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Composition analysis of falsified chloroquine phosphate samples seized during the COVID-19 pandemic



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ABSTRACT

The proliferation of falsified medicines can cause serious public health issues, particularly in the context of a global pandemic such as the actual COVID-19 pandemic. Our study involved eight chloroquine phosphate medicines seized in Cameroon, Democratic Republic of Congo and Niger during March and May 2020. These suspect samples were first analyzed in a screening phase using field tools such as handheld Raman spectroscopy (TruScan) and then in a confirmation phase using laboratory tools such as hyper-spectral Raman imaging and High Performance Liquid Chromatography (HPLC). The results confirmed the falsified nature of the samples, highlighting the presence of metronidazole at low dose in four samples (16.6, 15.2, 15.2 and 14.5 mg/tab), too low levels of chloroquine in two samples (2.4 and 20.2 mg/tab), and substitution of chloroquine phosphate by paracetamol in one sample (255.7 mg/tab). The results also confirmed that four samples had been adulterated with paracetamol in trace amounts and two of them presented traces of chloramphenicol.

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1. Introduction

On 31 December 2019, a new coronavirus disease emerged from China and gradually spread, becoming a global pandemic. Thus, on 30 January 2020, the World Health Organization (WHO) announced a state of public health emergency of international scope. Today, more than 45 million people have already been infected by this disease [1–4].

The world is currently facing many challenges arising from this pandemic. Beyond the non-negligible economic consequences affecting governments and international trade in general, there are problems related to access and supply of high quality essential medicines and health products. Taking advantage of this opportunity, unscrupulous people are selling substandard and falsified medicines. According to some experts, this phenomenon constitutes a risk of a parallel pandemic to the COVID-19 pandemic [5–9].

Substandard and falsified medicines have a negative impact not only in terms of public health, but also in socio-economic terms [5,10,11]. Aware of these risks, international organizations such as the WHO and the European Medicines Agency (EMA) have drawn the attention of consumers, professionals and health authorities to the emergence of substandard or falsified vaccines, medicines, as well as falsified screening tests and laboratory reagents claiming to have COVID-19 disease prevention, detection and treatment properties [12,13].

Falsifiers who are indeed criminal gangs are always on the lookout for such situations that could provide them large profit margins no matter the impact on human lives. They take advantage of the scarcity of medicines and health products to infiltrate both the formal and informal markets [11].

Thus, a few time after the very controversial announcement of the treatment of COVID-19 disease with chloroquine phosphate and hydroxychloroquine sulfate [14,15], WHO has brought to the public's attention cases of falsified chloroquine in Burkina Faso, Cameroon, Niger, Democratic Republic of Congo (DRC) and France, thanks to the effectiveness of its Global Surveillance and Monitoring System (GSMS). A previous publication, at the origin of the WHO alert, showed about five falsified tableted chloroquine samples

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collected in Cameroon and DRC using thin layer chromatography (GPHF Minilab) as a screening method [16–18].

After the alert launched by the WHO, the Pharmaceutical Analytical Chemistry laboratory of the University of Liege was contacted in the frame of its WHO prequalification to carry out tests on seized samples of chloroquine medicines suspected of being falsified.

In the 1950s, resistance to this long-used molecule against malaria was observed in most areas of high malaria endemicity, leading to a change in treatment [19,20]. Among the phenomena increasing this resistance, falsification plays a non-negligible role. Indeed, it has been observed in Cameroon a phenomenon of resistance that was supposedly linked to falsified chloroquine tablets [21]. Several studies have highlighted the presence of poor-quality chloroquine on the African pharmaceutical market [22–25].

In recent years, special attention has been paid to vibrational spectroscopy methods (mainly Raman and near infrared spectroscopies) for the detection of falsified medicines. They have many advantages compared to conventional methods used to control the quality of medicines because of their non-destructive nature (no sample preparation is required), absence of consumable (no use of solvents) and speed [26,27]. Time is indeed an important factor in the detection of falsified medicines to reduce its impact on the population [28]. However, once confirmed falsified, further laboratory analyses must be undertaken to measure the risk to which the population is exposed.

