



HAL
open science

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

Guillaume Binson, Nicolas Venisse, Alexis Sauvaget, Astrid Bacle, Pauline Lazaro, Antoine Dupuis

► To cite this version:

Guillaume Binson, Nicolas Venisse, Alexis Sauvaget, Astrid Bacle, Pauline Lazaro, et al.. Preparation and physicochemical stability of 50 mg/mL hydroxychloroquine oral suspension in SyrSpend() SF PH4 (dry). *International Journal of Antimicrobial Agents*, 2020, 56 (6), pp.106201. 10.1016/j.ijantimicag.2020.106201 . hal-03003546

HAL Id: hal-03003546

<https://hal.science/hal-03003546>

Submitted on 19 Nov 2020

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Highlights

- Hydroxychloroquine has been proposed as a potential agent to treat COVID-19 patients
- Oral drug administration of solid forms may be comprised in many patients
- Liquid formulation of hydroxychloroquine is not commercially available
- Compounded hydroxychloroquine oral suspension is stable over 60 days

Journal Pre-proof

Preparation and physicochemical stability of 50 mg/ml hydroxychloroquine oral suspension in Syrspond pH4 dry

Guillaume Binson^{1,2}, Nicolas Venisse^{2,3}, Alexis Sauvaget^{1,2}, Astrid Baclé⁴, Pauline Lazaro¹,
Antoine Dupuis^{1,2*}

¹University Hospital of Poitiers, Pharmacy department, 2 rue de la milétrie, 86021 Poitiers,
France

²CIC Inserm 1402, HEDEX Group, 2 rue de la milétrie, 86021 Poitiers, France

School of Medicine and Pharmacy, University of Poitiers, Poitiers, France

³University Hospital of Poitiers, Pharmacokinetics department, 2 rue de la milétrie, 86021
Poitiers, France

⁴Univ Rennes, Inserm, EHESP, Irset (Institut de recherche en santé, environnement et
travail) - UMR_S 1085, 2 Avenue du Pr Léon Bernard, 35043 Rennes, France; Pôle
Pharmacie, Centre Hospitalier Universitaire, 2 rue Henri Le Guilloux, 35033 Rennes, France.

*Corresponding author. Tel: +33 5 49 43 37 68; fax: +33 5 49 45.39 72

E-mail address: a.dupuis@chu-poitiers.fr

Abstract

In the context of the SARS-CoV-2 pandemic, hydroxychloroquine has been proposed as a potential agent to treat COVID-19 patients. Older adults are more susceptible to COVID-19 and some patients may require admission in intensive care units, where oral drug administration of solid forms may be compromised in many COVID-19 patients. However, 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 dry pH4® 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 ($5 \pm 3^{\circ}\text{C}$). 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.

Keywords: hydroxychloroquine; oral suspension; SARS-CoV-2 infection; stability-indicating assay

1. Introduction

Hydroxychloroquine, a derivative of chloroquine first synthesized 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. While hydroxychloroquine has 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 effect of hydroxychloroquine showed that it can efficiently inhibit SARS-CoV-2 infection [2,3]. Starting in China in December 2019, the outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2/2019-nCoV) has become a pandemic, posing a serious threat to global public health. Therefore several publications 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 in certain situations [9–11].

To our knowledge hydroxychloroquine is only available as 200 mg film-coated tablets. However, for many patients (seniors, difficulty swallowing, intensive care unit), the use of a liquid formulation is required but no commercially 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 number: 1742-B02-344675) was purchased from Fagron (France), and hydroxychloroquine sulfate powder (batch number: 1811P018) from Inresa (France). Sterile water was purchased from Fresenius (Versylene®, France) and ammonium acetate from Sigma-Aldrich (France). 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. The 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 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, in order to limit microbiological contamination.

