Kinetics of Absorption of a New Once-a-Day Formulation of Theophylline in the Presence and Absence of Food

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Abstract □ Two three-way crossover studies were done to characterize the drug release characteristics of Monospan (3M Pharmaceuticals, St. Paul, MN) capsules, a new once-a-day theophylline formulation. In the first study, 22 healthy males received single 450-mg doses of Monospan in the presence and absence of a high-fat breakfast; the same dose of Somophyllin (Fisons, Rochester, NY) immediate-release liquid was given to fasted subjects as a reference. The second study involved 29 healthy males given a single dose of 900 mg of Monospan in the presence and absence of the same high-fat meal; Theo-24 (G. D. Searle and Co., Skokie, IL) capsules were given to fasted subjects as a reference. The results of both studies showed that food did not affect the absorption of theophylline from Monospan; peak concentration, time to peak concentration, and area under the serum concentration–time curve were all unchanged. The absorption rates were similar with both strengths and dietary conditions and showed that theophylline was absorbed slowly from Monospan at a constant rate (~3.2%/h) over 24 h. Absorption continued past 24 h, and the extent of absorption from Monospan compared with that from each reference averaged 88% or higher. A good correlation ($r > 0.980$) was observed for Monospan between the amount absorbed in vivo and the amount released in the in vitro dissolution test, a result that demonstrates the precise rate control of Monospan. We conclude that Monospan is a suitable once-a-day formulation that can be taken without regard to food.

The aim of an oral extended-release dose form is to provide consistent drug release over the entire dosing interval, regardless of the existing physiological and dietary conditions. Ideally, the drug release rate should be independent of concentration (zero order) and drug absorption should be complete and dissolution rate limited.[1] For such control to be achieved, the dose form itself must be the limiting factor in drug absorption. 3M Pharmaceuticals (St. Paul, MN) has developed an oral extended-release technology that uses a microencapsulated drug to achieve the above-mentioned goals.[2] The drug is uniformly distributed in beadlets approximately 1 mm in diameter and coated with a rate-controlling membrane consisting of pharmaceutically acceptable materials. The rate of drug release from these beadlets approaches zero order after a certain period of time and is pH independent.

Theophylline was chosen as a test drug for this technology because of the desired once-a-day dosing interval. Twenty-four hours allows sufficient time to demonstrate consistency of the rate of drug absorption throughout the gastrointestinal tract and is a good test of dissolution rate-limited absorption. In addition, several twice-a-day theophylline formulations and both once-a-day formulations marketed in the United States are associated with changes in the rate of drug absorption in the presence of food.[3,4] Because theophylline is a drug with a narrow therapeutic index, it would be most desirable to maintain relatively constant serum drug levels that are unaffected by the presence of food.[4]

Targeting controlled oral drug absorption over a 24-h period, however, implies that absorption must continue unaffected as the drug moves through the upper gastrointestinal tract, large bowel, and colon. Literature studies have established that theophylline can be efficiently absorbed throughout the gastrointestinal tract, specifically from the large bowel[5] and colon.[6] In addition, it has been shown that drugs that alter gastrointestinal tract transit time can affect the rate but not the extent of theophylline absorption.[7] On the basis of these studies, the objective of maintaining theophylline absorption for 24 h was deemed feasible.

This report describes two clinical studies of the 3M Pharmaceuticals extended-release theophylline formulation (Monospan) conducted with healthy volunteers. These studies were conducted on the basis of single-dose guidelines that were established during U.S. Food and Drug Administration–industry workshops on oral controlled-release dose forms.[8,9] Drug administration immediately after a high-fat breakfast was included in these studies to stress the formulation.[10,11] Also, a sufficient number of serum samples were included in the absorptive phase to establish an in vitro–in vivo correlation, if one existed.

Experimental Section

Materials—Somophyllin oral liquid equivalent to 90 mg of anhydrous theophylline per 5 mL (Fisons, Rochester, NY), Theo-24 300-mg anhydrous theophylline capsules (G. D. Searle and Co., Skokie, IL), Monospan 300-mg and 450-mg anhydrous theophylline capsules, the TDx theophylline II reagent system, which is a fluorescence-polarized immunoassay (Abbott Laboratories, North Chicago, IL), and an anhydrous theophylline reference standard (USP) were used in these studies. All reagents were analytical grade.