Our study is focused on eight suspect samples: four from Yaoundé and Douala in Cameroon, one from Kinshasa in DRC, and three from Niamey in Niger. These suspect chloroquine samples were seized by local authorities as being part of the WHO alert list.

For the analysis of these suspect samples, we have adopted an analysis strategy based on two types of methods: screening phase using handheld Raman spectrophotometer and a confirmatory analysis to obtain information on the qualitative composition of both organic and inorganic chemicals of the seized samples [29,30]. HPLC–UV was used to obtain quantitative information of the identified active pharmaceutical ingredients and a screening LC–MS method was used to confirm the hyperspectral imaging results.

2. Material and methods

2.1. Samples

The suspect chloroquine samples were all in tablets dosage form. They are described in Table 1. Some samples were contained in blisters, some in boxes and some were unpackaged. The samples, once seized, were sent by courier service to the author's laboratory. Once received, they were stored at room temperature before analysis.

2.2. Data acquisition

2.2.1. Handheld Raman spectroscopy

Handheld Raman analyses were performed using a TruScan RM spectrophotometer (Thermo Scientific, USA). The acquisition parameters were automatically selected by the device. When available, ten tablets were analyzed per sample. Otherwise, all tablets were analyzed.

The tablets were scanned directly either through the blister (when samples were inside a blister, samples F–G) or out of the blister (when samples were without blisters, samples A–E). Spectra were preprocessed by the Savitzky–Golay first derivative (window size: 15, polynomial order 2) before comparison with the database over the spectral range 463–1853 cm^{-1} using the Pearson's correlation coefficient. The database used throughout the study for

Table 1
Description of samples.

Country and city of origin	N° of samples	Stated product name	Dosage	Stated manufacturer	Batch N°	Manufacturing date	Expiring date	Type of facility found in	Collected by	Date of collection
Cameroon, Douala	A	Chloroquine phosphate tablets USP	100mg	Laboratoire Jiangsu Pharmaceutical INC. China	660	May-17	May-21	General Hospital of Douala	LANACOME	MARCH 2020
Cameroon, Yaoundé	B	Chloroquine phosphate tablets	250 mg	Astral pharmaceuticals	EBT 2512	Jan-19	Oct-22	Informal market	LANACOME	MARCH 2020
	C	Chloroquine phosphate tablets USP	250 mg	Laboratoire Jiangsu Pharmaceutical INC. China	660	May-17	May-21	Informal market	LANACOME	MARCH 2020
DRC, Kinshasa	D	Chloroquine phosphate tablets USP	100mg	Laboratoire Jiangsu Pharmaceutical INC. China	660	Sep-18	Sep-22	Informal market	LANACOME	MARCH 2020
	E	Chloroquine phosphate	250 mg	Brown & Burk Pharmaceutical limited	655622	Nov-18	Nov-22	Charitable organization	Inspection Générale de la Santé (DRC) LANSPEX	MARCH 2020
Niger, Niamey	F	Samquine 100, chloroquine phosphate	100mg	-	NBJT 01	Nov-19	Oct-22	Informal market	LANSPEX	MAY 2020
	G	Chloroquine phosphate tablets B.P.	100mg	-	NBJT 02	Nov-19	Oct-22	Informal market	LANSPEX	MAY 2020
	H	Niruquine, Chloroquine phosphate tablets	100mg	-	Unreadable	Sep-19	Aug-22	Informal market	LANSPEX	MAY 2020

Raman spectra comparison (Truscan or Raman imaging spectra) is a homemade database containing 165 API and excipients.

