KYAMBOGO UNIVERSITY

PHYSICOCHEMICAL ASSESSMENT OF THE QUALITY OF ALBENDAZOLE TABLETS ON THE UGANDAN MARKET

BY

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DECLARATION

This dissertation is my original work and has never been presented for a degree award in any other university. Where other people's work has been used, this has been acknowledged in references.

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APPROVAL

This Dissertation has been submitted to the Directorate of Research and Graduate Training for examination with the approval of the following university supervisors.

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DEDICATION

This work is dedicated to my parents: Mr. and Mrs. Paul Manirakiza and the entire Manirakiza family upon whose constant wisdom and providence, I rely for help.

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I thank the almighty God for His providence and blessings during this course.

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ABBREVIATIONS

API	Active Pharmaceutical Ingredient
BP:	British Pharmacopoeia
CRS	Chemical Reference standard
GMP:	Good Manufacturing Practices
HPLC:	High Performance Liquid Chromatography
IP:	International Pharmacopoeia
NDA	National Drug Authority
ODS:	Octadecyl silane
RSD:	Relative Standard Deviation
S.D:	Standard Deviation
STP	Standard testing procedure
U.V:	Ultra-violet
USP:	United States Pharmacopoeia
WHO:	World Health Organization
MHRA:	Medicines Health Regulation Agency

ABSTRACT

Albendazole tablets are listed by World Health Organization as essential medicines effective for treatment for parasitic worm infections and are indeed widely used in many public deworming campaigns in Uganda.

"Albendazole tablets being a high-volume consumption product coupled with the fact that they cure illnesses often referred to as those of the poor make them have a very high risk of being counterfeited. Despite this highly associated risk, there is no comprehensive assessment and documentation available on the quality of Albendazole tablets on the Ugandan market.

In this study, both qualitative and quantitative assessments were performed to evaluate the quality of different brands of Albendazole tablets sold in wholesale pharmacies in Kampala, Uganda. A visual inspection checklist was used for the assessment of the physical attributes and packaging requirements. Ultraviolet-Visible Spectroscopy (UVS) and High-Performance Liquid Chromatography (HPLC) were used for confirmation of the presence and amount of the Active Pharmaceutical Ingredient (API)."

A total of 40 batches of Albendazole tablets from 10 different brands were collected and evaluated. All brands of Albendazole tablets, except one, had acceptable physical characteristics. All the 10 brands (40 batches) passed the assay test, with average assay values ranging from 95.9 % (383.6 mg/mg) (to 99.5 % (398 mg/mg). Eight (20 %) batches failed the disintegration test. Three brands (30 %) of 10 brands failed the dissolution test with percentage dissolution values ranging from 0.0 % (0 mg/mg to 79 % (316 mg/mg). The most significant revelation of this study was the batches of Albendazole chewable tablets that did not completely dissolve as demonstrated by dissolution values ranging from 0% to 1%.

In conclusion, the Ugandan market had Albendazole tablets of both good and bad quality in circulation. This calls for regulatory enforcement to ensure that all these products that did not meet the specifications are recalled from the market and the manufacturers cautioned.

CHAPTER ONE

INTRODUCTION

1.1 Background

"Drugs play a very significant role in saving lives of people and animals, restoring health, preventing diseases and epidemics (Sagar, Zafar & Singh, 2006). Uganda has a national drug policy of 2000 and a national drug authority act of 1993 which mandates the National Drug Authority to ensure that at all times essential drugs are supplied at a cost-effective price and are of the right quality, efficacy and safety. Medicines of poor quality can reach the market through substandard production of legitimate drugs due to inadequate quality-control and quality assurance processes in manufacturing facilities, as well as by deliberately fraudulent practices (Bahtraore, 2012). The cardinal duty of drug regulators is to protect the public by ensuring that only quality medicines are produced by pharmaceutical manufacturers. This duty is performed by assessing the physicochemical properties of medicines (Yimer, &Anbessa, 2019)." Counterfeit or substandard drugs pose danger to the patient upon administration, since they are not fit for the purpose and hence do not offer relief to the patient (Kassahun, Asres & Ashenef, 2018). Reports from the World Health Organization (WHO) show that counterfeit, spurious and substandard medicines contribute to over 50 % of the world's drug market. Most of these are reported in third world countries, a fact attributed to lack of or poor effective regulation and a weak enforcement capacity existing in these countries (Glass, 2014). In addition, due to high costs and lack of availability of medicines, consumers in developing countries are more likely to seek out these inexpensive options (DiMasi,Grabowski &Hansen, 2015). This in turn impacts public health negatively since there is potential of increasing drug resistance and negating all the efforts that have already gone into the provision of medicines that are used to treat life threatening conditions in developing countries (World Health Organisation, 2015).

"Robust quality control and assurance of drugs in most third world countries is an often neglected issue (Erhun & Babalola, 2001). Among the most neglected drugs by regulators in third world countries are those for tropical diseases given that there is limited funding from the international bodies. This is evidenced by the reported high prevalence of parasitic infections in Africa. More than 1.5 billion people, or 24 % of the world's population, are infected with soil-transmitted helminth infections (Vercruysse, Duchateau, Spiegeleer, Levecke, 2015). Millions of people especially pre-school-age and middle school age children live in areas with high transmission rates of these parasites and need treatment and preventive interventions. In Uganda, studies have shown an overall infection of soil transmitted helminth infections as high as 26 %. In these studies, the leading parasitic infections were due to hook works reported to be at 18.5 % and Lumbricoides 9.8 % (Ojja *et al*., 2018; Adriko *et al., 2018)"*

The WHO recommended medicines, Albendazole chewable tablets and mebendazole chewable tablets, are effective, inexpensive and easy to administer by non-medical personnel, for example teachers, making them the most preferred medicines used in mass medication around the world and Uganda in particular (WHO, 2015). However, studies have shown that the dissolution properties of Albendazole chewable tablets on the market are poor (WHO, 2017). In 2011, a survey was conducted by WHO on medicines for neglected tropical diseases. It showed that 57 % of the products tested failed to comply with dissolution test requirements (WHO, 2015). This consequently affected the treatment negatively given that dissolution is an indicator parameter on the drug availability upon administration.

A study conducted in Ethiopia produced results consistent with global studies where 8 of 19 (42 %) batches of Albendazole tablets tested did not comply to dissolution test (Seifu, Kabede, Bacha & Melaku, 2019). Consequently, the quality assessment of Albendazole

tablets on the Ugandan market will go a long way on providing vital information on the quality of one of the most used drugs for deworming.

1.2 Statement of the problem

"Medicines that are most prone to substandard and counterfeit production are those that are massively used and those that attract little or no attention from local and international regulatory agencies. Albendazole tablets are preferred in deworming campaigns and are often referred to as medicines for neglected infections in third world countries hence making them highly susceptible to counterfeit and substandard production.

Despite this highly associated risk, there is no comprehensive assessment and documentation available on the quality of Albendazole tablets on the Ugandan market. Therefore, the need to assess the quality of Albendazole is of a great public health importance as this will generate data upon which informed decisions will be taken both by regulators and those who prescribe this essential medicine."

1.3 Objectives of the study

1.3.1 General Objective

To assess the quality of albendazole tablets on the Ugandan market.

1.3.2 Specific objectives

The general objective was achieved through the following specific objectives:

i. To screen by physical examination all collected batches of albendazole tablets and their packaging materials for defects and compliance to authorized packaging and labelling requirements.

ii. To determine the disintegration time of albendazole tablets.

iii. To determine the amount of active pharmaceutical ingredient that dissolves in albendazole tablets.

iv. To determine the amount of active pharmaceutical ingredient present in Albendazole tablets.

1.4 Significance of the study

Effective regulatory decisions are taken on the basis of sound scientific information available on the quality of medicines in circulation in the market. Given that analysis of medicines in Uganda is very expensive and all medicines on the Ugandan market are not tested prior to registration; regulatory decisions are based mainly on documentation received from manufactures and inspections carried out prior to licensing.

This study seeks out to establish the baseline data on the quality of albendazole tablets on the market through physical and chemical analysis of selected brands of albendazole tablets on the Ugandan market.

This study is therefore of a very great significance since it provided vital information on the status of the quality of Albendazole tablets on the Ugandan market.

1.5 Justification of the study

Ensuring the quality of Albendazole tablets is crucial for the safety of patients. Albendazole tablets are commonly used to treat infections caused by parasites. Tablets that are of poor quality do not contain the correct amount of active ingredient and could contain harmful impurities, leading to ineffective treatment and being potentially harmful to the sick who consume them.

Efficacy of Albendazole tablets is directly linked to their quality. Tablets that do not contain the amount of active ingredient that meets specifications or those that are not properly formulated can result in suboptimal treatment outcomes. This research therefore was aimed at

assessing the quality of Albendazole tablets to give assurance that patients receive the appropriate dosages fit for potent treatment.

Therefore, the physical-chemical quality assessment of Albendazole tablets on the Ugandan market is justified since it will provide valuable scientific insights and contribute to the advancement of pharmaceutical knowledge. This will in turn contribute to improved testing methods, quality control procedures, and drug design techniques for Albendazole tablets and other similar medications and ultimately lead to ensuring safe, efficacious quality medicines.

1.6 Hypothesis

Null Hypothesis (H_0); All brands of Albendazole Tablets circulating on the Ugandan market have all Critical Quality Attributes that are within specifications hence being therapeutically equivalent.

Alternative Hypothesis (Ha); All brands of Albendazole Tablets circulating on the Ugandan market do not have Critical Quality Attributes that are within specifications hence they are therapeutically un- equivalent.

CHAPTER TWO

LITERATURE REVIEW

2.1 Parasitic organisms

Parasites are organisms that survive by living in, on or off other organisms commonly known as hosts. Some parasites do not noticeably affect their hosts. A number of these parasites have their growth, reproduction through invasion of organ systems that make their hosts sick, resulting in a parasitic infection (Graczyk, Knight, & Tamang , 2005).

Multi host parasites can infect and exploit different types of hosts. These types refer to different variants for example genotypes or phenotypes within the same host species or to different host species. Most emerging diseases are caused by parasites, some of which infect multiple host species (Gandon, 2004).

Symptoms of parasitic infections vary depending on the organism and the organ of the host attacked. The symptoms vary from mild to very strong symptoms with varying degrees of pain. Some infections like the sexually transmitted infection Trichomoniasis produces no symptoms in as much it can be fatal in advanced stages. Toxoplasmosis may cause flu-like symptoms, including swollen lymph nodes and muscle aches or pains that can last for over a month (Loukas *et al.*, 2016).

"All infections by parasites are mainly due to three types of organisms: protozoa, helminths and ectoparasites. Some infections caused by protozoa include giardiasis. This is a serious infection that can be contracted from drinking water infected with Giardia protozoa (Gandon, 2004). Multi-celled organisms that can live in or on the outside of a host's body are known as Helminths. They are more commonly known as worms. They include flatworms, tapeworms, thorny-headed worms, and roundworms. Multi-celled organisms that live on or feed off the host's skin are known as ectoparasites. They include some insects and arachnids, such as mosquitoes, fleas, ticks, and mites (Kabatereine *et al*., 2005)."

Parasitic infections are mainly spread in a number of ways. Helminths and protozoa are mainly spread through contaminated water sources, food, waste piles, soil, and body fluids. Some can be passed through sexual contact. There is a number of insects that act as a vector, or carrier, of the disease. For example, malaria is caused by parasitic protozoa that are transmitted by mosquitoes when they feed on humans (Weaver, May, & Ellis, 2017).

2.2 Parasitic infections by worms

Parasitic infections by worms known as helminthic infections do affect more than a billion people worldwide, many of them children reference. Children are affected most because of their regular exposure to soil and other contaminated surfaces (Seifu, Kabede, Bacha, &Melaku, 2019).

Soil-transmitted helminth infections are among the commonest infections worldwide. Transmission is through eggs present in human faeces which consequently percolate through the soil. Species that mainly infect people are the roundworms and the whipworms (Soukhathammavong *et al*., 2012).

Soil-transmitted helminths rank high among the world's most important causes of physical and intellectual growth retardation. Their detrimental effect notwithstanding, these infections are still neglected both by the medical and public health interventions. This neglect stems mainly from the fact that people mostly affected are the world's most impoverished, particularly those who live on less than US$2 per day (Bethony *et al*., 2006).

More than 1.5 billion people, or 24% of the world's population, are infected with soil-transmitted helminth infections (Ndibazza *et al*., 2010). Mass deworming using the most recommended drugs of albendazole and mebendazole remains the most cost–effective and current global control strategy (Soukhathammavong *et al*., 2012).

2.3 Treatment of parasitic infections by worms

Medicines used to cure helminths in humans are known as anti-helminths. The best available remedy in control and prevention of Soil Transmitted Helminthics (STH) infections is the regular administration of one of the four antihelminthics recommended by the World Health Organization (WHO) which are mebendazole, albendazole, levamisole or pyrantel that belong to a drug class of benzimidazoles (Oxberry, Reynoldson, & Thompson, 2000).

Benzimidazoles belong to a class of heterocyclic, aromatic compounds that share a fundamental structure of a six-membered benzene fused to five-membered imidazole moiety (Locatelli *et al*., 2004). Benzimidazoles (BZ), Mebendazole (MEB) and Albendazole(ALB) are the most frequently used anthelmintics for treatment of STH infections (Vercruysse, Duchateau, Spiegeleer, & Levecke, 2015).

2.4 Albendazole Tablets

Albendazole is an anthelmintic or anti-worm medication. It prevents newly hatched insect larvae from growing or multiplying in one's body (Alderman, Konde-Lule, Sebuliba, Bundy, & Hall, 2006). Albendazole tablets are a needed treatment. Albendazole is an effective treatment for a range of parasitic diseases that represent a significant public health burden (WHO, 2015). Both albendazole and mebendazole are donated to National Ministries of Health through WHO in all endemic countries for the treatment of all children of school age.

2.4.1 Chemistry of Albendazole

Albendazole, $C_{12}H_{15}N_3O_2S$, is a methyl-[5-(propylthio)-1H-benzoimidazol-2-yl] carbamate (Refer to Fig. 2.1). It is synthesized through the heterocyclization of a derivative of phenylenediamine to a derivative of benzimidazole. This is achieved through the reaction of 3-chloro-6-nitroacetanylide with propylmercaptane to make 3-propylthio-6-nitroacetanylide. (Vandana, Yalavarthi, Vadlamudi, Kalluri, & Rasheed, 2017).

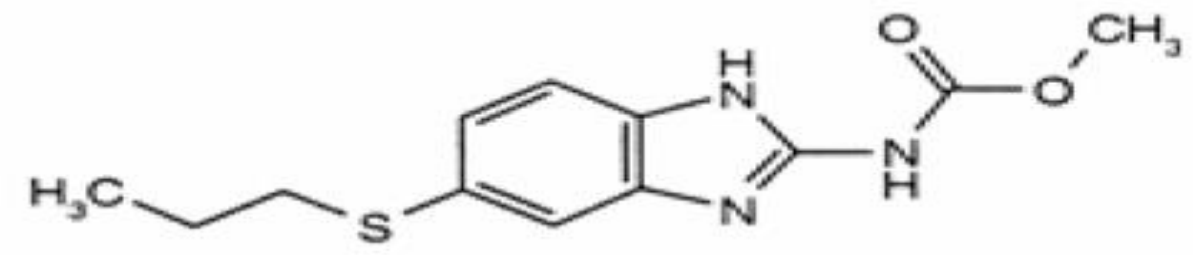

Fig. 2. 1: Structure of Albendazole ($C_{12}H_{15}N_3O_2S$) (WHO,2015)

2.4.2 Physical Properties of Albendazole

Albendazole is an off-white crystalline powder and is odorless. Its melting point is 207-211°C (decomposition). Albendazole is slightly soluble in organic solvents but it is insoluble in water (Medicamentos & Ciencias, 2015).

2.4.3 Mode of action of Albendazole

Albendazole is a member of the benzimidazole group of parasiticidal agents that disrupts parasite energy metabolism. This is achieved mainly through specific degenerative alterations in worm cells by binding to colchicine-sensitive sites of β-tubulin, a constituent cell protein, consequently inhibiting its assembly into a micro tubulin. The specific action of Albendazole against parasitic cells rather than mammalian cells is attributed to its preferential binding to parasitic β-tubulin (Jobert, 2002).

