ADSORPTION CHARACTERISTICS OF THE FLUOROQUINOLONE ANTIBACTERIAL AGENTS.

BY

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APRIL 2006

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A THESIS SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS OF THE MASTER OF SCIENCE DEGREE IN PHARMACEUTICAL CHEMISTRY, FACULTY OF PHARMACY, UNIVERSITY OF BENIN, BENIN CITY, NIGERIA.

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CERTIFICATION

We certify that this research work titled “Adsorption Characteristics of the Fluoroquinolone Antibacterial Agents” was carried out by AFOLABI ADEREMI BASIRU of the Department of Pharmaceutical Chemistry . We also certify that this thesis satisfied the partial requirements for the award of the Master of Science degree in pharmaceutical chemistry.

…….. ……..……

DR. C.J. EBOKA DR. C.J. EBOKA

CHIEF SUPERVISOR HEAD OF DEPARTMENT

DEDICATION

WITH GRATITUDE TO ALMIGHTY GOD, I DEDICATE THIS WORK TO THE SWEET MEMORY OF MY LATE FATHER, MR RAJI OJO AFOLABI (1919-1987) WHOSE LOVE AND RESPECT FOR EDUCATION KNEW NO BOUND.

A.B. Afolabi.

ACKNOWLEDGEMENTS

My profound gratitude goes to the almighty Allah for His continued support and sustenance. I am eternally grateful to Him for seeing me through another hurdle which initially seemed to be a mirage.

My sincere appreciation goes to my chief supervisor, Dr. C.J. Eboka for his unquantifiable assistance and advice throughout the course of this work. I thank God for your patience, thoroughness and amiable disposition.

I am eternally grateful to my mother Mrs Munirat Ajitoni Alake Afolabi who in every circumstance continues to urge me for patience and perseverance. I so much cherish your attitude of always highlighting the positive aspect of an otherwise precarious situation. I am grateful to my uncle evangelist Joseph Oladokun Olowolagba for his unrelenting assistance and fatherly advice. My gratitude also goes to my senior sisters Mrs Falilat Omolara Lawal and Mrs Taibat Arolayo Olaniyi for their assistance and encouragement. Other members of this wonderful family – Ayo, Taye, Bayo, Ramota, Kola, Temilade, Fasilat and Wasiu - are not left out.

I deeply thank the managements of Sam Pharmaceuticals, Ilorin and Nigeria – German Chemicals, Lagos for supplying the pure powders of ciprofloxacin, norfloxacin and ofloxacin used for this work. I also thank Messrs Anyaebene and Osifeso both of Biochemistry Department for their assistance.

My special thanks go to my lecturers – Prof. E.O.P. Agbakwuru, Prof. J.I. Ogonor (late), Prof.S.A. Adelusi and Dr. C.O. Usifoh

I appreciate my colleagues – Abiodun Falodun, Henry Okeri, Peter Alonge, Lucky Okunrobo, Smart Johnson, Bro. Buniyamin Ayinde, Gabriel, Fabian, Friday and others.

My sincere thanks also go to other members of staff – Mr.Umoru, Mrs Tina Obi, Odeka, Doris, Sister Ann, Pastor Ukoh, J. Umoru and Prof. E.E. Obaseki-Ebor for their assistance and co-operation in the use of the laboratory facilities.

I wish to acknowledge the contribution of my wife, Bukky and my son, Kolade whose continued support and understanding remain the oasis and fulcrum of my strength. I also thank my friends – Bayo Atanda, Kayode Oladipo, Kayode Amuda, Remi Yusuff, Idris Oyewo and Adebisi Sampson – for their enduring love and support.

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To those people who I ought to have acknowledged, I tender my unreserved apology as I count very much on your understanding.

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A.B. Afolabi.

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ABSTRACT

Bioavailability of orally administered fluoroquinolones has been shown to be hampered by factors that reduce gastro-intestinal absorption of the drugs. These factors include the presence of metallic drugs or agents which result in the formation of drug-cationic chelate complexes in the gut which make the fluoroquinolone molecules unavailable for absorption. Similarly, concurrent administration of some drugs alongside adsorbents like activated charcoal reduces the amount of the drug that could be absorbed from the gut due to binding of the drug molecules to the adsorbent. Binding capacities of adsorbents have also been known to be dependent on their surface polarity and surface area. Concomitant administration of fluoroquinolones with adsorbents would result in the binding of the fluoroquinolones on the adsorbents and thereby making the adsorbed fluoroquinolones to be unavailable in the right proportion required to effect the desired antibacterial activity. The ensuing therapeutic failure therefore, is of grave concern to the patient who would not derive value for his money and in some critical circumstances suffer an irreparable damage to his health. However, the phenomenon is of great importance in the management of cases of accidental ingestion and over dosage involving fluoroquinolones.

The aim of this work therefore, is to evaluate the extent to which adsorption of fluoroquinolones viz ciprofloxacin, ofloxacin and norfloxacin could be affected by common adsorbents such as activated charcoal (carbon), bentonite and kaolin. The experimental conditions were simulated to mimic normal human Gastro-Intestinal Tract (GIT) environment by using 0.1M hydrochloric acid (HCl) at 37oC and constant shaking. Definite amounts of fluoroquinolones were treated with graded amounts of adsorbents

over a period of time during which samples were taken at regular intervals to determine the drug concentrations which were measured by Ultraviolet/Visible (UV) absorption of the samples at wavelengths of their maximum absorption.

The results obtained showed that activated carbon and bentonite exhibited a high degree of adsorption to the three fluoroquinolones while kaolin showed poor binding capacities to the three compounds. The result was evaluated in accordance with the Langmuir adsorption isotherm in line with similar works earlier carried out. The implication of these findings is two fold:

1. The high binding capacities exhibited by activated carbon and bentonite to ciprofloxacin, ofloxacin and norfloxacin supported the view that the two adsorbents are good antidotes in cases of accidental ingestion of these antibacterial agents. However, these adsorbents should be avoided during fluoroquinolone therapy as they will bind the fluoroquinolones and therefore lead to therapeutic failure.
2. The poor binding capacities exhibited by kaolin to ciprofloxacin, ofloxacin and norfloxacin reduces the apprehension about therapeutic failure during concurrent administration with the fluoroquinolones.

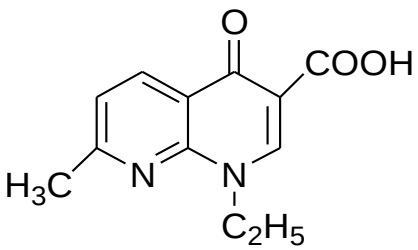
CHAPTER 1

INTRODUCTION AND LITERATURE REVIEW.

1.1 INTRODUCTION

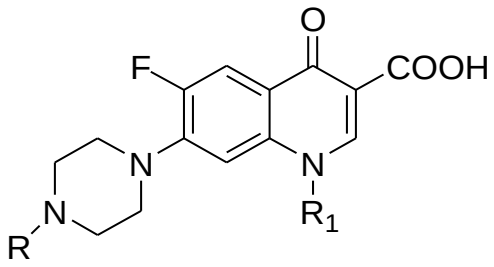
The quinolones are a group of potentially valuable antibacterial compounds. They are developed from nalidixic acid (Figure 1), a 1,8-naphthyridine which is a urinary tract antibactarial agent. Quinolones have much broader antibacterial spectrum than their predecessor and have found useful application in the treatment of genito-urinary tract infections, respiratory, bone and joint infections as well as skin and soft tissue infections. (1)

The addition of fluorine atom to the original quinolone structure at the carbon-6 (C_6) position and piperazino ring at C_7 position has yielded a new class of antimicrobial drugs (fluoroquinolones) which exhibit a broader antimicrobial spectrum and improved pharmacokinetic properties (2). The traditional quinolone antibacterial agents which included nalidixic acid (Negram), Cinoxacin (Cinobac) and Oxolinic acid have their clinical uses limited to the primary indications in the treatment of urinary tract infections. However the enhanced antimicrobial activity achieved with the introduction of fluoroquinolones has extended their uses beyond this traditional indication as they are effective in a wider variety of infectious diseases including skin and respiratory tract infections.(3). As a result of this as well as their excellent safety and tolerability profile, fluoroquinolone antibacterial agents have become popular alternatives to penicillin and cephalosporin derivatives in the treatment of various infections due to unpalatable anaphylactic reactions commonly associated with the latter's use. (4) Fluoroquinolones are broad-spectrum antibacterial agents with considerable activity against Gram-positive and Gram-negative organisms, especially *Pseudomonas aeruginosa* as well as in the treatment of certain infections such as pneumonia (5 - 7).

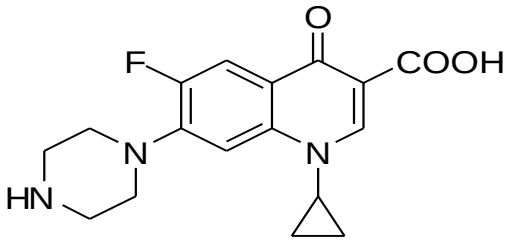


Nalidixic acid

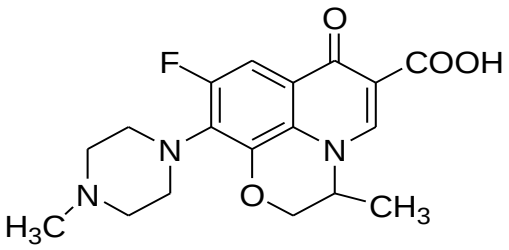
Figure 1: Nalidixic acid



Norfloxacin, R=H, $R_1 = C_2H_5$
Perfloxacin, $R=CH_3$ $R_1 = C_2H_5$
Amifloxacin, $R=CH_3$ $R_1 = NHCH_3$



Ciprofloxacin



Ofloxacin

Figure 2 : Examples of Quinolone Antibacterial agents.

1.2 CLASSIFICATION OF QUINOLONES.

1:2:1 MICROBIOLOGICAL CLASSIFICATION

This classification takes into account the expanded antimicrobial spectrum of the newer fluoroquinolones and their clinical indications. Introduced in 1997, it is useful to the physicians when empirically prescribing these drugs or evaluating new agents introduced into the market (8). Drugs in each group are similar in antimicrobial activity, while a significant new group of pathogens is added to the coverage with each successive generation.

First Generation

Members of this group include cinoxacin and nalidixic acid which are the oldest and least often used quinolones. Their use has been restricted to the treatment of uncomplicated urinary tract infections due to minimal serum concentrations achievable with them. They require more frequent dosing than the newer quinolones, and are more susceptible to the development of bacterial resistance. They are not recommended for use in patients with poor renal functions because of toxicity as a result of serum accumulation arising from significantly reduced urinary excretion.(2, 9).

Second Generation

This includes ciprofloxacin, ofloxacin, enoxacin, lomefloxacin and norfloxacin. They possess increased Gram-negative activity as well as some Gram-positive and atypical pathogen coverage. Compared with first-generation drugs, these agents have broader clinical applications in the treatment of complicated urinary tract infections and pyelonephritis, sexually transmitted diseases, selected pneumonias and skin infections (4). Ciprofloxacin is the most potent fluoroquinolone against *Pseudomonas aeruginosa* (10,11). It is a useful alternative to parenterally administered antibiotics for the treatment of osteomylitis caused by susceptible organisms due to its good penetration into bone after oral administration. Ofloxacin has the greatest activity against *Chlamydia trachomatis* of all the second generation agents, while the two (ciprofloxacin and ofloxacin) remain the most widely used second generation quinolones because of their availability in oral and intravenous formulations. (4). In spite of the concern expressed over incidence of adverse effects of fluoroquinolones on the joints based on experimental evidence in young animals, a study that was carried out on more than a thousand children who received ciprofloxacin revealed no arthropathies (12).

Third Generation

Members of this group include levofloxacin, gatifloxacin, moxifloxacin and sparfloxacin. These agents are separated into a third class because of their expanded activity against gram-positive organisms, particularly penicillin sensitive and penicillin resistant *Streptococcus pneumoniae*, and atypical pathogens

such as *Mycoplasma pneumoniae* and *Chalamydia pneumoniae* (7,13,14). Although they retain broad Gram-negative coverage, third generation quinolones are less active than ciprofloxacin against pseudomonas species (4).

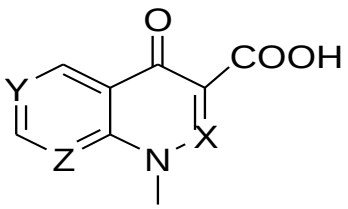
Fourth Generation

Trovafloxacin is currently the only member of this generation. While maintaining the Gram-positive and Gram-negative activity of the third generation quinolones, it adds significant antimicrobial activity against anaerobes. Its activity against pseudomonas species is comparable to that of ciprofloxacin (15,16) Trovafloxacin is available as an oral tablet and its prodrug, alatrofloxacin (Trovan IV) in an intravenous formulation, but due to concern about its hepatotoxicity, its use should be reserved for life or limb-threatening infections requiring in-patient treatment and the duration of treatment should not be longer than 14 days (17).

1:2:2 CHEMICAL CLASSIFICATION.

Chemistry of Quinolones.

General chemical structure of the quinolones is as shown in scheme 3 below:



	X	Y	Z
Quinolines	C	C	C
Cinolines	N	C	C
Naphthyridines	C	C	N
Pyridopyrimidines	C	N	N

Figure 3: General Chemical Structure of the Quinolones

1. Naphthyridrines

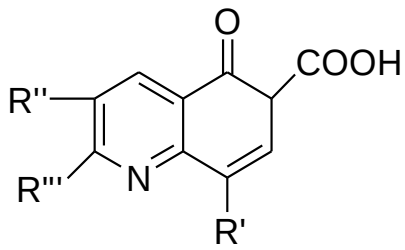


Figure 4 : Naphthyridines

2. Cinolines:

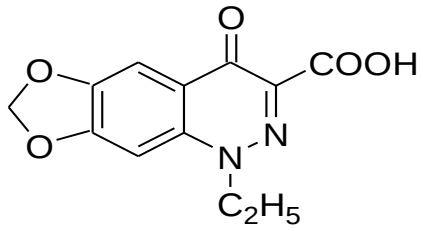


Figure 5: Cinolines e.g Cinoxacin

3. Pyridopyrimidines: e.g piromidic acid and pipemidic acid.

Piromidic acid is the first derivative of this group. It is slightly more active than nalidixic acid but less tolerated in-vivo (18).

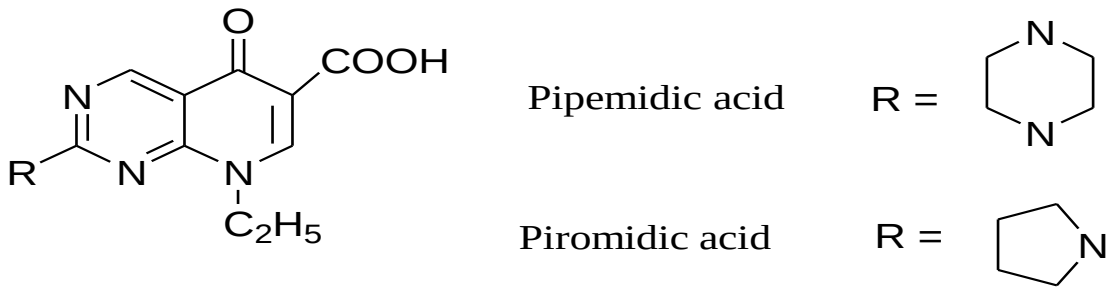


Figure 6: Pyridopyrimidines

4. Quinolines: Examples of earlier quinolones are oxolinic acid and acrosoxacin.

Acrosoxacin is more active in-vitro than Nalidixic acid but it is very rapidly metabolized in-vivo (18).

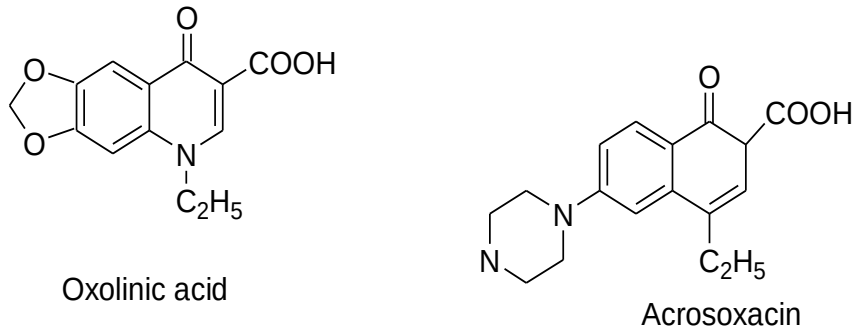
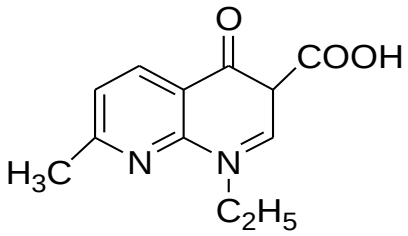


Figure 7: The Quinolones

Chemistry of Fluoroquinolone Antibacterial Agents.

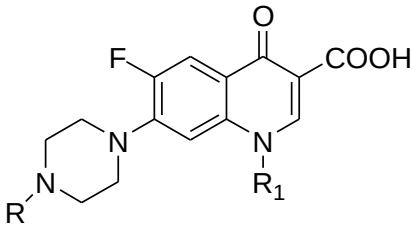
This group of antibacterial agents is developed from nalidixic acid, a 1,8-naphthyridine.



Nalidixic acid

Figure 8: Nalidixic acid

Examples of drugs in this group include:



Norfloxacin, R=H, $R_1 = C_2H_5$
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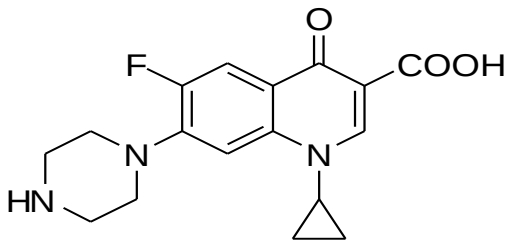
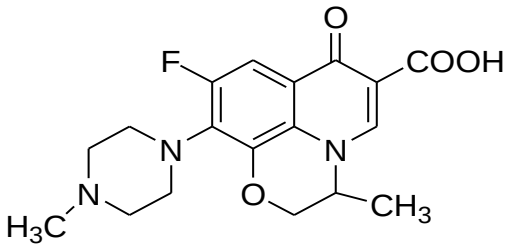


Ciprofloxacin



Ofloxacin

Figure 9: Examples of fluoroquinolones

The introduction of a fluorine atom at position C_6 and piperazine ring at C_7 leads to increased in-vitro antibacterial activity. Their antimicrobial action has been suggested to be due to their ability to bind directly to bacterial DNA (Deoxyribonucleic acid), inhibiting bacterial DNA gyrase, thereby destroying the bacteria at the point of DNA replication and also inhibit RNA (ribonucleic acid) synthesis. (1)

New Fluoroquinolones include the following:

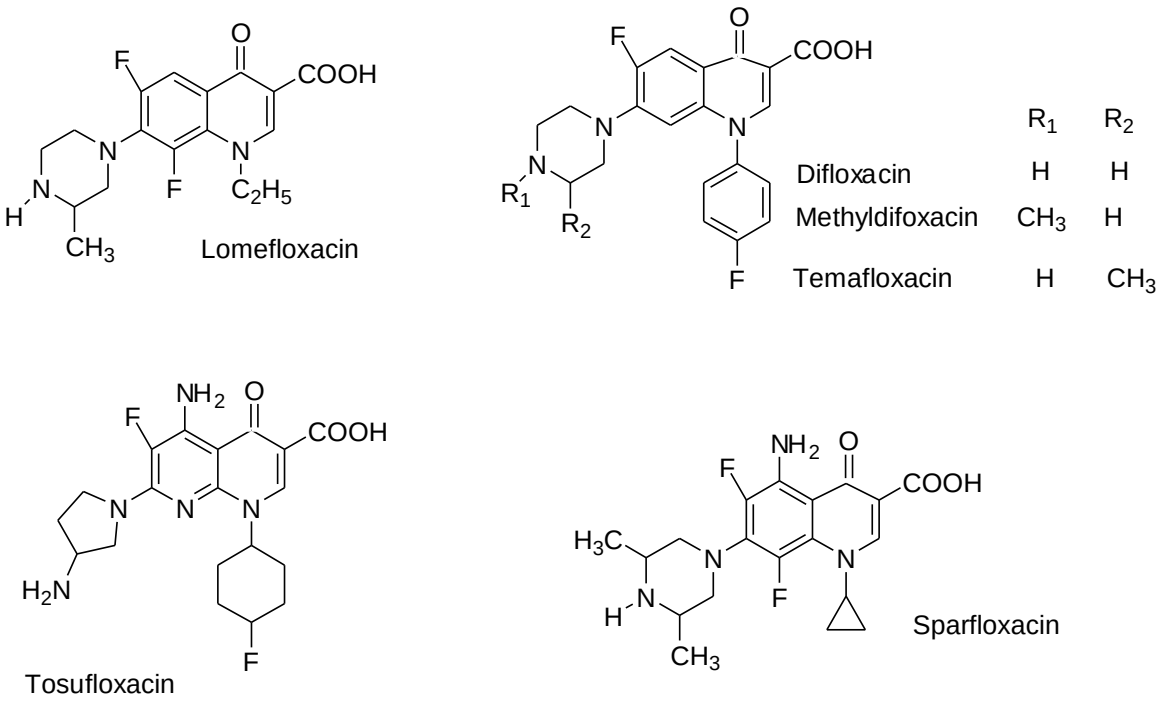


Figure 10: Structural formulae of some newer Fluoroquinolones(19,20,21)

Nomenclature of the Quinolones.

