Case study with chloroquine and hydroxychloroquine by using a thermal aerosolization process coupled to SUPER SESI–HR-MS

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ABSTRACT

Introduction and Objectives

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in January 2020 as the cause of the SARS-like atypical pneumonia called coronavirus disease 2019 (COVID-19).
- Recent publications have brought attention to the possible benefit of chloroquine (CQ) and its analog hydroxychloroquine (HCQ) in treatment of patients infected by this coronavirus.
- Previous research has demonstrated a narrow margin between the therapeutic and toxic doses of CQ and HCQ.
- In this study, we investigated the feasibility of developing inhalable forms of the antiviral drugs CQ and HCQ.

Methods

- The drugs were solubilized in an appropriate carrier 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 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 (MS).
- Transfer rate was assessed from the analyses of the chemicals present in the aerosol trapped in a Cambridge filter pad, by using liquid chromatography (LC) coupled to accurate mass detection.

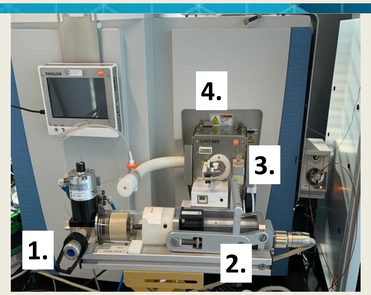
Conclusions

- ✓ Both CQ and HCQ solutions showed good potential for thermal aerosolization.
- ✓ These formulations are currently undergoing further improvements in parallel with transfer rate optimization related to thermal aerosol generation and gas/liquid phase partitioning.
- ✓ The developed methods and protocol for thermal drug aerosolization could have potential applications in treatment of infected people.

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. **2020**, *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*.

AEROSOL GENERATION

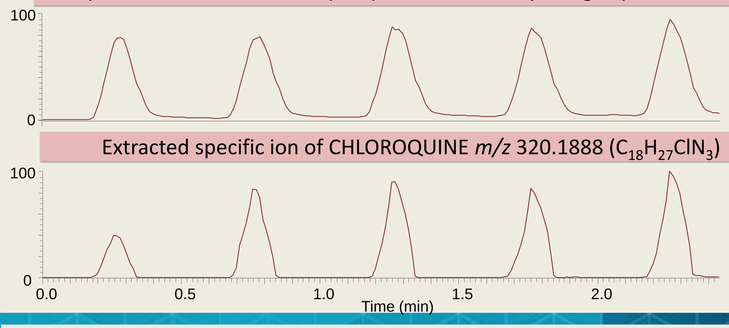


1. Connection for device with drug formulation.
2. PDSP pump generates the aerosol.
3. Super SESI ionizes the compounds present in the aerosol.
4. Q Exactive HF MS detects compounds in real time with high-resolution accurate-mass measurements.

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

Puff volume: 20 mL; **Interval between the puffs:** 30 s

5 puffs obtained with PDSP pump and detected by using Super SESI–HR-MS

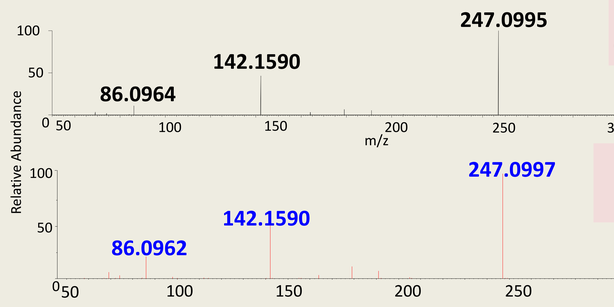


TIC Intensity
6.35 E^9

Extracted specific ion of CHLOROQUINE *m/z* 320.1888 ($C_{18}H_{27}ClN_3$)

Ion Intensity
1.04 E^7

PRESENCE OF DRUG CONFIRMED BY TANDEM MS (CQ example)



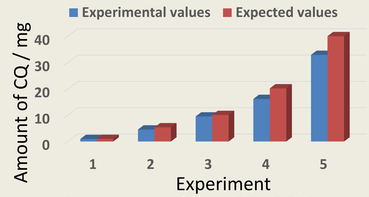
Experimental data
Fragmentation of *m/z* 320.2
With collision energy HCD @ 40

Mass spectral library reference (nist_msms) Chloroquine
$[M+H]^+$ HCD @ 32V P = 320.2

SOLUBILIZATION EFFICIENCY

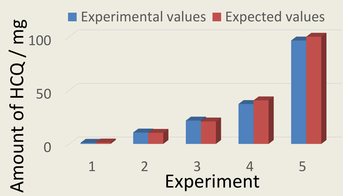
- The goal was to assess the possibility for increasing the drug concentration in the carrier before aerosolization
- 5 concentrations were evaluated:
  CQ: 1 - 5 - 10 - 20 - 40 mg/mL
  HCQ: 1 - 10 - 20 - 40 - 100 mg/mL
- Solubilized in 1 mL of an appropriate carrier (ultrasonic bath, 30–60°C)
- LC–HR-MS quantitative analysis of CQ/HCQ

CHLOROQUINE



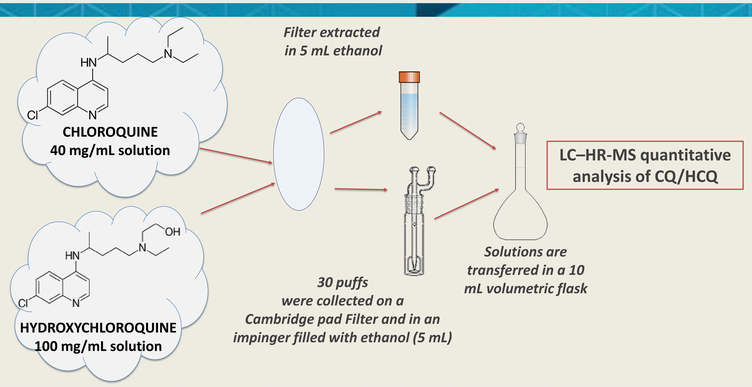
Accuracy values: 80–96%

HYDROXYCHLOROQUINE



Accuracy values: 78–104%

TRANSFER RATE ASSESSMENT



TRANSFER RATE RESULTS

CHLOROQUINE
78 ± 8 %

HYDROXYCHLOROQUINE
103 ± 5 %

Competing Financial Interest: The research described in this poster was sponsored by Philip Morris International