Drug release profiling of microspheres

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BENG 221

November 28th, 2014

Introduction:

Drug release is a crucial consideration in the design of any new pharmaceutical drug delivery system. Microencapsulation of compounds has become a popular technique in recent years, allowing for sustained release of a drug over time, consistent control over the drug release profile, and targeted delivery of a drug to its active site. Microencapsulation is a term commonly used two describe two distinct forms of structures: microspheres and microcapsules. A microsphere tends to refer to a homogeneous structure consisting of one continuous phase, whereas a microcapsule refers to a reservoir-like structure with a well-defined core and membrane [1]. Depending on the encapsulating material and drug type, the release kinetics of these structures may depend on drug dissolution, solute diffusion (and osmosis), polymeric matrix swelling, and material degradation. In the case of microcapsules, the drug release profile may be predictably modeled by Fick's Law when diffusion is assumed as the rate-limiting step [2]. Our goal is to examine the various diffusion-controlled drug release profiles that can be attained through the use of a microsphere system.

Primary models for microsphere drug release:

Microcapsules are described as reservoir devices, which may be modeled as either constant or non-constant activity sources. When first in contact with an aqueous solution, water permeates the microcapsule membrane and begins the dissolution of the drug core. If all of the drug is dissolved quickly, the system may be modeled as a non-constant source [Figure 1] which follows first-order release kinetics [2][3]. As drug diffuses across the membrane into a perfect sink, the resulting decreased concentration gradient reduces the rate of diffusion, causing an exponential decay of drug release rate over time. Conversely, if dissolution of the drug has limited solubility, only part of the drug will be dissolved initially and the system can be modeled as a constant source [Figure 2] with zero-order release kinetics [2][3]. The concentration gradient into a perfect sink will remain constant so long as undissolved drug remains in the reservoir.

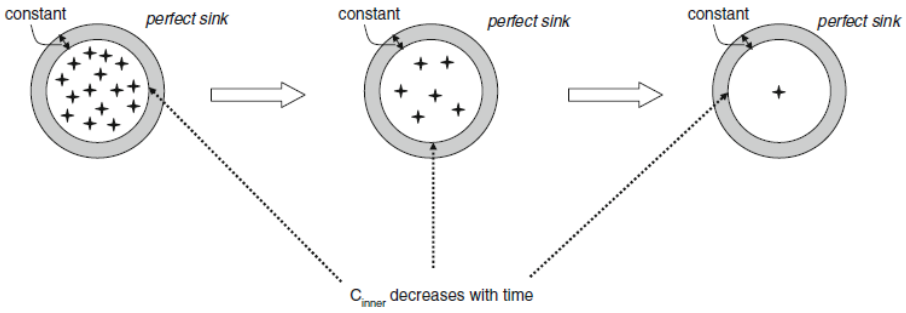


Figure 1: Microcapsule modeled as a reservoir with a non-constant activity source. [2]

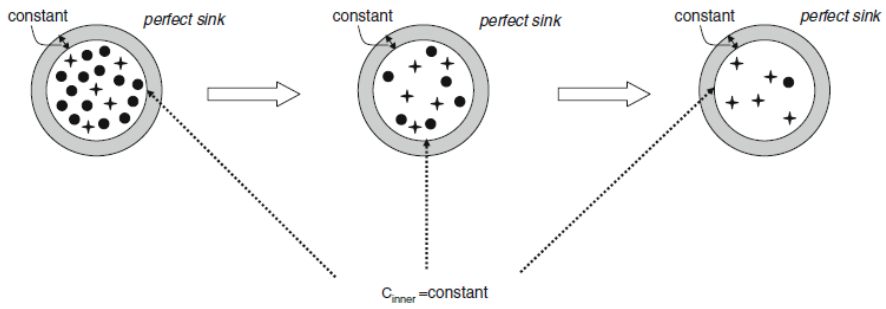


Figure 2: Microcapsule modeled as a reservoir with a constant activity source. Circles represent undissolved drug.[2]

Of further consideration for the drug release kinetics is the initial drug loading of the membrane. Depending upon the relation between the initial distribution of diffused drug within the membrane and the reservoir release profile, the system may experience either a burst effect (higher initial release rate) or a lag-time effect (lower initial release rate) [2][3]. These two conditions are demonstrated in Figure 3 for a zero-order release profile.

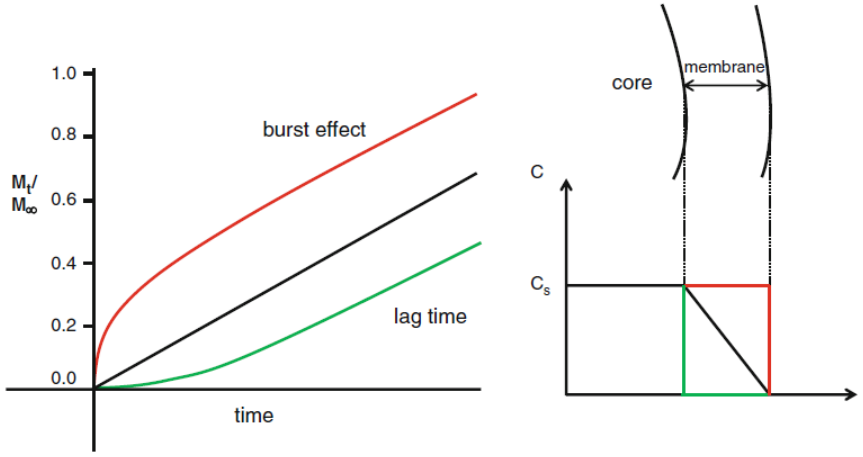
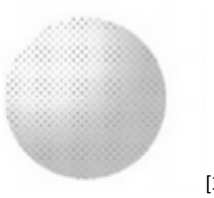


Figure 3: Initial burst and lag-time effects for constant-activity source microcapsule reservoirs [2]

The focus of this report will be monolithic solutions. Monolithic solutions describe microspheres that comprise of a fully spherical matrix, as opposed to a microsphere with only a polymer-matrix membrane. Monolithic solutions have the drug homogenously distributed throughout the sphere and contain an amount of drug that can be instantly dissolved. This often a poor drug delivery system, as the release kinetics are not zero-order, but this is also the easiest type of microsphere to model.



