Stability and Aerosol Performance of an excipient-free dry powder of Tigecycline for local delivery in lung infections

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Background

- Lower respiratory tract infections are the 4th leading cause of death across the world [1].

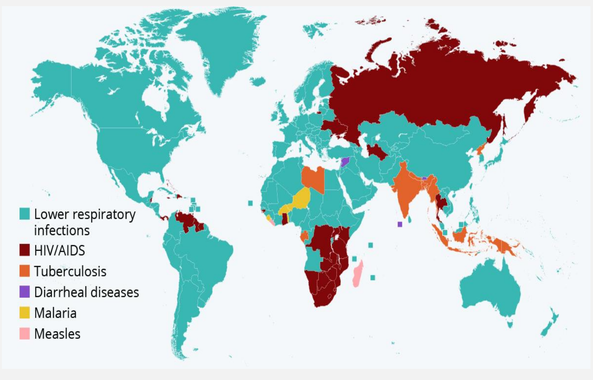


Figure 1: Transmittable diseases causing the biggest health burdens

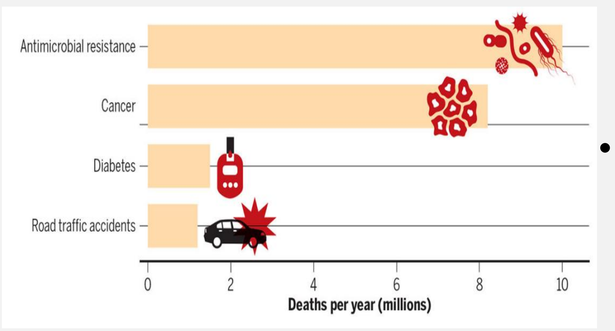


Figure 2: Annual global mortality projected for 2050

- Tigecycline (TIG) is a broad-spectrum glycylcycline antibiotic that is susceptible to a wide variety of infections including *Streptococcus pneumonia*, non-tuberculosis mycobacteria, and *Stenotrophomonas maltophilia* [2].
- Currently, TIG is only available as a lyophilized powder for injection for the treatment of skin and abdominal infections and is only stable for a maximum of 48 hours once reconstituted [3,4].
- The labelled dose of TIG is 100 mg initial dose followed by 50 mg every 12 hours [4]. Pulmonary delivery of TIG will help reduce this dose to as low as 10 mg.

Research Goals

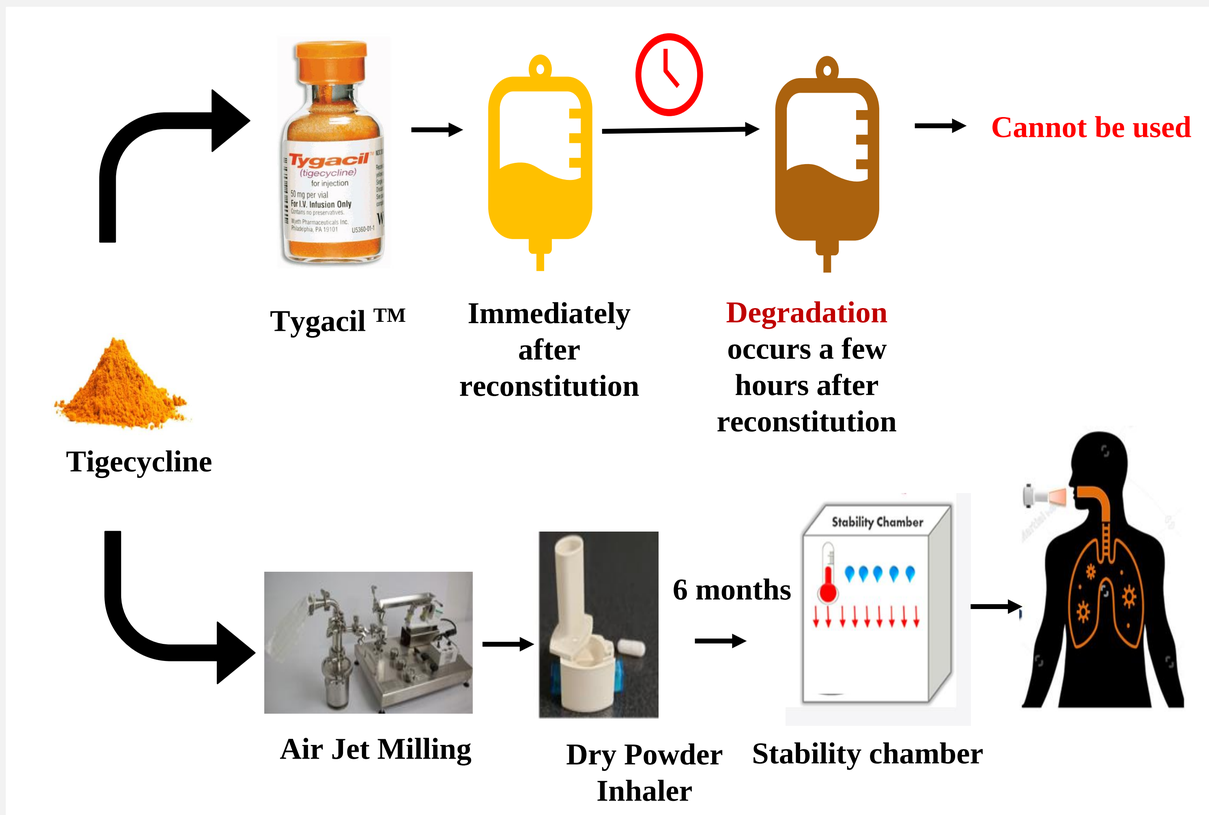


Figure 3: Comparison between the conventional and proposed processing methods [5]
Commercial IV formulation of TIG is only stable for 6 – 48 hours after reconstitution. The proposed method will utilize a dry-milling technique and test long-term storage stability for local delivery in the lung

