Carboxymethylation of *Phoenix dactylifera* L palm tree cellulose and its evaluation as pharmaceutical suspending agent

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Addis Ababa, Ethiopia

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A Thesis Submitted to Department of Pharmaceutics and Social Pharmacy, School of Pharmacy, College of Health Sciences, Addis Ababa University as Partial Fulfillment of the Requirements for the Masters of Science Degree in Pharmaceutics under the supervision of Prof. Anteneh Belete, Dr. Tesfaye Gebriel, and Mr. Yonas Brhane

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This is to certify that the thesis undertaken by Nurlgn Yesuf, entitled "Carboxymethylation of *Phoenix dactylifera* L palm tree cellulose and its evaluation as pharmaceutical suspending agent" and submitted in partial fulfillment of the requirements for the Degree of Master of Science in Pharmaceutics complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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Abbreviation and Acronyms

AA	Acetic Acid
AGU	Anhydroglucose Unit
ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredients
BP	British Pharmacopoeia
CMC	Carboxymethyl cellulose
C-CMC	Commercial Carboxymethyl cellulose
CC-C	Commercial cellulose
CrI	Crystallinity index
EFB	Empty fruit branch
EFDA	Ethiopian Food and Drug Authority
FA	Formic acid
FTIR	Fourier Transform Infrared
IPA	Isopropanol
L-CMC	Carboxymethyl cellulose prepared from Phoenix dactylifera L tree leaves
L-C	Cellulose extracted from *Phoenix dactylifera L* tree leaves
LB-C	Cellulose extracted from *Phoenix dactylifera L* leaves base
INR	Inversion not required
LB-CMC	Carboxymethyl cellulose prepared from Phoenix dactylifera L Leaf base
NaCMC	Sodium carboxymethyl cellulose
HPMC	Hydroxypropylmethyl cellulose
DS	Degree of Substitution
DSC	Differential Scanning Calorimetry

MA	Methanol
MBZ	Metronidazole benzoate
MCA	Monochloroacetate
SEM	Scanning electron microscope
RPM	Revolution per minute
TGA	Thermogravimetric Analysis
USP	United State Pharmacopoeia
UV	Ultraviolet – Visible
XRD	X-Ray Diffraction
WHO	World health organization

Abstract

Phoenix dactylifera L palm tree is a plant with great sustainability and renewability in nature and widely spread across much of Middle East, tropical Africa including Ethiopia. Its fiber biomass mainly comprises lignocellulose, and used as an alternative source of cellulose. The objective of this study was to extract and characterize cellulose from the leaves and leaf base of local *Phoenix dactylifera* L palm tree; modify the extracted cellulose to carboxymethyl cellulose (CMC) and evaluate the CMC as pharmaceutical suspending agent. Leaves and leaf base of *Phoenix dactylifera* L palm tree were individually subjected to extraction of cellulose, followed by the carboxymethylation process by utilizing monochloroacetic acid and sodium hydroxide. Characterization techniques including Fourier Transform Infrared Spectroscopy, Scanning electron microscopy, X-Ray Diffraction, and Thermogravimetric Analysis were employed to assure the successful extraction of cellulose as well as the modification of cellulose to CMC. The percent of cellulose yields on a dry weight basis was found to be 36.7 $\pm$ 0.97 % for cellulose extracted from palm tree (*Phoenix dactylifera* L) leaves and 41.3 $\pm$ 1.08 % from leaf base. The maximum degrees of substitutions of CMC were 0.889 for (Carboxymethyl cellulose derived from *Phoenix dactylifera* L tree leave) (L-CMC) and 0.667 (for Carboxymethyl cellulose derived from Phoenix dactylifera L Leaf base cellulose (LB-CMC)) based on dry weight conditions. The yield of CMC ranged from 0.889 $\pm$ 0.003 g/g (for L-CMC) to 0.179 $\pm$ 0.001 (for LB-CMC).

L-CMC and LB-CMC were evaluated as suspending agents in metronidazole benzoate suspensions. The suspensions were prepared using 0.5%, 1%, 1.5%, and 2% w/v of L-CMC, and LB-CMC, and compared with suspensions prepared from commercial carboxyl methyl cellulose (C-CMC) in similar concentrations. The resulting suspensions were evaluated for their visual appearance, pH, sedimentation volume (%), rheology, redispersibility, and *in vitro* drug release profile, and also stability studies at accelerated condition were performed for 3 months. The flow rate and redispersibility of the metronidazole benzoate suspension prepared with L-CMC were significantly lower than those with C-CMC and higher than those prepared with LB-CMC at 1 % w/v suspending agent concentrations($p>0.05$). The sedimentation volume of the formulations was in the order of C-CMC > L-CMC> LB-CMC ($p>0.05$). Additionally, the dissolution rate profiles of all the prepared metronidazole benzoate suspensions remained similar to the Negazole, Camezola, and Metrogly with $f_2 > 50$.

The results indicate successful carboxymethylation of palm tree cellulose, and yielding CMCs with desired physicochemical properties as pharmaceutical suspending agent.

Keywords: *Phoenix dactylifera* L palm tree, Cellulose, carboxyl methyl cellulose, suspending agent

1. Introduction

1.1. Polymers

Currently, the increasing number of scientific studies about renewable industrial material resources is mainly due to the limited availability of raw materials and the growing concern about greenhouse gas emissions. Hence, creating more productive, moderate, and ecologically feasible innovations to change lignocellulose biomass into chemical businesses that can be valuable to numerous segments of society is an important challenge (Coseri 2017). Due to its greater availability and lower price, lignocellulose biomass from agro-industrial waste products is a desirable alternative (De Freitas *et al.*, 2017).

Today, the request of the green industry to create low-cost, eco-friendly materials from bio waste is increasing with interest (Rizwan *et al.*, 2017). It has been obtained from various agricultural waste such as empty fruit branches (EFB), banana, sago waste orange peels, cotton waste, and palm tree leaves (Abouloula *et al.*, 2018). The use of common crude materials for the synthesis of polymers and polymer-based items has been one of the foremost crucial interests in recent times (Siqueira et al. 2010). The use of biomass-based materials has received honest attention due to their availability, relatively low cost, and favorable sustainability profile (Bing *et al.*, 2012).

Cellulose is among the most commonly occurring polymers, accessible around the world. This polymer is considered to be renewable and has high yearly production. It is considered to be the main source of raw materials (Cao *et al.*, 2009). Celluloses are obtained from major ordinary sources such as cotton and wood. These sources have been utilized for a long time in the generation of cellulose and its derivatives for typical mechanical applications, primarily in pharmaceutical, cosmetic, textile, and paper businesses. However, the overuse of such sources by competing businesses, such as energy, and/or deforestation, globally has expanded the requirement for alternative sources of cellulose from lignocellulose herbaceous plants, crops, and/or non-woody plants (Jmel *et al.*, 2019).

Carboxymethylcellulose (CMC) is derived from cellulose, a natural polysaccharide, with a large number of carboxymethyl groups added to the cellulose polymer chain. Sodium carboxymethyl cellulose (NaCMC) is an anionic water-soluble polymer that is commonly produced through the

reaction of a cellulose alkali with sodium monochloroacetate (Luna-Martínez *et al*., 2011). Due to their water solubility, high availability, nontoxicity, biological and environmental compatibilities, and low cost, CMC and derived sodium salt have been widely employed as natural components in several technological applications, such as pharmaceuticals, cosmetics, and the textile industry (Zheng *et al.*, 2015). The combination of biocompatibility, biodegradability, chemical stability, and solubility in the physiological environment of CMC has significantly extended its utility for advanced biomedical applications, including tissue engineering, drug carrier and delivery, and wound dressing, among others (Monier *et al*., 2016).

Many researchers have done CMC synthesis from alternative sources of industrial waste products such as sugarcane (De Freitas *et al*., 2017), rice husk (Das *et al*., 2014), wheat straw, corn husk, and palm trees. There should be considerable interest in finding cheaper alternative methods to produce CMC. Recently, the cultivation of palm trees has tremendously increased in Ethiopia, and huge amounts of palm tree leaves and leaf bases are either thrown away as waste or burned. This is causing environmental pollution. However, these will have great pharmaceutical, cosmetic, and textile applications with low-added value (Cao *et al*., 2007).

1.2. Cellulose

The most prevalent naturally occurring organic material in the world is cellulose. Nature generates between 100 and 1000 billion metric tons of cellulose annually, according to estimates. Numerous published articles on cellulose preparation and analysis techniques, molecular structure, physical, chemical, and biological characteristics, functioning, and usage have been the focus of much research over many years. French chemist Anselme Payen first extracted cellulose from plant material in 1839. He claimed that although cellulose and starch have the same basic structure, they are structurally and physically distinct (Kafle *et al*., 2014).

In the primary walls of growing plant cells, the glucose polymer is assembled into long micro fibrils. These micro-fibroils are encompassed by a non-cellulosic matrix of lignin and hemicellulose. As a result of the proximity of the three components, sources of cellulose are usually known as lignocellulose materials. In lignocellulose material, cellulose is reinforced along with hemicelluloses and lignin by covalent bonding, different intermolecular bridges, and van der Waals strengths. Their basic composition changes with climatic and development conditions (Thomas *et al*., 2013).

The world has a great interest in cellulose since it and its directives are biodegradable, abundant in nature, renewable and also have low natural impacts (Battisti *et al.*, 2018). Cellulose has the greatest advantage because of its interesting mechanical properties, which additionally have promising impacts on the creation of green polymer composites that are ecologically friendly. Lignocellulose biomass, fundamentally composed of cellulose, hemicellulose, and lignin, is the most abundant renewable bio resource fabric accessible on earth (Alotabi *et al*., 2020). In such lignocellulose materials, the cellulose fiber is surrounded in a composite structure, which is composed of different non-cellulosic cementing materials such as lignin, pectin, hemicelluloses, as well as other carbohydrate polymers (Abdel-Halim 2014). Cellulose micro fibrils have disarranged (amorphous) and highly ordered (crystalline) regions. Within the crystalline regions, the cellulose chains are tightly packed together by strong and highly complicated intra- and intermolecular hydrogen bond systems, whereas the amorphous spaces are routinely distributed along micro fibrils (Xu *et al.*, 2020). The features of cellulose are generally governed by the source plant and extraction technique (Oliveira *et al*., 2016).

Cellulose is a long-chain polymer containing (1→4)-linked β-glucopyranosyl residues. Up to 100 cellulose chains are gathered together to create long lean basic structures (fibrils) (Su *et al*.,. 2015).. Fundamentally, cellulose could be a linear homopolymer with the equation of $(C_6H_{10}O_5)_n$ conformational structure. The repeating units made up of D-glucose that does not break up in water, but can easily degraded by microbial, chemicals, and parasitic. The atomic chains of cellulose are biosynthesized through self-assembly; they turn into micro fibrils that are made up of crystalline as well as amorphous polymorphism. The adjacent cellulose particles stabilized and adjusted with hydrogen bonds (Fernandes *et al*., 2011). As a result of hydrogen bonds that are associated with the structure of molecular cellulose, it neither melts nor dissolves readily in common organic solvents (Kumar *et al.*, 2013).

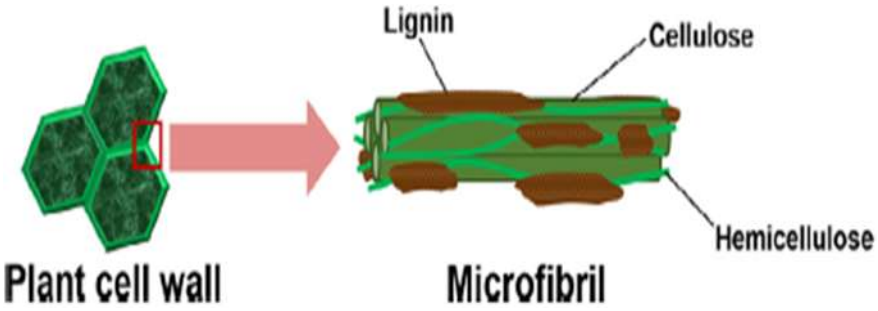

Figure 1: Main structure of plant cell wall in lignocellulose biomass.

In any case, the composition and substance of these three components are changed due to the contrast in species, types, and sources of lignocellulose biomass (Langan *et al.*, 2014).

1.2.1. Molecular structure of cellulose

The main component of lignocellulose biomass is cellulose. Unlike glucose in other glucan polymers, the repeating unit of the cellulose chain is the disaccharide cellobiose. Its structure comprises broad intramolecular and intermolecular hydrogen bonding systems, which firmly link the glucose units. Since almost half of the natural carbon within the biosphere is displayed within the cellulose frame, the transformation of cellulose into fuels and important chemicals has vital significance (El Nahrawy *et al.*, 2020).

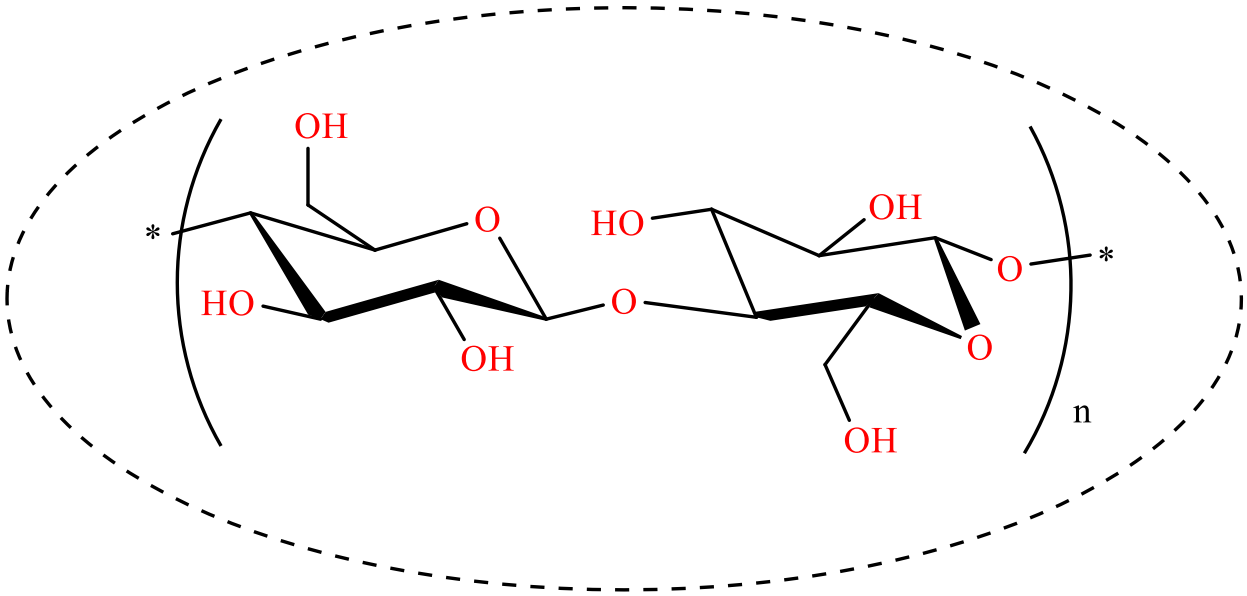

Figure 2: Molecular structure of cellulose.

Cellulose may be a linear polysaccharide comprising D-anhydroglucopyranose units (AGU), which are connected by β - (1 → 4) - glycosidic bonds (Lu *et al.*, 2013). An anhydroglucose unit

(AGU) may be a single sugar atom in a polymer and displayed from three accessible hydroxyl bunches. The primary OH on $C_{(6)}$ and the two auxiliary OHs on $C_{(2)}$ and $C_{(3)}$. These hydroxyl groups at C-6, C-2, and C-3 positions can experience the common place responses known for primary and secondary alcohols. The bridging and the ring oxygen atoms are predominantly included in intramolecular and intermolecular interactions, basically hydrogen bonds, and in the degradation reaction (Klemm *et al.,* 1998).

The anhydroglucose unit, the cellulose monomer, is made up of three hydroxyl groups that are strongly hydrogen bonded both with the adjacent glucose unit in the same chain as well as with other chains, creating what is known as intramolecular hydrogen bonding networks and intermolecular hydrogen bonding networks, respectively (Moon *et al.,*2011). These hydrogen bonding systems are strong and firmly pressed within the crystalline parts of cellulose fibrils which lead to the intense, solid, stringy, and insoluble in water, and highly resistant to most organic solvents in plant cell walls (Lavoine *et al.,* 2012). There are numerous morphologies of cellulose due to the broad orientation of the glucose molecules and hydrogen bonding systems in cellulose. The source of lignocellulose biomass and the method of treatment both affect the variety of cellulose morphology (Phanthong *et al.,* 2018). The amorphous and crystalline domains make up the two phases of cellulose, which are thought to be a two-phase system. The degree of crystallinity greatly affects the physico-chemical behavior of cellulose. It directly affects swelling, water binding, and the accessibility of chemical derivatization. Therefore, the degree of crystallinity is a crucial factor that must be taken into account when considering the manufacture and use of cellulose (Cybulska *et al.,* 2011).

The naturally produced crystalline cellulose can have two polymorphic structures: I_α and I_β. Algae and lower plants produce mostly I_α allomorph, whereas higher plants produce mostly I_β allomorph. Cellulose II is produced by treating cellulose I_α and I_β with high concentrations of alkaline and neutralizing with ammonia or obtained by coagulation with water of a fully dissolved cellulose solution in strong ionic solvents. When cellulose I or II is treated with liquid ammonia, they convert to II_I and III_{II}, respectively. Another polymorphic form is cellulose IV. It is reported to be formed through high-temperature treatments of cellulose III in glycerol. Certain young primary cell walls of cotton were claimed to produce IV cellulose IV (Kim *et al.,* 2013).

1.2.2. Methods of cellulose extraction

The main technological goal in all biomass processing techniques is to extract the cellulose material from the plant at a fair yield without suffering significant losses. Generally speaking, this procedure is referred to as "treatment" or "pretreatment" of the biomass (Ramos, 2003). Pretreatment can be defined as the depolymerization and solubilization of hemicellulose polymers, as well as the disruption of the cell wall matrix, which connects carbohydrates and lignin. The compact lignocellulose structure is damaged during the pretreatment process, exposing the cellulose fiber (Amin *et al*., 2017). Pretreatment also changes the degree of crystallinity of cellulose (Ramos, 2003). The four main categories of pretreatment technologies are physical, chemical, physico-chemical, and biological. The most typical application of techniques is a combination of two or more of the same or separate categories (Ibrahim *et al.*, 2013).

Mechanical operations, microwave radiation, and ultrasonic pretreatment are examples of physical pretreatment techniques. Mechanical pretreatment is one of the most commonly used physical pretreatments. In the first mechanical step of all pretreatment procedures, the biomass is broken down using a combination of chipping, grinding, and milling (Ganesh *et al.,* 2012). Ultrasound-assisted extraction can be explained by the mechanical action of ultrasound on the cell wall, resulting in increased accessibility and extractability of the hemicellulose and lignin components (Liu *et al*. 2006). Because of the heat produced and the large number of collisions caused by the oscillation of polar molecules and ion movement, microwave radiation also can speed up biological, chemical, and physical processes. However, the lignocellulose material's dielectric characteristics have an impact on how well it performs (Amin *et al.,* 2017).

Physicochemical pretreatment methods, including liquid hot water pretreatment, steam explosion, ammonia explosion, and supercritical fluid pretreatment, can also be used in cellulose extraction. Liquid hot-water pretreatment uses water at elevated temperatures and high pressures to maintain its liquid form and promote the disintegration and separation of the lignocellulose matrix. The pretreatment of liquid hot water can take place at temperatures between 160 ° C and 240 °C for periods between a few minutes and an hour. Another method for treating lignocellulose material is a steam explosion, which involves high-pressure treatment followed by a sharp pressure decrease. It is the most popular pretreatment technique used to depolymerize

lignocellulose material because it helps to release the links between cellulose, hemicellulose and lignin (Amin *et al.*, 2017).

Biological pretreatment with bacteria (Actinomycetes) has been observed to be effective on grasses. Commercial sources of the enzymes needed to break down plant cell walls include fungi. A lengthy residence period of 10 to 14 days, the necessity for incredibly exact growing conditions, and the need for a vast space are some of the drawbacks of biological pretreatment that make it less appropriate for industry. The fact that parts of the carbohydrates are eaten by microbes is another potential drawback. If the biomass has a low lignin content, biological pretreatment can be used as a first step, as a default pretreatment in combination with another pretreatment method, or on its own (Amin *et al.*, 2017).

Chemical, alkali, or acid pretreatment methods are the most commonly used, with the primary goal of removing lignin and/or hemicellulose (Ibrahim *et al.*, 2013). Alkaline pretreatment uses bases including sodium, potassium, calcium, and ammonium hydroxide. When an alkali is used, the ester and glycoside side chains degrade, changing the structure of the lignin and causing swelling, partial crystallization, and partial solvation of the hemicellulose and cellulose (Brodeur *et al.,* 2011). Acid pretreatment involves the use of concentrated or diluted acids to weaken the hard structure of the lignocellulose material. Sulfuric, hydrochloric, phosphoric, acetic, formic, and nitric acids are the most frequently used acids (Brodeur *et al.*, 201). One of the chemical pretreatment methods is acid pretreatment. Acid pretreatments have been part of the overall process of fractionating the components of lignocellulose biomass, as they can remove lignin and hemicellulose (Brodeur *et al.,* 2011).

Cellulosic pulp and other products can be produced by fractionating lignocellulose materials using the acetic or formic acid processes. Atmospheric pressure is suitable for the process. Distillation makes it simple to recover the process's spent acid and reuse it. The technique has been used to separate lignocellulose materials from cellulose, hemicellulose, and lignin (Jahan *et* al., 2011). Thus, the combination of formic and acetic acid can be utilized as an alternative way to extract cellulose from lignocellulose materials as it has a low environmental impact, low investment costs, and produces cellulose with a high yield, low residual lignin content, high brightness, and strong strength (Hidayati *et al.,* 2017).

1.2.3. Cellulose Modifications and Cellulose Derivatives

Native cellulose is big and fibrous, making it a poor candidate for direct usage in several pharmaceutical applications. Solubility, stability, flow property, and density are among the factors that are greatly impacted. To make these better cellulose physicochemical characteristics, a variety of derivatives have been created. Hydrolysis of amorphous portions with mineral acids and substitution of hydroxyl groups with different functional groups are commonly used methods of modification (Klemm *et al.*, 1998).

The pharmaceutical and cosmetic sectors employ semi-synthetic derivatives of cellulose. The two primary classes of cellulose derivatives with varying physicochemical and mechanical properties are cellulose ethers and cellulose esters. These polymers are broadly used in the formulation of dosage forms and healthcare products. These substances play significant roles in a variety of pharmaceutical products, including extended and delayed-release coated dosage forms, extended and controlled-release matrices, and osmotic drug delivery systems (Cabrales *et al.*, 2020).

Chemical modification of cellulose is one method of the production of value-added products. Several biodegradable cellulose derivatives, such as CMC, HPMC, and cellulose acetate, can be produced from cellulose after chemical modifications. Worldwide, there is a great deal of interest in the manufacturing of cellulose derivatives, primarily because cellulose is abundant in nature, biodegradable, and has a smaller environmental impact than polymers made from fossil fuels (Nabili *et al.*, 2017).

1.2.4. Palm Tree as a Source of Cellulose

Biomass waste from different palm tree species (Date palm, *Phoenix dactylifera L., genuineness of Elaeis,* and others) is one of the most promising sources for the production of various chemicals, including cellulose (35%-74.7%), hemicellulose, and lignin. These trees produce enormous amounts of garbage, much of which is now composted and utilized for traditional crafts or burned, polluting the environment in the process. Thus, the numerous waste components of palm trees can be utilized to create new sustainable byproducts like cellulose. This would result in a high-value biomaterial with exceptional physical and chemical qualities, as well as significant economic and environmental benefits (Cabrales *et al.*, 2020).

As a member of the *Arecaceae family* of trees, the date palm (*Phoenix dactylifera L*) is considered a symbol of life in the desert since it can withstand hot temperatures, water stress and salinity better than many other fruit trees. Due to its importance to human communities, health benefits, the ability to produce in harsh semi-arid and arid conditions, and the variety of subsistence goods that can be made from its fruits and other parts of the giant palm, it is one of the most valuable domesticated fruit trees (Al-khayri *et al.*, 2015).

The production of date palms worldwide is rising. For example, it saw an increase in production from 1.8 million metric tons in 1961 to 2.8 million metric tonnes in 1985 and then to 5.04 million metric tonnes in 2001. The world's date palm production was about 8.06 million metric tonnes on roughly 1.149 million hectares of land covered by palm tree (Al-Farsi & Lee, 2008a). The primary agricultural endeavour in the hot, arid regions of the world that boosts a nation's foreign exchange revenues is the development of date palms. According to the report by Pariona, Egypt is the world's leading producer of date palms, producing over 1.1 million metric tons annually and earning $41.8 million from the export of fresh date fruits. In a similar vein, fresh date palm exports from Saudi Arabia and Iraq to the global market were around $94.3 and $77.5 million, respectively (Pariona, 2017).

the growth of date palm output in Ethiopia is incredibly increasing, but the actual annual production is not recorded in any statistical database due to the lack of attention paid by the Ethiopian government in general. Governmental and non-governmental organizations have not carried out any research or outreach initiatives. The date palms employing traditional farming methods that they have learned from their parents and grandparents over the years. According to studies, no training sessions or extension services are provided to agro-pastoralists on date palm cultivation, management, and postharvest handling procedures, which are crucial for the effective production of date palm (Alemdar & Sain, 2008).

Since ancient times, a crop of palm trees has been developed. According to the most reliable evidence from Mesopotamia, date palm development probably started as early as 3000 BC. The date palm can be found throughout the Nile Valley of Egypt, and Egyptian hieroglyphics have long used its frond as an image. The date palm also has significance in the Islamic religion, dates are mentioned many times within the Quran, Muslims break the long fasting days within the month of Ramadan with dates, in the Christian religion, palm trees are utilized for the celebration

of Easter Sunday (Al-Farsi and Lee, 2008). Palm trees height is estimated to be between 20 and 30 meters, and it is widely cultivated in semi-arid and dry regions, including the United States, the Middle East, and countries in North Africa. These trees can have a lifespan of more than 100 years (Hachaichi *et al.*, 2021).

Figure 3: Palm tree, dried leaves and green leaves of palm trees (left to right) (alotaibi *et al.*, 2019).

According to some research, traders from Yemen and Sudan brought the date palm to Ethiopia from Middle Eastern nations around 200 years ago. Since then, agro-pastoralists have been cultivating it primarily in the Afar, Somali, Dire Dawa, Gambella, and Benishangul-Gumuz regions. The cultivation of date palms, particularly in the Afar region, has a long history. Particularly good areas for date palm production include the Danakil Depression's Afambo, Asayita, Gewane, and Amibara districts along the Awash River. Furthermore, the presence of the Awash River in the area provides a fantastic opportunity for the establishment and growth of small-scale and large date palm plantations in the Afar region (Lemlem *et al.*, 2018).

After planting or product collection, palm trees can generate more than 200,000 tonnes of waste annually (branches, stalks, and trunks). These agricultural wastes can be used to create inexpensive, ecologically acceptable materials for a variety of uses, including textiles, sports equipment, automobile parts, pharmaceuticals, and cosmetic products (Amroune *et al.* 2021). Thus, the various components of palm tree trash can be used to produce new sustainable by products like cellulose. This would result in a high-value biomaterial with outstanding physical and chemical capabilities, as well as significant financial and environmental benefits (Alotaibi *et al.*, 2019).

Figure 4: The process of hand pollination of date palm (Lemlem *et al.,* 2018).

A variety of compounds can be produced from palm trees, including cellulose (35%–74.7%, depending on the method of extraction and the part of the palm tree used), hemicellulose, and lignin (Alotaibi *et al.,* 2019). The plant cell wall is essentially composed of cellulose, which delivers support and rigidity to the structures of the plants (Bolio-López *et al.,* 2015). Cellulose is characterized by good thermal resistance, high mechanical properties, low cost, low density, and is renewable and biodegradable (Fardioui *et al.*, 2016).

Alternative sources of cellulose were investigated from the leaves and leaf bases of palm trees, which are rich in lignocellulose resources in Ethiopia and can be collected in an efficient and environmentally friendly manner.

In this study, the type of palm tree used as lignocellulose biomass for cellulose extraction and CMC preparation was a species called "*Phoenix dactylifera L*. palm tree," as authenticated by Addis Ababa University's Department of Plant Biology and Biodiversity Management.

1.3. Carboxymethyl Cellulose

Due to their high accessibility and desirable chemical and physical qualities like biocompatibility, biodegradability, and chemical soundness, modified cellulose products are widely used in several commercial applications in the food, textile, paper, and pharmaceutical industries (Saha, *et al.*, 2020). The most promising cellulose derivative is CMC. Because of its distinctive surface qualities, mechanical strength, customizable hydrophobicity, viscous characteristics, availability and abundance of raw ingredients, and inexpensive synthesis procedure. It is now widely employed in a variety of cutting-edge application disciplines, including the food, paper, textile, and pharmaceutical industries, biomedical engineering, waste water treatment, energy production and storage, and other areas (Rahman *et al*., 2021).

At the molecular level, the major difference between CMC and cellulose is that there are only some anionic carboxymethyl groups (i.e., -CH_2COOH) in the CMC structure that replace the hydrogen atoms from some hydroxyl groups present in the pristine cellulose infrastructure. CMC was first synthesized in 1918. However, the commercial production of these all-important polymeric materials was first depicted in Germany in the early 1920s (Zhang *et al.,* 2013). Sodium carboxymethyl cellulose is an anionic, water-soluble polymer. Due to its ability to increase viscosity, sodium carboxymethyl cellulose is frequently utilized in oral and topical medicinal formulations. To suspend powders intended for topical, oral, or parenteral treatments, viscous aqueous solutions are utilized (Hussain *et al.,* 1991).

A survey of the literature reveals that carboxymethylation reactions could be carried out in different types of solvent media, usually water, or water-miscible organic solvents with a small quantity of water. Solvents such as ethanol, methanol, butanol, isopropanol, and acetone have been investigated. Isopropyl alcohol was a solvent of choice due to its unique carboxymethylation properties, and it was also used in most other studies (Heinze and Pfeiffer, 1999). The origin of the parent cellulose has been confirmed as one of the factors that influence degree of substitution, and the carboxymethylation process; other factors include reagent concentration, reaction temperature, type of organic solvent, and reaction time (Lawal *et al.,* 2007).

1.3.1. Preparation of Carboxymethyl Cellulose

Purified CMC is a free-flowing, tasteless, odorless powder with a white-to-cream color that is used in many different industries (Stigsson *et al.,* 2001). The process of making CMC involves reacting alkali cellulose that has swelled in aqueous NaOH with an excess of an organic solvent (such as ethanol or isopropanol) and monochloroacetic acid (Heinze, and Pfeiffer, 1999). Hydroxyl groups in cellulose are usually replaced by carboxymethyl groups in the order of C2>C6>C3 (Ho, and Klosiewicz, 1980).

