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Short Communication

Preparation and physicochemical stability of 50 mg/mL hydroxychloroquine oral suspension in SyrSpend® SF PH4 (dry)

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ABSTRACT

In the context of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, hydroxychloroquine has been proposed as a potential agent to treat patients with COVID-19 (coronavirus disease 2019) caused by SARS-CoV-2 infection. Older adults are more susceptible to COVID-19 and some patients may require admission to the intensive care unit, where oral drug administration of solid forms may be compromised in many COVID-19 patients. However, a liquid formulation of hydroxychloroquine is not commercially available. This study describes how to prepare a 50 mg/mL hydroxychloroquine oral suspension using hydroxychloroquine sulfate powder and SyrSpend® SF PH4 (dry) suspending vehicle. Moreover, a fully validated stability-indicating method has been developed to demonstrate the physicochemical stability of the compounded hydroxychloroquine oral suspension over 60 days under refrigeration (5 ± 3 °C). Finally, use of the proposed oral suspension provides a reliable solution to perform safe and accurate administration of hydroxychloroquine to patients with SARS-CoV-2 infection.

1. Introduction

Hydroxychloroquine, a derivative of chloroquine first synthesised in the 1950s, belongs to the group of antimalarial agents exhibiting therapeutic effects in other diseases besides malaria [1]. Both drugs are mainly used in the treatment of numerous rheumatic diseases, including systemic lupus erythematosus. Whilst hydroxychloroquine has a similar chemical structure and mechanisms of action, it has been shown to be much less toxic than chloroquine. Among its numerous therapeutic effects, hydroxychloroquine was found to be effective against some viral infections. Recently, in vitro evaluation of the antiviral effects of hydroxychloroquine showed that it can efficiently inhibit severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [2,3]. Starting in China in December 2019, the outbreak of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 (formerly 2019-nCoV) has become a pandemic, posing a serious threat to global public health. Therefore, several studies have proposed hydroxychloroquine as a potential agent to treat COVID-19, even though robust clinical data are still needed to support its efficacy [2,4–7]. Accordingly, several treatment strategies including hydroxychloroquine are being considered and evaluated in numerous clinical trials [8], and hydroxychloroquine has been included in some national guidelines for treating COVID-19 patients in certain situations [9–11].

To our knowledge, hydroxychloroquine is only available as 200 mg film-coated tablets. However, for many patients [seniors, those with difficulty swallowing, intensive care unit (ICU) patients] use of a liquid formulation is required, but no commercial liquid formulations of hydroxychloroquine are currently available. Only one paper reports the preparation of a liquid hydroxychloroquine formulation but at a strength not optimal to treat COVID-19 patients [12]. Therefore, the aim of this study was to evaluate the feasibility of compounding a 50 mg/mL hydroxychloroquine oral suspension and to demonstrate its physicochemical stability.

2. Materials and methods

2.1. Chemicals and reagents

SyrSpend® SF PH4 (dry) (batch no. 1742-B02-344675) was purchased from Fagron (France) and hydroxychloroquine sulfate pow-

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der (batch no. 1811P018) was from Inresa (France). Sterile water was purchased from Fresenius (Versylene®, France) and ammonium acetate was from Sigma-Aldrich (France). High-performance liquid chromatography (HPLC)-grade acetonitrile and methanol were purchased from Carlo Erba (France) and ultrapure water was provided using a Direct-Q UV3 water purification system (Millipore®, France).

2.2. Feasibility study

Oral liquid dosage forms were compounded by a pharmacist at a target concentration of 50 mg/mL. Since hydroxychloroquine sulfate is poorly soluble in water, use of a suspending vehicle was mandatory in order to prepare a liquid dosage form. Oral suspensions were prepared according to the following standard operating procedure. First, the exact amount of hydroxychloroquine sulfate powder was weighed in order to obtain the targeted concentration. Then, hydroxychloroquine sulfate powder was added to 13 g of SyrSpend® SF PH4 (dry) and was triturated in a mortar until homogeneity was achieved. Subsequently, sterile water was gently added while stirring continuously until reaching a final volume of 200 mL in a class A volumetric flask (200 ± 0.5 mL). Finally, the suspension was bottled in a 100 mL Amber type I glass container. The entire procedure was carried out in a clean area to limit microbiological contamination.

