



## Data Article

# Data on chloroquine/hydroxychloroquine content in compounded oral suspension after filtration and centrifugation



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## ABSTRACT

The COVID-19 outbreak is spreading worldwide pushing the national healthcare systems to find effective protocols to prevent contagion and to reduce the patients' mortality and the severity of long-term effects. In the absence of authorised pharmacological treatments, chloroquine, and hydroxychloroquine, which are known as anti-malaria drugs, had been widely used off-label until concerns about their efficacy/safety limited their use to hospitalized patients affected by severe COVID-19. Regardless of their clinical use, their manipulation is necessary since the pure drug substance is not always promptly available and most of the drug products available on the market are tablets designed to be ingested; no liquid dosage forms are available. These are needed for children and the enteral nutrition of inpatients of intensive care units. Considering that both chloroquine and hydroxychloroquine are BCS class I, proper procedures for purifying the preparation from the insoluble excipients may be adopted to avoid clogging of a nasogastric tube and to reduce the drug content variability in the administered doses. The data in this article indicate that compounded oral suspensions containing chloroquine and hydroxychloroquine can

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be filtered and/or centrifuged without altering the drug assay of the preparation.

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## Specifications Table

Subject	Pharmacology, Toxicology and Pharmaceutical Science
Specific subject area	Pharmaceutical Science
Type of data	Table, Text
How data were acquired	High-pressure liquid chromatography (HPLC)
Data format	Raw and analysed
Parameters for data collection	Data on the drug assay of the compounded oral suspensions containing chloroquine and hydroxychloroquine before and after filtration and centrifugation
Description of data collection	The drug suspensions were prepared by manipulating chloroquine and hydroxychloroquine tablets. The impact of filtering and centrifuging was tested on three-vehicle suspensions. The samples were analysed by HPLC.
Data source location	Milan, Italy
Data accessibility	Data with the article. Raw data and chromatograms with supplementary materials

## Value of the data

- The data provide evidence on the impact of filtration or centrifugation on the assay of chloroquine and hydroxychloroquine suspension obtained by industrial tablet trituration followed by dispersion of the powder in different aqueous vehicles.
- The data can be useful for healthcare professionals to compound oral solution/suspension of highly water-soluble drug substance when an authorized solid dosage form is used as drug source or the commercial-available drug product has to be manipulated to meet clinical needs.
- The data are insights for further studies focused on the development of new dosage forms indicated for an inpatient with a nasogastric tube or paediatric patients

## 1. Data description

*Ad hoc* pharmaceutical dosage forms suitable for paediatric patients or non-cooperative patients with a nasogastric tube used for the administration of nutrients are often absent. This complicates the management of the therapy pushing the pharmacist to prepare a suitable drug product starting from the raw material or manipulating, after a risk assessment evaluation, other industrially-produced solid dosage forms such as tablet, capsules, pellets and granules [1]. In this case, the dosage form must be triturated, e.g. in a mortar, and the obtained powder dispersed in an appropriate vehicle. The final preparation can be a solution, if all components are soluble, or a suspension. In this second case, three different scenarios are possible: a) both drug and excipients are not enough soluble and remain suspended in the vehicle b) the drug is not soluble in the vehicle and remains suspended, whereas the excipients are solubilized; c) the drug is soluble, but the excipients do not remain suspended in the vehicle. For scenarios a) and b), the activities of the compounding pharmacist should include an in-depth assessment of the physico-chemical properties of both drug substance and excipients to select the most suitable vehicle for guaranteeing the physicochemical stability of the suspension and its re-suspendability over the time [2]. In the scenario c), the adoption of proper procedures for purifying the preparation from the insoluble excipients could be considered to avoid risks related to the clogging of the naso-

**Table 1**

Data on the assay of chloroquine extemporaneous suspensions after filtration. The extemporaneous suspensions were obtained dispersing the crushed tablets in different aqueous vehicles (i.e., purified water, CMC, FOSP). An aqueous solution made of the pure drug substance was used as a control. The data are expressed as a mean percentage and relative standard deviation (RSD%) of three batches of suspension.