The highest possible DS is 3, and it is used to compare the characteristics of derivatives of cellulose (Salmi *et al*., 1994). The preparation of highly substituted CMC requires careful consideration of the carboxymethylation conditions. The most typical DS obtained in commercial CMC is often between 0.4 and 1.4 (Silva *et al.,* 2004). To create better commercial

products, researchers are working to find different strategies to increase the degree of substitution for CMC.

Production of CMC goes through the following steps: alkylation, carboxymethylation, neutralization, purification, and drying. NaOH and sodium monochloroacetate ($ClCH_2COONa$) were reacted with cellulose fibers in a solvent medium for the first two stages of the reaction. With the solvent isobutyl-isopropyl alcohol. Next, acetic acid is used in the neutralization process, which is purified with 96% ethanol. The drying stage is then completed by heating the mixture in an oven set to 60 ^{o}C. The DS value determines the quality of solubility (Pribadi, 1985).

Several factors, including the value of DS, purity, and the presence of functional groups, indicate the quality of the final CMC. The kind of reaction media, the MCA concentrations, the reaction time, and the reaction temperature all have an impact on the value of DS. The CMC is of higher quality when the value of DS is larger(Barai *et al.*, 1997).

1.3.2. Applications of CMC

CMC has a wide range of uses in the food and pharmaceutical industries and is harmless. CMC is used as a thickening, suspending, stabilizing, and film-shaping operator in the pharmaceutical business(Ramos *et al.*,2003). NaCMC is an anionic water-soluble polymer with a high purity of 99.5%. NaCMC is widely used in oral and topical pharmaceutical formulations due to its viscosity-increasing properties. It is used to suspend powders intended for either topical, oral, or parenteral applications (Hussain *et al.*, 1991). CMC has been used to build up and maintain the viscosity of pharmaceutical semi-solids and liquid dosage forms. The most important factor that affects the viscosity is the concentration of the polymer in the solution (Guo *et al.*, 2015).

During the preparation of semi-solid or liquid dosage forms, if the sodium NaCMC is dissolved in water and then the solute is added, the solute has only a small effect on the viscosity. However, if the solute is dissolved before adding the sodium carboxymethyl cellulose, it inhibits polymer dissolution, and a solution of lower viscosity is obtained (Guo *et al.*, 2015).

1.4. Suspension dosage forms

Medication non-adherence can result in therapeutic failure, an extended course of treatment, and higher medical expenses. Adherence to a treatment regimen is significantly influenced by factors

such as medicine palatability and convenience of administration for pediatric patients (Winnick *et al.*, 2005).

Most drugs taken by young patients are not intended for use in paediatric settings. Consequently, physicians are frequently forced to utilise adult dose forms, including tablets and capsules, since there are insufficient dosage formulations suitable for use with paediatric patients. Nevertheless, younger paediatric patients cannot or will not swallow these dose forms (Mennella & Beauchamp, 2008). Additionally, the paediatric patient is not given enough dosage flexibility with these dosage forms. The majority of paediatric patients' prescriptions are dosed according to their body weight or surface area. Because oral liquid formulations allow for more dosage flexibility, they are therefore recommended(Parrott, 1971).

Suspending agents are (i) inorganic materials, (ii) synthetic compounds, or (iii) polysaccharides. A pharmaceutical suspension is a biphasic liquid or semi-solid dose form that contains uniformly distributed, finely divided, insoluble solid drug particles in a liquid or semi-solid medium. The internal, or disseminated, phase is composed of insoluble solid drug particles (Duganath *et al.*, 2010).

Suspension is a preparation that has uniformly dispersed, finely divided drug particles that display a minimum level of solubility. Some suspensions are offered in ready liquid form, which means they have already been dispensed through a liquid carrier with or without stabilizers and other ingredients. In the United States Pharmacopeia, this preparation is referred to as an "oral suspension" (USP). Other medications are offered as dry powders that can be reconstituted as needed. In the USP, this product is designated as "For Oral Suspension (Ansels, 2005). The manufacture and development of a suspension must take into account numerous physical and chemical factors to meet its medicinal criteria. To maintain consistent dispersibility (Kawashima et al. 1991) or to prevent the caking of the medication particles during shelf life (Jaber *et al.*, 2017), several suspending agents are typically added to the dispersion medium. A coarse dispersion is the typical definition of a pharmaceutical suspension (Singh *et al.*, 2014).

In a family of dispersed systems known as suspensions, a finely divided material is uniformly dispersed in a liquid dispersion medium. Depending on the size of the particles, suspensions can be classified as having coarse or colloidal dispersion. Typically, coarse suspensions are those with particles larger than or equal to 1 μm, whereas colloidal suspensions are those with particles

smaller than or equal to 1 μm. Pharmaceutical suspensions can be generically categorized as parenteral suspensions, topical suspensions, or oral suspensions, depending on their intended method of delivery (Chandrasekar *et al* ., 2015).

Dry powder oral suspension that can be reconstituted can be used right away. These are dry formulations that need water to be added when being dispensed. The reconstituted system is the preferred formulation when medication stability is a top priority. If kept in the refrigerator after reconstitution, these systems have a brief but serviceable lifespan (Singh *et al.,* 2014). Reconstitutable oral systems demonstrate adequate chemical stability of the drug throughout the product's shelf life, avoid physical stability issues associated with solubility, pH, and compatibility with other ingredients, and also reduce the weight of the finished product because the aqueous vehicle is not present. As a result, transportation costs may be reduced (Lieberman, *et al.,* 1994). The reason why the drug is given in dry form rather than a solution is that the dry form allows for longer storage of the substance without it degrading too quickly. They claim that such solutions have a limited shelf life (Singh *et al.*, 2014).

Suspensions are essential types of pharmaceutical dosage forms. The advantages of suspension dosage forms include efficient intramuscular depot therapy, effective hydrophobic drug dispensing, avoidance of co-solvent use, masking of unpleasant taste, and resistance to drug degradation with hydrolysis, oxidation, or microbial activity. Additionally, compared to solutions, suspension products can integrate a substantially higher concentration of medicines. Suspension dosage forms have several drawbacks, including the potential for dose fluctuation, the need for a large storage space, and a lack of elegance. Products prepared as dry powders for reconstitution with water before dispensing are commonly called oral suspensions reducing the rate of medication degradation in an aqueous medium (Kulshreshtha *et al.,* 2010).

In an ideal scenario, the internal phase would not sediment during storage and would instead be evenly distributed throughout the dispersion medium. However, the suspension's thermodynamic instability makes this all but impossible. The system becomes unstable due to the surface free energy of the particles in the suspension, which causes particle settling. The overall surface area and the interfacial tension between the liquid medium and the solid particles both affect the system's free energy. As a result, the system tends to reduce its surface area to reduce its free energy, which is accomplished via the development of agglomerates. Depending on the attractive

and repellent forces present in the system, this can result in flocculation or aggregation (Shakeel *et al.,* 2020). The particles in a flocculated suspension form floccules, which are loosely attached. By long-range van der Waals forces of attraction or physical adsorption of macromolecules, the particles are joined together. Fast-settling flocculated suspensions are quickly re-dispersed with mild agitation. To ensure consistent dosing, this characteristic is particularly desirable in a pharmaceutical solution. On the other hand, a deflocculated suspension remains dispersed for a longer period, but sedimentation results in the creation of a closely packed arrangement that results in caking. This has a substantially higher energy barrier than a flocculated suspension, making further re-dispersion problematic (Chandrasekar *et al.,* 2015).

Structured vehicles are aqueous dispersions of natural and synthetic gums. Its viscosity rises when the gums are evenly distributed throughout the aqueous medium. As a result, they are sometimes referred to as thickening agents. The settling of the individual suspension particles is delayed by the continuous medium's thickness. The structured vehicles are also referred to as suspending agents for this reason. Methylcellulose, CMC, gelatin, and tragacanth are the polymers that are most frequently utilized in pharmaceutical suspensions to serve as a structured vehicle. These polymers are safe, non-toxic, and compatible with a variety of active ingredients (Doye *et al.,* 2020). An ideal suspending agent would have low viscosity at high shear rates and high viscosity at minimal shear rates. The agents should display thixotropic and pseudo plastic flow behavior from a rheological perspective. The majority of polymers employed as suspending agents, such as gelatin, tragacanth, or alginates, are hydrocolloids that display pseudo-plastic flow behavior. They make the suspension more viscous and retard settling (Kumar and Yagnesh 2016).

In conclusion, flocculated suspension sediment is more quickly and is simpler to re-disperse than a deflocculated solution, which settles more slowly and is more challenging to do so. Stokes' law can be used to calculate the rate of particle sedimentation (Kumar and Yagnesh 2016).

$$v = d\frac{2(p1-p2)g}{18\eta} \quad \text{.....Eq(1)}$$

Where V is the terminal velocity of sedimentation (cm/s), d is the diameter of the particle (cm), *p1 and p2* are the densities of the suspended particles and the medium, respectively, g is the

acceleration due to gravity, and η is the viscosity of the medium. The suspension having a viscosity within the range of 200 -1500 milipoise is readily pourable (Aulton, 2002).

Ethiopia markets and prescribes a lot of pharmaceutical suspensions, which suggests that a lot of suspending agents are needed. The majority of the currently employed suspending agents, such as acacia, sodium alginate, sodium carboxymethylcellulose, tragacanth, and xanthan gum, are imported and typically costly. To reduce the quantity of imported components and the cost of the dosage form, new suspending agents based on readily available domestic materials, such as cellulose, are being developed. Also, it is advantageous to those who grow cellulose containing plants. Additionally, it might be a valuable addition to the body of prior research on suspension in the literature.

1.5. Metronidazole Benzoate

Metronidazole benzoate (MBZ) is a 5-nitroimidazole bioactive compound used as an antiparasitic and antibacterial therapeutic agent. This drug exhibits biological activity against strains of both Gram-positive and Gram-negative bacteria, particularly against anaerobic and microaerophilic cocci (Turgut & Özyazici 2004)(1–3 Because MBZ, an ester derivative of metronidazole, has a blander taste than the bitter base of the drug, patients are more likely to accept it (Aloumanis *et al.*,2008). For this reason, formulations of oral suspensions have been created.

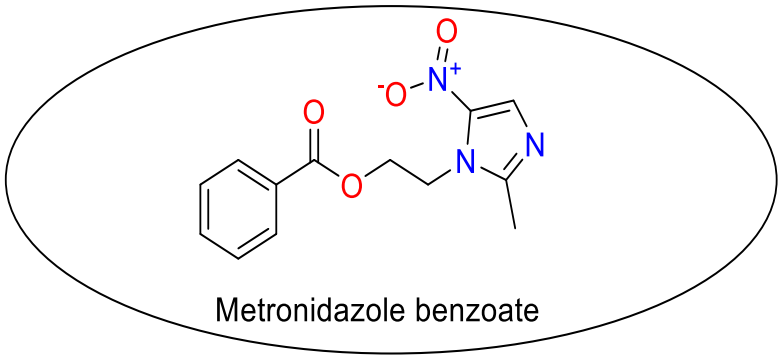

Figure 5: The chemical structure of Metronidazole Benzoate.

MBZ presents poor solubility in water (Bempong et al. 2005). MBZ can be classified as a class IV drug in the Biopharmaceutical Classification System (BCS) based on its solubility and absorption characteristics; it is regarded as poorly soluble and poorly permeable (Da Silva,

2016). For BCS class IV drugs, dissolution is dependent on the drug's acidic or basic nature, solubility, and formulation factors (Tsume *et al.,* 2014). Consequently, drugs in this class may have dissolution issues that limit *in vivo* absorption (Bredael *et al.,* 2014). Pediatric patients who are considering taste masking technology also face additional biopharmaceutical risks when taking poorly soluble pediatric medications, such oral suspension. Taste masking technology raises the possibility of variations in bioavailability and may have a dissolution rate-limiting effect (Purohit, 2012).

As far as we are aware, no report has been created on the potential use of carboxymetyl cellulose developed from palm tree leaves and leaf base as a suspending agent. Hence, the present study is aimed at evaluating the plant palm tree leaves and leaf base CMC as alternative suspending agents in metronidazole benzoate suspensions. Because metronidazole benzoate has an unpleasant taste, is practically water-insoluble, and has low bioavailability, it was chosen as the model drug for this investigation. It is therefore a good candidate to produce suspension dosage form based on its physicochemical qualities (Brhane *et al.,* 2014).

1.6. Statement of the Problem

The fundamental pharmacodynamics characteristics of pharmaceutical substances are not altered by drug delivery methods, but by using the right excipients, they may alter the pharmacokinetic characteristics to affect the pharmacodynamic performance. It can be difficult to choose the right excipients since they must focus on the desired qualities, including functionality, material consistency, regulatory acceptance, cost, availability, and sources, during the therapeutic product development phase (Katdare & Chaubal, 2006).

Cellulose is being increasingly used in different industrial applications on a global scale. Because wood (from conventional sources) is the primary source of cellulose, consumption is increasing worldwide, which contributes to further deforestation. It is getting harder to meet the high demand from conventional resources as cellulose and its derivatives usage rises. Globally, the availability of forest resources is diminishing while demand for cellulose and its derivatives is rising. To avoid using wood directly, which will exacerbate deforestation, these problems drive scientists to search for alternate fiber resources, especially non-wood ones (byproduct biomass from plants) (Uma Maheswari *et al.,* 2012).

The manufacturing of CMC using locally and naturally existing materials is due to the strong demand for cellulose and modified cellulose products like CMC in the pharmaceutical industry (Katdare & Chaubal, 2006). However, the Ethiopian pharmaceutical industries have relied on the import of pharmaceutical-grade cellulose and modified cellulose products, including CMC, which can create a burden on foreign currency and a shortage of these excipients.

The purpose of the present research is to investigate the suitability of the palm tree as a source of CMC. Every year in Ethiopia, large amounts of CMC are imported to meet domestic demand, and the importance of CMC is increasing day by day (Fakrul & Mondal , 2013). Therefore, there is a need to produce CMC from cheap locally available raw materials, such as palm trees, on a large scale(Monier *et al.,* 2016).

1.7. Significance of the Study

For the goal of producing cellulose and its derivatives, numerous plant species have already been studied. Palm tree leaves and leaf bases were considered as cellulose sources due to their abundance, availability, renewability, and low cost. The useful properties of cellulose and its modified products, such as CMC, which are derived from lignocellulose biomass, have recently attracted a great deal of attention in both research and industrial areas. These characteristics include good mechanical qualities, a sizable surface area, an abundance of hydroxyl groups that may be modified, and organic qualities that are environmentally friendly (Phanthong *et al.,* 2018).

It has a great deal of potential to eliminate imports and make these excipients easily accessible for local pharmaceutical manufacturers to create pharmaceutical-grade cellulose powder and CMC with the desired properties from locally accessible renewable lignocellulose biomass. All pharmaceutical manufacturing companies in Ethiopia import almost all pharmaceutical excipients (including CMC) from abroad. This requires a large amount of foreign currency, which in turn can put a considerable burden on the country's economic growth. Apart from the impact on foreign currency, the ordered chemicals may not be delivered timely because of problems encountered in shipment, transportation, customs procedures, and other related issues. Hence, the substitution of the imported excipients with locally produced ones will be economical in terms of both time and money.

This study will examine the local palm tree leaves and leaf base as a potential source of cellulose through the extraction of cellulose fiber and the preparation of carboxyl methylcellulose (CMC), assess CMC as suspending agent and look into CMC as an excipient for use in pharmaceuticals.

Moreover, the study offers recommendations for efficient cellulose extraction and CMC production techniques from palm tree leaves and leaf base biomass, including the most likely pharmaceutical uses. Generally, the present study reports on the physico-chemical properties of the prepared cellulose and CMC in comparison with those of commercial cellulose and CMC and evaluates CMC as a potential source of suspending agents in Metronidazole benzoate suspension dosage formulations.

1.8. Research Questions

Therefore, this research tries to answer the following questions.

1) What is the yield of cellulose and CMC extracted from *Phoenix dactylifera* L. palm tree leaves and leaf bases?

2) What are the physicochemical characteristics of extracted cellulose and CMC prepared from the leaves and leaf bases of the *Phoenix dactylifera* L. palm tree?

2. Objectives

2.1 General objective

- To extract and characterize cellulose from *Phoenix dactylifera* L palm tree leaves and leaf bases, and to prepare and characterize the corresponding CMC, and evaluate it as a suspending agent.

2.2 Specific Objectives

- To extract and characterize the cellulose from *Phoenix dactylifera* L. palm tree leaves and leaf base.
- To prepare and characterize CMC from the leaves and leaf base of the cellulose extracted from *Phoenix dactylifera* L. palm tree.
- To evaluate and compare CMC extracted from *Phoenix dactylifera* L. palm tree leaves and leaf bases with commercial CMC as suspending agents.

- To compare the dissolution profile of the prepared metronidazole suspensions with the CMC of *Phoenix dactylifera* L. palm tree leaves and leaf base with commercial suspensions (Camezol 125 mg/5 ml, Negazole 125 mg/5 ml, and Metrogyl 125 mg/5 ml).

3. Materials and methods

3.1. Materials

Phoenix dactylifera L. palm tree leaves and leaf base were collected from the Afar region, Asayta zone, North East Ethiopia. The samples were authenticated by Addis Ababa University (Botany Department) with the local name Temir, and assigned authentication number of NY001.

Pure sodium hydroxide (HiMedia, Mumbai, India), formic acid (98%) (Central Drug House (P) Ltd. New Delhi, India), commercial cellulose and hydrogen peroxide 30% (Carlo erba reagents, France), Monochloroacetic acid (Sigma-Aldrich, Germany), glacial acetic acid (Riedel de Haën, Germany), acetone and sodium hydroxide 97% (HiMedia, Mumbai, India), isopropanol (99.5%) (Indenta Chemicals, India), HCl 37% (BDH, England), phenolphthalein solution (1 %) (Alpha Chemoka, India), formic acid (98%) (Central Drug House (P) Ltd. New Delhi, India), commercial SCMC (C-SCMC) (UNI-CHEM Co. Ltd., South Korea), nitric acid 69-70%, iodine 99%, methanol 99.9% (LOBA CHEMIE Laboratories, India), and absolute ethanol (Fisher Scientific, UK) were used as received.

For the formulation of metronidazole suspensions, metronidazole benzoate powder (Hubei, India), Tween 80 (polysorbate 80), sodium saccharin (Blue Jed), and sucrose (ELD)., sorbitol 70% (India), propyl glycol (Dow) were received from EPHARM, Ethiopia, and methylparaben (Ari) and propylparaben (Ari) were also received from Julphar Pharmaceutical Manufacturing, Ethiopia.

For comparative dissolution profile study, commercial metronidazole suspensions (Camezole 125mg/5ml, Negazole 125mg/5, and Metrogyl 125 mg/5 ml) were received from a local Pharmacy in Addis Ababa, and all the products were within their shelf life at the time of the study.

3.2. Methods

3.2.1. Extraction of cellulose from *Phoenix dactylifera* L palm tree leaves and leaf base

The local collected *Phoenix dactylifera* L palm tree leaves and leaf base samples were washed with distilled water to remove dust, dried in an oven (Kottermann® 2711, Germany) at 60 °C for

48 h, cut into smaller pieces, and then further treated with a cutting machine to reduce sample size as well as increase surface area of the sample.

Cellulose fibers were extracted from the *Phoenix dactylifera* L palm tree leaves and leaf base following a three-stage treatment as reported by (Gabriel *et al.,* 2020), with slight modifications. The prepared sample was treated with extraction solvents in three stages as described below. With three alkali treatment conditions (A, B, C, D, E and F) were followed to extract the cellulose from the by-products, and the extracted celluloses were designated as A, B, C, D, E, and F, respectively, as shown in Table 1.

3.2.1.1. Alkaline pretreatment

An alkaline pretreatment was carried out in a 3 L flask containing 5%, 10% and 17.5% NaOH solutions in a solid-to-liquid ratio of 1:10 (w/v) of dry material in a water bath at 90 °C for 1.5 h. The fiber was filtered through nylon cloth and then thoroughly washed with hot distilled water (Gabriel *et al.,* 2022).

3.2.1.2. Treatment with formic acid, acetic acid and hydrogen peroxide

The pulps were then subjected to a 2:1:2 solution containing 20% acetic acid (AA), 20% formic acid (FA) and 7.5% H_2O_2 in a water bath at 90 °C for 1.5 h, with a byproduct-to-liquor ratio of 1:10. To separate the cooking liquor, which includes lignin and hemicellulose, from the cellulose, the delignified pulps were filtered and then cleaned with hot distilled water (Gabriel *et al.*, 2022).

3.2.1.3. Bleaching

The pulps were bleached by treating them with 7.5% H_2O_2 in a separate alkaline medium containing 5% and 10% NaOH solutions in a 1:10 fiber ratio. The pulps were treated for 30 min at room temperature and then for 60 min in a water bath at 70 °C. Finally, to eliminate any remaining lignin, the pulps were repeatedly cleaned with hot, distilled water. They were then dried at 60 °C in an oven until their weight remained constant.

Table 1: Extraction conditions of *Phoenix dactylifera* cellulose from palm tree leaves and leaf base.

Extraction condition of cellulose from palm tree leaves and leaf base						
Stage	A-	B-	C-	D-	E-	F-
I	5 % NaOH	5% NaOH	10 %NaOH	10 %NaOH	10 %NaOH	17.5 % NaOH
II	20%FA/ 20%AA/ 7.5%H_20_2 (2:1:2)	20%FA/ 20%AA/ 7.5%H_20_2 (2:1:2)	20%FA/ 20%AA/ 7.5%H_20_2 (2:1:2)	20%FA/ 20%AA/ 7.5% H_20_2 (2:2:1)	20%FA/ 20%AA/ 7.5% H_20_2 (2:1:2)	20%FA/ 20%AA/ 7.5% H_20_2 (2:1:2)
III	7.5 % H_20_2 in 5 % NaOH	7.5 % H_20_2 In 10%NaOH	7.5 % H_20_2 in 5 % NaOH	7.5 % H_20_2 In 10%NaOH	7.5 % H_20_2 in 10 % NaOH	7.5 % H_20_2 in 5 % NaOH

NaOH: Sodium hydroxide, AA: Acetic acid, FA: Formic acid, H_2O_2: water.

3.2.2. Preparation of Carboxymethylcellulose

Initially, a mixture of 2.5 g of crushed cellulose (with extraction condition E) and 50 ml of isopropanol and 50 ml of methanol was used to determine the effect of solvent media on DS prepared. To create alkali cellulose, 10 ml of a 30% NaOH solution was carefully added to the mixture while it was being stirred for 30 min at 25 °C. Subsequently, 2.85 g of sodium monochloroacetic acid was added to the mixture while stirring for 15 min in a ratio of 1:1.14 (cellulose:MCA). Reaction temperatures were moderately adjusted to range from 55 °C to 70 °C for reaction durations of 60 to 180 min as shown in Table 2. The mixture was decanted, and the CMC was placed in 40 ml of absolute methanol under stirring to dissolve impurities. After 40 min, pure acetic acid was added to neutralize the mixture. The mixture was filtered and washed three times with 40 ml of 96 % ethanol and washed again with 40 ml of absolute methanol to remove unwanted salts. Finally, the CMC was dried in an oven (Yeasmin & Mondal, 2015).

Table 2: Reaction condition used for carboxyl methylation of palm tree leaves and leaf base.

Reaction Condition	Cellulose source	Reaction media	Reaction temperature (°C)	Reaction time (h)
L –M-55-3	Leaves	Methanol	55	3
LB-M-55-3	Leaf base	Methanol	55	3
L–I-55-3	Leaves	Isopropanol	55	3
LB-I-55-3	Leaf base	Isopropanol	55	3
L–I-55-1	Leaves	Isopropanol	55	1
LB-I-55-1	Leaf base	Isopropanol	55	1
L –I-70-3	Leaves	Isopropanol	70	3
LB-I-70-3	Leaf base	Isopropanol	70	3

3.2.3. Identification of Cellulose and Carboxymethylcellulose

3.2.3.1. Organoleptic characteristic

After cellulose extraction was finished, each type of sample was examined for color, odor, and physical appearance.

3.2.3.2. Identification for cellulose

Cellulose identification tests were done according to USP guidelines. Twenty grams of zinc chloride and 6.5 g of potassium iodide were dissolved in 10.5 mL of distilled water. Then, 0.5 g of iodine was added to 2 g of the sample and it was shaken for 15 min. The sample was placed on a watch glass and dispersed in 2 ml of iodinated zinc chloride solution (USP, 2021).

3.2.3.3. Determination of percent yield of cellulose and CMC

The percent yield of extracted cellulose and CMC from *Phoenix dactylifera* L palm tree leaves and leaf base was calculated using the following formula as indicated in Equation 2 & 3 (Huang, 2017).

$$Yield\ of\ Cellulose\ (\%) = \frac{(\text{weight of dry cellulose reside(g)}) * 100}{\text{Weight of original sample residue fibers (g)}} \quad \text{Eq(2)}$$

$$\text{Yield of CMC (\%)} = \frac{(\text{Weight of CMC obtained (g)}) * 100}{\text{Weight of dried Cellulose used (g)}} \quad \text{Eq(3)}$$

3.2.3.4. Fatty and waxy matter

To determine the amount of extractives, solvent extraction was used (60 mL of acetone was used for every 1 g of dried biomass sample), and the temperature was maintained at 50 °C for two hours. The sample was then dried in an oven (105 °C –110 °C) until it reached a consistent weight. The amount of extractives is shown by the weight difference before and after the extraction (Mansor *et al.,* 2019).

3.2.3.5. Klason lignin

To determine the amount of lignin, each gram of the sample (extractive-free dried biomass) was mixed with 30 ml of 98% sulfuric acid. The sample was kept at room temperature for 24 h. It was boiled at 100 °C for 1 h. The mixture was filtered, and then the residue was washed until the sulfate ion in the filtrate was undetectable (by titrating a 10% barium chloride solution), followed by drying it to a consistent weight. The lignin content is expressed as a percentage of the residue's weight. Assuming that the only elements of the total biomass are extractives, hemicellulose, lignin, and cellulose, the quantity of cellulose is then determined by the difference (Yang *et al.,* 2006).

3.2.3.6. Hemicellulose Content

To determine the amount of hemicellulose, 1g of dried biomass without extractives was mixed with 150 mL of sodium hydroxide (0.5 M NaOH) for 3.5 h at 80 °C. Then, the sample was repeatedly washed with distilled water until it reached a neutral pH and dried to a constant weight. The difference between the sample weight before and after treatment was taken as the amount of hemicellulose (Yang *et al.,* 2006).

3.2.3.7. Water soluble components

To estimate the water-soluble components, the plant material was boiled in distilled water for 2 h on a hot plate, filtered, and then dried at 105 °C until a constant weight was obtained.

% Water Soluble Components = $(W_1/W_0)*100$……..…..…Eq(4)

where W_0 is the original weight of the sample (before treatment) and W_1 is the weight reduction (Mansor *et al.,* 2019).

3.2.3.8. Degree of substitutions for Carboxymethylcellulose

1 gram of Carboxymethylcellulose was weighed and added to a 250-mL beaker, followed by 50 mL of 95% ethanol, and stirred. Then, 5 mL of 2 M nitric acid was added, and the mixture was stirred for 10 min at room temperature. Using a magnetic hot plate, the mixture was brought to a boil for five minutes, stirred again for twenty minutes, and then allowed to settle. Following the solution's settling, the residue was cleaned with 100 millilitres of 95% ethanol to get rid of the salts and acid. After being cleaned with methanol and placed to a beaker, the precipitate was boiled to eliminate the alcohol. The precipitate-filled beaker was dried for three hours at 90 °C in the oven. (0.5 g perciptaed CMC) was weighed in a 250-ml Erlenmeyer flask, and 100 ml of distilled water was added and stirred. 25 ml of 0.5M sodium hydroxide were added and boiled for 20 min. Then, the heated solution was titrated with 0.3 M HCl by using phenolphthalein as an indicator to observe the color change from Mexican pink (dark pink) to colorless. The DS of CMC was calculated using the equations below (Pushpamalar *et al.,* 2006).

$$DS = \frac{0.162 \times A}{1 - 0.058 \times A} \quad \text{Eq (6)}$$

$$A = \frac{BC - DE}{F} \quad \text{Eq (7)}$$

where A is the milliequivalents of consumed HCl per gram of specimen; B is the volume of NaOH added; C is the molarity of NaOH; D is the volume of consumed HCl; and E is the molarity of HCl used; F is the CMC in grams; 162 is the molecular weight of the anhydroglucose unit, and 58 is the net increment in the anhydrous glucose unit for every substituted carboxymethyl group.

3.2.3.9. Determination of Moisture Content

One gram of CMC was placed on a pre-weighed petri dish and weighed. The petri dish was placed in an oven, and heated at 105 °C for 2 h. After being removed from the oven, its weight was determined, and drying was continued until a constant weight was obtained. The percentage of moisture was calculated as follows (ASTM, 2003).

$$Moisture\ (\%) = \frac{(\text{Mass loss on heating (g)}) * 100}{\text{Weight of Sample used (g)}} \quad \text{Eq(8)}$$

3.2.3.10. pH Determination

Using 100 ml of distilled water, two grams of CMC powder were manually shaken for 5 min. Using a pH meter (Phy-Ph-004, China), the pH of the supernatant liquid was measured. The mean value of the determinations made in triplicate was finally calculated.

3.2.3.11. Ash Value Determination

The ash value in the CMC was measured by taking 0.5 g of the dried sample into the dried crucible, and the sample was pre-ashed in a fume hood at 650 ^{o}C. When the sample ceased giving off smoke, it was heated to 600 °C in a muffle furnace and left for 2 h. The ash content was determined using the following equation once the sample had turned to ash (Yeasmin & Mondal 2015).

$$\text{Ash content (\%)} = \frac{(\text{wt.of ash}) * 100}{\text{wt.of sample}} \quad \text{Eq(9)}$$

3.2.4. Characterisation of Cellulose and Carboxymethylcellulose

3.2.4.1. Fourier-Transform Infrared (FTIR) spectroscopy studies

Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy (ATR-FTIR), supported by a system that can control instrument testing environment conditions (supply filtered, dried, and carbon monoxide-free air with relative humidity less than 20%), was used to conduct an infrared absorption identification test. With a wave number range of 400 to 4000 cm^{-1}, ATR FTIR (tensor II, broker Germany) was used to scan the FTIR spectra of the sample. For the FTIR scanning test, all sample types (pretreated raw material, extracted sample, and CMC) were evaluated. Each sample under test had its FTIR absorption spectra compared to a reference standard prepared concurrently.

