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Report

Theophylline-Controlled Release Preparations and Fatty Food: An *in Vitro* Study Using the Rotating Dialysis Cell Method

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The *in vitro* dissolution behavior of four controlled-release theophylline products was investigated utililzing the rotating dialysis cell method. The effects of pH, oil, and enzymes on the dissolution profiles were studied. The wide range of pH values and the content of oil and enzymes in the dissolution media in the dialysis cell, which functioned as an *in vitro* model, were simulated to mimic physiological changes due to food along the entire gastrointestinal tract. Treatment with oil affected the dissolution behavior of Uniphyl and especially Theo-Dur Sprinkle but had little or no effect on the dissolution profiles of Theo-Dur tablets and Theo-24 capsules. The *in vitro* observations of the oil effect were related to the food effect obtained from published *in vivo* studies. The rotating dialysis cell can be a useful tool in studying factors which may be responsible for dissolution-related food effects on the absorption of controlled-release products.

KEY WORDS: theophylline; controlled release; food effect; *in vitro* dissolution; rotating dialysis cell.

INTRODUCTION

The effect of food on the bioavailability of controlled-release (CR) theophylline preparations in humans has been the subject of many recent studies (1–9). The mechanisms of the food-induced changes which have been reported, either increasing (4–7), decreasing (4,8), or not changing (1,9) bioavailability compared to fasting conditions, are not clear. Recently an *in vitro* model which intended to correlate the *in vivo* observations and the *in vitro* dissolution was reported (10,11). In somewhat modified form the model was applied to the CR preparations of propranolol (12).

In the present study we employed a novel rotating dialysis cell method in an effort to further develop an *in vitro* system that would simulate food-induced physiological changes responsible for the dissolution behavior of theophylline CR preparations. In this system, the product with a small volume of fluid is contained in a small dialysis cell which is mobilized by continuous horizontal rotation in a dissolution vessel (Fig. 1). Through the cell membrane the product is continuously in contact with the dissolution medium. The fluid used inside the dialysis cell can be changed to simulate the following gastrointestinal conditions.

pH Effect. By changing the pH values of the fluid from 1.2 to 7.8, pH profiles are obtained to demonstrate the dissolution behavior along the entire gastrointestinal tract (GIT) under fasting conditions.

Food Effect. By adding oil to the fluid, the fatty component of a meal is simulated.

Enzymes and Bile Salts. These can also be added to the small volume of fluid in addition to the oil to mimic food-induced changes in the different parts of the GIT.

Under normal conditions an empty human stomach has an average pH value between 1.2 and 2.5 during the day. When food is ingested, the pH rises to about 4.5 but, shortly afterward, decreases to less than 2.5 again due to the supply of gastric acid. In order to simulate the gastric excretion of pepsin as a result of food, pepsin can be added to the oil in addition to low-pH medium. At the entrance to the proximal small intestine, however, the pH is about 6.6 (±0.5) due to the excretion of bicarbonate. It further increases to 7.5 (±0.4) along the proximal and distal intestine (13). Bile salts enter the GIT at the duodenum and are necessary for the digestion of lipids. The better *in vitro* simulation in alkaline pH medium thus requires the addition of bile salts.

EXPERIMENTAL

Theophylline CR Products

Four CR preparations were selected for this study. All were of the same strength, 200 mg. They included Theo-Dur tablets (Key Pharmaceuticals Inc., Lot P7138, Product A), Uniphyl tablets (Purdue Frederick, Lot FM6, Product B), Theo-Dur Sprinkle capsules (Key Pharmaceuticals Inc., Lot P7161, Product C), and Theo-24 capsules (Searle, Lot 1087-834, Product D).

