بسم الله الرحمن الرحيم

Sudan University of Science and Technology

College of Graduate Studies

كلية الدراسات العليا

Tracing of Photochemical Reaction of Some Sudanese Pharmaceutical Product

متابعة التفاعلات الكيميو ضوئية لبعض المنتجات الصيدلانية السودانية

A Thesis Submitted for the Fulfilment of the Requirements of the Master Degree in Chemistry

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سورة نوح الاية 15-16

DeDication

I dedIcate thIs work to,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,

My father , Mother ,,,,,,,,,,,,,,,

Brothers, sister,,,,,,,,,,

And friends.,,,,,,,,,

ACKNOWLEDGEMENTS

Thank god for giving me the will, strength, patience to go through all obstacles in order to complete this research project.

First of all, I would like to express my deepest gratitude to Dr. Elmugdad Ahmed Ali for his supervision, valuable and critical ideas. Useful comments and helpful guidance throughout my research.

My appreciation extends to all staff of Quality Control and Quality Assurant in General Medicines Company for their continuous help.

Abstract:

Pharmaceuticals are subject to degradation by light, heat and time. There is a danger of their passage to environment mainly the aquatic ecosystem. Five drugs (active ingredients) amoxicillin, carbamazepine, ciprofloxacin, cefradine and mefenamic acid were selected to study their photodegradation in the aqueous solution by uv-vis spectrophotometry. The separated moieties in HPLC were compared with a standard samples in sunlight and in dark conditions. The amoxicillin is found to be more stable than the other drugs. The photoproducts were identified by GC-MS to amoxicillin and carbamazepine: For amoxicillin as amoxicillin penicilloic acid ($C_{16}H_{21}N_3O_6S$). For carbamazepine, the degraded compounds are of molecular weights 196 and 256. Kinetic study of half-lives by equation are of the first order was reached $t_{½}$ AMX 693 h, CBZ 693h, CIP 31.5h, CEF 9.24h and MEF 173h.

المستخلص:

تخضع المنتجات الدوائية لعمليات التفكك بالضوء والحرارة والزمن. وتسرب هذه المركبات يؤثر على البيئة خاصة البيئة المائية. تم إختيار خمس عينات (المواد الفعالة) الأموكسيسلين و الكاربوميزابين والسفرادين والسيبرفلوكساسين وحمض الميفنميك لمتابعة تفككهم الضوئى في الوسط المائي بواسطـــــــــــــــة مطيافية الأشعـــة فوق البنفسجية والمرئية . وتمت مقارنة المكونات المنفصله بجهاز كروماتوغرافيا السائل عالي الضغط مع عينات قياسية في ضوء الشمس و في ظروف العتمة (الظلام) . وجد أن الأموكسسلين أكثر ثباتا من المركبات الأخرى و تم تشخيص بعض المركبات المتفككة للأموكسيسلين والكاربوميزابيين بواسطة بمطياف الكتلة الموصلكرامتوغرافيا الغاز بالنسبة للأموكسيسلين : كحمض بنسلونوك الاموكسيسلين(C_{16} $H_{21}N_3O_6S$) أما بالنسبة لكاربوميزابين فقد انفصل مركبين بالأوزان الجزيئة 196و256 من غير معرفة تسميتهما لعدم وجود مرجعية. وبدراسة حركية التفاعل لعمر النصف بالمعادلة من الرتبة الاولي وجد أن عمر النصف:

AMX 693 h, CBZ 693h, CIP 31.5h, CEF 9.24h, MEF 173h

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List of Abbreviations:

R&D:	Research and development.
AMX:	Amoxicillin.
USP:	united States pharmacopeia.
WHO:	World health organization.
CBZ:	Carbamazepine.
CIP:	Ciprofloxacin.
CEF:	Cefradine.
MEF:	Mefenamic acid.
STP:	Sewage treatment plant.
DOM:	Dissolved organic matter.
PPCPs:	Pharmaceutical and personal care products.
PAC:	Powdered activated carbon.
KF:	Freundlich constant.
ESI-MS:	Electrospray mass spectrometry.
NOM:	Natural organic matter.
UV:	Ultraviolet.
VIS:	Visible.
uv-vis:	Ultraviolet and Visible.
UPLC-MS:	Ultra performace liquid chromatography.
DSC:	Differential scanning calorimetry.

MCR.ALS: Multivariate curve resolution alternating least squares.

QSPR: Quantitative structure property relationship.

HPLC: High pressure liquid chromatography.

GC.MS: Gas chromatography mass spectrometry.

NMT : Not more than

WWTP: Waste water treatment plant.

Chapter one

1.1 :Introduction:

1.1.1 :Pharmaceutical Industry:

The pharmaceutical industry develops, produces, and markets drugs or pharmaceuticals licensed for use as medications (John et al. 2007).

Pharmaceutical companies are allowed to deal in generic or brand medications and medical devices. They are subject to a variety of laws and regulations regarding the patenting, testing and ensuring safety and efficacy and marketing of drugs.

The progress of medicine has been the development of the pharmaceutical industry. In the past two decades, emphasis has placed on medicinal, chemical, biological, and pharmacological research to such an extent that this era is recognized, more than any other comparable period in history, for the new and effective drugs that have come from scientific laboratory investigators, into the hands of physicians, who prescribe them to health of people. Their manufacture has been made possible by an industry whose highly skilled chemists, pharmacists, and chemical engineers are being challenged to discover more and better products for the benefit of humankind, the human life span has increased since 1900 from a life expectancy of 49 years to the present 70 years (Shreve & Brink 1975).

The pharmaceutical industry is one of the most important sectors of the heath care worldwide. Pharmaceutical materials are all manufactured in very small quantities relative to other types of compounds, but their dollar value is exceedingly high.

The pharmaceutical industry must invest more in research and development than any other industry to discover innovative drugs and therapies to fulfill medical need. Because of the high Research & Development cost and meet growth expectations and goals for new product launches, many companies are constantly reorganizing their research operations to be more effective.

Competition between companies arises not only from new products but also from generic drugs. Generic products are copies of the original products. They are products by specialized manufacturers, after the patent of the original product is expired or when it is not patented in certain countries (Ali, Ali &Speight 2005).

The use drugs to relieve pain and to ward off death are interwoven with the ancient superstition that evil spirits cause disease. The healing powers of Mythological personages, particularly of Aesculapius,
Son of Apollo, were sought in primitive cultures. The papyrus Ebers, which takes us back to the beginning of recorded history in the Nile Valley ,contains drug formulas with as many as 35 ingredients , including botanicals ,minerals, and animal products. A few of the minerals, such as sulfur, magnesia and soda, still appear in current pharmacopeias. It was the Greeks, however who through Hippocrates and Galen, made an effort to approach therapy rationally rather than mystically. Paracelsus, born in 1493, who experimented both in the laboratory and the clinic, may be looked upon as the founder of chemotherapy.
Three centuries later, while Liebig and his students in Germany were synthesizing biologically active compounds method for experimental medicine were developed in France by Bernard, Magendie, and others.
Although the American pharmaceutical industry had made a modest beginning in 1786, the synthetic organic Chemicals ether and chloroform were not used for anesthesia until the 1840s.three years after the end of the Civil War, the first integrated industrial synthetic organic manufacturing operation was established in the United States .in the meantime Pasteur, in studying the fermentation of beet sugar to alcohol, formulated the germ theory of disease and developed techniques for bacteriological study. The groundwork for modern pharmaceutical research was begun in1881with the establishment of a scientific division of Eli Lilly and Co. The shortage of important drugs such as veronal and Novocaine, caused by the entry of the united states into world war I, precipitated expansion of the pharmaceutical industry into successful effort to produce the synthetic chemicals needed .
Development of insulin, liver extract, and the short-acting barbiturates were milestones of the next decade, sulfa drugs vitamins were rapidly added many product lines during the 1930s. Blood plasma, new antimalarials, and the dramatic development of penicillin resulted from the demands of war. But the spectacular surge of new product which included steroid hormones, tranquilizers vaccines, and medium –spectrum antibiotics, came after World War II. Research has now been stepped up to find more efficient drugs for

the unconquered maladies arthritis cancer, heart condition, high blood pressure, hepatitis and diseases among other (Shreve & Brink 1975).

1.1.1.1: Classification and the chemistry of pharmaceutical product:

(i) The analgesics:

Analgesics represent an important class of drugs that is used primarily for the relief of severe pain .They are classified as narcotic and non-narcotic. The opiates are perhaps the oldest drugs known to man .Opium contain a complex mixture of almost 25alkaloids. The principal alkaloid in the mixture, and the one responsible for analgesic activity, is morphine. Pure morphine is especially good for analgesics good for treating dull, constant pain, and pain, and periodic pain. Unfortunately, it has a large number of said effects, which include the depression of the respiratory center, excitation, nausea, euphoria, dependence, and other.

(ii) Antiallergy and antiasthmatic drugs:

Allergic reactions occur when the body's immune system reacts to a foreign substance that is typically not toxic. Antihistamines such as Claritin ,Hismanal and Zyrtec are used to relieve allergies , such as seasonal hay fever and other form of allergies , by counteracting the effect of histamines in the body that are the transmitters of the allergic symptoms. The first generations of antihistamines, known as piperadines, include azatadine hydroxyzine HCl and others. The second generation of antihistamines includes stronger drugs that inhibit the release of histamine and other inflammatory mediators from several cell types. Examples of the group include terfenidine and loratadine.

(iii) Anti-bacteriais and antibiotics:

The fight against bacterial infection is one of the greatest stories of medicinal chemistry. Bacteria were first identified in the 1670s by Van Leeuwenhoek, following his invention of the miscroscope .Sulfonamides (known as sulfa drugs) represent the best example of antibacterial agents before the discovery of penicillin.

(iv) Anti-depressants:

The new era of therapeutics for the treatment of depression began in the late 1950s with the introduction of both the monoamine oxidase inhibitors and the tricyclic antidepressants. The first monoamine oxidase inhibitor was

iproniazid, which initially was used as an antituberculosis drug until it was observed that patients taking it exhibited excitement and euphoria. Some of the major drugs in the category of monoamine oxidase include phenelzine, moclobemide toloxatone and others.

(v) Antiepileptics:

Epilepsy is a disease that characterized by recurring convulsive seizures Phenobarbital, posses specific usefulness in epilepsy. In general barbituric acid derivatives are synthesized from phenylethylmalonic diethyl ester. Other drugs are also used for the treatment of epilepsy, phenytoin, carbomazepine and valproic acid is well-known anticonvulsants.

(vi) Antihypertensive:

Antihypertensive drugs are grouped into four main categories that include adrenergic blockers (e.g. cardura, minizide), adrenergic stimulants (e.g. aldoclor, clorpres) adrenergic blockers (e.g. normodyne) angiotensin converting enzyme inhibitors (e.g. aceon, captopril) and angiotensin converting enzyme inhibitors with calcium channel blockers (e.g. nifedipine tarka).

(vii) Antiulcer:

The methods available for treating ulcers were limited and unsatisfactory before the introduction of the cimetidine program in 1964. Ulcers are localized erosions of the mucous membrane of the stomach. For a long time it was not known how these ulcers arise , but the presence of gastric acid (HCl), released by cells known as parietal cells in the stomach aggravates the problem and delays recovery . In the 1960s, sodium bicarbonate or calcium carbonate was used to neutralize gastric acid.

(viii) Antipsychotic agents:

These drugs are usually used to treat patients with psychotic or other serious related illnesses. They have common side effects such as muscle spasms, restlessness, and Parkinsonism. However, these drugs are considered safe, because the side effects are transient. Clozaril, is the most active drug with almost percent incidence of agranulocytosis .Other antipsychotics agents such as geodon, thiothixene and zyprexa are also widely used as antipsychotic drugs.

(ix) Diuretics:

Diuretics are highly efficient drugs for the treatment of edema associated with congestive heart failure. They are also used to increase the volume of urine excreted by the kidneys. For example, duranide a dichlorinated benzene disulfonamide is an oral carbonic anhydrase inhibitor.

(x) Contraceptives:

Millions of women throughout the world take contraceptives the most common type of oral contraceptive is acombination of a synthetic estrogen such as mestranol or ethinylestradiol and aprogestin such as levonorgestrel or norethynodrel. The contraceptives are sold under different trade names such as Levlen, Brevicon, Modicon, Necon, ovcon, and other.

(xi) Vitamins:

Vitamin B1 is essential for daily growth and the prevention of beriberi. The commercial vitamin B1is obtained by the condensation of 6-amino-5-bromomethyl-2-methylpyrimidine hydrobromide with 5-(hydroxyethyl)-4-methylthiozole (Ali, Ali &Speight 2005).

1.1.1.2: Dosage forms of pharmaceutical product:

The most common dosage forms for pharmaceutical product include tablets, capsules, liquids, cream, ointment, as well as aerosols, patches and injectable dosages.

(i) Tablets: tablets are most popular type of dosage form, since they offer convenience, stability accuracy and precision and bioavailability of the active ingredients. Tablets are prepared by combining the active ingredient with filler such as sugar or starch and a binder, such as corn syrup or starch. The filler is added to ensure that the active pharmaceutical ingredient is diluted to the correct concentration. A binder is needed to bind tablet particles together. In addition a lubricant such as magnesium stearate or polyethylene glycol may be added to facilitate equipment operation, or to slow disintegration or dissolution of the tablet in the stomach.

(ii) Capsules:

the most common solid oral dosage form after tablets is the capsule. There are two forms of capsule

- Soft –gelatin capsules that contain Glycerol as well gelatin maintain plasticity even when dried.
- Hard capsules are formed by dipping metal pins in to solution of gelatin a specific temperature.

Hard capsules are made in to sections, cap and body which are then filled. Soft-gelatin capsules have their shell formed and filled in succession in one manufacturing procedure. Soft-gelatin capsules are generally filled with non-aqueous solutions. Soft- shelled capsules are formed by placing two continuous gelatin films between rotary die plates .Commercially filled soft gelatin capsules come in a wide choice of sizes and shapes they may be round ,oval , oblong, tube, or suppository-shaped .

(iii) Liquid dosage forms: The liquid products are prepared by dissolving the ingredients in the appropriate solvent systems. Dyes, flavors sweeteners, and antimicrobial preservatives are added to mask unpleasant taste or appearance and to prevent mold and bacterial growth. The final products are stored in large tanks before final packaging .If the liquid is used for injection or ophthalmic use the liquid must be sterilized .solutions for external or oral use do not require sterilization but generally contain antimicrobial preservatives.

(iv) Creams, ointments, and pastes: Cream is semisolid emulsions and is either oil-in- water or water-in-oil. Generally the ingredients of the two phases are heated separately 70-80°C while they are mixed and stirred vigorously to achieve emulsification. A solid ingredient can be added to the appropriate phase before emulsification or may be dispersed at some point after the emulsification step.

Ointments are prepared by melting together the active ingredient with a base such as petroleum derivative or max. The powder drug components are added while stirring and the mixture is cooled. The product then is passed

through a roller mill to achieve the particle size range desired for the dispersed solid.

(v) Suppositories: Suppositories are semirigid and plastic dosage forms designed to be delivered to body cavities such as the rectum, vagina, or urethra. They either melt at body temperature (cocoa butter) or are dissolved in the cavity (polyethylene glycols or glycerogelatin) Suppositories can be used for systemic therapy (rectal Suppositories) or for local treatment.

(vi) Parenteral dosage forms: Parenteral dosage forms are administered by injection into body fluid systems. They are of special utility for unconscious patients (Ali, Ali &Speight 2005).

(vii) Suspenations: suspension is liquid preparations that consist of solid particles dispersed throughout a liquid phase in which the particles are not soluble dosage form officially categorized as suspension are designated as such if they are not included in other more specific categories of suspension such as Oral suspensions , topical suspension ,etc.

Oral suspensions are liquid preparation containing solid particles dispersed in liquid vehicle, with suitable flavoring agents, intended for oral administration (USP 2007).

1.1.2: Drugs selected:

1.1.2.1: Amoxicillin $3H_2O$:

Amoxicillin is an antibiotic useful for the treatment of a number of bacterial infections.

It is a moderate-spectrum, bacteriolytic, β-Lactam antibiotic in the amino penicillin family used to treat susceptible Gram positive and Gram-negative bacteria. It is usually the drug of choice within the class because it is better-absorbed, following oral administration, than other β-lactam antibiotics. Amoxicillin is susceptible to degradation by β-lactamase-producing bacteria, which are resistant to a narrow spectrum of β-lactam antibiotics, such as penicillin. For this reason, it is often combined with clavulanic acid, a β-lactamase inhibitor. This drug combination is commonly called co-amoxiclav. Combining the drugs increases effectiveness by reducing susceptibility to β-lactamase resistance.

Side effects include an increased risk of yeast infections and, when used in combination with clavulanic acid, diarrhea (Gillies et al .2014).

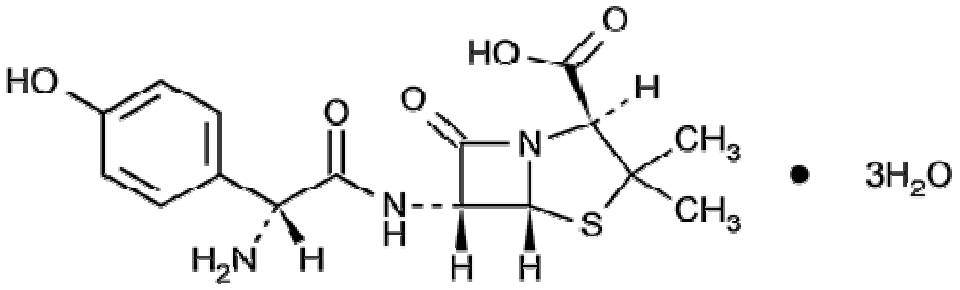
Amoxicillin is one of the most common antibiotics prescribed for children. The drug first became available in 1972. It is on the World Health Organization's List of Essential Medicines, a list of the most important medications needed in a basic health system (WHO 2013).

(i) Appearance: white, practically odorless, crystalline powder.

(ii) Solubility: slightly soluble in water and in methanol, insoluble in benzene, in carbon tetrachloride, and in chloroform. (USP 2007)

The amoxicillin molecular formula is $C_{16}H_{19}N_3O_5S \cdot 3H_2O$ and the molecular weight is 419.45

(iii) Chemical Structure:



(iv) Use of Amoxicillin:

Amoxicillin is an orally absorbed broad-spectmm antibiotic with a variety of clinical uses including ear, nose, and throat infections and lower respiratorytract infections. As a chemical modification of ampicillin, which is poorly absorbed after oral administration, amoxicillin is better absorbed by the gastrointestinal tract than ampicillin. Amoxicillin is prescribed for the treatment of infections of beta lactamase-negative stains, which are bacterial strains that do not possess the ability to produce beta-lactamase enzymes. Amoxicillin is semi-synthetic penicillin obtaining its antimicrobial properties from the presence of a beta-lactam ring. Amoxicillin and other penicillin-like antibiotics target bacterial cell walls. Beta-lactam antibiotics bind to and inhibit the enzymes needed for the synthesis of peptidoglycan, a component of bacterial cell walls as bacteria multiply and divide, the

defective walls cannot protect the organism from bursting in hypotonic environments and cell death occurs (Mores 2003).

It is also used to prevent bacterial endocarditis in high-risk people having dental work done, to prevent Streptococcus pneumoniae and other encapsulated bacterial infections in those without spleens, such as people with sickle-cell disease, and for both the prevention and the treatment of anthrax (American Society 2011).

These recommendations have not appeared to have changed the rates of infection for infectious endocarditis (Thornhill et al .2011).

Amoxicillin and amoxicillin-clavulanate have been recommended by guidelines as the drug of choice for bacterial sinusitis, but most sinusitis is caused by viruses, for which amoxicillin and amoxicillin- clavulanate are ineffective, and the small benefit gained by Amoxicillin may be overridden by the adverse effects. (Ahovuo et al.2014).

Amoxicillin is occasionally used for the treatment of skin infections, such as acne vulgaris. It is often an effective treatment for cases of acne vulgaris that have responded poorly to other antibiotics, such as doxycycline and minocycline

1.1.2. 2: Carbamazepine:

Carbamazepine was discovered in 1953 by Swiss chemist Walter Schindler. (Smith, Howard 2009). It is available as a generic medication and is not very expensive. It is on the WHO Model List of Essential Medicines, the most important medications needed in a basic health system (WHO 2013)

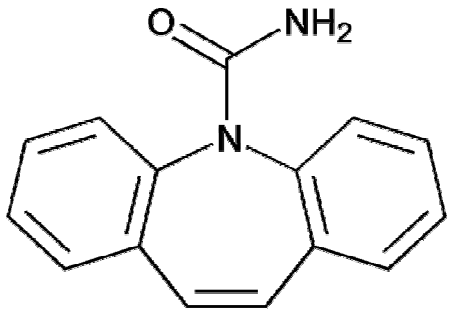
Carbamazepine is a first generation anticonvulsant used in the treatment of epilepsy and trigeminal neuralgia. (Aurora et al. 2007)

(i) Appearance: White to off white powder.

(ii) Solubility: in soluble in water, soluble in alcohol and acetone.

The Carbamazepine molecular formula is $C_{15}H_{12}N_2O$ and the molecular weight 236.27 (USP 2007)

(iii) Chemical structure:



(iv) use of Carbamazepine:

Epilepsy is one of the most common neurological disorders, affecting about 50 million people worldwide. Phenobarbital, one of the first compounds utilized in the treatment of epilepsy, was introduced in 1912. Since then, several antiepileptic drugs have been developed, but only some of them have become established. It is estimated that the majority of epileptic patients are treated with only four drugs (Antonio et al .2002)

1.1.2.3: Ciprofloxacin Hydrochloride:

Ciprofloxacin is an antibiotic that can treat a number of bacterial infections. It is a second-generation fluoroquinolone (Ball 2000).

Its spectrum of activity includes most strains of bacterial pathogens responsible for respiratory, urinary tract, gastrointestinal, and abdominal infections,including Gram-negative (Escherichiacoli, Haemophilus influenzae, Klebsiella pneumoniae, Legionella pneumophila, Moraxella catarrhalis, Proteus mirabilis, and Pseudomonas aeruginosa), and Gram-positive (methicillin-sensitive, but not methicillin-resistant Staphylococcus aureus, Streptococcus,pneumoniae, Staphylococcus epidermidis, Enterococcus faecalis, and Streptococcus pyogenes) bacterial pathogens. Ciprofloxacin and other fluoroquinolones are valued for this broad spectrum of activity, excellent tissue penetration, and for their availability in both oral and intravenous formulations. (Brunton, Lazo& Parker 2005).

