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THEO-DUR® AND THEO-DUR SPRINKLE™: CONTROLLED-RELEASE DELIVERY SYSTEMS FOR THEOPHYLLINE

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Therapy with theophylline has been optimized through the use of controlled-release formulations. Previous to the introduction of sustained-release theophylline products, frequent dosing of the drug was mandatory in most patients. This was as a result of the short elimination half life for this drug in a large segment of the population and a relatively narrow therapeutic range for optimal pharmacological response.

As recently as the early 70's analytical work with this drug was rather limited and its pharmacokinetics poorly understood. Work by Dr. Richard Ogilvie, however, established a linear correlation between the logarithm of the serum concentration and pulmonary function [1]. The design of dosage regimens based on the total body clearance of theophylline was also suggested by studies performed by

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Ogilvie and by Jenne and his coworkers [2,3]. The variability in the clearance of this drug was not fully appreciated until Ellis, Koysooko, and Levy reported their results of a study in 30 pediatric patients [4]. They found a mean elimination half life of only 3.7 hr, but the individual values ranged from 1.4 to 7.8 hr. Similar studies with adult asthmatics resulted in a mean half life of 8.2 hr with a range of 6.1 to 12.8 hr [5]. It is quite obvious that theophylline violates the rules which are frequently quoted to exclude drugs from sustained release formulations; that is, you do not incorporate into a sustained release product a drug with a short or a long half life. Given the large doses required for theophylline therapy and the narrow therapeutic index, it would seem that theophylline is indeed a poor candidate for controlled-release. The wide patient acceptance of controlled-release theophylline testifies to the contrary. Thus, some of the historical rules or guidelines must be reevaluated in light of our current formulation technology.

Key Pharmaceuticals' first contribution in the sustained-release theophylline market was Theo-Dur®. Figure 1 is a diagram of a Theo-Dur tablet which illustrates the composition of the tablet. The tablet consists of pellets embedded in a base which contains a fraction of the dose as well as excipients to control the release of theophylline.

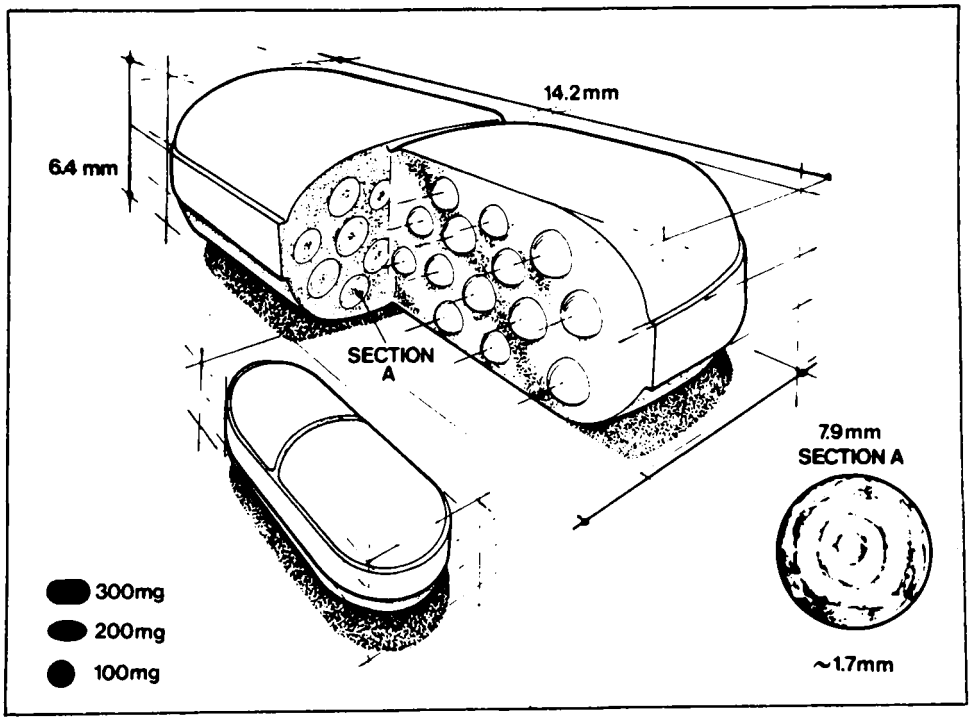

FIGURE 1

Schematic diagram of a 300 mg Theo-Dur Tablet.

