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A MATHEMATICAL MODEL FOR DISINTEGRATION OF SOLID DOSAGE FORMS USING A CASCADING DISINTEGRATION APPARATUS

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ABSTRACT

A modification in basket-rack assembly is proposed that enables one to develop the mathematical model for disintegration of solid dosage form. Once the parameters of the model is known, the true disintegration rate constant can be determined. The method is based on the assumption of deaggregation of solid dosage forms in a cascading system.

INTRODUCTION

Although disintegration is considered to be important in the absorption of orally administered solid dosage forms, few studies can be found in the literature regarding the mathematical expression of disintegration profiles. One of the difficulties

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in developing such an expression and calculating the true disintegration rate constant is the abstraction of the basket-rack apparatus. In 1970, Sandell (1) proposed that a disintegration test should be: "....developed and improved so that it will express the ability of tablets and capsules to disintegrate and deaggregate in such a way that the original drug particles are formed." He performed some preliminary studies using 30mm diameter Plexiglass tube containing three sieves. The sieve openings were 2mm, 0.5mm and 0.1mm, respectively. The tube was raised and lowered 1cm every 10 seconds in water at 37°C. After a period of time, the granules on the sieves were dried and the amount on each sieve was determined. This approach, with some modifications, combined with the basket-rack apparatus can be used to characterize the dynamic process of disintegration. It is also worth noting that his definition of disintegration test is very much in accord with the one in USP XXI (2).

In this article the basket-rack assembly has been modified to include the superimposed sieves. The modified apparatus has been used to develop a mathematical model based on the assumption of deaggregation of solid dosage forms. It has been suggested that the apparatus and the model can be used to observe the disintegration profile of a given solid dosage form and to define the true disintegration rate constant.

EXPERIMENTAL

The basket-rack assembly of USP disintegration apparatus (Van-Kel Industries, Inc.) was modified to include the following details. Each tube was divided into 3-5 compartments by miniature sieves arranged in tier of equal distance. The tubes can actually be cut to form the miniature sieves. The sieves were equipped with meshes of 5,7,10,20, with arithmetic mean of opening of 3.4mm, 2.4mm, and 1.4mm, thus giving four grade sizes of aggregates. The rest of the equipment was assembled as described in USP. The speed of the motor and the length of the stroke to move the basket containing the six compartmentalized tubes, up and down, was at the rate of not less than 28 and not more than 32 complete cycles per minute. However, the distance of the stroke did not exceed the height of the first compartment. To operate the apparatus coated placebo tablets were placed in the apparatus (one per tube in the first compartment with the sieve opening of 4mm). The basket was then set in motion under the same conditions described in USP XXI (2). The weight size distribution as function of time was determined by removing the tubes at different time intervals and drying and weighing the aggregates. A frequency distribution can then be imposed on the various states, in effect, a percentage of the total disintegration capability was assigned to each state.

THEORY

If we assume that these fractionated aggregates characterize the state of the solid dosage form during the disintegration, then state 1, retained in all compartments of # 1, is the percentage of aggregates of size N (i.e., 3.4); state 2, retained in all compartments of # 2, is the percentage of aggregates of size N-1 (i.e., 2.4), and so on. The last state is assumed to be the totally disintegrated state. Associated with each state is a decay rate constant, Ki, that represents the probability of the aggregates to be sieved through a particular compartment. The process of disintegration is assumed to take place in the following manner: the aggregates of size 3.4mm are reduced to 2.4mm and the aggregates of 2.4mm are reduced to 1.4mm all along the chain of states until the aggregates are no longer larger than the sieve opening of the last compartment. We have in essence a cascading effect of larger particle size to smaller particle size.

The set of differential equations that describe the disintegration process in the cascading apparatus where Pi (i = 1,..,4) is the percent of aggregates at each state is

$$\frac{dP_1}{dt} = -K_1P_1, \qquad (1)$$

$$\frac{dP_2}{dt} = K_1P_1-K_2P_2, \qquad (2)$$

$$\frac{dP_3}{dt} = K_2P_2 - K_3P_3, \tag{3}$$

$$\frac{dP_4}{dt} = K_3P_3, \tag{4}$$

These are a set of linear first-order differential equations. We can consider two ways of developing the solution of Eq 1-4. The first one is when we consider one tube and one tablet. The solution would then be the classical mono- and bi-exponential decays as follows

$$P_1 = P_0e^{-K_1t} \tag{5}$$

$$P_2 = \frac{P_0K_1}{K_1-K_2}(e^{-K_2t} - e^{-K_1t}) \tag{6}$$

$$P_3 = \frac{P_0K_2}{K_2-K_3}(e^{-K_3t} - e^{-K_2t}) \tag{7}$$

with the initial conditions of $P_1 = P_0$, $P_2 = 0$ and $P_3 = 0$ at $t = 0$.