Ciprofloxacin is used alone or in combination with other antibacterial drugs in the empiric treatment of infections for which the bacterial pathogen has not been identified, including urinary tract infections and abdominal

infections among others. It can also treat infections caused by specific pathogens known to be sensitive.

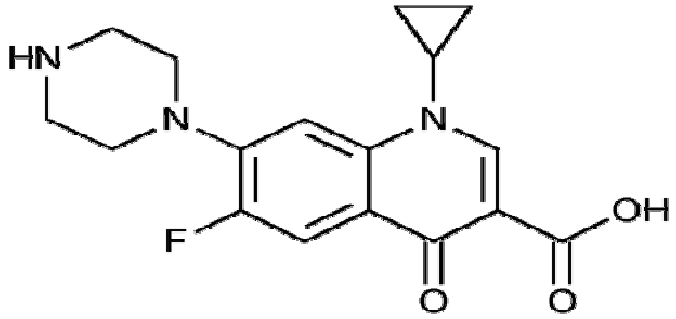
(i) Appearance:

Faintly yellowish to light yellow crystals

(ii) Solubility: sparingly soluble in water, slightly soluble in acetic acid and in methanol, vary slightly soluble in dehydrated alcohol, practically insoluble in acetone, in acetonitrile, in ethyl acetate, in hexane, and in methylene chloride.

The ciprofloxacin hydrochloride molecular formula is $C_{17}H_{18}FN_3O_3.HCl$ and the molecular weight is 367.8 (USP 2007)

(iii) Chemical Structure:



.HCl

(v) Use the ciprofloxacin hydrochloride:

Ciprofloxacin is used to treat a wide variety of infections, including infections of bones and joints, endocarditis,gastroenteritis, malignant otitis externa, respiratory tract infections, cellulitis, urinary tract infections, prostatitis, anthrax, and chancroid.

Ciprofloxacin only treats bacterial infections; it does not treat viral infections such as the common cold. Although for certain uses including acute sinusitis, lower respiratory tract infections and uncomplicated gonorrhea, ciprofloxacin is not considered a first-line agent.

Ciprofloxacin occupies an important role in treatment guidelines issued by major medical societies for the treatment of serious infections, especially those likely to be caused by Gram-negative bacteria, including Pseudomonas aeruginosa. For example, ciprofloxacin in combination with metronidazole

is one of several first-line antibiotic regimens recommended by the Infectious Disease Society of America for the treatment of community-acquired abdominal infections in adults (American Society2011).

1.1.2.4: Cefradine (Cephradine):

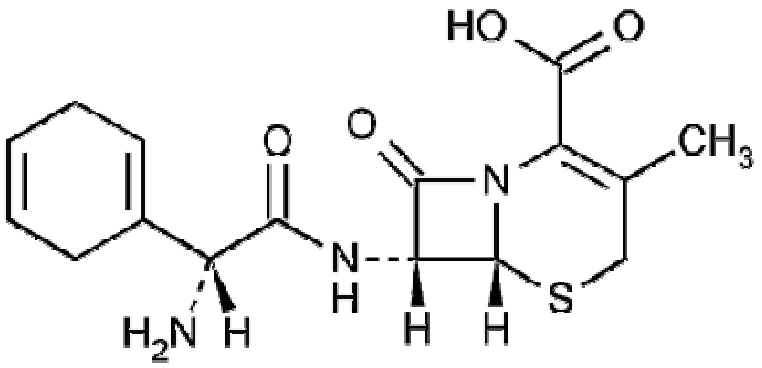
Cefradine is included among the first generation cephalosporins, which is active against a wide range of Gram-positive and Gram-negative bacteria including penicillinaseproducing Staphylococci (Sultana, Arayne & Afzal 2003) .The cephalosporins are a rapidly proliferating group of antimicrobial agents. They are widely used because they are similar to the penicillins in their structure and mode of action, but have the added advantages of being relatively resistant to the beta-lactamase and of possessing bactericidal activity against a broad spectrum of pathogenic microorganisms, many of which are not susceptible to the penicillins. (Callaghan 1979).

(i) Appearance: White to off -white, crystalline powder.

(ii) Solubility: Sparingly soluble in water, very slightly soluble in alcohol and in chloroform, practically insoluble in ether.

The Cefradine molecular formula is $C_{16}H_{19}N_3O_4S$ and the molecular weight is 349.41 (USP 2007)

(iii) Chemical structure:



(vi) Use the Cefradine:

It has similar spectrum of activity to cefalexin. Respiratory tract infections (e.g. Tonsillitis, pharyngitis, and lobar pneumonia) caused by group A beta-hemolytic streptococci and S. pneumoniae (formerly D. pneumonia). (Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Velosef is generally effective in the eradication of streptococci from the nasopharynx; substantial data establishing the efficacy of Velosef in the subsequent prevention of rheumatic fever are not available at present.) Otitis media caused by groupA beta-hemolytic streptococci, S. pneumoniae (formerly D. pneumoniae), H. influenzae, and staphylococci. Skin and Skin Structure Infections caused by staphylococci (penicillin-susceptible and penicillin-resistant) and beta-hemolytic streptococci. Urinary Tract infections, including prostatitis, caused by E. coli, P. mirabilis, Klebsiella species, and enterococci (S. faecalis). The high concentrations of cephradine achievable in the urinary tract will be effective against many strains of enterococci for which disc susceptibility studies indicate relative resistance. It is to be noted that among beta-lactam antibiotics, ampicillin is the drug of choice for enterococcal urinary tract (E. faecalis) infection. (British National Formulary2003)

1.1.2. 5: Mefenamic Acid:

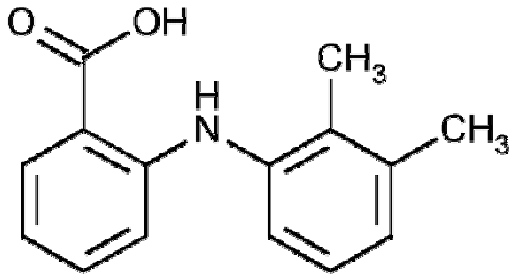
Mefenamic acid is a non-steroidal anti-inflammatory drug used to treat pain, including menstrual pain.

(i) Appearance: White to off white crystalline powder.

(ii) Solubility: soluble in solution of alkali hydroxide, sparingly soluble in chloroform, slightly soluble in alcohol and methanol practically in soluble in water.

The Mefenamic molecular formula is $C_{15}H_{15}NO_2$ and the molecular weight 241.29 (USP 2007)

(iii) Chemical structure:



(vii) Use of Mefenamic Acid:

Mefenamic acid decreases inflammation (swelling) and uterine contractions by a still-unknown mechanism. However it is thought to be related to the inhibition of prostaglandin synthesis. There is also evidence that supports the use of Mefenamic acid for perimenstrual migraine headache prophylaxis, with treatment starting 2 days prior to the onset of flow or 1 day prior to the expected onset of the headache and continuing for the duration of menstruation (Pringsheim, Davenport &Dodick 2008)

1.1.3: Photochemical Tracing:

Important developments in the study of photochemistry occurred in the early 1800s. In 1817 the German physicist Theodor von Grotthus recognized that in order for light to be effective in producing a chemical change it had to be absorbed. In 1841 the American chemist John William Draper studied the reaction between moist hydrogen and chlorine gases. This reaction was observed first about 1801 and may have been the first recognized photochemical reaction. Draper noted that after a certain inhibition period the rate of the reaction was proportional to the intensity of the light absorbed These observations led to the first law of photochemistry (the Grotthus-Draper law), which states that the amount of photochemical reaction is proportional to the quantity of light absorbed.

The development of the quantitative aspects of photochemistry began in earnest with the enunciation of the quantum theory by Max Planck in 1900 and its elucidation by Albert Einstein in 1905. Planck, who is regarded as the founder of the quantum theory, espoused that an atom or a molecule can absorb only fixed quantities (quanta) of light energy. This energy, E, he theorized, is proportional to the frequency, f, of the light. The energy of a single quantum of radiation is given by

$$E = h f$$

Where h is a proportionality constant that was named "Planck's constant." Five years later. Einstein proposed that light can be thought of as consisting of unusual particles called photons. Each photon of light is said to possess a quantum of energy given by the above relationship. These conclusions led to the second law of photochemistry, which states that the number of primary processes resulting from the absorption of light is equal to the number of photons absorbed. Exceptions to this rule sometimes occur (Kornblum2010).

1.1.3.1: Typical light sources for preparative photochemistry:

(i) The sun (300 – 1400 nm).

(ii) Low-pressure mercury (Hg approx. 10^{-5} atm) lamp: 185 nm (5%); 254 (95%).

(iii) Rayonet lamps (specific emission wavelength from secondary fluorescence emission, coated.

(iv) Medium pressure Hg (Hg vapor pressure 5 atm) lamps (distinct lines between 250 and 600 nm).

(v) High pressure Hg lamps (Hg vapor pressure approx. 100 atm; expensive, easily damaged) (emission 360 – 600 nm, broad).

(vi) Low- and high pressure sodium lamps (emission around 600 nm).

(vii) High power light emitting diodes (available at low cost for 650 to 400 nm; very narrow and intensive emission, long lifetime; UV-LED are currently still expensive (Konig 2013).

The relation between the number of molecules which undergo a particular photochemical reaction and the number of photons absorbed is the quantum yield ϕ.

$$\phi = \frac{\text{Number molecules undergoing a particular process}}{\text{Number of photon absorbed}}$$

The first step in a photochemical reaction is excitation of a molecule through absorption of one photon. Whether this excited molecule leads to a chemical reaction or returns to the original ground state depends upon its lifetime and potential intramolecular or intermolecular interactions within the system. Such processes can be accounted for by the energy relations between molecule and quantum- mechanical rules.

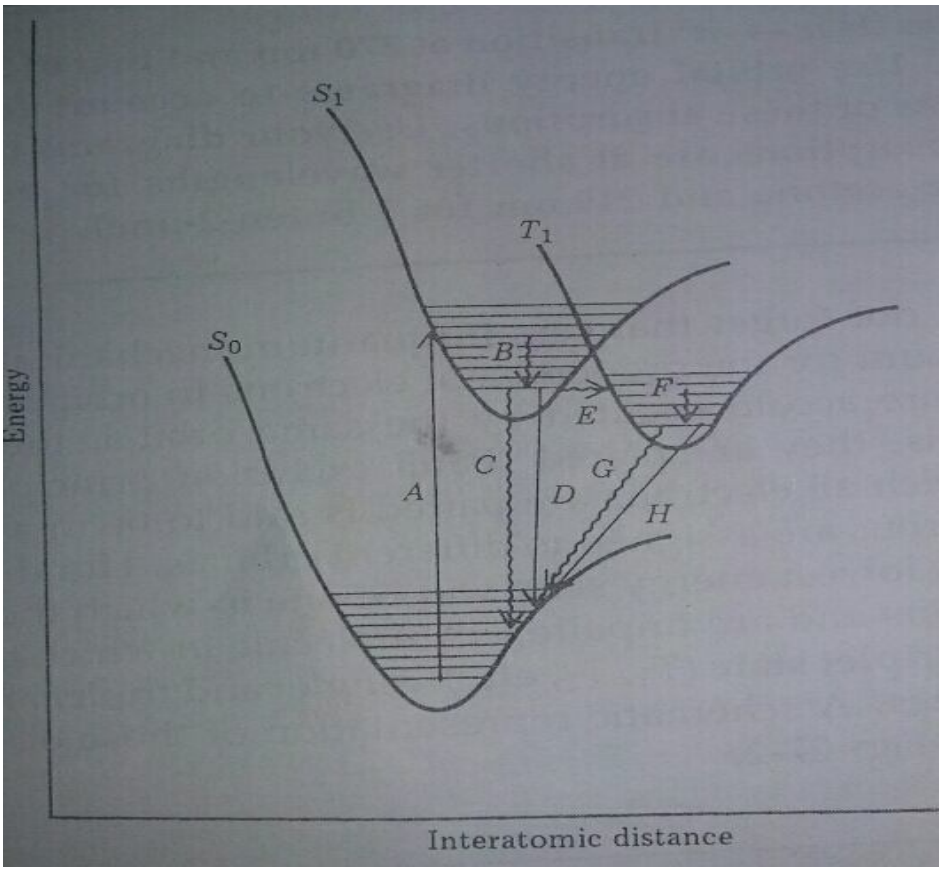


Fig. 1: Potential – energy curves and electronic transitions for a diatomic molecule.

A: $S_0 \rightarrow S_1$ excitation

B: Vibrational relaxation

C: $S_1 \rightarrow S_0$ radiation less decay

D: $S_1 \rightarrow S_0$ fluorescence

E: $S_1 \rightarrow T_1$ intersystem crossing

F: Vibrational relaxation

G: $T_1 \rightarrow S_0$ radiation less decay

H: $T_1 \rightarrow S_0$ phosphorescence

Consider the potential – energy diagram for the ground and excited states of a diatomic molecule (fig.1). The lowest point of each curve represents the equilibrium interatomic distance for that particular electronic configuration. `The excited states in which electron interaction are expected to be less favorable have somewhat longer interatomic distances. Horizontal lines within each curve represent slight differences in energy levels due to vibrational and rotational motions of the molecule.

The photo excitation process is very rapid it faster than a molecular vibration. Thus a molecule will initially have exactly the same interatomic distance in the excited state as it had in its original state (the Franck- Condon principle). The transition from ground state singlet to excited singlet is designated by line A in Fig.1. In this particular illustration of a vertical transition process the molecule ends up in one of the higher vibrational S_1 states .vibrational relaxation to the to the lowest S_1 state (wavy line B) occurs rapidly. A molecule in the excited singlet state has a typical lifetime of 10^{-9} to 10^{-6} s. During that time it may return to the ground state as electronic excitation energy is converted to vibrational energy (wavy line C) or expended in photoemission (line D). The photoemission of energy associated with an $S_1 \rightarrow S_0$ transition is known as fluorescence. Decay of an excited state to another state of the same multiplicity (singlet to singlet or triplet to triplet) is called internal conversion.

One of the important selection rules of spectroscopy predicts that singlet to-triplet transitions caused by the absorption of light are forbidden consequently light absorption by singlet ground-state molecules (S_0) is expected to produce only excited singlet-state molecules (S_1, S_2,etc.).

The excited singlet molecules may however, undergo intersystem crossing (wavy line E) a relaxation process in which they lose some of their energy and become triplet. Although intersystem crossing is a (forbidden) process it does occur with many excited molecules. Excited benzophenone for example converts almost completely from S_1 to T_1.

Intersystem crossing is a horizontal transition and therefore occurs with-out any initial change in energy level. Since the triplet state is normally of lower energy than the exited singlet $S_1 \rightarrow T_1$ transitions produce an excited molecule in one of the higher triplet vibrational state .rapid vibrational relaxation (wavy line F) leads to the lowest triplet vibrational level.

The lowest triplet is the lowest-lived of the electronic excited states decay of the triplet state to ground state many take place by radiation less process (wavy line G) or the photoemission (line H) known as phosphorescence . because molecules in the T1 state decay more slowly than in other excited states, they are often the species which undergoes the chemical reaction. (Pine 1987)

1.1.3.2: Photochemical Reactions:

A photochemical sequence can be divided into three parts:

(i) Absorption of light to produce an electronically excited molecule.

(ii) Primary photochemical processes that involve the excited molecule.

(iii) Secondary (or dark) reactions of the species produced by the primary process.

Photochemical reactions are usually uni-molecular or bimolecular. In uni-molecular reaction and electronically excited molecule a chemical change without involving other molecules. The chemical reaction can be regarded as a type of nonradiative decay process. Photolysis, the cleavage of bonds as a result of photoactivftion, and intramolecular rearrangement are typical uni-molecular photoreactions.

In a bimolecular photoactivftion a molecule in an excited state usually reacts with a ground – state molecule .the ground – state molecule may be an unexcited form of the excited molecule or some other constituent of the reaction mixture .Reaction between tow excited molecules is not common , since each excited molecules is present in low concentration in ordinary photochemical experiments.

- **Photoreduction :**

The excited state of the carbonyl groups of many aldehydes and ketones are excellent hydrogen atom abstractors. The reaction resemble those of ketyl free radicals. We saw that ketyls generated by alkali metals can dimerize to form pinacols. Similar chemistry is promoted by photo activation (Pine 1987)

Example:

$$(C_6H_5)_2C{=}O \xrightarrow{h\nu} (C_6H_5)_2C{=}O^{*1} \xrightarrow{Intersystem\ crossing} (C_6H_5)_2C{=}O^{*3}$$

$$(C_6H_5)_2C{=}O^{*3} + C_6H_5CH_3 \rightarrow (C_6H_5)_2C\cdot\text{-}OH + C_6H_5C\cdot H_2$$

Benzophenone ketyl Benzyl free radical

$$2(C_6H_5)_2C\text{–}OH \rightarrow (C_6H_5)_2C(OH)\text{–}C(OH)(C_6H_5)_2$$

Benzpinacol

$$2C_6H_5CH_2 \rightarrow C_6H_5CH_2CH_2C_6H$$

Bibenzyl

$$(C_6H_5)_2C\cdot\text{-}OH + C_6H_5C\cdot H_2 \rightarrow (C6H_5)_2C(OH)\,CH_2C_6H_5$$

Benzyldiphenyl carbinol

- **Photolysis:**

Irradiation of molecule often leads to hemolytic bond cleavage and free-radical intermediates. Acetone, for example, undergoes photolytic cleavage at the carbon –carbon bond alpha to the carbonyl group. The process, which often referred to as Norrish type I cleavage, leads to on alkyl and an acyl free radical.

$$CH_3\overset{O}{\overset{\|}{C}}CH_3 \xrightarrow{h\nu} CH_3C^{\bullet} + \cdot CH_3$$

Norrish type I cleavage

O

‖

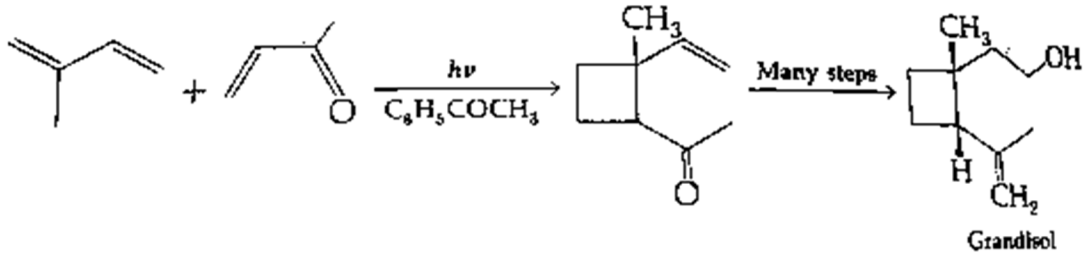
CH3C.→.CH3+CO

|⟶CH3-CH3

$_{.CH3}$

- **Cycloaddition:**

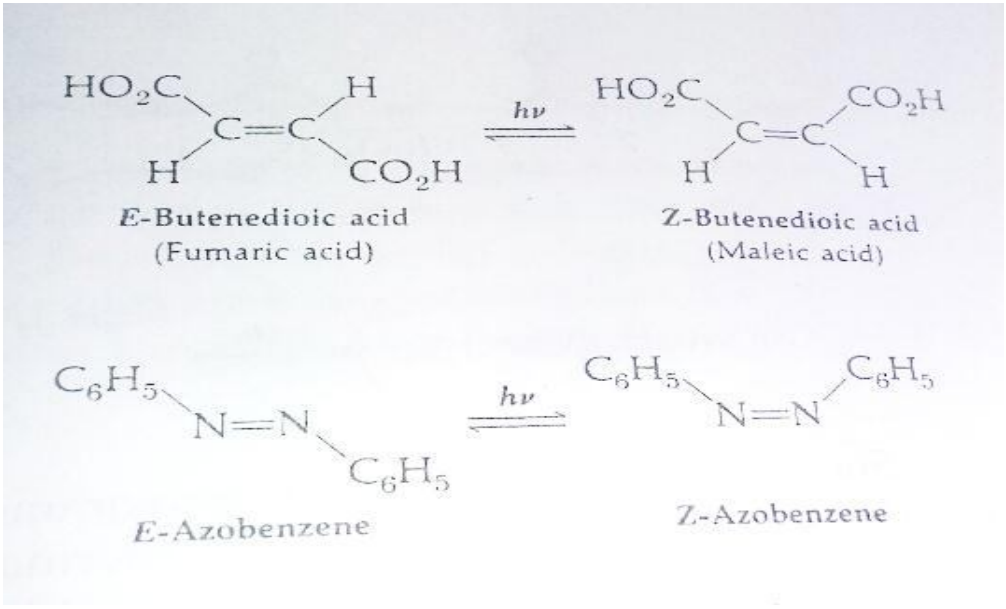
Photochemical Cycloaddition of alkenes to form four –membered rings has been used in many synthesis sequences. For example, a key step in one of the syntheses of grandisol, a sex- attractant pheromone emitted by male boll weevils was acetophenone –sensitized formation of the requisite cyclobutane (Pine 1987).



Grandisol

- **Isomerization and Rearrangement:**

Geometrical Isomerization is atypical photoreaction of many olefinic compounds. The reaction is promoted by direct irradiation of the substrate as well as by photosensitized energy transfer. In some simple alkenes the E isomer absorbs energy more effectively and at a slightly different wavelength than does Z isomer. it is therefore sometimes possible to at least partially convert an E isomer to its thermodynamically less stable Z form – a technique known as optical pumping. (Pine 1987)



1.1.4: Phototransformation of Pharmaceutical in Environment Water:

Since years, it is known that pharmaceuticals and their active metabolites occur in the environment. Pharmaceuticals occur in rivers, coastal waters, and sewage, not only from human and animal excretion but also through discarding of unused drugs and the release from production sites. They end up in surface water mainly through discharge of sewage treatment plant (STP) Effluent.

Additional to effects measured directly on exposed organisms, other concerns have been raised with the occurrence of pharmaceuticals and their active metabolites in the environment. A major problem is the development of resistances. Antibiotic resistant genes, for example against Sulfamethoxazole and Trimethoprim have already been discovered in STP effluents and downstream of STPs (Blum 2013).

Furthermore, there is great concern about the transformation and degradation by light (photodegradation) and microorganisms (biodegradation) of these pharmaceuticals in the environment, since biodegradation, and photodegradation are the main removal pathways of pharmaceuticals in the natural aquatic environment and their degradation pathways are essential to

predicting the fate and the environmental impacts of these contaminants in natural waters (Blum 2013).

