INTERACTION STUDIES BETWEEN TWO ANTIBIOTICS AND A COMMERCIAL HERBAL PRODUCT

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BEING A DISSERTATION SUBMITED IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE AWARD OF DOCTOR OF PHARMACY (PHARM.D) DEGREE OF THE UNIVERSITY OF BENIN, BENIN CITY, NIGERIA.

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CERTIFICATION

This is to certify that this work was carried out by Okedusi Damilola Deborah in the Department of Pharmaceutics and Pharmaceutical technology, Faculty of Pharmacy, University of Benin, Benin City in partial fulfillment of the award of the Pharm. D degree of the university

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DEDICATION

This work is dedicated to Almighty God, whose grace and infinite mercies have guided me throughout this journey of academic pursuit.

ACKNOWLEDGEMENT

I would like to express my deepest gratitude to Almighty God, whose unwavering grace and guidance have been the cornerstone of my academic journey. His divine presence has illuminated my path and granted me the strength to persevere through the challenges encountered during this pursuit of knowledge.

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Lastly, to my cherished friends, Pat, Greta, Tobe, Daniel, Martins, Maro, Trust, Erica, Nat, and all my classmates, I extend my heartfelt thanks. Your camaraderie, support, and encouragement have created an enriching academic environment. Together, we have shared

the triumphs and challenges of this educational journey, and I am grateful for the bonds we have forged.

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ABSTRACT

Introduction: In the realm of modern healthcare, the integration of herbal remedies with conventional pharmaceuticals presents a dynamic and potentially influential interplay.

Purpose: This study aimed to investigate the interaction between Beta Cleanser Bitters and two antibiotics, ciprofloxacin and amoxicillin.

Method: Commercial brands of Ciprofloxacin, amoxicillin and Beta Cleanser Bitters were purchased and evaluated for the physiochemical properties. The interaction between the antibiotics and Beta Cleanser Bitters were evaluated using the disintegration time test and dissolution studies. Further interactions studies were carried out using absorbance inference studies and FTIR studies.

Results: The presence of Beta Cleanser Bitters showed no contrasting effects on the disintegration times of the two drugs. For ciprofloxacin in the presence of Beta Cleanser Bitters, the dissolution drug release remained relatively stable and no significant difference while for amoxicillin there was a decrease in drug release in the presence of the bitters. FTIR analysis revealed similarity in spectra, suggesting minimal chemical interactions between amoxicillin and Beta Cleanser Bitters and for Ciprofloxacin, revealed difference in spectra, indicating an interaction.

Conclusion: The study suggests that Beta Cleanser Bitters may exert some influence on the dissolution and disintegration behavior of ciprofloxacin and amoxicillin, though chemical interactions appear to be limited.

CHAPTER ONE

1.1 INTRODUCTION

Herbal products, botanical products, or phytomedicines are items manufactured from botanicals, or plants, that are used to treat illnesses or preserve health. An herbal supplement is a product made from plants that is only intended for internal use (Abdel-Aziz *et al*., 2016). They fall under the umbrella of complementary and alternative medicine. Numerous prescriptions and over-the-counter medications are also created from plant materials, but they only have purified chemicals and are subject to FDA regulation (Marcus, 2016). Whole plants or plant components may be found in herbal supplements. Herbal supplements are available in a variety of forms, including dried, chopped, powdered, liquid, capsules, and tinctures, and can be consumed in a number of ways. brewed as tea, used topically as creams, gels, or lotions (Hadady, 2020).

It has been customary since the beginning of time to employ plants, plant parts, and isolated phytochemicals to prevent and treat a variety of illnesses. There are 121 such active drugs in use, and it is believed that around 25% of medications prescribed globally are derived from plants. 11% of the 252 pharmaceuticals on the WHO's list of essential medications are only made from plants. Almost 80% of people in Africa and Asia rely on traditional medicines for their primary healthcare (Sen and Chakraborty, 2017).

In India, the use of herbal remedies or traditional medical practices is prevalent in the rural areas (approximately 80%). The Indian herbal business uses about 960 different plant species, 178 of which are employed in substantial quantities that exceed 100 metric tonnes annually. The Indian herbal market is expanding (Nautiyal *et al*., 2020).

Herbal medications can be divided into three categories based on the makeup of their active metabolites. The first group includes drugs that are used crudely. The second category of herbal medications consists of the active components that have been extracted after plant extracts have been processed. These are pure molecules and are typically more potent pharmacologically. The third class of herbal medicines for which information on acute and long-term animal toxicity trials is available.

A regional workshop on the regulation of herbal medicines, sponsored by the WHO regional office for South East Asia, recommended a classification system for herbal pharmaceuticals in 2003. Herbal medications can be broadly divided into four kinds, including imported goods with a herbal medicine base, systems-based herbal medicines, modified herbal medicines, and indigenous herbal medicines. Due to their long history of use in the community, indigenous herbal medicines are well known in terms of their composition, methods of treatment, and dosage.

Since herbal medications have been used for a very long time in the systems of Ayurveda, Unani, and Siddha, efficacy assessments are not necessary for local usage. In terms of dose form, mode of administration, herbal medicinal components, techniques of preparation, and medical purposes, modified herbal medicines indicate modifications to the form of traditional herbal medicine. These should be safe and effective according to national regulatory standards. Depending on the modification(s), pre-clinical and clinical data may or may not be required.

Raw components and finished products used in imported herbal medicines must be registered and marketed in the countries of origin. The national authorities of the importing nation must receive safety and efficacy data. It is particularly important that the final two categories of herbal medications comply with good manufacturing practices (GMP). India is renowned for exporting herbal medications in systems, such as ayurveda medicines, to many

regions of the world in addition to standardized herbal extract and raw materials. Even though the use of herbal pharmaceuticals is growing over the world, reports of their negative effects and adulteration have raised questions about their widespread use and are preventing their commercialization. Additionally, these pharmaceuticals' regulatory processes varied from country to country. The current study makes an effort to determine both the regulatory framework for the commercialization of these pharmaceuticals as well as the development of technical standards in the manufacture of herbal drugs (Sahoo *et al*., 2010).

1.2 DRUG INTERACTIONS

Drug interactions happen when the concurrent administration of items like foods, drinks, or other medications alters the way a drug works. The reason is frequently the drug's specific receptors' blockage or reduced ability to function. Due to this, medication molecules are influenced to bind to secondary targets, which may have a variety of undesirable side effects. Drug effects on a person cannot be as expected due to food interactions, drug-drug interactions, and other factors. beverages and nutritional supplements they take (drug-nutrient/food interaction) or a different ailment they are dealing with (drug-disease interaction). A drug interaction occurs when a chemical alters a drug's action. This means that neither the causes nor the consequences independently generate a new impact or change. These interactions could occur via accident, abuse, or a failure to comprehend the chemical makeup of the relevant chemicals. The ability of the body to utilize a certain diet or prescription can be affected by food-drug interactions, which are known to cause serious side effects. This knowledge is common among doctors and pharmacists. Changes in pharmacokinetic, pharmacological, or other parameters may have an impact on the patient or their pharmacodynamic properties when there are interactions between clinically relevant medications that could be dangerous.

Drug interactions can sometimes induce adverse drug reactions, however this is less often and may be used against some patients. Information from numerous reviews was gathered for the literature review of new studies on the connections between certain foods and certain medications. Details on the numerous interactions between meals are provided in this review. Doctors and pharmacists must take great care when deciding which medications to recommend to patients in order to give them the maximum benefit feasible (Bais and Mali, 2023).

1.2.1 Types of Drug-Drug Interactions

Drug interaction could be pharmacokinetics or pharmacodynamics in nature (Oga *et al*., 2016). By having the same (agonistic) or a blocking (antagonistic) impact on tissues, one drug can change how sensitive or receptive they are to another drug in pharmacodynamic interactions. Although they may occur intracellularly, these effects typically take place at the receptor level. A drug typically modifies the distribution, protein binding, metabolism, or excretion of another medication in pharmacokinetic interactions. Drug availability and persistence at receptor sites change as a result. Pharmacokinetic interactions change the size and duration of the effect but not its nature. They are often predicted based on knowledge of the individual drugs or detected by monitoring drug concentrations or clinical signs *(Petric, 2021).*

i. Drug–drug interactions:

Drug-drug interactions (DDIs) are one of the most prominent reasons for ADRs, and we found that the elderly are more likely to experience these manifestations because of polytherapy. In fact, polytherapy makes therapeutic management more complex, increasing the chance of clinically meaningful medication interactions that could lead to the

development of adverse drug reactions (ADRs) and either decrease or improve clinical efficacy.

The patient is at risk of developing more adverse drug reactions (ADRs) because of the "prescribing cascade," which happens when an ADR is misdiagnosed and new, potentially unneeded medications are given.

DDI can be divided into two categories:

Pharmacokinetics: Consists of absorption, distribution, metabolism, and excretion; each of these processes is connected to either toxicity or treatment failure.

Pharmacodynamic interaction: may be divided into three subgroups: (1) direct effect at receptor function, (2) interference with a biological or physiological control process and (3) additive/opposed pharmacological effect (Palleria *et al.,* 2013).

ii. Drug herb interactions:

The term "drug-herb interactions" describes how herbal supplements may affect the pharmacokinetics or pharmacodynamics of prescription medications. For patients to be safe and to receive quality healthcare, it is essential to comprehend these relationships.

