European Journal of Pharmaceutical Sciences 68 (2015) 51–55

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Modeling accelerated and decelerated drug release in terms of fractional release rate

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ARTICLE INFO

Article history:
Received 4 August 2014
Received in revised form 21 October 2014
Accepted 1 December 2014
Available online 5 December 2014

Keywords:
Dissolution testing
Accelerated drug release
In vitro–in vivo correlation (IVIVC)
Time scaling

ABSTRACT

The model of a proportional change in fractional dissolution rate was used to quantify influences on the vitro dissolution process. After fitting the original dissolution profile with an empirical model (inverse Gaussian distribution), acceleration and deceleration effects due to dissolution conditions or formulation parameters could be described by one parameter only. Acceleration of dissolution due to elevated temperature and deceleration by increasing the content of glyceryl monostearate in theophylline tablets are presented as examples. Likewise, this approach was applied to in vitro–in vivo correlation (IVIVC). It is shown that the model is appropriate when the plot of the in vivo versus in vivo times is nonlinear and can be described by a power function. The results demonstrate the utility of the model in dissolution testing and IVIVC assessment.

1. Introduction

The fractional dissolution or release rate function, $k(t)$, is defined as the dissolution rate divided by the fraction undissolved. This concept was previously used to classify models of dissolution profiles (Lansky and Weiss, 2003) and to characterize the dissolution process (Weiss et al., 2014). Here it will be shown that accelerated (decelerated) drug release can be described by a proportional increase (decrease) in fractional dissolution rate, i.e., $\alpha k(t)$ with a constant factor $\alpha > 1$ (acceleration) or $\alpha < 1$ (deceleration). The purpose of this article is twofold; firstly, to apply this approach to dissolution processes in vitro by fitting data where drug release is accelerated due to elevated temperature (Quist and Östling, 2002) or decelerated by increasing the content of glyceryl monostearate (GMS) in theophylline tablets (Weiss et al., 2014). Secondly, to show that this modeling concept can be effectively applied to in vitro–in vivo correlation (IVIVC) when in the time scaling approach the relationship between $t_{\text{in vivo}}$ and $t_{\text{in vitro}}$, $t_{\text{in vivo}} = \phi(t_{\text{in vitro}})$, i.e. the Levy plot (Levy et al., 1965), is nonlinear. While in most cases a linear time transformation proved sufficient (Brockmeier et al., 1985; Schliecker et al., 2004; Nishimura et al., 2007; Jantratid et al., 2009; Cardot and Davit, 2012), several reports have found that ϕ is a convex function, i.e., the Levy plot shows an upward curvature (Drewe and Guitard, 1993; Humbert et al., 1994; Hemmingsen et al., 2011; Cardot and Davit, 2012; Kakhi et al., 2013; Klancar et al., 2013). It will be shown in this study that this means that dissolution is decelerated in vivo ($\alpha < 1$), or respectively, accelerated in vitro, and that the Levy plot can be described by a power function.

The approach is as follows: first, the dissolution profile $F_1(t)$ started off with is fitted by an inverse Gaussian distribution or a sum of two inverse Gaussian (any other empirical function would be also suitable); second, the in vitro release profile with accelerated (decelerated) drug release, $F_2(t)$, or the in vivo absorption profile, $F_{\text{in vivo}}(t)$, is fitted using the proportional fractional dissolution rate model. When, as in this examples, the fit was successful, only one parameter (α) has to be estimated (in some cases additionally a lag-time t_0). That means, changes in the shape of the release profile can be characterized by one adjustable parameter only.

In principle, the concept is analogous to the Cox proportional hazard model (Kumar and Klefsjö, 1994), which was previously used in IVIVC (Dunne et al., 1997, 1999).

2. Material and Methods

2.1. Model

The present analysis exploits the concept of dissolution time distribution. When denoting the amount of drug released up to time t by $A(t)$, the normalized in vitro dissolution profile becomes $F(t) = A(t)/A(\infty)$ and can be regarded as the cumulative distribution function of a random variable T (the time until a randomly selected molecule of drug enters solution)

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http://dx.doi.org/10.1016/j.ejps.2014.12.003
0928-0987/

Nomenclature

$A(t)$	amount of drug released up to time t	t_0	lag-time
$F(t)$	normalized dissolution profile $[A(t)/A(\infty)]$, cumulative distribution function of random release time	MDT	mean dissolution time
		RD^2	relative dispersion of dissolution time
$f(t)$	density function (dF/dt)	IG	inverse Gaussian distribution
$k(t)$	fractional release rate	IVIVC	in vitro–in vivo correlation
α	factor to $k(t)$	GMS	glyceryl monostearate
t	time		

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

and $f(t) = dF(t)/dt$ is the corresponding probability density function. It is convenient to take $F(t)$ from a parameteric family of distribution functions. The inverse Gaussian distribution (IG) was used previously as an empirical model of the dissolution time distribution of drug formulations in vivo and in vitro (Weiss, 1996; Lotsch et al., 1999; Wang et al., 2008). The cumulative distribution function of the IG can be expressed in terms of the standard normal distribution, Φ,