2.2.2. Raman hyperspectral imaging

Before being analyzed by Raman imaging, tablets were glued on a microscope slide and their surface was milled using a Leica EM Rapid milling system equipped with a tungsten carbide miller (Leica Microsystems GmbH).

Raman hyperspectral imaging experiments were performed on a Labram HR Evolution (Horiba scientific) equipped with an EMCCD detector (1600 × 200-pixel sensor) (Andor Technology Ltd.), a Leica 50x Fluotar LWD objective and a 785 nm laser with a power of 45 mW at sample (XTRA II single frequency diode laser, Toptica Photonics AG).

A mapping of 150 × 150 pixels per sample was performed and the spectra were then analyzed by Multivariate Curve Resolution-Alternating Least Square (MCR-ALS) in order to find the pure spectra of the constituents as well as their spatial distribution. The Raman data were corrected by an Asymmetric Least Square baseline correction ($p: 1 \times 10^{-5}$, $\lambda: 3 \times 10^4$). The pre-processed data were first compared to the laboratory database.

Following the first comparison, the data were analyzed by MCR-ALS. Three MCR-ALS models were successively computed with 10, 30 and 50 components respectively. Non-negativity on concentration and spectra were used as constraints. The different resolved spectra were then preprocessed by the Savitzky-Golay first derivative (window size: 15, polynomial order 2) before comparison with the database over the spectral range 463–1853 cm^{-1} using the Pearson's correlation coefficient. A correlation coefficient of one corresponds to a perfect correlation. The identification of chloroquine phosphate was confirmed by a second comparison in the 810–1160 cm^{-1} spectral range. Indeed, chloroquine phosphate presented very good discrimination towards chloroquine sulfate (correlation coefficient of 0.30) and hydroxychloroquine sulfate (correlation coefficient of 0.17) in this spectral range (see Fig. S9). The total analysis time was about 16 h per sample.

Raman imaging was used to detect as much compounds as possible (both organic and inorganic) in order to obtain a composition of the sample as complete as possible.

2.2.3. HPLC

Assays were performed on a HPLC system comprising a Waters 2695 separation module coupled to a Waters 2996 photodiode array detector from Waters Corporation (Eschborn, Germany). The HPLC methods are detailed in Tables S1–S3 in Supplementary data. The double information of retention times and UV spectra of detected peaks allowed a formal identification of the active ingredients of the different samples compared to reference substances.

A screening confirmatory LC–MS analysis of the samples was performed. The LC–MS equipment was composed of a Dionex Ultimate 3000 (Thermo Scientific) with an MS detector Amazon Speed ETD (Bruker). The details of the LC–MS method are given in Table S4.

3. Results and discussion

3.1. Description of samples

Samples A, B, C and D from Cameroon and samples F, G and H from Niger correspond to the WHO 04/2020 alert samples from these two countries. The samples came from both the informal sector (B, C, D, F, G, H) and the formal sector (A and E). See photos in Supplementary data S1–S8.

Samples A, C and D have the same reported manufacturing laboratories and lot numbers as samples I, II, IV and V collected by Gnegel et al. [18]. Sample D in particular has the same information

