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Mathematical expression of tablet dissolution profiles

J.R. Leary * and S.D. Ross **

* *Revlon Health Care (U.K.) Ltd., Shalford, Surrey and ** Department of Chemistry, Chelsea College, University of London, London (U.K.)*

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Summary

The process of tablet dissolution may adequately be expressed in terms of two consecutive stages, the first having a time-dependent rate, and the second being a simple first-order process. By utilizing tables of first and second differences, the rate constants of these processes may easily be determined from dissolution profiles. The practical use of the method is discussed.

Introduction

In a previous work (Leary et al., 1983), tables of first and second differences have been used to determine the rate constants of various consecutive zero-order and first-order processes. Earlier workers have considered that the process of drug dissolution from a tablet matrix is best represented by one of two mechanisms:

$$\overset{\frown}{A \rightarrow B \rightarrow C} \rightarrow P \qquad A \rightarrow B \rightarrow P \qquad (1,2)$$

where A, B, C and P represent tablets, large particles or aggregates, small particles or fines, and solution, respectively. Rakowski (1906) solved the differential equations which result from mechanism 1 if all processes along the main stem are first-order, and processes off the main stem are considered to have negligible effect. He arrived at the following equation for the final product:

$$[P] = 1 - \frac{k_1' k_1'' e^{-k_1 t}}{ab} + \frac{k_1'' k_1 e^{-k_1' t}}{ca} - \frac{k_1 k_1' e^{-k_1'' t}}{bc} \qquad (3)$$

where the reaction scheme is $A \rightarrow B \rightarrow C \rightarrow P$ with first-order rate constants k_1, k_1',

k_1'', respectively; a, b, and c are $(k_1' - k_1)$, $(k_1'' - k_1)$, and $(k_1'' - k_1')$, respectively, and [A] at time zero is unity.

Leary et al. (1983) compared the results generated by using this scheme with results obtained by using mechanism 2 with first-order rate constants k_1 and k_1', respectively. If the third process of the first scheme is fast relative to the other two processes, then reducing the mechanism to a two-stage process still gives an adequate fit to the experimental data.

Goldsmith et al. (1978) have examined the use of Weibull, logarithmic-logistic, and logarithmic-normal plots in modelling dissolution data. They concluded that, although all of these methods provide reasonable representations of dissolution traces, the additional work involved in fitting the parameters to the data does not lead to any fresh information. They comment that the most useful result of such treatment is to provide a short description of the dissolution rate curves; but that this description can equally well be provided by the times at which specified fractions of the tablet are in solution.

We now go on to consider other possible mathematical models for tablet dissolution.

Methods and Results

Table 1 presents simulated data for 3 mechanisms. The first mechanism is that of 3 consecutive first-order processes. The rate constants given are in approximately the correct ratio to simulate the dissolution process: initial break-up of tablet into aggregates is relatively slow, but is followed by faster stages which are the production of fine particles, and their eventual dissolution. The formation of P, which is the amount of drug in solution, is given by Eqn. 3. The second mechanism is that of two consecutive first-order processes (2); for this mechanism, the expression for P is:

$$P = 1 + \frac{1}{k_1 - k_1'} \cdot \left(k_1' e^{-k_1 t} - k_1 e^{-k_1' t}\right) \tag{4}$$

The third mechanism is an extension of the second, and can be represented as:

$$\overset{\curvearrowright}{A \rightarrow B \rightarrow P} \tag{5}$$

This is a reasonable mechanism to examine, as we can consider that some drug will be dissolving directly from the tablet surface while the tablet itself is breaking down into granules. This surface dissolution will obviously be slow compared with the dissolution of the granules, as the granules will have a much larger surface area. The 3 differential equations for this process may be integrated to give:

$$[P] = 1 - \frac{1}{k_1' - k_1 - k_1''} \cdot \left((k_1' - k_1'') e^{-(k_1 + k_1'')t} - k_1 e^{-k_1' t}\right) \tag{6}$$

We can see quite clearly from Table 1 that, firstly, there is little advantage gained in

