DIFFUSION OF ASPIRIN-(ACETYLSALICYLIC ACID) BASED DRUGSIN SODIUM HYDROXIDE SOLUTION AT 25°C

BY

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DECLARATION

Declaration by the student

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DEDICATION

This work is dedicated to my parents, Dr and Mrs.Anditi; my siblings Stephen, Duncan Shellin and Godwin for their love, understanding and support during this study. Special dedication goes to my uncle the late Peter OngoroAnditi. I love you all.

ABSTRACT

Diffusion is a macroscopic motion of components of a system that arises from concentration difference and plays a vital role in drug migration in the bodygoverned by Fickian diffusion laws. This project considers effective mechanism leading to effective diffusion coefficient. The diffusion coefficient of aspirin based drugs was studied in basic NaOH of concentration range 0.01M to 0.1M and a relatively more concentrated set ranging from 0.1M to 1.0M were studied at 25^{o}C. The study looks into the rate of diffusion of coated and non-coated aspirin drugs in aqueous NaOH solution designated different letter heads A, B, C, D, and E. The objective of this work was to determine the diffusion coefficients of aspirin drugs at different concentrations range at 25^{o}C and to compare with those calculated from limiting ionic conductance at infinite dilution. The rate of diffusion was monitored by observing the boundary conditions of the indicator between the drug and solution. The problem statement is that there are various aspirin based drugs in the market and all have different amount of aspirin in them. The research sought to find out the rate of diffusion of the drugs and conclude if at all their values relate to their masses as per the diffusion law. In the study five (5) aspirin tablets collected from a local pharmacy in Eldoret town were used for the study. From the profile it was observed that as the time progressed the boundary increased fast for non-coated tablets compared to the coated ones. The boundary heights (x) at a time t and concentration are also recorded. The moving boundary method coefficients ranged from 2.780×10^{-6} cm^2 sec^{-1} to 6.995×10^{-6} cm^2 sec^{-1}, 2.196×10^{-6} cm^2 sec^{-1} to 6.092×10^{-6} cm^2 sec^{-1}, 2.138×10^{-7} cm^2 sec^{-1} to 6.576×10^{-7} cm^2 sec^{-1} , 3.241×10^{-10} cm^2 sec^{-1} to 1.617×10^{-10} cm^2 sec^{-1} and 1.378×10^{-10} cm^2 sec^{-1} to 2.172×10^{-10} cm^2 sec^{-1} for drugs aspirin A , B, C. D and E respectively. All the aspirin were found to give values according to Fickian mechanism. For the drug A (600mg) of aspirin the best value of diffusion coefficient of 6.995×10^{-6} cm^2 sec^{-1} at concentrated solution and 2.780×10^{-6} cm^2 sec^{-1} was observed at dilute range solutions while the values for coated drug E with 75 mg aspirin was found to be slightly lower. The fractional drug uptake is linear and independent of the sample of thickness when distance is plotted against time. A graph of x^2 against time was plotted which was used to calculate the diffusion coefficient. The experimental values of diffusion coefficient Do were in close agreement with the expected value from infinite dilution which was a general estimation of diffusion coefficients. Quantitative data was analysed using analysis of variance and chi-square statistical. Data was presented using table and graphs.The study found that the aspirin drug with the highest diffusion coefficient is drug A. In addition,conductometric technique was recommended to give more accurate results and similar method should be constituted with the use of other techniques such as TLC and spectrophotometric method for comparison purposes with the free diffusion and it is important for manufacturers to revalidate steps in the production process, for any critical control point in the production process leads to hydrolysis of aspirin.

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LIST OF ACRONYMS

Do	Diffusion Coefficient
EDTA	Ethylene DiamineTetra acetic Acid
FDA	Food and Drug Administration
FW	Formulae Weight
GMP	Good Manufacturing Practice
IUPAC	International Union of Science and Applied Chemistry
Ka	Dissociation Constant
Mol. wt	Molecular Weight
pH	Potential of Hydrogen
SPSS	Statistical Package for Social Science
TLC	Thin Layer Chromatography
UV	Ultra Violet
VIS	Visible Wavelength

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CHAPTER ONE

INTRODUCTION

1.1Background Information

Diffusion is a process by which substances are transferred from a region of high concentration to a region of low concentration through random molecular motion. It is a process that involves the existence of proportionality between the rate of flow across any cross section area A and concentration gradient expressed as that cross section. Awtry&Loscalzo, 2000) find diffusion to be a scientific term having roots in extremely broad range of disciplines. The concept subsumes the transport of entities as language, populations, genes and technology as well as heat, charge and atoms because of all this process involves a strong element ofrandomicity(Harned&Owen, 1958).

Diffusion in drug systems is described by Fick's second lawwhich in many cases can be analytically solved if experimental data as well as initial and boundary conditions are provided in order to yield an effective mass transfer coefficient. Inversely, when the value of this coefficient is known a mass transfer simulation can be performed and the distribution of concentration in time and space in the drug can be obtained by solving Fick's equation. Analytical solutions covering on varying specimen geometry are found in the most well-known book by (Crank, 1997).The so called effective diffusion coefficient has been used and misused in the drug literature, since drugs are characterised by complicated structure making the media involved and hence forth the mass transfer phenomena multiphase and multi component.

Consequently the general theory of diffusion must be diffusion process; the entropy is the only increase. In the most elemental spontaneous isothermal mixing, the volume energy and total mole numbers constant. It should not be surprising that the Gaussian

and error integral functions from probability play an important role in elemental diffusion theory. Basically solid liquid reactions are more complex than solid gas reactions and include a variety of technically important process such aselectrodeposition. When a solid reacts with a liquid the process involves the products forming a layer on solid surface or dissolving into the liquid phase(Kays, 2005) believed that the reaction products are partly or wholly soluble in the liquid phase, the liquid has access to the reacting solid and chemical reaction at the interface therefore becomes important in determining the kinetics.

The simplest solid-liquid reaction is the dissolution of a solid in a liquid. The rate of diffusion can be measured by a number of different methods by direct chemical analysis of samples at different distances after definite time intervals. The equations formally describing the diffusing migrations of atoms was proposed over a hundred years ago (Rinsema, 2004). No experimental data on diffusion was available then and Fick'sequation was written in conformity with molecular diffusion within liquids.

Fick's first law has the following form:

$$J = -D\frac{dC}{dX} \qquad (1.1)$$

Where ***J*** is called flux or diffusion flux or flow which is the rate of transfer per unit area of section (in kilograms per square meter per second), ***C*** is the concentration of diffusing substances (in grams per milliliter or grams per 100ml), and $x$is the space co-ordinate measured normal to the section and D is diffusion coefficient (in square centimeters per second). This is shown in equation 1.1, If ***J*** and *C* are both expressed in terms of the same unit of quantity, ***D*** is then independent of the unit and has dimensions length 2 times 1(Laidler&Meiser, 2006).

In Kenya as a result of trade liberalization and the boost in the local pharmaceutical manufacturing sector, people perceive the pharmaceutical market as a commodity market and an easy means of making profits. The general disregard to lay down rules of quality assurance and desire to reap huge financial profit and the motivating factors for quackery and faking makes it necessary for independent assessment of the quality of pharmaceutical products. Quality assurance is a wide ranging concept covering all matters that individually or collectively influence the quality of a product. Quality assurance incorporates good manufacturing practice (GMP), quality control as well as other factors including product design and development(Olaniyi, 2000) displays the purpose of quality assurance system is to ensure an absolute quality product such that each product tablet will contain the amount of active drug claimed on the label within the stated limit, as well as other essential parameters such as bioavailability of the product.

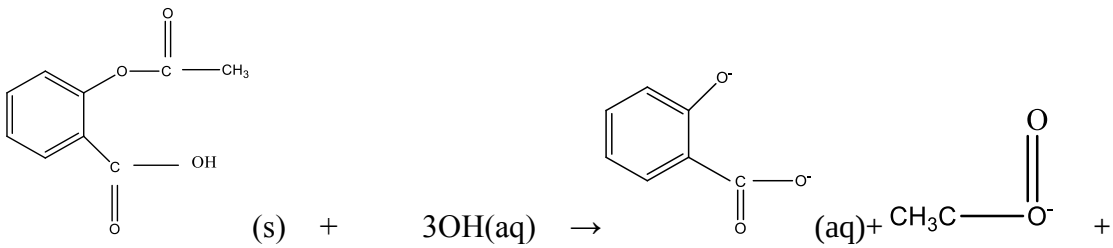
1.2Drug aspirin

Aspirin is a member of chemicals called salicylates.It is an extremely potent pyretic and anti-inflammatory agent in several species(Thun*et al.,* 2006).These chemicals have been known to people in medicine for centuries. Since its market introduction in 1899 under the trademark Aspirin®, acetylsalicylic acid has attained a leading worldwide position in the non-prescription treatment of pain, inflammation, and fever. It has proven effective as a general pain reliever, and it is routinely used in a wide range of painful conditions, including head, body and muscle aches, arthritis and many other common ailments (Rowland & Riegelman, 2007).

Today, aspirin is also taken by millions of people who benefit from its antithrombotic effect. Patients with a history of cardiovascular disease or stroke benefit from the lifesaving blood thinning properties of acetylsalicylic acid. The medical community

has increasingly recommended routine therapy with low-dose acetylsalicylic acid, which significantly reduces the risk of death from a cardiovascular event (Franeta*et al.,* 2002).

The aspirin content of commercial tablets is routinely determined using the acid/base titration method.Acetylsalicylic acid is readily hydrolysed in basic medium to yield the salicylate dianion(Reynolds,2005) according to the equation.



Aspirin salicylate dianion

One of the first and most influential physicians 'Hippocrates' wrote about the bitter powder extracted from willow back that could ease aches and pains and reduce fevers in 15th century BC (Moysich*et al.,* 2002).Figure1.1 shows salicylic acid.

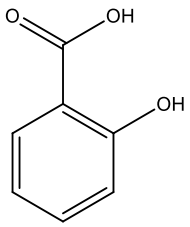


Figure 1.1: Salicylic acid (2- Hydroxybenzoic acid)

Table1.1 shows the types of drugs containing aspirin and other pain relieving components that were investigated in this work study.

