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Report

Analysis of *in Vitro* Dissolution of Whole vs. Half Controlled-Release Theophylline Tablets

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Controlled-release (CR) drug products dissolve more slowly than conventional-release products, reflecting their quality of sustaining a prolonged therapeutic effect. A frequent practice with scored tablets when only half the dosage is desired is to divide the tablet at the score mark and administer only half of the product. The dissolution characteristics of the divided tablets are unknown. It is only an assumption that the halved tablet behaves similarly to the whole tablet both *in vitro* and *in vivo*. A series of *in vitro* dissolution analyses was performed on whole and half CR theophylline tablets from different manufacturers. Statistical tests were carried out between the dissolution results of whole and those of halved tablets to determine whether the mean overall percentages dissolution (averaged over sampling times) were similar and whether the patterns of percentage dissolution over time were similar. The dissolution of halved tablets was slightly faster compared to that of intact (whole) tablets. However, these small differences were not large enough to cause concern or to require bioavailability studies.

KEY WORDS: controlled-release theophylline; dissolution; whole vs. half tablets; statistical analysis.

INTRODUCTION

Theophylline is widely used in the treatment of asthmatic patients of all ages. Because it is used prophylactically to prevent status asthmaticus over prolonged periods, controlled-release (CR) preparations of this drug are appropriate and are available from a number of manufacturers. It has a narrow therapeutic range, however, being most effective at plasma concentrations between 8 and 20 μg/ml. Careful titration of the dosage is required, particularly in children. Many of the CR theophylline tablets currently available are scored, and a frequent practice when only half the dosage is desired is to divide the tablet at the score mark and administer a fraction of the dose, especially in children. The *in vivo* absorption characteristics of the divided CR tablets are not known, and it is only an assumption that the halved tablets behave similarly to the intact whole tablets.

In many instances *in vitro* dissolution characteristics have been correlated/associated with *in vivo* performance of a product. However, there are only two published papers that have compared the bioavailability and dissolution of whole vs half of *one* manufactured theophylline CR product (1,2). Simons *et al.* found a slight but significant difference in the dissolution profile (10–20% in simulated gastric fluid and 4–12% in simulated intestinal fluid) but no significant difference in the bioavailability of the whole vs half tablet (1). Leeds *et al.* corroborated the lack of *in vivo* differences in administered whole vs half tablets of the same product (2).

Since there are a large number of controlled-release theophylline dosage forms marketed, where such a determination has not been made, it was the subject of this investigation. As a first step in understanding the behavior of halved tablets, the *in vitro* dissolution of the whole and halved CR theophylline products was determined. A series of *in vitro* dissolution analyses was performed on these tablets from several different manufacturers and the results were statistically analyzed.

METHODS

The following 300-mg CR theophylline tablets were used in the study: A, Theochron (Forest Labs); B, Theo-Dur (Key); C, Quibron (Mead Johnson); D, Sustaire (Roerig); E, Theocontin (Purdue Frederick); F, Labid (Baylor); G, Theolair (Riker); and H, Constant-T (Cord). Dissolution studies were performed using the USP paddle method at 50 rpm for all tablets (3). A six-gang chain-drive dissolution apparatus was used and the dissolution profiles of whole tablets and one part (weighed) of the tablets cut in half at the score mark were run for 12 hr in simulated gastric fluid (SGF; pH 1) and simulated intestinal fluid (SIF; pH 7.5) without enzymes. Hourly samples were removed and analyzed by a high-performance liquid chromatographic (HPLC) method and calculated as the percentage of the label claim dissolved.

Statistical Analysis

In vitro dissolution of whole vs half tablets was approached from two aspects:

