Journal of Natural Sciences Research www.iiste.org
ISSN 2224-3186 (Paper) ISSN 2225-0921 (Online)
Vol.5, No.13, 2015

Diffusion of Aspirin (ASA) Based Drugs in Sodium Hydroxide Solution at Ambient Temperature.

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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 body governed 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 x 10^{-6} cm^2 sec^{-1} to 6.995 x 10^{-6} cm^2 sec^{-1}, 2.196 x 10^{-6} cm^2 sec^{-1} to 6.092 x 10^{-6} cm^2 sec^{-1}, 2.138 x 10^{-7} cm^2 sec^{-1} to 6.576 x 10^{-7} cm^2 sec^{-1} , 3.241 x 10^{-10} cm^2 sec^{-1} to 1.617 x 10^{-10} cm^2 sec^{-1} and 1.378 x 10^{-10} cm^2 sec^{-1} to 2.172x 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 x 10^{-6} cm^2 sec^{-1} at concentrated solution and 2.780 x 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.

Key words: Diffusion, Aspirin, Acetylsalicylic acid, Diffusion Coefficient, Sodium Hydroxide, Fickian Mechanism,

1. INTRODUCTION

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. Diffusion as a scientific term has roots in an 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 of randomicity (Harned and Owen, 1958).
Diffusion in drug systems is described by Fick's second law which 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 (Crank., 1975). 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 as electro deposition. When a solid reacts with liquid the process involves the products forming a layer on solid surface or dissolving into the liquid phase. If 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 (Kays, 2005).

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, 1999). No experimental data on diffusion was available then and Fick's equations was written in conformity with molecular diffusion within liquids (Jost., 1960).
Fick's first law has the following form:

$$J = -D\frac{\partial \phi}{\partial x}$$

Where J (diffusion current is the amount of substance passing through a reference substance of unit time mol/m^{2-s}, x is the co-ordinate perpendicular to surface area where D is the diffusion coefficient length^{2}time^{-1} (m^2/s) and Ø (for ideal mixtures) is the concentrations in dimensions of (amount of substance) length $^{-3}$, i.e. (mol /m^3). The diffusion coefficient controls the rate of diffusion. The dc/dx is the rate change of concentration in the x direction and minus sign indicates the flow from a higher to lower concentrations (Ladler and Meiser, 1982).
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.
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.

2. OBJECTIVES

The main objective was to determine the diffusion coefficients of aspirin drugs in sodium hydroxide solutions of different concentration range at 25^0C. The specific objectives were outlined as below.

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.

3. MATERIALS AND METHOD

Two concentration sets of base were prepared; dilute and concentrated. To each sample two drops of methyl orange was added and the solution mixed in a disposable plastic curettes of cross section 10cm^3 and capacity 4.50ml while closed using a fitted stopper. The procedure was repeated with different concentrations of NaOH upto 0.01M. The contents were kept in an oven at a regulated temperature of 25^oC.
An accurately weighed mass of commercial aspirin tablets was dropped into each of the cuvettes and time recorded at different intervals where boundary height between the alkaline and acidic parts of solutions formed.

4. 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.

4.1 Results

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 concentration of a simple case of solution containing a single solute. 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, for instance the x direction. In an adjacent volume the same volume may be moving in reverse direction. If the concentration in the first volume is greater than in the second, the overall effect is that more particle moving are leaving the first element for second and hence a net flow of solute in the x direction ,the direction of decreasing concentration. This was governed by Fick's law.

4.1.1 Experiment with Sodium Hydroxide solution from 0.01M TO 0.10M

The research showed typical data from a run using sodium hydroxide after an initial period of about one hour 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 (figure 1-figure 8) the slopes of these plots were found to be dependent on the basic concentrations.

The rates of diffusion of aspirin in sodium hydroxide solutions increased with increased concentration of the base: - a solution that, agreed with expectations of diffusions with chemicals reactions.

4.1.2 Experiments with Sodium Hydroxide solution from 0.10 M TO 1.0 M

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

1. 0.10-0.40M: acid has quantities of aspirin that are higher than those of the base into the solutions therefore the aspirin diffuses to the meniscus.
2. 0.50M base is in a class of its own: this type of behavior is 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 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 the concentrations increased, the plots could not yield straight lines as the boundaries started dropping due to the fact that the base begins to diffuse into the acid.

