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Research paper

A method for modeling in vitro dissolution profiles of drugs using gamma distribution

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Abstract

A method of fitting in vitro dissolution profiles of drugs, in a constant pH medium, to the incomplete gamma function by the Levenberg-Marquardt method based on χ^2 criterion is proposed, and a computer program, written in ANSI FORTRAN-77 standard computer language, is developed. The method provides, besides the best-fit representation of the drug dissolution profile, also corresponding instantaneous dissolution rate, mean dissolution time, its variance, and other dissolution parameters of interest. The use of the proposed method is illustrated with a typical set of in vitro dissolution data. Routine drug production quality control has shown that the method provides good representation of disparate dissolution profiles. © 1997 Elsevier Science B.V.

Keywords: Drug dissolution modeling; Dissolution parameters; Drug quality control; Incomplete gamma function; Levenberg-Marquardt method

1. Introduction

Various in vitro studies of dissolution profiles of drugs, and their correlation to the corresponding in vivo results [1–3], may involve fitting dissolution profiles (percentage of drug dissolved as a function of time) to a model function that depends on several adjustable parameters. The model function is chosen to represent the experimental data conveniently and, more or less, accurately. This is done in order to effectively obtain various dissolution parameters such as, among others [4–6], 20 or 80% dissolution times, dissolution rate and mean dissolution time together with its variance. Model fitting is usually based on the maximum likelihood estimation method and can be achieved efficiently, for a given nonlinear model function, by the Levenberg-Marqardt method based on χ^2 criterion [7]. This method was used recently [8] in an interactive program for pharmacokinetic modeling. Here, we describe its application to a specific model function, namely to the (suitably modified) incomplete gamma function [9]. This is based on the observation that in practice, in vitro dissolution profiles in a constant pH medium have habitually the shape of a typical (cumulative) probability distribution function. We have found in routine drug production quality control that the incomplete gamma distribution, depending on two adjustable parameters, often provides a convenient, flexible and sufficiently general model function which makes mathematically consistent use of the available experimental data possible. This concerns especially the extrapolation of the dissolution data to infinite time, a procedure which always leads to (unknown) errors. Thus, the proposed method provides a procedure to predict the total amount of drug dissolved. In this paper we present the key equations on which the proposed method of fitting dissolution profiles to the incomplete

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gamma function by the Levenberg-Marquardt method is based, describe briefly a computer program which was developed, illustrate its use on a representative set of in vitro dissolution data and, finally, present discussion and conclusions.

2. Theoretical development

As a convenient model function representing in vitro dissolution data in a constant pH medium, we propose the following function

$$G(t) \equiv P(\alpha^2, \beta^2 t) \tag{1}$$

Here, t is time, α and β are two adjustable parameters ranging from $-\infty$ to $+\infty$, and $P(a, x)$ is the incomplete gamma function as defined in [9]. Basic properties of this function, together with its computer implementation, are well documented in [7]. We only note that the flexibility of this trial function (as exemplified e.g. by Fig. 6.2.1 in [7]) often provides good representation of disparate dissolution drug profiles. The time derivative of this model function

$$g(t) \equiv \frac{\mathrm{d}G(t)}{\mathrm{d}t} = \frac{\beta^{2\alpha^2}\, t^{\alpha^2-1}\, e^{-\beta^2 t}}{\Gamma(\alpha^2)} \tag{2}$$

is also of considerable importance since it provides, after optimal α and β are determined, the instantaneous dissolution rate of a drug, and leads to the following two simple expressions for the mean dissolution time and mean squared dissolution time

$$\langle t \rangle = \left(\frac{\alpha}{\beta}\right)^2, \qquad \langle t^2 \rangle = \frac{\alpha^2(\alpha^2+1)}{\beta^4} \tag{3}$$

Additionally, one obtains the measure of the width of the $g(t)$ curve (i.e. the variance of the mean dissolution time) in the form

$$\sigma^2 = \langle t^2 \rangle - \langle t \rangle^2 = \left(\frac{\alpha}{\beta^2}\right)^2 \tag{4}$$

The latter could be, more or less successfully, correlated to the corresponding in vivo variance of the mean residence time [6]. It is evident that all these quantities can be obtained quite easily, once the optimal values the two adjustable parameters, α and β, are determined. Since the trial function $G(t)$ is nonlinear, this task can be achieved using the maximum likelihood estimation method performed by the Levenberg-Marqardt method. The maximum likelihood estimation method determines, in the present context, the parameters which maximize the probability that the particular dissolution data set could have occurred. This leads [7] to the minimization of the χ^2 as a criterion of best fit, where

$$\chi^2 = \sum_{i=1}^{n} \left(\frac{y_i - G(t_i)}{\sigma_i}\right)^2 \tag{5}$$

Here, (t_i, y_i) with $i = 1, 2, \ldots, n$, represent the experimental dissolution data points, each with its own standard deviation σ_i. (It is assumed that the y_i values are scaled down so as to fall in the interval from 0 to 1, with e.g. $y_i = 0.5$ indicating that 50% of drug is dissolved). It is seen that the inverse value of (the square of) the standard deviation for each data point is used as the weighing factor for each term in the sum (when the standard deviation is constant, the equation for χ^2 is equivalent to the usual least-squares equation).