Vehicle	Filter	Drug assay (%)		RSD (%)	
		4 mg/ml	25 mg/ml	4 mg/ml	25 mg/ml
Control	–	101.1	100.7	1.8	10.9
	0.2 $\mu\text{m}$ , NYL	104.2	102.1	4.6	1.5
	0.2 $\mu\text{m}$ , PES	101.4	99.6	1.7	1.3
	0.45 $\mu\text{m}$ , PP	101.2	100.2	1.0	0.9
	0.45 $\mu\text{m}$ , PTFE	101.5	99.7	3.1	0.9
Water	–	101.3	106.9	2.4	10.0
	0.2 $\mu\text{m}$ , NYL	99.9	101.2	1.5	3.4
	0.2 $\mu\text{m}$ , PES	100.4	102.1	2.1	3.4
	0.45 $\mu\text{m}$ , PP	100.0	100.9	0.6	2.5
	0.45 $\mu\text{m}$ , PTFE	100.0	99.3	0.7	0.3
CMC	–	108.0	114.0	7.3	6.4
	0.2 $\mu\text{m}$ , NYL	102.4	103.7	0.9	1.0
	0.2 $\mu\text{m}$ , PES	104.3	100.4	1.7	2.5
	0.45 $\mu\text{m}$ , PP	104.4	105.5	1.7	3.7
	0.45 $\mu\text{m}$ , PTFE	103.4	102.6	1.6	3.9
FOSP	–	97.7	103.7	2.1	7.1
	0.2 $\mu\text{m}$ , NYL	105.4	103.3	2.4	5.8
	0.2 $\mu\text{m}$ , PES	100.4	97.9	2.9	2.7
	0.45 $\mu\text{m}$ , PP	99.7	99.0	3.9	2.2
	0.45 $\mu\text{m}$ , PTFE	99.4	102.3	2.7	3.1

gastric tube and consequently heterogeneity of the drug dose. However, filtration may affect the drug concentration due to retention of the drug by the filter if the compatibility between drug and filter membrane has not been previously verified. In the last months, chloroquine and hydroxychloroquine, which are authorised for malaria and certain autoimmune diseases, have been extensively used for the management of COVID-19. However, since concerns about efficacy/safety of antimalarials have been reported in the literature [3], the use of hydroxychloroquine has been advised against, limiting the use in hospitalized patients affected by severe COVID-19 [4].

In the absence of industrially-produced liquid dosage forms, the commercial tablets have been ground to allow the administration to non-cooperative patients. Both drugs are classified in BCS Class I (i.e. water-soluble and well-absorbed). Thus, they appear as an interesting case to evaluate the advantages/disadvantages of clarification after aqueous dispersion of the triturated tablets.

Herein, the impact of filtration and centrifugation on the drug assay of oral chloroquine/hydroxychloroquine suspensions obtained by tablet manipulation is presented. The impact of filtration was investigated on filters which are like those commonly used in the compounding laboratories and as in-line filters for volumetric pump devices by using suspensions of different concentrations and aqueous vehicles. The centrifugation was applied as a method for purifying the preparation from insoluble excipients only if difficulties in filtering were observed during the experiments. The physicochemical stability of the suspensions overtime was not investigated since the existing literature suggested that both drugs are stable in aqueous systems for months [5].

Tables 1 and 2 reported the data on assays of both chloroquine and hydroxychloroquine before and after filtration with syringe filters made with a different pore size (i.e., 0.2, 0.45  $\mu\text{m}$ ) and membrane material. Data were obtained by using membranes made of nylon (NYL), polyether-sulfone (PES), polypropylene (PP), polytetrafluoroethylene (PTFE).

The data show that none of the tested filters affects the assay of both drugs, which remain within the  $\pm 10\%$  range of the declared one as prescribed by both USP and Ph. Eur. [6,7]. No significant differences are observable among the different vehicles or in comparison to the con-

**Table 2**

Data on the assay of hydroxychloroquine extemporaneous suspensions after filtration. The extemporaneous suspensions were obtained dispersing the crushed tablets in different aqueous vehicles (i.e., purified water, CMC, FOSP). Drug solution in water was used as a control. The data are expressed as a mean percentage and relative standard deviation (RSD%) of three batches of suspension.