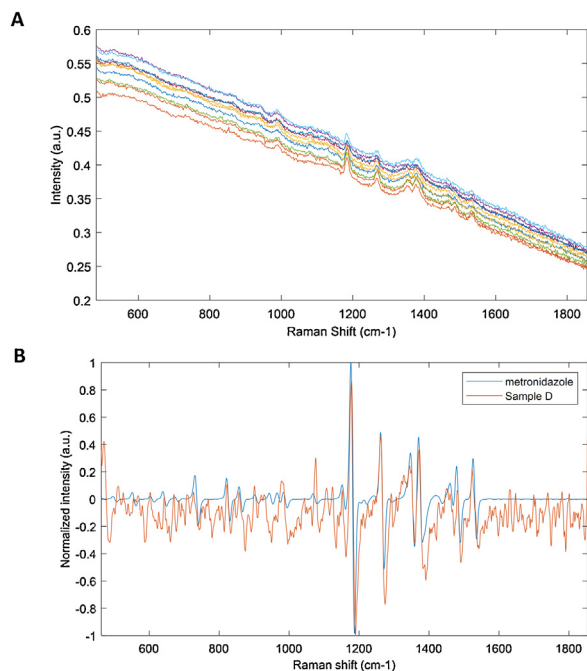


Fig. 1. A) Raw Raman spectra measured with the handheld Raman spectrometer on the ten intact tablets without blister of sample D. B) Preprocessed Raman spectrum of a typical tablet of sample D overlaid with metronidazole Raman spectrum from the database. The intensities were normalized to ease the visual comparison.

(manufacturer's laboratory, lot number, date of manufacture and expiry date) as sample V from Gnegel et al. [18], but with differences in the declared active ingredient content (100 and 250 mg respectively).

Not all samples from Niger included information on the manufacturing laboratories. For sample H, the secondary packaging did not have a lot number but the inscription \bar{S} on Blister. On the blisters, this information was not readable, thus highlighting the product traceability problem in medicines falsification.

As in the study by Gnegel et al. [18], these suspect samples came from both the formal and informal sectors.

3.2. Samples analysis

Considering the results in Table 2, in samples A, B, C and D from Cameroon, metronidazole and starch were identified as the major constituents with correlation coefficient > 0.5 (See Table S5 for detailed Truscan results). Figs. 1–3 show typical preprocessed Raman spectra of samples measured with the handheld device. The spectra were overlaid with reference Raman spectra of chemicals from the database. As one can see, handheld Raman spectra have a rather low signal to noise (SNR) ratio due to the high fluorescence background (see Fig. 1A). This low SNR implies that the detection of the pharmaceutical ingredient is sometimes difficult or may be hindered by a stronger signal by a main constituent. This finding may be seen in Table S5 when looking at the results obtained for different tablets of a sample. Nevertheless, this first screening step enabled the confirmation of falsification of samples A – E because of the presence of a wrong API. Samples F–H were considered as suspicious since the signal of chloroquine phosphate was very small or undetectable.

Raman imaging confirmed the presence of metronidazole in samples A–D together with excipients such as starch, magnesium stearate, calcium carbonate, talc, and calcium phosphate. In addition, sample B showed the presence of paracetamol and chloramphenicol and sample D contained paracetamol (see Table 2).

Table 2
Analysis results of the different techniques per sample.

Handheld Raman spectroscopy	Raman Imaging	LC-MS	LC-UV
metronidazole , starch metronidazole	metronidazole , starch, magnesium stearate metronidazole , paracetamol , chloramphenicol , starch, magnesium stearate, calcium phosphate	metronidazole metronidazole , chloramphenicol , paracetamol metronidazole	metronidazole 16.6 mg/tablet metronidazole 15.2 mg/tablet
metronidazole , starch metronidazole , starch paracetamol	metronidazole , starch, magnesium stearate, calcium phosphate, calcium carbonate metronidazole , paracetamol , starch, magnesium stearate paracetamol , sodium benzoate, microcrystalline cellulose, starch	metronidazole , paracetamol paracetamol , chloramphenicol , chloroquine , aspartame chloroquine	metronidazole 15.2 mg/tablet metronidazole 14.5 mg/tablet paracetamol 255.7 mg/tablet
starch	chloroquine phosphate , starch, calcium carbonate, magnesium stearate, talc, calcium phosphate	chloroquine	chloroquine 2.4 mg/tablet
starch	chloroquine phosphate , paracetamol , starch, calcium carbonate, magnesium stearate, talc, calcium phosphate	chloroquine	chloroquine 20.2 mg/tablet
chloroquine phosphate , calcium carbonate	chloroquine phosphate , starch, calcium carbonate, magnesium stearate, talc, sodium bicarbonate, titanium dioxide (rutile), sodium sulfate	chloroquine	chloroquine 99.2 mg/tablet paracetamol 0.2 mg/tablet

