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CO-ENCAPSULATION OF INDOMETHACIN/ ETHYL ESTER OF INDOMETHACIN AND ALPHA-BISABOLOL IN POLYMERIC NANOCAPSULES: SELECTIVE AND CYTOTOXIC EFFECT IN GLIOMA CELLS

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Introduction: Gliomas are the commonest tumor of the central nervous system. A modern approach for the treatment of these tumors is the use of modified-release drugs systems, which have nanocapsules as a highlight. Recently in our research group demonstrated a promising approach, based on the nanoencapsulation of non-steroidal anti-inflammatory drugs for the treatment of gliomas. The results showed that drug-loaded nanocapsules were more effective than a drug solution, without presenting the side effects of chemotherapy. Studies revealed that alpha-bisabolol has a strong cytotoxic effect on several cell lines.
Objective: In the present work we propose as a novel strategy intended to treat gliomas, a multidrug-loaded nanocapsule formulation co-encapsulating indomethacin, indomethacin ethyl ester and alpha-bisabolol. So, the first step of investigation was focused on the physico-chemical characterization of formulations. We considered the hypothesis of obtaining a synergic effect against glioma cells by means of the simultaneous nanoencapsulation.
Materials and Methods: Nanocapsule suspensions were prepared by interfacial deposition of polymer. After preparation, the pH values of nanocapsule suspensions were determined using a potentiometer. The particle size, polydispersity and zeta potential of the systems were determined by photon correlation spectroscopy (PCS). The particle size was also determined using a Nanosight®- Nanoparticle Tracking Analysis (NTA). The total content of indomethacin, indomethacin ethyl ester and alpha bisabolol in the formulations were measured by HPLC. The morphological analysis was conducted by transmission electron microscopy. The formulation was evaluated by a Turbiscan LAb®. The glioma cell lines (U138-MG and C6) were obtained from ATCC (American Type Culture Collection). For evaluate the cytotoxic and antiproliferative effects of formulations we used the MTT and cell counting assays. The cell death was evaluated by iodide propide incorporation.
Results and Discussion: All formulations presented acid pH due to the characteristics of its components. The average diameter was submicrometric (closed to 200 nm) and it is in agreement with literature data for nanocapsules formed by the interfacial deposition method. We obtained a polydispersity index of 0.063. NTA analysis showed an average diameter of 192 nm, quite similar to one found by PCS. The contents of indomethacin, indomethacin ethyl ester and alpha bisabolol measured in the nanocapsule were respectively 0.561, 0.455 and 18.20. It was observed values of 96.44%, 97.98% and 99.36% of encapsulation efficiency, for indomethacin, indomethacin, ethyl ester and alpha bisabolol, respectively. Transmission electron microscopy showed the formation of vesicular particles containing indomethacin, indomethacin ethyl ester and alpha bisabolol. It was observed in the Turbiscan analysis a small variation in the amount of backscattered light during the analysis time compared to the initial time, indicating that the samples do not tend to instability phenomena. Our results performed with glioma cell lines suggest that alpha-bisabolol is more cytotoxic when compared to indomethacin or indomethacin ethyl ester. The alpha-bisabolol treatment causes a significative antiproliferative effect that culminate in cell death.
Conclusion: The results of this study demonstrate the feasibility of nanocapsules containing indomethacin, indomethacin ethyl ester and alpha-bisabolol using the technique of interfacial deposition of poly-(ε-caprolactone). Nanocapsules had similar characteristics to those prepared using the same drug-loading method, as demonstrated by the physical-chemical and morphological characterization of the formulation. Moreover preliminary results suggest that alpha-bisabolol may be considered a potential candidate for glioma treatment, further investigations are necessary to determine the appropriate doses for therapy of gliomas.
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