American Journal of Analytical Chemistry, 2019, 10, 415-422
https://www.scirp.org/journal/ajac
ISSN Online: 2156-8278
ISSN Print: 2156-8251

Quality Control of Quinine in Pharmaceutical Forms Tablets Find East of the Democratic Republic of Congo

Lucien Murhula Namegabe[1*], Mireille Tumusifu Kadhesi[2], Pacifique Murhula Hamuli[2,3], Aladdin Ombeni Mahano[4], Paul Brioen[2]

[1]Department of galenic Pharmacy, Official University of Bukavu, Bukavu, DRC
[2]Faculty of Medicine and Pharmacy, Official University of Bukavu, Bukavu, DRC
[3]Medicinal Plant Research and Drug Development at PAU-UI, University of Ibadan, Ibadan, Nigeria
[4]Analytical Chemistry and Food Sciences Laboratory, Official University of Bukavu, Bukavu, DRC
Email: *murhulan@yahoo.fr

How to cite this paper: Namegabe, L.M., Kadhesi, M.T., Hamuli, P.M., Mahano, A.O. and Brioen, P. (2019) Quality Control of Quinine in Pharmaceutical Forms Tablets Find East of the Democratic Republic of Congo. *American Journal of Analytical Chemistry*, **10**, 415-422.
https://doi.org/10.4236/ajac.2019.109029

Received: August 16, 2019
Accepted: September 16, 2019
Published: September 19, 2019

Abstract

The present study focuses on the quality control of quinine in the compressed pharmaceutical forms circulating in eastern Democratic Republic of Congo. The analyses performed on the collected samples included disintegration of the tablets, identification of quinine in the formulations by color reaction methods and thin-layer chromatography. The quantitative analysis was performed by spectrophotometric and volumetric methods. The most significantly observed findings were abnormalities of release; underdosing, overdosing and absence of the active ingredient, Which brings us to the conclusion that more than 30% of the samples analyzed are of inferior quality and adulterated.

Keywords

Quality-Control Quinine Tablets

1. Introduction

Malaria is a parasitic infection transmitted through the bite of plasmodium infected female anopheles mosquito, the infection causes intermittent fevers. Malaria remains the most important tropical parasites, about 300 to 500 million people are infected and claims 1.5 to 2.7 million lives per year. Almost 80% of cases are registered in sub-Saharan Africa, where most cases are children under five and pregnant women [1].

Artemisinin-based Combination Therapy (ACT) is exceptionally indicated for

true resistance or a formal contraindication to quinine [2]. An estimated 1 in 10 medical products circulating in low- and middle-income countries is either substandard or falsified, according to new research from World Health Organization (WHO). Since 2013, WHO has received 1500 reports of cases of substandard or falsified products. Of these, antimalarials and antibiotics are the most commonly reported. Most of the reports (42%) come from the WHO African Region, 21% from the WHO Region of the Americas, and 21% from the WHO European Region [3]. In the Democratic Republic of Congo (DRC), a pharmaceutical manufacturing company installed since 1998 was sued in October 2018 for the counterfeiting of quinine and the company manager was arrested [4]. There are several reasons for counterfeiting in Democratic Republic of Congo (DRC), such as the failure of quality control institutions for inadequately equipped medicines; influence peddling and political pressure on or within the control and repression bodies of counterfeit drug dealers; the population mostly under or uninformed about the circulation of fake medicines; the impoverished population faces a high morbidity which leads to inaccessibility to health care and services, hence the massive use of local and other illicit pharmacies; Counterfeit medicines cost less.

Quinine is an antimalarial that is the most counterfeit drug class on the planet according to the World Health Organization (WHO).

The objective of this study is to undertake control quality of quinine in the compressed pharmaceutical forms available for sale in three cities in eastern Democratic Republic of Congo (Bukavu, Goma and Uvira).