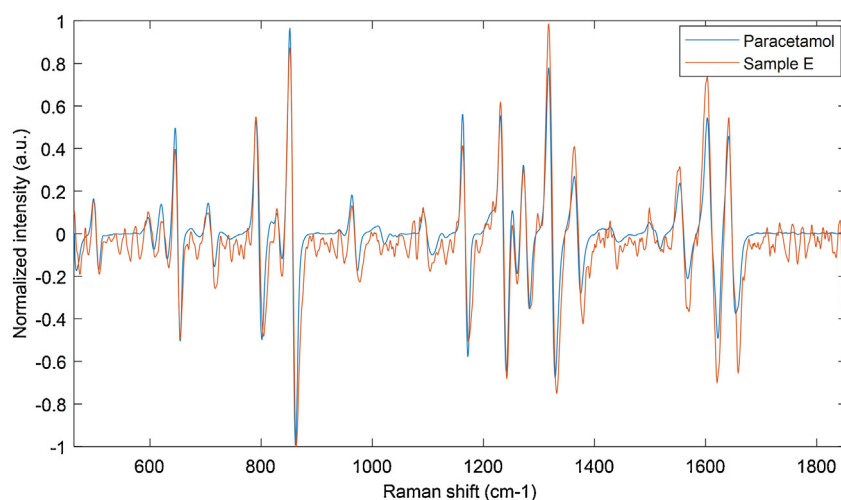


Fig. 2. Preprocessed Raman spectrum of a typical tablet of sample E overlaid with paracetamol Raman spectrum from the database. The intensities were normalized to ease the visual comparison.

Paracetamol and chloramphenicol were present at trace amount since they are present in a very few number of pixels of the chemical images (see Fig. 4A). HPLC-UV analysis quantified metronidazole levels of 16.6, 15.2, 15.2 and 14.5 mg per tablet in samples A, B, C and D respectively. No paracetamol was found in the HPLC-UV analysis of samples A–D. This might be explained by the very low amount of paracetamol together with the probable heterogeneity of samples. Indeed, this contamination possibly occurred during the production of the tablets highlighting the poor quality. Possibly not all tablets are contaminated.

The metronidazole contents of samples A, B, C and D from Cameroon are all close to the metronidazole contents obtained by Gnegel et al. [18] for samples IV and V also from Cameroon although the packaging is different. All these samples from Cameroon may possibly have the same source.

In sample E, handheld Raman spectroscopy identified paracetamol. Hyperspectral imaging confirmed this result with a correlation coefficient of 0.95. It also revealed the presence of excipients such as sodium benzoate and microcrystalline cellulose. HPLC assay confirmed these results with a paracetamol content of 255.72 mg per tablet. LC–MS also identified the presence of chloroquine (in trace amounts), chloramphenicol and aspartame. These compounds were not detected by Raman imaging possibly because of the high fluorescence background and high Raman scattering char-

acter of paracetamol possibly masking the signal of trace level API's [31]. However, the probable heterogeneity among tablets may also explain the discrepancies between the LC-UV, LC–MS and Raman experiments.

For samples F and G, the TruScan identified only starch. In sample H, the presence of calcium carbonate was detected. However, the presence of chloroquine may be confirmed when looking at the specific spectral range 1300 – 1800 cm^{-1} with an average correlation coefficient of 0.84 (see Fig. 3b and Table S5).

Raman imaging results showed the presence of chloroquine phosphate in samples F, G and H with correlation coefficients of 0.95, 0.98 and 0.99 respectively. The spectra were tested against chloroquine sulfate and hydroxychloroquine sulfate in the spectral range 810 – 1160 cm^{-1} to ensure the identification of chloroquine phosphate salt.