1.1.4.1: Biodegradation (Biotransformation):

Biotransformation can be direct or co-metabolic. In the direct transformation, microbes use a compound as a carbon and energy source.
Whereas in the co-metabolic transformation, certain microbes gain energy from more abundant and easily degradable organic com. Hence, the way the microbial community may work is dependent on presence of other substrates simultaneously in the same habitat, i.e. on trophicor saprobic set-ups.
Biotransformation is considered to be the main process for removing
Pharmaceuticals, both in WWTPs and in the aquatic environments Microbial transformation of pharmaceuticals varies from recalcitrant, like clofibric acid and carbamazepine, to readily transformed, like ibuprofen, Ketoprofen and paracetamol. The biotransformation is often slower in anaerobic conditions. Hence, it is important to predict the fate of pharmaceuticals both in aerobic and anaerobic environments (Lahti 2012).
It should be noted that the biodegradation products can be more harmful than the substance.

1.1.4.2: Photodegradation (Phototransformation):

It can be distinguished between two different mechanisms of photodegradation: direct and indirect photolysis. In direct photolysis, the pharmaceutical molecule absorbs solar radiation, which leads to a break-up of the molecule Indirect photolysis involves naturally occurring molecules (photosensitizers) such as nitrate; generating strong reactive oxygen species' like for example singlet oxygen ($1O_2$), hydroxyl radical (·OH), or peroxyl radicals (·OOR) under solar radiation. Humic acids can reduce the rate of
Phototransformation by absorbing light and acting as an inner filter estimated the dependence of photodegradation from the light intensity. For this purpose they exposed samples of diclofenac diluted in water at different light intensities, simulating different geographical latitudes and different seasons. Shows that the geographical position does not really matter for the efficiency of photo-degradation in summer time, but that huge

Differences between different latitudes especially in wintertime can occur. Low light intensities far north in wintertime can reduce the efficiency of photodegradation dramatically. The adsorption spectrum of diclofenac and UV- radiation overlap in the 300 to 330 nm range this is the wavelength that dominates the photodegradation. Determined experimentally a first order Depletion rate of 0.8 h-1 for diclofenac, and other studies showed results in the same order of magnitude, also when the results are depending on the experimental setup, especially of the size of exposed flasks. Light intensity is strongly depending on the weather found a much slower decrease of diclofenac on rainy, cloudy days compared to sunny days. Photodegradation is also depending on the depth of the water column. Samples exposed in the German lake Goitsche showed a 97% decomposition of Diclofenac over a two-week period in 50 cm depth. In the same time in one meter depth only about 30% of the diclofenac decomposed. (Jiskra 2008)

The hardness of the water is also postulated to influence indirect photolysis. Carbonate radicals, resulting out of a reaction of hydroxyl ions with carbonate or bicarbonate ions, can perform as scavengers for hydroxyl radicals and delay or even stop transformation.

Important factors which can influence the transformation of pharmaceuticals in general are the amount of compound, extinction coefficient of the compound at a specific wavelength, temperature, intensity and wavelength of light, in relation with the latitude, season and weather as well as the water column and turbidity. Nevertheless, experiments have shown that the total specific light absorption rate did not show large variances in summer at different latitudes in the northern hemisphere, but big differences in other seasons.

1.1.4.3: Kinetics

Direct photolysis is a decay reaction $A \xrightarrow{h\nu} B + C$ and follows first-order kinetics, whereas the order of indirect photolysis depends on the number of reactants present. However, as the pharmaceuticals are present in large excess compared to possible reactants, pseudo-first order can be assumed. In both cases the reaction rate (r) can be described with equation (2) (Blum 2013).

$$r = \frac{dcrel}{dt} = k * c_{rel} \qquad \text{Eq. (2)}$$

Where k equals the reaction constant and c_{rel} equals the relative concentration of reactant A. After integration the concentration $c_{rel}(t)$ gives an exponential decay with $c_{rel}(0)$ as initial concentration.

$$c_{rel}(t) = c_{rel}(0) * e^{-kt} \qquad \text{Eq. (3)}$$

Reaction constant (k) is determined from the function's slope and the half live ($t_{1/2}$) concludes from the rate constant with equation (4).

$$t_{1/2} = \ln(2)/k \qquad \text{Eq. (4)}$$

Phototransformation, the focus of this master project, has already been studied for some drugs and half-life.

1.2: Literature Review

Photochemical and titanium dioxide photocatalysed degradation of amoxicillin in water under natural and simulated sunlight, In contrast amoxicillin remained photo stable under direct photolysis, while degrading significantly in the presence of titanium dioxide. The amoxicillin degradation study was conducted in July 2010 with 6 hours of exposure to direct natural sunlight (UV level of 7) (Kockler et al .2012). Similarly to the result in the solar simulator the degradation of amoxicillin in the photocatalytic reaction exceeded that of experiment in the absence of catalyst. A photocatalytic degradation of 78% was achieved after 6 hours of illumination. An increase of 7% upon direct photolysis after 6 hours was attributed to a concentration effect caused by condensation of water on the polyethylene wrap covering the petri-dish. The results therefore confirm that AMX is stable on exposure to direct natural sunlight in aqueous solution and that a photocatalyst is needed to initiate photochemical degradation. Amoxicillin is a widely used antibiotic and has been detected in natural waters (Haomin et al.2010). Its environmental fate is in part determined by hydrolysis, and, direct and indirect photolysis. The hydrolysis rate in distilled water and water to which five different isolated of dissolved organic matter (DOM) was added, were evaluated. In the five different DOM solutions hydrolysis accounted for 5-18% loss of amoxicillin. Direct and indirect photolysis rates were determined using a solar simulator and it appeared that indirect photolysis was the dominant loss mechanism. Direct photolysis, in a solar simulator, accounted for 6-21% loss of amoxicillin in the simulated natural waters.

Detection of numerous pharmaceutical and personal care products (PPCPs) in the environment has gained a public attention due to their known and or potential adverse impacts on ecological and public health. Previous studies consistently demonstrate the prevalence of pharmaceutical in the environment but we do not yet know how concentration vary over time within a given system. The adsorption characteristics of pharmaceutical in soils and ground Water is of great importance environmentally, because such

process is Associated with the ecotoxicity, degradation, transportation, and Bioaccumulation of them in the soil environment. Adsorption of Ibuprofen Amoxicillin, and Caffeine was studied and the following results were obtained:

- Amoxicillin and Ibuprofen soil adsorption in this study was increased with increasing temperature versus time.
- The study showed that caffeine soil- adsorption is lower than that in Ibuprofen and amoxicillin with increasing temperature, due to its high water solubility.
- The more amoxicillin hydrolysis was at pH 4-7 with highly adsorption at pH 1.5 and 12.
- The kinetics and equilibrium of adsorption of ibuprofen, amoxicillin and caffeine were best described using first – order reaction and Freundlich isotherm.
- Amoxicillin concentrations decreased dramatically and rapidly in each rate among the one year and 15 –year columns, than ibuprofen due to its nature highly degradable compound.
- It was observed that the concentration of caffeine were obviously larger than that in ibuprofen and amoxicillin among the one year and 15-year's columns this is because that caffeine is more water soluble , despite it didn't reach ppm.
- During the columns study the leachate from those columns found less than 1ppm and this mean that there will be no environmental effects of those pharmaceuticals on the ground water (Halimeh 2012)

The combination of powdered activated carbon (PAC) and TiO_2 has been tested for synergistic antagonistic effects in the photocatalytic degradation of carbamazepine, clofibric acid and iomeprol. Synergistic effects are thought to be caused by rapid adsorption on the PAC surface followed by diffusion to the TiO_2 surface and photocatalytic degradation.

The Freundlich constant KF was used for comparing the sorption properties of the three substances and it was found that KF for clofibric acid was 3 times lower than for carbamazepine and iomeprol, regardless of the kind of

PAC used. A PAC with a distinct tendency to form conglomerates was selected so that a high percentage of the PAC surface was in direct proximity to the TiO_2 surface. The photocatalytic degradation of the pharmaceutically active compounds studied followed pseudo-first order kinetics. Synergistic effects only occurred for clofibric acid (factor 1.5) and an inverse relationship between adsorption affinity and synergistic effects was found. High affinity of the target substances to the PAC surface seemed to be counterproductive for the photocatalytic degradation (Ziegmann & Frimmel 2010) Carbamazepine, a widely consumed psychotropic pharmaceutical, is one of the most commonly detected drugs in the environment. To better assess the environmental persistence of carbamazepine in aqueous matrices, the effect of pH and dissolved oxygen on the direct photodegradation rate of this pharmaceutical was evaluated in this study, using simulated solar irradiation. In order to follow the degradation and the emergence of photoproducts, a micellar electrokinetic chromatography based method was developed, consisting on the use of a dynamically coated capillary column. The developed methodology showed good repeatability and efficiency in the separation of carbamazepine and photo irradiation products. Also, seven photodegradation products were identified by electrospray mass spectrometry (ESI-MS), including the known carcinogenic acridine that was produced under all the pH and oxygenation levels studied and one newly identified photoproduct. This paper gives new insights into the role of dissolved oxygen on the photodegradation rate of carbamazepine. The results indicate that acidic pH, combined with the absence of dissolved oxygen in the aqueous matrix, results in very high direct photodegradation rates. At basic pH, dissolved oxygen does not interfere with the process and very low rates were observed. At environmentally relevant conditions, carbamazepine was shown to persist in the environment from 4.5 to 25 days (Calisto et al. 2010)

Photodegradation of four pharmaceuticals (i.e. carbamazepine, ibuprofen, ketoprofen and 17α-ethinylestradiol) in aqueous media was studied using a solar light simulator (Xe lamp irradiation) and sunlight experiments. These experiments were carried out in river and seawater and compared to distilled

water. The latter was used to evaluate the direct photodegradation pathways. (Matamoros et al .2008).

Photocatalytic experiments on the pharmaceutical pollutant carbamazepine (CBZ) were conducted using sol-gel nitrogen-doped TiO2-coated glass slides under a solar simulator. CBZ was stable to photodegradation under direct solar irradiation. No CBZ sorption to the catalyst surface was observed, as further confirmed by surface characterization using X-ray photoelectron spectroscopic analysis of doped surfaces. When exposing the catalyst surface to natural organic matter (NOM), an excess amount of carbon was detected relative to controls, which is consistent with NOM remaining on the catalyst surface. The catalyst surface charge was negative at pH values from 4 to 10 and decreased with increasing pH, correlated with enhanced CBZ removal with increasing medium pH in the range of 5 to 9. A dissolved organic carbon concentration of 5 mg/L resulted in ~20% reduction in CBZ removal, probably due to competitive inhibition of the photocatalytic degradation of CBZ. At alkalinity values corresponding to $CaCO_3$ addition at 100 mg/L, an over 40% decrease in CBZ removal was observed. A 35% reduction in CBZ occurred in the presence of surface water compared to complete suppression of the photocatalytic process in wastewater effluent. (Avisar et al. 2013)

The photocatalytic degradation of Carbamazepine (CBZ), 5*H*-dibenzo[b,f]azepine-5- carboxamide, under near Uv-Vis and UV irradiation is studied using P_{25}, synthesized TiO_2 (anatase and rutile), mechanical mixtures and composites of oxidized-multi-walled carbon- nano-tube :anatase, and ZnO suspensions as catalyst, to identify intermediates, and to elucidate its degradation mechanism. Factors affecting the kinetics of the process, such as the type and load of photocatalyst, and the presence of dissolved O_2 or addition of cooxidants (H_2O_2), have been compared. Optimal conditions for degradation were obtained using P25 (0.5g/L), 5mM of H_2O_2 or 50% O_2 (v/v), with rate constants *ca*. 0.3144 min-1 and 0.2005 min-1, respectively. Complete removal of CBZ was achieved, showing the efficiency of the photocatalytic process. Ten photoproducts of CBZ were assigned by using high resolution mass spectrometry, the most important of

which identified as 10,11-dihydro- CBZ-10,11-epoxide, in accordance with the literature. The reaction mechanism includes previous proposals, and accounts for the pathways giving rise to the identified photoproducts. (Martinez et al .2010)

The developed UPLC-MS/MS method enables the determination of Ciprofloxacin, Moxifloxacin, Norfloxacin and Ofloxacin in the presence of photodegradation products and identification of photodegradation products. The method meets the acceptance criteria for validation which guarantees correct analysis results. It has been shown that the tested fluoroquinolones occurring in the presence of excipients undergo photodegradation under the influence of UVA radiation. Photodegradation follows the kinetics of a first order reaction. The results obtained by UPLC-MS/MS and the calculated kinetic parameters k and t0.1 and t0.5 have shown that photodegradation of Moxifloxacin is faster than Ciprofloxacin, Norfloxacin and Ofloxacin. Greater susceptibility of Moxifloxacin to photodegradation process has also been shown by DSC method. It seems that the differences obtained during the photodegradation of tested fluoroquinolones may be connected with the presence of inorganic components in the tablet powder such as Fe_2O_3 and TiO_2 (Hubicka et al. 2013)

To compare Ciprofloxacin attenuation efficiency, Ciprofloxacin solutions mixed with TiO_2 nanoparticles were irradiated with two different light sources: a UV lamp and ordinary electric bulb. Insignificant degradation was witnessed when irradiations were made in absence of TiO_2. In contrast, prominent Ciprofloxacin degradation was detected in the presence of 0.01 mg/ml of TiO_2. Close to 90 % and 70 % of its original concentration was eradicated in 120 inutes when the irradiation basis used was a UV lamp and Ordinary electric bulb respectively. Without the use of TiO_2 nanoparticles, irradiation by UV lamp sources was also significant. The antibactacterial activity of chosen microorganisms was radically inhibited when exposed to Ciprofloxacin solution treated with photocatalyst for the short periods of irradiation. (Hayder et al .2012)

The Ciprofloxacin acts mostly against the Gram positive but rarely against the Gram negative bacteria. The concentration ranging from 50-500 ppm of

the ciprofloxacin was exposed to the sun light and UV radiation. The duration of the exposure for the degradation, was 1 to 7 hrs. The UV rays (15W and 30W) lamps were used for the study. The degradation was determined by the by zone of inhibition. The maximum degradation was demonstrated by the exposure of UV

After 6 h duration. The photodegradation was also at its maximum after 6 h of exposure. The UV and the photodegradation proved to be the significant mode to control the pollution in the environment caused by Ciprofloxacin residue. (Singh & Gupta 2014)

Data obtained by uv-vis and fluorescence were processed by MCR-ALS using the so called (data fusion) approach, i.e. the data were simultaneously analyzed. MCR-ALS made it possible to obtain the concentration profiles of the species involved in the reaction and the corresponding pure spectra (both uv-vis and fluorescent). From the results it can be seen the typical degradation profile of ciprofloxacin and also the presence of four photodegradation products. Three of them are intermediate products and the forth is the final product. All the species have different uv-vis spectra. However, fluorescence spectra related to ciprofloxacin and the first two intermediate products are quite similar. The third intermediate product has a different fluorescence spectra and the final product is not fluorescent. From the results also it can be seen that the photodegradation was more effective at higher pH. These preliminary results are promissory as a start point to Study the kinetic degradation of the fluoroquinilones in several media. (Razuc, Garrido& Band 2013).

In a weak acidic medium (pH 4.0) photochemical reaction of cephradine occurs under the irradiation of ultraviolet light, forming a fluorescent product (γ_{ex} = 334 nm, γ_{em} = 442 nm). Based on this fact, a new photochemical fluorimetric method was developed for the determination of cephradine. The linear relationship between the fluorescence intensity and the concentration of cephradine is over the range of 0.01 – 4.0 μg/ml. The detection limit is 0.66 ng/ml (n = 11) and the relative standard deviation is 0.72% (n = 8). This method is simple and sensitive, and has been successfully applied to the determination of cephradine in urine samples.

Mechanism of the photochemical reaction was also discussed. (Cai et al.1998)

Pharmaceuticals and personal care products are an emerging class of environmental pollutants. Photolysis is expected to be a major loss process for many of these compounds in surface waters, including the common non-steroidal anti-inflammatory drug mefenamic acid. The direct photolysis solar quantum yield of mefenamic acid was observed to be $1.5 \pm 0.3 \times 10^{-4}$. Significant photosensitization was observed in solutions of Suwanee River fulvic acid and Mississippi River water, as well as for the model photosensitization compounds 3′-methoxyacetophenone, 2-acetonaphthone and perinaphthenone. Quenching, sparging and light-filtering experiments suggested a direct reaction of mefenamic acid with excited triplet-state dissolved organic matter as the major photosensitization process. The persistence of the model photosensitizer suggests that the photosensitization by perinaphthenone occurs either by triplet-energy transfer or an electron transfer followed by rapid regeneration of the sensitizer. Due to its low quantum yield, the loss of mefenamic acid in sunlit natural waters is expected to depend on both direct and indirect photodegradation processes. (Werner, McNeill & Arnold 2004)

The occurrence of pharmaceuticals in natural waters is a potential threat to human nutrition and ecosystem quality. The persistence of the acidic pharmaceuticals gemfibrozil, naproxen and mefenamic acid was studied in surface waters of Maracaibo Lake and Tule reservoir (Venezuela) under laboratory conditions. A quick and easy analytical method was developed for the determination of the acidic drugs at microgram per liter levels using aqueous derivatization, liquid–liquid extraction and gas chromatography–mass spectrometry. Pharmaceuticals degradation followed a pseudo first-order kinetic and their half-lives were calculated for every experimental condition. Under sunlight, naproxen and mefenamic acid were degraded at moderate rates with half-lives from 9.6 ± 0.5 to 27.0 ± 6.6 days, while gemfibrozil had a higher persistence ($t_{1/2} = 119.5 \pm 15.6 - 288.8 \pm 61.3$ days).(Araujo et al.2009)

(Blum 2013) developed a quantitative-structure-property-relationship (QSPR) models to relate molecular features of pharmaceuticals to phototransformation half-lives determined from 8 h UV-exposure and to further experimentally investigate half-lives of those which were stable after 8 h UV-exposure. Additionally the half-life of the metabolite Oseltamivir carboxylate was first predicted with the developed models and then experimentally investigated.

First 2D and 3D molecular descriptors were correlated to the rate of phototransformation. The descriptors covered physico-chemical properties, atom and bond counts, structural fragments, molecular connectivities, surface and volume characteristics, partial charges and quantum-chemistry based descriptors. For the group of 30 stable pharmaceuticals experimentally determined half-lives ranged between 6 hours for Amitriptyline in unfiltered Umea river water and 37 days for Carbamazepine in buffer.

The Phototransformation of diclofenac was considered as a first order reaction and rate was determined by HPLC, the half-life of the drug in distilled water was found to be 2.47 h and 5.33h in river water. The increase of half -live in river water is attributed to the shielding effect of suspended materials that are present in river water. (Zamazam 2014)

1.3: Objective of the Research:

The objectives of the work is:

1- Follow the Photodegradation of five drugs under sunlight and dark conditions through uv-vis spectrophotometry, high pressure liquid chromatography and Gas chromatography mass spectrometry.

2- Identification of some of the degraded products.

3- Kinetic measurement of the half-life drugs. .

Chapter Two

2.1: Selection Pharmaceuticals:

The drugs used in this study were selected because it is used in abundance in Sudan, prescribed or unprescribed .The drugs were also selected according to its impact on the environment. Since the solar radiation in Sudan is very intensive, we do expect to find high Phototransformation of the pharmaceuticals used in this study.

2.2: Sampling of pharmaceutical (n plan):

Sampling of pharmaceutical in the study used the plan sampling of the starting material (active materials).

The n plan should be used with great caution and only when the material to be sampled is considered uniform and supplied a recognized source .samples can be withdrawn from any part of the container (usually from the top layer). The n plan is based on the formula $n = 1 + \sqrt{N}$, where N is the number of sampling units in the consignment. The value of n is obtained by simple rounding. A minimum number of container needs to be sampled, e.g. if N is less than or equal to 4 then every container is sampled. According to this plan original sample are taken from n sampling units selected at random and these are subsequently placed in separate sample containers. The control laboratory inspects appearance of the material and tests the identity of each original sample according to the relevant specification. If the results are concordant, the original sample s is combined into a final, composite sample from which an analytical sample is prepared, the remainder being kept as a retention sample. (WHO 2005)

2.3: Materials:

(i) Samples:

- Amoxicillin Trihydrate (Assay 99.2%), Aurobindo, India.
- Carbamazepine (Assay 99.52 %), Bajaj Healthcare LTD, India.
- Cephradine Monohydrate (Assay 99.0 %), MCM Pharma, Germany.
- Ciprofloxacin Hydrochloride (Assay 99.5 %), Aarti Drugs Limited, India.

- Mefenamic Acid (Assay 99.9%), Shin Poong Pharmaceutical CO., LTD, Korea.

(ii) Chemicals

- Ethanol 100%, Chem Lab, Belgium.
- Phosphoric Acid, Daejung chemicals and Metals CO., LTD, Korea.
- N. Hexane, Lab Tech, India.
- Potassium Di hydrogen orthophosphate, Lab Tech, India.
- Sodium Lauryl Sulfate, Wako Pure Chemical Industries, Korea.
- Sodium Acetate, Tedla Company, INC, Ohio.
- Methanol (HPLC), J.T.Baker, USA.
- Acetonitrile (HPLC), J.T.Baker, USA.
- Ethyl Acetate, Oriental Chemical Industry, Korea.
- Acetic Acid Glacial, J.T.Baker, USA.
- Triethylamine, Daejung Chemical and Metal CO, LTD, Korea.
- Potassium Hydroxide, Tedla Company, INC, Ohio.
- Distilled Water, pass of analysis by USP

(iii) Equipment and Instruments:

- Balance, Mattler AE 240, Switzerland.
- Volumetric flask (250, 500, 1000 ml) Pyrex glass.
- Separatory funnel Pyrex glass.
- Glass tubes.
- Membrane filters 45µm.
- UV-Visible Spectrophotometer, S110.30-0103006P,Scino CO,LTD, Korea.
- pH-meter 3510, 37560, Jenway, UK.
- Power sonic 405,100-220, Hwashin, Korea.
- HPLC, 05240, VARIAN, USA.
- GC.MS.QP2010 +, Shimadzu.

2.4: Methods:

- **UV-VIS Spectrophotometric method** :

Two samples of the same concentration were prepared. Sample one exposed directly to sunlight, the other sample kept in the dark condition in room temperature. Then the absorptions of the samples were measured at appropriate times.

- **HPLC Method :**

The sunlight samples and the dark condition samples were subjected to separation by HPLC and compared to the standards.

- **GC-MS Method:**

Some components of each photoproduct were identified by GC-MS.

- **Kinetics:**

The kinetic of the reaction for the sunlight samples were measured by following the change in the initial concentration of the drug against time by uv-vis spectrophotometer.

