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An empirical model for dissolution profile and its application to floating dosage forms

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ABSTRACT

A sum of two inverse Gaussian functions is proposed as a highly flexible empirical model for fitting of in vitro dissolution profiles. The model was applied to quantitatively describe theophylline release from effervescent multi-layer coated floating tablets containing different amounts of the anti-tacking agents talc or glyceryl monostearate. Model parameters were estimated by nonlinear regression (mixed-effects modeling). The estimated parameters were used to determine the mean dissolution time, as well as to reconstruct the time course of release rate for each formulation, whereby the fractional release rate can serve as a diagnostic tool for classification of dissolution processes. The approach allows quantification of dissolution behavior and could provide additional insights into the underlying processes.

1. Introduction

In vitro dissolution testing is used to determine the release characteristics of the product over time. When mechanistic models are not available, empirical models of the release profile can be very helpful to extract quantitative information on the dissolution process (Costa and Sousa Lobo, 2001; Lánský and Weiss, 2003; Dokoumetzidis et al., 2006). Fitting such models to cumulative release data allows estimation of parameters like mean dissolution time and reconstruction of the time course of release rate. These models can be classified in terms of the shape of the fractional dissolution rate function (Lánský and Weiss, 2003). However, when we tried to describe the release profiles of floating multi-layer coated tablets of theophylline (Kriangkrai et al., unpublished results; Sungthongjeen et al., 2008), it turned out that the time course of release rate showed a multimodal shape and none of the known models (Costa and Sousa Lobo, 2001; Gao, 2011; Lánský and Weiss, 2003; Papadopoulou et al., 2006) consistently described our data. Thus, it is the purpose of this paper to find a more flexible model for fitting drug dissolution data. As an example we describe the effect of different amounts of the anti-tacking agents talc or glyceryl monostearate on mean dissolution time and release rate as a function of time. Data fitting was performed using nonlinear mixed effects modeling, the advantages of which in dissolution testing have been pointed out elsewhere (Adams et al., 2002; Wang et al., 2008).

2. Materials and methods

2.1. Model development

Denoting the amount of drug released up to time t by $A(t)$, the normalized in vitro dissolution profile $F(t) = A(t)/A(\infty)$ can be regarded as the cumulative distribution function of a random variable T (the time until a randomly selected molecule of drug enters solution)

$$F(t) = Pr\{T \le t\} \tag{1}$$

The inverse Gaussian distribution (IG) has been used to model the dissolution time distribution of slow release formulations in vivo and in vitro (Wang et al., 2008; Weiss, 1996; Weiss et al., 2012). The cumulative distribution function of the IG which can be expressed in terms of the standard normal distribution Φ as

$$F(t) = \Phi\left(\sqrt{\frac{MDT}{RD^2 t}}\left(\frac{t}{MDT} - 1\right)\right) + e^{2/RD^2}\,\Phi\left(-\sqrt{\frac{MDT}{RD^2 t}}\left(\frac{t}{MDT} + 1\right)\right) \tag{2}$$

where $\Phi(x) = (1/\sqrt{2\pi}\int_{-\infty}^{x} e^{-u^2/2}du$; $MDT = E(T)$ and $RD^2 = \mathrm{Var}(T)/\mathrm{MTT}^2$ represent the mean and relative dispersion of the dissolution

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time distribution, respectively, defined as $E(T) = \int_0^\infty (1 - F(t))dt$ and $\mathrm{Var}(T) = 2\int_0^\infty t\ (1 - F(t))dt - E(T)^2$.

In the present case, however, the IG model failed to fit the terminal phase of the dissolution curve. Thus, we were looking for an extension of this model. Since mixture distributions provide a powerful tool for generating flexible distributions, we used a mixture of two IG (2IG model)

$$F_{2IG}(t) = A(t)/A(\infty) = pF_1(t) + (1-p)F_2(t) \quad (3)$$

where the functions $F_i(t)$ are given by Eq. (2) and $0 < p < 1$ is a mixing parameter, i.e., $F_{2IG}(t)$ represents a two-point distribution with probability p of outcome F_1 (IG_1) with parameters MT_1, RD_1^2 and probability $(1-p)$ of outcome F_2 (IG_2) with parameters MT_2, RD_2^2, where the IG with the longer MT accounts for the tail part of the dissolution data. The mean and relative dispersion of dissolution time of the mixture inverse Gaussian, i.e. sum of two inverse Gaussian (Eq. (3)), is then given by

$$MDT = p\mathrm{MT}_1 + (1-p)\mathrm{MT}_2 \quad (4)$$

and

$$RD^2 = \frac{p(RD_1^2+1)\mathrm{MT}_1^2 + (1-p)\left(RD_2^2+1\right)\mathrm{MT}_2^2}{MDT} - 1 \quad (5)$$

More insights in the kinetics of the release process can be get from the rate of drug release as function of time, i.e., the density function of the dissolution time distribution $f(t) = dF/dt$. For the mixture of two inverse Gaussian (Eq. (3)), we obtain

$$f_{2IG}(t) = qf_1(t) + (1-q)f_2(t) \quad (6)$$

with

$$f_i(t) = \sqrt{\frac{MDT_i}{2\pi RD_i^2 t^3}} \exp\left[-\frac{(t-MDT_i)^2}{2RD_i^2 MDT_i t}\right] \quad (7)$$

Especially useful for characterizing the properties of a dissolution model is the fractional or relative dissolution rate function is defined as

$$k_{2IG}(t) = \frac{f_{2IG}(t)}{1 - F_{2IG}(t)} \quad (8)$$

assuming a complete dissolution of the applied dose. The shape of relative dissolution rate function allows a classification of dissolution models and a diagnosis of which mechanistic models would be compatible with the data (Lánský and Weiss, 2003).