Dissolution—In vitro dissolution studies were conducted with a commercially available USP XXII dissolution apparatus (Distek, North Brunswick, NJ) at a basket speed of 100 rpm. Six intact capsules were exposed to 0.1 N hydrochloric acid for the first 1.5 h and subsequently to 0.05 M pH 7.5 phosphate buffer for the rest of the study. The medium was kept at 37 °C, and all sampling was done automatically. The absorbances of the samples were read in a Hewlett-Packard 8450A UV spectrophotometer and subsequently converted to percentages of theophylline released as a function of time by use of software provided by Hewlett-Packard (DODIS*). The algorithm corrected for the change in dissolution volume and for the amount of solute dissolved in the removed sample.

Clinical Studies—Two studies were conducted with different healthy human volunteers. All subjects were required to be nonsmoking males between 18 and 55 years of age. Health was judged on the basis of prestudy medical history, physical examination, clinical laboratory tests, and electrocardiograms. Body weight had to be at least 70 kg and within 10% of the ideal. Subjects were not allowed to have smoked tobacco or marijuana within the past year and were prohibited from ingesting alcohol and methylxanthine-containing foods and beverages for 48 h before and during a dosing period. All subjects gave informed consent, and each protocol was approved by an independent investigational review board.

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Study Procedures—Subjects for both studies were domiciled the night before each dosing period and remained domiciled for the duration of that period's blood sampling schedule. The subjects began fasting at 10 p.m. the night before dosing and took their doses with 6 oz of water. No food was allowed until 4 h postdosing, unless the treatment required a high-fat breakfast. The breakfast consisted of two fried eggs, two strips of bacon, one slice of buttered toast, 2 oz of hash brown potatoes, and 8 oz of milk. All meals were standardized and given at specified times. Water was allowed ad libitum.

Adverse experiences were queried at the time of each blood sampling and recorded throughout both studies. Clinical laboratory tests were performed before each dosing period and at the end of the studies. Standard laboratory tests were done for hematology, blood chemistry, and urinalysis.

The design of each study follows.

Study A—The first study was an open-label, single-dose, three-period crossover design with a 7-day washout between dosing periods. Each subject was randomly assigned to one of six dosing sequences based on a balanced Latin-square design for 24 subjects. Each subject received in random order a 450-mg theophylline dose as one Monospan capsule after an overnight fast, as one Monospan capsule immediately after the high-fat breakfast, and as 12.5 mL of Somophyllin liquid (equivalent to 225 mg of anhydrous theophylline), taken at time zero and 6 h after an overnight fast. Two subjects dropped out of the study before dosing period 2 and were replaced. Of the 26 subjects who entered the study, 22 completed it. Four subjects dropped out of the study for personal reasons, not related to any adverse event.

Study B—The second study was also an open-label, single-dose, three-period crossover design but with a higher theophylline dose and a once-a-day reference. Each subject was randomly assigned to one of six dosing sequences based on a balanced Latin-square design for 30 subjects. Each subject received in random order a 900-mg theophylline dose as three 300-mg Monospan capsules after an overnight fast, as three 300-mg Monospan capsules immediately after the same high-fat breakfast as that described above, and as three 300-mg Theo-24 capsules after an overnight fast. Of the 31 subjects entering the study, 29 completed it. One subject dropped out of the study during dosing period 1 and was replaced, and one additional subject did not complete the study. Neither discontinuation was related to any adverse event.

Serum Analysis—Blood samples were collected over 72 h after each drug administration. Serum theophylline levels were determined by use of the Abbott TDx fluorescence polarization immunoassay, modified for greater sensitivity.[12] Before use, the TDx method was compared with an existing HPLC method[13] and found to provide comparable results (slope = 1.05, $r > 0.969$). Over 300 serum samples, including all samples from four randomly selected subjects, were compared. The entire assay range was tested in this validation.

