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## ORAL DELIVERY OF AMPHOTERICIN B COCHLEATES: DEVELOPMENTAL STATUS

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Cochleate vehicles are stable precipitates, composed of naturally occurring lipids (phosphatidylserine, PS) and calcium with a spiral multilayered structure that presents no internal aqueous space. Their unique structure stabilizes molecules, provides protection from hazardous environmental conditions, enzymatic degradation and even allows lyophilization to a powder without changes in their structure. Previously we have reported that oral amphotericin B cochleates, (CAMB), showed excellent activity in murine models of clinically relevant invasive fungal infections and low toxicity: disseminated candidiasis, disseminated aspergillosis, and central nervous system cryptococcosis. In those studies cochleate technology for drug delivery was still at an early stage, and the CAMB formulations were being prepared from expensive, synthetic phospholipids using a research “bench level” protocol.

Our long term goals are to prepare CAMB as a commercially viable product, using a scalable manufacturing protocol producing stable suspensions, reconstitutable lyophilized powders, and capsules. To this end several significant milestones have been achieved. Expensive synthetic PS has been replaced with soy derived PS. A simplified, four step “solvent drip” manufacturing process has been developed. Also, cochleates are naturally hydrophobic and tend to form aggregates in aqueous suspension when dried or lyophilized. Hence, a major goal has been to find excipients that are compatible with cochleate formulations and could stabilize particle size and prevent aggregation. Several standard excipients were investigated without success. For example, trehalose, routinely used to stabilize liposome formulations, did not inhibit cochleate aggregation following lyophilization. However, it was found that methyl cellulose, (MC), added to cochleate formulations subsequent to calcium addition, stabilized CAMB particle size in suspension. Also, following lyophilization and reconstitution with water, MC at concentrations between 0.2% and 0.4% yielded suspensions with particle size characteristics very similar to the initial suspension. MC also stabilized CAMB particle size in the presence of antimicrobials such as parabens, which tend to enhance aggregation.

It is anticipated that significant quantities of GMP CAMB will soon be available allowing the preclinical studies supporting the filing of an IND. Supported by SBIR Grant # 2 R44 AI46040-02