ISSN No:-2456-2165

Mathematical Model of the Role of Peristalsis in Intestinal Drug Absorption

Enobong E. Joshua, Ubon A. Abasiekwere
Department of Mathematics and Statistics,
University of Uyo, Uyo, Nigeria

Abstract:- In this paper, we formulate a broad-based mathematical model for drug absorption in the intestine based on the peristaltic motion of the drug-carrying intestinal fluid which is approximately sinusoidal. Using the background of Fick's laws and perturbation methods, an initial – boundary value problem is formulated and solved and the drug concentration, $Q(x,t)$ at a distance x along the intestinal tract at time t determined. In doing this, we use the result of drug absorption in the gastro-intestinal tract for constant velocity of the intestinal fluid [14]. The solution is analyzed for various frequencies (or wave numbers) of the peristaltic wave for the drug indomethacin. The results do not show marked deviations for low frequencies; but for large frequencies, it has been observed that the absorption is more rapid. Thus, the results show that with higher peristaltic wave frequency, the drug particles that had diffused into intestinal fluid are more in contact with the villi surrounding the intestinal lumen and hence absorption is enhanced.

Keywords:- *Mathematical model, peristalsis, drug absorption, intestinal.*

I. INTRODUCTION

The study of drug absorption, metabolism and distribution in the human system has continuously been of paramount importance to the pharmaceutical and medical sciences. Drugs act as supplements to food particularly where there is deficiency in the required nutrients for body building and growth. Like food, drugs are digested through enzymatic action into substances which can be absorbed and assimilated by the body. The routes of penetration of drugs or other substances into the organism can be enteral or parenteral.

In this paper, we shall concentrate on the enteral administration and in particular, the oral administration. This is vital because most drugs are commonly ingested orally, even though more rapid therapeutic effect is obtained through parenteral administration [1].We shall consider the digestive process which modifies food or drugs and enables them to be absorbed into the bloodstream for distribution throughout the body. We shall consider the mechanical movements of the gastro-intestinal tract and their role in moving the intestinal contents along, to be acted upon successively by a series of enzyme and then the churning movements which expose all parts of the semi-liquid mass to the large absorbing surface of the intestine for absorption.

The small intestine which forms the greater portion of the gastro-intestinal tract measures just over 5 metres long in an adult as given by Ross and Wilson ([2], [3]) and a host of other sources. Further, they give the diameter as about 2.5cm and that of the large intestine as more than twice as wide in parts. In this work we shall use the generally accepted length of about 5 metres for the small intestine. The small intestine consists of three sections – the upper part which connects it to the stomach, called the duodenum which is about 25cm long; the middle part, called jejunum which measures about 2 metres, and the lower part, the ileum, which links the large intestine through the ileocaecal valve. It is of length about 3 metres [2]. The small intestine has three main functions:

- To complete the digestion of food or nutrients
- To absorb the digested material
- To move the chyme through it from one end to another.

It has an extended absorption area of about 300 square metres [3]. Its mucosa is covered by finger-like projections called *villi* which constitute the anatomical and function unit that ensures intestinal absorption of nutrients and drugs.

In the large intestine, which measures about 1.5 metres in an adult, there occur both peristalsis and churning movements somewhat like those of the small intestine [9]. It is designed to absorb most of the water from the remaining chyme.

II. GASTRO-INTESTINAL RHYTHMS

Spontaneous rhythms occur in all parts of the digestive tract right from the oesophagus which moves the food materials to the stomach by the process of peristalsis [4]. These rhythms are commonly called "slow waves". The frequency and wave shapes of these waves vary considerably between the organ and species being studied. For example, Linkens [5] states that the canine stomach has narrow pulse-like waves of about 0.08Hz, while the human stomach produces square-like waves of about 0.05Hz.

The commonest rhythmic movement displayed in the alimentary canal is called peristalsis. The word peristalsis, according to Fung and Yih[6], stems from the Greek word "peristaltikos" which means clasping and compressing. In

ISSN No:-2456-2165

physiology it may be described as a progressive wave of contraction seen in tubes provided with longitudinal and transverse muscular fibres. Nancy Roper [7] defines it as the characteristic movement of the intestines by which the contents are moved along the lumen. It consists in a narrowing and transverse shortening of a portion of the tube, which then relaxes while a lower portion becomes shortened and narrowed. Kapur[8] defines peristaltic flow as the motion generated in the fluid contained in a distensible tube when a progressive wave of area contraction and expansion travels along the wall of the tube.