The second approach, that is more realistic and proposed in this article, is when we consider the whole apparatus or series of the apparatus. In this case, one places tablets in the apparatus, one at a time, and sets the apparatus in motion, one at a time. Therefore, P_i^0 is the initial condition of state i and $P_4^0 = 0$ at time equal to zero. Ki (i = 1,...,4) represents the disintegration rate constants with K_4 equal to zero. The

solution to Eq 1-4, for the totally disintegrated solid dosage form is

$$P_4 = K_1K_2K_3P_1^0\left[\frac{e^{-K_1t}}{(-K_1)(K_3-K_1)(K_2-K_1)} + \frac{e^{-K_2t}}{(-K_2)(K_3-K_2)(K_1-K_2)}\right.$$

$$\left. + \frac{e^{-K_3t}}{(-K_3)(K_2-K_3)(K_1-K_3)} + \frac{1}{(K_3)(K_2)(K_1)}\right] + K_2K_3P_2^0\left[\frac{e^{-K_2t}}{(-K_2)(K_3-K_2)}\right.$$

$$\left. + \frac{e^{-K_3t}}{(-K_3)(K_2-K_3)} + \frac{1}{(K_3)(K_2)}\right] - P_3^0[e^{-K_3t}-1]. \qquad (8)$$

The general solution to a set of differential equations as shown by Eq 1-4 in closed form is

$$Pi = \sum_{J=1}^{i} \sum_{m=1}^{i} \frac{(K_J^{\cdot}-K_{i+1}\cdots K_{i-1})(e^{-K_mt})(P_J^0)}{(K_i-K_m)(K_{i-1}-K_m)\cdots(K_J^{\cdot}-K_m)} \qquad (9)$$

where $m \geq J^{\cdot}$. When $J^{\cdot} = m$, $(K_J^{\cdot}-K_m) = 1$ (3).

When presented as percent remaining to disintegrate, the equation should be written as % remaining to disintegrate = 100 - Pi, where Pi is the last state to be considered. The fraction dissolved during disintegration can be considered negligible or can be subtracted from 100, that is, % remaining to disintegrate = (100 - % dissolved during disintegration) - Pi. In a cascading process, the value for K which indicate the rate of transition from one state into the next, differs for each state. There are also differences between tubes in the basket-rack assembly. For example, K_3 in the first tube

may be smaller than K_3 in the second tube. We assume, however, that overall K_3 is an average rate constant for state 3 in all of the tubes.

For practical purposes Eq 8 can be reformulated so that we can form the series

$$Y(t) = X_1 + X_2e^{-K_1t} + X_3e^{-K_2t} + K_4e^{-K_3t} \quad (10)$$

$$\text{where } X_2 = \frac{-K_2K_3P_1^0}{(K_3-K_1)(K_2-K_1)} \quad (11)$$

$$X_3 = \frac{-K_1K_3P_1^0}{(K_3-K_2)(K_1-K_2)} - \frac{K_3P_2^0}{(K_3-K_2)} \quad (12)$$

$$X_4 = \frac{-K_1K_2P_1^0}{(K_2-K_3)(K_1-K_3)} - \frac{K_2P_2^0}{(K_2-K_3)} - \frac{K_2P_2^0}{(K_2-K_3)} - P_3^0 \quad (13)$$

$$X_1 = P_1^0 + P_2^0 + P_3^0 \quad (14)$$

From previous discussion, it is known that the sum of P_i^0 must be equal to 100%. Therefore, we may set $X_1 = 100$ and estimate the coefficients in Eq 10 by equating it to be the % remaining to disintegrate. Thus,

$$100\% - \%\ \text{remaining to disintegrate} = X_1 + X_2e^{-K_1t} + X_3e^{-K_2t} + X_4e^{-K_3t} \quad (15)$$

Since $X_1 = 100\%$ at $t = 0$, Eq 15 can be rewritten as

$$-\%\ \text{remaining to disintegrate} = X_2e^{-K_1t} + X_3e^{-K_2t} + X_4e^{-K_3t} \quad (16)$$

RESULTS AND DISCUSSIONS

To illustrate the use of previously discussed technique, we shall assume the system of placebo tablets with the following characteristics and parameters.

The true disintegration rate constant can then be calculated as

$$K_d = (0.7)(0.05) + (0.2)(0.35) + (0.1)(0.5)$$

$$K_d = 0.155 min^{-1}$$

Experimentally this would be the result. Obviously, given the output from an experiment, we must first estimate the proper number of terms to use. This may be done by trying a number of schemes and evaluating the error functions. All estimates of the parameters can be improved by using iterative techniques. The computer fitting of the data provides a satisfactory way of estimating disintegration rate constant and percent of aggregates in a given compartment.

The applicability of this technique as a formulation tool should be investigated. The attention must be given to the pattern of disintegration profile, and how the pattern is influenced by the formulation and the manufacturing factors. The disintegration rate constant, calculated by this method, reflects the disintegration profile and the particle size distribution. Theoretically, the dissolution rate constant

TABLE 1

Size Weight Distribution and Rate Constants of the Placebo Tablets

Arithemtic Mean of Opening	Sieved Number (Passed/Retained)	Pi %	Ki (Min^{-1})
3.4	5/7	70	0.05
2.4	7/10	20	0.35
1.4	10/20	10	0.5

is a function of surface area. Therefore, the correlation between the dissolution rate constant and the rate constant for disintegration, calculated by the cascading system, can be more meaningful. Further works are in progress to determine the applicability of the method.

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