Intramuscular Administration of Paliperidone Palmitate Extended-Release Injectable Microsuspension Induces a Subclinical Inflammatory Reaction Modulating the Pharmacokinetics in Rats

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ABSTRACT: The present study aims at elucidating the intricate nature of the drug release and absorption following intramuscular (i.m.) injection of sustained-release prodrug nanocrystals/microcrystals. A paliperidone palmitate (PPP) long-acting suspension was characterized with regard to particle size ($D_{v,50}$ = 1.09 μm) and morphology prior to i.m. injection in rats. The local disposition was rigorously investigated by means of (immuno)histochemistry and transmission electron microscopy while the concurrent multiphasic pharmacokinetics was linked to the microanatomy. A transient (24 h) trauma-induced inflammation promptly evolved into a subclinical but chronic granulomatous inflammatory reaction initiated by the presence of solid material. The dense inflammatory envelope ($CD68^+$ macrophages) led to particle agglomeration with subsequent drop in dissolution rate beyond 24 h postinjection. This was associated with a decrease in apparent paliperidone (PP) absorption (near-zero order) until 96 h and a delayed time of occurrence of observed maximum drug plasma concentration (168 h). The infiltrating macrophages phagocytosed large fractions of the depot, thereby influencing the (pro)drug release. Radial angiogenesis ($CD31^+$) was observed throughout the inflammatory rim from 72 h onwards and presumably contributed to the sustained systemic PP concentrations by maintaining a sufficient absorptive capacity. No solid-state transitions of the retrieved formulation were recorded with X-ray diffraction analysis. In summary, the initial formulation-driven prodrug (PPP) dissolution and drug (PP) absorption were followed by a complex phase determined by the relative contribution of formulation factors and dynamic physiological variables. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci

Keywords: prodrugs; nanoparticles; muscle; disposition; biocompatibility; pharmacokinetics; paliperidone palmitate; sustained release; histopathology; inflammation

INTRODUCTION

Extended-release drug formulations for intramuscular (i.m.) administration, more specifically aqueous crystalline nano- and microsuspensions of poorly soluble compounds, have emerged during the last decade as viable and attractive alternatives to oral drug delivery systems.[1] These products aim at achieving stable therapeutic drug exposure for long periods of time (i.e., weeks to months), while enhancing patient compliance and minimizing adverse effects, which is especially relevant in the case of chronic or life-long therapies.[2] Nano- and microsuspensions for parenteral injection consist of (pro)drug nano- or microcrystals dispersed into a buffered aqueous vehicle containing relatively low amounts [drug/stabilizer ratios (w/w) varying from 1:3 to 50:1] of generally recognized as safe and stabilizing excipients (surfactants and/or polymers).[3] Using top-down milling techniques, it is possible to tailor the mean particle dimensions and size distribution to achieve optimal release kinetics, thus enabling steady therapeutic plasma concentrations for the desired period of time.[4] However, in case the active pharmaceutical ingredient (API) intended for prolonged i.m. release has a reasonable aqueous solubility, artificial reduction of the dissolution rate by conversion of the API to a poorly soluble salt or prodrug is required.[5] The aspired overall release rate of the active moiety is then determined by the dissolution velocity (modulated by both solubility and particle size of the salt or prodrug particles) along with the chemical or enzymatic stability of the derivative compound. The atypical antipsychotic paliperidone (PP) has accordingly been formulated as microcrystals of the extremely poorly soluble palmitoyl ester prodrug [paliperidone palmitate (PPP), Invega Sustenna®, Xeplion®, Janssen Pharmaceuticals Inc.].[6] This dosage form accomplishes sustained plasma concentrations for up to 4 weeks.[7] Even longer dosing intervals are attainable, with a 3-month formulation of PPP currently undergoing phase 3 clinical trials.

Although crystalline suspensions constitute a seemingly simple, yet elegant and effective way to parenterally deliver drugs and offer some distinct benefits compared with

Abbreviations used: API, active pharmaceutical ingredient; *AUC*, area under the (plasma concentration vs. time) curve; *CL/F*, weight-normalized apparent drug clearance; C_{MAX}, observed maximum drug plasma concentration; $D_{v,50}$, median equivalent sphere diameter; HE, haematoxylin and eosin; i.m., intramuscular; LAI, long-acting injectable; LD, laser diffraction; ORO, Oil Red O; PBPK, physiologically based pharmacokinetic; PLM, polarized light microscopy; PPP, paliperidone palmitate; PP, paliperidone; PS, polystyrene; s.c., subcutaneously; SEM, scanning electron microscopy; TEM, transmission electron microscopy; $T_{1/2}$, apparent terminal half-life in plasma; T_{MAX}, time of occurrence of observed maximum drug plasma concentration.

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alternative formulation strategies, their fate and local *in vivo* behavior following i.m. injection remain elusive. The general knowledge that the biological environment has the potential to modulate the drug release and absorption after i.m. dosing is not new. Nonetheless, a coherent mechanistic description of the variables affecting muscular drug absorption and their interrelationships does not exist. The limited work that has hitherto been carried out to identify the key factors influencing i.m. drug disposition originates from the 1980s or earlier and has been reviewed elsewhere.[8–11] For solid sustained-release parenteral depots, it is generally assumed that the drug absorption rate is predominantly controlled by the dosage form itself (e.g., particle size, solubility, etc.), therefore implying dissolution rate-limited pharmacokinetics (as opposed to absorption or perfusion rate limitation).[11,12] However, the situation *in vivo* is likely to be more complicated, especially because very long exposures to living (viz. reactive) biological tissues can be expected for these slowly dissolving drug particles. The pharmacokinetics (mean absorption time, etc.) could consequently be influenced by a plethora of interrelated parameters, both biological and formulation dependent.[11] The influence of biological factors on drug absorption is supported by recent observations following subcutaneous implantation of nanocrystals.[13,14] Additionally, nonclinical and clinical data available on file at Janssen Research & Development revealed discrepancies between predicted *in silico* and observed *in vivo* pharmacokinetics. Those differences cannot be attributed solely to formulation effects.[7] Moreover, indications of a foreign body reaction were evidenced in preclinical animal models. Surprisingly, no meticulous studies assessing the biological response elicited by i.m. drug nano- or microcrystals have been reported to date.