Dissolution Studies

Dissolution tests were carried out in the Pharma-Test

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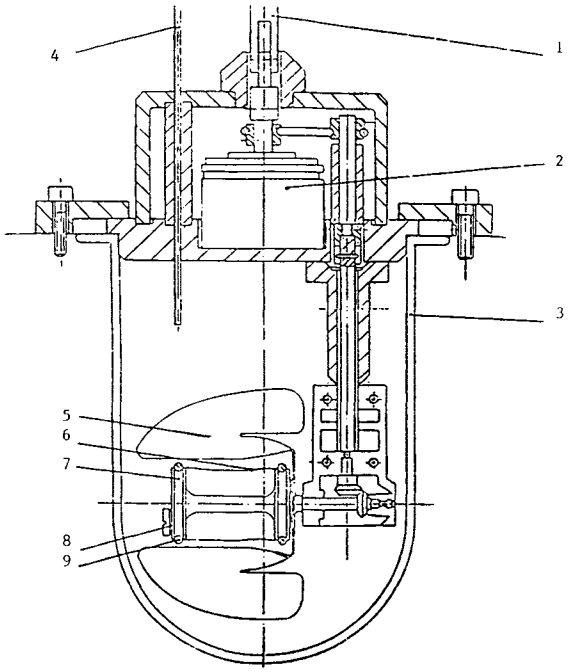

Fig. 1. Illustration of a rotating dialysis cell apparatus for the *in vitro* testing. 1, Drive shaft; 2, gear drive; 3, glass vessel; 4, temperature sensor; 5, agitator plate; 6, dialysis membrane; 7, O-ring; 8, dialysis cell; 9, plastic insert supporting membrane.

Dissolution Test Instrument (PTW-S, Scientific Instruments & Technology Corp., Piscataway, N.J.).

The apparatus consists of six rotating dialysis cells which emerge in the dissolution vessels. The cell was originally developed for the study of drug release from hydrophobic carrier preparations, e.g., suppositories (14). It enclosed a small volume (up to 30 cm^3) of inner fluid by means of a dialysis membrane (Durapore, HPLV 0.45 μm). The cell rotates horizontally in a larger volume of test medium (outer medium) which has the same pH as the inner volume. The rotating speed was set at 100 rpm, which gives 50 horizontal rotations per minute of the cell (50 hrpm). The smaller inner volume was 10 ml, whereas the larger outer volume was 900 ml. Both media were maintained at 37 ± 0.5°C.

pH profiles were obtained by placing the product inside the dialysis cell with 10 ml of buffer at pH 1.2 (for simulated gastric fluid without pepsin) and buffers at pH 4.5, 5.4, 6.8, 7.5, and 7.8, respectively. These buffers were prepared according to USP XXI procedures (15). The dissolution tests were conducted for up to 8 hr, with sampling at each hour.

Simulation of *in Vitro* Food Effect

Peanut oil in the inner test medium representing dietary fat was used to simulate fatty food. Like the other long-chain triacylglycerides, peanut oil is an insoluble amphiphile which forms a thin lipid film on the substrate in an aqueous solution. Like many other vegetable oils, it is a mixed triacylglyceride, with the attached fatty foods being oleic (56%), linoleic (26%), palmitic (8.3%), and stearic (3.1%) acids and small percentages of arachidic, behenic, and lignoceric acids. A concentration of 10% was selected on the basis of previous experience with peanut oil (12).

Gastric conditions following food intake were simulated in *in vitro* by placing the oil into the buffer with 0.32% pepsin, the buffer being either pH 1.2 or 4.5. Parallel tests were run with oil in buffer only, without pepsin, in order to separate the effects of the two.

Intestinal food-induced conditions were simulated by adding bile salts to the buffers, the pH being 6.8, 7.5, or 7.8. For the simulation of the effect of bile salts in the test system, the sodium salt of taurocholic acid (Sigma Chem. Co.) at a concentration level of 10 m*M* was used. All simulations were made by using different media inside the dialysis cells. The outer media were only buffers at various pH's and did not contain oil or enzymes.

