W4142

# Measurements to Support Regulatory Submissions for Filing Investigational New Drugs: An Example, Using New Salts of Bedaquiline


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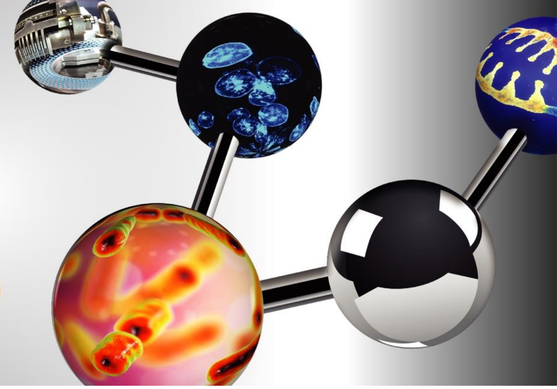


## PURPOSE

- Bedaquiline is used in the treatment of multidrug resistant tuberculosis (TB)
- The fumarate salt is currently the only available commercial drug product
- Research in our laboratories unveiled new salts of bedaquiline, which offers additional information on the bedaquiline system
- Research focused on developing control strategies for specifications for the new benzoate and maleate salts
- The International Conference on Harmonization (ICH) Q 6 document provides guidance on specifications for new drug substances (DS) and new drug products (DP)
- Specifications are described as a list of conformance criteria that will assure a new DS or DP will meet its intended purpose
- ICH Q6 aims to establish a set of global specifications for DS and finished products (DP)
- Common tests are physicochemical properties, particle size, test for chirality and polymorphic forms

## OBJECTIVES

- To increase the knowledge space for the newly formed benzoate and maleate salts
- Generate preliminary data that are critical for the quality attributes of the new salts

## METHODS

- Conducted preliminary small scale synthesis of bedaquiline benzoate and maleate salts
- Elucidated the powder structure of salts using X-ray diffractometry (XRD) of powder crystals of the new salts
- Confirmed composition of bulk samples with powder XRD, solid state NMR and FT-IR
- Assessed chemical purity through melting point determination
- Conducted thermal analysis with TGA, DSC, and HSOM
- Determined hygroscopicity with water sorption experiments at 0% and 75% RH
- Assessed water content by Karl-Fischer titration
- Elucidated salts' morphology using stereo and polarized light microscopy
- Investigated chemical and physical stability of the new salts

## RESULTS

***Fig. 1 Structural elucidation of the new bedaquiline salts***
***a****: single crystal structure of bedaquiline benzoate. One fully occupied and one partially occupied water molecule are present in the lattice elucidated from X-ray diffractometry. The chemical formula is $C_{32}H_{32}BrN_2O_2 \cdot C_7H_5O_2 \cdot 1.166(H_2O)$; the molecular weight is 698.70 g/mol*
***b****: single crystal structure of bedaquiline maleate, as a 0.5 hydrate elucidated from X-ray diffractometry. The chemical formula is $C_{32}H_{32}BrN_2O_2 \cdot C_4H_3O_4 \cdot 0.476(H_2O)$; the molecular weight is 680.17 g/mol*

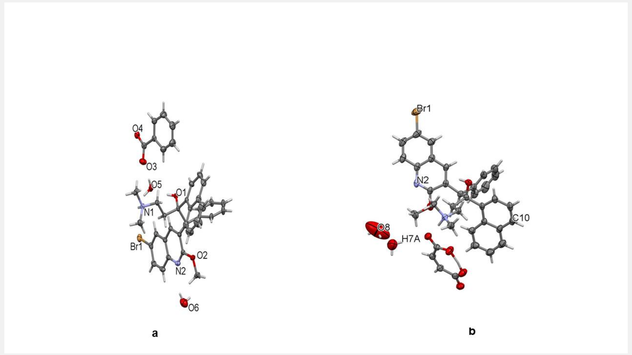



***Fig. 2 Spectral confirmation for structural composition of the new bedaquiline salts***
***a****: Rietveld Refinement of powder X-ray diffractogram of bedaquiline benzoate matched the fingerprint pattern obtained from the single crystal structure of the salt.*
***b****: Rietveld Refinement of powder X-ray diffractogram of bedaquiline maleate matched the fingerprint pattern obtained from the single crystal structure of the salt.*