The majority of the active drug, however, is found in the pellets which are coated before being blended with the base and compressed into tablets. Theo-Dur is available as scored tablets in 100, 200, and 300 mg strengths.

Dr. Welling has already discussed in his paper in this publication data illustrating the zero-order release kinetics of Theo-Dur after a single dose. Figure 2 summarizes the results of a multiple-dose study with Theo-Dur in six healthy subjects [6]. The study was a 3-way crossover comparing Theo-Dur to an elixir reference product and a sustained-release capsule. All medications were dosed

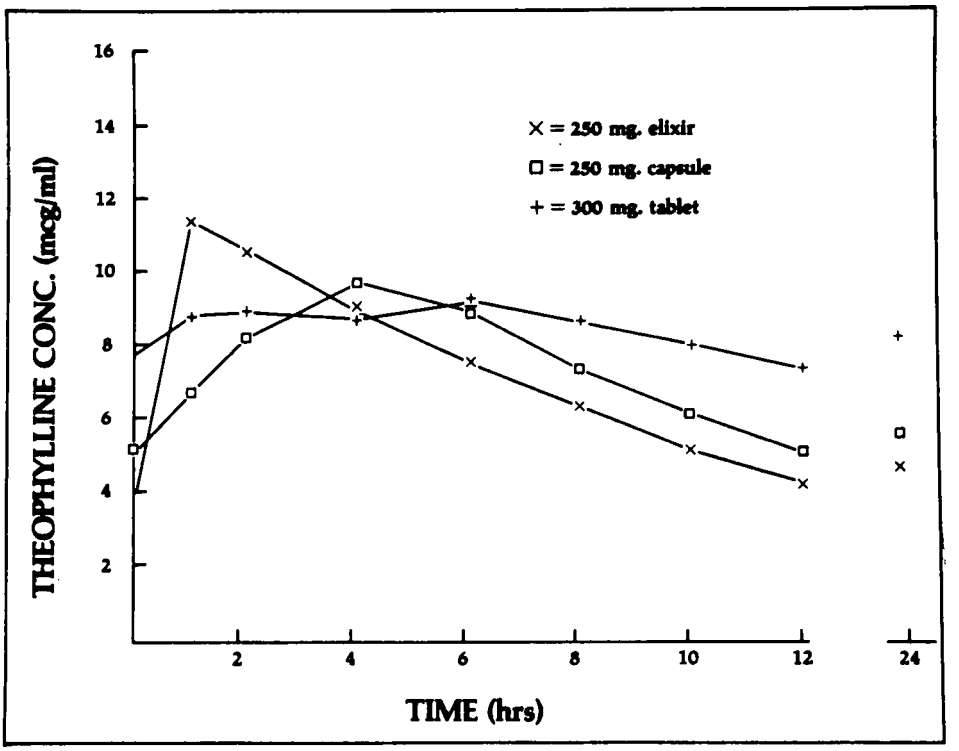

FIGURE 2

Theophylline serum concentrations obtained after dosing every 12 hours for 4 days. The 24 hr sample was collected 12 hours after the evening dose on the morning of Day 5. Each serum concentration represents the mean of six subjects. The tablet used was Theo-Dur 300 mg; the capsule was Slo-Phyllin Gyrocaps 250 mg.

every 12 hours for 4 days before characterization of the plasma concentration-time profile. The degree of fluctuation of the plasma levels at steady state was significantly greater for the immediate release product and the capsule. The difference between the maximum and minimum serum concentrations for the reference, capsule and Theo-Dur were 7.6, 4.7, and 1.4 μg/ml respectively. The doses used

in this study were conservative; 250 mg for the elixir and capsule and 300 mg for the tablet. If larger doses had been used, the differences between the maximum and minimum serum levels would be even greater.

