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Modeling of supersaturated dissolution data

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Abstract

A recursion equation which relies on the population growth model of dissolution is used for the analysis of supersaturated dissolution data. The concentration–time data of dissolution experiments are initially transformed to fractions of dose dissolved-generations by adopting an appropriate time interval as the time step of the recursion equation. A computer program is used to derive estimates for the maximum fraction of dose dissolved and the fraction of dose remaining in solution at steady state. Good fittings were observed when this equation was applied to phenytoin and nifedipine supersaturated dissolution data obtained from literature.

Keywords: Dissolution; Supersaturation; Modeling; Population growth model; Difference equation

1. Introduction

Dissolution testing is an integral component of the pharmaceutical product development process. It is used as a quality control procedure in pharmaceutical production and as a surrogate for in vivo bioavailability, and bioequivalence when in vitro–in vivo correlations have been established.

Considerable interest has been shown in the modeling of dissolution data. Numerous approaches have been reported over the years to describe mathematically the drug dissolution profiles. The standard methods in the dissolution data analysis are the cubic root law, the square root time equation, and several modifications of the simple exponential function (Noyes et al., 1897; Hixon et al., 1931; Higuchi, 1961; Gibaldi and Feldman, 1967; Goldsmith et al., 1978; Peppas, 1985; Sathe et al., 1996; Jorgensen and Christensen, 1996). Various models have been also described for the analysis of S-shaped dissolution profiles (Wagner, 1969; Langenbucher, 1972; Leary and Ross, 1983; Kervinen and Yliruusi, 1993; Djordjevic and Mendas, 1997).

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The dissolution data are basically of monotonic nature (the drug concentration or the fraction of drug dissolved is increasing with time) and therefore the corresponding modeling approaches rely on monotonic functions. However, non-monotonic dissolution profiles are frequently observed in studies dealing with coprecipitates of drugs with polymers, solid dispersion formulations and dissolution of salts in buffers (Wuster and Taylor, 1965; Finholt and Solvang, 1968; Yamamoto et al., 1976; Fujii et al., 1991; Suzuki and Sunada, 1998). The dissolution profiles of these studies usually exhibit a supersaturation phenomenon; namely, an initial rapid increase of drug concentration to a maximum followed by a progressive decline to a plateau value. To the best of our knowledge, no modeling approach for supersaturated dissolution data has yet been reported. Therefore, the necessity of developing a modeling approach for supersaturated dissolution data is apparent.

In this work, the proposed technique for modeling supersaturated dissolution data relies on the difference equation of the population growth model of dissolution reported recently (Dokoumetzidis and Macheras, 1997). In this model, the variable of interest, mass dissolved, is not considered as a continuous function of time, but is a function of a discrete time index specifying successive generations.

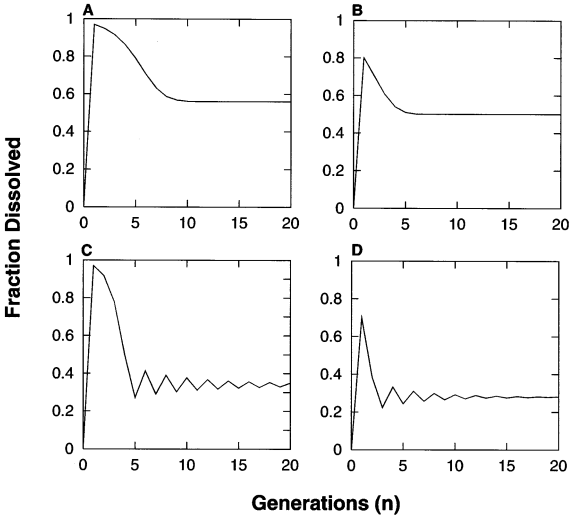

Fig. 1. Plots of the dissolved fraction Φ_n as a function of generations, n, using Eq. (1) with r and θ/X_0 values satisfying the inequality $\theta/X_0 < r < 2/((X_0/\theta) - 1)$: (A) $r = 0.97$, $\theta/X_0 = 0.56$; (B) $r = 0.8$, $\theta/X_0 = 0.5$; (C) $r = 0.97$, $\theta/X_0 = 0.34$; (D) $r = 0.7$, $\theta/X_0 = 0.28$.