The results also agree with the square root relationship for the diffusions into a semi-infinite medium involving the dimensionless parameter (Crank., 1975):

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 is proportional to the square of its distance from the surface where the diffusion occurs.

Table 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 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 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: 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 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	1.0
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 6: 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.

Figure 1: Graph of x^2 versus time for 0.1M to 1.0M sodium hydroxide solutions for drug A.

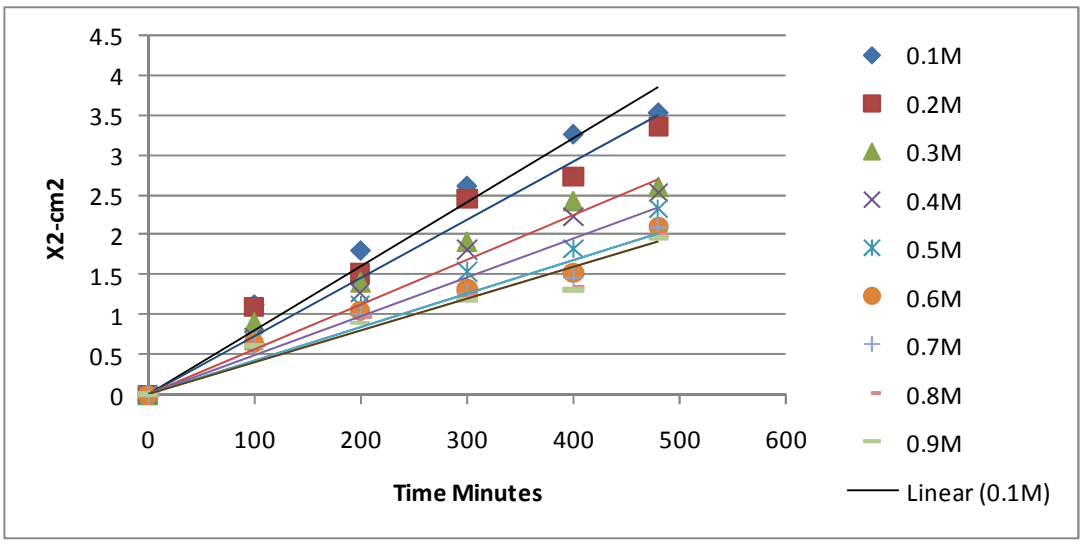


Figure 2: Graph of x^2 versus time for 0.01M to 0.1M sodium hydroxide solutions for drug A.