With each batch of unknown serum samples, four control standards supplied by Abbott plus a sample spiked at a lower concentration were analyzed. The results were consistently within established limits and agreed well for all batches. In addition, 10% of the unknown samples were randomly selected and analyzed in duplicate, and most replicates agreed within 10%. Replicate values for a given sample were averaged.

Data Analysis—Standard methods of calculating pharmacokinetic parameters were used.[14] The apparent terminal serum half-life values were determined from at least three and usually four or more analytically significant datum points in the terminal phase of the log plasma concentration–time curves by calculation of the least-squares regression line. Values were rejected when the coefficient of determination of the regression line was <0.85. The area under the plasma concentration–time curve was calculated by use of the trapezoidal rule from time zero to the last analytically significant concentration and extrapolated to infinity (AUC_∞).

Absorption rate constants and the fraction of the dose absorbed were determined by the method of Wagner-Nelson.[14] Study A included an immediate-release reference so that a true elimination rate constant could be calculated for each individual. In study B, the elimination rate constant was the mean value obtained for 87 subjects given Somophyllin liquid in other studies (3M historical data). The value used was 0.092/h. Absorption rate constants for zero-order and first-order absorption models were calculated from the least-squares regression line through the appropriate data set.

All pharmacokinetic calculations were performed with internal computer programs. All programs are documented and have been validated with test cases.

Statistical Analyses—The parameters studied to compare the treatments in each study were peak concentration, time to peak concentration, AUC_∞, and serum drug levels at each time point.

For both studies, each pharmacokinetic parameter was compared by an analysis of variance for a three-period crossover with sequences, subjects within sequences, periods, and treatments as factors in the model. The subjects-within-sequences mean square was used as the error term in the test of sequence effects. Treatment effects with $p \leq 0.05$ were considered significant. Follow-up multiple comparisons were made by use of Student-Newman-Keuls tests (study A) or t tests or least-squares means (study B) at an alpha level of 0.05.[15]

Variances among the treatments for each parameter were compared by use of the Pitman-Morgan test for correlated variances.[16] When significant differences were found among the variances, the data were subjected to a rank transformation for further testing. Ninety percent confidence intervals were determined for the AUC_∞ values; two one-sided t tests were performed, and the higher p value was reported.

All statistical analyses were performed with SAS versions 5.16 and 5.18 (SAS Institute, Inc., Cary, NC).

Results

Dissolution—The in vitro rates of release of theophylline from Monospan and Theo-24 in the dissolution medium are shown in Figure 1. Under the selected conditions, which simulate the pH changes as a dose form moves through the gastrointestinal tract, Theo-24 showed a faster rate of release than did Monospan after the 1.5-h pH change. In contrast to Theo-24, Monospan did not demonstrate any pH sensitivity. About 50% of the drug load was released in 3 h with Theo-24 and 7 h with Monospan.

Statistics—The analyses of variance applied to all the pharmacokinetic data to test for significant sequence effects yielded no significant effects in either study. In addition, no significant period effects were observed in study A. In study B, period effects were only observed for several serum concentrations and the first-order absorption rate constant. These period effects were judged to have no influence on the comparisons of the treatments in this study. All statistical comparisons in study B were done with the least-squares means because of an unbalanced number of subjects in the treatment groups.

Serum Drug Levels—Serum theophylline levels after the 450-mg single doses in study A are shown in Figure 2. The differences in the curves reflect the expected differences between an immediate-release product (given as two divided doses) and an extended-release product. There was no evi-

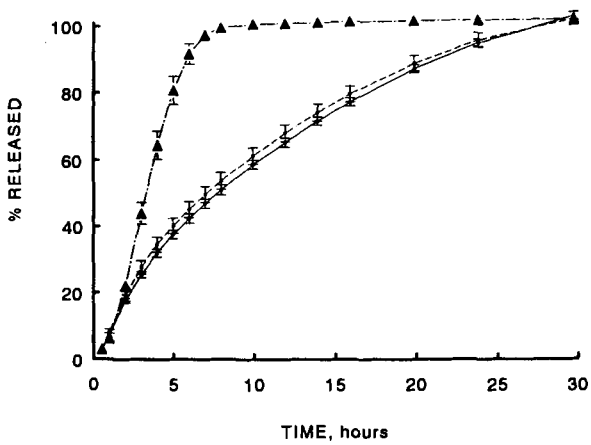

Figure 1—Dissolution profiles for 300-mg capsules of Theo-24 (▲) and 300-mg (— ○ —) and 400-mg (- - ● - -) capsules of Monospan. Each point is the mean ± SD for six determinations.