2. Material and Method

2.1. Material

2.1.1. Apparatus

SHIMADZU UV-1280 spectrophotometer, coupled to a computer, ERWEKA-APPARATEBAU disintegration apparatus, 254 nm UV lamp of the Merck KGaA type, D-64271 Darmstadt, F.R. Germany,

2.1.2. Reagent

Reagents and analytical grade products were used:

Concentrated sulfuric acid batch B-3901 Leuven, 6172, BELGIUM, 98%, density 1.84; Hydrochloric acid from PANREAC QUIMICA SAU, E-08211 Castellar del Valles (Barcelona), 37%, density 1.19; Ethanol 96% Vergallt MEK Carl Roth GmbH + Co.kg, 97% NaOH Extra pure LOBA CHEMIE PVT. LTD, Mumbai, Quinine Sulfate Powder from the pharmakina puré company according to the European Pharmacopoeia

2.2. Method

2.2.1. Sample

This is an experimental study involving analytical comparison of 20 batches of quinine in compressed pharmaceutical form sold in South Kivu and North Kivu

pharmacies and hospitals

2.2.2. Identification of Quinine in Tablets

By color reaction: We mixed each sample with 5 ml of water, then add a drop of concentrated sulfuric acid. The resulting solution was stirred, placed it in a dark room and exposed to 366 nm UV light; the observance of a stong white blue florescence indicated the presence of quinine, otherwise quinine is absent [5].

Preparation of sample solutions:

Preparation of the stock test solution of a 500 mg drug: a 500 mg tablet was grinded into a fine powder, then transferred into 50 ml volumetric flask. Distilled water of 5 ml was added into the flask followed by the addition of 45 ml methanol. The test solution obtained had a concentration of 10 mg/ml.

Preparation of test solution of the stock at 250 mg: we reduced a complete tablet to powdered form and extracted the powder obtained with 2 ml of water and then 23 ml of methanol using graduated pipettes and a 50 ml bottle as the test solution container of the stock.

Preparation of stock test solution at 300 mg: reduce a 300 mg tablet to a powder, pour it into a 50 ml flask and extract with 3 ml of water then 27 ml of methanol using pipettes.

Preparation of the test use test: we took 1 ml of the test solution from the stock and added 7 ml of methanol [6].

2.2.3. Preparation of Solutions for the Determination of the Calibration Curve

Quinine sulfate is a molecule possessing the chromatophore group because of its chemical structure (**Figure 1**), which gives the possibility of analysis by spectrophotometry.

The specific absorbance of quinine sulfate in 0.1 N HCl is 136 in the 1 cm long tank for a 1 g solution in 100 ml to 348 nm [7] [8] [9]. 100 mg of quinine sulfate powder considered as reference was dissolved in 100 ml of 0.1 N HCl. After homogenization, the diluted solutions are prepared from this standard solution called SM. **Table 1** summarizes the preparation of the solution.

Table 1. Preparation of solutions for the determination of the calibration graphic.

N°	Preparations for solutions	Concentration (mg/ml)	Dilution
S1	10 ml SM/100ml	0.1	10
S2	40 ml S1/50ml	0.08	12.5
S3	40 ml S2/50ml	0.064	15.6
S4	25 ml S1/50ml	0.05	25
S5	25 ml S3/50ml	0.032	31.25
S6	20 ml S5/50ml	0.016	65.5

Ab = Absorbance.

Molecular formula. $(C_{20}H_{24}N_2O_2)_2$, H_2SO_4, $2H_2O$

Relative molecular mass. 783.0

Graphic formula.

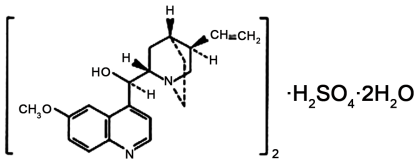

Figure 1. Structure of quinine sulfate [14].

2.2.4. Quantitative Analysis of Quinine in the Drug

Assay by Alcalimetry

A quantity of powder containing quinine sulfate corresponding to 400 mg of PA was weighed and dissolved in a mixture of 10 ml of ethanol and 5 ml of chloroform, then titrated with 0.1 N sodium hydroxide in the presence of phenolphthalein. The appearance of a persistent pink color marks the end of the titration. Each ml of NaOH consumed is equivalent to 37.325 mg of quinine sulfate $(C_{20}H_{24}N_2O_2)_2{\cdot}H_2SO_4{\cdot}2H_2O$) [10].

