: Create a novel nanocapsule formulation incorporated in a thermo-sensitive hydrogel composite for the administration of a hydrophobic drug such as olanzapine.
Materials and Methods: Lipid-core nanocapsules were prepared by the interfacial deposition of preformed polymer method. Poly(ε-caprolactone)(Mw=65.000), caprylic/capric triglyceride, olanzapine and Lipoid S-75® were dissolved in acetone (27mL) at 42ºC. This phase was injected into 53mL of an aqueous phase containing polysorbate 80 under magnetic stirring at room temperature. After 10min, the suspension was concentrated under reduced pressure to 10mL. The particle size, polydispersity index and zeta potential were determined at 25ºC using Zetasizer®. The thermo-sensitive hydrogel (Pluronic F127®) was dispersed in the drug-loaded nanocapsules at 5ºC and maintained for 24 hours at 5ºC. As a control, a hydrogel containing Pluronic F127® without nanocapsules were also prepared. The total concentration of F127 was maintained between 15% and 22% (w/w). To determine the sol–gel transition behavior, 2.0mL of F127® solution in water or the nanocapsule suspension was transferred to a test tube and put in a water-bath with temperature raising from 5ºC to 60ºC at a rate of 0.5ºC/min. Olanzapine-loaded nanocapsules prepared and the respective hydrogel containing 18% of Pluronic F127® was evaluated by a Turbiscan Lab at 20ºC (suspension and hydrogel) or at 37 ºC (hydrogel) using the scan mode.
Results and Discussion: Olanzapine-loaded nanocapsules presented macroscopic homogeneous aspect like milky yellowish opalescent liquids. After preparation, analysis by photon correlation spectroscopy showed a mean particle size of 157nm and low polydispersity index (0.07). Its potential zeta was negative (-23.9mV) indicating stable suspensions. The thermo-sensitive hydrogels with concentrations below 18% did not gel up to 60ºC. On the other hand, concentrations above 18% promote the formation of the hydrogel. The hydrogel containing the nanocapsules showed a lower sol-gel transition temperature compared to the aqueous dispersion. The injectable gel must have a suitable gelation temperature (30–36ºC) to be a liquid at room temperature and to form a gel phase instantly in the body. Hydrogels prepared with Pluronic F127® at 18%, with a gelation temperature of 31ºC, were chosen for the next characterization step. The relative physical stability of olanzapine-loaded nanocapsules and the respective hydrogel containing Pluronic F127® at 18% was evaluated by multiple light scattering analyses. The transmittance signal was null for all samples, from $t = 0$ to $t = 1$ h, indicating that backscattering profiles (*BS*) can be considered for their characterization. Variation of the backscattering signal was below 1% in the middle of the cell for all formulations indicating that no aggregation or coalescence of the droplets occurred. In addition, only variation of the backscattering signal lower than 2.5% at the bottom and at the top of the cuvette were observed, showing that no significant sedimentation and clarification occurred, respectively, even if the hydrogel was analyzed at 37ºC. These results demonstrate the physical stability of the formulations.
Conclusions: Olanzapine-loaded lipid-core biodegradable nanocapsules were successfully prepared using Pluronic F127® at 18% promoted the formation of a thermo-sensitive hydrogel suitable to be used as an injectable depot. The developed formulation presents high potential to be used as an intramuscular drug delivery system for hydrophobic drugs as olanzapine.