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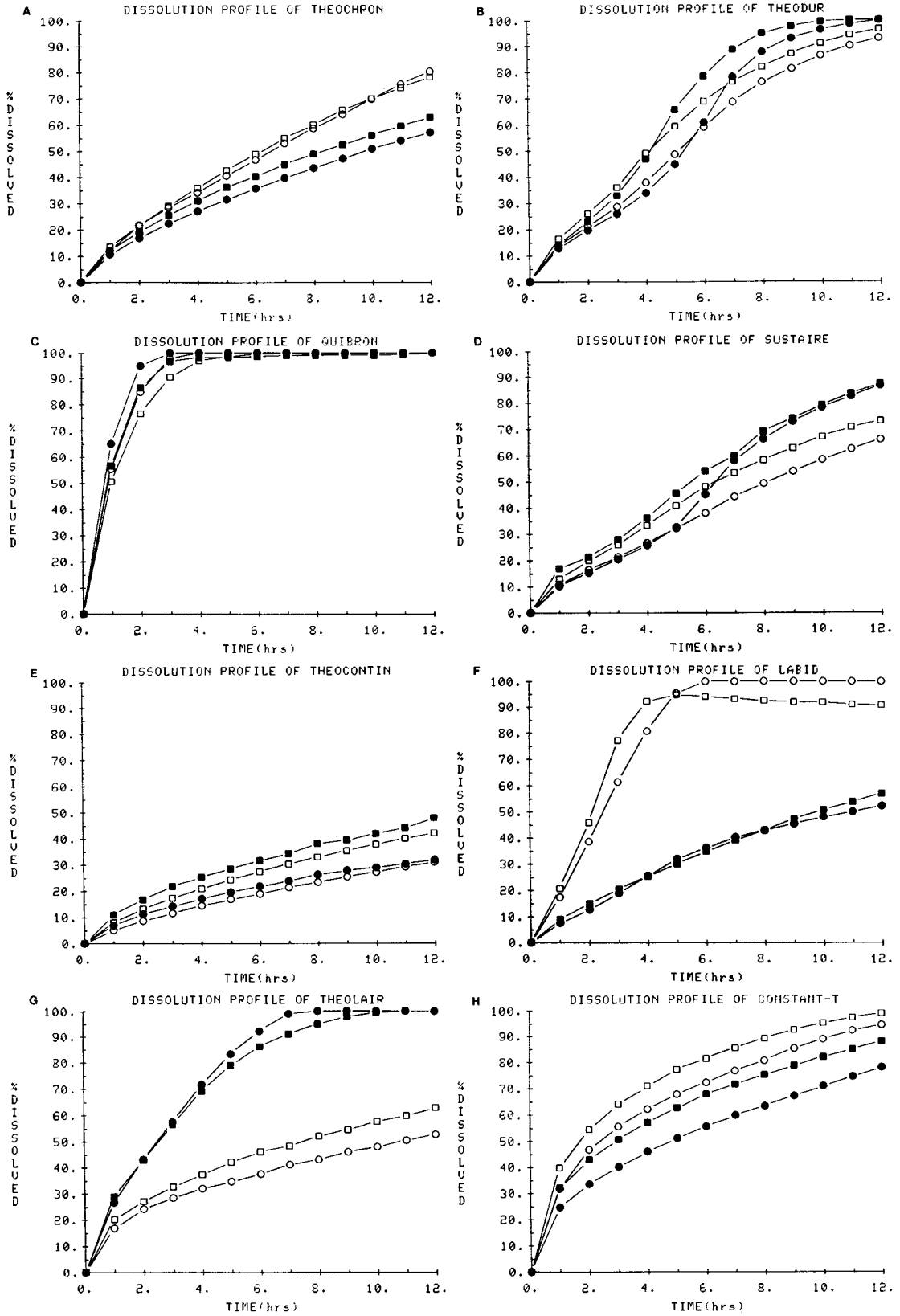

Fig. 1. Dissolution profiles of whole and half CR theophylline products A–H. (○) SGF whole; (□) SGF half; (●) SIF whole; (■) SIF half.

(1) Are the overall mean dissolution values, averaged over all time points, similar for both half and whole tablets?
(2) Are the patterns of the percentage dissolution vs time curves similar for half vs whole tablets?

For each product and each medium, a repeated-measures (split plot) analysis of variance was carried out (4). A similar analysis of blood-level measurements in a bioavailability study was discussed by Westlake (5). The total variability in the data was partitioned as follows.

Source of variability	df
Between tablets	
Half vs whole (averaged over time points)	1
Between-tablet averages within tablet types (= error a)	10
Within tablets	
Times	11
Half vs whole × time ("parallelism")	11
Error b	110

Error a, which is an estimate of between-tablet variability, was used to test the hypothesis that half and whole tablets do not differ with respect to average dissolution, averaged over the 12 time points, using an F test. It was also used to form 95% confidence intervals for the average difference between half and whole tablets, averaged over time points. Error b, which is an estimate of within-tablet variability, was used to test the hypothesis that the average difference between whole and half tablets did not change from time to time, i.e., the hypothesis that the profiles were essentially parallel. This was an F test formed from the parallelism mean square from the analysis of variance.

