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THE RELATIONSHIP OF THEOPHYLLINE RELEASE WITH TABLET SURFACE AREA AND ASPECT RATIO FROM A NEW MATRIX TABLET FORMULATION

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INTRODUCTION

We have recently described a method for making wax-matrix based controlled-release (C/R) tablets containing theophylline[1,2] as an extension of the use of a process described some while ago[3]. The process itself is readily conducted on manufacturing batch sizes of up to 300kg and is capable of producing tablets having reproducible performance on both an intra- and inter-batch basis[4].

Many mathematical approaches have been made in an attempt to describe the release characteristics of matrix C/R formulations,

most notably the model for a diffusion controlled process, first described by Higuchi[5] and subsequently used to describe release characteristics of many types of products[6,7].

$$Q=\left[\frac{D\varepsilon}{\gamma}(2A-Cs)-Cs.t\right]^{\frac{1}{2}} \qquad \text{.....Eqn 1}$$

where Q is the amount of drug released per unit area of tablet exposed to drug solvent

D is the dissolution coefficient of the drug in the permeating fluid,

ε is the porosity of the matrix

γ is the tortuosity of the matrix

A is the concentration of drug in the matrix

Cs the solubility of drug in the dissolution medium

t is time.

A simple equation of the type: $M_t/M_f = Kt^n$ ..... Eqn 2

where M_t mass of drug released at time, t

M_f = final mass of drug released from dosage form

K = a nonlinear dissolution coefficient

n = an exponent term, descriptive of the net release mechanism operative with the dosage form

has recently been described[8] and appears to have wide applicability to describe drug release data from monolithic matrix products.

OBJECTIVE

This presentation shows the usefulness of the equation to assess comparative release characteristics of a series of tablets compressed at different sizes in relation to their surface area and aspect ratio.

METHODS:

(1): TABLET FORMULATION

The formulation contains 90.6% of Theophylline (anhydrous) B.P. in a glyceryl stearate matrix: 0.8% of Magnesium Stearate B.P. has been used as a lubricant. Granulation was carried out by a patented process (3) described previously. Tablets were compressed on a single punch Manesty F3 machine, using circular, normal concave punches of appropriate diameter, without surface markings.

(2): SOLUTION RATE TESTS

Solution rate studies on individual C/R theophylline tablets have been conducted using Apparatus 2 of the USP XXI[9] at a paddle rotation speed of 80 rpm, using 500ml volumes of dissolution medium, pH 1.2 (2h), followed by phosphate buffered medium (pH 7) to the completion of the test.

(3): THE CALCULATION OF BICONVEX TABLET SURFACE AREA

A biconvex tablet can be considered as a right circular cylinder with a segment of a sphere, cut by a single plane, attached at each end. The surface area, A_1, of the curved surface of a cylinder is given by

$$A_1 = D\,h \qquad \text{.....(Eqn 3)}$$

where D = diameter

h = height of the cylinder.

The surface area, A_2, of the convex surface of a segment of a sphere is given by

$$A_2 = (r^2 + h^2) \quad \text{.....(Eqn 4)}$$

where r is the radius of the plane surface of the segment

h is the maximum height of the segment from the plane surface.

A simple means of calculating the surface area of a biconvex circular tablet, A_T, is therefore to combine equations 3 and 4 and simplifying to give the expression

$$A_T = 2\pi\left[(0.5D)^2 + (0.5\ (T-E))^2\right] + DE \quad \text{.....(Eqn. 5)}$$

Tablet surface areas have been calculated from eqn. 5. This method of calculation has the virtue of simplicity in that tablet diameter (D) and total thickness (T), as indicated in Figure 1, are easily measured using a micrometer, and the depth of the tablet edge (E) can be readily measured using a travelling microscope.

RESULTS

(1): THE RELATIONSHIP OF THE NONLINEAR DISSOLUTION COEFFICIENT, K, WITH TABLET SURFACE AREA

The relationship of the nonlinear dissolution coefficient, K, which is the fraction released at unit time (1) and is, in this