In order to verify that the formulations were providing correct dispersion of hydroxychloroquine sulfate powder in the suspending vehicle, hydroxychloroquine strengths in the compounded preparations were assessed. In this way, concentrations ($n=3$) of three different batches were determined for the oral liquid dosage form, using high performance

liquid chromatography coupled to ultraviolet spectrometry (HPLC-UV) methods described below. One milliliter oral suspension samples (n=3), collected after shaking (30 s) in order 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 supernatants were then diluted in water (1:100, v:v) before injection onto the column. According to the United States Pharmacopoeia, 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

In order to investigate the physical and chemical stability of hydroxychloroquine oral suspension, three bottles from different batches of hydroxychloroquine suspensions 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. One milliliter oral suspension samples (n=3), collected after shaking (30 s) in order 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 Pharmacopoeia, 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, in order to check the initial color and opalescent aspect of the suspension.

2.4. Analytical method development and validation

A stability-indicating method, using isocratic high performance liquid chromatography coupled to u.v. spectrometry (HPLC-UV), has been developed, validated and performed to

determine hydroxychloroquine concentrations. Separation was performed using a Purospher[®] 5 µm RP-18 endcapped column (150 x 4.6 mm, Merck). The mobile phase consisted of a mixture of 0.1M 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). 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.

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 (3-D) chromatogram and to perform a peak purity check test. The 3-D chromatograms obtained from stored suspensions were then compared to 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 hydroxychloroquine concentration in the compounding vehicles. Initial 100 µg/mL hydroxychloroquine solution was prepared in water. This 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 the 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 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 a Student t test ($\alpha = 0.05$) to assess matrix effect.

2.4.3. Accuracy and limit of quantification

Accuracy was investigated by assessing precision and trueness of the method. Quality controls (QC) were prepared in water at a level of 50 $\mu\text{g/mL}$, 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 five days for intermediate precision ($n=15$). Trueness was assessed by determination of the percent recovery of the expected concentrations of QC used during precision study. Quantitation limit was calculated based on the standard deviation of the y-intercept and the slope in order to set the limit of quantification.

3. Results

3.1. Method validation

Calibration curves obtained with water working solutions provided adequate linearity over the studied range since correlation coefficients were greater than 0.9999 and residual values were lower than 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 matrix effect due to the suspending vehicles, 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, relative standard deviation obtained at the quality control level during repeatability and intermediate precision studies were equal to 4.5% and 2.9%, respectively. The mean percent recoveries obtained at the quality control level during the trueness study were equal to 100.7% and 101.3% for repeatability and intermediate precision, respectively. The quantitation limit was equal to 0.91 mg/mL. However, to be more conservative, the limit of quantification was set as the lowest point of the calibration curve (6.25 mg/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 the 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 higher than 95%, meaning that oral suspensions were chemically stable up to at least 60 days under refrigerated storage (5 ± 3 °C). In addition, according to FDA guidelines [15], an estimated shelf life of 100 days may be established since the earliest time at which the lower one-sided 95 percent 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 3-D chromatogram analysis and purity check test of the peaks, no degradation products were coeluting with hydroxychloroquine (Fig. 3). Moreover, for all samples, hydroxychloroquine concentration remained within 95 to 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 color 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 at least 60 days.

4- Discussion

Liquid formulation of hydroxychloroquine is not commercially available and only one paper from 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 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 suspension in order to provide an oral liquid dosage form. One major disadvantage of suspension dosage form is the risk of the settling of drug particles, producing 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 higher than 5% of expected drug strength. Thereby, these results demonstrate that the oral formulation compounded using Syrspend® SF PH4 Dry as a suspending vehicle provides 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 U.S. Pharmacopeia [13], meaning that hydroxychloroquine oral suspension was stable up to at least 60 days under refrigeration ($5 \pm 3^{\circ}\text{C}$). 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 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 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 in intensive care units [17], where oral drug administration of solid forms may be compromised in many COVID-19 patients. In case of lack of 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 with commercially available tablets, the liquid formulation of hydroxychloroquine compounded by our team is suitable to perform personalization of an optimal dosing regimen, particularly in view of reaching appropriate target blood level 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.

Journal Pre-proof

Acknowledgment

We wish to thank Jeffrey Arsham, an American scientific translator, for his highly helpful reading of our original text.

Declarations

Funding: This work was supported by internal funding.

Competing Interests: All authors report no potential conflicts of interest.

Ethical Approval: Not required.