Herbal products have been absorbed more and more into Western medicine, supported by a usage history that precedes the creation of written records and the idea that "natural" guarantees safety. Consumers frequently self-administer these drugs together with traditional medications without telling their doctor(s) or other healthcare professional(s). Such herb-drug combos may have undesirable effects if the herbal product disturbs the function of transporters and/or enzymes that metabolize drugs. Even though these kinds of herb-drug interactions are becoming more widely recognized, there is no established method for predicting and assessing these interactions. As a result, pharmaceutical research on the processes behind herb-drug interactions is still lacking. Due to the heterogeneity in herbal

product composition, uncertainty around the causal elements, and frequently limited understanding of the pharmacokinetics of the causal constituents, evaluating the liability of herbal product interaction is difficult. These restrictions are further complicated. Integration of this information into in silico models that estimate the pharmacokinetics of individual constituents should facilitate prospective identification of herb–drug interactions (Brantley *et al.,* 2014).

1.2.2 Pharmacovigilance of herbal medicine:

Pharmacovigilance is defined as 'the study of the safety of marketed drugs under the practical conditions of clinical usage in large communities' (Mann and Andrews, 2002). The goal is to increase safety monitoring and find drug adverse events that had gone unnoticed while being assessed in clinical trials. These techniques were designed to monitor pharmaceutical drugs, but they are also used to assess the safety of other treatments, such as herbal remedies, blood products, vaccines, and even medical devices.

The reports of suspected toxicity and adverse events have increased along with the usage of herbal medications. Such unintended effects may result from (i) side effects, which are typically detectable by pharmacodynamics and frequently predictable; (ii) reactions brought on by overdose, prolonged use, tolerance, dependence, and addiction (detectable either by pharmacodynamics or pharmacovigilance); (iii) hypersensitivity, allergic, and idiosyncratic reactions; (iv) intermediate and long-term toxic effects, including liver; and (v) any number of other factors.

In addition, there is an ongoing problem with unexpected toxicity of herbal products due to quality issues, including use of poor quality herbal material, incorrect or misidentified herbs, incorrect processing methods, supply of adulterated or contaminated herbs or products (Shaw, 2010). By establishing GMP standards for production, better regulation can partially alleviate

these quality difficulties. However, medical herbs and products come from a variety of nations with varying production standards and regulatory enforcement, so low-quality goods are likely to continue to be an issue.

The safety of herbal medicines has become an issue for the regulatory authorities, as serious effects have been reported, including hepatotoxicity, renal failure and allergic reactions (Perharic *et al*., 1995, Nortier and Vanherweghem, 2007). The World Health Organisation, recognising the growing importance of the use of herbal medicines worldwide developed guidelines for the monitoring of herbal safety within the existing pharmacovigilance framework (WHO, 2004).

1.3 BACTERIAL INFECTIONS

1.3.1 SEXUALLY TRANSMITTED INFECTIONS

Infections caused by a variety of microorganisms, including viruses, bacteria, fungus, and protozoa, are among the most contagious infections. The prevalence of bacterial sexually transmitted illnesses has been steadily rising in recent years around the globe. The most prevalent bacterial sexually transmitted infection in the world is chlamydia. Multi-drug resistant gonorrhea strains have spread rapidly around the world. The greatest barriers to the prevention and treatment of sexually transmitted diseases are caused by *Neisseria gonorrhoeae,* which has a high level of antibiotic resistance. This makes it possible for untreatable infections to develop and pose a severe threat to public health in the future. The first-line treatment for syphilis is still penicillin because there is no known penicillin resistance.

One of the most contagious illnesses, sexually transmitted diseases (STDs), also referred to as "venereal diseases," are brought on by a variety of microorganisms. Bacteria, viruses, fungi, and protozoa are indeed the pathogens of STDs (Tenaw, 2022). These bacteria can pass from

one person to another by bodily fluids like blood, sperm, vaginal discharge, and others. Due to this, sexually transmitted infections (STIs) are spread from one person to the next through close physical contact, mostly but not exclusively during sexual activity. Ejaculation does not have to occur for STIs to be transmitted from person to person (Amu and Adegun, 2015).

1.3.2 TYPES OF SEXUALLY TRANSMITTED DISEASES

1.3.2.1 Chlamydia

Chlamydia is caused by Chlamydia trachomatis infection. This widespread infection can spread by anal, vaginal, and oral intercourse. Additionally, during labor, a newborn may contract it (Kriesel *et al*., 2016).

Chlamydia typically has no symptoms, but if it is left untreated, it can lead to infertility and other problems (Mishori *et al.,* 2012). With early therapy, it is simple to cure. If symptoms do show up, they could be something as simple as a change in vaginal discharge or burning discomfort when urinating. If chlamydia develops as a result of anal sex or spreads from another part of the body, it can also infect the rectum. According to (Dela *et al*., 2019), this may result in rectal pain, rectal bleeding, or rectal discharge.

1.3.2.2 Syphilis

The bacterium *Treponema pallidum* is the cause of syphilis. Early treatment is essential to avoid long-term problems and irreversible damage because it is a potentially dangerous illness (Franjic, 2019).

Typically, there are four stages. A person may experience a circular, firm sore at the infection site in the early stages, which is typically around the genitalia, anus, rectum, or mouth. This often lasts three to six weeks. Since the sore is frequently painless and can be concealed, for example in the vagina, it might not be noticeable. At any moment throughout the infection, the pathogen can spread. An unborn child can contract syphilis during pregnancy.

At the second stage, symptoms like a non-itchy rash of rough, brownish or red spots on the palms of the hands or soles of the feet, lesions in the mucous membranes like the mouth, vagina, or anus, swollen lymph nodes, hair loss, headaches, weight loss, muscular aches, exhaustion, and fever may also appear.

While the symptoms vanish during the latent stage, the germs are still present in the body and can still harm the body.

Life-threatening problems can affect the brain, neurological system, eyes, heart, and a number of other organs in the tertiary stage. Which body area the syphilis affects will determine the symptoms at this stage. On average, symptoms start to show up about 21 days after the bacteria was transmitted, but they can take anywhere from 10 to 90 days to do so (Mattei *et al.,*2012).

1.3.2.3 GONORRHEA

One of the earliest human illnesses is gonorrhea, which has been mentioned in the Bible since the Old Testament (Morgan and Decker, 2016). The term "gonorrhoeae" was originally used by the Greek physician Galen (130–200 AD) to refer to a "unwanted excretion of semen"(Barlow *et al.*,1978). The slang term "the clap" dates back to 1378 and comes from Les Clapiers, a prostitution-heavy neighborhood in Paris.1 the responsible agent Gram-negative diplococcus *Neisseria gonorrhoeae* has a clear preference for the mucosal surfaces of people (Unemo *et al.,* 2014). It still frequently causes cervicitis in women and men, which can result in widespread infection as well as pelvic inflammatory disease (Morgan *et al.*, 2016).

The spread of gonorrhea can occur during anal, vaginal, or oral intercourse. Gonorrhea can also cause pink eye if a person contacts a part of their body that is infected and then touches their eye (Ikokwu *et al*., 2023). Additionally, when giving delivery, a baby could contract this

illness. In warm, wet bodily regions like the vagina, penis, mouth, rectum, and eye, *N. gonorrhoeae* thrive. Sexual interaction can help spread this virus (Sheet, 2017).

Although symptoms are rare, they may include: pain when urinating, discharge, vaginal swelling, and bleeding between periods. (Dombrowski *et al.,* 2021). If the rectum is affected, symptoms include anal itching, pain during bowel movements, discharge, and an infection brought on by oral sex that can cause throat pain and enlarged lymph nodes (Budkaew *et al.,* 2019).

Infected women may develop pelvic inflammatory disease (Curry *et al.,* 2019). In contrast, the tube where sperm are stored in males, the epididymis, may become inflamed. Fertility may be impacted by either illness (Barak *et al*., 2016).

Once a person has gonorrhea, the germs can spread through physical contact to other persons and to other regions of the body. Antibiotic therapy typically helps to clear the infection (Gibson *et al.,* 2014).

1.3.3 DRUGS USED IN THE MANAGEMENT OF INFECTIONS

1.3.3.1 FLUOROQUINOLONES

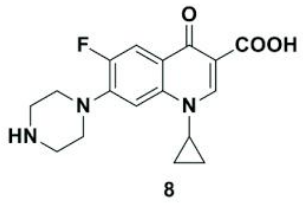
Ciprofloxacin

In the age of antibiotic resistance and human immunodeficiency virus infection, the management of sexually transmitted diseases (STDs) has advanced to a new level. *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Treponema pallidum* are three widely found STD pathogens that have not yet been completely eradicated by a single antibiotic. Among the fluoroquinolones that are currently on the market, ciprofloxacin, ofloxacin, lomefloxacin, and enoxacin all exhibit excellent in vitro activity (MIC90 0.06 micrograms/ml) and excellent in

vivo efficacy against *N. gonorrhoeae*, including isolates that are multi-resistant (penicillinase-producing N. gonorrhoeae (MacDougall, 2022).