2. Theoretical development

The population growth model of dissolution (Dokoumetzidis and Macheras, 1997) relies on the concept of the discontinuous birth in successive generations, n, of the dissolved drug molecules from the population of the drug molecules in the solid state. According to this model, the dissolution process is described by the recursion equation:

$$\Phi_{n+1} = \Phi_n + r(1 - \Phi_n)(1 - \Phi_n X_0/\theta) \quad (1)$$

where X_0 is the dose (total amount of drug), θ is the amount of drug in solution corresponding to the saturation solubility of the drug in the dissolution medium, r is a dimensionless proportionality constant, and Φ_n, Φ_{n+1} denote the fractions of dose dissolved at generations n and $n+1$, respectively; the generation number n takes values beginning with zero for $t = 0$. Eq. (1) has two steady-state solutions, $\Phi_{ss} = 1$ when $\theta/X_0 \geq 1$ and $\Phi_{ss} = \theta/X_0$ when $\theta/X_0 < 1$. Because of the nature of the model, the first step is always $\Phi_{n=1} = r$, and r is always lower than 1, i.e. the theoretical top boundary of Φ_n. When either $r < \theta/X_0 < 1$ or $r < 1 < \theta/X_0$, Eq. (1) follows the typical pattern of dissolution curves, i.e. a monotonic exponential increase of Φ_n asymptotically reaching the steady state, namely 1 or θ/X_0.

However, for values of r in the range $\theta/X_0 < r < 2/((X_0/\theta) - 1)$ (Dokoumetzidis and Macheras, 1997), the first step is higher than the plateau value followed by a progressive decrease to the plateau (Fig. 1A,B). Thus, Eq. (1) can be used for the analysis of supersaturated dissolution data which exhibit this type of behavior, i.e. an initial rapid increase of drug concentration to a supersaturated maximum with a subsequent decline to a plateau. For θ/X_0 and r values that are close enough, the descending part of the dissolution curve is smooth, concaving either upwards (Fig.

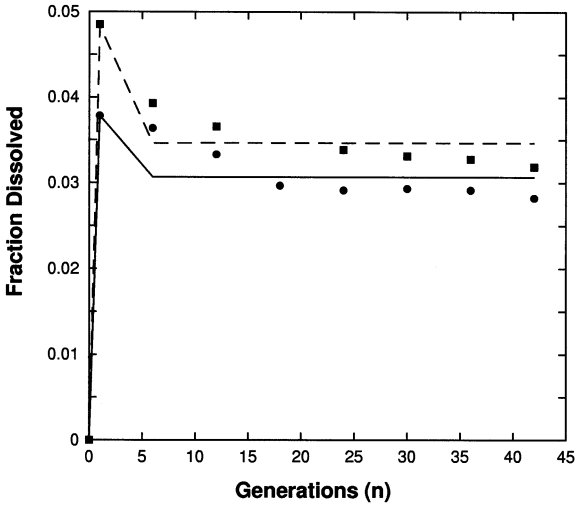

Fig. 2. Plot of the dissolved fraction Φ_n as a function of generations, n (time step 4 h) using Eq. (1) for the dissolution of phenytoin ground mixture with microcrystalline cellulose in 50 ml of JP VIII disintegration medium at 37°C. ●, 50 mg of the ground mixture; ■, 150 mg of the ground mixture (Yamamoto et al., 1976). Fitted lines of Eq. (1) are drawn over the experimental data (●, solid line; ■, dashed line).

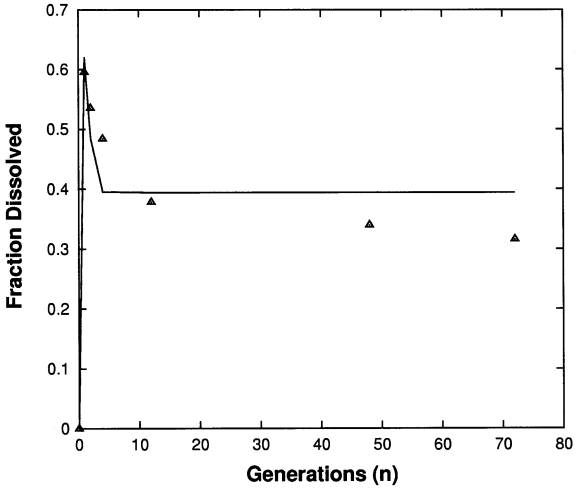

Fig. 3. Plot of the dissolved fraction Φ_n as a function of generations, n (time step 2.5 min) using Eq. (1) for the dissolution of 109 mg phenytoin sodium salt powder in 1 l of JP VIII disintegration medium at 37°C (Yamamoto et al., 1976). Fitted line of Eq. (1) is drawn over the experimental data.

1B) or initially downwards and then upwards (Fig. 1A); this decline can also take the form of a fading oscillation when r is close to $2/((X_0/\theta)-1)$ (Fig. 1C,D).

