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Nonlinear data fitting for controlled release devices: an integrated computer program

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Abstract

A computer program, MSFIT, was developed for nonlinear fitting of release data from controlled release devices. The program is written in the C language, based on the high level user-interface Macintosh operating system. Five popular release models are implemented in the program. Initial estimates of the parameters are obtained by linear transformation followed by linear fitting of the fraction released-time data. Nonlinear model fitting is based on the maximum likelihood estimation method and is performed by the Levenberg-Marquardt method based on the χ^2 criterion. Several methods are available to aid the evaluation of the fitting results. The MSFIT program was used for the nonlinear fitting of several release data sets and results were satisfactory.

Keywords: Nonlinear fitting; Sustained release; Microspheres; Release models; Macintosh computer program

1. Introduction

Microencapsulation has been utilized for a long time as a method of achieving sustained release in a wide variety of applications, including pharmaceutical dosage forms. A sustained release microencapsulation device can take various geometries, including slab, cylinder, hemisphere and sphere. However, spherical devices, widely known as microspheres, is one of the most popular preparations for controlling the release of pharmaceuticals.

Microspheres, intended to be used as controlled release drug delivery systems, need to be tested for their release properties and the release data are usually fitted to nonlinear models. Several nonlinear equations are available for this purpose. Since no computer program is available specifically for nonlinear fitting of drug release data, fitting is usually done by linear transformation of the data followed by computer fitting using linear regression programs. One of the drawbacks of this method is that the fitting is based on the transformed data and thus may not be mathematically accurate for the original data. For example, when the data is transformed into its logarithm form before the fitting, the fitting depends more heavily on the data with smaller values than that with larger values by a logarithm factor. By reviewing the literature, it can be seen that standard deviations of the data were usually not taken into

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account when linear fitting was done. A more efficient program is needed for the use of the standard deviations. Furthermore, the fitting of the actual data to the model can not be graphically seen since the data has to be transformed to the linear form in order to use the existing programs. Also, the commonly used linear fitting programs fit the data to a straight line with an intercept that is in many cases different from zero. This may create a source of error depending on the release model used. The details will be discussed later in this article. Because of the different models available for modeling of the release data, there is a dire need for a computer program for nonlinear model fitting specifically used for controlled release devices. We have recently developed an integrated program for fitting release data from sustained release matrices. The program, MSFIT, is easy to use. It runs on the Macintosh operating system and takes advantage of the high-level user-interface of the system. The aim of this paper is to introduce the MSFIT program and evaluate its performance. Several sets of release data were fitted using the MSFIT program and the results were satisfactory.

2. General description

2.1. Nonlinear fitting algorithm

An algorithm based on maximum likelihood estimation is used for nonlinear model fitting in the MSFIT program. The algorithm calculates the parameters which maximize the probability that the experimental data set could have occurred. Since the probability of the data set is the product of the probabilities of each point, it can be written as:

$$P = \prod_{i=1}^{N} \left\{ \exp\left[-\frac{1}{2}\left(\frac{y_i - y(x_i)}{\sigma_i} \right)^2 \right] (\Delta y) \right\}$$

where σ_i is the standard deviation for each data point (x_i, y_i) and Δy is a constant factor. To maximize P in the above equation, one can minimize the negative of its logarithm (L), where

$$L = \left[\sum_{i=1}^{N} \frac{[y_i - y(x_i)]^2}{2\sigma_i^2} \right] - N \log(\Delta y)$$

Since N and Δy are constants, minimizing the above equation is equivalent to minimizing the following equation (the process is called chi-square, χ^2, fitting or weighted least-squares fitting):