1.3.3.1.1 Mechanism of action

The bacterial DNA gyrase and topoisomerase IV are the targets of quinolone antibiotics (Mohammed *et al.,* 2019). Topoisomerase IV, which dissociates linked daughter DNA molecules produced by DNA replication, is the main target for many gram-positive bacteria. In contrast, DNA gyrase is frequently a gram-negative microbe's main target for quinolones. To counteract too positive supercoiling that might happen during DNA replication, the gyrase adds negative supercoils to the DNA (Cozzarelli, 1980). At concentrations that coincide well with those needed to prevent gyrase-mediated DNA supercoiling, the quinolones, as a drug metal complex. (MacDougall, 2022)



8

Figure 1 Ciprofloxacin structure

1.3.3.1.2 Antimicrobial activity

When first introduced, fluoroquinolones were effective bactericidal agents against the majority of gram-negative bacteria, including Proteus, E. coli, Klebsiella, as well as different species of Salmonella, Shigella, Enterobacter, and Campylobacter. Due to the frequency of E. coli and Proteus spp. in some areas, fluoroquinolones may not be dependable for empiric therapy, similar to how resistance to TMP-SMX has steadily reduced the coverage that these drugs provide (Olson *et al.*, 2009). Although these medications were formerly the go-to treatment for *Neisseria gonorrhoeae* infections, resistance has grown to the point where most nations no longer advise using them for gonorrhea empiric therapy (Centers for Disease

Control and Prevention, 2021). Levofloxacin and ciprofloxacin have enough anti-Pseudomonas spp. action to be used in systemic infections (MacDougall, 2022).

1.3.3.1.3 Pharmacokinetics

The majority of quinolones are effectively absorbed when taken orally. Within 1 to 3 hours after an oral dose, the fluoroquinolones reach their peak serum levels. Quinolones are widely distributed, with concentrations in urine, kidney, lung, and prostate tissue as well as stools, bile, macrophages, and neutrophils that are higher than those seen in serum. The time to peak serum concentrations may be delayed by food. The presence of several fluoroquinolones in human breast milk raises the possibility of nursing infants receiving significant exposure due to their good absorption. With the exception of moxifloxacin, quinolones are primarily excreted via the kidney; hence, doses must be modified for renal failure (MacDougall, 2022)

1.3.3.2 PENICILLINS

1.3.3.2.1 Description

Antibiotics classified as penicillins are a subset of the larger class of medications known as beta-lactam antibiotics. Penicillins function by attaching to peptidoglycan molecules found on bacterial cell walls. Penicillin hinders the proteins in the cell wall from properly reassembling when the bacteria divide, leading to cell rupture and rapid death of the germs (Lima *et al*.,2020).

The only penicillins that come from *P. chrysogenum* fungus are natural penicillins Two types of natural penicillin exist; Penicillin G natural (benzylpenicillin) and Phenoxymethylpenicillin or (Penicillin V). In the laboratory, semi-synthetic penicillins are created to imitate the chemical components of *P. chrysogenum* (Fierro *et al.,* 2022). The semi-synthetic penicillins comprise:

- Semisynthetic penicillins are divided into four classes, which include antibiotics like ampicillin and amoxicillin that are frequently administered. These includes:
- Aminopenicillins, which include hetacillin, ampicillin, and amoxicillin
- Antistaphylococcal penicillins including:Cloxacillin, dicloxacillin, nafcillin, and oxacillin
- Broad-spectrum penicillins (ticarcillin, carbenicillin, mezlocillin, and piperacillin)
- Inhibitor of beta-lactamases (clavulanic acid)

1.3.3.2.2 Mechanism of Action

The interpeptide linking of peptidoglycan, a powerful structural component found solely in bacterial cell walls, is what penicillins and other beta-lactam antibiotics inhibit. A bacterium's cell walls are physically brittle, prone to collapse, and likely to dissolve without intact peptidoglycan cross-links when it tries to divide. Penicillins do not harm human eukaryotic cells because they lack cell walls.This is the concept of selective toxicity of penicillins (Prescott, 2013).

1.3.3.2.3 Antimicrobial Activity

The ability of aqueous penicillin G to treat staphylococcal and streptococcal infections was a significant pharmacologic achievement. The creation of penicillinase-resistant penicillins, such as methicillin, oxacillin, and nafcillin, in which an acyl side chain prevented rupture of the -lactamase ring, was motivated by the introduction of Staphylococcus aureus that produces penicillinase. The subsequent need for gram-negative antibacterial action led to the development of the aminopenicillins (such as ampicillin and amoxicillin). Their spectrum included Proteus mirabilis, Shigella, Salmonella, Listeria, Haemophilus, and Neisseria. The carboxypenicillins (carbenicillin, ticarcillin, and temocillin) and ureidopenicillins (mezlocillin, azlocillin, piperacillin, and apalcillin) were created as a result of the search for a penicillin with additional antimicrobial activity against Enterobacteriaceae and Pseudomonas

aeruginosa. Last but not least, adding a -lactamase inhibitor (such as clavulanic acid or sulbactam) to an aminopenicillin or ticarcillin has broadened their antibacterial spectral range (Copete-Pertuz *et al.,* 2018)

1.3.3.2.4 Pharmacokinetics

In plasma, penicillin has minimal protein binding. Penicillins vary in their bioavailability, with penicillin G having a low bioavailability (below 30%) and penicillin V having a higher bioavailability (between 60 and 70%) (Levison, 2000)

Penicillin is eliminated by the kidneys and has a brief half-life. This means that to maintain optimal levels of penicillin in the blood, it must be dosed at least four times each day. Therefore, early guidelines on how to administer penicillin advised injections as frequently as every three hours. Dosing penicillin has been compared to trying to fill a bath with the plug out. Since much bigger doses of penicillin are now inexpensive and readily available, this is no longer necessary, however continuous use of infusions is recommended for this reason (Walton *et al.,* 2007).

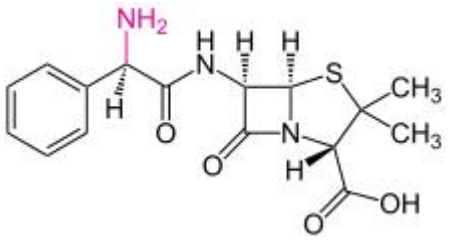


Figure 2 Amoxicillin structure

1.4 BETA CLEANSER BITTERS

BETA CLEANSER BITTER is a life transforming herbal formula that transform lives to vibrant ones.

It is a powerful blend of some premium quality herbs well formulated to reduce free radical damage and harmful toxins in the body, thereby supporting the immune system and help the body to resist diseases.

COMPOSITION

Aloe Vera

Moringa Oleifera

Excipients

INDICATIONS

-For Waist and Joint Pains

-For Fibroid

-For sexually transmitted infections e.g. Staphylococcus. Gonorrhea, Syphilis, Candidiasis, especially previously poorly treated ones

-Helps in abating constipation.

-The Moringa helps in treatment and prevention of diabetes

-Helps in thyroid disorders

-Boosts fertile sperm production in men

-Tighten mental clanty and improves retentive memory.

-For malaria and Typhoid

-For irregular menstrual Period and Painful Menstrual Cramps

1.5 QUALITY CONTROL TEST FOR CAPSULES

Quality control is primarily concerned with ensuring quality from raw materials and finished products, quality assurance of processes, analytical equipment and good laboratory practices. Quality control is the collective name for all actions done to guarantee the identification and purity of a certain pharmaceutical product. These methods might be as simple as carrying out a single chemical experiment to identify and check for the presence of a specific medicinal component or as a complex as the requirements of pharmacopoeia monographs. Quality control is necessary for both conventional and herbal medicinal products, since the end users

remain the same. The quality control test for capsules include weight uniformity, friability test, Disintegration test, Dissolution test.

1.5.1 Weight uniformity

Testing for weight consistency involves weighing and computing the individual weights of 20 capsules selected at random from a batch of capsules. This test is used to estimate the content of active ingredients per capsule. It is based on the assumption that the active ingredient is homogeneously dispersed through the contents of a batch of capsules. In the test, a specific number of capsules are weighed then their contents are emptied and the shells are reweighed and then the weight of the fill is calculated.

1.5.2 Friability test

Capsules are often subjected to tumbling motion during coating operation. They are also vulnerable to abrasion and friction during packaging process, handling and transportation. Capsules friability test is devised to examine to resistance of these tablet to abrasion

1.5.3 Disintegration test

This is the time it takes for a capsule to disintegrate when immersed in some test fluid. Capsule disintegration testing is routinely carried out to provide information for both quality control process and drug development. It is a test used to indicate whether a capsule will release its content in vivo.

1.5.4 Dissolution test

Dissolution test measures the rate at which the active drug passes into solution. The USP was the first to introduce such a test.

1.6 PRINCIPLES AND THEORY OF ABSORPTION

Numerous substances are capable of absorbing visible or ultraviolet light. The absorbance of a solution increases as the attenuation of the beam increases. The route length and the concentration of the absorbing specie are directly inversely proportional to absorbance. Absorbance is based on Beer Lambert's law. Beer Lambert's Law may simply be written as:

A = Ebc

A- absorbance

E - molar absorptivity

b - path length of the sample

c - concentration of the compound in solution

Molecules absorb light at different wavelengths. The chromophores that are present in the molecule are represented by a number of bands in the absorption spectra.