Table 1.1: Types of drugs

Drug	Aspirin	Paracetamol	Caffeine
A	600	300	50
B	400	200	50
C	300	200	50
D	75		
E	100		

Aspirin is one of the most common over the counter medicines in the world (Rinsema, 2004). In fact since its industrial production by Bayer company in 1899 it has dominated the market of inexpensive pain killers. The story of the development of aspirin at Bayer is well known and has been told over and over again (Gennaro, 2003).

1.3 Profile of active ingredients of sample

1.3.1 Aspirin

Aspirin is a white crystalline, powder or colourless crystal, with a melting point at about 12°C. It has a dissociation constant Ka 3.5 (25^{o}C).Aspirin has a solubility of 3.3 g/dm^3 of water, 142.9 g/dm^3 of acetone, 50.0 g/dm^3 of ether and 58.8g/dm^3 of chloroform (Vane *et al.,* 2007).Figure1.2 shows the structure of aspirin.

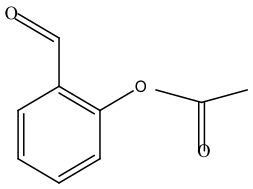


Figure 1.2: Aspirin

1.3.2 Paracetamol

This is the second essential constituent of the drug. Figure1.3 shows the structure of paracetamol.

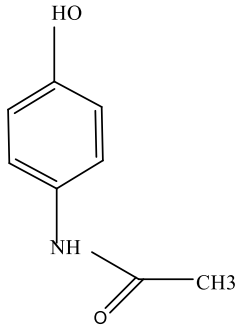


Figure 1.3: The structure of Paracetamol

Paracetamol is a white crystalline powder with a melting range 168-172^{o}C. Paracetamol is very soluble in chloroform and practically insoluble in either. In acidic aqueous medium, it dissipates a minimum UV absorption at 245nm. However in alkaline aqueous medium there is a maximum UV absorption dissociation constant ofKa 9.5 at 25^{o}C (Cussler, (1997).

1.3.3 Caffeine

Figure1.4 shows the structure of caffeine.

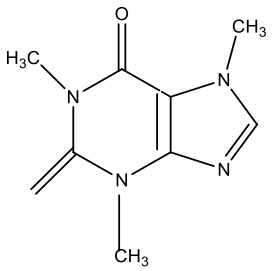


Figure 1.4: Structure of Caffeine

Caffeine is a white crystalline powder or silky white crystals sublimes readily sparingly soluble in water, freely soluble in boiling water and slightly soluble in ethanol. It dissociates in concentrated solutions of alkali benzoates or salicylates (Mirgiardi*et al.*, 2002).At room temperature it is odourless, slightly bitter, and sublimes at 178ºC. According to(Gennaro, 2003)caffeine has melting point range of 235°C-239°C.

1.3 Statement of the problem

Drug aspirin is defined by the Food and Drug Administration (FDA) as a derivative of salicylic acid. Compounds of salicylic acid are found in some plants, notably white willow and meadowsweet. The use of aspirin has become more prominent in recent years, due to the increased production. Aspirin is used as pain killer, fever reliever and for rheumatic conditions. However, consumers and scientists across the globe have raised questions about the necessity and safety and effectiveness and efficiency of the drug. It is important to realize, that drug aspirin are extensively investigated and carefully regulated by various regulating bodies and various international organizations to ensure that they are effective and not substandard. Additionally, aspirin based drugs are labelled by law so as, in theory at least, to enable the consumer to avoid their consumption in case they experience any diverse effects. However, the specific diffusion coefficients of each drug based aspirin should be known.

1.4 Objectives

1.4.1 General Objective

The main objective was todetermine the diffusion coefficients of aspirin drugs in sodium hydroxide solutions of different concentration range at 25^0C.

1.4.2 Specific Objectives

1. To compare the experimental diffusion coefficients in relation with those calculated from conductance at infinite dilution.
2. To compare the concentration with the diffusion coefficient.
3. To compare the diffusion coefficient between the coated and non coated aspirin.

1.5 Justification

Drug aspirin plays a vital role in human body and must only be used in limited quantities. However; the effective rates of diffusion and efficiency of these drugs remain a concern to both consumer and the regulatory federal authorities and international organizations. Though the intake of drug is basically a diffusion process less research has been done to specify the rates of diffusion.

This research seeks to use moving indicator method to obtain boundary heights and their respective diffusion coefficients from subsequent graphical plots which would be used as reference data, and since it is easier to thermostat to that temperature the correlation to conductances can be extrapolated to 36-37^{o}C. According to Harned& Owen, 1958, transport phenomena of drugs and other important biological materials are a significant link between the processing of these materials and the quality and safety of the products. The diffusion coefficient obtained from the research will form a set of data base for reference and would be an alternative method for laboratories not equipped with expensive materials in the aim to preserve security of the consumers, especially in the developing countries.

1.6 Scope of Study

The chemical scope of study was limited to five drugs containing aspirin in different amounts whereby each was designated a letter representing their company of manufacture. The concentration range was carried out at 25^{0}C.Ideally this study could be conducted at various temperatures but time and financial constraints dictated a single case study. The decision to use aspirin could limit its generalizability but it should be useful for exemplification.

CHAPTER TWO

LITERATURE REVIEW

2.1 Diffusion Coefficient

There is an evidence of diffusion coefficients being essential to the order of predictive problem, which further justifies the devotion of this section of research,(Kirkaldy& Young, 2005). It summarizes that material would be found in monographs of diffusion in solutions.

One of the departures from this primary research is to place particular emphasis on the application and useful initial boundary value problems from a wide range of disciplines. The mathematics of diffusion by (Crank, 1997) gives essential reference works in developing and extending practical application.

(Meyerink& Friedlander,2004) provide a review on experimental data for mass transfer rate of substance which dissolves from the wall of a pipe into water or aqueous solution of sodium hydroxide in fully developed turbulent flow. Data for aspirin in fully developed case without chemical reactions is also recorded.

(Florence&Rowland, 2002) reviewed four single crystals of aspirin of varied weight where order of release, dilution rate constant, diffusion coefficient and time were investigated. It offers results on diffusion coefficient and indicates Fickian diffusion model being displayed by single microcapsules.

A comprehensive examination on diffusion of aspirin was presented by(Lee & Kim, 2007) through a membrane whereby the permeation salicylic acid in chitosan device was determined in glass diffusion cell with two compartments of equal volume. Drug release studies were conducted in a beaker containing sodium hydroxide solution. The results provided diffusion coefficients and proved that diffusion was through pores. According to Broadhurst,*et al.*,2008dispersion time and the region of dispersion were

sampled on aspirin tablets in water whereby they suggested tablets dispersed for five minutes and stirred to reduce overdosing.

Kituyi & Irina, 1993 investigated the diffusion coefficients of calcium chloride and Zinc Sulphate in aqueous EDTA at 25^0C whereby the rate of diffusion was monitored by observing the boundary conditions. They investigated the rate of diffusion and compared the diffusion coefficient with those of calculated limiting conductance.

Finally (Bouhsain*et al.*,2006) expounded on a simple, rapid, economical, precise and accurate method for spectrophotometric simultaneous determination of aspirin in combined dosage forms, by first order derivative spectroscopy and area under a curve where by the analysis of authentic samples containing aspirin showed no interference from common additives and excipients and was easily adopted for routine quality control analysis.

Diffusion is a macroscopic motion of components of a system that arises from concentration difference. It is a process that involves the existence of proportionality between the rate of flow across any cross-section with a unit area and concentration gradient expressed in the equation (Kays, 2005).

$\frac{dc}{dx}$ at that cross section where

dc –change in concentration, dx – change in cross-section

(Harris, 2008) denotes that if solutions of different concentrations are brought into contact with each other the solute molecules tend to flow from regions of higher concentration to regions of lower concentration and there is ultimately an equalization of concentration.

Between the time when a drug is administered and when it’s eliminated from the body, it must diffuse through a variety of membranes that act primarily as lipid live barriers. A major criterion in evaluation of the ability of a drug to penetrate these lipid

membranes is its diffusion coefficient. An activity of a drug is a function of its ability to cross membranes, and interact with the receptor. As a first approximation, the more effectively a drug crosses the membranes the greatest its activity. There is also optimum diffusion coefficient for a drug in which it most affectively permeates and thus shows greatest activity. The values of diffusion coefficient below the optimum diffusion result in decreased lipid solubility, and the drug will remain localized in the first aqueous phase it contracts. The values larger than the optimum result in poorer aqueous solubility but enhanced lipid solubility, and the drug will not partition out of lipid membrane hence it gets in. Drugs with a diffusion coefficient higher or lower than the optimum are in general poorer candidates for formulation into extended release dosage forms. The experimental uncertainty for aspirin drugs in the diffusion coefficient is approximately $\pm$ 1 x 10^{-9} cm^2s^{-1} (Rinsema, 2004).

2.1.1The Measurement of diffusion coefficient

Diffusion coefficient is the amount of solute that diffuses across a unit area in one second under the influence of unit concentration gradient. The solutions of diffusion equation are useful for experimental determination of diffusion coefficients (Crank, 1997).

In the capillary tube open at one end and containing solutions immersed in a well stirred larger quantity of solvent and the change of concentration in the tube is monitored, the solute diffuses from the open end of the capillary at a rate that can be calculated by solving the diffusion equation with the appropriate boundary conditions so D may be determined. Several methods are used to calculate diffusion coefficient.

It involves the following techniques:-

2.1.1.1 The capillarity technique

A capillary tube, open at one end and containing a solution is immersed in a well stirred larger quantity of solvent and change of concentration in the tube is monitored. The solution diffuses from the open end of the capillarity at a rate that can be calculated by solving the diffusion equation with appropriate boundary conditions, so D may be determined (Harned& Owen, 1958).

2.1.1.2 Diaphragm technique

In the technique, the diffusion occurs through the capillary pores of a solute and solvent whose concentrations are monitored and then related to the solutions of the diffusion equation corresponding to this arrangement (Kidson & Kirkaldy 2005).