3.2.4.2. X-ray diffraction (XRD)

The diffraction pattern of the cellulose and CMC powder was investigated using an X-ray diffractometer (XRD7000 X-ray diffractometer MAXima, SHIMADZU Corporation, Japan) at 40 KV to determine the crystalline or amorphous nature of cellulose and CMC.

The Segel or peak height method was simply used for the calculation of crystallinity index (CrI) based on the following equation (Karimi & Taherzadeh 2016).

$$CrI = 100 * \frac{(I200-IAM)}{I200} \quad \text{Eq(10)}$$

Where I_{200} represents the maximum intensity of diffraction of the peak (I_{200}, 2Θ= 22.7◦), while I_{AM} represents the amorphous material when the intensity is minimum between the 200 and 110 peaks (I_{AM}, 2Θ = 19◦).

3.2.4.3. Thermogravimetric analysis (TGA)

The thermal properties of cellulose and CMC were determined using a thermogravimetric analyzer (DTG-60H, SHIMADZU, Japan) for TGA. The samples were heated from room temperature to 700 ^{o}C with a scanning rate of 10 ^{o}C/ min under a nitrogen atmosphere (Deepa *et al*., 2011).

3.2.4.4. Environmental Scanning Electron Microscopy (ESEM)

The Morphological analysis of cellulose and CMC is commonly observed using scanning electron microscopy (SEM) under vacuum conditions and at a voltage of 20 kV. All images were taken at magnifications of 100 X, 600X (Haafiz *et al.,* 2013).

3.2.4.5. Excipient compatibility study

The compatibility of the prepared excipients (L-CMC, and LB-CMC) with the Metronidazole benzoate and other prepared excipients used during formulation was checked by preparing a 1:1 ratio with FTIR. During the compatibility study, the samples were stored at accelerated condition for 30 days (40°C±2°C/75%±5% RH) (Rignall, 2017).

3.2.5. Preparation of Metronidazole benzoate suspensions

The composition of the MBZ suspensions is given in Table 3. The suspensions are grouped into three groups: L-CMC (carboxyl methyl cellulose prepared from *Phoenix dactylifera* L palm tree leaves with DS of 0.889), LB-CMC (carboxyl methyl cellulose prepared from *Phoenix dactylifera* L palm tree leaf base with DS of 0.667), and C-CMC (commercial carboxyl methyl cellulose). Each group has four formulations (LCMC-E1-LCM-E4, LB-CMC-E1-LB-CMC-E4, and CC-CMC1-CC-CMC4). The letters L-CMC, LB-CMC, and CC-CMC indicate the type of suspending agent, while the numbers 1, 2, 3, and 4 represent 0.5, 1, 1.5 and 2% (w/v) concentrations, respectively, of the suspending agents.

The formulas listed in Table 3 were used to prepare suspension formulations that contained metronidazole benzoate. First, a smooth paste was formed using a mortar and pestle by triturating the specified amount of suspending agent and metronidazole benzoate with 10 ml of a solution that contained 15 g sucrose, 0.1 mL Tween 80, and 0.07 g of sodium saccharine. Then, with continuous trituration, 30 ml of a 70% sorbitol solution was added to the prepared paste. This was followed by the addition of the preservative solution (methyl and propylparaben in propylene glycol). Subsequently, the mixture created was put into a 125-mL amber-colored bottle, adjusted to 100 mL volume with distilled water, and shaken vigorously for 5 min (Rishabha *et al* ., 2010).

Table 3: Compositions of metronidazole benzoate suspension formulation.

Formulation ingredients	Composition
Metronidazole benzoate	4.00 (w/v)
Suspending agents	0.5,1,1.5 and 2% (w/v)
Methyl paraben	0.18 (% w/v)
Propyl paraben	0.02 (% w/v)
Propylene glycol	2 (% v/v)
Tween 80	0.05 (% v/v)
Sodium saccharine	0.07 (% w/v)
Sucrose	15 (% w/v)
Sorbitol	(70%, w/v) 30 ml
Distilled water	Qs 100 ml

3.2.6. Evaluation of metronidazole benzoate suspensions

3.2.6.1. Appearance and pH of the suspensions

Metronidazole suspension was re-dispersed by shaking. Then, color and homogeneity were visually examined (Yahaya *et al.* 2023). The pH of all developed suspensions was measured using a digital pH meter (Achor, and Aminu, 2023).

3.2.6.2. Flow rate

The flow rate (ηα in ml-1/s) of each suspension sample was determined by calculating the timerequired for flow through a 10 ml pipette (Mann *et al.,* 2007).

$$\text{Flow rate} = \frac{V}{t} \quad \text{.....Eq(11)}$$

V = volume of the sample in the pipette (in mL), t = time (in seconds) required for the 10 mL suspension to totally elute out of the pipette (Ayorinde & Odeniyi, 2017).

3.2.6.3. Construction of calibration curves

Linearity was evaluated in the range (0.0106, 0.0142, 0.0177, 0.0213, 0.0248, and 0.0284) μg mL^{-1} using MBZ standard stock solution (0.325967 μg mL^{-1}) in dissolution media. Linearity was estimated using linear regression analysis. All analyses were performed in triplicate.

3.2.6.4. Dissolution profile

The dissolution studies were carried out using a method described elsewhere (Zietsman *et al.,* 2007) which is based on the USP (2021) monograph for metronidazole tablets, with modification of the method to include apparatus II (Labindia analytical instrument, India). Paddle rotation speed was 100 RPM, the temperature of the apparatuses was adjusted to 37^0 + 0.5 and the dissolution medium used was 0.1N HCl (900 mL). A 5 ml sample equivalent with 201 mg MBZ was taken at 10, 20, 30, 45, and 60 min. The sample was withdrawn from the dissolution vessel using a syringe, filtered with filter paper to remove dissolved particle, and dissolution samples were measured at 232 nm using a UV spectrophotometer (All454601989 CD, Japan). The averages of six determinations were used.

3.2.6.5. Sedimentation volume

A 20 ml of each suspension formulation was placed in 25 mL graduated cylinder and allowed to stand at room temperature. The sedimentation volumes (%) of the formulations were recorded daily for seven days, and every week for a total of four weeks. The readings of the sedimentation volumes (%) were taken where the clear supernatant started to become cloudy upon descending from the top surface of the suspension. The sedimentation volume was calculated as follows (Kumar *et al.*, 2009).

$$sedimentation\ volumes = \frac{Ultimate\ sediment\ volumes * 100}{Inital\ volume} \quad \text{.....Eq(12)}$$

3.2.6.6. Redispersibility

A 20 mL sample of a suspension formulation was placed in a 25 mL measuring cylinder and allowed to settle over separate periods of a week and a month. To evaluate redispersibility, the cylinders were manually inverted 180 degrees on the seventh day and again after a month. The effectiveness of redistributing the sedimented metronidazole benzoate particles was measured by counting the number of complete rotations required to achieve a uniform suspension. The results provided are the averages from three separate measurements(Saeedi *et al.*, 2003).

3.2.6.7. Assay of metronidazole suspension

The concentration of total metronidazole benzoate in the suspensions was measured using the HPLC method, in accordance with BP 2021. 150 mL of methanol and 5 mL of each metronidazole benzoate suspension were combined, and 250 mL of distilled water was added after mixing. The mixture was centrifuged for 10 minutes at 1000 rpm. Methanol (60%) was used to dilute one to ten volumes. After that, these samples were subjected to triplicate HPLC analysis (HPLC, Shimadzu, Japan) (BP, 2021).

3.2.7. Stability of metronidazole suspension

Accelerated stability studies were conducted on the metronidazole suspensions containing (1%) CMC from leaves, leaf base, and CC-CMC under environmental conditions using International Conference on Harmonization (ICH) guidelines. The accelerated conditions were 40 ± 2°C and 75 ± 5% RH. Samples were collected at 0, 30, 60, and 90 days after storage and tested to detect changes such as pH, drug content, particle size and physical appearance in storage conditions, as defined in the ICH Guidelines (ICH, 2003).

3.2.7.1. Particle Size and Size Distribution

Particle size analysis was measured using a Malvern Mastersizer 2000 laser diffraction particle size analyzer (Malvern Instruments Ltd, Worcestershire, WR14 1XZ, UK). 500 mL distilled water was used to immerse the sampling. Background reading was done with the dispersing medium (distilled water). Then, a small amount of metronidazole suspension was dispersed into the soaking distilled water till an obscuration of 10-30 % was achieved. The mean particle size of samples was determined. Determinations were done in triplicates and average values with corresponding standard deviations were calculated (Ogaji & Hoag 2011).

3.2.7.2. Assay of metronidazole suspension

Using the HPLC procedure as outlined in BP 2021, the suspensions were tested for total metronidazole benzoate concentration. Each 5 mL metronidazole benzoate suspension was diluted with 150 mL of methanol. 250 mL of distilled water was then added while the mixture was still being mixed, and the mixture was centrifuged for 10 min at 1000 rpm. One volume was diluted to yield ten volumes using 60% methanol. The samples were subsequently subjected to triplicate HPLC analysis (HPLC, Shimadzu, Japan) (BP,2021).

3.2.7.3. pH determination of metronidazole suspension

Metronidazole suspension was re-dispersed by shaking. The pH of all prepared suspensions was measured using digital pH meter (Achor, and Aminu, 2023).

3.2.8. Statistical analysis

Three sets of experiments were carried out, and the results were shown as mean ± standard deviation (SD). OriginPro 9.6.5 (Origin Lab Corporation, MA, USA) and Minitab version 21.04 were used to analyse all of the data presented in this study, which were the averages of triplicate determinations. One-way Analysis of Variance (ANOVA), was used to compare the outcomes. To compare the variations in the MBZ suspensions' properties, the Tukey test was employed. P values less than or equal to 0.05 were deemed significant at the 95% confidence interval.

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4. Results and Discussion

4.1. Physico-Chemical Characterization of Cellulose and Carboxymethyl cellulose

4.1.1 Chemical composition of palm tree leaves and leaf base by products

The amounts of extractives, hemicellulose, and lignin in palm tree leaves and leaf bases are shown in Table 4.

Table 4: Chemical composition of untreated palm tree leaves and leaf base from *Phoenix dactylifera L* palm tree.

Plant part	Fatty and waxy matters contents	Lignin contents	Hemicellulose contents	Water soluble contents	Cellulose contents
Leave	10	17	22.3	8	36.7
Leave base	8	19	20	6	41.3

As seen in Table 4, palm tree leaves contain a higher amount of hemicellulose, water-soluble contents, and fatty and waxy matter, but a lower amount of lignin compared to palm leaf bases.

4.1.2. Percent Yield of Cellulose

During the preliminary study, six different pretreatment conditions at different concentrations and ratios were used for the isolation of cellulose from date palm tree leaves and leaf bases. Extraction condition E (stage 1): 10% NaOH Stage 2 (20% FA/20% ACC/7.5% H_20_2 (2:1:2); stage;3 (7.5% H_2O_2 in 10% NaOH) was the most effective one according to the yield and organoleptic property. Similar results were obtained by Gabriel *et al.*, (2021).

the type of extraction solvent, the period or duration of the extraction, and the extraction temperature, all have a major impact on the percent yield and purity of cellulose and CMC (Radotić and Mićić, 2016). In this study, the same cellulose and CMC methods and processes (as stated in the materials and methods section) were applied to all types of *Phoenix dactylifera* L palm tree leaves and leaf base parts. After completion of the steps of the extraction process, the

percent of cellulose yields on dry basis were found to be 36.7 ± 0.97 from palm tree (*Phoenix dactylifera* L) leaves and 41.3 ± 1.08 from leaf base following extraction condition E, respectively.

4.1.3. Organoleptic characterization

The organoleptic properties of the prepared cellulose from the leaves and leaf base of *Phoenix dactylifera* L palm tree samples fulfilled USP/NF specifications (USP 30/NF 25, 2007). Both the prepared cellulose from the leaves and leaf base were white, odorless, and the physical appearance of cellulose is fibrous, as shown in Figure 6 and Table 4.

Figure 6: Cellulose extracted from palm tree leaves, leaf base and commercial cellulose.

Table 5: Organoleptic Characteristics of cellulose from palm tree leave, leaf base and commercial cellulose.

Source	Color	Oder	Appearance
Leaves	White	Odorless	Fibrous
Leaf base	White	Odorless	Fibrous
Commercial cellulose	White	Odorless	Fibrous

4.1.4. Identification for cellulose

The result of the identification test for the sample was in agreement with USP 30/NF 25 (2007) specifications. The cellulose extracted from palm tree leaves and leaf base with an iodinated zinc chloride solution turned to violet-blue color, confirming the presence of cellulose in the sample as shown in Figure 7 below. According to USP 30/NF 25 (2007), there must be violet-blue color in the iodinated zinc chloride solution.

Figure 7: Identification test result with iodinated zinc chloride for Cellulose extracted from *Phoenix dactylifera* L leave (left) and leaf base (right),

4.1.5. Chemical composition of palm tree leaves and leaf base by products

The amounts of extractives, hemicellulose, and lignin in palm tree leaves and leaf bases are shown in Table 5.

Table 5: Chemical composition of untreated palm tree leaves and leaf base from *Phoenix dactylifera L* palm tree.

Plant part	Fatty and waxy matters contents	Lignin contents	Hemicellulose contents	Water soluble contents	Cellulose contents
Leave	10	17	22.3	8	36.7
Leave base	8	19	20	6	41.3

4.1.6. Ash value, loss on drying pH of CMC

Inorganic impurities/ash value, loss on drying, and pH value of CMC from *Phoenix dactylifera* L palm tree leaves and leaf base were determined as per the USP method of analysis. As it is shown in Table 6, the inorganic impurities/ash value, loss on drying, and pH value of CMC from *Phoenix dactylifera* L palm tree leaves were found to be within the USP acceptance. the ash value (residue on ignition) for CMC isolated from the leaf base was found to be relatively higher

due to the physical rigidity or intact nature of the leaf base parts of *Phoenix dactylifera* L, resulting in difficulty in removing the lignin and hemicellulose parts of the leaf base (USP-NF 2021).

Table 6: Some physico-chemical properties of L-CMC (Carboxymethyl cellulose extracted from Phoenix dactylifera L tree leave), LB-CMC (Carboxymethyl cellulose extracted from Phoenix dactylifera L Leaf base), and C-CMC (Commercial Carboxymethyl cellulose).

Physicochemical test parameter	**Source of CMC and test results**			**USP– NF(2021) Acceptance Criteria**
	From leave	**From leave base**	**C-CMC**	
Ash Value (%)	0.045	0.052	0.04	Less than 0.1 %
pH value	6.849 ± 0.03	6.964 ± 0.02	6.85 ± 0.01	6.5-8.5
Loss on Drying (%)	6.9	7.8	6.3	Less than 8.0%

USP– NF: united states pharmacopeia – National formulary

Ash, pH, and loss on drying of L-CMC, LB-CMC, and CC-CMC were performed and are presented in Table 6. All those values were within the USP/NF specification (USP-NF, 2021).

4.1. 7. Properties of Carboxymethylcellulose

CMC was prepared from the celluloses previously extracted from the *Phoenix dactylifera* L palm tree leaves and leaf base by products, following the two steps of carboxymethylation: first, alkalization by NaOH, then etherification using MCA under heterogeneous conditions (Yeasmin & Mondal 2015). Alkalization is carried out using NaOH to activate OH groups on cellulose molecules and function as developers, while carboxymethylation is accomplished by adding sodium monochloroacetate (Futeri, 2016). In the alkalization step, native cellulose's crystalline structure is destroyed to create amorphous alkalized cellulose (Cell-O-Na+), which allows MCA to permeate more readily and improve the carboxymethylation process (Wenehenubun *et al.*, 2015). Furthermore, the influence of reaction time, reaction temperature, and types of reaction medium on DS was investigated in the preliminary work.

The as-obtained CMC was a free-flowing, tasteless, odorless, and white to almost white (Figure 8) granular powder. The CMC samples meet the requirements given in pharmacopoeias, being soluble in water and forming a very viscous solution (BP, 2022b).

The average number of substituents per AGU, or cellulose monomer unit, is known as the DS, and it represents the quantity of carboxymethyl group formed. The DS is between zero and three since each AGU has three hydroxyl groups at carbon numbers 2, 3, and 6 (Wahyuni *et al.*, 2019). The CMC derived from palm tree leaves had greater DS values under the same carboxymethylation circumstances than the CMC derived from palm tree leaf bases under all examined reaction conditions, suggesting that origin influences the DS (Table 7).

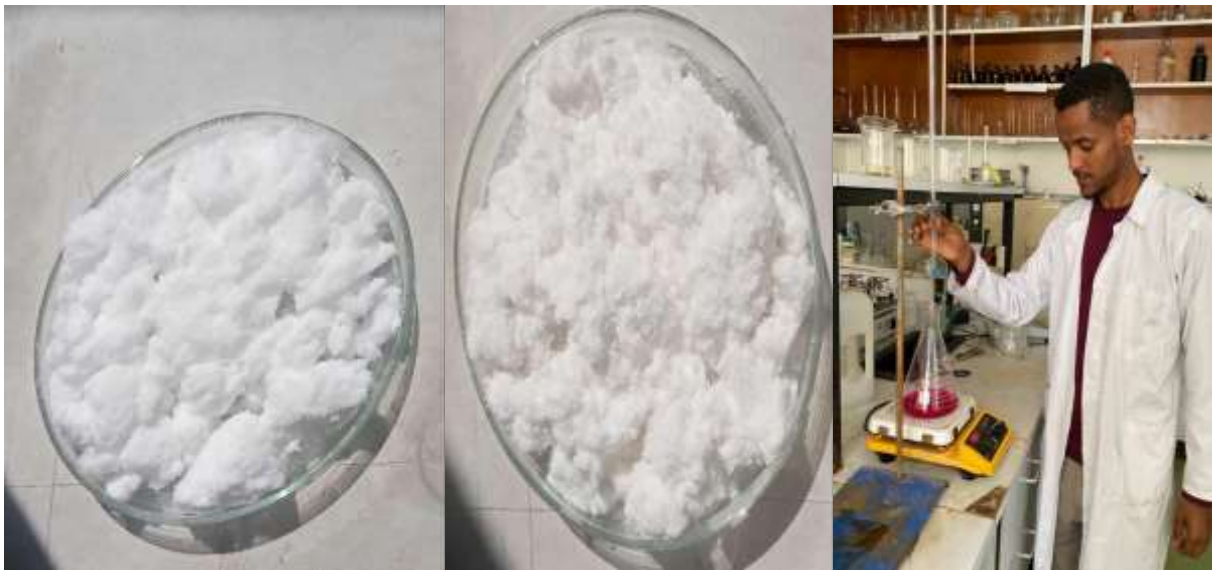


Figure 8: L-CMC (Carboxymethyl cellulose extracted from *Phoenix dactylifera* L tree leave), LB-CMC (Carboxymethyl cellulose extracted from *Phoenix dactylifera* L Leaf base), and procedure for determination DS of CMC (from left to the right).

The highest DS (0.889) was obtained for the palm tree leaf when the reactor content was run at 55 °C for 3 h using ISPA as reaction medium (LB-I-55-3); on the other hand, the least DS (0.179) was obtained for the palm tree leaf base in methanol as reaction medium (LB-M-55-3), which is 0.179.

The yield of CMC ranged from 0.889 $\pm$ 0.003 g/g (for L-CMC) to 0.179 $\pm$ 0.001 (for LB-CMC) based on dry weight conditions as indicated in Table 7. The DS as well as % yield of CMC products were dependent on the source of cellulose at similar carboxymethylation condition.

Table 7: Reaction condition used for carboxyl methylation of palm tree leaves and leave base and the resulting DS and yield.

SN	Reaction Condition	Cellulose source	DS	Yield (g/g)
1	L –M-55-3	Leaf	0.290 ± 0.008	1.296 ± 0.036
2	LB-M-55-3	Leaf base	0.179 ± 0.001	1.281 ± 0.026
3	L –I-55-3	Leaf	0.889 ± 0.003	1.447 ± 0.048
4	LB-I-55-3	Leaf base	0.667 ± 0.018	1.365 ± 0.054
5	L–I-55-1	Leaf	0.334 + 0.003	1.242 ± 0.012
6	LB-I-55-1	Leaf base	0.311+0.011	1.281 ± 0.020
7	L –I-70-3	Leaf	0.456+0.008	1.334 ± 0.060
8	LB-I-70-3	Leaf base	0.433+0.009	1.342 ± 0.042

Table 7 indicates that the selection of organic solvent had a significant impact on DS as well. This may be attributed to ISPA's superior capacity to dissolve the etherifying agent and increase cellulose swelling and viscosity in comparison to methanol. Moreover, DS increased with the increase in reaction time. The increase in the reaction time from 1 h to 3 h resulted in an enhanced period of contact between the etherifying reagent and the cellulose molecules. It is also reasonable that longer reaction times enhance cellulose swelling and ultimately improve the homogeneity of the reactants. However, in other studies, no remarkable increases were observed in DS after 3 h of reaction time (Lawal *et al.,* 2008).

The maximum DS (0.889) was achieved at 55 °C. The DS was higher because of the high swelling ability, which enhances the diffusion and absorption abilities of into cellulose fibers at 55 °C. Unfortunately, the thermal breakdown of carboxymethyl cellulose at temperatures greater than 55 °C confers poorer DS. A similar trend of carboxymethylation of cellulose has been observed from previous work on different materials (Tijsen *et al.,* 2001).

The cellulose's capacity to swell may be the cause of the increase in DS with time. By improving the contact time between etherifying agents and cellulose, MCA in the carboxymethylation reaction might diffuse and absorb over a longer reaction period (Yeasmin & Mondal, 2015).

The CMC was modified by varying the reaction parameters to enhance the carboxymethylation reaction of palm tree plant parts (leaves and leaf base) extracted from cellulose to get a higher value of DS. Since the industrial application of CMC is based on its DS value, DS is the most significant quality indicator of the synthesized CMC (Haleem *et al.,* 2014). The CMC prepared from modified palm tree leaves registered a DS value of 0.889 which was higher than other CMC studies prepared from wheat straw (DS= 0.789) (Li *et al.,* 2019), Eucalyptus nitens (DS= 0.32) (Yáñez *et al.,* 2018), sugarcane bagasse (DS= 0.73) and palm kernel cake (DS= 0.37) (Huang et al. 2017).

Another study showed that low DS CMC (< 0.40) was insoluble, while CMC with DS higher than 0.4 was soluble in water (Yeasmin & Mondal, 2015). As a result we can use as suspending agents in metronidazole suspension.

4.1.8. FTIR spectroscopic properties

Infrared spectroscopy is a pharmacopoeia technique of priority for identification tests of organic compounds. It is a very efficient and effective technique. The main goal of the FTIR spectroscopy test was to identify or determine the functional groups of the cellulose and CMC. Lower (500–1700 cm-^{1}) and higher (2800-3500 cm^{-1}) IR-spectral areas are typically regarded as being crucial for characterizing cellulose and CMC (Mohamad *et al.,* 2013).

For comparison, chemical functionality tests were conducted on both raw palm tree leaves and leaf base powders, as well as the extracted celluloses and modified CMCs. The FTIR spectra of commercial cellulose, and the leaves and leaf base extracted cellulose of the *Phoenix dactylifera* L palm tree (recorded in the range of 4500–400 cm^{-1}) are shown in Figures 9 and 10, respectively. The similarities between the raw plant parts, extracted cellulose, and commercial cellulose, except absorbed water in the case of the raw plant parts, indicate that the samples have comparable chemical compositions. It is possible that the absorption band at 1610 cm^{-1} in the raw palm tree leaves and leaf base (Figure 9) is attributable to the absorbed water's bending mode (Sun *et al*. 2005).

The C=C aromatic skeletal vibrations, which are typical of lignin, are frequently represented by two peaks at 1509-1609 cm^{-1} and 1433 cm^{-1}, respectively. Since the cellulose spectrum lacks the recognizable bands of lignin, it is possible to claim that the polymer has been completely removed by chemical treatments. The absence of peaks at 1730 cm-1, which are attributable to the acetyl and uronic ester groups of the hemicelluloses or the ester linkage of carboxylic groups of the ferulic and p-coumaric acids of lignin and/or hemicelluloses, supports the purity of separated cellulose even further (Sun *et al.*, 2005).

All samples exhibited broad band between 3150 $cm^{-1,}$ and 3400 cm^{-1} on FTIR spectra due to O-H stretching vibration peaks as shown in Figures 9 & 10. The absorption bands near 2852 cm^{-1} and 2923 cm^{-1}, comes from the stretching vibrations of C-H_2 that are symmetric and asymmetric, respectively. The band at 1023 cm^{-1} is due to C-O stretching vibrations for the raw palm tree sample (leaves and leaf base), extracted as well as commercial cellulose is seen in Figure 9 (Alemdar & Sain, 2008). Distinct FTIR spectra of cellulose extracted from the leaves and leaf base of *Phoenix dactylifera* L palm tree compared to commercial cellulose (as a reference standard) as presented in Figure 10.

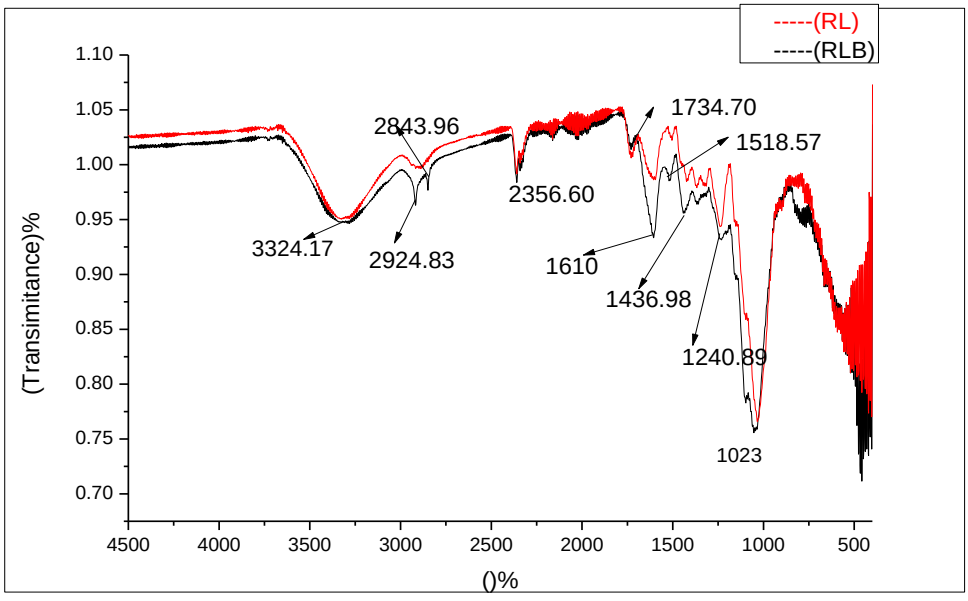


Figure 9: FTIR result for raw palm leaves (RL) powder and raw palm leaf base (RLB) powder.

Untreated plant byproducts displayed characteristic peaks around 1734 cm^{-1}, 1518 cm^{-1}, and 1240 cm^{-1}, in contrast to the recovered cellulose spectra. The acetyl and uronic ester groups of

hemicellulose are responsible for the peak of about 1734 cm^{-1}, which denotes the connections between ferulic acid, p-coumaric acid, or (p-) hydroxycinnamic acids and lignin. The lignin functional groups, such as aromatic rings, are indicated by the bands about 1518 cm^{-1}, and 1240 cm^{-1}. The absence of the lignin's distinctive bands (1518, 1240 cm^{-1}) in the spectra of the isolated celluloses suggests that lignin was removed from the byproducts. Various study groups reported similar results as well (Abdel-Halim, 2014).

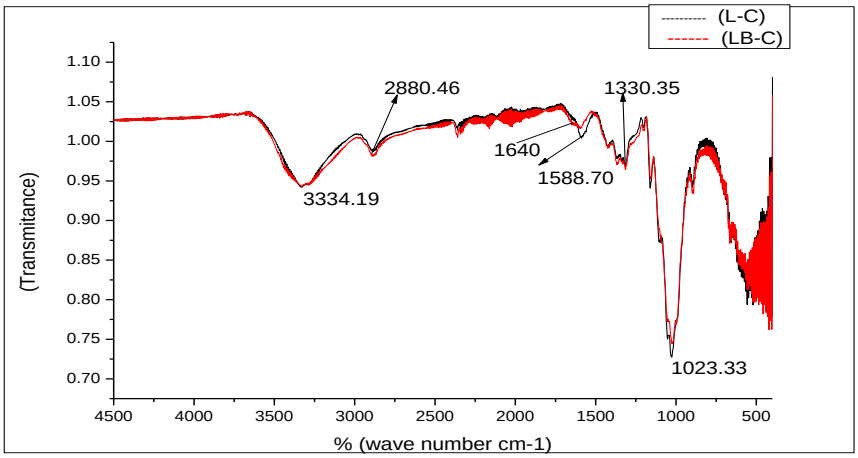


Figure 10: FTIR of extracted cellulose from palm tree leaves (L-C) and palm tree leave base (LB-C).

According to the FTIR spectra comparison, vibrational band assignment shown in the Figure 9, 10 & 11, the FTIR identification test for each type of cellulose obtained from palm tree parts (leave & leaf base), and commercial cellulose confirms to be comparable to one another. The broad absorption band observed at 3324 cm^{-1} is caused by the stretching vibration of C-O-C in the main backbone of the skeletal group. The transmittance peaks around 3324 cm^{-1}, 2924 cm^{-1}, 1610 cm^{-1}, and 1320 cm^{-1} are associated with the properties of pure cellulose, according to the extracted cellulose and commercial cellulose spectra. It shares chemical properties with commercial cellulose as well as other compounds. The FTIR spectra patterns of all the extracted cellulose samples were strikingly similar, with the commercial cellulose showing that the combined extraction condition did not affect the chemical functioning (Gabriel *et al.*, 2022).

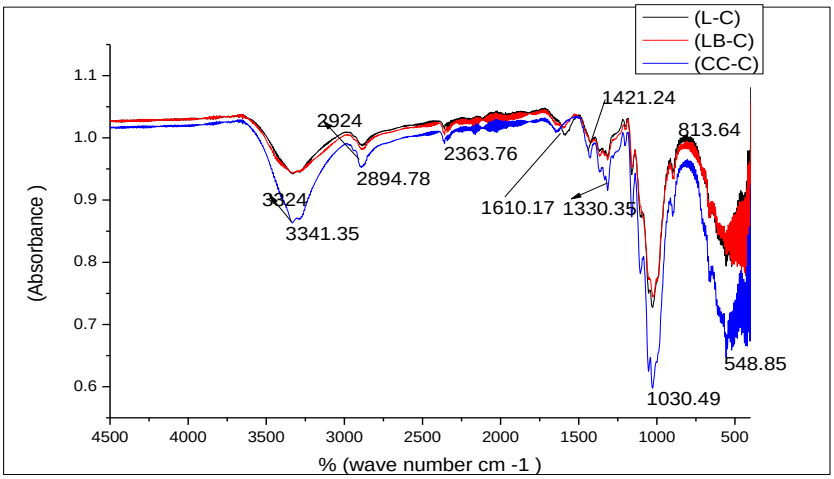


Figure 11: FTIR results for extracted cellulose from (L-C) palm tree leaves, (LB-C) leave base and (CC-C) commercial cellulose, respectively.

