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Comparative in vitro dissolution profiles of marketed Artemether–Lumefantrine adult-dose tablets in Kinshasa, Democratic Republic of the Congo

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ABSTRACT

Introduction

Despite advances in clinical care, therapeutic strategies, and governmental interventions, malaria remains a significant public health concern—particularly in Africa, which consistently ranks highest in global morbidity and mortality reports from the World Health Organization. In the Democratic Republic of the Congo (DRC), malaria is one of the leading causes of medical consultations. This is largely due to the ineffectiveness of some antimalarial medications, which are often of substandard quality, contributing to therapeutic failures and the emergence of drug-resistant *Plasmodium* strains. Artemisinin derivatives are the mainstay of antimalarial therapy, with artemether–lumefantrine being the most commonly used oral formulation.

Purpose

This study aimed to evaluate the *in vitro* dissolution profiles of various artemether–lumefantrine brands available on the Congolese pharmaceutical market.

Methods

Fourteen brands of artemether–lumefantrine tablets at 80/480 mg and two at 20/120 mg dosage strengths were subjected to pharmaceutical quality control tests, including mass uniformity, friability, and disintegration. Qualitative and quantitative analyses were performed using high-performance liquid chromatography with diode-array detection (HPLC-DAD). Dissolution testing was conducted in 0.005 M HCl with 2% Myrj 52 at pH 1.2. Comparative dissolution profiles were assessed using similarity (f_2) and difference (f_1) factors.

Results

All samples complied with pharmaco-technical standards and demonstrated dissolution profiles comparable to the reference formulation ($f_1 < 15$; $f_2 \geq 50$).

Conclusion

The artemether–lumefantrine generics available on the Kinshasa market exhibit similar *in vitro* dissolution characteristics to the reference product, supporting their potential interchangeability.

INTRODUCTION

Malaria remains a parasitic infection with staggering global mortality and morbidity statistics (Randall & Seidel, 1985). Every year, 200 to 400 million malaria cases are recorded worldwide, resulting in over 500,000 deaths (Kayentao et al., 2022). In 2016, the global burden of malaria was estimated at 216 million cases and 445,000 deaths, compared to 212 million in 2015, 228 million in 2018, and 229 million in 2020 (Resende et al., 2019; Thellier et al., 2020; Amin et al., 2013). The highest prevalence is recorded in sub-Saharan Africa, followed by Asia, Central and South America, and finally the Mediterranean region (Girma et al., 2022; Leroy et al., 2014; Heng et al., n.d.; Karnad et al., 2018).

A recent World Health Organization (WHO) report published in 2023 indicated that 249 million malaria cases were reported in 2022—an incidence rate of 58 cases per 1,000 inhabitants. Of these, 233 million cases (approximately 94%) occurred in the WHO African Region, with Nigeria (27%), the Democratic Republic of the Congo (12%), Uganda (5%), and Mozambique (4%) accounting for the majority (Venkatesan, 2024). Children under 5 years old and pregnant women are the most vulnerable groups (Akpa et al., 2020). The African region also bears the brunt of malaria-related mortality, accounting for about 91% of global malaria deaths (Seo et al., 2022; Ogbuanu et al., 2024). Despite the encouraging progress made over the past decade in reducing malaria incidence and mortality in several endemic regions, especially in sub-Saharan Africa (Karnad et al., 2018), several challenges hinder effective malaria control. The widespread availability of falsified and substandard antimalarial drugs, as well as the emergence of drug resistance, remain significant barriers (César et al., 2008). Artemisinin-based combination therapies (ACTs) are currently recommended by WHO as the first-line treatment for *Plasmodium falciparum* malaria, but the effectiveness of treatment depends heavily on the quality of the drugs administered.

Estimates suggest that between 10% and 40% of all antimalarial drugs are falsified or substandard (Salami et al., 2023). A meta-analysis by Kaur et al. (2015) found that approximately 35% of antimalarial drugs were of poor quality. Another study indicated that 9.5% of antimalarial drugs assessed were either substandard or falsified (Petersen et al., 2017).

In the Democratic Republic of the Congo (DRC), the Ministry of Health has raised public alerts about suspected cases of low-quality antimalarial drugs (falsified, degraded, or mislabelled) since 2016. A study by Congolese researchers reported that 19% (14 out of 75) of antimalarial samples analysed were non-compliant. Furthermore, of the 124 registered trademarks reviewed, 46.0% (57) were unlicensed, and 14.5% (18) had expired licences (*PMC, n.d.*).