References

- [1] Ben-Zvi I, Kivity S, Langevitz P, Shoenfeld Y. Hydroxychloroquine: From Malaria to Autoimmunity. *Clin Rev Allergy Immunol* 2012;42:145–53. <https://doi.org/10.1007/s12016-010-8243-x>.
- [2] Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis Off Publ Infect Dis Soc Am* 2020. <https://doi.org/10.1093/cid/ciaa237>.
- [3] Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov* 2020;6. <https://doi.org/10.1038/s41421-020-0156-0>.
- [4] Zhou D, Dai S-M, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. *J Antimicrob Chemother* 2020:dkaa114. <https://doi.org/10.1093/jac/dkaa114>.
- [5] Garcia-Cremades M, Solans BP, Hughes E, Ernest JP, Wallender E, Aweeka F, et al. Optimizing hydroxychloroquine dosing for patients with COVID-19: An integrative modeling approach for effective drug repurposing. *Clin Pharmacol Ther* 2020. <https://doi.org/10.1002/cpt.1856>.
- [6] Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020:105949. <https://doi.org/10.1016/j.ijantimicag.2020.105949>.
- [7] Gautret P, Lagier J-C, Parola P, Hoang VT, Meddeb L, Sevestre J, et al. Clinical and microbiological effect of a combination of hydroxychloroquine and azithromycin in 80 COVID-19 patients with at least a six-day follow up: A pilot observational study. *Travel Med Infect Dis* 2020:101663. <https://doi.org/10.1016/j.tmaid.2020.101663>.
- [8] Zhai P, Ding Y, Wu X, Long J, Zhong Y, Li Y. The epidemiology, diagnosis and treatment of COVID-19. *Int J Antimicrob Agents* 2020. <https://doi.org/10.1016/j.ijantimicag.2020.105955>.

- [9] Nicastrì E, Petrosillo N, Bartoli TA, Lepore L, Mondì A, Palmieri F, et al. National Institute for the Infectious Diseases “L. Spallanzani”, IRCCS. Recommendations for COVID-19 clinical management. *Infect Dis Rep* 2020;12. <https://doi.org/10.4081/idr.2020.8543>.
- [10] Avis relatif aux recommandations thérapeutiques dans la prise en charge du COVID-19 (complémentaire à l'avis du 5 mars 2020) n.d.:23. [https://www.hcsp.fr/Explore.cgi/Telecharger?NomFichier=hcspa20200323_coronsarscov_recomthrap.pdf.]
- [11] Hinton DM. Food and Drug Administration. FDA Emergency use authorization (EUA) of chloroquine and hydroxychloroquine. 28 Mar 2020. [<https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>]
- [12] McHenry AR, Wempe MF, Rice PJ. Stability of Extemporaneously Prepared Hydroxychloroquine Sulfate 25-mg/mL Suspensions in Plastic Bottles and Syringes. *Int J Pharm Compd* 2017;21:251–4.
- [13] Allen, L.V., Jr.; Bassani, G.S.; Elder, E.J.; Parr, A.F. Strength and Stability Testing for Compounded Preparations. *US Pharmacop.* 2014, pp. 1–7. [<https://www.usp.org/sites/default/files/usp/document/FAQs/strength-stability-testing-compounded-preparations.pdf>]
- [14] Abraham, J. International Conference on Harmonisation of Technical Requirements For Registration of Pharmaceuticals for Human Use. In *Handbook of Transnational Economic Governance Regimes*; Brouder, A., Tietje, C., Eds.; Brill: Leiden, The Netherlands, 2009; pp. 1041–1054. ISBN 978-90-04-16330-0.
- [15] Guidance for industry #219 (VICH GL51) Statistical Evaluation of Stability Data. US Food Drug Adm 2019. [<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-219-vich-gl51-statistical-evaluation-stability-data>]
- [16] McElnay JC, Mukhtar HA, D'Arcy PF, Temple DJ, Collier PS. The effect of magnesium trisilicate and kaolin on the in vivo absorption of chloroquine. *J Trop Med Hyg* 1982;85:159–63.
- [17] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA* 2020;323:1061. <https://doi.org/10.1001/jama.2020.1585>.
- [18] Bourdenet G, Giraud S, Artur M, Dutertre S, Dufour M, Lefèbvre-Caussin M, et al. Impact of recommendations on crushing medications in geriatrics: from prescription to administration. *Fundam Clin Pharmacol* 2015;29:316–20. <https://doi.org/10.1111/fcp.12116>.
- [19] Stubbs J, Haw C, Dickens G. Dose form modification – a common but potentially hazardous practice. A literature review and study of medication administration to older psychiatric inpatients. *Int Psychogeriatr* 2008;20:616–27. <https://doi.org/10.1017/S1041610207006047>.
- [20] Matysiak-Luśnia K, Lysenko Ł. Drug administration via enteral feeding tubes in intensive therapy - terra incognita? *Anaesthesiol Intensive Ther* 2014;46:307–11. <https://doi.org/10.5603/AIT.2014.0050>.
- [21] Perinel S, Launay M, Botelho-Nevers É, Diconne É, Louf-Durier A, Lachand R, et al. Towards Optimization of Hydroxychloroquine Dosing in Intensive Care Unit COVID-19 Patients. *Clin Infect Dis* 2020:ciaa394. <https://doi.org/10.1093/cid/ciaa394>.