Smith (22) proposed to use the 4-quinolones as generic name for all these compounds so that there is a common term thus facilitating the discussion on these drugs as shown below:

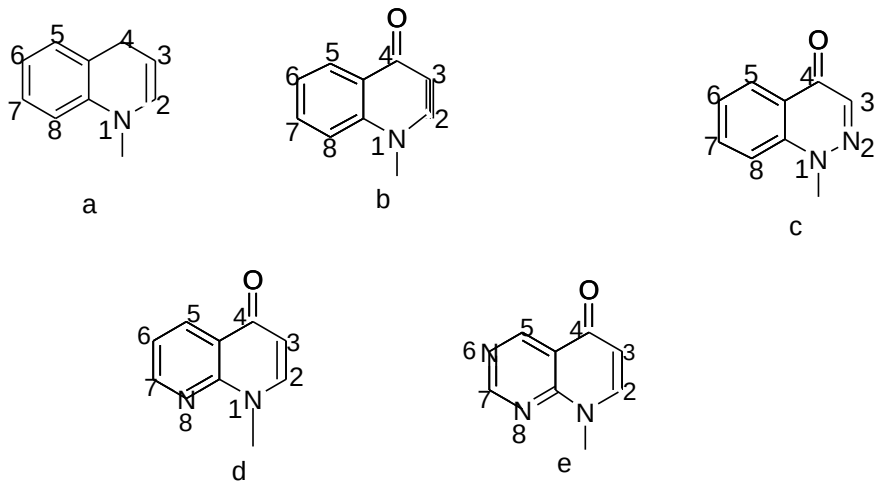


Figure 11: Nomenclature.

11a. The structure of quinoline and its numbering system
11b. 4-oxo-1,4 dihydroquinoline or 4-quinolone.
11c. 2-aza-4-quinolone
11d. 8-aza-4-quinolone
11e. 6,8-diaza-4-quinolone.

1.3 STRUCTURE – ACTIVITY RELATIONSHIP (SAR).

In 1977 R. Albercht (23) published an extensive review of structure activity relationships, antibacterial activity, and synthetic chemistry of nalidixic acid-type antibacterial agents (Quinolone antibacterial agents)

They are structurally characterized by a bicyclic heteroatomic system as shown below:

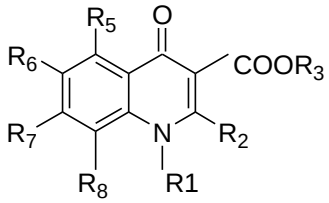


Figure 12: Bicyclic heteroatomic system.

Modifications of the group which occupy the R_1, R_2, R_3, R_4, R_5, R_6, R_7 & R_8 positions have been successful in yielding potent antibacterial agents.

(1) N-1 Position

Presence of nitrogen atom in position 1 is paramount to effective antibacterial activity as substitutions with other elements have not been successful (24,25).

Also substitution on the nitrogen atom in position 1 is important as unsubstituted compounds bring about tautomerism which results in little or no effect (23)

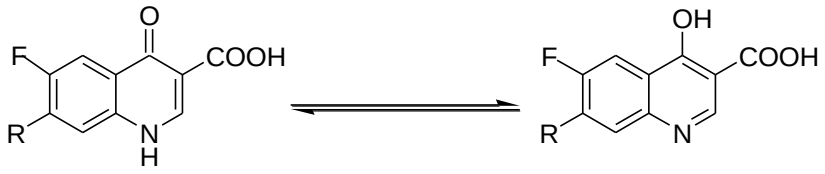


Figure 13: Formation of Tautomers by N-1 unsubstituted compounds.

Wolfson and Hooper (26) reported that an ethyl group substitution on N-1 gives optimal activity. Substitution at position N-1 yielded the following results:

Very active - Cyclopropyl

Active - Ethyl (C_2H_5). Methylamine ($NHCH_3$) , Fluoroethyl (C_2H_4F)

Less active - Methyl (CH_3), and groups larger than propyl group (C_3H_7)

(2) Substitution in the 2-position.

Substitution in this position has been favourable in yielding potent antibacterial agents. However, recently, derivatives in which the C-2 substituents are part of a ring have been reported and found to be very potent broad-spectrum antibacterial agents (23,24). For example, benzothiazol [3,2-a] quinolones where C-2 is linked via sulphur atom to a benzene ring that is in turn affixed to N-1 (Figure14) possess high antibacterial potency (24)

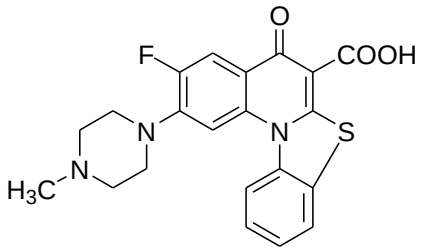


Figure 14: Benzothiazolo [3,2-a] quinolone derivative.

3. **Substitution on the C-3 Position.**

The presence of a carboxylic group in position 3 and a ketone group at position 4 are critical to the maintenance of antibacterial activity in all quinolones as modification leads to loss of activity as they are necessary for the binding of quinolones to the DNA (Deoxynucleic acid) gyrase (27,28).

However, modification of the carboxylic acid when the compound contains a cyclopropyl group at R_1 position and the piperazine ring at R_7 position has led to an outstanding potent series of products. For example, the thiazolidone analogue of ciprofloxacin (scheme 13) is ten times more potent in-vitro than ciprofloxacin (23).

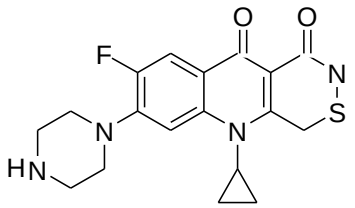


Figure 15: Thiazolidone analogue of Ciplofloxacin.

(4). **Substitution of the 4-oxo group**: This has resulted to loss of antibacterial activity.

(5). **Substituents in C-5 position.**

Until recently, only a few examples of 5-substituted quinolones were reported and no systematic structure activity relationships developed.

A 5-amino group in a 6,8 –difluoroquinolone (Figure 14) confers excellent overall potency with some improvements over the 5-hydrogen substituents, but these results cannot be generalized to other quinolone nuclei (29,30).

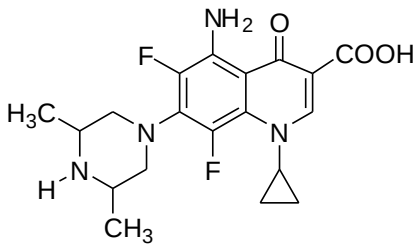


Figure 16: 6,8-difluoroquinolone derivative (Sparfloxacin)

6. **Substituents at position C-6.**

Substitution at this position is very important and crucial for antibacterial activity of the quinolones. The activity improves when a nitro (NO_2) group is introduced, and increases further with a chlorine atom but the highest activity is achieved with a fluorine atom.

7 **Substitution at the C-7 position**.

Substitution at the C-7 position yields compounds which are highly active and this position has undergone the greatest modification on the bicyclic ring structure. Poor antibacterial activity was observed when a hydrogen, chlorine, methyl, methylamino or hydrazine group was the substitute. However, there has been excellent in-vitro activity with a piperazinyl, pyrolyl, thiazolidinyl or thiamorpholinyl group at this position.

8. Substitution in the C-8 position

In most of the currently available compounds, there is only hydrogen present in the C-8 position. Fluorine derivatives have slightly decreased in-vitro activity, but they have increased in vivo absorption and longer half-lives (31,32). In the N-cyclopropyl series, C- 8 fluorine derivatives have greater in-vitro antibacterial activity on gram-positive bacteria and better in-vivo efficacy. (33,34). Substitution of a 3-amino pyrolidin-1-nyl group at position 7 with a chlorine group at position 8 yields a compound AM1091 or clinafloxacin (scheme 17) which has increased activity against *Enterobacteriaceae* species, *Staphylococcus aureus*, *Streptococcus pneumonia* and *Bacteroideae* species with only a modest decrease in activity against *Pseudomonas aeruginosa* compared to ciprofloxacin.

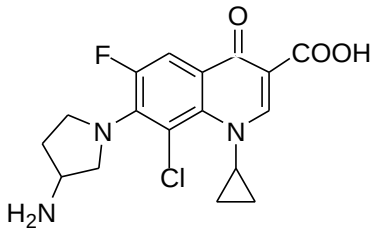


Figure17: Structure of AM1091 (Clinafloxacin)

When substitution at the C-8 position is combined with R1 position to form a heterocyclic ring, there is good activity as in ofloxacin which is a furo-[2,3,9] quinoline derivative fused with 1,4-oxazine rings (23).

1.4 PHARMACOKINETICS OF FLUOROQUINOLONES.

By definition, pharmacokinetics is the branch of pharmaceutical sciences concerned with the mathematical characterization of the time course of drug absorption, distribution, metabolism and excretion as well as the relationship of these processes to the intensity and time course of therapeutic or toxic response in animals and man. The World Health Organization (WHO) study group defines pharmacokinetics as the study of absorption, distribution, metabolism and excretion of drug (35). Knowledge in this branch of pharmaceutical science like others has grown rapidly over the past decades with the acceptance by the clinicians such as clinical pharmacists, physicians, clinical pharmacologists and other health science specialists who utilize drugs in their practices of pharmacotherapy and its applications in pharmacotherapeutic management of patient in a clinical setting. This growth has been phenomenal such that it has now been accepted that pharmacokinetic is a very important and compulsory part of information about any drug product.

Fluoroquinolone antibacterial agents have improved pharmacokinetic parameters when compared with the original quinolones. They are rapidly and almost completely absorbed from the gastro-intestinal tract. As a result of this, peak serum concentrations obtained after oral administration are very close to those achieved with intravenous administration (3). Consequently, the oral route is generally preferred in most cases, hospitalized patients should be switched from intravenous to oral formulation as soon as they can tolerate oral medications.

Absorption of orally administered fluoroquinolones is decreased significantly from the gastrointestinal tract when these agents are concurrently administered with aluminium, magnesium, calcium, iron or zinc, because of the formation of drug-cationic chelate complexes. (3,9). The problem can be overcome largely by ensuring that the products containing these metal ions are administered at least four hours before or two hours after oral administration of fluoroquinolones.

Fluoroquinolones have a large volume of distribution and thus concentrate in tissues at levels that often exceed serum drug concentrations. Penetration is particularly high in renal, lung, prostrate, bronchial, nasal, gall bladder, bile and genital tract tissues. (5,6,7) Urine drug concentrations of some fluoroquinolones, such as ciprofloxacin and ofloxacin may be as much as 25 times higher than serum drug concentrations. Consequently, these agents are especially useful in treating urinary tract infections (6)

Distribution of the fluoroquinolones into respiratory tract tissues and fluids is of particular interest because of the activity of these agents against common respiratory tract pathogens. Trovafloxacin penetrates non-inflamed meninges and may therefore have a future role in the treatment of bacterial meningitis (5,15).

The half-lives and routes of administration of some quinolone antibiotics are shown in the Table below:

		Half-life	Route of Administration
1	Nalidixic acid	60-90 minutes	Oral
2	Cinoxacin	1.1-2.7 hours	Oral
3	Norfloxacin	2.3 - 5.5 hours	Oral
4	Lomefloxacin	7 - 8.5 hours	Oral
5	Enoxacin	3.3 - 7 hours	Oral
6	Ofloxacin	5 – 8 hours	Oral and Intravenous
7	Ciprofloxacin	3- 5.1 hours	Oral and Intravenous
8	Levofloxacin	6 hours	Oral and Intravenous
9	Sparfloxacin	21 hours	Oral and Intravenous
10	Gatifloxacin	7 hours	Oral and Intravenous
11	Moxifloxacin	12 hours	Oral and Intravenous
12	Trovafloxacin	7.8 hours	Oral and Intravenous

Table 1: Half-lives and routes of administration of some quinolone antibacterial agents (4)

The long half-lives of the newer fluoroquinolones allow once or twice daily dosing. The quinolones vary with respect to the relative contribution of renal and non-renal pathways for their elimination. Only ofloxacin and levofloxacin are exclusively eliminated by the kidney. (2,6,7). Renal and non-renal (gastro-intestinal or hepatic) mechanisms are responsible for the elimination of nalidixic acid, cinoxacin, norflaxacin, ciprofloxacoin, enoxacin, lomefloxacin, gatifloxacin, moxifloxacin and sparfloxacin.

Dosage adjustments based on estimated creatinine clearance values must be made for the agents with significant renal elimination. In such cases, administrating the usual dose at an extended time interval is recommended. (4)

Trovafloxacin is eliminated primarily by hepatic mechanism (16). Approximately 50 percent of a Trovafloxacin dose is conjugated in the liver, 43% is excreted unchanged in the faeces (15). Significant hepatic disease may increase the elimination half-life of trovafloxacin. Dosage adjustments are required in patients with mild to moderate cirrhosis. No data are available on patients with severe liver disease (16).

Increased serum concentrations of fluoroquinolones have been noted in the elderly. The usual cause is the somewhat decreased volume of distribution and decreased renal function in older persons. However, dosage adjustments based on age alone is not recommended (4).

ADVERSE/SIDE EFFECTS.

The most common adverse effects of the fluoroquinolones are nausea, vomiting and diarrhoea, which occur in 3 to 6 percent of recipients. (6). Other more serious but less common side effects are central nervous system effects (headache, confusion and dizziness), cardiotoxicity (sparfloxacin) and hepatotoxicity (trovafloxacin) (4).

Concern about the adverse effects of quinolones on the joints is based primarily on experimental evidence in young animals. These drugs are therefore not recommended for use in patients younger than 18 years or in pregnant or lactating women. However, no arthropathies were observed in a study in which more than 1000 children received ciprofloxacin (12).

MODE OF ANTIBACTERIAL ACTIVITY.

The fluoroquinolones are bacterial antibiotics that act by specifically targeting DNA gyrase (9). The mechanism of action by which fluoroquinolones bring about their bactericidal action is by inhibiting the bacterial topoisomerase II (DNA gyrase) enzyme.

Topoisomerases are responsible for continuous introduction of negative super coils into DNA. This is an ATP dependent reaction that requires both strands of the DNA to be cut to permit passage of a segment of DNA through the break; the break is then reset. Fluoroquinolones decrease the introduction of negative super coils into DNA and cause rapid cessation of DNA

synthesis by interfering with the propagation of DNA replication (12). In contrast to amino glycosides and beta-lactams, some fluoroquinolones are active against dormant and replicating bacteria (6).

Fluoroquinolones exhibit a post-antibiotic effect following bacterial exposure to inhibitory concentrations. The anti-bacterial effect continues for approximately two to three hours after bacteria are exposed to these drugs, despite sub-inhibitory concentrations. The duration of the post-antibiotic effect may be increased with longer bacteria-drug exposure and higher drug concentrations (4).

BACTERIAL RESISTANCE

Both Gram-positive and Gram-negative bacteria have been reported to be resistant to quinolones. This resistance appears to be the result of one of these three mechanisms.

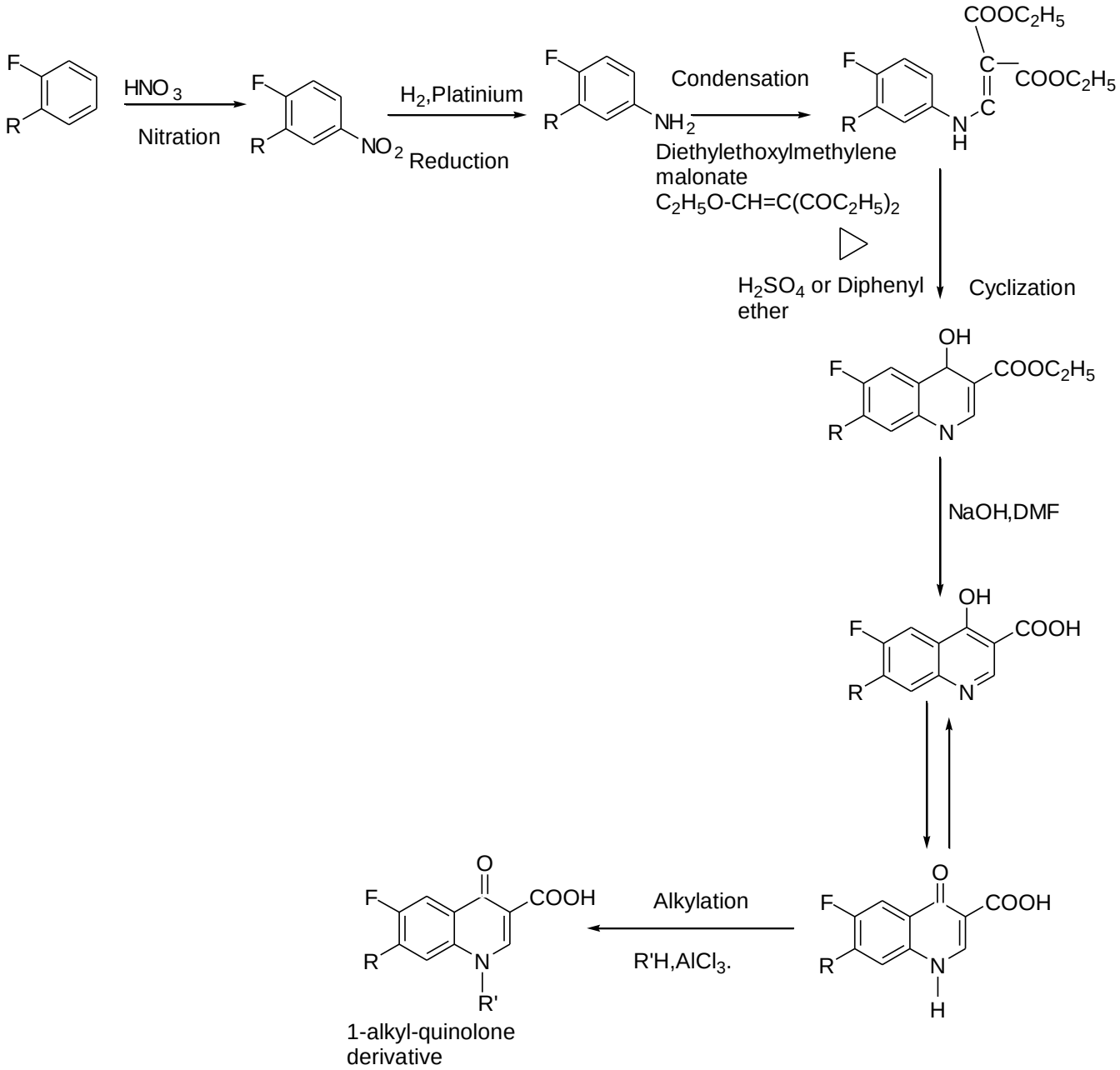
1. Alternatives in the quinolone enzymatic target (DNA gyrase)
2. Decreased outer membrane permeability.
3. Or the development of efflux mechanisms (13,36)

The accumulation of several bacterial mutations (DNA gyrase and bacterial permeability) has been associated with the development of very high minimum inhibitory concentrations to ciprofloxacin in isolates of *Staphylococcus aureus*, *Enterobacteriaceae* species and *Pseudomonas aeruginosa* (37).