2.4.1: Amoxicillin Trihydrate:

(i) Preparation of Calibration Curve:

For quantitative calculation of Amoxicillin Trihydrate a standard calibration curve was prepared. The absorbance was read by uv-vis spectrophotometer at wavelength 230 nm of series dilutions (standard drug) of Amoxicillin Trihydrate 0.015, 0.020, 0.025, 0.030 and 0.035 mg/ml in distilled water, then the calibration curve was constructed.

(ii) Phototransformation method:

- Natural sunlight:

A sample of Amoxicillin Trihydrate 0.0147g equal (0.0125g amoxicillin) was dissolved in 500 ml distilled water (con 0.025 mg/ ml) exposed directly

to sunlight in the period 1 February 2014 -1 June 2014 in Khartoum absorption was recorded every three hours for period 408hours.

- Dark condition :

Another sample of amoxicillin Trihydrate 0.0147g equal (0.0125g amoxicillin) was dissolved in 500ml distilled water (con 0.025 mg/ ml) and kept in dark condition in room temperature (NMT 30^0 C) in the period 1 February 2014 -1 June 2014 absorption was recorded every three hours.

(iii) HPLC method:

Mobile phase diluent and Acetonitrile (96:4)

Diluent : Dissolve 13.6 g of monobasic potassium phosphate in 2000 ml of distill water and adjust with a 45%w/w solution of potassium hydroxide pH(5.0±0.1),the flow rate of elution was 1.5 ml /min UV detector at 230 nm column C18 (4.6mm-250mm) inject 10µl.

Sample solution: The sample in sunlight and sample in dark was filtered with 0.45µm membranes and then injected in HPLC directly.

Standard solution: dissolve 0.0147g of amoxicillin Trihydrate in 500ml distilled water (Con 0.025 mg/ ml).

(iv) GC-MS Method:

Sample preparation:

15 ml of sunlight sample was separated by liquid –liquid extraction with 10 ml n-hexane, 5 ml of the organic phase was filtered with 0.45µm nylon membranes and read by GC-MS.

Working conditions of GC- MS:

GC-2010

- Column fused silica capillary column (30mx0.25 mm i.d.,0.25µm.
- Liquid phase: methyl silicone or 5%phenlmethyl silicone.

- Column oven temperature :50˚C
- Injection temperature :230˚C
- Injection mode : split
- flow control mode :Pressure
- Pressure:69.4 kpa
- total flow : 63.0 ml/min
- column flow:1.22ml/min
- linear velocity : 40.0 cm/sec
- purge flow : 1.0 ml/min
- spit ration :50.0
- high pressure injection :0ff
- carrier gas saver :off
- splitter hold :off
- oven temp .program

Rate	Temperature (˚C)	Hold time (min)
-	50.0˚C	4.00
6.00	100˚C	0.00
15.0	280˚C	0.00

(ii) GCMS-QP 2010 plus

- ion source temp :200.00˚C
- Interface temp :250.00 ˚C
- solvent cut time : 3.00min
- detector gain mode: relative
- detector gain :0.00kv
- Threshold :1000

(iii) MS:

- Start time :3.50 min
- End time :24.30 min

- ACQ mode : scan
- Event time : 0.5b sec
- Scan speed :1250
- Start m/z :40.00
- End m/z :600.0

2.4.2: Carbamazepine:

(i) Preparation of Calibration Curve:

For quantitative calculation of Carbamazepine a standard calibration curve was prepared. The absorbance was read by uv-vis spectrophotometer at wavelength 285 nm for series dilutions (standard drug) of Carbamazepine 0.005, 0.010, 0.015, 0.020 and 0.025 mg/ ml in sodium lauryl sulfate solution 1%, then the calibration curve was constructed.

(ii) Phototransformation method:

- Natural sunlight:

A sample of Carbamazepine 0.008g was dissolved in 1000ml Sodium Lauryl Sulfate Solution 1% (con 0.008 mg/ ml) exposed directly to sunlight in the period 26 May 2014 -22 September 2014 in Khartoum absorption was recorded every six hours for period 312 hours.

- Dark condition :

Another sample of Carbamazepine 0.008g e was dissolved in 1000ml Sodium Lauryl Sulfate Solution 1% (con 0.008 mg/ml)and Kept in dark condition in room temperature (NMT 30 ^{0}C) in the period 26 May 2014 -22 September 2014 in Khartoum absorption was recorded every six hours for period 312 hours.

(ii) HPLC method:

Mobile phase: water, methanol and acetonitrile (550:350:100)

The flow rate of elution was 0.6 ml /min UV detector at 230 nm column C18 (4.6mm-150 mm) inject 10µl.

Sample solution: The sample in sunlight and sample in dark was filtered with 0.45 µm membranes and then injected in HPLC directly.

Standard solution: dissolve 0.008g of Carbamazepine in 1000 ml Sodium Lauryl Sulfate Solution 1% (con 0.008 mg/ ml)

(iv) GC-MS Method:

Sample preparation:

50 ml of sample in sunlight was separated by liquid –liquid extraction after end in 20 ml from ethyl acetate 5 ml of the organic phase filtered with 0.45µm nylon membranes and read by GC-MS.

Working condition of GC- MS:

(i) GC-2010

- Column fused silica capillary column (30mx0.25 mm i.d.,0.25µm.
- Liquid phase: methyl silicone or 5%phenlmethyl silicone.
- Column oven temperature :80.0˚C
- Injection temperature :280.00˚C
- Injection mode : split
- flow control mode :Pressure
- Pressure:90.0 kpa
- total flow : 70.3 ml/min
- column flow:1.32ml/min
- linear velocity : 42.3cm/sec
- purge flow : 3.0 ml/min
- spit ration :50.0
- high pressure injection :0ff
- carrier gas saver :off
- splitter hold :off

- oven temp .program

Rate	Temperature (˚C)	Hold time (min)
-	80.0˚C	1.00
25.00	225.0˚C	1.00
1.00	231.0˚C	0.00
10.00	280.0	5.00
45.00	320.0	3.00

(ii) GCMS-QP 2010 plus

- ion source temp :200.00˚C
- Interface temp :230.00 ˚C
- solvent cut time : 3.00min
- detector gain mode: relative
- detector gain :0.00kv
- Threshold :1000

(iii) MS Table:

- Start time :3.50 min
- End time :27.50 min
- ACQ mode : scan
- Event time : 0.50sec
- Scan speed :1666
- Start m/z :40.00
- End m/z :800.0

2.4.3: Ciprofloxacin Hydrochloride:

(i) Preparation of Calibration Curve:

For quantitative Calculation of ciprofloxacin HCl a standard calibration curve was prepared. The absorbance was read by uv-vis spectrophotometer at wavelength 276 nm of series dilutions (standard drug) of ciprofloxacin HCl 0.001, 0.003, 0.005, 0.007and 0.009 mg/ ml in distilled water, then the calibration curve was constructed.

(ii) Phototransformation method:

- Natural sunlight:

A sample of ciprofloxacin HCl 0.0029g equal (0.0025g ciprofloxacin) was dissolved in 500ml distilled water (con 0.005mg/ ml) exposed directly to sunlight in the period 17 June 2014 -29 June 2014 in Khartoum absorption was recorded every six hours for period 54 hours.

- Dark condition :

Another sample of ciprofloxacin HCl 0.0029g equal (0.0025g ciprofloxacin) was dissolved in 500 ml distilled water (con 0.005 mg/ ml) and kept in dark condition in room temperature (NMT 30 ^{0}C) in the period 17 June 2014 -29 June 2014 absorption was recorded every six hours for period 54 hours.

(iii) HPLC method:

Mobile phase: 0.025 M phosphoric acid adjusted with triethylamine PH 3.0±0.1 and acetonitrile (87:13)

The flow rate of elution was 1.0 ml /min UV detector at 278 nm column C18 (4.6-250mm) inject 10µl.

Sample solution: The sample in sunlight and sample in dark was filtered with 0.45 µm membranes and then injected in HPLC directly.

Standard solution: dissolve 0.0029g of ciprofloxacin HCl in 500ml distilled water (Con 0.005 mg/ ml).

2.4.4: Cephradine monohydrate:

(i) Preparation of Calibration Curve:

For quantitative Calculation of cephradine monohydrate a standard calibration curve was prepared. The absorbance was read by uv-vis spectrophotometer at wavelength 255 nm of series dilutions (standard drug) of cephradine monohydrate 0.005, 0.01, 0.015, 0.02and 0.025 mg/ ml distilled water, then the calibration curve was constructed.

(ii) Phototransformation method:

- Natural sunlight:

A sample of cephradine monohydrate 0.0105g equal (0.010g cephradine) was dissolved in 500 ml distilled water (con 0.02mg/ ml) exposed directly to sunlight in the period 17 June 2014 -9July 2014 in Khartoum absorption was recorded every six hours for period 102 hours

- Dark condition :

Another sample of cephradine monohydrate 0.0105g equal (0.010g cephradine) was dissolved in 500cm^3 distilled water (con 0.02 mg/ ml) and Kept in dark condition in room temperature (NMT 30 ^{0}C)in the period 17 June 2014 -9 July 2014 absorption was recorded every six hours for period 102 hours.

(iii) HPLC method:

Mobile phase: 1ml Acetic acid (5M), 17ml sodium acetate (3.62 w/v), 200ml methanol and 782 Water.

*Acetic acid: 4 ml acetic acid in 100ml water.

The flow rate of elution was 1.0 ml /min UV detector at 254 nm column C18 (4.6-25cm) inject 10µl.

Sample solution: The sample in sunlight and sample in dark was filtered with 0.45 µm membranes and then injected in HPLC directly.

Standard solution: dissolve 0.0105g of cephradine monohydrate in 500ml distilled water (Con 0.02 mg/ ml).

2.4.5: Mefenamic Acid:

(i) Preparation of Calibration Curve:

For quantitative Calculation of Mefenamic Acid a standard calibration curve was prepared. The absorbance was read by uv-vis spectrophotometer at wavelength 230 nm of series dilutions (standard drug) of Mefenamic Acid 0.005, 0.010, 0.015, 0.020and 0.025 mg/ ml in Ethanol 50%, then the calibration curve was constructed.

(ii) Phototransformation method:

- Natural sunlight:

A sample of Mefenamic acid 0.0018g was dissolved in 250ml Ethanol 50% (con 0.0072mg/ml) exposed directly to sunlight in the period 20 October 2014 -31 December 2014 in Khartoum absorption was recorded every six hours for period 294 hours

- Dark condition :

Another sample of Mefenamic Acid 0.0018g was dissolved in 250ml Ethanol 50%(con 0.0072 mg/ ml) and Kept in dark condition in room temperature (NMT 30 ^{0}C)in the period 20 October 2014 -31 December 2014 absorption was recorded every sex hours for period 294 hours.

(iii) HPLC method:

Mobile phase: Methanol and water (70:30)

The flow rate of elution was 1.25 ml /min UV detector at 270nm column C18 (4.6-250mm) inject 10µl.

Sample solution: The sample in sunlight and sample in dark was filtered with 0.45 µm membranes and then injected in HPLC directly.

Standard solution: dissolve 0.0018g of Mefenamic acid in 250ml Ethanol 50% (con 0.0072 mg/ ml).

Chapter Three

3.1 :Results:

After the absorption was read for each standard the calibration curve was constructed as followed.

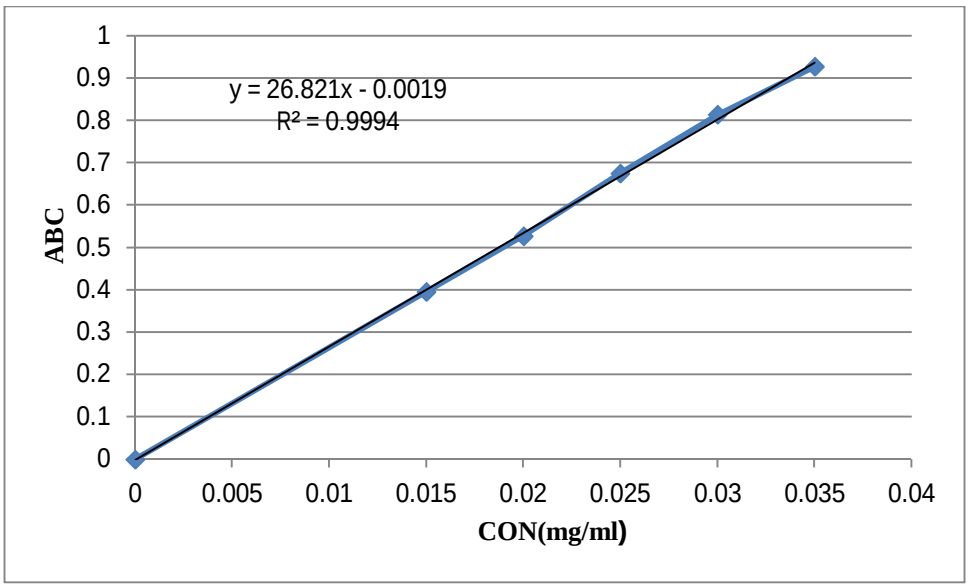


Fig 3.1.1 The Calibration Curve of AMX.

Time(h)	ABS
0	0.6679
12	0.661
24	0.6446
36	0.6347
48	0.6338
60	0.6154
72	0.65
84	0.632
96	0.6374
108	0.6271
120	0.6195
132	0.6156
144	0.6192
156	0.6188
168	0.5937
180	0.5844
192	0.5988
204	0.5738
216	0.5573
228	0.5456
240	0.5317
252	0.5318
264	0.5174
273	0.5082
282	0.4802
291	0.4733
300	0.4398
309	0.4491
318	0.4429
327	0.4343
336	0.4224
345	0.4024
354	0.3944
363	0.3602
369	0.3588
372	0.3629
381	0.356
390	0.3625
399	0.2967
408	0.3707

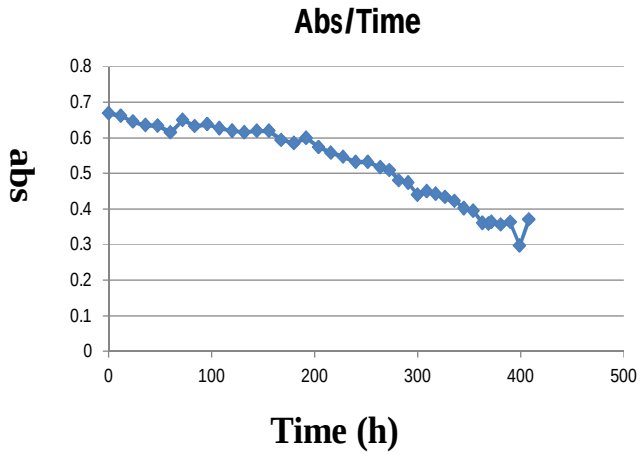


Fig. 3.1.2 The results of the absorption, and the curve of AMX in sunlight.

time(h)	CON(mg/ml)
0	0.025
12	0.0247
24	0.0241
36	0.0237
48	0.0237
60	0.023
72	0.0243
84	0.0236
96	0.0238
108	0.0234
120	0.0231
132	0.023
144	0.0231
156	0.0231
168	0.0222
180	0.0218
192	0.0224
204	0.0214
216	0.0208
228	0.0204
240	0.0199
252	0.0199
264	0.0193
273	0.0184
282	0.0173
291	0.0171
300	0.0159
309	0.0162
318	0.016
327	0.0157
336	0.0152
345	0.0145
354	0.0143
363	0.013
369	0.0129
372	0.013
381	0.0128
390	0.013
399	0.0106
408	0.0133

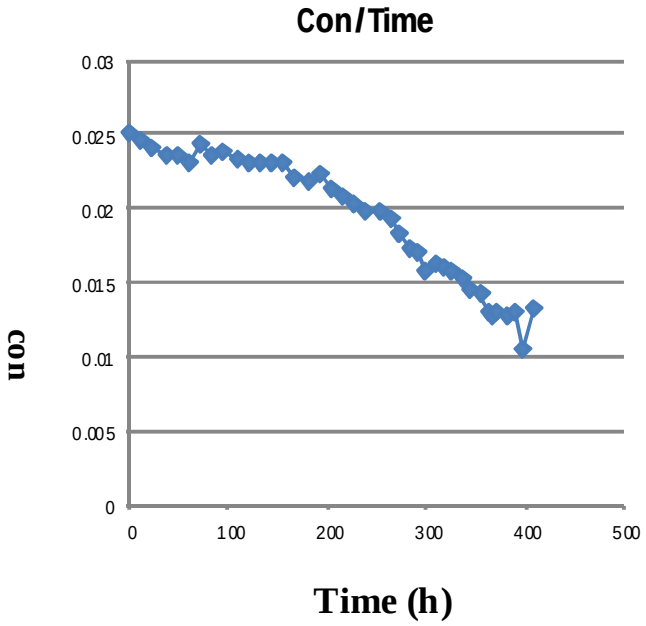


Fig. 3.1.3 The results of the concentration, and the curve of AMX in sunlight.

Time(h)	ABS
0	0.6746
12	0.6731
24	0.6758
36	0.6742
48	0.6604
60	0.6338
72	0.6546
84	0.6335
96	0.6217
108	0.5981
120	0.5958
132	0.5331
144	0.5206
156	0.5181
168	0.498
180	0.5034
192	0.496
204	0.4888
216	0.4785
228	0.4772
240	0.4703
252	0.4676
264	0.4666
273	0.4623
282	0.452
291	0.4436
300	0.4234
309	0.4462
318	0.4625
327	0.4548
336	0.4521
345	0.4437
354	0.4545
363	0.4306
369	0.447
372	0.448
381	0.4437
390	0.4019
399	0.3752
408	0.3923

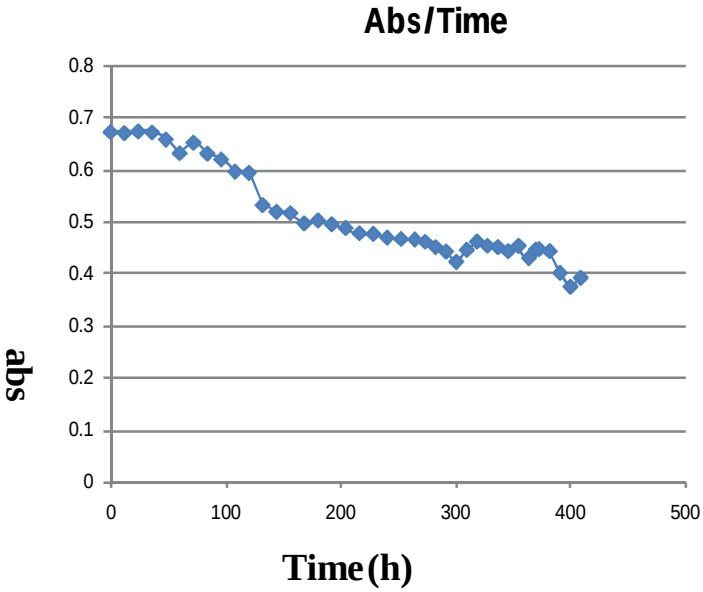


Fig. 3.1.4 The results of the absorption, and the curve of AMX in dark sample.

time(h)	CON(mg/ml)
0	0.025
12	0.0249
24	0.025
36	0.02498
48	0.0245
60	0.0235
72	0.0243
84	0.0235
96	0.023
108	0.0222
120	0.022
132	0.0198
144	0.0193
156	0.0192
168	0.0185
180	0.0187
192	0.0184
204	0.0181
216	0.0177
228	0.0177
240	0.0174
252	0.0173
264	0.0173
273	0.0171
282	0.0167
291	0.0164
300	0.0157
309	0.0165
318	0.0171
327	0.0169
336	0.0168
345	0.0164
354	0.0168
363	0.016
369	0.0166
372	0.0166
381	0.0164
390	0.0149
399	0.0139

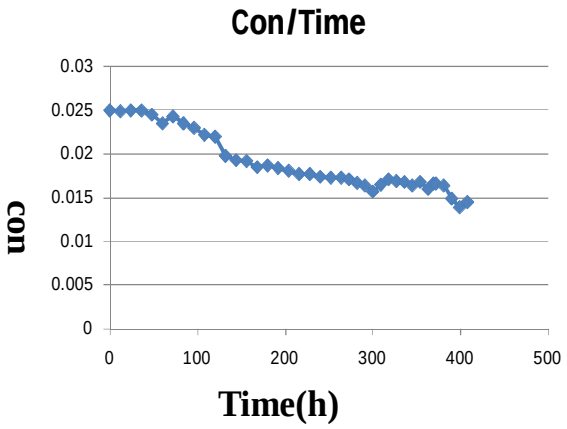
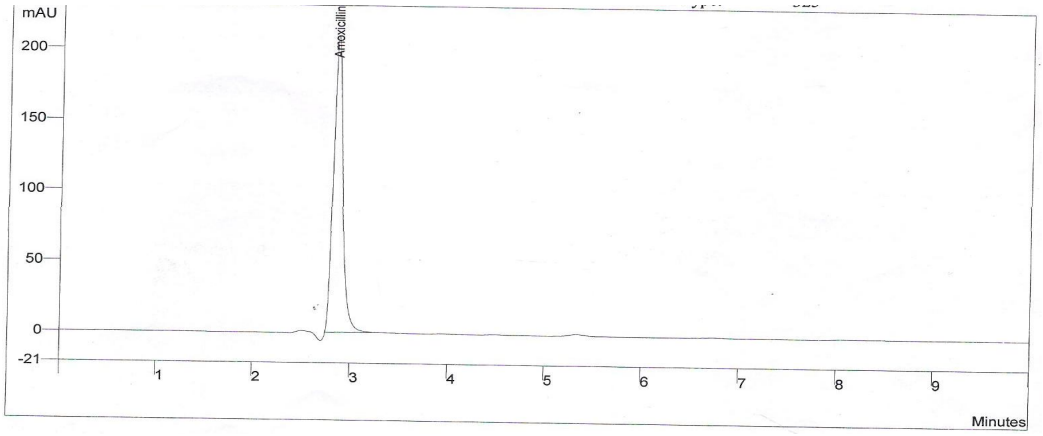
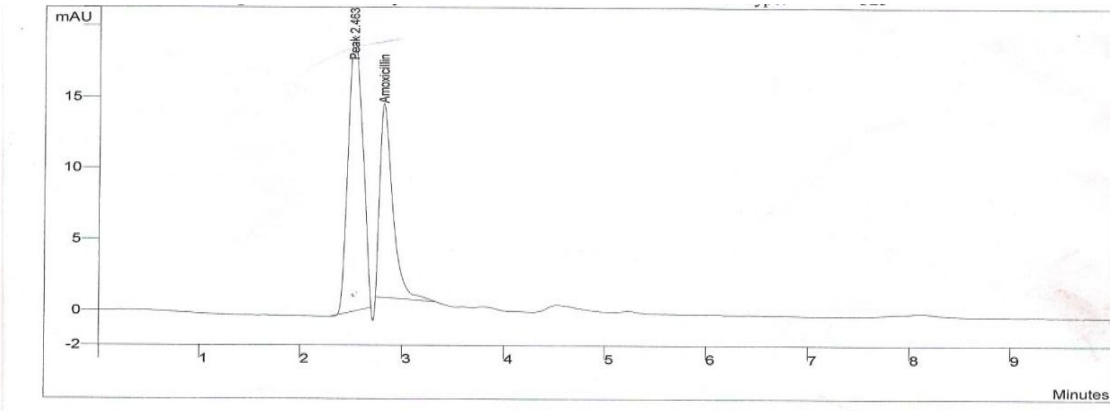


Fig.3.1.5The results of the concentration and the curve of AMX in dark sample.

