An Ultra-long-acting prodrug of Buprenorphine for Opioid Dependence

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INTRODUCTION

Opioid use disorder (OUD) is a national health emergency in the United States. While treatments for OUD exist, there remains a high unmet need for long-acting (LA) formulations and therapies to manage the abuse of emerging potent synthetic opioid compounds. Buprenorphine (BUP) is an approved, safe, and effective treatment for OUD, and available in multiple forms, including daily oral, once-weekly to once-monthly injectables. However, approximately 35-50% of patients discontinue therapy prior to six months [1]. Side effects of existing LA formulations that utilize organic solvents are major limitations. As such, we created organic solvent-free ultra-long-acting BUP prodrug formulations.

METHODS

A library of lipophilic prodrugs of BUP was synthesized by esterification. The synthesized prodrugs were characterized and nano-formulated using biocompatible surfactants to produce stable aqueous nanosuspensions. Pharmacokinetics (PK) and biodistribution profiles of the lead candidate were evaluated in Sprague Dawley (SD) rats following a single intramuscular (IM) injection. Drug levels in plasma and brain tissues were quantified using validated UPLC-MS/MS methods.

RESULTS

The BUP prodrug powders were synthesized in high chemical yields of >60%. The water-insoluble prodrugs exhibited significantly higher lipophilicity compared to BUP and were efficiently converted to BUP when incubated in plasma from different species. Surfactant-stabilized prodrug nanosuspensions were room temperature stable over a 3-month observation period. Notably, single injections of the lead prodrug nanosuspension (NM6BUP) at 45 and 90 BUP eq. mg/kg in Sprague-Dawley rats produced dose-proportional exposures, sustaining therapeutic concentrations of BUP above the efficacious C_{trough} levels for approved doses of BRIXADI and SUBOXONE for over 182 days (Figure 3). Notably, NM6BUP aqueous nanosuspension also exhibits sustained BUP levels in an ongoing PK study where SD rats were administered a single subcutaneous injection (Figure 4), underscoring the potential for self-administration.

LEARNING OBJECTIVES

Novel prodrug and formulation approaches could potentially extend the apparent half-life of BUP.

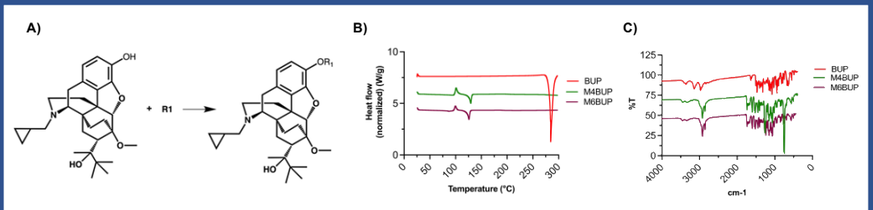

Figure 1: BUP prodrugs synthesis and characterization: **A)** BUP prodrugs were synthesized by conjugating BUP to biocompatible linkers through an esterification reaction. **B)** Overlay of differential scanning calorimetry (DSC) of BUP, M4BUP, and M6BUP at a ramp of 10° C from 30-300° C. **C)** Overlays of Fourier-transformed infrared (FT-IR) spectrum of BUP, M4BUP and M6BUP, identifying the specific functional group at prodrug moieties.