2.1.1.3 Special laser scattering technique

A dynamic light scattering can be used to investigate the diffusion of polymers in solutions. Consider two polymer molecules being irradiated by a lesser beam. Suppose that a time t the scattered waves from these particles interfere constructively at the detector leading to a larger signal. However, as the molecule move through the solution the scattered waves may interfere destructively at another time t and result in no signal. When this behaviour is extended to a very large number of molecules in solutions, it results in fluctuation in light intensity that depends on the diffusion coefficient D which is a measure of the rate of molecular motion (Jost, 1960).

2.1.1.4 Free diffusion methods

In this method one may use the electrophoresis apparatus, the analytical ultracentrifuge or a special diffusion apparatus. A sharp line is formed between a solution containing macromolecules and a zone of solvent either by glass particles or by sedimentation. As centrifuging is continued at low speed, the solute is permitted to

diffuse across the present plane at constant temperature in a vibration free system (Laidler&Meiser 2006).

2.1.1.5 The Statistical view of diffusion

An intuitive picture of diffusion is the particles moving in a series of small steps and gradually migrating from their original position. This idea is explored using a model in which the particles can jump through a distance λ in a time T, the total distance travelled by a particle t is therefore tλ/T. However, the particles will not necessarily be found at that distance from the original. The direction of each step may be different and the let distance travelled must take the charging direction into account, if the discussion is simplified by allowing the particles to travel only along a straight line (the x-axis) and for each step (to the left or right) to be through the same distance λ, then one dimensional random walk is obtained in (Laidler & Meiser, 2006).

2.2 Fick's laws of diffusion

The German physiologist Adolf Eugen Fick (1829-1901) formulated in 1855 two fundamental laws of diffusion.

2.2.1 Fick's first law

The rate of diffusion dr/dt of a solute across an area A known as the diffusion flux and given the symbol $\boldsymbol{J}$ whereby;

$$\boldsymbol{J} = -\boldsymbol{D}\frac{\boldsymbol{dC}}{\boldsymbol{dX}} \textit{(2.1)}$$

Where $\boldsymbol{J}$ is called flux or diffusion flux or flow which is the rate of transfer per unit area of section (in kilograms per square meter per second), $\boldsymbol{C}$ is the concentration of diffusing substances (in grams per millilitre or grams per 100ml), and $x$is the space co-ordinate measured normal to the section and D is diffusion coefficient (in square

centimeters per second). This is shown in equation 2.1. If ***J*** and *C* are both expressed in terms of the same unit of quantity, ***D*** is then independent of the unit and has dimensions length 2 times 1. (Kidson&Kirkaldy, 2005).

2.2.2 Fick's second law

Fick's second law relates the rate of change of composition with time to the curvature of the concentration profile: Concentration increases with time in those parts of the curvature and decreases where curvature is negative. as given by (Jost, 1960).

$$c = \frac{c_o}{2(\pi D_t \, t)^{1/2}} \exp\left(-\frac{x^2}{4D_t t}\right) \qquad (2.2)$$

This is Ficks second law if D is constant.

Some of the diffusing substances is immobilized if it reacts in the diffusion medium. In the simplest cases, the concentration of the immobilized substances S, would be directly proportional to the concentration C of the substances that is free to diffuse (Crank, 1997) hence

$$S = RC \qquad (2.3)$$

A chemical reaction that would slow down the diffusion process implies that the overall diffusion would be slower than the simple diffusion. This study describes the diffusion of commercial aspirin in sodium hydroxide solution at 25^{o}C at various concentrations.

The rates of diffusions were monitored using methyl orange indicator.

2.3 Diffusion and Conductivity-Nernst-Einstein Equation

The binary diffusion coefficient of the electrolyte, D, can be expressed in terms of the diffusion coefficients of the ionic species (Glasstone*et al.,* 2006).The diffusion

coefficient for a salt, $\mathbf{D_{salt}}$ may be calculated from the $\mathbf{D_+}$ and $\mathbf{D_-}$ values of the constituent ions by the relation

$$\boldsymbol{D_{salt} = \frac{(z_+ + |z_-|)D_+ D_-}{z_+ D_+ + |z_-| D_-}} \qquad \textbf{(2.4)}$$

The diffusion coefficient is concentration dependent and at infinite dilution its value is the tracer diffusion coefficient D^o. For solutions of simple, pure electrolytes (one positive and one negative ionic species) such as NaCl, equivalent ionic conductivity $\boldsymbol{\Lambda^\circ}$ which is the molar conductivity per unit concentration of charge, is defined as

$$\boldsymbol{\Lambda^\circ = \lambda_+ + \lambda_-} \qquad \textbf{(2.5)}$$

Where $\boldsymbol{\lambda_+}$and$\boldsymbol{\lambda_-}$are equivalent ionic conductivities of the cation and anion. The more general formula is

$$\boldsymbol{\Lambda^\circ = \nu_+ \lambda_+ + \nu_- \lambda_-} \qquad \textbf{(2.6)}$$

Where $\mathbf{\nu_+}$ and $\mathbf{\nu_-}$ refer to the number of moles of cations and anions which one mole of electrolyte gives a rise in the solution.

In electrolytic solutions, salts dissociate and diffuse as ions and molecules depending on the degree of dissociation. The theory of salt diffusion is elaborated mainly for dilute solutions in which the degree of dissociation is close to one. Thus, the diffusion coefficient for a simple salt that is infinitely diluted can be found using the *Nernst-Heckell equation:*

$$\boldsymbol{D_{AB} = \frac{RT}{Fa^2} \frac{1/n_+ + 1/n_-}{1/\lambda_+^{\,0} 1/\lambda_-^{\,0}}} \qquad \textit{(2.7)}$$

where D_{AB} is the diffusion coefficient, defined as the proportionality factor between the molecular flow of dissolved salt and the gradient of its molecular concentration, cm^2/s; T, the temperature, K; Fa, the Faraday number, n_+ and n_-, the cation and anion

valences; λ_+^0 and λ_-^0, the limit (under an infinite dilution) ionic conductions of cation and anion, cm^2/Ω mol (Kidson&Kirkaldy, 2005).

The diffusion coefficient for a strong electrolyte at infinite dilution is calculated by the formula (Kays, 2005)

$$D_o = \frac{8.936\times10^{-10}T(\gamma_1+\gamma_2)\lambda^\circ_1\lambda^\circ_2}{\gamma_1 z_1(\lambda_1+\lambda_2)} \quad (2.8)$$

Where T is the absolute temperature, γ_1 and γ_2 are the number of the cations and the anions from the dissolution of one molecule of the electrolyte, z_1 is the cationic charge and λ_1 and λ_2 is the equivalent cationic and anion limiting conductance (Singleton, 2006).

2.4 Diffusion as a time dependent process

Fick's law and its analogues for the transport of other physical properties rate to the flux under the influence of gradients they therefore describe time independent processes. In time dependent diffusion process some distribution of concentration of temperature is established at some moment and then allowed to disperse without replacement for example when a metal bar is heated rapidly at one end and the thermal energy is conducted through the bar or when a layer of solute is spread on the surface of a solvent and the concentration in the solution changes as it dissolves. In order to treat a time dependent diffusion of matter the arguments are easily modified to apply to other properties (Harris, 2008).

2.5 Diffusion in solution

The more soluble a drug is, the more quickly it passes from the digestive system into the bloodstream after being swallowed. Aspirin is a weak acid and methyl orange

indicator was found to be a suitable indicator. The solute spontaneously diffuses from a region of high concentration to one of low concentration. Chemically speaking the driving force of diffusion is the gradient of potential, but it is more usual to think of the diffusion of solutes in terms of gradient of their concentration. Although no individual solute particle in a particular volume shows a preference for motion in a particular direction, a definite fraction of molecules may be considered to be moving in any particular direction. This is governed by Fick's law.

2.6Diffusion and the human body

The dependence of life processes on diffusion mechanisms could not be more prevalent. Diffusion occurs throughout the human body, and without it, cells and body tissue could not get important nutrients for survival, the eyes would dry out, and many medicines could not be absorbed into the body (Harris, 2008).

From severe illness to a common headache, medicines are universally used to alleviate pain or cure sickness around the world. For medicines taken orally as pills, the medicine must somehow find its way into the bloodstream. Once in the stomach, if the pill capsule is a time release mechanism, the medicine must first diffuse out of the capsule. Once in the stomach, the medicine from the pill is absorbed into the lining of the stomach and then into the bloodstream, both processes involve diffusion(Watson, 2009).

2.7 Rates of diffusion

A number of diffusion projects lead to information about the size and shape of macromolecules in solution. The first of these will be considered in the diffusion of macromolecules across a well-defined boundary in a solvent. In such discussions the issue of diffusion coefficient comes into play as it is a measure of the rate with which

a material diffuses across a unit cross section area as a result of a unit concentration gradient. The relation of aqueous phase reaction process to diffusion can be recognized by first focusing on a particular molecule A and asking about the rate with which B molecules would diffuse to it. The diffusion coefficient is characteristic, therefore for the given solvent at a given temperature of diffusing tendency of the solute in solution (Miller *et al.,* 2002).

2.8 Molecular Size and diffusivity

A drug must diffuse through a variety of biological membranes during its time course in the body. In addition to diffusion through these biological membranes drugs in many extended release systems must diffuse through a rate controlling matrix. The ability of a drug to diffuse is called diffusivity(Watson, 2009).

Diffusion coefficient, D is a function of its molecular size (or molecular weight). The value of diffusion is related to the size and shape of drugs. Generally values of diffusion coefficient for intermediate molecular weight 150-400mg through flexible aqueous solutions range from 10^{-6} to 10^{-9} cm^2 $sec^{-1}$with a value of order 10^{-8} being most common. A value of order 10^{-6} is typical for drugs through water as the medium. For drugs with molecular weight greater than 500mg, their diffusion coefficients in many polymers are frequently so small that they are difficult to quantify, that is less than 10^{-12} cm^2sec^{-1}. Thus the higher the molecular weight drugs should be expected to display very slow release kinetic in extended release devices using diffusion through aqueous solution as releasing mechanism (Gennaro, 2003).