To verify that the formulations were providing correct dispersion of hydroxychloroquine sulfate powder in the suspending vehicle, the hydroxychloroquine strength in the compounded preparations was assessed. In this way, concentrations ($n = 3$) of three different batches were determined for the oral liquid dosage form, using HPLC coupled to ultraviolet spectrometry (HPLC-UV) methods as described below. Three oral suspension samples (1 mL), collected after shaking (30 s) to obtain uniform dispersion of the hydroxychloroquine sulfate powder, were diluted in water (1:10 v:v), centrifuged at 3500 × *g* for 10 min and the supernatants were then diluted in water (1:100 v:v) before injection onto the column. According to the US Pharmacopeia, dose content uniformity is verified if every compounded preparation contains no less than 90% and no more than 110% of theoretical strength [13].

2.3. Stability study

To investigate the physical and chemical stability of hydroxychloroquine oral suspension, three bottles from different batches of hydroxychloroquine suspension were stored throughout the study duration under controlled refrigeration (5 ± 3 °C) (temperature was monitored daily).

Hydroxychloroquine concentrations were determined at Days 0, 3, 7, 11, 14, 30 and 60 using the HPLC-UV methods described below. Three oral suspension samples (1 mL), collected after shaking (30 s) to obtain uniform dispersion of hydroxychloroquine sulfate powder, were diluted in water (1:10 v:v), centrifuged at 3500 × *g* for 10 min and the supernatants were then diluted in water (1:100 v:v) before injection onto the column.

According to the US Pharmacopeia, compounded preparations are considered to be stable if the drug concentration remains within 90–110% of the initial value (Day 0) [13].

In addition, physical appearance was investigated by visual inspection performed in a transparent glass vial to check the initial colour and opalescent aspect of the suspension.

2.4. Analytical method development and validation

A stability-indicating method, using isocratic HPLC-UV, has been developed, validated and performed to determine hydroxychloroquine concentrations. Separation was performed using a Purospher® 5 μm RP-18 end-capped column (150 × 4.6 mm; Merck). The mobile phase consisted of a mixture of 0.1 M ammonium acetate:acetonitrile:methanol (40:15:45 v:v:v) and the flow rate was set at 1 mL/min. The chromatographic system consisted of a Waters 1525® solvent delivery pump and a Waters 717® autosampler (set at 30 μL) connected to a Waters 2996® photodiode array detector (Waters, France). The wavelength of the detector was set at 340 nm. Chromatographic data were recorded and processed using Empower® software integrator. The system was operated at ambient temperature.

The stability-indicating capability of the method was evaluated by verifying that degradation products did not coelute with intact hydroxychloroquine. Hydroxychloroquine oral suspension was subjected to severe stress (heat, acidic and basic conditions, oxidation) in accordance with ICH Q1 (R2) international guidelines [14]. To ensure that no degradation products were coeluting with hydroxychloroquine, a photodiode array detector was used to obtain a three-dimensional (3D) chromatogram and to perform a peak purity check test. The 3D chromatograms obtained from stored suspensions were then compared with those obtained with initial extemporaneous suspensions.

Validation of the analytical method was performed in accordance with ICH Q2 R(1) international guidelines using the following criteria: linearity and accuracy (precision and trueness) and specificity of the method [14].

2.4.1. Calibration curve

A calibration method was performed to assess the hydroxychloroquine concentration in the compounding vehicles. An initial 100 μg/mL hydroxychloroquine solution was prepared in water. The latter was then diluted in water to obtain a six-point calibration curve (0, 6.25, 12.5, 25, 50 and 100 μg/mL). The calibration curve range was chosen according to the target concentration of hydroxychloroquine in diluted oral suspension set at 50 μg/mL. Calibration curves were generated by linear least-squares regression of the peak area versus hydroxychloroquine concentration profiles.

2.4.2. Linearity and matrix effect

Five calibration curves were prepared on five different days. Linearity was assessed through analysis of the coefficient of determination (r^2), *y*-intercept and slope of the linear regression line, and residual values (expressed as the percentage of the theoretical value).

Matrix effect was assessed by comparing calibration curves prepared in water versus calibration curves obtained using SyrSpend® SF PH4 (dry). Dilution was performed using water solution containing 0.1% of the suspending vehicle in order to mimic the exact composition of samples obtained after dilution of the oral suspensions before HPLC-UV analysis. The *y*-intercept and slope of linear regression lines were compared using Student's *t*-test ($\alpha = 0.05$) to assess the matrix effect.