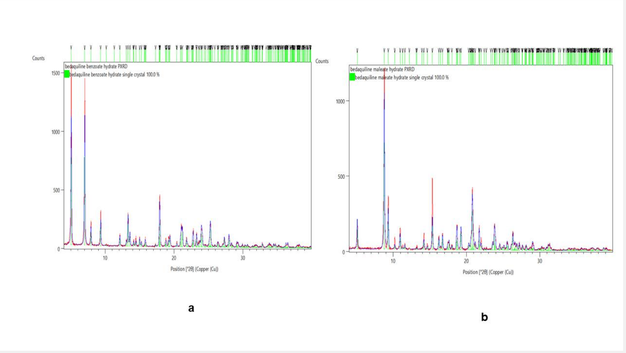



***Fig. 3 Differential Scanning Calorimetry for the new bedaquiline salts***
***a****: Endothermic maxima at 109.33 ℃ and 124.73 ℃ corresponding to solvent evaporation and melt of bedaquiline benzoate salt prepared from acetonitrile. Value is close to melting range of 128 ± 1 ℃, obtained for the benzoate salt.*
***b****: Melting endotherm maximum from bedaquiline maleate salt at 142.6 ℃ prepared from slow evaporation from THF. Value is close to melting range, 143 ± 1 ℃, obtained for the maleate salt.*

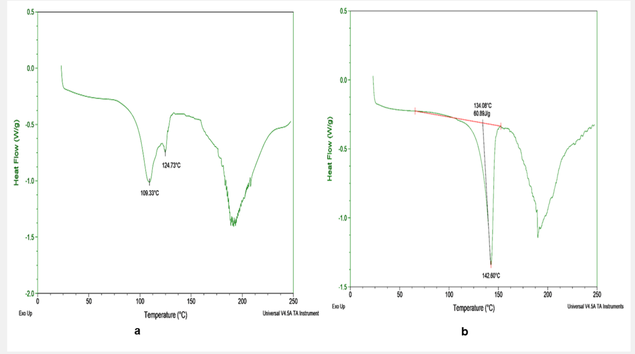



***Fig. 4 Thermogravimetric Analysis (TGA) for the new bedaquiline salts***
***a****: TGA for bedaquiline benzoate; salt lost ~ 0.30mg weight when sample was heated up to 140ºC. Moisture loss was close to the salt's water content, 3.33%, obtained from Karl Fischer determination.*
***b****: TGA for bedaquiline maleate; salt lost ~ 0.030mg weight when sample was heated up to 140ºC. Moisture loss was close to the salt's water content, 2.94%, obtained from Karl Fischer determination*

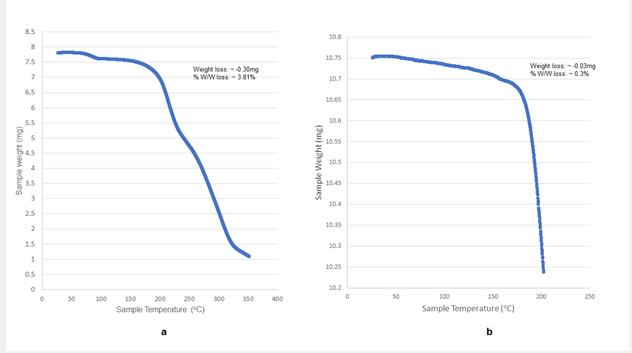
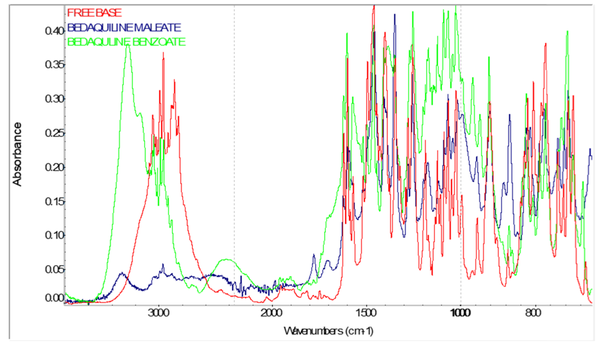



***Fig. 5 Fourier Transform Infra-Red (FT-IR) spectroscopy confirmed formation of the new bedaquiline salts***
*Reflection/absorption infrared spectra of free base (red) and bedaquiline benzoate (green) and ATR infrared spectrum of bedaquiline maleate (blue)*




## CONCLUSIONS

1. Data generated serve as preliminary specifications for controlling quality for the benzoate and maleate salts of bedaquiline
2. Preliminary results suggest promising data for moving the newly formed bedaquiline benzoate and maleate salts into pharmacokinetic studies in animal models.

## REFERENCES


1. Okezue M, Smith D, Zeller M, Byrn SR, Smith P, Bogdanowich-Knipp S, Purcell DK, Clase KL. Crystal structures of salts of bedaquiline. *Acta Cryst.* C 2020, 76(11) 1010-1023.
2. Zeller M, Bogdanowich-Knipp S, Smith P, Purcell DK, Okezue M, Smith DT, Byrn SR, Clase KL. Maleate salts of bedaquiline. *Acta Cryst.* E 2021, 77(4), 433-445.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