3. Results and discussion

Eq. (1) was applied to supersaturated dissolution data obtained from the literature in order to derive estimates for the dimensionless parameters r and θ/X_0. Initially, the drug concentration values were transformed to the corresponding dissolved fractions of dose, Φ_n, and plotted as a function of the generations, n. The transformation of sampling times to generations, n, was achieved by adopting the time needed to reach maximum concentration (equivalent to maximum fraction of dose dissolved) as the time step of Eq. (1). Initial estimates for parameters r and θ/X_0 were derived by reading the maximum and lowest values of Φ_n, respectively. These values were further used as starting points to a computer program, written in QUICKBASIC, to determine the best parameter estimates. The programme searches for values of r and θ/X_0, optimizing the minimization of the sum of squared discrepancies between the observed values and the values given by the model. The program can be obtained by the authors upon request.

Fittings of Eq. (1) to the data taken from the literature for dissolution of phenytoin ground mixture with microcrystalline cellulose and phenytoin sodium salt powder (Yamamoto et al., 1976), as well as nifedipine solid dispersions with nicotinamide and polyvinylpyrolidone (Suzuki and Sunada, 1998), are shown in Figs. 2–4. The estimated parameters values are listed in Table 1. The three parameters used to describe the supersaturated dissolution data are r, θ/X_0 and the time step. The latter is quoted in the legends of Figs. 2–4 for each one of the data sets. The value of r denotes the maximum fraction of dose which is dissolved in a time interval equal to the time step used. The value of θ/X_0 corresponds to the plateau value, which is the fraction of dose remaining in solution at steady state.

However, the use of Eq. (1) should not be considered as a panacea for modeling non-monotonic dissolution curves. Obvious drawbacks

of the model using Eq. (1) are: (i) the data on the ascending limb of the dissolution curve, if any, should be ignored; (ii) the inherent error involved, since the time required to reach the maximum value of the dissolved fraction of drug is adopted as the time interval between successive generations; (iii) the time values of the data points which can be used for fitting purposes should be integer multiples of the time step adopted. Moreover, caution should be exercised by prospective users of the method since when r takes values much larger than θ/X_0, Eq. (1) exhibits chaotic behaviour following the period doubling bifurcation (Macheras et al., 1996; Glass and Mackey, 1988). For example, Eq. (1) leads to chaos when $\theta/X_0 = 0.25$ and r is higher than 0.855. Despite the aforementioned disadvantages, Eq. (1) offers the only approach which can be used to describe supersaturated dissolution data.

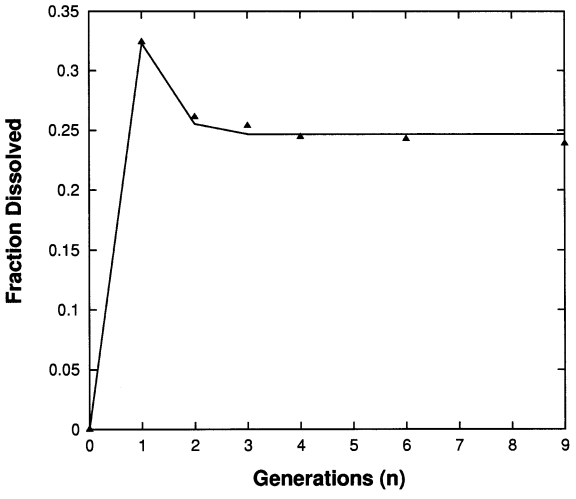

Fig. 4. Plot of the dissolved fraction Φ_n as a function of generations, n (time step 5 min) using Eq. (1) for the dissolution of nifedipine solid dispersion with nicotinamide and polyvinylpyrolidone (1:3:1), in 900 ml of distilled water (Suzuki and Sunada, 1998). Fitted line of Eq. (1) is drawn over the experimental data.

Table 1
Estimates for r and θ/X_0 derived from the fitting of Eq. (1) to supersaturated dissolution data taken from the literature

Reference	r	θ/X_0	Root mean square error
Yamamoto et al. (1976)[a]	0.038	0.031	2.44×10^{-3}
Yamamoto et al. (1976)[b]	0.048	0.035	2.24×10^{-3}
Yamamoto et al. (1976)[c]	0.620	0.394	5.38×10^{-2}
Suzuki and Sunada (1998)[d]	0.323	0.246	5.04×10^{-3}

[a] Phenytoin ground mixture, 150 mg.
[b] Phenytoin ground mixture with microcrystalline cellulose, 50 mg.
[c] Phenytoin sodium salt powder, 109 mg.
[d] Nifedipine solid dispersion formulation with nicotinamide and polyvinylpyrolidone.

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