Spectrophotometry Assay

A test portion of the powder containing 100 mg of Quinine sulfate was dissolved in 100 ml of 0.1 N HCl. After homogenization, a dilution of 5 ml in 100 ml of 0.1 N HCl was carried out, using spectrophotometer, the absorbance was read at 348 nm. The reference product was treated in the same way and under the same conditions.

3. Results

3.1. Qualitative Analysis of Quinine

Compressed dosage forms dosed at 100 mg, 250 mg, 300 mg and 500 mg quinine sulfate were the subject of this quality control work. The chipping loss was performed, 16 samples gave a loss value of less than 1% while the results of lots 7, 12, 13 and 20 were greater than 1%.

In 0.1 M HCl, all tablets disintegrated within 30 minutes except samples Nos. 3, 17, 18, 19 and 20 which broke up more than 45 minutes later.

With regard to identification tests, **Table 2** shows the results obtained for the identification by the color reaction and by thin-layer chromatography. For the colored reaction the results are represented by the sign (−) which reflects the absence of the blue fluorescence after exposure to the light of the UV lamp at 254 nm and sign (+) signifies the presence of a light blue fluorescence after exposure to light from the UV lamp at 254 nm.

3.2. Quantitative Analysis

3.2.1. Graphic Calibration

Proceeding in the same way as described in the methodology (**Table 1**), a calibration curve was drawn up. The linearity is found in the concentration range of 0.016 and 0.1 mg/ml (**Figure 2**) with a regression coefficient of 0.999.

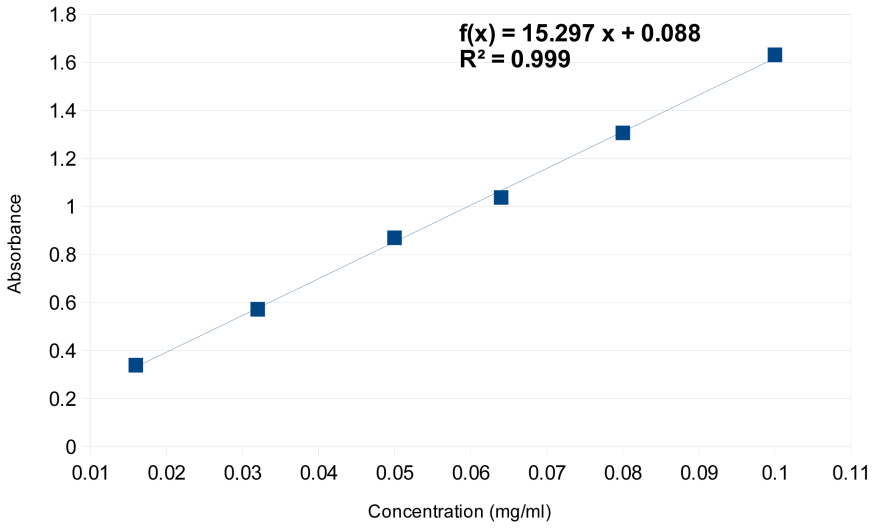

Figure 2. Calibration curve.

Table 2. Tests on quinine samples in compressed pharmaceutical form.

Lot	Quinine per tablet (mg)	Crumbling (%)	Disintegration	Identification test	
				Color reaction	Thin-layer chromotography (front report)
1	300	0.28	30	–	**0.8**
2	300	0.015	30	–	**0**
3	300	0.24	**45**	+	0.4
4	300	0.45	3	+	0.4
5	100	0.03	30	+	0.4
6	300	0.08	5	+	0.4
7	300	**1.67**	7	+	0.4
8	300	0.6	10	+	0.4
9	300	0.3	7	–	**0**
10	300	0.29	5	+	0.4
11	500	0.3	30	+	0.4
12	500	**5.48**	30	+	0.4
13	300	**2.21**	9	+	0.4
14	300	0.16	9	+	0.4
15	250	0.08	30	+	0.4
16	500	0.45	14	+	0.4
17	500	0.38	**49**	+	0.4
18	500	0.77	**75**	+	0.4
19	300	0.65	**125**	–	**0.7**
20	500	1.07	**50**	+	0.4