TABLE 1

COMPARISON OF SIMULATED DISSOLUTION DATA FOR 3 DIFFERENT PROCESSES

t (min)	$[P]_1$	$[P]_2$	$[P]_3$
0	0	0	0
2	0.016	0.017	0.019
4	0.056	0.058	0.062
6	0.110	0.113	0.118
8	0.170	0.174	0.180
10	0.233	0.236	0.243
12	0.295	0.299	0.306
14	0.355	0.358	0.366
16	0.412	0.415	0.423
18	0.465	0.467	0.476
20	0.513	0.516	0.525
22	0.558	0.560	0.569
24	0.599	0.601	0.610
26	0.637	0.639	0.647
28	0.671	0.672	0.681
30	0.702	0.703	0.712
32	0.730	0.731	0.740
34	0.756	0.757	0.765
36	0.779	0.780	0.787
38	0.800	0.801	0.808
40	0.819	0.820	0.827

$[P]_1$ = [P] from 3 consecutive first-order processes; $k_1 = 0.05\ min^{-1}$, $k_1' = 0.2\ min^{-1}$, $k_1'' = 10\ min^{-1}$.
$[P]_2$ = [P] from 2 consecutive first-order processes; $k_1 = 0.05\ min^{-1}$, $k_1' = 0.2\ min^{-1}$.
$[P]_3$ = [P] from 2 consecutive first-order processes in parallel with one first-order process; $k_1 = 0.05\ min^{-1}$, $k_1' = 0.2\ min^{-1}$, $k_1'' = 0.001\ min^{-1}$.

using the third stage in a scheme such as 1, and, similarly, there is little gained by including the direct dissolution of the tablet into solution as in mechanism [5].

The two rate constants of Eqn. 4 are obtainable from tables of the first and second forward differences of the raw data (Leary et al., 1983). The curve thus generated will show a point of inflection, at which time $d^2[P]/dt^2$ will be zero, leading to the relationship:

$$k_1 e^{-k_1 t_s} = k_1' e^{-k_1' t_s}$$

where t_s is the time at the point of inflection. This can be substituted into the expression for d[P]/dt, giving:

$$\frac{d[P]}{dt} = k_1 e^{-k_1 t_s} = k_1' e^{-k_1' t_s} \quad (7)$$

These two equations may be solved by graphical or other means to yield values for k_1 and k_1'.

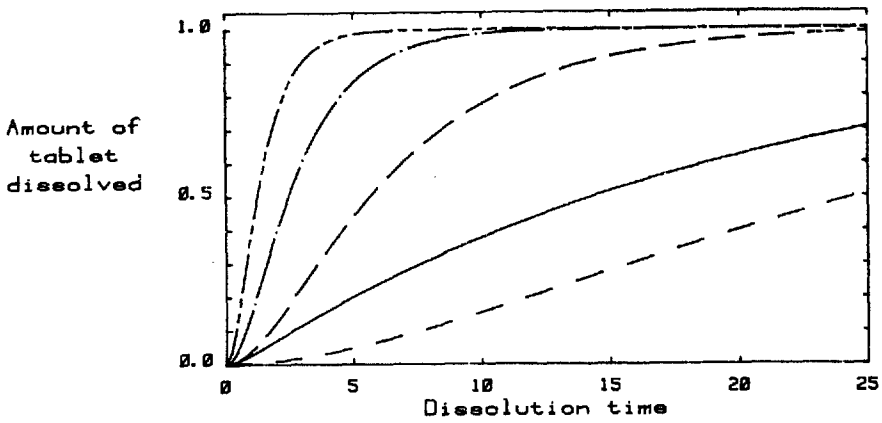

Fig. 1. Examples of dissolution traces generated by two first-order processes.
———, $k_1 = 0.05\ min^{-1}$, $k'_1 = 2.00\ min^{-1}$;
— · — · —, $k_1 = 1.00\ min^{-1}$, $k'_1 = 0.50\ min^{-1}$;
- - - - - -, $k_1 = 0.05\ min^{-1}$, $k'_1 = 0.10\ min^{-1}$;
— - - — - -, $k_1 = 1.00\ min^{-1}$, $k'_1 = 2.00\ min^{-1}$;
— — —, $k_1 = 0.20\ min^{-1}$, $k'_1 = 0.50\ min^{-1}$.

