Thermal aerosolization of chloroquine and hydroxychloroquine and pharmacokinetic prediction of inhaled aerosols

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INTRODUCTION

Studies have suggested that antimalarial drugs chloroquine (CQ) and hydroxychloroquine (HCQ) are effective against SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) in vitro, and both drugs were initially recommended for therapeutic and prophylactic treatment of COVID-19. Previous research has demonstrated a narrow margin between the therapeutic and toxic doses of CQ and HCQ

OBJECTIVES

- Develop inhalable formulations of CQ and HCQ.
- Evaluate the efficiency and stability of thermal aerosols.
- To predict the pharmacokinetics of inhaled CQ and HCQ aerosols.

METHODS

Aerosol Generation

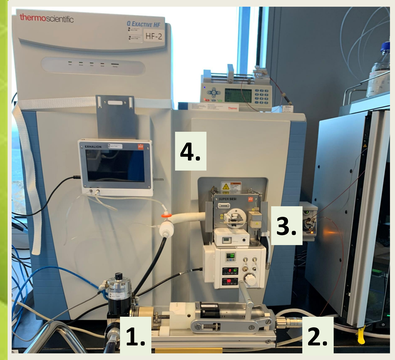
- The drugs were solubilized in propylene glycol and subjected to thermal aerosolization to generate an aerosol.
- The liquid formulation was evaporated by heating and subsequently cooled, which triggered nucleation and condensation processes that led to aerosol formation.
- The aerosol was generated and assessed by using a programmable dual syringe pump (PDSP) coupled to the aerosol generation device, which guaranteed active drawing of a specified volume of air.
- The chemicals were detected by using secondary electrospray ionization (SUPER SESI) interfaced with a Q Exactive HF mass spectrometer (high resolution MS).
- The drug delivery and stability of drugs (HCQ & CQ) were assessed by analyzing the chemicals present in the aerosol particles trapped on a Cambridge filter pad, using liquid chromatography (LC) coupled to MS (off-line LC-HR-MS measurements).

Physiologically Based Pharmacokinetics (PBPK) models

- A PBPK model for each compound was developed by incorporating respiratory tract physiology and lysosomal trapping parameters.

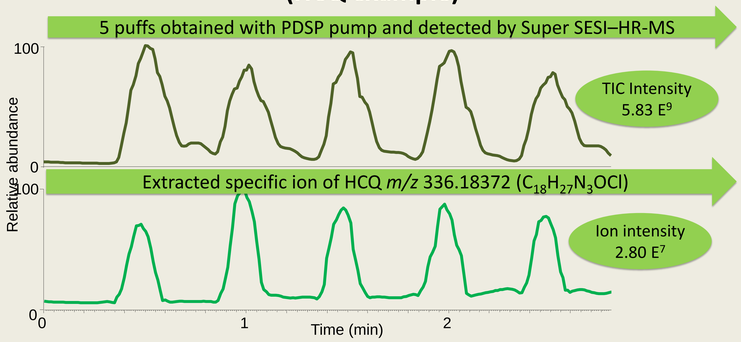
RESULTS

AEROSOL GENERATION

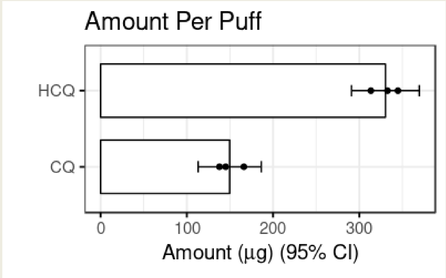


1. **Connection for device with drug formulation**
2. **PDSP pump generates the aerosol**
3. **Super SESI ionizes the compounds present in the aerosol**
4. **Q Exactive HF MS detects compounds in real time with high-resolution accurate-mass measurements**

AEROSOLIZATION CONFIRMED BY SUPER SESI–HR-MS (HCQ example)