Resistance to quinolones can also develop because of alterations in bacterial permeability and the development of efflux pumps. This resistance mechanism is shared with antimicrobial agents structurally unrelated to the quinolones, such as the beta-lactams, tetracyclines and chloramphenicol. Cross-resistance among the quinolones is expected, but the extent to which the minimum inhibitory concentration is affected varies from one agent to another. Therefore, the bacterial susceptibility and pharmacokinetic profiles of each quinolone should be considered in determining the effectiveness of specific agents. (2)

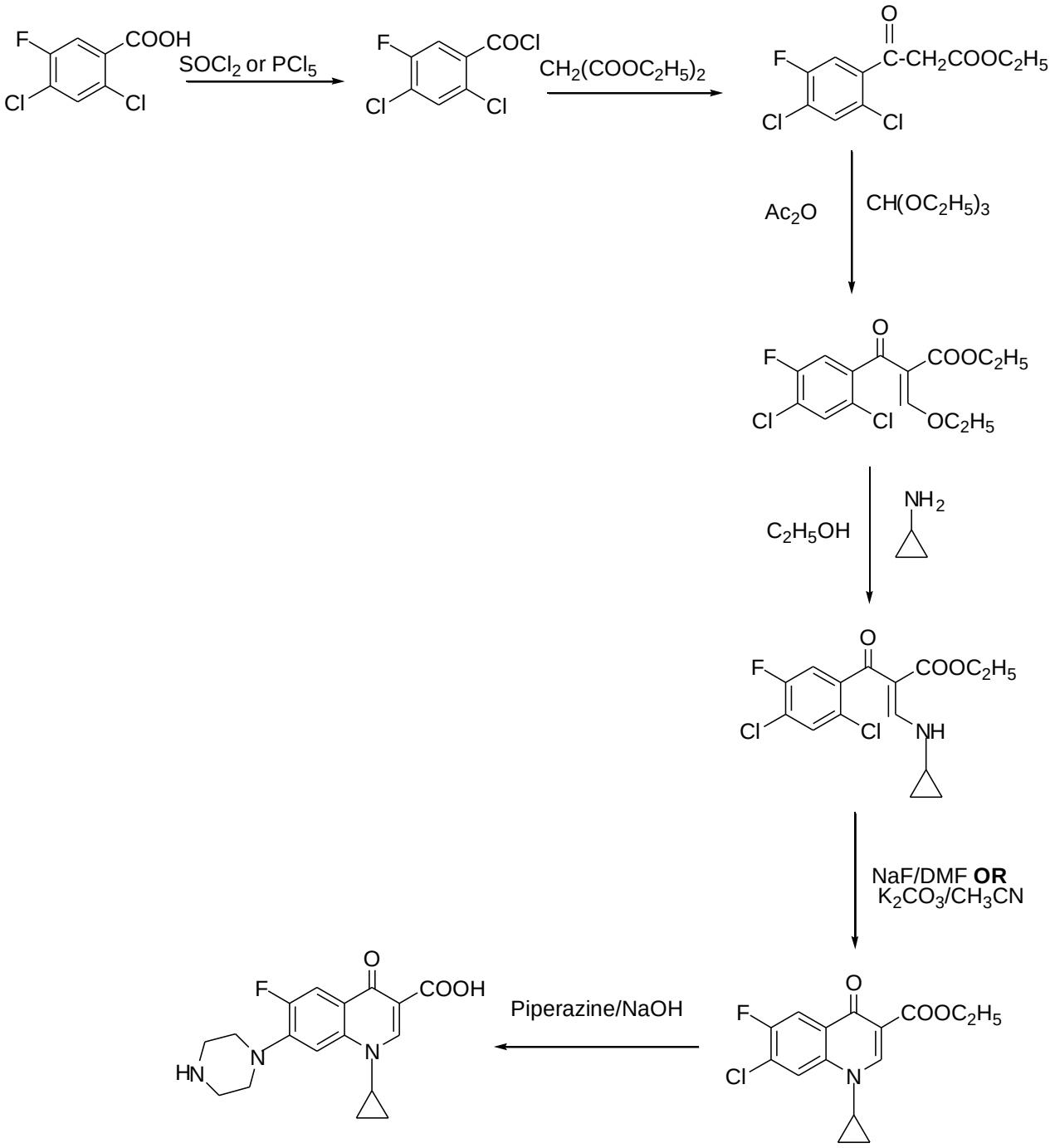
1.5 **SYNTHESIS OF QUINOLONES.**

The general method of synthesis of quinolones is as shown below (22).



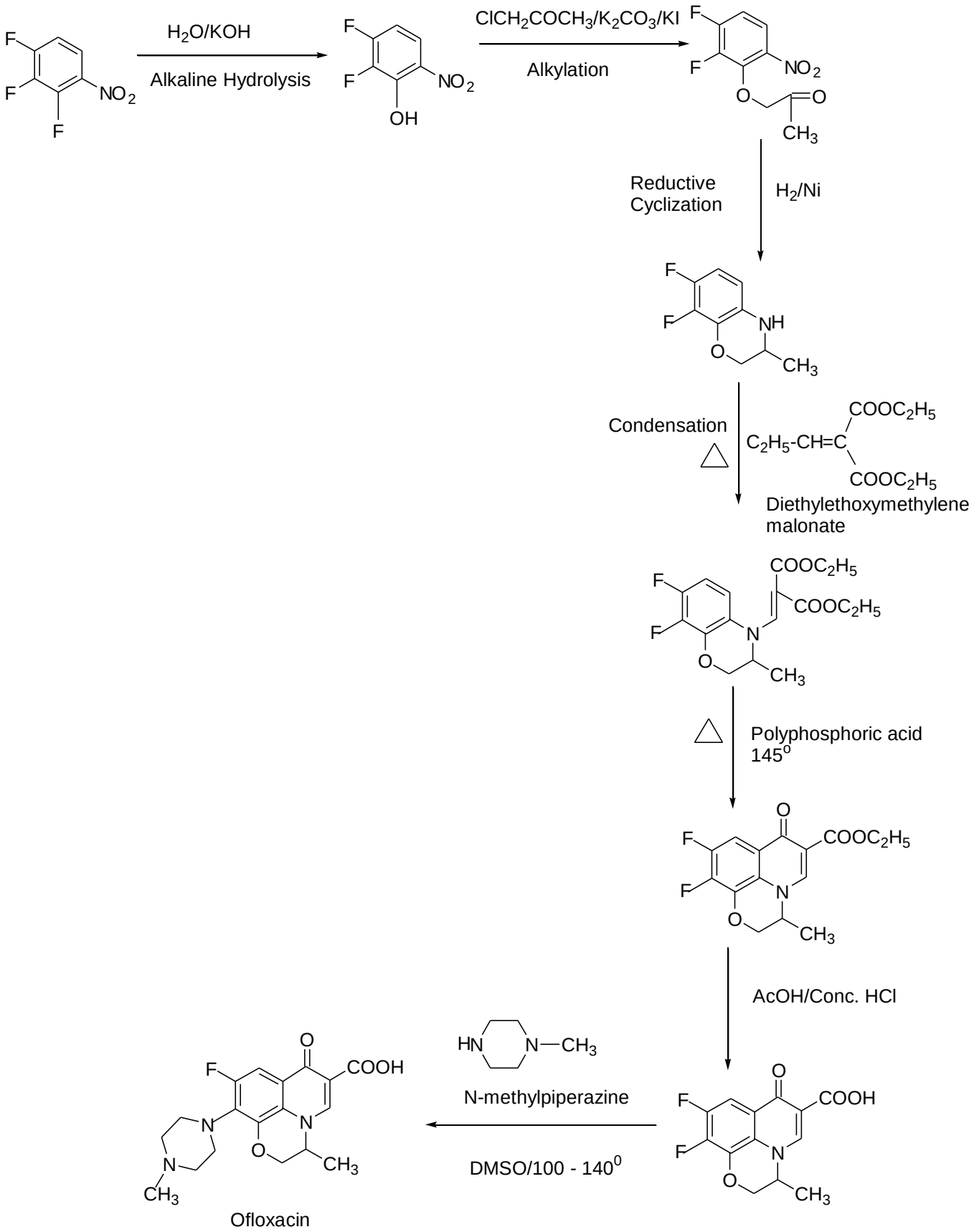
Scheme 1: General Method of Synthesis of the Quinolones.

A new synthetic method has been reported for the preparation of ciprofloxacin which solved some of the difficulties in the method reviewed above. The starting compound is 2,4-dichloro-5-fluorobenzoic acid (23) as shown below:



Scheme 2: Synthesis of Ciprofloxacin

In the case of ofloxacin synthesis, the starting compound is 2,3,4-trifluoronitrobenzene (23) as shown below:



Scheme 3: Synthesis of Ofloxacin

1.7 METHODS OF ANALYSIS OF THE FLUOROQUINOLONES.

Many methods have been employed for the analysis of the fluoroquinolones in biological fluids such as plasma, saliva, urine and semen. These methods include microbiological, chemical and instrumental among others.

The microbiological assay employs agar diffusion methods in which the minimum inhibitory concentration is determined by measuring the zone of inhibition on the agar plate. The British Pharmacopoeia 1988 (38) recommends a procedure for the microbiological assay of fluoroquinolones which was suitably modified in 1991 by Okhamafe et al (39).

The chemical and instrumental methods include colorimetry (40, 41), fluorimetry (42) spectrophotometry (43, 44), and high performance liquid chromatography (HPLC) (45, 46).

Chromatography is a procedure that permits the resolution of solute mixtures depending on the degree to which the various solutes are adsorbed, partitioned or exchanged between the original solution otherwise called the “moving phase” and a second solid or liquid phase called the “stationary phase”. In adsorption chromatography, the solute mixture is allowed to pass through a column of the adsorbent (e.g. alumina, magnesium oxide, charcoal), which acts as the stationary phase. The various solute species present in the solution will come off at the bottom of the column in the reverse order of their adsorptive affinity for the particular adsorbent used. In the light of this, those solutes with little or no affinity for the solid phase will pass through the column and will be present in the initial effluents while the strongly adsorbed solutes will be retained by the column and pass out in the final effluent. Separation of components of original solution is thus effected by collecting fractions of the solution exiting from the bottom of the column. This is most efficiently carried out with the aid of technological advancement in High Performance Liquid Chromatography (HPLC).

Spectrophotometric method of evaluation is based on the fact that when organic molecules in solution or as a liquid are exposed to light in the visible and ultraviolet regions of the electromagnetic spectrum, they absorb light of particular wavelength, depending on the type of electronic transition that is associated with the absorption. The wavelength of absorption is dependent on the chemical structure, type of bond and availability of electrons which are characteristic of the molecule. The intensity of absorption represents the concentration of such a molecule in the test medium.

Exploiting the chromophoric centers in fluoroquinolones which are centres of light absorption, Eboka (43) developed a spectrophotometric method for the assay of ciprofloxacin. This method has been found to be quick, accurate and precise. Spectrophotometric method was therefore, used in this study as HPLC, though fast, accurate and precise is not readily available in most local laboratories.

1.5 ADSORPTION/LANGMUIR ISOTHERMS.

Interface is a terminology that comes into play whenever phases exist together and it is used to describe the boundary between them. In most cases the properties of the molecules forming the interface often vary from those in the bulk of each phase. Several types of interface can exist, depending on the forms of the two adjacent phases which could either be solid, liquid or gas. E.g.

S/N	PHASES	TYPES AND EXAMPLES
1.	GAS/GAS	No interface possible
2.	Gas/Liquid	Liquid surface, body of water exposed to atmosphere
3.	Gas/Solid	Solid surface, table top exposed to the atmosphere
4.	Liquid/Liquid	Liquid-Liquid interface, emulsion
5.	Liquid/Solid	Liquid-Solid interface, suspension
6.	Solid/Solid	Solid-Solid interface, Powder particles in contact

Table : Classification of Interfaces

Although solid/solid interfaces have practical significance in pharmacy, (e.g. the adhesion between granules, the preparation of layered tablets and the flow of particles), little information is available to quantify these interactions. This is partly due to the fact that the surface region of materials in the solid state is quiescent as against the turbulence that exists at the surfaces of liquids and gases. (47)

Interfacial phenomena in pharmacy and medicine are significant factors that affect adsorption of drugs onto solid adjuncts in dosage forms, penetration of molecules through biologic membranes, emulsion formation and stability, and dispersion of insoluble particles in liquid media to form suspensions.

Adsorption in Liquid Interfaces

In the liquid state the cohesive forces between adjacent molecules tend to pool them together while the adhesive forces between the molecules at the surface or interface with molecules of the matter constituting the other phase tend to pull them apart. The overall effect therefore depends on which of the forces prevail.

Certain molecules and ions, when dispersed in the liquid, move on their own accord to the interface. Their concentration at the interface then exceeds their concentration in the bulk of the liquid. Such a phenomenon where the added molecules are partitioned in favour of the interface is termed adsorption while such molecules or ions are termed surface-active-agents, surfactants or amphiphiles.

Adsorption at Solid Interfaces

Adsorption of material as solid interfaces may take place from either an adjacent liquid or gas phase. The study of adsorption of gases is concerned in such diverse applications as

- the removal of objectionable odours from rooms and foods
- operation of gas masks and
- measurement of the dimensions of particles in a powder.

In the same manner, the principles of solid/liquid adsorption are utilized in

- decolourizing solutions,
- adsorption chromatography.
- detergency and wetting.

In many ways, adsorption of materials from a gas or liquid onto a solid surface is similar to that discussed under liquid surfaces.

The degree of adsorption of a gas by a solid depends on the chemical nature of the adsorbent (the material used to adsorb the gas), the surface area of adsorbent, the temperature and partial pressure of the adsorbed gas.

The types of adsorption are generally recognized as physical (van der Waals) adsorption and chemical adsorption or chemisorption.

Physical adsorption is usually reversible leading to a process of desorption which is the removal of adsorbate from the adsorbent by increasing the temperature and reducing pressure.

Chemisorption, on the contrary, is irreversible as the adsorbate is attached to the adsorbent by primary chemical bonds.

Adsorption of solute molecules from solution by solid substrates as demonstrated by drugs such as dyes, alkaloids, fatty acids and even inorganic acids and bases which are adsorbed from solution onto solids such as charcoal and alumina may be treated in the same manner as solid/gas interface. The relationship between the amount of molecules physically adsorbed on a solid and the equilibrium pressure or concentration at constant temperature yields an adsorption isotherm when plotted.

One of the major draw backs of oral administration of fluoroquinolone is the impairment of gastro intestinal absorption due to concurrent administration of the drugs with cation containing formulations which normally results in the formation of drug-cation complex (chelate). Adsorption is another phenomenon with likelihood of similar implication for administration of fluoroquinolones through the oral route.

The use of solids for removing substances from either gaseous or liquid solutions has been widely employed in different facets of human endeavours from time immemorial. This process is known as adsorption and it involves essentially “preferential partitioning of substances from the gaseous or liquid phase onto the surface of a solid substrate”. From the early days of using bone char for decolorization of sugar solutions and other foods, to the later implementation of activated carbon for removing nerve gases from the battle-field, and to many other applications today, adsorption phenomenon has become a useful tool for purification and separation. (48,49).

The process of adsorption involves separation of a substance from one phase accompanied by its accumulation or concentration at the surface of another. The adsorbing phase is the adsorbent and the material concentrated or absorbed at the surface of that phase is the adsorbate. There is a need to appreciate the difference between adsorption and absorption. While the former is the preferential partitioning of substances from the gaseous or liquid phase onto the surface of a solid substitute, the latter is a process in which material that is transferred from one medium to another (e.g. liquid) , interpenetrates the second phase to form a “solution”. Adsorption thus refers to the binding of molecules or particles to a surface while absorption on the other hand is a process of filling of pores in a solid (48,49). The term sorption is therefore a general expression encompassing both processes.

Adsorption phenomena are operative in most natural, physical, biological and chemical systems and adsorption operations employing solids such as activated carbon and synthetic resins are widely used in industrial applications and for purification of water and waste-water. Physical adsorption is caused mainly by van der Waals forces and electrostatic forces between adsorbate molecules and the atoms or molecules which compose the adsorbent surface. Thus adsorbents are characterized first by surface properties such as surface area and polarity (50). Since surface area is proportional to the particle size, the smaller the particle size the greater will be the surface area that is made available for the adsorption process.

A large specific surface area is preferable for providing large adsorption capacity, but the creation of a large internal surface area in a limited volume inevitably gives rise to a large number of small sized pores between adsorption surfaces (48, 49). The size of the micro pores determines the accessibility of adsorbate molecules to the internal adsorption surface; therefore the pore size distribution of micropores is another property for characterizing adsorptivity of adsorbents.

Surface polarity corresponds to affinity with polar substances such as water or alcohols. Polar adsorbents are thus called hydrophilic and alumino-silicates such as zeolites, porous aluminia-silica gel or silica-alumina are examples of adsorbents of this type. Conversely non-polar adsorbents are generally “hydrophobic” which connotes that they have more affinity with oil or hydrocarbons than water. Example of adsorbents of this type includes carbonaceous adsorbents, polymer adsorbents and silicalite.

Other adsorbents commonly found in pharmaceutical and industrial usage include activated carbon (charcoal) bentonite and kaolin.

In adsorption, the binding to the surface is usually weak and reversible due to the operation of van der Waals and electrostatic forces. Just about anything including the fluid that dissolves or suspends the material of interest is bound, but compounds with colour, those that have taste or odour tend to bind strongly. Compounds that contain chromogenic groups (atomic arrangement that vibrates at frequencies in the visible spectrum) very often are adsorbed on activated carbon. (51). Decolorization can be wonderfully efficient by adsorption and with negligible loss of other materials.

A surface that is already heavily contaminated by adsorbates is not likely to have much capacity for additional binding (52). Thus, freshly prepared adsorbents are mostly preferred to achieve utmost adsorptivity. Charcoal made from roasting wood differs from activated carbon in that its surface is contaminated by other products but further heating will drive off these compounds to produce a surface with high adsorptive capacity. Spent activated carbon is thus regenerated by roasting, but the thermal expansion and contraction disintegrate the structure, so some carbon is either lost or oxidized. Temperature effects on adsorption are thus profound and measurements are usually at a constant temperature.

LANGMUIR EQUATION

In the analysis of data obtained in various processes of adsorption, a number of relationships have been established between the amount of adsorbents required to produce a level of adsorption and concentration of the substance of interest in the chosen medium. These relationships are referred to as isotherms due to the fact that they were obtained at a constant temperature. Among these isotherms are Langmuir and Frenndlich equations.

Langmuir derived a relationship between the rate of adsorption, amount of material adsorbed, or amount of adsorbent used to achieve a particular level of adsorption and concentration of the material of interest in the fluid. All these were based on some quite reasonable assumptions, which are: a uniform surface, a single layer of adsorbed material and constant temperature.

The rate of attachment to the surface should be proportional to driving force times an area. The driving force is the concentration in the fluid, and the area is the amount of bare surface. If the fraction of covered surface is θ, the rate per unit of surface is:

Rate of adsorption = $K_aC (1 - \theta)$---------- (1)

The loss from the surface is proportional to the amount of surface covered.

Rate of desorption = $K_d \theta$ ---------- (2)

Where K_a and K_d are rate constants for adsorption and desorption, respectively.

C =concentration in the fluid

θ = fraction of the surface covered.

Derivation of the Langmuir Equation..

At equilibrium, the rate of adsorption equals the rate of desorption,therefore,

$K_d\theta = K_aCeq\ (1 - \theta)$ ---------- (3)

Solving for θ, we obtain

$$\theta = \frac{K_a\ Ceq}{K_d + K_a\ Ceq}$$ ---------- (4)

By dividing the numerator and denominator by K_d

$$\theta = \frac{K_a/K_d\ Ceq}{K_d/K_d + K_a/K_dCeq}$$ ---------- (5)

$$\theta = \frac{K_a/K_d\ Ceq}{1 + K_a/K_dCeq}$$ ---------- (6)

K_a/K_d is the ratio of rate of adsorption and desorption which is K_1.

