QUALITY ASSESSMENT OF DIFFERENT BRANDS OF AREMETER LUMEFANTRINE MARKETED AROUND BENIN CITY METROPOLIS

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CERTIFICATION

This is to certify this is an original research work carried out by **IZEVBIGIE LAWSON OSAWEUSE** in the Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Benin, in partial fulfillment of the requirements for the award of Doctor of Pharmacy (Pharm D) degree.

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DEDICATION

This project work is dedicated to God Almighty for the gift of life and strength throughout this project, and to my entire family and friends for standing by me through the tough times and the process.

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I express my deepest gratitude to God and to everyone who contributed to the success of this project. To my late dad, Izevbigie Dickson, I would give anything for you to see me reach this milestone, and my mum Queen Izevbigie. I am more than grateful for everything. To my elder brother, Oscar Izevbigie, thank you for everything you do. Also, to my other siblings, Jacklynn, Harold, and Russell Izevbigie.

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ABSTRACT

Background: Artemether-lumefantrine (AL) is the first-line treatment for uncomplicated malaria throughout Nigeria. The rise of substandard and falsified medicines endangers patient safety, effective treatment, and antisubstitution for decreased susceptibility to effective treatment. This study evaluated *in-vitro* pharmaceutical quality of artemether-lumefantrine brands that are marketed in Benin City.

Methods: Sixteen (16) brands of artemether-lumefantrine tablets were procured from Patented and Proprietary Medicine Vendors (PPMVs) and retail pharmacies licensed through NAFDAC throughout Benin City. Samples were evaluated based on pharmacopoeial standards of visual/organoleptic packaging and tablet assessment, weight uniformity, tablet hardness, friability, disintegration time, *in-vitro* dissolution and assay for % purity of active pharmaceutical ingredients.

Results: All 16 brands were NAFDAC-approved and presently active. All samples passed critical evaluative tests associated with weight uniformity, dissolution (all >80% in 60 min), and % purity (assay) with all brands within pharmacopoeial standards of 90.0% - 110.0% meaning active pharmaceutical ingredients are accounted for. However, significant quality concerns were raised as 1 brand (Biolumefar) failed the friability test (3.00% weight loss) due to compromised mechanical integrity. 1 brand (Contrine plus) failed disintegration time analysis as the average time elapsed was >30 min according to pharmacopoeial standards. Finally, a statistically significant difference was found in tablet hardness across all brands (range: 6.50 LP to 11.33 kP).

Conclusion: Overall, findings present inconsistent quality. While it is a positive outcome that no brands failed the assay for content of active ingredients, the failure of two brands in the most critical physical assessments - one for friability and one for disintegration - indicates inferior manufacturing processes and quality control standards. Therefore, there is a continued need for post-market surveillance from NAFDAC to ensure all AL products in circulation are quality compliant to avoid malarial treatment failures secondary to drug resistance.

CHAPTER 1

1.0 INTRODUCTION

Malaria is a massive problem, threatening the lives of people in Nigeria, accounting for an average of 225,000 deaths annually in the country. Artemether-lumefantrine is very effective against Plasmodium falciparum and drug-resistant strains, which has been demonstrated by multiple studies. It has been assigned as the first-line drug for the treatment of uncomplicated malaria by the World Health Organization (WHO) (A. Mgbahurike, 2017). The massive production and sale of counterfeit and substandard antimalarial drugs have undermined the efforts to control malaria in Nigeria and other sub-Saharan countries in Africa, leading to failure of treatment, increased morbidity, and drug resistance (Aladin Ombeni Mahano et al, 2021).

There is a growing concern in Africa and neighbouring countries, which has been highlighted by multiple studies regarding the quality of artemether-lumefantrine formulations that are publicly available in the market in various pharmacies. In a study in 2023, it was observed that only 50-55% of all AL tablet brands sampled in Kaduna state met the requirements of the international pharmacopoeia for content, even when they passed the requirements for packaging and physical assessments (Umar Rayyanu et al, 2023). Similarly, a different study from the southern part of Nigeria found that though all the AL met the requirements standard for artemether, only 80% of them met the same requirements for lumefantrine, with only 40% satisfying the dissolution criteria, and these all indicate the presence of substandard products in the market (O. Izevbekhai et al. 2017).

The widespread availability of these substandard AL ruins patient outcomes and may cause an acceleration in the development of antimalarial drug resistance, posing a massive risk to public health. These findings underscore the urgent necessity for continuous quality assessment and regulatory enforcement to ensure that only safe and effective AL brands are accessible to the population, particularly in malaria-endemic regions like Benin City (O. Izevbekhai et al. 2017).

1.1 What is Malaria

When considering the world's most pressing public health issues, malaria stands out as one of the most serious, and one hundred percent of the time it's caused by Plasmodium parasites that spread through the bites of female Anopheles mosquitoes. Coming hotfooting in second to AIDS, this disease is costing the world dearly, and even though it can be prevented and treated, the toll on global health, economic stability and progress is crippling. the people living in the tropics and subtropics, and especially those in sub-Saharan Africa are hit the hardest. Well-known statistics are unable to do justice to the reality of the impact of malaria, and don't show the chilling number of fatalities and illnesses, the economic devastation it wreaks and the problems that threaten to undo years of advances in combatting this disease.

One of the major contributors to malaria-related deaths can be seen through the yearly records of instances and fatalities, visually describing the human price of the illness. The World Malaria Report 2023 of the World Health Organization (WHO) states that the global number of malaria cases in 2023 is estimated to be 263 million, which is the cause of 597,000 deaths (WHO, 2023). The data indicate significant changes in the reduction of cases and deaths since 2000, when 2.1 billion cases and 11.7 million deaths were averted, but after a few years of stagnation, the situation remains very serious, and the numbers are still quite high (WHO, 2023). The statistics are most tragic as the people who suffer most are the children under five. Children below five years are the most susceptible group making up about 76% of malaria deaths in the African Region of the WHO in 2023 (WHO, 2023). This means that a child dies of malaria approximately every minute. Besides this, pregnant women also get hammered as malaria puts the way

to severe anemia, maternal death, stillbirth, and low birth weight. Tragically, malaria has a very unequal distribution in terms of geography worldwide. The WHO African Region is the one that has to bear the heaviest and most disproportionate share of the worldwide burden and makes up the estimated 94% of all malaria cases and 95% of all malaria deaths in 2023. According to WHO (2024). Only four countries, namely Nigeria, the Democratic Republic of Congo (DRC), Uganda, and Mozambique, were responsible for almost half of the cases worldwide. This extreme concentration is due to a combination of factors such as: an appropriate climate for vector mosquitoes to carry on with their cycle, the dominance of Plasmodium falciparum, the most lethal parasite causing malaria, and frequently under-resourced health systems that are challenged with methods for surveillance, diagnosis, and treatment (WHO, 2023). The extent of the difference in the geographic distribution of the disease highlights malaria as a disease of inequity, which is inevitably linked to poverty and lack of healthcare access.

Besides the cost to human life, malaria places an enormous economic burden on the affected populations, which keeps them locked in the poverty cycle. The economic consequences of the disease are felt on a global scale and at a local level too. Malaria is said to be the cause of the loss of GDP worth US$12 billion a year just in Africa (Malaria Consortium, n.d.). This "growth penalty" is considered to reduce the speed of the economic growth rate in the countries with a high level of malaria transmission by about 1.3% annually (Malaria No More UK, n.d.). Most of the malaria-ridden countries can see the disease carving out as much as 40% of the share of their public health expenditure.

However, the costs at the level of households are terrible. The despaired families first need to buy drugs, pay for transport to the clinics, and protective measures such as insecticide-treated nets (ITNs) if they want to stay alive and healthy.

The situation is worsened by the indirect costs resulting from the wages lost and the time not worked or spent at school, thus, a family's economic resilience weakens further and the poverty which is passed from one generation to another becomes more and more ingrained. Besides all those problems, the fight against malaria is weakening in some parts of the world and progress is even reversing in those places. The main causes of this are the convergence of a multitude of biological, environmental, and financial threats.

One of the biological threats is the development of mosquito resistance to pyrethroids, which is the main insecticide in ITNs, as well as the emergence of partial parasite resistance to artemisinin-based combination therapies (ACTs), which are the first-line treatment for P. falciparum malaria (WHO, 2023). Climate changes are the major environmental factors in this case that are allowing the geographical spread of the mosquitoes carrying malaria to new altitudes and areas, and thus increasing the number of people exposed to the disease.

Besides that, extreme weather events can severely damage the infrastructure of the malaria control programs and lead to huge surges in cases, e.g. when the flooding is catastrophic as in Pakistan in 2022 (WHO, 2023). After all, we should not disregard the chronic underfunding of the global response. Malaria control total funding in 2023 was around US$4 billion, while the target was to achieve US$8.3 billion, so the amount that was secured made it very difficult to keep up the necessary pace (WHO, 2024).

The health burden is quantified in the number of lives that are lost, primarily those of young children, which reach hundreds of thousands every year. The economic burden is the one that takes the vitality of entire nations and communities away. Besides being a complex challenge, biological resistance, climate change, and the continuation of funding gaps are some of the factors that threaten the progress made. Newly developed vaccines undoubtedly are critical sources of hope, but they should not be considered as a silver bullet. The freeing of mankind from the malaria scourge requires the continuation and even the increase of the global commitment to closing the resource gap, strengthening health systems, and ensuring that the life-saving tools are accessible to the most vulnerable populations who are in need.

1.2 Artemether Lumenfarine

The fixed-dose combination of artemether and lumefantrine (AL) has been the most common first-line treatment of uncomplicated Plasmodium falciparum malaria, on which modern malaria control strategies primarily rely for their implementation. The Role and Mechanism of Artemether-Lumefantrine.

1.2.1 The Role and Mechanism of Artemether-Lumefantrine

The effectiveness of artemether-lumefantrine depends on the clever "one-two punch" combination, which leverages the distinct characteristics of its two active ingredients to achieve a very high cure rate while preventing the emergence of drug resistance (M. Duraisingh et al, 2019).

