P-069 Novel Inhaled Liposomal Ciprofloxacin Formulations for Personalized Therapy

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Introduction, Methodology & Discussion

Management of chronic lung infections and prevention of infectious exacerbations that lead to lung tissue destruction and further decline in lung function are desirable for long-term quality of life outcomes in a number of disease conditions including cystic fibrosis (CF) and non-CF bronchiectasis (BE).

To that end, Aradigm developed two aqueous, liposomal formulations to increase the concentration and duration of action of ciprofloxacin in the lung:

- **Lipoquin,** ciprofloxacin encapsulated in liposomes and
- **Pulmaquin**, a combination of free ciprofloxacin and Lipoquin to provide both a high peak and a sustained release profile of ciprofloxacin in the lungs (Figure 1).

Nebulization using the PARI LC Sprint nebulizer and PARI TurboBoy-S compressor did not compromise the integrity of the liposomes nor the vesicle size distribution in Lipoquin or Pulmaquin[2].

In a 6-month, Phase 2b, randomized double-blind, placebo-controlled trial (ORBIT-2), 42 BE patients were dosed once-daily with either 210 mg Pulmaquin or placebo for three cycles of 28 days on treatment, followed by 28 days off treatment. Pulmaquin was well tolerated, demonstrated potent anti-pseudomonal microbiological efficacy (Figure 2), and delayed the time to first pulmonary exacerbation (Figure 3)[3]. Phase 3 trials are ongoing (ORBIT-3 and -4).

In this study we describe a simple method to attenuate the release rate of ciprofloxacin by incorporation of drug nanocrystals within the vesicles. Instead of changing the liposome composition, or adding excipients to rigidify the membrane or change its permeability, a formulation containing cryoprotectant (sucrose) was developed that could be frozen, and upon thawing, the ciprofloxacin encapsulated in the liposomes formed nanocrystals (Figure 4). These liposomes possessed slower In Vitro Release (IVR) profiles due to the combination of both a dissolution and a diffusion rate-controlling step (Figure 5). The addition of non-ionic surfactant prior to freeze-thaw led to reduced nanocrystal size within the vesicles and an additional means to modify the release profile.

Preparations of 12.5 mg/ml Lipoquin containing 90 mg/mL sucrose and various concentrations of non-ionic surfactant were formulated between pH 4.9 to 5.3, stored frozen, and thawed prior to use. These thawed formulations, before and after mesh nebulization, and after subsequent refrigerated storage for up to three months, were characterized in terms of liposome structure by cryo-TEM imaging, vesicle size by dynamic light scattering, drug encapsulation by centrifugation-filtration, and IVR[4] performance. These formulations were robust to PARI e-Flow mesh nebulization (Figure 6), and formed respirable aerosols with a volume mean diameter (VMD) of ~3.8-3.9 µm and a geometric standard deviation (GSD) of ~1.7.

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2. Cipolla D, Wu H, Chan J, Chan H-K, and Gonda I. (2013) Liposomal Ciprofloxacin for Inhalation Retains Integrity Following Nebulization. *Respiratory Drug Delivery Europe 2013*, 237-242. Eds, RN Dalby, PR Byron, J Peart, JD Suman, SJ Farr, and PM Young. Davis Healthcare Int'l Publishing, River Grove, IL. Berlin, Germany, May 21-24, 2013.

3. Serisier DJ, Bilton D, De Soyza A, Thompson PJ, Kolbe J, Greville HW, Cipolla D, Bruinenberg P, and Gonda I. (2013) Inhaled, Dual-Release Liposomal Ciprofloxacin in Non-Cystic Fibrosis Bronchiectasis (ORBIT-2) – a Randomised, Double-Blind, Placebo-Controlled Trial. *Thorax.* 68; 9: 812-817

4. Cipolla D, Wu H, Eastman S, Redelmeier T, Gonda I and Chan HK. (2014) Development and Characterization of an In Vitro Release Assay for Liposomal Ciprofloxacin for Inhalation. *J. Pharm. Sci.* 103; 1: 314-327. doi:10.1002/jps.23795.