Analysis of Theophylline in the Dissolution Samples

Theophylline was determined by reversed-phase high-performance liquid chromatographic (HPLC) method as described in a previous study (10). The system consisted of a Waters autosampling HPLC system (Waters Associates, Milford, MA) with a 22-cm C-18 RP column (Brownlee Labs, Santa Clara, CA). The mobile phase was made up of acetonitrile and 0.05 *M* acetate buffer, pH 4.8 (8:92). The theophylline was measured at 254 nm (Waters Model 440 absorbance detector) at 0.1 AUFS. Injected volume was 50 μl. At a 1.5-ml/min flow rate, theophylline was eluted at about 5 min under these conditions. The validation of the method gave an overall reproducibility of less than 2% coefficient of variation. An internal standard was not used due to the satisfactory performance of the autosampler. Theophylline concentrations were calculated by comparing the peak areas to those of known concentration standards.

RESULTS AND DISCUSSION

Product A consists of beads, approximately 1 mm in diameter, embedded in a tablet matrix. The tablet surface appears to be smooth, but on breaking, the intact beads are clearly seen.

During the dissolution testing, tablet disintegration occurs slowly. The process is complete at the end of 8 hr and the individual beads are free of matrix material. The rate of disintegration varies according to the conditions of the experiment. The tablet remained intact for 4 hr in alkaline pH and longer when the dissolution medium contained oil and bile salts. In the lower-pH media the tablet disintegrated into several large fragments by 4 hr. Disintegration was more rapid in the presence of oil and pepsin.

Effect of pH on Dissolution. Previous studies (10,16) employing conventional apparatus demonstrated pH-independent dissolution behavior. The dissolution profiles obtained in the present study, however, were significantly higher in alkaline-pH than in low-pH media. The amounts dissolved after 8-hr testing were 83 ± 2 and 82 ± 9% at pH 6.8 and 7.8, respectively, compared to only 44 ± 2 and 54 ± 1% at pH 1.2 and 4.5, respectively (Table I).

Effect of Oil. The addition of 10% peanut oil to the buffer in the cell increased both the initial rate of dissolution and the overall dissolution profile at lower-pH media. In alkaline-pH media, however, the initial dissolution decreased, generating a somewhat more sigmoidal dissolution profile, but the overall dissolution was unaffected. The initial

Table I. Dissolution Profiles of Controlled-Release Theophylline Products Under Simulated Physiological Conditions

