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Modeling the controlled release of drug embedded in a plate-like polymer matrix

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Abstract

The controlled release of over-loaded drug in a plate-like polymer matrix, the Higuchi's problem, is investigated theoretically. Taking the advantage of Landau transformation, we restore the concentration profile of drug in a polymer matrix, the rate of release of drug from the polymer matrix, and the temporal variation of location of the moving boundary taking the external mass transfer resistance into account. The applicability of the series of moving boundaries, a numerical approach often adopted, is examined. We found that it may become ineffective when the over-loading of drug in a polymer matrix is too small. In contrast, our method has no such limitation. We conclude that assuming the transfer of drug to occur at a pseudo-steady-state condition is inadequate if the degree of over-loading for drug is low or the external mass transfer resistance is significant.

Keywords: Desorption; Higuchi model; Interface; Mathematical modelling; Polymer; Moving boundary problem

1. Introduction

The controlled release of an over-loaded drug system is first investigated by Higuchi (1961, 1963). For the delivery of drug from a plate-like polymer matrix, Higuchi's model can be illustrated as Fig. 1, where c_s is the saturated concentration of drug in polymer matrix, c_u is the over-loaded undissolved drug concentration, x is the depth into the polymer matrix, $2L$ is the thickness of polymer matrix, x_m and $(2L - x_m)$ are the moving fronts of saturated concentration, and $(c_s + c_u)$ is the initial loading of drug. In Higuchi's analysis the time for the dissolution of drug is neglected, so is the external mass transfer resistance, and the environment outside the polymer matrix, where the drug is released to, is treated as a perfect sink, that is, the concentration of the environment is kept at some constant value. The assumption of no external mass transfer resistance implies that the concentrations of drug at both $x = 0$ and $x = 2L$ are constant. As illustrated in Fig. 1, Higuchi assumed that the concentration of drug in the environment is zero, and consequently, that at $x = 0$ and at $x = 2L$ both vanish. Under a pseudo-steady-state assumption, the concentration profiles in the diffusion zones, $0 < x < x_m$ and $(2L - x_m) < x < 2L$, are linear. In this case, Higuchi arrived at the following expression for the temporal variation of x_m:

$$x_m = 2\sqrt{\frac{Dtc_s}{c_s + 2c_u}}, \tag{1}$$

where D is the diffusivity of drug in polymer matrix, and t is time. This expression is valid only before the two moving fronts coincide. A pseudo-steady-state approximation is frequently adopted to solve analytically other drug release systems with more confined conditions (e.g., Roseman and Higuchi, 1970; Tojo, 1985; Zhou and Wu, 2002).

The diffusion problem can be solved analytically without assuming a pseudo-steady-state condition. Paul and

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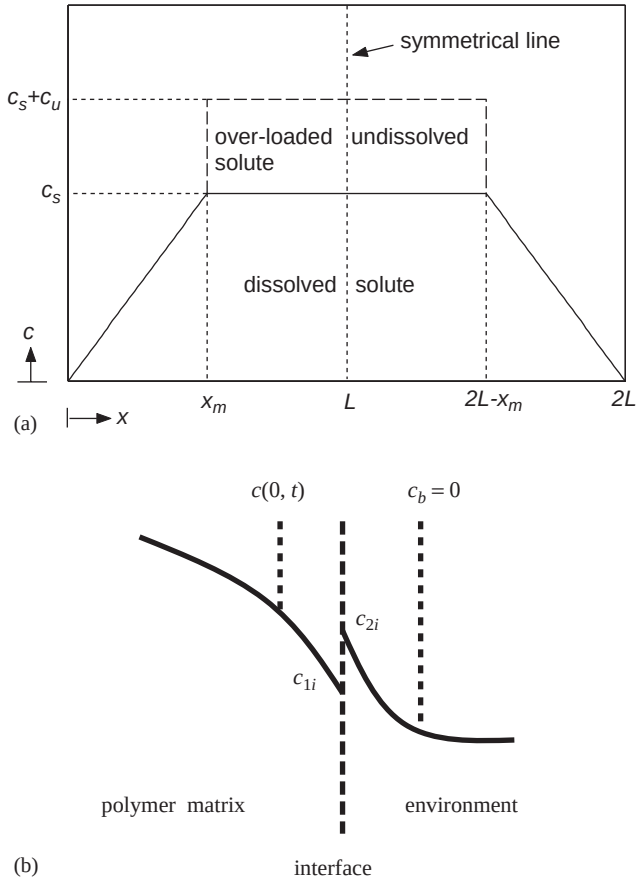

