European Journal of Pharmaceutics and Biopharmaceutics 117 (2017) 77–90

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Research paper

Use of mesoporous cellular foam (MCF) in preparation of polymeric microspheres for long acting injectable release formulations of paliperidone antipsychotic drug

Stavroula Nanaki [a], Maria Tseklima [a], Zoe Terzopoulou [a], Maria Nerantzaki [a], Dimitrios J. Giliopoulos [b], Konstantinos Triantafyllidis [b], Margaritis Kostoglou [b], Dimitrios N. Bikiaris [a,*]

[a] Laboratory of Polymer Chemistry and Technology, Aristotle University of Thessaloniki, GR-54124 Thessaloniki, Macedonia, Greece
[b] Laboratory of General and Inorganic Chemical Technology, Aristotle University of Thessaloniki, GR-54124 Thessaloniki, Macedonia, Greece

ARTICLE INFO

Article history:
Received 29 December 2016
Revised 10 March 2017
Accepted in revised form 14 March 2017
Available online 4 April 2017

Keywords:
PLA
PLGA
Mesoporous cellular foam (MCF)
Microspheres
Paliparidone
Long acting injectable
Antipsychotic drug

ABSTRACT

In this study, high surface area mesoporous silica foam with cellular pore morphology (MCF) was used for injectable delivery of paliperidone, an antipsychotic drug used in patients suffering from bipolar disorder. The aim was to enhance paliperidone solubility and simultaneously to prepare long active intractable microspheres. For this reason paliperidone was first loaded in MCF silica, and the whole system was further encapsulated into PLA and PLGA 75/25 w/w copolymer in the form of microspheres. It was found that paliperidone, after its adsorption into MCF, was transformed in its amorphous state, thus leading to enhanced in vitro dissolution profile. Furthermore, incorporation of the drug-loaded MCF to polymeric microparticles (PLA and PLGA) prolonged the release time of paliperidone from 10 to 15 days.

1. Introduction

Mesoporous silica nanoparticles (MSN) have attracted much attention due to their use as potential drug delivery systems [1], drug targeting [2,3], gene transfection [4–7], tissue engineering [7–9] and cell tracking [9–12]. Their unique properties, such as high surface area, uniform pore, particle size distribution, good biocompatibility and easily functionalized surface, render them ideal for drug delivery systems [13–17]. MSN have already been used for the delivery of active compounds through oral [18–20] and intravenous [21,22] route. Studies have been conducted concerning cytotoxicity of silica-based nanoparticles. Several in vitro studies have convincingly demonstrated that mesoporous [23] and colloidal silica-based nanoparticles [24] do not affect cell viability or plasma membrane integrity at concentrations adequate for potential pharmacological applications. However, there were observed differences in hepatotoxic effects, that apart from other factors, might be accounted for by the distinct characteristics of particle size [25], surface charge [26], or both. Ivanov et al. [27] showed that intravenous administration of silica nanoparticles at a dose of 7 mg/kg was not associated with any changes in hematological parameters or serum biochemical markers over a period of 60 days post-infusion.

Among mesoporous silica nanoparticles, Mobil Composition of Matter (MCM)-41 and Santa Barbara Amorphous (SBA)-15 with a two dimensionally ordered hexagonal arrangement of cylindrical pores of uniform size (typically 2–10 nm) disposed parallel to each other, are probably the most investigated materials [28–30]. Mesocellular foam nanoparticles (MCF) are a MSN category with spherical structure and a continuous three-dimensional pore system, having already been used for oral delivery of drugs [31,32] showing enhanced drug loading efficiency compared to SBA-15. This is due to the high specific area that MCF nanoparticles have, based on their cellular form.

Paliperidone (9-hydroxy-risperidone) belongs to the class of typical antipsychotics and is the major metabolite of the already well-established risperidone that has very similar receptor activity. As a second generation antipsychotic, paliperidone is effective in treating both positive and negative symptoms of schizophrenia, with an increased safety effect towards extrapyramidal symptoms. According to its structure, paliperidone acts as a weak base whose solubility drops down with pH increase. For that reason, paliperidone is administrated in two forms; in oral form, present on the

* Corresponding author.
E-mail address: dbic@chem.auth.gr (D.N. Bikiaris).

http://dx.doi.org/10.1016/j.ejpb.2017.03.016
0939-6411/

market as a 24-h extended-release tablet [33,34] and in injectable form (Invega Sustenna), marketed by Janssen, where paliperidone is in the form of paliperidone palmitate. The last formulation (Xeplion), which was approved by FDA few years ago, is injectable once-monthly and is used for acute and/or maintenance treatment of schizophrenia. Paliperidone palmitate is present in the form of nano-/micro-suspension and, after intramuscular injection, releases the active moiety, paliperidone, by hydrolysis, which is absorbed into the systemic circulation. The obstacle of the proper formulation is related to cellular uptake, observed in all nano-microcrystal formulations, that apart from safety reasons, also affects drug release and/or prodrug stability. More precisely, Darville et al. [35] investigated the local disposition and PK of Xeplion in rats and found that the elicited injection site reaction consisted of an acute inflammation that was followed by a chronic inflammatory reaction. Also, large amounts of crystalline PP-LAI particles were found within the infiltrating macrophages, enhancing the scenario that the sudden drop in dissolution rate of the drug and its potential absorption ought to cause accumulation of the drug in macrophages. The same group investigated the co-administration of liposomal clodronate and sunitinib in order to inhibit the depot infiltration and nano-/microparticle phagocytosis by macrophages, and the neovascularization of the depot, respectively [36]. It was found that liposomal clodronate significantly decreased the rate and extent of the granulomatous inflammatory reaction, while sunitinib treatment completely suppressed the granulomatous reaction. A solution to retain the therapeutic concentration of paliperidone in plasma can be a depot-like system which will allow the drug to be released in a controlled manner. Polymeric microparticles are a promising tool to this direction for a variety of drugs.