To implement the Levenberg-Marquardt method for minimizing χ^2, the partial derivatives of the trial function with respect to the fitting parameters, $\partial^{\mathrm{G}}/\partial\alpha$ and $\partial G/\partial\beta$, are also needed. We determine the former numerically, and the latter from

$$\frac{\partial G}{\partial \beta} = 2\frac{\alpha^2}{\beta}\,[G(t) - I] \tag{6}$$

A computer program was developed along these lines. The input data for the program consist of n triples (t_i, t_i, σ_i) representing dissolution data, and of an initial guess for the adjustable parameters, α and β. (Incidentally, we remark that often in practice one has to fit the dissolution profiles many times, each time with a slightly different shape; in this case, previous best-fit parameters usually provide a good initial guess for the next profile). The output, after successful fitting, consists essentially of only two numbers that succinctly summarize the experimental data, namely the estimated best-fit values of the parameters α and β (from these, everything else follows, Eqs. (2) and (3) Eq. (4)) together with their uncertainties and computed best-fit χ^2 value.

Finally in this section, we remark that the nonstandard notation for the parameters of the incomplete gamma function, adopted in Eq. (1), is advantageous for the numerical work since the Levenberg-Marquardt method, in order to work properly, requires an unrestricted range of parameters.

3. Results and discussion

We illustrate the use of the proposed method, of fitting dissolution profiles to the incomplete gamma function by the Levenberg-Marquardt method, with a typical set of in vitro dissolution data. A number of dissolution profiles was determined, under the same conditions, for a single 250 mg chloramphenicol capsule (locally produced by ICN Galenika) in 900 ml 0.1 M hydrochloric acid by the rotating basket method (using ERWEKA Dissolution Tester DT6), and according to BP-93 specifications at 100 rpm. Each dissolution profile consisted of $n = 13$ data points, regularly sam-

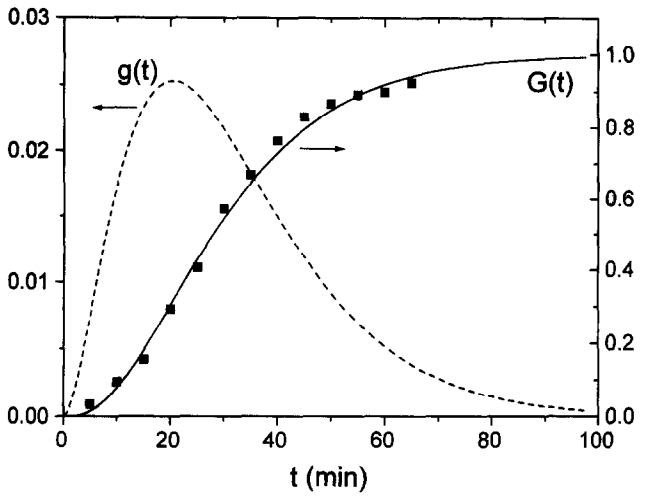

Fig. 1. Fit of mean in vitro dissolution measurements (squares) of single 250 mg chloramphenicol capsule in 900 ml 0.1 M hydrochloric acid, by the rotating basket method at 100 rpm, to the incomplete gamma function by the Levenberg-Marquardt method. Solid curve represents best-fit dissolution profile, $G(t)$, that was obtained, and dashed curve, $g(t)$, represents corresponding dissolution rate of chloramphenicol. Right hand ordinate pertains to the experimental data and $G(t)$, left hand ordinate to $g(t)$.

pled at 5 min time intervals from $t_1 = 5$ min to $t_{13} = 65$ min. At each t_i, the mean value of the percentage of the drug dissolved and corresponding standard deviation σ_i were determined, yielding n triples (t_i, y_i, σ_i) (represented by squares in Fig. 1) that served as the input data. The largest standard deviation was less than 0.02. After supplying an initial guess for the adjustable parameters, α and β, the computer program yields estimated best-fit values of the two parameters, together with their uncertainties

$$\alpha = 1.6850 \pm 0.0043, \qquad \beta = -0.2999 \pm 0.0002$$

and best-fit 'χ^2' value of $\chi^2 = 172.9$. The two optimum parameter values give, using Eqs. (1) and (2), the best-fit model function $G(t)$ representing the dissolution profile, and its time derivative, $g(t)$, representing the instantaneous dissolution rate of chloramphenicol (both shown in Fig. 1). Also, one readily obtains the corresponding mean dissolution time and (square root of) its variance, from Eqs. (3) and (4), respectively

$$\langle t \rangle = 31.6 \text{ min}, \qquad \sigma = 18.7 \text{ min}.$$

Other quantities of interest, such as e.g. 80% dissolution time, can also be obtained quite easily. Routine drug production quality control has shown that the proposed method leads to similar results for in vitro dissolution profiles of various other drugs such as diazepam tablets, ampicillin capsules and promethazine hydrochloride tablets.

It should be pointed out that the uncertainties introduced by the errors in the experimental data are reflected in the uncertainties of the best-fit parameters. Their large values indicate either bad fitting, large standard deviations, problems within the dissolution data, or, indeed, improper model function (in this last case the incomplete gamma function being simply an inadequate model).

Finally, we remark that if the model function, $G(t)$, provides a good description of the dissolution data, then it might also be profitable to compute another quantity related to the third moment of the frequency function $g(t)$, namely skewness of dissolution time distributions from [9]

$$\text{Skew} = \left\langle \frac{t - \langle t \rangle}{\sigma} \right\rangle^3 = \frac{2}{\alpha} \tag{7}$$

Apparently, this quantity will gain in importance in future pharmacokinetic investigations [10].

The computer program that implements the proposed method of fitting dissolution profiles to the incomplete gamma function by the Levenberg-Marquardt method, and written in standard ANSI FORTRAN-77, is available upon request from the authors. This should run without modification on any computer which implements this standard.

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