Artemether (The Fast-Acting Agent): It is a characteristic following an artemisinin derivative, that of being "fast-acting shock trooper" for artemether. In this manner, the drug is incorporated and in the shortest time possible it has already begun its effect, it could be said that artemether positions and rapidly accomplishes its powerful assault on the parasites in the bloodstream. In fact, the main achievement of the organism biomass reduction, that is, the rapid destruction of the parasites, is the one that leads to the alleviation of the symptoms, like fever resistance of which is most often resolved in the period of 24 hours. Nevertheless, the very short half-life of artemether limits its presence to relatively few hours (White, N. J., 1997).

Lumefantrine: the task of lumefantrine is to ensure the continuation of the therapeutic effect and, hence, it achieves this by action on the area that has already been disinfected but is left there with few parasites to clean. It adopts the most diligent procedure in

dealing with the survivors of an attack (which in this case is the small number of remaining parasites); that is, those that have managed to escape the initial artemether assault will be exterminated by lumefantrine. (White, N. J. (1997).

This combination strategy cannot be outdated. Basically, the artemether is the agent that in a very short time, saves the patient's life, by reducing the parasite load rapidly, while lumefantrine is the component that ensures a "radical cure" by stopping the recrudescence (the infection returning from the surviving parasites) (White, N. J. (1997). The reason for the extremely low chance of a parasite developing resistance to both drugs at the same time is that they have combined two drugs with different mechanisms of action (WHO, 2015) Besides, the fact that it is a fixed-dose combination (FDC)—one single tablet containing both drugs—is an important public health advantage, as it not only makes the treatment simple but also guarantees that patients are taking both drugs together, which is necessary for adherence (WHO, 2015).

1.3 Importance of Drug Quality

The power of artemether-lumefantrine to cure rests solely on the quality of the product given. A good quality medicine is a product which has the correct active pharmaceutical ingredients (APIs) in the correct dosage, is free from contaminants, and is made in a way that the drug can be properly absorbed by the body (bioavailability).

The - spread of Substandard and Falsified (SF) medicines is one of the greatest difficulties the world faces in the fight against malaria (WHO, 2017).

1.4 Counterfeit and Substandard Medicines

Counterfeit medications, also known as fake medications, are defined a medicinal products which have be deliberately and fraudulently (falsely) labelled with respect to identity and sources, and may be produced or packaged to contain wrong active ingredients, insufficient active ingredients or no active ingredients at all. A counterfeit medication is therefore a fake or unauthorized replica of a genuine product usually made by someone other than the genuine manufacture in some sub-sahara African countries linke Nigeria. that closely resembles the original product in terms of appreance and packaging inorder to deceive unsuspecting customers into believing that they are authentic products.

Counterfeit medicines pose a significant threat to public health worldwide, particularly in developing countries due to its high as these medicines can be proliferation ineffective, toxic or even life-threatening.

Estimate suggests that counterfeit medicines can constitute up to 30% of the medicine substandard medicine on the other hand, are authorized pharmaceutical products that fail to meet the required standards and specifications for quality efficacy and safety due to issues encountered during their manufacturing, storage and low distribution. As such, substandard medicines are genuine products that do not meet quality

standards, often due to manufacturing or quality control issues (Almuzani et al, 2021).

1.4.1 Rationale for counterfeiting of medicines in sub-Sahara Africa

Several reasons have been attributed to the very high prevalence of counterfeit and fake medicines in Sub-Sahara African countries, like Nigeria and they include (Akunyili et al, 2007)

i. Financial gain: Counterfeiting of medicines is a very lucrative business, with estimates suggesting that Nigeria alone, Loses around two hundred billion naira (N200 billion) annually to manufacturer and distributors of counterfeit medicines.

ii. Weak regulatory framework: Inadequate legislation, poor enforcement and corruption amongst drivers of healthcare systems can facilitate the entry and proliferation of counterfeit medicines.

iii. High demand and limited access to quality healthcare services and products may subject patients to become vulnerable to counterfeit medicines

iv. Poor health-seeking behavior: A lot of patients in Nigeria and most sub-sahara African counterfeit are low income earners and as such priortise cheap and unverified medicines over legitimate, potentially life-saving products. In Nigeria for examples, majority of patients patronize quacks and local drug peddlers than registered

pharmacies to meet their medication needs which make them prone to purchasing fake/counterfeit medicines.

v. Poor supply chain management: Nigeria's porous borders and inadequate tracking systems enable counterfeit medicines to enter easily into the drug market. The high dependence on informal/inefficient distribution channels and drug markets in Nigeria such as the Onitsha open drug market in south eastern Nigeria. The idumota medical market in western Nigeria etc increase the risk of proliferation of counterfeit medicine substantially.

vi. Lack of Awareness: Limited public awareness about the prevalence and dangers of counterfeit medicines contribute to their high demands insufficient public awareness campaigns by regulatory agencies and professional bodies contribute immensely to low awareness especially amongst rural community dwellers.

vii. Orgnised crime: Transnational organized crime groups exploit Nigeria's weak regulatory environment to flood the market with counterfeit medicines which can be best combated with international synergy and collaboration with organisations like the world health organisation (WHO) and the Interpol to arrest all such

criminals across the entire supply chain, thus safeguarding public health and ensuring efficacy of treatment options.

1.4.2 Countries involved in the counterfeiting of medicines

Through counterfeit medicines pose a global challenge and may be multifaceted in nature, some countries are known globally to be a conducive hub for the manufacturing and /or distribution of counterfeit and substandard medicines and they include (OECD & European Union Intellectual Property Office. (2020).

i. China: Which have been identified as a major source of counterfeit medicines accounting for about 27.6% of reported incidents
ii. India: Known as the pharmaceutical capital of the world is reputed for producing counterfeit medicines, with estimate suggesting up to 35% of its products are questionable
iii. Pakistan: A major drug production hub globally is also linked to counterfeit medicine trade with reports of toxic cough syrup production
iv. Indonesian: Associated with counterfeit medicine production, contributing significantly to global health risks.
v. Mexico: A Latin America country known essentially for the production of vaccines has issued alerts for falsified predictions including hepatitis B vaccines

vi. Nigeria: Struggles essentially with counterfeit medicine penetration and proliferation and in some cases have reported the production and sace of counterfeit medicines that have affected public health resulting in several deaths and disabilities.

1.4.3 Ways of Addressing the Proliferation of Substandard and Counterfeit Medicines in Sub-Saharan Africa

1. Strengthening Regulatory Frameworks: Enhance the capacity of national medicines regulatory authorities (NMRAs) to enforce compliance with quality standards and safety regulations.
2. Improving Supply Chain Management: Establish efficient supply chain systems that include storage, distribution, and tracking of medicines to prevent loss and ensure accessibility.
3. Implementing Quality Assurance Protocols: Develop and enforce quality assurance measures for all stages of medicine production, distribution, and sale.
4. Enhancing Pharmacovigilance: Create systems for monitoring the efficacy and safety of medicines in real-time to identify and address substandard products swiftly.

5. Capacity Building and Training: Provide training for healthcare professionals and stakeholders in pharmaceutical quality, regulatory compliance, and detection of counterfeit medicines.
6. Collaboration and Partnerships: Foster partnerships among governments, NGOs, and the private sector to share resources, knowledge, and best practices for combating counterfeit medicines.
7. Public Awareness Campaigns: Educate the public about the dangers of counterfeit drugs, encouraging them to purchase medications from reputable sources.
8. Leveraging Technology: Use technology, such as mobile apps and blockchain, to trace the origin of medicines and ensure their authenticity.
9. Strengthening Local Manufacturing: Encourage local production of medicines to reduce dependence on imports and improve quality control.
10. Policy and Legislation: Advocate for stronger enforcement of anti-counterfeiting laws and support for policies that promote access to quality medicines (WHO, 2018).

1.4.4 Approaches to Identifying and Trading Sources of Substandard and Counterfeit Medicines in Nigeria

1. Strengthening Regulatory Framework

- Enhance Legislation: Ensure existing laws are robust and specific to counterfeiting and substandard practices.
- Enforcement: Empower regulatory agencies like the National Agency for Food and Drug Administration and Control (NAFDAC) to enhance enforcement of laws.

2. Establishing a Surveillance System

- Market Surveillance: Conduct regular inspections of pharmacies, hospitals, and drug stores to monitor product quality.
- Adverse Event Reporting: Create a system for healthcare professionals and consumers to report suspected counterfeit or substandard medications.

3. Strengthening the Supply Chain

- Traceability Systems: Implement track-and-trace systems to verify the origin and authenticity of medicines.
- Supplier Auditing: Conduct thorough audits of manufacturers and distributors to ensure compliance with quality standards.

4. Increasing Awareness and Education

- Public Campaigns: Educate healthcare providers and the public about the dangers of counterfeit medicines and how to identify them.

- Training: Provide training for pharmacists and healthcare professionals on recognizing counterfeit products.

5. Utilizing Technology

- Mobile Applications: Develop apps for consumers and healthcare workers to verify the authenticity of medicines through codes or barcodes.
- Digital Platforms: Use blockchain technology to create secure, tamper-proof records of medicine distribution.

6. Collaborating with Stakeholders

- Partnerships: Collaborate with international organizations (e.g., WHO, INTERPOL) and NGOs to share intelligence on counterfeit networks.
- Pharmaceutical Companies: Work with pharmaceutical manufacturers to establish anti-counterfeiting measures and assist in tracking.

7. Encouraging Community Involvement

- Empower Local Communities: Engage community health workers to monitor and report illicit drug activities.
- Consumer Education: Promote awareness campaigns at community levels to educate consumers about safe medicine practices.

8. Implementing Regulatory Frameworks

- Good Distribution Practices (GDP): Ensure all stakeholders in the supply chain adhere to established GDP guidelines.
- Quality Control Testing: Establish protocols for routine quality testing of medicines in the market.

9. Reporting and Data Collection

- Centralized Database: Create a national database to track reports of counterfeit and substandard medicines.
- Data Analysis: Regularly analyze data to identify trends and hotspots for counterfeiting.

10. Legal Action and Penalties

- Prosecute Offenders: Implement legal actions against individuals and organizations involved in the manufacture and distribution of counterfeit medicines.
- Public Disclosure: Inform the public of actions taken against counterfeiters to discourage further offenses (Onyesum et al, 2019).

