A Diffusion-based Model Theory of Passive-Targeted Drug Delivery in Solid Tumors

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A model theory of passive-targeted drug delivery in sphere-shaped solid tumors is introduced on the basis of Fick's law of diffusion, with appropriate boundary and initial conditions. For a uniform initial concentration inside the tumor, the concentration is obtained as a function of time and radial position. The concentration is shown to approach the equilibrium distribution as the time elapses, as is expected by the Gedanken Experiment. The time-evolution rate is found to be determined by the diffusion coefficient of the drug in the tissue, the size of the tumor, the volume of the drug-injected region, and the concentration gradient at the boundary.

Key Words: Drug delivery, Solid tumors, Fick's law, Concentration

INTRODUCTION

Recently we have experienced great progress in drug development in conjunction with advancement of the other fields of technology. It is well known that development of drug is usually accompanied by that of delivery systems.[1-3] The two primary objectives of delivery systems are to increase patient compliance and to enhance drug efficacy and tolerance.[4] Although quite many methods achieving these goals have been reported so far, there still remain some problems. One of the interesting problems attracting the present authors lies in the "targeted drug delivery",[5-23] since targeting of toxic drugs to their specific site of action reduces the adverse side effects on healthy tissues and increases the drug uptake by the targeted cells.[4]

Targeted drug delivery problems include the active targeting based on the chemical interaction such as ligand-receptor interaction and biologic pair interaction, the first passive targeting focused on optimization of release condition such as controlling PH and enzymes, and the second passive targeting based on physical enhancement of concentration on the site in problem such as accumulation of drug. molecules in solid tumors.[24,25] Among the transport mechanisms involved in the second passive targeted delivery, diffusion may be the most dominant one, to the knowledge of the present authors.

In this paper we will present a model equation of drug diffusion in solid tumors. Note that we will limit ourselves only to the diffusion in the system here. First, we will set up a diffusion equation on the basis of Fick's theory.[26,27] We will show how the drug is administered to the site by taking into account the proper accommodation of a appropriate volume of drug solutions. For that purpose the proper boundary and initial conditions will be introduced, which will be followed by the analytic solution. The next part shall be devoted to some numerical applications with an example introduced in accordance with physical reality. Finally some further discussions and concluding remarks will be given with future plan of further studies.

A MATHEMATICAL MODEL

We consider a sphere-shaped solid tumor of radius b and take the center of the tumor as the origin of the spherical coordinates (r, θ, ϕ), as shown in Fig. 1. If we assume that

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the distribution of concentration is isotropic, then the system is spherically symmetric and the $\theta-$ and ϕ-dependence can be suppressed. Thus we can express the concentration simply in terms of radical coordinate r and time t only as $u\ (r,\ t)$. Now we suppose that initially the proper amount of drug is administered with a ultrasonic endoscope attached-injector in order that the initial concentration $u\ (r,\ 0)$ may be limited within a narrow region specified by $\leq a$.

As the system is spherically symmetric we may assume that the diffusion coefficient D_0 is constant. Then following Fick's idea,[26,27] we start with the equation of diffusion for the drug concentration $u\ (r,\ t)$ in the spherical coordinates as

$$D_0\left[\frac{\partial^2 u}{\partial r^2}+\frac{2}{r}\frac{\partial u}{\partial r}\right]=\frac{\partial u}{\partial t}\quad [0\leq r<b,\ t>0]. \tag{1}$$

If the concentration in the background tissue is u_m, the following boundary conditions (BC I, BC II) and intial condition (IC) can be adopted:

$$\text{BC I: } u\ (r,\ t) \text{ is bounded as } r\rightarrow 0. \tag{2}$$

$$\text{BC II: } \left.\frac{\partial u}{\partial r}\right|_{r=b}=-h\left[u(b,\ t)-u_m\right],\ (h>0,\ t>0) \tag{3}$$

$$\text{IC: } u(r,\ 0)=\begin{cases} u_0+u_m & (0<r<a) \\ u_m & (a<r<b)\ . \end{cases} \tag{4}$$

It should be noted that if $u_m=0$ then $u\ (r,\ 0)=u_0$, implying that the initial concentration within the small sphere $(r<a)$ is constant. And the constant $h\ (h>0)$ is introduced in order to include the concentration gradient at $r=b$ in the physically acceptable manner.