Fig. 1 presents curves which have been generated from Eqn. 4, and shows the effect of different values for k_1 and k'_1. It can be seen that, in all of these curves, the portion of the trace before the point of inflection does not show the same type of curvature as is seen in most dissolution traces. These curves in fact only resemble dissolution curves of tablets which can be said to disintegrate very quickly.

Fig. 2 shows dissolution traces of tolbutamide 500 mg tablets B.P. ('Pramidex' tablets, Berk Pharmaceuticals). The traces were generated using the method of Randall and Goldsmith (1975); the dissolution medium was 1 litre of phosphate buffer at pH 7.5, and the amount of drug in solution was monitored at 228 nm.

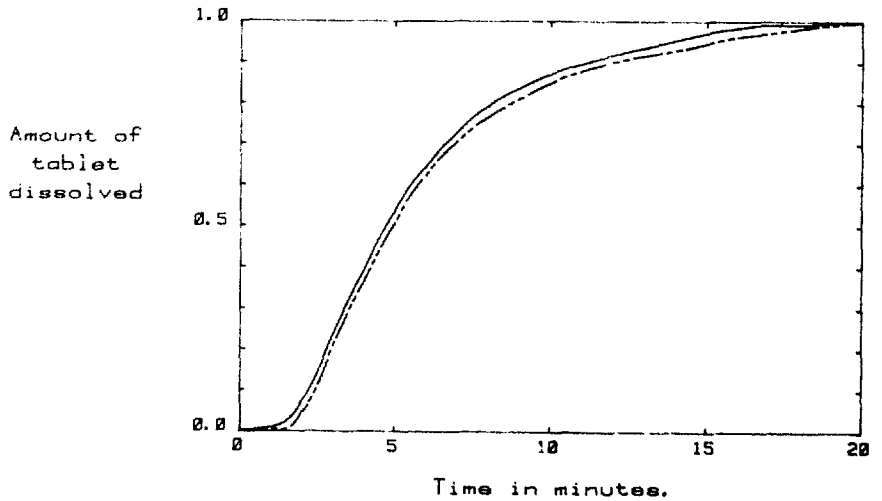

Fig. 2. Two dissolution traces of tolbutamide tablets: these data are presented in Table 3.

These traces are representative of the dissolution traces shown by a variety of generic drugs; particularly in respect of the degree of curvature of the first part of the trace. However, the model described above cannot be applied, as Eqn. 7 has no roots for the data from these points of inflection. This agrees with the observation above: which is that this model generates traces which resemble those from rapidly disintegrating tablets, but that it is not appropriate for the majority of dissolution profiles seen. Consequently we can conclude that an expression such as Eqn. 3 is not an adequate explanation for, or model of, the dissolution process for all types of tablet.

The initial processes of tablet dissolution

If the process of tablet dissolution is actually observed in a suitable apparatus, we can see that, for a short period, very little appears to happen to the tablet. After a while the tablet starts to disintegrate into granules, and this process can usually be seen to accelerate until a time is reached when the tablet has apparently lost its original form. Consequently, the first process of tablet dissolution must be represented by a reaction yielding a curve such as that in Fig. 3. Three schemes giving curves of the required shape are:

$$\frac{d[A]}{dt} = -k([A]_0 - [A]) \tag{8}$$

$$\frac{d[A]}{dt} = -\frac{k}{[A]} \tag{9}$$

$$\frac{d[A]}{dt} = -kt \tag{10}$$

Eqn. 8 relates the rate of disappearance of tablet to the amount of tablet which has dissolved. It is somewhat difficult to use; the reaction apparently never starts, as the initial rate of disappearance of [A] is zero. Eqn. 9 can be interpreted as the rate