"Albendazole leads to the impairment of glucose uptake by the adult and larval forms of the parasites leading to depletion of their glycogen storage. As a consequence, the production of adenosine trisphosphate decreases because of insufficient glucose and leads to death of the parasite. When in higher concentrations, Albendazole also disrupts parasitic metabolic pathways through inhibition of metabolic enzymes involved in Krebs cycle, including malate dehydrogenase and fumarate reductase (Palomares, Palencia, Ambrosio, Ortiz, & Jung-Cook, 2006)."

Albendazole does prevent the formation of the spindle-fiber that is needed for the alignment of chromatin during the cell division process, which is essential in inhibition of cell division, egg production and development, and hatching of existing eggs. Lack of spindle formation also leads to reduced intracellular transport and cell motility (Martínez-Espinosa, Arguello-Garcia, Saavedra, & Ortega-Pierres, 2015).

In comparison to other agents in the benzimidazole group, such as mebendazole, Albendazole shows a higher activity in a single oral dose of 400 mg against ascariasis, hookworm infection and enterobiasis, trichuriasis which consequently results in either the worms' impairment or death (Sawatdee *et al.,* 2019)**.** Albendazole binds to intracellular tubulin, selectively affecting helminths and inhibiting essential absorptive functions in the organism (WHO, 2011).

2.4.4 Pharmacokinetics of Albendazole

"Absorption of Albendazole in animals and humans is rapid, within 2-3 hours in humans, rats and sheep. Food enhances absorption up to 5-fold in humans and animals (World Health Organization, 2002). Clearing of the parent drug is usually rapid in all species, however, the one for metabolites, albendazole sulphoxide and sulphone, is slower. Formation and elimination of sulphoxide is important because it is believed to be the main active form of the drug. The half-life time of sulphoxide is 8-12 hours in humans. This is replicated in humans except that the rate of formation of the positive enantiomer, which appears to be more biologically active than the negative form, is more rapid in humans and domestic animals than in laboratory animals (WHO, 2015)."

Albendazole tablets upon uptake are oxidized into two enantiomers, namely: R(+) albendazole sulphoxide by the aid of flavin-containing monooxygenase and S (-) Albendazole Sulphoxide with the aid of an enzyme known as cytochrome P450

oxidases (Cyt P450) . In humans, the most abundant enantiomer is the R (+) one and is the one that furnishes the drug with its pharmacological activity or potency. Albendazole sulphoxide is further oxidized into Albendazole Sulhone which is inactive by the aid of Cytochrome P450 and later other metabolites before excretion as illustrated in Fig. 2.2 below.

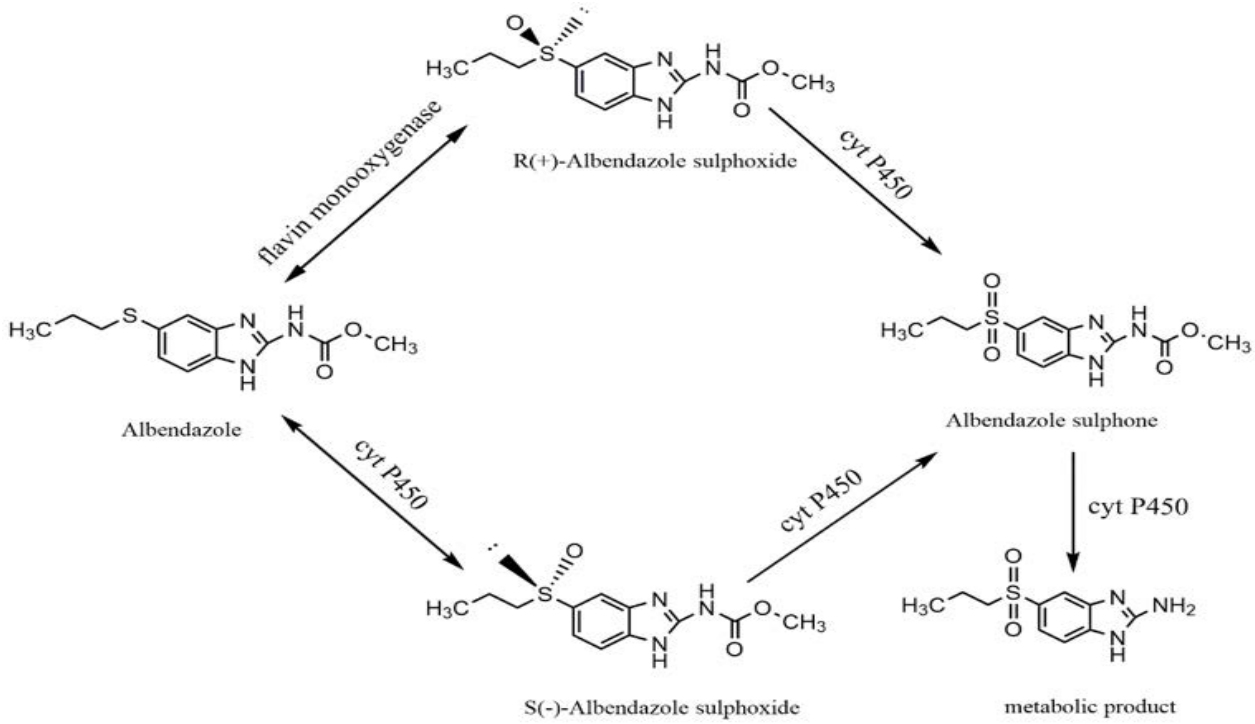

Fig 2. 2: Pharmacokinetics of Albendazole (WHO,2015)

2.4.5 Brands of Albendazole tablets marketed in Uganda

Albendazole tablets in Uganda are marketed through 15 different brands which are registered by the National Drug Authority. From these 15 brands that appear on the register, ten brands were found in circulation in pharmacies in big major outlets at the point of sampling were all sampled and form part of this study.

These brands are Zentel, Zepar, Alben, D-worm, Agozole, Albasol, BG-zole, Alzol, Wormee-4, Vorm-400, Vermikil, Anthel, Alzentel, Womnil, Alphin DS, and Zestaval.

2.5 Counterfeit Medicines

Counterfeit medicines are fake medicines (DiMasi, Grabowski, & Hansen, 2015). These may be contaminated during production and through the chain of production or contain the wrong or no active ingredient. This includes those that have the right active ingredient but contain the wrong dosage quantities which could be lower or higher than the required . (Mukhopadhyay, 2007). Counterfeit drugs are illegal and are harmful to people's health. Most substandard healthcare products have been toxic in nature with either fatal levels of the wrong active ingredient or other toxic chemicals (WHO, 2017).

"Substandard, falsified and spurious medicines and healthcare products are usually produced in very unhygienic conditions by unqualified and unauthorized personnel These counterfeits are difficult to detect given that they are designed in a way that their appearance is identical to the genuine product and may not cause an obvious adverse reaction. However, they often will fail to properly treat the disease or condition for which they were intended, and can lead to serious health consequences including death (Kopp, 2010). The World Health Organization (WHO) estimates that 50% of medicines available via internet are fake (El-Jardali *et al*., 2015)."

2.5.1 Counterfeit Albendazole Tablets on the Market

Albendazole tablets and oral suspensions are the most preferred choice of treatment against worms (WHO, 2011). This coupled by the massive deworming campaigns that most countries have taken to curb the prevalence of worms in children, makes Albendazole a high risk formulation for counterfeiting across the globe (Kabatereine *et al.*, 2005). This has been evidenced by a number of studies that have been conducted both in Africa and the rest of the world.

Studies conducted in Yemen on seven albendazole brands and tested against the British Pharmacopeia (BP) quality control standards showed that five brands met the BP disintegration criteria, whereas only two brands (29%) complied with BP quality control parameters of the dissolution specifications, while (71%) failed to fulfill the quality control standards. Similar results have been obtained in studies conducted in Rwanda and Bangladesh. The revelation of substandard formulations at purchase time is attributed to errors in manufacturing (Gamil , 2018).

"In 2019, several other studies conducted in the horn of Africa to assess the efficacy of albendazole using in vivo or in vitro techniques reported low efficacy. Low efficacy is normally associated with either development of drug resistance by parasites or low quality of the administered drugs. In the study done in Ethiopia, low efficacy was attributed to poor drug release profiles (Seifu, Kebede, Bacha, & Melaku, 2019)."

In Kenya, Albendazole suspension for veterinary use accounted for all the failures (8.9%) in the anthelmintics category while among the antiprotozoals, nitazoxanide tablets were noncompliant with specifications, which is an indicator that counterfeit or substandard drugs are present in the East African Region (Caudron *et al.*, 2008).

Gross adulteration of Albendazole has been reported in the West African region. A study aimed at examining the quality of nine brands of veterinary albendazole boluses commonly used in Nigeria, revealed that 78 % of the brands tested failed bolus weight uniformity test, none of the brands passed hardness test and only 44 % passed the dissolution test (Fidelis & Bosha, 2014).

The findings from these studies therefore underscore the importance of assessing the chemical and physicochemical quality of drugs, especially albendazole before they are accessed by the public for administration. Despite these numerous studies, it should be noted

that there is little or no information documented about the physio-chemical attributes of Albendazole tablets on the Ugandan market, despite their reported massive use as the most preferred drugs of choice for deworming both people and animals (Kabatereine *et al.*, 2005).

2.6 Regulation of Medicines in Uganda

The sole responsibility of ensuring that the people of Uganda have access to safe, effective and quality medicines and healthcare products lies entirely with National Drug Authority. The National Drug Authority (NDA) was established in 1993 by the National Drug Policy and Authority Statute which in 2000 became the National Drug Policy and Authority (NDP/A) Act, Cap. 206 of the Laws of Uganda (2000 Edition). The Act established a National Drug Policy and National Drug Authority to ensure the availability, at all times, of essential, efficacious and cost-effective drugs to the entire population of Uganda, as a means of providing satisfactory healthcare and safeguarding the appropriate use of drugs (NDP/A, 2000).

"The mandate of NDA is achieved through testing of all medicines, registering all medicines on the National Registry prior to market authorization, inspection of all manufacturing facilities both local and foreign and through active pharmacovigilance, where all complaints from clinicians, hospitals and all who interface with the drugs are registered and investigated".

Due to the expensive nature of testing of medicines, not all drug molecules are tested annually but rather the testing is done as a phased-out approach based on the risk profile assessment of all medicines on the Ugandan market. The fundamental shortfall of this approach is that medicines of a particular molecule not tested in a given period can be counterfeited and go un-noticed, both by the regulator and the public till when adverse effects are registered.

“Assessment of the quality attributes of albendazole tablets on the Uganda market is thus warranted given that for a long period this study has not been conducted despite the many failures reported in the region and the globe (Fidelis & Bosha, 2014). These failures led to a revision of the WHO specifications for albendazole tablets as captured in the latest edition of the International Pharmacopeia, which made it mandatory for all the tablets to pass the given requirements for dissolution among others. This was a fundamental shift from the long held notion, that chewable tablets did not require to meet the dissolution requirements for solid dosage forms (WHO, 2015).”

2.7 General Methods used in physical and chemical Analysis of medicines

2.7.1 Screening through observation of physical characteristics of medicines.

Safe, efficacious and quality medicines should contain the appropriate amount of active pharmaceutical ingredient (API), required physical characteristics like uniformity of shape, uniformity of size and be free from surface contamination, breaks, cracks or splits (Seifu, Kabede, Bacha, & Melaku 2019). This ensures that the medicines administered are of consistent dosage to patients to meet their intended purposes for use.

“The manufacturers are required to provide sufficient information on the packaging material including the product name, amount of API, the indications, contra-indications, storage conditions, manufacturing and expiry dates, Batch number, manufacturer’s name and address, and leaflet insert or patient information leaflet. This information is not only paramount to the patients consuming tablets for their understanding and appreciation but it has been found as an important screening tool by health workers for counterfeits at the last point of administration in the supply chain. Studies in Lubumbashi showed that health workers discovered many counterfeit medicines in circulation based on the details of packaging information which were in Arabic and French. These ordinarily would be meant for Arabic or French speaking countries (Mwamba, Duez, & Kalonji, 2016)”

2.7.2 Confirmation of the Presence of the Active Pharmaceutical Ingredient in Tablets

Active pharmaceutical ingredients are the most important component of tablets; given that they are the ones that furnish tablets with curative or treatment activity. It is therefore, imperative, that particular tests for discriminate identification are performed prior to quantitative determination.

These tests are of paramount importance because there is a possibility of occurrence of certain related substances or impurities which have a very close structural resemblance. These related substances or impurities can contribute to high assay or dissolution values during quantitative analysis.

2.7.3 Disintegration test for tablets and capsules

Complete disintegration refers to the state in which any residue of the drug unit, except those due to fragmentation of insoluble coatings or capsule shell, remaining on the screen of the test apparatus are a soft mass (Kimaro *et al*, 2019). Disintegration in the human body refers to the mechanical breakdown of a compressed tablet into small granules upon ingestion. It involves breakdown of the inter particulate bonds, which are created in the compression process of the tablet manufacturing cycle.

"It is hence a good starting point to briefly reflect on the physical changes that take place during the compaction process which include particle rearrangement, elastic deformation, plastic deformation, and fragmentation of particles, as well as the formation of inter particulate bonds (Markl & Zeitler, 2017). Although disintegration does not necessarily translate into dissolution of the drug, it is a rate limiting step for dissolution. It is important for tablets to disintegrate within specified period in order for dissolution to take place effectively (Fidelis & Bosha, 2014)"

2.7.4 Dissolution

The physicochemical process that determines the rate and extent in which the drug substance from solid state is transferred into a solution is known as dissolution (Khuluza, Kigera & Heide, 2017). Dissolution tests offer concrete knowledge on the drug-release characteristics of a drug formulation, or batch of a product, under prescribed test conditions. Compliance with a dissolution test offers confidence that the active ingredient will dissolve in an aqueous medium within a prescribed amount of time when the preparation is subject to mild agitation.

"Dissolution is a critical factor that can affect efficacy of drugs against parasites given that it is a measure of availability of the active pharmaceutical ingredient in solution, a precursor to uptake by the patient. For drugs like Albendazole chewable tablets that have low solubility and high permeability, dissolution is the rate-limiting step for drug absorption. High dissolution and solubility values obtained through dissolution testing translate into a high blood concentration due to sufficient availability of the drug and consequently clinical effectiveness to the patient against the parasite (Vercruysse, Duchateau, Spiegeleer & Leveck*et*, 2015)".

The dissolution process is a precursor for absorption unless drug administration is by a solution. It should be noted that even solutions should have a minimum level of dissolution to prevent precipitation in the stomach contents or in blood. Needless to say, all drugs must dissolve first before absorption into the blood stream can occur (Kimaro, Tibalinda, Shedafa, Temu, & Kaale, 2019)

2.7.5 Assay

Assay test is performed in pharmaceutical analysis to ascertain the amount of active pharmaceutical ingredient available in a pharmaceutical product. If the amount of the API of drug is within the acceptance range, there is high assurance that the drug upon administration will be efficacious thereby producing the desired and intended healing effects on the patient.

This equally leads to a cost effective treatment process which saves both the resources used for treatment and the time spent by the patient while sick hence increased productivity (Seifu *et al.,* 2019).

"If a drug contains a higher than the expected amount of API, it is not safe and may be toxic due to overdose uptake. On the other hand, if the drug has lower amount of API, there is less assurance of it serving its curative purpose. This does not only lead to longer treatment periods and an un necessary high expenditure on treatment costs but could equally lead to other adverse conditions as a result of drug treatment failure and ultimately death (Geerts & Grtseels, 2000). Determination of assay of medicines can be done using a number of methods, namely: Titration, UV-Spectrometry, Gas Chromatography and high performance liquid chromatography (Bonfilio, Araujo, & Salagado, 2010)"

2.7.6 Measurement of mass

Tests that involve the measurement of mass require the use of balances of the required capacity and sensitivity corresponding to the degree of accuracy sought.

When weighing quantities of 50 mg or more that need to be accurately weighed, an analytical balance of 100-200 g capacity and 0.1 mg sensitivity is required. When weighing quantities of less than 50 mg that need to be accurately weighed, an analytical balance of 20 g capacity and 0.001 mg sensitivity is required (WHO, 2019). During analysis, a lot of caution and care should be taken since it is a critical stage in ensuring that accurate weights are used. To ensure this, balances only calibrated with standard masses should be used.