The diffusion coefficient is a very important application of chemical and equipment design involving mass transfer process. However, there is limited experimental data of commercial aspirin diffusion coefficients in the literature. Therefore, the reserarch

investigation correlating experimental data and development of a prediction model are of practical and theoretical significance (Rahme*et al.,* 2005).

2.9 Variation of mass transfer coefficient during diffusion process

The variation of mass transfer coefficients is experimental essential for commercial aspirin. The studies were made in the same conditions with those presented by the previous determinations(Bockris& Reddy, 2003).

These were represented by a plot of square distance vs. the time and the diffusion coefficient calculated. The values of these coefficients as well as tablets surface area as a result of their mass decrease through diffusion process (Watson, 2009).

There was gradual increase of the mass transfer coefficients during the diffusion process. That was explained by decreasing of aspirin amounts, which leads to change of the limit layer thickness (Singleton, 2006).

2.10 Concentration and volume

Fick's law states that diffusion moves in one direction (Vane, 2007). The clearance or absorption rate of a diffusing molecule is directly linked to area, A of the solution exposed to the absorbing membrane, the diffusion coefficient, and the concentration gradient or the difference between the drug concentration at the injection site and its concentration in the blood flowing past the injection site. A drug concentration in blood is usually assumed to be a very small component to that at the injection site because of drug dilution in the fluids of distribution, metabolism and excretion. The amount absorbed per unit area would be greater for the more concentrated solution. Investigation has shown the influence of both factors, volume and concentration on the other hand when volume was held constant and concentration varied the solution having lower concentration (Thun *et al.,* 2006).

CHAPTER THREE

MATERIALS AND METHODOLOGY

3.1 Reagents and chemicals

Commercial aspirin and sodium hydroxide were purchased from local pharmacy and Sigma-Aldrich respectively. Methyl orange was supplied by Kobian scientific. All the reagents were of analytical grade and were used without further purification. Double distilled and deionized water was used in preparing solutions.

3.2 Apparatus

Weighing measurements were carried out using analytical weighing balance (MRC Laboratory equipment manufacturers, Israel) and plastic disposable cuvettes with cross $1cm^2$ and 4.5ml capacitysection. The pH values were determined using pH 211-Microprocessor pH meter (HANNA Instruments, Mauritius).

3.3 Experimental procedures

3.3.1Diffusion

Two concentration sets of0.01 to 1.0M NaOH were prepared; dilute and concentrated. To each sample two drops of methyl orange was added and the solution mixed in a disposable plastic cuvettes of cross section $1cm^2$ by4.5mlcapacity, mixed and allowed to stand for over night while closed using a fitted stopper at 25˚C so as to attain thermal and mechanical equilibrium. The procedure was repeated with different concentrations of NaOH upto1.0M.

Accurately weighed masses of commercial aspirin tabletweredropped into each of the cuvettes and time recorded at different intervals where boundary height between the alkaline and acidic parts of solutions formed.

3.4 Preparation of standard solutions

A stock solution of 1.0M NaOH was prepared by dissolving 0.4g in 1litre of double distilled water. Concentrations (0.01-0.9M) were made by suitable dilution of the stock solution. All solutions were left to stand for ten minutes and incubated at 25˚C. Fresh solutions were prepared for each set of experiments.

3.5Research design

The research was carried out in a classical experimental design which focused on two variables: the independent variable (they cause intervention) and dependent variables (outcome). The purpose to the design was to remove influence of other variables so that the effect of other interventions can be seen clearly,(Singleton, 2006). The study considered boundary height as dependent variables, temperature, pH and time as independent variables, solubility of drug aspirin as intervening variables.

Pre-test and post-test measurements ofboundary height were carried out at the start and at the end (at infinity),respectively. However, the experimental procedures were conducted in thermal equilibrium conditions and methyl orange indicator was carefully dropped for each aspirin mixture at 25˚C. Diffusion coefficients were determined using linear regression plots of dependent variables against time.

3.6 Data collection and statistical analysis

The data collected from the laboratory where the research was carried out, were analyzed by plotting scatter graphs and managed using the Microsoft Excel. Descriptive statistics including frequency tables was used to analyse the data obtained. They have a considerable advantage over complex statistics since they are easily understood (Bell & Rhodes, 2005). Kerlinger, 2008 also holds that the most widely used and understood standard proportion is the percentage.

CHAPTER FOUR

RESULTS AND DISCUSSION

4.1 RESULTS

4.2 Experiment with sodium hydroxide solution from 0.01M to 0.1M

The typical data from a run using sodium hydroxide after an initial period of about one hour showed the rate of rising of the hydroxide was proportional to time and was dependent on the concentration of the bases and the weight of the commercial aspirin tablet. When the square of the height of the boundaries were plotted against time, straight lines passing near the origin were obtained whose slopes were found to be dependent on the base concentrations.

The rates of diffusion of aspirin in sodium hydroxide solutions increased with increased concentration of the basicsolution, a relationship that agreed with expectations of diffusion with chemical reactions (Kays, 2005).

The results also agree with the square root relationship for the diffusions into a semi-infinite medium involving the dimensionless parameter by (Crank,1997), in two aspects;

1. The distance obtained by any given concentration was proportional to the square root of the time.
2. The time needed for any point to reach a given concentration was proportional to the square of its distance from the surface where the diffusion occured.

4.3 Experiments with sodium hydroxide solution from 0.1M to 1.0M

The results of the basic solutions with concentration between 0.1M and 1.0M may be classified into three groups.

1. 0.1-0.4 M: acid had quantities of aspirin that were higher than those of the base into the solutions therefore the aspirin diffused to the meniscus.
2. 0.5 M base is in a class of its own: this type of behavior observed when the number of moles of moles of aspirin is equal (or almost equal) to those of moles of OH^- in the basic solutions of the steady state at which the boundary remains at the some positions for a long time. The interval indicates a situation where the rate of diffusion of the aspirin is exactly counter balanced by the rate of diffusion of the base.
3. 0.6M - 1.0M base: the amounts of base in such solutions usually exceed the quantity of acid in the tablet. Hence initially the acid diffuses into the base to a

height that depends on the concentration of the base, after which the tablet begins to diffuse into the alkali.

When the squares of the boundaries were plotted against time, straight lines passing near the origin were obtained as shown in appendix 1 to appendix 8**.**

The experimental conditions are for an amount of diffusing substance deposited at the time t=0 in the plane x=0 approximating to those of a reflection boundary (Bockris & Reddy, 2003).This is reported by experimental conditions are expressed as ;

$$\frac{n}{n_{total}} = \frac{1}{(\pi Dt)^{1/2}} e - x^2/4Dt \qquad (4.1)$$

Where n is the number of ions at a distance x at a time t and n_{total} is the total number of ions placed in the plane x = 0 at the time t = 0.In the present work, n and n_{total} are

constant. Therefore the plot of$x^2$with t gives a straight line whose slope equals -4D', where D' is the diffusion coefficient at a given acid concentration. Hence:

$$\boldsymbol{D = \frac{slope}{4}} \qquad (4.2)$$

Using equation 4.2 the D_o values for acid concentrations are as shown in table 4.1. The correlation coefficients for the graphs were between 0.990 and 0.997.

The plots of boundary height squared against time for the drug of concentration ranging from 0.01 to 0.1 for the aspirin drug A to E are shown from the data obtained from tables 4.1 to 4.8

Table 4.1: Data of drug A in NaOH between 0.1 M and 0.9 M

Molarity of NaOH	**0.1**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**
Time in Minutes	Boundary Height in cm^2								
100	1.13	1.1	0.91	0.72	0.67	0.65	0.63	0.62	0.62
200	1.81	1.52	1.41	1.27	1.11	1.05	1	0.98	0.9
300	2.62	2.47	1.92	1.82	1.54	1.32	1.27	1.23	1.2
400	3.27	2.74	2.43	2.24	1.83	1.53	1.47	1.35	1.31
480	3.54	3.37	2.61	2.53	2.32	2.11	2.1	2	1.98

Table 4.2: Data of drug A in NaOH between 0.01 M and 0.1 M

Molarity of NaOH	**0.01**	**0.02**	**0.03**	**0.04**	**0.05**	**0.06**	**0.07**	**0.08**	**0.09**	**0.1**
Time in Minutes	Heights of Boundaries in cm^2									
100	0.82	0.74	0.68	0.42	0.38	0.35	0.32	0.32	0.3	0.3
200	1.52	1.23	0.86	0.54	0.42	0.38	0.35	0.33	0.32	0.3
300	2.25	1.5	1.27	0.64	0.48	0.45	0.41	0.39	0.38	0.35
400	2.44	1.87	1.46	1.23	0.98	0.62	0.58	0.53	0.49	0.45
420	2.83	1.48	1.52	1.48	1.23	1	0.98	0.95	0.9	0.82

Table 4.3: Data of drug B in NaOH between 0.1 M and 1.0 M.

Molarity of NaOH	**0.1**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**
Time in Mins.	Heights of Boundaries in cm^2									
0	0.53	0.5	0.42	0.38	0.35	0.32	0.3	0.3	0.3	0.3
100	0.82	0.68	0.58	0.48	0.42	0.4	0.36	0.34	0.32	0.3
200	1.35	1.23	1.1	0.98	0.85	0.78	0.7	0.62	0.53	0.5
300	2	1.78	1.57	1.45	1.36	1.28	1.18	1.11	1	0.82
400	2.48	2.3	2.19	2.11	2.05	2	1.92	1.72	1.68	1.32
420	2.5	2.45	2.32	2.27	2.15	2.12	2	1.91	1.82	1.62

Table 4.4: Data of drug B in NaOH between 0.01 M and 0.1 M

Molarity of NaOH	**0.01**	**0.02**	**0.03**	**0.04**	**0.05**	**0.06**	**0.07**	**0.08**	**0.09**	**0.1**
Time in Minutes	Boundary Height in cm^2									
100	1.47	1.45	1.43	1.4	1.36	1.34	1.34	1.32	1.3	1.3
200	2.3	2.15	2.11	2	1.89	1.76	1.64	1.54	1.5	1.45
300	3	2.87	2.72	2.61	2.57	2.47	2.38	2.28	2.2	2.15
400	3.82	3.57	3.35	3.28	3.16	3	2.86	2.74	2.68	2.6
420	4	3.72	3.65	3.58	3.47	3.38	3.28	3.17	3.1	3.03

Table 4.5: Data of drug C in NaOH between 0.1 M and 1.0 M.