$$\chi^2 = \sum_{i=1}^{N} \left(\frac{y_i - y(x_i)}{\sigma_i} \right)^2$$

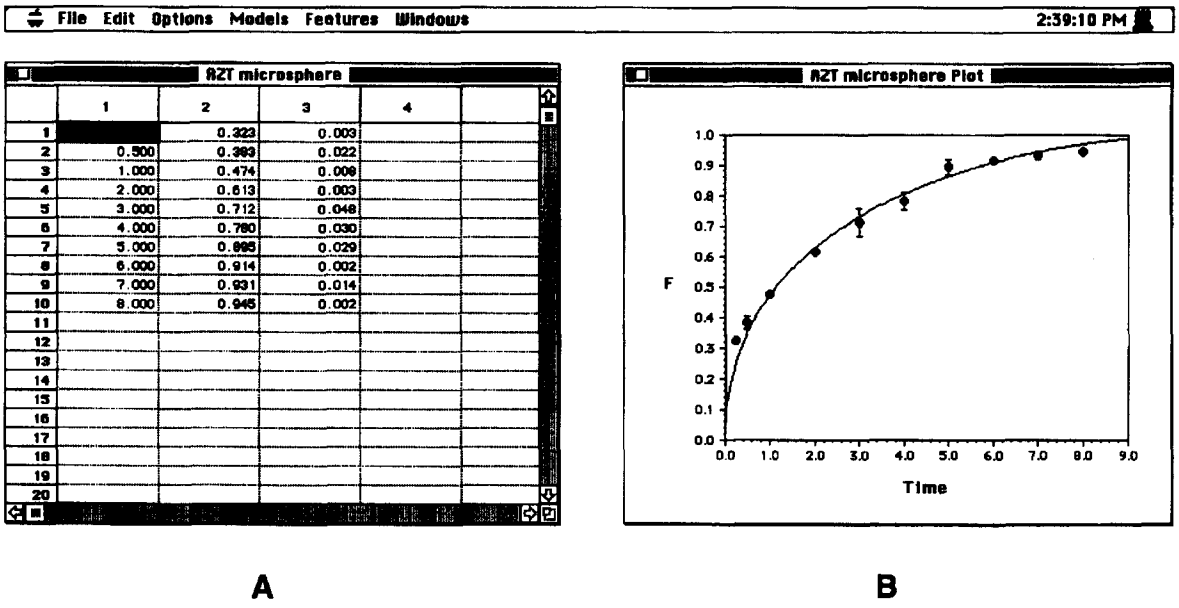
If the standard deviation, σ_i, is constant within the data set, the equation is equivalent to the least square equation:

$$LS = \sum_{i=1}^{N} (y_i - y(x_i))^2$$

The MSFIT program uses minimization of the χ^2 as the criterion of 'best fit'. The estimated initial parameters (obtained using either the automatic estimation mode or the manual input mode) are first employed to generate estimates which result in a relatively small χ^2. Iterations are then made until a minimum χ^2 is obtained. The Levenberg-Marquardt method (Press et al., 1988) is used in the MSFIT program for minimizing the χ^2. This method represents a compromise between the linearization (or Taylor series) method and the steepest descent method and appears to combine the best features of both (Press et al., 1988). The fitting algorithm was described in detail in Press et al's book (Press et al., 1988) and was used in the pharmacokinetic program, PharmK (Lu and Mao, 1993). It should be noted that the success of reaching the minimum χ^2 is, in many cases, dependent on the initial parameter estimation. An initial parameter estimation that is too far from the true value may cause the iterations to stop at local minima. The estimation from the linear regression approach implemented in the MSFIT program usually gives a sufficient initial estimation.

2.2. Release models

There are several models which can be used for description of the release profiles from controlled release devices. The choice of a specific model for the data set from a particular controlled release



	1	2	3	4
1		0.323	0.003	
2	0.500	0.393	0.022	
3	1.000	0.474	0.009	
4	2.000	0.613	0.003	
5	3.000	0.712	0.048	
6	4.000	0.780	0.030	
7	5.000	0.895	0.029	
8	6.000	0.914	0.002	
9	7.000	0.931	0.014	
10	8.000	0.945	0.002	
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				

Fig. 1. A brief description of the general operating procedure for nonlinear model fitting with the MSFIT program. (A) is a representative data-entry window. After a release model is selected from the Model menu, a graphic display of the fitting results is generated (B). The features of the graph can be manipulated using the Features menu. Other options such as data conversion, scatter plot, etc. are also available in the Options menu.

formulation depends on shape of the graphics and the underlying controlling mechanism. Here we will only discuss the mathematical form of those models implemented in our program.

2.2.1. Baker and Lonsdale equation (Higuchi's model for spherical matrices)

The Baker and Lonsdale equation (Baker and Lonsdale, 1974) which was derived from Higuchi's model (Higuchi, 1963) describes the drug release from sustained release microspheres:

$$\tfrac{3}{2}[1-(1-F)^{2/3}]-F=kt$$

Here F is the fraction of drug released at any time t. The constant k is equal to $3DC_S/r_o^2C_o$, where, D is the diffusion coefficient, C_s is the drug solubility in the polymer, r_o is the radius of the device and C_o is the initial concentration of the drug in the polymer matrix.