1.6.1 UV Visible spectrometry

This spectrometric method follows Beer Lambert's law's guiding principles. Both qualitative and quantitative goals can be served by it. Molecular absorption spectroscopy is based on the measurement of the transmittance or absorbance of fluids contained in transparent cells. The concentration of the analyte can be determined by measuring the absorbance at a single wavelength. In order to identify the wavelength of maximum absorption, a wavelength scan is first carried out with the reference solution. The wavelengths of known standard solutions at various concentrations are determined, and they are then utilized to create a calibration curve that will later be used to extrapolate the concentration of the unknown.

1.7 AIM AND OBJECTIVE OF THE STUDY

The aim of the study is to investigate any interactions between Beta Cleanser Bitters with ciprofloxacin and amoxicillin.

The objectives of the study are;

- To investigate the effect of Beta Cleanser Bitters on the disintegration time of ciprofloxacin and amoxicillin.
- To determine the effect of Beta Cleanser Bitters on the drug release of ciprofloxacin and amoxicillin.
- To determine the type of interaction that exist between Ciprofloxacin, amoxicillin and Beta Cleanser Bitters.
- To investigate the interaction between Beta Cleanser Bitters and ciprofloxacin and amoxicillin using FTIR and UV Spectrometry.

CHAPTER TWO

MATERIALS AND METHOD

2.1 MATERIALS

Amoxicillin and ciprofloxacin pure powder samples were gift samples from the Nigeria Army production company, Bonny camp, Lagos, Nigeria. Ciprotab® 500 mg, manufactured by V.S. International Pvt. Ltd and Amoxil™ 500 mg manufactured by Medreich Limited, Virgonagar, Bangalore, India, were both purchased from Ep pharmacy, Federal Government Girls College Road, Benin City. Beta Cleanser Bitters produced by S.Joesylv concerns Limited and purchased from an online marketer in Lagos. 0.1N HCl were obtained from Pyrex Lg Scientific supply company, Benin City.

Table 1 shows the labelled information on amoxicillin

Name of Product	Amoxil™
Batch no	A10900
Manufacture date	09/2021
Expiry date	08/2026
NAFDAC reg no	04- 2481

Table 2 shows the labelled information on Ciprotab®

Name of product	Ciprotab® 500
Batch no:	C012023
Manufacture date :	03/2022
Expiry date :	02/2025
NAFDAC Reg no :	04-0723

Table 3 shows the information on Beta Cleanser Bitters

Name of Product	Beta Cleanser
Batch no	BCC001
NAFDAC Reg no	A7-0738L
Manufacture date	July 2022
Expiry date	June, 2025

2.2 METHOD

2.2.1 Preliminary Investigation

This involves the initial phase of examining the commercial brands of the drugs to be used in the investigations to deduce their physical properties and determine if the drugs meet standard.

2.2.2 Weight uniformity

Twenty (20) capsules of ciprofloxacin were randomly selected and weighed individually to obtain a mean weight. The percentage variation of each capsule from the mean was then calculated. The same procedure was repeated for amoxicillin capsules.

2.2.3 Friability

Five randomly selected capsules were dusted and weighed together and placed in the Roche friabilator (Lianing, China), and operated for 4 minutes and 25 rpm. The capsules were de-dusted and weighed again. The percentage weight loss was calculated.

2.2.4 Disintegration time test

Six ciprofloxacin capsules were placed in the Manesty disintegration chamber (Liverpool, England) in a disintegration medium (distilled water) at 37±1°C. The disintegrating machine was switched on and with the aid of a stopwatch; the time it took each capsule to pass through the mesh was observed and recorded.

2.2.5 Dissolution test

The dissolution test was done in the dissolution apparatus (Calivar, United States) using the modified paddle method with medium containing 900mls of 0.1N sodium hydroxide to a pH of 6.8 ± 0.1; with sink conditions maintained at a temperature of 37°C ± 1°C. One capsule was placed in a vessel and at various time intervals of 5, 10, 15, 30, 45 minutes, 1 hour, 5mls

of the solution was withdrawn and replaced with 5mls of the fresh dissolution medium. The absorbance values of the filtered portion of the samples were read at 298nm and 362nm for amoxicillin and ciprofloxacin respectively using the UV-visible spectrophotometer against the blank solution of the medium. The concentration of the drug present in the solution at each given time was determined from the calibration plot previously obtained with pure samples of ciprofloxacin and amoxicillin.

The dissolution test was also carried out with the components of Beta herbal cleansers; *Aloe vera, Moringa oleifera*. The resulting solution was used to carry out the dissolution time test for the drugs. The absorbance values of the filtered portion of the samples were read at 362nm and 298nm using UV-visible spectrophotometer against the blank solution of the medium for ciprofloxacin and amoxicillin respectively.

2.2.6 Absorbance interference study

Ciprofloxacin and amoxicillin

Different concentrations of ciprofloxacin in micrograms/ml were prepared in 0.1N HCl and amoxicillin in micrograms/ml by dissolving 0.625g of the pure samples in 6.25ml of 0.1N HCl as stock solution. The resultant concentrations were read in the UV-visible spectrophotometer T-70 (United Kingdom) at 362nm and 298nm for ciprofloxacin and amoxicillin respectively. Duplicate readings were obtained and mean values were plotted to obtain a straight line graph.

Ciprofloxacin plus Beta bitter cleanser

Different concentrations of ciprofloxacin were prepared by dissolving 1g Beta bitter cleanser in 100ml of 0.1NHCl containing 100mg ciprofloxacin and the resultant concentration were

read in the UV visible spectrophotometer at 362 nm. Duplicate readings were obtained and mean values were plotted to obtain a straight line graph.

The same procedure was repeated using ciprofloxacin and 1g of the various individual components of Beta bitters (*Aloe Vera, Moringa Oleifera*)

Amoxicillin plus Beta bitter cleanser

Different concentrations of amoxicillin were prepared by dissolving 1g Beta bitter cleanser in 100ml of 0.1NHCl containing 100mg amoxicillin and the resultant concentration were read in the UV visible spectrophotometer at 298nm. Duplicate readings were obtained and mean values were plotted to obtain a straight line graph.

The same procedure was repeated using amoxicillin and 1g of the various individual components of Beta bitters (*Aloe Vera, Moringa Oleifera)*

2.2.7 FTIR Analysis

Dried Beta Bitters powder, pure ciprofloxacin powder and their admixture were subjected to FTIR analysis using the potassium bromide tablet method (FTIR-4100 Spectrophotometer, Shimadzu Co. Japan). To create a 200 mg weight powder, five milligram powder samples were combined with dried potassium bromide. A tablet made from the powder was compressed using a Sigma potassium bromide press before being put in the spectrophotometer's sample container and scanned at a range of 4000 - 750 cm-1. The same procedure was repeated with amoxicillin pure samples.

CHAPTER THREE

RESULTS AND DISCUSSION

3.1 PRELIMINARY EVALUATION

Table 4, Table 5 and Table 6 below shows the result of preliminary studies of some physiochemical properties of ciprofloxacin (Ciprotab®), amoxicillin (Amoxil™) capsules and Beta Cleanser Bitters respectively. The capsules were elegant in their organoleptic properties and showed a mean weight variation, percentage friability values that meets the BP specifications with regards to these parameters (BP, 2003).

Tablet Properties	Result
Colour	White
Texture	Smooth
Taste	Slightly bitter
Writing on surface of capsule	CIPROTAB
Total Weight of 20 capsules (g)	16.204
Mean Weight of 20 capsules (g) ±SD	0.810 ± 0.01
Friability test (%)	0.041

Table 4 Physiochemical Properties of ciprofloxacin (Ciprotab®) capsules

Tablet Properties	Results
Colour	White
Texture	Smooth
Taste	Slightly bitter
Writing on the surface of capsule	AMOXIL 500
Total Weight of 20 capsules (g)	13.758
Mean Weight of 20 capsules (g) ± SD	0.688 ± 0.01
Friability test (%)	0.034

Table 5 Physiochemical Properties of amoxicillin (Amoxil™) capsules

Tablet Properties	Results
Colour	Green
Texture	Smooth
Taste	Slightly bitter
Odour	Pungent
Total Weight of 20 capsules (g)	7.76
Mean Weight of 20 capsules (g) ± SD	0.388 ± 0.01
Friability test (%)	0.034

Table 6 Physiochemical Properties of Beta Cleanser Bitters

3.2 COMPARATIVE STUDIES

3.2.1 Disintegration time test

In the absence of Beta Cleanser Bitters, ciprofloxacin exhibited a disintegration time of approximately 9.53 minutes, with a standard deviation of ± 2.9 minutes. This serves as a baseline for comparison. In the presence of Beta Cleanser Bitters (9.52 ± 2.15 mins), there was a negligible change in disintegration time. Introducing *Aloe vera* led to a slightly prolonged disintegration time of 10.74 minutes, indicating a modest delay in disintegration compared to the baseline. Similarly, the inclusion of *Moringa oleifera* resulted in a disintegration time of 10.43 minutes, with a standard deviation of ± 1.31 minutes. This suggests a minimal effect on disintegration compared to the baseline.