Then, $$\theta = \frac{K_1\ Ceq}{1 + K_1\ Ceq}$$ ---------- (7)

Since it is difficult to measure θ experimentally, we can make use of the fact that X/m is proportional to θ at equilibrium i.e. ($\theta \propto X/m$).

Therefore, the useful form of the equation is:

$$X/K_2m = \frac{K_1Ceq}{1 + K_1Ceq}$$ ---------- (8)

where K_2 is the binding affinity factor.

So, $$X/m = \frac{(K_1K_2).Ceq}{1 + K_1Ceq}$$ ---------- (9)

Where Ceq is the equilibrium concentration of the free drug, X/m is the amount of drug adsorbed by the quantity of the adsorbent used while K_2 and K_1K_2 are constants.

By finding the reciprocals,

$$\frac{1}{(X/m)} = \frac{1 + K_1Ceq}{K_1\ K_2Ceq}$$ ---------- (10)

Rearranging, we have,

$$\frac{Ceq}{(X/m)} = \frac{1 + K_1Ceq}{K_1\ K_2}$$ ---------- (11)

$$\frac{Ceq}{(X/m)} = \frac{1}{K_1 K_2} + \frac{K_1 Ceq}{K_1 K_2} \quad \text{---------- (12)}$$

Therefore the linear form of the Langmuir equation is:

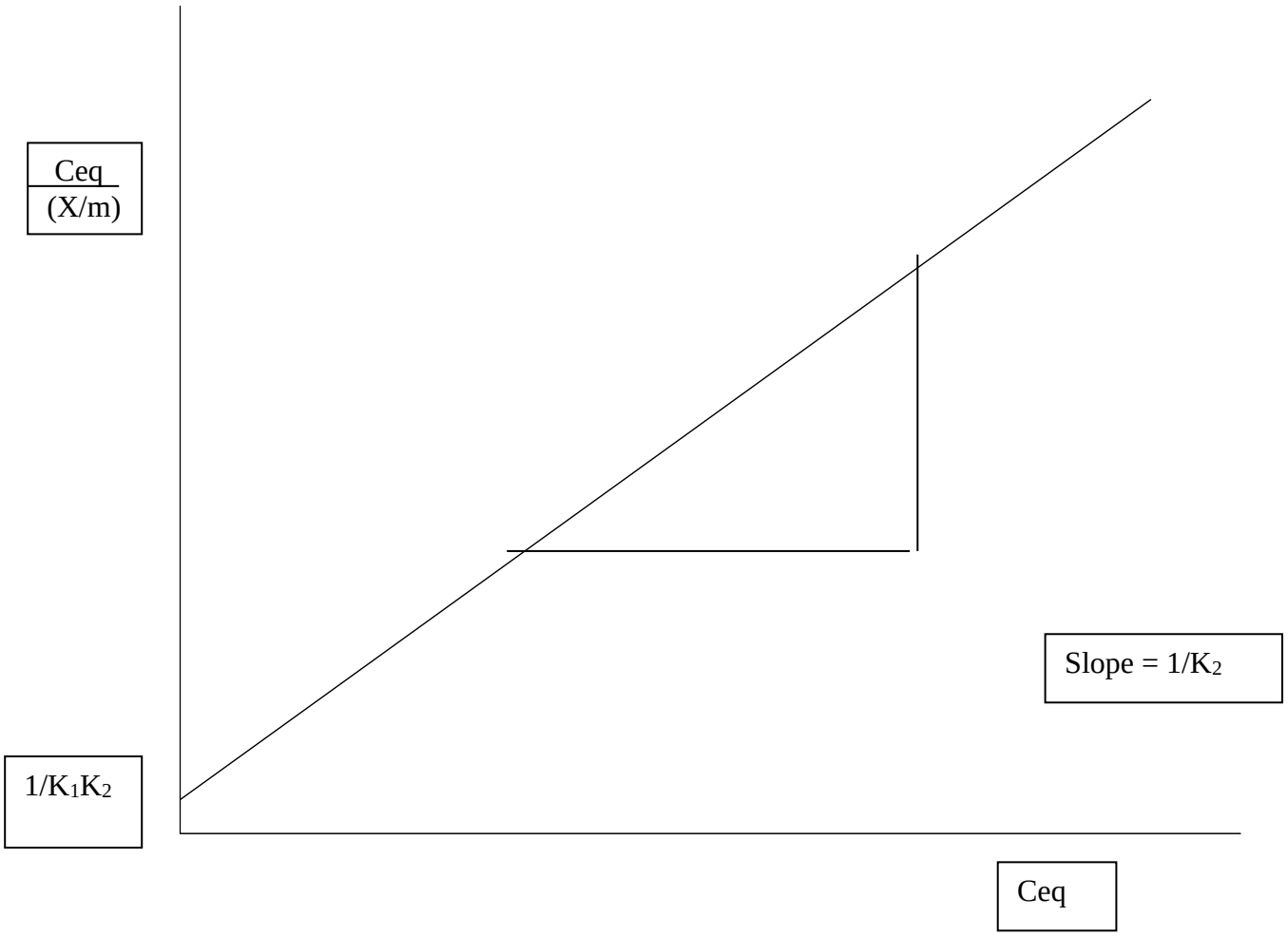
$$\frac{Ceq}{(X/m)} = \frac{1}{K_1 K_2} + \frac{Ceq}{K_2} \quad \text{---------- (13)}$$

Where Ceq = free drug concentration in solution at equilibrium.

X/m = amount of drug adsorbed (X) by quantity of adsorbent used (M).

K_2 and K_1K_2 are constants evaluated from reciprocals of the respective isotherm slope and intercept values of the regression equation.

A plot of Ceq/(X/m) versus Ceq should indicate a straight line of slope $1/ K_2$ and an intercept of $1/ K_1K_2$. The graph shows data points and lines fitted to both Freundlich and Langmuir equations.



OBJECTIVES OF THE STUDY

The important roles by fluoroquinolone antibiotics in the treatment of bacterial infections especially those caused by *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Chlamydia* species which hitherto have been described as obstinate cannot be over-emphasized. The need to therefore ascertain the interaction of adsorbents commonly employed in pharmaceuticals with these fluoroquinolones formed the basis of this study. The use to which the outcome could be put can be viewed from several perspectives. One is to prevent concomitant administration of these antimicrobial agents with any adsorbent which adversely affects their pharmacokinetic profiles as a result of strong binding of the fluoroquinolones to the adsorbents. This will reduce the amount of free drug available to the patient and thus reduce the optimal therapeutic benefit for the patient. Also, these adsorbents could be of valuable assistance in cases of over dosage or accidental ingestion of any of these antimicrobial agents.

Thus this work was designed to generate basic data that could be used for such cases. On the other hand, the results could be used in the development of sustained release dosage form of the fluoroquinolones.

General Objectives:

The general objectives of this study are to cast an overview of the likelihood of therapeutic failure in the administration of fluoroquinolone antibacterial agents in the management of infections caused by susceptible bacteria, due to sub clinical level of bio-availability of the drug. The aim is to proffer solutions to such identified loopholes with a view to enhancing ultimate benefit to the patient. Furthermore, fluoroquinolones play more prominent role in the management of a number of medical conditions that are amenable to the use of antibacterial agents. This is largely due to their considerable patient tolerability, safety and excellent pharmacokinetic profile. However, the need to curtail accidental ingestion and overdosage of this group of antibacterial agents or to nib it in bud whenever it arises, can not be over emphasized.

Specific Objectives

The specific objectives of this study are as follows:

1. To prevent concomitant administration of these anti bacterial agents with any adsorbent which could adversely affect their pharmacokinetic profiles as a result of strong binding affinity between the two entities. This is because the ensuing binding between the fluoroquinolone drug molecule and the adsorbent in the patient GIT could reduce the amount of free fluoroquinolone molecule that is available for absorption into the blood stream.
2. To establish the level of adsorption affinities between fluoroquinolone antibacterial agents used in this study (ciprofloxacin, ofloxacin and norfloxacin) and adsorbents used (activated charcoal, bentonite and kaolin) in order to make a pronouncement on the desirability or otherwise of any of the adsorbents in cases of accidental ingestion or overdosage involving any of the fluoroquinolones.
3. To use the data generated to explore the probability of development of sustained release dosage forms of the fluoroquinolones by employing desorption mechanism as a follow up to the initial adsorption of the drug molecules on appropriately suitable adsorbent.

CHAPTER II

EXPERIMENTAL

2.1 EQUIPMENT\MATERIALS

Equipment:

Equipments used in carrying out this study include:

B & T Hot Air Oven (England), Metler Toledo Weighing Balance (England), Gallenkamp Thermostated Shaker Bath (England) and Spectronic 21D Milton Roy UV/visible Spectrophotometer.

Materials:

The materials used include:

Samples of industrial grades of adsorbents such as activated carbon (charcoal) powder (BDH, England), bentonite powder(Merck, Germany) and heavy kaolin powder (Merck, Germany).

Pharmaceutical grades of the fluoroquinolones antibiotic powders used were obtained. Ciprofloxacin and norfloxacin (from Sam pharmaceuticals Ilorin, Nigeria) and ofloxacin (from Hoeschst Germany, through Nigeria-German Chemicals, Ota, Nigeria).

Hydrochloric acid (May & Baker, England).

2.2 METHODOLOGY:

SAMPLE PREPARATION

Samples of adsorbents were subjected to thorough drying by placing them in the hot air oven at 100^0C for 3hours and allowed to cool overnight in a dessicator prior to usage.

The thermostated shaker was thoroughly cleaned and water level in the water bath appropriately adjusted. The thermostat was then set at 37^{o}C and switched on for at least an hour before the commencement of the experiment.

a. Determination of the analytical wavelengths of the fluoroquinolones by obtaining wavelengths of maximum absorption in an automated manner.

b. Beer's Calibration plot.

50mg of the fluoroquinolone powder was weighed into a 100ml volumetric flask and made up to volume with 0.1M HCl to form the stock solution. A set of six 25ml volumetric flasks containing 0.0, 0.5, 1.0, 1.5, 2.0 and 2.5ml respectively of the stock solution were made up to volume with 0.1M HCl. A further 1 in 10 dilution of the resulting solutions were made and UV absorbance measured at predetermined wavelength of maximum absorption for the compound in question.

The result thus obtained for each compound is plotted in graph of absorbance versus concentration (Beer's plot) which served as calibration plot for the experiment.

c. ADSORPTION STUDIES:

100mg of the fluoroquinolone powder is weighed into a 100ml volumetric flask and made up to volume with 0.1 M HCl. 15ml of the resulting solution was pipetted into each of the four 25ml volumetric flasks to which graded amounts of the adsorbent have been placed. To each of another set of four 25ml volumetric flasks in which the same graded amounts of the adsorbent had been placed was added 15ml of 0.1M HCl to serve as blank.

The two sets of the volumetric flasks were thoroughly mixed and immediately transferred into a thermo-stated water bath with shaker set at 37^0C $\pm$ 0.2 and 80 oscillations per minute. Samples (0.5ml) of the supernatant solution were thereafter taken at regular time intervals of 0,15minutes, 30minutes, 60minutes and 120minutes for activated charcoal and then intervals of 0, 2hours, 24hours, 48hours and 72hours for bentonite and kaolin, after allowing the flasks to stand for 2minutes so as to obtain a clear supernatant solution.

Appropriate dilutions of the withdrawn supernatant solutions were made for UV spectrophotometric absorbance measurement at wavelength of maximum absorption (norfloxacin = 274nm, ciprofloxacin = 277nm and ofloxacin = 278nm).

The duration of the experiment with bentonite and kaolin was 72hours and that of activated charcoal was 2hours.

From the absorbance values obtained, concentration of the fluoroquinolones in the presence of the adsorbents were determined by interpolating from the Beer's plots and then appropriate Langmuir plots were carried out for the computation of the required constants.

CHAPTER III

RESULTS

3.1 The results of the determination of wavelengths of maximum absorbance for ciprofloxacin, norfloxacin and ofloxacin are shown in Table 3.1.

3.2 The absorbance values for standard concentrations of ciprofloxacin, norfloxacin and ofloxacin are shown in Tables 3.2.1 – 3.2.3 and the calibration plots of absorbance against concentration are shown in Figures 3.2.1 – 3.2.3, respectively.

3.3 The results of absorbance of ciprofloxacin in the presence of graded amounts of activated carbon at different times and the ensuing computations are shown in Table 3.3 and the Langmuir and equilibrium plots for these results are shown in Figures 3.3A and 3.3B respectively.

3.4 The results of absorbance of ciprofloxacin in the presence of graded amounts of bentonite at different times and the ensuing computations are shown in Table 3.4 and the Langmuir plot for these results are shown in Figure 3.4.

3.5 The results of absorbance of ciprofloxacin in the presence of graded amounts of kaolin at different times and the ensuing computations are shown in Table 3.5 and the Langmuir plot for these results are shown in Figure 3.5.

3.6 The results of absorbance of norfloxacin in the presence of graded amounts of activated carbon at different times and the ensuing computations are shown in Table 3.6 and the Langmuir plot for these results are shown in Figure 3.6.

3.7 The results of absorbance of norfloxacin in the presence of graded amounts of bentonite at different times and the ensuing computations are shown in Table 3.7 and the Langmuir plot for these results are shown in Figure 3.7.

3.8 The results of absorbance of norfloxacin in the presence of graded amounts of kaolin at different times and the ensuing computations are shown in Table 3.8 and the Langmuir and equilibrium plots for these results are shown in Figures 3.8A and 3.8B respectively.

3.9 The results of absorbance of ofloxacin in the presence of graded amounts of activated carbon at different times and the ensuing computations are shown in Table 3.9 and the Langmuir plot for these results are shown in Figure 3.9.

3.10 The results of absorbance of ofloxacin in the presence of graded amounts of bentonite at different times and the ensuing computations are shown in Table 3.10 and the Langmuir and equilibrium plots for these results are shown in Figures 3.10A and 3.10B respectively.

3.11 The results of absorbance of ofloxacin in the presence of graded amounts of kaolin at different times and the ensuing computations are shown in Table 3.11 and Langmuir plot for these results are shown in Figure 3.11.

3.12 The results of the summary of various constants obtained from the Langmuir plots for the fluoroquinolones against the 3 adsorbents employed are shown in the Table 3.12.

3.13 The results of the comparison of graphical analysis and regression equation calculation for the constants obtained are shown in the Table 3.13.

3.14 The results of the unit binding capacities and optimum binding capacities of the fluoroquinolones against the employed adsorbents are shown in Table 3.14.

Table 3.1: Result of the determination of wavelengths of maximum absorbance for ciprofloxacin, ofloxacin and norfloxacin.

S/No.	Drug sample	Wavelength of Maximum Absorption
1.	Ciprofloxacin	277nm
2.	Ofloxacin	278nm
3.	Norfloxacin	274nm

Table 3.2.1: The absorbance values for standard concentrations of ciprofloxacin.

Concentration (mg/ml)	Absorbance values
0	0
0.001	0.105
0.002	0.230
0.003	0.330
0.004	0.453
0.005	0.566

Absorbance readings were taken at 277nm.

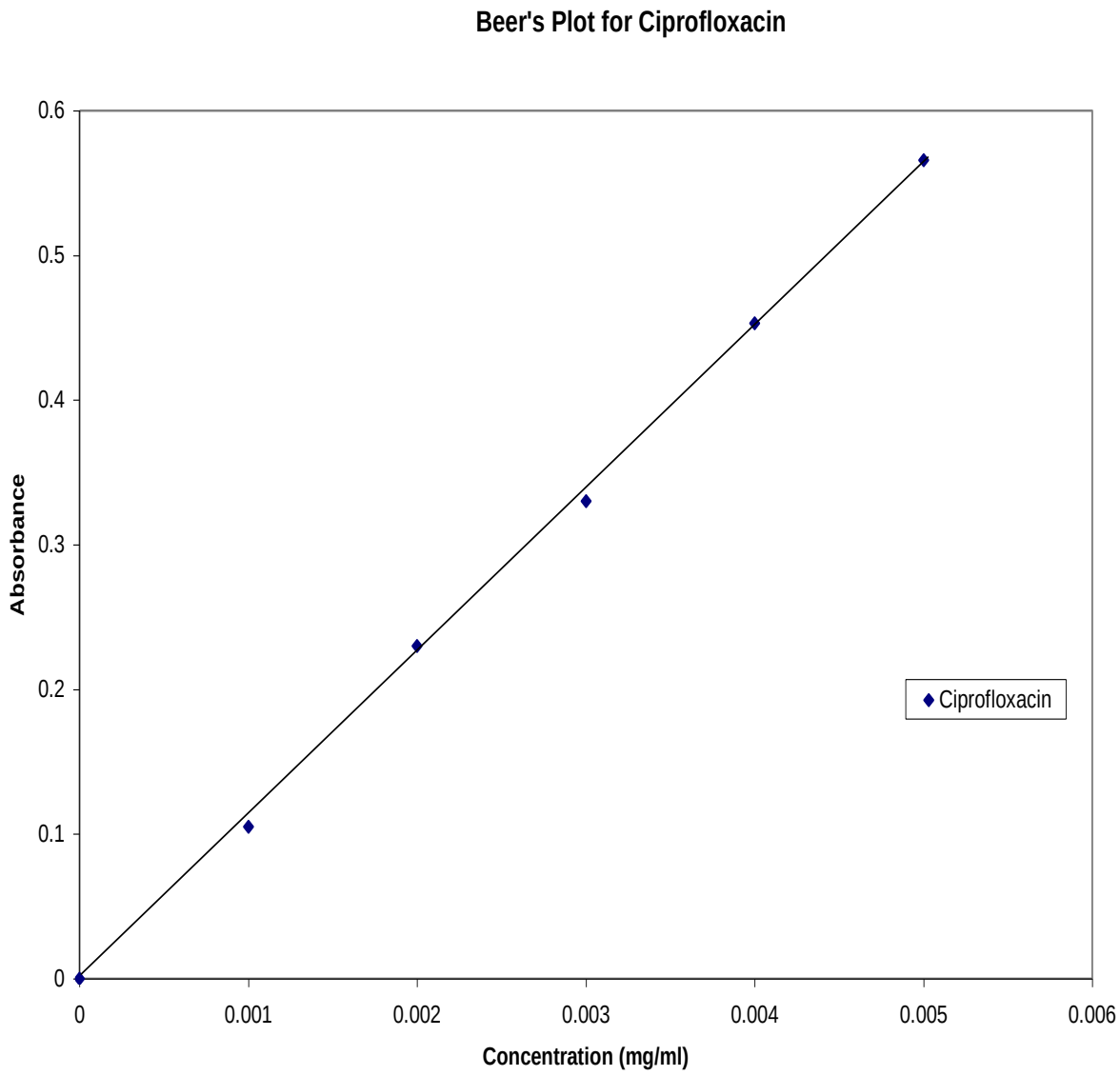

Beer's Plot for Ciprofloxacin
Absorbance
0.6
0.5
0.4
0.3
0.2
0.1
0
0
0.001
0.002
0.003
0.004
0.005
0.006
Concentration (mg/ml)
Ciprofloxacin

Figure 3.2.1

Table 3.2.2: The absorbance values for standard concentrations of ofloxacin.

Concentration (mg/ml)	Absorbance values
0	0
0.001	0.062
0.002	0.105
0.003	0.162
0.004	0.220
0.005	0.258

Absorbance readings were taken at 278nm.