A comparison of the areas under the serum concentration-time curves (AUC) at steady state after dose normalization revealed no statistical differences; thus, both the capsule and tablet were completely absorbed. As has been emphasized by both Dr. Robinson and Dr. Welling there is a potential source of error in trying to estimate elimination rate constants from single doses of medication with prolonged duration of absorption. A single-dose bioavailability study may thus provide misleading information if the AUC to infinity is extrapolated with a rate constant calculated from the sustained-release dose, since absorption may be continuing. Ideally, drug level monitoring in such cases should be carried out well beyond the product's absorption phase. Since theophylline has a substantial intra-subject variation in elimination, there is a risk also in using the elimination rate constant from the immediate release reference product. A multiple dose design avoids these complications and offers the most convenient and best assessment of bioavailability for a sustained-release product.

Figure 3 shows the mean serum concentration-time profile for theophylline in 20 pediatric patients, after

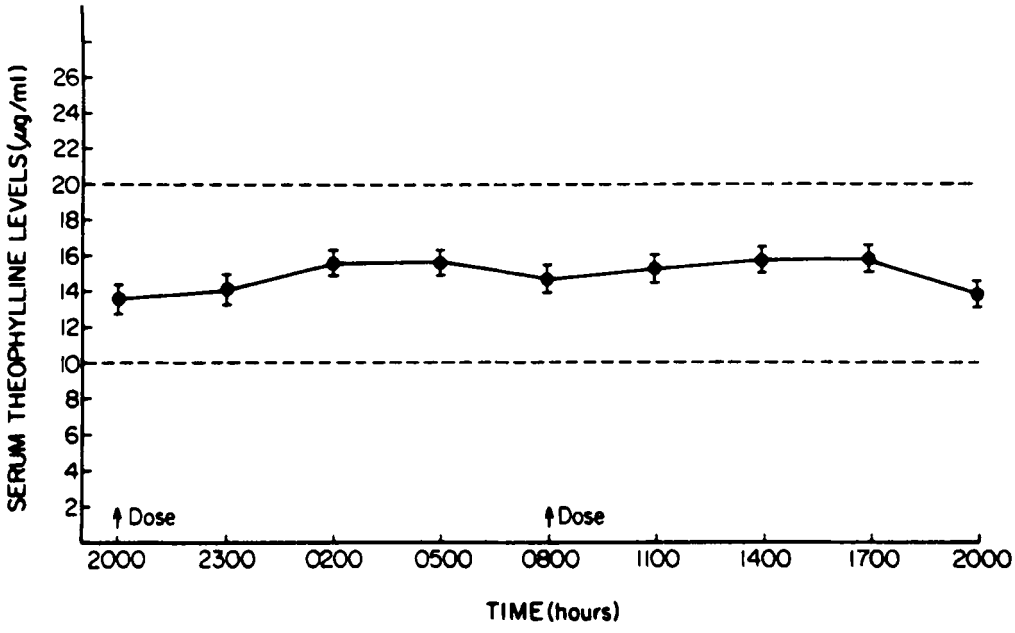

FIGURE 3

Mean serum theophylline concentrations for 20 pediatric asthmatic patients (± S.E.M.) dosed every 12 hours with Theo-Dur tablets. (Reprinted with permission from Reference 7).

dosing every 12 hr with Theo-Dur [7]. In this study, blood samples were drawn over 24 hours thus characterizing two doses at steady state. The stability of the serum concentrations with twice-a-day dosing suggested the usefulness of this product in pediatric therapy. These patients, however, were old enough to be able to swallow tablets. For those pediatric or geriatric patients who have difficulty in swallowing intact tablets or capsules, such controlled-release preparations offer no advantages.

Theo-Dur Sprinkle™ was designed for those patients who experience difficulty in swallowing tablets or capsules.

It is intended to be used sprinkled on soft food which can then be easily swallowed by a patient. To facilitate dose titration,the product is available in 50,75,125, and 200 mg strengths. It is packaged in oversized capsules to enable patients to open the capsules without spilling of the contents. Figure 4 is a photomicrograph of Theo-Dur Sprinkle pellets taken shortly after dispersal in water. The pellets range in size from 600 to 800 microns and as seen in Figure 4 are quite spherical in shape. They are