2.2. Tablet formulation and release study

The novel model was applied to theophylline data from in vitro dissolution experiments of floating multi-layer coated tablets based on gas formation (Kriangkrai et al., unpublished results). Details on the tablet design and the drug release studies can be found there. Briefly, the floating multi-layer coated tablets were based on gas formation (Sungthongjeen et al., 2008). The system consists of a drug-containing core tablet coated with a protective layer (hydroxypropyl methylcellulose), a gas forming layer (sodium bicarbonate) and a gas-entrapped membrane (Eudrgit® RL30D), respectively. Upon contact with the acidic medium (e.g. 0.1 N HCl), the fluid permeated into the gas forming layer through the outer gas-entrapped membrane. Carbon dioxide was liberated via neutralization reaction and was entrapped in the polymeric membrane. Consequently, the swollen tablets with a density less than 1.0 g/mL floated and maintained the buoyancy. While the tablet floated on the medium, the drug was released from the system. Since tackiness problem of the floating tablets occurred in our previous study (Kriangkrai et al., unpublished results.), anti-tacking agents were used to solve this problem.

Release experiments were performed by using 900 ml of 0.1 N HCl (pH 1.2) as the medium in USP apparatus II (Vankel Model VK-7000, Vankel, USA) at 37 ± 0.5 °C and 50 rpm. The amount of theophylline release was measured at predetermined time intervals and was then assayed with UV/visible spectrophotometer (Varian, Australia) at a wavelength of 270 nm using a 1.0 cm quartz cell. A minimum of three replicates were carried out for each formulation. Here, as an example, we analyze theophylline release data of formulations containing 0%, 5%, 10%, 20% and 30%, of the anti-tacking agents talc and glyceryl monostearate (GMS), respectively.

2.3. Fitting of release data

In data fitting, a lag time was t_0 was introduced into the 2IG model (Eqs. (2) and (3)), to account for the delay in drug release (to first detectable concentration). The six adjustable parameters of the 2IG model (t_0, p, MT_1, RD_1^2, MT_2, and RD_2^2) were estimated

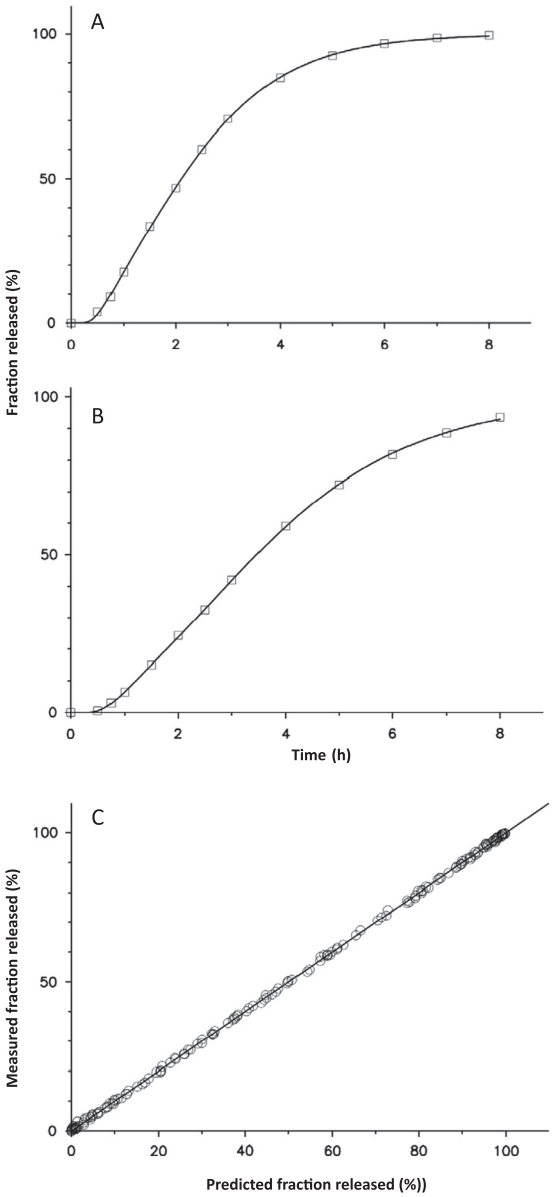

Fig. 1. Typical fits of the 2IG model to normalized cumulative theophylline release from formulations containing no (A) and 30% talc (B). The goodness-of-fit plot (C) summarizes all fits of the talc group, i.e. data of 15 release profiles ($R^2 = 0.9999$).