FTIR spectra for each type of cellulose extracted from palm tree leaves and leaf base in comparison with the commercial cellulose are presented in Figure 11. This indicates that the FTIR spectra of cellulose and commercial cellulose were found to be similar. All extracted cellulose and commercial cellulose FTIR test results confirm that all types of cellulose and commercial cellulose were found to be similar in their chemical nature, and the extraction treatment and process were found to be effective without affecting the chemical structure and nature of cellulose fragments of the lignocellulose materials.

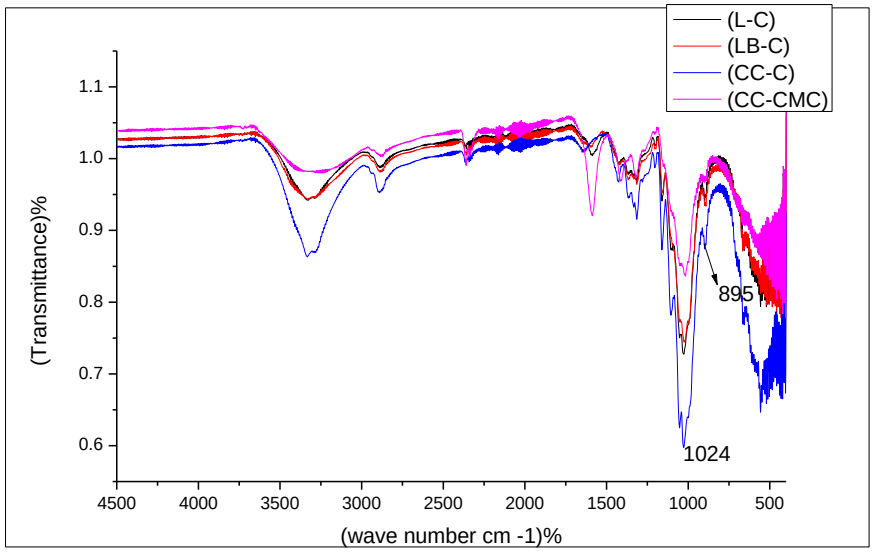


Figure 12: FTIR result for extracted cellulose from (L-C) palm tree leaves, (LB-C) leaf base, (CC-C) commercial cellulose, and (CC-CMC) commercial CMC, respectively.

The band at 1024 cm^{-1} is detected for cellulose and CMC due to vibrations of the C-O molecule. All of the samples also exhibit a faint band at 895 cm^{-1} for the rocking vibrations caused by C-H bonds, which are unique to the glucoside connections between glucose units in cellulose (Alemdar & Sain, 2008).

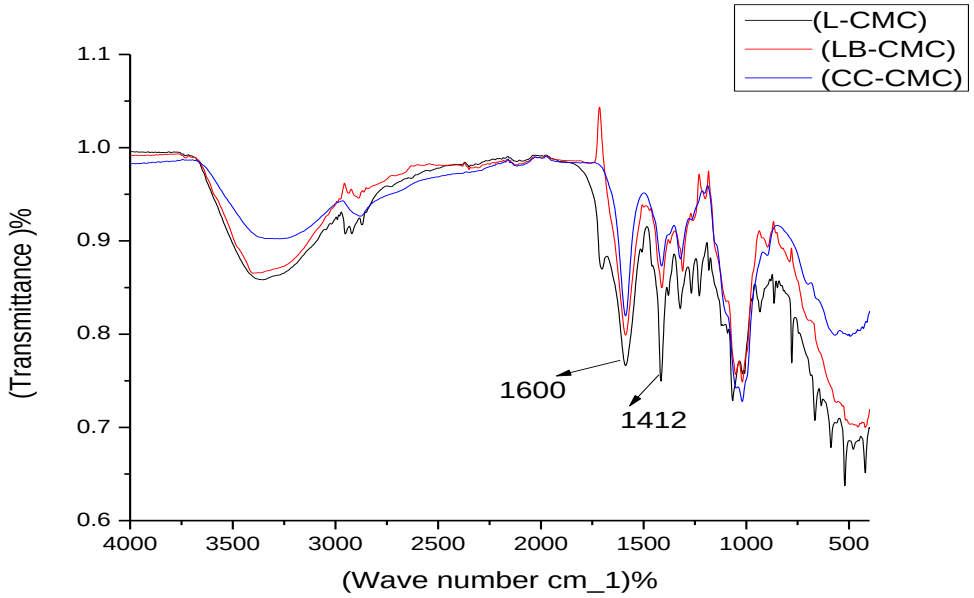


Figure 13: FTIR spectra of modified CMC from the (L-CMC) palm tree leaves and (LB-CMC) leaf base, and Commercial CMC (CC-CMC).

All the extracted cellulose as well as the modified CMC exhibited peaks in the range of 2800–2900 cm^{-1} and 3200 –3400 cm^{-1} which are related to the stretching vibrations of the CH groups stretching within each glucose unit and the OH of the polyhydroxylated saccharide backbone, respectively (Chumee & Seeburin, 2014 Abouloula *et al.*, 2018). Additionally, it was previously reported that the presence of peaks in the range of 1590-1640 cm^{-1} and 1390-1450 cm^{-1}, which correspond to the COO and CH_2 absorption bands, respectively, proved the presence of carboxymethyl substituents in CMC as shown in figure 13 (Candido & Gonçalves, 2016). Following etherification, there is a drop in the strength of the absorption band about 3335 cm^{-1} as a result of the conversion of cellulose I to II, a notable loss in crystallinity, and/or the production of amorphous components as a result of the weakening of hydrogen bonds between cellulose chains (Demesa, A.G., 2018).

4.1.9. Crystallinity analyses

X-ray diffraction analysis was done to identify the crystalline and amorphous natures of cellulose and CMC (Oun & Rhim, 2015). The diffraction pattern of crystalline cellulose exhibits strong signals with sharp peaks, whereas the amorphous (non-crystalline) component is characterized by weaker and broader signals (Karimi & Taherzadeh, 2016).

The amorphous amount is shown by the background, and the crystalline amount is represented by the peaks. The crystalline composition was eliminated throughout the modification procedure of L-CMC and LB-CMC, as demonstrated by the diffraction patterns. It was notable that the cellulose was semi-crystalline in nature (Parid *et al.*, 2018). All of the characteristic peaks of the original cellulose nearly disappeared and were converted into an amorphous phase (Kinate & Cornelius, 2019), and 47.7% (Parid *et al*., 2018).

Table 8: X-ray diffraction pattern of cellulose, and Carboxymethyl cellulose.

Source of polymer	CrI (%)
CC-Cellulose	64.836
L-Cellulose	63.616
LB-Cellulose	61.374

Because of the cellulose's altered nature during isolation, which changed it from crystalline to amorphous, the crystallinity of the cellulose declined following the alkaline pre-treatment and bleaching process (Candido & Gonçalves, 2019). The diffraction patterns of CMC exhibited destruction in the crystalline structure of the original cellulose. All the characteristic peaks of cellulose (CC-Cellulose, L-Cellulose, and LB-Cellulose with CrI 64.836, 63.616, and 61.374 respectively) had almost disappeared and transformed into an amorphous phase after carboxymethylation. The amorphous phase was obtained in the synthesized L-CMC and LB-CMC, as was the case with commercial CMC. Since the higher DS of CMC decreased the crystallinity, this may be the result of the etherification reaction of CMC expanding the breaking of hydrogen bonds at the hydroxyl group of cellulose with sodium monochloro acetic acid (Palamae *et al.*, 2017). Since reduced crystallinity indicates higher solubility, CMC has superior solubility as a result. Cellulose molecules are immersed in an alkaline solution during the carboxymethylation process. The cellulose granules' expansion puts strain on the nearby cellulose molecules' crystals, which tends to deform them. Their crystalline structure breaks up,

and their double-helical area uncoils or dissociates as a result of further expansion (Fang *et al.*, 2002).

In comparison to L-CMC, the results show that LB-CMC has the most ordered cellulose structure. In addition to increasing crystallinity, this may result in stronger hydrogen bonds between adjacent cellulose chains, packing the cellulose structure more densely.

Figure 14 shows the XRD patterns of cellulose extracted from the palm tree leaves and leaf base. The cellulose fibers showed the typical characteristic peaks around 2θ values of 15.5°, 22.5°, and 34.5° (Veeramachineni *et al.,* 2016). The XRD peaks of the modified CMC from palm tree leaves and leaf base samples showed a broad and typical diffraction signal around 2θ = 20.5°, followed by other strong peaks around 29.5° and 32° (Basu *et al.,* 2018).

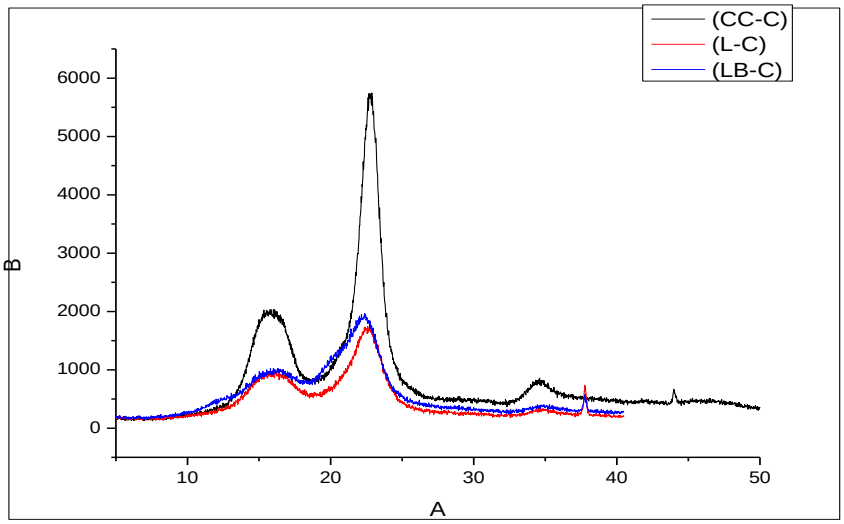


Figure 14: XRD results for (CC-C) commercial cellulose, (C-L) cellulose extracted from leaves of palm tree, and respectively (C-LB) cellulose extracted from leaf base of palm tree.

The modified CMC samples had peaks of lower intensity than the cellulose precursor samples. This is most likely caused by swelling that occurs before the carboxymethylation process, as well as the damage that alkalization causes to the crystalline structure of cellulose and the breaking of hydrogen bonds (Tuan Mohamood *et al.,* 2021).

As the DS increases, the crystallinity of CMC diminishes. This phenomenon may be caused by hydrogen bonds breaking or broadening as a result of carboxymethyl substitution at the hydroxyl

groups in cellulose. The crystallinity of cellulose was associated with the inter- and intra-molecular hydrogen bonds of cellulose (Rachtanapun & Suriyatem, 2009).

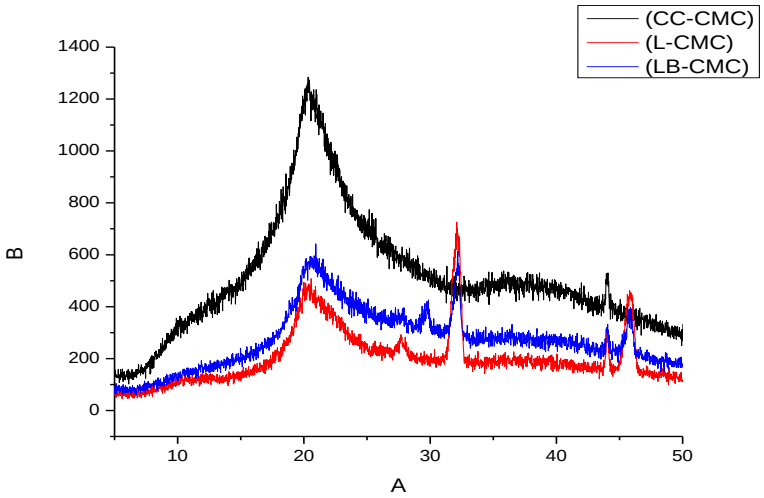


Figure 15: XRD results for Commercial CMC (CC-CMC), Leaves CMC (L-CMC), and leaf base CMC (LB-CMC).

4.1.10. Thermal stability analysis

Each type of cellulose and modified CMC from *Phoenix dactylifera* L palm tree leaves and leaf base were tested for their thermal properties using thermal analysis in comparison with commercial cellulose and commercial CMC, respectively, as standards.

The thermo gravimetric analysis (TGA) provides a method for the determination of mass change in the polymer as a function of time and temperature. These methods take into account processes that happen at the materials' molecular level (Princi *et al.*, 2005). The thermal analysis of cellulose and CMC is important to determine their future applications. TGA are commonly used methods to investigate the thermal and degradation properties of cellulose and CMC samples (Trache *et al.*, 2016). The thermal studies of cellulose and CMC by TGA are presented in Figure 16.

The cellulose samples presented three weight loss regions, as shown in Figure 16. The initial weight loss (6.72 to 13.6 %) in the region (26.19 to 147 °C) is mainly due to moisture evaporation and the loss of water adsorbed to the plant materials. The second curve indicates the dehydration, decarboxylation, depolymerization, and decomposition of glycosyl units in cellulose in the range of 179–347 ^{o}C, followed by the char residue formation in the range of 350–700 ^{o}C (Trache *et al.*, 2016).

The first stage of weight loss in the TGA curve was noted in the temperature range of 26 ^{0}C-92 ^{o} C, 26 ^{0} C-75 ^{o} C, and 26 ^{0}C -147 ^{O}C, 28 ^{0}C-82 ^{O}C, 28 ^{0}C - 82 ^{O}C, and 28-105 ^{O}C for L-C, LB-C, CC-C, L-CMC, LB-CMC and CC-CMC respectively, with corresponding weight loss of 13.17 %, 13.6 %, 6.72 %, 9.69 %, 9.82 % and 9.42 %. The evaporation of loosely bound water on the surface of the samples is responsible for the presence of this endothermic peak on thermograms of cellulosic and modified CMC materials (Nwajiobi *et al.*, 2019).

The second decomposition peak of L-C, LB-C, CC-C, L-CMC, LB-CMC, and CC-CMC appeared at 162 ^{o}C-313 ^{o}C, 152 ^{o}C-309 ^{o}C, 150 ^{o}C-347^{o}C, 179^{o}C-309^{o}C, 164 ^{o}C-311 ^{o}C, and 241 ^{o}C-313 ^{o}C, respectively. These temperature ranges demonstrated polymer depolymerization, decarboxylation, and breakdown (Kian *et al.*, 2017). Low to moderate temperatures cause the degradation of cellulosic materials. Early decomposition of hemicelluloses begins below 400 ◦C followed by pyrolysis of lignin (Haafiz et al., 2014). According to this finding, cellulose with higher crystallinity showed greater heat stability. This may be due to the absence of hemicellulose and lignin, as well as the removal of the amorphous part present in the cellulose during the acid hydrolysis process (Zheng *et al.*, 2018).

50% weight loss decomposition of cellulose and CMC occurred at L-C (309.5 ^{o}C), LB-C (288.7 ^{o}C), CC-C (328.3 ^{o}C), L-CMC (311.3 ^{o}C), LB-CMC (311.3 ^{o}C), and CC-CMC (294.3 ^{o}C). The significant elimination of less stable hemicellulose and lignin is most likely the cause of pure cellulose's and CMC's comparatively enhanced heat stability (Sun *et al.*, 2004).

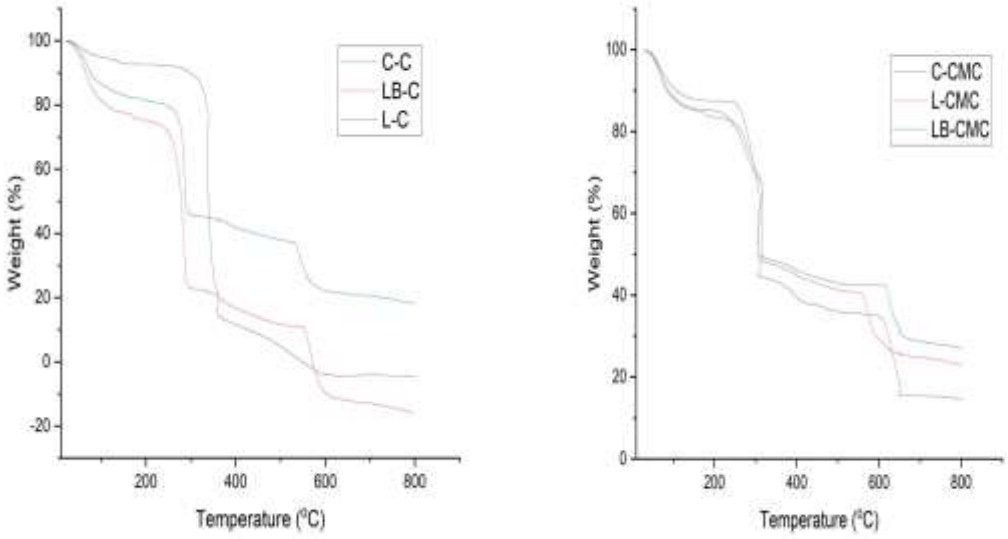


Figure 16: Thermogravimetric analysis (TGA) of; Cellulose extracted from *Phoenix dactylifera* L tree leave (L-C), Cellulose extracted from *Phoenix dactylifera* L leave base (LB-C), Commercial cellulose (CC-C) (the left side), Carboxymethyl cellulose extracted from *Phoenix dactylifera* L tree leave (L-CMC), Carboxymethyl cellulose extracted from *Phoenix dactylifera* L Leaf base(LB-CMC), and Commercial Carboxymethyl cellulose (CC-CMC) (the right side).

4.1.11. Morphological Analysis

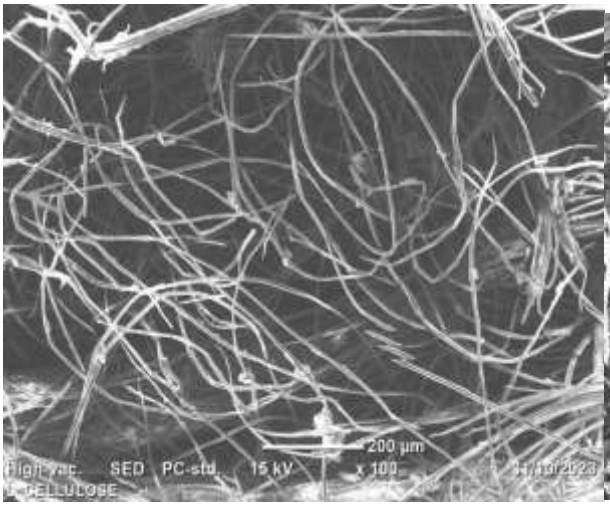
Morphological analysis of extracted cellulose and modified CMC from *Phoenix dactylifera* L palm tree (leaf, and leaf base) was done by Scanning Electron Microscopy (SEM) with 100X and 600X magnification power. SEM image analysis results with different Magnification power are shown in Figures 17 and 18, respectively.

The molecular, supramolecular, and morphology of cellulose structures determine its mechanical and physical characteristics (De Freitas *et al.*, 2017). Particle morphology is an important property in the characterization and identification of pharmaceutical excipients.

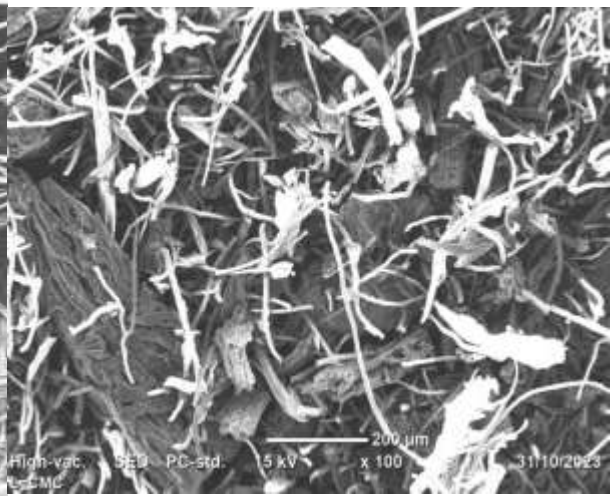
Because of the alkaline and bleaching processes employed in the cellulose extraction procedure, the cellulose extracted from the palm tree leaves and the leaf base had a rough outer surface with twisted and ruptured fibers (Tasaso, 2015). In comparison to cellulose, the modified CMC made from palm tree leaves and leaf bases had a somewhat lower roughness. This outcome was brought about by a shift in the crystallinity of cellulose, which created an electrostatic repulsion

between the fibres and gave the etherifying agent access to the cellulose polymer chain (Yáñez *et al.*, 2018).

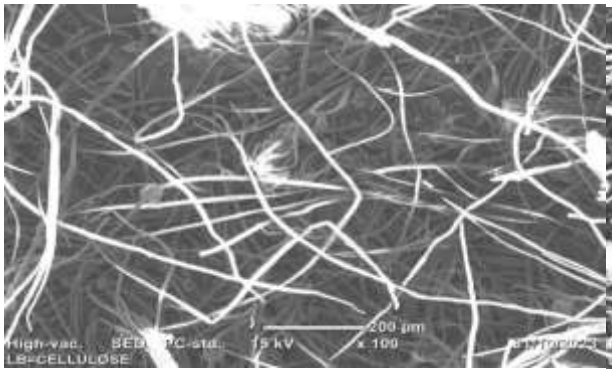
The surface roughness between cellulose and CMC was slightly different. This was caused by the cellulose being extracted and bleached with strong chemicals at high temperatures before being used in the carboxymethylation process. Generally speaking, modified CMCs were smoother than the extracted cellulose. This result was caused because cellulose crystallinity was changed due to the etherifying agent having higher access to the cellulose molecules for the carboxymethylation process (Lawal *et al.*, 2008).



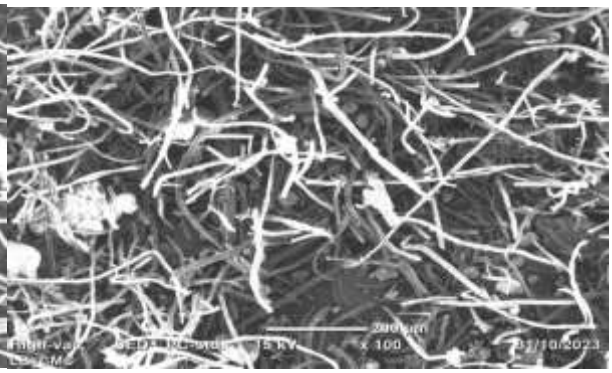
L-C



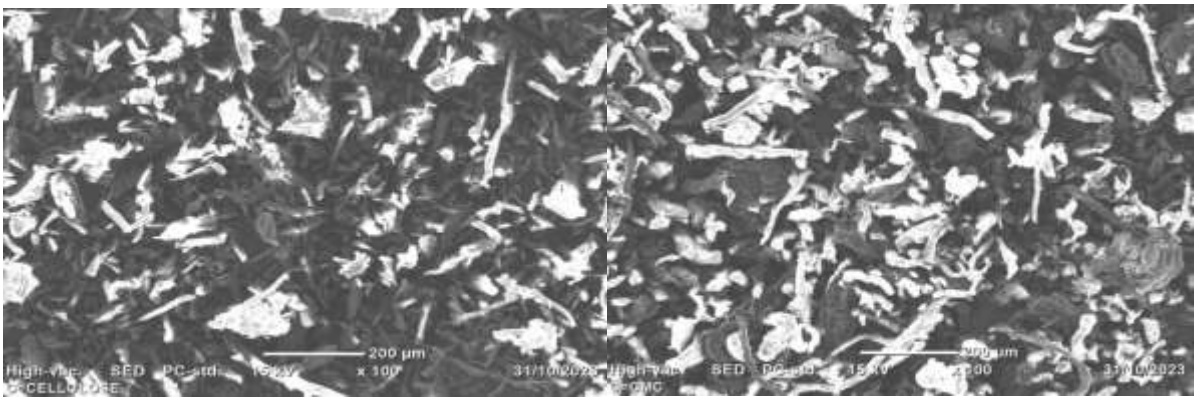
L-CMC



LB-C

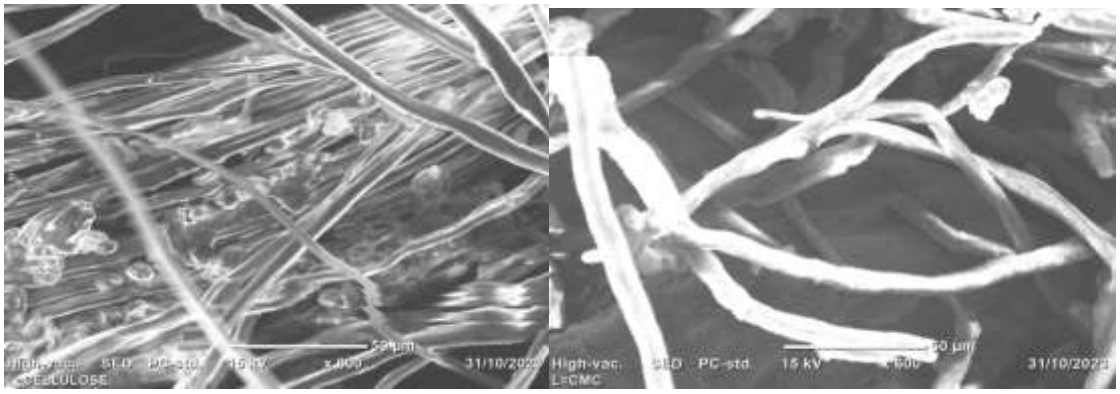


LB-CMC

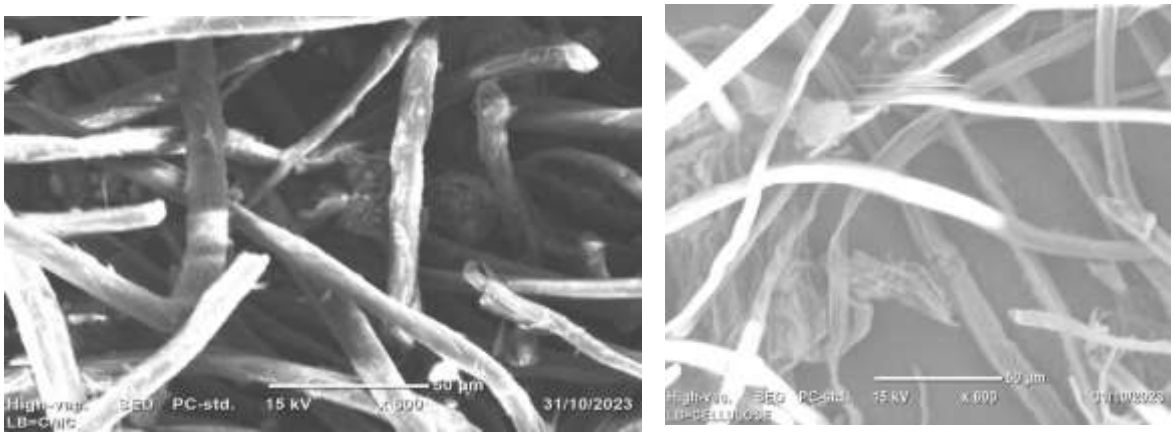


CC-C CC-CMC

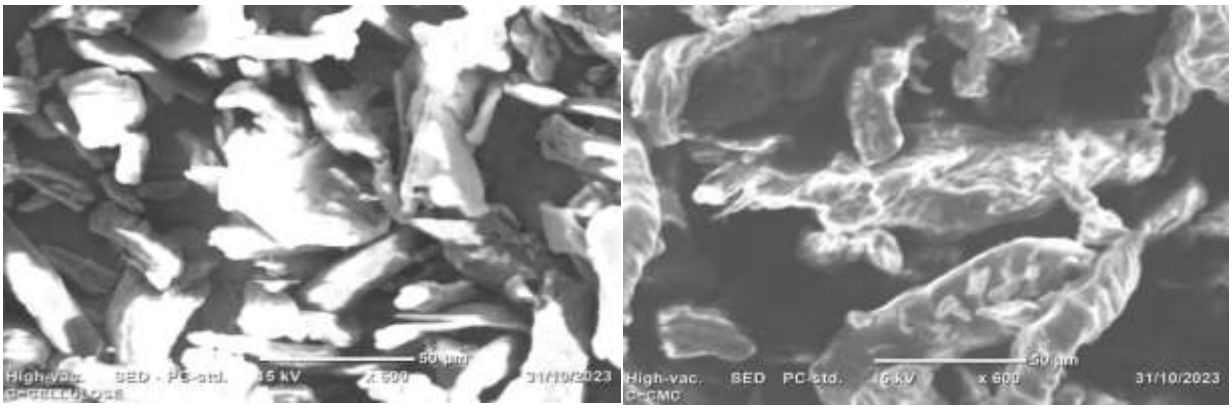
Figure 17: 100X SEM images of Cellulose extracted from *Phoenix dactylifera* L tree leave (L-C), Cellulose extracted from Phoenix dactylifera L leave base (LB-C), Commercial cellulose(CC-C), Carboxymethyl cellulose extracted from *Phoenix dactylifera* L tree leave (L-CMC), Carboxymethyl cellulose extracted from *Phoenix dactylifera* L Leaf base(LB-CMC), and Commercial Carboxymethyl cellulose (CC-CMC), respectively.



L-C L-CMC



LB-C LB-CMC



CC-C CC-CMC

Figure 18: 600X SEM images of Cellulose extracted from *Phoenix dactylifera* L tree leave (L-C), Cellulose extracted from *Phoenix dactylifera* L leave base (LB-C), Commercial cellulose(CC-C), Carboxymethyl cellulose extracted from *Phoenix dactylifera* L tree leave (L-CMC), Carboxymethyl cellulose extracted from *Phoenix dactylifera* L Leaf base(LB-CMC), and Commercial Carboxymethyl cellulose (CC-CMC), respectively.

4.1.12. Excipient compatibility study

The purpose of drug-excipient compatibility study is to explain, as quickly as possible, real and possible interactions between potential formulation excipients and the API. This is an important risk reduction exercise early in formulation development.