Molarity of NaOH	**0.1**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1**
Time in Minutes	Boundary Height in cm^2									
100	0.48	0.45	0.44	0.42	0.4	0.38	0.3	0.3	0.3	0.3
200	0.91	0.72	0.65	0.54	0.47	0.4	0.35	0.33	0.31	0.31
300	1.37	1.28	1.15	1.1	1	0.86	0.78	0.65	0.58	0.55
400	1.72	1.62	1.56	1.46	1.4	1.28	1.2	1.15	1.1	1
480	1.92	1.88	1.78	1.68	1.54	1.5	1.46	1.35	1.29	1.19

Table 4.6: Data of drug C in NaOH between 0.1 M and 1.0 M.

Molarity of NaOH	**0.1**	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1.0**
Time in Minutes	Boundary Height in cm^2									
100	0.82	0.74	0.68	0.42	0.38	0.35	0.32	0.32	0.3	0.3
200	1.52	1.23	0.86	0.54	0.42	0.38	0.35	0.33	0.32	0.3
300	2.25	1.5	1.27	0.64	0.48	0.45	0.41	0.39	0.38	0.35
400	2.44	1.87	1.46	1.23	0.98	0.62	0.58	0.53	0.49	0.45
420	2.83	1.48	1.52	1.48	1.23	1	0.98	0.95	0.9	0.82

Table 4.7: Data of drug D in NaOH between 0.01 M and 0.1 M.

Molarity of NaOH	**0.01**	**0.02**	**0.03**	**0.04**	**0.05**	**0.06**	**0.07**	**0.08**	**0.09**	**0.1**
Time in Minutes	Boundary Height in cm^2									
100	0.1	0.1	0.1	0.1	10	0.1	0.09	0.09	0.09	0.09
200	0.24	0.2	0.18	0.15	0.13	0.12	0.1	0.1	0.1	0.1

Table 4.8: Data of drug E in NaOH between 0.01 M and 0.1 M.

Molarity of NaOH	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.1
Time in Minutes	Boundary Height in cm^2									
100	0.32	0.3	0.3	0.28	0.27	0.25	0.2	0.2	0.19	0.19
200	0.54	0.46	0.38	0.32	0.3	0.28	0.24	0.2	0.2	0.2
300	0.71	0.68	0.48	0.42	0.4	0.33	0.3	0.28	0.25	0.23
400	1	0.86	0.76	0.64	0.58	0.42	0.39	0.34	0.3	0.27
480	1.98	1.56	1.37	1.26	1.15	1.1	1	0.87	0.78	0.58

The calculated D values from the plot of x^2 with time for each aspirin drug with respective base concentrations are given in Tables 4.9 to Table 4.19 by multiplying the D_o values by the square roots of the base concentrations. The results of the data analysis both from laboratory were presented in frequency tables and scatter graphs.

Table 4.9: Data of basic concentrations and diffusion coefficient for drug A (0.01 M to 0.1 M).

Mass (grams)	Concentration	Slope V $\times 10^{-4}$	D $\times 10^{-5}$ [D']	Square roots	D' x square root $[OH^-]$ Do$\times 10^{-6}$
1.120	0.01	9.42	0.75	√0.01	7.50
1.121	0.02	6.50	5.17	√0.02	7.31
1.120	0.03	5.46	4.36	√0.03	7.55
1.122	0.04	4.90	3.91	√0.04	7.82
1.120	0.05	4.39	3.52	√0.05	7.88
1.121	0.06	3.54	2.84	√0.06	6.98
1.121	0.07	3.05	2.42	√0.07	6.42
1.120	0.08	2.80	2.23	√0.08	6.30
1.122	0.09	2.57	2.05	√0.09	6.14
1.122	0.10	2.40	1.91	√0.10	6.05
					Total D_o value 69.95×10^{-6} cm^2sec^{-1}

Average D_o value 6.995×10^{-6} cm^2sec^{-1}

Table 4.10: Data of basic concentrations and diffusion coefficient for drug A (0.1 to 1 M).

Mass (grams)	Concentration	Slope V ×10 $^{-5}$	D × 10 $^{-6}$ [D']	Square roots	D' x square root [OH$^-$] Do×10 $^{-6}$
1.120	0.1	7.19	5.72	√0.1	1.81
1.121	0.2	5.91	4.69	√0.2	2.10
1.120	0.3	5.53	4.40	√0.3	2.41
1.122	0.4	5.18	4.14	√0.4	2.62
1.120	0.5	4.87	3.87	√0.5	2.72
1.121	0.6	4.68	3.74	√0.6	2.90
1.121	0.7	4.46	3.56	√0.7	2.98
1.120	0.8	4.58	3.64	√0.8	3.26
1.122	0.9	4.62	3.67	√0.9	3.48
1.122	1.0	4.40	3.52	√1.0	3.52

Total D_o value 27.80×10^{-6} cm^2sec^{-1}

Average D_o value of 2.780×10^{-6} cm^2sec^{-1}

Table 4.11: Data of basic concentrations and diffusion coefficient for drug B (0.01 to 0.1 M).

Mass (grams)	Concentration	Slope V ×10 $^{-4}$	D × 10 $^{-5}$ [D']	Square roots	D' x square root [OH$^-$] Do×10 $^{-6}$
0.701	0.01	8.59	6.84	√0.01	6.84
0.699	0.02	6.03	4.79	√0.02	6.77
0.711	0.03	4.74	3.76	√0.03	6.52
0.701	0.04	4.05	3.22	√0.04	6.43
0.702	0.05	3.42	2.74	√0.05	6.13
0.699	0.06	3.12	2.49	√0.06	6.10
0.711	0.07	2.84	2.26	√0.07	5.98
0.701	0.08	2.60	2.07	√0.08	5.86
0.702	0.09	2.21	1.76	√0.09	5.27
0.701	0.10	1.99	1.59	√0.10	5.02

Total D_o value 60.92×10^{-6} cm^2sec^{-1}

Average D_o value 6.092×10^{-6} cm^2sec^{-1}

Table 4.12: Data of basic concentrations and diffusion coefficient for drug B (0.1 to 1 M).

Mass (grams)	Concentration	Slope V ×10 $^{-5}$	D × 10 $^{-6}$ [D']	Square roots	D' x square root [OH^-] Do× 10 $^{-6}$
0.701	0.1	6.16	4.90	√0.1	1.55
0.699	0.2	5.72	4.69	√0.2	2.10
0.711	0.3	4.87	3.88	√0.3	2.17
0.701	0.4	4.24	3.40	√0.4	2.15
0.702	0.5	3.98	3.17	√0.5	2.24
0.699	0.6	3.67	2.92	√0.6	2.26
0.711	0.7	3.42	2.73	√0.7	2.28
0.701	0.8	3.27	2.59	√0.8	2.32
0.702	0.9	3.17	2.52	√0.9	2.39
0.701	1.0	1.03	2.50	√1.0	2.50

Total D_o value 21.96×10^{-6} cm^2sec^{-1}

Average D_o value 2.196×10^{-6} cm^2sec^{-1}

Table 4.13: Data of basic concentrations and diffusion coefficient for drug C (0.01 to 0.1 M).

Mass (grams)	Concentration	Slope V× 10 $^{-5}$	D × 10 $^{-6}$ [D']	Square roots	D' x square root [OH^-] Do×10 $^{-7}$
0.641	0.01	8.59	6.84	√0.01	6.84
0.639	0.02	6.04	4.81	√0.02	6.80
0.641	0.03	4.91	3.91	√0.03	6.77
0.640	0.04	4.20	3.35	√0.04	6.70
0.641	0.05	3.76	2.99	√0.05	6.68
0.641	0.06	3.36	2.67	√0.06	6.54
0.641	0.07	3.05	2.43	√0.07	6.44
0.639	0.08	2.83	2.26	√0.08	6.40
0.640	0.09	2.65	2.11	√0.09	6.32
0.640	0.10	2.49	1.98	√0.10	6.27

Total D_o value 65.76×10^{-7} cm^2sec^{-1}

Average D_o value 6.576×10^{-7} cm^2sec^{-1}

Table 4.14: Data of basic concentrations and diffusion coefficient for drug C (0.1 to 1.0 M).

Mass (grams)	Concentration	Slope V ×10 $^{-6}$	D × 10 $^{-7}$ [D']	Square roots	D' x square root [OH$^-$] Do× 10 $^{-7}$
0.641	0.1	5.96	4.74	√0.1	1.50
0.639	0.2	5.74	4.58	√0.2	2.05
0.641	0.3	4.76	3.80	√0.3	2.08
0.640	0.4	4.14	3.32	√0.4	2.10
0.641	0.5	3.83	3.04	√0.5	2.15
0.641	0.6	3.58	2.85	√0.6	2.21
0.641	0.7	3.35	2.67	√0.7	2.23
0.639	0.8	3.20	2.57	√0.8	2.30
0.640	0.9	3.12	2.49	√0.9	2.36
0.640	1.0	3.02	2.40	√1.0	2.40

Total D_o value 21.38×10^{-7} cm^2sec^{-1}

Average D_o value 2.138×10^{-7} cm^2sec^{-1}

Table 4.15: Data of basic concentrations and diffusion coefficient for drug D (0.01 to 0.1 M).