Vehicle	Filter	Drug assay (%)		RSD (%)	
		4 mg/ml	25 mg/ml	4 mg/ml	25 mg/ml
Control	–	99.6	99.4	3.2	3.5
	0.2 µm, NYL	102.5	98.6	2.8	1.8
	0.2 µm, PES	104.0	97.0	3.2	2.9
	0.45 µm, PP	101.5	98.8	1.3	2.5
	0.45 µm, PTFE	106.1	97.9	2.2	5.1
Water	–	104.8	112.2	3.0	14.3
	0.2 µm, NYL	101.4	98.1	2.4	5.4
	0.2 µm, PES	102.1	99.4	3.7	2.7
	0.45 µm, PP	101.3	98.6	2.9	7.2
	0.45 µm, PTFE	101.1	95.4	2.8	7.2
CMC	–	100.5	100.5	7.4	13.9
	0.2 µm, NYL	104.2	101.4	1.2	9.4
	0.2 µm, PES	103.2	102.3	1.4	5.0
	0.45 µm, PP	101.4	99.1	3.5	8.1
	0.45 µm, PTFE	101.5	98.2	2.7	5.2
FOSP	–	99.9	96.4	0.5	4.2
	0.2 µm, NYL	97.8	94.3	2.9	6.6
	0.2 µm, PES	102.5	96.1	2.0	5.7
	0.45 µm, PP	99.5	96.7	3.6	1.2
	0.45 µm, PTFE	96.6	103.2	5.8	8.9

**Table 3**

Data on the assay of chloroquine, and hydroxychloroquine extemporaneous suspensions (25 mg/ml) after weak centrifugation (3000 rpm, 25 °C, 5 min). The extemporaneous suspensions were obtained dispersing the crushed tablets in different aqueous vehicles (i.e., purified water, CMC, FOSP). The data are expressed as a mean percentage and relative standard deviation (RSD%) of three batches of suspension.

Vehicle	Drug assay (%)		RSD (%)	
	Chloroquine	Hydroxychloroquine	Chloroquine	Hydroxychloroquine
Water	101.8	102.8	5.0	3.3
CMC	102.0	98.6	3.2	5.3
FOSP	103.6	98.7	3.9	3.8

control solution. However, it is noteworthy that the most significant deviations and inter-sample variability from the expected assay were observable for no filtered suspensions, suggesting that filtration may improve the reproducibility of the preparation dosing at the patient's bedside. Moreover, the experimental data seemed to suggest good compatibility between the drug substances and the membrane filters.

However, the experimental evidence suggested that 25 mg/ml suspensions were more difficult in filtering than 4 mg/ml ones with a higher risk of filter clogging. For high-concentration suspensions, centrifugation can be an alternative method for eliminating the inactive suspended particulates. Table 3 reported the data on assays of both chloroquine and hydroxychloroquine after weak centrifugation. As reported, the drug assay in the supernatant was within specification for both drugs, regardless of the vehicle viscosity.

## 2. Experimental design, materials, and methods

### 2.1. Materials

Clorochina Bayer (Bayer AG, I). 250 mg chloroquine bisphosphate. Excipients: corn starch, talc, magnesium stearate, hypromellose, macrogol 400, titanium dioxide [8].

Plaquenil (Sanofi S.p.A., I). 200 mg hydroxychloroquine sulphate. Excipients: lactose monohydrate, povidone, corn starch, magnesium stearate, Opadry OY-L-28900 (hypromellose, macrogol 400, titanium dioxide, lactose monohydrate) [8].

Syringe filters with 0.2  $\mu\text{m}$  nylon (NYL) membrane, 0.2  $\mu\text{m}$  polyethersulfone (PES) membrane, 0.45  $\mu\text{m}$  polypropylene (PP) membrane, and 0.45  $\mu\text{m}$  polytetrafluoroethylene (PTFE) membrane were purchased by VWR International (I). Sodium carboxymethyl cellulose (CMC), trisodium citrate dihydrate, citric acid, and Fast Oral Solution Puccini (FOSP) were purchased by Farmalabor (I). All other chemicals/solvents used in the study were analytical grade and used without further purification.

