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Doxycycline microparticles for potential use in neurodegenerative diseases

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1. Introduction

Neurodegenerative diseases are a group of chronic, progressive disorders characterized by the gradual loss of neurons that affect specific regions of the brain, leading to deficits in memory, movement and cognition functions.

Doxycycline (DOX) has proven to be able to reduce the progression and severity of disease in different experimental models of neurodegeneration, mainly due to its anti-inflammatory effects [1], which include the reduction of cytokine release and the inhibition of MMPs [2]. Previous studies have shown that doses ranging between 20-40 mg/day while maintaining the anti-inflammatory effect do not cause bacterial susceptibility. According to this if the drug is encapsulated within microparticles, the desired therapeutic effect could be achieved with very small amounts and the risk of side effects and bacterial resistance could be prevented. However, commonly used techniques for the elaboration of microparticles usually lead to low encapsulation efficiency values (EE) of hydrophilic drugs. In this study various parameters were investigates to enhance DOX encapsulation within poly (D, L-lactide-co-glycolide) (PLGA) microspheres prepared by solvent extraction-evaporation and double emulsion (water/oil/water) techniques.

2. Materials and methods

For the preparation of DOX microparticles different amounts of PLGA 502 were dissolved in 2 ml DCM or a co-solvent ratio composed of 0:1, 1:3 or 1:5 (EtOH: DCM).

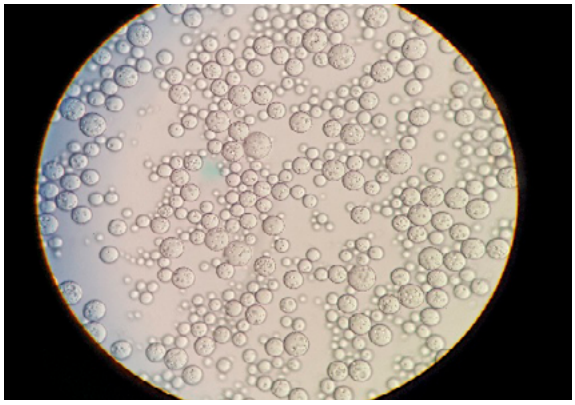

Fig. 1. Doxycycline microparticles

DOX was dissolved in 0.5 ml PBS and added to the polymer solution. The mixture was emulsified for 2 min at 5,000 rpm to form the (W1/O) emulsion and then slowly added into an aqueous solution containing polyvinyl alcohol (PVA) with NaCl and emulsified again at 5,000 rpm for 3 min at room temperature to form the W1/O/W2 emulsion. The pH of the external phase was adjusted to 5.5, 7.0 and 9.0 by adding NaOH or HCl solutions. Solvent removal and hardening of the particles were achieved by stirring in a magnetic stirrer for 2.5 h at 300 rpm. Then, the microspheres were isolated by filtration using 3.0 μm filters and washed with distilled water three times to remove the excess PVA. The microspheres were then freeze-dried at −55 °C in a vacuumed sealed flask for 24 h and stored at −20 °C for further analysis (encapsulation efficacy, particle size and DOX in vitro release). Particle

size was measured in a microtrac s3500 device. The amount of drug encapsulated after extraction with methanol was quantified in an spectrophotometer at 355 nm.

3. Results and Discussion

3.1. Particle size analysis

Particle size ranged from 19.20-68.36 μm being influenced by w/v percentage of polymer used in the formulation and the emulsion time. However, the overall results showed that the size of the microparticles did not have a significant effect on encapsulation.

3.2. Encapsulation efficacy (EE)

EE ranged from 0.6 % to 94.10 % being influenced by the amounts of co-solvent and electrolyte used in the preparation of the formulations.

3.3. In vitro release study

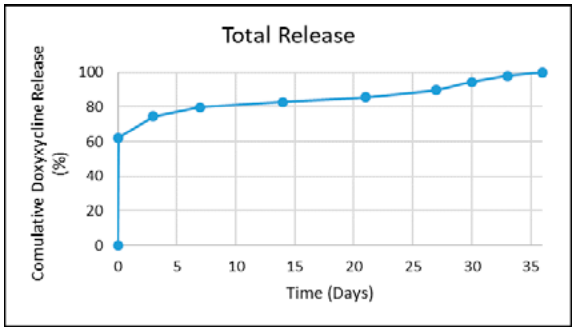

Fig. 2. In vitro DOX release from a formulation of PLGA microparticles.

All DOX formulations exhibited high burst releases during the first hr with a slow and controlled release occurring (Fig.2). The lowest burst release was 28.07 % and the highest 74.16 %. The most influential factor in reducing this burst release was the pH of the W2 phase, with the lowest value in the formulations prepared in acidic pH. On the other hand, increasing the percentage of PVP in the external phase accelerated the release of DOX within the first hour.

4. Conclusions

Due to the hydrophilic nature of DOX, a significant amount of the drug is lost during the double emulsion method when preparing PLGA microparticles. Moreover, some of the formulations obtained which presented high EE values, did not show adequate results in the vitro release tests due to the high initial burst effect obtained which could be explained by the large amount of the drug that is adsorbed onto the surface of the particles. n In this study, by providing an electrolyte-containing basic environment, the solubility of the drug in aqueous medium was minimized. In addition, the initial burst was controlled as well as the in vitro release of DOX for at least one month. The results of this study provide the conditions for entering the next phase of research, namely animal studies, kinetic studies, evaluation of drug penetration into the CNS and evaluation of the neuroprotective effects of this new delivery system developed for DOX.

Acknowledgments

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