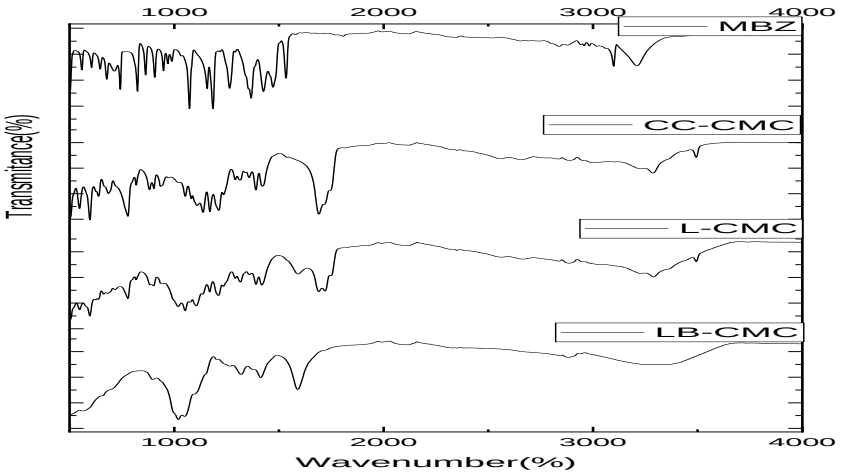


Figure 19: FTIR result for Metronidazole benzoate (MBZ), Carboxymethyl cellulose extracted from Phoenix dactylifera L tree leave (L-CMC), Carboxymethyl cellulose extracted from

Phoenix dactylifera L Leaf base (LB-CMC), and Commercial Carboxymethyl cellulose (CC-CMC) respectively from top to the bottom.

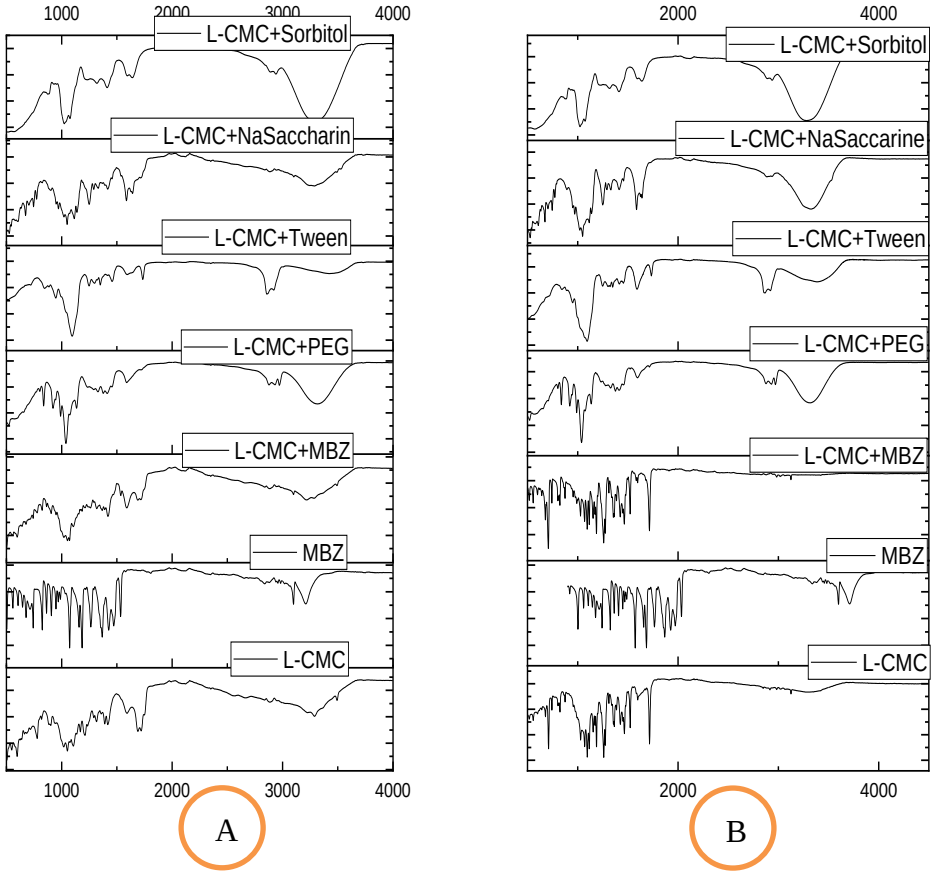


Figure 20: FTIR results of Compatibility test for L-CMC at 0 (A) and 1 (B) month.

In the spectrum of CMC, there are peaks of different intensities at 2800–2900 cm^{-1} and 3200–3400 cm^{-1} which, respectively, are related to the stretching vibrations of the CH groups stretching within each glucose unit and the OH of the polyhydroxylated saccharide backbone. Additionally, the presence of peaks in the range of 1590-1640 cm^{-1} and 1390-1450 cm^{-1}, which correspond to the COO and CH_2 absorption bands, respectively, proved the presence of carboxymethyl substituents in CMC (Figure 20 and 21).

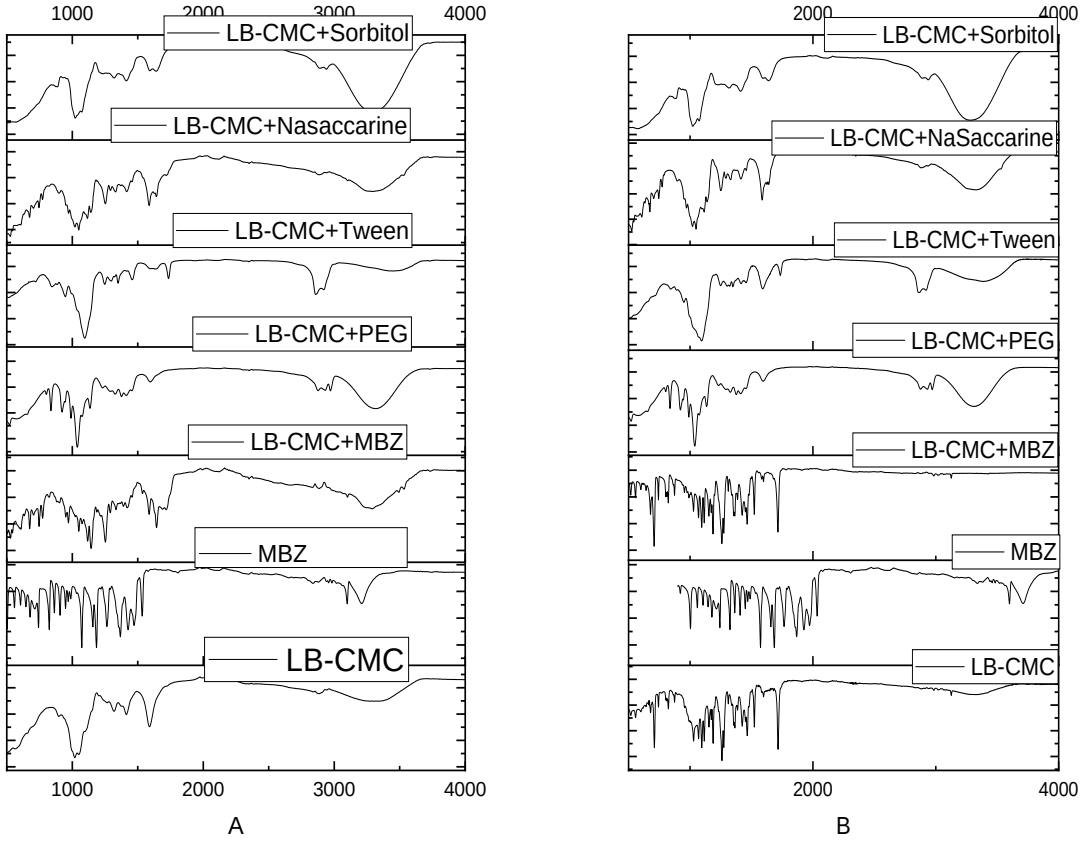


Figure 21: FTIR result of Compatibility test for LB-CMC at 0 (A) and 1 (B) month, respectively.

According to FTIR results, sorbitol, Na Saccharine, Tween 80, PEG and MBZ were found to be compatible with the developed excipient of L-CMC and LB-CMC. If the main peaks of the drug are also included in the spectrum of the drug-excipient physical mixtures, it is an indication of the absence of possible interactions between the active drug and excipients (Doğantürk *et al.*, 2006). The characteristic peaks of L-CMC and LB-CMC were unchanged or preserved in mixtures of L-CMC with Sorbitol, L-CMC with PEG, L-CMC with MBZ, and L-CMC with Na saccharine. Also, for LB-CMC with Sorbitol, LB-CMC with PEG, LB-CMC with MBZ, and LB-CMC with Na Saccarine (Figure 20, and 21).

1L =CMC from leaves, 1/LB=CMC from leaf base **2=MBZ**
1C= Commercial CMC

3L = CMC from leaves + MZ, **4L = CMC from leaves + PEG,**
3LB =CMC from leaf base +MBZ **4LB = CMC from leaf base +PEG**

5L = CMC from leaves +Tween, **6L= CMC from leaves +Sodium saccharine,**
5LB = CMC from leaf base +Tween **6LB= CMC from leaf base + Sodium saccharine**

7 L= CMC from leaves +Sorbitol, 7LB= CMC from leaf base + Sorbitol

Figure 22: Compatibility study sample pictures at 1 month .

The distinctive bands at 1464 cm^{-1} and 710.78 cm^{-1}, which indicate the existence of the aromatic ring related to C-C vibrational modes, were displayed by pure MBZ. The prominent absorption bands of carbonyl C=O stretching vibrations at 1715.71 cm^{-1} identified the ester linkage. Additionally, the C-O group bands at 1275.93 cm-^{1}, 1260.50 cm^{-1}, and 1188.17 cm^{-1} describ the benzoate ester. The aromatic C-N stretching vibrations were shown by absorption bands at 1427.35 cm^{-1}. The bands at 1070.51 cm^{-1} and 1522.83 cm^{-1}, respectively, indicated the presence of the aliphatic C-N vibrations and the nitro group. It is possible, therefore, to conclude that there was no meaningful interaction between the medication and the prepared excipients.

During the compatibility study of the prepared excipients. There were no changes in color, odor, texture and physical appearance of the prepared excipients as shown in (Figure 22). From this we can conclude that the prepared excipients (L-CMC, and LB-CMC) are chemically compatible with other excipients and with Metronidazole Benzoate.

4.2. Preparation of metronidazole benzoate suspension formulations

4.2.1. Appearance and pH of the suspensions

All metronidazole benzoate suspension formulations prepared with L-CMC (with DS of 0.889), LB-CMC (with DS of 0.667), and CC-CMC suspending agents showed good homogeneity with white-creamy color.

From Table 9, the pH of all MBZ suspensions formulated with L-CMC, LB-CMC, and CC-CMC suspending agents were within the range of 5.45 ± 0.02 to 6:22 ± 0.03. It could be observed that

throughout the course of the study, pH appeared to be in the acidic to neutral region. The pH of the formulated suspension is within the acceptance range of BP which is in the range of 5.0-6.5 (BP, 2021). There was also no significant change in the pH values as the concentration of the suspending agent increased in all the batches of formulation. These showed that CMC does not significantly affect the pH of the suspensions at different concentrations.

Table 9: pH of MBZ suspension with different suspending agents at different concentrations.

S.No	Formulation	Suspending agent concentrations (% w/v)	Mean pH ± SD
1	F1CC	0.5	6.25 ± 0.04
2	F1L	0.5	5.85 ± 0.03
3	F1LB	0.5	5.55 ± 0.02
4	F2CC	1.0	6.34 ± 0.03
5	F2L	1.0	5.76 ± 0.01
6	F2LB	1.0	5.47 ± 0.01
7	F3CC	1.5	6.45 ± 0.12
8	F3L	1.5	5.75 ± 0.03
9	F3LB	1.5	5.47 ± 0.03
10	F4CC	2.0	6.23 ± 0.03
11	F4L	2.0	5.74 ± 0.02
12	F4LB	2.0	5.45 ± 0.02

4.2.2. Rheology and Flowability of the Suspensions

The suspensions are classified as low viscosity, intermediate viscosity, and high viscosity based on their rate and extent of flow out of the pipette. It is assumed that the suspension has a low viscosity if it comes out from the pipette solely by gravity, in which case flow rates need to be determined. It is said to have intermediate viscosity if it partially emerges. However, the suspension is said to have a high viscosity if it does not exit the pipette (Femi-Oyewo *et al.*, 2004).

As presented in Table 10, the flow rate increased with a decrease in the concentration of the suspending agents. The flow rates of metronidazole benzoate suspension containing LB-CMC were higher than those containing L-CMC, and CC-CMC. When equal amounts of suspending agent were used, the flowability of the suspensions was in the order of LB-CMC > L-CMC> CC-CMC. This indicates that suspensions prepared from LB-CMC have better pourability from

containers than L-CMC, and CC-CMC. The flowability difference among the formulations might be due to the difference in the viscosity of suspending agents used.

Table 10: Flow rate of the suspension formulations at different suspending agent concentrations.

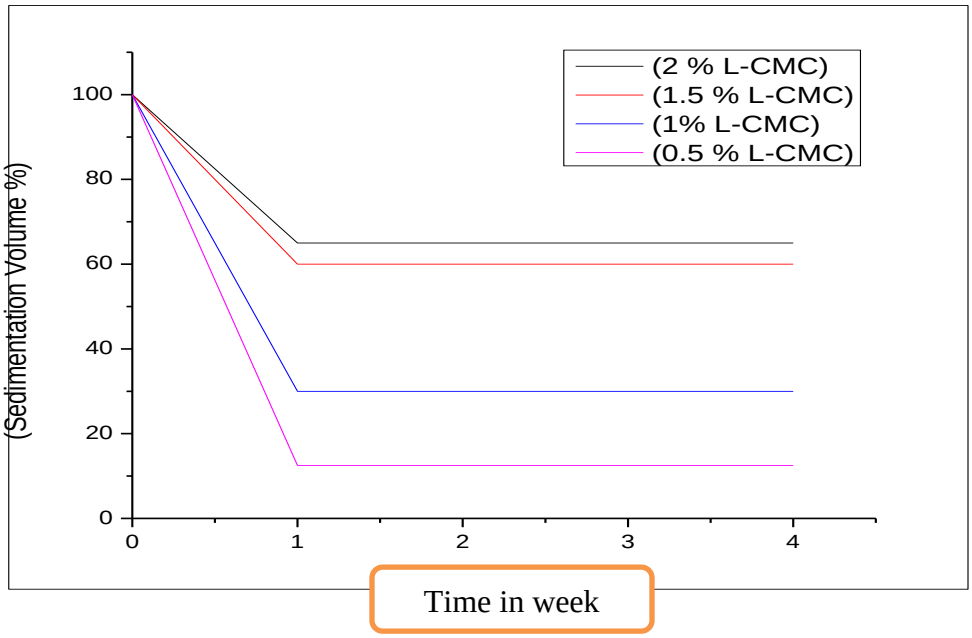
Concentration of suspending agents (% w/v)	Flow rate ml/s (mean ± SD)		
	CC-CMC	L-CMC	LB-CMC
0.5%	0.52±0.01	0.66±0.01	0.83±0.00
1%	0.23±0.00	0.49±0.02	0.62±0.01
1.5%	Intermediate	0.28±0.00	0.58±0.01
2%	Viscous	Intermediate	0.33±0.02

CC-CMC: Commercial Carboxymethyl cellulose, L-CMC: Carboxymethyl cellulose extracted from *Phoenix dactylifera* L tree leaves, LB; Carboxymethyl cellulose extracted from *Phoenix dactylifera* L Leaf base

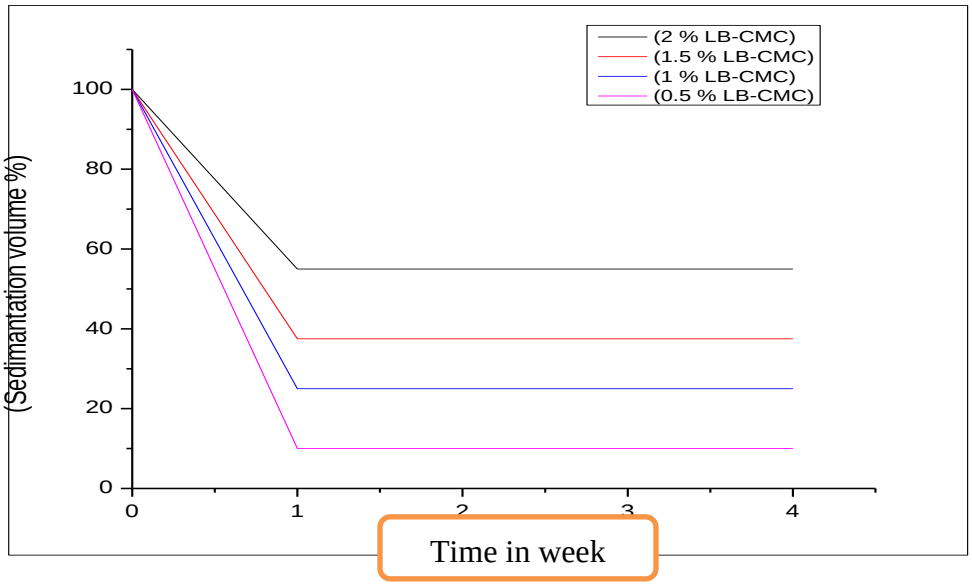
For pharmaceutical suspensions to be stable, pourable, or dosed accurately, the apparent viscosity is crucial. The quick sedimentation of dispersed particles reduces with increasing apparent viscosity of suspensions, causing the particles to stay suspended for longer period of time (Ayorinde & Odeniyi, 2017).

4.2.3. Sedimentation volume of the suspensions

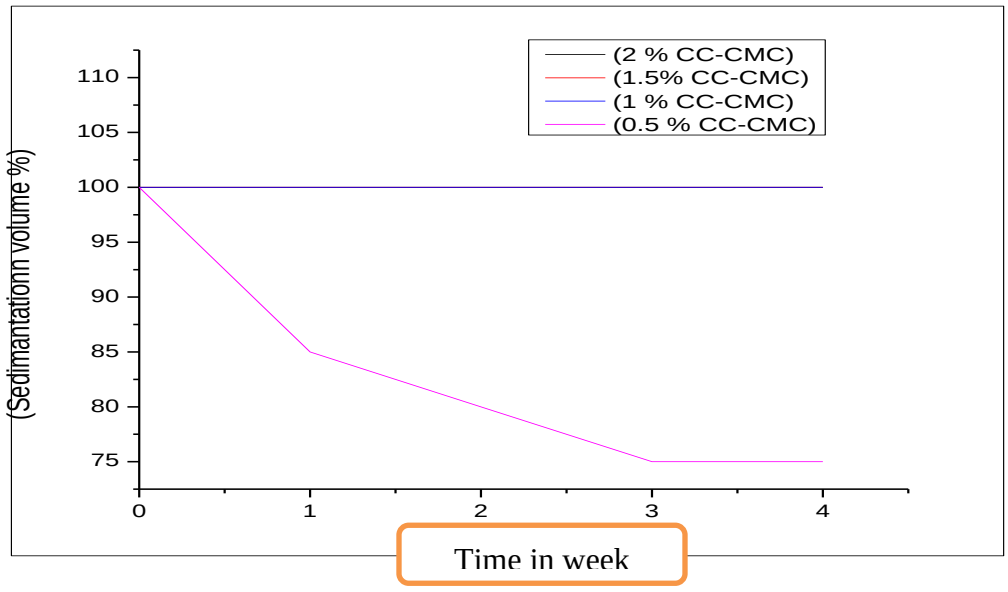
Sedimentation volume is the height of the sediment after it has settled to the original height of the suspension in the cylinder (Aremu and Oduyela ,2015). Figure 24 displays the average sedimentation volume measured for the formulations at various suspending agent concentrations. The outcome demonstrates that at some point during the process, the particles settle to create sediments. This is most likely the result of interactions between the suspended particles, which ultimately produced energy. This is in conformity with observations of Tabibi and Rhodes (1995) who defined energy of interaction V_T between two particles as Suspension sample produced using L-CMC and the LB-CMC showed a lower sedimentation volume when compared with those prepared using CC-CMC at all concentrations of prepared samples (Aremu and Oduyela, 2015).


(2 % L-CMC)
(1.5 % L-CMC)
(1% L-CMC)
(0.5 % L-CMC)
(Sedimentation Volume %)
100
80
60
40
20
0
0
1
2
3
4
Time in week

(a)


(2 % LB-CMC)
(1.5 % LB-CMC)
(1 % LB-CMC)
(0.5 % LB-CMC)
(Sedimantation volume %)
100
80
60
40
20
0
0
1
2
3
4
Time in week

(b)



(c)

Figure 23: The sedimentation volumes (%) of MBZ suspensions prepared at different concentration of suspending agents (a) Carboxymethyl cellulose extracted from *Phoenix dactylifera* L Leaves (L-CMC), (b) Carboxymethyl cellulose extracted from *Phoenix dactylifera* L Leaf base (LB-CMC), and (c)Commercial Carboxymethyl cellulose (CC-CMC) respectively from top to the bottom.

Suspension samples containing the CC-CMC at concentrations 0.5, 1, 1.5, and 2 % (w/v), respectively showed higher sedimentation volumes when compared with those of the corresponding concentrations of L-CMC and LB-CMC. Generally, the sedimentation volumes of all the formulations were of the order CC-CMC > L-CMC >LB-CMC ($P<0.05$).

All CC-CMC containing formulations remained completely suspended except at 0.5 % CC-CMC over the 4 week the study. There was a rapid sedimentation of all L-CMC, and LB-CMC containing formulations in the first week and a slight decrease to the next consecutive weeks of storage.

It can be seen from the profiles that the sedimentation volumes (%) of suspensions increased with increase in the concentrations of the suspending agents. As seen in the Figure 24, 0.5 % LB-CMC showed faster sedimentation rate and lower sedimentation volume, while 1% CC-CMC, 1.5 % CC-CMC, and 2 % CC-CMC showed 100% sedimentation volumes.

The viscosity of the medium increased with concentration, slowing the rate of sedimentation, which is why the volume of sedimentation increased as the concentration of the suspending agents increased. This finding is consistent with the outcomes documented in other studies (Kittipongpatana *et al*., 2006; Rishabha *et al*., 2010; Nep and Conway, 2011). At all concentrations of the suspending agents, CC-CMC provided higher sedimentation volume than L-CMC, and LB-CMC.

4.2.4. Re-dispersibility of Suspensions

For pharmaceutical suspensions to be administered homogeneously and with consistent, accurate drug dosage, it is crucial that the suspensions be easily redispersible (Brhane *et al.*, 2014). The homogeneity of pharmaceutical suspensions at the moment of administration plays a significant role in their dose uniformity and precision. Redispersibility is a crucial component of the medicinal quality of diluted suspensions since they have a tendency to settle (Deicke & Süverkrüp, 2000). Since suspensions tend to settle over time, it is intended that they can be easily re-dispersed with a little shake or stir to produce a homogenous suspensionTable 11 shows the degree of inversions needed to redistribute the prepared suspensions after a week, and a month. The degree of inversions required to achieve a complete re-dispersion for L-CMC, LB-CMC and CC-CMC containing formulations was increased as concentration increased after one week and one month storage time. The study's results further show that, the formulations comprising of L-CMC were easier to redisperse than those containing LB-CMC. However, at higher concentrations, both L-CMC and LB-CMC-containing formulations did not sediment for the first week of storage and did not require dispersion. These results suggest that the increment in viscosity of the L-CMC and LB-CMC formulations contributed to retarding the settling velocity of the particles. Comparative research on air-dried and freeze-dried *Grewia mollis* gum using CC-CMC, xanthan gum, and acacia gum as suspending agents in ibuprofen suspensions showed similar findings (Kumar, and Singh, 2010). Additionally, it was shown that for all formulations, the degree of redispersibility decreased with increasing storage time.

Table 11: Redispersibility of the suspensions after a week and a month.

Concentration of suspending agents (% w/v)	Rate of redispersibility (cycles) (mean ± SD)					
	After a week			After a month		
	CC-CMC	L-CMC	LB-CMC	CC-CMC	L-CMC	LB-CMC
0.5%	5 ± 3	7 ± 1	10 ± 2	15 ± 1	23 ± 3	25± 2
1%	INR	5 ± 2	7 ± 1	12 ± 3	19 ± 2	21 ± 3
1.5%	INR	INR	4 ± 3	INR	11 ± 1	15 ± 2
2%	INR	INR	INR	INR	INR	INR

4.2.5. Preparation of calibration curves

Linearity was tested by analysis of MBZ standard solutions in the concentration of 0.0106 $mg.mL^{-1}$, 0.0142 $mg.mL^{-1}$, 0.0177 $mg.mL^{-1}$, 0.0213 $mg.mL^{-1}$, 0.0248 $mg.mL^{-1}$, 0.0284 $mg.mL^{-1}$. The method showed linear correlation (r^2 =0.9996) and statistical analysis revealed a significant linear regression and no significant deviation from linearity ($p>0.05$) as shown in Figure 24.

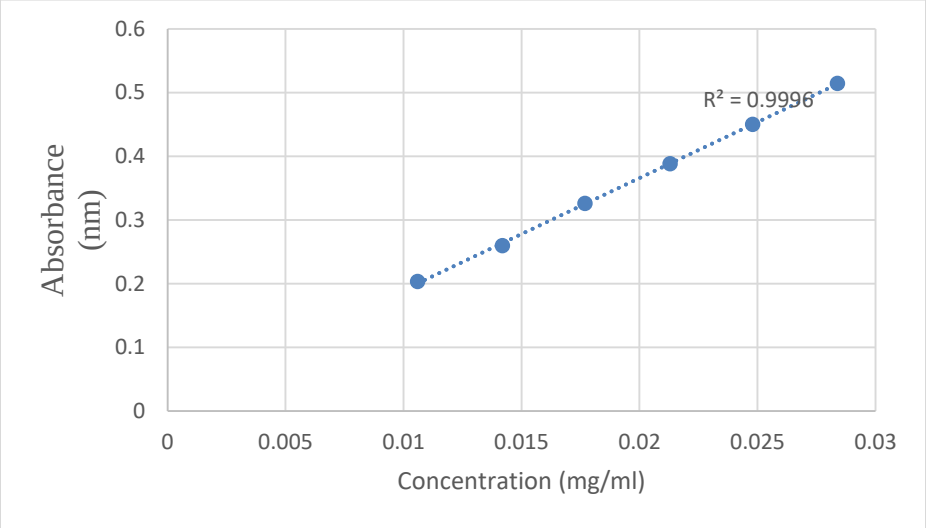


Figure 24: Calibrationcurve for MBZ, with medium of 0.1 N HCl (simulating gastric fluid), at 254 nm wavelength.

4.2.6. Dissolution profile of suspensions

Figures 25-29 demonstrate that formulations with lower suspending agent concentrations experienced a faster release rate. The release of the API is expected to occur more slowly in the more viscous preparations. This might be explained by the formulations becoming more viscous as the suspending agent increases in concentration. Furthermore, at the same doses, the drug

release profiles from MBZ suspension formulations containing LB-CMC as a suspending agent were higher than those comprising L-CMC and CC-CMC ($p < 0.05$).

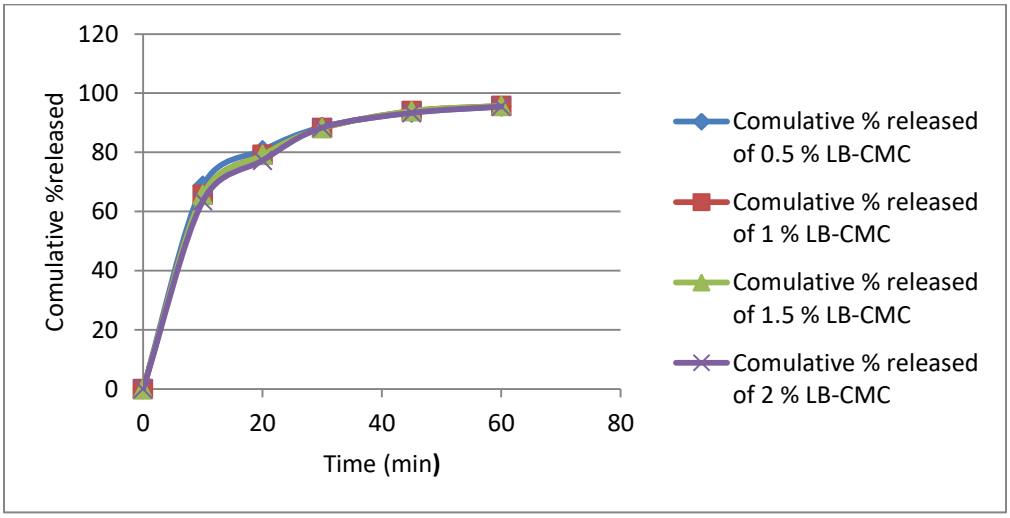


Figure 25: Drug release profiles of metronidazole benzoate suspension formulations containing LB-CMC as suspending agent.

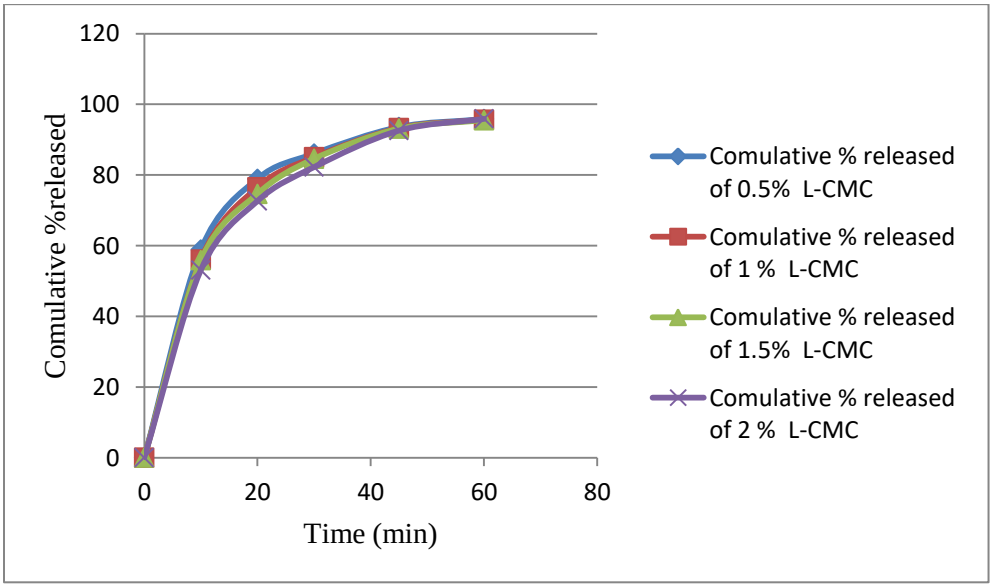


Figure 26: Drug release profiles of metronidazole benzoate suspension formulations containing L-CMC as suspending agent.

