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Kinetic Model Identification of Drug Release from Microcapsules Using the Nonlinear Regression Search Procedure

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INTRODUCTION

Drug release from microcapsules has been shown by several investigators to follow either a square-root-of-time equation (*1,2*) or a first-order kinetic equation (*3,4*). Other authors (*5*) have found that the kinetic data from microcapsules agree both with first-order and square-root-of-time equations. Application of the differential rate treatment (*6*) was needed in order to distinguish between the two kinetic release models. It was found that kinetic data actually conformed with the first-order equation.

PROCEDURES

Microcapsules of acetylsalicylic acid were prepared using ethylcellulose as a coating polymer. Microencapsulation was effected by coacervation using the temperature reduction process in the presence of polyethylene (*7*). Individual film-coated microcapsules were obtained, the release data for which are reported in Table 1. These microcapsules

TABLE 1
Kinetic Data of Acetylsalicylic Acid Microcapsules (91% Content)[a]

t, min	Q', amount released, %
5	16.4
10	26.7
15	36.5
20	45.0
25	52.0
30	58.4
35	63.8
40	68.7
45	72.5

[a]The experimental drug release conditions were identical to those described in (5).

exhibit release profiles that conform with both kinetic models (Table 2A). The differential mathematical treatment, based on the relationship analysis of the release rates (dQ'/dt) as a function of the amount released (Q') or the reciprocal of the amount released ($1/Q'$), is therefore required. However, a geometrical estimation of the release rates is considered fastidious and is subject to considerable error. An algebraic method is preferable. The latter is applicable only if the first-order and square root equations are validated. Since at this stage of the analysis, no distinction can be made between the two kinetic models and only one of them is correct, the release rates should be calculated by differentiation of the two equations. Two sets of release rate data are obtained. Obviously

TABLE 2
Mechanism of Drug Release from Microcapsules[a]

A		B, correlation coefficients of plots of rate dQ'/dt			
		First-order differential rates[c]		Square-root differential rates[d]	
First-order release constant $min^{-1} \times 10^2$	Square-root release constant, percent $\cdot$ $min^{-1/2}$	versus $1/Q'$	versus Q'	versus $1/Q'$	versus Q'
2.76(0.999)[b]	12.64(0.998)[b]	0.909	0.999	0.996	0.949

[a](A) Linearization of kinetic release data by first-order equation [ln $(100 - Q') = k_1 t$] and square-root-of-time equation ($Q' = kt^{1/2}$), (B) comparison of linearity obtained from plots of release rate against the reciprocal amount ($1/Q'$) and the amount (Q') of drug released for the two kinetic models respectively.

[b]Correlation coefficients.

[c]Calculated from $dQ'/dt = 100k_1e^{-k_1t}$,

[d]Calculated from $dQ'/dt = k/2t^{1/2}$. (These equations were obtained by differentiation of the above kinetic equations respectively).

these calculations yield two different release rate values for each point on the initial release curve and only one of them approaches the real value of this point obtained by measuring the slope of the tangent extracted from the experimental Q' vs time curve. Unfortunately, this method failed to distinguish between the two kinetic models, as is shown in Table 2B, where four possibilities were examined. In this case, it appears that the differential rate treatment is not sensitive enough to differentiate between the two models, which probably exhibit close release profiles.

An alternative and more adequate statistical method for release mechanism identification that uses the kinetic experimental results obtained without any further transformation is presented. It is considered more valid and accurate than the previous differential rate treatment. Since two kinetic models are expected, the chi-square χ^2, test which is useful for comparison purposes, should be used. It is in fact a measure of the deviation of the expected curves from the experimental curve. The expected curves are calculated by a curfit computer program that consists of a least squares fit to a nonlinear function with a linearization of the fitting function through the kinetic parameters. According to this method, the optimal parameter values are obtained by minimizing χ^2 with respect to each of the parameters simultaneously. The smallest χ^2 value yielded during the comparison will designate the correct release

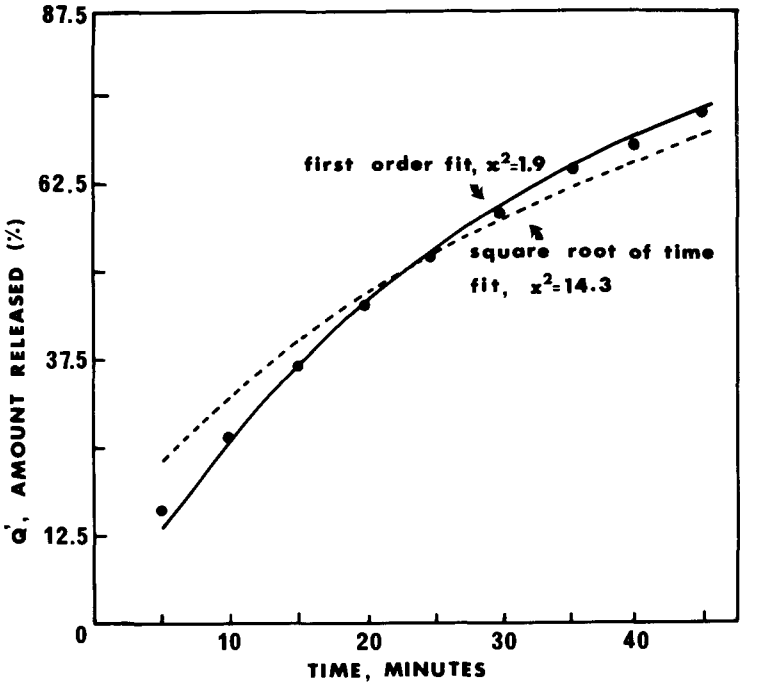

Fig. 1. Fitting and comparison of predicted release curves to observed kinetic data (•) reported in Table 1.

model. The expected amounts released from microcapsules are calculated by means of the first order:

$$Q' = W_o\ (1 - e^{-k1t})$$

and square-root-of-time equations, respectively, and compared to the observed amounts released.

The graphical results reported in Fig. 1 clearly indicate that acetylsalicylic acid release from microcapsules definitely follows the first-order kinetic model, as is also confirmed by the low resultant value of χ^2 obtained (Fig. 1).

This work shows again that the data on drug release from microcapsules agree with both kinetic models and that a more stringent statistical test is needed in order to distinguish between the two models. It is recommended to examine the applicability of both the first-order and square-root-of-time equations during kinetic data analysis for drug release from microcapsules. If both plots are linearly acceptable, then a further mathematical test is required in order to avoid ambiguity and provide useful information on the correct release mechanism.

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