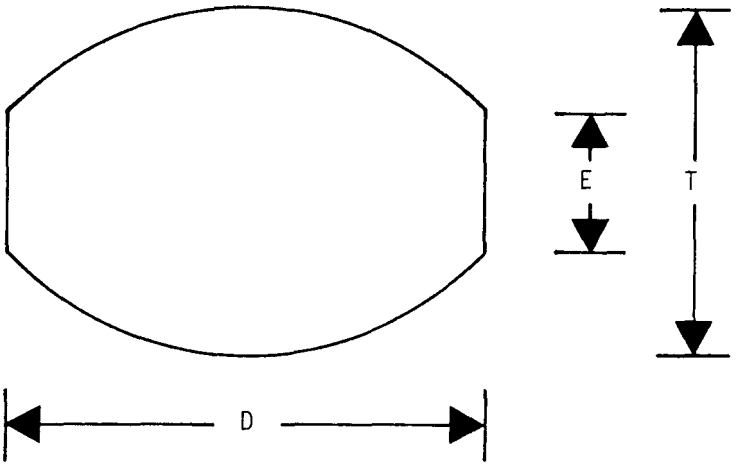

FIGURE 1

Dimensions for Simple Calculation of Tablet Surface Area

TABLE 1

The Relationship of Nonlinear Dissolution Coefficient, K, with Tablet Surface Area

Tablet dimensions		Nonlinear dissolution coefficient K (fraction released)		
diameter mm	surface area mm^2	mean	upper 95% confidence limit	lower 95% confidence limit
4.78	62.06	0.2887	0.2667	0.3097
6.96	116.87	0.2018	0.1995	0.2081
7.93	150.15	0.1737	0.1565	0.1910
9.51	209.33	0.1858	0.1585	0.2131
10.28	231.89	0.1652	0.1469	0.1835
11.90	292.20	0.1679	0.1604	0.1754
18.97	733.35	0.1043	0.0862	0.1224

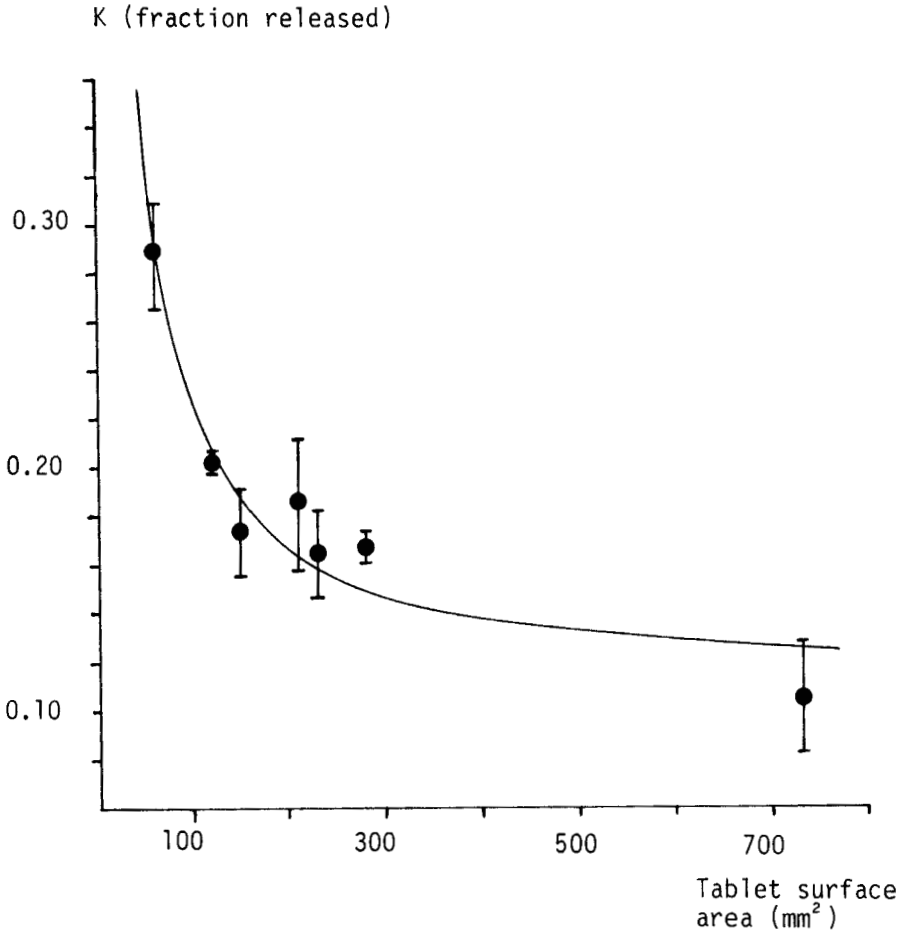

FIGURE 2

The Relationship of Nonlinear Dissolution Coefficient, K (mean ± 95% confidence limits) with Tablet Surface Area

circumstance, independent of the units of the exponent term, n, with tablet surface is shown in Table 1 and Figure 2. The relationship exhibiting the best correlation, indicates that K is inversely proportional to the surface area of the tablets ($r=0.938$; $p<0.001$).