2.7.7 UV- visible Spectrophotometric analysis

The technique of Ultraviolet-visible spectrophotometry is one of the most frequently employed technology used in pharmaceutical analysis. The wavelength used ranges from 190 nm - 380 nm for ultraviolet radiation and 380 nm-800 nm for visible radiation Since most pharmaceutical active ingredients possess chromophore groups, they can be determined

directly in the ultraviolet region without the need for a derivatization reaction. The above coupled with common availability of the instrumentation, the simplicity of procedures, economy, speed, precision and accuracy of the technique make spectrophotometric methods attractive and some of the most sought after analytical techniques (Bonfilio *et al*., 2010)

2.7.7.1 UV-Visible spectrophotometry instrumentation

"All spectrophotometers are designed to permit sufficient amounts of monochromatic radiant energy to be passed through the test sample in a suitable form and to enable the measurement of the fraction of that energy that is transmitted (Atole & Rajput, 2018). Spectrophotometers comprise an energy source, a dispersing device with slits for wavelength band selection, a cell or holder for the test substance, detectors of radiant energy, connected to amplifiers, and measuring and recording devices. Some instruments are manual while others are designed for automatic operation. These analytical instruments are available for use in the visible region of the spectrum, normally 380 nm to about 700 nm, and in the visible and ultraviolet regions of the spectrum, usually ranging from 190 nm to about 700 nm (WHO, 2019)".

The Beer-Lambert law forms the backbone upon which all analytical absorption spectrophotometry is conducted. The law states that, the absorbance of a solution of a substance is related to the path length of the solution through which the light passes and to its concentration.

Mathematically: A= a*b*c

A = Absorbance

a= specific absorbance concentration in %w/v

b= Path length in cm

c= concentration in %w/v

The law holds when monochromatic light is used and the solution used is diluted and stray light is excluded. Plotting absorbance against concentration for a cell of unit thickness, usually 1cm gives a straight line passing through the origin. This is termed the calibration curve. The calibration curve can be used for the determination of the concentration of an unknown sample when the absorbance has been determined.

2.7.8 Chromatography

Chromatographic processes entail the distribution of a solute between two phases, one of which is the mobile phase and the other one being the stationary phase. The stationary phase performs through adsorption, partition ion exchange, or gel permeation. Application of chromatographic process in many pharmaceutical applications ranges from simple to complex operations that involve separation of active drug substances from their matrices. In pharmaceutical analysis, types of chromatography that are useful are categorized into three broad groups, namely: Thin Layer Chromatography, High Performance Liquid Chromatography and Column Chromatography (MHRA, 2019; WHO, 2019)

"Column chromatographic methods involve the adsorbent being packed into a column, which may be of the traditional open type or may be closed normally with the capacity to withstand considerable pressures which enables the mobile phase to be pumped through the column at high pressures. Gas chromatography is a unique case of column chromatography in that the mobile phase is a gas rather than a liquid and the solutes must be volatile or converted upon application of high temperatures to derivatives that are volatile. (United States Pharmacopoeial Convention, 2019)"

2.7.8.1 Thin Layer Chromatography

Thin-layer chromatography is a type of chromatography in which a stationary phase that consists of an appropriate material is spread as a uniform thin layer through a support of

glass, metal or plastic. When a mixture of analytes is spotted and dried on the plates, the drugs move across the plate at different rates depending on the extent of adsorption or the degree of partitioning on the plates and their solubilities in the mobile phase.

Some of the stationary phases used for TLC include Silica gel, cellulose, Alumina (aluminum oxide), magnesium silicate, ion exchange resins and reversed phases like paraffin and octadecyl silane (ODS). TLC is one of the most widely used techniques for the separation of pharmaceutical products and their identification. This method of characterization has gained popularity and favor as an analytical method because of its simplicity, reliability as well as the simple method location procedures (WHO, 2019).

2.7.8.2 High performance liquid chromatography

High-performance liquid chromatography (HPLC) is a separation technique based on the differential distribution of solutes in both the stationary and mobile phases. The HPLC instrumentation is fundamentally made up of a mobile phase reservoir, high-pressure pumps, injectors, a column, a detector and a signal-recorder (MHRA, 2019).

"High performance liquid chromatography is the most preferred analytical technique in pharmaceutical analysis due to its high sensitivity, resolution, turn-over of analysis and the ability to store raw data generated in a safe and reproducible format.(Bonfilio, Magali, Rudy et al., 2010). HPLC consist of high-pressure pumps, injector systems, columns with varying stationary phases, and detectors. pumps function by delivering measured amounts of mobile phase at a constant flow rate as predetermined in the method. Due to the high pressures involved, the design of the tubings should be in a certain way to withstand very high pressures. (United States Pharmacopoeial Convention, 2019)."

CHAPTER THREE
MATERIALS AND METHODS

3.1 Study Area and Sampling

3.1.1 Study Area

“The study was conducted on batches from different brands of Albendazole tablets on the Ugandan market randomly picked from the wholesale pharmacies in the divisions of Kampala City Council Authority. The study was conducted from July 2019 to March 2020. Kampala is the capital and largest city of Uganda and it is located in the Central Region of Buganda. Geographically, Kampala is located in the southern part of Uganda, approximately 1,270 meters (4,170 feet) above sea level. The city is home to various ethnic groups, with the majority belonging to the Baganda ethnic group, who consequently have significant influence on the culture and history of Kampala given the close linkages to Buganda’s cultural seat, Bulange, Mengo. The city also hosts several museums and cultural centers, such as the Uganda Museum, which showcase the country's history, art, and traditions. The city's economy is diverse, with key sectors including services, trade, manufacturing, and agriculture. Kampala City Council Authority is home to head offices of many banks, insurance companies, and other financial institutions and her central business district is a major revenue collection area for the country given the booming wholesale and retail trade in the area.”

3.1.2 Sampling

Sampling was conducted from wholesale pharmacies in divisions of Kampala Capital City Council as shown in Figure 3.1. All brands of Albendazole tablets found in pharmacies in KCCA were sampled. These wholesale pharmacies form the core of distribution of

Albendazole tablets to the rest of the country since they are the sole wholesalers for all the brands that were sampled for this particular study.

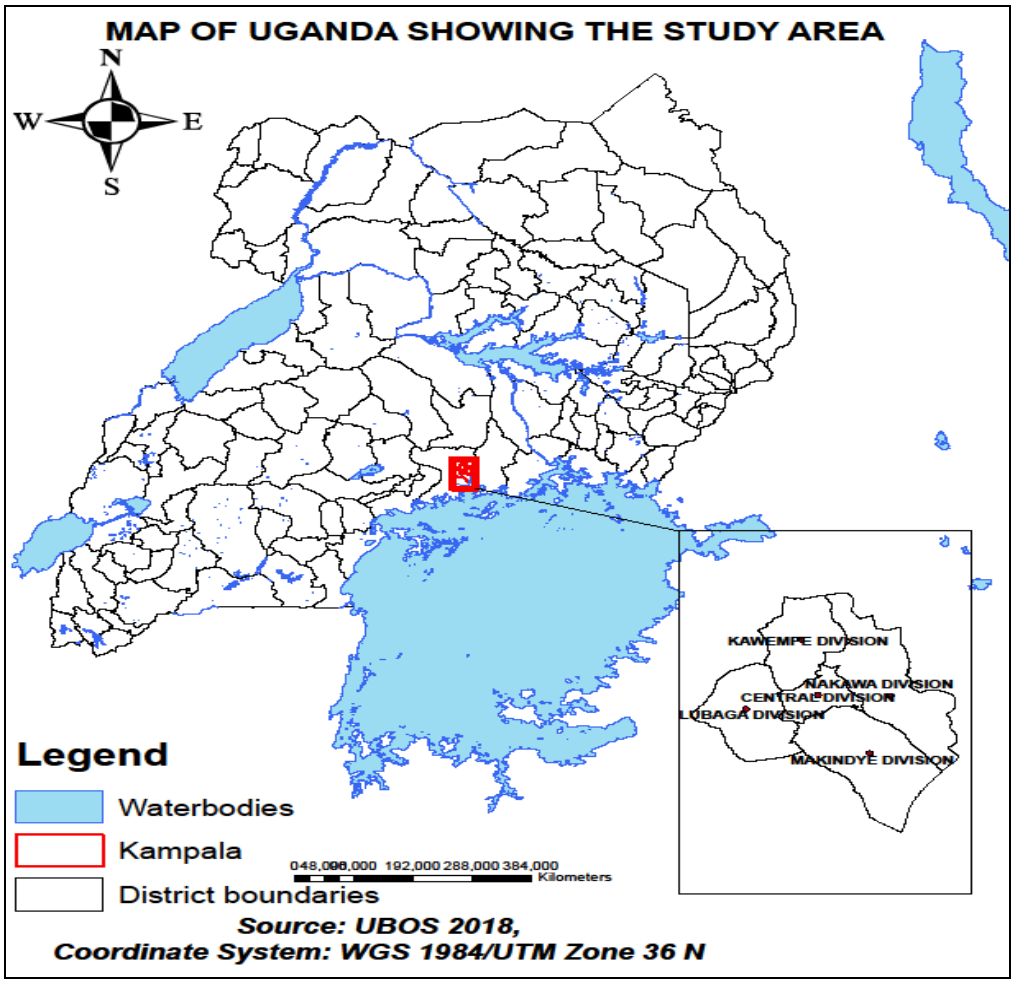

Fig 3. 1: A map showing Kampala City Council Authority

3.1.2.1 Sample collection

For comprehensive analysis, all brands and batches found in circulation in Kampala City Council Authority Wholesale pharmacies were sampled. Brands Albasol, Alzol-400, Vermikil and Anthel were picked from Kawempe, Nakawa, Lubaga and Makindye respectively while brands Zepar, Wormee, Olworm, Zeben, Albendazole-GSK and Albendazole 400 were picked from the Central Division.

A total of 40 batches of Albendazole tablets were randomly sampled from major whole sale pharmacies. These batches were from 10 different brands and 100 tablets were collected per

each batch. A total sample size of 4000 tablets from 40 batches was collected and used for analysis as illustrated in table 3.1 below.

Table 3. 1: Details of the samples collected

BRAND	NUMBER OF BATCHES	TABLETS COLLECTED
ALBASOL	3	300
ALZOL-400	4	400
VERMIKIL	8	800
ANTHEL	3	300
ZEPAR	3	300
WORMEE	4	400
OLWORM	3	300
ZEBEN	3	300
ALBENDAZOLE-GSK	6	600
ALBENDAZOLE 400	3	300
Total	**40**	**4000**

3.2 Sample Analysis

The methods of analysis were adopted from the International Pharmacopeia (2019) and the United States Pharmacopeia (2019) and later as an approved testing procedure by National Drug Quality Control Laboratory, Mulago, NDA/DLS/STP-M/027, Revision Number 01.

3.2.1 Screening by physical examination

All samples were assessed by examination of their physical attributes. These physical attributes were shape, uniformity of size, uniformity of color and presence of cracks or splits. Packaging and labelling information was also examined. This information included presence of dosage statement, batch number, physical address, manufacture date, expiry date, storage information and leaflet insert or patient information leaflet.

3.2.2 Disintegration

Six tablets randomly selected from each batch were placed in each of the six tubes of the Disintegration tester (Electrolab, India, Model-EDI 2SA, NDA/7620/18). The apparatus was operated using water from a Millipore-Elix purification water machine (Merk, Molsheeim, France, Model-SDS 350, NDA/7576/13) as the immersion fluid and maintained at a temperature of 35–39 °C. At the end of the test, each of the six tubes was lifted from the fluid and the dosage units observed.

Dosage units are said to have disintegrated completely if no whole masses of the drug are observed.

3.2.3 Dissolution

3.2.3.1 Standard solution preparation

Eleven (11) mg of Albendazole CRS (Sigma Aldrich, St. Louis, USA, Lot Number-LRAA9078) as weighed into a 25-mL volumetric flask, then 10 mL of Acidified methanol (Acidified methanol was prepared by transferring 50 mL of methanol (Merk, Germany, Cas No. 67-56-1) HPLC grade into a 100-mL volumetric flask, adding 2 mL of concentrated hydrochloric acid (VWR, France, Paris, Lot No. 19B184026) and diluted with methanol to volume. The contents were mixed and shaken to dissolve. The resultant solution was diluted with 0.1 M hydrochloric acid to 25 mL and sonicated for 15 minutes.

1mL of the resultant solution was pipetted to a 50-mL volumetric flask, diluted with 0.1 M sodium hydroxide (Lot No. B1792498006, Merk, Darmstadt, Germany) to the 50-volume mark, and sonicated for 5 minutes using a sonicator (Life care, India, NDA/7605/18).

3.2.3.2 Preparation of sample solutions

Randomly, 6 tablets were chosen from the available sampled blister packs. One tablet was introduced into each of the six vessels of the dissolution tester (Erweka, Germany, Model-DT 800) and dissolution tester (Erweka, Germany, Model DT 1614). The dissolution tester apparatus was operated using the dissolution conditions below:

(a) Apparatus: Type 2 (paddle type apparatus)

(b) Medium: 900 mL of 0.1M hydrochloric acid;

(c) Temperature: $37.0^0C \pm 0.5^0C$

(d) RPM: 50 RPM

(e) Time: 30minutes

A sample (about 30ml) was drawn and immediately filtered using a Whatman filter paper (MN 615, diameter 150 mm). Sampling was done within a tolerance of ±2% of the run time discarding the first 5ml of the filtrate.

1 mL for 400 mg strength or 2 mL for 200 mg strength was transferred and a portion of the solution filtered to a 50-mL volumetric flask, diluted with 0.1 M sodium hydroxide (Merk, Darmstadt, Germany, Lot B1792498006) to the mark and mixed.

Using the UV/Vis Spectrophotometer (Fischer Evolution 3000 UV-VIS, USP/NDA/01), the absorbencies of the final solutions were measured. The absorbance of the standard and sample solutions was determined in five and three replicates respectively at the fixed wavelength;

maximum and minimum absorbances at about 308 nm and 350 nm respectively using a 1cm cell and 0.1 M sodium hydroxide as the blank.

Acceptance limit: Not less than 80 % of the labeled amount of $C_{12}H_{15}N_3O_2S$ is dissolved in 30 minutes.

The percentage amount of Active Pharmaceutical Ingredient that Dissolved was calculated suing the following formula:

$$\text{Amount of API} = \frac{\text{Sample Solution Absorbance X Standard Solution Concentration x100}}{\text{Standard Solution Absorbance X Sample Solution Concentration}}$$

3.2.4 Assay Test

3.2.4.1 Preparation of standard solutions

In duplicate, about 20 mg of Albendazole reference Standard (Sigma-Aldrich, Lot Number: LRAA9078), was weighed and transferred into a 10-mL volumetric flask. 1 mL of sulfuric acid in methanol [sulfuric acid in methanol was prepared by mixing of 1 mL of concentrated sulfuric acid (Sigma-Aldrich, Germany, 98% w/w) and 99 mL of methanol (Merk, Germany] and 5 mL of methanol were added and shaken to dissolve. The solution was diluted with methanol to 10 mL volume, and mixed to dissolve.

5.0 mL of this stock solution was transferred to a 50-mL volumetric flask, diluted with methanol to the 50 mL volume mark, and mixed.

3.2.4.2 Sample extraction

Twenty tablets randomly picked from the pack of each batch were weighed and finely powdered. A weighed portion of the powder equivalent to about 100 mg of Albendazole was transferred to a 50-mL volumetric flask. 5 mL of sulfuric acid in methanol and 20 mL of methanol were added to aid the dissolving and extraction of the active pharmaceutical

ingredient, and the contents shaken for 15 minutes using an orbital shaker. The sample solution was diluted with methanol to volume, and mixed using a vortex mixer for 5 and filtered.

Five mL of the clear filtrate was transferred into 50-mL volumetric flask, diluted with methanol to volume, and mixed.