Methods

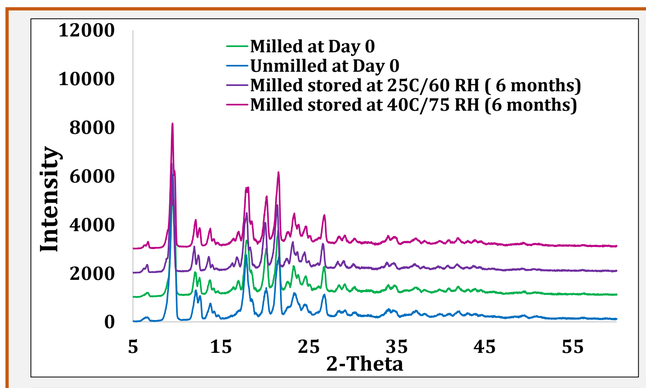
Parameter	Measurement Technique	Method
Micronization	Air Jet Mill	75 psi grind pressure, 65 psi feed pressure, and 1 g/min feed rate [6]
Particle Size	Laser Diffraction (HELOS RODOS)	Pressures from 0.5-3 bar
Stability	Differential Scanning Calorimetry (DSC)	35-350° C at 10 degree/minute
Crystallinity	Powder X-ray Diffraction (PXRD)	5 to 60 degrees at 2 degree/minute
Aerosol Performance	Next Generation Impactor (NGI)	93 L/min at a pressure drop of 4 kPa
6-month storage stability	DSC, PXRD, NGI, HPLC, TGA	Same as above

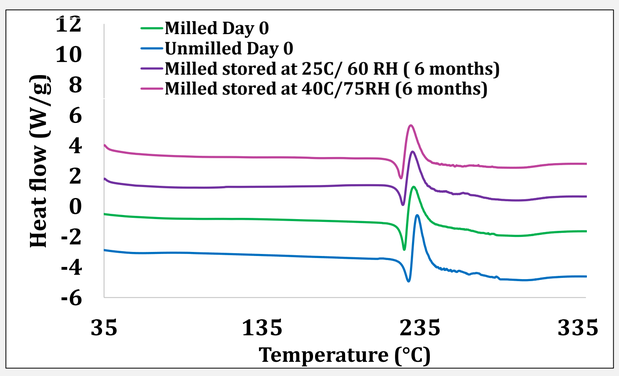
Results

Table 1: Geometric and Aerodynamic particle size of TIG powders

Method	Parameter	Milled At Day 0	Unmilled At Day 0
RODOS (0.5 bar)	Dv50 (µm)	2.76 ± 0.2	5.98 ± 0.7
NGI (4 kPa)	Mass Median Aerodynamic Diameter (MMAD) (µm)	1.90 ± 0.2 **At 6 months** 25°C/60% RH: 1.6 ± 0.4 40°C/75% RH: 1.3 ± 0.1	5.74 ± 0.7
NGI (4 kPa)	Fine Particle Fraction (FPF) (%)	95.08 ± 0.08 **At 6 months** 25°C/60% RH: 78.9 ± 0.9 40°C/75%RH: 73.5 ± 0.2	31.70 ± 1.8
NGI (4 kPa)	Emitted Fraction (EF) (%)	90.15 ± 0.1	90.20 ± 0.3

- Dv50 for milled particles was half of the unmilled TIG particles at 0.5 bar
- The MMAD for unmilled powders was ~3-fold higher than that of milled powders at Day 0
- At Day 0, the EF remained high for milled and unmilled powders while the FPF was ~3-fold higher for milled powders
- The FPF and MMAD of milled powders remained comparable to Day 0 upon storage at accelerated and intermediate conditions for 6 months





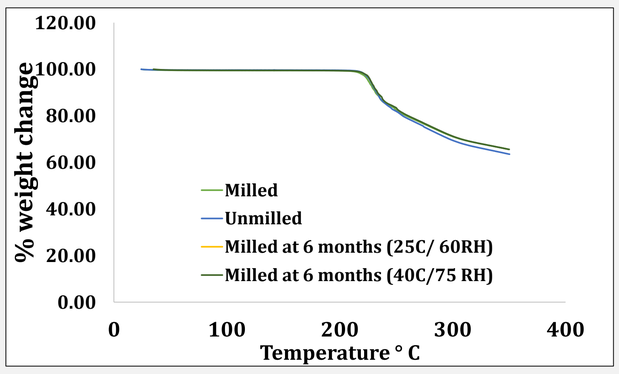


Figure 4: A) PXRD B) DSC C) TGA of TIG powders

- The HPLC data revealed that milled TIG powders remained stable upon processing and storage at intermediate (25°C/60% RH) and accelerated (40°C/ 75% RH) conditions for 6 months. All groups had a single peak at 4.9 minutes and no additional peaks were seen throughout the chromatogram indicating the absence of degradants (data not shown)
- PXRD and DSC analysis after processing and storage revealed that TIG remained crystalline and did not degrade at 6 months (Figure 4 A, 4B)
- The TGA analysis revealed that TIG is non-hygroscopic and has very little potential to adsorb moisture. The water content did not change and remained at zero for TIG powders upon storage and processing.

Conclusions

- TIG was successfully prepared as an excipient free, high dose dry powder for inhalation with enhanced aerosolization efficiency.
- It was found to be stable upon storage at 25°C/60%RH and 40°C/75% RH for 6 months and maintained its aerosolization efficiency.
- Additionally, TIG has little propensity to adsorb ambient moisture thereby protecting it from degradation upon storage even in high humidity conditions

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