Counterfeit and substandard medicines represent a global health threat, reportedly causing up to one million deaths annually. While rare in the Global North, they remain prevalent and deadly in the Global South. WHO estimates that approximately 30% of medicines marketed in Africa are falsified or substandard. Cameroon reports the highest proportion (7.1%), followed by the DRC (2.7%) and Nigeria (1.1%) (Africa Check., 2024; Médicaments Contrefaits, 2013; Petersen et al., 2017).

Beyond the issue of falsification, another challenge in malaria treatment is the poor dissolution of some antimalarial drugs. The artemether-lumefantrine combination, although widely used, suffers from low oral bioavailability due to limited solubility and permeability (*PMC, 2024*; Rivelli et al., 2018). In a quality assessment study of ten brands of artemether-lumefantrine tablets, although eight brands (80%) met dosage specifications for both active ingredients, only four (40%) passed the dissolution test (Izevbekhai et al., 2017; Ahmed et al., 2024; Salami et al., 2023).

Dissolution is a critical factor in drug performance, as it directly affects in vivo bioavailability. Effective dissolution is vital for proper absorption, optimal bioavailability, and therapeutic efficacy. As such, the dissolution test serves as a cornerstone of drug quality assurance. Drugs with dissolution issues are deemed substandard and may cause therapeutic failure, complications, resistance, and financial losses. According to recent findings, the DRC ranks second only to Cameroon in the circulation of substandard medicines in Africa, highlighting the need to assess the dissolution profiles of artemether-lumefantrine tablets sold in Kinshasa (Ikechuku et al., 2024; Viljoen et al., 2024; Mavungu et al., 2019).

While the International Pharmacopoeia provides a monograph for analysing artemether-lumefantrine combination tablets, it lacks a standard method for dissolution testing due to the poor solubility of lumefantrine (International Pharmacopoeia, n.d.). Artemether is poorly soluble in water, and lumefantrine is practically insoluble (International Pharmacopoeia, n.d.). To overcome this limitation, Umapathi et al. (2011) developed and validated a dissolution method using an acidic medium and Myrj 52 (polyoxyl 40 stearate), which will be employed in this study.

The objective of this study is to determine the in vitro dissolution profiles of generic artemether-lumefantrine tablets marketed in Kinshasa and evaluate their similarity to the originator product to ensure their efficacy in malaria treatment.

METHODS

Reagents and Chemicals

HPLC-grade acetonitrile, 36% hydrochloric acid, 85% phosphoric acid, sodium hexanesulfonate R, and sodium dihydrogen phosphate R were obtained from Merck (Darmstadt, Germany). Myrj 52 (polyoxyl stearate 40) was sourced from Welming Pharmaceuticals (Bombay, India). Ultra-pure water was produced using a Milli-Q Plus 185 system (Massachusetts, MA, USA).

Equipment

Dissolution experiments were conducted using a Dissolutest DISS-06 apparatus (Hangzhou, China). Qualitative and quantitative analyses of the active ingredients were carried out using an HPLC-DAD system from Merck Hitachi (Antwerp, Belgium), controlled by Chromaster software (Antwerp, Belgium). An XBridge C18 chromatographic column (100 × 4.6 mm, 3.5 µm) from Waters (Milford, MA, USA) was used. An electronic balance (GRAM FV-220C) was provided by IPESAGE SAS (Paris, France), and an IKA® C-MAG MS4 agitator was supplied by Grosseron SAS (Paris, France).

Sample Collection

Various lots of tablets were purchased from pharmaceutical depots in the city of Kinshasa.

Preparation of Solutions

Dissolution Medium

The dissolution test was performed using 2% w/v of Myrj 52 (polyoxyl stearate 40) in 0.005 M hydrochloric acid. Aliquots of 5.0 mL were taken at four different time points over a period of 120 minutes (30, 60, 90, and 120 minutes). After each sampling, an equal volume of the dissolution medium was added to maintain the total volume in each vessel. The samples were filtered using a 0.45 µm PTFE syringe filter (Whatman). A pH of 1.2 was used for the medium.