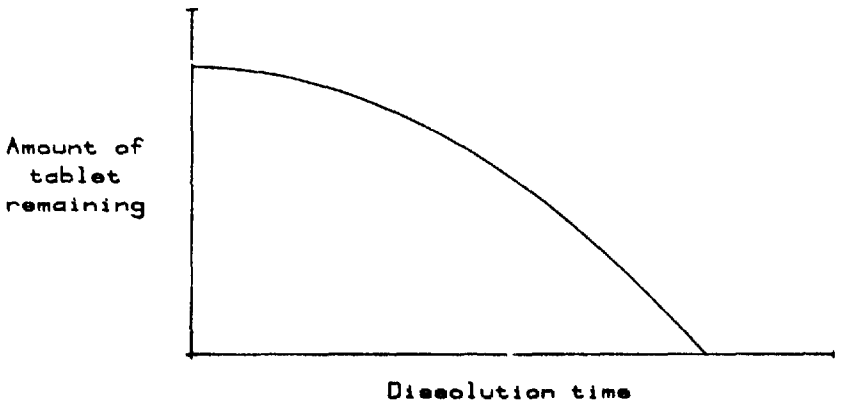

Fig. 3. A graphical representation of the physical process of a tablet dissolving.

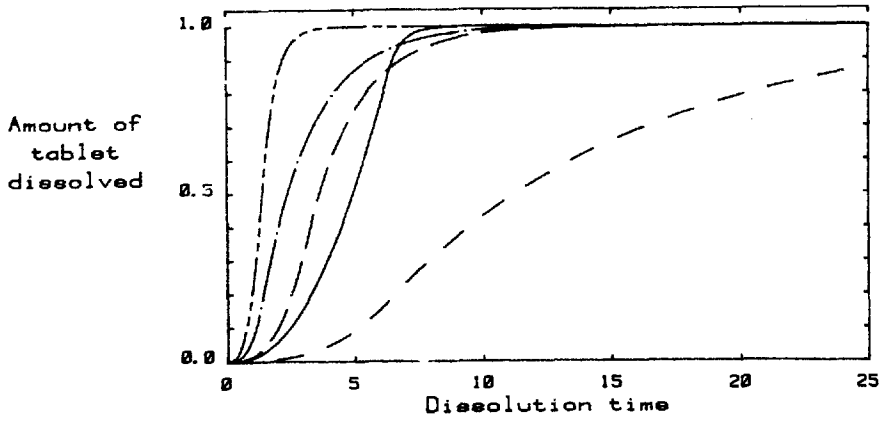

Fig. 4. Some examples of dissolution traces generated by the proposed equations.
———, $k = 0.05\ min^{-2}$, $k_1 = 2.00\ min^{-1}$;
— · — · —, $k = 1.00\ min^{-2}$, $k_1 = 0.50\ min^{-1}$;
- - - - - -, $k = 0.05\ min^{-2}$, $k_1 = 0.10\ min^{-1}$;
— - - — - -, $k = 1.00\ min^{-2}$, $k_1 = 2.00\ min^{-1}$;
— — —, $k = 0.20\ min^{-2}$, $k_1 = 0.50\ min^{-1}$.

of disappearance of the tablet being inversely proportional to the amount of tablet remaining. Using this mechanism leads to complex integrations if combined with other processes. Eqn. 10 shows that the rate of disappearance of tablet increases linearly with time; and combining this first stage with other processes yields relatively simple expressions for the amount of tablet in solution. As the purpose of this work is to provide a simple, yet adequate, model of the dissolution process, we shall now consider the application of Eqn. 10 to tablet dissolution. The use of this equation also permits the determination of rate constants from forward differences.

We may now represent the process of tablet dissolution by mechanism 2, with the first process being time dependent as in Eqn. 10, and the second process being first-order. Integration of these differential equations gives:

$$[P] = \frac{1}{2}kt^2 - \frac{k}{k_1^2}(k_1 t + e^{-k_1 t} - 1) \tag{11}$$

This equation holds until $t = t_L = (2/k)^{1/2}$, after which time [P] is given by:

$$[P] = 1 - B_L\, e^{-k_1 z} \tag{12}$$

where B_L is the concentration of B at t_L, and $z = t - t_L$.
The first and second differentials of these expressions can be used to find k and k_1 from experimental data. From Eqn. 11:

$$\frac{d[P]}{dt} = kt - \frac{k}{k_1}(1 - e^{-k_1 t}) \tag{13}$$

$$\frac{d^2[P]}{dt^2} = k(1 - e^{-k_1 t}) \tag{14}$$

and from Eqn. 12:

$$\frac{d[P]}{dt} = k_1 B_L e^{-k_1 t} \tag{15}$$

$$\frac{d^2[P]}{dt^2} = -k_1^2 B_L e^{-k_1 t} \tag{16}$$

By inspection of Eqns. 14 and 16, the second differential changes sign at time t_L, and hence k can be found as $k = 2/t_L^2$. At any time after t_L, using Eqns. 12 and 15:

$$k_1 = \left(\frac{d[P]}{dt}\right) / (1 - [P]) \tag{17}$$

Table 2 shows the treatment of simulated data for this reaction scheme. The first and second forward differences have been used to regenerate the rate constants, k and