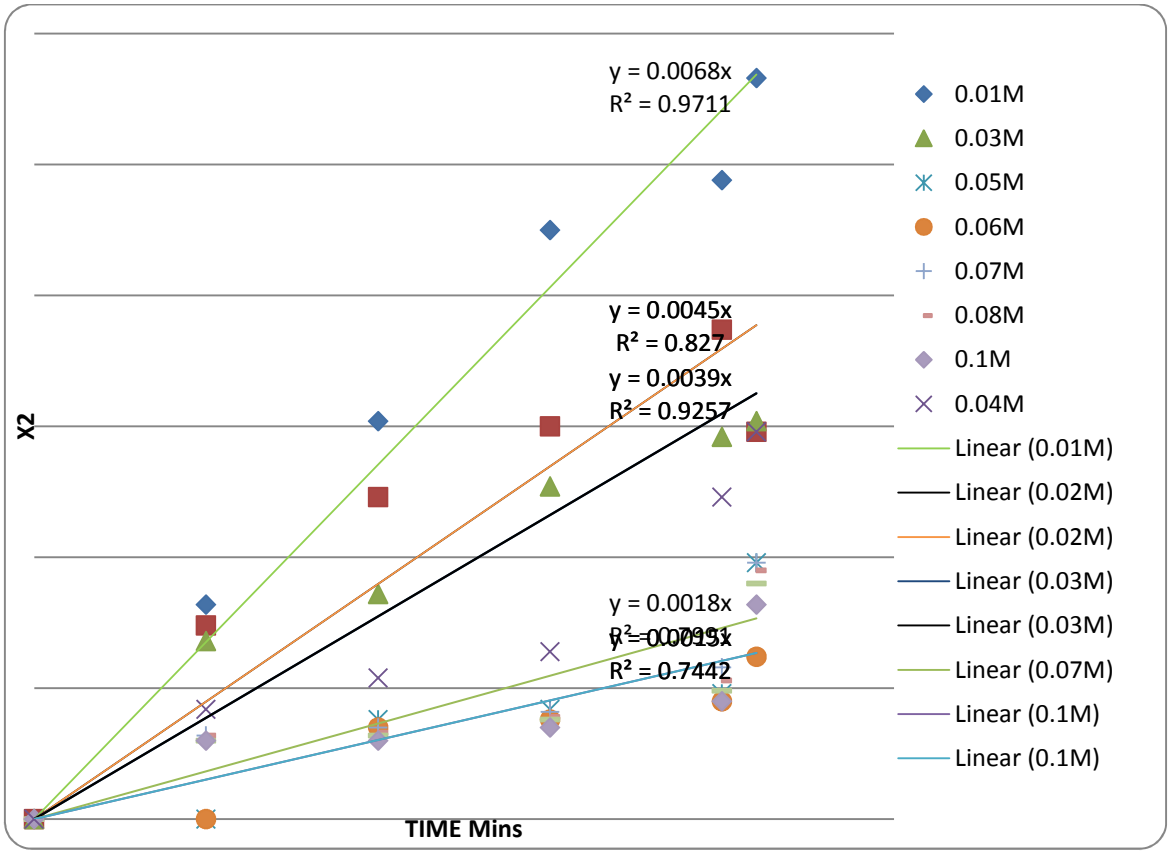


Figure 3: Graph ofs x^2 versus time for 0.1M to 1.0M sodium hydroxide solutions for drug B.

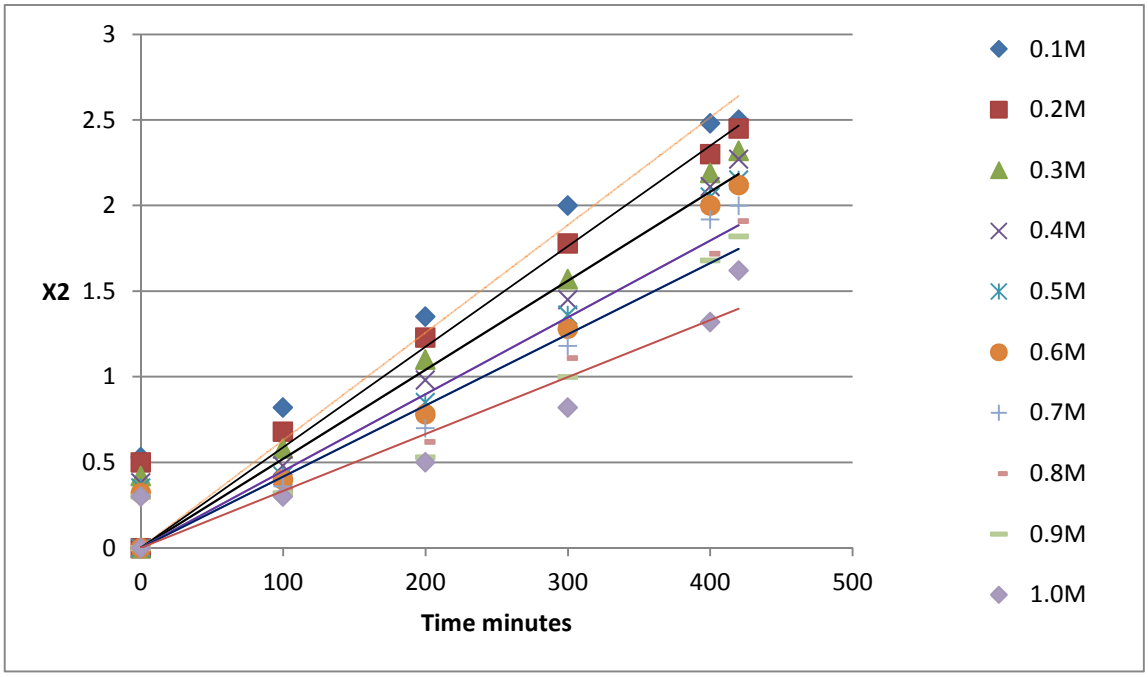


Figure 4: Graph of x^2 versus time for 0.1M to 1.0M sodium hydroxide solutions for drug C.