(1)



(2)



(3)

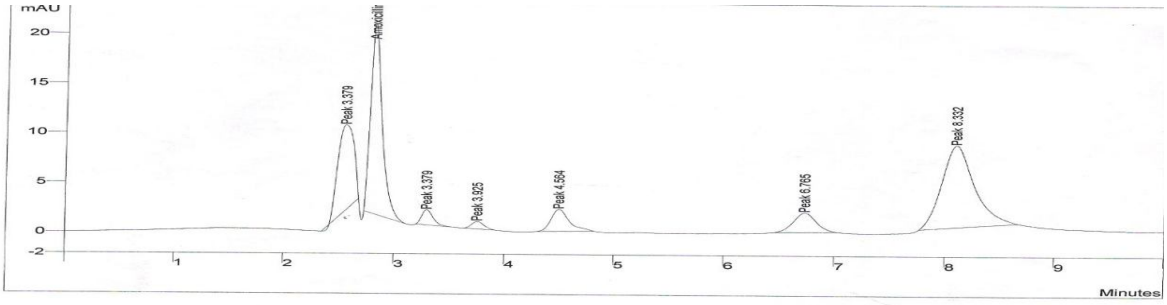


Fig. 3.1.6 HPLC chromatograms of AMX standard (1) and sample in sunlight (2) and sample in dark (3).

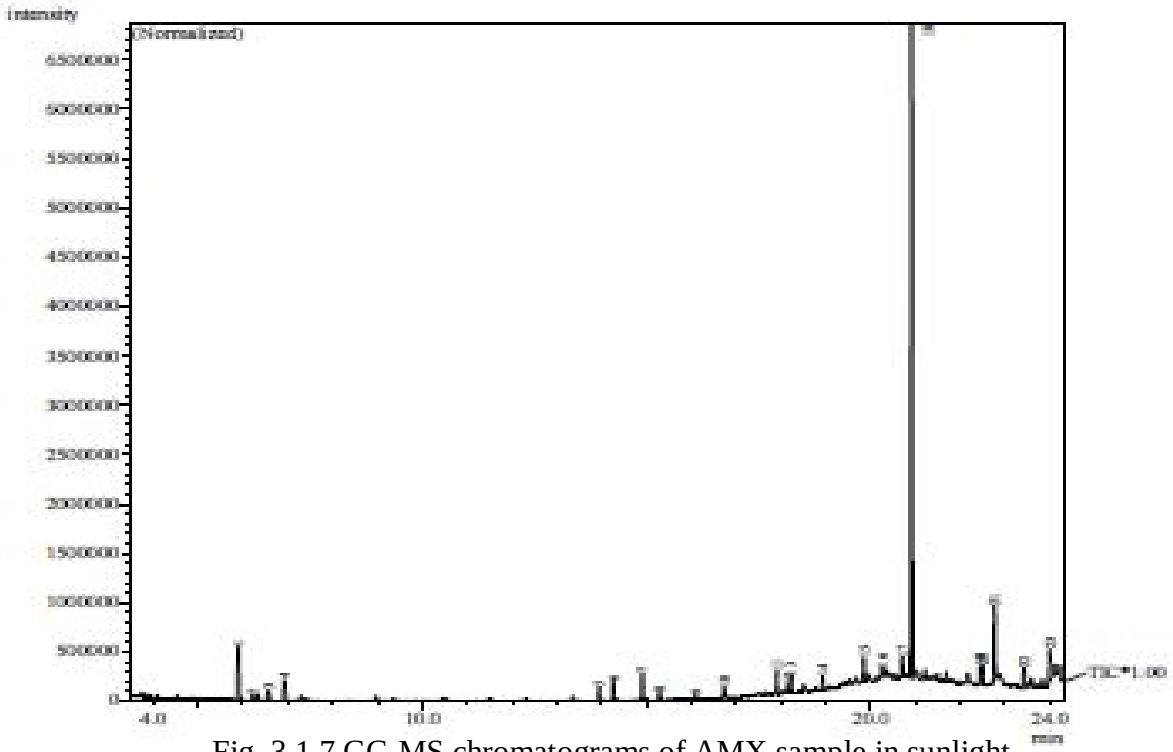


Fig. 3.1.7 GC-MS chromatograms of AMX sample in sunlight.

- Kinetics :
  $T_{1/2}$ = 693h

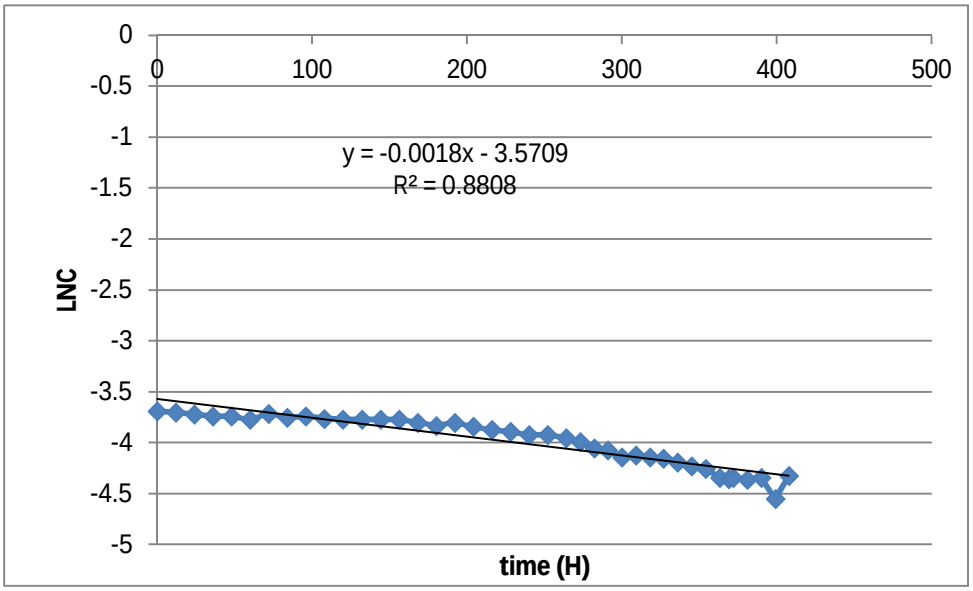


Fig. 3.1.8 Kinetic curve of AMX in sunlight

After the absorption was read for each standard the calibration curve was constructed as followed.

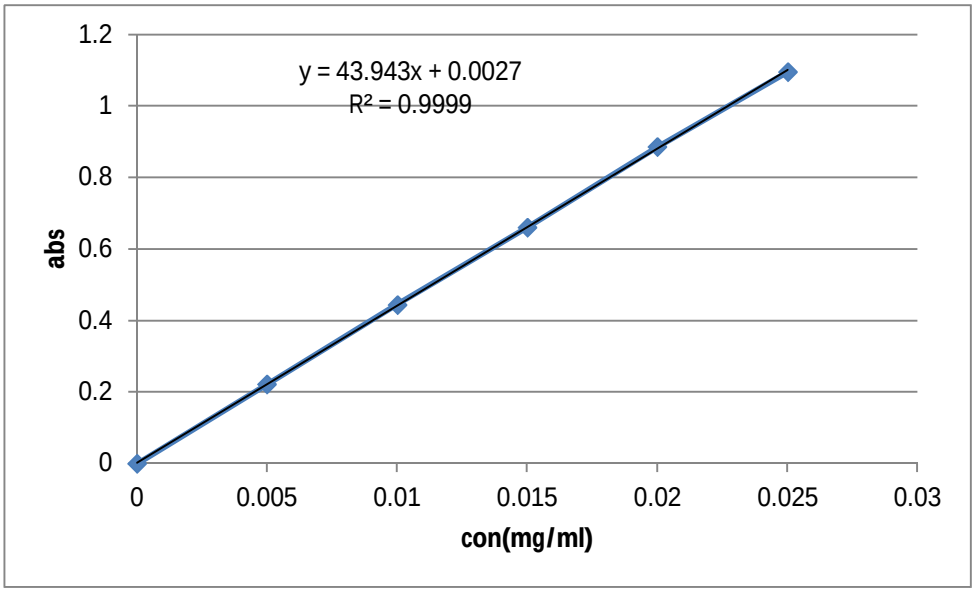


Fig 3.1.9 the calibration curve of CBZ.

Time(h)	ABS
0	0.3743
12	0.3704
24	0.3615
36	0.3595
48	0.3285
60	0.3292
72	0.3338
84	0.331
96	0.3226
108	0.3266
120	0.3019
132	0.3078
144	0.3108
156	0.3065
168	0.3052
180	0.2864
192	0.2974
204	0.2659
216	0.2796
228	0.2726
240	0.2704
252	0.2574
264	0.2738
276	0.2198
288	0.2388
300	0.2339
312	0.2286

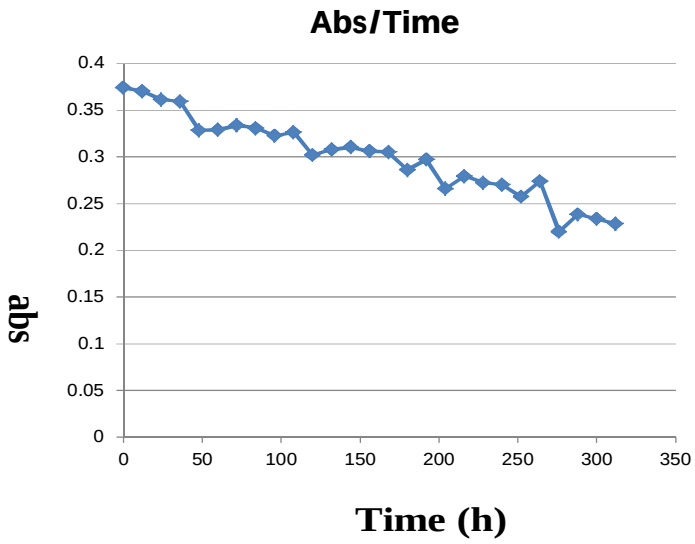


Fig. 3. 1.10 The results of the absorption, and the curve of CBZ in sunlight.

Time(h)	Con (mg/ml)
0	0.008
12	0.00792
24	0.00773
36	0.00768
48	0.00702
60	0.00703
72	0.00713
84	0.00707
96	0.0069
108	0.00698
120	0.00646
132	0.00658
144	0.00664
156	0.00655
168	0.00652
180	0.00612
192	0.00636
204	0.00568
216	0.00598
228	0.00582
240	0.00578
252	0.0055
264	0.00585
276	0.00469
288	0.0051
300	0.00499
312	0.00489

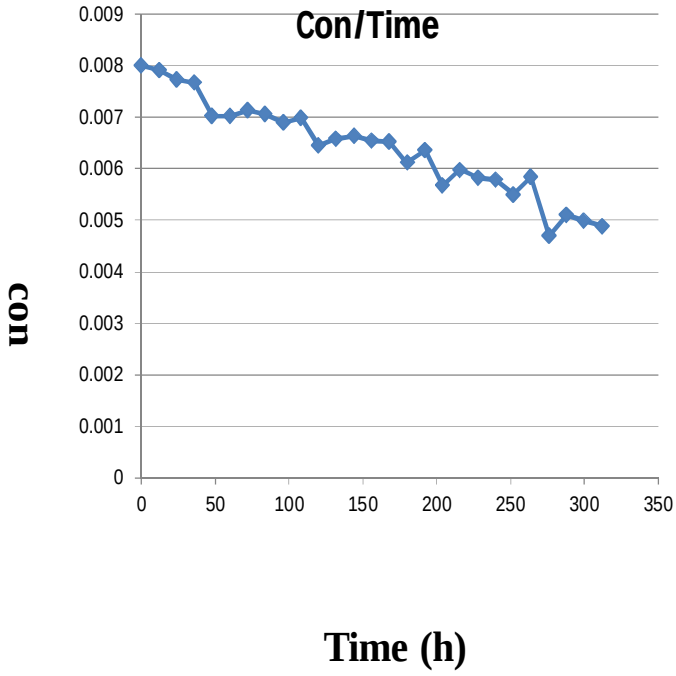


Fig. 3.1.11 The results of the concentration, and the curve of CBZ in sunlight.

Time(h)	ABS
0	0.3713
12	0.3704
24	0.3729
36	0.371
48	0.3694
60	0.3618
72	0.3694
84	0.3566
96	0.3626
108	0.3544
120	0.356
132	0.3609
144	0.3662
156	0.3615
168	0.3581
180	0.3508
192	0.3579
204	0.3518
216	0.3609
228	0.3625
240	0.3671
252	0.3621
264	0.3661
276	0.3404
288	0.3648
300	0.3633
312	0.3535

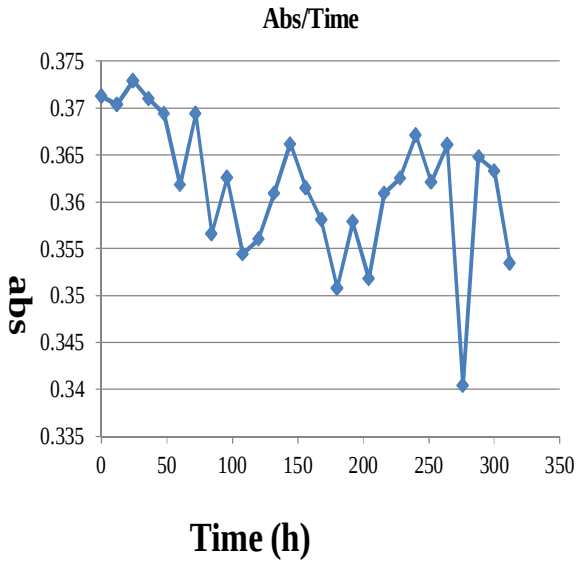


Fig. 3.1.12The results of the absorption and the curve of CBZ in dark sample.

Time(h)	Con (mg/ml)
0	0.008
12	0.00798
24	0.00803
36	0.00799
48	0.00796
60	0.0078
72	0.00796
84	0.00768
96	0.00781
108	0.00763
120	0.00767
132	0.00777
144	0.00789
156	0.00779
168	0.00771
180	0.00756
192	0.00771
204	0.00758
216	0.00778
228	0.00781
240	0.00791
252	0.0078
264	0.00788
276	0.00733
288	0.00786
300	0.00783
312	0.00762

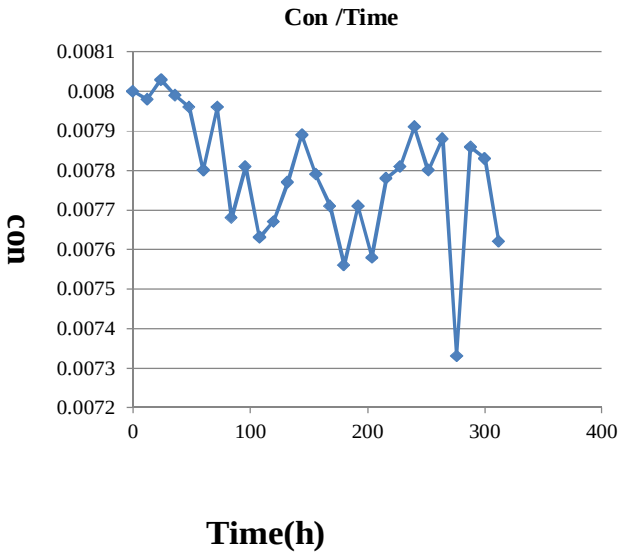
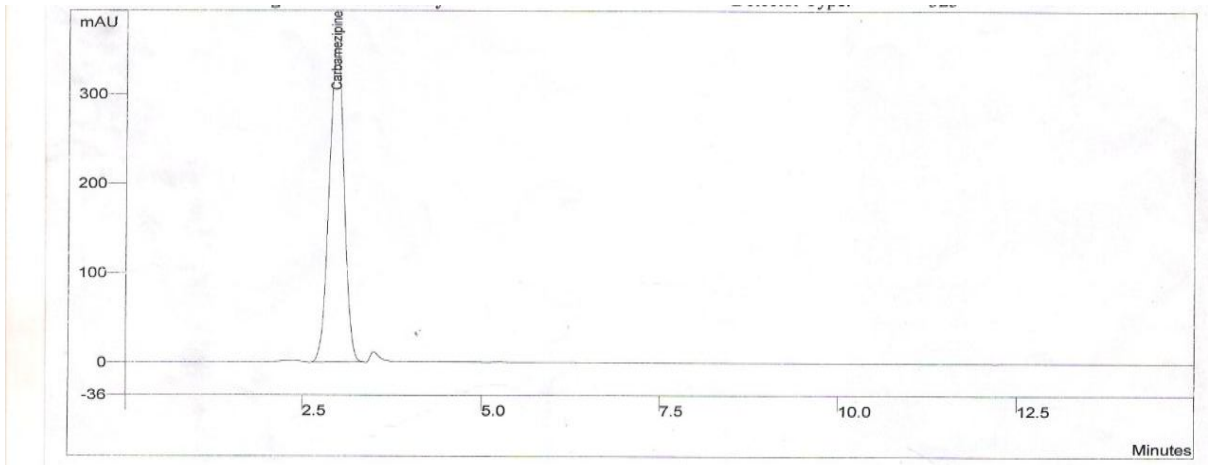
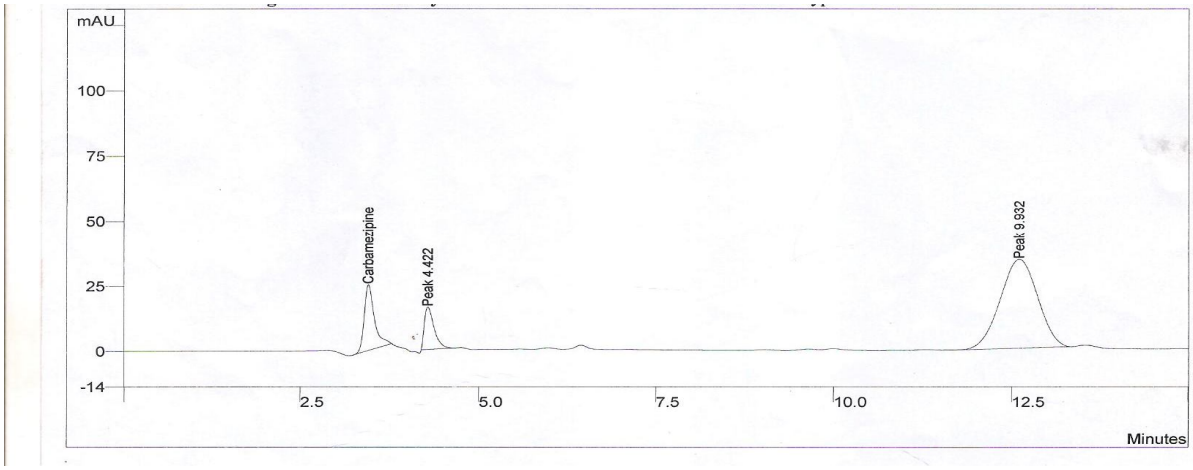


Fig. 3.1.13The results the concentration, and the curve of CBZ in dark sample.

(1)



(2)



(3)

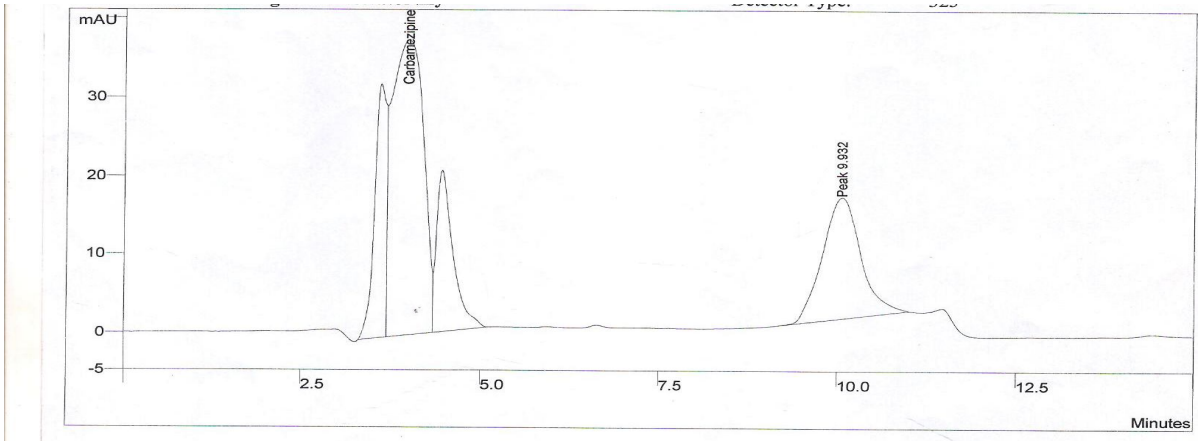


Fig. 3.1.14 HPLC chromatograms of CBZ standard (1) and sample in sunlight (2) and sample in dark (3)

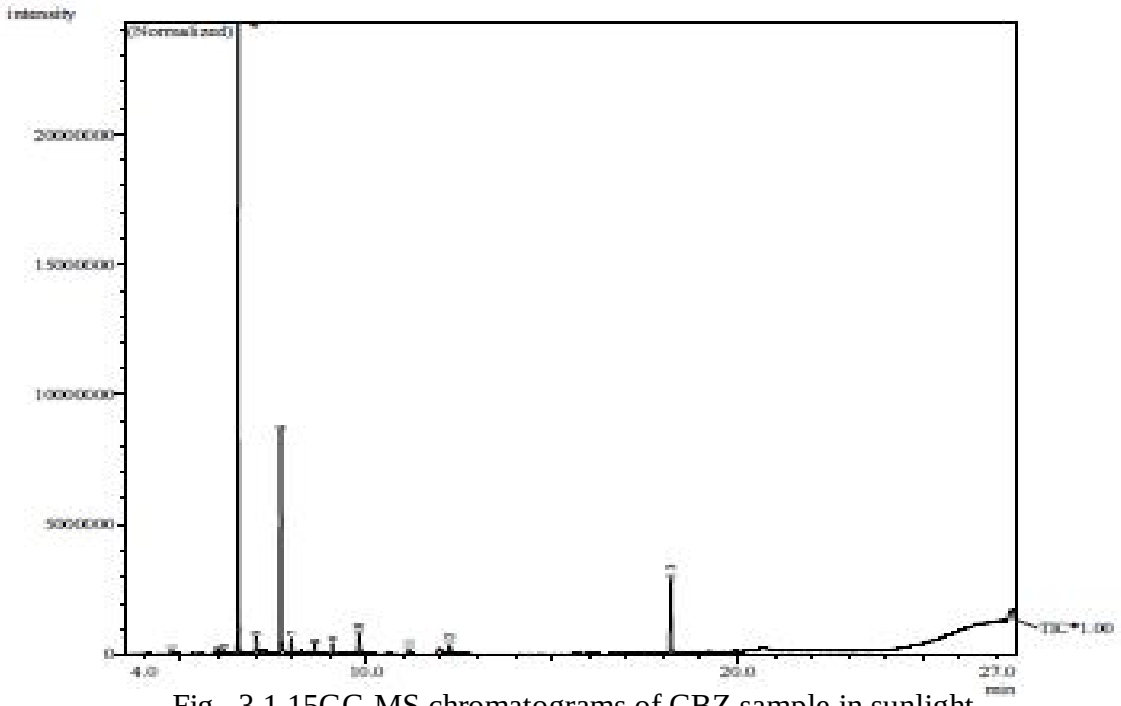


Fig. 3.1.15GC-MS chromatograms of CBZ sample in sunlight.