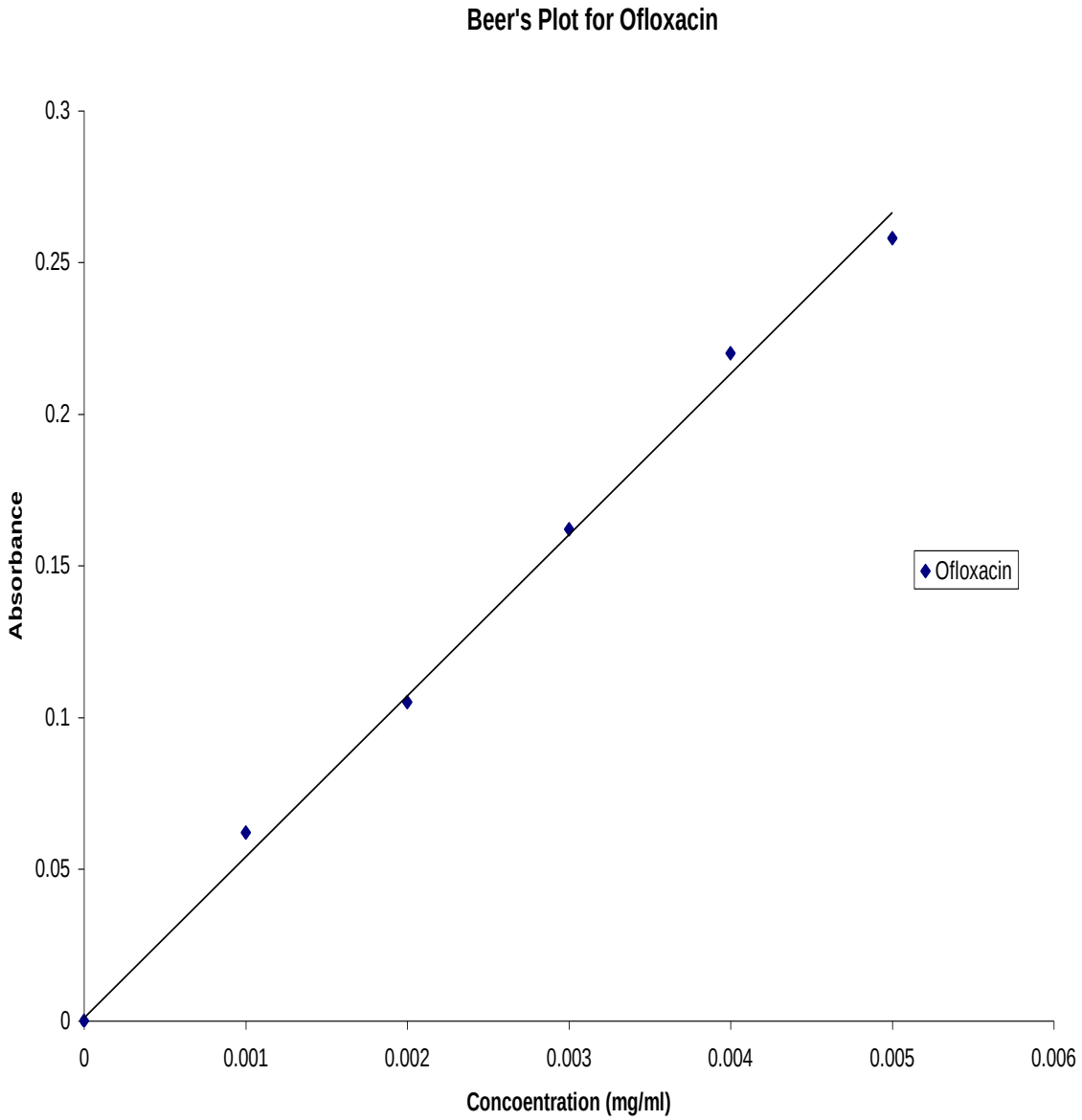

Beer's Plot for Ofloxacin
Absorbance
0.3
0.25
0.2
0.15
0.1
0.05
0
0
0.001
0.002
0.003
0.004
0.005
0.006
Concoentration (mg/ml)
Ofloxacin

Figure 3.2.2

Table 3.2.3: The absorbance values for standard concentrations of norfloxacin

Concentration (mg/ml)	Absorbance values
0	0
0.001	0.084
0.002	0.179
0.003	0.259
0.004	0.331
0.005	0.422

Absorbance readings were taken at 274nm.

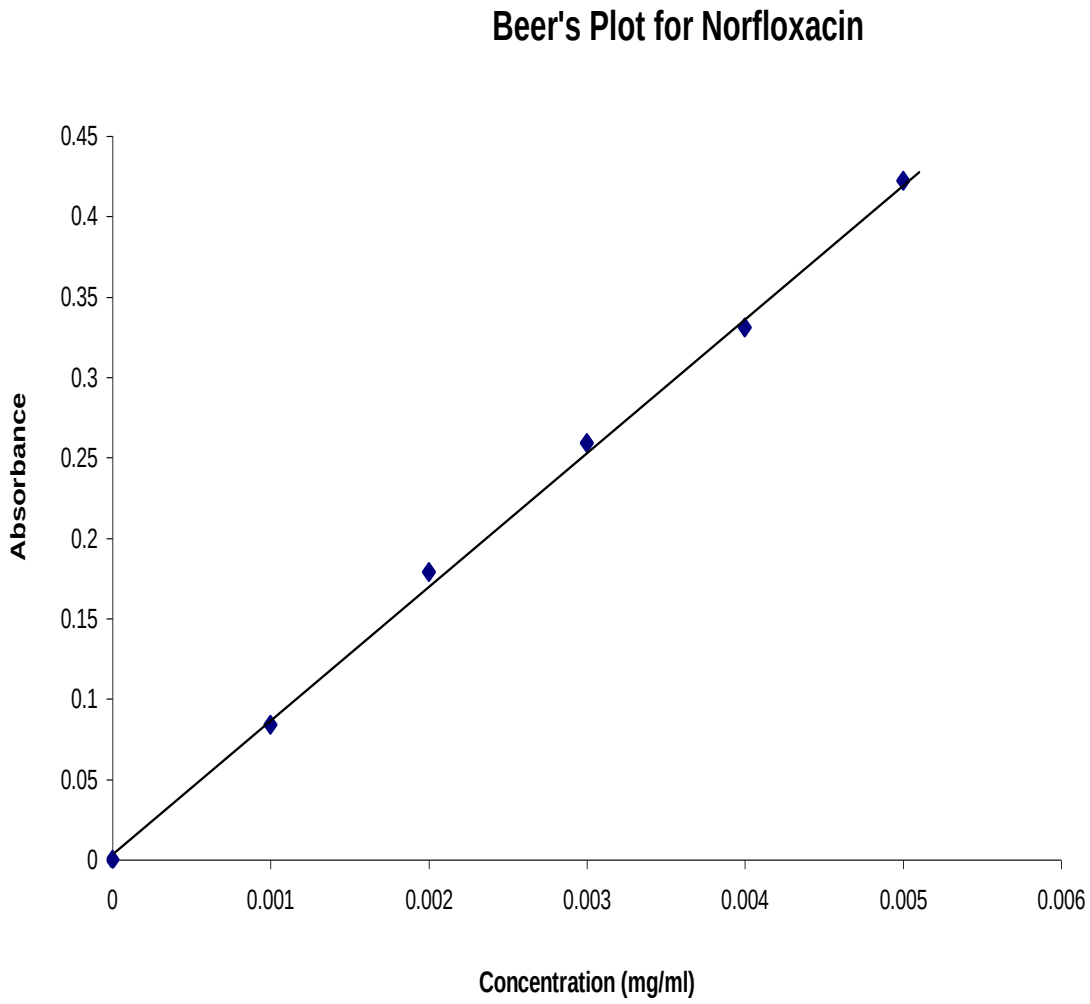


Figure 3.2.3

TABLE 3.3 ABSORBANCE OF CIPROFLOXACIN SHOWING ITS LEVEL OF ADSORPTION TO ACTIVATED CARBON.

Time	Flask	Amount of Adsorbent (m) mg	Absorbance (nm)	Concentration	Ceq mg/ml	Amount left mg	Amount adsorbed (X) mg	X/m	Ceq/X/m mg/ml
0min	1	0.00	0.495	0.0044	0.88				
	2	31.50							
	3	61.00							
	4	102.10							
15mins	1	0.00	0.490	0.00435	0.87	13.05	-	-	-
	2	31.50	0.294	0.0026	0.52	7.80	5.25	0.1667	3.12
	3	61.00	0.183	0.0016	0.32	4.80	8.25	0.1353	2.37
	4	102.10	0.063	0.00055	0.11	1.65	11.40	0.1117	0.99
30mins	1	0.00	0.479	0.00425	0.85	12.75	-	-	-
	2	31.50	0.268	0.0024	0.48	7.20	5.55	0.1762	2.72
	3	61.00	0.170	0.0015	0.30	4.50	8.25	0.1353	2.22
	4	102.10	0.063	0.00055	0.11	1.65	11.10	0.1087	1.01
1hour	1	0.00	0.495	0.0044	0.88	13.20	-	-	-
	2	31.50	0.279	0.0025	0.50	7.50	5.70	0.1810	2.76
	3	61.00	0.143	0.0013	0.26	3.90	9.30	0.1525	1.71
	4	102.10	0.058	0.0005	0.10	1.50	11.70	0.1146	0.87
2hours	1	0.00	0.493	0.00435	0.87	13.05	-	-	-
	2	31.50	0.251	0.00225	0.45	6.75	6.30	0.2000	2.25
	3	61.00	0.113	0.001	0.20	3.00	10.05	0.1648	1.21
	4	102.10	0.048	0.00045	0.09	1.35	11.70	0.1146	0.79

Absorbance readings were taken at 277nm.

Fig 3.3: A Typical Langmuir PLot for Ciprofloxacin in the Presence of Activated Carbon.

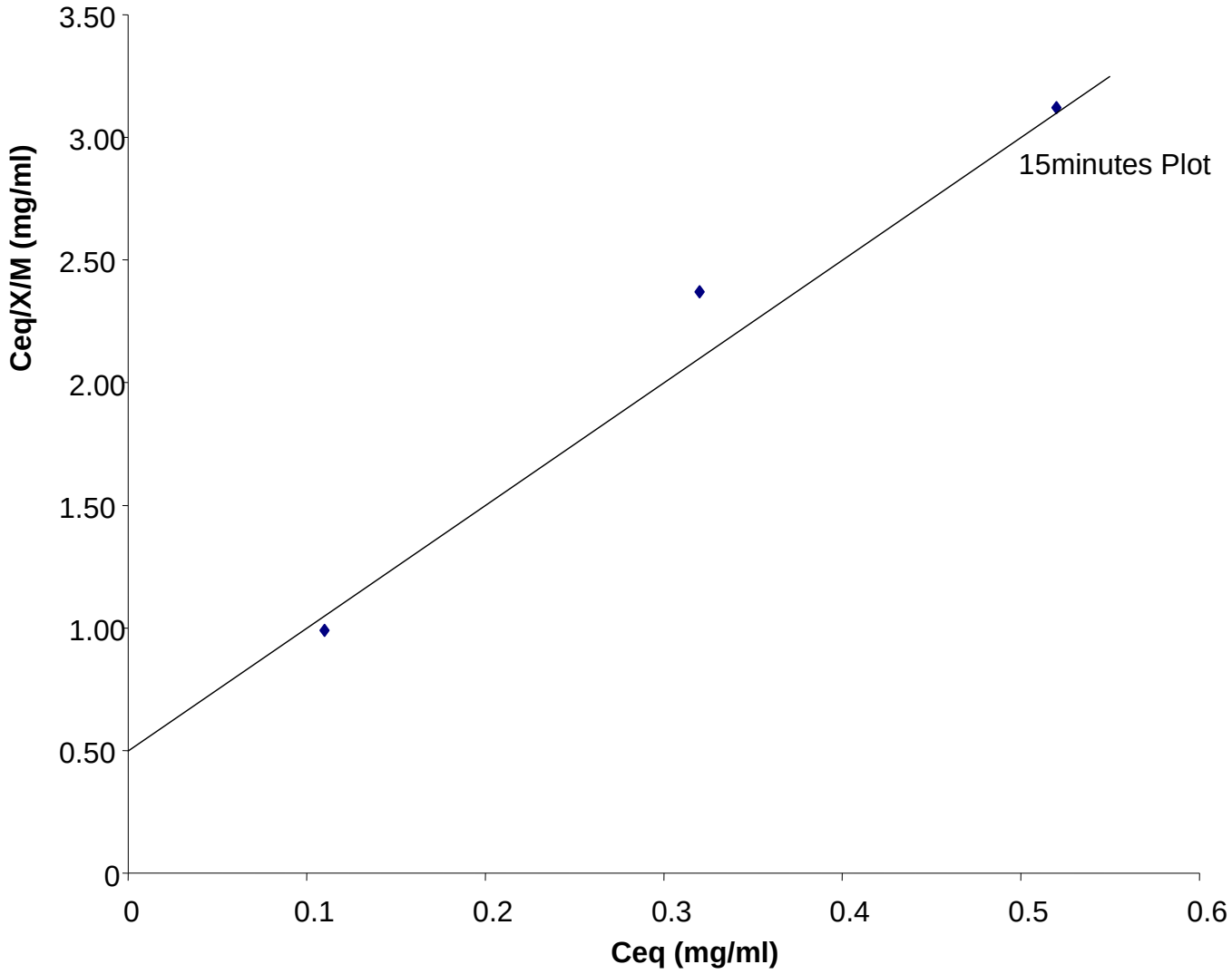


Figure 3.3A

Equilibrium Plot for Ciprofloxacin in the Presence of Activated Carbon.

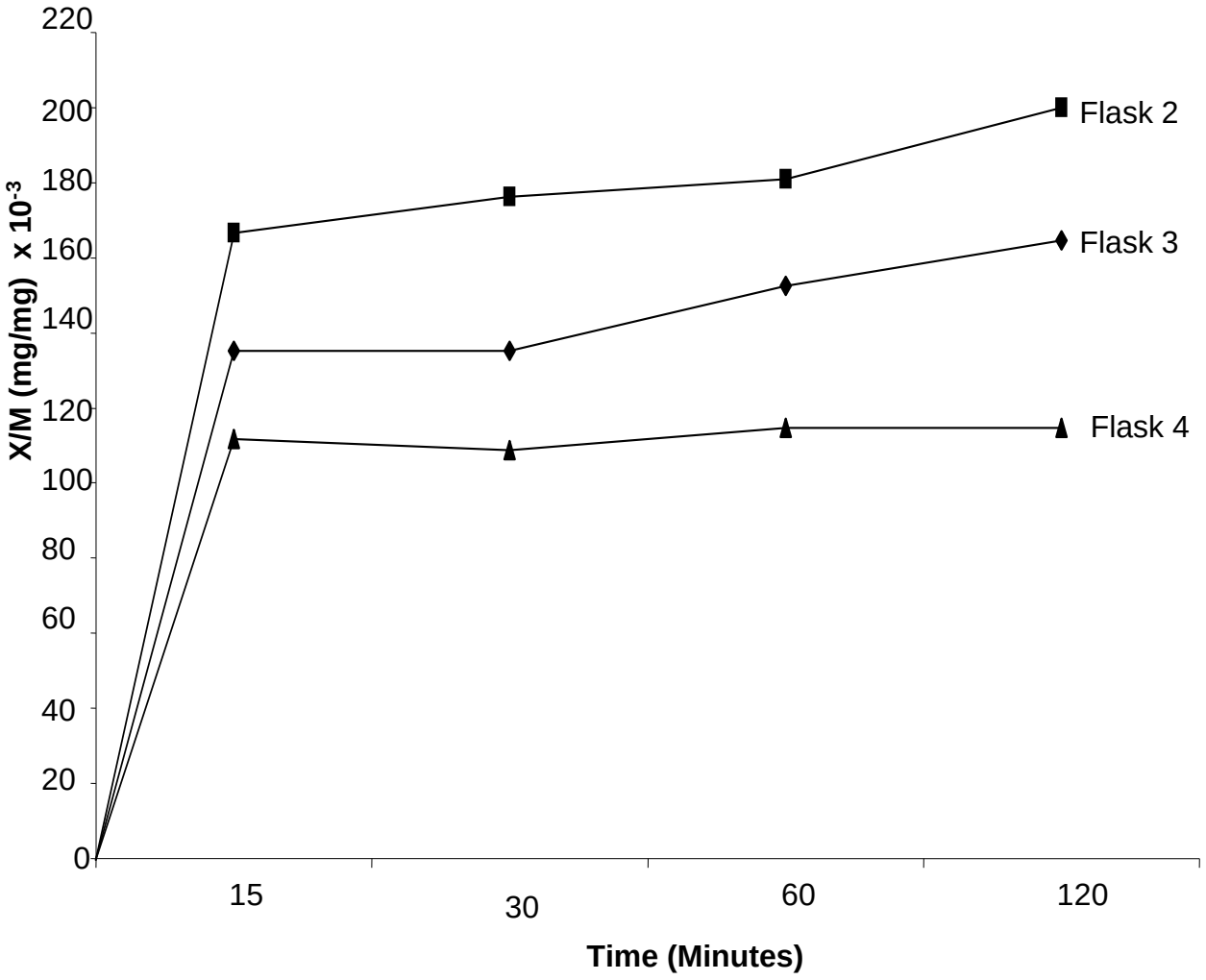


Figure 3.3B

TABLE 3.4. ABSORBANCE OF CIPROFLOXACIN SHOWING ITS LEVEL OF ADSORPTION TO BENTONITE.

Time	Flask	Amount of Adsorbent (m) in mg	Absorbance (nm)	Concentration (mg/ml)	Ceq (mg/ml)	Amount left (mg)	Amount adsorbed (X) mg	X/m	Ceq/X/m mg/ml
0hour	1	0.00	0.530	0.00475	0.95				
	2	30.80							
	3	61.30							
	4	101.50							
2hours	1	0.00	0.525	0.00465	0.93	13.95	-	-	-
	2	30.80	0.360	0.0032	0.64	9.60	4.35	0.1412	4.53
	3	61.30	0.175	0.00155	0.31	4.65	9.30	0.1517	2.04
	4	101.50	0.03	0.0003	0.06	0.90	13.05	0.1286	0.47
24hour	1	0.00	0.499	0.0045	0.9	13.5	-	-	-
	2	30.80	0.257	0.0023	0.46	6.9	6.6	0.2143	2.15
	3	61.30	0.141	0.00125	0.25	3.75	9.75	0.1591	1.57
	4	101.50	0.022	0.0002	0.04	0.6	12.9	0.1271	0.31
48hours	1	0.00	0.550	0.0049	0.98	14.7	-	-	-
	2	30.80	0.304	0.0027	0.54	8.1	6.6	0.2143	2.52
	3	61.30	0.168	0.0015	0.3	4.5	10.2	0.1664	1.80
	4	101.50	0.005	0.0005	0.1	1.5	13.2	0.1301	0.77
72hours	1	0.00	0.437	0.0039	0.78	11.7	-	-	-
	2	30.80	0.262	0.0023	0.46	6.9	4.8	0.1558	2.95
	3	61.30	0.128	0.0011	0.22	3.3	8.4	0.1370	1.61
	4	101.50	0.002	0.0002	0.04	0.6	11.1	0.1094	0.37

Absorbance readings were taken at 277nm.

Fig 3.4: A Typical Langmuir Plot for Ciprofloxacin in the Presence of Bentonite.