1.4.5 Ports of Entry for Substandard and Counterfeit Medicines into Nigeria

1. Land Borders: Nigeria shares extensive land borders with several countries (e.g., Benin, Niger, Chad, and Cameroon), which are common routes for smuggling.

2. Sea Ports: Major Sea ports, like the Lagos Port Complex (Apapa and Tin Can Island), as well as ports in Port Harcourt and Calabar, sometimes serve as entry points for counterfeit medicines.
3. Airports: International airports, especially Nnamdi Azikiwe International Airport (Abuja) and Murtala Muhammed International Airport (Lagos), are points of entry for pharmaceutical imports (Nounkeu et al, 2022).

1.4.6 Strengthening Measures to Combat the Entry of Substandard and Counterfeit Medicines into Nigeria

1. Enhanced Customs Inspection: Increase the capacity of customs officials to inspect and verify the authenticity of pharmaceutical imports. Use advanced scanning technologies and training programs to help identify counterfeit products.
2. Collaboration with Health Agencies: Foster stronger collaboration between the National Agency for Food and Drug Administration and Control (NAFDAC) and customs authorities for better coordination in monitoring and regulatory enforcement.
3. Border Surveillance and Patrols: Increase surveillance and patrols along land borders to deter smuggling activities and intercept illicit shipments.

4. Public-Private Partnerships: Engage the private sector in strengthening the supply chain and improving reporting mechanisms for suspected counterfeit products.
5. Awareness Campaigns: Conduct awareness campaigns to educate both the public and healthcare professionals about the risks of counterfeit medicines and how to recognize them.
6. Use of Technology: Implement tracking systems, such as barcoding and serialisation, to trace medicines from manufacturers to end-users, ensuring that any counterfeit products can be quickly identified.
7. Training and Capacity Building: Provide comprehensive training for health officials, customs personnel, and law enforcement on identifying counterfeit medicines and understanding regulatory frameworks.
8. Legal Frameworks: Strengthen legislation and penalties related to the manufacturing, distribution, and sale of counterfeit medicines to deter illegal activities.
9. Regional Cooperation: Collaborate with neighboring countries to share intelligence and best practices for combatting the influx of counterfeit medicines across borders.

10. Strengthening Local Manufacturing: Encourage local production of medicines to reduce reliance on imports and enhance quality control measures (WHO,2018; Onyesum et al, 2019).

1.4.7 Commonly Counterfeited Drugs

1. Antimalarials:

- Examples: Artemisinin-based combination therapies (ACTs), Chloroquine, and Quinine.
- Reason: High prevalence of malaria; significant demand drives counterfeit production.

2. **Antibiotics:**

- Examples: Amoxicillin, Ciprofloxacin, and Metronidazole.
- Reason: Over-the-counter availability leads to misuse and high demand.

3. **Analgesics**:

- Examples: Pain relievers like Paracetamol and Ibuprofen.
- Reason: Common use for various ailments makes them attractive targets.

4. **Antiretrovirals**:

- Examples: Drugs used in HIV treatment, such as Tenofovir and Efavirenz.
- Reason: Increasing prevalence of HIV/AIDS and the need for ongoing treatment.

5. **Diabetes Medications**:

- Examples: Metformin, Insulin.
- Reason: Rising rates of diabetes create a significant market.

6. **Cardiovascular Drugs:**

- Examples: Statins, Antihypertensives.

- Reason: Chronic conditions and long-term use contribute to demand.

7**. Vaccines:**

- Examples: Childhood vaccines and newer COVID-19 vaccines.

- Reason: High immunization needs and the value of vaccines make them a target (WHO, 2017).

Health Implications:

- **Increased Morbidity and Mortality**: Patients consuming ineffective or harmful drugs can suffer adverse health outcomes or die from untreated conditions.
- **Antimicrobial Resistance:** Substandard antibiotics contribute to resistance, making infections harder to treat.
- **Healthcare Costs:** Increased treatment costs due to complications from counterfeit medicines burden healthcare systems.
- **Loss of Trust**: Erosion of trust in healthcare systems can lead to lower patient compliance and utilization of legitimate services (WHO, 2017).

1.5 Impact of Substandard and Falsified Medicines

There is an international consensus that counterfeit/substandard or falsified medicines pose a serious health challenge and threat to both individual health and public health in general. The nature of these fraudulent drugs ranges from those containing wrong dosage of active ingredients, wrong active ingredients or active ingredients of low quality and purity which when taken, may at best, fail to help improve the patient's disease condition or at worst, bring about avoidable morbidity and mortality as well as drug resistance (Guta Tefera 2002). Any product which contains a dangerous contaminant that is injurious to health (including an excessively high level of the expected API) will pose an immediate hazard to the individual taking it. Patients may equally die or suffer a longer bout of disease, if their disease condition remain untreated because the medications, they take contains no API or the quantity of API present is at sub-therapeutic concentration (Ghanem N 2019).

Use of substandard and falsified medical products can also lead to increased prevalence of infectious diseases due to the non-prevention, cure or control of such diseases as a result of the use of counterfeit prophylactic agents such as vaccines which leave people unprotected against future diseases.

Use of substandard antimicrobial agents which contain either low or erratic drug doses or doses that have been diluted to sub-therapeutic concentrations can selectively allow the growth of resistant strains of pathogenic organisms thereby leading to future antimicrobial resistance (Bate R et al 2016).

Another major impact of the use of substandard and falsified medicines is the loss of public confidence in medication and in health systems generally. Where doubts about quality of medicines lead people to stay away from particular health facilities, refuse vaccination for their children and wards or fail to take treatment as prescribed leading to non-compliance or adherence to the dosage regimen that could further impact their health negatively (Ghanem N. 2019).

There is also the socioeconomic consequence of the use of substandard and falsified medicines which result in loss of monies spent purchasing such drugs and the direct costs of additional treatment that may be required to properly manage the disease conditions with other drugs and/or the cost of hospitalization and loss of man hours that may results from the development of adverse drug reactions to the fraudulent products. This is especially worse for developing countries where 80% of the population still depend on out-of-pocket payment for their medications and do not enjoy the benefits on a health insurance coverage. (WHO 2017).

1.6 Prevalence of Substandard and Falsified Medicines in the Nigerian Health Sector

The National Agency for food and Drug Administration and Control (NAFDAC), has said that Nigeria has a 15 to 20 percent of fake, substandard and falsified medicines in the market (NAFDAC factsheet, 2019). This represents a very high amount of fake and counterfeit medicines circulating freely in the Nigerian drug market. This is occasioned by a tremendous rise in the unpatriotic business of the illegal manufacture, importation and distribution of targeted substandard and falsified medicines within the country. The classes of medicines usually targeted include Antimalarials, Antibiotics,

Antihypertensives, Antidiabetic agents and several Analgesics and life style modification and enhancement drugs (WHO 2011).

The public health implications of these substandard products are numerous and include increased hospital admissions, prolonged stay in the hospital, development of multi drug resistance, treatment failures and even death.

1.7 Nafdac's Strategy to Improve Drug Security in Nigeria

The national agency for food and drugs administration and control (NAFDAC) has over the years adopted various strategies for combating the spread of fake and counterfeit medicines in Nigeria by embarking on various activities such as;

1. Public enlightenment campaigns.
2. Improving the laws governing the production, importation and distribution of drugs in Nigeria and other administrative regulations.
3. Stopping the importation of fake and substandard drugs from the source (Country of origin/production).
4. Inspection of oversea drug production facilities and issuing pre-shipment clearances for imported drugs.
5. Restriction of the number of points of entry to ensure proper surveillance.
6. Confiscation and destruction of fake drugs already in circulation and prosecution of local vendors.
7. Cooperation with local banks to acquire NAFDAC clearance and financial document for drug imports.
8. Monitoring quality standards among local manufacturer.
9. Modernization and strengthening of regulatory processes.

10. Streamlining and strict enforcement of drug registration guidelines.

11. Improved recruitment, training and supervision of regulatory staff.

Strict sanctioning of erring and corrupt staff (Akuniyi 2002).

1.7.1 The Causes of Poor Quality

A disastrous situation that is complicated and tangled is what results from giving a patient a poor-quality artemether-lumefantrine tablet:

For the Patient (Treatment Failure): The first and foremost impact is the continuation of the disease in the patient. An infection dose that is not enough will not be able to kill the infection. In the case of a child, this could be the difference between speedy recovery and rapid progression of the disease from mild to severe (e.g. cerebral malaria, severe anemia, multi-organ failure), which most of the time leads to death.

For Public Health (Drug Resistance): This is the threat that can eventually lead to the extinction of humanity. When the parasites encounter low levels of the drug, only the weakest ones are killed, while the "stronger" or more tolerant ones remain. This, in fact, is "selection pressure." Those who survive subsequently reproduce and transfer their tolerance until a fully resistant strain becomes dominant and spreads. The use of poor-quality antimalarials is the main cause of artemisinin resistance and, as a result, the problem of making our entire class of last-line drugs useless is going to be bigger than ever (WHO 2023). .

For the System (Economic and Social Loss): Large amounts of money—both from the international donors and the families—are being wasted on ineffective treatments. The erosion of people's trust in the healthcare system is, however, a more significant impact.

When "official" medicines from the clinic, which are expected to work, fail, people may decide not to seek formal care anymore and thus may resort to unproven traditional remedies or unregulated markets, thereby further deepening the health crisis.

1.7.2Meeting Quality Standards: The Who Prequalification Programme

Ensuring drug quality in the face of such high stakes is not only a concern of the manufacturer's but also a global health security necessity. National Regulatory Authorities (NRAs) are the main gatekeepers in each country; however, many of them lack sufficient resources.

The World Health Organization (WHO) Prequalification (PQ) Programme was created to address this issue and acts as a main global standard. It is a service that evaluates the quality, safety, and effectiveness of drugs. The manufacturer is required to provide a large amount of data (a "dossier") and also be subjected to tough inspections of the manufacturing plant.