Figure captions

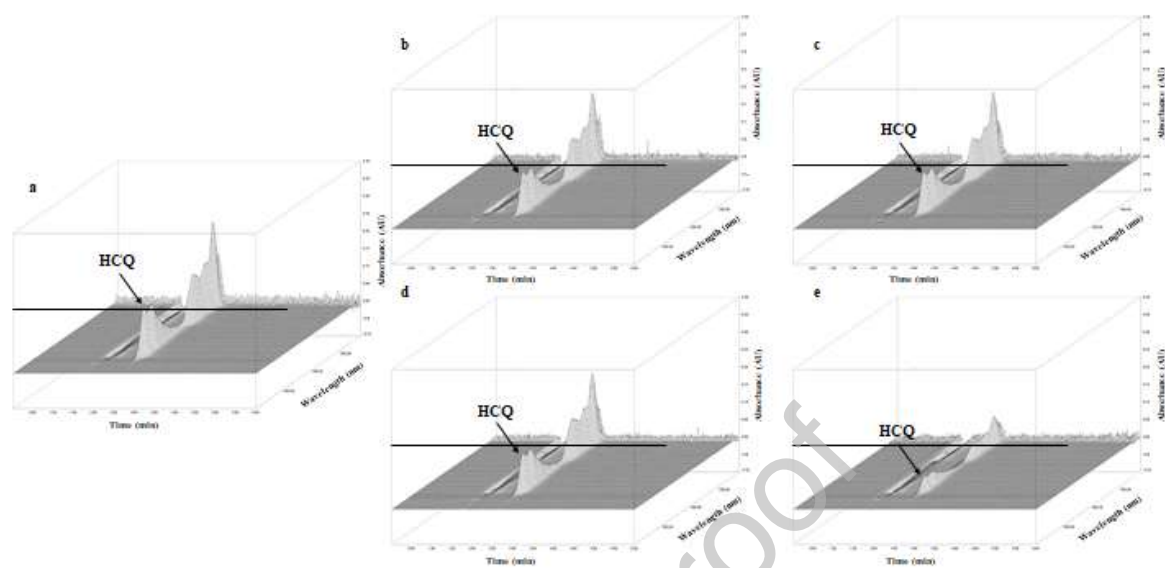


Fig. 1. Three-dimensional chromatograms obtained for hydroxychloroquine (HCQ) oral suspensions after applying different stress conditions: no stress(a), HCl 0.75 M for 5 min (b), NaOH 0.5 M for 5 min (c), H₂O₂ 1% for 2.5 h (d) and 80°C for 1.5 h (e). Dark line indicates the control absorbance at 340 nm.