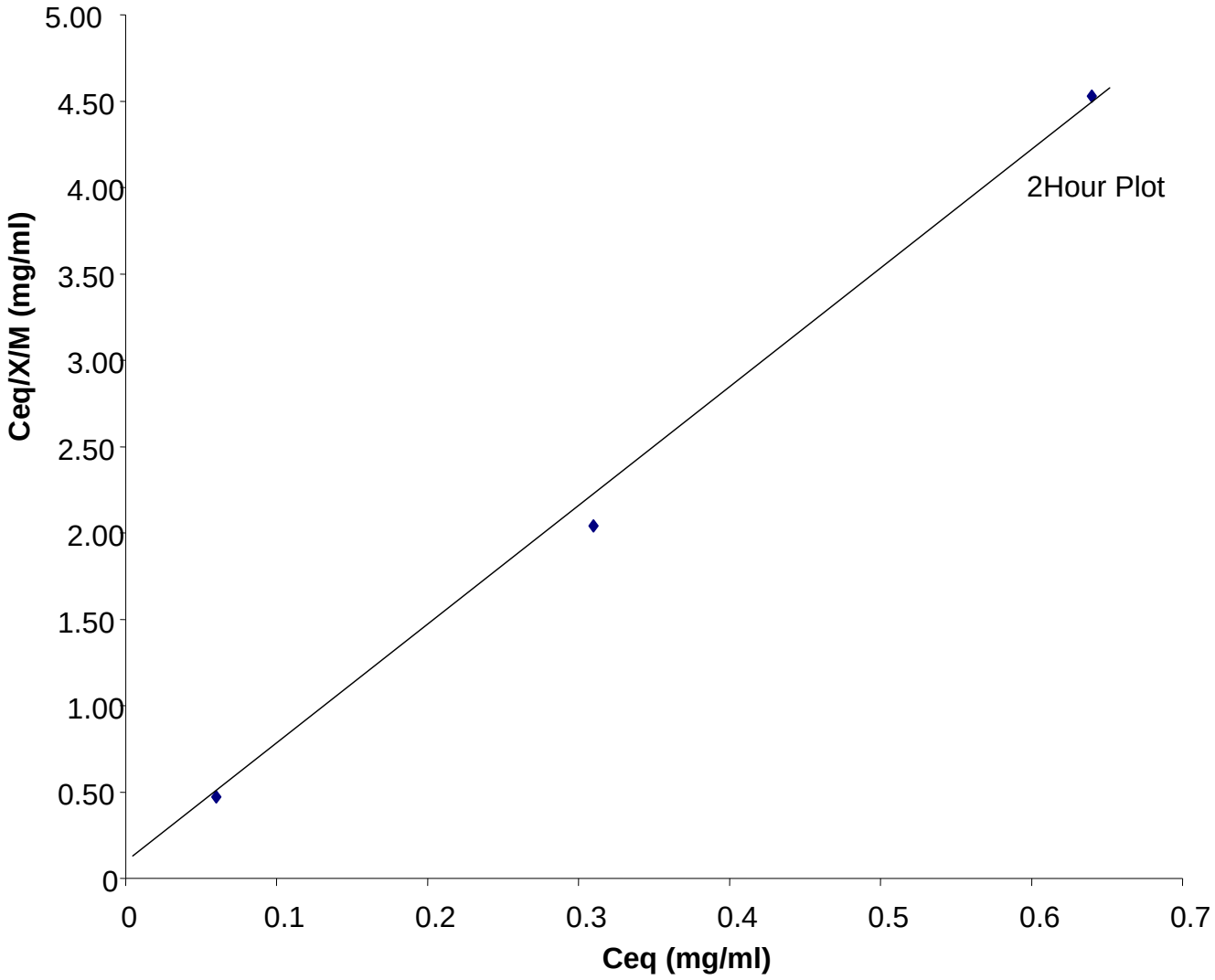


TABLE 3.5. ABSORBANCE OF CIPROFLOXACIN SHOWING ITS LEVEL OF ADSORPTION TO KAOLIN.

Time	Flask	Amount of Adsorbent (m) in mg	Absorbance (nm)	Concentration.	Ceq (mg/ml)	Amount left mg	Amount adsorbed (X) mg	X/m	Ceq/X/m mg/ml
0hour	1	0.00	0.447	0.00395	0.79				
	2	401.70							
	3	801.50							
	4	1200.90							
2hours	1	0.00	0.413	0.00365	0.73	10.95	-	-	-
	2	401.70	0.326	0.0029	0.58	8.7	2.25	0.0056	103.50
	3	801.50	0.240	0.00215	0.43	6.45	4.50	0.0056	76.60
	4	1200.90	0.180	0.0016	0.32	4.8	6.15	0.0051	62.50
24hour	1	0.00	0.448	0.00395	0.79	11.85	-	-	-
	2	401.70	0.354	0.00315	0.63	9.45	2.40	0.0060	105.40
	3	801.50	0.267	0.00235	0.47	7.05	4.80	0.0060	78.50
	4	1200.90	0.208	0.00185	0.37	5.55	6.30	0.0052	70.50
48hours	1	0.00	0.453	0.004	0.80	12.0	-	-	-
	2	401.70	0.350	0.0031	0.62	9.3	2.70	0.0067	92.20
	3	801.50	0.267	0.00235	0.47	7.05	4.95	0.0062	76.10
	4	1200.90	0.187	0.00165	0.33	4.95	7.05	0.0059	56.20
72hours	1	0.00	0.511	0.0045	0.90	13.5	-	-	-
	2	401.70	0.383	0.0034	0.68	10.2	3.30	0.0082	82.80
	3	801.50	0.287	0.00255	0.51	7.65	5.85	0.0073	69.90
	4	1200.90	0.191	0.0017	0.34	5.10	8.40	0.0070	48.60

Absorbance readings were taken at 277nm.

Fig 3.5: A Typical Langmuir Plot for Ciprofloxacin in the Presence of Kaolin.

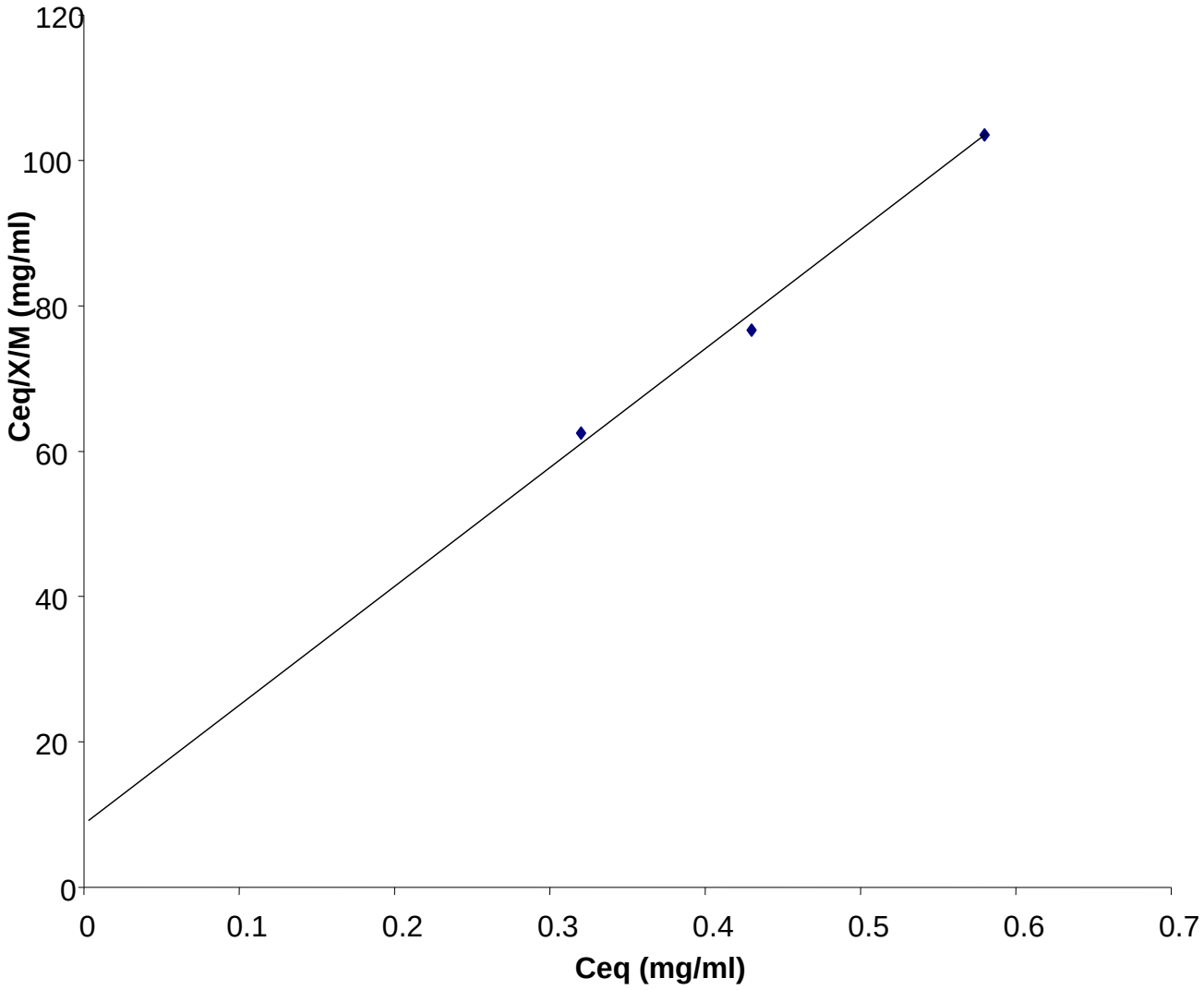


TABLE 3.6. ABSORBANCE OF NORFLOXACIN SHOWING ITS LEVEL OF ADSORPTION TO ACTIVATED CARBON.

Time	Flask	Amount of Adsorbent (m) mg	Absorbance (nm)	Concentration	Ceq mg/ml	Amount left mg	Amount adsorbed (X) mg	X/m	Ceq/X/m mg/ml
0min	1	0.00	0.420	0.005	1.00	15.00			
	2	32.00							
	3	61.80							
	4	102.30							
15mins	1	0.00	0.423	0.005	1.00	15.00	-	-	-
	2	32.00	0.312	0.0037	0.74	11.10	3.90	0.1219	6.10
	3	61.80	0.182	0.00215	0.43	6.45	8.55	0.1384	3.10
	4	102.30	0.082	0.001	0.20	3.00	12.00	0.1173	1.70
30mins	1	0.00	0.418	0.005	1.00	15.00	-	-	-
	2	32.00	0.297	0.0035	0.70	10.50	4.50	0.1406	5.00
	3	61.80	0.154	0.00185	0.37	5.55	9.45	0.1529	2.40
	4	102.30	0.068	0.0008	0.16	2.40	12.60	0.1232	1.30
1hour	1	0.00	0.414	0.00495	0.99	14.85	-	-	-
	2	32.00	0.269	0.0032	0.64	9.60	5.25	0.1641	3.90
	3	61.80	0.123	0.0015	0.30	4.50	10.35	0.1675	1.80
	4	102.30	0.062	0.00075	0.15	2.25	12.60	0.1232	1.20
2hours	1	0.00	0.422	0.005	1.00	15.00	-	-	-
	2	32.00	0.265	0.00315	0.63	9.45	5.55	0.1734	3.60
	3	61.80	0.115	0.0014	0.28	4.20	10.80	0.1748	1.60
	4	102.30	0.065	0.0008	0.16	2.24	12.60	0.1232	1.30

Absorbance readings were taken at 274nm.

Fig 3.6: A Typical Langmuir Plot for Norfloxacin in the Presence of Activated Carbon.

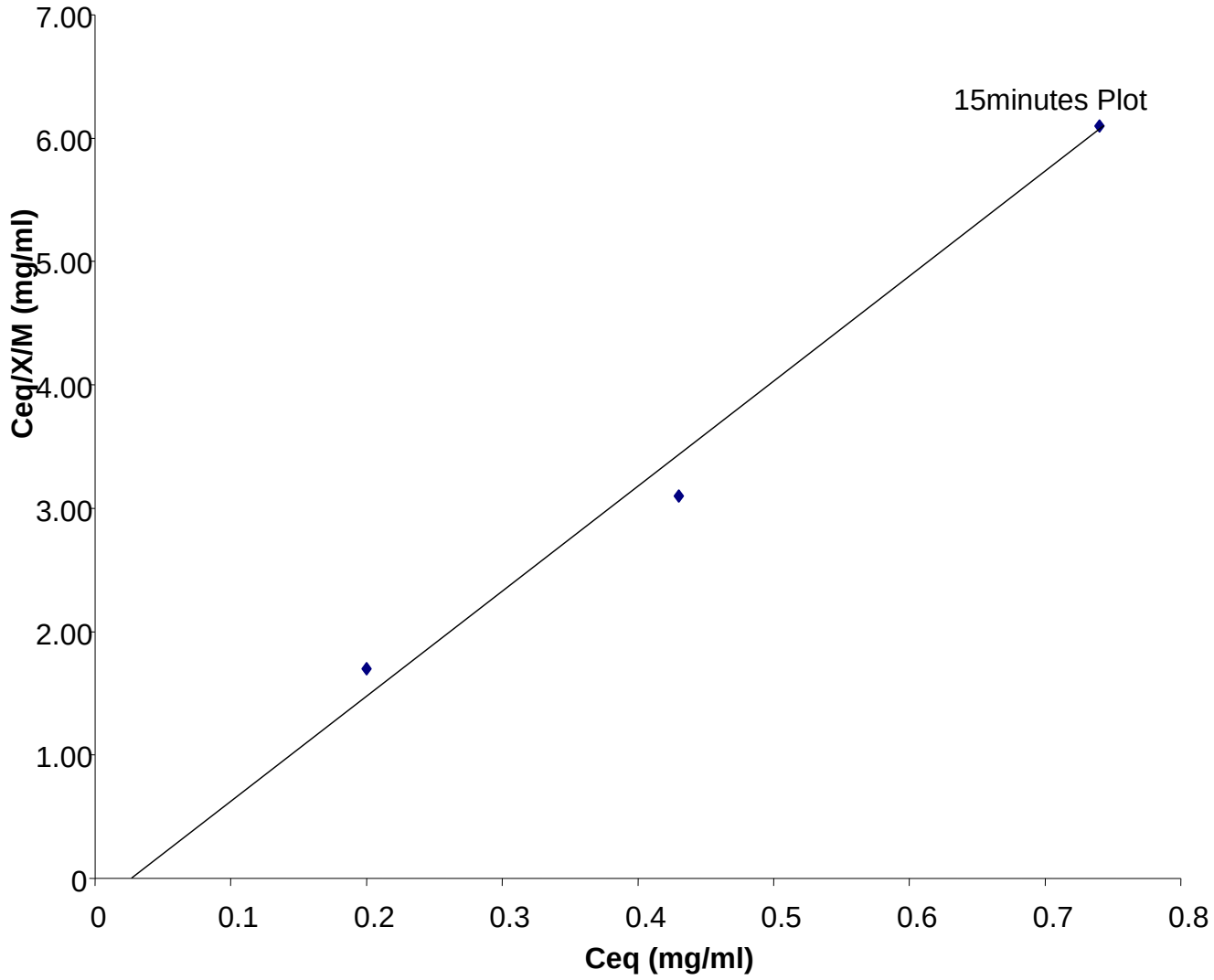


TABLE 3.7. ABSORBANCE OF NORFLOXACIN SHOWING ITS LEVEL OF ADSORPTION TO BENTONITE.

Time	Flask	Amount of Adsorbent (m) in g	Absorbance (nm)	Concentration.	Ceq (mg/ml)	Amount left in mg	Amount adsorbed (X) mg	X/m	Ceq/X/m mg/ml
0hour	1	0.00		0.0055	1.1				
	2	31.80							
	3	61.00							
	4	100.50							
2hours	1	0.00	0.468	0.0056	1.12	16.80	-	-	-
	2	31.80	0.344	0.0041	0.82	12.30	4.50	0.1415	5.80
	3	61.00	0.177	0.00215	0.43	6.45	10.35	0.1697	2.53
	4	100.50	0.046	0.00055	0.11	1.65	15.15	0.1508	0.73
24hours	1	0.00	0.443	0.00525	1.05	15.75	-	-	-
	2	31.80	0.306	0.0037	0.74	11.10	4.65	0.1462	5.06
	3	61.00	0.170	0.00205	0.41	6.15	9.60	0.1574	2.61
	4	100.50	0.040	0.0005	0.10	1.50	14.25	0.1418	0.71
48hours	1	0.00	0.424	0.005	1.00	15.00	-	-	-
	2	31.80	0.291	0.00345	0.69	10.35	4.65	0.1462	4.72
	3	61.00	0.160	0.0019	0.38	5.70	9.30	0.1525	2.49
	4	100.50	0.021	0.00025	0.05	0.75	14.25	0.1418	0.35
72hours	1	0.00	0.412	0.0049	0.98	14.70	-	-	-
	2	31.80	0.265	0.00315	0.63	9.45	5.25	0.1651	3.82
	3	61.00	0.153	0.0018	0.36	5.40	9.30	0.1525	2.36
	4	100.50	0.017	0.0002	0.04	0.60	14.10	0.1403	2.85

Absorbance readings were taken at 274nm.

Fig 3.7: A Typical Langmuir Plot for Norfloxacin in the Presence of Bentonite.

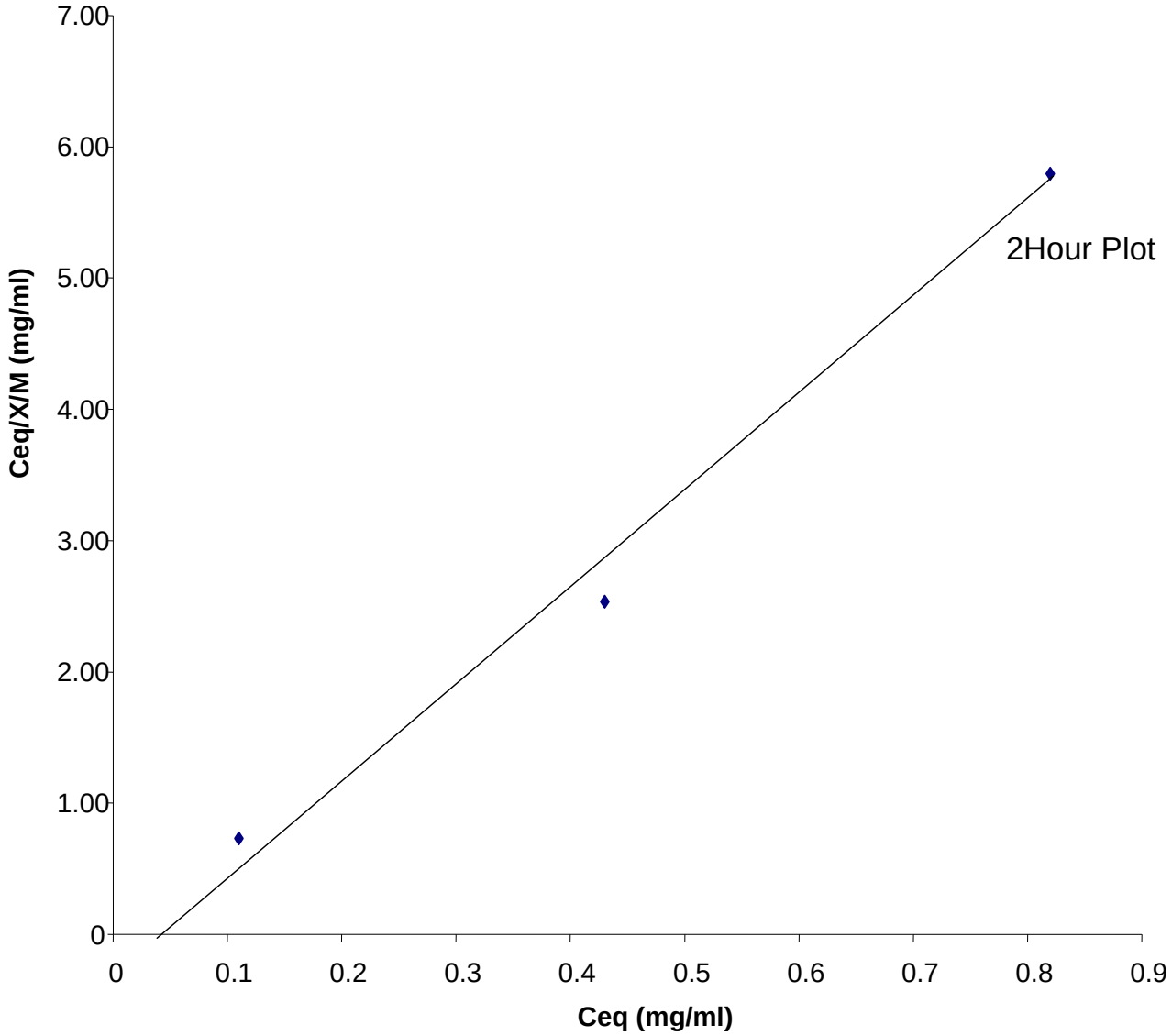


TABLE 3.8. ABSORBANCE OF NORFLOXACIN SHOWING ITS LEVEL OF ADSORPTION TO KAOLIN.