The amount of Assay was calculated using the formulae below:

$$Assay = \frac{Actual\ Sample\ Concentration}{Theoretical\ Sample\ Concentration}$$

$$Actual\ Sample\ Concentration = \frac{Response\ of\ Sample\ X\ Concentration\ of\ Standard}{Response\ of\ Standard}$$

$$\text{Concentration of Standard} = \frac{Wstd\ x\ 5x\ PS}{10\ x\ 5}$$

$$Theoretical\ Sample\ Concentration\ = \frac{Wspl\ xLC\ X1\ X5}{Awt\ x\ 50\ \ X\ 50}$$

$$\text{Amount of API/Assay} = \frac{(\text{Rspl x Wstd x5 x 5 x 50 xAvg.wt x Pstd x100})}{\text{Rstd x10x50xSpl.WtxLC}}$$

Where;

Rspl = Response of sample

Rstd = Response of standard

Wstd. = Actual weight of standard taken

Spl.wt. = Actual weight of sample taken

Avg.wt = Average weight

Pstd = Potency of the standard

LC = Label Claim

5, 10 and 50 were volumes in which the respective dilutions for both sample and standard were made to arrive at the final concentrations used.

3.2.4.3 HPLC analysis of albendazole samples

The blank, standard and sample solutions obtained above were injected into the HPLC system (Agilent, USA, Model 1260 series) fitted with a Variable Wavelength Detector using the following chromatographic conditions:

(a) Equipment: HPLC- UV Detector

(b) Column: 25cm X 4.6mm; 5µm-L1 (C18) packing, Luna Phenomenex column (PL/C18/034).

(c) Column temperature: 30 ^{0}C

(d) Injection volume:10µl

(e) Detector wave length: UV 254nm

(f) Flow rate: 1.5 ml/minute

Mobile phase: 0.50 g of monobasic ammonium phosphate (Fluka Chemicals, Dorset, UK) was dissolved in 400 mL of water. 600 mL of methanol (Merk, Germany) was added, mixed, and filtered using Whatman filter papers (Vile Parle, Mumbai), discarding the first 15 mL of the filtrate. The clear filtrate was degassed before use.

3.3 Quality Assurance and Quality Control of the Testing Process

To ensure that the results obtained in this study were valid, reliable, accurate and reproducible, the following measures were put into consideration.

3.3.1 Testing procedure

The standard testing procedure used was an approved test method adopted from the International pharmacopeia and the United States pharmacopeia bearing a document number [NDA/DLS/STP-M/027] valid up to 25/02/2023.

3.3.2 Analytical Instruments used

All instruments used were calibrated and were within validity periods.

3.3.3 Samples

All samples analysed were at least six months away from their expiry dates, collected from facilities authorized with licenses from National Drug Authority and all brands collected were from authorized manufacturers and these are on the updated National Drug Authority register of 2019/2020.

3.3.4 System suitability Parameters

Before analysis was performed for both dissolution and assay, the following system suitability parameters and their respective limits were complied with.

3.3.4.1 Assay by Agilent HPLC

The system suitability was determined by evaluating data obtained from the replicate injections of the 100% standard solutions. The precision was evaluated by computing the Relative Standard Deviation for response factors and retention times of 5 replicate injections of standard solutions A and B as shown in appendix 25 and appendix 26.

Table 3.2 shows the specifications for each of the parameters used to assess system suitability before conducting the Assay test.

Table 3. 2: System suitability parameters for the Assay test

System Suitability Parameter	Specification
Relative standard deviation for peak area response for standard solutions A and B	NMT 2.0%
Relative standard deviation for the retention time of the principal peak in the standard solutions	NMT 2.5 %
Relative standard deviation for peak area response for standard solution A including the bracketing standards	NMT 2.0 %
Theoretical plates for the principal peaks in the standard solution	NLT 2000
Tailing factor for the principal peaks in the standard solutions	NMT 2.0%
Similarity factor for the standard solution prepared in duplicate	0.98 to 1.02

3.3.4.2 Dissolution test by UV-visible spectrophotometer

Table 3. 3: System suitability parameters for the Dissolution test

System Suitability Parameter	Specification
Relative standard deviation for the five replicate readings for the standard solutions	NMT 2.0%
Similarity factor for the standard solution prepared in duplicate	0.98 to 1.02

3.4 Data Analysis

Comprehensive data analysis of the different data sets generated was performed using IBM SPSS statistics version 21.0 for Windows (IBM Corp., Armonk, NY, USA and Microsoft Excel 2016 by employing ANOVA.

3.4.1 Analysis of Variance (ANOVA) test

The ANOVA test was employed as a statistic tool in determining the relationship between the means of the different groups of data involved.

The result of the ANOVA formula offers information used to determine whether multiple groups of data are similar or varies. This involves two hypotheses: the null and the alternative (Henson, 2015)

Before the data generated is subjected to the ANOVA test, the following assumptions must be tested and met;

1. There should be normal distribution of the population from which the samples are drawn.

2. All samples collected should be independent of each other.

3.There should be homogeneity of variance.

Of specific interest in this study, is the comparison of the brands using the means obtained from the quantitative tests of Assay, Disintegration and Dissolution. This comparison is of great importance since it leads to drawing informed conclusions about batch to batch variability and the equivalency of the different brands of the same drug molecule in the same market (Kim, 2014)

CHAPTER FOUR

RESULTS AND DISCUSSION

4.1 Screening

4.1.1 Physical characteristics of tablets batches

All the batches from the 10 brands that were tested passed the uniformity of shape, uniformity of size, uniformity of color tests and all of them had no surface contamination. Only 1 batch B5, representing 25 % of brand ALB 2 (1 of the 4 samples tested) had cracked tablets.

This is as shown in Figure 4.1

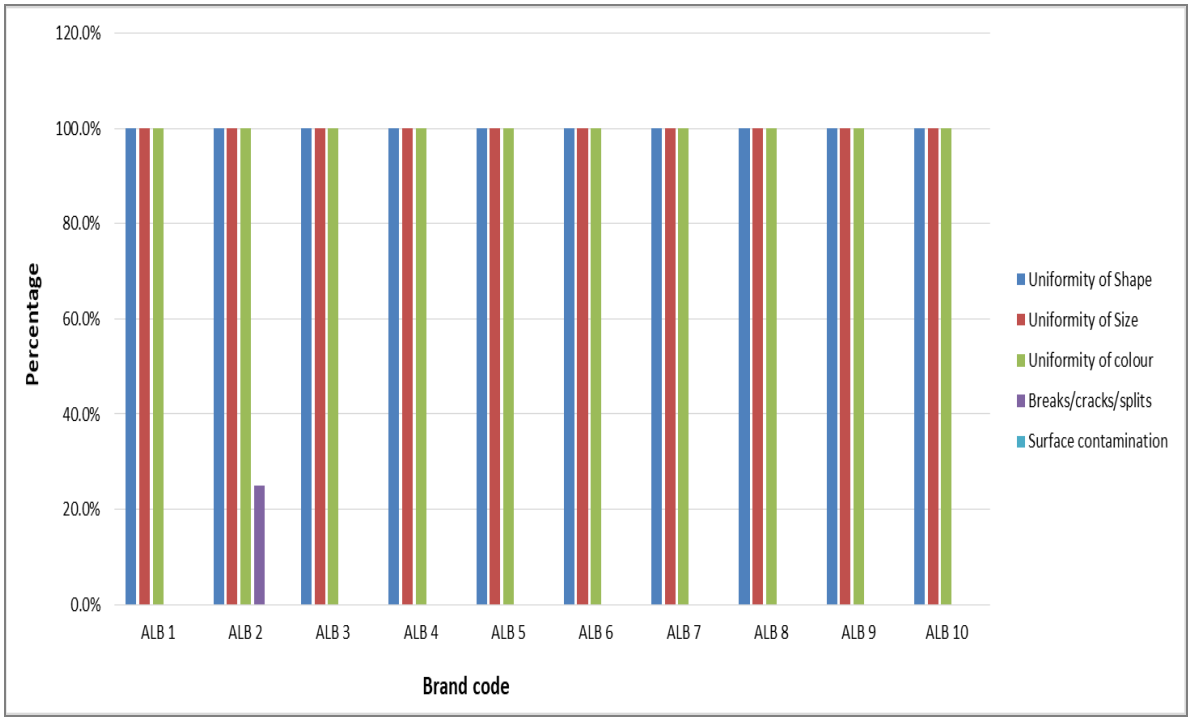

Fig 4. 1: Physical characteristics of tablets of the different brands of Albendazole tablets

4.1. 2 Packaging and Labeling

All batches of the different brands that were assessed were found compliant with the packaging and labeling requirements as shown in Figure 4.2. These requirements included presence of Dosage statement, Batch number, Physical address, Manufacture expiry date, Storage information and Leaflet insert.

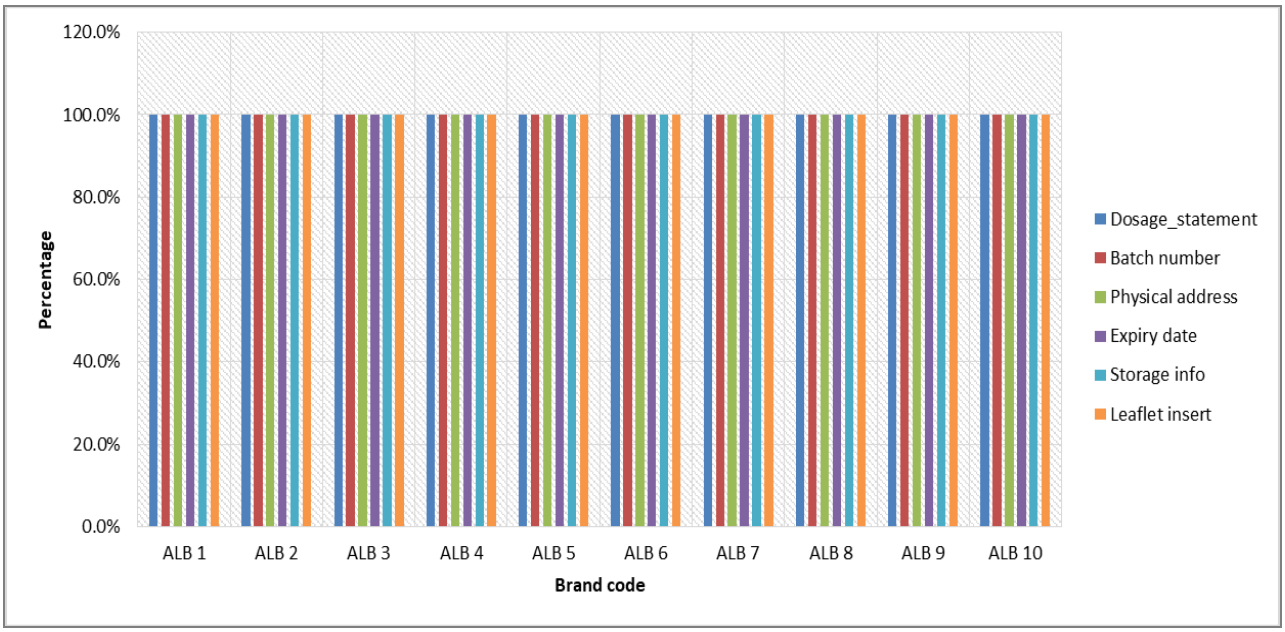

Fig 4. 2: Packaging information and labeling for the different brands of Albendazole

In this study, all the brands evaluated met the labelling requirements and physical characteristics apart from one which was consistently observed to have cracked tablets. This ultimately compromises the dosage content and ultimately points to a poorly controlled manufacturing process that cannot effectively identify and isolate these manufacturing defects before they are taken to market.

Safe, efficacious and quality medicines should contain the appropriate amount of active pharmaceutical ingredient (API), required physical characteristics like uniformity of shape,

uniformity of size and be free from surface contamination, breaks, cracks or splits (Seifu *et al*., 2019)

This ensures that the medicines administered are of consistent dosage to patients to meet their intended purposes for use.

The manufacturers should also provide sufficient information on the packaging material including the product name, amount of API, the indications, contra-indications, storage conditions, manufacturing and expiry dates, Batch number, manufacturer's name and address, and leaflet insert or patient information leaflet. This information is not only paramount to the patients consuming tablets for their understanding and appreciation but it has been found as an important screening tool by health workers for counterfeits at the last point of administration in the supply chain.

"Similar studies carried out on the continent demonstrate the role played by preliminary analysis of physical characteristics and packaging materials in identification of counterfeits. In Lubumbashi, health workers discovered many counterfeit medicines in circulation based on the details of packaging information which were in Arabic and French. These ordinarily would be meant for Arabic or French speaking countries (Mwamba, Duez, & Kalonji, 2016). In a study done in Ethiopia, 10% the Albendazole brands did not have compliant physical characteristics and 20% lacked Patient leaflet information (Seifu *et al.*, 2019). Results from this study were however different from a study done to assess the physicochemical quality of metformin Hydrochloride tablet brands available in Jimma town which showed total compliance to the specifications of packaging and physical characteristics of medicines (Yimer, Anbessa, Sultan, & Belachav, 2020)."

In conclusion, the different studies above point to the fact that despite screening being a cheap, non-destructive and quick test, it can be a pointer to compliant or substandard medicines when carried out and it is also a great tool of quality checks by the end-user health workers and patients when trained, since many medicines deteriorate along the supply and storage chains.

4.2 Disintegration of Albendazole tablets

All eight batches of brand ALB 3 failed the Disintegration test having failed to totally disintegrate into pulpable fragments within 15 minutes. This was a representation of twenty percent of the batches and ten percent of brands. Brand ALB 8 brand had the lowest average disintegration of 0.63 minutes (SD=0.01). Brand ALB 3 had the highest average disintegration of 182 minutes (SD=1.93). This is as illustrated in Table 4.1 and Figure 4.3 respectively. Among the batches that failed, batches B10 and B13 took the longest time of 184 minutes to disintegrate while batch B14 took the shortest to disintegrate after 180 minutes as illustrated in Figure 4.4 here below.

Table 4. 1: Disintegration time of the brands of Albendazole tablets

Brand	T Mean/ min	Minimum	Maximum
ALB 1	2.87±0.17	2.75	3.07
ALB 2	4.28±0.35	3.93	4.60
ALB 3	182.00±1.93	180.00	184.00
ALB 4	6.75±1.07	6.02	7.98
ALB 5	3.28±0.70	2.50	3.85
ALB 6	9.06±0.52	8.50	9.55
ALB 7	1.68±0.03	1.65	1.72
ALB 8	0.63±0.01	0.62	0.65
ALB 9	0.96±0.07	0.83	1.05
ALB 10	0.91±0.17	0.75	1.08

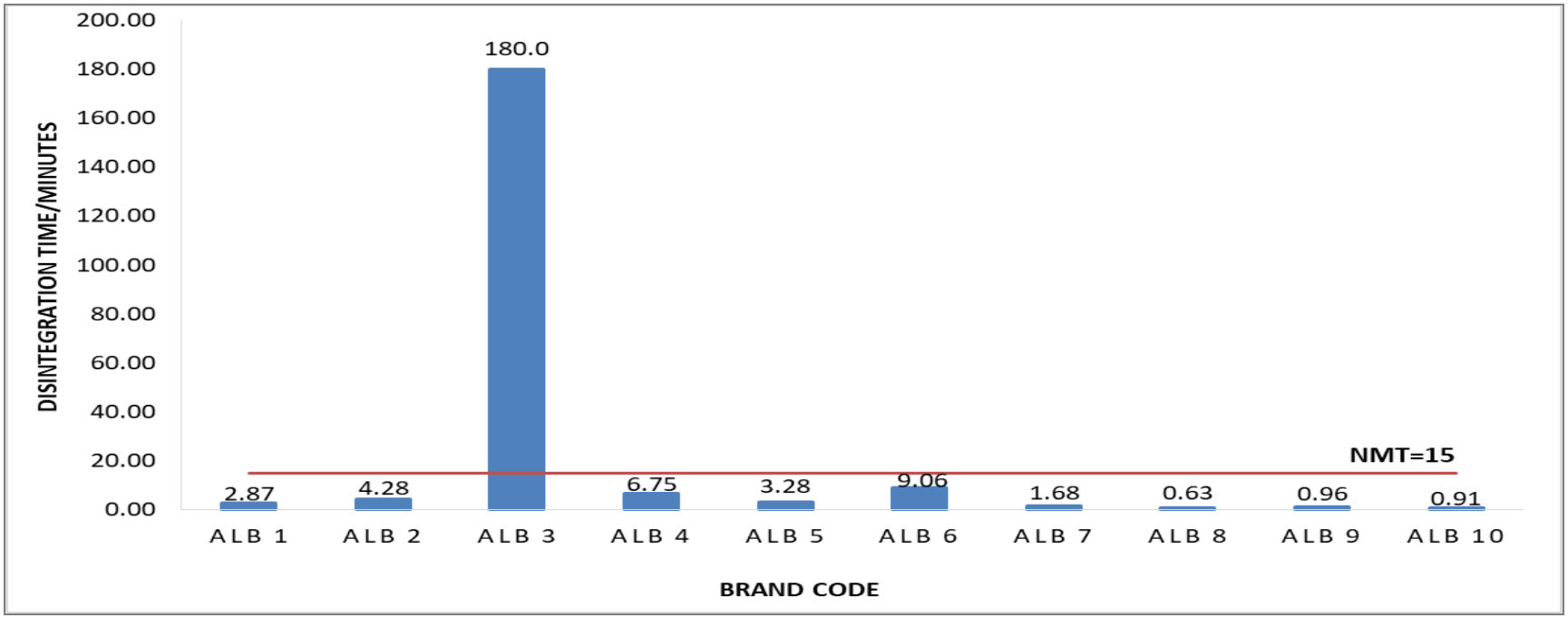

Fig 4. 3: A bar graph showing Disintegration time of the brands of Albendazole chewable tablets