Given the complexity of the i.m. environment, it is of paramount importance to carefully consider and understand the likely interactions between long-acting injectable (LAI) nano- or microcrystals and the surrounding biological matrix. Hence, it was the aim of the current study to obtain, for the first time, fundamental, but indispensable knowledge, on the *in vivo* behavior of long-acting i.m. injectable microcrystals. For this, a thorough *in vivo* evaluation in rats of the local disposition, as well as the possible interactions with inflammatory cells, of PPP microcrystals (as the commercially available Xeplion® long-acting i.m. suspension) was performed. Fluorescent polystyrene (PS) microbeads and a blank vehicle solution were used for comparison. The dosage forms were characterized with regard to particle size and morphology using laser diffraction (LD) measurements and scanning electron microscopy (SEM) prior to administration. Rats were injected with the various formulations and ultrasonography was used in an attempt to characterize the formulation depot *in vivo*. The administration sites and draining lymph nodes were isolated to evaluate the local disposition of the microparticles by means of histology, (immuno-)histochemistry, and transmission electron microscopy (TEM). Plasma samples were additionally collected to try correlating those observations with the resulting systemic exposure profile. Finally, the solid state of the retrieved formulation depot was verified by X-ray diffraction (XRD) analysis. The implications of the findings are discussed in light of the traditional presumptions and valuable insights are obtained on the complex *in vivo* drug release and absorption mechanisms resulting in the atypical pharmacokinetic profiles.

MATERIALS AND METHODS

Materials

Paliperidone palmitate racemate (PubChem CID: 9852746; Supporting Information, Fig. S1), PP racemate (PubChem CID: 115237), R215639 (^{13}C and deuterated PP analogue) and a sterile PPP long-acting injectable microcrystal suspension (PPP-LAI, Xeplion®, volume-weighted mean hydrodynamic diameter ($D_{v,50}$) of 1.09 ± 0.01 μm) were kindly donated by Janssen Pharmaceutica NV (Beerse, Belgium). Fluoresbrite® 1 μm yellow-green fluorescent plain PS microspheres were purchased from Polysciences Europe GmbH (Eppelheim, Germany). Polysorbate 20 was obtained from Applichem GmbH (Darmstadt, Germany). Polyethylene glycol (PEG) 4000 (Ph. Eur. grade) was purchased from BASF (Ludwigshafen, Germany). Sodium chloride, sodium dihydrogen phosphate monohydrate, sodium phosphate dibasic, sodium hydroxide, 10% (v/v) neutral-buffered paraformaldehyde, Gill's haematoxylin No. 3, eosin Y (1%, w/v, aqueous solution), alcoholic 0.1% (w/v) eosin Y with 0.1% (w/v) phloxin solution, Oil red O (ORO), Giemsa stain solution, sodium cacodylate trihydrate, uranyl acetate dihydrate, ammonium formate, formic acid, 2-propanol, tetrahydrofuran, and xylene were all provided by Sigma–Aldrich Chemie GmbH (Steinheim, Germany). Citric acid monohydrate (Ph. Eur. grade) and denaturated ethanol were acquired from Chem-Lab NV (Zedelgem, Belgium). Paraformaldehyde, glutaraldehyde 25% (v/v), propylene oxide, and the Agar® 100 resin kit, all of electron microscopy grade, were purchased from Agar Scientific Ltd. (Stansted, UK). Osmium tetroxide was obtained from Electron Microscopy Sciences Inc. (Hatfield, Pennsylvania). Lead(II) nitrate and trisodium citrate dihydrate for preparation of Reynold's lead(II) citrate and the Elastica Van Gieson staining kit were acquired from Merck KGaA (Darmstadt, Germany). Isoflurane was ordered from Piramal Healthcare Ltd. (Northumberland, UK). Acetonitrile, methanol, and ethanol were provided by VWR International BVBA (Leuven, Belgium). Type I ultrapure deionized water obtained from an Elgastat Maxima system was used (Elga LabWater VWS Ltd., High Wycombe, UK). All chemicals and organic solvents were of analytical purity and HPLC grade, respectively, unless otherwise specified.

Formulation of Injectable Microsuspensions

The commercially available PPP-LAI microsuspension was used as obtained (endotoxin load <2.33 IU/mg). To be able to discriminate between histopathological responses mediated by the introduction of particulate material and bioactive solutes, a PS suspension of identical strength, with same vehicle composition and similar particle size, was prepared. Briefly, 250 mg of PS particles were sterilized by triple rinsing, centrifugation (4°C for 10 min at 4000*g*) and resuspension in 70% (v/v) ethanol. Finally, the PS particles were aseptically resuspended in 1.60 mL of sterile vehicle solution. The vehicle solution was obtained by dissolving 12 mg/mL polysorbate 20, 30 mg/mL PEG 4000, 5 mg/mL citric acid monohydrate, 5 mg/mL sodium phosphate dibasic, 2.5 mg/mL sodium dihydrogen phosphate monohydrate, and 2.87 mg/mL sodium hydroxide in water, followed by filtration through a sterile 0.2-μm single use syringe filter. All suspensions were isotonic and had a neutral pH.

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