Prequalified products are those that comply with the strictest international standards. International purchasing agents such The Global Fund to Fight AIDS, Tuberculosis and Malaria and UNICEF, procure almost exclusively medicines that obtained the WHO prequalification. The system put in place is a way to ensure that the billions of dollars invested in global health go towards buying products that are safe and effective, thus, making the patients safe and the drugs secure from the resistance threat. To conclude, artemether-lumefantrine is a robust and necessary weapon in the war against malaria. Nevertheless, it is just as effective as its quality.

Maintaining and implementing high-quality standards through programs like the WHO Prequalification is an indispensable factor in the global malaria plan—crucial for both saving lives now and conserving our most potent treatments for the future.

1.7.3 Quality Control of Tablet Formulations

Tablets are the most widely utilized and easy-to-use form of medication delivery. Yet, their minimalistic look is deceptive as the manufacturing process is intricate and requires high precision. The effectiveness of a tablet to provide a drug safely and efficiently is based on the tablet having the right dose, releasing it at the correct rate, and being physically strong. To achieve this, pharmaceutical manufacturers carry out a stringent Quality Control (QC) program, which is a set of standardized tests performed to ensure that every batch of tablets fulfills all the safety, quality, and efficacy requirements. (e.g. BP, 2023; USP, 2023).

These examinations may be comprehensively classified as "official" tests, which are mandatory by national and international pharmacopoeias (for example, the United States Pharmacopeia [USP] or British Pharmacopoeia [BP]), and "unofficial" tests, which are not a universal requirement by all pharmacopoeias and are vital for in-process control and providing a high-quality, stable product.

1.7.4 Ensuring Safety and Efficacy:

Tablets are by far the most common and easiest method of delivering medication. However, their simple facade is a complex manufacturing process where accuracy is very important. A tablet's functionality to provide a drug safely and effectively depends on it having the right dose, releasing it at the drug proper rate, and being physically strong. To

ensure this, pharmaceutical companies put in place a stringent Quality Control (QC) system, which is a series of standard tests aimed at checking that each batch of tablets is in accordance with safety, quality, and efficacy requirements.

The tests performed on the tablets can be divided to two major categories: first, "official" tests, which are mandatory according to national and international pharmacopoeias (e.g., United States Pharmacopeia [USP], British Pharmacopoeia [BP]), and second, "unofficial" tests, which are not required by all pharmacopoeias, but are of great importance for in-process control and product consistency and quality.

1. 8 Chemical Method of Analysis of Drugs

Chemical methods of drug analysis are mainly used for constant analysis with high accuracy and reliability. However, they can be complicated and time consuming and are not conducive for automation. They are nevertheless, the most dependable as they are easy to conduct and far less expensive when compared to the instrumental techniques. The chemical method of analysis includes mainly the gravimetric, titrimetric and pH determination (Joda *et al* 2018).

Gravimetric Analysis and Testing

It refers to the separation of the components of the drug compound to be tested and relating the extent of the content or composition of each component by determining their individual masses. Gravimetric analysis is performed by getting a certain weight of the sample, using an appropriate method to separate the desired component from other components in the sample, then converting it into a certain form of weight and finally obtaining the content of the component by weighing (USP <731>)

Titrometric Analysis

Acid-based titrometry refers to determining the composition of a drug substance according to the extent of consumption of certain standard solution by volume measurement it involves dropping a reagent solution with a known accurate concentration into the solution of the tested drug substance until the chemical reaction is complete. Based on the concentration of the reagent solution used and its volume, one can obtain the content of the measured component.

Acid – base titrations are the most widely used chemical method of analysis of drug samples in the industry during drug production as it is commonly used in the analysis of raw materials, intermediate products and finished products in pharmaceutical quality control (QC) laboratories (USP <541>).

pH value determination method

pH is the negative logarithm of the hydrogen ion activity of a solution and it is used to indicate the acidity or alkalinity of a solution. The device used for pH measurement is called the pH meter or acidity meter and it consists of two pares namely, a pH indicator. The pH measurement cell is a primary cell consisting of a glass electrode, a saturated calomel electrode and the solution to be measured. The glass electrode is the indicating electrode while the calomel electrode is the reference electrode which is used as a reference for indicating the potential of the electrode.

The pH value determination method has now been included as a standardization technique for drugs in the pharmacopoeia of various countries of the world (USP <791>).

INSTRUMENTAL METHOD OF ANALYSIS OF DRUGS

The instrumental methods of drug analysis is used for micro and trace analysis of drugs with high sensitivity. It mainly includes optical methods, chromatographic methods ad spectrophotometric methods (Skoog *et al* 2007).

Official (Pharmacopoeial) Tests

These tests are a must for any product that is going to be marketed legally. They mainly concentrate on the essential features that influence the drug's therapeutic effectiveness and the patient's safety directly.

Assay (Content of Active Ingredient): This test is the one and only to verify the import of the drug. It performs the chemical analysis of the drugs in order to find the exact concentration of the active pharmaceutical ingredient (API) in the tablets (Nilam A. Nikam et al. 2025).

Technique: The method which is most commonly used and most accurate is High-Performance Liquid Chromatography (HPLC). Sample Preparation: Some tablets (e.g., 20) are pulverized to obtain a fine and homogeneous powder. A definite quantity of this powder is then accurately weighed and mixed with a certain solvent (called the diluent) to prepare a solution (M. Uddin et al. 2016).

Analysis: The prepared solution is fed into the HPLC instrument. The HPLC pump forces the solution through a column loaded with a material specially made for this purpose. The various compounds (the API and the excipients) in the sample interact differently with the material in the column, thus they are separated. A detector (in most cases a UV-Vis detector) records the API when it leaves the column and at this moment a peak is formed on the chromatogram is produced.

Quantification: The size of this peak is directly proportional to the amount of the API. The extent of this peak is contrasted with the peak extent of a Certified Reference Standard (CRS) is that the CRS is the pure API of a known concentration.

Sample Preparation: Twenty tablets are ground into a homogeneous powder. Then, an accurate portion of the powder is measured and mixed with a certain solvent to prepare a solution (the solvent is called a diluent) (Nilam A. Nikam et al. 2025).

HPLC

Analysis: The preparing solution is placed in the HPLC instrument. The HPLC pump transports the solution through a column filled with the material specially chosen for this purpose. The individual compounds (the API and the excipients) interact differently with the material in the column and as such they are separated. A detector (usually a UV-Vis detector) records the API when it comes out of the column and at this moment a peak is formed on the chromatogram is produced (M. Uddin et al. 2016).

Quantification: This peak's size, or more accurately the "area" of this peak is directly proportional to the concentration of the API. The extent this peak is compared to the peak extent of a Certified Reference Standard (CRS) which is a pure sample of the API at a precisely known concentration.

Specification: The test result needs to be within a small range set by the pharmacopoeia, normally between 90.0% and 110.0% of the content stated on the label (e.g., a 100 mg tablet should contain 90.0 mg to 110.0 mg of the API) (M. Uddin et al. 2016)

1.8 Tools for Quality Control of Pharmaceutical Drug Products

Specific tools and methods were used to carry out the study and these includes: test for uniformity of weight and content, hardness, friability, disintegration and dissolution tests. These, together with the concept of quality assurance, shall be discussed briefly in the section below.

Uniformity of Weight and Content: The combined effect of these tests is to ensure that all tablets in a batch are within reasonable limits of the same potency. A perfect manufacturing procedure would yield a batch of tablets having identical weight and medicament content.

In practice, the values of these parameters for individual tablets deviate about the mean values for the whole batch. Such deviations will be of acceptable magnitude if correctly formulated and prepared granules are compressed on properly maintained equipment. Ideally, the quality of a batch of tablets would be assessed by determining the potency of each tablet in a truly representative sample; however, the analysis of a large number of tablets by conventional means would be both costly and time consuming.

The standard for uniformity of content are framed to take in to account processing difficulties, variations in the purity of drugs, accuracy of the assay methods and the size of the sample relative to that of the typical manufacturing batch.

Tablet hardness test

Tablet hardness test involves the mechanical strength of the tablets. It is load required to crush the tablet when placed on its edge and it is an indication of the ability of the tablet to resist stress during transportation, storage and use (Abhilash, 2018). Don 2011

however, explains that the crushing strength is the most widely used in nomenclature. He defines it as the compression force which when applied is placed upon affixed anvil and then is transmitted to it by means of a moving plunger. Examples of commercially available instruments for measuring the crushing strength of tablets include; stokes (Monsanto), strong cobb, Pfizer, Erweka and Schleuniger equipment.

Friability test

Friability is defined as the percentage of weight loss by tablets due to mechanical action during the test tablets are weighed before and after the test and the friability is expressed as a percentage loss on pre-test tablet weight. Friability also refers to the ability of the compressed tablet to avoid fracture and breaking during transport (Clement *et al,* 2011; Don, 2011). It is the tendency of the tablet to powder; chip or fragment and this can affect the elegance, consumer acceptance of the tablet, and also add to tablet weight variation and content uniformity problems. Friability is a property that is related to[1] the hardness of the tablet. The friability test involves an instrument called the friabilator, which is use to evaluate the ability of the tablet to withstand abrasion in packaging, handling, shipping. The USP states that conventional compressed tablets that loss less than 0.5% to 1% of their weight after 100 revolutions are generally considered acceptable (USP, 2004).

1.8.4 Disintegration Test: Features common to the tests described in most literature are: an aqueous disintegration medium, agitation of the tablet or medium to simulate peristalsis and means for recognizing the endpoint, that is, complete disintegration.

In the context of tablets technology, disintegration implies penetration of the tablet by an aqueous liquid, disruption of internal bonds and the subsequent breakdown of the tablet.

In other words, disintegration, though a poor guide, can be used to predict the biological availability of a drug. It is a rate limiting step in the course of drug utilization for conventional products (Hiola *et al* 1996)

1.8.5 Dissolution Rate Tests: With Proper attention to operating conditions, dissolution tests provide valuable in vitro data for the development of pharmaceutical products, an indication of relative potential in vitro performance and means for quality control. Certainly, there is now considerable evidence to show that in a given series of products, the one with the highest dissolution rate will probably produce the most rapid and intense response in vivo. Bales et al (1967) compared suspension and tablet formulation of salicylamide and demonstrated that there in vivo behaviour were in parallel with their in vitro dissolution rates.