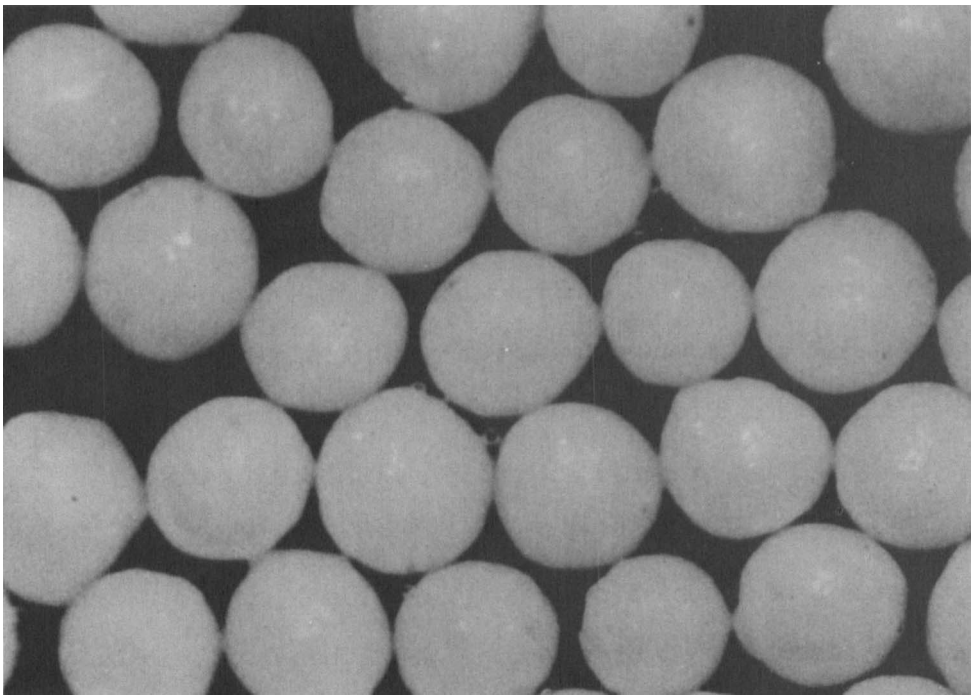

FIGURE 4

Photomicrograph of Theo-Dur Sprinkle Pellets taken immediately after dispersal in water. The size of the pellets range from 600-800 microns.

prepared using a fluidized bed coating technique which allows the active drug to be coated onto sucrose crystals. The polymer coating which controls the release of theophylline is sprayed on after the active drug layer has been applied.

The theophylline release characteristics of this product were determined by dissolution testing through an apparatus designed by Key's Methods Development Laboratory and is based on a previously reported method [8]. The method utilizes the rotating paddle dissolution apparatus as described in the U.S.P. XX. The USP Method, however, was modified to avoid problems normally encountered with pelletized or microencapsulated formulations, such as floating of the pellets on the surface of the dissolution media and adhesion of the pellets to the walls of the flask or shaft of the paddle. A stationary stainless steel, 40 mesh basket is suspended in simulated intestinal fluid, and the pellets are placed inside the basket. Serial sampling of the fluid is performed to obtain a cumulative percent dissolved-time profile. Figure 5 is a diagram of the apparatus used in these studies while Table 1 lists a typical dissolution profile for a lot of Theo-Dur Sprinkle.

Linear regression of the data gave a correlation coefficient of 0.994 indicating that the product released theophylline with apparent zero order kinetics. The slope

