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Modeling the Effect of Coincident Drug-Release Rate and Absorption in Intestinal Lumen

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Abstract: ***Drug release rate and diffusion are paramount in the delivery of drugs to site of need, whether the drug administration isenteral or parenteral. These phenomena affect the drug absorption. It has been established that the rate of absorption also plays an important role in the drug release process. Although many of the mathematical models take into account the perfect sink condition, in a real system this assumption may not be true as there are many physiological parameters which may affect the drug delivery process. This study establishes that the desirable situation for drug effectiveness and efficacy is when the drug release rate is small compared to the diffusion rate.***

Keywords: drug, release rate, absorption, modeling, intestinal lumen

1. Introduction

The successful treatment of a particular disease state depends on the maintenance of effective drug concentration level in the body for which a constant and uniform supply of drug is desired [7]. Drug-delivery systems deliver medications to specific parts of the body and control the rates that drugs are released. Understanding how the drug is released from the delivery vehicle is crucial for achieving good results. However, the behavior of drug-delivery systems can vary extensively, depending on their surroundings [12].

Mathematical modeling of these drug delivery systems could help us understand the underlying mass transport mechanisms involved in the control of drug release. Mathematical modeling also plays an important role in providing us with valuable information such as the amount of drug released during a certain period of time or when the next dosage needs to be administered; thus potentially reducing the number of *in-vitro* and *in-vivo* experiments, which in some cases are infeasible.

A sustained drug release is defined as being one in which a drug is initially made available to the body in an amount sufficient to cause the desired pharmacological response as rapidly as is consistent with the properties of the drug determining its intrinsic availability for absorption; and one which provides for maintenance of activity at the desired level [9].

The drug absorption model is given by

$$\frac{\partial Q}{\partial t} = D\frac{\partial^2 Q}{\partial x^2} - U\frac{\partial Q}{\partial x} - \nu\, Q(x,t) \quad (1)$$

where Q is the drug concentration, D the diffusion constant, U the fluid velocity and ν the kinematic viscosity of the fluid. One of the initial boundary conditions of the drug concentration is given [6] by

$$Q(0,t) = Q_0 e^{-\alpha t}\ ,\ \alpha > 0, t > 0 \quad (2)$$

where α is related to the rate of drug release and Q_0, the initial concentration of drug in the stomach as it passes through the pyloric sphincter. We can rewrite (1) in the form

$$\frac{\partial^2 Q}{\partial x^2} - \frac{U}{D}\frac{\partial Q}{\partial x} - \nu\frac{Q}{D} - \frac{1}{D}\frac{\partial Q}{\partial t} = 0 \quad (3)$$

with initial and boundary conditions as

$$\begin{aligned} &Q(x,0) = 0, \quad 0 < x < \infty \\ &Q(0,t) = Q_0 e^{-\alpha t}, \ \alpha > 0, \ t > 0 \quad (4) \\ &Q(\infty,t) = 0, \quad t > 0 \end{aligned}$$

Using appropriate methods, for example, Laplace transforms, we obtain the solution of the diffusion-absorption model as

$$Q(x,t) = \frac{1}{2}Q_0\, e^{-\alpha t}\left\{ e^{\frac{Ux}{2D}\left(1-\sqrt{1+\frac{4D}{U^2}(\nu-\alpha)}\right)} erfc\left(\frac{x - Ut\sqrt{1+\frac{4D}{U^2}(\nu-\alpha)}}{2\sqrt{Dt}} \right) + e^{\frac{Ux}{2D}\left(1+\sqrt{1+\frac{4D}{U^2}(\nu-\alpha)}\right)} erfc\left(\frac{x + Ut\sqrt{1+\frac{4D}{U^2}(\nu-\alpha)}}{2\sqrt{Dt}} \right) \right\} \quad (5)$$

Traditional delivery systems are characterized by immediate and controlled drug release kinetics. Accordingly, drug absorption is essentially controlled by the body's ability to assimilate the therapeutic molecule and thus drug concentration in the different body tissues such as the blood, typically undergoes an abrupt increase followed by a similar decrease. However, the purpose of controlled release systems is to maintain drug concentration in the blood or in target tissues at desired values as long as possible. In other words, they are able to exert control on the drug release rate and duration [4]. Drug release kinetics follows a well defined behaviour in order to supply the maintenance dose enabling the attainment of the desired drug concentration. This step is considerably influenced by drug removal kinetics due to different factors such as metabolism.

Mathematical description of the entire drug release process is rather difficult, because of the number of physical characteristics that must be taken into consideration. These include the polymer swelling, polymer erosion, drug

dissolution/diffusion characteristics, drug distribution inside the matrix, drug/polymer ratio and system geometry. ([2],[1], [11]). Norman Loney and Susarla worked on the effect of absorption on drug release from polymer matrix and obtained interesting results [8].

We note that drugs are often stored in polymers (like capsules). They are stored in dry, shrunken state. In this condition the drug present in the dry polymeric network in the form of microcrystals, nanocrystals or amorphous state, cannot diffuse through the network meshes. Upon contact with the release fluids (water or physiological media) the polymer swells and drug dissolution takes place.

2. Comparing Drug Release Rate with Diffusion Rate

We shall assume that the process of drug release from the spherical matrix into the gastrointestinal tract is controlled by diffusion. Where the drug particles are encapsulated within a polymer matrix the liquid from the compartment enters the polymer matrix, dissolving the drug within the matrix thus enabling it to release. The drug is also assumed to release with a constant diffusivity.