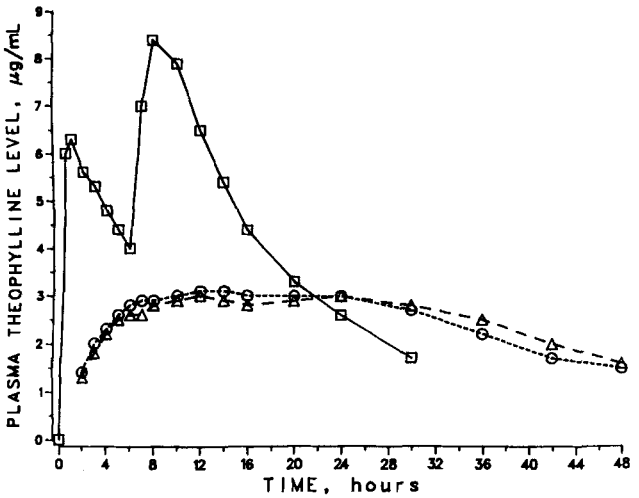

Figure 2—Mean serum theophylline concentrations in 22 subjects given 225 mg of Somophyllin liquid (□) at time zero and 6 h or one 450-mg Monospan capsule (○ [subjects who had fasted] and △ [subjects who had been fed]).

dence of dose dumping or loss of rate control with Monospan; on the contrary, serum theophylline levels with Monospan were very consistent from 6–30 h.

Different serum theophylline level profiles were also seen for the two once-a-day products in study B (Figure 3), a result that probably reflects their different dissolution rates. Serum theophylline levels with Monospan were twice as high as in study A, in direct proportion to the dose increase. Peak serum theophylline levels with Monospan were again observed to be very consistent, in this case occurring between 10 and 24 h.

Rate of Absorption—Peak theophylline levels with Monospan (Table I) were significantly lower than those with the corresponding doses of Somophyllin (study A) or Theo-24 (study B), and the times to peak levels were significantly longer with Monospan, although much of the differences were arbitrary because of the prolonged flatness of the Monospan peak level. These results are consistent with the slow, continued absorption of theophylline from Monospan, as the plot of the fraction of the dose absorbed versus time for study B shows (Figure 4).

Monospan absorption kinetics could be fit equally well to a zero-order or a first-order model. Approximately 3% of the dose was absorbed per hour in a linear fashion for up to 30 h (Table I). A slightly better fit of the Theo-24 data was obtained with the first-order model. The absorption half-lives were estimated to be 6.3 h for Theo-24 and 9.9 h for Monospan.

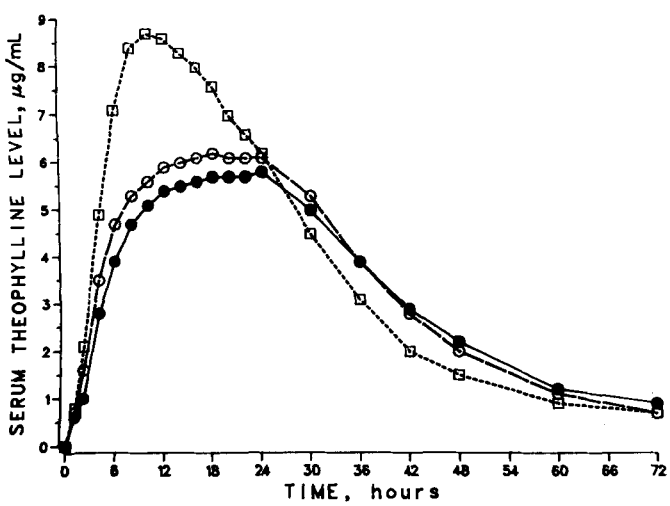

Figure 3—Mean serum theophylline concentrations in 29 subjects given a single 900-mg dose of theophylline as Monospan (○ [subjects who had fasted] and ● [subjects who had been fed]) or Theo-24 (□).

