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A novel mathematical model considering change of diffusion coefficient for predicting dissolution behavior of acetaminophen from wax matrix dosage form☆

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ABSTRACT

From wax matrix dosage forms, drug and water-soluble polymer are released into the external solvent over time. As a consequence, the pore volume inside the wax matrix particles is increased and the diffusion coefficient of the drug is altered. In the present study, we attempted to derive a novel empirical mathematical model, namely, a time-dependent diffusivity (TDD) model, that assumes the change in the drug's diffusion coefficient can be used to predict the drug release from spherical wax matrix particles. Wax matrix particles were prepared by using acetaminophen (APAP), a model drug; glyceryl monostearate (GM), a wax base; and aminoalkyl methacrylate copolymer E (AMCE), a functional polymer that dissolves below pH 5.0 and swells over pH 5.0. A three-factor, three-level (3^3) Box–Behnken design was used to evaluate the effects of several of the variables in the model formulation, and the release of APAP from wax matrix particles was evaluated by the paddle method at pH 4.0 and pH 6.5. When comparing the goodness of fit to the experimental data between the proposed TDD model and the conventional pure diffusion model, a better correspondence was observed for the TDD model in all cases. Multiple regression analysis revealed that an increase in AMCE loading enhanced the diffusion coefficient with time, and that this increase also had a significant effect on drug release behavior. Furthermore, from the results of the multiple regression analysis, a formulation with desired drug release behavior was found to satisfy the criteria of the bitter taste masking of APAP without lowering the bioavailability. That is to say, the amount of APAP released remains below 15% for 10 min at pH 6.5 and exceeds 90% within 30 min at pH 4.0. The predicted formulation was 15% APAP loading, 8.25% AMCE loading, and 400 μm mean particle diameter. When wax matrix dosage forms were prepared accordingly, the predicted drug release behavior agreed well with experimental values at each pH level. Therefore, the proposed model is feasible as a useful tool for predicting drug release behavior, as well as for designing the formulation of wax matrix dosage forms.

1. Introduction

Wax matrix dosage forms constructed by insoluble lipids, a wax base, have attracted attention in the pharmaceutical field because this formulation has a number of advantages: organic solvent-free preparation, non-toxicity, and cost effectiveness (Shiino et al., 2010). To date, various wax matrix dosage forms have been developed for controlled release, taste masking, or both (Kayumba et al., 2007; Xu et al., 2008).

Generally, drug diffusion within wax matrix particles has been considered to be the rate-controlling step of drug release from wax matrix particles, and many studies have investigated the kinetics of drug release from wax matrix dosage forms on the basis of the Higuchi equation (Higuchi, 1961) or Fick's second law of diffusion (Crank, 1975). Yajima et al. (1996) reported that isokinetic erosion derived from polymer characteristics was the rate-controlling step of drug release, and they derived a mathematical model similar to the cube-root law. However, the applicability of Yajima's model is limited to a narrow set of conditions, such as those in the initial stages of dissolution; for long dissolution times, diffusion becomes the dominant step controlling drug release. Against this background, we recently succeeded in deriving a mathematical model that incorporates diffusion and erosion theory, where a decrease in particle diameter of wax matrix particles over time is assumed to predict the kinetics of drug release from wax matrix

Abbreviations: APAP, acetaminophen; GM, glyceryl monostearate; AMCE, aminoalkyl methacrylate copolymer E; TDD, time-dependent diffusivity; SEM, scanning electron microscope; AIC, Akaike's information criterion.

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particles (Agata et al., 2011). Although this model exhibited good agreement with all experimental values pertaining to APAP release at pH 4.0 and pH 6.5, a concern about the initial conditions of this mathematical model remains; namely, that changes of particle diameter are much less likely to occur in wax matrix particles than is assumed in the model. However, another possibility is that an increase in pore volume inside wax matrix particles, rather than a decrease in particle diameter, is involved in the release of drugs from wax matrix particles. Thus, development of a mathematical model that considers time-dependent diffusivity (TDD) is considered to be worth investigated.

So far, a number of mathematical models that consider time- or position-dependent diffusivity have been investigated. For instance, as TDD models, semi-empirical models that consider an increase in pore volume within a cylindrical wax matrix have been analyzed (Siepmann et al., 2008; Verhoeven et al., 2009). In addition, a semi-empirical model that considers a time-dependent changes of polymer molecular weight within wax matrix particles has also been derived (Raman et al., 2005). Although these models represent realistic drug release kinetics, since experimentally determined pore volumes or the initial concentration distribution within the wax matrix dosage forms must be substituted into the models, experiments to obtain these physicochemical parameters are needed. Because previous models are formulated by numerical methods designed to handle more complex processes, the obtained solutions are approximated values and specific knowledge about the mathematics and programming is necessary. Therefore, a new model is required that is easy to formulate and that can obtain a good fit for a variety of general pharmaceutical formulations.