By setting up the trial solution as $u\ (r,\ t)=[V\ (r,\ t)+\Psi(r)]/r$, $V\ (r,\ t)$ being the transient solution and $\Psi(r)$ the steady-state one, we easily obtain the final solution as

$$u(r,\ t)=u_m+\sum_{n=1}^{\infty}A_n\frac{\sin\alpha_n r}{\alpha_n r}\exp\left[-\alpha_n^2 D_0 t\right] \tag{5}$$

where the coefficients A_n are given as

$$A_n=2u_0\frac{\sin\alpha_n a-\alpha_n a\cos\alpha_n a}{\alpha_n b-\sin(\alpha_n b)\cos(\alpha_n b)} \tag{6}$$

and the α_n are the eigenvalues determined by

$$\alpha_n b=(1-bh)\tan\alpha_n b. \tag{7}$$

If we introduce dimensionless parameters γ, β_n and χ as

$$\gamma=a/b,\ \beta_n=\alpha_n b,\ x=r/b$$

then we have for $0\leq\chi<1$

$$\frac{u(x,\ t)-u_m}{u_0}=\sum_{n=1}^{\infty}B_n\frac{\sin(\beta_n x)}{\beta_n x}\exp\left(-\frac{\beta_n^2 D_0}{b^2}t\right) \tag{8a}$$

where

$$B_n=2\frac{\sin\gamma\beta_n-\gamma\beta_n\cos\gamma\beta_n}{\beta_n-\sin\beta_n\cos\beta_n}\ . \tag{8b}$$

This equation can be used for numerical solution. If any experimental values of a, b, h and D_0 are available, the concentration can be pictorialized in terms of r and t. In the next section we will give an example which is physically acceptable and examine the $r-$ and $t-$dependence more in details.

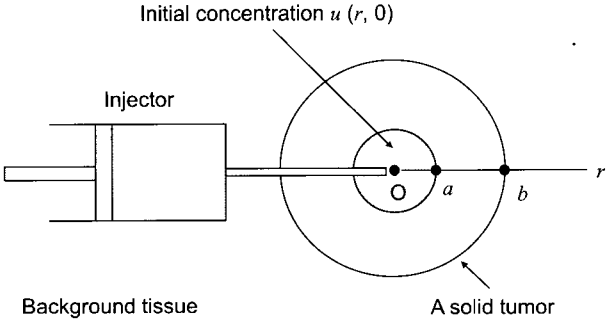

Fig. 1. Rough sketch of the system.

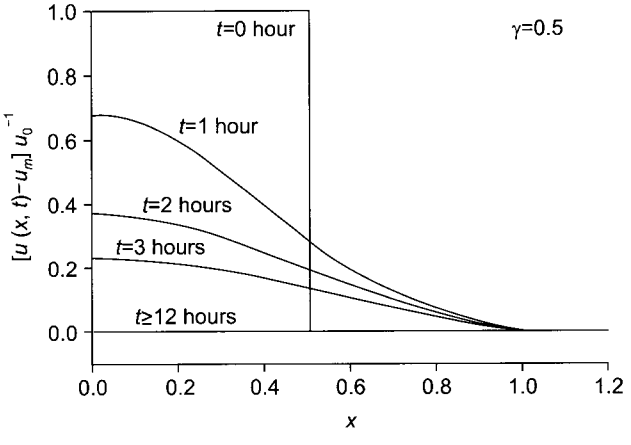

Fig. 2. $u\ (x,\ t)$ vs. x at t=1, 2 and 3 hours for γ=0.5.

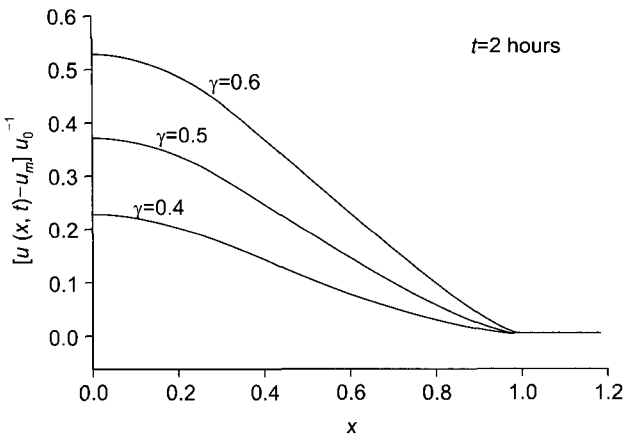

Fig. 3. u (x, t) vs. x for various values of γ at t=2 hours.