Extent of Absorption—Less theophylline was absorbed from Monospan taken in the fasting state than from either Somophyllin or Theo-24 under similar conditions (Table I). The ratios of the individual AUC_∞ values with Monospan to those with Somophyllin and Theo-24 were 0.88 ± 0.19 (mean ± SD) and 0.97 ± 0.22, respectively.

The AUC difference reached statistical significance for the comparison with Somophyllin. However, the 90% confidence intervals for the mean AUC_∞ values for the Monospan treatments were 78–96%; the mean value for Somophyllin (study A) and 89–100%; the mean value for Theo-24 (study B); these results indicate little clinical significance in the AUC difference.

Effect of Food—As Figures 2 and 3 and Table I show, the serum theophylline level profiles and all pharmacokinetic parameters were essentially unchanged when Monospan was administered immediately after a high-fat breakfast. The only significant difference between the treatments with or without food was with the peak concentration in study B. Although statistically significant, the actual difference was quite small.

The absorption rate constants for theophylline were not significantly changed when Monospan was administered with food. The largest difference in the rate of theophylline absorption from Monospan was seen in study A (Table I), and examination of the fractions of the dose absorbed over time in the presence and absence of food (Figure 5) revealed that this rate difference was indeed small.

In Vitro–In Vivo Correlation—To test for dissolution-controlled absorption, we compared the amount of drug dissolved in vitro with the amount of drug absorbed in vivo (fasting conditions) at a given time point for the lots of Monospan and Theo-24 used in these studies. A good linear correlation was seen for the 450-mg dose of Monospan over 30 h in study A (Figure 6); the coefficient of determination of the regression line was 0.9955. The slope of this line was 0.799. A similar slope (0.765) and a similar correlation (r = 0.9832) were seen for the 300-mg capsule lot of Monospan used in study B. These correlations were unaffected by the in vivo food treatment. In contrast, no correlation between the dissolution and absorption rates could be established for Theo-24.

Safety—All adverse experiences in both studies were mild to moderate in severity and resolved without sequelae and without medical intervention. All of the adverse experiences that were drug related were of the type commonly associated with theophylline (headache, nausea, lightheadedness, tiredness, restlessness). No subject withdrew from a study because of an adverse experience.

In study A, more adverse experiences were reported during the Somophyllin dosing period, despite division of the dose. The food treatment did not appreciably affect the incidence of adverse experiences with Monospan.

Discussion

One goal of the 3M oral extended-release beadlet technology was to have the dose form control its own absorption rate by dissolution rate-limited absorption. This characteristic would allow the selection of the desired formulation on the basis of dissolution data alone. Clinical studies would be limited to testing just the target formulation, saving time and money in drug development.

The demonstration of a linear correlation between dissolution and absorption for 30 h with Monospan indicates that beadlet technology is capable of achieving this goal. The

Table I—Pharmacokinetic Summary

Parameter	Value, Mean ± SD, for the Indicated Drug in Study[a]:					
	A, 450-mg Dose			B, 900-mg Dose		
	Somophyllin, Fasted	Monospan		Theo-24, Fasted	Monospan	
		Fasted	Fed		Fasted	Fed
Peak level, μg/mL	8.4 ± 1.1	3.3 ± 0.7	3.2 ± 0.6	9.0 ± 2.2	6.6 ± 1.7	6.1 ± 1.6
Time to peak level, h	2.3 ± 1.0	14.6 ± 6.4	15.2 ± 7.3	10.7 ± 2.8	18.8 ± 5.0	19.2 ± 5.4
Absorption rate constant (zero order), %/h	—	3.0 ± 0.4	2.7 ± 0.4	3.9 ± 0.5	3.3 ± 0.5	3.2 ± 0.5
Absorption rate constant (first order), per h	—	0.063 ± 0.021	0.050 ± 0.014	0.11 ± 0.05	0.07 ± 0.03	0.07 ± 0.03
AUC_T, μg · h/mL	141 ± 43	119 ± 43	124 ± 41	253 ± 92	238 ± 76	226 ± 78
AUC_∞, μg · h/mL	156 ± 48	135 ± 47	139 ± 44	263 ± 96	250 ± 82	239 ± 85

[a] Fasted, subjects who had fasted; fed, subjects who had been fed.