[3]

Figure 4:A monolithic solution microsphere, the drug is homogenously distributed throughout the spherical matrix

A monolithic dispersion is similar to a monolithic solution. The difference is the amount of drug inside the spherical matrix. If there is enough drug inside the sphere for the drug concentration to reach the solubility limit and still have undissolved drug inside the matrix, the microsphere is known as a monolithic dispersion. These microspheres have zeroth-order release kinetics while there is still undissolved drug inside the matrix, which is highly desirable.

[3]

Figure 5:A monolithic dispersion microsphere, not all of the drug can be dissolved at once due to the solubility limit

Examples of Microcapsule Drug Applications:

Targeted Drug Delivery – Chemotherapeutics in the brain:

Drug delivery and stability pose significant challenges in the treatment of carcinomas of the brain. Systemically delivered chemotherapeutic agents tend to have low response rates due to the interference of the blood-brain barrier, low chemical stability of the drug, systemic side-effects, low drug distribution profiles, and small payloads of drug to the brain [4]. Arthroscopic delivery of chemotherapeutic polymer microspheres is one potential solution to address these issues. Current techniques include the Gliadel wafer, but it is limited by its large size and low drug distribution and payload. Further, the efficacy of the Gliadel wafer has been shown to be quite low [5]. The development of biodegradable, controlled release, polymeric microcapsules for implantation into the brain is currently an area of great interest, with many groups conducting research on the topic.

In particular, one group has attempted to functionalize doxorubicin-loaded PLGA microcapsules with folic acid to improve their targeting of tumor cells [6]. According to their research, the DOX release rate increased in an environment of lower pH [Figure 4]. They theorized that this may be due to DOX having a higher solubility under acidic pH than physiological pH. Due to the slightly acidic nature of the tumor microenvironment, this quality could be valuable in vivo. Note that the drug release profile exhibits first-order release kinetics.

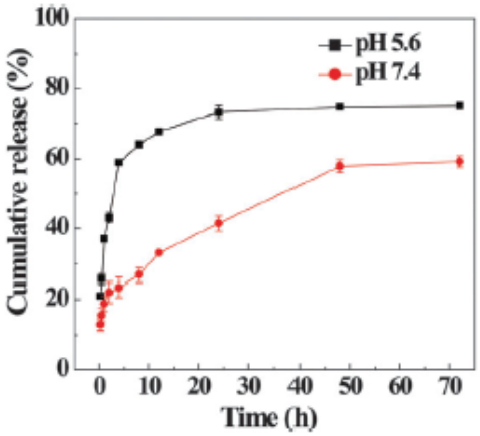


Figure 5 – In vitro release of DOX from PLGA–DOX–PEI–PEG–FA HMs as a function of time under different pH conditions. The initial drug load was 80.1%. [6]

Controlled Drug Delivery – Delivery of drugs with low therapeutic index:

One area of extreme significance for microcapsule drug delivery is in the controlled release of drugs with a low therapeutic index. The therapeutic index (TI) is a comparison of the amount of therapeutic agent necessary for an effective dosage to the amount that causes toxicity. The most basic form of this ratio is as follows:

$$TI = MTD/MED$$

where MTD and MED are the minimum toxic dose and minimum effective dose, respectively

In such cases, an ideal drug release profile is a zero-order release kinetic, maintaining the plasma concentration at a value between the MED and the MTD.

Burst effects may occur when microcapsules have been stored for long enough for drug to permeate the membrane. This can be especially dangerous with drugs that have very regimented release profiles (such as those with low therapeutic index) because it causes a spike in the concentration of drug released initially. One example of a drug with a low TI is theophylline, a bronchodilator used in the treatment of asthma and COPD. It has a “narrow” therapeutic index (less than 2) [7], making proper dosing of the drug essential. Several studies have been conducted to find the ideal membrane material for both zero-order release kinetics

and stability of theophylline microcapsules over time (no burst effect) [8][9]. The release profiles of two examples are given below [Figure 5].

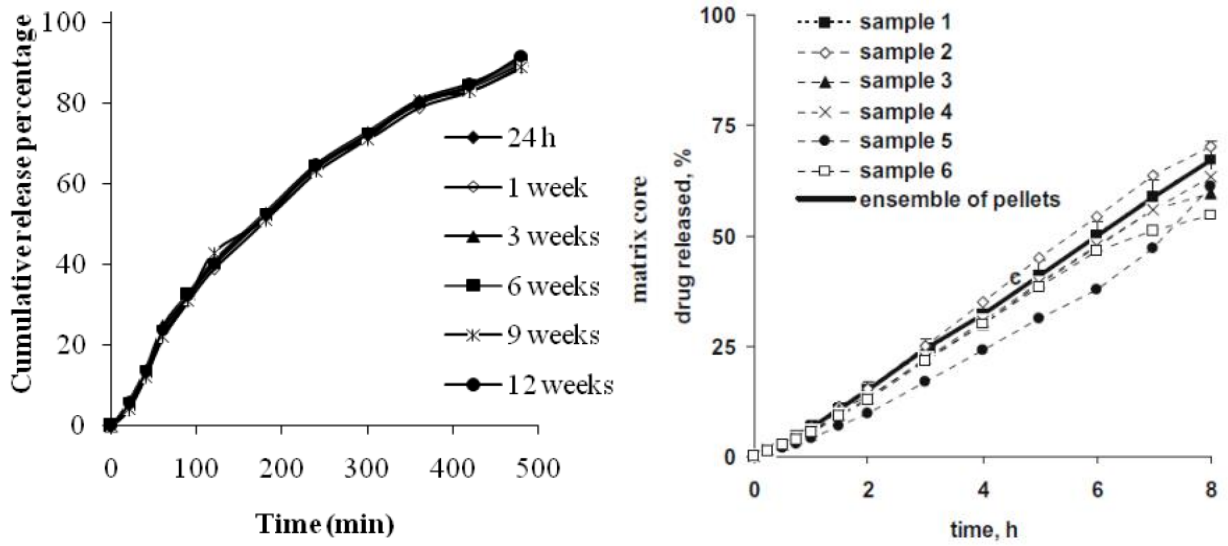


Figure 6 – *(left)* Release profiles of ethyl cellulose microcapsules taken at different times post-fabrication. [8] *(right)* Theophylline release from single pellets (taken every 2 hours) as well as an ensemble of pellets in 0.1 N HCl from drug matrix cores, coated with ethylcellulose:PVA-PEG graft copolymer 85:15 (coating level: 15%). [9]

Sustained Drug Delivery – Encapsulation of drugs of low half-life:

Drugs with a low half-life must be taken often, due to their tendency to denature quickly in the body. Insulin is one example, with type I diabetes patients often requiring pulmonary administration of fast-acting insulin prior to each meal and at least one long-acting subcutaneous injection of insulin per day [10]. Repeated injections may have a variety of side-effects, the worst of which being tissue necrosis, bacterial infection, or nerve damage [11]. Aside from its fast degradation rate, insulin also has a low therapeutic index, so proper dosing is essential.