Time (hr)	pH	Untreated	Mean % dissolved (SD)[a] 10% oil	Oil + pepsin	Oil + bile salts
		Product A			
1	1.2	16.3 (1.6)	22.2	15.3 (1.2)	NA
2		22.2 (3.4)	31.8	26.4 (2.4)	
3		25.8 (6.2)	36.9	34.3 (2.7)	
4		30.6 (2.6)	43.7	41.7 (5.5)	
5		31.4 (3.2)	48.0	45.2 (3.8)	
6		36.4 (1.8)	50.7	49.1 (5.9)	
7		40.5 (2.4)	58.4	51.0 (5.9)	
8		44.4 (2.1)	60.7	55.8 (7.2)	
1	4.5	13.3 (0.4)	12.4	13.2 (0.7)	NA
2		18.9 (0.3)	23.3	22.1 (1.2)	
3		26.0 (1.0)	29.7	27.9 (2.1)	
4		29.8 (1.1)	34.6	32.7 (2.4)	
5		39.5 (1.2)	40.8	39.7 (3.4)	
6		39.9 (0.6)	45.2	48.7 (3.5)	
7		48.4 (2.6)	47.8	53.8 (3.2)	
8		54.0 (0.8)	52.8	58.8 (2.6)	
1	6.8	18.3 (1.8)	10.8	NA	14.5 (1.7)
2		34.6 (1.5)	26.7		35.9 (2.4)
3		45.7 (3.6)	35.2		48.6 (5.1)
4		52.8 (6.7)	55.7		56.6 (7.6)
5		62.2 (6.9)	64.7		60.2 (8.7)
6		70.3 (6.6)	70.4		71.2 (6.8)
7		79.7 (4.3)	79.2		78.3 (3.4)
8		83.4 (2.2)	85.5		80.6 (1.5)
1	7.8	16.6 (2.3)	7.9	NA	15.7 (0.5)
2		29.0 (4.9)	23.1		37.3 (1.8)
3		39.4 (3.4)	42.4		54.1 (3.1)
4		52.5 (2.5)	55.3		65.1 (5.5)
5		65.7 (9.9)	69.6		73.7 (7.2)
6		71.2 (5.4)	73.6		79.2 (3.6)
7		75.0 (7.2)	80.2		86.1 (3.1)
8		82.3 (9.0)	85.1		90.2 (2.9)
		Product B			
1	1.2	8.1 (0.3)	10.7 (1.8)	10.0 (1.6)	NA
2		15.0 (0.6)	22.4 (1.0)	21.9 (2.0)	
3		20.5 (1.2)	35.0 (0.3)	33.7 (2.3)	
4		26.6 (0.5)	43.3 (0.3)	47.6 (4.8)	
5		32.7 (1.7)	51.1 (0.0)	59.1 (3.6)	
6		33.2 (3.1)	57.9 (0.8)	67.3 (4.1)	
7		42.5 (5.0)	66.5 (2.2)	75.0 (3.0)	
8		47.3 (6.7)	73.5 (4.1)	84.6 (2.6)	
1	4.5	6.9 (0.1)	7.1 (1.7)	5.3 (1.0)	NA
2		13.8 (1.8)	18.6 (4.2)	21.0 (4.1)	
3		21.7 (5.5)	28.8 (5.5)	34.1 (5.2)	
4		24.5 (0.7)	35.1 (7.9)	44.1 (6.1)	
5		35.7 (12.6)	47.0 (9.6)	55.0 (8.2)	
6		39.7 (12.4)	50.1 (9.8)	63.2 (6.3)	
7		43.7 (14.9)	55.4 (12.9)	69.3 (7.8)	
8		43.8 (17.3)	62.1 (12.8)	74.0 (6.4)	
1	6.8	9.2 (1.1)	9.9 (1.4)	NA	12.0 (2.1)
2		19.6 (6.0)	20.3 (4.1)		25.6 (6.3)
3		24.7 (6.2)	28.2 (5.0)		39.5 (11.6)
4		32.0 (4.8)	36.7 (7.1)		51.4 (15.4)
5		36.8 (9.8)	44.3 (9.1)		59.2 (15.8)
6		42.3 (11.0)	51.8 (10.4)		66.9 (15.0)
7		50.4 (3.9)	55.5 (8.7)		69.4 (11.6)
8		59.1 (3.8)	62.4 (10.7)		75.1 (11.3)
1	7.8	8.6 (1.2)	4.6 (0.1)	NA	9.2 (0.2)
2		17.6 (3.1)	11.1 (0.2)		14.8 (0.5)
3		28.1 (3.9)	18.0 (1.0)		21.9 (1.8)
4		39.0 (1.4)	26.6 (0.1)		30.9 (4.6)
5		43.0 (8.2)	32.3 (0.2)		39.1 (7.0)
6		50.7 (3.6)	36.5 (0.3)		46.2 (9.6)
7		56.0 (9.0)	41.4 (0.5)		54.8 (8.2)
8		61.1 (8.7)	46.3 (0.7)		60.7 (5.9)
		Product C			
1	1.2	4.4 (0.4)	0.3	0.8 (0.1)	NA
2		14.5 (1.0)	0.9	1.7 (0.1)	
3		26.4 (1.1)	1.7	3.3 (0.3)	
4		39.1 (1.9)	2.7	6.9 (1.5)	
5		49.8 (5.0)	3.9	7.6 (0.7)	
6		63.2 (3.4)	4.8	11.5 (1.8)	
7		71.3 (3.1)	6.0	13.6 (1.6)	
8		78.7 (2.5)	6.9	22.9 (4.0)	
1	4.5	3.0 (0.3)	0.4	0.2 (0.2)	NA
2		14.8 (0.3)	0.8	1.3 (0.2)	
3		24.7 (0.8)	1.2	2.7 (1.6)	
4		35.8 (0.9)	1.7	5.0 (3.0)	
5		46.5 (0.8)	2.4	7.2 (4.3)	
6		55.3 (2.1)	3.0	10.0 (5.6)	
7		66.4 (0.3)	3.8	12.5 (6.7)	
8		78.6 (3.7)	4.7	15.4 (7.0)	
1	6.8	5.2 (2.4)	0.0	NA	0.3 (0.3)
2		19.8 (2.5)	0.5		0.9 (0.4)
3		34.1 (2.8)	1.0		1.4 (0.6)
4		53.8 (4.0)	1.5		2.1 (0.6)
5		66.9 (4.4)	2.3		3.2 (0.7)
6		82.2 (6.4)	3.2		4.5 (0.8)
7		86.5 (1.7)	4.2		5.8 (0.8)
8		90.9 (2.0)	5.3		7.0 (1.0)
1	7.8	6.7 (0.5)	0	NA	0.8 (0.4)
2		23.0 (0.6)	0.5		3.4 (2.1)
3		41.6 (2.6)	1.0		1.3 (0.7)
4		59.3 (1.6)	1.7		2.0 (1.3)
5		70.6 (0.7)	2.7		3.2 (2.1)
6		79.7 (2.2)	4.5		5.2 (3.0)
7		85.8 (1.0)	6.5		7.1 (4.1)
8		89.3 (1.2)	8.6		10.2 (4.3)
		Product D			
1	1.2	3.8 (0.3)	3.1	2.7 (0.4)	NA
2		9.0 (0.3)	8.8	8.0 (0.9)	
3		15.2 (0.5)	15.0	14.3 (1.0)	
4		21.1 (1.1)	20.8	20.8 (1.0)	
5		27.0 (0.7)	27.6	27.5 (1.1)	
6		32.9 (0.7)	33.1	32.8 (1.0)	
7		39.7 (2.0)	39.2	38.5 (1.0)	
8		45.4 (0.7)	44.3	43.6 (0.5)	
1	4.5	3.5 (0.3)	2.4	2.5 (0.1)	NA
2		8.5 (0.8)	6.6	6.8 (0.4)	
3		14.4 (0.9)	12.1	9.7 (0.4)	
4		19.8 (2.0)	17.3	19.0 (0.5)	
5		26.1 (2.4)	23.0	22.6 (0.3)	