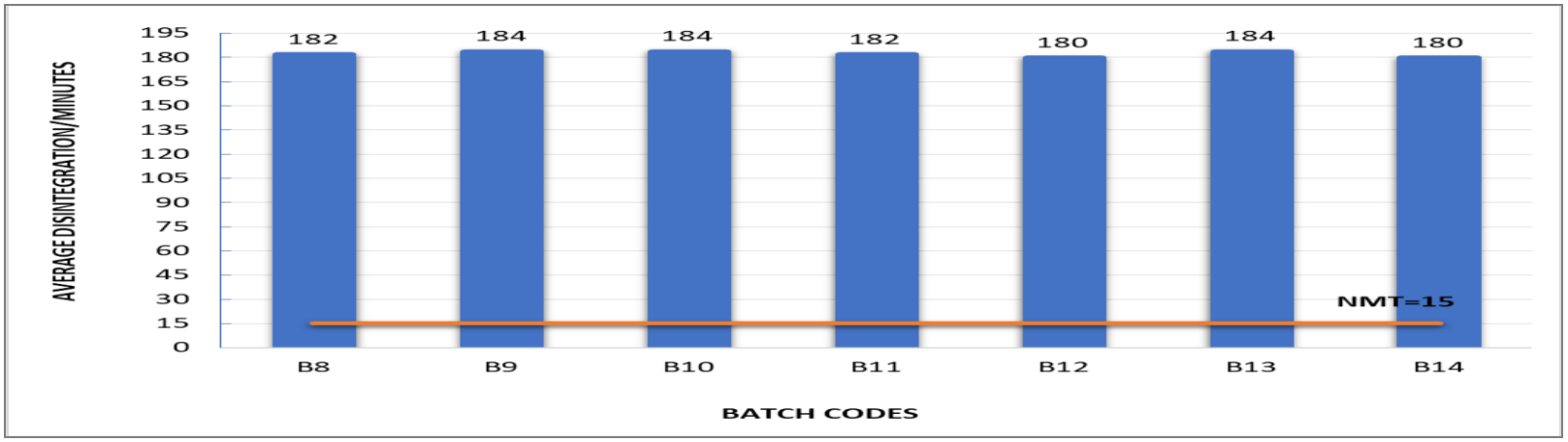

Fig 4. 4: A bar graph showing the batches of Albendazole chewable tablets that failed the Disintegration test

4.2.1 Summaries of batches that passed

A total of 32 samples passed the disintegration test with an average of 3.4 minutes The range for the average disintegration among the batches that pass was 0.62 minutes to 9.55 minutes. This is as illustrated in figure 4.5 below.

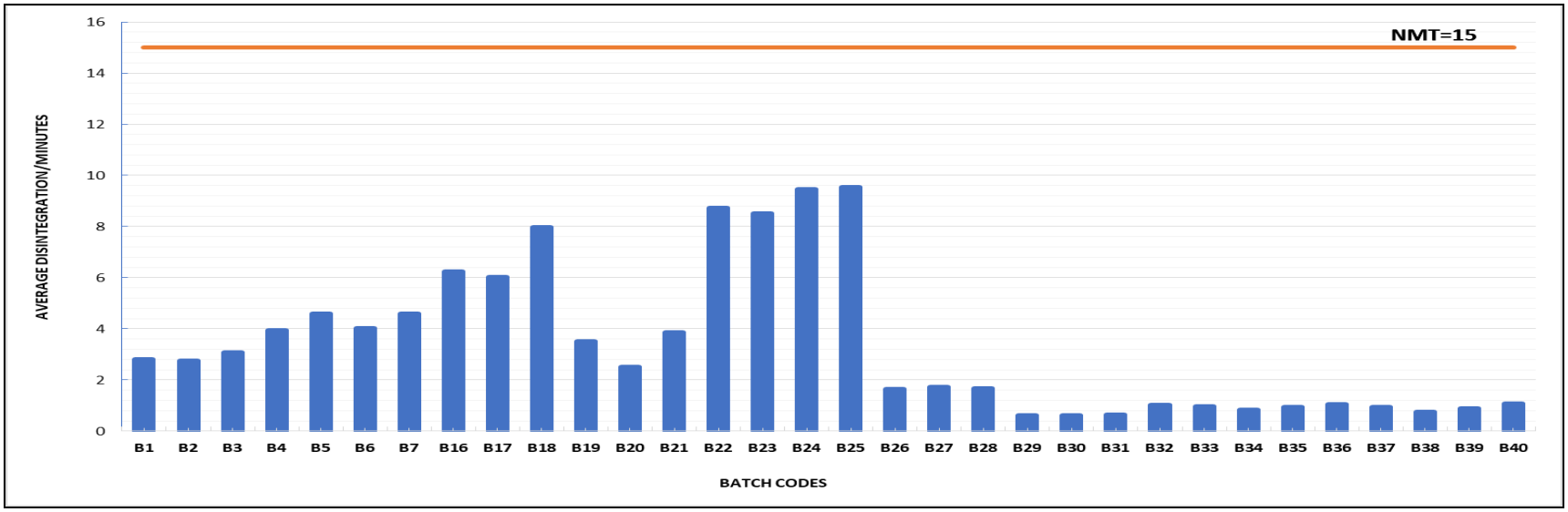

Fig 4. 5: A bar graph showing the batches of Albendazole chewable tablets that passed the Disintegration test

Brand ALB 8 had the lowest average disintegration of 0.63 minutes (SD=0.01) and ALB 3 ghad the highest average disintegration of 182 minutes (SD=1.93).

Analysis of variance at the 95 % Confidence interval of the 10 brands revealed a significant difference in the average integration among the different Albendazole brands ($P<0.05$). This shows a variation in the different manufacturing processes of the different brands that are in circulation on the Ugandan market.

The eight batches that failed the disintegration test had an average disintegration time of 182 minutes (SD=1.93). The range for the average disintegration among the batches that failed was 180 to 184 minutes.

A total of 32 samples from 9 brands passed the disintegration test with an average of 3.4 minutes (SD=2.9). The range for the average disintegration among the batches that passed was 0.62 minutes to 9.55 minutes.

A regression analysis performed on the disintegration results and the respective dissolution results of the brands showed a positive correlation between disintegration and dissolution. A one-minute increase in the disintegration time reduces dissolution rate by 1.70%. The coefficient of determination (R-Squared = 0.775) implies that disintegration is an important factor that explains over 77% of the dissolution rate. The relationship was statistically significant at 5% level of significance ($F=130.52$, $P<0.0001$).

“Therefore, to improve dissolution rate, disintegration of the tablets should be carefully controlled to fall within the prescribed time of 15 minutes, given that the disintegration process is an integral step in ensuring, and indeed maximising, the bioavailability of the API from the majority of solid dosage forms.

Disintegration time of Albendazole can be improved through addition of suitable disintegration agents in the manufacturing formulation, which promote the breakup of the

tablets into small granules and their constituent particles within the prescribed time (Markl, 2017)."

The disintegration results in this study are found to be consistent with similar studies in Yemen, Nigeria and Bukavu that have been reported on the disintegration of Albendazole. In Yemen, 22.6 % of the brands in circulation in 2017 were found to be failing disintegration (Gamil, 2018). In Nigeria, it was reported that 22.2 % of common Albendazole boluses in circulation were found non-compliant to the disintegration test (Fidelis &Bosha, 2014). In a pharmaceutical study carried out in Bukavu, 66.7 % of Quinine sulfate, Artemether and Lumefantrine tablets in circulation were found to be non-compliant with disintegration quality (Mahano *et al.*, 2021) The results from this study were however different from those obtained from two studies carries out in Ghana and Pakistan. In a quality assessment of antimalarial medicines in retail pharmaceutical outlets, all medicines tested complied to the disintegration test (El-Duah and Ofori., 2012) In Pakistan, assessment on different brands of Ciprofloxacin revealed that all the tested samples complied (Agha *et al*., 2017).

In conclusion, disintegration test which is a key predictor of how the active pharmaceutical ingredient incorporated into a solid form with other excipients is released should be controlled. The varying disintegration times are due to the amount and type of excipients as well as the different modes in the manufacturing process, all which should be mixed in a manner to ensure appropriate and timely release of the drug (Kassahun, Asres, & Ashenef, 2018).

4.3 Dissolution of Albendazole of tablets

Out of the ten brands of Albendazole chewable tablets that were tested for dissolution, 8 brands (80%) passed the test.

Two brands (20 %) of the brands failed the dissolution test. These two ; Brand ALB 3 and brand ALB 6 consisted of 16 batches (40 %) of the total 40 batches analysed. This is as demonstrated in Figure 4.6 below.

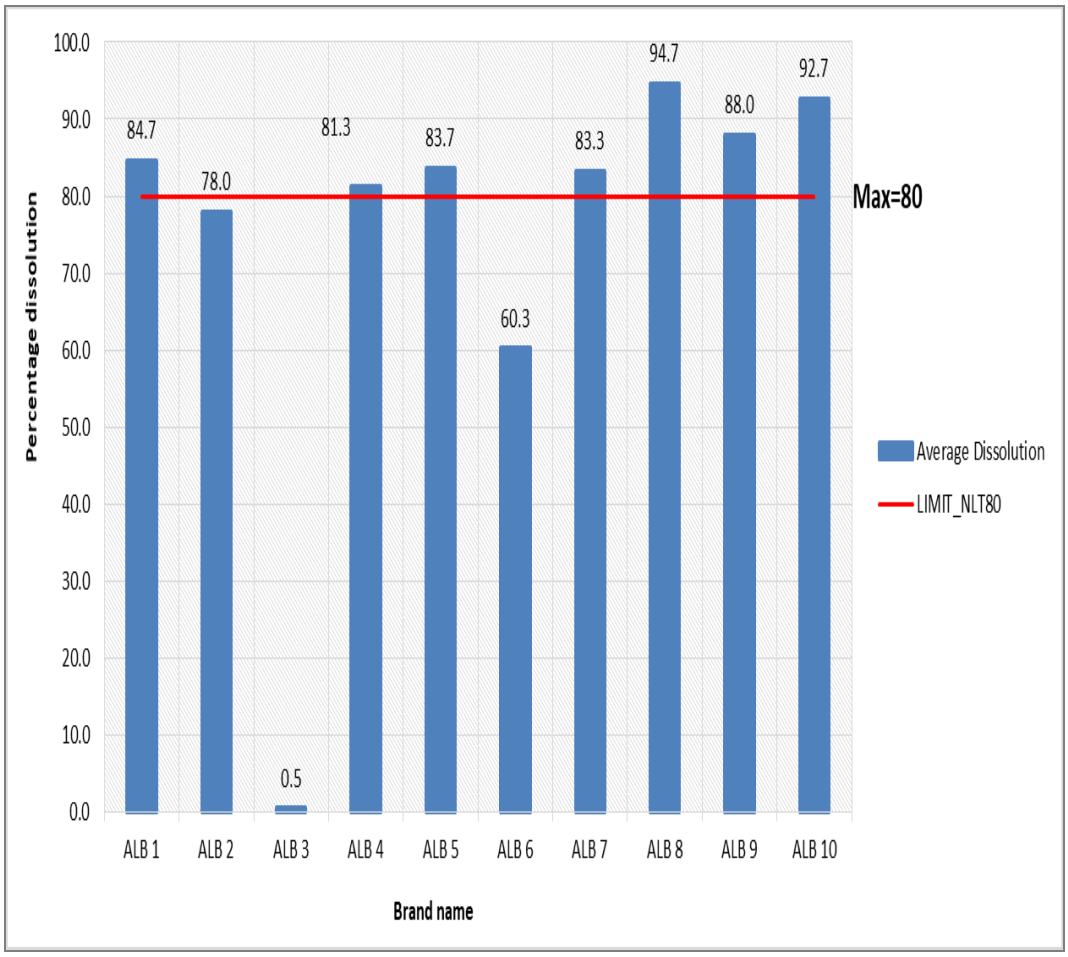

Fig 4. 6: A bar graph showing of the average amount of Albendazole that dissolved per brand

4.3.1 Samples that passed the dissolution test

Among the brands that passed; ALB 8 demonstrated a higher dissolution rate of 94.7% (about 378.7 mg out of 400 mg). This was followed by ALB 10 with 92.7% dissolution rate (370.7 mg out of 400 mg). The average dissolution rate for the 24 batches which passed dissolution test was 87.0% (SD=4.87) ranging from 80.0% to 96.0 %.

This is as illustrated in Fig 4.7 below.

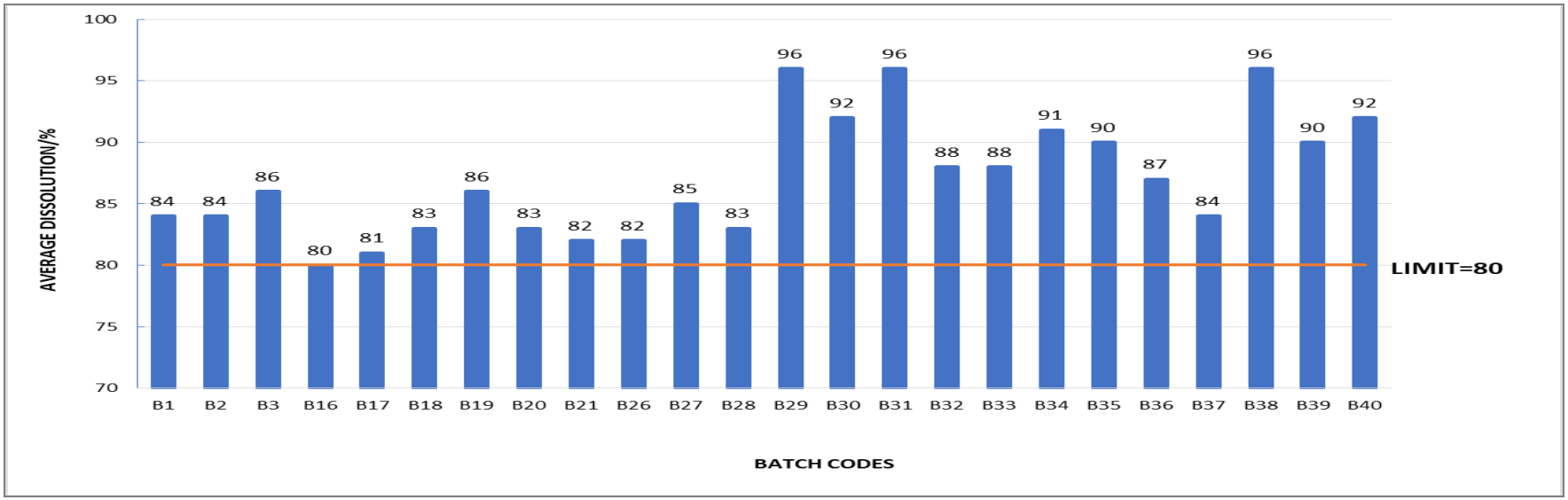

Fig 4. 7: A bar graph representation of the batches of Albendazole chewable tablets that passed the dissolution test

4.3.2 Summary statistical Analysis of the batches that failed dissolution test

A total of 16 batches failed the dissolution test with an average percentage dissolution of 34.8 %. This is an average dissolution of 139.2 mg/mg. The lowest scored 0.0 % while the highest among the batches that failed dissolution test scored 79.0% against a specification of Not Less 80 % (320 mg/mg) of the label claim should dissolve after a period of 30 minutes. This is demonstrated in Figure 4.8 below.