The observation that amoxicillin alone and in the presence of Beta Cleanser Bitters exhibited similar disintegration times, while the presence of individual components *(Aloe vera and Moringa oleifera*) led to reduced disintegration times, suggests a nuanced interaction between amoxicillin and the herbal components.

This phenomenon may be attributed to the specific properties of *Aloe vera* and *Moringa oleifera*, which could potentially enhance the disintegration process. *Aloe vera*, known for its mucilaginous properties, may act as a lubricant or swelling agent, facilitating the rapid disintegration of the tablet. Similarly, *Moringa oleifera*, rich in bioactive compounds, might have a similar effect, potentially aiding in the breakdown of the tablet structure (Upadhyay, 2017). The absence of a significant alteration in disintegration time in the presence of Beta Cleanser Bitters as a whole might indicate a complex interplay of different components within the herbal mixture. It's possible that while *Aloe vera* and *Moringa oleifera* exerted an influence, other constituents (excipients) in Beta Cleanser Bitters may have counteracted or balanced out their effects.

These findings emphasize the importance of understanding the specific interactions between pharmaceutical components and herbal additives, as they can greatly influence the performance of the final product.

Notably, the presence of Beta Cleanser Bitters showed no contrasting effects on the disintegration times of the two drugs, but presence of *Aloe vera* and *Moringa oleifera* reduced the disintegration time of amoxicillin, indicating a potential drug-specific interaction. These observations suggest the need for further investigation into the underlying mechanisms driving these interactions.

Table 7 below shows the result of the disintegration time of ciprofloxacin and amoxicillin in the presence and absence of Beta Cleanser Bitters.

Table 7 disintegration test

Drugs	Absence of Beta Cleanser Bitters(mins)	Presence of Beta Cleanser Bitters(mins)	Presence of *Aloe vera* (mins)	Presence of *Moringa oleifera* (mins)
Ciprofloxacin	9.53 ± 2.9	9.52 ± 2.15	10.74 ± 1.18	10.43 ± 1.31
Amoxicillin	4.34 ± 0.64	4.02 ± 1.50	3.54 ± 0.20	3.27 ± 0.23

Values are ± standard deviations

3.2.2 DISSOLUTION STUDIES

Drug dissolution takes place over a period of time and shows drug release. This process is necessary before a medication may be absorbed or have a pharmacological effect. The rate and degree of drug absorption for immediate release dosage forms is determined by the rate of drug release and dissolution in relation to the velocity of transit through the intestine and by the small intestine's permeability profile (Sinko, 2006).

From Figure 3, It is observed that at all time points, the presence of Beta Cleanser Bitters, *Aloe vera*, and *Moringa oleifera* did not significantly alter the dissolution profile of ciprofloxacin when compared to the control (ciprofloxacin alone). The dissolution remained relatively stable over the evaluated time intervals. This suggests that, in this experimental context, these herbs may not significantly influence ciprofloxacin's drug release characteristics.

From Figure 4, It is observed that at all time points in the presence of Beta Cleanser Bitters, the drug release of amoxicillin decreases compared to amoxicillin alone. However, the presence of *Aloe vera* and *Moringa oleifera* alone did not significantly affect the drug release properties of amoxicillin. This may be likely because there is an interaction between *Aloe vera*, *Moringa oleifera* and excipients present in the Beta Cleanser Bitters causing the decrease in amoxicillin’s drug release.

It is important to acknowledge that this study was conducted under specific experimental conditions. Variations in factors such as pH, temperature, and formulation composition may yield different results.

The dissolution study for the interaction between ciprofloxacin and amoxicillin with Beta herbal cleanser is as shown below;

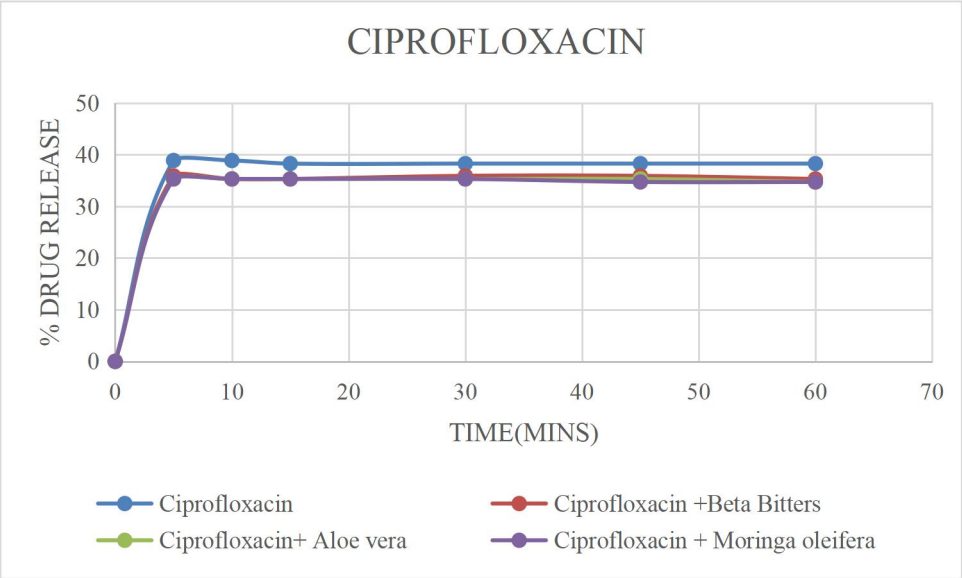


Figure 3 shows the dissolution plots for ciprofloxacin alone and in the presence of Beta herbal bitters and its individual components

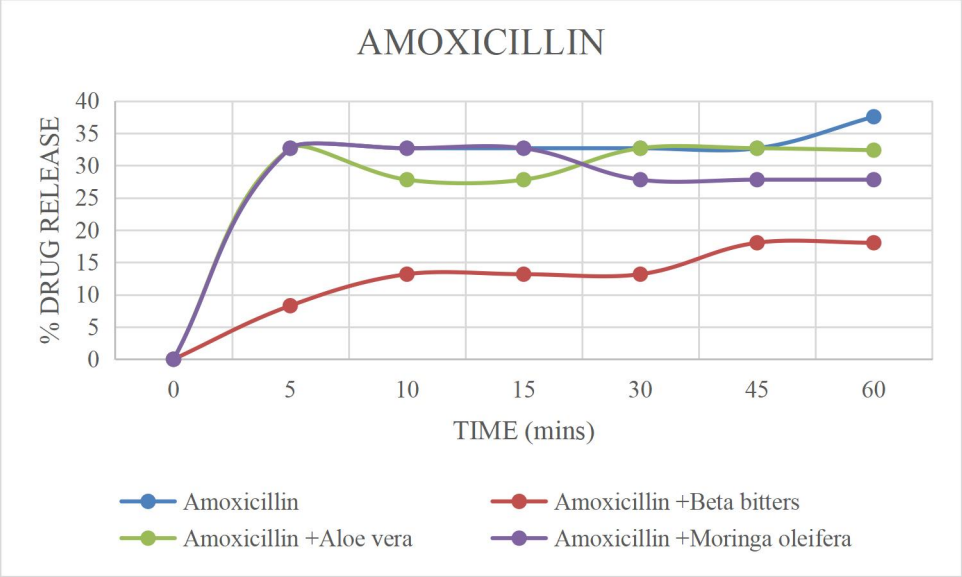


Figure 4 shows the dissolution plots for amoxicillin alone and in the presence of Beta herbal bitters and its individual components

3.3 ABSORBANCE INFERENCES STUDIES

A comparison of the absorbance of the various dilutions of the stock solutions of ciprofloxacin and the mixtures of ciprofloxacin with either Beta Cleanser Bitters, *Aloe vera* or *Moringa oleifera* is shown in Figure 5 below.

The absorbance inference test was also conducted to assess the relationship between concentration and absorbance for amoxicillin in the presence of Beta Cleanser Bitters, including the individual components *Aloe vera*, and *Moringa oleifera*. The results are summarized in the Figure 6 below.