In man, peristalsis occurs in the oesophagus, stomach, small and large intestines and rectum in the alimentary canal [9]. Some worms use peristaltic motion as a means of locomotion. The ureter passes urine from the kidney to the bladder by peristalsis. Some biomedical instruments such as some heart-lung machines are designed to use peristaltic motion to pump blood or other fluids. Throughout the length of the small intestine rhythmic movements are of two main kinds, namely, peristaltic waves and the churning movements called rhythmic segmentation. Peristaltic waves occur slowly moving the digested materials onward.

Fung and Yih[6] investigated the phenomenon of peristalsis for arbitrary wavelengths and small amplitudes while Shapiro, *et al*[10] considered peristaltic pumping in a tube under long wavelength approximation and for very small Reynolds number. These studies showed that the average flux over a time period is increased by increasing the amplitude of the peristaltic wave. On their own part, Radhakrishnamacharya, *et al*[11] presented a model to study the peristaltic transport of a Newtonian fluid through a circular tube of varying cross-section and having two mild constrictions. Their result showed that the pressure rise over a wavelength and the shear stress on constrictions increase as the amplitude of the peristaltic wave and the thickness of the constrictions are increased.

III. MODEL FORMULATION

We shall set out to determine the concentration of a drug which diffuses through the intestinal fluid, is absorbed into the walls of the gastro-intestinal tract and is carried by the fluid flow which moves according to the pattern prescribed by the peristaltic motion of the walls of the tract. We shall concentrate on the absorption within the small intestine. We make the following assumptions for the formulation of our model.

- The physical and chemical properties of the drug including its extent of solubility, ionization state and molecular size and shape are accounted for by diffusion, *D*.
- The rate of absorption ν' is assumed constant for any particular drug. The intestine is anatomically adapted for absorption of drugs and other substances due t the presence of a large number of villi covering a surface area of over 300 m^2. Wagman[12]and other medical experts confirm that absorption or assimilation of foods is almost completed before the substance leaves the small intestine.
- Since the small intestine is extremely long relative to its width and other organs and the rate of flow of the intestinal fluid, we assume that x lies between zero and infinity.
- The time when the drug crosses the stomach through the pyloric sphincter into the duodenum shall be taken as initial time while the time it leaves for the large intestine shall be taken as infinity due to the length of the small intestine.
- From experimental results we can assume that the concentration of drug decreases exponentially due to diffusion and absorption, so that $Q(\infty, t) = 0$ and at initial time, no drug is expected in the compartment under discussion, so that $Q(x, 0) = 0$.

  However, at $x = 0$,

  $$Q(x, t) = Q_a e^{-\alpha t} \qquad (3.1)$$

  Where $\alpha > 0$ and is related to the rate of stomach emptying or drug release, and Q_a is the initial concentration of the drug in the stomach.

- The velocity U of fluid flow is modified from its constant nature, by the effect of peristalsis to assume a sinusoidal form. During the peristaltic motion of the walls of the intestine, its contents including the fluid are carried along in the direction of motion.

Hence the velocity can be represented in wave-form as

$$U = U_0 \left\{1 + \varepsilon \cos \tfrac{2\pi}{\lambda}(x - \sigma t)\right\},\ \varepsilon \ll 1 \qquad (3.2)$$

(in accordance with Schlichting[13] and Kapur[8]), where U_0 is the velocity at the unperturbed flow which is constant. Thus a progressive wave of amplitude $U_0\varepsilon$, velocity σ and the wavelength λ passes along the tube in the positive x-direction. If$\sigma = 0$, the wall of the tube becomes a fixed cosine wave, so that

$$U = U_0 \left\{1 + \varepsilon \cos \tfrac{2\pi}{\lambda} x\right\},\ \varepsilon \ll 1 \qquad (3.3)$$

$\mathcal{E}$ accounts for the perturbation on the flow which produces the peristaltic wave motion. Since $\mathcal{E}$ is small, the resulting amplitude of the wave is small. By nature of the peristalsis the wavelength λ is small as compared to the distance between the walls, resulting in the wave number, $n = \dfrac{2\pi}{\lambda}$.