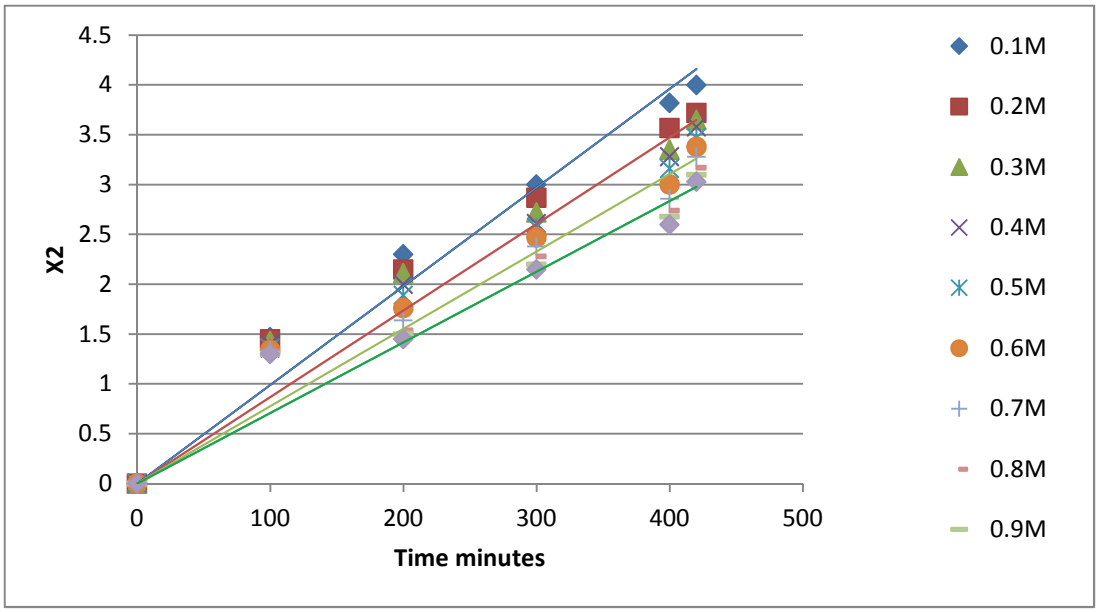


Figure 5: Graph of x^2 versus time for 0.1M to 1.0M sodium hydroxide solutions for drug C.