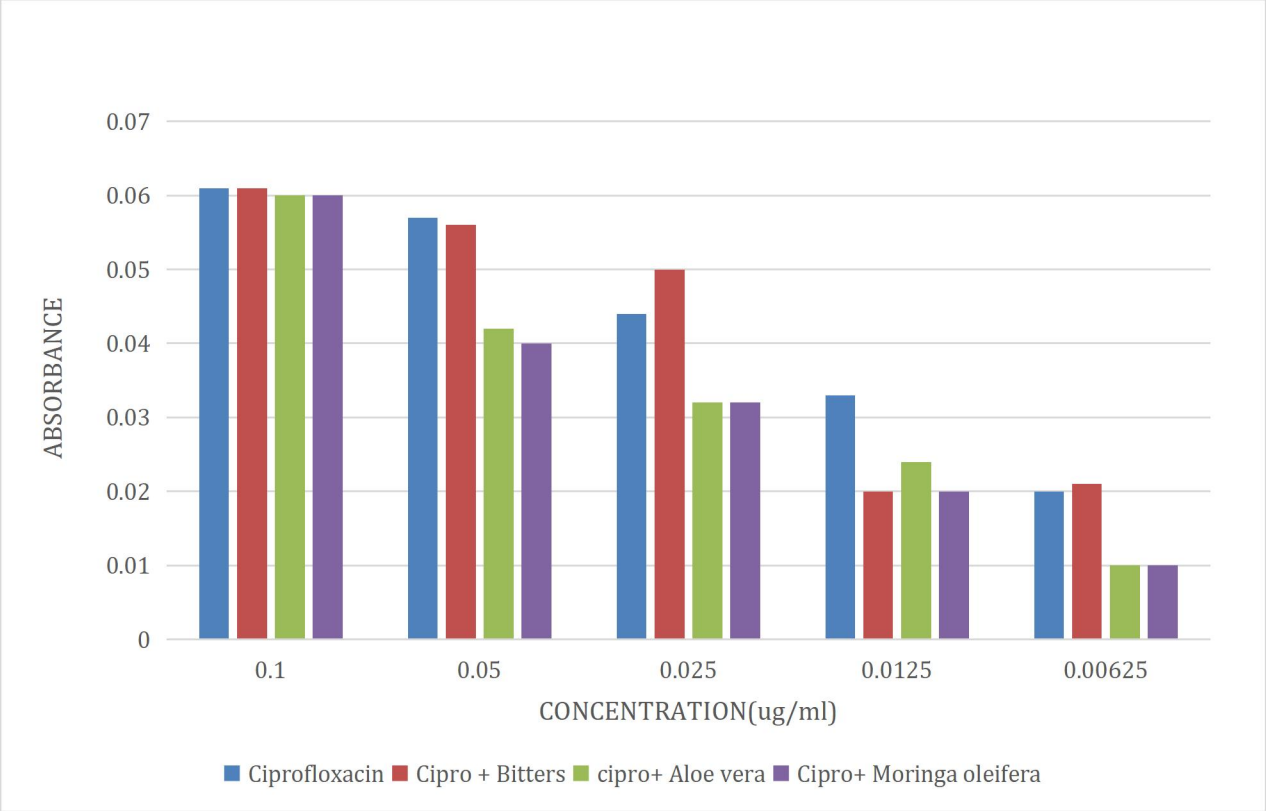


Figure 5 A comparison of the absorbances of solutions of ciprofloxacin and mixture of Beta Cleanser Bitters, Aloe vera or Moringa oleifera

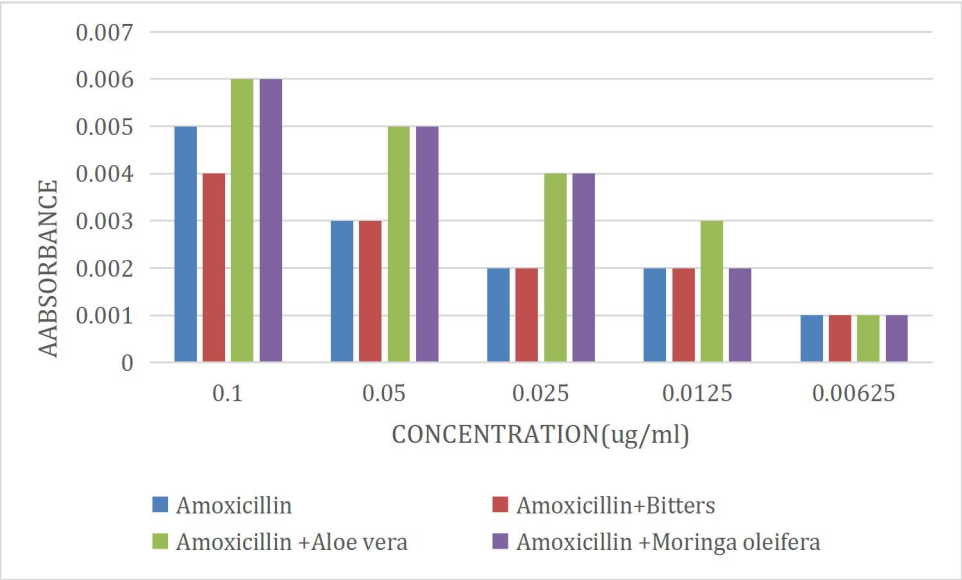


Figure 6 A comparison of the absorbances of solutions of amoxicillin and a mixture of Beta Cleanser Bitters, Aloe vera or Moringa oleifera

The results indicate a clear concentration-dependent relationship for ciprofloxacin and amoxicillin, in line with the Beer-Lambert's law, which states that absorbance is directly proportional to concentration. As expected, as the concentration of ciprofloxacin and amoxicillin decreases, so does the absorbance.

When assessing the impact of the additives on ciprofloxacin from Figure 5, it is observed that the presence of Beta Cleanser Bitters, *Aloe vera*, and *Moringa oleifera* did not induce substantial deviations in the absorbance profiles of ciprofloxacin across the tested concentrations. This suggests that, under the conditions of this experiment, Beta Cleanser Bitters do not significantly influence the absorption characteristics of Ciprofloxacin.

When considering the impact of the additives on amoxicillin from Figure 6, it is notable that the presence of Beta Cleanser Bitters did not lead to substantial alterations in the absorbance profiles of amoxicillin across the tested concentrations. But with the individual components of the herbal drugs, *Aloe vera*, and *Moringa oleifera,* there was an increase in the absorbance profiles of amoxicillin. This suggests that, under the conditions of this experiment, the bitters do not significantly influence the absorption characteristics of amoxicillin but the individual components does.

However, it is important to note that further investigations may be warranted to explore potential interactions under different experimental conditions or with a broader range of concentrations.

3.4 FTIR STUDIES

The spectrum obtained from ciprofloxacin (Figure 7) exhibits numerous troughs. A comparison of the spectra of ciprofloxacin and the admixture of ciprofloxacin and Beta

Cleanser Bitters (Figure 8) shows a significant increase in the number of peaks of the ciprofloxacin spectrum, an indication of a possible interaction.

The spectrum obtained from amoxicillin (Figure 9) exhibits numerous peaks. A comparison of the spectra of amoxicillin and the admixture of amoxicillin and Beta Cleanser Bitters (Figure 10) shows no significant difference (little differences) in the number of peaks of the amoxicillin spectrum, while a similarity in FTIR spectra between a drug and an herbal component suggests that their chemical structures are similar or unchanged after interaction, it doesn't conclusively prove the absence of interaction.