Considering the boundary conditions: $Q(x, 0) = Q(\infty, t) = 0$ and since $0 \le x \le L$, where L represents the length of the intestine, without loss of generality, we can assume that

ISSN No:-2456-2165

$$n' = \frac{k\pi}{L}, \quad k = 0, 1, 2, \ldots \tag{3.4}$$

where n' is the wave number. Thus, by non-dimensional zing we obtain

$$n = n'L = k\pi \quad k = 0, 1, 2, \ldots \tag{3.5}$$

The case $k = 0$ yields a constant velocity. We can then write (3.3) as

$$U = U_0\{1 + \varepsilon \cos n'X\}, \ \varepsilon \ll 1 \tag{3.6}$$

If we let the drug concentration be $\overline{Q}(X,T)$, the rate of drug release α', the rate of absorption ν' and diffusion constant D', we can formulate the absorption model from the above considerations with the given velocity profile in relation (3.6) as

$$D'\frac{\partial^2 \overline{Q}}{\partial X^2} - U_0\{1 + \varepsilon \cos n'X\}\frac{\partial \overline{Q}}{\partial X} - \nu'\overline{Q} - \frac{\partial \overline{Q}}{\partial X} = 0 \tag{3.7}$$

with boundary conditions

$$\begin{aligned} &\overline{Q}(X,0) = 0, \ 0 < X < \infty \\ &\overline{Q}(0,T) = Q_a e^{-\alpha T}, \quad \alpha' > 0, T > 0 \\ &\overline{Q}(X,T) \to 0 \ \text{as} \ \ X \to \infty, T > 0 \end{aligned} \tag{3.8}$$

Where Q_a is the initial concentration of the drug. This is the formulation we now need to solve.

IV. SOLUTION OF MODEL PROBLEM

We shall now analyze the model (3.7) with (3.8) and solve the resulting problem. Laplace transform methods will be used on the resulting second order differential equation. First of all we introduce non-dimensional quantities.

$$\begin{aligned} &x = \frac{X}{L}, t = \frac{TU_0}{L}, \ D = \frac{D'}{LU_0} \\ &\nu = \frac{\nu' L}{U_0}, \alpha = \frac{\alpha' L}{U_0}, \ Q = \frac{\overline{Q}}{Q_a} \end{aligned} \tag{4.1}$$

Where L is the length of the intestine. Using (4.1) we write (3.7) in non-dimensional form as

$$DLU_0 Q_a \frac{\partial^2 Q}{\partial x^2}\frac{1}{L^2} - U_0[1 + \varepsilon \cos\frac{n}{L}xL]Q_a\frac{\partial Q}{\partial x}\frac{1}{L} - \frac{\nu U_0}{L}Q_a Q - \frac{U_0}{L}\frac{\partial Q}{\partial t}Q_a = 0$$

$$\Rightarrow \frac{Q_a U_0}{L}\left[D\frac{\partial^2 Q}{\partial x^2} - (1 + \varepsilon \cos nx)\frac{\partial Q}{\partial x} - \nu Q - \frac{\partial Q}{\partial t}\right] = 0$$

And since $\frac{Q_a U_0}{L} \neq 0,$ we have

$$D\frac{\partial^2 Q}{\partial x^2} - (1 + \varepsilon \cos nx)\frac{\partial Q}{\partial x} - \nu Q - \frac{\partial Q}{\partial t} = 0 \tag{4.2}$$

where $Q = Q(x,t),$ and the initial and boundary conditions (3.8) become

$$\begin{aligned} &Q(x,0) = 0, \quad 0 < x < \infty \\ &Q(0,t) = e^{-\alpha t}, \alpha > 0, t > 0 \\ &Q(x,t) \to 0 \text{ as } x \to \infty, t > 0 \end{aligned} \tag{4.3}$$

For uniform flow, that is, when $\varepsilon = 0$ in (4.2) we obtain

$$D\frac{\partial^2 Q_0}{\partial x^2} - \frac{\partial Q_0}{\partial x} - \nu Q_0 - \frac{\partial Q_0}{\partial t} = 0 \tag{4.4}$$

Where Q_0 is the concentration when $\varepsilon = 0$. The conditions (4.3) are also applicable here since they have no term in ε.