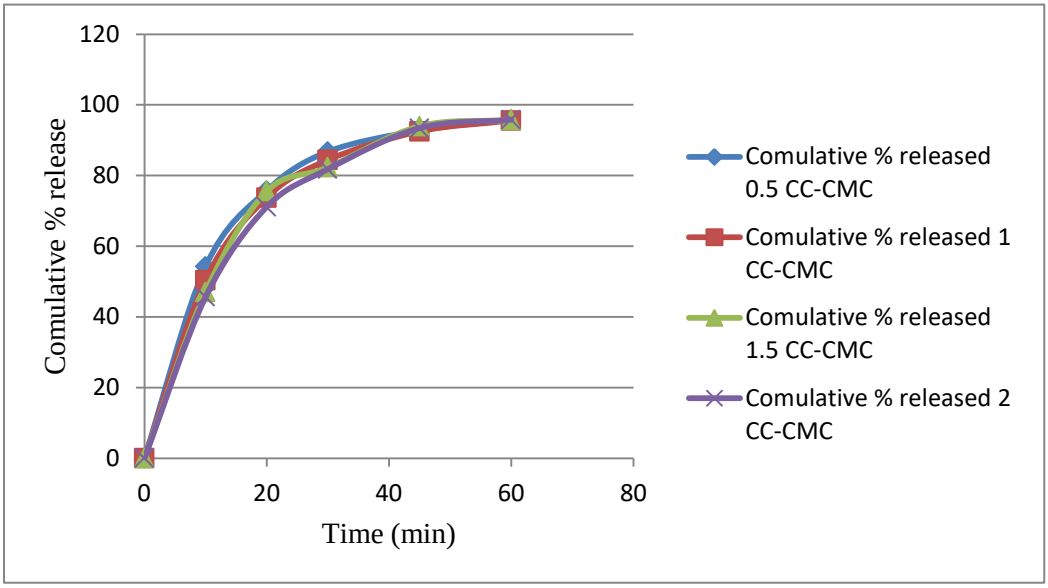


Figure 27: Drug release profiles of metronidazole benzoate suspension formulations containing CC-CMC as suspending agent.

The drug release profile of the metronidazole benzoate suspension is directly impacted by the suspending agent's concentration. At lower concentrations of the suspending agent, the suspension exhibited faster initial drug release for all L-CMC, LB-CMC and CC-CMC based MBZ Suspension. This is likely due to lower viscosity, allowing the drug particles to dissolve more easily and readily.

Higher concentrations of suspending agents (L-CMC, LB-CMC and CC-CMC) increased the viscosity of the suspension, which slowed down the drug release rate. This can be explained by the development of a more gel-like matrix, which restricts the movement and dissolution of drug particles (Okoye., et al 2014).

At an optimal concentration, the suspending agent provided sufficient viscosity to maintain uniform drug distribution without appreciably slowing down the drug release rate. Similar studies (Brhane, Y., 2020) have shown that the concentration of suspending agents have important impact to control drug release profiles of MBZ suspension. The findings of this study align with previous research, confirming that optimal concentrations of suspending agents are key to achieving desired release characteristics.

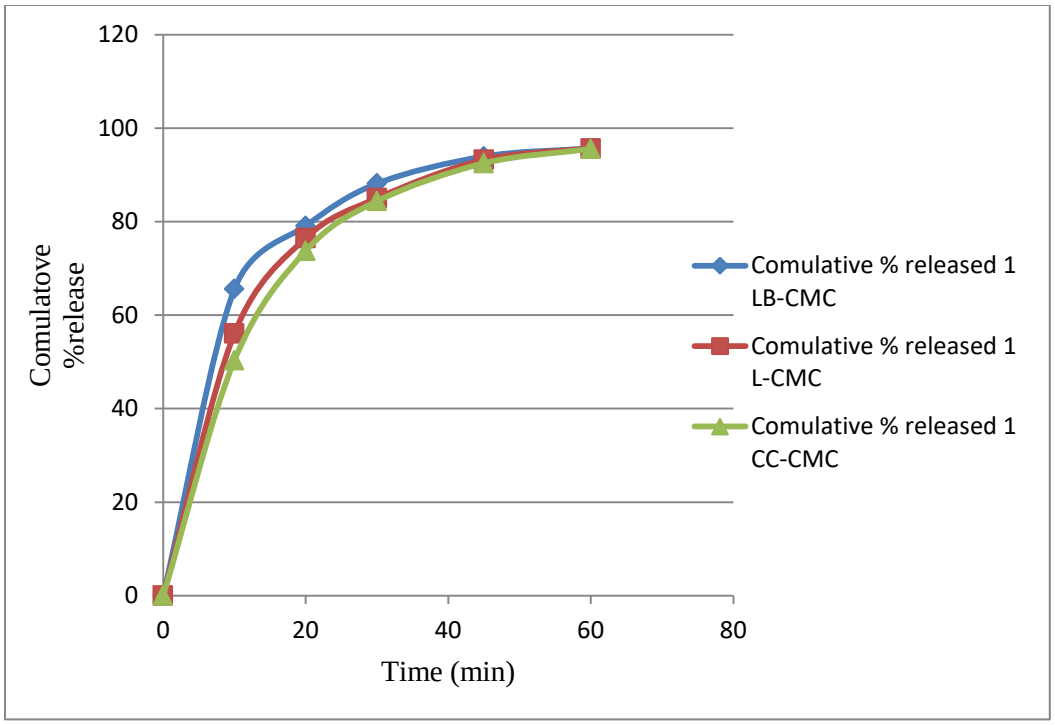


Figure 28: Drug release profiles of metronidazole benzoate suspension formulations for 1 % L-CMC,1 % LB-CMC and 1% CC-CM.

Metronidazole benzoate suspension with 1% CC-CMC has relatively moderate viscosity. On the other hand, Metronidazole benzoate suspension with 1% LB-CMC is relatively less viscous which may cause relatively faster drug release profile as shown in Figure 28.

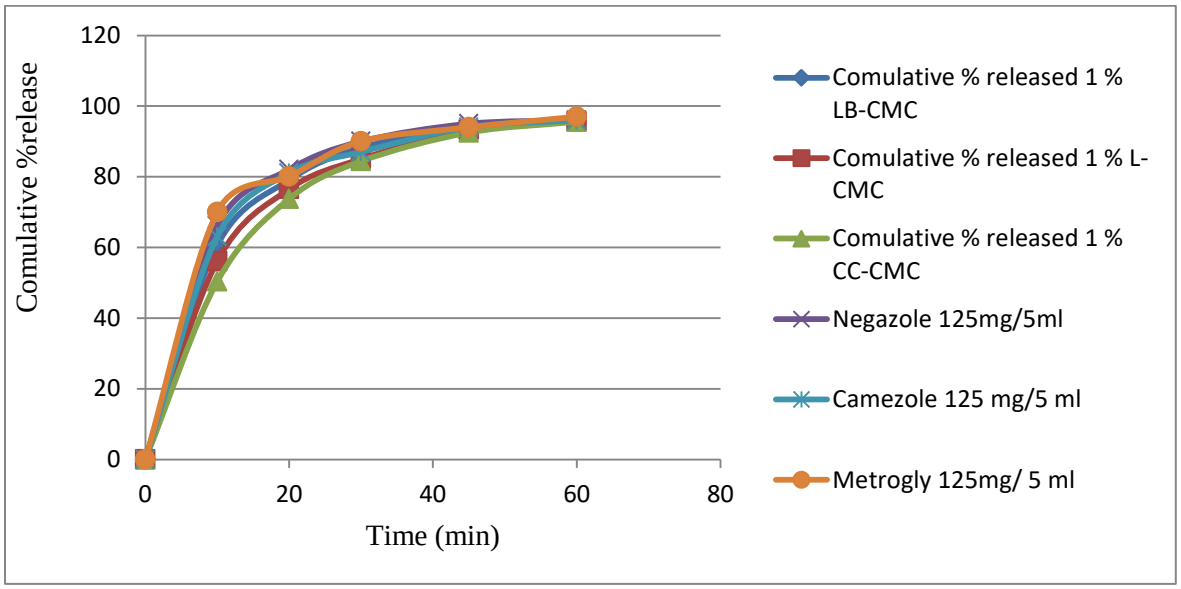


Figure 29: Drug release profiles of metronidazole benzoate suspension formulations and

products from the market, Negazol 125 mg/5 ml, Camezol 125 mg/5 ml, and Metrogyl 125 mg/5ml respectively in comparison with 1 % L-CMC,1% LB-CMC and 1% CC-CMC.

At the specified time, all metronidazole suspensions included in this study released 85% of the labeled dose. The assay results were within the pharmacopoeia limit for all metronidazole benzoate oral suspension products. Statistical results of the assay of metronidazole benzoate oral suspensions showed that there is no significant difference between all products ($P > 0.05$).

The dissolving profiles of the prepared metronidazole benzoate suspensions with (1 % L-CMC, 1 % LB-CMC, and 1 % CC-CMC) are comparable to those of the commercially available products Metrogly, Camezola, and Negazole. When compared to these commercial products, our results show that all prepared suspensions achieved similar (f2) value, which was greater than 50, indicating very similar dissolution patterns.

This study successfully demonstrates that the prepared metronidazole benzoate suspensions have similar dissolution profiles to Negazole, Camezola, and Metrogly, indicating potential similar dissolution profile. Metronidazole benzoate suspension formulations that havebeen evaluated all exhibit good quality, as evidenced by their passing with all pharmacopoeial standards.

4.2.7. Stability of metronidazole suspension

Tables 12, 13 and 14 present the stability study results of MBZ suspension formulations containing 1% L-CMC, 1% LB-CMC, and 1% CC-CMC as suspending agents. The bulk visual appearance as well as the odor of all suspension formulations remained the same (creamy white and odorless, respectively). There was no color change in all metronidazole benzoate suspension formulations. Furthermore, both the pH and drug content were within the pharmacopeial limits, and the formulations were found to be stable at accelerated condition for three months.

The pH range stated in BP (2021) for metronidazole benzoate suspension formulation is in the range of 5.0-6.5. Similarly, at all storage conditions, the changes in average assay recovery of the suspension formulations were within the acceptable range (90.0 to 110.0%) as shown in Table 12 (Boonme et al., 2000; Vu *et al.*, 2008). The suspension formulations stored under the same condition showed no significant change ($p>0.05$) in mean particle size throughout the study period as shown in Table 14.

4.2.7.1. Assay of metronidazole suspension

Calibration curve of HPLC was tested by analysis of BMZ standard solutions in the concentration of 0.0301 mg.mL−1, 0.0397 mg.mL−1, 0.05 mg.mL−1, 0.0598 mg.mL−1, 0.0697 mg.mL−1. The method showed linear correlation (r^2 =1) and statistical analysis revealed a significant linear regression and no significant deviation from linearity (p>0.05) as show in figure 30.

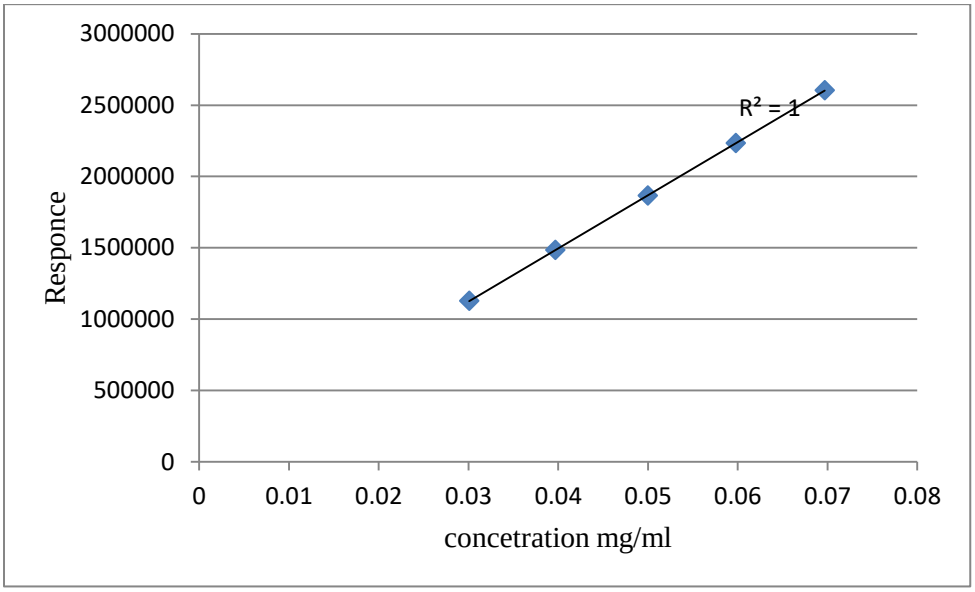


Figure 30: Calibration curve of MBZ for assay using HPLC Solution: 0.1% (v/v) glacial acetic acid in water, Mobile phase: Acetonitrile and Solution A (40:60), Column: 4.6-mm × 15-cm; 5-µm packing L1, Column temperature: 30°, Flow rate: 1.0 mL/min, Injection volume: 5 µL

The changes in average assay recovery of the metronidazole suspension formulations were within the acceptable range (90.0 to 110.0%) as shown in Table 12. The suspension formulations stored under the same condition also showed no significant change (p>0.05) in assay throughout the study period.

Table 12: Assay values of metronidazole benzoate suspensions stored at 40 ºC / 75 % relative humidity for 3 months.

Formula	Storage condition	% recovery mean± SD			
		0 Month	1 Month	2 Month	3 Month
1% CC-CMC	40 ºC /75% RH	96.19± 0.86	96.22± 0.23	96.22± 0.07	95.99± 0.03
1% L-CMC		95.52± 0.52	95.51± 0.25	95.50± 0.04	95.29± 0.11
1% LB-CMC		96.00± 0.50	95.96± 0.12	95.92± 0.09	95.76± 0.13

4.2.7.2. pH determination of metronidazole suspension

As shown in Table 13, all formulations of metronidazole benzoate suspension showed pH alterations that fall within an acceptable range. The pH range of 5.0–6.5 is specified in BP (2021) for the formulation of metronidazole benzoate suspension.

The pH level is pivotal in determining the stability of suspension formulations, especially within the pharmaceutical industry. Its significance spans across several crucial aspects, including chemical stability, physical characteristics, microbiological integrity, and ingredient compatibility within the formulation (Vázquez-Blanco et al., 2018).

Table 13: pH values of metronidazole benzoate suspensions stored at 40 ºC / 75 % relative humidity for 3 months.

Formula	Storage condition	PH			
		0 Month	1 Month	2 Month	3 Month
1% CC-CMC	40 ºC /75% RH	6.34± 0.03	6.39± 0.01	6.42±0.01	6.45± 0.02
1% L-CMC		5.76± 0.01	5.78± 0.02	5.80± 0.02	5.85± 0.00
1% LB-CMC		5.47± 0.01	5.49± 0.01	5.52± 0.03	5.58± 0.01

4.2.7.3. Particle Size and Size Distribution

The MBZ suspensions are sold commercially in anhydrous form. Hoelgaard and Moller state that the conversion of the anhydrous form to monohydrate is what causes the increase in MBZ particle size in aqueous suspension; this conversion has only been observed in oral suspensions that have been stored at 4°C for approximately three months, while the suspension that has been stored at 40°C did not exhibit any modification.(Hoelgaard & Møller 1983). The suspension formulations stored under 40 ºC / 75% RH condition also showed no significant change ($p>0.05$) in mean particle size throughout the study period as shown in Table 14.

Table 14: Particle size of metronidazole benzoate suspensions stored at 40 ºC / 75% relative humidity for 3 months.

Formula	Storage condition	Particle size (µm) (mean ± SD)			
		0 Month	± SD	3 Month	± SD
1 % CC-CMC	40 ºC /75% RH	50.53	1.53	48.95	0.66
1 % L-CMC		52.02	1.00	52.35	0.72
1 % LB-CMC		53.48	1.79	51.40	0.97

5. Conclusion

The percent of cellulose yields on a dry weight basis was found to be 36.7 $\pm$ 0.97 % for cellulose extracted from palm tree (*Phoenix dactylifera* L) leaves and 41.3 $\pm$ 1.08 % from leaf base. The maximum degrees of substitutions of CMC were 0.889 (for Carboxymethyl cellulose derived from *Phoenix dactylifera* L tree leave) and 0.667 (for Carboxymethyl cellulose derived from Phoenix dactylifera L Leaf base cellulose (LB-CMC)) based on dry weight conditions.

The characterization of the synthesized CMCs confirmed the successful introduction of carboxymethyl groups onto the cellulose backbone, as evidenced by Fourier-transform infrared spectroscopy (FT-IR), scanning electron microscope (SEM), X-ray diffraction (XRD), and thermo gravimetric analysis (TGA).

The evaluation of the L-CMC and LB-CMC as suspending agents showed their promising pharmaceutical application. The prepared CMCs from leaves and leaf base of *Phoenix dactylifera* L palm tree exhibited good appearance, pH, sedimentation volume (%), rheology, redispersibility, and *in vitro* drug release profile. Dissolution studies of the suspension formulations showed that all suspensions have achieved $\geq$ 85% drug release within 1 h period.

The performance of the prepared L-CMC and LB-CMC as suspending agents was compared with CC-CMC and the results show the promising performance of the synthesized CMCs. Additionally, the dissolution rate profiles of all the prepared metronidazole benzoate suspensions remained comparable to the Negazole, Camezola, and Metrogly with $f_2 > 50$.

The bulk visual appearance as well as the odor of all suspension formulations remained the same (creamy white and odorless, respectively). There was no color change in all metronidazole benzoate suspension formulations. Additionally, the formulations were shown to be stable at an accelerated situation for three months, and both the pH and drug concentration were found to be within the pharmacopeial limitations.

Future paths for research can include investigating potential uses for these CMCs in drug delivery systems and other pharmaceutical formulations, as well as further preparing the carboxymethylation method to improve the characteristics of the synthesized CMCs.

According to this study results, it can be concluded that the leaf, and leaf base lignocellulose biomass of the *Phoenix dactylifera* L palm tree were found to be the good sources of cellulose

and CMC, with a relatively higher yield, purity, and pharmaceutical suspending agent capacity. The *Phoenix dactylifera* L palm tree's leaves, and leaf bases can be considered as a reliable, sustainable, and promising source for producing high-quality pharmaceutical suspending agent without harming the environment.

6. Suggestions for further work

Due to scarcity of resource and shortage of time, further work suggestion for the carboxymethylation of *Phoenix dactylifera* L palm tree celluloses from leaves and leaf base and the evaluation of the carboxymethyl celluloses (CMCs) as pharmaceutical suspending agents are listed below.

Long-Term Stability; this study did not look at the long-term stability of CMCs in pharmaceutical solutions. Subsequent investigations might concentrate on assessing the stability of CMC-based suspensions over extended storage periods under various environmental conditions. This will provide important information on the shelf-life and storage requirements of CMC based pharmaceutical formulation.

Scale-Up Considerations; This study does not address the scale-up of the carboxymethylation process or the practicality of manufacturing CMCs for industrial uses on a wider scale, although these are important issues for future industrial application. To enable the possible commercialization of pharmaceutical products based on CMC, factors including cost-effectiveness, process scalability, and regulatory compliance need to be taken into account.

Regulatory constraints; although the potential of CMCs as pharmaceutical excipients was investigated, this study was not intended to address regulatory issues related to the approval and adherence of CMC-based formulations to pharmaceutical regulations.

Future studies that address these issues may improve our knowledge on the Carboxymethylation of *Phoenix dactylifera* L palm tree celluloses and evaluation of the CMCs as pharmaceutical suspending agents and also capacity to use CMCs made from leaves and leaf base celluloses of the *Phoenix dactylifera* L palm tree in pharmaceutical formulations and other related fields. This will ultimately contribute to the development of pharmaceutical formulations that are safer, more effective, and sustainable.

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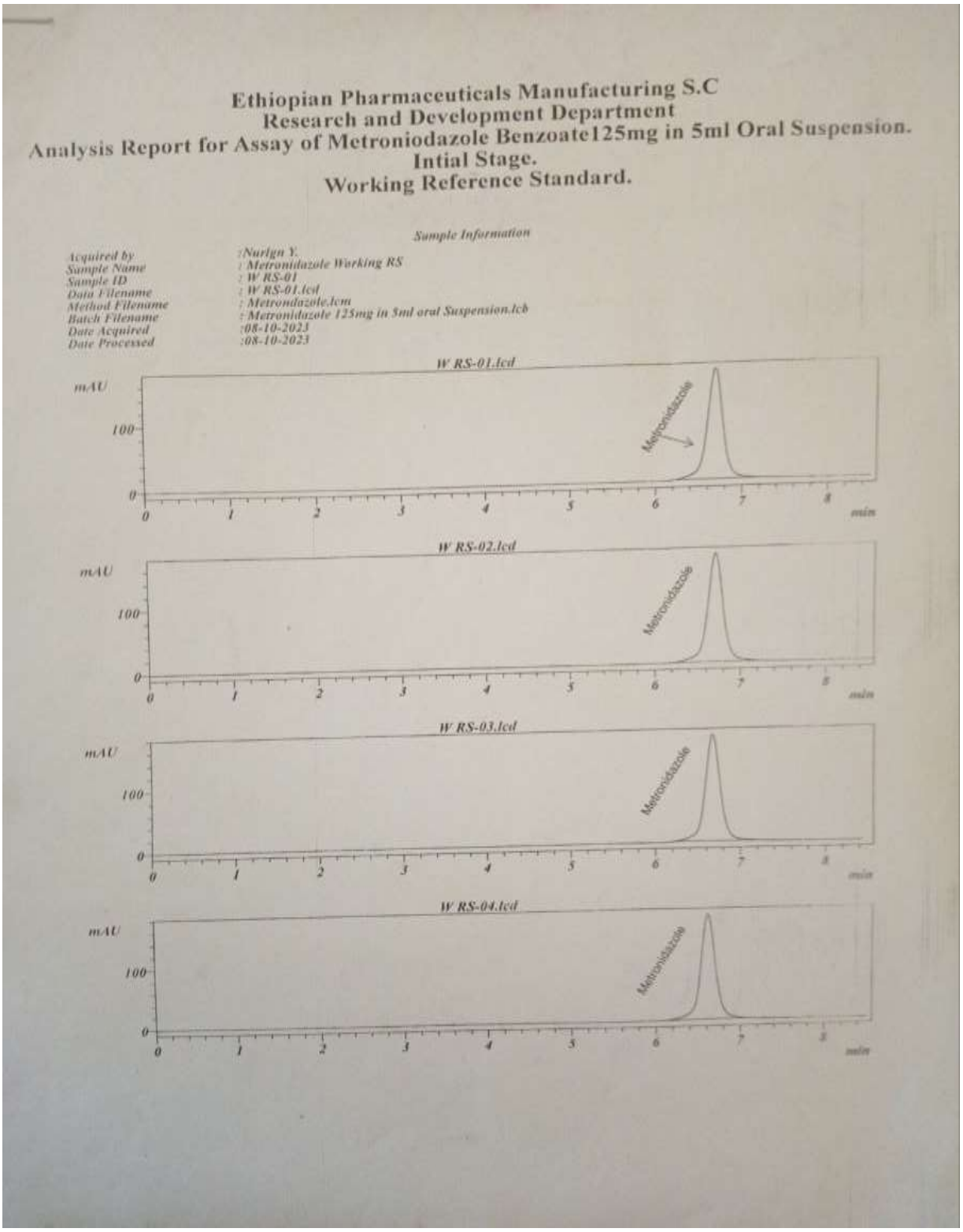
Annex

Assay result to metronidazole benzoate suspension 125mg/5 ml



Ethiopian Pharmaceuticals Manufacturing S.C
Research and Development Department
Analysis Report for Assay of Metroniodazole Benzoate125mg in 5ml Oral Suspension.
Intial Stage.
Working Reference Standard.

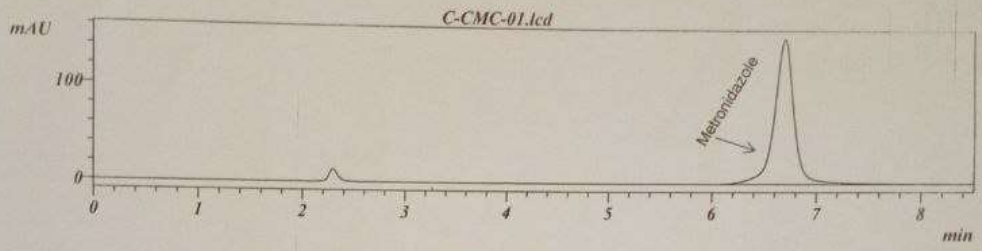
Sample Information

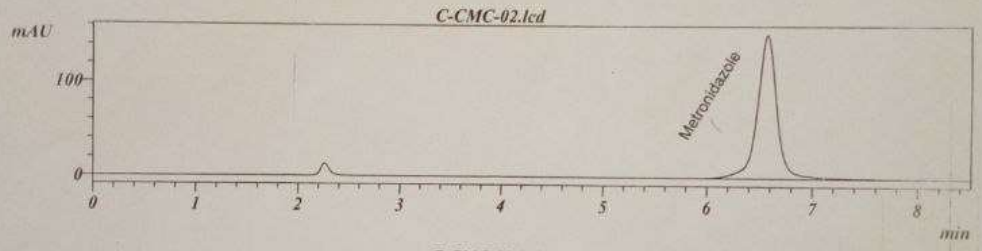
Acquired by	*:Nurign Y.*
Sample Name	*: Metronidazole Working RS*
Sample ID	*: W RS-01*
Data Filename	*: W RS-01.lcd*
Method Filename	*: Metrondazole.lcm*
Batch Filename	*: Metronidazole 125mg in 5ml oral Suspension.lcb*
Date Acquired	*:08-10-2023*
Date Processed	*:08-10-2023*

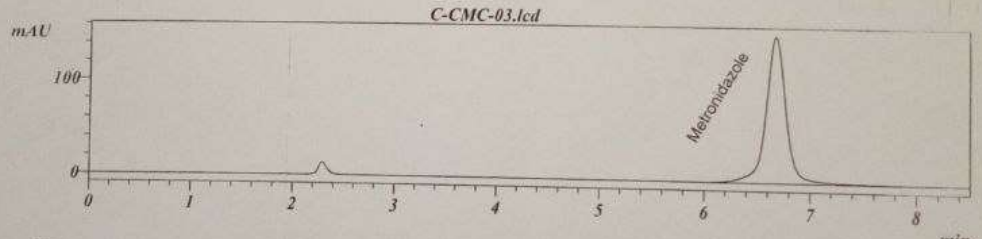
Ethiopian Pharmaceuticals Manufacturing S.C
Research and Development Department
Analysis Report for Assay of Metroniodazole Benzoate125mg in 5ml Oral Suspension.
Intial Stage.
B.No.C-CMC

Sample Information

Acquired by	*:Nurlgn Y.*
Sample Name	*: Metronidazole 125mg in 5ml oral Suspension*
Sample ID	*: C-CMC-01*
Data Filename	*: C-CMC-01.lcd*
Method Filename	*: Metrondazole.lcm*
Batch Filename	*: Metronidazole 125mg in 5ml oral Suspension.lcb*
Date Acquired	*:08-10-2023*
Date Processed	*:08-10-2023*





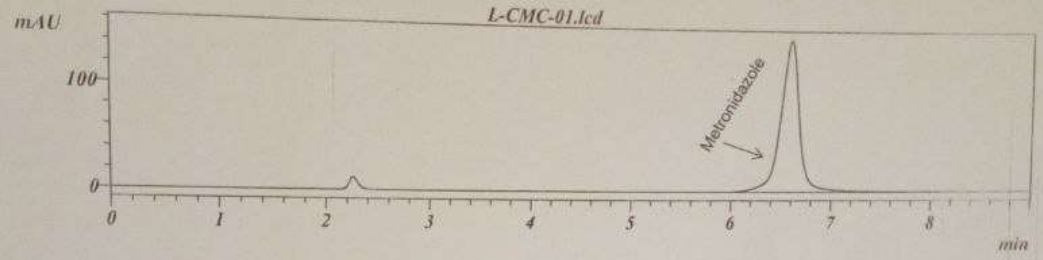


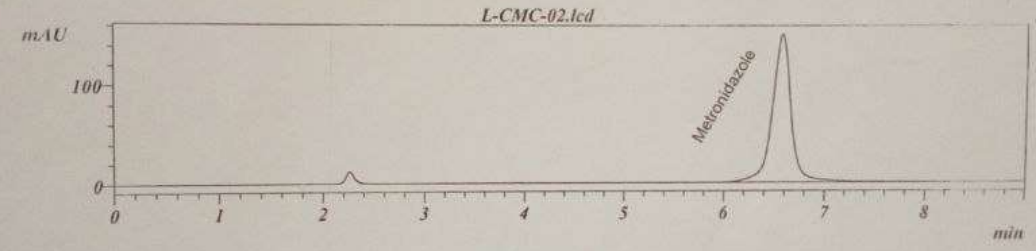
<< PDA >>
ID#1 Compound Name: Metronidazole

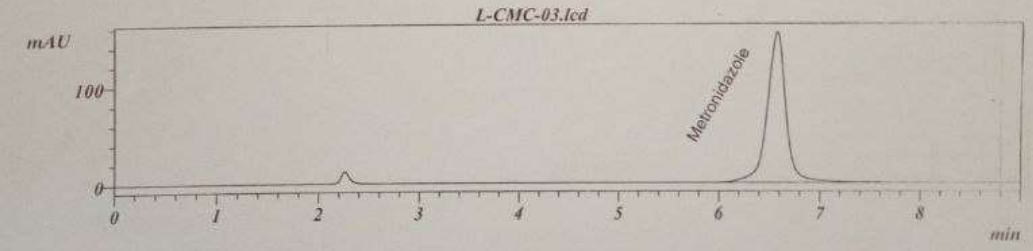
Data File Name	*Sample Name*	*mple*	*Ret. Time*	*Tailing Factor*	*er of Theoretical Plate*	*Area*	*Conc.*
C-CMC-01.lcd	*Metronidazole 125mg i*	*C-CM*	*6.673*	*0.966*	*6661*	*2028617*	*96.665*
C-CMC-02.lcd	*Metronidazole 125mg i*	*C-CM*	*6.561*	*0.975*	*6615*	*1998544*	*95.232*
C-CMC-03.lcd	*Metronidazole 125mg i*	*C-CM*	*6.673*	*0.966*	*6661*	*2028868*	*96.677*
Average			*6.636*	*0.969*	*6646*	*2018676*	*96.192*
%RSD			*0.972*	*0.552*	*0.403*	*0.864*	*0.864*

Ethiopian Pharmaceuticals Manufacturing S.C
Research and Development Department
Analysis Report for Assay of Metroniodazole Benzoate125mg in 5ml Oral Suspension.
Intial Stage.
B.No.L-CMC