The equation has been fitted to release data from various microspheres formulations (Jun and Lai, 1983; Leelarasamee et al., 1986; Chang et al., 1986; Shukla and Price, 1989, 1991; Dubernet et al., 1990). Linear fitting was usually used after calculating the quantity corresponding to the expression on the left side of the equation at each time point.

2.2.2. Peppas equation

The Peppas equation (Peppas, 1985) represents a general data fitting approach for drug release:

$$F=kt^n$$

where, F is the fraction released at time t, k is a constant incorporating structural and geometric characteristics of the controlled release device, and n is the release exponent, that may be used to indicate the mechanism of drug release.This is a general semiempirical equation that is not based on a certain model, a certain geometry or a single mechanism. It is usually used to analyze release data from polymeric devices, when the mechanism of release is not well known or when more than one type of release may be involved (Orienti and Zecchi, 1993; Franz et al., 1987).

Number	Time	F Released	Std. Deviation	Prediction
1	0.2500	0.3232	0.0030	0.2518
2	0.5000	0.3831	0.0220	0.3466
3	1.0000	0.4738	0.0075	0.4708
4	2.0000	0.6133	0.0034	0.6268
5	3.0000	0.7119	0.0408	0.7302
6	4.0000	0.7800	0.0300	0.8060
7	5.0000	0.8944	0.0290	0.8638
8	6.0000	0.9143	0.0016	0.9085
9	7.0000	0.9312	0.0140	0.9430
10	8.0000	0.9449	0.0019	0.9688

Calculation using the Baker-Lonsdale equation

Equation: $3/2\left[1-(1-F)^{2/3}\right]-F=K*t$

K = 0.0478

FITTING ITERATION

K	Chi-Square
INITIAL PARAMETERS:	
0.0440	1027
7 ITERATIONS (3 for re-fitting); LF(1,2) = 10.000, 5.000; Conv. = 0.00010	
0.0474	760.9094
0.0478	759.2088
0.0478	759.2088
0.0478	759.2088
0.0478	759.2088
0.0478	759.2088
0.0478	759.2088

UNCERTAINTY, SD AND CONFIDENCE INTERVAL

K
ESTIMATED PARAMETERS:
0.0478
UNCERTAINTY: (SD (Y) input: Column #3):
0.0002
STANDARD DEVIATION OF EACH PARAMETER:
0.0022
95% CONFIDENCE INTERVAL: (univariate)
0.0427
0.0529
95% CONFIDENCE INTERVAL: (plane)
0.0427
0.0529

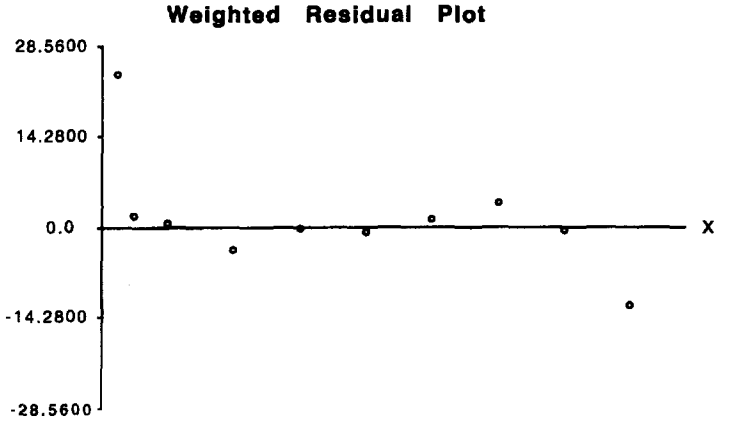


Fig. 2. The output file for fitting of the AZT data to Baker and Lonsdale Equation.

2.2.3. Hixon and Crowell equation

Hixon and Crowell originally derived the following equation to describe the dissolution of solid particles (Hixon and Crowell, 1931).

$$1-(1-F)^{1/3}=kt$$

where, F is the fraction dissolved at time t and k is a constant.

This equation has been used by some researchers to describe the release of drugs from spherical matrices that have been compressed into tablets and satisfactory results were obtained (Touitou and Donbrow, 1982; Franz et al., 1987). The use of this model is based on the assumption that the rate of release is limited by the rate of dissolution of the drug particles and not by diffusion through the polymer matrix.

