Accepted Manuscript

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Davin Rautiola, James C. Cloyd, Ronald A. Siegel

PII: S0168-3659(18)30532-7
DOI: doi:10.1016/j.jconrel.2018.09.013
Reference: COREL 9465

To appear in: *Journal of Controlled Release*

Received date: 26 April 2018
Revised date: 8 August 2018
Accepted date: 14 September 2018

Please cite this article as: Davin Rautiola, James C. Cloyd, Ronald A. Siegel , Conversion of a soluble diazepam prodrug to supersaturated diazepam for rapid intranasal delivery: Kinetics and stability. Corel (2018), doi:10.1016/j.jconrel.2018.09.013

Conversion of a soluble diazepam prodrug to supersaturated diazepam for rapid intranasal delivery: kinetics and stability

Davin Rautiola[a], James C. Cloyd[b,c], and Ronald A. Siegel[a,d,*] siege017@umn.edu

[a]Department of Pharmaceutics, University of Minnesota, Minneapolis, MN 55414, USA

[b]Department of Experimental and Clinical Pharmacology, University of Minnesota, Minneapolis, MN 55414, USA

[c]Center for Orphan Drug Research, University of Minnesota, Minneapolis, MN 55414, USA

[d]Department of Biomedical Engineering, University of Minnesota, Minneapolis, MN 55414, USA

[*]Corresponding author at: Department of Pharmaceutics, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455, USA.

ABSTRACT

The low aqueous solubility of diazepam (DZP) presents a challenge in formulating nasal sprays without the use of organic solvents. One approach to overcome this challenge involves co-administration of a soluble prodrug, avizafone (AVF), with a converting enzyme to produce supersaturated DZP at the site of administration. In addition to overcoming solubility issues, the supersaturated state of DZP provides an increased driving force for enhanced permeation across nasal mucosa. However, supersaturated solutions are metastable, and there is a limit to the degree of supersaturation (S) that can be reached without causing spontaneous phase separation of the solute. The aim of this article was to determine how formulation parameters affect the rate of DZP supersaturation, maximum degree of supersaturation, and phase separation kinetics. A model enzyme, *Aspergillus*