Acquired by	*:Nurign Y.*	*Sample Information*
Sample Name	*: Metronidazole 125mg in 5ml oral Suspension*	
Sample ID	*: L-CMC-01*	
Data Filename	*: L-CMC-01.lcd*	
Method Filename	*: Metrondazole.lcm*	
Batch Filename	*: Metronidazole 125mg in 5ml oral Suspension.lcb*	
Date Acquired	*:08-10-2023*	
Date Processed	*:08-10-2023*	







<< PDA >>
ID#1 Compound Name: Metronidazole

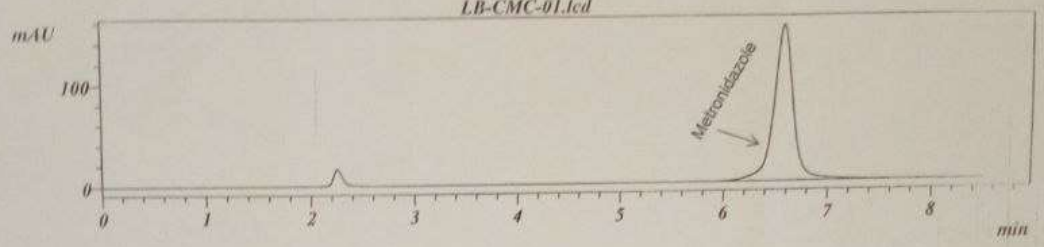
Data File Name	*Sample Name*	*mple*	*Ret. Time*	*Tailing Factor*	*er of Theoretical Plate*	*Area*	*Conc.*
L-CMC-01.lcd	*Metronidazole 125mg i*	*L-CM*	*6.562*	*0.989*	*6623*	*2004488*	*95.515*
L-CMC-02.lcd	*Metronidazole 125mg i*	*L-CM*	*6.558*	*1.002*	*6611*	*2004893*	*95.535*
L-CMC-03.lcd	*Metronidazole 125mg i*	*L-CM*	*6.558*	*1.002*	*6611*	*2004756*	*95.528*
Average			*6.560*	*0.998*	*6615*	*2004712*	*95.526*
%RSD			*0.036*	*0.716*	*0.108*	*0.010*	*0.010*

Ethiopian Pharmaceuticals Manufacturing S.C
Research and Development Department
Analysis Report for Assay of Metroniodazole Benzoate125mg in 5ml Oral Suspension.
Intial Stage.
B.No.LB-CMC

Sample Information

Acquired by	*:Nurlgn Y.*
Sample Name	*: Metronidazole 125mg in 5ml oral Suspension*
Sample ID	*: LB-CMC-01*
Data Filename	*: LB-CMC-01.lcd*
Method Filename	*: Metrondazole.lcm*
Batch Filename	*: Metronidazole 125mg in 5ml oral Suspension.lcb*
Date Acquired	*:08-10-2023*
Date Processed	*:08-10-2023*

LB-CMC-01.lcd



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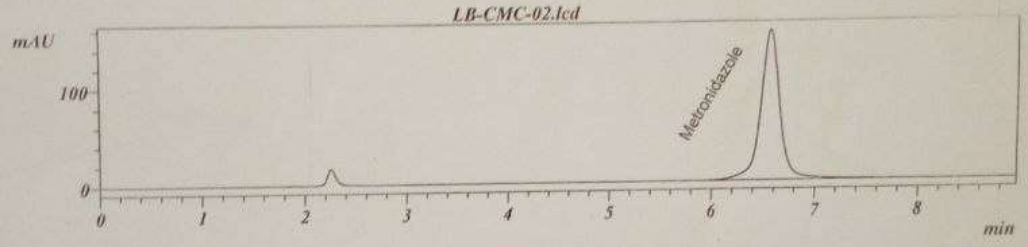
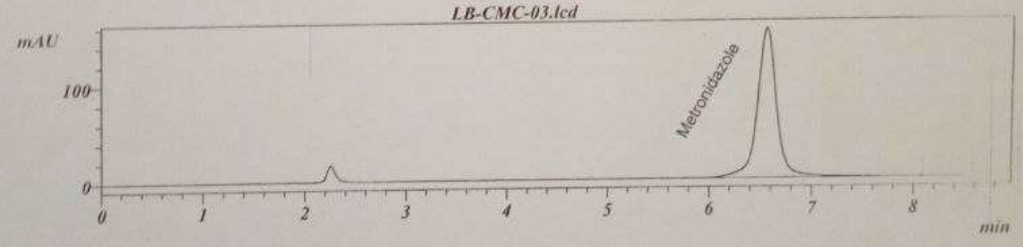
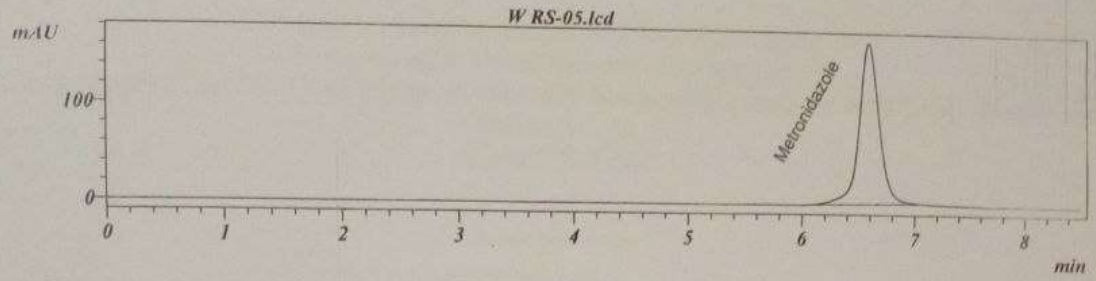


LB-CMC-03.lcd



<< PDA >>
ID#1 Compound Name: Metronidazole

Data File Name	Sample Name	mple	Ret. Time	Tailing Factor	er of Theoretical Plate	Area	Conc.
LB-CMC-01.lc	Metronidazole 125mg i	LB-C	6.559	0.984	6597	2020793	96.292
LB-CMC-02.lc	Metronidazole 125mg i	LB-C	6.562	0.978	6653	2020467	96.277
LB-CMC-03.lc	Metronidazole 125mg i	LB-C	6.559	0.984	6606	2002903	95.440
Average			6.560	0.982	6619	2014721	96.003
%RSD			0.026	0.355	0.458	0.508	0.508



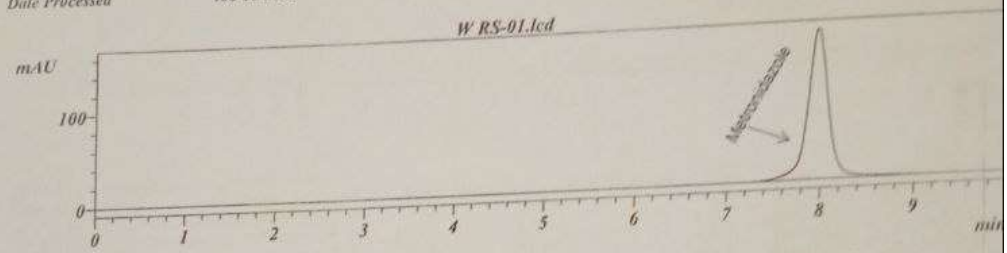
<< PDA >>
1D#1 Compound Name: Metronidazole

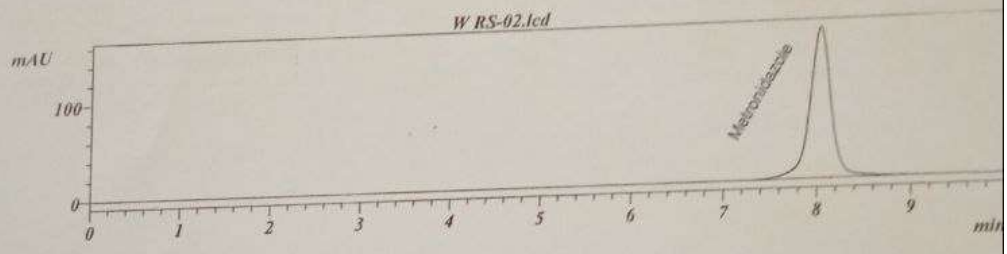
Data File Name	Sample Name	mple	Ret. Time	Tailing Factor	er of Theoretical Plate	Area	Conc.
W RS-01.lcd	Metronidazole Working	W RS	6.682	0.971	6760	2121426	100.000
W RS-02.lcd	Metronidazole Working	W RS	6.706	0.962	6708	2131577	100.239
W RS-03.lcd	Metronidazole Working	W RS	6.675	0.971	6774	2122700	99.881
W RS-04.lcd	Metronidazole Working	W RS	6.617	0.966	6808	2109910	99.889
W RS-05.lcd	Metronidazole Working	W RS	6.592	0.965	6787	2106160	100.360
Average			6.655	0.967	6767	2118355	100.074
%RSD			0.721	0.399	0.552	0.486	0.216

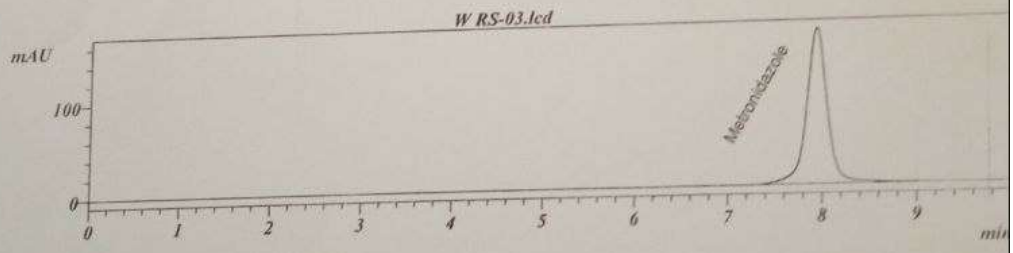
Ethiopian Pharmaceuticals Manufacturing S.C
Research and Development Department
Analysis Report for Assay of Metronidazole Benzoate 125mg in 5ml Oral Suspensi
1st Month Stability sample(accelarated Time).
Working Reference Standard.

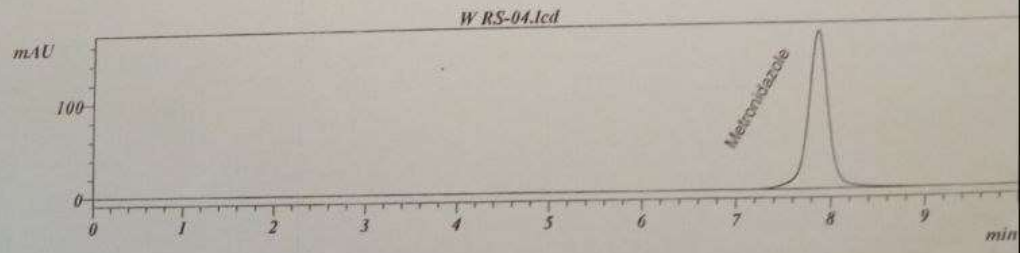
Sample Information

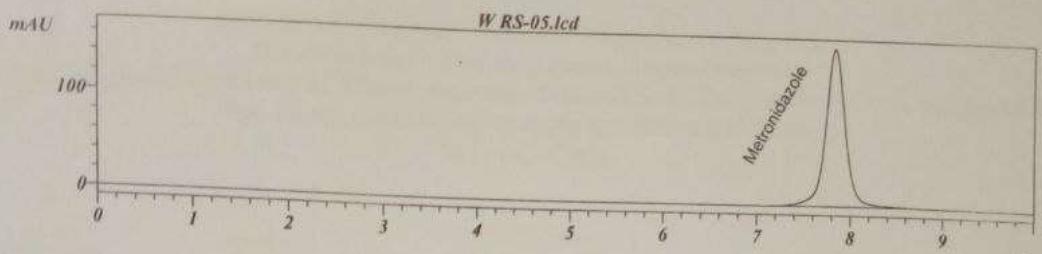
Acquired by	*:Nurlegn N.*
Sample Name	*: Metronidazole Working RS*
Sample ID	*: W RS-01*
Data Filename	*: W RS-01.lcd*
Method Filename	*: Metrondazole.lcm*
Batch Filename	*: Metronidazole 125mg in 5ml oral Suspension.lcb*
Date Acquired	*:08-11-2023*
Date Processed	*:08-11-2023*

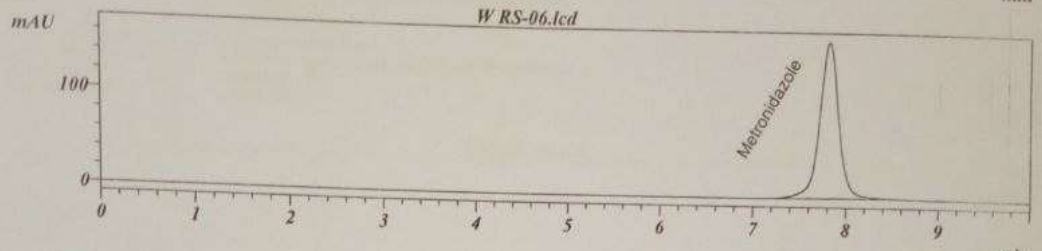












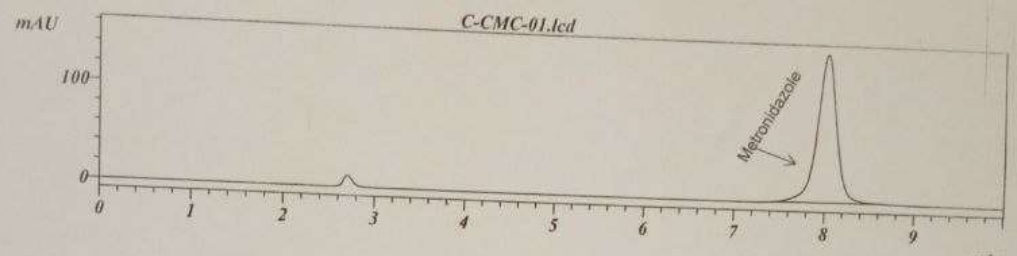
<< PDA >>
ID#1 Compound Name: Metronidazole

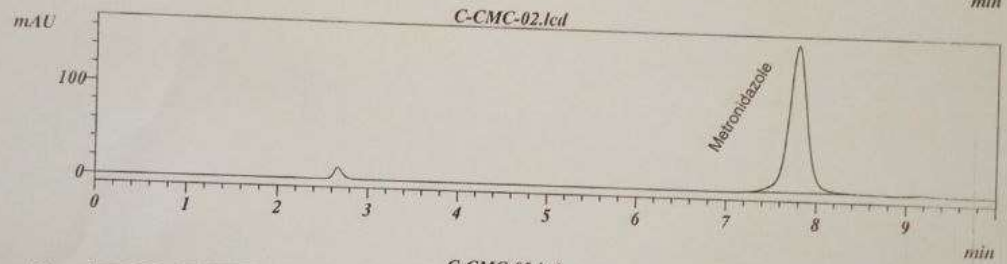
Data File Name	Sample Name	mple	Ret. Time	Tailing Factor	er of Theoretical Plate	Area	Conc.
W RS-01.lcd	Metronidazole Working	W RS	7.973	0.960	7006	2450259	100.000
W RS-02.lcd	Metronidazole Working	W RS	8.034	0.950	6766	2443983	99.872
W RS-03.lcd	Metronidazole Working	W RS	7.948	0.966	7045	2446742	99.990
W RS-04.lcd	Metronidazole Working	W RS	7.862	0.975	7063	2419367	100.179
W RS-05.lcd	Metronidazole Working	W RS	7.837	0.977	7118	2400488	100.366
W RS-06.lcd	Metronidazole Working	W RS	7.812	0.978	7171	2375317	100.124
Average			7.911	0.968	7028	2422693	100.088
%RSD			1.105	1.162	2.004	1.244	0.174

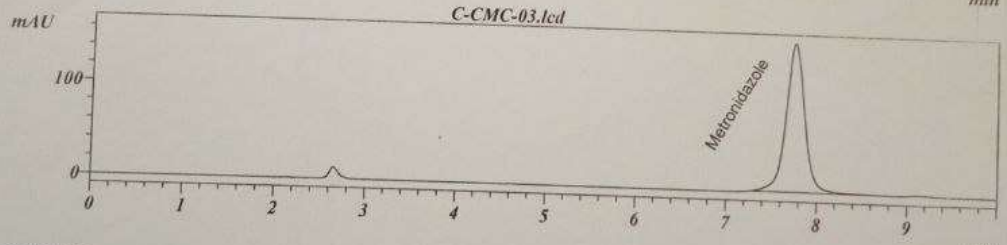
pH = 5.72

Ethiopian Pharmaceuticals Manufacturing S.C
Research and Development Department
Analysis Report for Assay of Metronidazole Benzoate 125mg in 5ml Oral Suspension.
1st Month Stability sample(accelarated Time).
B.No.C-CMC

Acquired by	*:Nurlegn N.*	*Sample Information*
Sample Name	*: Metronidazole 125mg in 5ml oral Suspension*	
Sample ID	*: C-CMC-01*	
Data Filename	*: C-CMC-01.lcd*	
Method Filename	*: Metrondazole.lcm*	
Batch Filename	*: Metronidazole 125mg in 5ml oral Suspension.lcb*	
Date Acquired	*:08-11-2023*	
Date Processed	*:08-11-2023*	







<< PDA >>
ID#1 Compound Name: Metronidazole

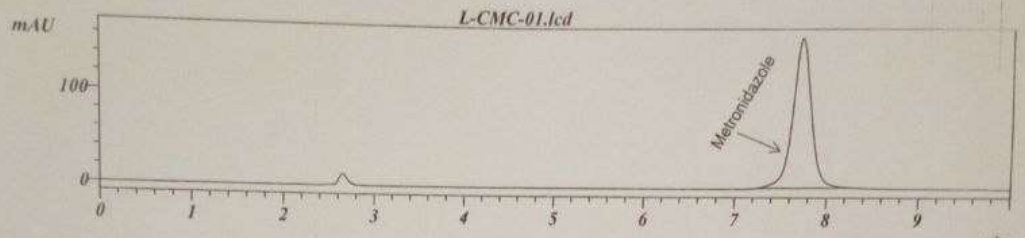
Data File Name	*Sample Name*	*mple*	*Ret. Time*	*Tailing Factor*	*er of Theoretical Plate*	*Area*	*Conc.*
C-CMC-01.lcd	*Metronidazole 125mg i*	*C-CM*	*8.006*	*0.955*	*7002*	*2288315*	*96.457*
C-CMC-02.lcd	*Metronidazole 125mg i*	*C-CM*	*7.781*	*0.988*	*7248*	*2282074*	*96.194*
C-CMC-03.lcd	*Metronidazole 125mg i*	*C-CM*	*7.755*	*1.004*	*7238*	*2277863*	*96.016*
Average			*7.847*	*0.982*	*7163*	*2282750*	*96.222*
%RSD			*1.761*	*2.540*	*1.950*	*0.230*	*0.230*

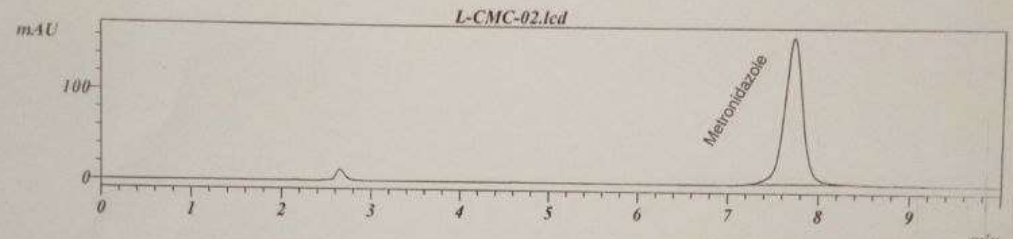
pH = 5.69

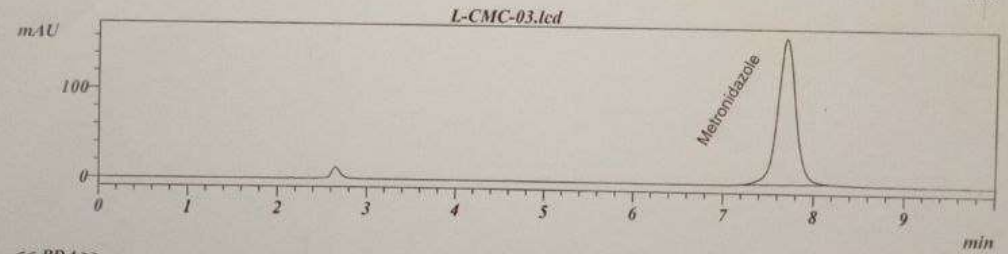
Ethiopian Pharmaceuticals Manufacturing S.C
Research and Development Department
Analysis Report for Assay of Metronidazole Benzoate 125mg in 5ml Oral Suspension.
1st Month Stability sample(accelarated Time).
B.No.L-CMC

Sample Information

Acquired by	:Nurlegn N.
Sample Name	: Metronidazole 125mg in 5ml oral Suspension
Sample ID	: L-CMC-01
Data Filename	: L-CMC-01.lcd
Method Filename	: Metrondazole.lcm
Batch Filename	: Metronidazole 125mg in 5ml oral Suspension.lcb
Date Acquired	:08-11-2023
Date Processed	:08-11-2023







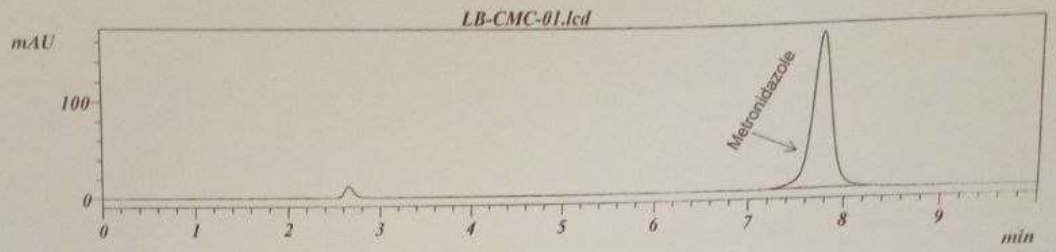
<< PDA >>
ID#1 Compound Name: Metronidazole

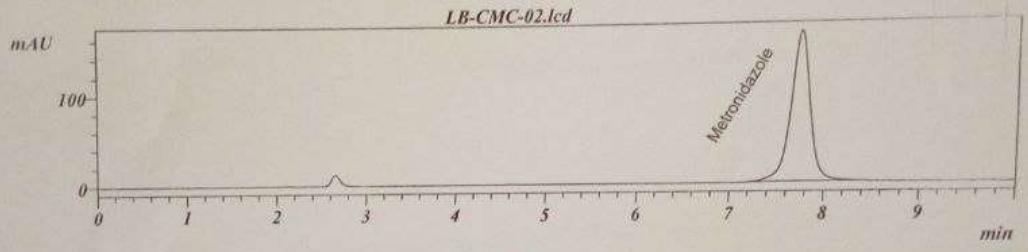
Data File Name	Sample Name	mple	Ret. Time	Tailing Factor	er of Theoretical Plate	Area	Conc.
L-CMC-01.lcd	Metronidazole 125mg i	L-CM	7.715	1.004	7331	2264465	95.451
L-CMC-02.lcd	Metronidazole 125mg i	L-CM	7.706	1.008	7348	2269948	95.683
L-CMC-03.lcd	Metronidazole 125mg i	L-CM	7.692	1.004	7377	2263401	95.407
Average			7.704	1.005	7352	2265938	95.514
%RSD			0.145	0.251	0.314	0.155	0.155

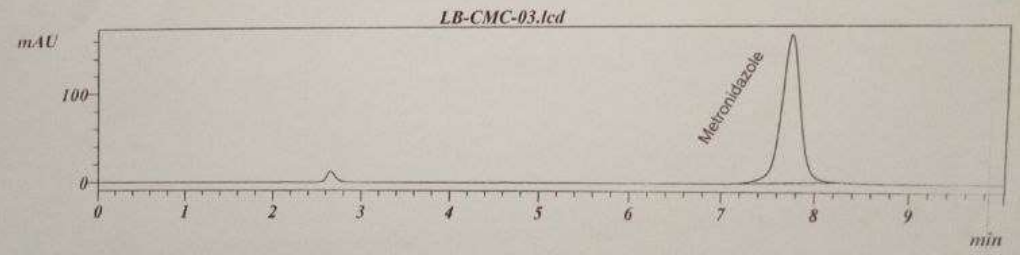
Ethiopian Pharmaceuticals Manufacturing S.C
Research and Development Department
Analysis Report for Assay of Metronidazole Benzoate 125mg in 5ml Oral Suspension.
1st Month Stability sample(accelarated Time).
B.No.LB-CMC

Sample Information

Acquired by	*:Nurlegn N.*
Sample Name	*: Metronidazole 125mg in 5ml oral Suspension*
Sample ID	*: LB-CMC-01*
Data Filename	*: LB-CMC-01.lcd*
Method Filename	*: Metrondazole.lcm*
Batch Filename	*: Metronidazole 125mg in 5ml oral Suspension.lcb*
Date Acquired	*:08-11-2023*
Date Processed	*:08-11-2023*







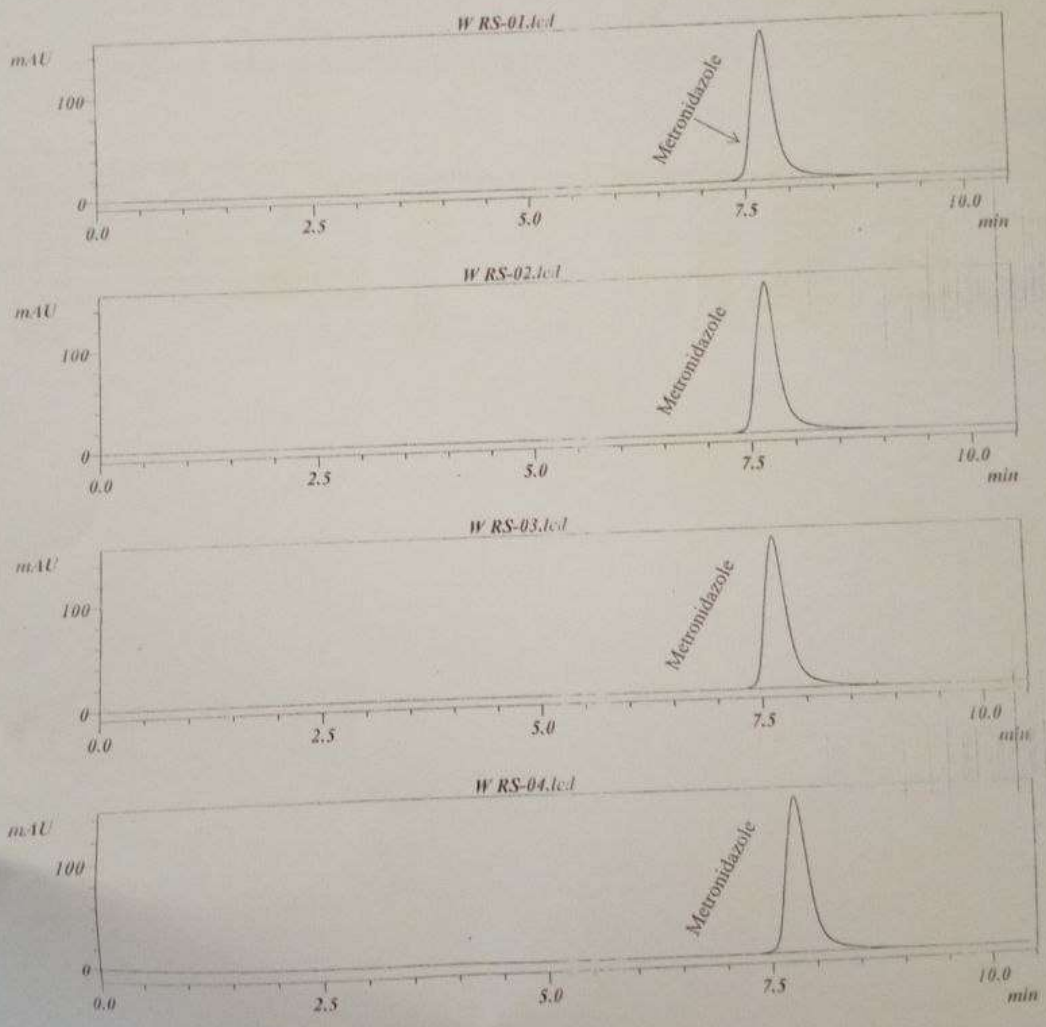
<< PDA >>
ID#1 Compound Name: Metronidazole

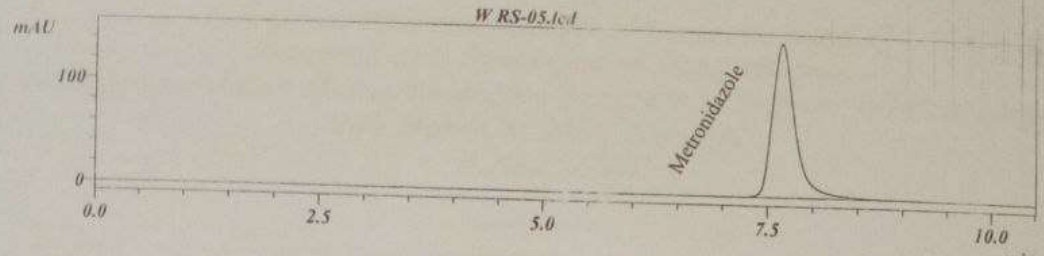
Data File Name	*Sample Name*	*mple*	*Ret. Time*	*Tailing Factor*	*er of Theoretical Plate*	*Area*	*Conc.*
LB-CMC-01.lc	*Metronidazole 125mg i*	*LB-C*	*7.742*	*0.989*	*7271*	*2277303*	*95.993*
LB-CMC-02.lc	*Metronidazole 125mg i*	*LB-C*	*7.734*	*1.003*	*7304*	*2273560*	*95.835*
LB-CMC-03.lc	*Metronidazole 125mg i*	*LB-C*	*7.724*	*0.990*	*7303*	*2279149*	*96.070*
Average			*7.734*	*0.994*	*7292*	*2276671*	*95.966*
%RSD			*0.116*	*0.753*	*0.260*	*0.125*	*0.125*

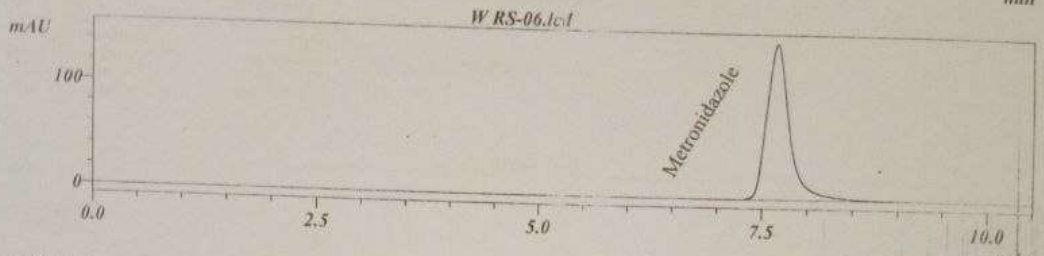
Ethiopian Pharmaceuticals Manufacturing S.C
Research and Development Department
Analysis Report for Assay of Metronidazole Benzoate 125mg in 5ml Oral Suspension.
2nd Month Stability Sample.
Working Reference Standard.

