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Indomethacin microencapsulation in polymeric blends of PLGA502 and PEOT-PBT multiblock copolymer

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1. Introduction

Indomethacin (IND) is a non-selective non-steroidal anti-inflammatory drug (NSAIDs) with high anti-inflammatory, antipyretic and analgesic activity. It has been widely used in the therapeutical management of moderate to severe rheumatic disorders, including rheumatoid arthritis, osteoarthritis and gouty arthritis. Nonetheless, its use as a first-line and long-term therapy is limited by its dose-dependent severe gastrointestinal, renal and hematologic adverse effects [1]. Local administration via intra-articular (I.A.) injection can be an alternative to achieve high drug concentrations into the joint, but the high clearance rate of most drugs limits its use as a long-term administration route.

Microencapsulation seems to be an excellent approach to overcome those limitations, allowing us to increase the retention time of the drug into the joint and to achieve a controlled drug delivery profile [2]. Nonetheless, IND microencapsulation in PLGA was previously reported, showing a high drug delivery rate [3].

This work aims to prepare and characterize IND-loaded microspheres made of a polymeric blend of PEOT-PBT and PLGA502 with convenient features to achieve an intra-articular long-term delivery profile.

2. Materials and methods

2.1. Preparation of microspheres

Indomethacin-loaded microspheres were fabricated by coaxial ultrasonic atomization. Briefly, both channels of a dual-feed nozzle were fed with a 3 % polymeric blend dispersion in CH2Cl2 composed for a mixture of PLGA502 and 1000PEOT70PBT30 at different ratios, obtaining a spray that was collected over a PVA stirring solution. Indomethacin was dissolved in the polymeric dispersion atomized through the inner channel (0.1 g IND/g polymer), whereas the outer dispersion remained drug-free. The contribution of each channel to the total flow rate (1 ml/min) and PEOT PBT/PLGA502 ratio was set accordingly to an experimental design. Finally, the solvent was removed under continuous stirring, and microparticles were isolated and dried under vacuum.

A central composite rotatable and orthogonal statistical experimental design was built to assess the influence of flow rate through each channel (0.22 – 0.78 ml/min) and polymeric composition (PLGA502; 14.64 – 85.36 %) on particle size, encapsulation efficiency and drug delivery profile. Experimental results were fitted to a quadratic multiple regression model and optimal formulations were selected by surface response methodology.

2.2. Characterization of microspheres

All formulations obtained were characterized in terms of particle size (laser diffraction), surface morphology (SEM), process yield and encapsulation efficiency. Physicochemical interactions between PEOT-PBT and PLGA502 and between IND and the polymeric matrix were characterized by FTIR. Also, thermal analysis of IND, Empty and IND-loaded MPs was performed by DSC. Changes in the degree of crystallinity of the drug and polymers after microencapsulation were assessed by X-ray diffraction.

Cell compatibility of the microspheres was tested by XTT assay in THP-1 cells previously differentiated into macrophages. Further, the phagocytic capacity of THP-1-derived macrophages in the presence of microspheres was evaluated.

3. Results and Discussion

All formulations included in the experimental design were successfully prepared, exhibiting high process yield (78.2 – 88.5 %) and encapsulation efficiency (81.3 – 56.2 %). Particle size analysis showed a polydisperse distribution with a mean diameter ranging between 22.8 and 82.6 µm. Experimental data of encapsulation efficiency (E.E) and Mean Diameter (d(v,0.5) have successfully fitted a multiple regression quadratic model. Surface response graphs were constructed to assess the influence of formulation parameters over the microspheres' properties (Figure 1).

SEM micrographs showed spherical particles with a porous surface (Figure 2). Further studies by RAMAN confocal microscopy are being carried out to determine the distribution of PLGA502, PEOT-PBT and Indomethacin within the microparticles.

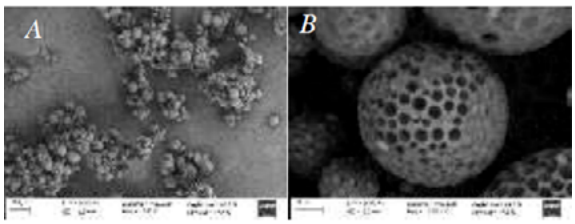

Fig. 2. SEM micrographs of IND-loaded microspheres (central point). A)500x B)3000x

DSC thermogram of commercial crystalline IND showed an endothermic peak around 161 ºC (Tm). X-ray diffractogram confirmed its crystalline state, showing the characteristic diffraction pattern of γ-polymorph of IND. The absence of significant differences between DSC thermograms of empty and IND-loaded microspheres suggested that the drug is dispersed into the polymeric matrix in an amorphous form with the independence of the polymeric blend composition. These results support those of X-ray diffraction, where the typical diffraction pattern of crystalline IND was not detected in IND-loaded microcapsules, corroborating the amorphous state of the microencapsulated drug. The absence of polymer-polymer and drug-polymer chemical interactions were confirmed by FTIR, suggesting that the polymeric blend is a simple mixture of polymers.

Microspheres' biocompatibility was assessed in THP-1 derived macrophages after 24 hours of

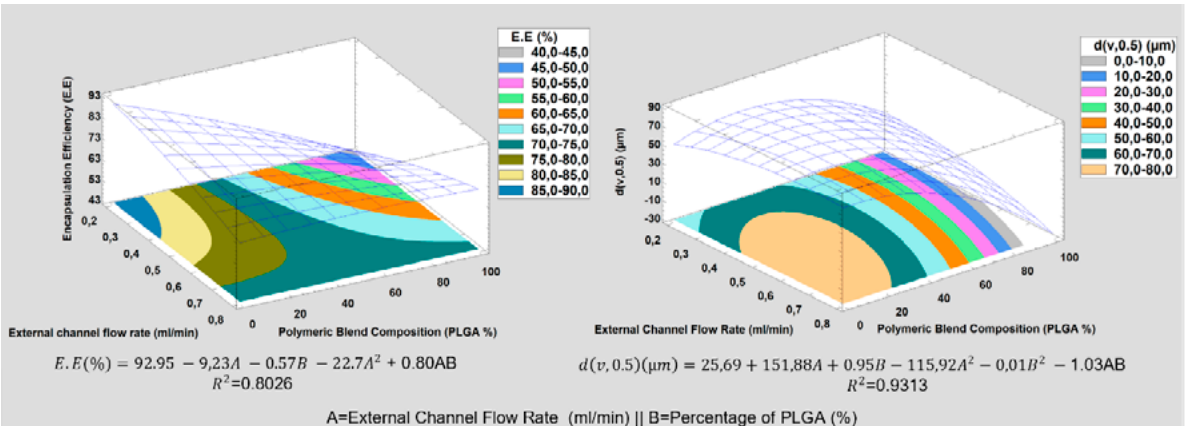

Figure 1- Surface-response graphs for encapsulation efficiency and particle size of IND-loaded microspheres prepared by ultrasonic atomization accordingly to the experimental design

co-incubation, achieving high viability rates (95-100 %). Also, microparticles were found to be extensively phagocyted by THP-1 cells.

4. Conclusions

Indomethacin-loaded microparticles with suitable properties for intra-articular administration were successfully obtained. Also, in vitro drug delivery studies are being performed.

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