In the process of diffusion solid drug particles come in contact with the GI tract and a saturated layer of drug solution is created very quickly in the surface of particles in the liquid immediately surrounding them (called the diffusion layer). The drug molecules then diffuse through the GI content to the lipoidal membrane where diffusion across the gastro intestinal membrane and absorption into the circulation takes place[5].

Hence, we are set to analyze the solution of the diffusion – absorption model obtained as the concentration of the drug in the gastrointestinal tract at any time *t*[6].

$$Q(x,t)=\frac{1}{2}Q_0\,e^{-\alpha t}\left\{e^{\frac{Ux}{2D}\left(1-\sqrt{1+\frac{4D}{U^2}(\nu-\alpha)}\right)}erfc\left(\frac{x-Ut\sqrt{1+\frac{4D}{U^2}(\nu-\alpha)}}{2\sqrt{Dt}}\right)+e^{\frac{Ux}{2D}\left(1+\sqrt{1+\frac{4D}{U^2}(\nu-\alpha)}\right)}erfc\left(\frac{x+Ut\sqrt{1+\frac{4D}{U^2}(\nu-\alpha)}}{2\sqrt{Dt}}\right)\right\}$$

We shall consider two cases as follows:
1) When the drug release rate is equivalent to the diffusion rate, i.e. $\alpha=\nu$ so that $\nu-\alpha=0$
2) When the release rate is very small compared to the diffusion rate, i.e. $\alpha \ll \nu$

These scenarios are similar to those examined by [3] concerning the rapid dissolution of solid particles and the rate of absorption and the slow dissolution of solid particles and rate of absorption. In each case he noted that the rate of absorption is controlled by the rate of diffusion into the GI tract. We shall now consider these cases in terms of drug release rate.

Case 1: If the drug release rate is equivalent to the diffusion rate

This case arises if the drug is released at the same rate at which it is absorbed into the blood stream through the intestinal lumen. On simplification of Equation (5), we obtain

$$Q(x,t)=\frac{1}{2}Q_0\,e^{-\alpha t}\left\{erfc\left(\frac{x-Ut}{2\sqrt{Dt}}\right)+e^{\frac{Ux}{D}}erfc\left(\frac{x+Ut}{2\sqrt{Dt}}\right)\right\} \quad (6)$$

It can be observed here that the result gives the predominance of two constants, the speed of the fluid, $U$and the diffusion constant, D. By the nature of the complementary error function, Equation (6) becomes equivalent to the case in which the movement of the fluid is very large compared to the rate of diffusion. The first term in the bracket of this equation can be clearly seen to approach zero as $\frac{U}{D}\to\infty$. The second term becomes very large due to the term $e^{\frac{Ux}{D}}$ and hence in the limit, $Q(x,t)$ becomes very large. As discussed in [6], this scenario may not encourage absorption since the elimination of the drug can occur as it arrives at the site to give room for more drug to be released into the system. Besides, the implication of the vanishing of the absorption term is that the drug would be swept away from the intestinal epithelium by the excessive speed of the fluid, U. This is therefore not a desirable case in drug absorption.

Case 2: If the drug release rate is small compared to the diffusion rate

We now consider the case in which $\alpha \ll \nu$. Thus, $\frac{\alpha}{\nu}\to 0$ and we obtain the solution of (1) with condition (2) for the drug concentration as

$$Q(x,t)=\frac{1}{2}Q_0\,e^{-\alpha t}\left\{e^{\frac{Ux}{2D}\left(1-\sqrt{1+\frac{4D\nu}{U^2}}\right)}erfc\left(\frac{x-Ut\sqrt{1+\frac{4D\nu}{U^2}}}{2\sqrt{Dt}}\right)+e^{\frac{Ux}{2D}\left(1+\sqrt{1+\frac{4D\nu}{U^2}}\right)}erfc\left(\frac{x+Ut\sqrt{1+\frac{4D\nu}{U^2}}}{2\sqrt{Dt}}\right)\right\} \quad (7)$$

where the symbols have their usual meanings and the complementary error function is given by

$$erfc(\xi)=\frac{2}{\sqrt{\pi}}\int_{\xi}^{\infty}e^{-\lambda^2}d\lambda\,.$$

An analysis of this result shows the predominance of the absorption term. Using particular drug pharmacokinetic data we can plot a graph of $Q(x,t)$ against t with fixed distance, x in order to predict the drug concentration at any time. This case enhances appropriate absorption of the drug and leads to its effective utilization in the body.

3. Conclusion

The drug release rate plays a key role in drug absorption. Drugs are designed with these phenomena of speed of drug release and diffusion rates as important pharmacokinetic parameters. The case when the drug release rate is very large compared to the diffusion rate, i.e. $\alpha \gg \nu$, has been seen to coincide with the case when the diffusion rate is equivalent to the release rate. That case is undesirable as drug particles can easily be swept away without any therapeutic effect. It has been noted that the most important parameters in accessing drug absorption in the gastrointestinal tract after oral or rectal administration are the diffusion coefficient$D$, the absorption rate ν , and the rate α , of drug released into the intestinal tract ([10], [6]). We conclude that drug release rate influences the rate of absorption in the gastrointestinal tract, particular if the release rate is gradual compared to the rate of diffusion.

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