Encapsulation of insulin can offer some protection from the environment and enzymes of the body, improving its release profile significantly. Long-acting pulmonary applications of insulin could be a possibility with the creation of microcapsules as a dry powder inhaler formulation. The use of PLGA to create insulin microcapsules shows promise, as in vitro studies of the drug release profile suggest a reasonable drug release profile and a safe burst condition [Figure 7] [10][11].

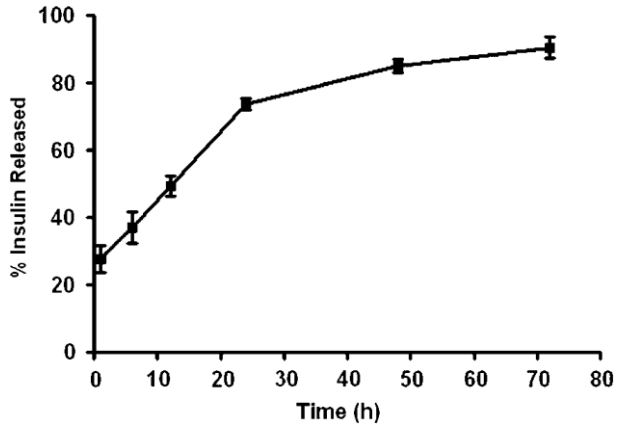


Figure 6 – Sustained release profile of insulin from PLGA microspheres in vitro [10]

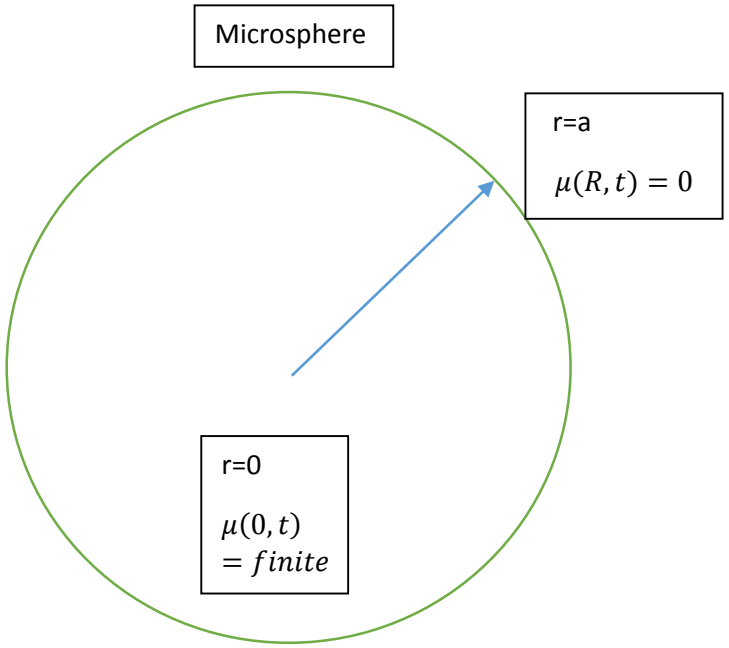
Description of the Model:

Having established the importance of controlling the drug release profile of microsphere, we modeled a solid microsphere matrix that was homogenously doped with a solid drug, a monolithic solution microsphere. As time proceeds, the surrounding medium permeates into the matrix and dissolves the drug, allowing for diffusion of the drug to the outside of the sphere. For simplicity sake, we assume that the external medium permeates throughout the whole sphere at the initial condition, so that the drug concentration is exactly at the solubility limit throughout the sphere at time 0. We assumed that the external liquid medium was well mixed, so that it acted as a perfect sink. Further, we assumed no imperfections in the membrane of the microcapsule and that there was no significant degradation of the membrane over time. Finally, because of the release profile of our microsphere is ideally symmetrical in all angular directions, we modeled the diffusion using the 1D spherical diffusion equation:

$$\frac{\partial \mu}{\partial \mathrm{t}} = \frac{D}{r^2}\frac{\partial}{\partial \mathrm{r}}\left(r^2\frac{\partial \mu}{\partial \mathrm{r}}\right) + \frac{1}{r^2\sin\phi}\frac{\partial}{\partial \phi}\left(sin\phi\,\frac{\partial \mu}{\partial \phi}\right) + \frac{1}{r^2\sin^2\phi}\left(\frac{\partial^2 \mu}{\partial \theta^2}\right)$$

0 0

The two-dimensional representation of the model is as follows:



- Boundary Conditions:
  $\mu\,(a\,,t\,)=0 \quad \mu\,(0,t\,)$ is finite
- Initial Condition:
  $\mu\,(r\,,0)=u_0$ for r ∈ [0, R]

We used the following values for the variables for analysis, taken from ranges of possible values established by the literature.

Parameter	Variable	Value
Diffusion coefficient	D	0.01 µm^2/s
Radius of microcapsule	R	62.5 µm
Saturated Concentration	U_0	244 mol/m^3

Equation Repertoire:

Fick's Second Law of Diffusion: $\frac{\delta \varphi}{\delta t} = D\frac{\delta^2 \varphi}{\delta x^2}$

- predicts how diffusion causes the concentration to change with time

Noyes-Whitney Equation: $\frac{dm}{dt} = A\frac{D}{d}(C_s - C_b)$

- m:mass of dissolved material
- t: time
- A: surface area of the interface between the dissolving substance and the solvent
- D: diffusion coefficient
- d: thickness of the boundary layer of the solvent at the surface of dissolving substance
- C_s : concentration of substance on surface
- C_b : concentration of substance in bulk of solvent

Sturm-Liouville Equation: $\frac{\delta}{\delta x}[p(x)\frac{\delta y}{\delta x}] + [w(x) - q(x)]y = 0$

- is a constant and w(x) is a known function called either the density or weighting function
- solutions (with appropriate boundary conditions) of are called eigenvalues and the corresponding $u(x)$ eigenfunctions. The solutions of this equation satisfy important mathematical properties under appropriate boundary conditions

