Intratympanic Injection Drug Delivery System for Extended Steroid Delivery to the Inner Ear

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Background & Objectives

- There are no FDA-approved drugs for the treatment of inner ear diseases that afflict millions of Americans every year.
- In their place, physicians often prescribe drugs off-label that – whether delivered orally or through local injection to the ear - lack safety data and show widely variable clinical responses.
- Here, we describe Orbis Biosciences’ innovative inner ear drug delivery platform – a system comprised of drug-loaded microspheres suspended in a Fast Film-forming Agent (FFA) that localizes microspheres to the Round Window Membrane (RWM) in the middle ear.
- This system could enable cost-effective, local delivery and extended-release of new and existing drugs, thereby providing physicians and patients new safe and effective treatments for debilitating diseases of the inner ear.

Experimental Methods

- Uniform microspheres were prepared using a modified melt-spray technique of Orbis’ Precision Particle Fabrication technology.
- Betamethasone and PLGA was first dissolved in dichloromethane (DCM) and 50:50 poly (D,L-lactic-co-glycolic acid) (PLGA) then processed through a coaxial Precision Particle Fabrication nozzle. Simultaneously, the wax matrix jet was acoustically excited using an ultrasonic transducer controlled by a frequency generator that produced regular disruptions in the polymer jet (Figure 1).
- PLGA-drug particles were combined with a FFA mixture and tested in vitro and in vivo.
- In vitro betamethasone release from the microsphere/FFA‘vehicle’ was determined as a function of microsphere size on a Franz cell dissolution apparatus fitted with cellulose acetate membranes.
- In vivo FFA adhesion studies were conducted using anesthetized C57/BL6 mice. 2.0µL of the FFA/microsphere-suspension was delivered directly above the RWM with a Hamilton Syringe. The mice were kept stationary for 5 minutes before being sutured up. The mice were kept alive and active for either 21 or 35 days, upon which necropsy was performed to visually and histologically evaluate the adhesion of microspheres with and without FFA.

Results

- Uniform microspheres were created using a novel process enabled by Orbis’ Precision Particle Fabrication Technology (Figure 2A).
- In vitro betamethasone release from Precision Particle Fabrication microspheres demonstrated that microsphere size can influence betamethasone release (Figure 2B).
- At 21 and 35 days, mice treat with microspheres suspended in the FFA had microspheres localized directly on the RWM with a thin film as intended (Fig. 3A,C).
- Negative control mice displayed no visible microspheres, indicating that the particles had migrated away from the surgical site due to lack of an FFA component (Fig. 3B,D).
- Staining indicated that the microspheres and FFA caused no significant inflammatory response. The intensity of TNF-α and IL-6 development was similar between the groups (data not shown), and H&E revealed no discernible changes in hair cell anatomy or apparent tissue reaction (Fig. 4A, B).

Conclusion

- Using Precision Particle Fabrication, an injectable, extended release intratympanic delivery system was developed that can localize drug-loaded microspheres to the RWM of mice for greater than 35-days with minimal inflammatory response.

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