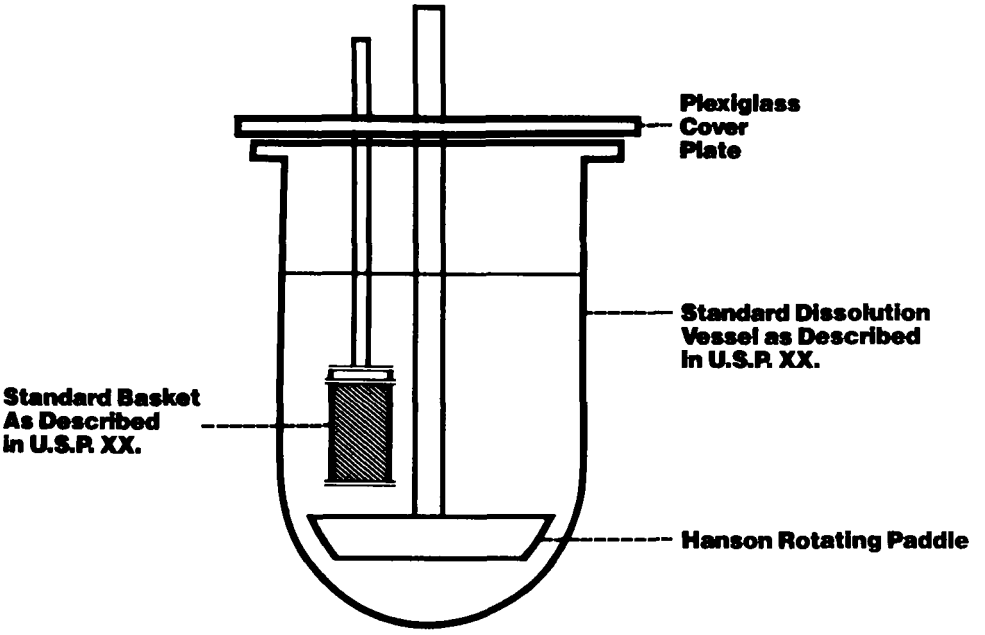

Diagram of the Fixed Basket Dissolution Apparatus

FIGURE 5

Dissolution apparatus used for testing the release rate of theophylline from Theo-Dur Sprinkle.

Table 1

Dissolution Profile for Lot F

time	Mean Cumulative Fraction Dissolved (n=6)
0	0.0
1	0.122
2	0.273
4	0.589
6	0.841
8	0.990

$r^2 = 0.988$
$m = 0.129$
$b = 0.017$

of the dissolution profile served as a quantitative measure of the dissolution rates. The validity of the method was established by testing products with different levels of coating and demonstrating that dissolution was faster with less coating.

Studies to evaluate the bioavailability of different formulations were conducted at the University of Tennessee in collaboration with Arthur Straughn, Pharm.D. A typical pilot study consisted of a two way crossover comparing 500 mg of an immediate release standard to 500 or 600 mg of Theo-Dur Sprinkle. The dose of the controlled-release product was sprinkled onto a tablespoonful of applesauce which fasting subjects swallowed with water. Serial blood sampling was carried out for at least 30 hours, and serum concentrations were assayed in duplicate using the EMIT® procedure. The results of a bioavailability study are illustrated in Figure 6. As may be seen from the plot of the mean serum concentration time curves, Lot F of Theo-Dur Sprinkle had a lower maximum concentration and a larger time to peak, both of which are characteristics of a prolonged time for absorption. To best evaluate the absorption kinetics of this product, the serum profiles were transformed using a modification of the Wagner-Nelson Equation[9]. The Wagner-Nelson equation may be written as

$$\frac{A_t}{V} = C_t + \beta \int_0^t C \, dt \qquad \text{(Eq. 1)}$$

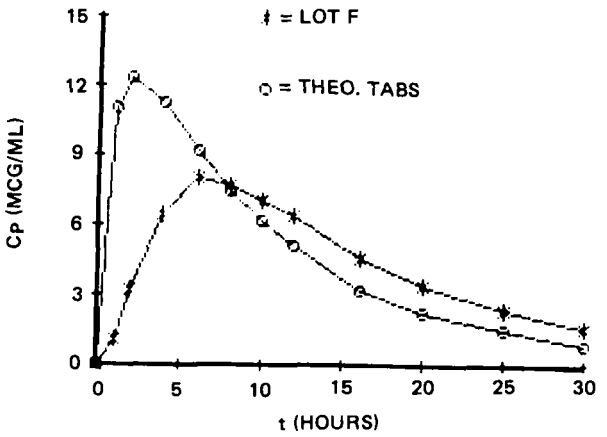

FIGURE 6

Serum concentration-time profile for Theo-Dur Sprinkle (asterisks) and an immediate release reference tablet (circles) obtained in a typical bioavailability study. The points are mean concentrations obtained in six subjects.