2.4.3. Accuracy and limit of quantification

Accuracy was investigated by assessing precision and trueness of the method. Quality controls (QCs) were prepared in water at a level of 50 μg/mL according to diluted oral suspension concentrations. Precision was assessed through determination of the relative standard deviation (RSD) of the mean concentration determined for each QC, on the same day for repeatability ($n = 5$) and over 5 days for intermediate precision ($n = 15$). Trueness was assessed by determination of the percent recovery of the expected concentrations of QC used during the precision study. The limit of quantitation (LoQ) was calculated based on the standard deviation of the *y*-intercept and the slope in order to set the LoQ.

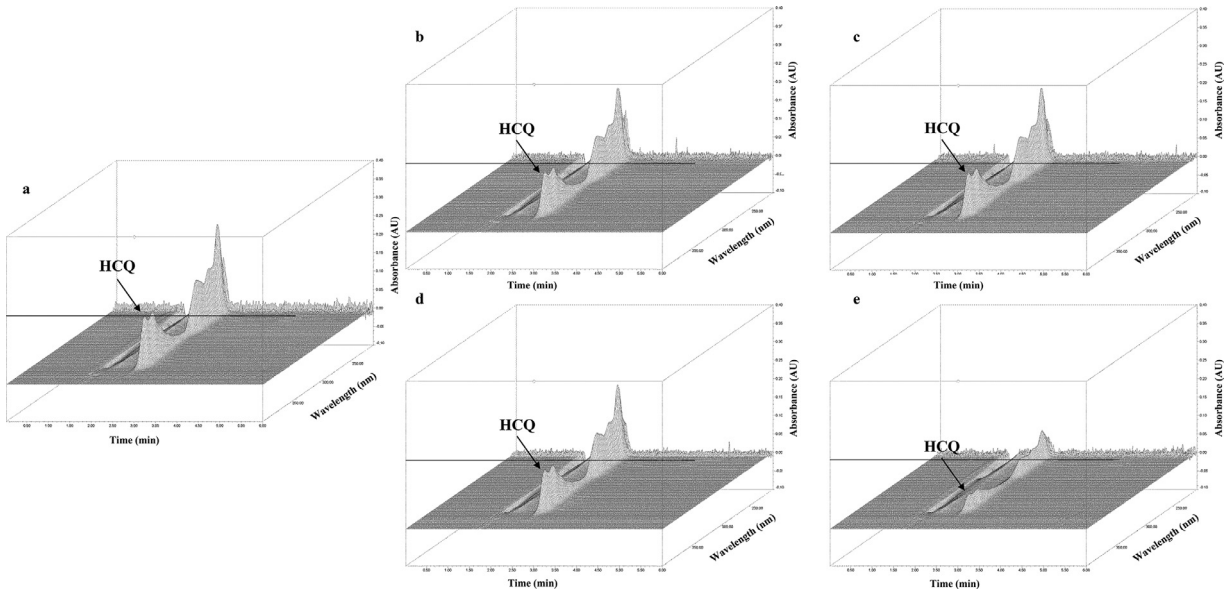

Fig. 1. Three-dimensional chromatograms obtained for hydroxychloroquine (HCQ) oral suspensions after applying different stress conditions: (a) no stress; (b) 0.75 M HCl for 5 min; (c) 0.5 M NaOH for 5 min; (d) 1% H_2O_2 for 2.5 h; and (e) 80 °C for 1.5 h. The dark line indicates the control absorbance at 340 nm.

3. Results

3.1. Method validation

Calibration curves obtained with water working solutions provided adequate linearity over the studied range since correlation coefficients were >0.9999 and residual values were <4% of the nominal value. The mean equation of the linear regression line was:

$$y = 57303(\pm 936)x + 18064(\pm 5234),$$

and correlation coefficients (r^2) of the linear regression line were equal to 0.99996 (± 0.00002), on average.

The slope and *y*-intercept values provided by calibration curves prepared in SyrSpend-SF PH4 (dry) (57284 ± 250 and 23297 ± 14377 for slope and *y*-intercept, respectively) were not statistically different from those provided by calibration curves obtained using water ($P = 0.97$ and $P = 0.52$ for slope and *y*-intercept, respectively). These results are in accordance with the absence of a matrix effect due to the suspending vehicle, which implies that calibration curves may be performed using hydroxychloroquine water solutions.

The analytical method was accurate as demonstrated by precision (repeatability and intermediate precision) and trueness studies. Indeed, RSD obtained at the QC level during repeatability and intermediate precision studies was equal to 4.5% and 2.9%, respectively. The mean percent recoveries obtained at the QC level during the trueness study were equal to 100.7% and 101.3% for repeatability and intermediate precision, respectively. The LoQ was equal to 0.91 mg/mL. However, to be more conservative, the LoQ was set as the lowest point of the calibration curve (6.25 μg/mL).