RESULTS AND DISCUSSION

The results of dissolution profiles of whole and half tablets in SGF and SIF are shown in Fig. 1, and the statistical analyses in Tables I and II. The dissolution differences were in the range of 1–13% in most cases, between half vs whole tablets. For the most part the dissolution of the whole and half tablets appears to be similar in SGF and SIF with the exception of Products F and G. When the data were analyzed by overall mean averaged over all time points, a number of products showed statistically significant differences. Dissolution of whole vs half tablets for Products E, G, and H in SGF demonstrated highly significant differences ($P < 0.0001$) and product B showed a significant difference in SGF ($P < 0.05$). In SIF, a dissolution profiles of whole vs half tablets of Products E and H showed highly significant differences, while Products A and C were significantly different. When the same type of analysis was performed on the pattern or curve similarity of whole vs half tablets, it was determined that in SGF only Product D did not show differences, with Products B, C, E, F, G, and H being highly significantly different. In SIF only Products D and F showed no significant differences in pattern and the remainder were highly significantly different. The mean dissolution curves did not always appear to correspond with the statistical analysis, particularly the differences noted with Product C and the lack of difference with Product D. This is due to the variance of the six tablets analyzed in each case. As can be seen in Table I, there are differences both in the mean dissolution averaged over all time points and in the pattern between SIF and SGF for most of the products. Only Products D and F show no statistically significant difference in mean dissolution when compared in the two dissolution media.

Table I. P Values for the Comparison of Half vs Whole Tablets

	SGF		SIF	
Product	Avg[a]	Pattern[b]	Avg[a]	Pattern[b]
A	0.708	0.024	0.018	0.0003
B	0.015	0.0001	0.025	0.0001
C	0.212	0.0001	0.011	0.0001
D	0.36	0.967	0.434	0.615
E	0.0001	0.0001	0.0001	0.0001
F	0.345	0.0001	0.885	0.986
G	0.0001	0.0001	0.377	0.0004
H	0.0001	0.0001	0.0001	0.0001

[a] Comparison of average percentage dissolution over the 12 time points.
[b] Test for "parallelism" of the profiles over time.

It should be borne in mind that a significant difference (indicated by a P value < 0.05) indicates that the whole and half tablets truly differ, but it says nothing about the magnitude of that difference. For each of the eight products a confidence interval was determined for the differences observed between half vs whole tablets averaged over all time points (Table II). As previously mentioned, the presence or absence of statistically significant results when contrasted with the graphic representation could be due to the wide range of values shown by the confidence interval. Take, for example, the range shown by Product D and compare it with that shown by Product C. Whereas Product C showed statistically significant differences between half vs whole tablets in SIF and Product D did not, the range of the confidence interval for Product D is much greater than for Product C, and the differences may be merely a reflection of the greater variability of the Product D dissolution.

The dissolution testing of solid dosage forms serves as a screening tool for continuing bioavailability studies of the products. The CR preparations are approved based on bioavailability studies. The dissolution specifications of these CR preparations are established based on the dissolution behavior of the products that underwent bioavailability (approved) testing. The CR products dissolve slowly in the gastrointestinal (GI) tract and pass through a milieu of pH levels in the range of 1 to above 7. Since controlled-release tablets are not immediately absorbed by the body but proceed in partially undissolved form throughout the GI tract, the dissolution specifications should include results at varying pH levels to reflect physiological conditions surrounding the tablets *in vivo*. The CR tablets often are broken at score marks in order to adjust the required dosage administration, especially in children. Because of these various reasons and to understand the complex dissolution–absorption process in the GI tract, the dissolution of eight marketed whole and half CR theophylline products was studied, in SGF and SIF, under the same conditions and the results were compared.

Table II. Ninety-Five Percent Confidence Intervals for the Difference in Average Dissolution (over the 12 Time Points), Whole Minus Half Tablets

	SGF		SIF	
Product	Estimate	Conf. int.	Estimate	Conf. int.
A	0.76	−2.95, 4.46	4.40	0.714, 8.12
B	6.52	1.05, 11.99	7.78	2.3, 13.2
C	−2.51	−5.7, 0.695	−3.35	6.55, −0.152
D	7.23	−7.2, 21.6	5.07	9.3, 19.46
E	8.08	6.55, 9.6	10.10	8.5, 11.6
F	−2.46	−14.8, 9.83	1.18	−11.1, 13.47
G	−7.06	1.38, 12.74	−3.43	−9.11, 2.25
H	7.63	5.12, 10.13	10.72	8.21, 13.23

It is important to determine whether there are differences in the *in vitro* dissolution of whole and half tablets of CR theophylline products since such differences may lead to problems in *in vivo* absorption. If the dissolution of half tablets had been found to be much faster than that of whole tablets, it would suggest that breaking the tablet to adjust the dose should be avoided until proved safe with an appropriate bioavailability study.

Certainly there appears to be variability among products from different manufacturers and between results obtained with SGF and results with SIF. For certain manufacturers the dissolution of halved tablets was slightly faster compared to that of intact (whole) tablets. However, based on the confidence intervals for the average differences between halved and whole tablets, it was determined that the differences were not large enough to cause concern and to require bioavailability studies on halved tablets. This finding is in agreement with work done by previous workers (1,2).

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