We now solve (4.4) with (4.3) using Laplace transforms since the conditions for this method are fulfilled. We obtain

$$\hat{Q}_0(x,s) = \frac{1}{\alpha + s}\exp\left(\tfrac{x}{2D} - x\sqrt{\tfrac{1}{4D} + \tfrac{\nu + s}{D}}\right) \tag{4.5}$$

which on inversion becomes

$$\begin{aligned} Q_0(x,t) = \tfrac{1}{2}\, e^{-\alpha t + \frac{x}{2D}} \{ &\exp\left(-x\sqrt{\tfrac{1}{4D^2} + \tfrac{\nu - \alpha}{D}}\right) erfc\left(\frac{x}{2\sqrt{Dt}} - \sqrt{t\left(\tfrac{1}{4D^2} + \nu - \alpha\right)}\right) + \\ + &\exp\left(x\sqrt{\tfrac{1}{4D^2} + \tfrac{\nu - \alpha}{D}}\right) erfc\left(\frac{x}{2\sqrt{Dt}} + \sqrt{t\left(\tfrac{1}{4D^2} + \nu - \alpha\right)}\right)\Bigg\} \end{aligned} \tag{4.6}$$

Where $erfc[z]$ is the complementary error function of z defined by $erfc[z] = \frac{2}{\sqrt{\pi}}\int_z^\infty e^{-t^2} dt$. In order to solve the case of peristalsis, we seek solution for $\varepsilon \neq 0$.A series expansion of $Q(x,t)$ in ε representing a small perturbation on the steady solution yields

$$Q(x,t;\varepsilon) = Q_0(x,t) + \varepsilon Q_1(x,t) + \varepsilon^2 Q_2(x,t) + \ldots\ldots \tag{4.7}$$

Substituting in (4.2) and equating coefficients of like powers of ε yields the following equations:

$$D\frac{\partial^2 Q_0}{\partial x^2} - \frac{\partial Q_0}{\partial x} - \nu Q_0 - \frac{\partial Q_0}{\partial t} = 0 \tag{4.8}$$

$$D\frac{\partial^2 Q_1}{\partial x^2} - \frac{\partial Q_1}{\partial x} - \nu Q_1 - \frac{\partial Q_1}{\partial t} = \cos nx.\frac{\partial Q_0}{\partial x} \tag{4.9}$$

$$D\frac{\partial^2 Q_2}{\partial x^2} - \frac{\partial Q_2}{\partial x} - \nu Q_2 - \frac{\partial Q_2}{\partial t} = \cos nx.\frac{\partial Q_1}{\partial x} \tag{4.10}$$

etc.

since (4.8) has already been solved we now need to solve (4.9), together with initial and boundary conditions

$$\begin{aligned} &Q_1(x,0) = 0 \\ &Q_1(0,t) = 0, t > 0 \\ &Q_1(x,t) \to 0 \text{ as } x \to \infty, \ t > 0 \end{aligned} \tag{4.11}$$

again, using the Laplace transform methods. After a rigorous analysis, we finally obtain a simplified form of the result for $Q_1(x,t)$ as

$$Q_1(x,t)=\frac{e^{\frac{x}{2D}-\alpha t}}{4nD}\times$$

$$\left\{\left[D\sin(nx)-\frac{1}{n^2+\frac{1}{D^2}+\frac{4(\nu-\alpha)}{D}}\left(\left(\frac{1}{D}\sqrt{1+4D(\nu-\alpha)}+n^2D\right)\sin(nx)+n(\sqrt{1+4D(\nu-\alpha)}-1)(\cos(nx)-1)\right)\right]\times\right.$$

$$e^{\frac{-x\sqrt{1+4D(\nu-\alpha)}}{2D}}erfc\left(\frac{x}{2\sqrt{Dt}}-\sqrt{\left(\frac{1}{4D}+\nu-\alpha\right)t}\right)+\left[Dsin(nx)+\frac{1}{n^2+\frac{1}{D^2}+\frac{4(\nu-\alpha}{D}}\left(\left(\frac{1}{D}\sqrt{1+4D(\nu-\alpha)}+n^2D\right)\sin(nx)+n\left(\sqrt{1+4D(\nu-\alpha)}+\right.\right.\right.$$