Sample Information

Acquired by	: Nurlegn N.
Sample Name	: Metronidazole Working RS
Sample ID	: W RS-01
Data Filename	: W RS-01.lcd
Method Filename	: Metrondazole.lcm
Batch Filename	: Metronidazole 125mg in 5ml oral Suspension.lcb
Date Acquired	:08-12-2023
Date Processed	:08-12-2023







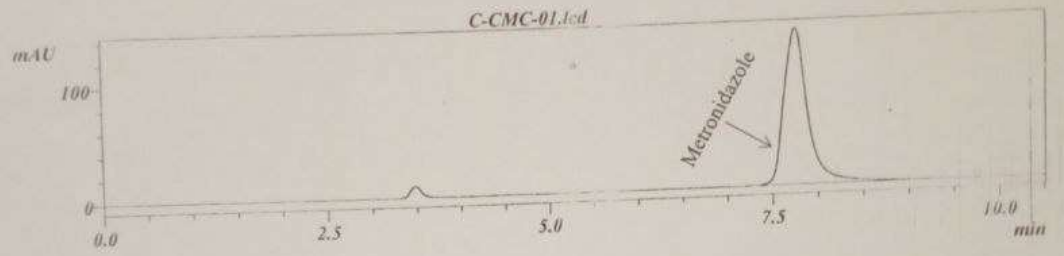
<< PDA >>
ID#1 Compound Name: Metronidazole

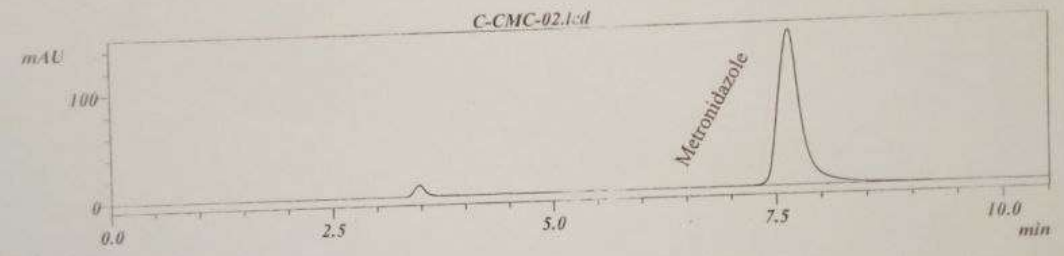
Data File Name	Sample Name	mple	Ret. Time	Tailing Factor	r of Theoretical Plate	Area	Conc.
W RS-01.lcd	Metronidazole Working W RS		7.699	1.430	4707	2595362	100.000
W RS-02.lcd	Metronidazole Working W RS		7.681	1.428	4739	2596910	100.185
W RS-03.lcd	Metronidazole Working W RS		7.671	1.439	4787	2595965	100.071
W RS-04.lcd	Metronidazole Working W RS		7.790	1.397	4684	2584077	99.782
W RS-05.lcd	Metronidazole Working W RS		7.655	1.431	4820	2599593	100.169
W RS-06.lcd	Metronidazole Working W RS		7.647	1.458	4837	2600396	100.167
Average			7.691	1.431	4762	2595384	100.062
%RSD			0.679	1.382	1.301	0.227	0.155

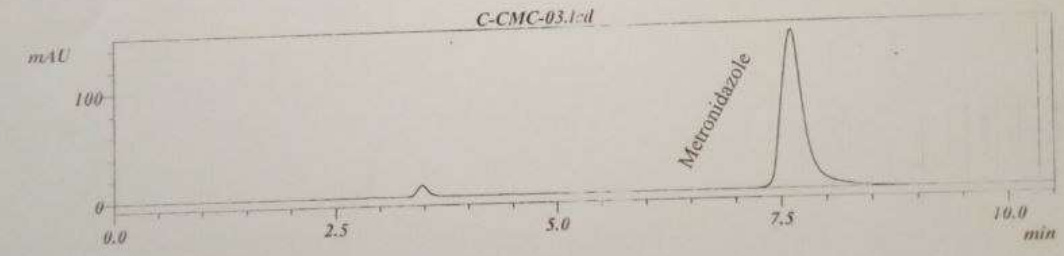
Ethiopian Pharmaceuticals Manufacturing S.C
Research and Development Department
Analysis Report for Assay of Metronidazole Benzoate 125mg in 5ml Oral Suspensio
2nd Month Stability Sample.
B.No.C-CMC

Sample Information

Acquired by	:Nurlegn N.
Sample Name	: Metronidazole 125mg in 5ml oral Suspension Assay
Sample ID	: C-CMC-01
Data Filename	: C-CMC-01.lcd
Method Filename	: Metrondazole.lcm
Batch Filename	: Metronidazole 125mg in 5ml oral Suspension.lcb
Date Acquired	:08-12-2023
Date Processed	:08-12-2023







<< PDA >>
ID#1 Compound Name: Metronidazole

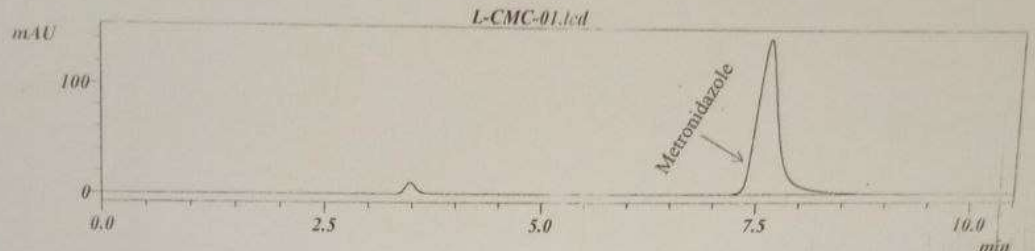
Data File Name	Sample Name	mple	Ret. Time	Tailing Factor	r of Theoretical Plate	Area	Conc.
C-CMC-01.lcd	Metronidazole 125mg i	C-CM	7.737	1.417	4697	2490303	96.161
C-CMC-02.lcd	Metronidazole 125mg i	C-CM	7.636	1.473	4867	2500201	96.307
C-CMC-03.lcd	Metronidazole 125mg i	C-CM	7.623	1.464	4842	2497620	96.208
Average			7.665	1.451	4802	2496041	96.225
%RSD			0.811	2.055	1.907	0.206	0.077

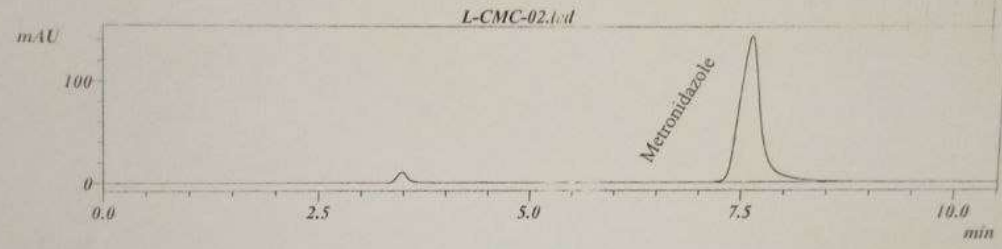
pH = 5.64

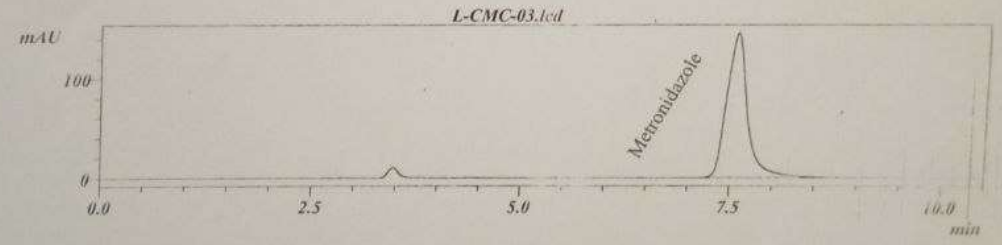
Ethiopian Pharmaceuticals Manufacturing S.C
Research and Development Department
Analysis Report for Assay of Metronidazole Benzoate 125mg in 5ml Oral Suspension
2nd Month Stability Sample.
B.No.L-CMC

Sample Information

Acquired by	:Nurlegn N.
Sample Name	: Metronidazole 125mg in 5ml oral Suspension Assay
Sample ID	: L-CMC-01
Data Filename	: L-CMC-01.lcd
Method Filename	: Metrondazole.lcm
Batch Filename	: Metronidazole 125mg in 5ml oral Suspension.lcb
Date Acquired	:08-12-2023
Date Processed	:08-12-2023







<< PDA >>
ID#1 Compound Name: Metronidazole

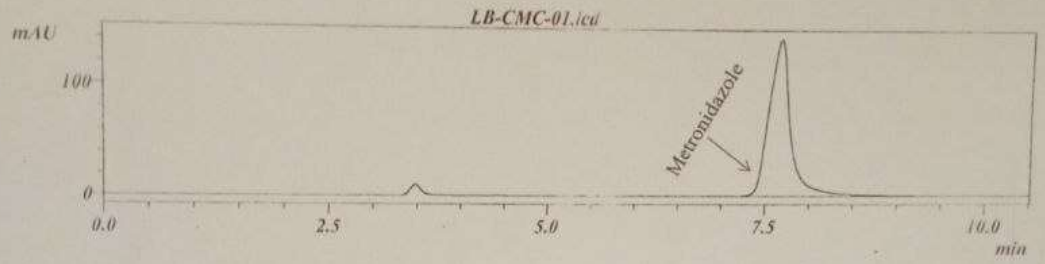
Data File Name	Sample Name	mple	Ret. Time	Tailing Factor	y of Theoretical Plate	Area	Conc.
L-CMC-01.lcd	Metronidazole 125mg i	L-CM	7.569	1.419	4911	2478204	95.460
L-CMC-02.lcd	Metronidazole 125mg i	L-CM	7.550	1.418	4884	2479645	95.515
L-CMC-03.lcd	Metronidazole 125mg i	L-CM	7.542	1.427	4909	2480493	95.548
Average			7.554	1.438	4901	2479447	95.508
%RSD			0.183	0.752	0.306	0.047	0.047

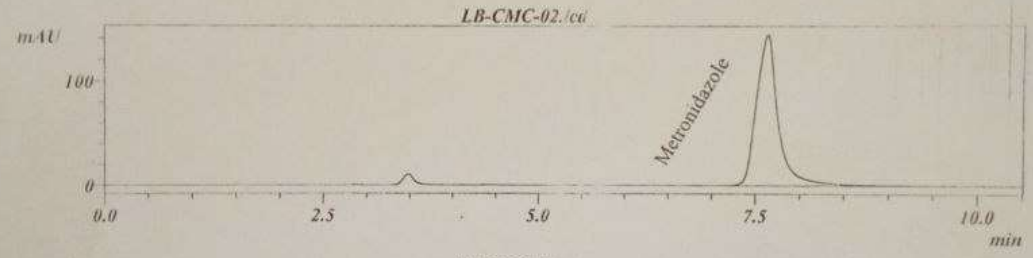
PH = 5.68

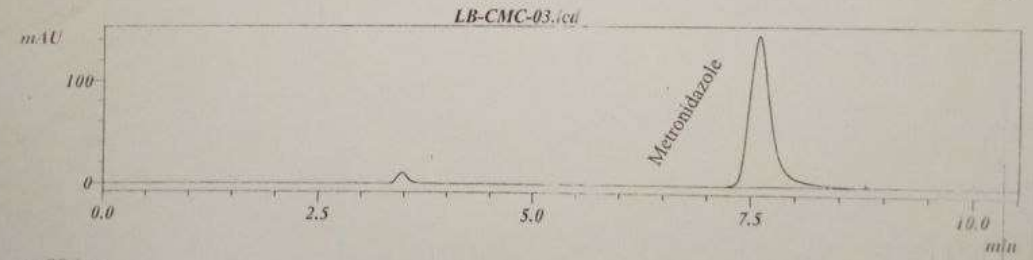
Ethiopian Pharmaceuticals Manufacturing S.C
Research and Development Department
Analysis Report for Assay of Metronidazole Benzoate 125mg in 5ml Oral Suspens
2nd Month Stability Sample.
B.No.LB-CMC

Sample Information

Acquired by	:Nurlegn N.
Sample Name	: Metronidazole 125mg in 5ml oral Suspension Assay
Sample ID	: LB-CMC-01
Data Filename	: LB-CMC-01.lcd
Method Filename	: Metronidazole.lcm
Batch Filename	: Metronidazole 125mg in 5ml oral Suspensio..lcb
Date Acquired	:08-12-2023
Date Processed	:08-12-2023







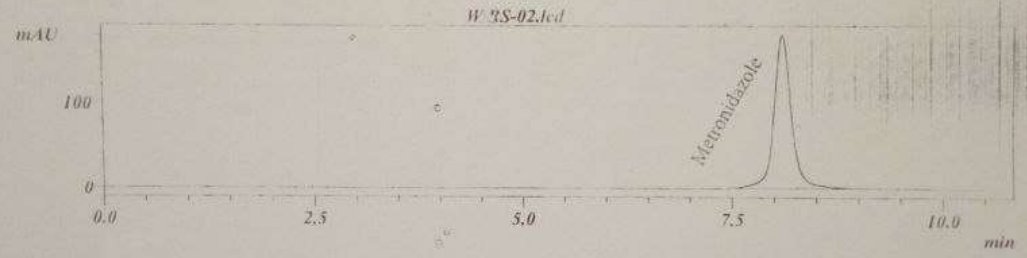
<< PDA >>
ID#1 Compound Name: Metronidazole

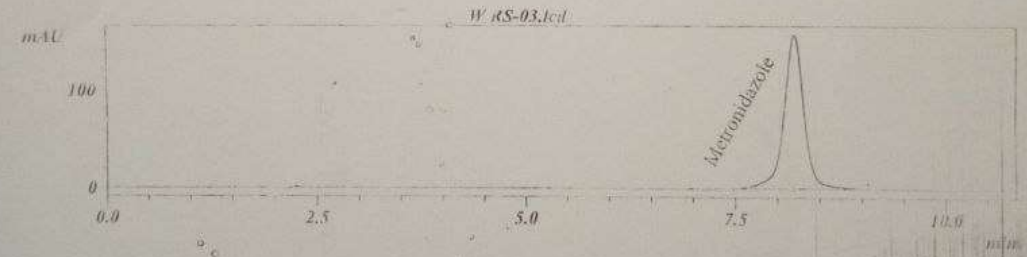
Data File Name	Sample Name	mple	Ret. Time	Tailing Factor	s of Theoretical Plate	Area	Conc.
LB-CMC-01.lc	Metronidazole 125mg in	LB-C	7.609	1.493	4906	2491648	95.978
LB-CMC-02.lc	Metronidazole 125mg in	LB-C	7.596	1.466	4871	2487591	95.821
LB-CMC-03.lc	Metronidazole 125mg in	LB-C	7.585	1.448	4878	2491297	95.964
Average			7.597	1.469	4885	2490179	95.921
%RSD			0.159	1.515	0.385	0.090	0.090

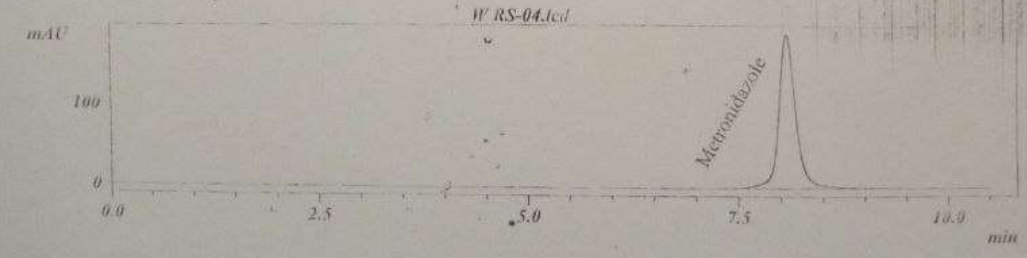
Ethiopian Pharmaceuticals Manufacturing S.C
Research and Development Department
Analysis Report for Assay of Metronidazole Benzoate 125mg in 5ml Oral Suspension.
3rd Month Stability Sample.
Working Reference Standard.

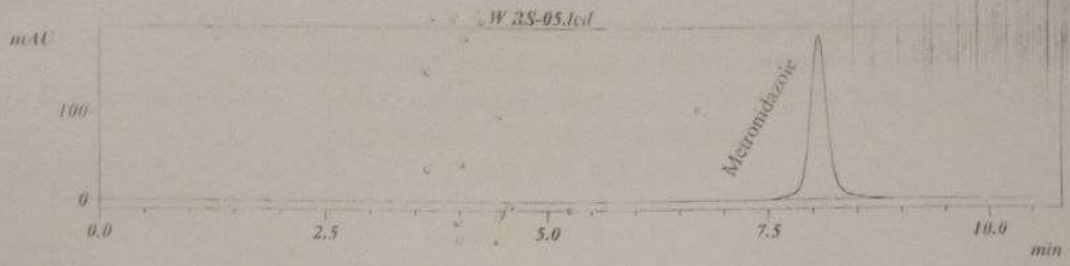
Sample Information

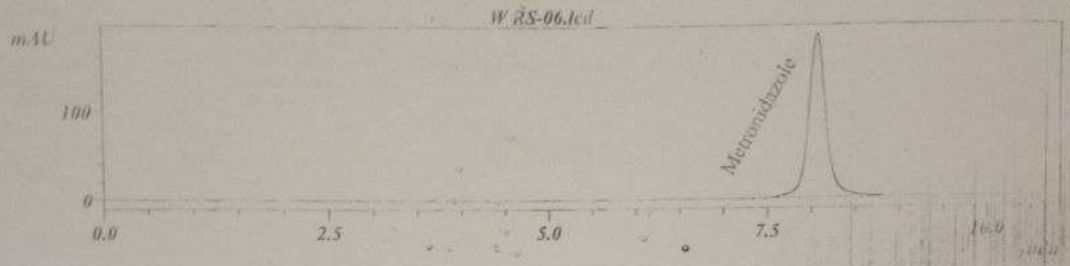
Acquired by	:Nurlegn N.
Sample Name	: Metronidazole Working RS
Sample ID	: W RS-01
Data Filename	: W RS-01.lcd
Method Filename	: Metrandazole.lcm
Batch Filename	: Metronidazole 125mg in 5ml oral Suspension.lcb
Date Acquired	:08-01-2024
Date Processed	:08-01-2024











<< PDA >>

ID#1 Compound Name: Metronidazole

Data File Name	Sample Name	mple	Ret. Time	Tailing Factor	e of Theoretical Plate	Area	Conc.
W RS-01.lcd	Metronidazole Working W RS		8.121	1.003	8142	2591802	100.000
W RS-02.lcd	Metronidazole Working W RS		8.107	1.050	8297	2590738	99.979
W RS-03.lcd	Metronidazole Working W RS		8.215	0.890	6293	2591696	100.011
W RS-04.lcd	Metronidazole Working W RS		8.055	1.077	8380	2600786	100.271
W RS-05.lcd	Metronidazole Working W RS		2.060	1.106	8346	2594657	100.028
W RS-06.lcd	Metronidazole Working W RS		8.052	1.121	8331	2595837	100.061
Average			8.106	1.041	7965	2594233	100.058
%RSD			0.734	8.201	10.336	0.144	0.108

pH = 5.60

Ethiopian Pharmaceuticals Manufacturing S.C
Research and Development Department
Analysis Report for Assay of Metronidazole Benzoate 125mg in 5ml Oral Suspension.
3rd Month Stability Sample.
B.No.C-CMC

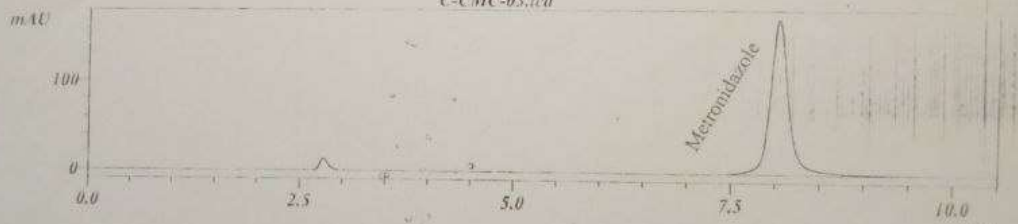
Sample Information

Acquired by	:Natiegn N.
Sample Name	: Metronidazole 125mg in 5ml oral Suspension Assay
Sample ID	: C-CMC-02
Data Filename	: C-CMC-01.lcd
Method Filename	: Metronidazole.lcm
Batch Filename	: Metronidazole 125mg in 5ml oral Suspension.lcb
Date Acquired	:08-01-2024
Date Processed	:08-01-2024

C-CMC-01.lcd

C-CMC-02.lcd

C-CMC-03.lcd



<< PDA >>

ID#1 Compound Name: Metronidazole

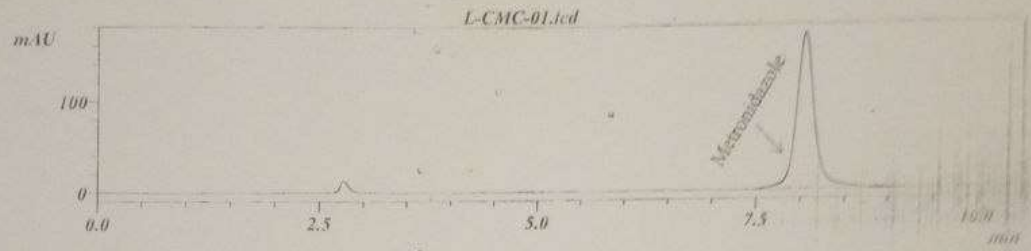
Data File Name	Sample Name	Sample ID	Ret. Time	Tailing Factor	# of Theoretical Plate	Area	Conc.
C-CMC-01.lcd	Metronidazole 125mg in 5ml C-CMC		8.047	1.158	8250	2490908	96.016
C-CMC-02.lcd	Metronidazole 125mg in 5ml C-CMC		8.047	1.159	8250	2491069	96.023
C-CMC-03.lcd	Metronidazole 125mg in 5ml C-CMC		8.037	1.176	8169	2489363	95.957
Average			8.044	1.164	8223	2490447	95.999
%RSD			0.069	0.878	0.565	0.038	0.038

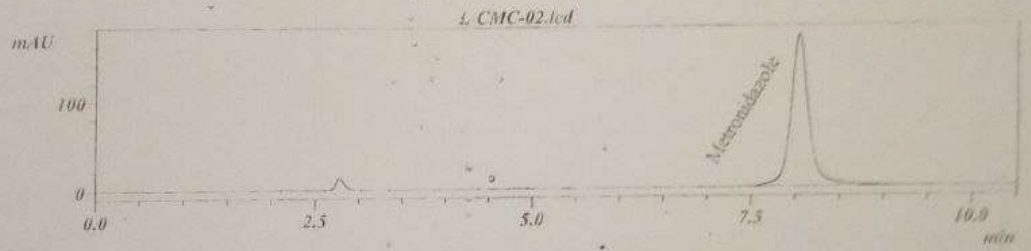
PH = 5.58

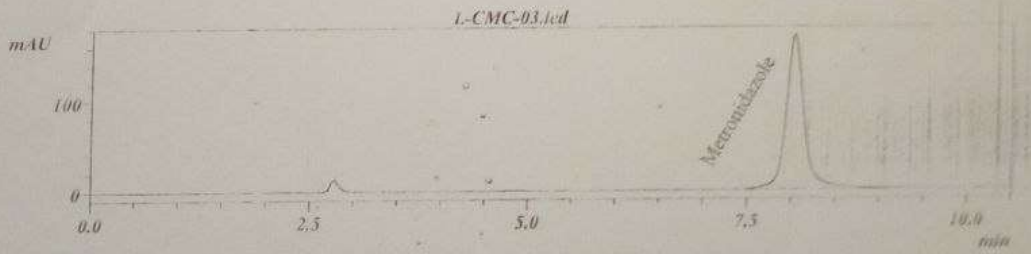
Ethiopian Pharmaceuticals Manufacturing S.C
Research and Development Department
Analysis Report for Assay of Metronidazole Benzoate 125mg in 5ml Oral Suspension
3rd Month Stability Sample.
B.No.L-CMC

Sample Information

Acquired by	:Nuriegn N.
Sample Name	: Metronidazole 125mg in 5ml oral Suspension Assay
Data Filename	: L-CMC-01.lcd
Method Filename	: Metronidazole.lcm
Batch Filename	: Metronidazole 125mg in 5ml oral Suspenston.lcb
Date Acquired	:08-01-2024
Date Processed	:08-01-2024







<< PDA >>
ID#1 Compound Name: Metronidazole

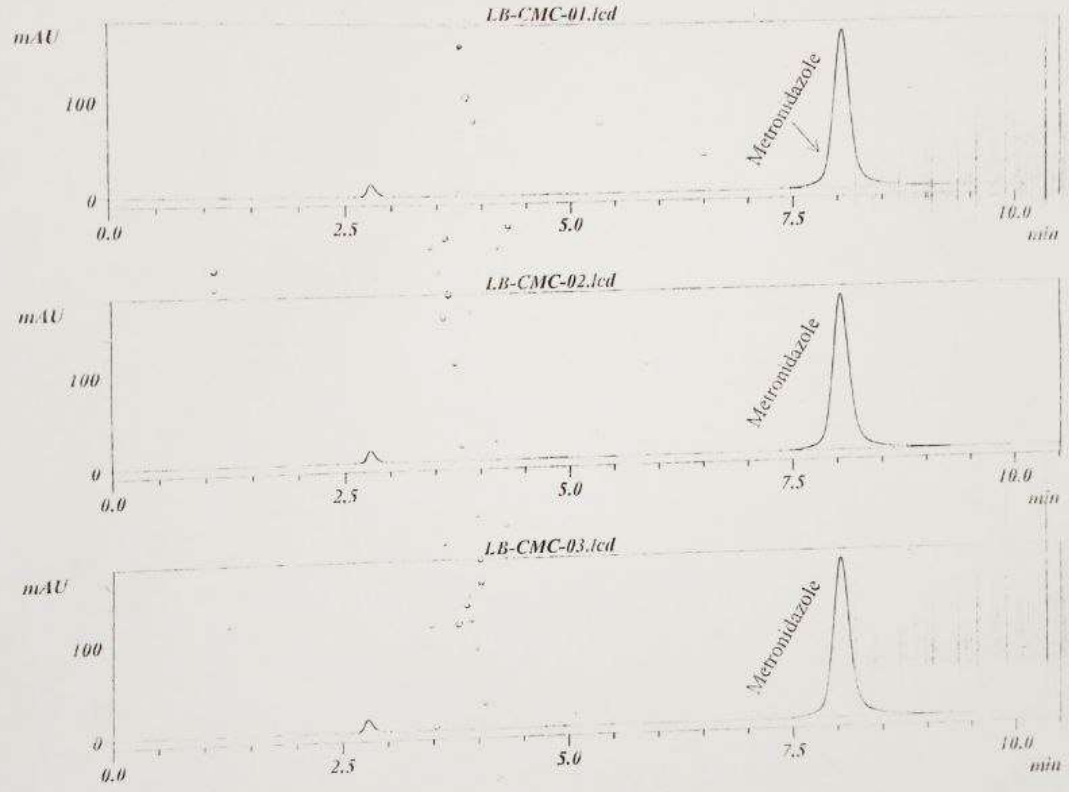
Data File Name	Sample Name	mple	Ret. Time	Tailing Factor	r of Theoretical Plate	Area	Conc.
L-CMC-01.lcd	Metronidazole 125mg in	LB-C	8.032	1.188	8217	2470434	95.227
L-CMC-02.lcd	Metronidazole 125mg in	LB-C	8.032	1.188	8218	2470761	95.240
L-CMC-03.lcd	Metronidazole 125mg in	LB-C	8.032	1.189	8216	2475623	95.427
Average			8.032	1.188	8217	2472273	95.298
%RSD			0.000	0.043	0.014	0.118	0.118

PH = 5.89

Ethiopian Pharmaceuticals Manufacturing S.C
Research and Development Department
alysis Report for Assay of Metronidazole Benzoate 125mg in 5ml Oral Suspension
3rd Month Stability Sample.
B.No.LB-CMC

Sample Information

Acquired by	: Nurhegn N.
Sample Name	: Metronidazole 125mg in 5ml oral Suspension Assay
Sample ID	: LB-CMC-01
Data Filename	: LB-CMC-01.lcd
Method Filename	: Metronidazole.lcm
Batch Filename	: Metronidazole 125mg in 5ml oral Suspension.lch
Date Acquired	: 08-01-2024
Date Processed	:08-01-2024



<< PDA >>
ID#1 Compound Name: Metronidazole

Data File Name	Sample Name	Ret. Time	Tailing Factor	# of Theoretical Plate	Area	Conc.
LB-CMC-01.lc	Metronidazole 125mg in LB-C	8.032	1.189	8213	2481105	95.639
LB-CMC-02.lc	Metronidazole 125mg in LB-C	8.032	1.190	8212	2484111	95.754
LB-CMC-03.lc	Metronidazole 125mg in LB-C	8.032	1.190	8211	2487689	95.892
		8.032	1.190	8212	2484302	95.762
Average		0.000	0.001	0.009	0.133	0.133
%RSD						

Metronidazol Benzoate 125mg/5ml Oral Suspension

Assay (As BP)

Method: HPLC

Mobil phase: 40:60 (1.25% w/v) Ammonium Acetate & methanol

12.5gm Ammonium Acetate in 1000 ml V. flask and Dissolve with water then adjust the pH = 7.0 with Dilute Acetic Acid of Ammo

Column: 25cm x 4.6mm ODS (octadecylsilyl silica gel)

Wave length: 310 nm.

Flow rate: 1.0 ml/min

injection Volum: 20 µl

Sample = 200mg (8ml) metronidazol / 250 ml + 150 ml meton then H2O centrifuge * 2.5ml / 25ml = 0.0 (60% met 40% H

125mg = 5ml
200mg = 8ml

Std → 62.5mg (40mg) metr. Benzo metr. / 50 ml + 1ml dimethyl formamide + 30 ml meton then H2O * 2.5ml / 25ml = 0.08 (60% meton 40% H2

200mg (metronidazol) = 312.5mg (metr. Ben
40mg (>>) = 62.5mg (>>

Det. By Melaku Wondaferash AAU.			
Collected by Nurlen Yesuf			
Code	**Local Name**	**Family**	**Scientific Name**
NY001	Temer	ARECACEAE	Phoenix dactylifera L.