Preparation of the Mobile Phase for HPLC-DAD Analysis

Ion Pair Reagent Preparation

In a 1000.0 mL volumetric flask, 5.65 g of sodium hexanesulfonate R and 2.75 g of sodium dihydrogen phosphate R were dissolved in approximately 900 mL of Milli-Q water. The pH was adjusted to 2.3 using phosphoric acid (105 g/L), and the volume was made up with Milli-Q water.

Elution Gradient Preparation

- **Mobile Phase A**: 700 volumes of the ion pair reagent and 300 volumes of acetonitrile R.
- **Mobile Phase B**: 300 volumes of the ion pair reagent and 700 volumes of acetonitrile R.

Table I:
Mobile Phase Elution Gradient (adapted from Umapathi et al., 2011)

Time (min)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0-28	60	40	Isocratic
28-29	60 to 0	40 to 100	Linear gradient
29-45	0	100	Isocratic
45-46	0 to 60	100 to 40	Return to initial composition
46-55	60	40	Isocratic re-equilibration

Dissolution Solvent Preparation for HPLC-DAD Analysis

In a 1000.0 mL volumetric flask, 200 mL of the ion pair reagent, 60 mL of Milli-Q water, and 200 mL of 1-propanol R were combined. The volume was brought up with acetonitrile R. The solution was stored at a temperature not below 20 °C.

Control Solution Preparation for HPLC-DAD Analysis

Exactly 20 mg of artemether RS and 120 mg of lumefantrine RS were accurately weighed into a 100.0 mL graduated

flask. Approximately 85 mL of the dissolution solvent was added, and the mixture was sonicated until fully dissolved, cooled to room temperature, and made up to volume.

Sample Preparation for HPLC-DAD Analysis

A 5 mL aliquot of the sample solution from the dissolution test was transferred into a 10.0 mL volumetric flask and diluted to volume with the dissolution solvent. The solution was filtered through a 0.45 µm filter, discarding the first millilitre of filtrate before injection into the HPLC-DAD system.

Analytical Method

Twelve tablets of each brand were used for the dissolution test. The dissolution volume was 900 mL, and the stirring speed was set to 100 r/min. Deaeration was performed by sonication.

HPLC-DAD was used for the qualitative and quantitative analysis of the active pharmaceutical ingredients. The mobile phase flow rate was set at 1.3 mL/min. Detection was performed at 210 nm for artemether and 380 nm for lumefantrine (Umapathi et al., 2011). The injection volume was 20 µL.

Data Processing

Data analysis was conducted using Microsoft Excel 2016. To confirm visual results and compare the dissolution profiles of generics with the reference (princeps), the **fit factor method** was used, based on the calculation of two factors: the difference factor (f_1) and the similarity factor (f_2).

Twelve tablets were analysed, and the average percentage release at each time point was calculated. Two dissolution curves were considered similar if f_1 was less than 15 and f_2 was greater than or equal to 50. The formulas for f_1 and f_2 were as follows:

$$f_1 = \frac{\sum_t^n (R_t - T_t)}{\sum_t^n R_t} \times 100$$

$$f_2 = 50 \times \log([1 + \frac{1}{n}\sum_t^n (R_t - T_t)^2]^{-0,5} \times 100)$$

Where n is the number of sampling points (n = 4 in this study), R_t is the percentage dissolved at time t for the reference, and T_t is the percentage dissolved at time t for the test formulation.

RESULTS

Presentation of the Samples Analysed

Table 2 presents the samples analysed in this study.

Table 2:
Presentation of the Samples Analysed

N°	Product	Manufacturer	Country of Origin	Lot	Expiry Date	AMM¥
1	Coartem 80/480 mg	Novartis	France	A019G1	09/2026	Yes
2	Cether-L 80/480 mg	New Cesamex	DRC	8211024	09/2027	Yes
3	Lumeart 40/240	Promed	DRC	4080	02/2027	Yes
4	Luther DP	Zest Pharma	India	AEH23024Q	06/2025	Yes
5	Lonart DS 80/480 b/6ces	Bliss GVS India	India	LD-638	06/2026	Yes
6	Arolum 80/480	Aura Lifecare Pvt.	India	R024	08/2025	No
7	Artetab	Healthy Drugs Pvt. Ltd.	India	BAZ	09/2025	
8	Cukether	Pharmacy of University Clinics of Kinshasa	DRC	0362024	06/2027	No
9	Arthefan 80	Phatkin	DRC	1023	07/2025	No
10	Combisunate 80/480	Ajanta Pharma Ltd.	India	C1293	07/2025	Yes
11	Davimether-L	S Kant Healthcare Ltd.	India	DOA12	08/2026	Yes
12	Alludoc 80/480 b/6ces	Dr Pharma	India	2191401	02/2026	Yes
13	Colart 80/480 b/6ces	GlaxoSmithKline	India	CWY024004	06/2025	Yes
14	Co-Arter 80/480 b/6ces	Pharma Plus	India	06	09/2025	
15	Lumart-E	Kim Pharma	DRC	LM21	08/2027	Yes
16	Lumiter DT	Oxalis Labs	India	L0321	07/2025	Yes