Helmholtz Equation: $x^2\frac{\delta^2 y}{\delta x^2} + 2x\frac{\delta y}{\delta x} + [x^2 - n(n+1)]y = 0$

- Solution to this equation are two linearly independent solutions called spherical Bessel functions j_n and y_n and are related to the ordinary functions J_n and Y_n by:
  - $j_n = \sqrt{\frac{\pi}{2x}}J_{n+\frac{1}{2}}(x)$
  - $y_n = \sqrt{\frac{\pi}{2x}}Y_{n+\frac{1}{2}}(x) = (-1)^{n+1}\sqrt{\frac{\pi}{2x}}J_{-n-\frac{1}{2}}(x)$
- The spherical Bessel functions can also be written as Rayleigh's Formulas

- $j_n = (-x)^n (\frac{1}{x}\frac{d}{dx})^n \frac{sin(x)}{x}$
- $y_n = -(-x)^n (\frac{1}{x}\frac{d}{dx})^n \frac{cos(x)}{x}$

- The first spherical Bessel function $j_0(x)$ is also known as the (unnormalized) sinc function
  - $j_0(x) = \frac{sin(x)}{x}$
- and
  - $y_0(x) = -j_{-1}(x) = -\frac{cos(x)}{x}$

In the modeling of drug release from drug delivery system, a reservoir system in particular, we begin with the 3 dimensional diffusion equation which can be derived from Fick's Second Law which predicts how diffusion causes the concentration to change with time.

$$\frac{\delta u(r,t)}{\delta t} = D\Delta u(r,t) \quad (1)$$

$$\Delta u(r,\varphi,\theta) = \frac{1}{r^2}\frac{\delta}{\delta r}(r^2\frac{\delta u}{\delta r}) + \frac{1}{r^2}sin\varphi\frac{\delta}{\delta\varphi}sin(\varphi\frac{\delta u}{\delta\varphi}) + \frac{1}{r^2}sin^2(\varphi)\frac{\delta^2 u}{\delta\theta^2} \quad (2)$$

By assuming that our system is spherically symmetric we eliminate the angular dependence of equation (2) and reduce equation (1) to one dimension

Therefore, $\Delta u(r,\varphi,\theta)$ becomes :

$$\Delta u(r) = \frac{1}{r^2}\frac{\delta}{\delta r}(r^2\frac{\delta u}{\delta r}) \quad (3)$$

Then,

$$\frac{\delta u(r,t)}{\delta t} = D\frac{1}{r^2}\frac{\delta}{\delta r}(r^2\frac{\delta u}{\delta r}) \quad (4)$$

Initial and Boundary Conditions

$u(r,0) = C \quad \frac{\delta u}{\delta r}|_{r=0,t} = 0 \quad u(R,t) = u_R(t) = 0$

Our reservoir system has zero flux at the center of the sphere, primarily due to an excess initial drug concentration, and a concentration constant at the boundary which is determined by the dissolution rate.

$$u_R(t) = \frac{(4\pi DKc_s R_0 R_1)}{R_0 - R_1} t \tag{5}$$

Note: the right side of equation (5) is derived from the Noyes-Whitney Equation[Modeling of diffusion controlled drug delivery], which quantifies the speed of a dissolution process. K is the partition coefficient between the reservoir and the membrane ($\frac{D_1}{D_2}$) and c_s is the solubility limit

In order to solve equation (4) with the given boundary conditions, we must can obtain a problem with zero boundary conditions, which can be achieve by separating $u(r,t)$ into two parts.

$$u(r,t) = u_T(r,t) + u_R \tag{6}$$

By considering u_R as a constant, the equation (6) has $\frac{\delta u_T}{\delta r}$ and $u_T(r,t)$ equal zero at r=0 and r=R respectively. Thus the equation will satisfy the differential equation (4) and the boundary conditions

With the assumption we use separation of variables to acquire our solution.

$$u_T(r,t) = P(r)T(t) \tag{7}$$

and obtain the following results

$$\frac{\delta u}{\delta t} = P(r)\frac{dT(t)}{dt} \quad \frac{\delta u}{\delta r} = T(t)\frac{dP(r)}{dr} \tag{8}$$

When we substitute our results into equation (1), we obtain

$$\frac{1}{D}\frac{1}{T(t)}\frac{dT(t)}{dt} = \frac{1}{P(r)}\frac{1}{r^2}\frac{d}{dr}\left(r^2\frac{dP(r)}{dr}\right) \tag{9}$$

The left side of equation (9) is a function of t only, while the right is a function of r only. This can only hold if, and only if, both sides are equal to a constant.

$$\frac{1}{D}\frac{1}{T(t)}\frac{dT(t)}{dt} = \frac{1}{P(r)}\frac{1}{r^2}\frac{d}{dr}\left(r^2\frac{dP(r)}{dr}\right) = -\lambda^2 \tag{10}$$

Note: we introduced $-^2$ because we suspect the displacement will oscillate in time

The first equation in (10) yields the following,

$$\frac{dT(t)}{dt} = -\lambda^2 DT(t) \tag{11}$$

which has the general solution

$$T(t) = Ce^{-\lambda^2 Dt} \tag{12}$$

The second equation in (10) can be solved as follows

$$\frac{d}{dr}r^2\frac{dP(r)}{dr} + \lambda^2 r^2 P(r) = 0 \tag{13}$$

When expanded, equation (13) becomes a Sturm-Liouville Equation with weight $\lambda^2 r^2$.