3.2.2. Quantitative Analysis of Quinine in Market Tablets

The results of the volumetric method are expressed in volume (average of volumes in ml) whereas those of the spectrophotometry are expressed in absorbance (average of absorbance) in Table 3. The contents were calculated for the volume taking into account of the equivalence given in the methodology and for the spectrophotometry taking into account the reference product which is quinine powder purity of the European Pharmacopoeia. Samples not containing quinine by identification were excluded from quantification.

4. Discussion

Our study was based on the quality control of twenty lots of quinine sulfate in compressed pharmaceutical forms dosed at 500 mg, 300 mg, 250 mg, 100 mg, for sale in the city of Bukavu, Goma, Uvira (Democratic Republic of Congo).

Table 3. Results of samples assay.

Lot	Quantification by spectrophotometry		Quantification by alkalimetry	
	Absorbance	Content ± SDS (%)	Volume consumed (ml)	Content (%)
1				
2				
3	0.67	101.8 ± 1.2	11.4	106.6
4	0.81	**123.3 ± 1.1**	13.4	**124.5**
5	0.61	92.7 ± 0.2	11.4	105.9
6	0.78	108.5 ± 1.2	10.5	97.9
7	0.62	94.2 ± 0.3	10.2	103.5
8	0.61	92.3 ± 4.6	11.1	95.2
9				
10	0.56	**84.7 ± 0.5**	8.5	**78.8**
11	0.64	96.7 ± 1.0	11	102.2
12	0.71	107.8 ± 1.8	10.5	97.9
13	0.6	91.3 ± 0.7	10.6	98.9
14	0.6	91.4 ± 0.5	10.8	100.3
15	0.68	103.09 ± 0.7	10	93.3
16	0.66	99.7 ± 2.0	10.4	97.05
17	0.67	101.6 ± 4.6	10.1	94.2
18	0.63	96.3 ± 7.3	10.1	93.8
19				
20	0.7	106.2 ± 0.1	10.8	100.2
Reference	0.66	100 ± 0.1	10.95	102.17 ± 0.7

With regard to the galenic tests, the uniformity of the masses gave us the compliant results because no tablet deviated from the limit required by the European Pharmacopoeia [11] which requires that the individual mass of the tablets ≥ 250 mg is within ±5%. And tablets ≤ 250 mg is within ±7%, and two out of 20 tablets may deviate from this percentage. This leads us to say that all our samples have satisfied the requirements of the pharmacopoeia compared to the uniformity of the masses.

Only 4 of the 20 quinine sulphate samples (20%) did not respond to the identification assay by both Quinine's color reaction and Quinine Thin Layer Chromatography (TLC) methods. This serious anomaly can lead to therapeutic failures and even cases of intoxication In Tanzania, a simila study showed that 11% of the Quinine samples analyzed did not respond to the identification test; similarly, one conducted in three African countries [12] showed that 1 in 39 (2.5%) of quinine drugs did not have the indicated active ingredient. In another study done in Bamako; 1 case of non-presence of quinine has been reported out of 24 (4%) [13]. In the light of the foregoing, it is noted that the counterfeit rate of circulating quinine is higher in the DRC than in other countries whose similar studies have been conducted.

The linearity was established by the least square regression method of the calibration curve. This standard curve was obtained over the range of concentrations from 0.016 to 0.1 mg/ml. The drawn curve gave an equation $Y = 15{,}297X + 0.088$ where the intercept and the slope are respectively 0.08 and 15.32; With a correlation coefficient (r) greater than 0.999 (**Figure 2**). The results show an excellent correlation between the absorbance and the concentration of the analyst.