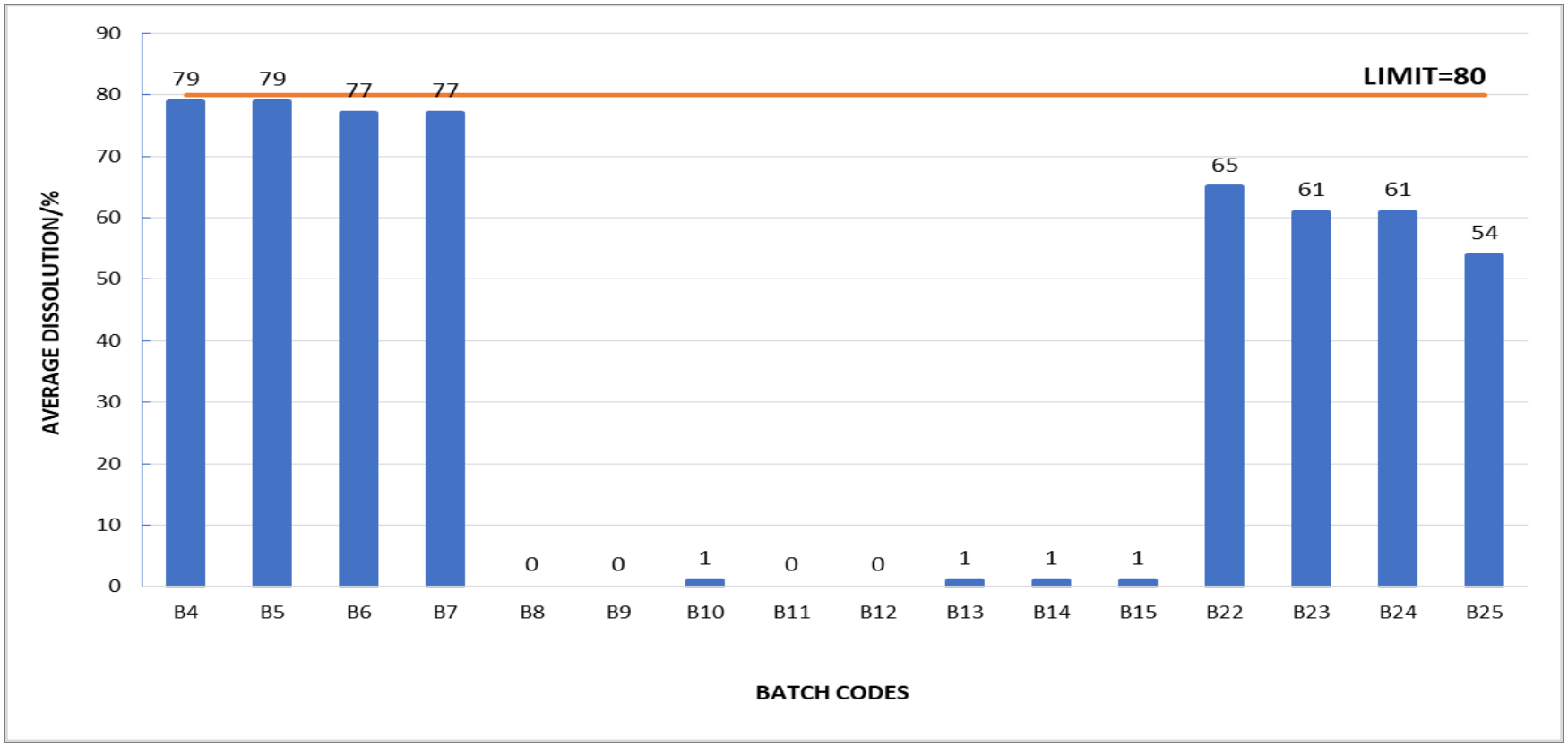

Fig 4. 8: A bar graph showing the batches that failed the dissolution test

In this study, 10 brands of Albendazole chewable tablets were tested and 3 brands (30%) of them failed the test with 7 (70%) of them passing. These three brands constituted 16 (40%) of the 40 total batches tested.

"Further analysis of variation by ANOVA among the brands that passed dissolution showed a significant difference in the dissolution rates (F=16.467, P=0.0001). This is a demonstration that despite these particular brands passing the dissolution test, they were greatly varying. This shows that the different manufacturing processes are equally very significantly different.

Of the 16 batches that failed 50 % of them had an average of 1% of Albendazole dissolving against the pre-determined minimum of 80%. This demonstrates a total failure of the manufacturing process at evaluating drug dissolution of these particular batches that did not ensure compliance to this critical efficacy parameter".

Equally, this further points to the quality control units of the manufacturing sites not being able to perform batch-wise quality control tests upon which batch releases to the market should be based upon.

This study in Uganda is consistent to similar studies that have been conducted in several countries like Yemen, Nigeria, Rwanda, Ethiopia and Bangladesh. In 2011 a survey of medicines for neglected tropical diseases by WHO showed that 57% of the products tested failed to comply with dissolution test requirements (WHO, 2015). Other studies carried out in Ethiopia, produced similar results, with 8 of 19 tested albendazole tablets (42%) failing to comply with the dissolution test (Suleman *et al.*, 2014).

In Rwanda, evaluation of dissolution of medicines in circulation on the market revealed that there was existence of substandard formulations at purchase time due to manufacturers' errors (Twagirumukiza *et al.*, 2009). In Nigeria, a similar study showed that two of the nine brands

evaluated for dissolution equally failed to release 80% of their drug contents within 30 minutes as outlined in the USP (Hambisa *et al.*, 2019). In the evaluation of physicochemical properties of some pediatric antimalarial drugs in Nigeria, it was found that there was 100 % failure of the dissolution test according to the specifications (Olajide, 2017) In Bangladesh, a quality evaluation of leading brands of ciprofloxacin tablets available pointed to a 60 % failure of the dissolution test.

This study in Uganda, like other studies across the world, shows that despite dissolution being a critical control parameter that should be carefully controlled during manufacturing and evaluated during quality control; there is a high prevalence of failure rates. These high failure rates are underlined by some formulations completely not dissolving as was noted in some brands of Albendazole tablets evaluated in this study.

Dissolution being the most critical preconditions for bioavailability of the drug to the absorption membranes and consequent uptake in patients to whom the drugs are administered, should comply at all times to the prescribed specifications (Medicamentos & Ciencias, 2015).

Therefore, the high failure rates of the dissolution test in some brands evaluated under this study calls for complete review of the manufacturing processes and production in puts employed by the affected manufacturing facilities. This is so because manufacturing inputs and their interaction with the API of interest greatly affect drug release and dissolution into solution (Yimer *et al.* ,*2020).*

4.4 Determination of the Amount of Albendazole Active Pharmaceutical Ingredient present

4.4.1 Identification of Albendazole Active Pharmaceutical Ingredient in Albendazole tablets

All the batches of the 10 brands of Albendazole chewable tablets were found to have the active pharmaceutical ingredient as summarized in Table 4.2

Table 4. 2: Average retention times of the different brands of Albendazole tablets

BRAND	HPLC RETENTION TIMES/minutes
ALB 1	13.012
ALB 2	12.998
ALB 3	12.893
ALB 4	12.978
ALB 5	12.897
ALB 6	13.014
ALB 7	13.001
ALB 8	13.008
ALB 9	12.968
ALB 10	13.112

Using the HPLC method, the chromatograms of the known Albendazole Chemical reference standard solutions and the ones of the sample solutions were examined.

The retention times of the principal peaks obtained in both were similar (± 5 %). The sample and standard chromatograms were also free from extraneous unidentifiable peaks as observed in Figures 4.9 and 4.10.

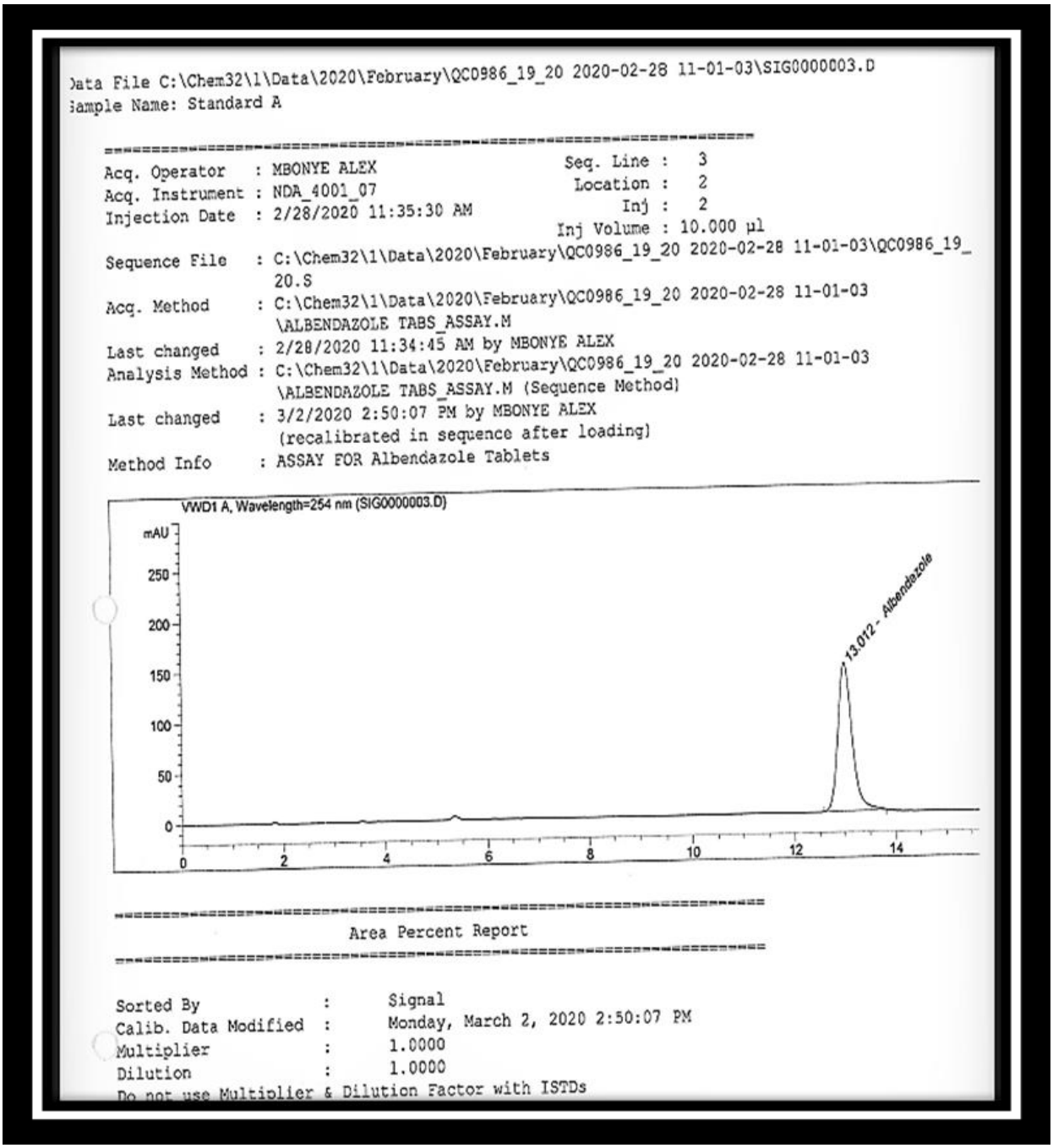

Fig 4. 9: A Standard Chromatogram showing the Retention time of Albendazole

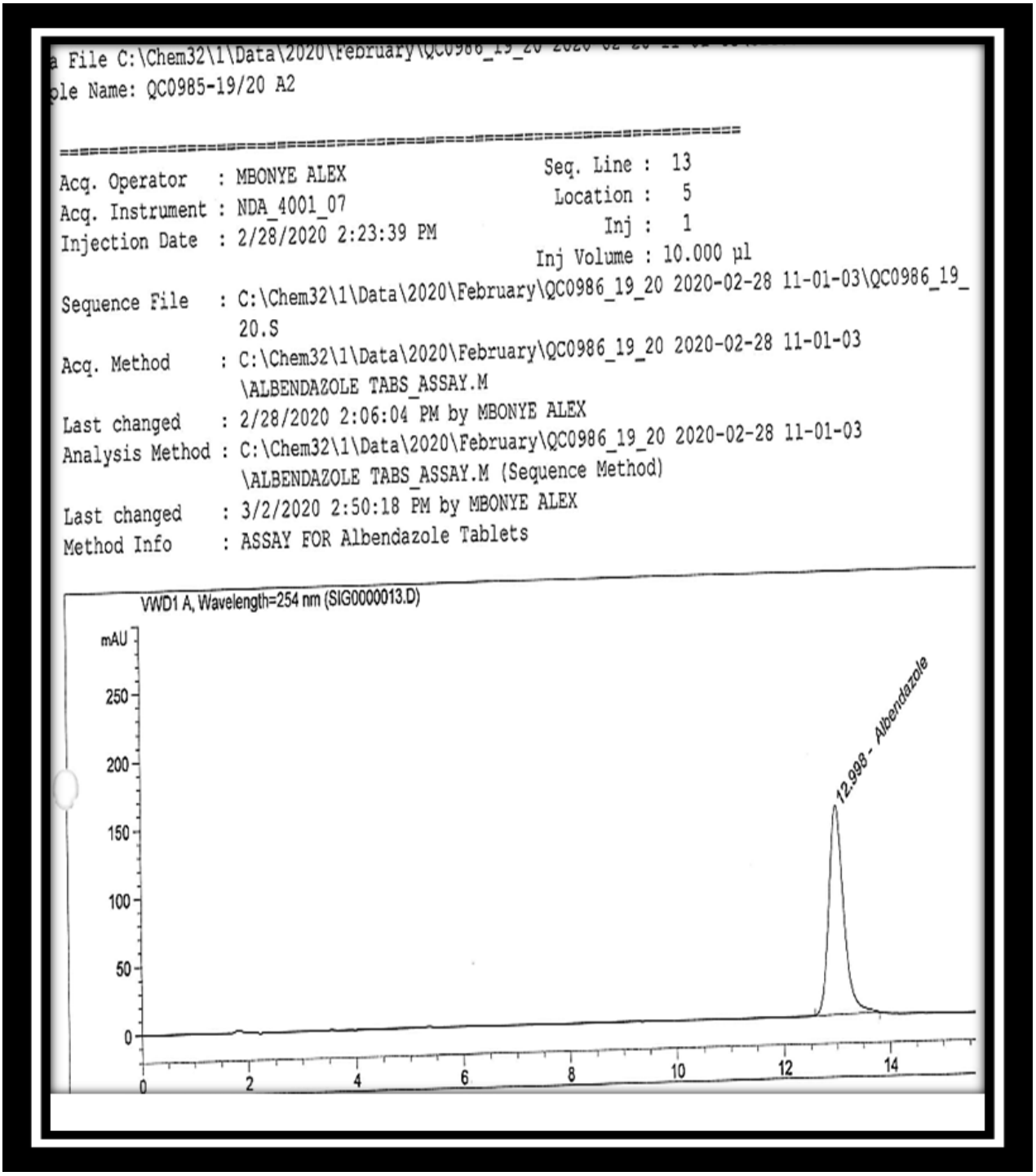

Fig 4. 10: A Sample chromatogram showing the Retention time of Albendazole

In this study, identification test for presence of Albendazole which is a major preliminary step to quantification was complied with by all samples. The confirmation of the presence of the active pharmaceutical ingredient is very key in ruling out un-intended quantification of the wrong drug substance of interest given that some pharmaceutical molecules with similar chemical structures might have similar peak shapes and retention times during chromatographic analysis.

4.4.2 Assay (Amount of Albendazole Active Pharmaceutical Ingredient)

All the 40 batches from the ten brands passed the assay test with ALB 6 having the least average assay (95.89 %,384 mg/mg) and ALB 7 having the highest average assay (99.52 %, 398 mg/mg) as presented in tables and figure 4.11 below.