Mass (grams)	Concentration	Slope V ×10 $^{-8}$	D × 10 $^{-10}$ [D']	Square roots	D' x square root [OH$^-$] Do×10 $^{-10}$
0.190	0.01	1.28	10.2	√0.01	1.02
0.190	0.02	1.05	8.34	√0.02	1.18
0.190	0.03	1.04	8.31	√0.03	1.44
0.191	0.04	1.21	8.00	√0.04	1.60
0.190	0.05	9.21	7.33	√0.05	1.64
0.191	0.06	8.16	6.49	√0.06	1.59
0.189	0.07	7.79	6.20	√0.07	1.64
0.191	0.08	6.36	5.06	√0.08	1.43
0.190	0.09	6.24	4.97	√0.09	1.49
0.191	0.10	6.12	4.87	√0.10	1.54

Total D_o value 14.57×10^{-10} cm^2sec^{-1}

Average D_o value 1.457×10^{-10} cm^2sec^{-1}

Table 4.17: Data of basic concentrations and diffusion coefficient for drug D (0.1 to 1 M).

Mass (grams)	Concentration	Slope V ×10 $^{-9}$	D ×10 $^{-10}$ [D']	Square roots	D' x square root [OH$^-$] Do× 10 $^{-10}$
0.190	0.1	1.52	12.2	√0.1	3.85
0.190	0.2	9.83	7.83	√0.2	3.50
0.190	0.3	8.03	6.35	√0.3	3.48
0.191	0.4	6.80	5.41	√0.4	3.42
0.190	0.5	6.00	4.78	√0.5	3.38
0.191	0.6	5.41	4.31	√0.6	3.34
0.189	0.7	4.94	3.93	√0.7	3.29
0.191	0.8	3.97	3.16	√0.8	2.83
0.190	0.9	4.00	3.18	√0.9	3.02
0.191	1.0	2.89	2.30	√1.0	2.30
				Total $D_o$value	32.41×10 $^{-10}$ cm^{2}sec^{-1}

Average $D_o$value 3.241×10 $^{-10}$ cm^{2}sec^{-1}

Table 4.18: Data of basic concentrations and diffusion coefficient for drug E (0.01 to 0.1 M).

Mass (grams)	Concentration	Slope V × 10 $^{-9}$	D × 10 $^{-10}$ [D']	Square roots	D' x square root [OH$^-$] Do×10 $^{-10}$
0.120	0.01	1.38	11.0	√0.01	1.1
0.121	0.02	1.00	7.8	√0.02	1.13
0.120	0.03	8.67	6.9	√0.03	1.19
0.121	0.04	7.79	6.2	√0.04	1.24
0.120	0.05	7.35	5.85	√0.05	1.31
0.121	0.06	7.07	5.63	√0.06	1.38
0.121	0.07	7.07	5.63	√0.07	1.49
0.120	0.08	6.98	5.55	√0.08	1.57
0.120	0.09	6.97	5.55	√0.09	1.64
0.121	0.10	6.87	5.50	√0.10	1.73
				Total D_o value	13.78×10 $^{-10}$ cm^{2}sec^{-1}

Average D_o value 1.378×10 $^{-10}$ cm^{2}sec^{-1}

Table 4.19: Data of basic concentrations and diffusion coefficient for drug E (0.1M to 1.0 M).

Mass (grams)	Concentration	Slope V×10 $^{-9}$	D ×10 $^{-10}$ [D']	Square roots	D' x square root [OH^-] Do× 10 $^{-10}$
0.120	0.1	1.16	9.23	√0.1	2.92
0.121	0.2	8.04	6.40	√0.2	2.86
0.120	0.3	6.11	4.87	√0.3	2.67
0.121	0.4	4.81	3.83	√0.4	2.42
0.120	0.5	3.93	3.13	√0.5	2.21
0.121	0.6	3.46	2.75	√0.6	2.13
0.121	0.7	3.0	2.40	√0.7	2.01
0.120	0.8	2.78	2.21	√0.8	1.98
0.120	0.9	1.72	1.37	√0.9	1.30
0.121	1.0	1.53	1.22	√1.0	1.22
				Total D_o value 21.72×10^{-10} cm^2sec^{-1}	

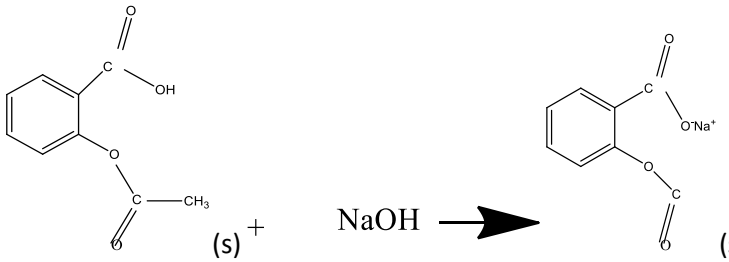
Average D_o value 2.172×10^{-10} cm^2sec^{-1}

4.4 DISCUSSION

4.4.1 Reactions of Aspirin (acetylsalicylic acid)

1. Neutralization: acid + base → salt + water

Aspirin+ (acetylsalicylic acid) + sodium hydroxide → a salt (sodium acetylsalicylate) + Water



$C_9H_8O_4(s)$ + NaOH (aq) → $C_9H_7O_4(s)$-Na+ + $H_2O(l)$

2. The neutralization reaction can be used to determine the amount of aspirin (acetylsalicylic acid) present in commercially available aspirin tablets using a back (indirect) titration method.

4.4.2 Diffusion coefficient of commercial aspirin from experimental data

The diffusion coefficients of commercial aspirin in aqueous solution at 25^{o}C were measured and the experimental results shown from table 4.1 to table 4.10.

At the same concentration, the diffusion of aspirin drugs vary. This can be explained from two aspects. At first, the diffusion coefficient is influenced by solute size. On the basis of simplest stokes Einstein equation, $D_{AB}=KT/6\pi_{o}h$, the smaller the molecular volume of the diffusion species, the larger the diffusion coefficient, upon inspection their molecular volume per weight gradually increases; therefore, their diffusivities are smaller and smaller.

Second, the diffusion coefficient can be advanced by the molecular polarity because the solute polarity can result in electrostriction in this experiment, the solvent was sodium hydroxide so the polar solute molecules combined adjacent sodium hydroxide molecules to produce larger aggregates which led to an increase of the effective diffusive volume and a decrease of diffusion coefficient. In aqueous solution aspirin can combine only a small quantity of sodium hydroxide molecules (Vane, 2007).

A number of diffusion projects lead to information about the size and shape of macromolecules in solution. The first of these was considered in the diffusion of macromolecules across a well defined boundary in a solvent. Experimentally diffusion is proportional to the concentration. In such discussions the issue of diffusion coefficient comes into play as it is a measure of the rate with which a material diffuses across a unit cross section area as a result of a unit concentration gradient. The relation of aqueous phase reaction process to diffusion can be recognized by first focusing on a particular molecule A and asking about the rate with which B molecules would diffuse to it. The diffusion coefficient is characteristic,

therefore for the given solvent at a given temperature of diffusing tendency of the solute (Miller*et al.*, 2002).

4.4.3 Comparison methods of diffusion coefficient for commercial aspirin

The diffusion coefficient for a strong electrolyte at infinite dilution may be calculated from the equation (4.3),

$$\mathbf{D_o = \frac{8.936\times10^{-10}T(\gamma_1+\gamma_2)\lambda^\circ_1\lambda^\circ_2}{\gamma_{1Z_1}(\lambda_1+\lambda_2)}} \qquad (4.3)$$

Where T is the absolute temperature,v_1, v_2arethenumbers of cations and anions from dissolution of one molecule of the electrolyte, z ,cationic charge Λ+ and Λ– equivalent cation and anion limiting conductances.

$$D_o = \frac{8.936\ x\ 10^{-10}T\times2(50\times10^{-04}\times36\times10^{-04})}{(50\times10^{-04}+36\times10^{-04})} \qquad (4.4)$$

$$=1.11\times10^{-9}\text{cm}^2\text{sec}^{-1}$$

$\Lambda^\circ = v_+\Lambda_+ + v_-\Lambda-$
(4.5)

$1\times50.08\times10^{-4} + 1\times36\times10^{-4}$

$=86.08\times10^{-4}\text{cm}^2\text{sec}^{-1}$

$$D = \frac{RT\Lambda}{Z2F2} \qquad (4.6)$$

$$D = \frac{8.936\ x\ 10^{-10}T\times2(86\times10^{-04})}{2(96000)^{\ 2}} \qquad (4.7)$$

$$=1.15\times10^{-9}\text{cm}^2\text{sec}^{-1}$$

$$D = \frac{2DA\times DB}{DA+DB} \qquad (4.8)$$

$$D = \frac{2\times9.58\times10-10\times1.33\times10-5}{9.58\times10-10+1.33\times10-5} \qquad =1.92\times10^{-9}\text{cm}^2\text{sec}^{-1} \qquad (4.9)$$

The Do values for sodium and salicylate are 1.33×10^{-5} and 9.58×10^{-10} cm^2sec^{-1} respectively while the limiting conductances are 50.08×10^{-4} and 36×10^{-4} m^2Smol^{-1}.The values obtained are close from the one from the moving boundary method. The effect of electrostatic interaction of electro neutrality is the retardation of diffusion of salicylate ions and the acceleration of the diffusion of Na^+.

4.4.4 Comparison of diffusion coefficient and concentration

The equations describing Fick's First Law are analogous to the general equation for a straight line with a negative slope that intersects the origin (y = -mx), and so the graph of this function resembled the plottings on appendix 9.

As mentioned earlier, the constant in the equation gets its own name, D (called the diffusion coefficient). D is something that needs to be measured, and it's different for each unique situation (a particular molecule in a particular medium at a particular concentration). For example, the diffusion coefficient of aspirin in sodium hydroxide was found to be varying inversely proportional to the concentration.

According to Fick's first law, these quantities were inversely proportional to each other and negative sign was the slope. In other words, when D is high the concentration was low.

4.5 Errors and assumptions

In the calculations, Do is assumed to be independent of concentration since the equation strictly applies under conditions where Do is independent of concentration. It is evident that Do varies with concentration.

There were two likely sources of error; namely, initial disturbances due to the dropping of the tablet aspirin and convective effects due to the size of the cells.

