Development of Long-Acting Injectable Ketamine Loaded PLGA Microparticles as a Non-opioid Analgesic

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Background/Objective:

Ketamine, a psychedelic, is a noncompetitive N-methyl-D-aspartate receptor antagonist that may also bind to mu opioid receptors. Historically, it has been used as an anesthetic (Ketalar®), although now has found uses as a novel, quick acting, antidepressant for treatment-resistant depression (Spravator®) and could be used as an adjuvant to opioid analgesia providing opioid-sparing effects. One major advantage over opioids is Ketamine does not suffer from respiratory depression and maintains patent airways during anesthesia. Ketamine is only available as a short-acting injectable solution or a nasal spray. Our goal is to develop a long-acting injectable form in a biodegradable matrix poly(lactic-co-glycolic) acid (PLGA) that does not have a burst release and provides 5-7 days of steady-state plasma levels.

Methods:

A mechanistic approach towards development of a long-acting injectable began with a solubility screen of Ketamine. Based on these results, experiments began with an oil in water emulsification with two theoretical drug loadings (25% and 40%) and two processing conditions – (1) aqueous extraction and (2) aqueous extraction, intermediate drying, and a 25% Ethanol wash. The formulations were characterized for drug loading, drug release, and crystallinity and imaged using scanning electron microscopy (SEM).

Results:

Minimal differences were noted in the release profiles between formulations. Although, a significant difference was noted between the two processing conditions, where the extra intermediate drying step and 25% ethanol wash resulted in a significant slowing of the drug release rate.

Conclusion and Implications:

The difference in release kinetics is hypothesized to be due to densification of the PLGA matrix, based on the increase in surface roughness/wrinkling in the SEM images, crystallinity increase, and on their respective powder x-ray diffraction patterns. Our preliminary results demonstrate the feasibility of a longer acting Ketamine using PLGA. Further refinement of these formulations and rodent pharmacokinetic studies will be done in future.