When designing test apparatus, means must be provided for agitating the dissolution medium, supporting the sample without impeding the flow of liquid and estimating the quantity of drug that has dissolved. Closed circuit systems have been devised, by e.g., Marshall and brook (1969), to take advantage of the methods that now exist for continuously monitoring concentrations of solutes in liquids.

Provision may also be made for replacing part of the dissolution medium from time or time or for changing its nature, both modifications are intended to give a closer simulation of actual conditions within the gastrointestinal tract.

1.9 Artemether-Lumefantrine Formulations in the Nigerian Market

As a key element of the national malaria treatment policy in Nigeria, artemether-lumefantrine (AL) is the most commonly recommended single agent and the first line

therapy of choice among Artemisinin-based Combination Therapy (ACT) **(Federal Ministry of Health [FMOH], 2020)**. This high demand has led to a large and diverse market for pharmaceuticals with many brands ranging from the original innovator product to a variety of generic versions.

The Innovator (Reference) Brand

Coartem® is the innovator, or reference, brand of artemether-lumefantrine.

Manufacturer: Novartis

significance: Coartem® was the first fixed-dose combination of artemether-lumefantrine to be developed and prequalified by the World Health Organization (WHO) **(Falade & Oduola, 2007)**. It is the standard product to which generic versions are usually compared in bioequivalence and quality studies.

Formulations: This product is very popular in Nigeria where it is sold in different dosages for varying age and weight groups such as:

Coartem® 20/120: (20 mg artemether / 120 mg lumefantrine) - Usually a pack of 24 tablets contains the normal amount of the dose.

Coartem® 80/480: (80 mg artemether / 480 mg lumefantrine) - With the higher power, the tablet helps to relieve the "pill burden" as only six tablets of a full course need to be taken by a patient.

Coartem® Dispersible: A dissolvable, sweetened tablet made just for infants and children, that facilitates adherence and gives dosing accuracy in a vulnerable group of patients.

1.9 Common Generic Brands in Nigeria

Numerous generics are very instrumental in ramping up accessibility and making the product affordable. These generics carry the same active pharmaceutical ingredients (APIs) as the innovator brand. Hence a product that is genuine and obtainable in the Nigerian market is essentially a NAFDAC-registered product or service. The National Agency for Food and Drug Administration and Control (NAFDAC) is the licensing agent for such products. **(NAFDAC, 1993)**. The list of generic brands provides just an indication of the existence of a market in no way reflects the entirety of the market but comprises the most common and widely available artemether-lumefantrine products in the Nigerian market, which can be purchased at pharmacies and hospitals:

Lonart®: (Produced by Greenlife Pharmaceuticals Ltd.) - A generic brand that is most popular and widely known in Nigeria.

Amatem®: (Produced by Elbe Pharma Nigeria Ltd.)

Lumartem®: (Produced by Bliss GVS Pharma Ltd.)

Artefan®: (Produced by Ajanta Pharma Ltd.)

Rofant®: (Produced by Fidson Healthcare Plc)

Combiart®: (Produced by Strides Pharma)

Laritem®: (Marketed by Lagos)

Artelum®: (Produced by Swiss Pharma Nigeria Ltd.)

Falcitem®: (Produced by Cipla)

Artecxin®: (Produced by Micro Labs)

1.10 The Critical Link to Quality and Regulation

The numerous brands available in the market is a good thing in terms of accessibility but at the same time, it poses a huge problem for quality control. This is the point where your previous query becomes very important.

The National Agency for Food and Drug Administration and Control (NAFDAC) is a regulatory body that ensures the quality, safety, and efficacy of all medicines available in Nigeria **(NAFDAC, 1993)**. Any brand, either a newly innovated one or a generic, has to go through NAFDAC's registration process. This process involves production of a dossier and undergoing quality control tests (e.g., assay by HPLC, dissolution, disintegration, and friability) as we have talked about.

Such regulatory monitoring is necessary as the Nigerian market is the lead target for Substandard and Falsified (SF) antimalarials (WHO 2017).

NAFDAC is always making public announcements to inform people of these risky products. For instance, previously, alerts were given to the falsified versions of artemether-lumefantrine, such as those found circulating under the names like "Aflotin" (NAFDAC, 2009) or substandard batches of "Artemetrin DS" (WHO, 2018), which people might be unaware of.

Hence, notwithstanding the large number of genuine and good proper-quality brands, we cannot take the QC tests lightly as it is not just a theoretical step in the manufacturer's

process. Besides theoretically, it is the main instrument that NAFDAC employs to shield the public from the products that are ineffective and unsafe. The inappropriate use of substandard AL tablets not only causes treatment failure with consequent death but also profoundly contributes to the problem of antimalarial drug resistance, which is a big threat to the sustainability of all ACTs in the future (WHO, 2023).

1.11 The Concept of Quality Assurance

Quality assurance, or QA for short, refers to a program for the systematic monitoring and evaluation of the various aspects of a project, service, or facility to ensure that standards of quality are being met (Ejaz *et al* 2017).

It is important to realize also that quality is determined by the program sponsor. QA cannot absolutely guarantee the production of quality products, unfortunately, but makes this more likely. Two key principles characterize QA: "fit for purpose" (the product should be suitable for the intended purpose) and "right first time" (mistake should be eliminated). QA includes regulation of the quality of raw materials, assemblies, products and components; service related to production; and management, production and inspection processes (Clement *et al* 2007).

Quality assurance refers to the process of making sure quality requirements have been fulfilled. Quality assurance aims to prevent mistakes and defects, as well as manage quality through defining processes, establishing standards, and developing guidelines for better quality management. Hence, quality assurance is focused on the process while quality control revolves around the product. There is also a contrast between how quality control is carried out compared to quality assurance. Quality control is often the responsibility of certain individuals in a pharmaceutical Organisation. These duties are

usually carried out by quality control specialists who undertake product testing and process validation. These professionals specialize in troubleshooting errors in medical products and making sure they comply with legal standards.

Quality assurance, on the other hand, involves an entire team with each member responsible for different quality assurance activities such as documentation, planning, project auditing and other forms of quality assessments. Quality assurance is thus more than just testing the quality of aspects of a product, service or facility. It analyses the quality to make sure it conforms to conforms to specific requirements and comply with established plans (Giri *et al* 2012).

1.12 Aim of Study

Assessment of different drugs of artemether lumefantrine found in Benin City

1.13 Objectives of the Study

1. To evaluate the organoleptic properties of artemether/lumefantrine
2. To access physical properties like weight uniformity, hardness, and friability.
3. Determine the disintegration time of the various brands.
4. To evaluate drug release using a dissolution test

1.14 Significance of the Study

As the study assesses the quality of a first-line antimalarial, artemether-lumefantrine, in Benin City, its impact on public health is very direct, and hence it becomes an indispensable one. One way it does so is by taking patient safety to the next level through the confirmation of the effectiveness of the drugs in circulation, thus averting treatment failures, complication cases, and death rates that could have been

avoided. In addition to that, the study is instrumental in pinpointing low-quality, low-dose tablets, which, in effect, lead to the fast spread of resistance to antimalarial drugs, which is one of the most significant threats to global health (WHO, 2023). At long last, the results will essentially be of great help in giving the much-needed local data to the regulatory bodies, such as NAFDAC, for them to be able to spot and take out counterfeit or substandard products from the market, thus not only ensuring the public's safety but also preserving their confidence in the healthcare system.

CHAPTER 2

2.0 METHOD

2.1 Materials:

Electronic weighing balance,

3 station Disintegration apparatus(Manesty machine limited, UK).

RC-3 Dissolution apparatus (NANBEI INSTRUMENT LIMITED, China).

Monsanto hardness tester (JAPSON, India).

Mortar and pestle

Roche Friabilator (NANBEI INSTRUMENT LIMITED, China).

Glass wares

Ultraviolet-Visible spectrometer.

HCl

Sodium lauryl sulphate.

2.2 Method

Different brands of artemether-lumefantrine (AL) tablets were sourced from registered retail pharmacies in Benin City metropolis and Patent and Proprietary Medicine Vendors (PPMVs) in a location-based manner.

In order to have a representative sampling, the metropolis were divided into the major Local Government Areas (LGAs) such as Oredo, Egor, and Ikpoba-Okha. Pharmacies and PPMVs in these LGAs were chosen through convenience or random sampling methods.

The samples of medicine were gotten via a "mystery shopper" style. In this case, I acted as a normal consumer and bought the drugs that were needed over the counter. By this means, ensure that the samples obtained are the ones that represent the stock of drugs that are available to the public.

the information from each sample of the collection was recorded in the following manner:

- Brand name of the drug
- Name and address of the pharmacy/vendor
- Date of purchase
- Date of manufacture and expiry
- Batch number
- NAFDAC registration number

2.2.1 Organoleptic properties

The organoleptic and visual examinations were conducted for the externally and physically checked characteristics of all the brands that were sampled.

First, the external packaging was checked for the following information: the manufacturer's name and address, batch number, manufacturing date, expiration date, NAFDAC registration number, and the printed text readability.

Then the tablets were checked. Ten tablets of each brand were randomly selected and visually inspected for the uniformity of their color, shape, and size. The identification of defects in the physical nature of the tablets, such as fragmentation, chips, spots, or mottling, was documented. Furthermore, the characterization of the scoring or monogram (brand markings) identification on the tablet surface was also noted.

2.2.2 Determination of Tablet Hardness (Crushing Strength)

The tablet hardness of the different samples was measured in this instance to get a mechanical strength evaluation of the tablets. For the test, a Monsanto-type hardness tester was used.

From each brand, randomly ten tablets were chosen. One by one, each tablet was placed diametrically between the fixed anvil and the moving jaw of the tester. A compressive force was applied by turning the screw knob manually and the force was increased slowly and steadily until the fracture of the tablet occurred.

The force (in Kiloponds, kp) at the calibrated scale, which caused the tablet to fracture was recorded. The operation was carried out on all ten tablets. The average hardness and standard deviation for each brand were then computed to determine the average crushing strength and its variation.

2.2.3 Determination of Tablet Disintegration Time

Disintegration test was carried out to find the time taken by the tablets to disintegrate into such small particles that can pass through a certain mesh.