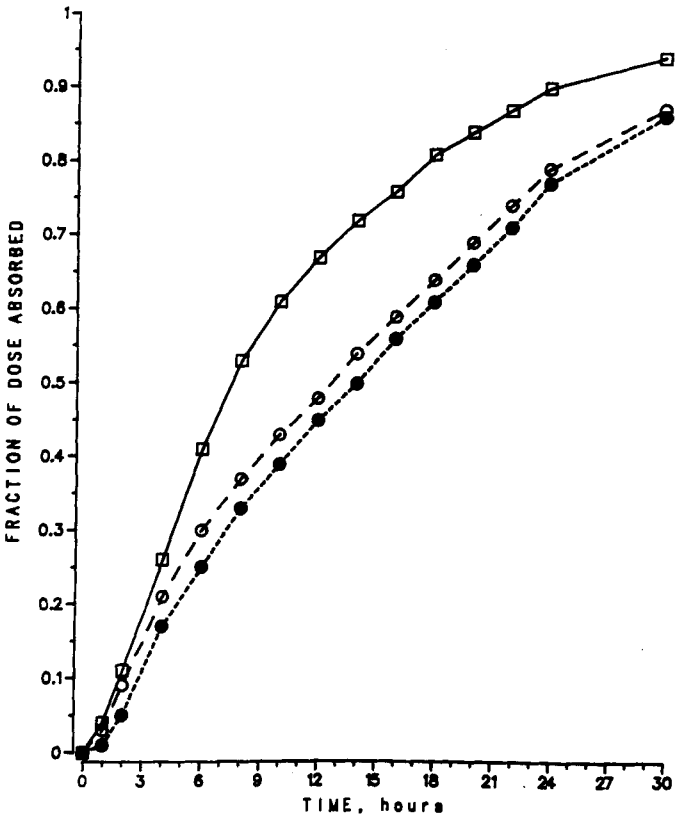

Figure 4—Mean fraction of the theophylline dose absorbed in 29 subjects after dosing with Monospan (○ [subjects who had fasted] and ● [subjects who had been fed]) or Theo-24 (□).

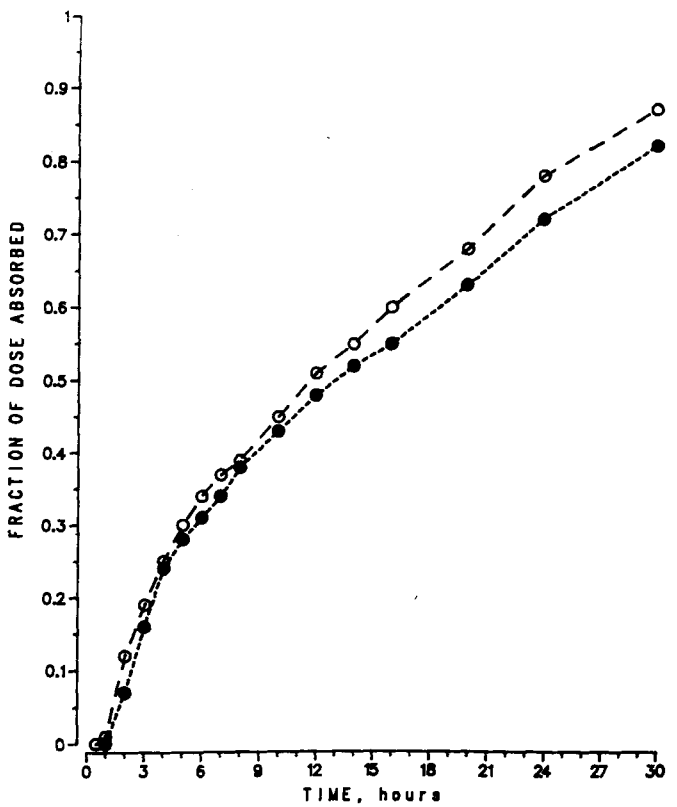

Figure 5—Mean fraction of theophylline dose absorbed in 22 subjects given one 450-mg Monospan capsule with (●) or without (○) food.