2.2.4. Higuchi equation of square root of time

The following equation was derived by Higuchi (1961) to describe the release of drugs diffusing through a planar system and it has occasionally been used to fit release data from some microspheres formulations.

$$F=k\sqrt{t}$$

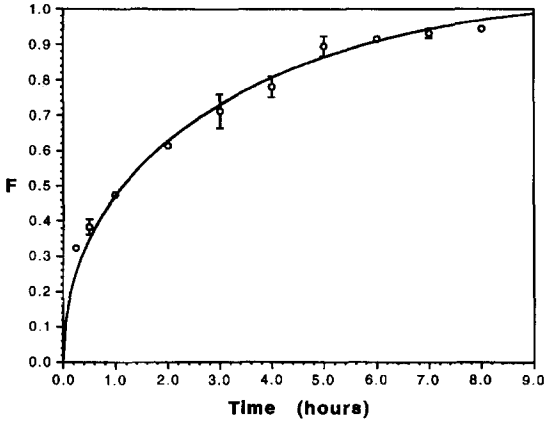


Fig. 3. Graphical representation of the fitting results (fraction of drug released vs time) of the AZT data to Baker and Lonsdale Equation. Vertical bars represent actual standard deviation of the data points.

The constant k is equal to $(2ADC_s)^{1/2}/M_o$. Here, A is the surface area of the device, D is the diffusion coefficient, C_s is the solubility of the drug in the polymer and M_o is the amount of the drug per unit area present initially in the system. Although the use of this equation for spherical matrices does not reflect any single release mechanism, some data showed good fitting (Mortada et al., 1988). This may indicate the possibility of superposition of two mechanisms or more. In this case, it may correspond to an exponent $n=0.5$ in the Peppas equation. A square root model may also describe the release from a monolithic solution in a spherical device, where the early time approximation results in a square root of time equation (Baker and Lonsdale, 1974).

2.2.5. First order equation

Occasionally, drug release data are fitted to a first-order decline model (Shah et al., 1987; Mortada et al., 1988). Since most microspheres consist of drug particles embedded in a polymer matrix, a first order release does not conform with a known mechanism for drug release from spherical matrices. One situation that can be described by first-order release kinetics is the nonconstant activity reservoir spherical device, where the drug solution is enclosed within a porous membrane through which diffusion occurs (Baker and Lonsdale, 1987).

For the fitting purpose, the first order release equation is

$$F=1-e^{-kt}$$

2.3. Fitting process and evaluation

The general fitting process can be briefly seen in Fig. 1. The release data is input via a 'spread sheet' type of input window. The fraction released and the corresponding time are input each in a separate column. After selecting a specific model, the computer calculates the initial estimation of the parameters using the linear transformation method. The initial estimated parameters are then refined via an iteration process to achieve a minimum χ^2. Subsequently, the MSFIT program gen-

Number	Time	F Released	Std. Deviation	Prediction
1	0.2500	0.1820	1.0000	0.1710
2	0.5000	0.2469	1.0000	0.2364
3	1.0000	0.3101	1.0000	0.3260
4	2.0000	0.4459	1.0000	0.4442
5	3.0000	0.4969	1.0000	0.5281
6	4.0000	0.6173	1.0000	0.5942
7	5.0000	0.6728	1.0000	0.6487
8	6.0000	0.7099	1.0000	0.6951
9	7.0000	0.7531	1.0000	0.7353
10	8.0000	0.7720	1.0000	0.7705
11	10.0000	0.8179	1.0000	0.8292
12	12.0000	0.8330	1.0000	0.8758

Calculation using the Baker-Lonsdale equation

Equation: $3/2\left[1-(1-F)^{2/3}\right]-F=K*t$

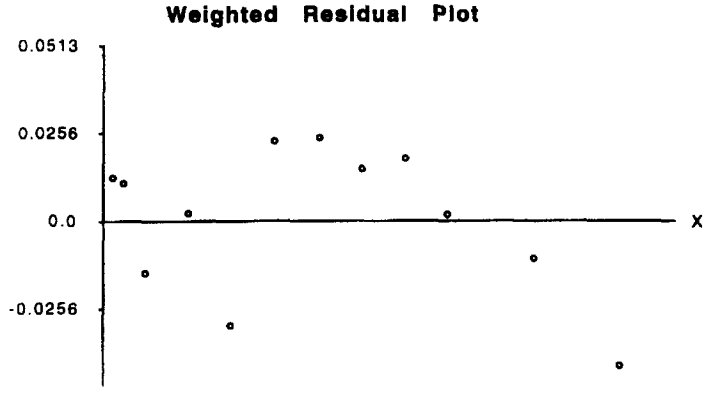
$K = 0.0209$

FITTING ITERATION

K	L-Square
INITIAL PARAMETERS:	
0.0190	0.0102
7 ITERATIONS (3 for re-fitting); LF(1,2) = 10.000, 5.000; Conv. = 0.00010	
0.0208	0.0051
0.0209	0.0051
0.0209	0.0051
0.0209	0.0051
0.0209	0.0051
0.0209	0.0051
0.0209	0.0051