$$\left.\left.\left.1\right)(\cos(nx)-1)\right)\right]e^{\frac{x\sqrt{1+4D(\nu-\alpha)}}{2D}}erfc\left(\frac{x}{2\sqrt{Dt}}+\sqrt{\left(\frac{1}{4D}+\nu-\alpha\right)t}\right)\Bigg\}+$$

$$+\frac{e^{\frac{x}{2D}-\left(\frac{1}{4D}+\nu+\frac{n^2D}{4}\right)t}}{D\left(n^2+\frac{1}{D^2}+\frac{4(\nu-\alpha)}{D}\right)}sin\left(\frac{nx}{2}\right)\left[(nD-i)erfc\left(\frac{x}{2\sqrt{Dt}}+\frac{in}{2}\sqrt{Dt}\right)+(nD+i)erfc\left(\frac{x}{2\sqrt{Dt}}-\frac{in}{2}\sqrt{Dt}\right)\right] \quad (4.12)$$

We observe that for $t=0$, $erfc\left(\frac{x}{2\sqrt{Dt}}\pm\sqrt{\left(\frac{1}{4D}+\nu-\alpha\right)t}\right)=0$ and $erfc\left(\frac{x}{2\sqrt{Dt}}\pm\frac{in}{2}\sqrt{Dt}\right)=0$ and hence $Q_1(x,0)$. Substitution of $x=0$ for $t\neq 0$ yields $Q_1(0,t)$ trivially. For the case $x\to\infty, t>0, erfc\left(\frac{x}{2\sqrt{Dt}}\pm\sqrt{\left(\frac{1}{4D}+\nu-\alpha\right)t}\right)\to 0$ and $e^{\frac{x(1-\sqrt{1+4D(\nu-\alpha)})}{2D}}\to 0$ since $1-\sqrt{1+4D(\nu-\alpha)}<0$. However, $e^{\frac{x(1+\sqrt{1+4D(\nu-\alpha)})}{2D}}erfc\left(\frac{x}{2\sqrt{Dt}}+\sqrt{\left(\frac{1}{4D}+\nu-\alpha\right)t}\right)\to 0\ as\ x\to\infty$ since the second term $erfc(\,)\to 0$ faster than the exponential goes to ∞. Other terms of (4.12) behave similarly and hence $Q_1(x,t)\to 0$ as $x\to\infty$, fulfilling the conditions (4.3).

Since $Q(x,t;\varepsilon)=Q_0(x,t)+\varepsilon Q_1(x,t)+\varepsilon^2Q_2(x,t)+\ldots\varepsilon\ll 1$, we obtain the first two terms of this expansion as

$$Q(x,t)=\frac{1}{2}e^{\frac{x}{2D}-\alpha t}\left[e^{\frac{-x\sqrt{1+4D(\nu-\alpha)}}{2D}}erfc\left(\frac{x}{2\sqrt{Dt}}-\sqrt{\left(\frac{1}{4D}+\nu-\alpha\right)t}\right)+e^{\frac{x\sqrt{1+4D(\nu-\alpha)}}{2D}}erfc\left(\frac{x}{2\sqrt{Dt}}+\sqrt{\left(\frac{1}{4D}+\nu-\alpha\right)t}\right)\right]+$$

$$+\varepsilon\frac{e^{\frac{x}{2D}-\alpha t}}{4nD}\left\{\left[Dsin(nx)-\frac{1}{n^2+\frac{1}{D^2}+\frac{4(\nu-\alpha)}{D}}\left(\left(\frac{1}{D}\sqrt{1+4D(\nu-\alpha)}+n^2D\right)\sin(nx)+n\left(\sqrt{1+4D(\nu-\alpha)}-1\right)(cosnx-1)\right)\right]e^{\frac{-x\sqrt{1+4D(\nu-\alpha)}}{2D}}erfc\left(\frac{x}{2\sqrt{Dt}}-\right.\right.$$

$$\left.\sqrt{\left(\frac{1}{4D}+\nu-\alpha\right)t}\right)+\left[Dsin(nx)+\frac{1}{n^2+\frac{1}{D^2}+\frac{4(\nu-\alpha)}{D}}\left(\left(\frac{1}{D}\sqrt{1+4D(\nu-\alpha)}-n^2D\right)\sin(nx)+n\left(\sqrt{1+4D(\nu-\alpha)}+1\right)(cosnx-\right.\right.$$