- Kinetics
  $T_{1/2}$=693h

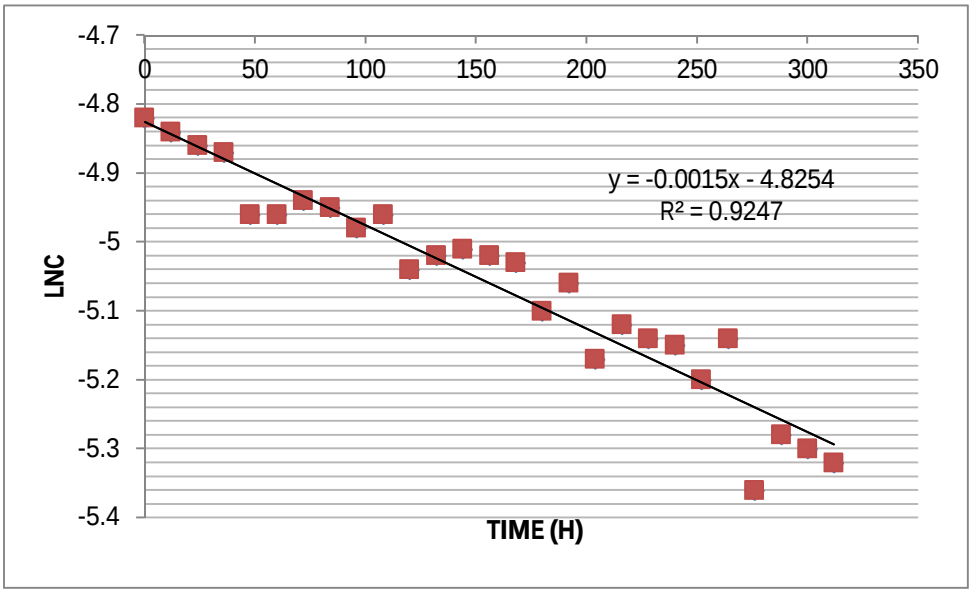


Fig. 3.1.16 The curve of the kinetics of CBZ in sunlight.

After the absorption was read for each standard the calibration curve was constructed as followed.

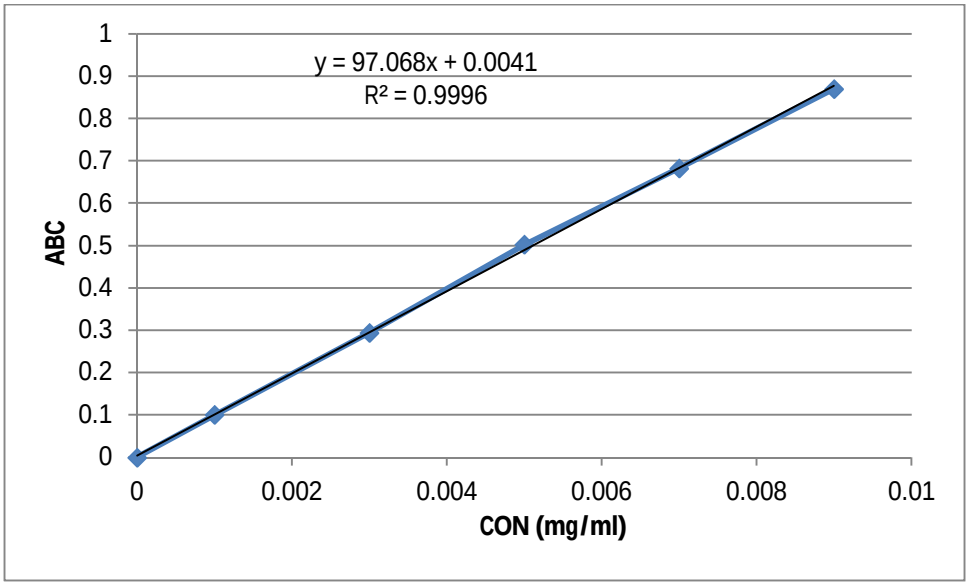


Fig. 3.1.17 The Calibration Curve of CIP.

Time (h)	ABC
0	0.513
6	0.28
12	0.2155
18	0.1826
24	0.15
30	0.1555
36	0.1288
42	0.1293
48	0.1227
54	0.1239

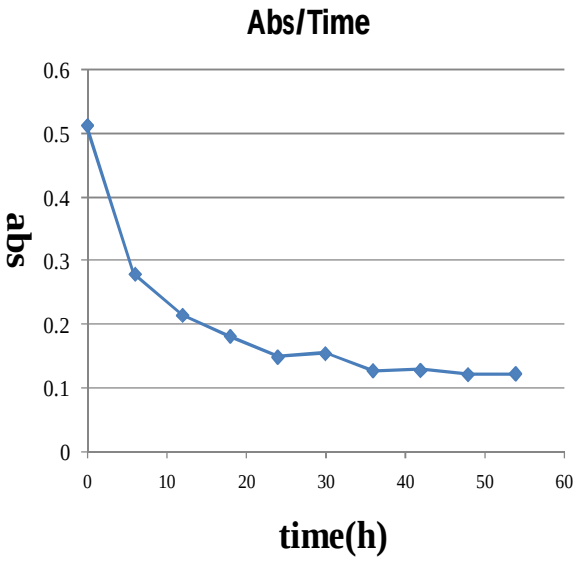


Fig. 3.1.18The results of the absorption and the curve of CIP in sunlight.

Time (h)	Con (mg/ml)
0	0.005
6	0.00272
12	0.0021
18	0.00177
24	0.00146
30	0.00151
36	0.00126
42	0.00126
48	0.00119
54	0.0012

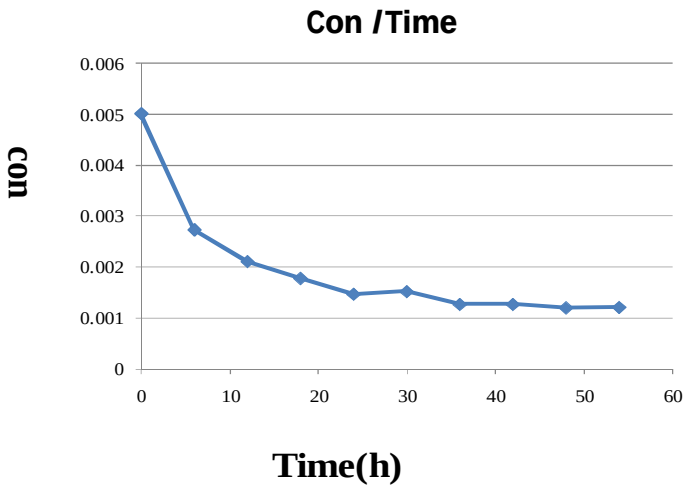


Fig. 3.1.19 The results of the concentration, and the curve of CIP in sunlight.

Time (h)	ABC
0	0.5139
6	0.5129
12	0.5188
18	0.5247
24	0.5087
30	0.5032
36	0.5069
42	0.5128
48	0.5075
54	0.505

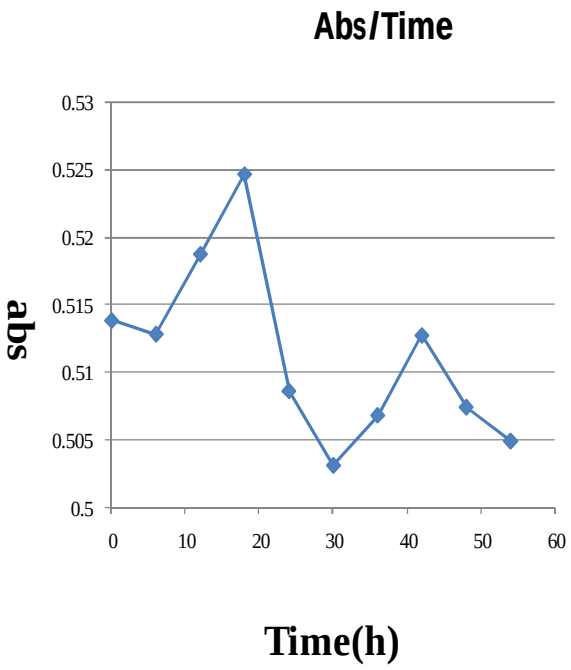


Fig. 3.1.20 The results of the absorption, and the curve of CIP in dark sample.

Time (h)	Con(mg/ml)
0	0.005
6	0.00499
12	0.00504
18	0.0051
24	0.00494
30	0.00489
36	0.00493
42	0.00498
48	0.00493
54	0.00491

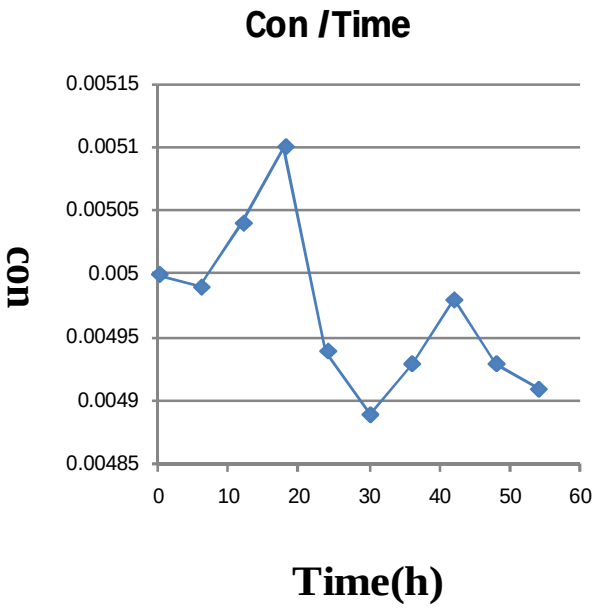
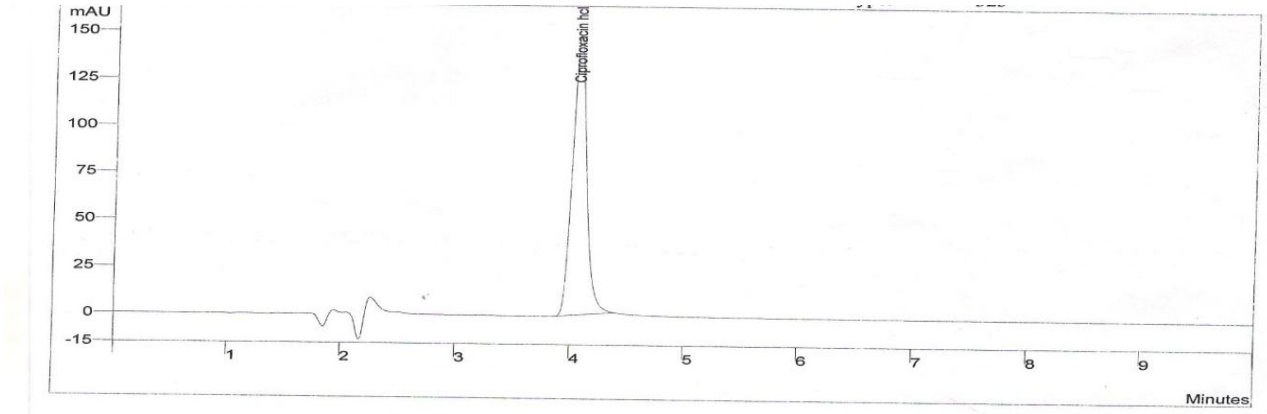
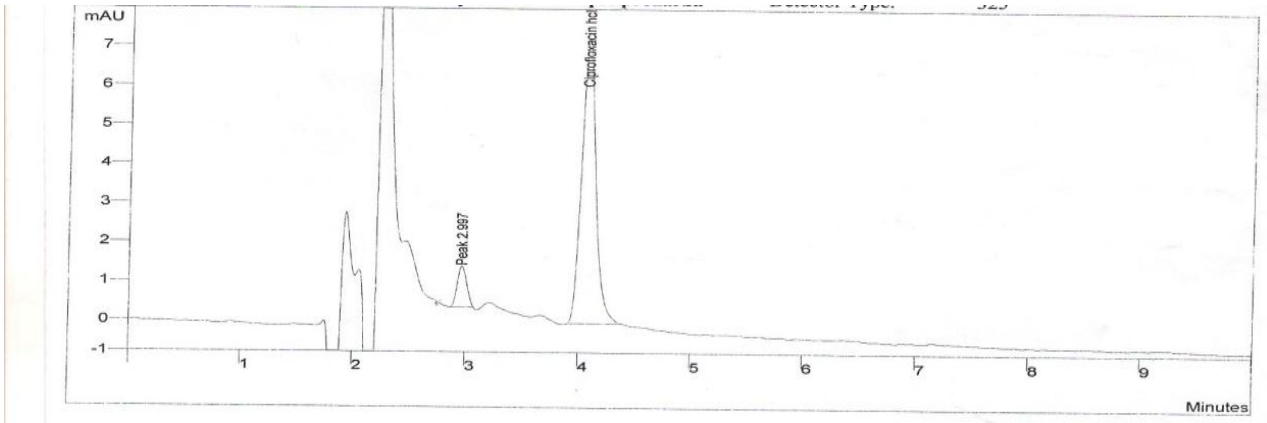


Fig. 3.1.21The results of the concentration and the curve of CIP in dark sample.

(1)



(2)



(3)

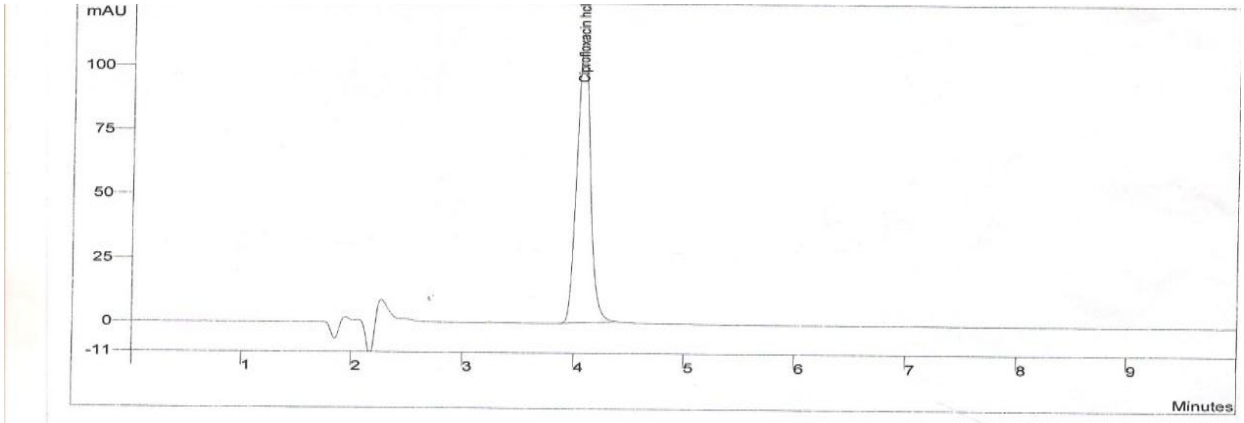


Fig. 3.1.22 HPLC chromatograms of CIP standard (1) and sample in sunlight (2) and sample in dark (3).

Kinetics:

$T_{1/2}$=31.5h

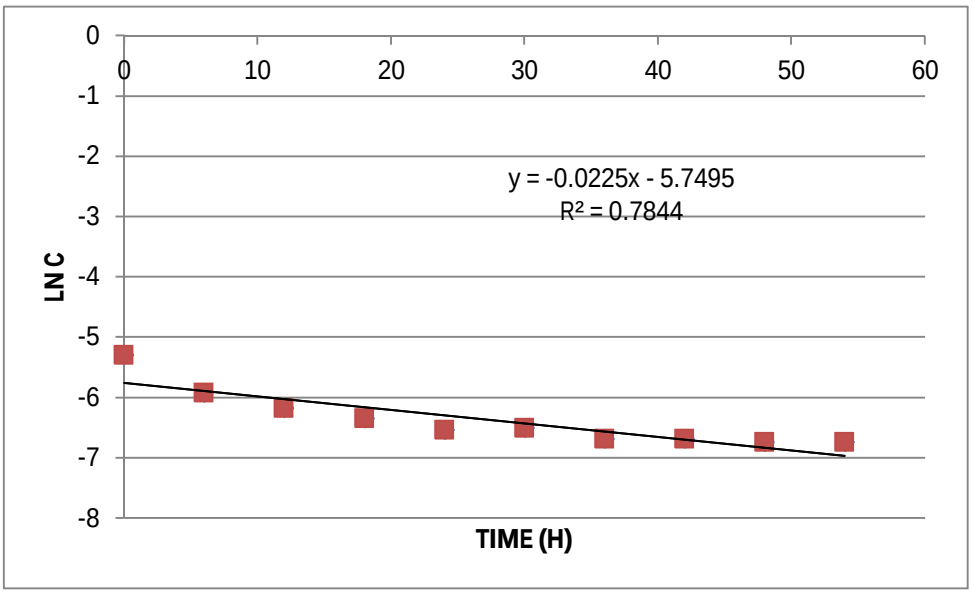


Fig. 3.1.23 The curve of the kinetics of CIP in sunlight.

After the absorption was read for each standard the calibration curve was constructed as followed.

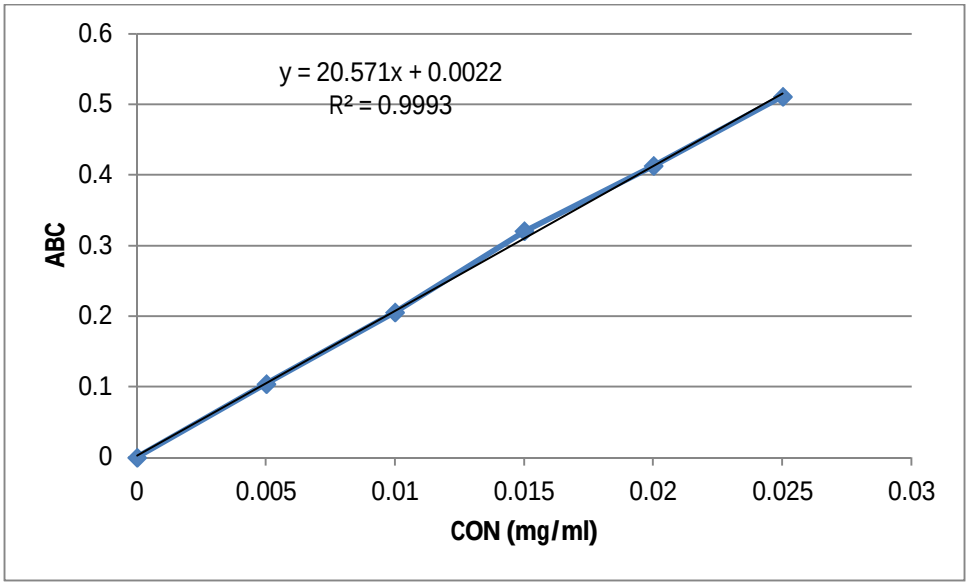


Fig. 3.1.24 The Calibration Curve of CEF.

Time (h)	ABS
0	0.4074
6	0.4063
12	0.3638
18	0.3429
24	0.3163
30	0.3044
36	0.2911
42	0.2742
48	0.2494
54	0.2317
60	0.1965
66	0.1929
72	0.177
78	0.1656
84	0.1476
90	0.1375
96	0.1215
102	0.1258

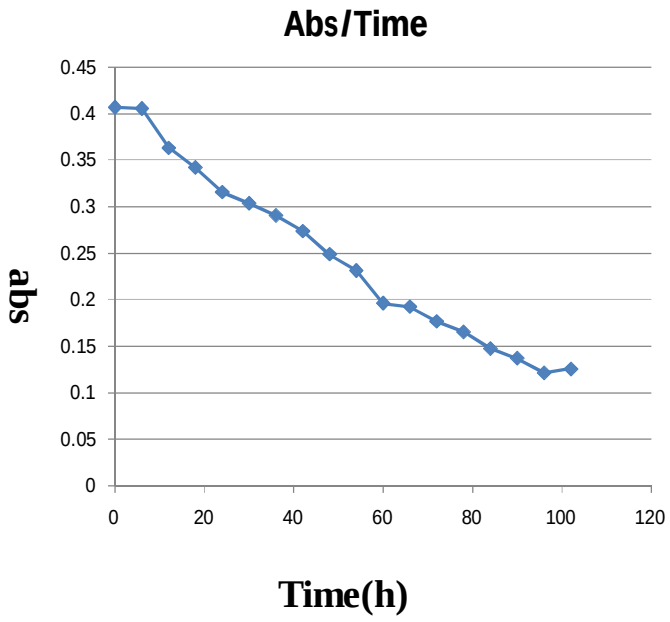


Fig. 3.1.25 The results of the absorption, and the curve of CEF in sunlight.