UNCERTAINTY, SD AND CONFIDENCE INTERVAL

K
ESTIMATED PARAMETERS:
0.0209
UNCERTAINTY: (SD (Y) input: Column #3):
0.0274
STANDARD DEVIATION OF EACH PARAMETER:
0.0005
95% CONFIDENCE INTERVAL: (univariate)
0.0196
0.0222
95% CONFIDENCE INTERVAL: (plane)
0.0196
0.0222



erates a graphical presentation of the model fitting on the computer screen. A high quality hardcopy of smoothly curved graphics can be obtained on LaserWriter printers. The user of the MSFIT program can interactively manipulate certain features of the graphics, such as adding labels, moving texts, rescaling, plotting standard error bars, or changing symbols for a publication-ready hardcopy. The MSFIT program can also be used to simulate the release profiles using known model parameter(s).

Several methods are used in the MSFIT program to aid the evaluation of the fitting results. The evaluation is particularly useful when statistical considerations are involved.

2.3.1. Graphical examination

Following the fitting process, a graphical presentation of the fitting results (in the form of fraction released-time curve) is displayed on the computer screen. Visual examination of the fraction released-time curve in the presence of the input data points can help one determine whether to reject the fitting results. It is noteworthy that although it is not correct to accept a fitting simply because the graph looks 'good', the fitting may be rejected if the graph looks 'bad'.

2.3.2. The uncertainty of the estimated parameter

The uncertainty of the estimated parameter is computed after the nonlinear fitting. The uncertainty of the estimated parameter is calculated as the square root of the diagonal elements of the matrix $[\alpha]^{-1}$, where $[\alpha]$ is a matrix of sums of cross-products of certain partial derivatives (Boxenbaum et al., 1974; Press et al., 1988). These uncertainties are introduced by the measurement errors in the data (Press et al., 1988). The computation is based on the normal distribution theory. As a result, the uncertainty tends to be optimistic. Nevertheless, if the uncertainty values are very large compared with the corresponding parameters, further examination is necessary. The large uncertainty values may indicate bad fitting, the wrong model is being used, large standard deviations, or problems within the data. Therefore, the uncertainty value may be helpful for the user to determine if the fitting is acceptable or further examination is required.

2.3.3. Confidence intervals of the estimated parameters

A confidence interval (CI) is a measure of the precision of an estimated parameter. It is calculated based on the linearized approximation (Draper and Smith, 1988). In the MSFIT program, 95% confidence intervals of the estimated parameter are computed using either the univariate method or the plane method (Boxenbaum et al., 1974). The former is computed according to the Student $t_{(\alpha,df)}$ statistics criterion:

$$\text{CI} = \text{Estimated parameter} \pm (t_{(\alpha,df)} \times \text{S.D.})$$

and the later according to the F(α,NP,df) statistics criterion:

$$\text{CI} = \text{Estimated parameter} \pm \sqrt{F_{(\alpha,NP,df)} \times NP \times (\text{S.D.})^2}$$

where NP is the number of parameters. The standard deviation of the ith estimated parameter, S.D._i, used in the calculation of the confidence interval is calculated using the following equation:

$$\text{S.D.}_i = \sqrt{S^2 \times a_{ii}}$$

where S^2 is the sum of the weighted squared residuals divided by the degrees of freedom and a_{ii} is the entry for the ith diagonal element of the matrix $[\alpha]^{-1}$. The confidence intervals so calculated are reported in the output file to aid the evaluation of the estimated parameters.

2.3.4. Examination of the residuals

The differences between the experimental data points and the corresponding values on the fitting curve are computed as the fitting residuals. The residual indicates the deviation of the original data from the fitting curve. An appropriate method to evaluate the fitting results is to plot the residuals at each data point. A weighted residual plot is generated by the MSFIT program to help the user determine the goodness of fit. The inverse value of the standard deviation for each data point is used as the weighting factor of each residual (Boxenbaum et al., 1974). An evenly distributed residual plot represents a satisfactory result for the fitting (Boxenbaum et al., 1974; Thakur, 1988).