If we substitute the aforementioned weight for a dimensionless variable such as $x^2 = \lambda^2 r^2$ .Then our Sturm-Liouville Equation becomes a Helmholtz Equation with $n = 0$

$$x^2 \frac{\delta^2 P(x)}{\delta x^2} + 2r \frac{\delta P(x)}{\delta x} + [x^2 - 0]P(x) = 0 \text{ for } n = 0 \qquad (14)$$

Note: granted that we modeled a spherically symmetric microcapsule, the anti-symmetric solutions have been eliminated hence the reason why $n = 0$

The solution to equation (14) consists of two linearly independent solutions called spherical Bessel functions j_n and y_n and are related to the ordinary functions J_n and Y_n by:

$$j_n = \sqrt{\frac{\pi}{2x}} J_{n+\frac{1}{2}}(x) \qquad (15)$$

$$y_n = \sqrt{\frac{\pi}{2x}} Y_{n+\frac{1}{2}}(x) = (-1)^{n+1} \sqrt{\frac{\pi}{2x}} J_{-n-\frac{1}{2}}(x) \qquad (16)$$

in which the general solution is the following

$$P(r) = AJ_0(r) + BY_0(r) \qquad (17)$$

To simplify these spherical Bessel functions we rewrote them using Rayleigh's Formulas

$$j_n = (-x)^n \left(\frac{1}{x}\frac{d}{dx}\right)^n \frac{sin(x)}{x} \qquad (18)$$

$$y_n = -(-x)^n \left(\frac{1}{x}\frac{d}{dx}\right)^n \frac{cos(x)}{x} \qquad (19)$$

with the first spherical Bessel functions $j_0(x)$ and $y_0(x)$, zeroth-order functions, being

$$j_0(x) = \frac{sin(x)}{x} \qquad (20)$$

$$y_0(x) = -j_{-1}(x) = -\frac{cos(x)}{x} \tag{21}$$

Thus the general solution becomes

$$P(r) = A\frac{sin(\lambda r)}{r} + B\frac{cos(\lambda r)}{r} \tag{22}$$

Now we will show that the proposed solution satisfies equation (13)

Differentiating the proposed solution gives

$$\frac{dP(r)}{dr} = \lambda A\frac{cos(\lambda r)}{r} - \lambda B\frac{sin(\lambda r)}{r} - A\frac{sin(\lambda r)}{r^2} - B\frac{cos(\lambda r)}{r^2} \tag{23}$$

Substituting the derivative of the proposed solution into equation (13) gives

$$\frac{d}{dr}r^2\frac{dP(r)}{dr} = \frac{d}{dr}r^2\left[\lambda A\frac{cos(\lambda r)}{r} - \lambda B\frac{sin(\lambda r)}{r} - A\frac{sin(\lambda r)}{r^2} - B\frac{cos(\lambda r)}{r^2}\right] \tag{24}$$

$$= \frac{d}{dr}\left[\lambda Arcos(\lambda r) - \lambda Brsin(\lambda r) - Asin(\lambda r) - Bcos(\lambda r)\right]$$

$$= \lambda Acos(\lambda r) - \lambda^2 Arsin(\lambda r) - \lambda Bsin(\lambda r) - \lambda^2 Brcos(\lambda r) - \lambda Acos(\lambda r) + \lambda Bsin(\lambda r)$$

$$= -\lambda^2 Arsin\lambda r - \lambda^2 Brcos(\lambda r) \tag{25}$$

Substituting this result (25) and the proposed solution (22) into equation (13) shows that the proposed solution indeed satisfies the differential equation

$$\frac{d}{dr}r^2\frac{dP(r)}{dr} = -\lambda^2 Arsinr - \lambda^2 Brcos(r)$$

$$\lambda^2 r^2 P(r) = \lambda^2 r^2\left[A\frac{sin(r)}{r} + B\frac{cos(r)}{r}\right] = \lambda^2 Arsinr + \lambda^2 Brcos(r)$$

Therefore,

$$\frac{d}{dr}r^2\frac{dP(r)}{dr} + \lambda^2 r^2 P(r) = 0$$

When evaluating the proposed solution (22) at r=0, the solution becomes infinite ($\frac{cos(\lambda r)}{r}|_{r=0} = \frac{1}{0} = \infty$). Thus in order to retain a finite solution at the center of the sphere we must set B=0.

Equation (7) becomes

$$u_T(r,t) = T(t)P(r) = ACe^{-\lambda^2 Dt}\frac{sin(r)}{r} = Ee^{-\lambda^2 Dt}\frac{sin(r)}{r} \qquad (26)$$

In order to satisfy the condition $u_T(R,t) = 0$

$$\frac{sin(\lambda R)}{R} = 0 \qquad (27)$$

Then,

$$\lambda R = n\pi \text{ or } \lambda_n = \frac{n\pi}{R}$$

The general solution for $u_T(R,t)$ is a sum of all eigenvalue solutions multiplied by a different constant E_n

$$u_T(r,t) = \sum_{n=1}^{\infty} E_n e^{-\lambda_n{}^2 Dt}\frac{sin(\lambda_n r)}{r} \qquad \text{with} \quad \lambda_n = \frac{n\pi}{R}$$

Thus $u(r,t)$ becomes

$$u(r,t) = \sum_{n=1}^{\infty}\frac{E_n}{r}sin(\frac{n\pi r}{R}) + u_R \qquad (28)$$

We must now satisfy the initial condition $u(r,0)$

$$u(r,0) = u_0(r) - u_R = \sum_{n=1}^{\infty} \frac{E_n}{r} sin(\frac{n\pi r}{R}) \quad (29)$$

The eigenfunctions $\frac{1}{r} sin(\frac{n\pi r}{R})$ form an orthogonal set of eigenfunctions. In addition, recall the Sturm-Liouville weighting factor r^2, that must be used in the orthogonality integral. Thus when we multiply both sides of equation (29) by $r^2 \frac{1}{r} sin(\frac{m\pi r}{R})$ and integrate over the boundary, we get the following

$$\int_0^R \left[u_0(r) - u_R\right] r^2 \frac{sin(\frac{m\pi r}{R})}{r} dr = \int_0^R \sum_{n=1}^{\infty} E_n r^2 \frac{sin(\frac{n\pi r}{R})}{r} \frac{sin(\frac{m\pi r}{R})}{r} dr$$

$$= E_m \int_0^R sin^2(\frac{m\pi r}{R}) dr \quad \text{for} \quad m = n \quad (30)$$

Solving for E_m and evaluating the integral in equation (30) yields the following results

$$E_m = \frac{\int_0^R \left[u_0(r) - u_R\right] r \, sin(\frac{m\pi r}{R}) dr}{\int_0^R sin^2(\frac{m\pi r}{R}) dr} = \frac{2}{R} \int_0^R \left[u_0(r) - u_R\right] r \, sin(\frac{m\pi r}{R}) dr$$

$$= \frac{2\left[u_0(r) - u_R\right]}{R} \int_0^R r \, sin(\frac{m\pi r}{R}) dr = \frac{-2R\left[u_0(r) - u_R\right] cos(m\pi)}{m\pi}$$

Now since $cos(m\pi)$ is 1 when m is even and -1 when m is odd, we can write the final result as follows