Table I. Continued

Time (hr)	pH	Untreated	Mean % dissolved (SD)[a] 10% oil	Oil + pepsin	Oil + bile salts
6		30.8 (1.3)	28.6	27.2 (0.5)	
7		34.5 (0.9)	35.0	31.3 (0.5)	
8		43.6 (1.5)	42.0	35.5 (1.2)	
1	6.8	3.1 (0.3)	2.7	NA	3.3 (0.3)
2		10.5 (0.7)	8.8		10.5 (0.7)
3		18.7 (0.7)	17.3		19.4 (1.2)
4		28.0 (1.9)	26.6		28.5 (1.5)
5		36.1 (1.2)	36.5		41.1 (2.2)
6		44.0 (0.5)	45.6		48.9 (4.9)
7		52.7 (1.1)	52.8		58.4 (2.8)
8		59.6 (1.2)	59.5		63.7 (3.8)
1	7.8	5.6 (0.2)	6.0	NA	5.9 (0.5)
2		20.4 (1.4)	20.3		22.5 (1.4)
3		40.4 (0.5)	40.6		14.3 (2.7)
4		58.7 (5.3)	59.2		62.8 (3.6)
5		70.8 (7.0)	75.3		78.9 (4.6)
6		88.8 (3.0)	90.6		86.9 (3.9)
7		93.4 (6.6)	94.7		91.3 (2.9)
8		99.3 (3.6)	98.3		96.8 (1.8)

[a] Mean values of three units except for those data without standard deviations (SD), which represent the averages of two units.

decrease in the rate of dissolution may be related to the enhanced disintegration in lower-pH medium, where in the presence of oil, a larger area becomes available for contact with the dissolution medium.

