INFLUENCE OF STRUCTURE AND SURFACE OF TERPOLYMER MATRICES ON RISPERIDONE RELEASE

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Introduction

Therapy with risperidone (RSP) is one of the frontline treatments for most psychotic disorders. It should be noted that RSP is administrated mainly in oral formulations, i.e., tablets and orodispersible tablets, capsules or solutions. Recently, implantable formulations with prolonged release have been proposed to improve the efficiency of current therapies. The most popular solutions are based on aliphatic polyesters, i.e., poly(lactide-co-glycolide) (PLGA) with various content of lactidyl and glycolidyl segments, and different configurations of lactide. Nowadays, only one medicinal product with RSP based on D,L-PLGA 75:25 microspheres is available on the market. There are various opinions on the efficiency of this product and the rationale for its administration, pointing to both advantages and disadvantages. It should be noted that microspheres cannot be removed in the event of clinical complications.

In this study, an alternative solution has been developed. A basic research on solid formulation obtained from terpolymer material, i.e., L-lactide−glycolide−trimethylene carbonate (PLLAGATMC) terpolymer has been performed. The use of terpolymer may open a broader possibility of obtaining a solid formulation with optimized mechanical properties and release profile.

Materials and methods

The matrices (10 mm diameter) were obtained from PLLAGATMC terpolymer in the molar ratio of termonomers 56.7:18.1:25.2. Terpolymer was synthesized at the Centre of Polymer and Carbon Materials of Polish Academy of Sciences in Zabrze in bulk with the use of $Zr(Acac)_4$ as a low toxic initiator. Matrices were prepared with the use of the solution casting method. RSP (Teva Kutno S.A.) was introduced in the amount of 0.11 g to 1 g of terpolymer matrix.

The matrices were incubated in a PBS buffer (pH 7.4) under constant agitation (240 revs per minute) at the temperature of 37°C. Before measurements, the matrices were air dried at room temperature in a laminar box and then under reduced pressure.

The amount of released RSP was determined by high-performance liquid chromatography using Elite LaChrom HPLC system (VWR Hitachi, Merck) with UV absorbance detector (Diade Array Detector L -2355, VWR Hitachi, Merck) set at 280 nm.

The changes in terpolymer composition and chain microstructure (the average length of L-lactidyl, glycolidyl and trimethylene carbonate blocks were determined by ^1H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy. ^1H NMR spectra were recorded at 600 MHz and ^{13}C NMR at 125 MHz with AVANCE II Ultra Shield Plus, Bruker 600 MHz spectrometer and a 5-mm sample tube. DMSOd6 was used as solvent.

Thermal characteristics of terpolymer matrices were assessed with DSC, using the TA DSC 2010 apparatus (TA Instruments, New Castle, DE) at a heating rate of 20°C/min, in the range from -20°C to +200°C, under nitrogen atmosphere (flow = 50 mL/min). The instrument was calibrated with high purity indium and gallium.

Glass transition temperature (Tg) was taken as the midpoint of the increase of the specific heat associated with the transition.

The matrices' morphology was assessed with a SEM (Quanta 250 FEG, FEI Company, USA). The micrographs were obtained under low vacuum. The samples stuck to the microscopic stubs with a double-sided adhesive carbon tape.

Results and discussions

The profile representing the cumulative release of RSP from terpolymer matrix showed a sigmoidal shape. Moreover, a burst effect was not noted.

The NMR study revealed changes in the composition for L-LA and GA during 127 days. The increase of L-LA with the decrease of GA was noted, i.e., from 56.7 to 63.0 and from 18.0 to 13.0, respectively. The least intense changes were found with respect to TMC.

The changes in the microstructure of the chain were also observed. The shortening of lactidyl blocks from 3.9 to 3.5 was noted during 127 days. The average length of the glycolidyl and trimethylene carbonate blocks remained unchanged (i.e., 1.1 and 1.5, respectively).

The DSC measurement shows to the changes in Tg from 39.9°C to 29.0°C during 127 days of degradation. This decrease demonstrated a gradual tendency.

SEM revealed the solid nature of native matrices without a differentiated morphology. Moreover, no pores were observed. Matrices degradation enhanced the diversity. However, no radical changes were noted.

The presented study exhibits a stable process of degradation. No intense changes in the analyzed parameters were shown. Moreover, a sigmoidal character of the curve showed RSP release without a burst effect, indicative of a great potential to obtain solid formulations obtained from PLLAGATMC terpolymer.

Conclusions

The results reveal the potential of PLLAGATMC in drug technology for the obtaining of an implantable biodegradable formulation for a prolonged release of RSP.

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