During the forced degradation study, no degradation products interfered with the hydroxychloroquine peak in terms of retention time and according to UV spectrum analysis and purity check test of the peaks (Fig. 1). Therefore, the method can be considered as a stability-indicating method according to international guidelines [14].

3.2. Feasibility and stability studies

Subsequent to preparation, the mean hydroxychloroquine concentration of the compounded oral suspensions was equal to 50.13 ± 0.69 mg/mL. Thereby, these results demonstrate reliability of the compounding and that no drug loss occurred during preparation.

Regarding chemical stability, no significant degradation of hydroxychloroquine occurred in the compounded oral suspensions (Fig. 2). Indeed, at Day 60 the mean percentage drug remaining was equal to 97.3 ± 1.3%, 98.4 ± 1.3% and 96.5 ± 0.4%, for oral suspension #1, #2 and #3, respectively. During the period of testing, the proportion of the initial hydroxychloroquine concentration remaining was >95%, meaning that oral suspensions were chemically stable up to at least 60 days under refrigerated storage (5 ± 3 °C). In addition, according to US Food and Drug Administration (FDA) guidelines [15], an estimated shelf-life of 100 days may be established since the earliest time at which the lower one-sided 95% confidence limit of the linear regression intersects the acceptance criterion of 90% at this time (Fig. 2). In accordance with this result, no degradation products were observed over the assessed period and, according to 3D chromatogram analysis and purity check test of the peaks, no degradation products were coeluting with hydroxychloroquine (Fig. 3). Moreover, for all samples the hydroxychloroquine concentration remained within 95–104% of the targeted strength, highlighting the fact that dose content remained uniform over time for all the compounded suspensions.

According to the physical stability study, no colour modification was observed and no precipitates or suspendability were retained over the storage period.

Overall, these results attest to the physical and chemical stability of the oral liquid dosage form stored at 5 ± 3 °C over ≥60 days.

4. Discussion

A liquid formulation of hydroxychloroquine is not commercially available and only one study by McHenry et al. reported the extemporaneous preparation of a liquid dosage form of hydroxychloroquine for oral use [12].

According to the doses proposed for COVID-19 patients (from 100 mg to 600 mg per dose), we chose to prepare oral liquid dosage forms at a target concentration (50 mg/mL) higher than