¥: Marketing Authorisation

Determination of Other Pharmaco-Technical Tests

Table 3 shows the results of pharmaco-technical tests performed on the samples.

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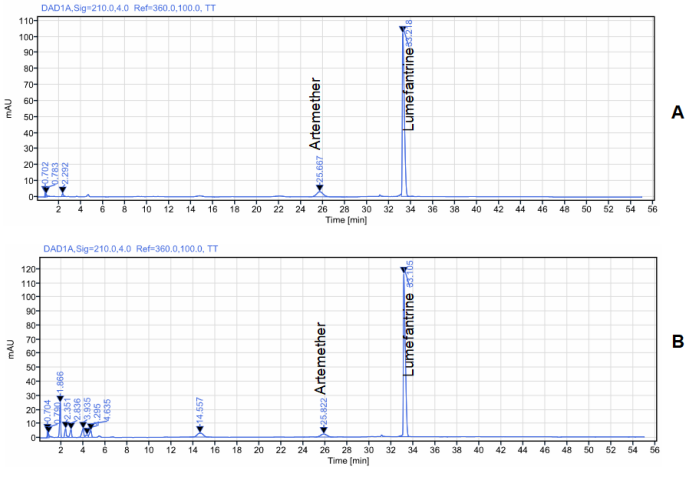
Table 3:
Results of Pharmaco-Technical Trials

N°	Product	Mass Uniformity (n = 20): Average Weight (g) / Deviation (%) Standard: ±5%	Friability (%) (n = 10) Standard: ≤1.0%	Melt Time (minutes) (n = 6) Standard: ≤15 minutes
1	Coartem 80/480 mg	0.9454/-1.5% to +2.5%	0.4	6
2	Cether-L 80/480 mg	0.8934/-1.0% to +1.1%	0.5	10
3	Lumeart 40/240	0.7765/-1.9% to +1.5%	0.3	7
4	Luther DP	0.9156/-3.6% to +1.9%	0.8	9
5	Lonart DS 80/480 b/6ces	0.8734/-3.5% to +1.2%	0.6	9
6	Arolum 80/480	0.8923/-3.0% to +2.9%	0.7	11
7	Artetab	0.8734/-2.7% to +2.9%	0.5	7
8	Cukether	0.8232/-1.9% to +1.1%	0.8	9
9	Arthefan 80	0.7840/-2.1% to +1.8%	0.5	10
10	Combisunate 80/480	1.0231/-2.9% to +3.7%	0.9	11
11	Davimether-l	0.9543/-3.2% to +3.8%	0.5	8
12	Alludoc 80/480 b/6ces	0.8734/-4.1% to +2.4%	0.6	7
13	Colart 80/480 b/6ces	0.8241/-1.9% to +1.5%	0.6	9
14	Co-Arter 80/480 b/6ces	1.185/-2.6% to +2.9%	0.7	7
15	Lumart-E	0.8562/-3.1% to +2.9%	0.5	6
16	Lumiter dt	0,9259/-1.7% to +2.3%	0,8	9

Identification of Active Ingredients by HPLC-DAD

Prior to performing comparative dissolution tests, the presence of active ingredients in the samples was confirmed using the HPLC-UV technique. All samples analysed contained the declared active ingredients, as the retention times of the controls matched those of the samples (artemether: 25 minutes; lumefantrine: 32 minutes). **Figure 1** shows the chromatograms of a sample and a control solution.

Figure 1:
Chromatograms of the control (A) and a sample under study (B)



Quantification of Active Ingredients by HPLC-DAD

Following identification, the quantification of active ingredients was carried out. **Table 4** presents the results for artemether and lumefantrine content in each sample.