3. Results and discussion

Several sets of release data were used to evaluate the MSFIT program. The data were mainly from sustained release microspheres formulations. In this paper, we will present the fitting results of two data sets for the Baker and Lansdale model. The fitting for other models have been proved satisfactory but the results are not presented due to the limitation in the paper length. The first set is release data obtained from sustained release zidovudine (AZT) microspheres prepared in our laboratory; and the second set is literature data from sustained release theophylline microspheres.

3.1. Data from AZT microspheres

The preparation method of these microspheres will be discussed in another publication (Abu-Izza et al., 1996). Release data from the microspheres of a particular formulation were fitted to the Baker and Lonsdale equation. Each data point was a mean of three repetitions, and the actual standard deviation was used to calculate the χ^2. The initial estimate of the constant K was generated by the MSFIT program in automatic estimation mode using the linear regression method. Alternatively, an initial estimate of the constant can be entered by the user. The initial estimate was equal to 0.044 (with a χ^2 of 1027.0). Subsequently, nonlinear fitting was carried out by the program and the final estimate of K was equal to 0.048 (with a χ^2 of 759.2). The output file for fitting the AZT data is given in Fig. 2 and a graphical representation of the nonlinear fitting of the same data is shown in Fig. 3. The output file shows the estimated value of the constant K. It also contains information on the fitting iteration, uncertainties, standard deviation of the constant K and its 95% CI as well. Both the output file and graphical presentation of the fitting results indicate that a good fitting was achieved.

It should be pointed out that one of the advantages of using the MSFIT program to fit the Baker and Lonsdale equation is the elimination of the intercept problem. When using the linear transformation method, an error is introduced if an intercept very different from zero is obtained since only the slope is used as the estimated parameter, K, and the intercept is assumed to be zero and dropped.

3.2. Data from theophylline microspheres

This data was obtained from a published article (Shukla and Price, 1991). The controlled release device was a spherical matrix with relatively high drug loading. In that paper the data was fitted to the Baker and Lonsdale equation after linear transformation. A good correlation coefficient was obtained. When fitted using the MSFIT program, the initial estimate of the parameter, K, obtained by linear transformation was equal to 0.019. Because no information was available on the standard deviation of this data set, a constant standard deviation of 1.000 was used. When a constant standard deviation is used, the χ^2 equation is equivalent to the least-square equation. The fitting results are not affected by the value of the constant; however, the uncertainties are dependent on that value. Changing the value of the constant standard deviation resulted in large changes in the values of uncertainties of the parameters. Therefore, it is recommended that true standard deviations be used when using the MSFIT program. Based on the initial estimation, nonlinear fitting was carried out by the program

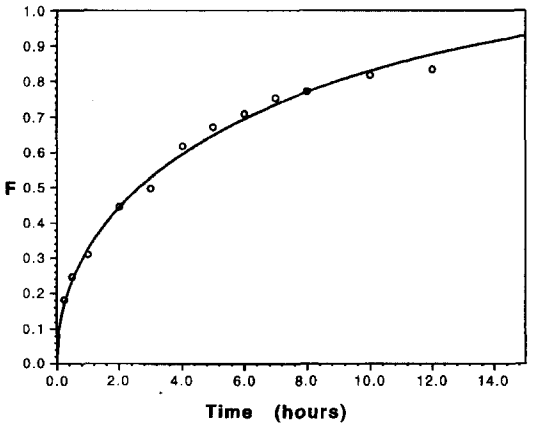


Fig. 5. Graphical representation of the fitting results (fraction of drug released vs time) of the theophylline data to Baker and Lonsdale Equation. A constant standard deviation of 1.0 was used.

and the final estimate was found to be 0.021. The output file from the theophylline data fitting is shown in Fig. 4; and a graphical representation of the fitting results is given in Fig. 5. The information obtained in Fig. 4 is similar to that obtained from Fig. 2. It can be clearly seen from the output file and the graphical presentation that the fitting is good.

4. Conclusions

The MSFIT program is a very useful and versatile tool for fitting release data from controlled release formulations. It is the first program available for specifically nonlinear fitting of release data, and it eliminates the disadvantages associated with the linear transformation method. Its user-friendly and high graphics-oriented features make the nonlinear model fitting very easy.

The MSFIT program is available from the authors with no charge. The interested reader should send a request with a blank disk to the authors to obtain this program.

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