Effect of Pepsin and Bile Salts. The addition of pepsin to the 10% oil dissolution mixture did not further affect the rate or extent of dissolution more than oil alone. However, the addition of bile salts to the buffer at pH 7.8 moderately improved the rate of dissolution (Fig. 2).

Product B is a matrix type of CR tablet. The drug is released by leaching out of the matrix, which remained intact throughout the 8-hr dissolution run.

Effect of pH on Dissolution. Previous work done in our laboratory (17) has shown that dissolution is incomplete regardless of agitation rate or media. There is evidence of better dissolution in alkaline-pH media at the present study (Table I).

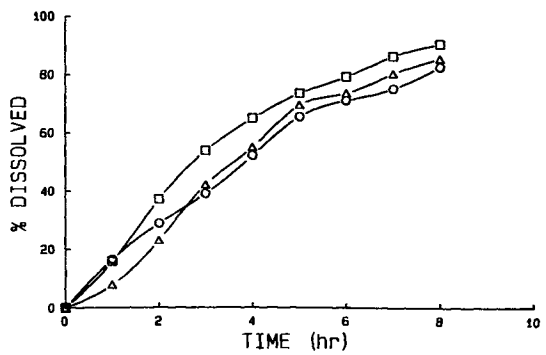

Fig. 2. *In vitro* dissolution profiles of product A under alkaline conditions (pH 7.8). Circles represent untreated, triangles represent treated with 10% oil, and squares represent treated with oil plus bile salts.

Effect of Oil, Pepsin, and Bile Salt. The addition of oil produced different effects in relation to the pH of the buffer. At pH 1.2 dissolution increased significantly and reached 73 ± 3% after 8 hr of dissolution, compared with 47 ± 7% in the absence of oil. Also, adding pepsin to oil at pH 1.2 led to a further increase (85 ± 3%) in dissolution (Fig. 3a). In alkaline pH 6.8 the effect of the oil was negligible. However, adding bile salt to the buffer raised the amount dissolved significantly, to 75 ± 11% (Fig. 3b). In a more alkaline pH (i.e., 7.8) both oil and bile salt addition resulted in a somewhat reduced dissolution profile of this product (Fig. 3c).

Product C is a capsule containing very finely divided beads, each representing a CR unit. In the therapy of child's asthma, the capsule is snapped open and the beads are sprinkled on a spoonful of apple sauce. Therefore the *in vitro* tests were run also by removing the hard gelatin capsule and placing the beads into the cell. The test medium was introduced, and the cell immersed in the outer medium for testing. For the oil treatment tests, the oil was applied to the beads, then the buffer containing either pepsin or bile salts was added.

Effect of pH on Dissolution. The pH profiles generally show a considerable time lag, indicating a delay in onset of dissolution which was not observed with the tablet forms (Table I). Since there is no capsule to cause this delay, this is presumably the "wetting" lag or the time needed for the beads to be sufficiently wetted in order for the dissolution process to be initiated. Dissolution then proceeds independent of pH, except for the slight increase in alkaline media. This dissolution behavior suggests a well-absorbed product under fasting conditions.

Effect of Oil. Addition of 10% oil drastically reduced the dissolution in all pH media. A similar effect was observed in our previous study when the CR beads of propranolol were subjected to oil treatment (12). In the presence of oil (ingested as a component of a fatty meal, for instance), the beads which are of a very small size become agglomerated and encapsulated by the oil droplets. In this way a large surface area of drug is lost for direct contact with the dissolution medium. This resulted in extremely low dissolution profiles (Table I).

Effect of Pepsin and Bile Salt. In the presence of pepsin or bile salts dissolution relatively improved at the last hours of the test. Since the oil could not be solubilized by the bile salt micelles, it is not clear in which way the addition of sodium taurocholate or pepsin could have improved the wettability and, consequently, the dissolution of the beads.

Product D consists of encapsulated beads, each of which represents a CR unit. The beads are larger in size than those in product C. Since in the therapeutic situation, the capsule is administered as an intact entity, the capsule was used intact for the dissolution tests.