Fig. 1. (a) Schematic representation of the controlled release device considered, where c is the concentration of drug in polymer matrix, c_s is the saturated concentration of drug in polymer matrix, c_u is the over-loaded undissolved drug concentration, x is the depth into the polymer matrix, $2L$ is the thickness of polymer matrix, x_m and $(2L-x_m)$ are the moving fronts of saturated concentration, and (c_s+c_u) is the initial loading of drug. (b) Schematic representation of the mass transfer problem under consideration.

McSpadden (1976), for example, solved the problem by resorting to the diffusion analogue of the change of state in heat conduction (Carslaw and Jaeger, 1959). They obtained

$$x_m = \eta^* 2\sqrt{Dt}, \tag{2}$$

where η^* is the root of $\sqrt{\pi}\eta^* \exp(\eta^{*2})\,\mathrm{erf}(\eta^*) - c_s/c_u = 0$, erf being the error function.

Without a pseudo-steady-state assumption, solving Higuchi's problem analytically can be nontrivial when additional constraints such as external mass transfer resistance and finite environmental volume are imposed, and relevant problems need to be solved numerically. Lee (1980), for example, solved Higuchi's problem based on a method of series of fixed boundaries under the condition when external mass transfer resistance is significant. This method was also adopted previously in an analogous heat conduction problems of solidification and melting systems (Longwell, 1958; Tao, 1967). However, as demonstrated later, this method may become inappropriate for the present diffusion transfer of drug if the rate of movement of the moving boundary, $\mathrm{d}x_m/\mathrm{d}t$, is too fast for x_m to be fixed in the series. Although the method of series of fixed boundaries can be modified by decreasing the time step in each of the fixed boundaries series, it is still questioned for the validity in its physical sense.

In this study the controlled release of an over-loaded drug system is investigated by extending previous analysis to the case when the external mass transfer resistance for the transport of drug can be significant. Coupled with a Landau transformation, the moving boundary problem is solved numerically based on a finite difference scheme. The applicability of present approach is examined through numerical simulation.

2. Theory

The controlled release device considered in the present work is the same as that of Higuchi shown in Fig. 1, except that the concentrations of drug at $x = 0$ and $x = 2L$ are not necessarily zero. The concentrations of drug at these two points depend on the external mass transfer resistance, and vary with time. The concentration of drug in the environment is assumed to be zero for simplicity. The symmetric nature of the problem under consideration suggests that only the interval $x = [0, x_m]$ needs to be considered. Assuming that the diffusivity of drug is constant, the diffusion transfer of drug can be described by

$$\frac{\partial c}{\partial t} = D\,\frac{\partial^2 c}{\partial x^2}, \tag{3}$$

where c is the concentration of drug in the interval $x = [0, x_m]$. The boundary conditions associated with Eq. (3) are assumed as

$$D\,\frac{\partial c}{\partial x}\bigg|_{x=0} = kc(0,t), \tag{4}$$

$$c = c_s, \quad x = x_m, \tag{5}$$

where k is the overall mass transfer coefficient for the transfer of drug from the polymer matrix–environment interface to the environment (Appendix A). The temporal variation of x_m can be represented by

$$c_u\,\frac{\mathrm{d}x_m}{\mathrm{d}t} = D\,\frac{\partial c}{\partial x}\bigg|_{x=x_m}. \tag{6}$$

The associated initial condition is $x_m = 0$ and $t = 0$. In the case the external mass transfer resistance can be ignored, Eq. (4) reduces to $c(0,t) = 0$. Eqs. (3)–(6) can be expressed further as

$$\frac{\partial C}{\partial T} = \frac{\partial^2 C}{\partial X^2}, \tag{7}$$

$$\frac{\partial C}{\partial X}\bigg|_{X=0} = B_m C(0,T), \tag{8}$$