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Figure 1: Pharmacokinetic profile of Pulmaquin vs Lipoquin in Healthy Subjects and Bronchiectasis Patients

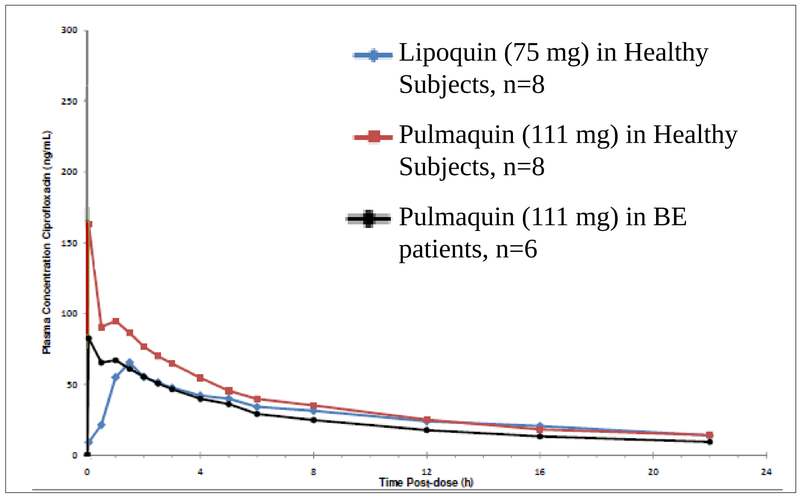


Figure 2: Pulmaquin has Significant Antimicrobial Effect

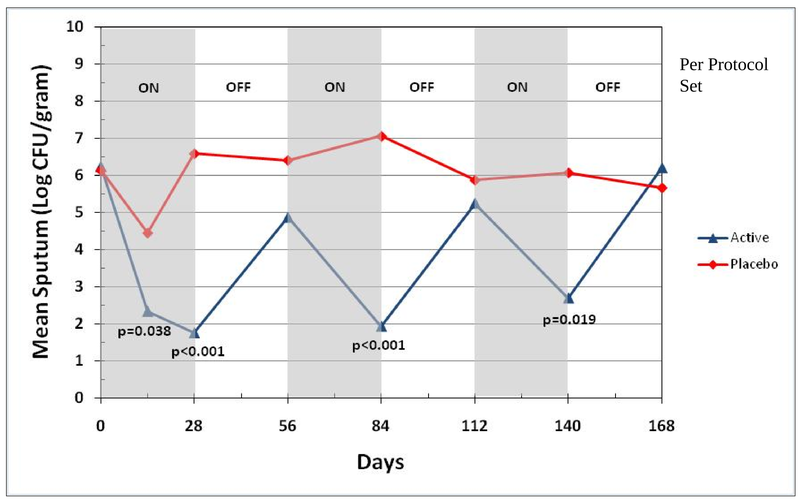


Figure 3: Pulmaquin Improves Time to First Exacerbation

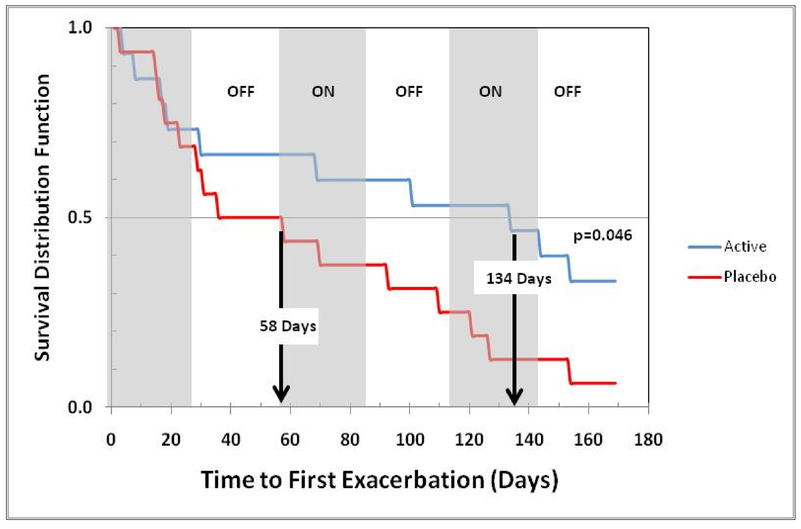


Figure 4: Cryo-TEM Images Confirm the Formation of Nanocrystals after Freeze-Thaw