Effect of pH on Dissolution. As prevously described in publications (5,10), the dissolution of this product is dependent on the pH of the medium. The profiles obtained in this study were low in acidic pH, intermediate at pH 6.8, and high at pH 7.8 (Table I). The time lag observed, although much shorter than that of product C, may be due partially to the presence of the hard gelatin capsule.

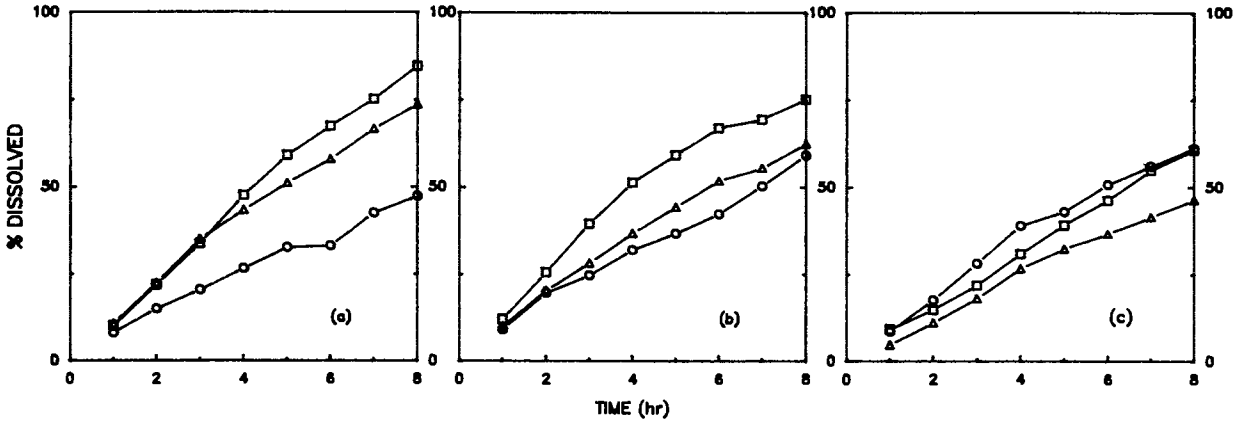

Fig. 3. Effect of oil treatment on the dissolution profiles of product B under acidic and alkaline media: (a) pH 1.2, (b) pH 6.8, and (c) pH 7.8. (○) Untreated; (△) treated with 10% oil; (□) treated with oil plus enzymes.

Effect of Oil, Pepsin, and Bile Salt. No significant oil effect was seen at any pH value. In a separate study, similar dissolution results were observed when acetate buffer (pH 4.5) was used instead of phosphate buffer (pH 4.5). The addition of pepsin or bile salts did not change the profiles to any significant degree (Table I).

Relation to the *in Vitro* Food Effects Obtained from Published Data

It has been reported that the coadministration of product A with different diets (i.e., high fat, low fat, liquid low fat, standardized breakfast, etc.) did not affect the overall bioavailability, although the time to peak level was slightly delayed (1,9). The present *in vitro* studies showed that although the oil initially decreased the dissolution rate in alkaline-pH media, the overall dissolution profile was not affected by the oil treatment. Figure 4 shows the relationship of the *in vivo* absorption obtained from Ref. 1 and the *in vitro* dissolution under alkaline pH in various simulated physiological conditions.

An increase in the bioavailability of product B has been reported as a result of food by Milavetz *et al.* (6) and Karim *et al.* (4). In Milavetz's study, the extent of absorption increased from 68 ± 7% during single dosing on an empty stomach to 83 ± 4% under nonfasting conditions. Similar results were also obtained during multiple dosing. In Karim's study a high-fat meal increased the bioavailability to 96 ± 46%, compared to 53 ± 23% in the absence of food. The profiles and the relationship of the *in vitro* dissolution data obtained from low-pH media and the *in vivo* absorption data obtained from Karim *et al.* (4) are illustrated in Figs. 5A and B, respectively. Since fatty food increased the bioavailability of this product, the nontreated *in vitro* data were corre-