where A_t is the amount of drug absorbed at time t; V is the volume of distribution; C_t is the serum concentration at time t, and β is the apparent first order rate constant of elimination. When $t = \infty$, Eq. 1 simplifies to

$$\frac{A_\infty}{V} = \beta \int_0^\infty C \, dt \qquad \text{(Eq. 2)}$$

If Eq. 1 is then divided by Eq. 2 the following results

$$\frac{A_t}{A_\infty} = \frac{C_t + \beta \int_0^t C \, dt}{\beta \int_0^\infty C \, dt} \qquad \text{(Eq. 3)}$$

The ratio of A_t/A_∞ is simply the fraction of the dose absorbed at time t, F_t, and Eq. 3 may be rewritten as

$$F_t = \frac{C_t/\beta + \int_0^t C\,dt}{\int_0^\infty C\,dt} \qquad \text{(Eq. 4)}$$

Using Eq. 4 the data in Figure 6 was transformed into a modified Wagner-Nelson plot; this may be seen in Figure 7. The data has been fitted by linear regression and it is apparent that the drug is being released at a fairly constant rate for 8-10 hours.

Since both the dissolution and in vivo data were plotted as a cumulative fraction of the dose-time profile, it was rather straight-forward to arrive at an in vitro/in vivo correlation. The cumulative fraction dissolved in vitro at a certain time point was plotted against the cumulative fraction absorbed in vivo at the same time point. Figure 8 demonstrates that a linear relationship exists between the fraction dissolved

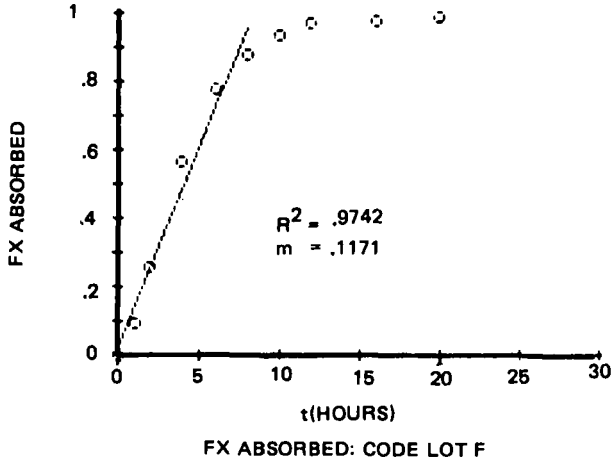

FIGURE 7

Modified Wagner-Nelson plot prepared from the data in Figure 6.

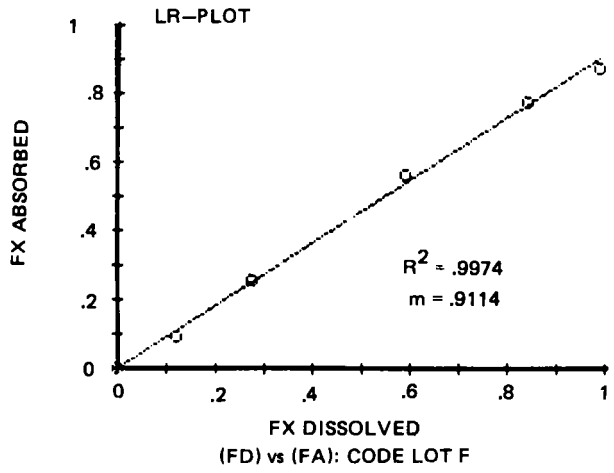

FIGURE 8

In vitro/In vivo correlation plot for Theo-Dur Sprinkle prepared from the data in Table 1 and Figure 7.

and fraction absorbed, $r^2 = 0.9974$. A similar relationship has previously been demonstrated by Levy et al. for aspirin [10]. Once an in vitro/in vivo correlation is established, it is possible to modify formulations and monitor them solely with dissolution studies. This greatly reduces the needs for costly and time consuming bioavailability trials.