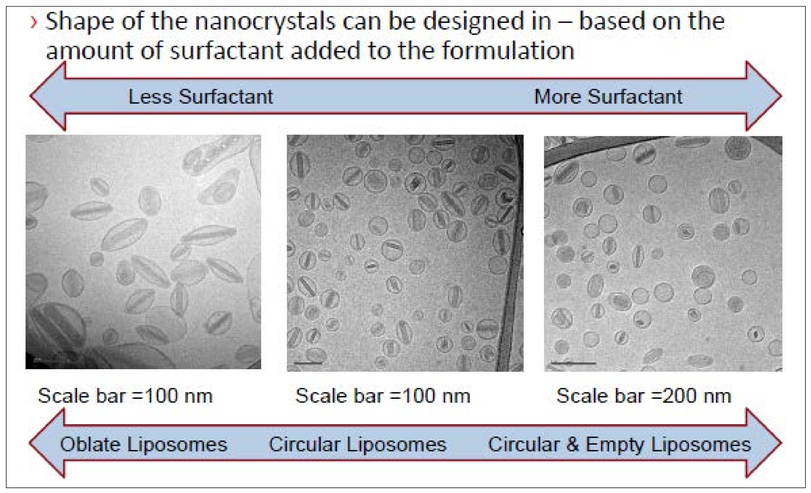
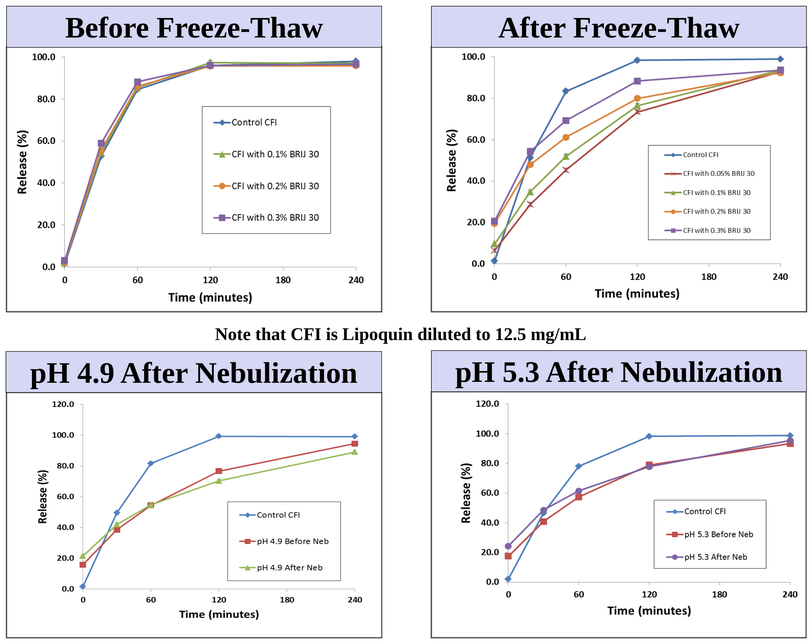
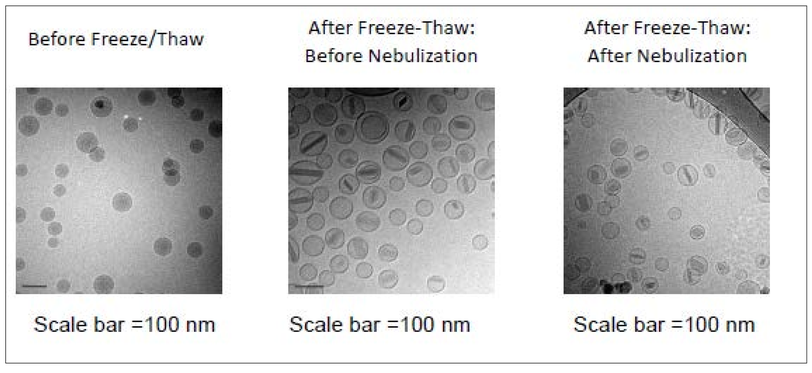


Figure 5: Nanocrystals Attenuate the In Vitro Release Profile



Note that CFI is Lipoquin diluted to 12.5 mg/mL

Figure 6: Cryo-TEM Images Before and After Nebulization



SUMMARY

▪ We have prepared liposomal ciprofloxacin formulations for inhalation that vary in their rate of release from immediately available to very slow, depending on the composition of the formulations and subsequent physical treatment. Our most recent development enables the modulation of release of the formulation already extensively tested in animal models and humans without the need to change the qualitative composition of the liposomes through nano-crystal engineering.
▪ The size and shape of the nanocrystals, and thus the rate of release (IVR), can be modified by the presence of non-ionic surfactant.
▪ PARI e-Flow mesh nebulization of the liposomes containing nanocrystalline ciprofloxacin forms respirable aerosols with a VMD of 3.8-3.9 µm and a GSD of 1.7.
▪ Their physicochemical properties (encapsulated nanocrystalline drug and slower IVR profiles) are retained after mesh nebulization.
▪ The new method has the potential to personalize therapy for patients by modulating the encapsulation and release properties of a liposomal drug product to suit an individual patient's needs.