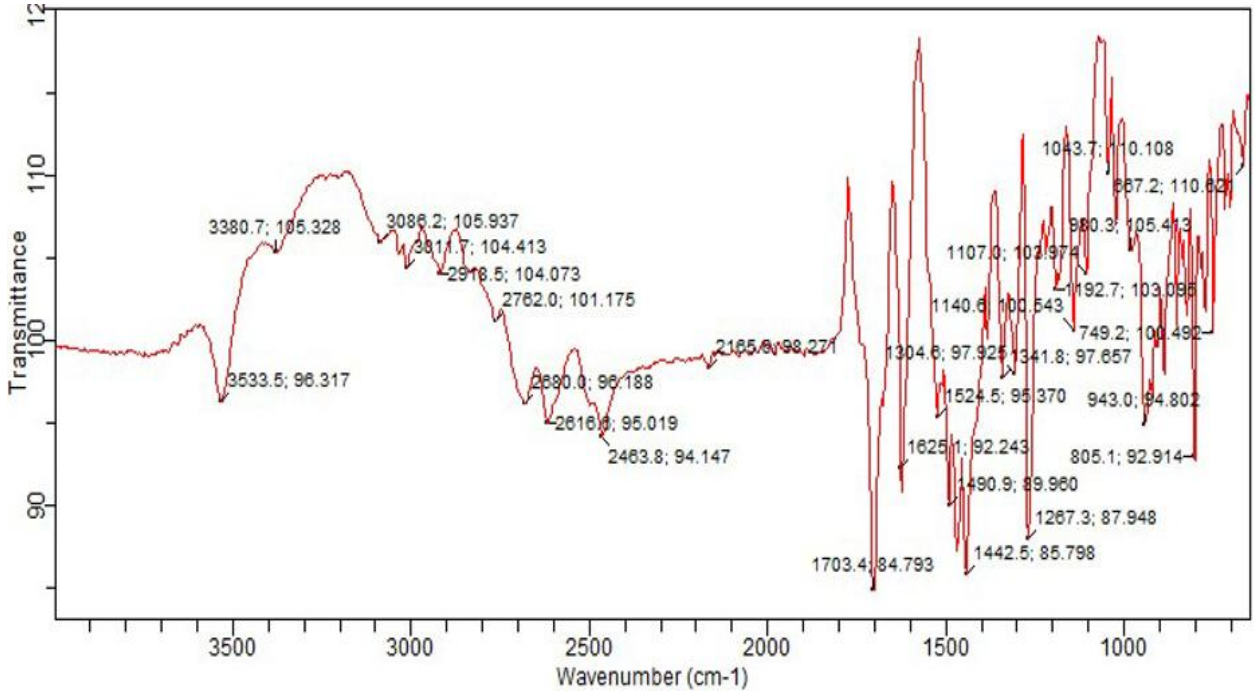


Figure 7 FTIR Spectroscopy of dried powder sample of Ciprofloxacin

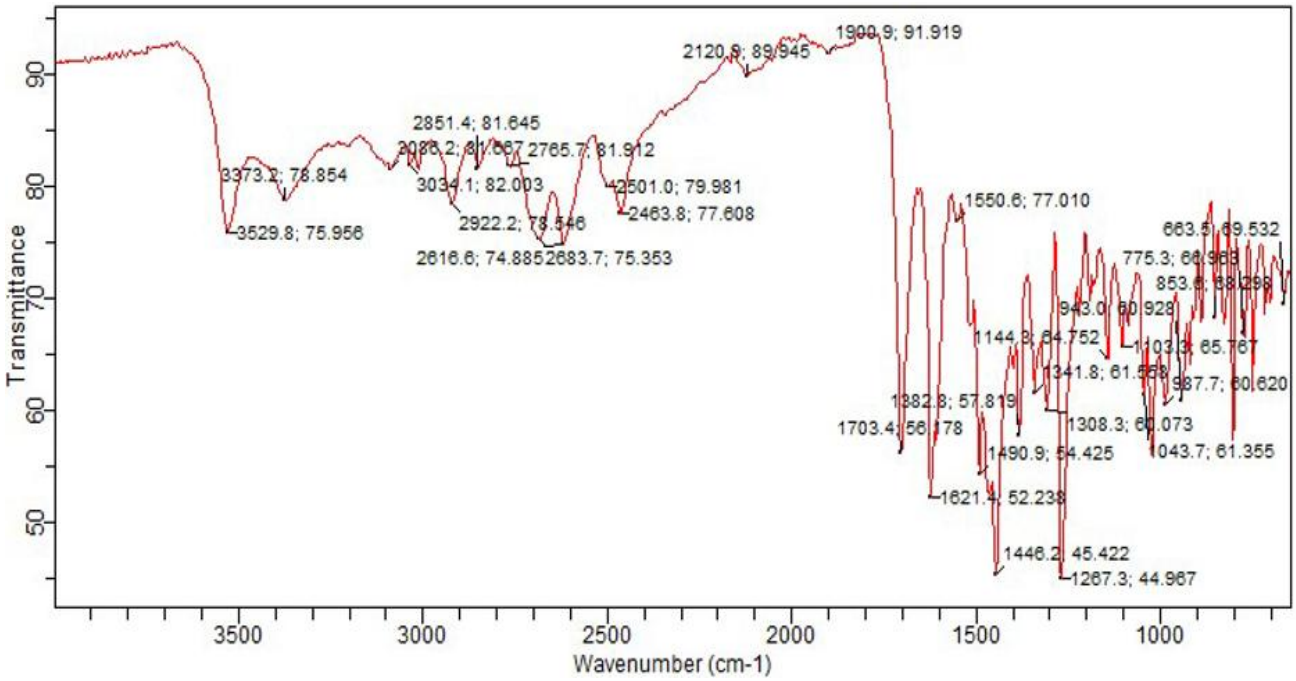


Figure 8 FTIR Spectroscopy of dried powder sample of ciprofloxacin and Beta herbal cleanser

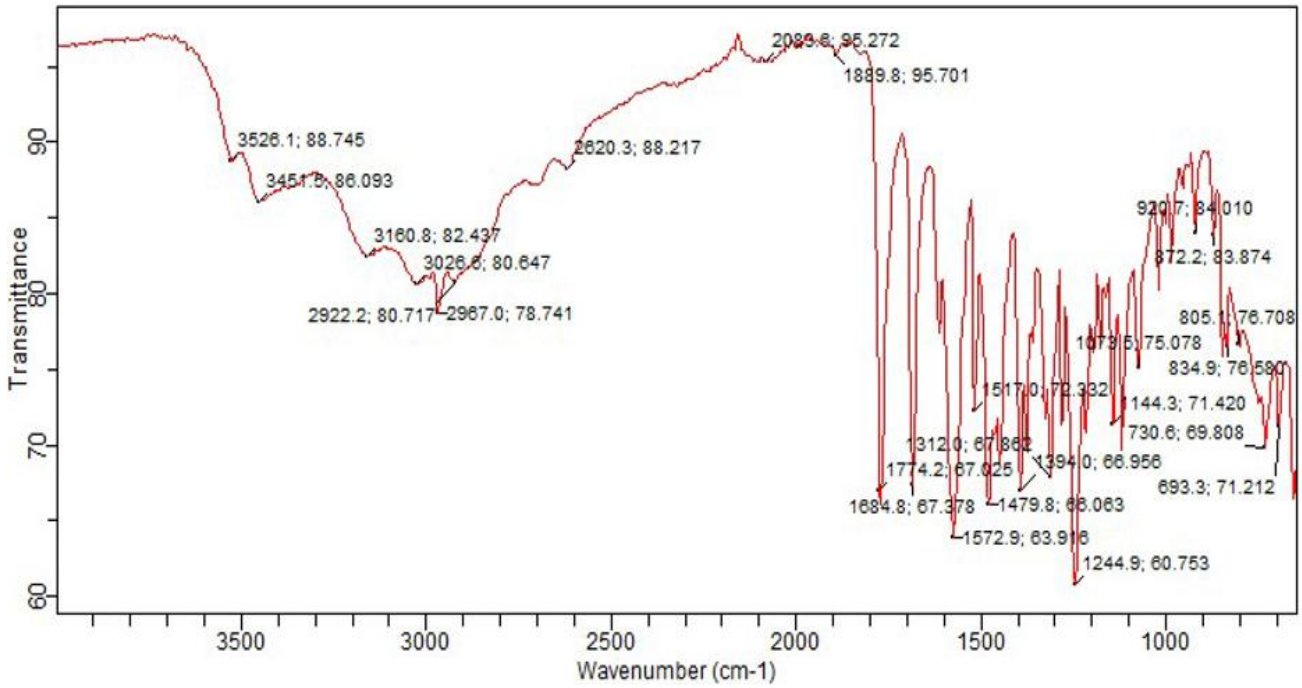


Figure 9 FTIR Spectroscopy of dried powder sample of amoxicillin

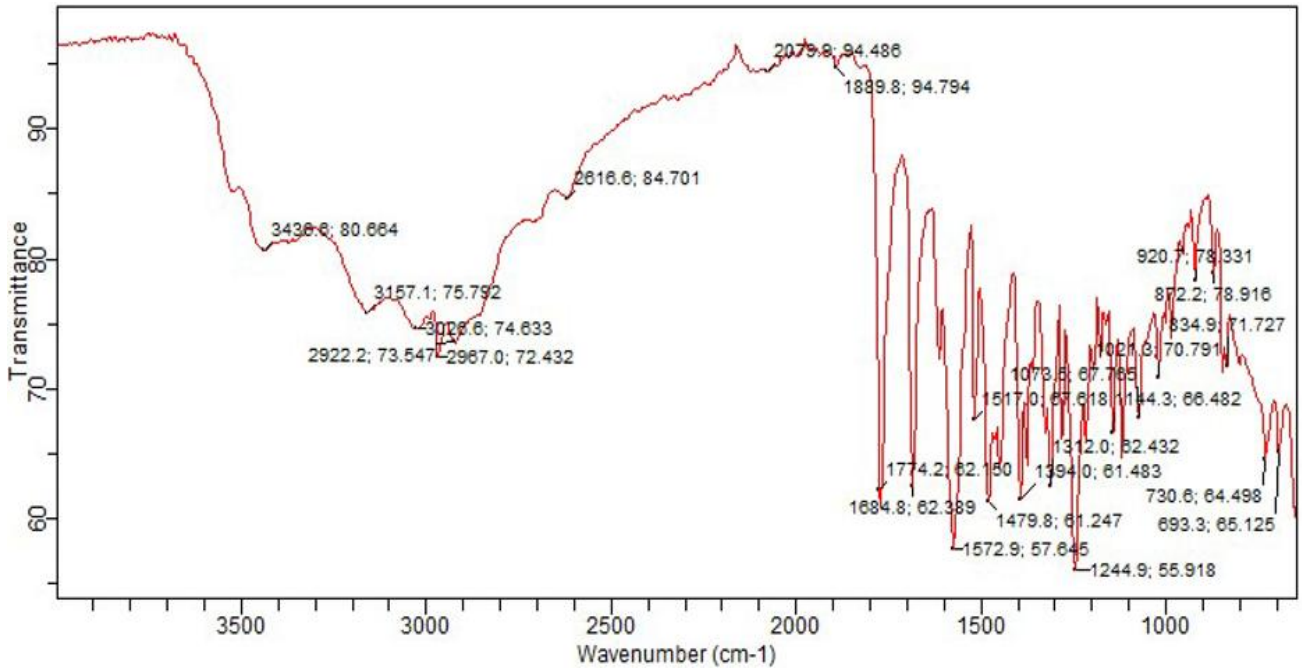


Figure 10 FTIR Spectroscopy of dried powder sample of amoxicillin and Beta herbal cleanser

CHAPTER FOUR

CONCLUSION

Based on the disintegration time results, the presence of Beta Cleanser Bitters showed no contrasting effects on the disintegration times of the two drugs, but presence of *Aloe vera* and *Moringa oleifera* alone reduced the disintegration time of amoxicillin, indicating a potential drug-specific interaction.