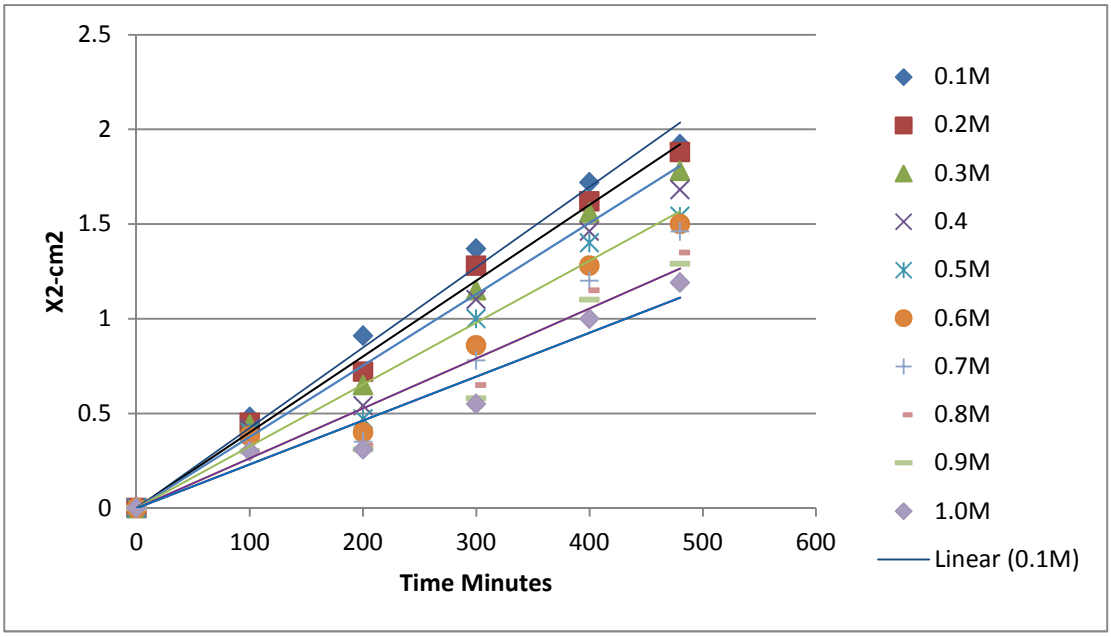


Figure 6: Graph of x^2 versus time for 0.1M to 1.0M sodium hydroxide solutions for drug D.

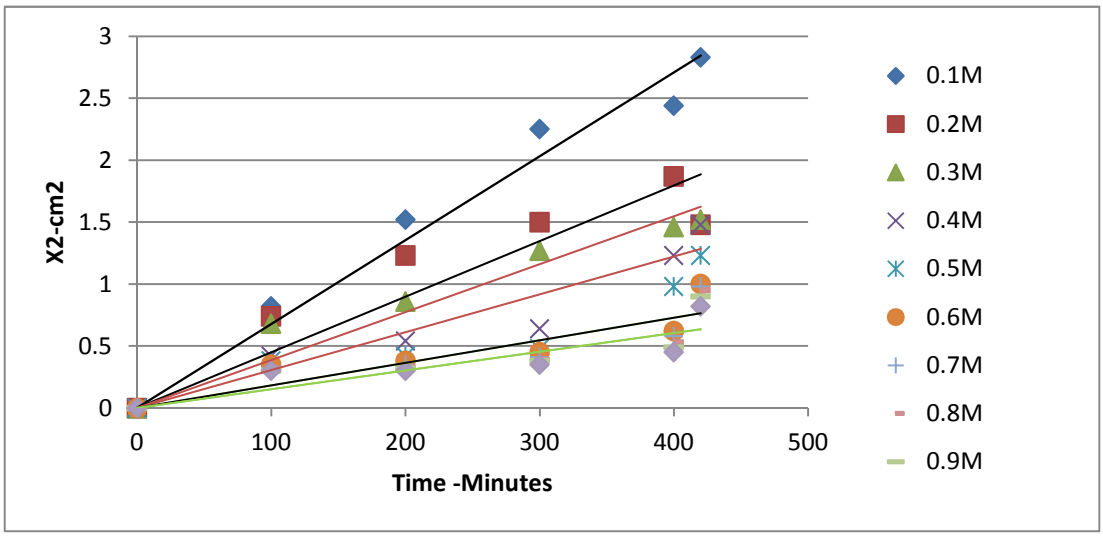


Figure 7: Graph of x^2 versus time for 0.01M to 0.1M sodium hydroxide solutions for drug D.