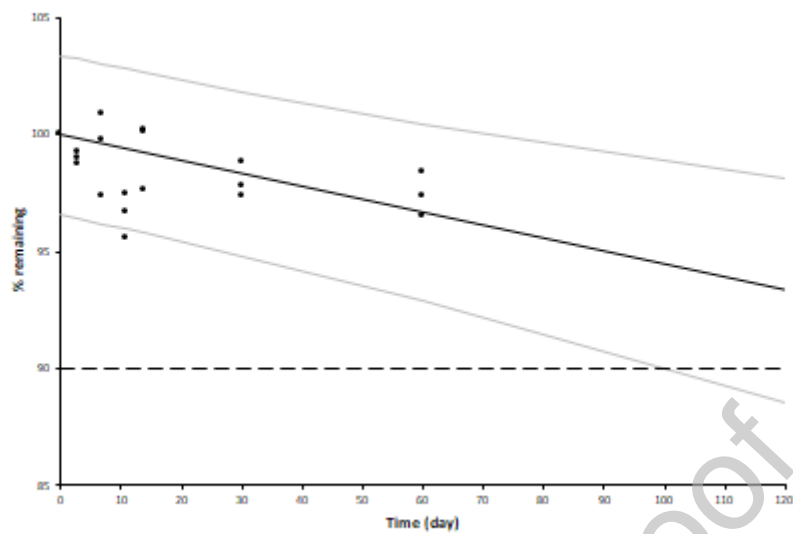


Fig. 2 . Chemical stability of hydroxychloroquine in compounded oral suspensions stored at 5 ± 3 °C. The plots represent the mean percentage drug remaining ($n=3$) for each batch. The solid dark line represents the linear regression of the percentage drug remaining versus time profile ($y = -0.0554x$).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

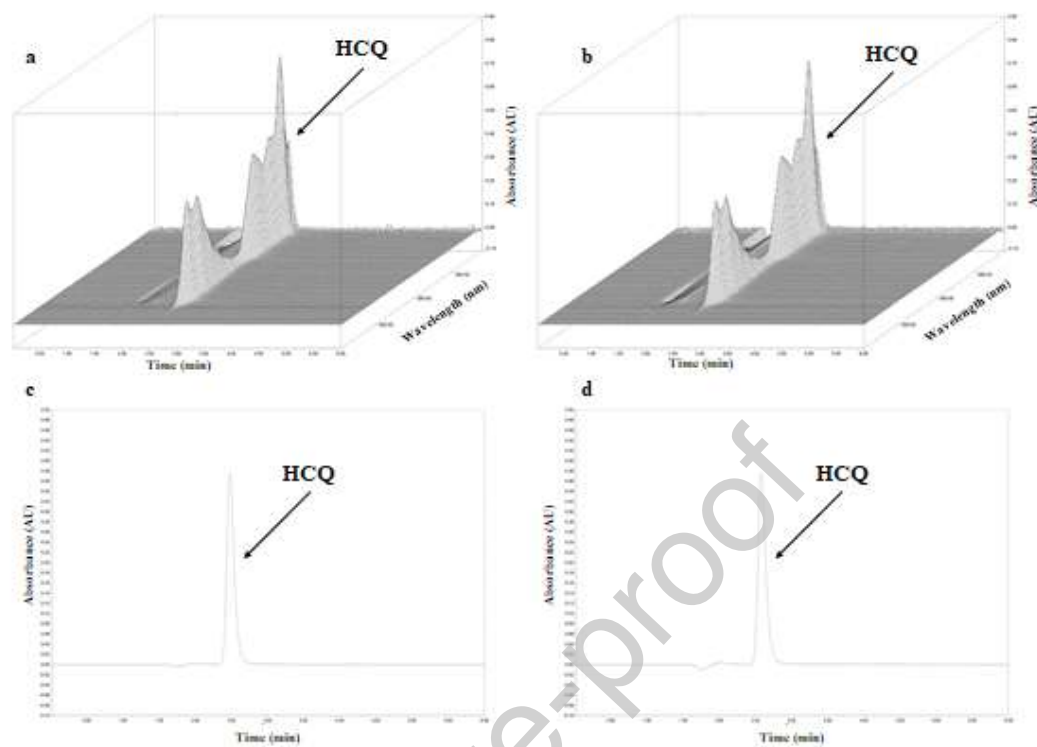


Fig. 3. Three-dimensional chromatograms obtained for hydroxychloroquine (HCQ) oral suspension #2 at day 0 (a) and at day 60 (b) and two-dimensional chromatograms obtained at day 0 (c) and at day 60 (d).