Time (h)	Con (mg/ml)
0	0.02
6	0.0199
12	0.0179
18	0.0168
24	0.0155
30	0.0149
36	0.0143
42	0.0135
48	0.0122
54	0.0113
60	0.0096
66	0.0095
72	0.0087
78	0.00813
84	0.0072
90	0.0068
96	0.0059
102	0.0061

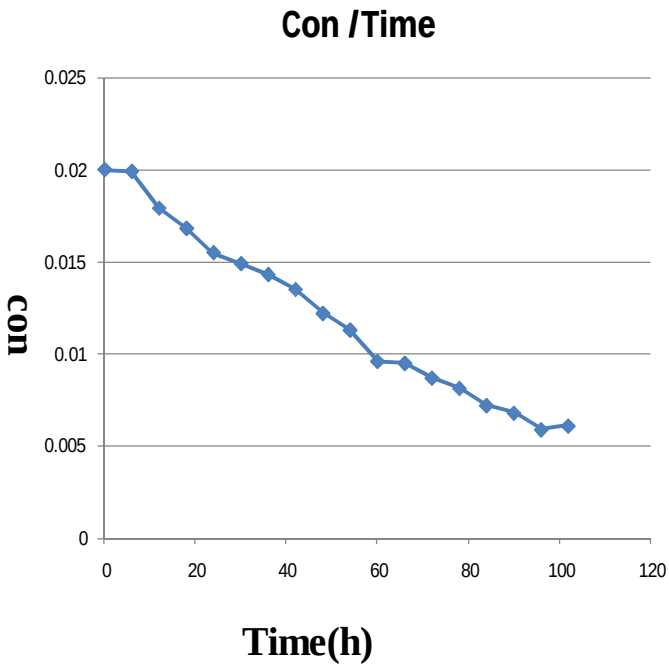


Fig. 3.1.26The results of the concentration and curve of CEF in sunlight.

Time (h)	ABS
0	0.4072
6	0.41
12	0.4084
18	0.4069
24	0.4019
30	0.3993
36	0.3969
42	0.3957
48	0.401
54	0.402
60	0.3949
66	0.3936
72	0.3949
78	0.3887
84	0.3751
90	0.3618
96	0.3439
102	0.3482

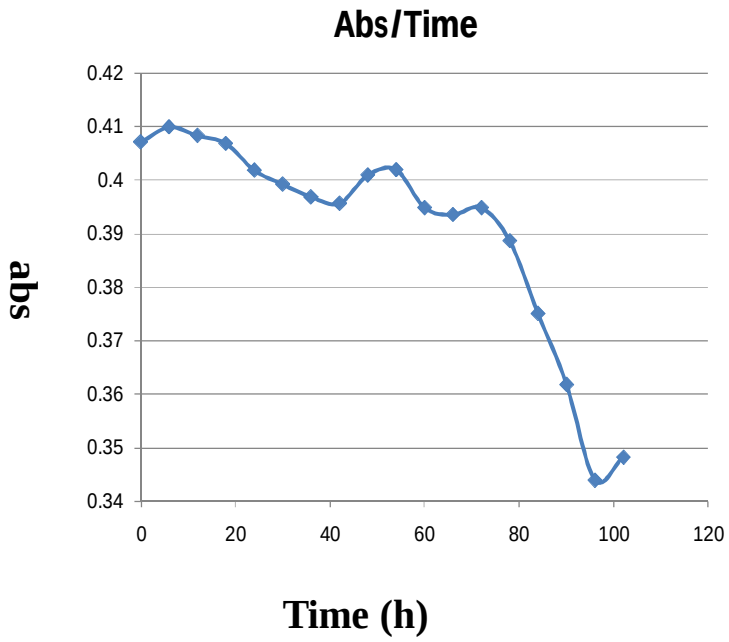


Fig. 3.1.2 The results of the absorption, and the curve of CEF in dark sample.

Time (h)	Con (mg/ml)
0	0.02
6	0.02
12	0.02
18	0.0199
24	0.0197
30	0.0196
36	0.0195
42	0.0194
48	0.0197
54	0.0197
60	0.0194
66	0.0193
72	0.0194
78	0.0185
84	0.0184
90	0.0178
96	0.0169
102	0.0171

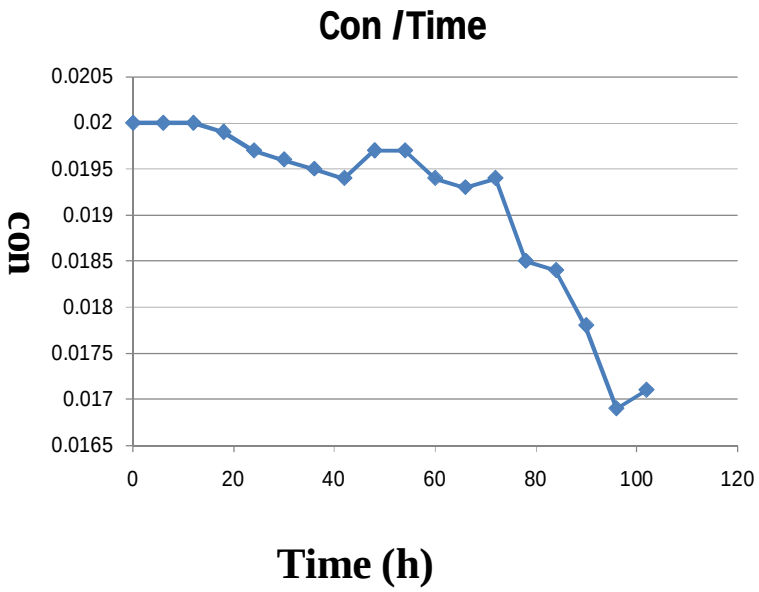
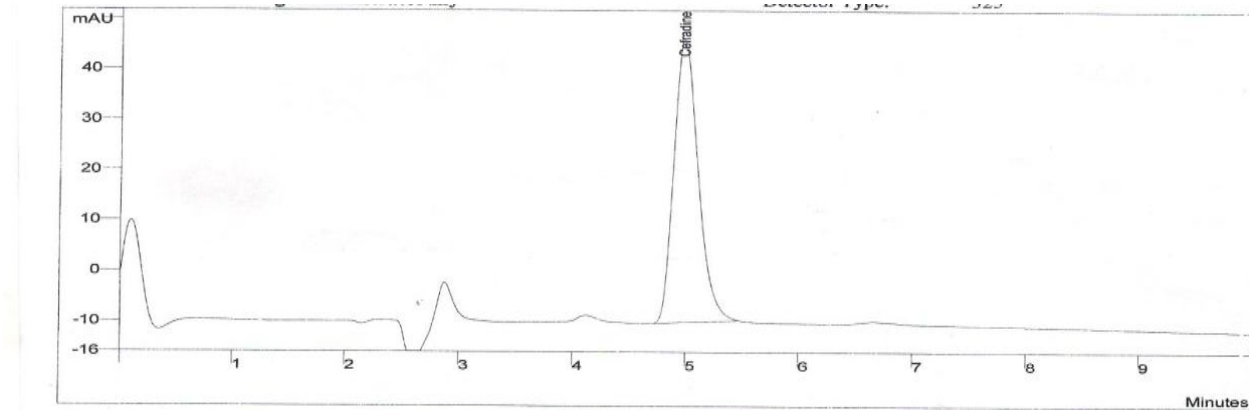
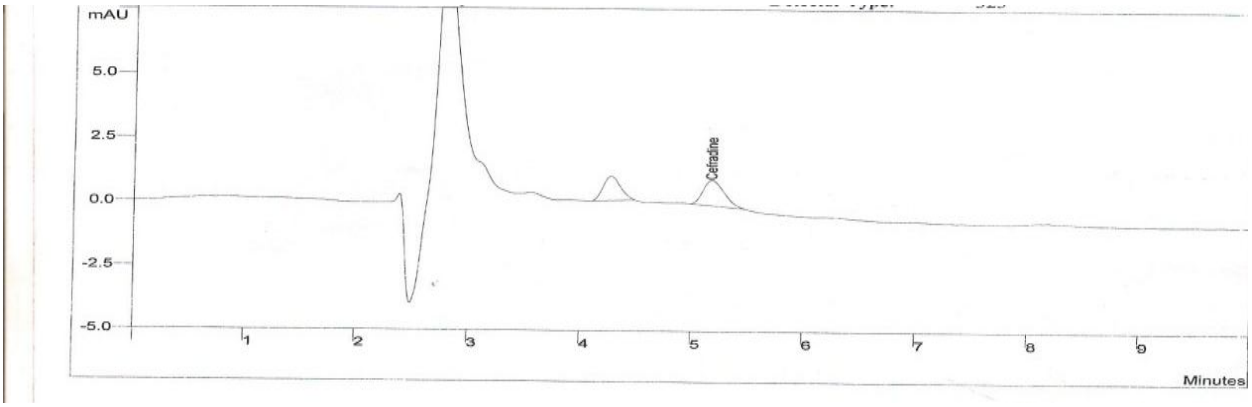


Fig. 3.1.28 The results of the concentration, and the curve of CEF in dark sample.

(1)



(2)



(3)

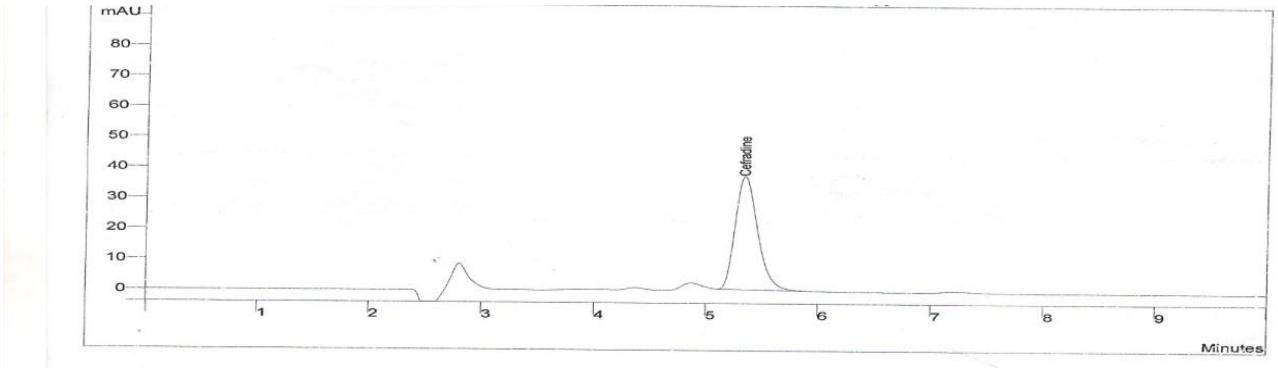


Fig. 3.1.29 HPLC chromatograms of CEF standard (1) and sample in sunlight (2) and sample in dark (3).

- Kinetics:
  $T_{1/2}$= 9.24 h

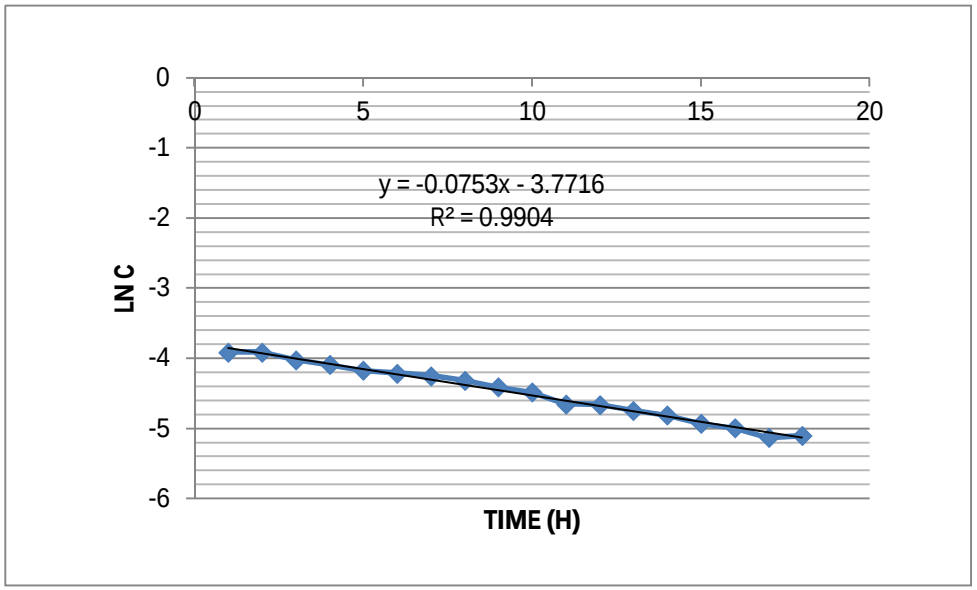


Fig. 3.1.30 the curve of kinetics of CEF in sunlight

After the absorption was read for each standard the calibration curve was constructed as followed.

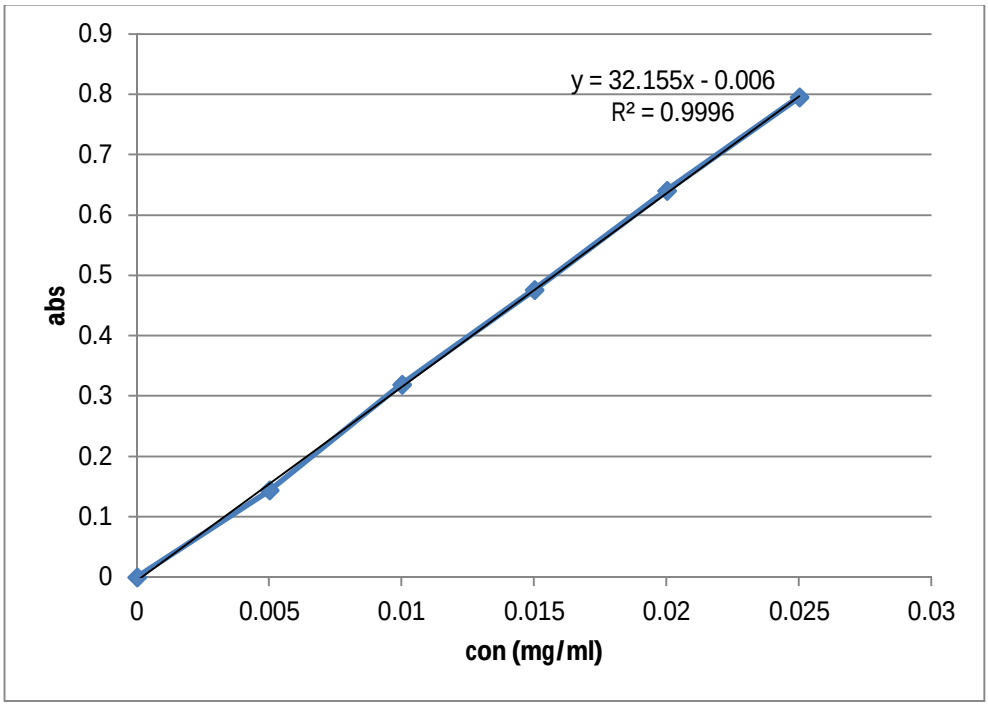


Fig. 3.1.31The Calibration Curve of MEF.

Time (h)	ABS
0	0.3261
6	0.2844
12	0.2692
18	0.255
24	0.2613
30	0.2621
36	0.2539
42	0.249
48	0.2585
54	0.2413
60	0.2299
66	0.2279
72	0.2676
78	0.2653
84	0.2743
90	0.2786
96	0.2412
102	0.3219
108	0.3165
114	0.2868
120	0.2919
126	0.2639
132	0.2921
138	0.2835
144	0.3305
150	0.3176
156	0.3208
162	0.3123
168	0.3263
174	0.3002
180	0.3289
186	0.3059
192	0.3038
198	0.2928
204	0.2608
210	0.2542
216	0.2335
222	0.2335
228	0.2579
234	0.2708
240	0.269
246	0.2476
252	0.2666
258	0.2697
264	0.1958
270	0.1524
276	0.3195
282	0.2946
288	0.3057
294	0.282

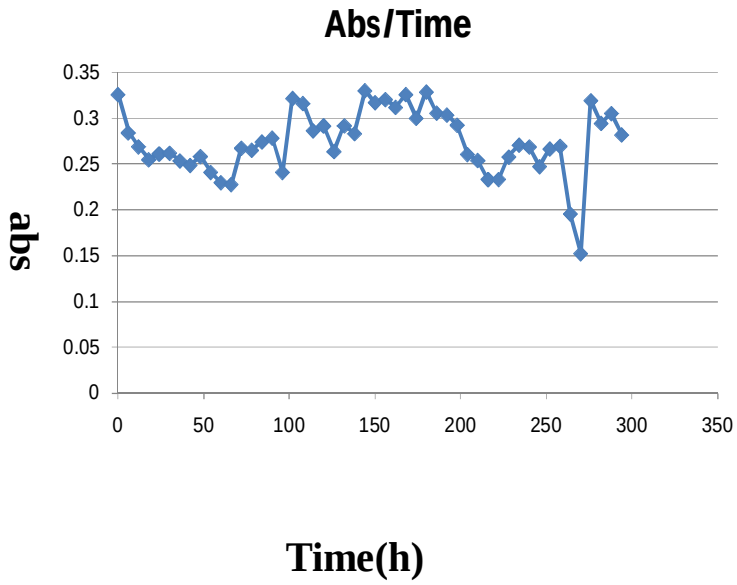


Fig. 3.1.32 The results of the absorption, and the curve of MEF in sunlight.

Time (h)	Con (mg/ml)
0	0.0072
6	0.0063
12	0.0059
18	0.0056
24	0.00575
30	0.00577
36	0.00559
42	0.00537
48	0.00569
54	0.00531
60	0.005
66	0.005
72	0.0059
78	0.00584
84	0.00604
90	0.00613
96	0.00531
102	0.00709
108	0.00697
114	0.00632
120	0.00641
126	0.00581
132	0.00643
138	0.00624
144	0.00728
150	0.00699
156	0.00707
162	0.00687
168	0.00718
174	0.00661
180	0.00724
186	0.00674
192	0.00673
198	0.00644
204	0.00574
210	0.00534
216	0.00514
222	0.00514
228	0.00568
234	0.00596
240	0.0059
246	0.0055
252	0.00587
258	0.00594
264	0.00431
270	0.00335
276	0.00703
282	0.00649
288	0.00673
294	0.00621

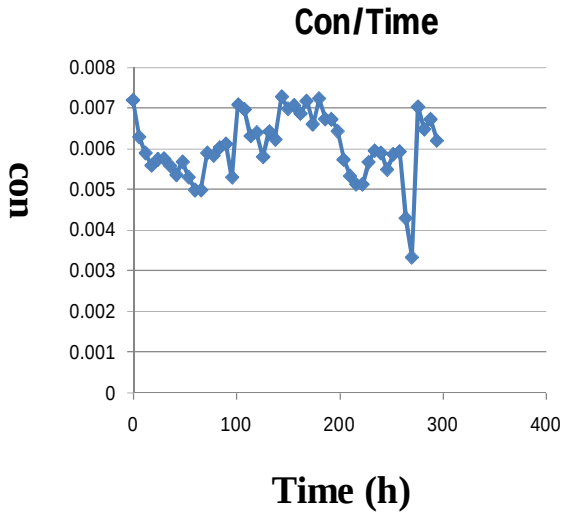


Fig. 3.1.33 The results of the concentration, and the curve of MEF in sunlight.

Time (h)	ABS
0	0.3261
6	0.3185
12	0.2941
18	0.2928
24	0.2952
30	0.2973
36	0.2944
42	0.2747
48	0.2876
54	0.2751
60	0.2588
66	0.2687
72	0.2827
78	0.2969
84	0.2907
90	0.278
96	0.2742
102	0.3483
108	0.3318
114	0.3269
120	0.3109
126	0.3098
132	0.3323
138	0.3271
144	0.3257
150	0.3251
156	0.3311
162	0.3719
168	0.3857
174	0.3618
180	0.3886
186	0.3709
192	0.3808
198	0.3782
204	0.3243
210	0.3122
216	0.3167
222	0.3272
228	0.348
234	0.3665
240	0.3491
246	0.3224
252	0.3548
258	0.3432
264	0.2805
270	0.2426
276	0.4137
282	0.3958
288	0.4127
294	0.3943

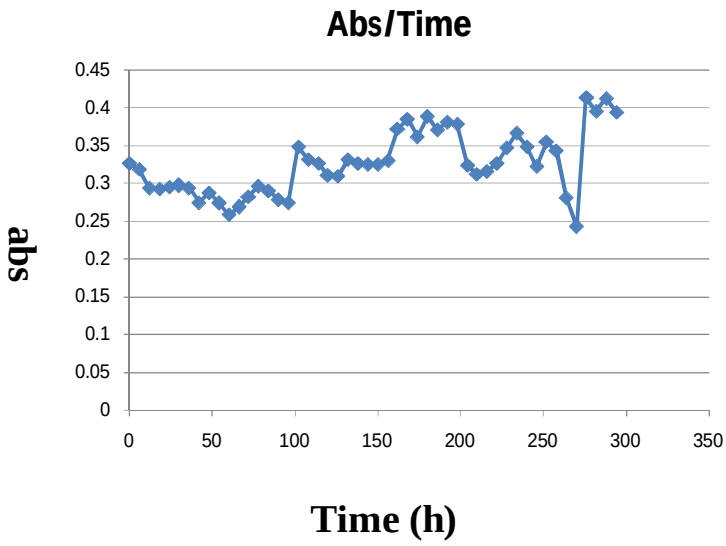


Fig. 3.1.34The results of the absorption and the curve of MEF in dark sample.