Polymeric microparticles are nowadays one of the most promising area in pharmaceutical field due to their advantages; ability to encapsulate either hydrophilic either hydrophobic drugs, administration through different pathways to patients (oral, nasal, inhalation, parenteral), maintenance of the therapeutic concentration of drugs (shorter half-life) in plasma for longer period of time by controlling their release. Moreover microparticles have larger surface to volume ratios and can be developed for the improvement of dissolution rate of practically insoluble drugs. To our knowledge, no injectable formulation of paliperidone alone has been studied, due to its low solubility.

In this study, in order to increase drug solubility, paliperidone was adsorbed in MCF. This formulation was further used for preparation of microspheres, using poly(L-lactic acid) (PLA) and poly(D,L-lactide-co-glycolide) 75/25 w/w (PLGA75/25) as polymeric matrices. PLA [37,38] and PLGA [39] are two approved by Food and Drug Administration (FDA) polymers, which are used particularly in injectable drug delivery systems due to their hydrolysis into lactic and/or glycolic acid inside human body. However, these polymers, due to their different chemical structure and physical properties, have completely different release properties. So, the aim was to establish which of these could act as long time release carrier in order to increase the therapeutic treatment of paliperidone.

2. Materials and methods

2.1. Materials and reagents

Pluronic P-123 (Poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol) triblock copolymer with average Mn ~ 5800 was acquired by Sigma-Aldrich and was used as the MCF mesostructure-directing agent, together with 1,2,3-trimethylbenzene (TMB, Fluka) which was utilized as co-surfactant and swelling agent, as well as ammonium fluoride (NH_4F, Merck) serving as mineralizing agent [40]. Tetraethyl orthosilicate (TEOS) was acquired by Merck and was used as the silica source of MCF. Poly(lactic acid) (PLA) and Poly(lactide-co-glycolide) (PLGA) 75/25 w/w copolymer were kindly donated by Corbion (Spain, Montmelo). Paliperidone was kindly donated by Pharmathen S.A (Athens Greece). All other reagents were of analytical grade.

2.2. Synthesis of MCF silica

The mesostructured cellular foam (MCF) silica was synthesized via a self-assembly method using non-ionic surfactant Pluronic P-123 as the structure directing agent, 1,2,3-trimethylbenzene (TMB) as swelling agent, ammonium fluoride (NH_4F) as mineralizing agent, and tetraethyl orthosilicate (TEOS) as the silica source, in acidic pH conditions [41]. In a typical procedure, P-123 was diluted in aqueous HCl 1.6 M followed by the addition of NH_4F and TMB. The mixture was stirred for 1 h at 40 °C. TEOS was then added and the stirring continued for another 20 h at 40 °C. The mixture was then transferred in an autoclave and heated at 100 °C for 24 h. The solid products were recovered by filtration and were washed with deionized water, followed by calcination in air at 500 °C, for 8 h, with a heating rate of 1 °C/min, in order to combust the organic templates.

2.3. Paliperidone loading procedure on MCF

Paliperidone, 100 mg in weight, was initially dissolved into a mixture of organic solvents isopropanol: DCM 75:25, 100 mL in volume. Mesoporous silica MCF, 100 mg, was inserted into the organic solution and the resulting dispersion was left under magnetic stirring for 24 h, under nitrogen atmosphere. Centrifugation at 4000 rpm for 10 min was followed and the sediment was allowed at room temperature till total evaporation of the solvent. The dried material was further washed with acetone in order to remove the quantity of paliperidone that was loosely deposited on the surface of MCF. The amount of adsorbed drug was determined by TGA.

2.4. Preparation of microspheres

Polymeric microspheres containing MCF with adsorbed paliperidone were prepared by solid-oil-water (s/o/w) modified double emulsification method. According to this procedure, 100 mg of polymer, PLA and PLGA 75/25 respectively, were dissolved in 5 mL of dichloromethane. 10 mg of MCF containing adsorbed paliperidone was inserted in the polymeric solution and dispersed using probe sonicator for 1 min. The dispersion was inserted dropwise in 100 mL of PVA solution, 1% w/v in concentration, and homogenized using homogenizer for 2 min. After that, it was added in 100 mL water and left under magnetic stirring till total evaporation of dichloromethane. After centrifugation at 8000 rpm for 10 min the microparticles were collected and washed three times with distilled water in order to remove traces of the residual solvent and PVA. The resulting microparticles were finally freeze-dried and then stored at 4 °C for further evaluation.

Microspheres of paliperidone, without the presence of MCF, were also prepared as described above for comparison reasons.

2.5. Characterization of MCF and MCF-paliperidone adsorbed

2.5.1. Thermogravimetric analysis (TGA)

Thermogravimetric analysis was carried out with a SETARAM SETSYS TG-DTA 16/18. Samples (6.0 ± 0.2 mg) were placed in alumina crucibles. An empty alumina crucible was used as reference. Paliperidone, MCF and MCF-Paliperidone were heated from ambient temperature to 600 °C in a 50 mL/min flow of N_2 at heating rate