### 2.2. Suspension preparation

A known number of tablets containing chloroquine or hydroxychloroquine were crushed in a mortar to obtain a fine and homogenous powder. The crushing procedures were carried out under hood by operators suitably equipped with proper personal protective equipment to avoid health risks associated with drug exposure. Then, the powder was precisely weighed to obtain suspension of 4 and 25 mg/ml when dispersed in 50 ml of one of the three vehicles selected, namely: purified water, 1% w/v CMC solution in pH 4.2 citrate buffer and FOSP. The preparations were mechanically mixed for 10 min at least to reach a homogenous whitish suspension. The obtained suspension was then stored in well-closed and light-resistant containers until use. The data resulted from the preparation of three suspension batches for each concentration.

### 2.3. Purification of the preparation

The drug-loaded suspensions obtained using both drug substance and manipulated tablets were purified by filtration and/or centrifugation to eliminate the precipitated insoluble materials.

#### 2.3.1. Filtration

Aliquots of the 4 and 25 mg/ml suspensions and control solutions were filtered by using four syringe filters, which differed by the membrane material and pore size (0.2, 0.45  $\mu\text{m}$ ). The filtrates were diluted with purified water (1:4 v/v for 4 mg/ml; 1:25 v/v for 25 mg/ml), mixed by vortex and then analysed in HPLC.

#### 2.3.2. Centrifugation

Aliquots of the 25 mg/ml suspensions were centrifuged at 3000 rpm, 25 °C for 5 min. The supernatant was then diluted with purified water (1:4 v/v for 4 mg/ml; 1:25 v/v for 25 mg/ml), mixed by vortex and then analysed in HPLC.

### 2.4. HPLC method

#### 2.4.1. Chloroquine

The drug quantification was performed using the analytical method described by Coelho and co-workers [9]. Briefly, an Agilent 1100 HPLC system equipped with an autosampler, a quaternary pump with degasser, a thermostated column compartment set at 40 °C, and a diode array

**Table 4**

Chromatographic condition of hydroxychloroquine (Gradient).

Time (min)	Solvent A%	Solvent B%
0	90	10
2	90	10
5	80	20
5.1	90	10
10	90	10

detector set at 250 nm (Agilent, US). A reverse-phase column C18 was used as the stationary phase (InertClone ODS (3), 250 × 4,6 mm, 5 μm, Phenomenex, US). A combination of methanol and phosphate buffer at pH 3 (0.01 M) plus 0.5% w/v of triethanolamine (75:25) was used as the mobile phase. The flow rate was set at 1.0 mL/min. The injection volume was 10 μL. The drug concentration was determined from three standard calibration curves in the range of 0.1–1.6 mg/ml. Chromatograms and analyses' raw data are reported in Supplementary materials.

#### 2.4.2. Hydroxychloroquine

The HPLC method used was derived for a method recently published by USP [10]. The drug quantification in suspensions was determined using an Agilent 1100 HPLC system equipped with a diode array detector at 254 nm (Agilent, US). A reverse-phase column was used as the stationary phase (InertClone ODS (3) C18, 5 μm, 4.6 × 150 mm, Phenomenex, US). The analyses were performed in gradient conditions by using a combination of acetonitrile and HPLC-water plus H<sub>3</sub>PO<sub>4</sub> (1:400) at pH 3 as the mobile phase (Table 4). The flow rate was set at 1.0 mL/min. The injection volume was 5 μL, and the column temperature fixed at 40 °C. The drug concentration was determined from three standard calibration curves in the range of 0.1–1.25 mg/ml. Chromatograms and analyses' raw data are reported in Supplementary materials.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships which have, or could be perceived to have, influenced the work reported in this article.

#### Ethics Statement

The reported data resulted from tests neither on animal models nor with human volunteers.

#### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dib.2020.106116.

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