success of the correlation can be attributed to the dissolution characteristics of the dose form, which is not 100% dissolved at 30 h. Several previous attempts to develop in vitro–in vivo correlations for theophylline used products whose dissolution characteristics were such that 100% of the dose was dissolved by 12 h or sooner, and these products could achieve correlations only for up to 4–5 h[17–20] or not at all.[21] Thus, our observation of a lack of in vitro–in vivo correlation for Theo-24 is consistent with these results, because this product had a 12-h dissolution profile in our study. We are aware of two studies that were able to establish in vitro–in vivo correlations for theophylline controlled-release products.[22,23] Significantly, these products required more than 12 h for 100% dissolution.

Literature studies have demonstrated that theophylline can be absorbed from the large bowel and colon.[5,6] Those studies focused primarily on the extent of drug absorption. The present studies extend our knowledge of theophylline kinetics by examining the rate of theophylline absorption from all regions of the gastrointestinal tract over 30 h. The Wagner-Nelson analysis of the Monospan data shows that the rate of theophylline absorption can be maintained constant and reliable for the entire gastrointestinal tract over an interval of 30 h. The linear in vitro–in vivo correlation further supports the conclusion that the absorption rate does not change as the dose form moves through the gastrointestinal tract.

The 3M theophylline beadlet formulation was also designed to be pH independent. This design resulted in a product that was independent of food effects in vivo, as demonstrated in the present two controlled studies done in accordance with U.S. Food and Drug Administration–industry guidelines.[8,9] Any significant food effect, if it existed, would have been apparent with a high-fat breakfast. Theo-24 has undergone similar studies and been shown to be substantially affected by food.[3,10] pH-dependent dissolution with Theo-24 has been reported.[3,24]

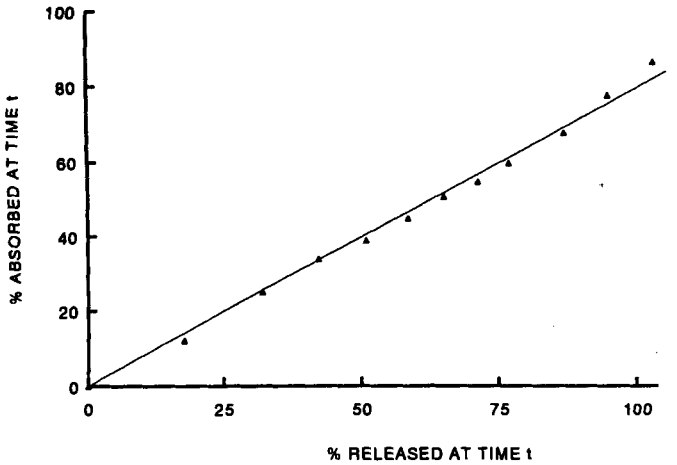

Figure 6—Correlation between the percent released in the dissolution assay for 450-mg Monospan capsules and the percent absorbed in 22 subjects given one 450-mg Monospan capsule without food (study A) at 0, 2, 4, 6, 8, 10, 12, 14, 16, 20, 24, and 30 h.

Because the 3M oral extended-release technology uses identical beadlets for all strengths, it was not surprising to observe essentially the same serum drug level profiles and rates of absorption for the two Monospan treatments. Likewise, it was not surprising to observe the good dose proportionality between the two unrelated studies. Consistency of product performance between individuals is predicted for an extended-release product that shows dissolution rate-limited, near zero-order absorption.[1]

The ultraslow drug release from Monospan made it difficult to estimate the extent of drug absorption, especially for the low serum drug concentrations observed in study A. For this reason, study B is the better estimate of the extent of absorption, but a multiple-dose study is needed to fully characterize the extent of theophylline absorption from Monospan.

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