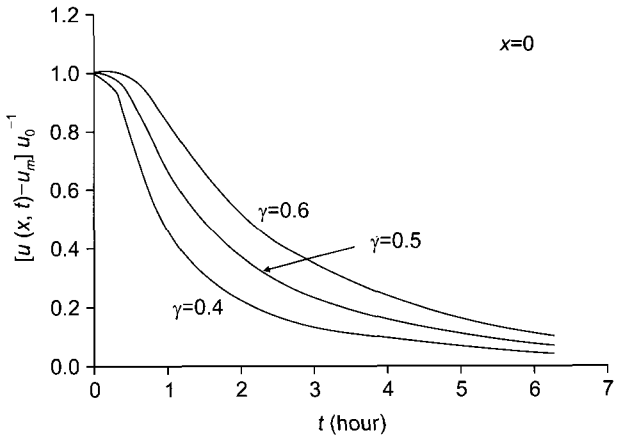

Fig. 4. u (x, t) vs. t for various values of γ at x=0.

AN EXAMPLE

As the coefficients of diffusion of most proteins and glucose in water lies in the order of $10^{-9}\sim10^{-10}$ m^2/s, we may choose D_0 for our drug in the tissue to be[28] $D_0=10^{-9}$ m^2/s. Now for demonstration we choose a fictitious system with $b=10^{-2}$ m, $\gamma=0.5$ and $h=10^6$ m^{-1}. In other words, the tumor has radius 1 cm, the radius of the drug-infused region is 0.5 cm and the thickness of the membrane located between the tumor and the surrounding medium (the background) is $1/h=10^{-6}$ m. Then we have $bh=10^4\gg1$ giving $\beta_n=-10^4\tan\beta_n$ in approximation. Thus we have the results as shown in Fig. $2\sim4$.

From Fig. 2 we see that for $\gamma=0.5$ u $(x, t)\fallingdotseq0$ at $t\geq12$ hours, which implies that the proper period of administration is 12 hours and the medicine can be injected this way twice a day. This means that if this method is adopted the time required for treatment for tumor can be reduced by increasing the frequency of administration. The reason why u $(x, t)=u_m$ for $r\geq b$ is that capacity of the background is assumed to be infinite.

Fig. 3 shows that u (x, t) at t=2 hours becomes smaller as γ decreases, implying that the decreasing rate of u (x, t) increases with decreasing γ. Note that in realistic situation the smaller value of γ is more recommended.

Fig. 4 shows that u (x, t) at the central part of the tumor decreases with t, as is expected. Note that this result is actually identical with that of Fig. 2.

FURTHER DISCUSSIONS

1. Background of the method adopted here

Although many types of tumor treatment are used, surgery is known to be the most effective and fastest one for early caught tumors. However, there is no guarantee that all microscopic extensions can be removed. In addition, there is more danger of metastasis in the case of malignant tumors when this method is used. The other methods such as radiation therapy and chemotherapy can be used in conjunction with the surgical treatment. But, as is well known, all these methods are accompanied by various adverse side effects such as nausia, vomiting, ulcer, diarrhea, depilation, marrow problem, anemia, hemorrhage and leukopenia.

The targeted drug delivery method is a part of chemotherapy that can reduce the adverse side effects to healthy organs. In the present targeted drug delivery, the highly toxic anti-tumor drugs are injected only into the limited volume specified by $r=a<b$ in order to protect the healthy tissues surrounding the tumor. Whether this method is successful depends mainly on making proper connection of the values of h defined in Eq. (3) which is closely related with the thickness of the macromembrane at the boundary of the tumor, u_0 (the concentration of the initially injected drug), and $\mu_n^2 D_0$ (the elimination rate constant). The way how these values can be determined shall be discussed in the next subsection in relation with the values of a, b, and u_m.

2. Location of the tumors and determination of U_0

Ultrasound machines equipped outside can be used to locate the tumors in the body without damaging the tissues. Note that when a pulse encounters a boundary between two tissues with different densities, reflections occurs. The sonogram can be obtained by scanning the waves and detecting the echoes generated. The frequency of the wave should be high enough to have better resolution. But super high frequency may cause some ill-effects, as claified below. The frequency of 5 MHz and intensity of about 10^{-2} W/m^2 may be appropriate for the human body.