In the present study, we attempted to derive a novel and versatile empirical mathematical model that considers TDD in wax matrix particles, on the basis of Fick's second law without any additional experiments. Since this model can be solved by an exact analytical method, calculations are straightforward. In addition, the model can provide insight into the drug release mechanism within wax matrix particles. By using a spray congealing technique, wax matrix particles were prepared with acetaminophen (APAP) as a model drug, glyceryl monostearate (GM) as a wax base, and aminoalkyl methacrylate copolymer E (AMCE) as a functional polymer that dissolves below pH 5.0 and swells over pH 5.0. The drug release behavior and the validity of the proposed TDD model were then investigated. Furthermore, we sought to predict the desirable kinetics of drug release from wax matrix particles by using a combination of the TDD model and a Box–Behnken design.

2. Theory

If we restrict ourselves to a case where the drug diffusion is radial in a single wax matrix particle, the diffusion equation for a sphere takes the form (Crank, 1975)

$$\frac{\partial c}{\partial t} = \frac{1}{r^2}\left\{\frac{\partial}{\partial r}\left(Dr^2\frac{\partial c}{\partial r}\right)\right\}, \tag{1}$$

where c denotes the concentration of a drug as a function of time t and radius r within the spherical wax matrix particle. Furthermore, D is the diffusion coefficient of drug.

If D can change over time during diffusion, the diffusion equation then becomes

$$\frac{\partial c}{\partial t} = \frac{D(t)}{r^2}\left\{\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right)\right\}. \tag{2}$$

Also, if the function T is defined as

$$T(t) = \int_0^t D(t)dt, \tag{3}$$

then $dT/dt = D(t)$. By the chain rule, Eq. (2) can be rewritten as

$$\frac{\partial c}{\partial T} = \frac{1}{r^2}\frac{\partial}{\partial r}\left(r^2\frac{\partial c}{\partial r}\right). \tag{4}$$

By setting

$$u = rc, \tag{5}$$

Eq. (4) is transformed into

$$\frac{\partial u}{\partial T} = \frac{\partial^2 u}{\partial r^2}. \tag{6}$$

From the assumption that APAP is uniformly distributed throughout the wax matrix particle at the start of the experiment, the initial condition for Eq. (6) is

$$u|_{t=0} = rc_0. \tag{7}$$

Here, C_0 represents the initial APAP concentration in the system. In addition, the boundary conditions for Eq. (6) follow from the assumption that perfect sink conditions are maintained throughout the experiment:

$$u|_{r=a/2} = 0. \tag{8}$$

Here, a represents the particle diameter. This initial value problem (Eqs. (6)–(9)) can be solved by Laplace transform or separation of variables, leading to

$$c(r,t) = \frac{-ac_0}{\pi r}\sum_{n=1}^{\infty}\frac{(-1)^n}{n^2}\exp\left(-\frac{4n^2\pi^2}{a^2}T(t)\right)\sin\frac{2n\pi}{a}r. \tag{9}$$

The absolute amount of APAP remaining in the system is given by

$$M = \frac{a^3c_0}{\pi}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left(-\frac{4n^2\pi^2}{a^2}T(t)\right). \tag{10}$$

Here, M represents the absolute remaining amounts of APAP in the system. For m wax matrix particles having equal diameter, the total amount of drug within the particles is given by

$$mM = m\frac{a^3c_0}{\pi}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left(-\frac{4n^2\pi^2}{a^2}T(t)\right), \tag{11}$$

and the initial total amount of drug is

$$M_{total} = m\frac{1}{6}\pi a^3c_0. \tag{12}$$

Therefore, the drug release ratio at time t is given by

$$R = 1 - \frac{6}{\pi^2}\sum_{n=1}^{\infty}\frac{1}{n^2}\exp\left(-\frac{4n^2\pi^2}{a^2}T(t)\right). \tag{13}$$

In this study, an empirical model that reflects the TDD is established. If rate of change of the diffusion coefficient constantly increase and/or decrease in first order proportion to diffusion coefficient, the empirical model is assumed as the following,

$$\frac{dD}{dt} = K - kD, \tag{14}$$

where K ($\mu m^2\ min^{-2}$) is the coefficient associated with the rate of increase of the diffusion coefficient, and k (min^{-1}) is the coefficient associated with the speed that the diffusion coefficient of the wax matrix particles reaches the maximum (K/k). If the diffusion coefficient is equal to zero at the start of the experiment, Eq. (14) can be solved to give

$$D(t) = \frac{K}{k}\{1 - \exp(-kt)\}. \tag{15}$$