Time (h)	Con (mg/ml)
0	0.0072
6	0.007
12	0.0065
18	0.0065
24	0.0065
30	0.00656
36	0.0065
42	0.006
48	0.00635
54	0.00607
60	0.00571
66	0.00593
72	0.00624
78	0.00656
84	0.00642
90	0.00657
96	0.00605
102	0.0077
108	0.00732
114	0.00722
120	0.00686
126	0.00684
132	0.00733
138	0.00722
144	0.00726
150	0.00718
156	0.00731
162	0.00821
168	0.00852
174	0.00798
180	0.00858
186	0.00819
192	0.0084
198	0.00725
204	0.00716
210	0.00711
216	0.00699
222	0.00722
228	0.00768
234	0.008
240	0.0077
246	0.00711
252	0.00783
258	0.00758
264	0.00619
270	0.00536
276	0.00913
282	0.00873
288	0.00911
294	0.0087

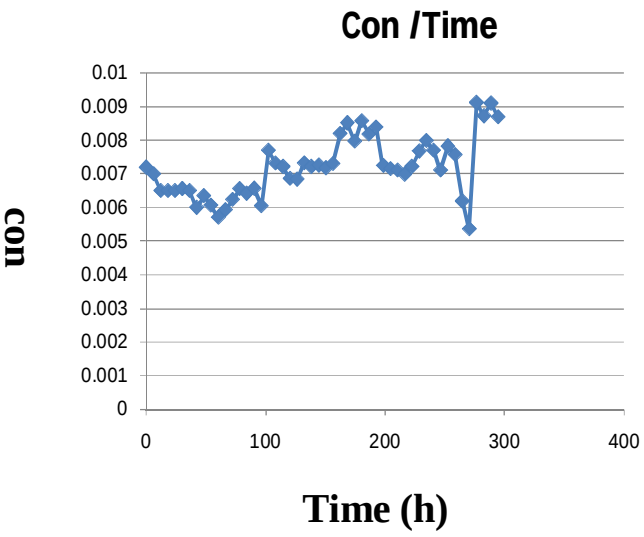
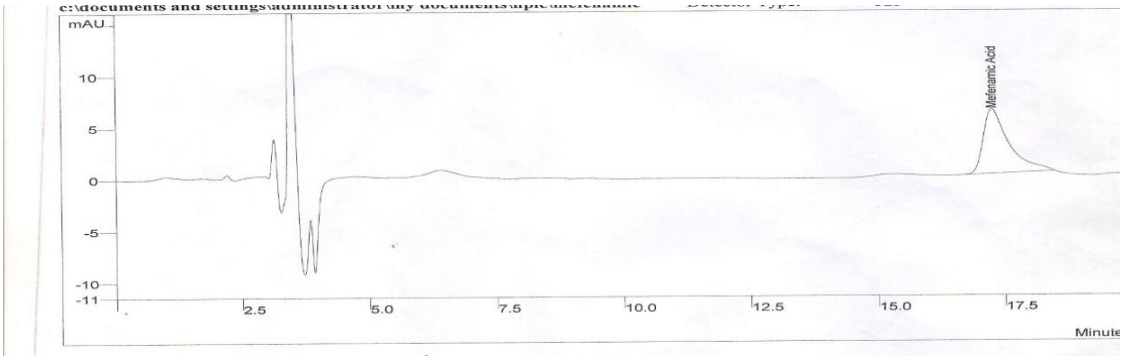
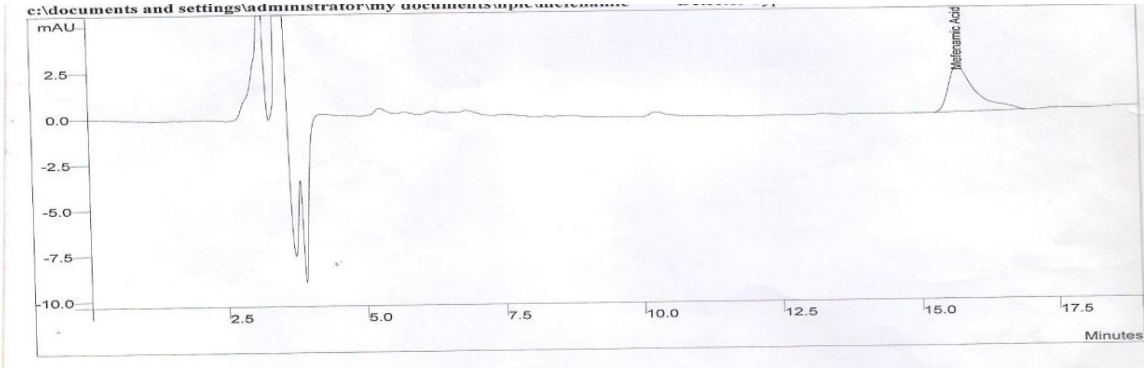


Fig. 3.1.35The results of the concentration and the curve of MEF in dark sample.

(1)



(2)



(3)

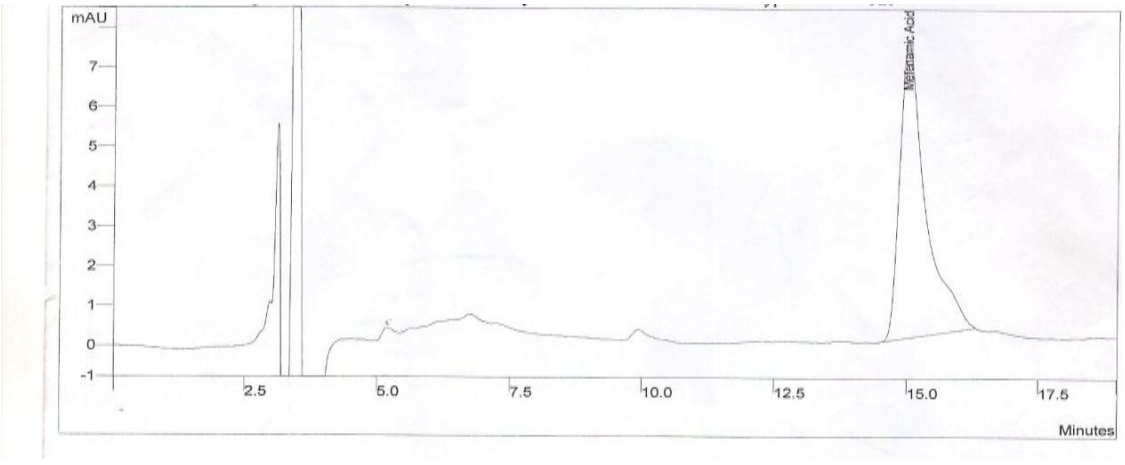


Fig. 3.1.36 HPLC chromatograms of MEF standard (1) and sample in sunlight (2) and sample in dark (3).

- Kinetics :

$T_{1/2}$ = 173 h

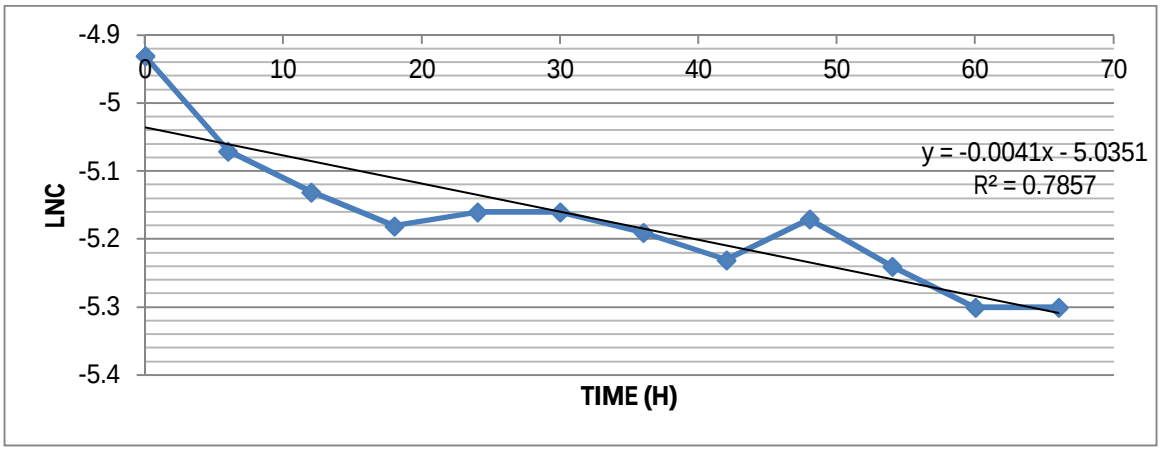


Fig. 3.1.37 The curve of kinetics of MEF in sunlight

3.2: Discussion:

After exposing the five drug samples to the experimental conditions mentioned above, the flowing findings were noted.

3.2.1: Amoxicillin:

In sunlight:

(i) uv-vis spectrophotometer:

When exposing the sample to sunlight the absorbance of the sample gradually decreased with time, indicating decrease in concentration. After 390 h it was noted that the sample turned turbid, and then the absorbance increased indicating its reappearance but with a loss of the amount which breaks. At 399 h a sharp decrease was noted, then again at 408 h the absorbance increased, this might be due to the partial breakage of the original compound, this could be confirmed by the two adjacent chromatograms of appearing at retention times 2.52 and 2.815 shown in Fig. 3.1.6. It is concluded that, there is almost a linear relationship between the absorbance and concentration.

(ii) HPLC:

When we compare the standard of AMX with the sample after 408 h, in addition to AMX, a new compound appeared at retention time 2.52 min.

(iii) GC-MS:

The appearance of the peak at 16.1 which has a molecular weight 382, might be due the breakage of C – N bond, followed by the entering of water molecule giving the compound amoxicillin penicilloic acid (C_{16} $H_{21}N_3O_6S$) .(Nagele & Moritz 2005)

(iv) Kinetics:

According to the first order equation the half-life of AMX was found to be 693 h.

In dark:

(i) uv-vis spectrophotometer:

There is a consistent decrease in absorbance with time, indicating decrease in concentration.

(ii) HPLC:

When we compare the standard of AMX with sample after 408 h, Appearance of different peaks (six peaks) at different times, indicating formation of six cleavage entities, these peaks may be due to certain chemical cleavages due to hydrolysis, hydrated, isomerization.

3.2.2: Carbomazepine:

In sunlight:

(i) uv-vis spectrophotometer:

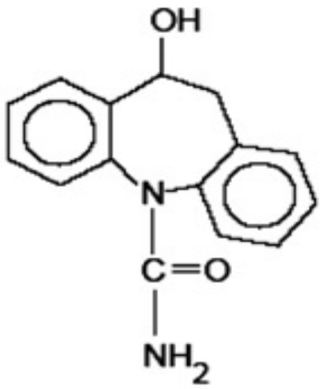
Exposing the sample to sunlight, the absorbance of the sample decreased with time from 0 to 252 h and increased at 264 h, then followed by decrease until 276 h. We conclude that concentration of CBZ sample in sunlight decreased with time.

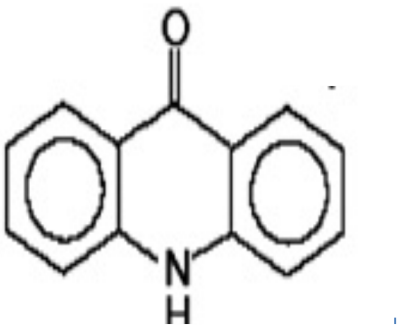
(ii) HPLC:

Comparing the standard of CBZ with sample, two peaks appeared at retention time 4.289 min. and 12.606 min.

(iii) GC-MS:

The two peaks appeared the first one at 7.983 min and it had molecular weight 196 due to direct photodegradation and hydrolysis of the original compound (I); and the second peak at 9.083 min and its molecular weight 256 due to successive cleavages of the original compound ending with a compound of the structure (II). (Petrovic & Barcelo 2007)





II I

(iv) Kinetics:

According to the First order equation the half -life of CBZ was found 693 h.

In dark:

(i) uv-vis spectrophotometer:

A noticeable up and down pattern of decrease and increase indicating a rapid cleavage of the compound.

HPLC:

One peak appeared at retention time 10.057 min.

3.2.3: Ciprofloxacin:

- **In sunlight:**

(i) uv-vis spectrophotometer:

Exposing the sample to sunlight, sharp decrease in the absorbance was noticed, followed by a regular decrease.

(ii) HPLC:

The technique is unable to detect any degraded compounds.

(iii) Kinetics:

According to the first order equation the half-life of CIP was found 31.5 h.

- **In dark :**

(i) uv-vis spectrophotometer:

No apparent change in concentration was noticed.

(ii) HPLC:

When we compare the standard of CIP with sample, an identical chromatogram of the standard appeared, indicating reasonable stability.

3.2.4: Cefradine:

- **In sunlight:**

(i) uv-vis spectrophotometer:

When exposing the sample in sunlight the absorbance of the sample was decreased with time, indicating photodegradation.

(ii) HPLC:

When we compare the standard of CEF with sample after 102 h did not appear any peak with CEF, the result is in accordance with (i).

(iii) Kinetics:

According to the first order equation the half-life of CEF was found 9.24 h.

- **In dark:**

(i) uv-vis spectrophotometer:

The reading of absorbance was decreased with time, also concentration decreased with time indicating degradation.

(ii) HPLC:

When we compare the standard of CEF with sample after 102 no other a peak with CEF.

3.2.5: Mefenamic Acid:

- **In sunlight:**

(i) uv-vis spectrophotometer:

Exposing the sample to sunlight, the absorbance of the sample decreased regularly with time from 0 to 264h, at 270h a noticeable decrease was noticed, which may indicates a cleavage in the original compound. After that the absorbance decreased and increased till 294h.

(ii) HPLC:

When we compare the standard of MEF with sample after 294 h no significant peaks appeared with MEF. This coincides with (i).

(iii) Kinetics:

According to the first order equation the half-life of MEF was found 173 h.

- **In dark:**

(i) uv-vis spectrophotometer:

There is a minor decrease in the absorbance at the beginning, then after that a noticeable increase was noticed till 294h.

The final concentration of MEF is more than initial concentration.

(ii) HPLC:

When we compare the standard of MEF with sample after 294h no peak with appeared MEF.

3.3: Conclusion:

The drugs active ingredients under study are complex organic compounds with varied bonding entities containing N, O, S, and F atoms. These will easily break when exposed to light energy or degraded with time.

Amoxicillin shows pronounced stability compared to other four compounds. This is conformity with pharmacopeia information (USP 2007).

Suggestions for further work:

- Detection of the presence of these compounds in water and soil environments.
- Identification of the photo-chemically degraded compound.
- Kinetic tracing of the fates of the degraded compounds in water streams and the soil.
- The fragments which appear for the other samples will be left for further studies.

References:

Ali, MF, Ali, BM &Speight, JG 2005, *Handbook of Industrial Chemistry organic chemicals*, McGraw Hill, New York.

Ahovuo, A, Rautakorpi, UM, Borisenko, OV, Liira, H, Williams, JW& Makela, M 2014, Antibiotics for acute maxillary sinusitis, *The Cochrane Library*, doi: 10.1002/14651858.CD000243.pub3. edit.

Aurora, JC, Graeme, MD, Mother well, WD & Jones, W 2007, Importance of molecular shape for the overall stability of hydrogen bond motifs in the crystal structures of various carbamazepine type drug molecules, *Crystal Growth & Design*, 2007, 7 (1), pp 100–107.

Antonio F, Ambrosio,1 ,Patrício Soares-da-Silva,2 Caetana M, Carvalho,1,and Arsélio P, Carvalho 2002, Mechanisms of Action of Carbamazepine and Its Derivatives, Oxcarbazepine, BIA 2-093, and BIA 2-024, *Neurochemical Research*,vol.27,no.1,pp.121-130.

Avisar, D, Horovitz,I ,Lozzi ,L, Ruggieri ,F, Baker, M, LaureAbel ,M & Mamane, H 2013,Impact of water quality on removal of carbamazepine in natural waters by TiON Photo-Catalytic thin film surfaces, *Journal of Hazardous Materials*,Vol.244-245,pp.463-471.

Araujo, L , Villa, N, Camargo, N, Bustos, M, Garcia ,T, Prieto, AJ 2009, . Persistence of gemfibrozil, naproxen and mefenamic acid in natural waters, *Environmental Chemistry Letters*, vol. 9 ,no. 1, pp. 13-18.

Ball, P 2000, Quinolone generations, natural history or natural selection, *Antimicrobial Chemotherapy*,vol.45,no.3,pp.17-24.

Brunton, L, Lazo, J, Parker, K 2005, *Goodman & Gilman's the Pharmacological Basis of Therapeutics*, McGraw-Hill, New York.

British National Formulary 45 March 2003.

Blum, K 2013, *Phototransformation of pharmaceuticals in the environment*, M.Sc. thesis, Umea University, Sweden

Callaghan, CH 1979, Description and classification of the newer cephalosporins and their relation with the established compounds. J. Antimicrob. Chemothe, *Antimicrobial Chemotherapy*, vol.5, no.6, pp. 635-671.

Calisto ,V, Domingues, RM, Emy, GL & Esteves, VI 2010, Direct photodegradation of carbamazepine followed by micellar electrokinetic chromatography and mass spectrometry, *Water Research,*vol.45,no.3,pp.1095-1104.

Cai, W, Ouyang, Y, Lin, X &XU, J 1998, Photochemical Fluorimetric Determination of Cephradine, *Analytical Letters,*vol.31,no.3,pp.439-450.

Gillies, M, Ranakusuma, A, Hoffmann, T, Thorning, S, McGuire, T, Glasziou, P& Del Mar, C 2014 , Common harms from Amoxicillin a systematic review and meta-analysis of randomized placebo-controlled trials for any indication, *CMAJ Medical Knowledge that matters*, Cmaj .140488.

Hayder, I, Ishtiaq A.Qazi,I, Awan, MA, Khan, MA, Turabi,2012, Degradation and Inactivation of Ciprofloxacin By photocatalysis using TIO2 Nanoparticles, *Journal of Applied pharmacy,*Vol.4,no.1,pp.487-497.

Haomin Xu, Cooper, WJ, Jung, J, W& Song, W 2010, Photosensitized degradation of amoxicillin in natural organic Matter isolate solutions, *water research,* vol.45.no.2, pp.632-938.

Halimeh, AS 2012, *Fate of Amoxicillin, Ibuprofen, and Caffeine in Soil and Ground Water Using Soil Columns*, M.Sc. thesis, An-Najah National University, Palestine.

Hubicka, U , Zmudzki, P, Talik, P, Zuromska-Witek, B & Krzek, J 2013, Photodegradation assessment of ciprofloxacin, moxifloxacin, norfloxacin and Ofloxacin in the presence of excipients from tablets by UPLC-MS/MS and DSC, *Chemistry Central*,vol.7,no.1,pp,133.

John, LM, Hasskarl, H, Bode, G, Klingmann, I & Zahn, M 2007, *Pharmaceuticals General Survey* ,Ullmann's Encyclopedia of Industrial Chemistry, Technology Wiley-VCH Weinheim, Doi:10.1002/14356007.a19273.pub2.

Jiskra, M 2008, Fate of the pharmaceutical diclofenac in the aquatic environment, *Biogeochemistry and Pollutant Dynamics* ,vol.21,pp.1-16.

Kornblum, Z C 2010, Photochemistry, Encyclopedia Americana. Retrieved July 24, 2010, from Grolier Online http://ea.grolier.com/article?id=0311750-00.

Konig, B 2013, *Organic Photochemistry*, Institut für Organische Chemie, Universidad Regensburg.

Kockler, J, Kanakaraju, D, Glass, B & Oelgemoller ,M 2012, Photochemical and photocatalytic Degradation of Diclofenac and Amoxicillin using natural and simulated sunlight, *Journal of sustainability science and management,* vol. 7. No 1, pp.23-29.

Lahti, M 2012, the Fate Aspects of Pharmaceuticals in the Environment Biotransformation, Sedimentation and Exposure of Fish, University of Jyvaskyla.

Martinez, C, Canle, ML ,Fernandez, MI, Santaballa, JA& Faria ,J 2010, Kinetics and Mechanism of aqueous Degradation of Carbamazepine by Heterogeneous Photocatalysis Using Nanocrystalline TiO2, ZnO and Multi-Walled Carbon Nanotubes-Anatase Composites, *Applied Catalysis, B:Environmental*, Vol.2,no.3-4,pp.563-571.

Matamoros, V, Duhec, A , Albaigés, J & Bayona, MJ 2008, Photodegradation of Carbamazepine, Ibuprofen, Ketoprofen and 17α-Ethinylestradiol in Fresh and Seawater, *Water Air and soil pollution* vol. 196, no. 1-4,pp.161-168.

Mores, AN 2003, *Fate and Effect of Amoxicillin in Space and Terrestrial Water Reclamation Systems*. Ph.D theses, Texas Tech University.

Nagele, E & Moritz, R 2005, Structure Elucidation of Degradation Products of the Antibiotic Amoxicillin with Ion Trap MSn and Accurate Mass Determination by ESI TOF. *American Society for Mass Spectrometry,* Vol. 16, pp. 1670-1676.

Pringsheim, T, Davenport, WJ, Dodick, D 2008, Acute Treatment and Prevention of Menstrually Related Migraine Headache Evidence-Based, review, *Neurology*, vol.70, no.17, pp.1555-1563.

Pine, SH 1987, *Organic Chemistry*, McGraw-Hill, New York.

Petrovic, M & Barcelo, D 2007,LC-MS for identifying photodegradation products of pharmaceuticals in the environment. *Trends in Analytical Chemistry,* vol.26,no.6, pp. 486-493.

Razuc, M F, Garrido BS. & Band, F, 2013. 37. M. F.Date Fusion Applied to the photodegradation study of ciprofloxacin using a tandem detection system (uv-vis and fluorescence and multivariate curve resolution. *Talant,* Volume 115, pp. 314-322.

Singh, GD & Gupta, KC 2014, Photo and UV degradation of Ciprofloxacin Antibiotic, *International Journal of Current Microbiology and Applied science* ,vol.3,no.6,pp.641-648.

Shreve & Brink 1975, *Chemical process Industries*, McGraw Hill, New York.

Sultana, N, Arayne, MS & Afzal, M 2003, Synthesis and Antibacterial Activity of Cephradine Metal Complyxes : Part I Complexes With Magnesium, Calcium, Chromiuma And Manganese , *Pakistan Journal of Pharmaceutical Sciences* ,vol. 16, no.1, pp.59-72.

The American Society of Health-System Pharmacists, Ciprofloxacin Hydrochloride, Retrieved 3 April 2011.

The American Society of Health-System Pharmacists, Amoxicillin , Retrieved3 April 2011.

Thornhill, MH, Dayer, MJ, Forde, JM, Corey, GR, Chu, VH, Couper, DJ& Lockhart, PB 2011, Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study, *BMJ* 342:d2392. Doi:10.1136/bmj.d2392.PMC 3086390. PMID 21540258 .

United States Pharmacopeia National Formulary, 2007.

WHO Model List of Essential Medicines, World Health Organization, October 2013, Retrieved 22 April 2014.

WHO Technical Report Series, No. 929, 2005.

Werner, J, McNeill, K, Arnold, WA 2004, Environmental photodegradation of mefenamic acid,*Chemoshere,*vol.58,no.10,pp. 1339-1346.

Zamazam, A 2014, Photochemical phate of Diclofenac pharmaceutical drug, M.Sc. Theses, University of Omdurman Islamic, Sudan.

Ziegmann, M, & Frimmel, FH 2010, Photocatalytic degradation of clofibric acid, carbamazepine and iomeprol using conglomerated TiO2 and activated carbon in aqueous suspension, *Water Sci. techonol.*,vol.(61), 1 , pp. 81-273.