The value of U_0 can be regulated by virtue of ultrasound and/or laser light generated by the probe. But we should pay attention so that the tip of the probe may not give damage to the healthy tissues during the passage. There is another point to be warned. The laser light and ultrasonic wave may cause to activate the growth of tumors. Note that for the energy $\triangle E$ required for formation of a tumor cell, the Kelvin temperature T should not exceed the value specified by $kT=\triangle E$, where k is the Boltzmann constant.

3. Determination of the other quantities

The first physical constant characterizing the drug is the diffusion coefficient D_0. We may guess that D_0 cannot be regulated optionally.

Another physical constant involved here is the elimination rate constant $K_{el}=\alpha_n^2 D_0=\beta_n^2 D_0/b^2$. For the most drugs usually used on the daily basis, this value is around 10^{-3} s^{-1}, and thus when b and D_0 are given, the eigenvalues β_n can be determined, which also determine the characteristics of the system [See Eq. (7)]. Note that the half life $T_{1/2}$ is given by $T_{1/2}=0.693/K_{el}$.

The quantity characterizing the tumor itself is h. When the drug is administered, the value of h should be taken into account. Among the various possible methods for measuring h, the RI (radio isotope) method may be the best. In this method, some appropriate RI materials are injected with the drug and the pattern of the concentration gradient across the barrier can be detected by the equipment located outside, and consequently the value of h can be obtained. The second best one is determining the half thickness $\triangle$ for the light absorption in the barrier, which, according to the Lambert-Beer law, is given by $\triangle(r)=0.693/\epsilon\cdot\tilde{u}(r)$, where ϵ is the molecular absorption coefficient and $\tilde{u}(r)$ is the molar concentration at $r>b$.

4. The problem left unsolved

The method dealt with in the present work is focused mainly on how to inject highly toxic anti-tumor drug. But it has not covered any chemistry of the process. In other words, determination of the macroscopic physical quantities appearing here must be based on molecular levels. And thus in order to fully understand these mechanisms the quantum-mechanical aspect of the structures of the drugs, healthy tissues, and unhealthy tissues should be known. This problem is beyond our ability and is left unsolved.

There is another problem unsolved here. How often and how much the drug should be administered depend on the half life (or the elimination rate constant) and the volume of distribution. In order to get proper information on these, we should have information on other factors such as the drug clearance and the renal and billiary excretion rates. It is to be regretted that all these should be left for future studies.

CONCLUDING REMARKS

So far we have introduced a model theory of passive-targeted drug delivery in sphere-shaped solid tumors on the basis of Fick's law of diffusion, with appropriate boundary and initial conditions. For the initial concentration U_0 of the highly toxic anti-tumor drugs injected into the limited volume inside the tumor, the distribution of concentration has been calculated. The result turned out to be quite physical [See Eq. (8) and Fig. (2)], as is expected by the Gedanken Experiment (thought experiment).

We have also discussed some physical aspects of the system in terms of the diffusion coefficient, the elimination rate constant and the concentration gradient at the boundary. As stated in the last section, we have not covered any chemistry involved in the system, due to lack of further information and our ability. All the unsolved problems shall be pursued continually.

It is to be regretted that the present theory can not be

compared with any other thoeries or experimental results since they are not available as yet. We hope that the related experiment would appear in the near future so that the present theory can be compared with it.

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단단한 종양 안에 수동 조준된 약물의 전달에 관한 확산에 기초한 모델 이론

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공모양의 단단한 종양안에서 수동조준된 약물의 전달에 관한 모델이론이 적절한 경계조건과 초기조건하에서 픽의 확산법칙으로부터 유도된다. 종양안의 농도는 초기값이 일정하면 시간과 지름의 함수로 나타난다. 생각실험(사고실험)으로부터 예측되는 바와 같이, 농도는 시간이 경과함에 따라 평형값에 접근한다. 시간에 따른 농도의 변화는 조직안의 약물의 확산계수, 종양의 크기, 주입된 약물의 양, 경계면에서의 농도의 물매(gradient)에 의해 결정된다.

중심단어: 약물의 전달, 단단한 종양, 픽의 법칙, 농도