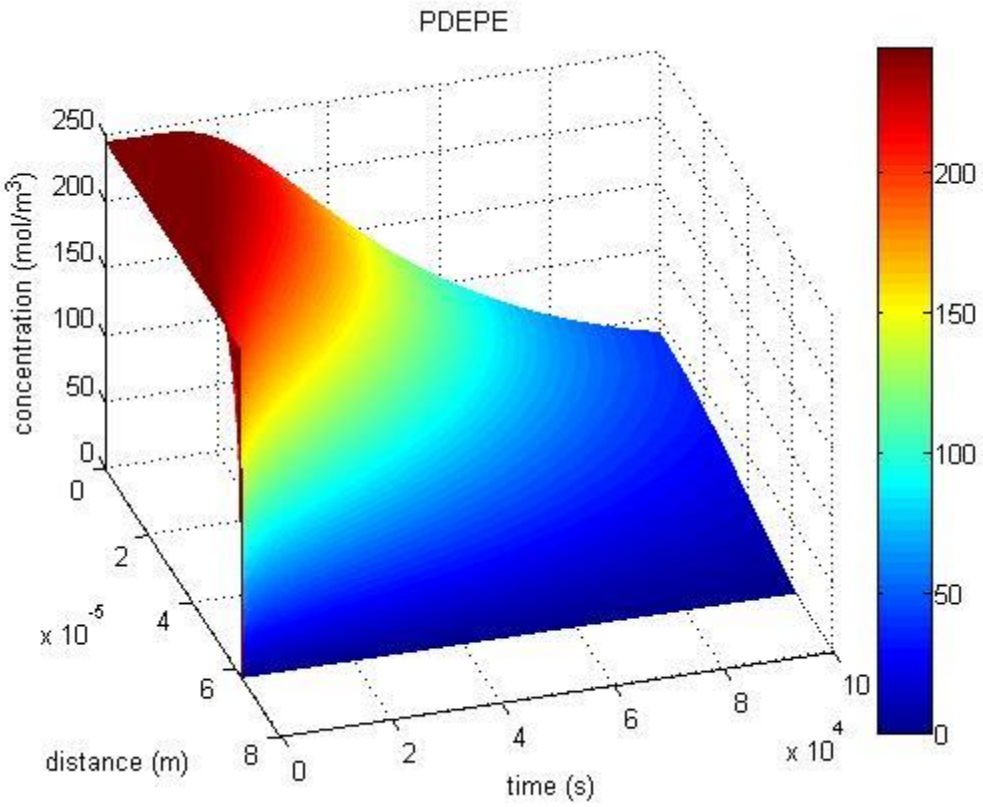
$$E_m = \frac{-2R\left[u_0(r) - u_R\right](-1)^m}{m\pi} \quad (31)$$

Substituting this result into equation (28) gives the solution to the diffusion equation when $u_0(r)$ is equal to a constant, and the concentration at the boundary u_R is zero

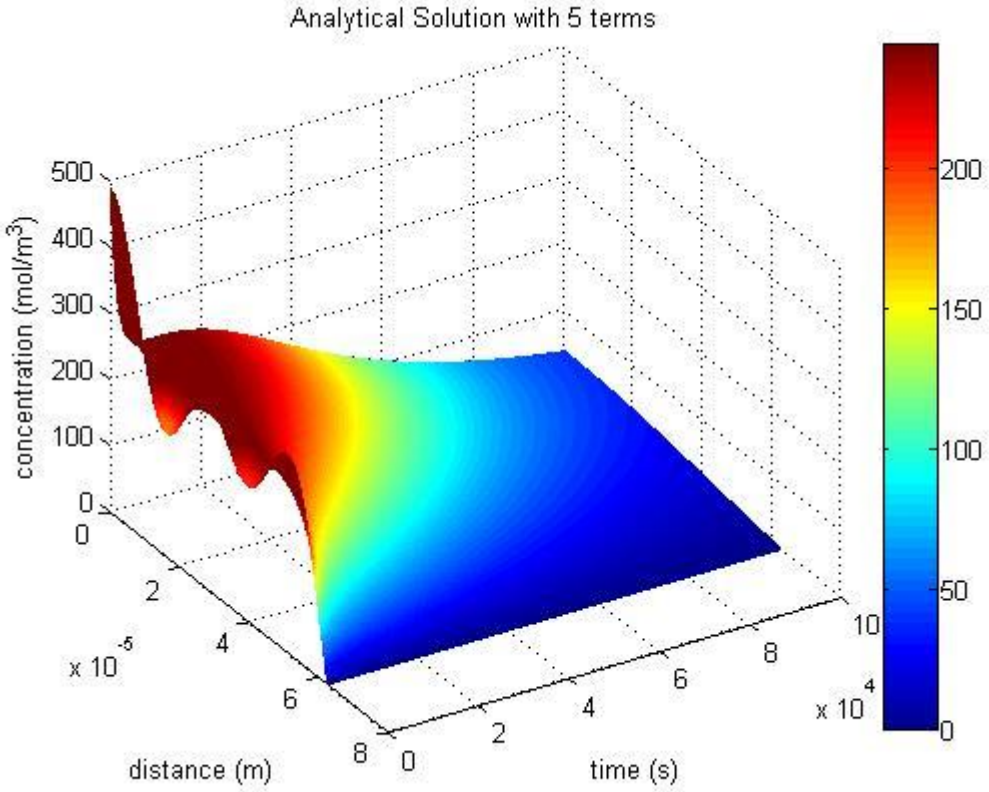
$$u(r,t) = \frac{-2R[u_0]}{\pi} \sum_{m=1}^{\infty} \frac{(-1)^m}{m} e^{-\lambda_n{}^2 Dt} \frac{\sin(\lambda_n r)}{r} \text{ with } \lambda_n = \frac{m\pi}{R}$$

Is our final solution.