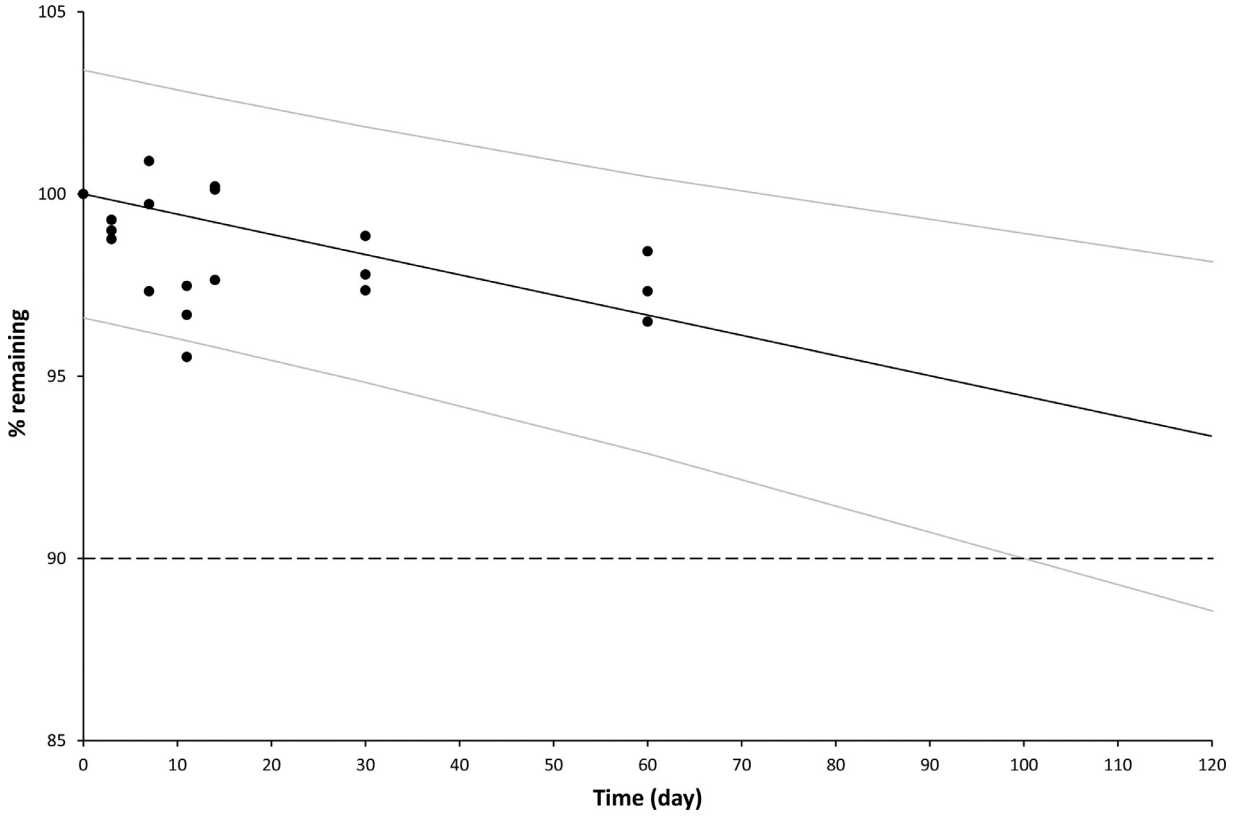

Fig. 2. Chemical stability of hydroxychloroquine in compounded oral suspensions stored at 5 ± 3 °C. The plots represent the mean percentage of drug remaining (n = 3) for each batch. The solid dark line represents the linear regression of the percentage drug remaining versus time profile (y = –0.0554x). The grey lines represent the 95% confidence limits for the linear regression. The dashed line represents the limit for the acceptance criterion of 90%.