TABLE 2

THE METHOD OF FORWARD DIFFERENCES APPLIED TO A 2-STAGE PROCESS WHERE THE FIRST STAGE HAS A TIME-DEPENDENT RATE

t (min)	[P]	First diff.	Second diff.	$[P]_{calc}$	Percent error
0	0				
		0.002			
1	0.002		0.008	0.002	0.0
		0.010			
2	0.012		0.017	0.012	0.0
		0.027			
3	0.039		0.022	0.038	0.1
		0.049			
4	0.088		0.028	0.085	0.3
		0.077			
5	0.165		0.032	0.159	0.6
		0.109			
6	0.274		0.019	0.264	1.0
		0.128			
7	0.402		−0.021	0.393	0.9
		0.109			
8	0.511		−0.019	0.505	0.6
		0.088			
9	0.599		−0.015	0.596	0.3
		0.073			
10	0.672		−0.013	0.670	0.2
		0.060			
11	0.732		−0.012	0.731	0.1
		0.048			
12	0.780		−0.008	0.780	0.0
		0.040			
13	0.820		−0.007	0.821	0.1
		0.033			
14	0.853		−0.007	0.853	0.0
		0.026			
15	0.879		−0.004	0.880	0.1
		0.022			
16	0.901		−0.004	0.902	0.1
		0.018			
17	0.919		−0.003	0.920	0.1
		0.015			
18	0.934		−0.003	0.935	0.1
		0.012			
19	0.946		−0.002	0.947	0.1
		0.010			
20	0.956		−0.002	0.957	0.1
		0.008			
21	0.964		−0.002	0.965	0.1
		0.006			
22	0.970			0.971	0.1

The column [P] has been calculated using $k = 0.05\ min^{-2}$, $k_1 = 0.2\ min^{-1}$. From the change in sign of the second forward difference, $t_L = 6.475$ min, hence $k = 2/6.475^2 = 0.0477\ min^{-2}$. At 13 min, which is twice the time at the point of inflection, the first forward difference (by interpolation) is $0.0365\ min^{-1}$, and (1 − [P]) is 0.180. From these, $k_1 = 0.0365/0.180 = 0.203\ min^{-1}$. The column $[P]_{calc}$ gives the values which result when these values of k_1 and k_1' are substituted into the original equation.

k_1, in the manner indicated in the preceding paragraph; and recalculated values for the amount of tablet dissolved are compared with the original values.

It is worth considering the usefulness of a 3-stage reaction scheme incorporating a time-dependent rate for the first stage. The rate constants for the 3 stages can be denoted by k, k_1, k_1'. It is only possible to regenerate these rate constants from experimental data if the assumption is made that $k_1' \gg k_1$. If this is so, then the addition of the third stage has very little effect on the final trace. However, if the assumption is not valid, the rate constants cannot be regenerated in this manner from the experimental data. Hence in either case, inclusion of a third stage in the reaction mechanism is not of value in finding a simple, yet adequate, model of the dissolution process.

Table 3 shows this treatment applied to the dissolution traces given in Fig. 2. For each trace, the recalculated values for the fractions of tablet dissolved agree well with the observed values; the difference between them is never greater than 3% of