CHAPTER FIVE

CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusion

From the research findings, it is concluded that the migration of drugs in NaOH is a diffusion process that obeys Fickian diffusion laws. The present work describe a simple, rapid and valid moving boundary method that gives D values that are close to those calculated from limiting conductance within experimental error. The diffusion process was dependent on time. For moving boundary method, D values varied inversely with concentration of NaOH solution and were sensitive to the molecular weight of the sample used. Though moving boundary method, D values could not be reliably estimated, they cluster around $1.9 \times 10^{-9} cm^2/s$, which gives reasonable but rough estimation of expected diffusion coefficients. In the method, investigation was done in accordance to the prerogative regulation of food and drugs in terms of linearity, accuracy and sensitivity.

Studies were performed which compared the method to experimentally obtained drug concentration data for five different drugsand showed that the method could reproduce experimental results extremely well.

Diffusion of drugs in a human body is critical to the pharmaceutical industry and although sophisticated drug distribution are available commercially, the method is significant and thus can serve as a stepping stone for future work. The method includes the latest theory about the diffusion in the body.

The research has demonstrated that this methodology is useful in characterizing the relevance of moving boundary method within the framework of a convective-diffusion model. The experimentally determined diffusion rates were found to be in good agreement with those values calculated and from limiting conditions within

experimental error. This model accounts for convective effects and provides an accurate picture of the physicochemical interactions occurring in the microenvironment at the tablet surface. The model also demonstrated a quantitative relationship between the expected diffusion rate and boundary height. Furthermore, plot analysis of the data demonstrated that the variability of the diffusion data tends to increase with increasing time during the diffusion process and that the relative magnitude of data dispersion was consistently higher at 0.1M than at 0.01 M.

These findings provide a basis to further develop and refine apparatus suitability test requirements using chemical calibrators. One can envision an acceptance range that is based not only on the statistical analysis of an experimental data set, but also on an interval that is based on the difference between the experimental value and the calculated value from the moving boundary technique.

All the aspirin tablet were found to produce values according to Fickian mechanism. For the drug A loaded with 600mg of aspirin the best value of diffusion coefficient being observed while the values for coated drug E with 75mg aspirin was found to be slightly lower.

A graph of x^2 against time was plotted which was used to calculate the diffusion coefficient. The experimental values of diffusion coefficient Do were within the experimental error as per those calculated from the limiting conductances. Aspirin which hydrolyses into salicylic acid and should therefore be protected by monitoring and controlling the moisture content during production.

In diffusion, individual particles are moving at random, the research was able to show that diffusion was also dependent on concentration and adhered to Fickian mechanism and net movement with the negative sign of D_O was a result of more particles moving from high to low concentration and diffusion is efficient only at very short distances.

5.2 Recommendations

Based on the findings of the study, the following recommendation can be made for policy and research.

(i) The method used was free diffusion but conductometric technique could be used which may even give a more accurate results.

(ii) A similar study should also be conducted involving more coated drug aspirin since only two were chosen for this research project.

(iii) A similar method should be constituted with the use of other techniques such as TLC and spectrophotometric method for comparison purposes with the free diffusion.

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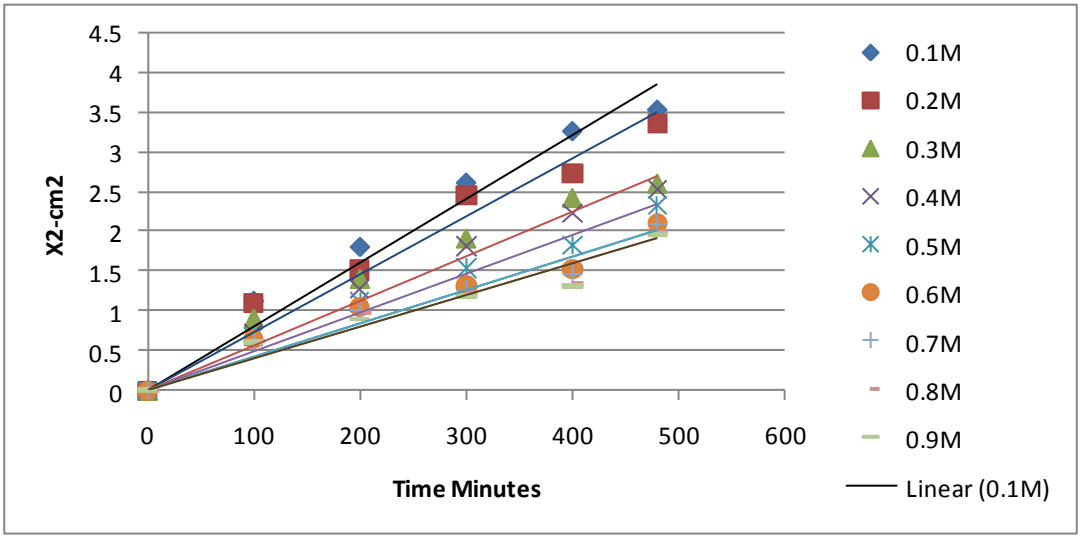
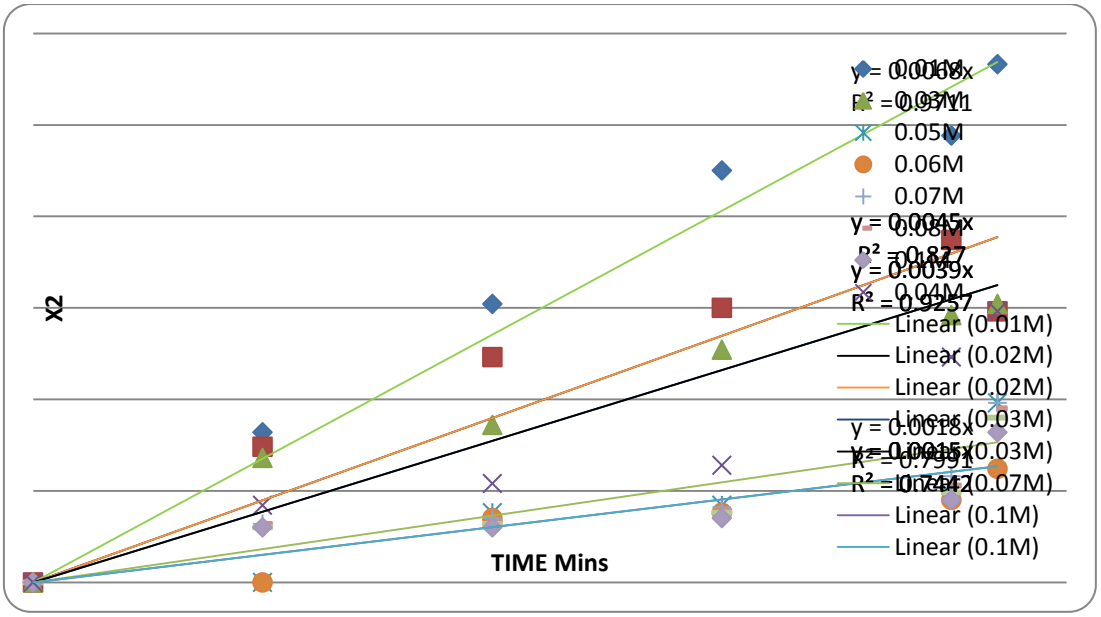
APPENDICES

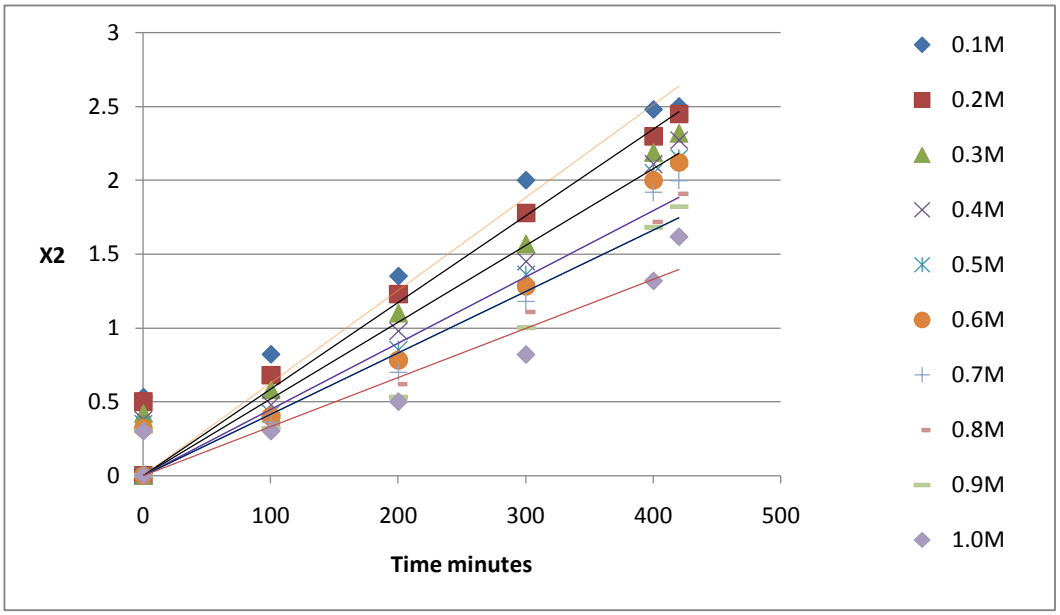
***APPENDIX I*: Graph of x^2 versus time for 0.1M to 1.0M sodium hydroxide solutions for drug A.**