Table 4:
Quantification of Active Ingredients in the Samples Analysed

N°	Product	Average percentage RSD¥ (%), n=3 Standard: 90.0 to 110.0%	
		Artemether	*Lumenfantrin*
1	Coartem 80/480mg	102.4 ± 1.2	101.0 ± 1.9
2	Cether-L 80/480mg	99.1 ± 1.7	102.3 ± 2.1
3	Lumeart 80/480	97.6 ± 2.0	98.0 ± 1.3
4	Luther DP	96.9 ± 1.8	100.7 ± 1.4
5	Lonart DS 80/480 b/6ces	98.2 ± 1.5	100.9 ± 3.1
6	Arolum 80/480	99.4 ± 1.5	103.2 ± 1.6
7	Artetab	103.1 ± 1.9	98.1 ± 1.4
8	Cukether 80/480mg	97.7 ± 1.1	98.9 ± 2.8
9	Arthefan 80/480mg	98.3 ± 2.2	101.8 ± 3.1
10	Combisunate 80/480	102.2 ± 2.7	99.4 ± 2.3
11	Davimether-l	98.1 ± 1.7	95.9 ± 2.4
12	Alludoc 80/480 b/6ces	101.5 ± 1.9	102.1 ± 1.4
13	Colart 80/480 b/6ces	103.3 ± 2.8	97.1 ± 2.1
14	Co-Arter 80/480 b/6ces	102.9 ± 2.9	96.8 ± 2.7
15	Lumart-E	96.9 ± 1.8	102.1 ± 2.4

¥: Relative Standard Deviation

All samples tested met the requirements for active ingredient content.

Dissolution Test

Dissolution Profiles

Figures 2 and **3** present the dissolution profiles of artemether and lumefantrine, respectively, for the samples tested.

Figure 2:
Dissolution Profiles of Artemether in the Products Studied

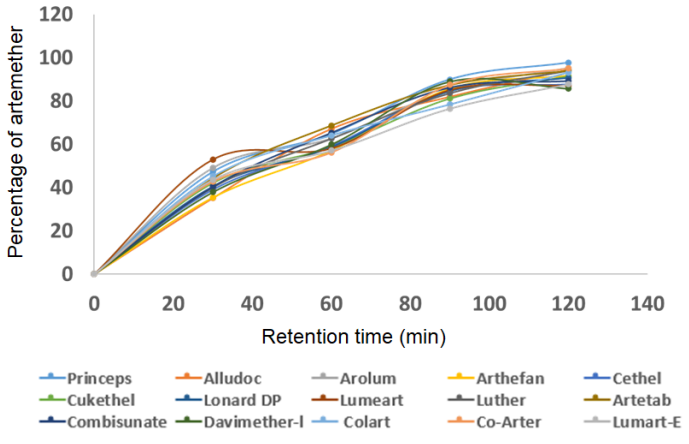


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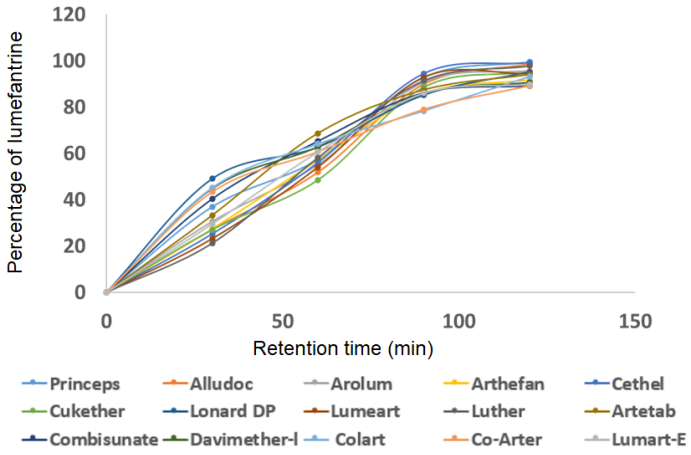
Figure 3:
Dissolution Profiles of Lumefantrine in the Products Studied



Similarity Test

Table 5 presents the results of similarity tests (f1 and f2 factors) between the princeps and generic formulations.

The f1 and f2 values shown in **Table 5** indicate that the dissolution profiles of the generics are similar to that of the reference (princeps) product, which is in line with acceptable pharmaceutical standards (Food and Drug Administration [FDA], 2021; World Health Organization [WHO], 2020).