TABLE 3

DISSOLUTION DATA TAKEN FROM THE TRACES IN FIG. 2

t (min)	First trace					Second trace		
	[P]	First diff.	Second diff.	$[P]_{calc}$	% error	[P]	$[P]_{calc}$	% error
0	0.000					0.000	0.000	0.0
		0.008						
1	0.008		0.058	0.009	0.1	0.007	0.008	0.1
		0.066						
2	0.074		0.092	0.067	0.7	0.047	0.062	1.5
		0.158						
3	0.232		0.001	0.214	1.8	0.203	0.197	0.6
		0.159						
4	0.391		−0.014	0.400	0.9	0.363	0.381	1.8
		0.145						
5	0.536		−0.036	0.542	0.6	0.507	0.524	1.7
		0.109						
6	0.645		−0.026	0.650	0.5	0.624	0.634	1.0
		0.083						
7	0.728		−0.018	0.733	0.5	0.705	0.719	1.4
		0.065						
8	0.793		−0.022	0.796	0.3	0.766	0.784	1.8
		0.043						
9	0.836		−0.008	0.844	0.8	0.810	0.834	2.4
		0.035						
10	0.871		−0.011	0.881	1.0	0.849	0.872	2.3
		0.024						
11	0.895		−0.003	0.909	1.4	0.878	0.902	2.4
		0.021						
12	0.916		−0.002	0.931	1.5	0.899	0.924	2.5
		0.019						
13	0.935		−0.001	0.947	1.2	0.916	0.942	2.6
		0.018						
14	0.953		−0.000	0.960	0.7	0.929	0.955	2.6
		0.018						
15	0.971		−0.005	0.969	0.2	0.946	0.966	2.0
		0.013						
16	0.984		−0.005	0.976	0.8	0.962	0.974	1.2
		0.008						
17	0.992		−0.008	0.982	1.0	0.972	0.980	0.8
		0.000						
18	0.992		0.006	0.986	0.6	0.983	0.984	0.1
		0.006						
19	0.998		−0.004	0.990	0.8	0.992	0.988	0.4
		0.002						
20	1.000			0.992	0.8	1.000	0.991	0.9

The values [P] are absorbance values from the traces presented in Fig. 1, which have been scaled to the value for the absorbance at t = 20 min. For the first trace, the second forward difference changes sign at t = 3.067 min (by interpolation), from which $k = 2/3.067^2 = 0.213$ min^{-2}. At 6 min, which is twice the time at the point of inflection, the first forward difference is 0.096 min^{-1}, hence $k_1 = 0.096/(1-0.645) = 0.270$ min^{-1}. In a similar manner, for the second trace, $k = 0.200$ min^{-2}, and $k_1 = 0.263$ min^{-1}. The values $[P]_{calc}$ have been generated from Eqns. 11 and 12 using these values for k and k_1, and the percentage error is the difference between [P] and $[P]_{calc}$, expressed as a percentage of the complete tablet.

the whole tablet. This difference can be caused in two ways, which are as follows.

The first possibility is that the applied equations are not an adequate model of the process. Randall and Goldsmith (1975) noted a type of trace shown by phenylbutazone tablets, where the tablet granules, after being released from the tablet matrix, remained as whole granules for a further induction period before disintegrating into fines and dissolving into solution. The trace thus generated shows 3 points of inflection. In general, if the model is not adequate, the differences between the observed and calculated values become large and also systematic.

The second possibility is that although the model is adequate, the rate constants have not been extracted accurately from the data. As k is determined only by the position along the time axis of the point of inflection, any error in noting this position will alter k, and hence the first part of the regenerated curve. This error may be minimized by careful selection of the time interval between the data points: if the interval is too great, there is only a small number of widely differing values for the second forward difference; but if the interval is too small, the second differences approach zero, and may fluctuate about zero because of the measurement errors in the ordinate. We have found that selecting the time interval in such a way that there are 4 or 5 ordinate values before the point of inflection usually gives a satisfactory value for k.

The rate constant k_1 may be determined at any time after the point of inflection, and the values determined at different times will normally vary. Several values should be determined, and their mean used in the regeneration of the curve; or, alternatively, a rule of thumb can be applied—such as determining k_1 when the time is twice that at the point of inflection.

Conclusion

A new mathematical model for dissolution traces has been proposed. This model is simple to apply, as the two parameters of the model may easily be determined directly from the experimental data. The regenerated traces have been shown to agree closely with the originals.

Although the parameters of the model are cast in the form of rate constants, there is no necessary implication that the process, in truth, takes place according to the mechanism proposed: the validity of the parameters as a means toward reproducing a dissolution trace is independent of any such assumption.

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