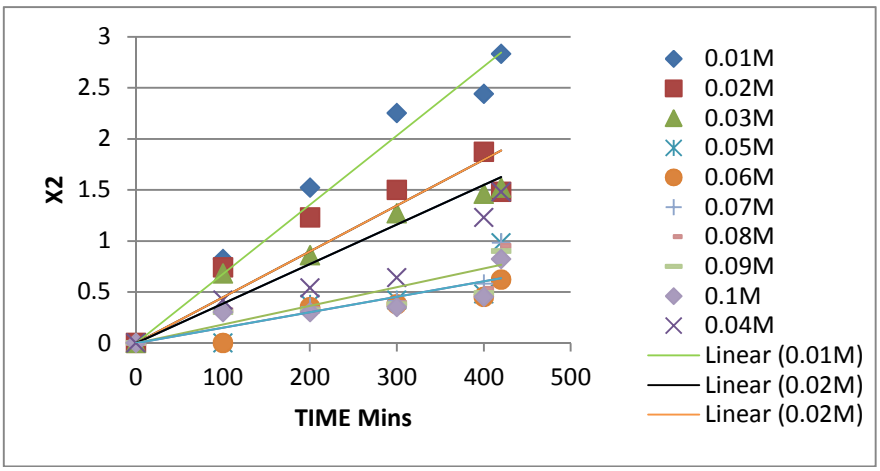
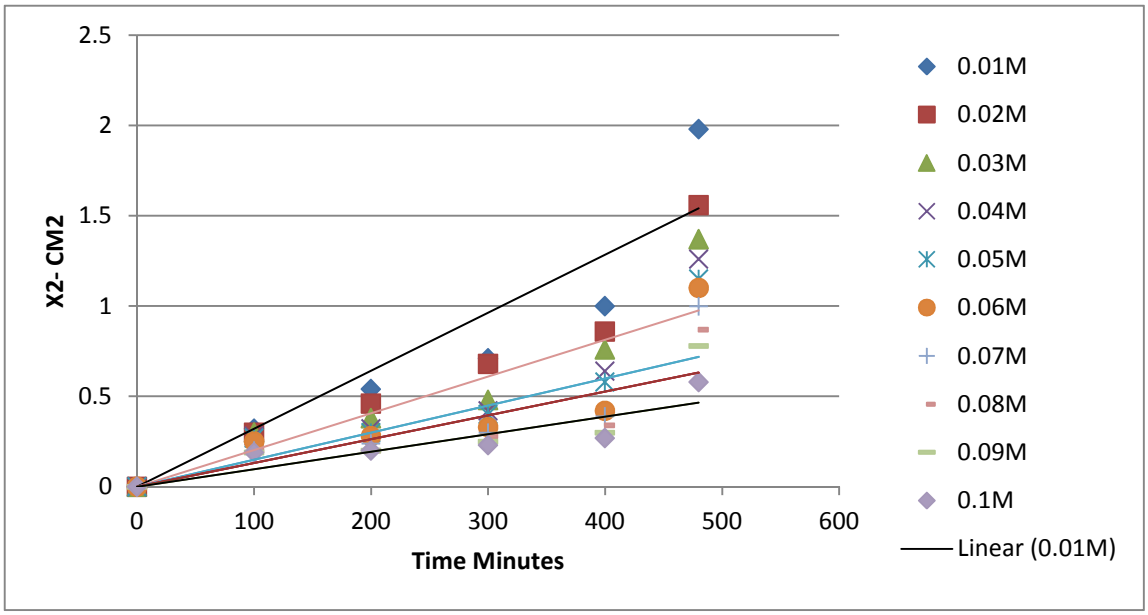


Figure 8: Graph of x^2 versus time for 0.01M to 0.1M sodium hydroxide solutions for drug E.