In previous studies with Theo-Dur tablets, an equation was derived which could be used to predict single dose serum concentration-time profiles from in vitro data [11]. This relationship could be used additionally to predict steady-state serum concentrations from single dose studies [11,12]. The equation is derived from the modified Wagner-Nelson Equation, Eq. 4. Expanding Eq. 4 and solving for C_t, the following equation results

$$C_t = F_t \beta \int_0^{\infty} C\,dt - \beta \int_0^{t} C\,dt \qquad \text{(Eq.5)}$$

The integral from 0 to time t can be defined in terms of the trapezoidal rule as follows in Eq. 6.

$$C_t = \beta \left[F_t \int_0^{\infty} C\,dt - \frac{\Delta t}{2}(C_t + C_{t-1}) - \int_0^{t-1} C\,dt\right] \qquad \text{(Eq.6)}$$

Where Δt is the time interval from the previous time point, t-1, to time t; C_{t-1} and C_t are the respective concentrations used to calculate the AUC for the time interval. The integral from 0 to t-1 represents the area prior to that obtained at time t. Rearranging Eq. 6 yields

$$C_t + \frac{\beta \Delta t}{2} C_t + \frac{\beta \Delta t}{2} C_{t-1} = \beta F_t \int_0^{\infty} C\,dt - \beta \int_0^{t-1} C\,dt \qquad \text{(Eq. 7)}$$

Eq. 7 can be further simplified to

$$C_t \left(\frac{\beta \Delta t}{2} + 1\right) = \beta F_t \int_0^{\infty} C\,dt - \beta \int_0^{t-1} C\,dt - \frac{\beta \Delta t}{2} C_{t-1} \qquad \text{(Eq. 8)}$$

The final relationship is obtained by solving for C_t

$$C_t = \frac{F_t \int_0^{\infty} C\,dt - \int_0^{t-1} C\,dt - \frac{\Delta t}{2} C_{t-1}}{\frac{\Delta t}{2} + \frac{1}{\beta}} \qquad \text{(Eq. 9)}$$

The F_t values obtained through Eq. 4 can then be used in Eq. 9 to generate C_t values at any time. Thus single dose data can be used to project steady-state serum curves and predict the results of a multiple dose study. Table 2 illustrates the similarity of projected serum concentrations

Table 2

Serum Theophylline Concentrations obtained after dosing with Theo-Dur Sprinkle every 12 hours for 5 doses and by projection with Equation 9

time,hr	Experimental C_{ss},µg/ml	Predicted C_{ss},µg/ml
48	6.2	5.8
49	6.6	5.8
50	6.2	5.5
52	6.8	6.2
54	7.0	7.3
56	6.8	7.3
60	5.4	5.8

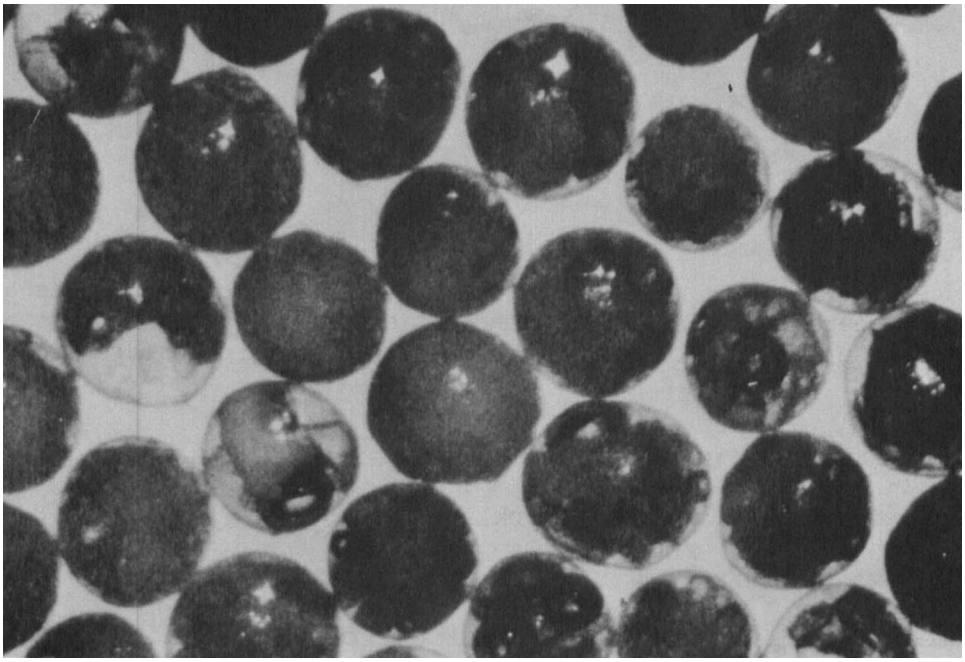

FIGURE 9

Photomicrograph of Theo-Dur Sprinkle after theophylline has begun to dissolve and diffuse through the polymer coating of the microspheres.