The content of active ingredient was determined for the 16 lots out of 20 possessing the active principle. Compared to the standard considered; only the content between 90% - 110% was considered to be compliant [14] [15] [16]. That is, from all the 16 lots analyzed, 2 were out of the norm, one over-dosed and the other under-dosed. The under-dosing represents about 6% which is consistent with the 5.5% and 6% reported by Mbadinga and WHO respectively. It should be noted that the under-dosing of antimalarial exposes the failure of treatments and the development of resistance. About Six-percent (6%) overdose found in our study, this corroborates the results found by Kounang [17] who recorded in his study a case of overdose of quinine. However, our finding contradicts with Mandingar, who reported no case of overdose [18]. Overdose of a drug may result in hazardous toxic effects. For instance, a single high dose of quinine may result in cinchonism, cardiac arrhythmia, decreased platelet count, severe allergic reactions [19].

5. Conclusion

Counterfeiting is a practice that is in full swing in African countries; the present study focused on the quality control of quinine in pharmaceutical dosage forms. At the end of this work, our results showed that nonconformity affects different formulations of quinine tablet. Asia has held most of our samples. This counter-

feiting of quinine mainly concerns overdose; underdosing and the absence of quinine in the formulations studied. The rate of non-compliance exceeds 30% of the formulations analyzed.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] WHO (2005) Expert Committee on Malaria. https://www.who.int/malarai/docs/ecr20frtoc.htm

[2] Yohimbi, J. and Olinga, U. (2015) la malaria: Aspect clinique et thérapeutique. https://www.louvainmedical.be

[3] WHO (2017) 1 in 10 Medical Products in Developing Countries Is Substandard or Falsified. https://www.who.int/news-room/detail/28-11-2017-1-in-10-medical-products-in-developing-countries-is-substandard-or-falsified

[4] https://www.voaafrique.com/amp/arrestation-pour-contrefacon-de-quinine-en-rdc/462353

[5] Global Pharma Health Fond e.V. (2008) GPHF Volume 1.

[6] Global Pharma Health Fond e.V. (2008) GPHF Volume 2.

[7] European pharmacopoeia (2001) European Pharmacopoeia, Addendum.

[8] Jakson, J.V. and Moss Swiddop, B. (1986) Clark's, Isolation and Identification of Drugs. 2nd Edition, The Pharmaceutical Press, London

[9] Florer, K. (1983) Analytical Profiles of Drug Substances. Academic Press, Cambridge, 557.

[10] Commission Belge de Pharmacopée (2002) Pharmacopée Belge. 4ème édition.

[11] Commission Européenne de Pharmacopée (2017) Pharmacopée Européenne. 9ème édition.

[12] WHO (1995) La qualité des médicaments sur le marché pharmaceutique africain-Étude analytique dans trois pays: Cameroun, Madagascar, Tchad-Série de recherche, No. 18. http://apps.who.int/medicinedocs/pdf/s2212f/s2212f.pdf

[13] Mbandinga, G. (2004) Contrôle qualité de l'Amodiaquine et de la Quinine, Thèse de doctorat en pharmacie, Université de Bamako, Bamako. http://www.keneya.net/fmpos/theses/2005/pharma/pdf/05P17.pdf

[14] International Pharmacopoeia (2018) WHO Department of Essential Medicines and Health Products. Eighth Edition. http://apps.who.int/phint/en/p/about/

[15] (2016) British Pharmacopoeia. The Stationery Office, London.

[16] (2005) United States Pharmacopoeia, First Supplement. 29ème Édition. http://ftp.uspbpep.com/v29240/usp29nf24s0_m72850.html

[17] Kouonang, M. (2005) Contrôle de qualité de trois antipaludiques dérivés de l'artemisinine, thèse de pharmacie, Université du Mali, Français.

[18] Madingar, P. and Madjim, D. (2010) Contrôle de qualité des médicaments: Cas des antipaludéens au Burkina. thèse de pharmacie, Bamako, 55.

[19] Gabriel, C., Posocco, V., Pparodi, B. and Bignardi, G. (2002) In Indentification of Degradation Products of Ibuprofen Arising from Oxidative and Thermal treatements.