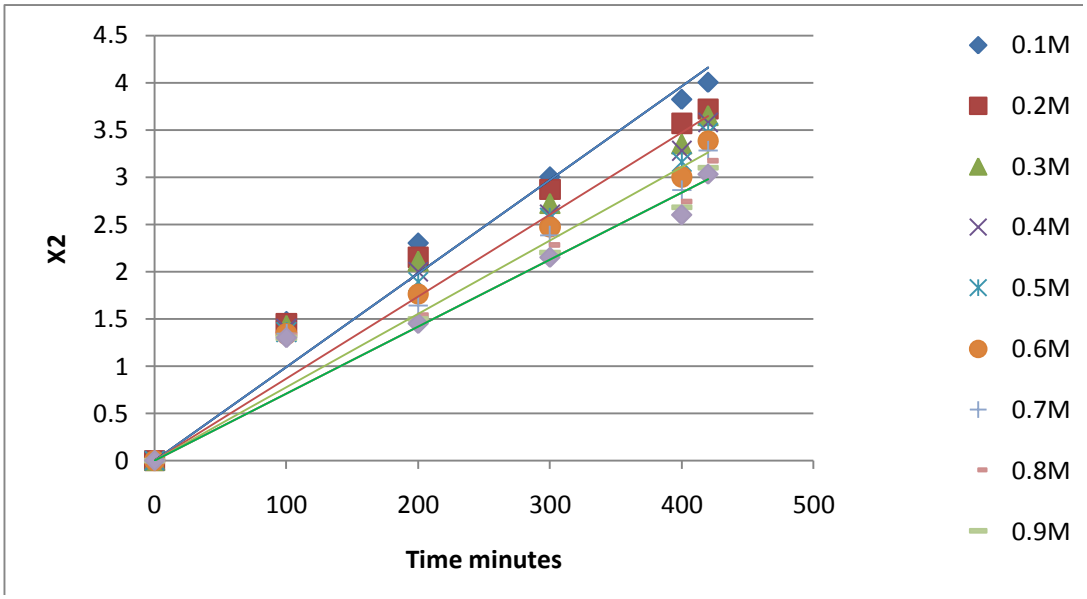
***APPENDIX II*: Graph of x^2 versus time for 0.01M to 0.1M sodium hydroxide solutions for drug A.**



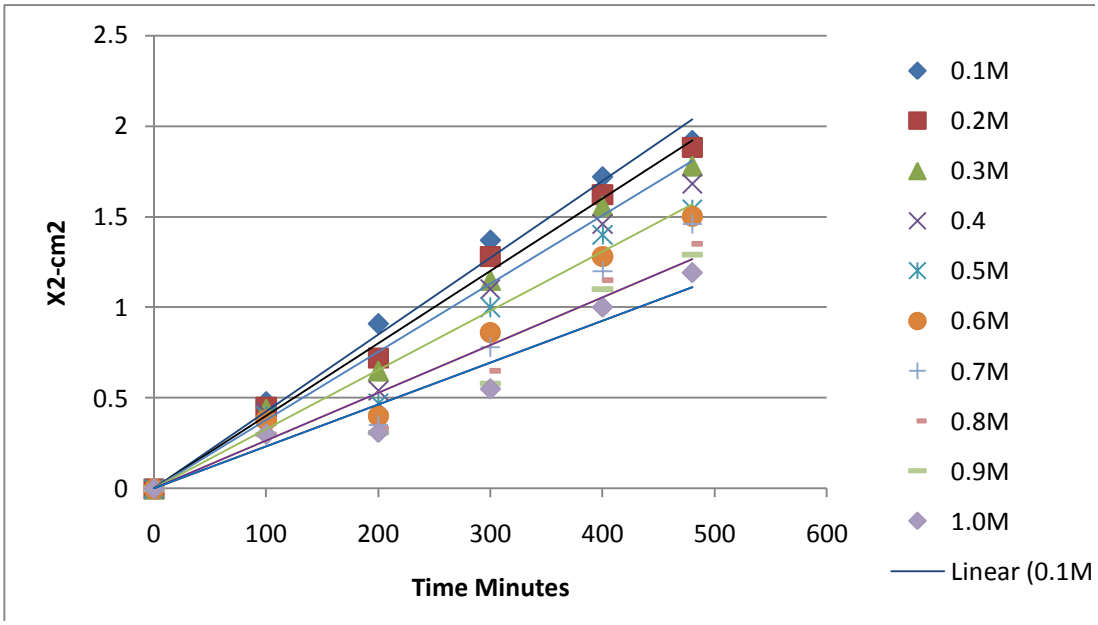
***APPENDIX III*: Graph of x^2 versus time for 0.1M to 1.0M sodium hydroxide solutions for drug B.**



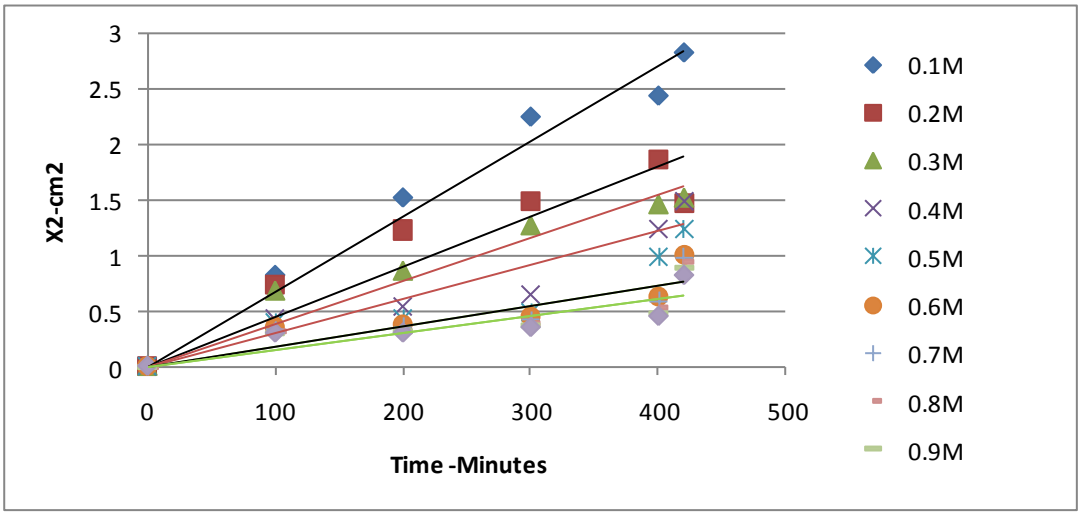
***APPENDIX IV*: Graph of x^2 versus time for 0.1M to 1.0M sodium hydroxide solutions for drug C.**



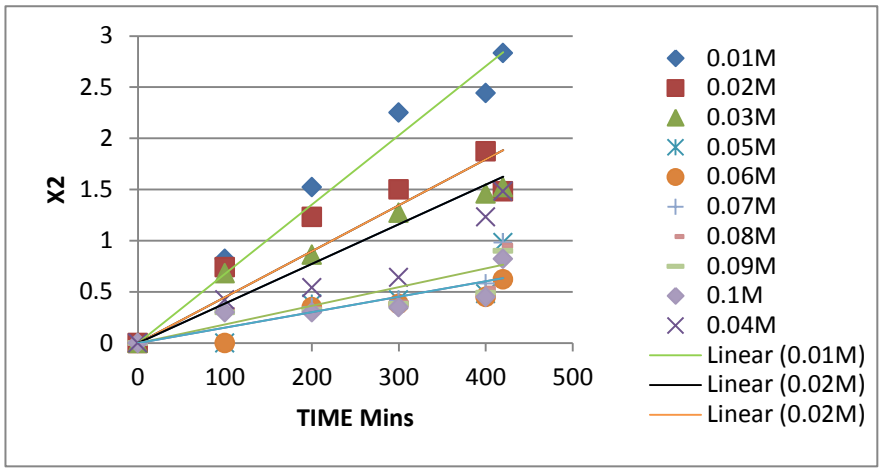
***APPENDIX V*: Graph of x^2 versus time for 0.1M to 1.0M sodium hydroxide solutions for drug C.**



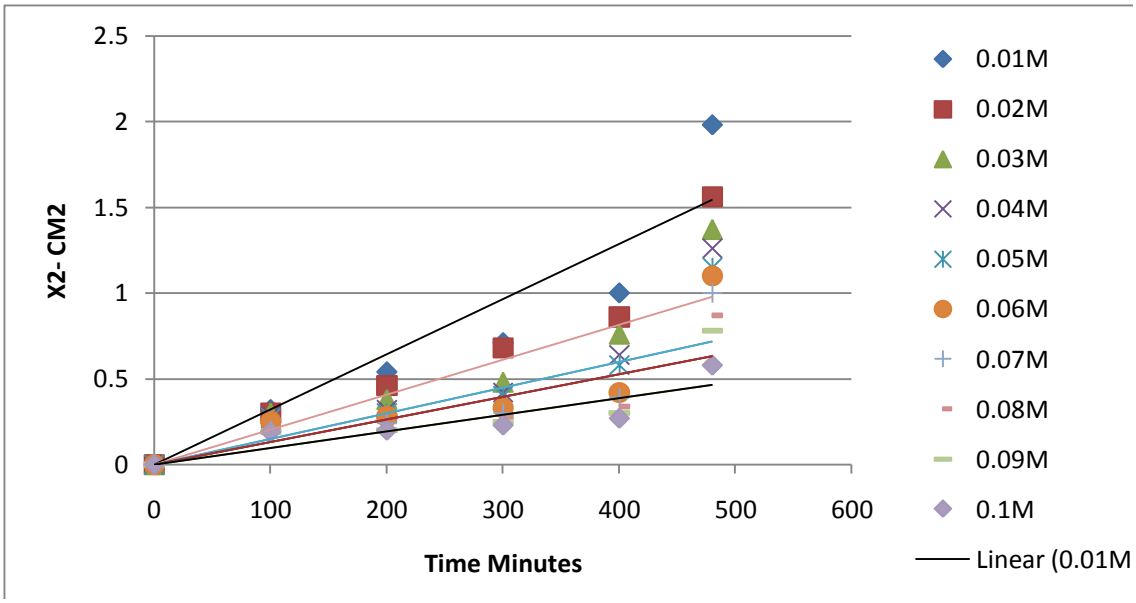
***APPENDIX VI*: Graph of x^2 versus time for 0.1M to 1.0M sodium hydroxide solutions for drug D.**



***APPENDIX VII*: Graph of x^2 versus time for 0.01M to 0.1M sodium hydroxide solutions for drug D.**



***APPENDIX VIII*: Graph of x^2 versus time for 0.01M to 0.1M sodium hydroxide solutions for drug E.**



***APPENDIX IX*: Graph of diffusion coefficient against concentration for drug aspirin.**