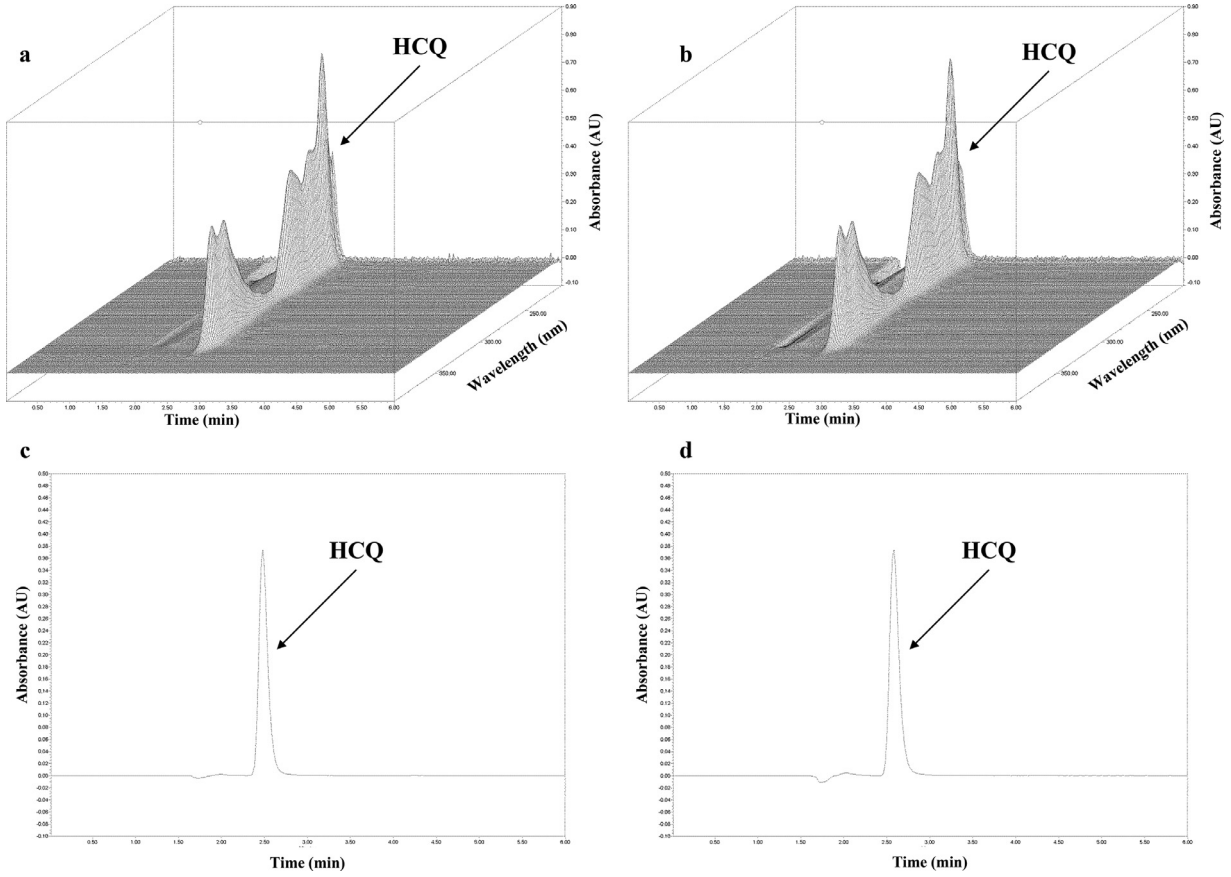

Fig. 3. (a,b) Three-dimensional chromatograms obtained for hydroxychloroquine (HCQ) oral suspension #2 at Day 0 (a) and Day 60 (b) and (c,d) two-dimensional chromatograms obtained at Day 0 (c) and Day 60 (d).

the formulations proposed by McHenry et al., thereby reducing by a factor of two the volume of administration required. Hydroxychloroquine is a hydrophobic compound, displaying poor solubility in water. Consequently, we had to compound the suspension in order to provide an oral liquid dosage form. One major disadvantage of the suspension dosage form is the risk of settling of drug particles, producing a non-homogeneous preparation leading to inaccuracy in dosage measurement. However, according to the feasibility study, dose content uniformity of the suspension was established since deviation of the concentration of the drug in the compounded preparations was never >5% of the expected drug strength. Thereby, these results demonstrate that the oral formulation compounded using SyrSpend® SF PH4 (dry) as a suspending vehicle provides a reliable dosage of hydroxychloroquine. Moreover, under our conditions, no significant degradation of hydroxychloroquine occurred in compounded oral suspensions. Indeed, during the period of testing, the proportion of the initial hydroxychloroquine concentration remaining was within the limit set by the US Pharmacopeia [13], meaning that hydroxychloroquine oral suspension was stable up to ≥60 days under refrigeration (5 ± 3 °C). In addition, an estimated shelf-life of 100 days may be proposed, supported by statistical analysis of the data. However, according to the manufacturer, the microbiological stability of oral suspensions compounded in SyrSpend® SF PH4 (dry) has been demonstrated under the same storage conditions and under the condition that the suspension is hygienically compounded and used for up to 60 days (statements provided by Fagron). Therefore, hydroxychloroquine oral suspension compounded in SyrSpend® SF PH4 (dry) can be assigned a maximum beyond-use date of 60 days. These results, the first to be obtained using a stability-indicating method, are in accordance with the durations of the different treatment strategies reported in the literature.

SyrSpend® SF PH4 (dry), a powder ensuring correct drug suspension and designed to prepare an oral liquid dosage form, was chosen since this marketed product is formulated mostly with starch, which is considered as an inert excipient. In contrast to many other vehicles, it does not contain any potentially harmful excipients such as alcohol, propylene glycol or benzoic acid, which render other formulations unsuitable for many patients. Thereby, the compounded oral suspension is particularly suitable for children requiring hydroxychloroquine administration. In addition, SyrSpend® SF PH4 (dry) does not contain any divalent cations, such as calcium or magnesium, which may interfere with the absorption of hydroxychloroquine and reduce its effectiveness [16]. Moreover, the low osmolality (<100 mOsm/kg; data not shown) displayed by our compounded liquid formulation of hydroxychloroquine minimises the risk of gastrointestinal side effects.

Older adults are more susceptible to COVID-19 and some patients may require admission to the ICU [17], where oral drug administration of solid forms may be compromised in many COVID-19 patients. In case of lack of a commercially available liquid formulation, crushing the solid oral form is a common practice to facilitate easier medication administration [18]. However, drug loss is frequently observed when tablets are crushed [19]. In addition, drug administration via enteral feeding tubes may be necessary for COVID-19 patients. Once again, crushed tablets may result in clogged tubing, leading to increased adverse events and decreased medication efficacy [20].

Finally, in contrast to commercially available tablets, the liquid formulation of hydroxychloroquine compounded by our team is suitable to perform personalisation of an optimal dosing regimen, particularly in view of reaching appropriate target blood levels in COVID-19 patients [21].

In light of all this, the compounded oral liquid formulation proposed in this study provides an appropriate and easy to use dosage form for oral hydroxychloroquine treatment, enabling safe and accurate hydroxychloroquine dose administration to patients with SARS-CoV-2 infection.

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