IN VITRO AND IN VIVO ASSESSMENT OF THE PROTOTYPE INTRANASAL PROMETHAZINE MICROCAPSULE FORMULATION

Jason Boyd¹, Brian Du², Zuwei Wang², Joe Mcdonough³, Ed Bowland⁴, Joe Persyn³ and Lakshmi Putcha⁵
¹Universities Space Research Association, Houston, TX, ²Wyle Laboratories, Life Sciences Systems and Services, Houston, TX, Southwest Research Institute, San Antonio, TX³, University of Texas, San Antonio, TX⁴, NASA-Johnson Space Center, Houston, TX⁵

Space Motion Sickness (MS) is commonplace in the U.S. manned space flight program. Typically, orally administration motion sickness medications have poor bioavailability and often have neurocognitive side effects at the recommended doses. Several drugs have been used for therapeutic management of SMS. Intramuscularly administered romethazine (PMZ) is perceived to have optimal efficacy with minimal side effects in space. A microcapsule intra-nasal gel dosage form of PMZ (INPMZ) was developed to offer a more effective noninvasive treatment for SMS. We evaluated in vitro and in vivo characteristics of the prototype INPMZ in preparation for an IND application to the FDA for phase I studies with the new dosage form.

In vitro studies included dissolution and diffusion studies with the dosage form using a DISTEK 5100 dissolution system and Hanson diffusion system, respectively.

Six groups of eight rats each were dosed for 3 days with three different doses of INSCOP, IM PMZ and placebo to determine toxicity and bioavailability. In vitro study samples were analyzed using a HPLC method and biological samples were analyzed for PMZ and metabolites with a LC/MS method, both methods were developed and validated in the laboratory.

Results from the in vitro studies indicated significant differences between the rate and extent of drug release from the diffusion and dissolution rates of the formulation. The diffusion rate was xx and the dissolution rate was xx. These results suggest diffusion of PMZ from the formulation is slower than its dissolution rate. This is due to the fact that Franz diffusion cell would allow the microcapsules to hydrate slowly in a humid environment, a condition that mimics that of the intra nasal drug delivery. Dissolution of PMZ microcapsules from the gel was relatively slow, about 45% of the loaded PMZ released from the gel by six hours.

Results from toxicology and bioavailability studies with INPMZ in rats revealed that the absorption from the IN dose is faster and greater than that from an equivalent IM dose. Bioavailability was linear for the three dose levels and clearance and volume of distribution from the IN and IM dosage forms was comparable?? (Jason to write his input)

Results from the toxicology data are presented separately. The overall results from this project indicate while the prototype dosage form meets the requirements for bioavailability and acute toxicity requirements, further modification of the dosage form is warranted to alleviate the toxicity after multiple/chronic dosing, and testing in a higher animal model such as dog will be also required before filing of an IND application for the new formulation.