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DEVELOPMENT OF APPROACHES TO CREATE INJECTABLE DEPOT FORMULATIONS OF RILPIVIRINE BASED ON POLYLACTIDES

Abstract

Relevance of the work. Recent years have seen a significant growth in research publications, dedicated to the development of injectable depot formulations for the therapy of chronic diseases. Depot formulations allow for reduced dosing frequency, compared to rapid-release dosage forms, by providing prolonged controlled drug release and prolonged maintenance of therapeutic concentrations in the blood. An important and relatively new field of application for injectable depot formulations is the treatment of human immunodeficiency virus (HIV) infection. HIV infection is one of the most serious public health problems, due to both the lack of radical treatment methods and poor patient adherence, which leads to HIV-1 replication. The relevance of this problem has driven the development of fundamentally new approaches to solving it.

The production of injectable depot formulations such as microspheres and implants based on polylactides, which are biodegradable and biocompatible copolymers of lactic and glycolic acids (PLGA), could be an excellent alternative approach. These depot formulations are characterized by controlled drug release through the selection of polylactides with suitable properties, physicochemical stability of the depots and the absence of the need for high concentrations of surfactants. Depot formulations based on PLGA microspheres and implants are complex objects whose main characteristic is the drug release rate. The release profile depends on many properties of the carrier, including its degradation rate in the body and hydrophobicity, which are determined by its chemical structure, surface area, shape and etc. However, approaches to the development of depot formulations of various drugs remain empirical as a rule, due to the variety of parameters that must be maintained to solve the pharmacological problem. Therefore, the development of a depot formulation of each specific drug requires long and labour-intensive experimental work.

The objective of the research is to develop a approach for the production of injectable depot formulations based on PLGA microspheres and in situ forming implants (hereinafter in situ implants) of the antiretroviral drug rilpivirine.

The achievement of this objective will be ensured by the following key **tasks:**

1) To develop methods for the production of PLGA-based microspheres and in situ implants with different rilpivirine release profiles.

2) To define the influence of parameters of the microfluidic process of PLGA microsphere production on their main physicochemical properties.

3) To determine the effect of macromolecular carrier composition on the in vitro release profile of rilpivirine from the developed depot forms for further control of the drug release rate.

4) To determine the effect of hydrolytic degradation of the carriers based on polylactides on the different phase of in vitro release profile of rilpivirine.

5) To evaluate the possibility of using polymeric depot formulations as an alternative to the nanocrystalline form of rilpivirine.

Scientific novelty. 1) For the first time, polylactide microspheres loaded with the antiretroviral drug rilpivirine were obtained by the microfluidic technique. The limiting technological parameters for obtaining PLGA microspheres with high rilpivirine loading were determined: PLGA content 2 %, rilpivirine content 13.8 mg per mg microspheres, organic and aqueous phase flow rate ratio 6.7.

2) For the first time, the influence of molecular weight, the nature of terminal group, the stoichiometric lactide:glycolide monomer ratio and PLGA content (for implants) on rilpivirine release profile from PLGA depot formulations based on microspheres and in situ implants has been found.

3) It was found that decreasing the molecular weight of PLGA, presence the terminal ester group and increasing the lactic acid fraction in PLGA from 50 to 75% resulted in a controlled monophasic rilpivirine release from PLGA in situ implants in accordance with the Peppas-Sahlin model and zero-order kinetics.

4) The possibility of using the obtained polylactide depot formulations of rilpivirine as an alternative to the nanocrystalline form of rilpivirine was demonstrated by comparing the experimental in vitro release profiles.

Theoretical and practical significance of the work. For the first time, a method for the preparation of narrowly dispersed polylactide microspheres loaded with rilpivirine with tunable drug release rate by using microfluidic technology has been proposed. It is shown that the phase flow rate ratio, polylactide and rilpivirine content in the organic phase are key parameters determining the physicochemical properties of the microspheres. The in situ implant composition parameters were determined to achieve monophasic rilpivirine release according to the dissolution profile of the nanocrystalline form of rilpivirine during one month.

The approaches developed in this study can be used to design and study polylactide depot formulations of other poorly soluble highly active drugs, opening a wide range of possibilities for practical application of the results obtained.

The main points for the defence.

1. A method for the preparation of narrowly dispersed polylactide microspheres with high rilpivirine loading and tunable characteristics by applying microfluidic system.

2. The conditions for the generation of injectable depot formulations of rilpivirine based on in situ implants with different rilpivirine release profiles.

3. Factors that significantly affect the rate of hydrolytic degradation of microspheres and implants and, consequently, the release rate of rilpivirine from polylactide carriers.

4. The conditions for the generation of in situ implants of rilpivirine with a monophasic release profile corresponding to the dissolution profile of rilpivirine nanocrystals.