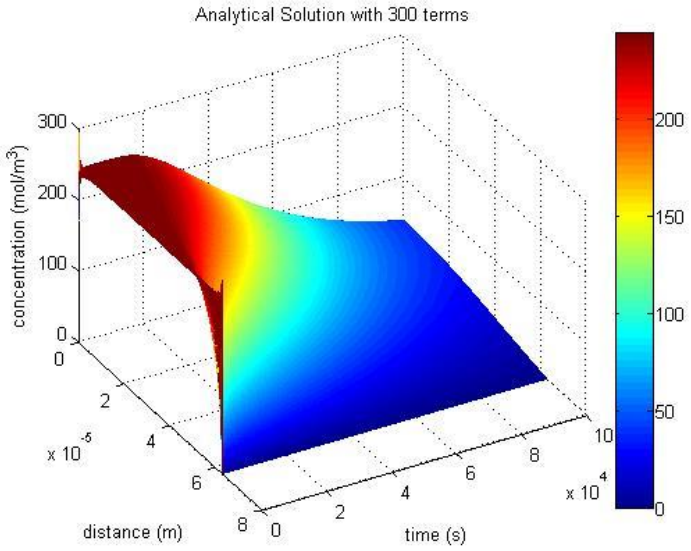
Graphs and Analysis:



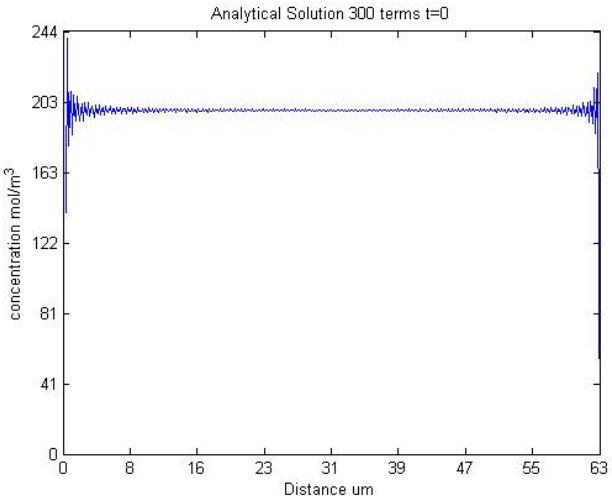
The matlab PDEPE solution above shows the concentration over space and time in the microsphere. The curve makes complies with intuition, as the initial condition is clearly shown, where the whole sphere is loaded with the same concentration of drug. There is an immediate discontinuity where the very edge of the sphere completely eludes all drug into the blood rushing by. As time goes on, the concentration inside the sphere eventually reaches zero. It takes much longer for the inside of the sphere to reach zero, which is expected. With our given constants, it takes about one day to reach an insignificant level of drug release from the microsphere.



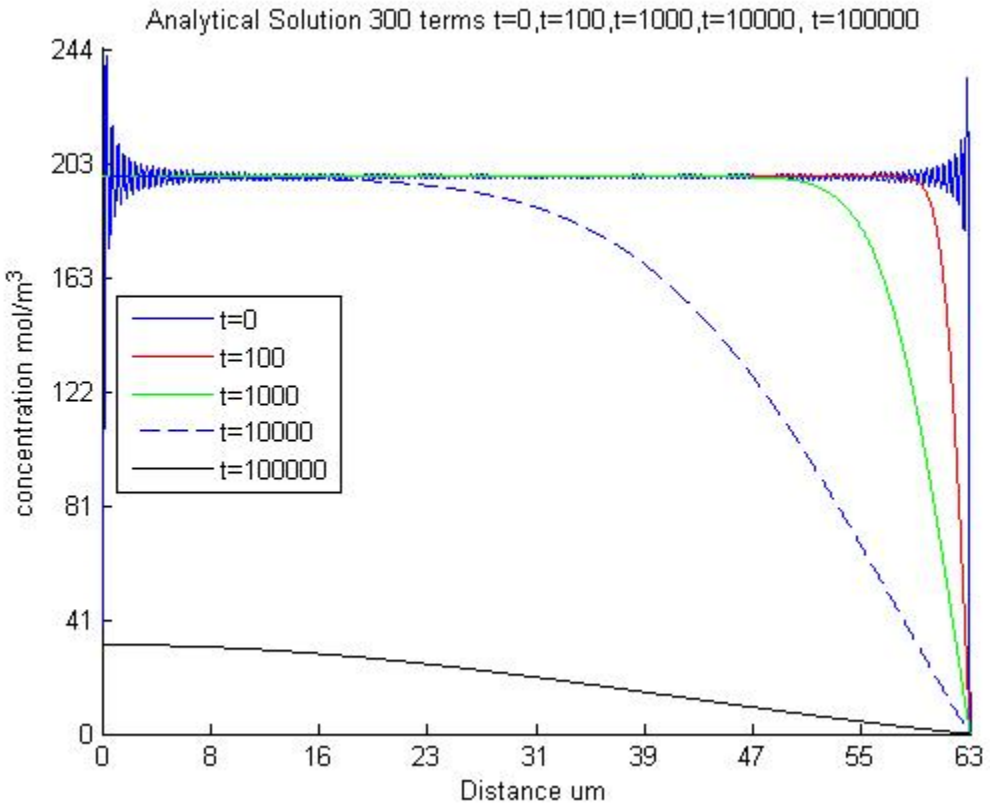
The analytical solution shows a similar profile to the PDEPE solution when time is greater than zero. This means our analytical solution is correct. Near t=0 the analytical solution resembles a sinusoidal function. This is expected, as the small number of summed terms cannot form the correct solution when t is small.



When 300 terms are used the analytical solution looks almost exactly like the PDEPE solution. There are some overshoots near the discontinuities.



As stated before, the analytical solution shows overshoots near the edges of the domain. This is a property of summing many sinusoidal functions, called Gibbs phenomenon. The overshoots will not disappear with any finite number of terms, but with an infinite number of terms our analytical solution will be completely accurate.



The figure above shows various slices of the analytical solution at several times. As time proceeds the total amount of drug inside the microsphere decreases. The drug