Time	Flask	Amount of Adsorbent (m) g	Absorbance (nm)	Concentration	Ceq mg/ml	Amount left mg	Amount adsorbed (X) mg	X/m	Ceq/X/m mg/ml
0hour	1	0.00	0.463	0.0055	1.10				
	2	403.20							
	3	801.50							
	4	1202.00							
2hours	1	0.00	0.461	0.0055	1.10	16.50	-	-	-
	2	403.20	0.386	0.0046	0.92	13.80	2.70	0.0067	137.00
	3	801.50	0.305	0.00365	0.73	10.95	5.55	0.0069	105.00
	4	1202.00	0.213	0.0025	0.50	7.50	9.00	0.0075	67.00
24hours	1	0.00	0.458	0.0055	1.10	16.50	-	-	-
	2	403.20	0.382	0.0045	0.90	13.50	3.00	0.0074	121.00
	3	801.50	0.309	0.0037	0.74	11.10	5.40	0.0067	110.00
	4	1202.00	0.207	0.0025	0.50	7.50	9.00	0.0075	67.00
48hours	1	0.00	0.455	0.00545	1.09	16.35	-	-	-
	2	403.20	0.362	0.0043	0.86	12.90	3.45	0.0086	100.00
	3	801.50	0.293	0.0035	0.70	10.50	5.85	0.0073	96.00
	4	1202.00	0.192	0.0023	0.46	6.90	9.45	0.0077	59.00
72hours	1	0.00	0.420	0.005	1.00	15.00	-	-	-
	2	403.20	0.355	0.00425	0.85	12.75	2.25	0.0056	152.00
	3	801.50	0.291	0.0035	0.70	10.50	4.50	0.0056	125.00
	4	1202.00	0.202	0.0024	0.48	7.20	7.80	0.0065	74.00

Absorbance readings were taken at 274nm.

Fig 3.8: A typical Langmuir Plot for Norfloxacin in the Presence of Kaolin.

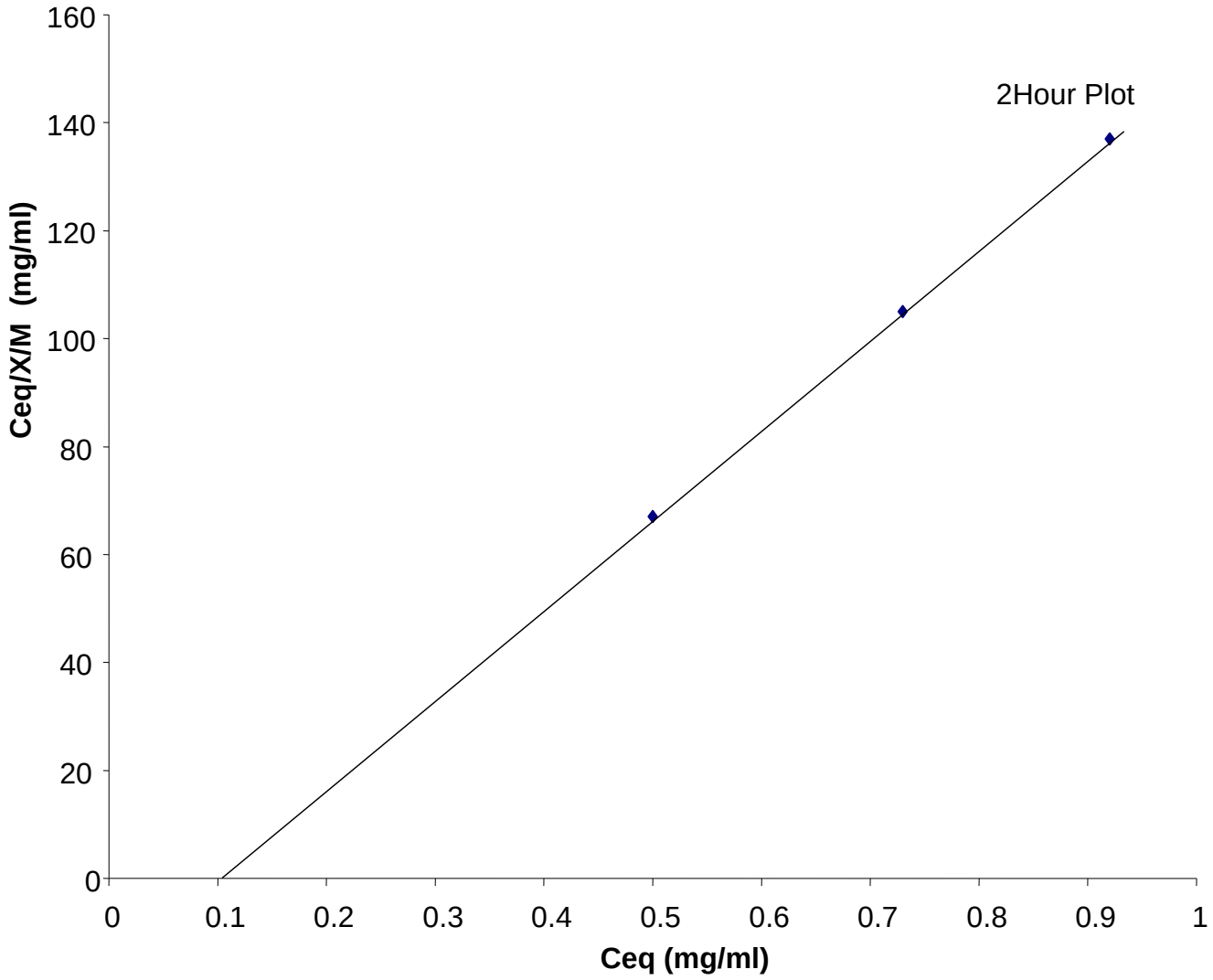


Figure 3.8

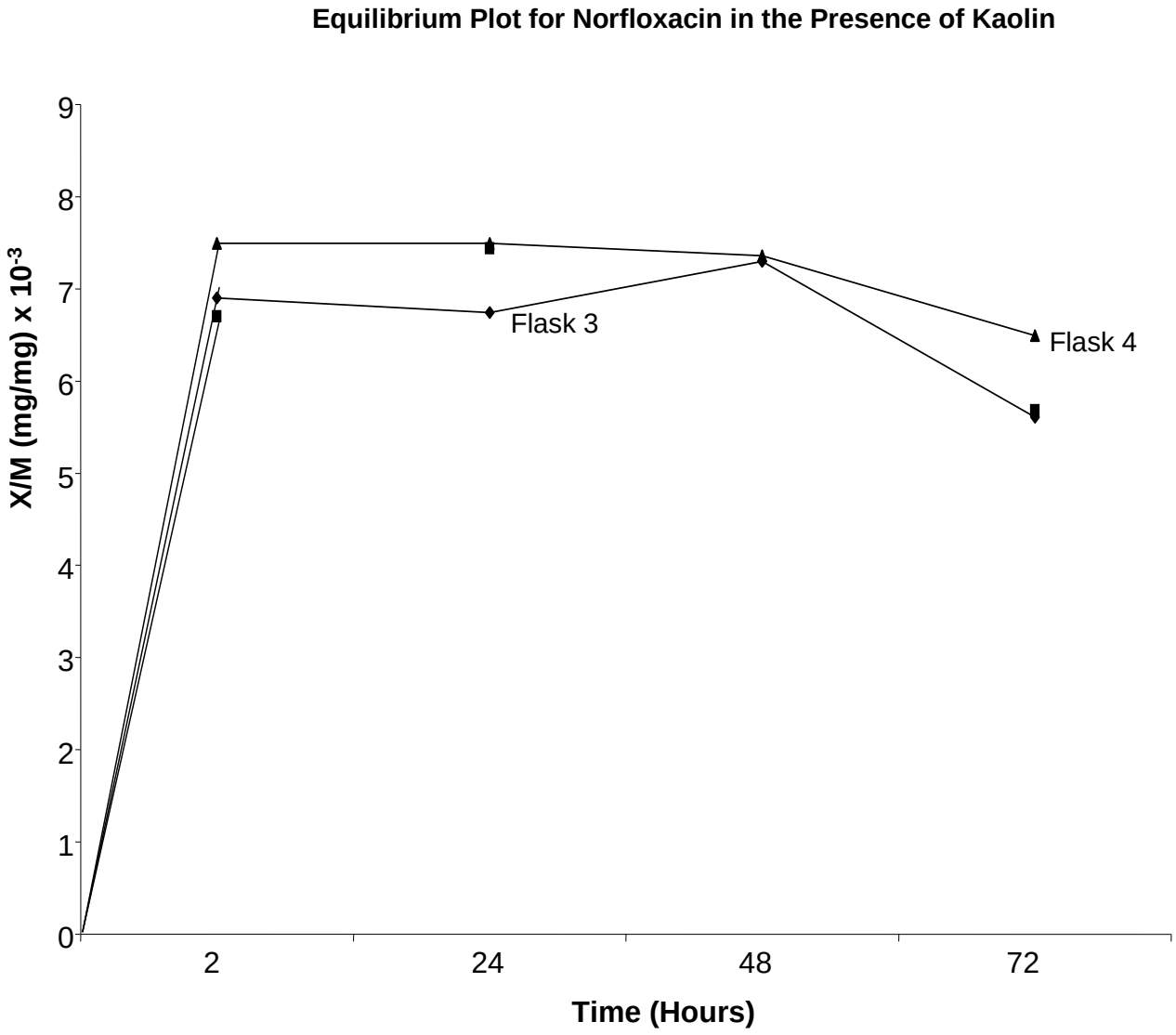

Equilibrium Plot for Norfloxacin in the Presence of Kaolin
X/M (mg/mg) x 10-3
9
8
7
6
5
4
3
2
1
0
2
24
48
72
Time (Hours)
Flask 3
Flask 4

Figure 3.8B

TABLE 3.9. ABSORBANCE OF OFLOXACIN SHOWING ITS LEVEL OF ADSORPTION TO ACTIVATED CARBON.

Time	Flask	Amount of Adsorbent (m) mg	Absorbance (nm)	Concentration	Ceq mg/ml	Amount left mg	Amount adsorbed (X) mg	X/m	Ceq/X/m mg/ml
0min	1	0.00	0.269	0.0051	1.02				
	2	31.50							
	3	61.00							
	4	102.10							
15mins	1	0.00	0.261	0.0049	0.98	14.70	-	-	-
	2	31.50	0.149	0.00285	0.57	8.55	6.15	0.1952	2.92
	3	61.00	0.087	0.00165	0.33	4.95	9.75	0.1598	2.06
	4	102.10	0.045	0.00085	0.17	2.55	12.15	0.1190	1.43
30mins	1	0.00	0.265	0.0050	1.00	15.00	-	-	-
	2	31.50	0.149	0.00285	0.57	8.55	6.45	0.2048	2.78
	3	61.00	0.079	0.0015	0.30	4.50	10.50	0.1721	1.74
	4	102.10	0.049	0.00095	0.19	2.85	12.15	0.1190	1.60
1hour	1	0.00	0.269	0.0051	1.02	15.30	-	-	-
	2	31.50	0.147	0.0028	0.56	8.40	6.90	0.2191	2.56
	3	61.00	0.070	0.0013	0.26	3.90	11.40	0.1869	1.39
	4	102.10	0.047	0.0009	0.18	2.70	12.60	0.1234	1.46
2hours	1	0.00	0.267	0.00505	1.01	15.15	-	-	-
	2	31.50	0.152	0.00285	0.57	8.55	6.60	0.2095	2.72
	3	61.00	0.067	0.00125	0.25	3.75	11.40	0.1869	1.34
	4	102.10	0.048	0.0009	0.18	2.70	12.45	0.1219	1.48

Absorbance readings were taken at 278nm.

Fig 3.9: A Typical Langmuir Plot for Ofloxacin in the Presence of Activated Carbon.

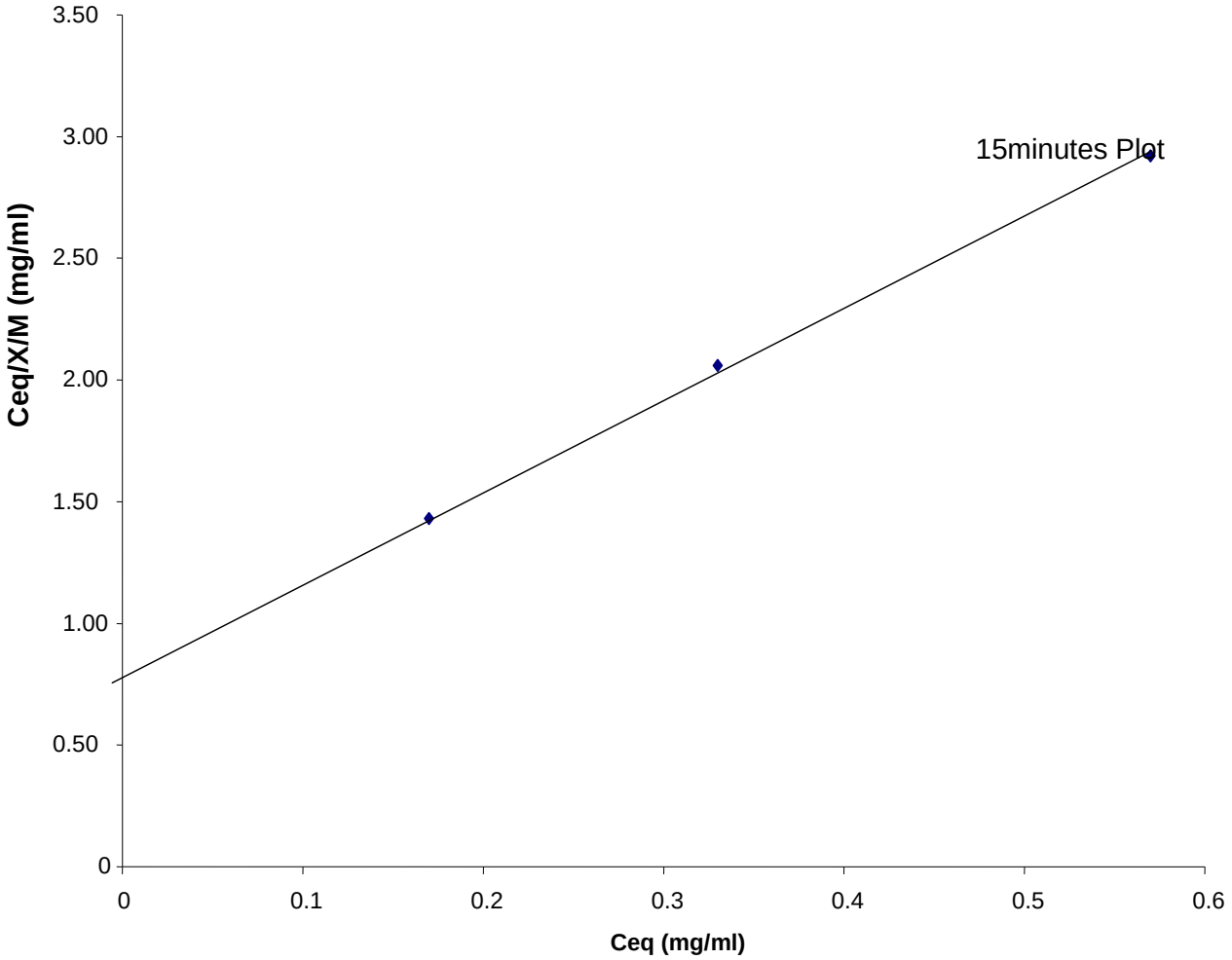


TABLE 3.10. ABSORBANCE OF OFLOXACIN SHOWING ITS LEVEL OF ADSORPTION TO BENTONITE.

Time (hours)	Flask	Amount of Adsorbent (m) mg	Absorbance (nm)	Concentration	Ceq mg/ml	Amount left mg	Amount adsorbed (X) mg	X/m	Ceq/X/m mg/ml
0	1	0.00	1.598						
	2	30.80							
	3	61.30							
	4	101.50							
2	1	0.00	1.590	0.003	0.60	9.0	-	-	-
	2	30.80	1.105	0.021	0.42	6.3	2.7	0.0877	4.79
	3	61.30	0.544	0.001	0.2	3.0	6.0	0.0979	2.04
	4	101.50	0.108	0.0002	0.04	0.6	8.4	0.0828	0.48
24	1	0.00	1.620	0.003	0.60	9.0	-	-	-
	2	30.80	1.080	0.0021	0.42	6.3	2.7	0.0877	4.79
	3	61.30	0.468	0.0009	0.18	2.7	6.3	0.1028	1.75
	4	101.50	0.054	0.0001	0.02	0.3	8.7	0.0857	0.23
48	1	0.00	1.590	0.003	0.60	9.0	-	-	-
	2	30.80	1.135	0.00215	0.43	6.45	2.55	0.0828	5.19
	3	61.30	0.515	0.00095	0.19	2.85	6.15	0.1003	1.89
	4	101.50	0.044	0.0001	0.02	0.30	8.70	0.0857	0.23
72	1	0.00	1.600	0.003	0.60	9.0	-	-	-
	2	30.80	1.080	0.0021	0.42	6.3	2.7	0.0877	4.79
	3	61.30	0.508	0.00095	0.19	2.85	6.15	0.1003	1.89
	4	101.50	0.035	0.0001	0.02	0.30	8.70	0.0857	0.23

Absorbance readings were taken at 278nm.

Fig 3.10: A Typical Langmuir Plot for Ofloxacin in the Presence of Bentonite

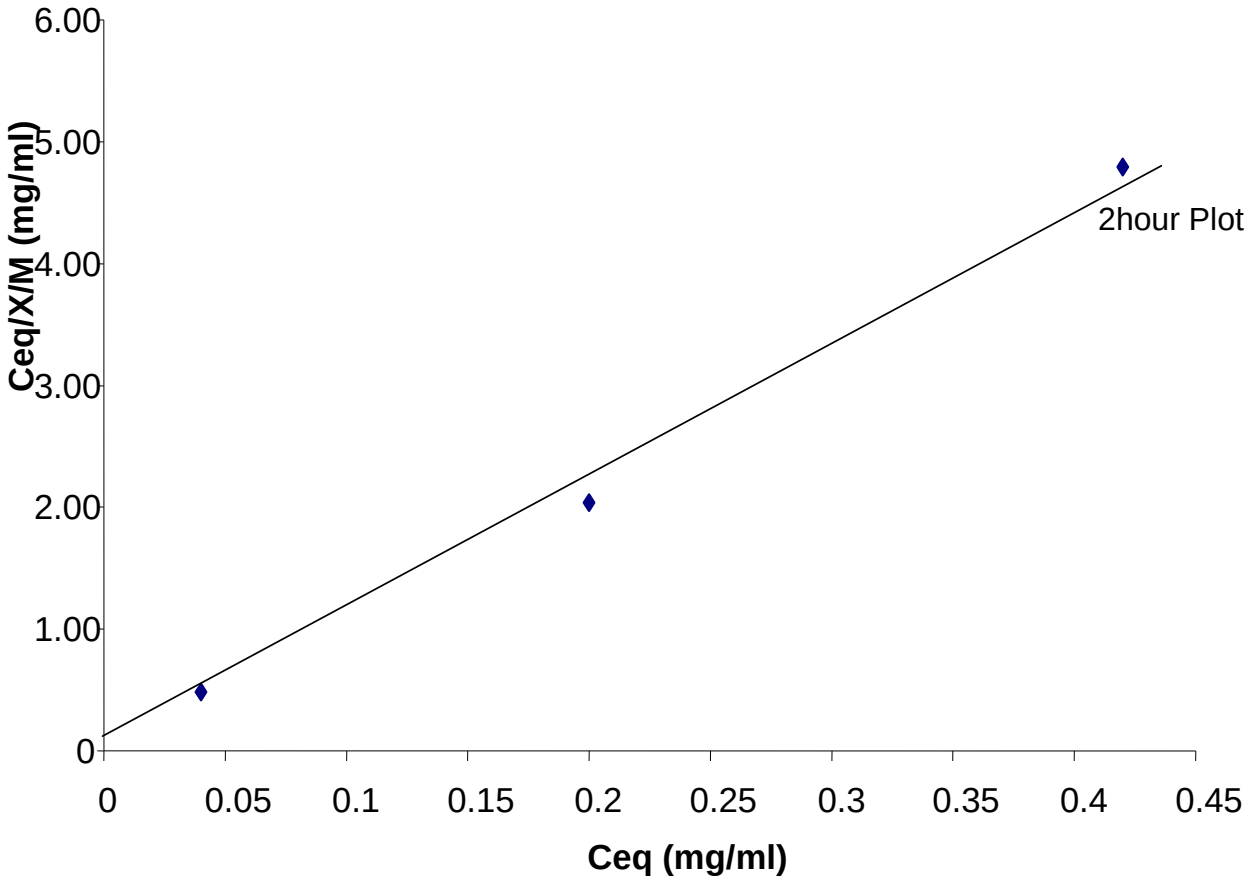


Figure 3.10A

Equilibrium Plot for Ofloxacin in the Presence of Bentonite.