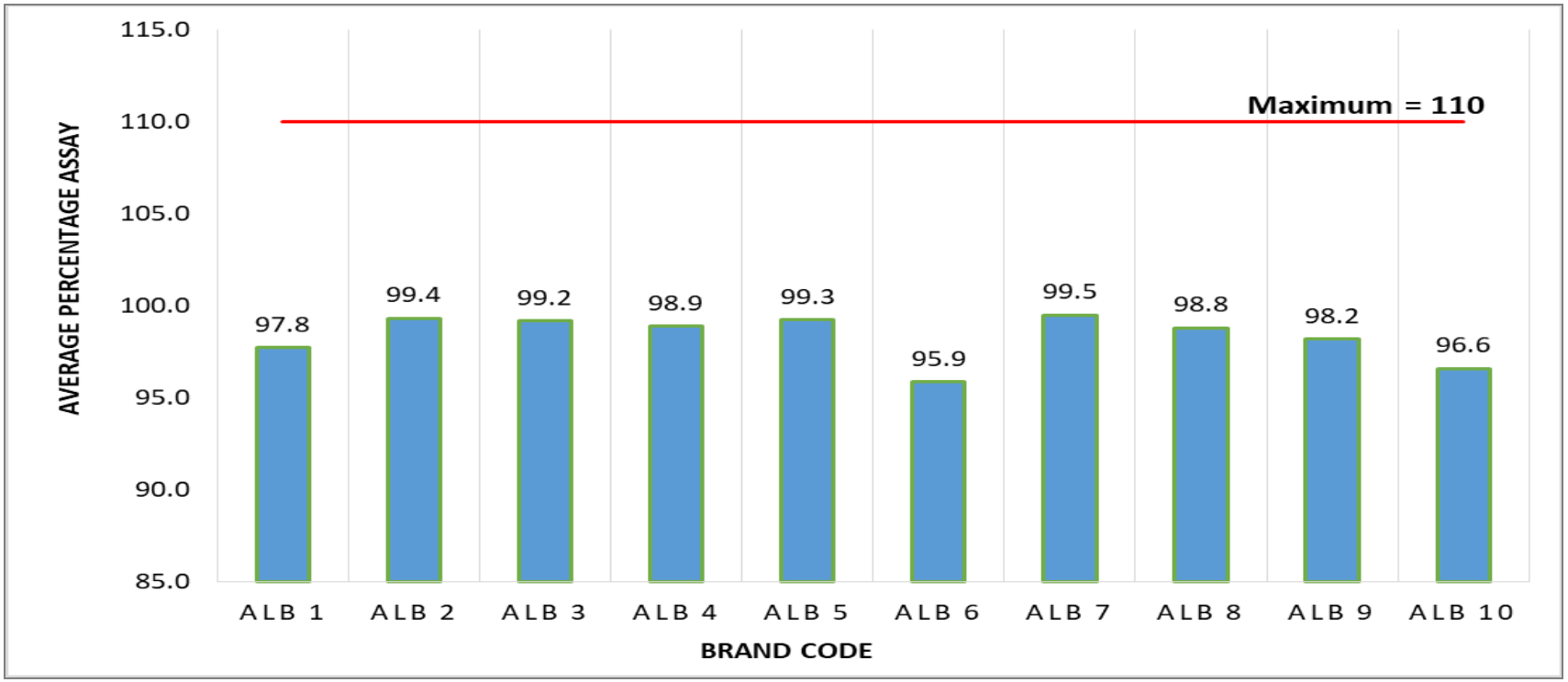

Fig 4. 11: A linear graph showing the average assay of the different brands of Albendazole chewable tablets

In this study, all the 40 batches from the ten brands analyzed passed the assay test with brand ALB 6 having the least average assay (95.9 %) and ALB 7 having the highest average assay (99.5 %). The corresponding amount of API present was 383.6 mg and 398.1 mg for the lowest and highest brands respectively. With the specifications giving a range of 90 % (360 mg) and 110 % (440 mg); the results obtained showed that all the ten brands (40 batches) had sufficient amount of API available.

Analysis of variance revealed a significant difference in average assay results by Albendazole brands ($P<0.05$). A multiple comparison test was done to test which brands had average assay results that were significantly different from each other. It was revealed that ALB 2 had significantly higher average assay than ALB 6 ($P=0.001$). ALB 3 had significantly higher average assay than ALB 6 ($P<0.0001$) and ALB 10 ($P=0.027$). ALB 4, ALB 5, ALB 7, ALB 8 and ALB 9 had significantly higher assay that ALB 6 ($P<0.05$). This shows that whereas all the ten brands passed the assay test, they greatly varied which points to different manufacturing processes.

Worth-noting is that all the 3 brands (16 batches) that failed the dissolution test passed the assay test. These three brands were Alb 2, Alb 3 and Alb 6 with average dissolution values of 78.0 %, 0.5 % and 60.3 % respectively against the dissolution specification of not less than 80 % of the API dissolved in 30 minutes. The corresponding average assay values were 99.35 %, 99.21 % and 95.89 % respectively against the assay specifications of (90.0 % -110.0 %). The explanation here is that medicines having the right amount of API as per their label claim is not sufficient to cause cure or treatment as long as the API in the matrix does not readily dissolve in solution.

This results into low bioavailability and consequently less or no uptake of the drug by the patient (Vandana *et al*., 2017).

The assay results obtained in this study of 100 % compliance are similar to what was reported in Ghana, Ethiopia, Pakistan, Yemen and Bangladesh (Abuye *et al*., 2020; Agha *et al.*, 2017; Kassahun *et al.*, 2018; Kuntworbe *et al*., 2018; Gamil, 2018; Uddin *et al*., 2017; Yimer *et al*., 2020).

They are however different to the results obtained from Ethiopia where 30 % of the Albendazole batches tested failed to comply (Seifu *et al.*, 2019). Similarly, in Lubumbashi of Democratic Republic of Congo, 56 % of the Albendazole tablets in circulation tested failed the assay test (Mwamba *et al*., 2016). Studies carried out in Nigeria, Ghana, Papua New Guinea, Bukavu and Togo showed assay test failures of 55.5 %, 50 %, 12.5 %,20 % ,48.3 %, 41.6 %, 92 % and 83.7 % respectively (Ajala *et al*., 2014; Boakye-Agyeman and Panas, 2017; Hetzel *et al*., 2014; El-Duah and Kwakye., 2012; Mahano *et al*., 2021; Olajide, 2017).

"In conclusion, the quality of Albendazole tablets circulating on the Ugandan market like other medicines is susceptible to quality failures given the high failures reported in countries around the globe. This is so because, a confirmed counterfeit on any market is a threat to the global supply chains since Uganda's production of conventional medicines is still very low. Therefore, regulatory authorities charged with ensuring the availability of safe and efficacious medicines should increase on the frequency of quality control tests that should be carried out. This should be combined by frequent good manufacturing practice inspections conducted on manufacturing sites since some failures point to complete failure of the manufacturing processes in producing medicines of the required physical and chemical properties according to the required specifications."

CHAPTER FIVE

CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

The major conclusion from this study is that some of the batches of Albendazole tablets in circulation in Uganda were not of the right quality due to failure comply with specifications for all the tests done.

In this study, under objective one, the importance of examination of physical attributes as a preliminary quality check was underscored. It was found out that some tablets can get to the market with physical defects which greatly affect their chemical quality attributes.

It was established, under objective two, that some tablets on the Ugandan market do not disintegrate into solution within the prescribed time and this posed a big threat to the efficacy of the dosages.

In this study, it was proven under objective three, that dissolution time quality test is the least compliant of all the quality parameters assessed. The fact that some batches did not dissolve at all in solution points to total failure of the manufacturing process.

A strong positive correlation between disintegration and dissolution quality tests was established in this study. This was due to the fact that all tablets that failed the disintegration test went on to fail the dissolution test .

This study further established under objective five that all the batches on market contained the required amount of active ingredient. However, it was found out through comparison that the 10 brands of Albendazole tablets in circulation were significantly different for the quality parameters assessed.

5.2 Recommendations

The high prevalence of substandard Albendazole chewable tablets in circulation in the regulated market in Uganda calls for major reforms in the process of registration, market authorization, post market surveillance and quality assurance of medicines in Uganda, mandate that lies with the National Drug Authority, Uganda. These recommendations therefore call for the actions of the authority as it dispenses its mandate of ensuring safe, efficacious and quality medicines.

1. It is hereby recommended that prior to registration and marketing authorization of medicines on the Ugandan market, these medicines should first be analysed comprehensively in the National Drug Quality Control laboratory to ascertain their quality.

2. A visual inspection tool should be developed, adopted and upon training passed on to end user health workers in their respective local languages to enable them carry out preliminary assessments before drugs are dispensed to patients. In this way, those tablets from particular batches which randomly escape the quality checks by the quality control and assurance of manufacturers will be handled. This will go a long way in completing the quality cycle during dispensing and most importantly crucial feedback to the regulators and timely in case substandard or counterfeit medicines are on the market.

3.Given that the high cost of pharmaceutical chemical analysis does not permit complete testing of all medicines on the Ugandan market by the regulatory authority, periodic rapid assessments are highly recommended. For instance, mobile laboratories, minilabs and other rapid assessment kits using techniques like Near Infra-Red can be employed regularly during post market surveillance.

4. Related drug molecules in the category of albendazole chewable tablets such as mebendazole should be sampled and analysed to ascertain their quality given that there could be a high chance of substandard products among those in circulation.

5. Efficacy studies should be carried out on different brands of Albendazole chewable tablets on the Ugandan market. The area of efficacy is one key area that has not been deeply studied in Uganda given the immense financial time resources required to conduct a scientific clinical trial. Such a study would reveal which brand is most effective as well as the level of drug resistance in Uganda by the parasites to Albendazole chewable tablets.

6. Given that all the samples in this study were collected from authorized wholesale pharmacies, studies on samples collected from the illegal market or un-licensed drug outlets should be conducted. Intelligence led investigations would help in identification of illegal drug premises and persons trading in medicines. This would be a great contribution to knowledge with regard to the extent of illegal drug premises and the quality of medicines traded therein.

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APPENDICES

Appendix 1: Physical Characteristics of tablets

BATCH CODE	Amount of API (mg/tablet)	Uniformity of Shape	Uniformity of Size	Uniformity of Colour	Breaks/cracks and splits	Surface contamination
B1	200	YES	YES	YES	NO	NO
B2	200	YES	YES	YES	NO	NO
B3	200	YES	YES	YES	NO	NO
B4	400	YES	YES	YES	NO	NO
B5	400	YES	YES	YES	YES	NO
B6	400	YES	YES	YES	NO	NO
B7	400	YES	YES	YES	NO	NO
B8	400	YES	YES	YES	NO	NO
B9	400	YES	YES	YES	NO	NO
B10	400	YES	YES	YES	NO	NO
B11	400	YES	YES	YES	NO	NO
B12	400	YES	YES	YES	NO	NO
B13	400	YES	YES	YES	NO	NO
B14	400	YES	YES	YES	NO	NO
B15	400	YES	YES	YES	NO	NO
B16	400	YES	YES	YES	NO	NO
B17	400	YES	YES	YES	NO	NO
B18	400	YES	YES	YES	NO	NO
B19	200	YES	YES	YES	NO	NO
B20	200	YES	YES	YES	NO	NO
B21	200	YES	YES	YES	NO	NO
B22	400	YES	YES	YES	NO	NO
B23	400	YES	YES	YES	YES	NO
B24	400	YES	YES	YES	NO	NO
B25	400	YES	YES	YES	NO	NO
B26	400	YES	YES	YES	NO	NO
B27	400	YES	YES	YES	NO	NO
B28	400	YES	YES	YES	NO	NO
B29	400	YES	YES	YES	NO	NO
B30	400	YES	YES	YES	NO	NO
B31	400	YES	YES	YES	NO	NO

B32	400	YES	YES	YES	NO	NO
B33	400	YES	YES	YES	NO	NO
B34	400	YES	YES	YES	NO	NO
B35	400	YES	YES	YES	NO	NO
B36	400	YES	YES	YES	NO	NO
B37	400	YES	YES	YES	NO	NO
B38	400	YES	YES	YES	NO	NO
B39	400	YES	YES	YES	NO	NO
B40	400		YES	YES	NO	NO

Appendix 2: Packaging information and labeling requirements for the different brands of Albendazole

BATCH CODES	Manufacture and expiry date	Batch Number	Storage Information	Leaflet insert	Physical Address	Dosage statement
B1	YES	YES	YES	YES	YES	YES
B2	YES	YES	YES	YES	YES	YES
B3	YES	YES	YES	YES	YES	YES
B4	YES	YES	YES	YES	YES	YES
B5	YES	YES	YES	YES	YES	YES
B6	YES	YES	YES	YES	YES	YES
B7	YES	YES	YES	YES	YES	YES
B8	YES	YES	YES	YES	YES	YES
B9	YES	YES	YES	YES	YES	YES
B10	YES	YES	YES	YES	YES	YES
B11	YES	YES	YES	YES	YES	YES
B12	YES	YES	YES	YES	YES	YES
B13	YES	YES	YES	YES	YES	YES
B14	YES	YES	YES	YES	YES	YES
B15	YES	YES	YES	YES	YES	YES
B16	YES	YES	YES	YES	YES	YES
B17	YES	YES	YES	YES	YES	YES
B18	YES	YES	YES	YES	YES	YES
B19	YES	YES	YES	YES	YES	YES
B20	YES	YES	YES	YES	YES	YES
B21	YES	YES	YES	YES	YES	YES
B22	YES	YES	YES	YES	YES	YES
B23	YES	YES	YES	YES	YES	YES

B24	YES	YES	YES	YES	YES	YES
B25	YES	YES	YES	YES	YES	YES
B26	YES	YES	YES	YES	YES	YES
B27	YES	YES	YES	YES	YES	YES
B28	YES	YES	YES	YES	YES	YES
B29	YES	YES	YES	YES	YES	YES
B30	YES	YES	YES	YES	YES	YES
B31	YES	YES	YES	YES	YES	YES
B32	YES	YES	YES	YES	YES	YES
B33	YES	YES	YES	YES	YES	YES
B34	YES	YES	YES	YES	YES	YES
B35	YES	YES	YES	YES	YES	YES
B36	YES	YES	YES	YES	YES	YES
B37	YES	YES	YES	YES	NO	YES
B38	YES	YES	YES	YES	NO	YES
B39	YES	YES	YES	YES	NO	YES
B40	YES	YES	YES	YES	NO	YES

Appendix 3: A Comparison of the brands of Albendazole chewable tablets that passed dissolution

Batch code	Mean (%)	Label claim (mg)	Amount dissolved (mg)	Std. Deviation	Median	Minimum	Max
ALB 1	84.7	200	169.3	2.31	168.0	168.0	172.0
ALB 4	81.3	400	325.3	6.11	324.0	320.0	332.0
ALB 5	83.7	200	167.3	4.16	166.00	164.0	172.0
ALB 7	83.3	400	333.3	6.11	332.00	328.0	340.0
ALB 8	94.7	400	378.7	9.24	384.00	368.0	384.0
ALB 9	88.0	400	352.0	9.80	352.00	336.0	364.0
ALB 10	92.7	400	370.7	12.22	368.00	360.0	384.0

Appendix 4: Amount released by the different batches of Albendazole chewable tablets

	% AMOUNT OF ALBENDAZOLE RELEASED IN 30 MINUTES						
BRAND CODE	TABLET	TABLET	TABLET	TABLET	TABLET	TABLET	AVERAGE
1	83	83	83	82	87	87	84
2	83	84	84	82	86	86	84
3	88	88	85	86	84	83	86
4	79	82	78	79	77	77	79
5	80	78	77	78	81	77	79
6	78	75	77	75	77	79	77
7	77	75	78	80	76	74	77
8	0	1	0	1	0	0	0
9	0	1	0	0	1	0	0
10	1	1	1	0	0	0	1
11	0	0	0	1	0	1	0
12	0	0	1	0	0	1	0
13	1	1	0	1	1	0	1
14	1	0	1	0	1	0	1
15	0	0	1	1	0	1	1
16	78	81	79	81	80	82	80
17	81	80	81	80	82	82	81
18	81	82	82	83	84	85	83
19	88	81	90	81	89	88	86
20	76	86	81	86	81	90	83
21	79	82	83	84	82	82	82
22	72	64	67	64	64	61	65
23	59	61	61	61	61	62	61
24	59	59	64	63	61	60	61
25	66	67	64	63	6	60	54
26	83	83	81	82	83	81	82
27	85	85	86	85	85	86	85
28	82	83	82	83	84	85	83
29	98	97	96	99	95	93	96
30	94	91	90	90	95	93	92
31	97	95	96	97	97	95	96
32	89	90	91	88	86	84	88
33	86	89	88	88	86	89	88
34	90	90	93	92	94	89	91
35	91	91	90	90	90	88	90
36	89	88	85	88	84	85	87
37	84	84	84	83	86	83	84
38	95	95	96	93	99	98	96
39	88	89	89	91	94	87	90
40	90	92	93	92	93	94	92