TABLE 2

The Relationship of Nonlinear Dissolution Coefficient, K, with Tablet Aspect Ratio

Tablet dimensions		Nonlinear dissolution coefficient K (fraction released)		
diameter mm	aspect ratio	mean	upper 95% confidence limit	lower 95% confidence limit
4.78	2.30	0.2887	0.2667	0.3097
6.96	2.96	0.2018	0.1995	0.2081
7.93	3.01	0.1737	0.1565	0.1910
9.51	3.29	0.1858	0.1585	0.2131
10.28	3.81	0.1652	0.1469	0.1835
11.90	4.65	0.1679	0.1604	0.1754
18.97	4.85	0.1043	0.0862	0.1224

(2): RELATIONSHIP OF NONLINEAR DISSOLUTION COEFFICIENT, K, WITH ASPECT RATIO

The tablet aspect ratio is the ratio of diameter to thickness. For the normal convex-faced tablets used in this study, the aspect ratio has been calculated as:

$$\text{Aspect ratio} = \frac{D}{(T.E)^{0.5}}$$

(D, T, E are as defined above).

The relationship of the nonlinear dissolution coefficient, K, exhibiting the best correlation with tablet aspect ratio is shown

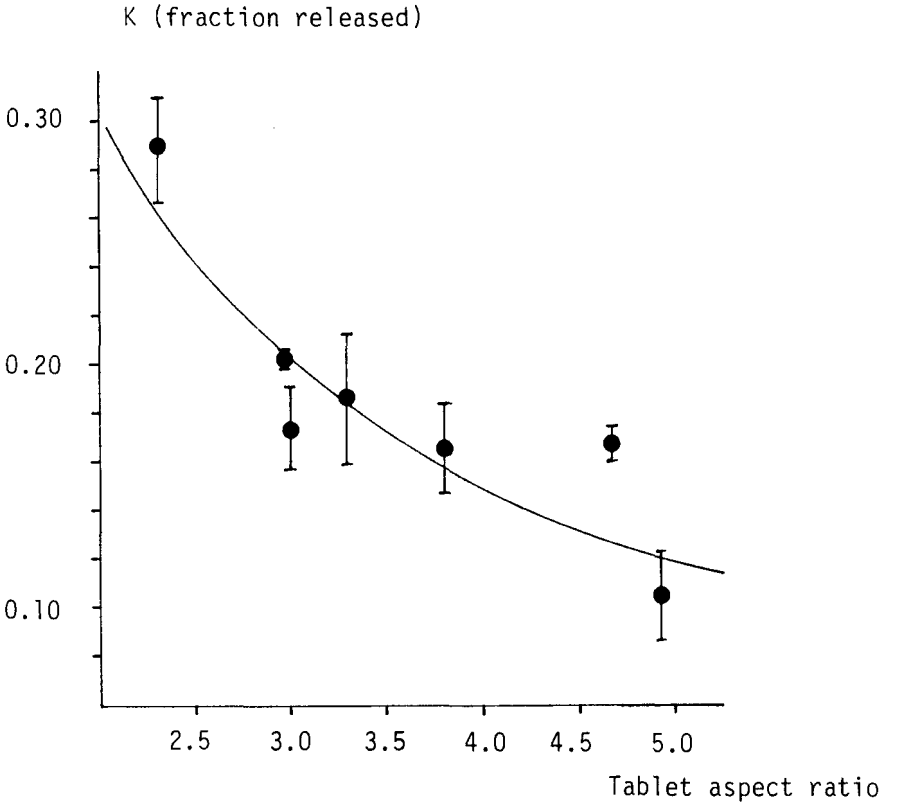

FIGURE 3

The Relationship of Nonlinear Dissolution Coefficient, K (mean ± 95% confidence limits), with Tablet Aspect Ratio

in Table 2 and Figure 3 and again indicates that K is inversely proportional to the aspect ratio ($r=0.869$; $p<0.001$).

Values of the nonlinear exponent term, n, for the tablets were 0.4923±0.0061 (mean±SEM) indicating that release was largely diffusion controlled[10] and no change in values in a manner related to tablet surface area or aspect ratio was evident over the relatively small range of aspect ratio values examined.

CONCLUSION

It is apparent that surface area exerts a high degree of influence on the solution rate characteristics of the tablets. The release occurs largely by a diffusion controlled process. Hence, the surface appears to act as a rate limiting parameter in relation to its effect on the uptake of the surrounding fluid medium and in terms of the relative volume of the tablets.

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