$$\left.\left.1)\right)\right]e^{\frac{x\sqrt{1+4D(\nu-\alpha)}}{2D}}erfc\left(\frac{x}{2\sqrt{Dt}}+\sqrt{\left(\frac{1}{4D}+\nu-\alpha\right)t}\right)\Bigg\}+\frac{\varepsilon}{D}\frac{e^{\frac{x}{2D}-\left(\frac{1}{4D}+\nu+\frac{n^2D}{4}\right)t}}{n^2+\frac{1}{D^2}+\frac{4(\nu-\alpha)}{D}}sin\left(\frac{nx}{2}\right)\times$$

$$\times\left[(nD-i)erfc\left(\frac{x}{2\sqrt{Dt}}+\frac{in}{2}\sqrt{Dt}\right)+(nD+i)erfc\left(\frac{x}{2\sqrt{Dt}}-\frac{in}{2}\sqrt{Dt}\right)\right]+O(\varepsilon^2) \quad (4.13)$$

(4.13) gives a two-term population approximation to the solution of the model problem and can be used to predict the concentration, $Q(x,t)$, of the drug at any point, x, along the lumen and at any time, t.

V. DISCUSSION OF RESULTS AND CONCLUSION

As earlier mentioned, the result obtained in (4.13) can be used to predict the absorption of drugs in the intestinal tract. This we can do by considering special cases regarding the drug, *indomethacin*. The results do not show marked deviations for low frequencies; but for large frequencies, it has been observed that the absorption is more rapid. Thus, the results show that with higher peristaltic wave frequency, the drug particles that had diffused into intestinal fluid are more in contact with the villi surrounding the intestinal lumen and hence absorption is enhanced.

REFERENCES

[1] Olinescu, R. (1977). Pharmacokinetic Aspects. In Voicu, V and Olinescu, R. EnzymaticMechanisms and Pharmacodynamics. Kent, England: Abacus Press.

[2] Ross, J. S. and Wilson, Kathleen (1981). Foundations of Anatomy and Philsiology (5th edition). London: Churchill Livingstone and ELBS.

[3] Labaune, Jean-Pierre (1989). Handbook of Pharmacokinetics. Chichester, England: Ellis Horwood Ltd.

ISSN No:-2456-2165

[4] Cheesbrough, Monica (1987). Medical Laboratory Manual for Tropical Countries, Vol.1(2nd edn.)
[5] Linkens, D. A. (ed.) (1987). Modelling of Gastro-intestinal Electrical Rhythms. In Biological Systems, Modelling and Control. London: Peter Peregrinus Ltd.
[6] Fung, Y. C. and Yih, C. S. (1968). Peristaltic Transport. J. Applied Mech.,(Trans. ASME). 669-675.
[7] Roper, Nancy (ed.) (1987). Churchill Livingstone Pocket Medical Dictionary (14th edn.). Edinburgh: Harcourt Brace & Co.
[8] Kapur, J. N. (1986). Mathematical Models in Biology and Medicine. New Delhi: Affiliated East-West Press (Pvt) Ltd.
[9] Carlson, A. J. and Johnson, V. (1947). The Machinery of the Body. Chicago: Univ. of Chicago Press.
[10] Shapiro, A. H., Jaffrin, M. Y. and Weinberg, S. L. (1969). Persitaltic Pumping with long Wavelengths at Low Reynolds Number. J. Fluid Mech. 37: 799 – 825.
[11] Radhakrishnamacharya, G., Shulka, J. B., Chandra, P. an Sharma, R. (1989). Effect of Multiple Constrictions on Peristaltic Transport of a Fluid through a Tube of Non-uniform Cross-section. In Sahay, K. B. and Saxena, R. K. (ed.) Biomechanics. New Delhi: Wiley Eastern Ltd.
[12] Wagman, R. J. (ed.) (1996). The Medical and Health Encyclopedia. Chicago, Illinois: J. G. Ferguson Pub. Co.
[13] Schlichting, H. (1960). Boundary Layer Theory. New York: Mc-Graw Hill Book Co. Inc.
[14] Joshua, E. E. (2008). Drug Absorption in the Gastro-Intestinal Tract: A Mathematical Model. J.Nig Math. Soc.,27,109-122.