The study suggests that Beta Cleanser Bitters may exert some influence on the dissolution and disintegration behavior of Ciprofloxacin, though chemical interactions appear to be limited. But for amoxicillin, the presence of Beta Cleanser Bitters caused a decrease in drug release. These findings offer valuable insights for pharmaceutical formulations involving these drugs and herbal components.

The presence of Beta Cleanser Bitters, *Aloe vera*, and *Moringa oleifera* did not induce substantial deviations in the absorbance profiles of ciprofloxacin across the tested concentrations. This suggests that, under the conditions of this experiment, Beta Cleanser Bitters do not significantly influence the absorption characteristics of Ciprofloxacin.

Furthermore, FTIR analysis provided valuable insights into potential chemical interactions. The spectra comparison revealed a notable similarity, suggesting minimal chemical alteration in the structure of ciprofloxacin and amoxicillin in the presence of Beta Cleanser Bitters. This implies that the herbal component may not induce significant changes in the chemical composition of the drugs.

Overall, the comprehensive evaluation of disintegration, dissolution, absorbance, and FTIR results sheds light on the behavior and interactions of ciprofloxacin and amoxicillin with Beta

Cleanser Bitters. These findings offer crucial insights for the development of pharmaceutical formulations incorporating these drugs and the herbal component. While the study provides a solid foundation, further investigations may be warranted to explore potential interactions under varied experimental conditions.

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APPENDIX

Appendix 1: Weights of 20 random capsules of ciprofloxacin (Ciprotab®) and amoxicillin (Amoxil™)

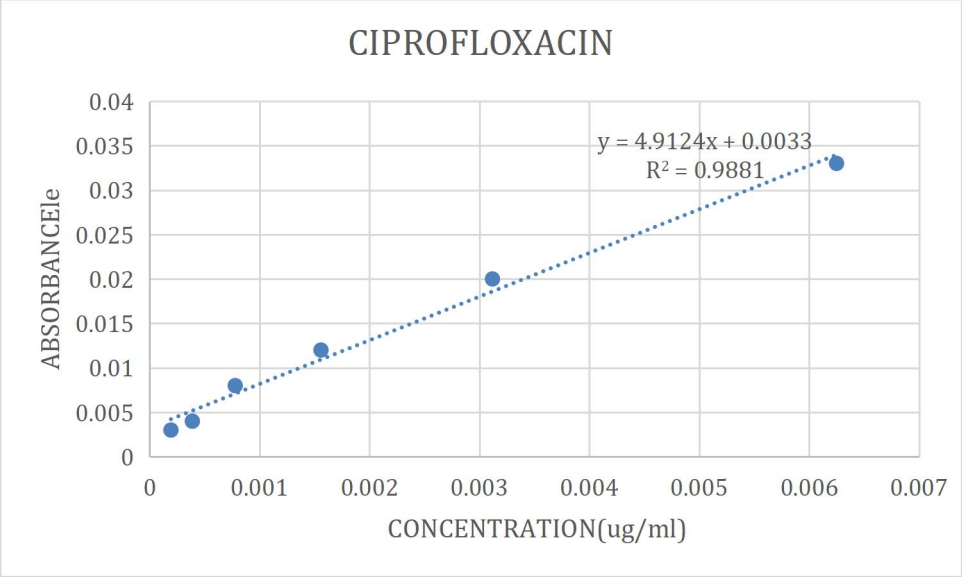
S/N	Ciprofloxacin(g)	Amoxicillin(g)
1	0.808	0.678
2	0.819	0.687
3	0.804	0.681
4	0.832	0.677
5	0.812	0.679
6	0.802	0.685
7	0.817	0.703
8	0.806	0.670
9	0.812	0.676
10	0.813	0.676
11	0.814	0.694
12	0.821	0.671
13	0.810	0.696
14	0.809	0.690
15	0.780	0.701
16	0.811	0.704
17	0.818	0.696
18	0.789	0.691
19	0.824	0.700
20	0.803	0.703

Appendix 2: Dilution and absorbance of ciprofloxacin (Ciprotab®) and amoxicillin (Amoxil™)

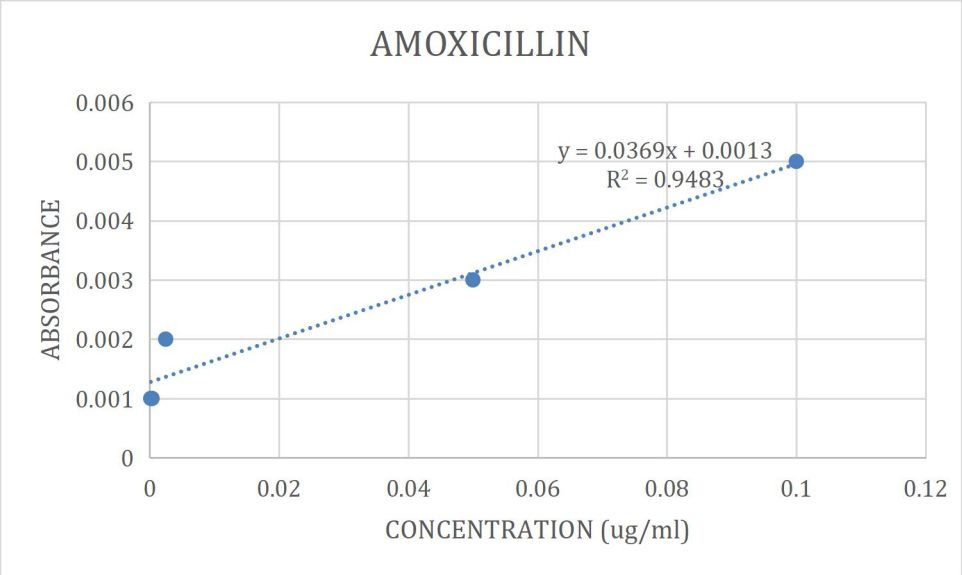
Concentration(ug/ml)	Absorbance for ciprofloxacin	Absorbance for amoxicillin
0.1%	0.005	0.057
0.05%	0.003	0.054
0.025%	0.002	0.044
0.0125%	0.002	0.033
0.00625%	0.002	0.020
0.003125%	0.002	0.012
0.0015625%	0.002	0.008
0.00078125%	0.002	0.004
0.00039062%	0.001	0.003
0.00019531%	0.001	0.001

Appendix 3: Calibration curve for pure samples of amoxicillin and ciprofloxacin

Calibration curve for Ciprofloxacin



Calibration curve for Amoxicillin



Appendix 4: Disintegration time test

Ciprofloxacin

Ciprofloxacin+ water (mins)	Ciprofloxacin+ Beta Cleanser Bitters	Ciprofloxacin+ *Aloe vera*	Ciprofloxacin + *Moringa oleifera*
5.67	6.65	8.63	8.4
6.97	7.42	10.12	9
8.2	8.5	10.78	10.75
9.97	10.72	10.88	10.85
12.63	11.17	11.83	11.58
13.73	12.67	12.25	12

Amoxicillin

Amoxicillin+ water(mins)	Amoxicillin+ Beta Cleanser Bitters	Amoxicillin+ Aloe vera	Amoxicillin+ Moringa oleifera
3.31	3.42	3.18	2.93
3.72	3.50	3.42	3.12
4.30	3.60	3.52	3.18
4.85	4.23	3.58	3.32
4.87	4.38	3.72	3.43
5	5	3.8	3.63

Appendix 5: Dissolution values

For ciprofloxacin

Time	Ciprofloxacin	Ciprofloxacin +Beta Bitters	Ciprofloxacin+ Aloe vera	Ciprofloxacin + Moringa oleifera
0	0	0	0	0
5	38.89	35.92	35.32	35.32
10	38.89	35.32	35.32	35.32
15	38.29	35.32	35.32	35.32
30	38.29	35.92	35.32	35.32
45	38.29	35.92	35.32	34.73
60	38.29	35.32	34.73	34.73

For Amoxicillin

Time (mins)	Amoxicillin	Amoxicillin +Beta bitters	Amoxicillin +Aloe vera	Amoxicillin +Moringa oleifera
0	0	0	0	0
5	37.56	8.29	32.68	32.68
10	32.68	0	27.81	27.81
15	32.68	0	27.81	32.68
30	32.68	0	32.68	32.68
45	32.68	0	32.68	27.81
60	37.56	0	37.56	27.81

Appendix 6: Absorbance Studies

Absorbance Studies result of Ciprofloxacin

Conc	Ciprofloxacin	Cipro + Bitters	Cipro+ Aloe vera	Cipro+ Moringa oleifera
0.1	0.061	0.061	0.06	0.06
0.05	0.057	0.056	0.042	0.04
0.025	0.044	0.05	0.032	0.032
0.0125	0.033	0.02	0.024	0.02
0.00625	0.02	0.021	0.01	0.01

Absorbance Studies result of Amoxicillin

Conc	Amoxicillin	Amoxi+Bitters	Amoxi +Aloe vera	Amoxi +Moringa oleifera
0.1	0.005	0.004	0.006	0.006
0.05	0.003	0.003	0.005	0.005
0.025	0.002	0.002	0.004	0.004
0.0125	0.002	0.002	0.003	0.002
0.00625	0.001	0.001	0.001	0.001