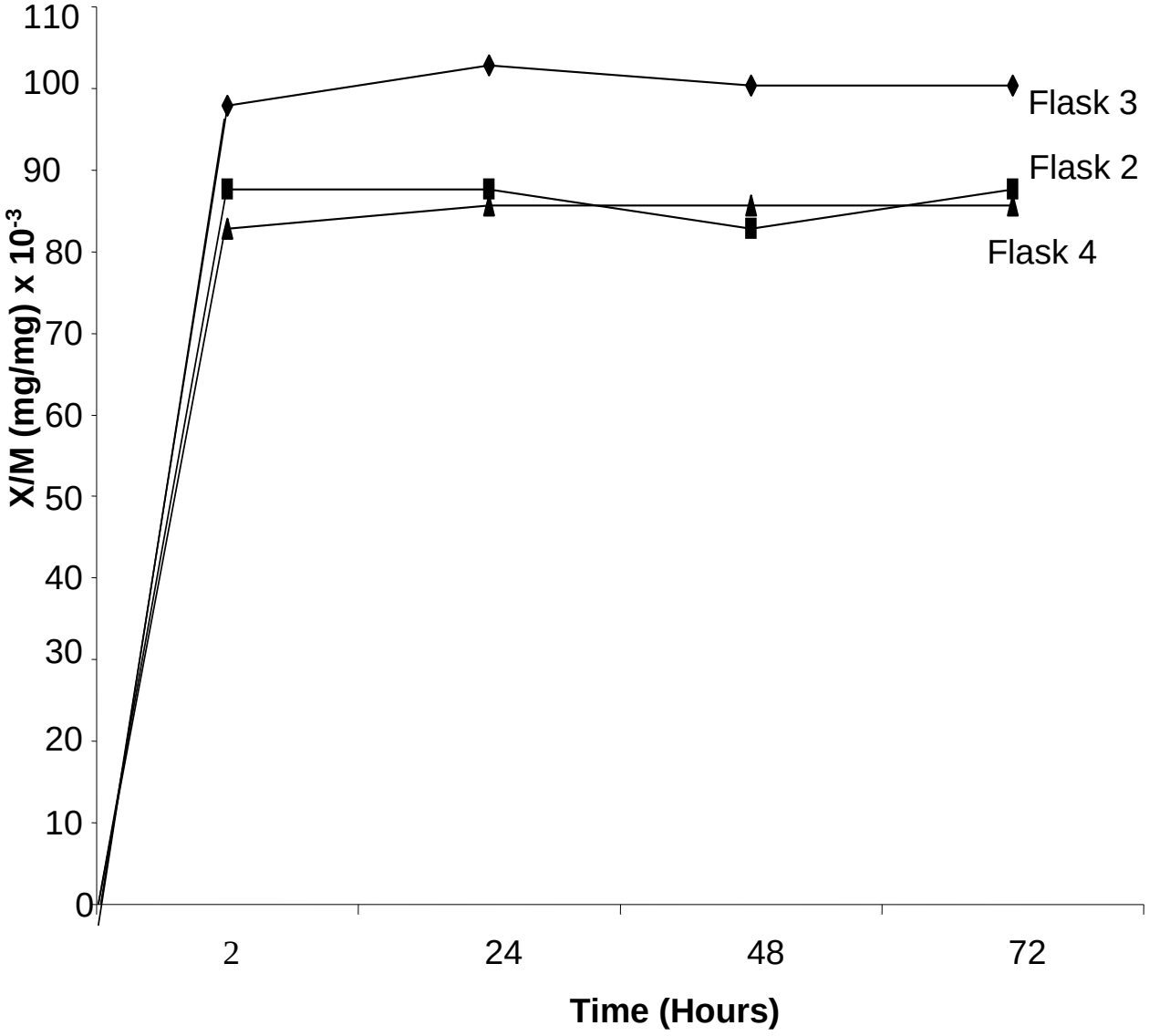


Figure 3.10B

TABLE 3.11. ABSORBANCE OF OFLOXACIN SHOWING ITS LEVEL OF ADSORPTION TO KAOLIN.

Time (hours)	Flask	Amount of Adsorbent (m) mg	Absorbance (nm)	Concentration	Ceq mg/ml	Amount left mg	Amount adsorbed (X) mg	X/m	Ceq/X/m mg/ml
0	1	0.00	0.156	0.00295					
	2	401.70							
	3	801.50							
	4	1,200.90							
2	1	0.00	0.162	0.00305	0.61	9.15	-	-	-
	2	401.70	0.160	0.00300	0.60	9.00	0.15	0.000373	1606.80
	3	801.50	0.154	0.0029	0.58	8.70	0.45	0.000561	1033.00
	4	1,200.90	0.091	0.0017	0.34	5.1	4.05	0.003372	100.80
24	1	0.00	0.166	0.00315	0.63	9.45	-	-	-
	2	401.70	0.159	0.003	0.60	9.00	0.45	0.001120	535.60
	3	801.50	0.155	0.00295	0.59	8.85	0.60	0.000749	788.10
	4	1,200.90	0.100	0.0019	0.38	5.70	3.75	0.003123	121.70
48	1	0.00	0.174	0.0033	0.66	9.90	-	-	-
	2	401.70	0.163	0.00305	0.61	9.15	0.75	0.001867	326.70
	3	801.50	0.155	0.00295	0.59	8.85	1.05	0.001310	450.40
	4	1,200.90	0.091	0.0017	0.34	5.10	4.80	0.003997	85.10
72	1	0.00	0.168	0.0032	0.64	9.60	-	-	-
	2	401.70	0.156	0.00295	0.59	8.85	0.75	0.001867	316.00
	3	801.50	0.148	0.0028	0.56	8.40	1.20	0.001497	374.00
	4	1,200.90	0.101	0.0019	0.38	5.7	3.90	0.003248	117.00

Absorbance readings were taken at 278nm.

Fig. 3.11: A Typical Langmuir Plot for Norfloxacin in the Presence of Kaolin

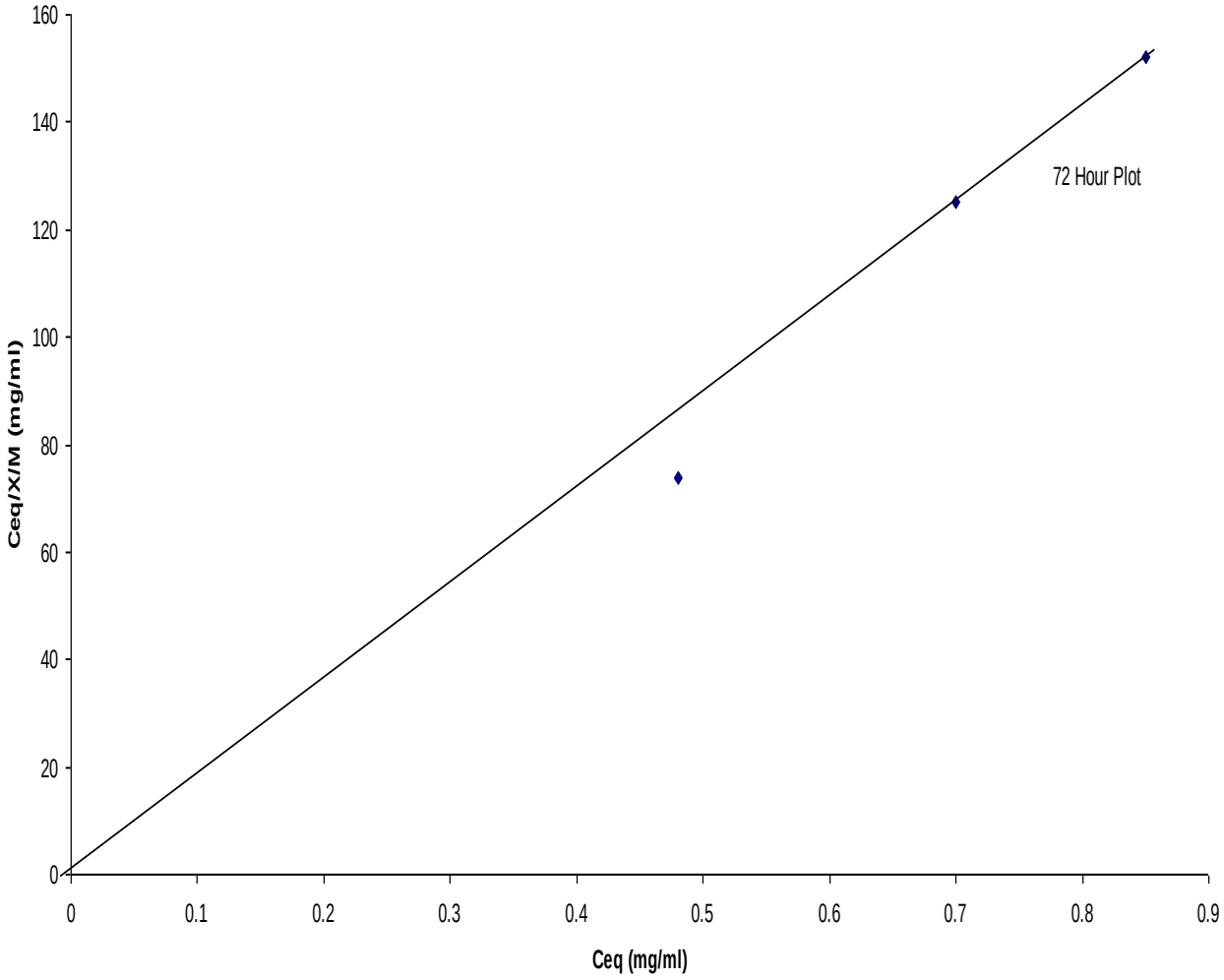


TABLE 3.12: SUMMARY OF K_1 AND K_2 VALUES OBTAINED FROM THE LANGMUIR EQUATION PLOTS.

DRUG - ADSORBENT	K_1	K_2 (mg/mg)	K_1K_2
CIPROFLOXACIN- ACTIVATED CARBON	10.19	0.1921	1.9572
OFLOXACIN- ACTIVATED CARBON	4.56	0.2693	1.1282
NORFLOXACIN- ACTIVATED CARBON	-63.09	0.1215	-7.6628
CIPROFLOXACIN- BENTONITE	17.68	0.2283	4.0361
OFLOXACIN- BENTONITE	-155.05	0.0876	-13.5870
NORFLOXACIN- BENTONITE	-30.94	0.1393	-4.3103
CIPROFLOXACIN- KAOLIN	15.28	0.0063	0.0961
OFLOXACIN- KAOLIN	-3.10	0.0002	-0.0006
NORFLOXACIN- KAOLIN	-6.64	0.0055	-0.0365

TABLE 3.13. COMPARISON OF K2 VALUES OBTAINED FROM GRAPHICAL AND REGRESSION EQUATION CALCULATIONS

	K_2 VALUES (mg/g)	
DRUG - ADSORBENT	OBSERVED	CALCULATED
CIPROFLOXACIN-ACTIVATED CARBON	222.22	192.07
OFLOXACIN-ACTIVATED CARBON	266.67	269.27
NORFLOXACIN-ACTIVATED CARBON	147.06	121.45
CIPROFLOXACIN-BENTONITE	200.00	228.26
OFLOXACIN-BENTONITE	100.00	87.63
NORFLOXACIN-BENTONITE	147.06	139.31
CIPROFLOXACIN-KAOLIN	8.33	6.29
OFLOXACIN- KAOLIN	0.37	0.20
NORFLOXACIN- KAOLIN	5.99	5.50

TABLE 3.14. UNIT/OPTIMUM BINDING CAPACITIES OF THE ADSORBENTS.

DRUG – ADSORBENT	UNIT BINDING CAPACITIES	OPTIMUM BINDING CAPACITIES
CIPROFLOXACIN-ACTIVATED CARBON	192.07mg/g	53.78 250mg tablets
OFLOXACIN- ACTIVATED CARBON	269.27mg/g	94.24 200mg tablets
NORFLOXACIN-ACTIVATED CARBON	121.45mg/g	21.25 400mg tablets
CIPROFLOXACIN-BENTONITE	228.26mg/g	63.91 250mg tablets
OFLOXACIN- BENTONITE	87.63mg/g	30.67 200mg tablets
NORFLOXACIN-BENTONITE	139.31mg/g	24.38 400mg tablets
CIPROFLOXACIN- KAOLIN	6.29mg/g	1.76 250mg tablets
OFLOXACIN- KAOLIN	0.20mg/g	0.07 200mg tablets
NORFLOXACIN- KAOLIN	5.50mg/g	0.96 400mg tablets

CHAPTER IV

DISCUSSION

As shown in the Table 3.141 above the binding capacities of the 3 adsorbents used (Activated charcoal, Bentonite and Kaolin) vary and revealed the extents to which the 3 fluoroquinolone antibacterial agents used (Norfloxacin, Ofloxacin and Ciprofloxacin) could be bound. Expectedly, activated charcoal exhibits a high binding capacity against the 3 drugs with binding capacities of 121.45mg/g, 269.27mg/g and 192.07mg/g for Norfloxacin Ofloxacin and Ciprofloxacin respectively. In the like manner, Bentonite shows very promising prospects in its binding capacity of 139.31mg/g for Norfloxacin, 87.63mg/g for Ofloxacin and 228.26mg/g for Ciprofloxacin.

Since large volumes of activated charcoal slurry may precipitate vomiting, one practice is to standardize the amount of charcoal by giving 1g of activated charcoal per each Kg body weight (53). In typical cases of accidental ingestion or over-dosage, information on the amount of drug ingested is seldom available; the focus therefore is to administer excess of the adsorbent at minimal risk of adverse effect (vomiting). Against this background, in a hypothetical case of an accidental ingestion or over-dosage in a man of an average body weight of 70kg, 70g of the activated charcoal would bind 21.25 400mg tablets of Norfloxacin, 94.24 200mg of Ofloxacin and 53.78 250mg tablets of Ciprofloxacin while the same quantity of Bentonite would bind 24.38 400mg tablets of Norfloxacin, 30.67 200mg tablets of Ofloxacin and 63.91 250mg tablets of Ciprofloxacin.

However, in this regard Kaolin does not appear to have good prospects as the binding capacities against the 3 fluoroquinolone antibacterial agents are very poor. It will therefore not serve any useful purpose as an antidote in cases of overdosage and accidental ingestion of any of the three drugs

The values of Langmuir constants (K_2 and K_1K_2) that were obtained as shown in Table 3.12 reveal relative similarity. K_2 values are observed to increase with the increase in binding capacities of the adsorbents or adsorption affinities between the fluoroquinolones and adsorbents which is the focal point of this work. As in the work of E.M.Sellers et. al on comparative drug adsorption by activated charcoal(53), the data were plotted according to the Langmuir equation as shown below:

$$\frac{Ceq}{X/m} = \frac{Ceq}{K_2} + \frac{1}{K_1K_2}$$

Where Ceq is the free drug concentration in solution at equilibrium

X\m is the amount of drug adsorbed by the quantity of adsorbent used

K_2 and K_1K_2 are constants which values were evaluated from the reciprocals of the respective isotherm slope and intercept values of the regression equation.

K_2 values obtained for ciprofloxacin, ofloxacin and norfloxacin against activated carbon and bentonite in this work are quite comparable to those obtained by E.M.Sellers et al for aspirin -262, amitriptyline - 133, chlordiazepoxide - 157, diazepam - 136, methaqualone - 179 and glutethimide – 252, all with activated carbon under a similar acidic condition and temperature of 37ºC. This thus infers that bentonite is as good as activated carbon as an antidote in handling cases of over-dosage or accidental ingestion involving ciprofloxacin, ofloxacin and norfloxacin. However, the same cannot be said of kaolin which K_2 values against the three drugs are in the range of 0.2 to 6.29, which thus confirms its poor adsorbing capacity or affinity.

Furthermore, the poor adsorbing capacity of kaolin was similarly attested to by Barr and Arnistal (54) in their work which investigated the adsorption of diphtheria toxin and several bacteria by various clays. They concluded that attapulgite, a hydrous magnesium aluminium silicate, was superior to kaolin as an intestinal adsorbent. The results of the adsorption of strychnine on activated attapulgite also showed more considerable affinity over halloysite (similar to kaolinite) and kaolin. The isotherm plot (Ceq/(X/m) against Ceq, smaller slope as in the case of attapulgite was an indication of better adsorption affinity as against halloysite and kaolin. (54)

Bentonite on the other hand showed a promising outlook in the formulation of a sustained release dosage form of the fluoroquinolone antibacterial agents. This could be achieved by reverse condition of initial adsorption between the adsorbent and the fluoroquinolone molecules. The ensuing desorption therefore, enhances the release of the otherwise bound

fluoroquinolone molecules for further absorption into the patient's blood steam at a pre-determined time intervals. However, this is outside the scope of this study.

Another point that was observed in the course of this work is the fact that there is a definite range of the quantity of adsorbent required for achieving desirable effect. This critical range shows that for each of the adsorbents used in this work, increase in the quantity of adsorbent above this range would not produce corresponding increase in amount of drug that is bound, but on the contrary has tendency to expose the patient to greater manifestation of adverse drug effects.

On the reproducibility of the results obtained, the double blind methods of providing a blank for each of the flasks used in this work had greatly helped in reducing to the barest minimum the incidence of experimental error that is normally encountered in a work of this nature. The result of this work is thus expected to be reproducible *invivo*. This was what informed the use of hydrochloric acid to make the medium acidic (pH =1) in order to mimic stomach acidic condition where absorption of medicaments takes place as well as keeping the flasks in a thermo stated shaker at 37^0C.

CONCLUSION

Activated charcoal and bentonite have been shown to possess very good binding capacities against norfloxacin, ofloxacin and Ciprofloxacin. In view of the immense role these versatile antibacterial agents have assumed in the treatment of various clinical conditions, the importance of these adsorbents in cases of accidental ingestion or over dosage of these fluoroquinolone antibacterial agents cannot be overemphasized. There is therefore an optimistic view that these adsorbents could be handy in any emergency situations involving these antibacterial agents.

This point is better outlined by the values obtained for adsorption affinities in both adsorbents for the three fluoroquinolone anti bacterial agents which are comparable to those obtained by E.M. Sellers et al (53) for activated charcoal with other drugs under similar conditions.

Bentonite in addition to the promising use in management of overdosage, it holds the possibility of use as lacquer in the formulation of sustained release dosage form of the fluoroquinolone anti bacterial agents.

Due to its weak binding capacities against norfloxacin. ofloxacin and ciprofloxacin, kaolin cannot be useful in any attempt at reducing the amount of these antibacterial agents that would be absorbed into the system through the GIT in cases of accidental ingestion or over-dosage. This finding is corroborated by Barr and Arnista (54) in their work which found attapulgite superior to kaolin as intestinal adsorbent.

CONTRIBUTION TO KNOWLEDGE

Activated charcoal and bentonite are very good adsorbents with considerable binding capacities for norfloxacin, ofloxacin and ciprofloxacin.

Bentonite could be as versatile as activated charcoal in handling cases of over dosage or accidental ingestion of norfloxacin, ofloxacin and ciprofloxacin. It also holds good prospects in formulation of sustained release dosage forms of these anti bacterial agents.

The prospects of employing kaolin as an adsorbing agent in the treatment of accidental ingestion or over-dosage involving norfloxacin, ofloxacin and ciprofloxacin is very poor.

Activated charcoal and bentonite will affect the pharmacokinetics of the fluoroquinolone anti bacterial agents because of strong binding. They should therefore not be concomitantly administered . However, because of weak adsorption of the fluoroquinolones on kaolin, kaolin will not alter the pharmacokinetics of the fluoroquinolones. Concomitant administration may not have too much adverse effects.

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