Appendix 5: Average Assay of the different batches of Albendazole chewable tablets

ASSAY OF ALBENDAZOLE BY HPLC			
BATCH CODE	**SAMPLE 1**	**SAMPLE 2**	**AVERAGE**
1	97.4	97.7	97.6
2	98.1	98.6	98.4
3	97.3	97.4	97.4
4	99.7	101.5	100.6
5	98.9	98	98.5
6	99.2	100.6	99.9
7	98.6	98.3	98.5
8	100	96.5	98.3
9	101.6	100.8	101.2
10	99.9	99.1	99.5
11	98.7	98.7	98.7
12	99.3	97.6	98.5
13	98.4	98.3	98.4
14	99	98.6	98.8
15	100.3	100.5	100.4
16	98.4	98.1	98.3
17	98.9	98.8	98.9
18	99.7	99.5	99.6
19	99	99	99.0
20	98.3	98.9	98.6
21	100.3	100.1	100.2
22	95.2	95.7	95.5
23	95.3	95.8	95.6
24	96.8	96.4	96.6
25	96	95.9	96.0
26	100.1	100.2	100.2
27	99	99.3	99.2
28	98.7	99.8	99.3
29	98.3	98.4	98.4

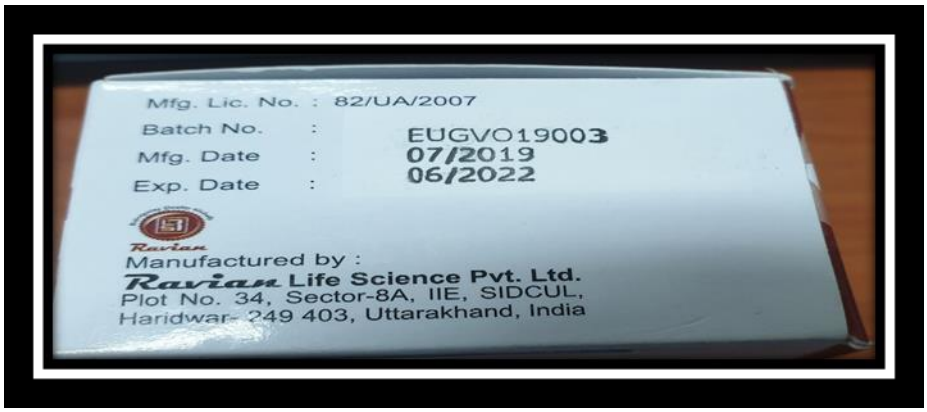
30	98.8	98.6	98.7
31	99.5	99.4	99.5
32	98.1	98.2	98.2
33	96.7	96.6	96.7
34	97	97.3	97.2
35	99.2	99.9	99.6
36	98.3	98.1	98.2
37	99.6	99.5	99.6
38	97.6	97.8	97.7
39	94.6	94.6	94.6
40	97.7	97.4	97.6

Appendix 6: Average actual amount of Albendazole present in the different batches of Albendazole chewable tablets

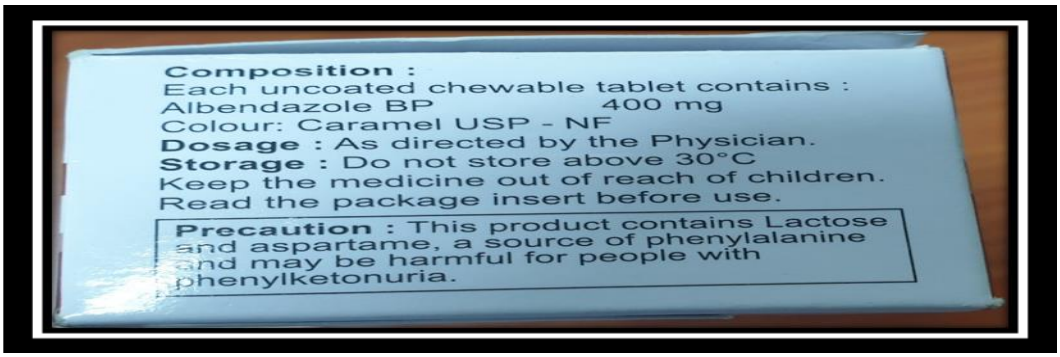
BATCH CODE	**LABEL CLAIM (mg)**	**ACTUAL /mg**	**minimum/mg**	**Maximum (mg)**
1	200	195.1	180	220
2	200	196.7	180	220
3	200	194.7	180	220
4	400	402.4	360	440
5	400	393.8	360	440
6	400	399.6	360	440
7	400	393.8	360	440
8	400	393	360	440
9	400	404.8	360	440
10	400	398	360	440
11	400	394.8	360	440
12	400	393.8	360	440
13	400	393.4	360	440
14	400	395.2	360	440

15	400	401.6	360	440
16	400	393	360	440
17	400	395.4	360	440
18	400	398.4	360	440
19	200	198	180	220
20	200	197.2	180	220
21	200	200.4	180	220
22	400	381.8	360	440
23	400	382.2	360	440
24	400	386.4	360	440
25	400	383.8	360	440
26	400	400.6	360	440
27	400	396.6	360	440
28	400	397	360	440
29	400	393.4	360	440
30	400	394.8	360	440
31	400	397.8	360	440
32	400	392.6	360	440
33	400	386.6	360	440
34	400	388.6	360	440
35	400	398.2	360	440
36	400	392.8	360	440
37	400	398.2	360	440
38	400	390.8	360	440
39	400	378.4	360	440
40	400	390.2	360	440

Appendix 7: Batch Number, Manufacturing, Expiry and Manufacturing Address details



Appendix 8: Active Pharmaceutical ingredient, Quantity and storage details



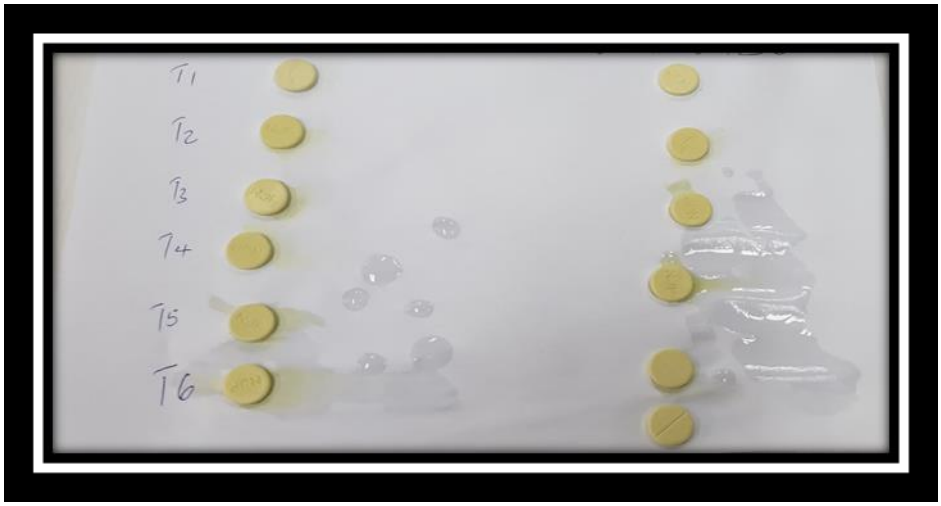
Appendix 9: Visual inspection revealing defective tablets

Chipped tablet observed during visual inspection

Appendix 10: Albendazole chewable tablets in the mortar being crushed for the assay test

Appendix 11: Samples for the Assay test undergoing filtration

Appendix 12: Tablets for Brand Alb 3 that did not dissolve at all after 30 minutes of testing

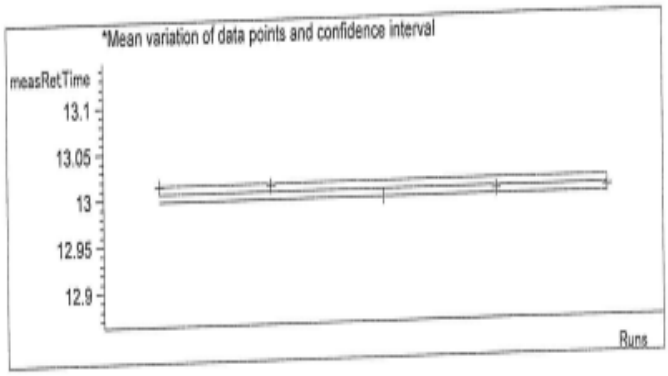


Appendix 13: Extended statistic report showing system suitability parameters for Retention time and Peak areas

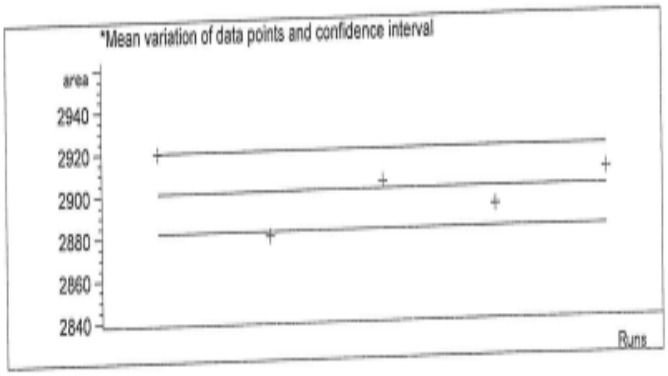
Run #	Location	Inj #	Inj. Date/Time	File Name	Sample Name
1	2	1	2/28/2020 11:18:42 AM	SIG0000002.D	Standard A
2	2	2	2/28/2020 11:35:30 AM	SIG0000003.D	Standard A
3	2	3	2/28/2020 11:52:19 AM	SIG0000004.D	Standard A
4	2	4	2/28/2020 12:09:07 PM	SIG0000005.D	Standard A
5	2	5	2/28/2020 12:25:56 PM	SIG0000006.D	Standard A
6	2	1	2/28/2020 3:47:51 PM	SIG0000018.D	Standard A

Compound: Albendazole (Signal: VWD1 A, Wavelength=254 nm)

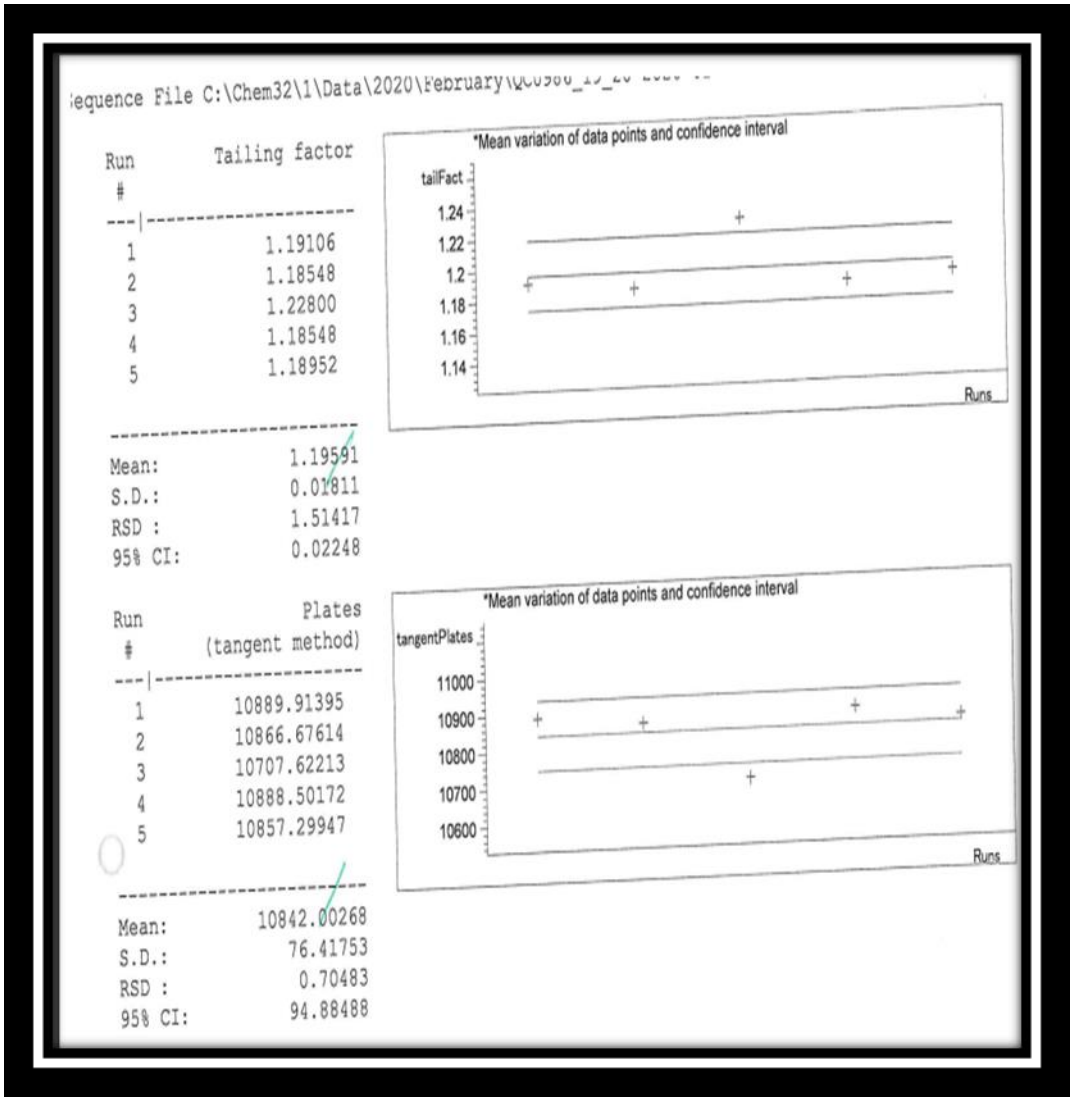
Run #	RetTime [min]
1	13.01345
2	13.01180
3	12.99717
4	13.00236
5	13.00347
Mean:	13.00565
S.D.:	0.00682
RSD :	0.05245
95% CI:	0.00847



Run #	Peak area [mAU*s]
1	2919.67212
2	2879.76782
3	2904.29272
4	2892.35498
5	2908.69751
Mean:	2900.95703
S.D.:	15.36452
RSD :	0.52964
95% CI:	19.07757



Appendix 14: Extended statistic report showing system suitability parameters for Tailing Factor and Theoretical plates



Appendix 15: Comparison of the brands of Albendazole chewable tablets that failed Disintegration

Measure	Value
Frequency	8
Average disintegration	182.0
Standard deviation	1.93
Minimum	180.0
Maximum	184.0

Appendix 16: Correlation between Disintegration and Dissolution

	Disintegration	**Dissolution**
Pearson Correlation	1	-0.880**
Sig. (2-tailed)		0.000
N	40	40
Pearson Correlation	-0.880**	1
Sig. (2-tailed)	0.000	
N	40	40

Appendix 17: Regression Analysis Disintegration and Dissolution

Measure	**Value**
Constant	304.81
Coefficient	-1.70
R-Squared	0.775
F-Statistic	130.52
P-Value	<0.0001

Appendix 18: Test for Normality of the Assay test results

Shapiro-Wilk		
Statistic	**Df**	**P-value**
0.962	40	0.204

Appendix 19: Test for Homogeneity of variances of the Assay test results

	Levene Statistic	df1	df2	Sig.
Based on Mean	1.675	9	30	0.139
Based on Median	0.513	9	30	0.854
Based on Median and with adjusted df	0.513	9	12.094	0.839
Based on trimmed mean	1.546	9	30	0.177

Appendix 20: ANOVA test of the Assay test results

	Sum of Squares	Df	Mean Square	F	P-value
Between Groups	52.391	9	5.821	5.862	<0.0001
Within Groups	29.793	30	0.993		
Total	82.184	39			