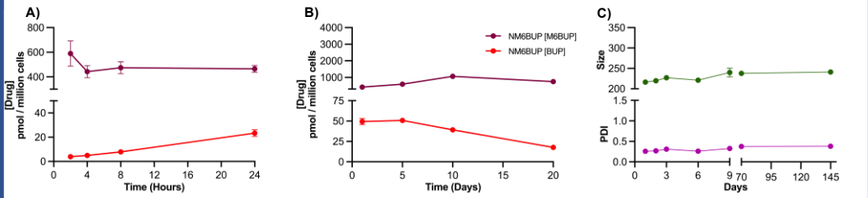

Figure 2: In-vitro characterization of BUP prodrug nanoformulations. A) NM6BUP uptake was measured in MDMs over 24 hours following a single treatment with 25 µM NM6BUP. **B)** NM6BUP retention was measured in MDMs over 20 days, following a single 8-hour treatment of 25 µM of NM6BUP. For the uptake and retention study, the intracellular BUP and M6BUP levels were quantified by UPLC-MS/MS, and results are expressed as Mean ± SEM, for n=3.**C)** Particle sizes, polydispersity indices (PDIs) of NM6BUP were measured at room temperature over 145 days using dynamic light scattering (DLS) to determine the long-term physiochemical stability of nanoformulation.

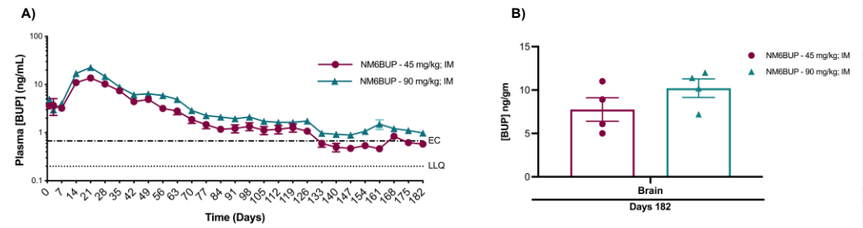

Figure 3: Pharmacokinetic profiles of single-dose NM6BUP in Sprague Dawley rats. A) Plasma exposure to active metabolite BUP over 182 days and **B)** Brain levels of BUP at 182 days, following 45 or 90 BUP eq. mg/kg single intramuscular doses of NM6BUP in Sprague-Dawley rats. Effective Concentration (EC) = 0.675 ng/mL, the clinically established effective concentration for BRIXADI [2]. LLQ = Lower Limit of Quantitation. Drug levels were determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS). The animal numbers in each group were n = 4. Data are presented as mean and SEM.

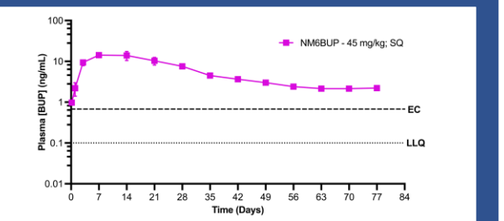

Figure 4: Pharmacokinetics of NM6BUP following a single subcutaneous injection in an ongoing study. SD rats were administered a single injection at a dose of 45 mg. BUP eq/ kg subcutaneously. Plasma BUP concentrations are being monitored biweekly by LC-MS/MS. Data are presented as mean ± SEM with n=4 animals each group.

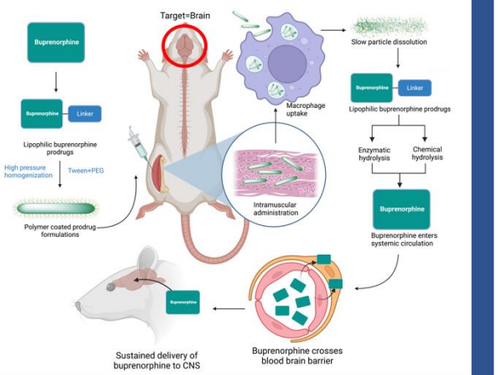

Figure 5: Systemic representation of BUP prodrug nanoformulations to improve BUP half-life: Nanoformulation creates a primary depot at the injection site, and macrophage infiltration at the injection site facilitates drug uptake and redistribution into secondary drug depots. Slow particle dissolution and subsequent rapid prodrug hydrolysis produce an ultra-long-acting BUP PK profile and drug delivery into the brain.

CONCLUSIONS

NM6BUP was identified from a prodrug library screening and has the potential to offer well-tolerated ultra-long-acting dose intervals of BUP. This profile could potentially improve patient convenience, adherence, medication compliance, and treatment outcomes.

ACKNOWLEDGEMENTS

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