The test was done with a pharmaceutical disintegration test apparatus conforming to pharmacopoeial requirements. Six tablets of each brand were selected at random. Each of the six tubes of the basket-rack assembly was loaded with one tablet. The basket-rack assembly was dipped in a beaker (1 liter) filled with distilled water - the disintegration medium. The medium was kept at a temperature of 37°C ± 2°C.

The machine was turned on, making the basket move up and down at the set frequency. The disintegration time was recorded when the tablet passed through the mesh completely or no residue (except the fragments of the insoluble coating) remained on the

mesh. The average disintegration time, along with the standard deviation for each brand, was determined.

Determination of Weight Uniformity (Weight Variation)

The weight uniformity test has been conducted to confirm the consistency of dosage units, i.e., the number of tablets in each brand, thus dose uniformity was ensured. The test was performed as per pharmacopoeial standards.

Twenty tablets were randomly selected from each brand; these tablets were weighed individually on a high-precision analytical weighing balance. The average (mean) weight for each brand was calculated from these 20 individual weights.

Subsequently, the percentage of deviation of the weight of each individual tablet from the established average weight was calculated. The results were compared with the standard pharmacopoeial limits to ascertain if the batch met the requirements for uniformity of weight.

2.2.4 Determination of Tablet Friability

It was the goal of the friability test to figure out how strong the tablets are physically and also to find out what percentage of the tablets would chip, crumble, or break if they are subjected to mechanical stress.

For this test a Roche-type friabilator was employed. For each tablet brand, a sample (20 tablets) was properly weighed (W1) after thorough dedusting. The tablets were placed in the friabilator drum.

2.2.5 Determination of Percentage Purity

The process began with the careful preparation of two key solutions. First, a Standard Solution was created to serve as the benchmark for 100% purity. This involves accurately weighing a precise amount of a Certified Reference Standard (CRS), which is a pure sample of the API, transferring it to a volumetric flask, and dissolving it in an appropriate HPLC-grade solvent to achieve a precisely known concentration. Second, a Sample Solution was prepared from the tablets being tested. A number of tablets (20), were weighed and ground into a fine, uniform powder. An amount of this powder equivalent to a single average dose was then accurately weighed and transferred to another volumetric flask. The same solvent was added, and the mixture was shaken to ensure the API is fully extracted from the tablet's fillers, or excipients. This mixture was then diluted to a final volume and filtered to remove any insoluble materials, which could otherwise damage the sensitive HPLC equipment, resulting in a clear sample solution.

Once the solutions were prepared, The HPLC system, which includes a pump, injector, column specific to the API, and a UV-Vis detector, is programmed with the correct parameters for the analysis, such as the solvent flow rate, column temperature, and detector wavelength. A precise volume of the Standard Solution was injected into the system, traveled through the column, and was measured by the detector, which records a "peak" on a chromatogram corresponding to its concentration. Following this, the exact same volume of the Sample Solution was injected and analyzed in the same manner, producing its own peak.

The instrument was run for 4 minutes at an average speed of 25 revolutions per minute (RPM), that is 100 revolutions in total. When the cycle was finished, the tablets were taken out, dedusted and weighed (W2) again.

The percentage of weight loss (Friability) was figured out through the use of the formula:

Friability (%) = [(W1 - W2) / W1] * 100

Generally, no more than 1.0% of the maximum average weight loss is regarded as acceptable.

2.2.6 Determination of Drug Dissolution

The in-vitro dissolution test was done to determine the rate and the total amount of the drug released (Artemether and Lumefantrine) from the tablets.

The dissolution test was conducted on a model RC-3, following the USP Apparatus 2 (Paddle Method) standards. The dissolution medium (e.g., 900 mL 0.1 N HCl containing 1% lauryl sulphate) was poured into each vessel to stimulate gastrointestinal conditions, and brought to a temperature of 37°C ± 0.5°C.

One tablet was given to each of the six vessels, and the device was operating at a set paddle speed (100 RPM). At various time intervals (15, 30, 45, and 60 minutes), a certain volume of dissolution medium was withdrawn from each vessel and filtered. The same volume of fresh, pre-warmed medium was put into each vessel immediately to keep the volume constant.

The concentration of Artemether and Lumefantrine in the sampled aliquots was determined by measuring the absorbance at this wavelength and comparing it against the standard solution

The content of Artemether and Lumefantrine in the taken samples was found UV-Visible Spectrophotometry using agilent at 254nm. The overall percentage of the drug dissolved at each time point was then determined.

2.3 Data Analysis

Quantitative data obtained from the hardness, friability, and disintegration time tests were analyzed using statistical software (Python scipy.stats and statsmodels). A One-Way Analysis of Variance (ANOVA) was performed to determine if there were statistically significant differences between the means of the 16 brands. The significance level (α) was set at 0.05. Where significant differences were detected ($p < 0.05$).

CHAPTEER 3

3.0 RESULT AND DISCUSSION

3.1 RESULT

The information on the labels of the different brands of Artemether/Lumenfatrine tablets was assessed for their pharmaceutical equivalence and quality assurance are as shown in Table 3.1. The information obtained showed that all ten (16) brands were within their shelf lives and validity period. It also showed that all samples collected for the study had the required NAFDAC approval numbers, which is a prerequisite for authentication.

The organoleptic properties of the different brands tested was shown in table 3.2 which shows the physical accessment of appearances

The result of the tableting properties of the ten different brands of diclofenac sodium such as uniformity of weight, hardness, (crushing strength) and friability are as shown in tables 3.3, 3.4 and 3.5 respectively. The ten brands were found to be uniform in weight and the weight variation as expressed as the standard deviation from the mean weight were found to be within acceptable limits of less than ± 5%.

The percentage friability result showed that fifteen of the sixteen brands had very negligible friability indicating that the tablets were well compact tablets and would be able to withstand the mechanical stress of handling, packaging and transportation without undergoing any form of capping, or lamination of the tablet surface, only biolumefar showed significant friability which indicates lower resistance to mechanical stress.

Table 3.1.: Labelling information of different brands of Artemether/Lumefantrine

Code	Brand name	Batch no.	Manufacturing date	Expiry date	NAFDAC no.	Country of origin
AL-1	Lynsunate	EB0027	02/2025	01/2028	A4-4854	India
AL-2	Artelum	A240220c/p1128	05/2024	04/2026	A11-100147	Nigeria
AL-3	Lumapil	T24078	10/2024	09/2027	B4-2275	Nigeria
AL-4	Arenax	VGT230194	10/2023	09/2026	A4-4854	Nigeria
AL-5	Artemeter plus	MP25576	06/2025	05/2028	B4-5719	Nigeria
AL-6	Cartef	JT357	08/2024	07/2027	A4-7395	UK
AL-7	Luter	CD06622	06/2023	05/2026	B4-3240	Malaysia
AL-8	Contrine	CR34002	05/2024	04/2027	B4-7566	India
AL-9	Clartem	240721	07/2024	07/2027	B4-5445	India
A-10	Co-mal	CO240901	09/2024	08/2027	B4-5283	Nigeria
AL-11	Malanter	MD25015	03/2025	02/2028	04-9927	India
AL-12	Lonart	C1AFM058	10/2023	09/2026	04-8827	India
AL-13	Shal'artem	45010055	04/2024	03.2027	A4-8201	India
AL-14	Biolumefar	3076	03/2023	02/2026	C4-0577	India
AL-15	Raimet	A4-200563	09/2023	08/2026	C4-1233	Switzerland
AL-16	Macalum	DYI4022045	07/2024	06/2027	C4-1565	India

3.1. Physical and Organoleptic Properties (Appearance)

First visual examination is a very simple and non-destructive preliminary quality screening. According to pharmacopeial standards, the tablets should look the same and be free from any kind of defects, which points towards the production being carried out under Good Manufacturing Practices (GMP).The physical properties of all tablets tested meet the GMP with consistency in the appearance of the tablets, showing no noticeable defects in Table 3.2

Table 3.2: Organoleptic properties of different brands of Artemether/Lumefantrine

Code	Color	Shape	Coating	Scoring
AL-1	Yellow	Oblong	Coated	No
AL-2	Yellow	Oblong	Uncoated	No
AL-3	Yellow	Round	Coated	Yes
AL-4	Yellow	Round	Uncoated	No
AL-5	Yellow	Round	Uncoated	Yes
AL-6	Yellow	Oblong	Uncoated	Yes
AL-7	Yellow	Oblong	Coated	No
AL-8	Yellow	Round	Uncoated	No
AL-9	Yellow	oblong	Uncoated	Yes
AL-10	Yellow	Round	Uncoated	No
AL-11	Yellow	Round	Coated	Yes
AL-12	yellow	Round	Coated	Yes
AL-13	Yellow	Round	Coated	Yes
AL-14	Yellow	Oblong	Coated	yes
AL-15	Yellow	Round	Coated	No
AL-16	Yellow	Round	Uncoated	Yes

3.2. Weight Uniformity

The uniformity of dosage units is a very important factor that allows for each patient to be given the appropriate dose with a minimum of variation. The test is performed according to the standard described in the United States Pharmacopeia (USP) general chapter <905> 'Uniformity of Dosage Units'. As the average weight of AL tablets is above 250 mg and the drug substance concentration is higher than 25%, the Weight Variation (WV) method should be used. The USP stipulates that no more than two of the ten tablets tested are allowed to deviate from the average weight by more than ±5%, and none of them can deviate by more than ±10% (USP 43-NF 38, 2020). The tablets tested showed uniformity of weight with none of the tablets showing a weight deviation of up to 5% as shown in table 3.3

Table 3.3: weight uniformity and standard deviation of various brands of Artemether/Lumefantrine

Code	Mean Weight (g) ± SD
Co-mal	0.990 ± 0.032
Lynsunate forte	0.790 ± 0.032
Arenax	0.684 ± 0.015
Artemeter plus	0.738 ± 0.020
Biolumefer	0.694 ± 0.015
Cartef	0.770 ± 0.021
Clartem- DS	0.894 ± 0.017
Lumepid	0.760 ± 0.026
Lonart	0.704 ± 0.012
Artelum combo	0.801 ± 0.014
Contrine plus	0.636 ± 0.007
Malanter DS	0.725 ± 0.007
Shal'artem forte	0.711 ± 0.021
Raimet	0.84 ± 0.05
Macalum	0.96 ± 0.05
Luter	1.08 ± 0.04

3.3. Hardness and Friability

Tablet hardness (or breaking force), along with tablet friability, are two closely related, interdependent, and most important mechanical properties, which are the basis for tablet integrity. Although hardness is usually a non-compendial test, it is very important for the development of formulations and quality control, as it is a way of proving that tablets through various stages of the production process, packaging, and transportation can be kept intact. Friability, standardized by USP <1216> 'Tablet Friability', determines the resistance of the tablet material to a wear process. The pharmacopeial limit for friability for most of the conventional tablets is set as a maximum weight loss of not more than 1.0% (USP 43-NF 38, 2020). Only the biolumefar tablet showed a friability greater than 1%. This failure indicates that the tablet is likely to chip or break before administration which leads to a loss of active drug and reduced patient compliance.