The fact that the handheld Raman spectrometer detected the presence of chloroquine only in sample H can be explained by the fact that in sample F and G, chloroquine phosphate was present only in small quantities with a content. Indeed, HPLC-UV estimated the contents at 2.4 mg and 20.2 mg per tablet respectively.

The presence of paracetamol in sample G was demonstrated by hyperspectral Raman imaging (see Fig. 4B), which was not the case by LC-UV or LC–MS. On the other hand, LC-UV results revealed the presence of paracetamol in sample H, which was not detected by

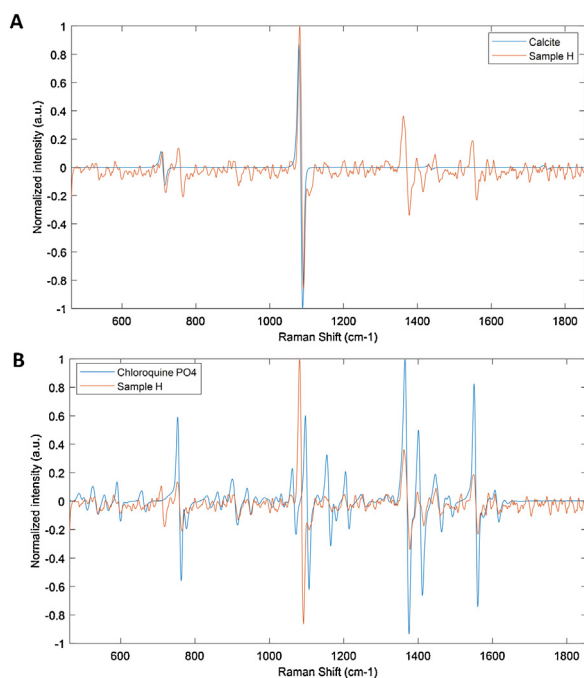


Fig. 3. A) Preprocessed Raman spectrum of a typical tablet of sample H overlaid with calcite Raman spectrum from the database. The intensities were normalized to ease the visual comparison. B) Preprocessed Raman spectrum of a typical tablet of sample H overlaid with chloroquine phosphate Raman spectrum from the database. The intensities were normalized to ease the visual comparison.

handheld Raman spectroscopy, hyperspectral Raman imaging or LC-MS demonstrating the heterogeneity of falsified samples.

Trace amounts of adulterating APIs in samples B, D, E G and H indicate contamination problems certainly resulting from the production of previous batches. This situation highlights the non-compliance with good manufacturing practices.

Metronidazole and paracetamol have certainly been used as a substitute for chloroquine as stated by Gnegel et al. to mimic its bitter taste [18]. Concerning sample E from DRC where chloroquine was substituted with paracetamol, the falsifiers certainly targeted its analgesic and antipyretic properties that could calm the pain

and fever that are part of the symptoms of COVID-19 disease and malaria.

Metronidazole levels are very low with amounts below 17 mg per tablet in samples A, B, C and D. Also in samples F and G, chloroquine levels are very low (2.4 mg and 20.2 mg per tablet respectively). These very low levels of active ingredients are prone to contribute to the emergence of antimalarial resistance problems [32].

Raman spectroscopy has been preferred to near-infrared spectroscopy because of the highly resolved spectra enabling a fast comparison with a pure compound spectral database [33–35]. In addition, Raman hyperspectral imaging has the advantage to give a deep insight in organic and inorganic compound composition of the tablets, making it possible to highlight the presence of substances likely to be toxic without a priori knowledge. However, this technique is long making it complicated to analyze several tablets per sample diminishing the representativity of the analysis. In addition, it suffers from the limitations of Raman spectroscopy such as fluorescence and low signal intensity possibly making difficult the analysis of some colored or degraded formulations.