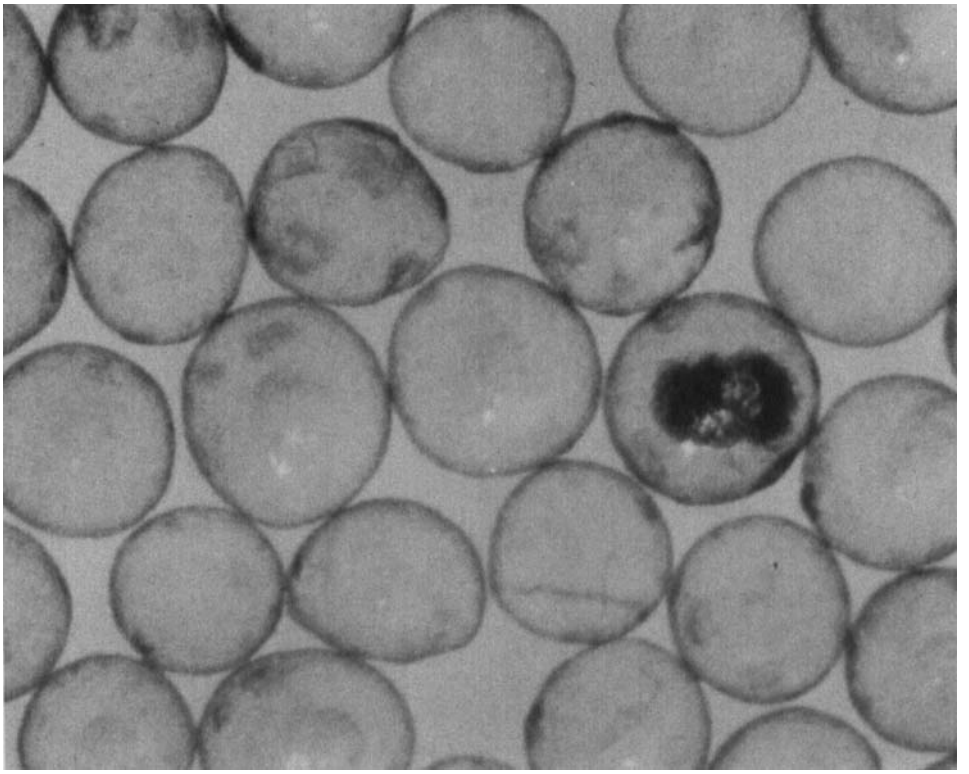

FIGURE 10

Photomicrograph of Theo-Dur Sprinkle after theophylline has completely diffused out of the microspheres. The dark spot on the pellet shows some theophylline remaining to dissolve.

at steady state versus the results obtained after a multiple dose study with Theo-Dur Sprinkle.

By altering the β in Eq. 9, this relationship can be used to predict the results of multiple dose studies in populations with different rate constants of elimination for theophylline. Equation 9 has been used successfully with Theo-Dur data obtained in adults to project steady state serum concentrations in children[12].

In closing, the following figures have been included to illustrate the dissolution of theophylline from Theo-Dur Sprinkle pellets. Figure 4, which was used to illustrate the spherical nature of Theo-Dur Sprinkle, is a photomicrograph taken immediately after the pellets were added to water. Figure 9 shows the pellets after they have been hydrated and theophylline has started to dissolve. The absence of theophylline in the pellets is seen as clear areas. The dissolution appears to be a random process in that some of the pellets in the center of the figure show little evidence of dissolution while other pellets have large gaps where the drug has dissolved and diffused through the polymer coating. Figure 10 illustrates what is seen after all the theophylline has dissolved. The microspheres are totally devoid of theophylline with the exception of one which shows a dark spot where some drug remains. At this stage the majority of the spheres seen are empty polymer sacks floating in the liquid.

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