There was a wide range of differences in the 16 brands' mean hardness values, as they went up from the lowest 6.5 kP (Lumepid) to an extremely high 11.33 kP (Luter). Most of the brands were within the normally acceptable range of 4–10 kP.

On the other hand, Luter exhibited the highest hardness, which was statistically significant ($p = 0.0003$) compared to the softer brands like Lumepid. Despite the fact that the brand passed friability with small (0.74%) weight loss, this too much hardness, which is normally caused by over-compression or too high binder concentration, can make the process of disintegration and thus, drug dissolution, difficult (Jouny et al., 2019). Represented in table 3.4 and 3.5

Table 3.4: mean hardness and standard deviation of various brands of artemether/lumefantrine

Code	Hardness (Kp) ± SD
Co-mal	7.62 ±1.25
Lynsunate forte	10.12 ± 0.63
Arenax	8.62 ± 0.48
Artemeter plus	10.25 ± 1.50
Biolumefer	8.88 ± 0.63
Cartef	6.25 ± 0.50
Clartem- DS	9.00 ± 0.82
Lumepid	6.50 ± 2.55
Lonart	9.25 ± 0.65
Artelum combo	9.00 ± 1.41
Contrine plus	9.12 ± 1.31
Malanter DS	7.62 ± 1.11
Shal'artem forte	10.00 ± 1.63
Raimet	7.17 ± 1.47
Macalum	7.6 ± 2.07
Luter	11.33 ± 0.58

Statistical analysis using ANOVA revealed a significant difference in the hardness profiles of the brands ($p = 0.0003$).

Table 3.5: percentage friability of various brands of artemether/lumenfatrine

Code	Friability (%)
Co-mal	0.96
Lynsunate forte	0.82
Arenax	0.29
Artemeter plus	0.28
Biolumefer	3.00
Cartef	0.39
Clartem- DS	0.56
Lumepid	0.45
Lonart	0.90
Artelum combo	0.38
Contrine plus	0.93
Malanter DS	0.40
Shal'artem forte	0.28
Raimet	0.91
Macalum	0.85
Luter	0.74

The One-Way ANOVA showed a statistically significant effect of brand on friability ($p = 0.015$).

3.4. Disintegration

Disintegration is the primary phase of drug release and subsequent drug absorption. In the case of uncoated, immediate-release tablets, the USP <701> 'Disintegration' test mandates that disintegration should be complete within 30 minutes in the given medium at 37°C (USP 43-NF 38, 2020).

The tablets tested showed good disintegration and passed the disintegration test with only Contrine failed the disintegration test, with a statistically significant delay ($p < 0.001$) compared to all other brands tested.. As shown in Table 3.6

Table 3.6: mean disintegration time and standard deviation of various brands of artemether/lumefantrine

Code	Mean Disintegration Time(Mins) ± SD
Co-mal	13.90 ± 0.99
Lynsunate forte	16.50 ± 0.01
Arenax	13.78 ± 1.54
Artemeter plus	12.60 ± 3.43
Biolumefer	18.52 ± 1.60
Cartef	13.16 ± 5.56
Clartem- DS	11.00 ± 0.02
Lumepid	11.71 ± 0.01
Lonart	13.06 ± 0.01
Artelum combo	11.73 ± 0.01
Contrine plus	30+
Malanter DS	12.5 ± 0.64
Shal'artem forte	9.6 ± 4.81
Raimet	5.57 ± 0.01
Macalum	7.8 ± 0.42
Luther	13.8 ± 0.76

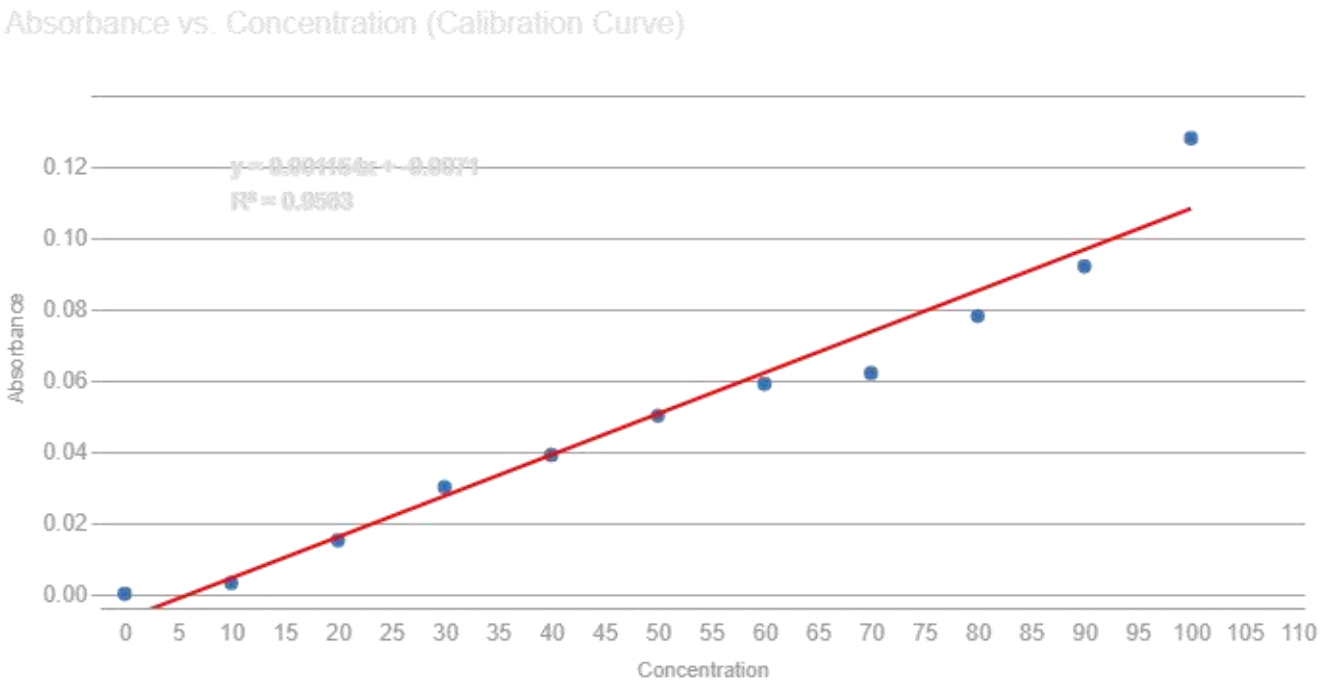
A highly significant difference was observed in the disintegration times ($p < 0.001$). Contrine took significantly longer to disintegrate (mean 42.00 min) than all other brands, exceeding the standard time for immediate-release tablets.

3.5. Dissolution

Dissolution test, which is described in detail in USP <711>, is considered the most important in-vitro parameter, from the point of view, it is used for the in-vivo bioavailability prediction of the drug. This is particularly the case for AL where lumefantrine is a Biopharmaceutics Classification System (BCS) Class II compound (low solubility, high permeability). Its absorption is limited by the dissolution rate, which makes this a test of direct therapeutic efficacy (Tender, 2017).

According to the USP monograph, dissolution of Artemether and Lumefantrine Tablets should be performed in a medium containing a surfactant (e.g., 1.0% sodium lauryl sulfate in 0.1 N HCl) to simulate the conditions of the gastrointestinal tract. A common pharmacopeial standard requires that not less than 80% (Q) of the labeled amount of both artemether and lumefantrine should be dissolved within 60 minutes.

Where lumefantrine dissolution is lacking, it directly points to plasma concentrations being below therapeutic levels. Since lumefantrine is the longer-acting partner drug that is responsible for the radical cure, its poor bioavailability is the main reason for treatment recrudescence and, thus, may also be the major source of the selection of artemisinin-resistant parasites (Djimdé et al., 2011). Using 254nm for both artemeter and lumefantrine.