4. Conclusion

Falsified samples of chloroquine phosphate seized by Cameroon, DRC and Niger during the COVID-19 pandemic were analyzed. In six samples, we noted the lack of chloroquine and its substitution by metronidazole (at sub-therapeutic levels) or paracetamol. In two samples, chloroquine phosphate was detected but at very low levels. In one sample, the chloroquine phosphate content was in conformity with the declared content. In addition to the major APIs present in the tablets, trace levels of paracetamol and chloramphenicol were detected in four and two samples respectively.

Non-compliance with good manufacturing practices and low levels of active ingredients reflect the desire from the falsifiers to make a profit without worrying about the unfortunate consequences that may happen to those who have consumed their product. This also demonstrates the speed with which falsifiers adapt their production to actual demand such as the chloroquine phosphate in the COVID-19 context. It appears that rather than producing new products with the correct API, falsifiers prefer to print new labels for their old bad quality products increasing their profits.

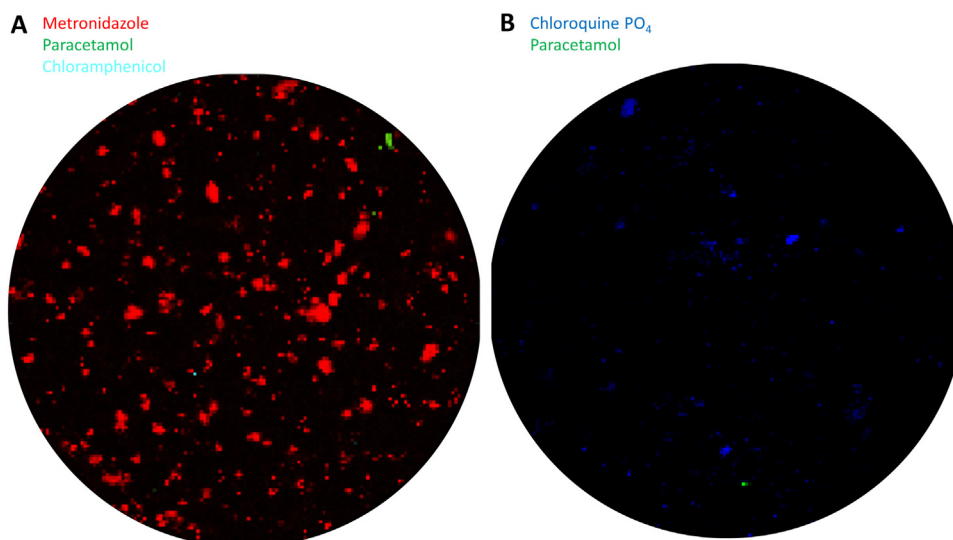


Fig. 4. A) Distribution map of metronidazole (red), chloramphenicol (cyan) and paracetamol (green) over a tablet of sample B. B) Distribution map of chloroquine phosphate (blue) and paracetamol (green) over a tablet of sample G.

In the frame of the COVID-19 pandemic, the need for specific products (allegedly treating the disease) may increase rapidly at a global scale. This constitute an opportunity for criminal groups and unscrupulous sellers to sell substandard and falsified medicines. In this context, the application of rapid, easy-to-use techniques such as Raman spectroscopy should make it possible to combat efficiently the resurgence of poor-quality medicines. However, handheld devices are not sensitive enough to detect trace level contaminants or low-dosed active ingredients. Therefore, hyperspectral imaging may help in this context providing also a "signature" of the product composition possibly allowing the grouping of falsification cases.

CRedit authorship contribution statement

C.A. Waffo Tchounga: Formal analysis, Investigation, Writing - original draft. **P.Y. Sacre:** Data curation, Formal analysis, Methodology, Investigation, Writing - review & editing. **P. Ciza:** Formal analysis, Investigation. **R. Ngono:** Resources. **E. Ziemons:** Resources, Supervision. **Ph. Hubert:** Resources, Project administration. **R.D. Marini:** Funding acquisition, Supervision, Project administration.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.jpba.2020.113761>.

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