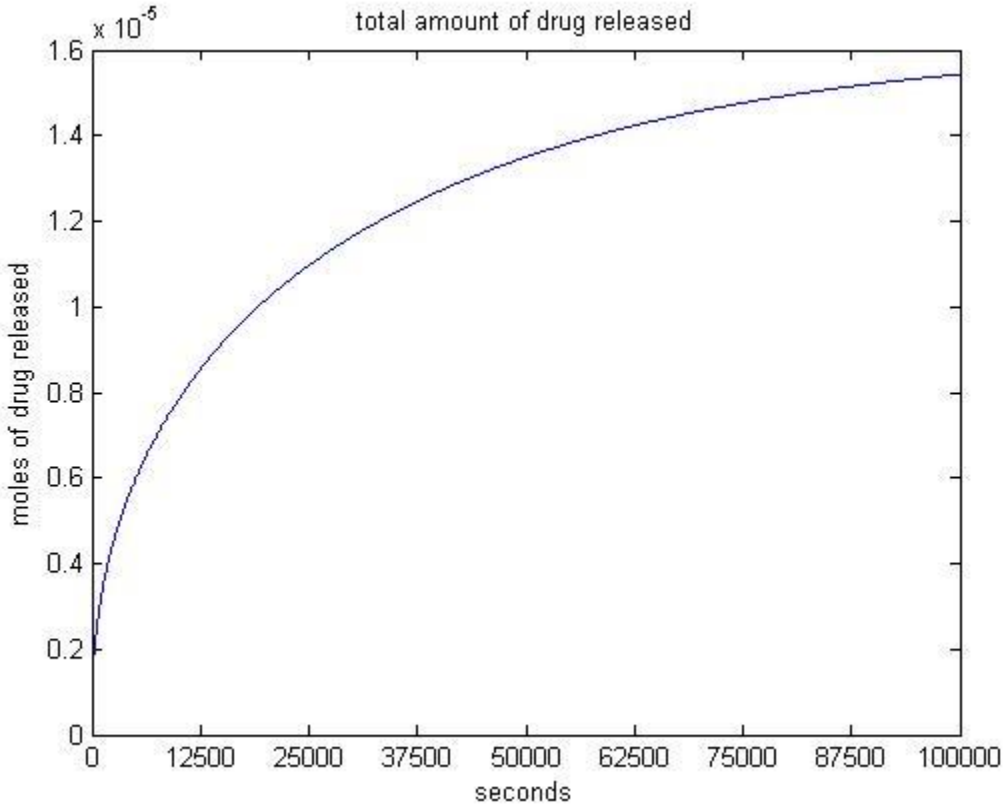
diffuses into the outer medium, which causes a gradient inside the sphere to be formed. The center of the sphere remains at the highest concentration, with a steady decrease to the surface of the sphere.

The release profile is very valuable information for designing microspheres.

To obtain the release profile:

$$Drug\ Released = 4\pi R^2 \int -D\frac{\partial \mu}{\partial r}|_R dt$$

We solved this computationally resulting in the following plot:



Initially, the sphere is fully loaded, which allows the greatest amount of drug delivery. Over time, the sphere is depleted and the release approaches zero.

Conclusion:

Microsphere design is an extremely promising endeavor, as it reduces the need for patient compliance, and can perform sustained release in difficult to reach areas. Carefully designing microspheres allows for a multitude of unique release profiles. One can make broad strokes and change the microsphere from a matrix to a reservoir system. The polymer can be changed, which would directly affect the diffusion coefficient and possible introduce degradation kinetics into the differential equation. The microcapsule does not even need to be a sphere, micro-slabs and micro-cylinders exhibit their own type of release profiles. Minor adjustments can create large effects as well. The initial concentration within the microsphere can change the activity source from non-constant to constant. Increasing the radius of the sphere can allow for more drug to be delivered over a longer period of time.

Our specific model demonstrated the concentration profile inside a matrix microsphere with a non-constant activity source. This problem was exactly solvable without the need of Bessel functions of the second kind due to the continuity at r=0. The release profile was non-linear, due to the depleting concentration on the inside of the sphere. Non-linear release profiles are not highly desirable in most situations, as it is simpler to maintain a therapeutic level of the drug with a linear release. The non-linear nature of the drug delivery can be circumvented by using a high initial amount of drug inside the spherical matrix, due to the solubility limit of the drug. This, however, would be a slightly harder problem to model.

Our mathematical model for this specific microsphere can be improved by including the increasing concentration of the drug on the outside of the sphere. We also only modeled the release of drug from one microsphere. In any practical situation many microspheres will be delivered at the same time, which would affect the outside concentration of the drug, and thus affecting the release kinetics.

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Code:

Analytical Solution Plotting

```
clc
clear
Rspan=linspace(0,62.5*10^-6,4000);
Tspan=linspace(0,100000,4000);
[r t]=meshgrid(Rspan,Tspan);
cs=244;
R=62.5*10^-6;
D=.01*10^-12;
sqlam=pi/R;
sol=0;

for m=1:300
sol=(((-1)^(m+1))/m).*exp(-((m.*sqlam).^2).*D.*t).*(sin(r.*m.*sqlam)./r) +
sol;


end

sol=(2*R*cs./pi).*sol ;

mesh(r,t,sol)
ylabel('time (s)')
xlabel('distance (m)')
zlabel('concentration (mol/m^3)')
title('Analytical Solution with 5 terms')

colorbar
caxis([0 244])


figure(33)

hold on
plot(sol(1,:),'')
plot(sol(5,:),'r')
plot(sol(41,:),'g')
plot(sol(401,:),'--')
plot(sol(4000,:),'k')

title('Analytical Solution 5 terms t=0,t=100,t=1000,t=10000, t=100000')
xlabel('Distance um')
ylabel('concentration mol/m^3')
    set(gca, 'XTicklabel', round(linspace(0,62.5,9)))
    set(gca, 'YTicklabel', round(linspace(0,244,7)))

%%

differ=diff(sol,1,2);
fluxr=differ(:,end);
for n=1:length(fluxr)-1;
    int(n)=trapz(-1.*fluxr(n:n+1));
end
```

```
%%
for n=2:length(int);
    int(n)=int(n-1)+int(n);
end
int=int.*4.*pi.*R.^2
figure(22)
plot(int)
title('total amount of drug released')
xlabel('seconds')
ylabel('moles of drug released')
set(gca, 'XTicklabel', round(linspace(0,100000,9)))
```

PDEPE Plotting, separate file

```
function pde1
a=0;
b=62.5*10^-6;
tend=100000;
xmesh=linspace(0,b,400);
tspan=linspace(0,tend,400);

sol = pdepe(2,@pdefun,@initialfun,@bcfun,xmesh,tspan);
u=sol(:,:,1);
figure(2)
surf(xmesh,tspan,u,'EdgeColor','none');

ylabel('time (s)')
xlabel('distance (m)')
zlabel('concentration (mol/m^3)')
title('PDEPE')

colorbar




function [c,f,s]=pdefun(x,t,u,DuDx)
d=.01*10^-12;
c=1./d;
s=0;
f=DuDx;

function u0=initialfun(x)
cs=244;
u0=cs;



function [pl,ql,pr,qr] = bcfun(xl,ul,xr,ur,t)
pl=0;
ql=0;
pr=ur;
qr=0;
```