All drugs tested showed good dissolution properties, meeting the standards as shown in Figures 3.1, 3.2, 3.3, 3.4 and 3.5

Figure 3.1 Standardization curve for artemeter

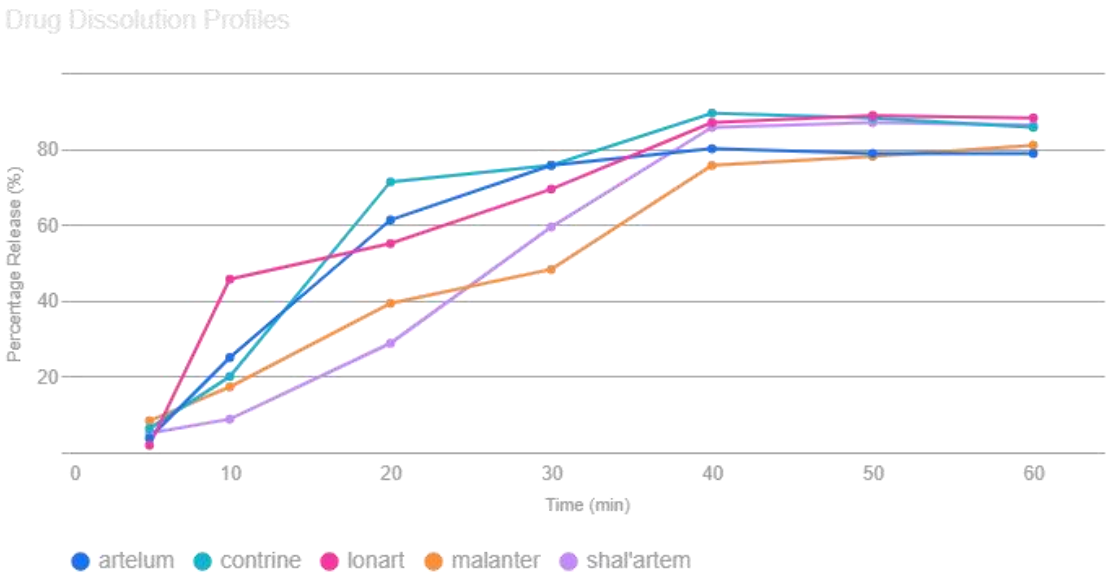


Figure 3.2: A graph of percentage of drug release (%) against time (min) for Artelum, contrine, malanter, and shal'aertem

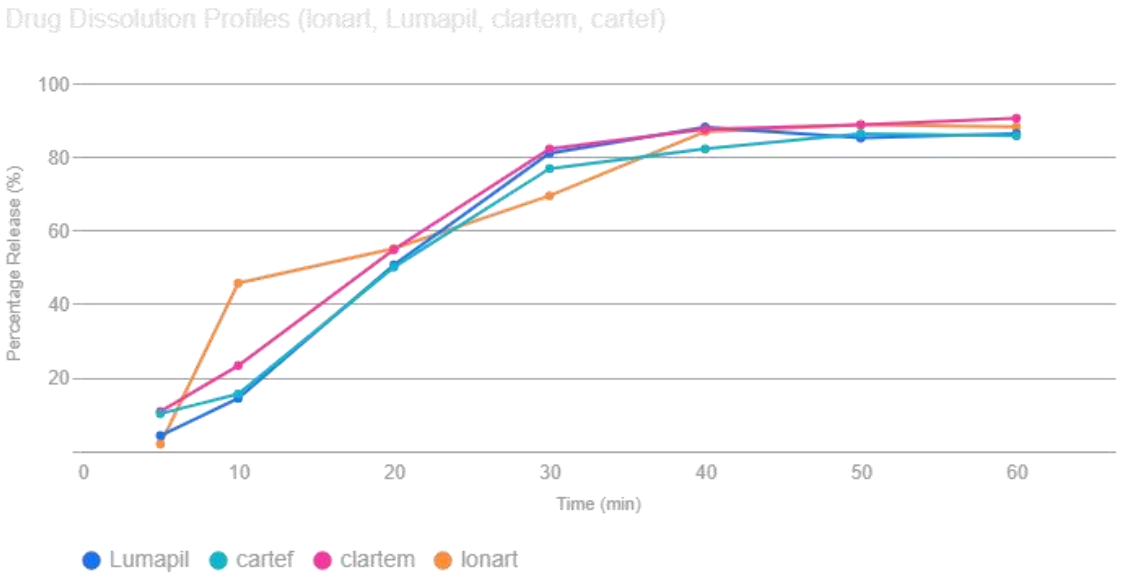


Figure 3.3: A graph of the percentage of drug release (%) against time (min) for Lumapil, cartef, clartem, and lonart.

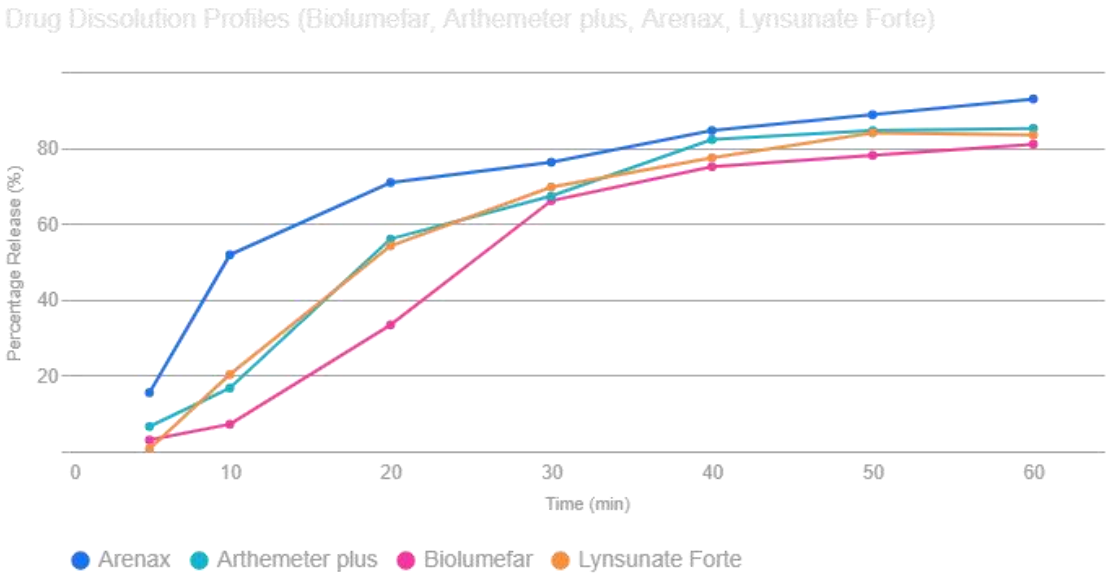


Figure 3.4: A graph of percentage of drug release (%) against time (min) for Arenax, artemether plus, biolumefar, and lynsynate forte

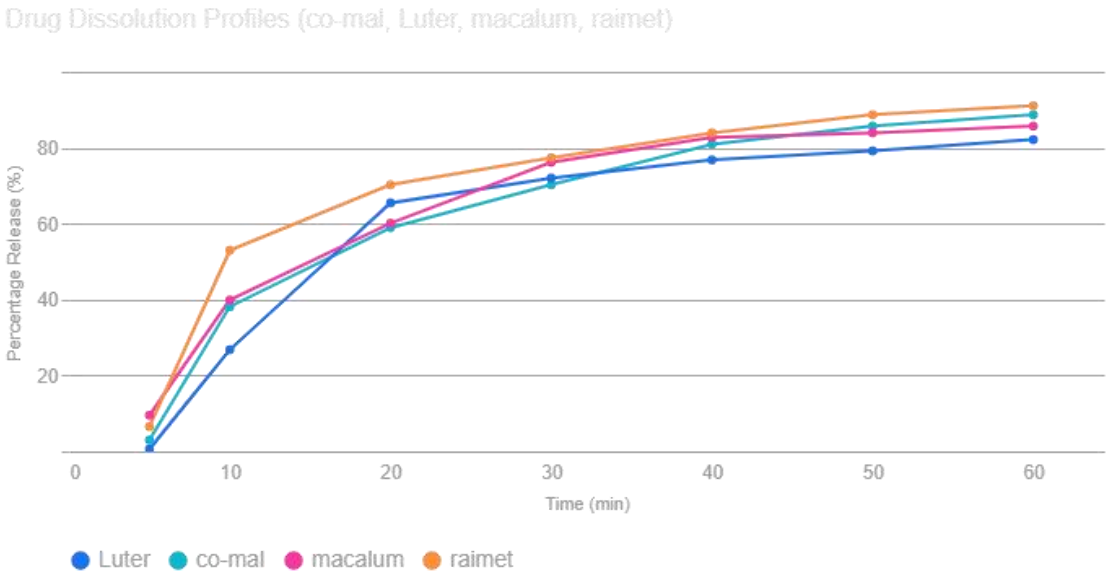


Figure 3.5: A graph of percentage of drug release (%) against time (min) for luter, co-mal, malaron, and raimet.

3.6. Percentage Composition (Assay)

Assay is the test that specifies the actual amount of the API in the tablets. It is the test which ensures that the products are not under-dosed or over-dosed. The pharmacopeial standard (e.g., USP 43-NF 38, 2020) for AL tablets defines that each tablet should contain 90.0% to 110.0% of the labeled amount of both Artemether (20 mg) and Lumefantrine (120 mg). From the result, all tablets contained a percentage composition of active ingredients within the 90.0% to 110.0% , which indicates that all the drugs are standard preparations as shown in Fig. 3.7

Table 3.7: Percentage composition of active ingredient in various brands of artemether/lumefantrine

Code	Percentage purity (%)
Co-mal	101.5%
Lynsunate forte	96.2%
Arenax	91.5%
Artemeter plus	97.8%
Biolumefer	98.4%
Cartef	95.6%
Clartem- DS	102.4%
Lumepid	98.5%
Lonart	95.6%
Artelum combo	102.4%
Contrine plus	98.1%
Malanter DS	97.3%
Shal'artem forte	104.2%
Raimet	96.6%
Macalum	93.8%
Luther	103.9%

CHAPTER 4

CONCLUSION

Overall, the *in-vitro* pharmaceutical quality assessment of the sixteen AL brands currently available to patients in Benin City reflects a mixed bag of quality. For example, it was reassuring that all 16 brands were NAFDAC-registered and not expired; however, quality metrics did not show such promising outcomes. Although each brand passed the necessary tests for weight uniformity and disintegration time, concerns for overall quality emerged. One brand (Biolumefar) failed the pharmacopoeial standard for friability, indicating that the brand was poorly mechanically suited and risked chipping and fragmentation as tablets, which could decrease dosage administered. Furthermore, since lumefantrine is a poorly soluble drug, this researcher is concerned about the high deviations between brands concerning tablet hardness and the dissolution tests where the therapeutic efficacy of such products relies upon it; however, all brands passed disintegration time. On the contrary, one brand is too hard (Luter), and one brand has disintegration time on the borderline (Contrine plus). These characteristics pose a concern for therapeutic efficacy by prolonging or not allowing the drug to be released.

While one brand failed a rudimentary quality assessment (friability), high deviations in hardness and dissolution quality among the brands show the need for active post-market surveillance from NAFDAC to preserve that all AL tablets in a patient's possession while in Benin City possess sufficient quality to, at best, treat malaria and, at worst, prevent treatment failure and antimalarial drug resistance.

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