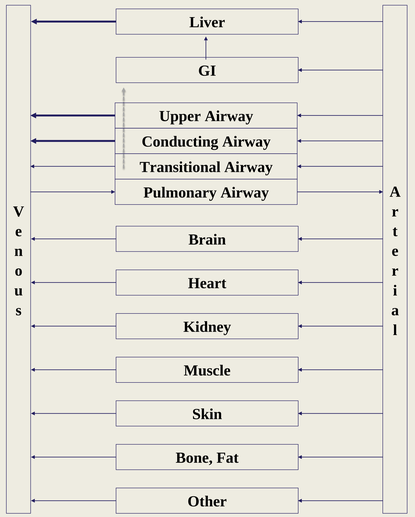


DRUG DELIVERY ASSESMENT

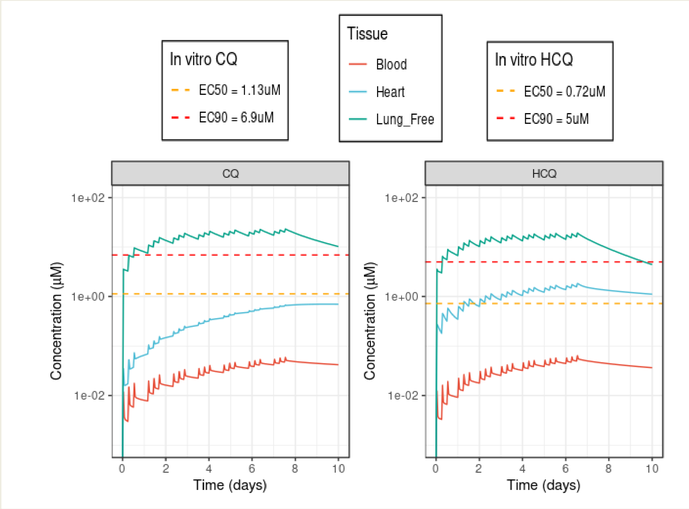


1. **Thermal aerosols were generated from 40 mg mL^{-1} CQ and 100 mg mL^{-1} HCQ liquid formulations.**
2. **149 µg (CQ) and 330 µg (HCQ) of the compounds were delivered per puff.**

PBPK MODEL



INHALATION DOSING REGIMEN



Conclusions

- ✓ Both CQ and HCQ solutions showed good potential for thermal aerosolization.
- ✓ No degradation products were observed.
- ✓ According to the prediction models, an inhalation dosing regimen of 20 puffs taken three times may yield therapeutically effective concentrations in the lungs.
- ✓ The developed protocol for thermal drug aerosolization could have potential applications in treatment of existing SARS-CoV-2 infection and/or as prophylactic treatment.

References

1. *"Pulmonary delivery of chloroquine and hydroxychloroquine aerosol to treat covid-19: in vitro experimentation to clinical dosing predictions"* A.R. Kolli, T. Zivkovic Semren, D. Bovard, S. Majeed, M. van der Toorn, S. Scheuner, P. Guy, A. Kuczaj, A. Mazurov, S. Frentzel, F. Martin, N. Ivanov, M. C. Peitsch, J. Hoeng. **2021**, *Submitted for peer-review publication*.
2. "Pharmaceutical formulation of chloroquine and its use" D. Bovard, S. Frentzel, P. Guy, J. Hoeng, A.R. Kolli, A. Kuczaj, S. Majeed, F. Martin, A. Mazurov, M.C. Peitsch, M. Van der Toorn, T. Zivkovic Semren **2020**, *IDF-02496*.
3. "Pharmaceutical formulation of hydroxychloroquine and its use" D. Bovard, S. Frentzel, P. Guy, J. Hoeng, A.R. Kolli, A. Kuczaj, S. Majeed, F. Martin, A. Mazurov, M.C. Peitsch, M. Van der Toorn, T. Zivkovic Semren **2020**, *IDF-02593*.