

Application of vibrational spectroscopy and chemometrics to assess the quality of locally produced antimalarial medicines in the Democratic Republic of Congo.

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1. Introduction

In recent decades, more than 15% of antimalarials marketed in low- and middle-income countries were of poor quality, in which quinoline derivatives and quinine-based formulations represent 21%. These molecules are used for severe and/or cerebral malaria, as well as for falciparum-resistant malaria treatment [1,2]. This research work deals with the opportunity of using vibrational spectroscopy techniques combined with chemometrics for the quality control of local production of antimalarial drugs. Near Infrared (NIR) spectroscopy was chosen for its low-cost and rapid testing properties as well as the possibility to transfer calibrations to handheld devices to control medicines directly on field [3,4].

2. Objectives

The objective was to develop and validate PLS regression models using NIR spectroscopy data to replace the high solvent consuming techniques such as HPLC. Indeed, routine HPLC analyses are difficult to perform in low- and middle-income countries due to the supply and price of reagents and solvents.

Furthermore, liquid chromatography devices often suffer from technical issues needing specialized technicians. The driven idea for the development of the quantitative method was the ease of implementation and use by low skilled staff together with the possibility to analyze different formulations of quinine; whether it is sulphate or hydrochloride salts.

3. Material and Methods

- Instrumentation:

Table 1 : Characteristics of NIR spectrophotometers

Code name	Vibrational spectroscopy	Manufacturer	Model	spectral range measured (nm)	data points	Weight (kg)	price (k€)
NIR A	FT-NIR	Bruker Optics	MPA (internal transmission)	800 - 2500	2203	benchtop	~ 100
NIR B	dispersive NIR	Innospectra	NIR-M-T1	900-1700	256	0.14	~ 2

- Methodology:

Multivariate analysis methods based on NIR spectroscopy have been developed and validated for the quality control of quinine based formulations manufactured and marketed in the Democratic Republic of Congo (DRC).

The samples are prepared by dissolution in an aqueous HCl 1N solution that is a cheap and easily available medium in low- and middle-income countries.

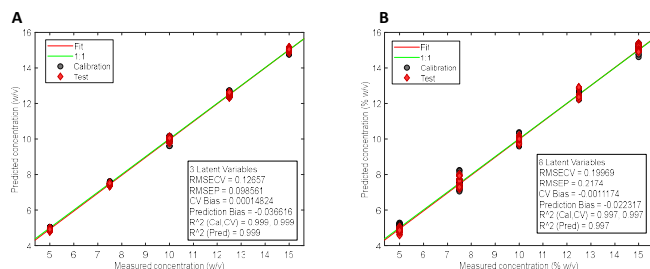
Calibration and validation samples were prepared by dissolving reference quinine sulfate and quinine hydrochloride in the presence of excipients using gravimetric data as reference. The final target concentration was 10 % w/v. Three series of validation were realized with five concentration levels. A background was measured between each series for the NIR A while the NIR B was shut down, restarted and warmed-up during 1 hour between each series.

After being validated, the method was used to analyze commercial quinine tablets and oral drops and intravenous solutions collected in the local market.

4. Results and discussion

Table 2. Figure of merits of PLS models.

	Included spectral range (cm ⁻¹)	Preprocessing
NIR A	[930-7500] [6200-5736]	SNV; Mean center
NIR B	[937-1584]	Savitzky-Golay 1st Derivative (order: 2; window: 17); SNV; Mean center



The developed method was successfully validated using the total error approach with acceptance limits of ± 10 %. The opportunity to use gravimetric data as reference allowed obtaining quantitative performances comparable to HPLC methods.

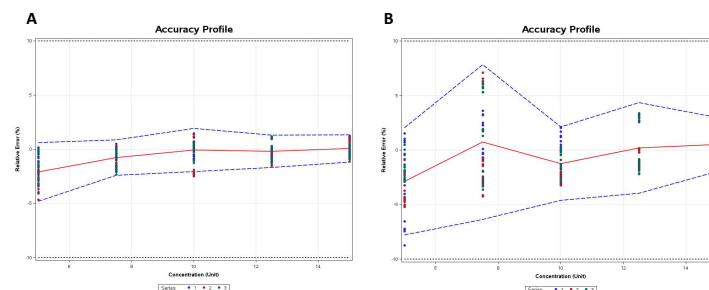


Figure 2. (a) Accuracy profile of the NIR-A quantitative PLS model and (b) Accuracy profile of the NIR-B quantitative PLS model. The plain red, dashed blue and dashed black lines represent the relative bias, the β -expectation tolerance limits ($\beta=95\%$) and the acceptance limits, respectively.

The method is considered as valid within the acceptance limits as shown in Fig 2. This approach gives the guarantee that the analytical error of each further measurement of unknown samples is included within the tolerance limits at the $\pm 10\%$ acceptance limits with a 5.0 % risk level.

Twenty samples collected in the local market were analyzed with the two validated PLS models. As shown in Table 3, the two methods generally predicted each sample correctly.

Thus demonstrating that the developed NIR methods could be applied on field by using handheld spectrometers.

Table 3. Results of quantification of 10 samples with NIR-A and NIR-B PLS models. Results are presented as predicted content of the label claimed (%) of the active ingredient.

Samples	Dosage forms	NIR-A	NIR-B
1	Tablets 300 mg	97.58	95.18
2	Tablets 300 mg	99.99	91.58
3	Tablets 300 mg	100.32	94.44
4	Tablets 300 mg	97.57	96.87
5	Tablets 300 mg	96.46	93.5
6	Tablets 500 mg	94.7	95.86
7	Tablets 500 mg	99.23	96.78
8	Tablets 500 mg	100.66	98.73
9	Tablets 500 mg	96.78	96.85
10	Tablets 500 mg	99.97	96.57
11	Oral drops 20%	103.15	100.76
12	Oral drops 20%	104.63	98.07
13	Oral drops 20%	103.81	99.06
14	Oral drops 20%	101.83	100.74
15	Oral drops 20%	104.64	101.77
16	Solution 500mg/2ml	105.17	103.21
17	Solution 500mg/2ml	105.33	99.43
18	Solution 500mg/2ml	105.6	99.01
19	Solution 500mg/2ml	105.77	102.33
20	Solution 500mg/2ml	105.12	99.35

Figure 3. Comparison of NIR-A and NIR-B predictions for local market samples

These results show that the developed models could quantitatively be used to analyze most of quinine formulations. The advantage of dissolving quinine is the possibility to analyze with the same PLS model both tablets, oral drops and intravenous solutions. This is not surprising since the liquid samples are constituted mainly of quinine dihydrochloride and water, whereas the excipients are less than 1% (W/V). Nevertheless, the present method is not applicable to the analysis of syrups.

5. Conclusion

- Considering the accuracy profile, NIR based on PLS regression model was successfully developed and validated using the total error approach with acceptance limits fixed at 10% at the 5 levels of the target concentration with both benchtop and low-cost handheld NIR transmission spectrophotometers.
- A comparison of developed methods showed that both could be used to verify the quality of quinine samples. 20 samples collected in the Congolese pharmaceutical market were analyzed by both techniques. All samples were conform since their quinine content was within $\pm 10\%$ of the theoretical value.
- This study constitutes the first step for the implementation of a field quality control method for quinine based medicines.

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