Table 5:
Similarity Test Results Between the Princeps and Studied Generics

Product		Alludoc	Arolum	Arthefan	Cether	Cukether	Lonard DP	Lumeart
Lumefantrin	F1	6,633773766	5,063713908	1,020408163	3,964992924	9,424991292	3,49365405	7,738668748
	F2	61,3988584	69,23919542	67,86810152	61,04778531	56,83013968	55,99274191	56,00070809
Artemeteher	F1	7,1	2,496712085	9,937928103	9,628562585	8,803392925	2,496712085	5,506262327
	F2	55,9	74,99570539	54,75087801	56,13011419	58,35474258	74,99570539	56,6990607
Product		Luther	Artetab	Combisunate	Davimether-l	Colart	Co-Arter	Lumart-E
Lumefantrin	F1	6,190358293	1,121119153	1,923594192	0,737326744	1,99337463	4,99393347	7,087346614
	F2	54,90627978	57,31178845	56,1256894	56,44015603	51,01192597	51,35601359	57,24964395
Artemeteher	F1	6,367479161	1,762601087	6,200635753	9,070342379	6,267373116	2,496712085	11,60636219
	F2	63,85108703	73,02518208	61,61323218	54,67121923	59,83732025	74,99570539	51,2540512

DISCUSSION

Pharmaceuticals must meet the standards of quality, efficacy, and safety as recommended by the World Health Organization (World Health Organization [WHO], n.d.). The dissolution of a drug is one of the quality criteria and influences its efficacy.

This study reports on the dissolution profiles of tablet forms of artemether-lumefantrine collected from wholesale establishments in Kinshasa, Democratic Republic of the Congo (DRC). The dissolution profiles were compared to those of the reference (princeps) product using the difference factor (f_1) and the similarity factor (f_2). Due to the insolubility of these samples in pH 4.5 and pH 6.8 media, only the pH 1.2 medium was used. The method used in the pH 1.2 medium confirmed the bioequivalence of these products, as the results showed a similarity between the dissolution profiles of all generic samples and the reference product.

These results may reflect an improvement in the quality of antimalarials resulting from strengthened regulations, enhanced import controls, and post-marketing surveillance conducted by the Congolese pharmaceutical regulatory authority in the DRC.

The findings of this study are consistent with those of a 2023 study conducted in Uganda on the quality of antimalarial lumefantrine, which also included some generics used in the current study. That study reported that all samples passed the dissolution test (International Pharmacopoeia, 2022).

However, the findings differ from those of a study conducted in Nigeria in 2017, which reported that 60% of artemether-lumefantrine-based antimalarials failed the dissolution test (Umapathi et al., 2011). The current study performed dissolution tests in the pH 1.2 medium, following the recommendation of the European Medicines Agency (European Medicines Agency [EMA], n.d.), whereas the Nigerian study used distilled water at 37°C as

the dissolution medium. This difference in methodology may explain the variation in results.

Low-quality antimalarial agents remain a problem in many sub-Saharan African countries. The results of this study demonstrate a significant advancement in the fight against malaria in the DRC. Nevertheless, while in vitro dissolution tests are essential to assess the release of the active ingredient, they only measure the rate and extent of drug dissolution in a simulated environment. These tests do not consider complex biological factors such as intestinal pH, intestinal motility, or food interactions. Therefore, in vitro bioequivalence does not always equate to in vivo therapeutic equivalence. We thus recommend complementing these studies with in vivo testing, especially when investigating suspect batches.

CONCLUSIONS

The objective of this study was to evaluate the quality of antimalarial drugs marketed in the DRC, specifically in Kinshasa, by determining the in vitro dissolution profiles of artemether-lumefantrine tablets collected locally. The tested samples exhibited a difference factor (f_1) of less than 15 and a similarity factor (f_2) greater than 50.

All tested generics demonstrated dissolution profiles similar to the reference product ($f_1 < 15$, $f_2 \geq 50$), supporting their interchangeability in clinical use without potential variation in in vivo effects.

Ethical Approval: Nil indicated.

Conflicts of Interest: None declared.

ORCID iDs:

Dhimbe, G. B.[1,2]:	Nil identified.
Ive, K. D.[1,2]:	Nil identified.
Tweni, B. E.[3]:	Nil identified.
Mankulu, K. J.[1,2]:	Nil identified.
Mbinze, J. K.[1]:	Nil identified.[2]

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