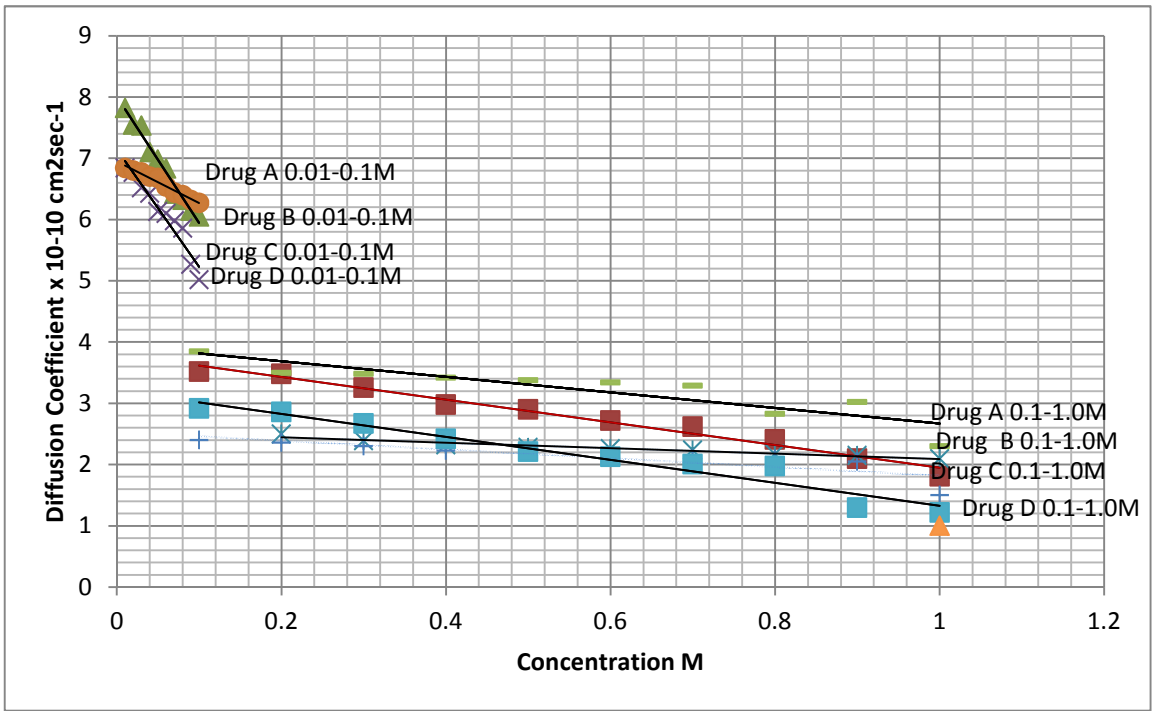
4.2 Comparison of diffusion coefficient and concentration

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 plotting on figure 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.

Figure 9: Graph of diffusion coefficient against concentration for drug aspirin.



Comparison methods of diffusion coefficient for commercial aspirin
The diffusion coefficient for a strong electrolyte at infinite dilution may be calculated from the equation below

$$D_o=\frac{8.936\,x10^{-10}T(v_{1+}v_2)h_1^0h_2^0}{v_1z_1(h_1^0+h_2^0)}$$

Where T is the absolute temperature,v_1,$v_2$arethenumbers of cations and anions from dissolution of one molecule of the electrolyte, z ,cationic charg $\Lambda+$ and $\Lambda-$ equivalent cation and anion limiting conductances.

$$D_o=\frac{8.936\,x10^{-10}T\times2(50\times10^{-04}\times36\times10^{-04})}{(50\times10^{-04}+36\times10^{-04})}$$

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

$\Lambda^\circ=v_+\Lambda_+ + v_-\Lambda$

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

$=86.08\times10^{-4}$

$$D = \frac{RT\Lambda}{Z2F2}$$

$$D=\frac{8.936\,x10^{-10}T\times2(86\times10^{-04})}{2(96000)^{\ 2}}$$

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

$$D=\frac{2DA\times DB}{DA+DB}$$

$$D=\frac{2\times9.58\times10^{-10}\times1.33\times10^{-5}}{9.58\times10^{-10}+1.33\times10^{-5}}$$

$=1.92\times10^{-9}$ cm^{2}sec^{-1}

The D values for sodium and salicylate are 1.33×10^{-5} and 9.58×10^{-10} cm^{2}sec^{-1} respectively while the limting conductances are 50.08×10^{-4} and 36×10^{-4} m^{2}Smol^{-1}.The values obtained are close from the one from the

moving boundary method. The effect of electrostatic interaction of electroneutrality is the retardation of diffusion of salicylate ions and the acceleration of the diffusion of Na^+.

4.3 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 x $10^{-9}cm^2/s$, 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 drugs and showed that the method could reproduce experimental results extremely well.

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.

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.

ACKNOWLEDGEMENT

My sincere gratitude goes to my supervisors Prof. Justin Irina and Dr. M.O. Okoth and Dr. S. T Lutta whose remarkable steadfast and insistence on perfection and innovation enabled me to think outside the box. I also thank the entire staff of Chemistry and Biochemistry- University of Eldoret for their assistance during the field work and my thesis write-up that ensured that the thesis was successfully written. They also came to my rescue at a time when in need of guidance, they have shown a keen interest in the progress of this work and besides the supervisory role they have been extremely vital in the building of my academic career throughout my postgraduate study. May you live long. I also wish to acknowledge Prof. J. L. Kituyi for their support during this research period to its successful completion.

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