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

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

$$E(T) = \int_0^\infty (1 - F(t))\,dt \text{ and}$$
$$\mathrm{Var}(T) = 2\int_0^\infty t(1 - F(t))\,dt - E(T)^2 \tag{3}$$

If the single IG does not fit the data sufficiently well, a sum of two IGs can be used (Weiss et al., 2014) analogously to the use of sums of exponentials to describe drug disposition curves. The 2IG model (mixture of two IGs) can be written as

$$F_{2\mathrm{IG}}(t) = pF_1(t) + (1-p)F_2(t), 0 < p < 1 \tag{4}$$

where the functions $F_i(t)$ are given by Eq. (2) and p is a mixing parameter. The mean and relative dispersion of dissolution time of the mixture inverse Gaussian, i.e. sum of two inverse Gaussian (Eq. (4)), is then given by

$$\mathrm{MDT} = p\mathrm{MT}_1 + (1-p)\mathrm{MT}_2 \tag{5}$$

and

$$\mathrm{RD}^2 = \frac{p(\mathrm{RD}_1^2 + 1)\mathrm{MT}_1^2 + (1-p)(\mathrm{RD}_2^2 + 1)\mathrm{MT}_2^2}{\mathrm{MDT}^2} - 1 \tag{6}$$

The fractional dissolution rate function $k(t)$ is defined as

$$k(t) = \frac{f(t)}{1 - F(t)} \tag{7}$$

and $k(t)dt$ gives the probability of release in $(t, t + dt)$ given the molecule has not been released until time t. Note that $F(t)$ is the IG (Eq. (2)) or 2IG distribution (Eq. (4)), respectively. The IG density function is given by

$$f_i(t) = \sqrt{\frac{\mathrm{MDT}_i}{2\pi \mathrm{RD}_i^2 t^3}}\exp\left[-\frac{(t - \mathrm{MDT}_i)^2}{2\mathrm{RD}_i^2 \mathrm{MDT}_i t}\right] \tag{8}$$

and for the 2IG model, one obtains

$$f_{2\mathrm{IG}}(t) = qf_1(t) + (1-q)f_2(t) \tag{9}$$

thus Eq. (7) can be written as

$$k_{2\mathrm{IG}}(t) = \frac{f_{2\mathrm{IG}}(t)}{1 - F_{2\mathrm{IG}}(t)} \tag{10}$$

Accelerated (decelerated) drug release is defined as proportional change in fractional release rate

$$k(t;\alpha) = \alpha k(t), \quad \alpha > 0 \tag{11}$$

where $k(t)$ is the 'baseline' rate, with acceleration for $\alpha > 1$ and deceleration for $\alpha < 1$, respectively. The distribution functions are then related as

$$F(t;\alpha) = 1 - [1 - F(t)]^\alpha \tag{12}$$

where $F(t)$ is the normalized in vitro dissolution profile under baseline conditions. This is illustrated in Fig. 1. For data fitting, an additional adjustable parameter, t_0, is introduced that accounts for a time delay

$$F(t;\alpha) = 1 - [1 - F(t + t_0)]^\alpha \tag{13}$$

Note that for fitting of in vivo release profile the bioavailability of the drug, $F_{\text{in vivo}}(\infty) \leqslant 1$, has to be taken into account:

$$F_{\text{invivo}}(t;\alpha) = F_{\text{invivo}}(\infty)\left(1 - [1 - F_{\text{invitro}}(t + t_0)]^\alpha\right) \tag{14}$$

2.2. Data analysis

Data were extracted from digitized figures or stem from our own studies (Weiss et al., 2014). Model parameters were estimated by maximum likelihood using the package ADAPT 5 (D'Argenio and Schumitzky, 2009). After fitting the baseline in vitro dissolution data by an inverse Gaussian distribution or a sum of two inverse Gaussians, the parameters were held fixed in fitting the data obtained under changed conditions by Eq. (13) or the in vivo by Eq. (14). (Note that the standard normal distribution, Φ, used in Eq. (2) is available in Fortran as implemented in ADAPT 5 as function NCDF.) If replicates of release profiles are available, the maximum likelihood expectation maximization population modeling module in ADAPT 5 was used. Estimates are presented with asymptotic standard deviations, or as mean and inter-experiment variability in the case of replicates.

3. Results

3.1. In vitro dissolution

3.1.1. Example 1: acceleration by temperature elevation

Quist and Östling (2002) studied the acceleration of dissolution of salicylic acid tablets by temperature elevation. First, using the IG model (Eq. (2)), the dissolution data measured at 37 °C (baseline conditions) were fitted; then the data measured at 57 °C were fitted by Eq. (13), holding the baseline parameters, MDT and RD^2,