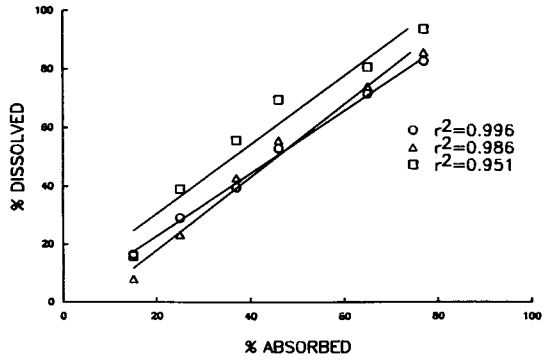

Fig. 4. Relationships of *in vitro* dissolution and *in vivo* absorption of product A at pH 7.8. Open circles represent untreated *in vitro* data versus *in vivo* fasting data, while open triangles and open squares represent *in vitro* oil- and oil plus bile salt-treated data versus *in vivo* fed data, respectively.

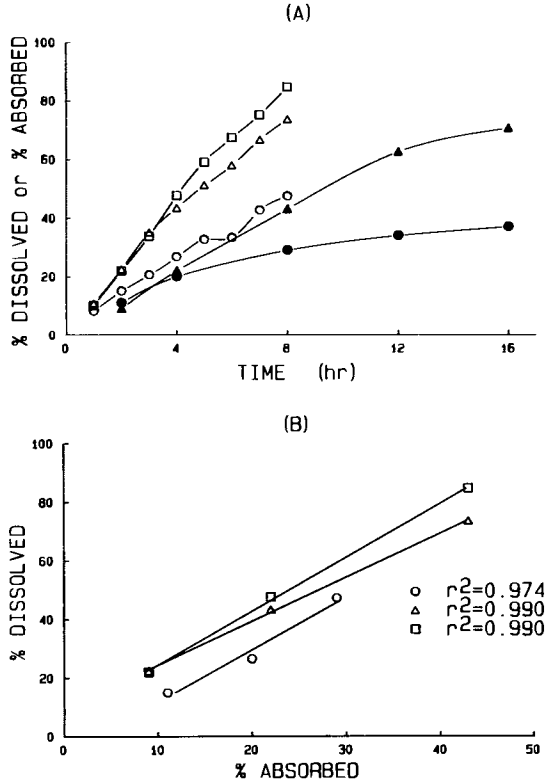

Fig. 5. (A) Profiles of *in vivo* dissolution of product B at pH 1.2 [(○) untreated; (△) treated with 10% oil and (□) treated with 10% oil plus pepsin] and *in vivo* absorption under fasting (●) and high-fat meal (▲). (B) Relationships between percentage dissolution and percentage absorption. Untreated data were plotted against fasting data (○), while oil (△)- and oil plus pepsin (□)-treated data were plotted against high-fat meal data (4), respectively.

lated with the fasting *in vivo* data, and the oil and the oil plus enzyme *in vitro* data were correlated with the fed *in vivo* data, respectively. The changes in dissolution due to the oil treatment mimics the changes in absorption due to the fatty meal. When product B is coadministered with food, there is an increase in gastric retention time: the tablet is retained longer in the stomach (as a large non-disintegrated unit) where the presence of oil promotes the dissolution of the active component out of the matrix.

Karim *et al.* (4) have reported that a high-fat meal decreased the bioavailability of product C to 53% of that in the fasting state. Pedersen (8) demonstrated a significant effect depending upon the type of meal on the absorption of this product: a wet meal consisting of a high water content slightly delayed the absorption but did not affect the bioavailability. A dry meal consisting of corn flakes and bread, however, not only delayed but also decreased the bioavailability and caused substantial interindividual variations (8). Timing of the meal was also critical and taking product C 5 min before, instead of immediately after, the meal reduced the food effect.

The dissolution profiles obtained in the present study under oil-treatment conditions were drastically reduced compared to those obtained in the absence of oil (Fig. 6A). These findings support the hypothesis that these beads require wetting in order to hydrate the coating so as to facilitate dissolution of the theophylline from the beads (8).

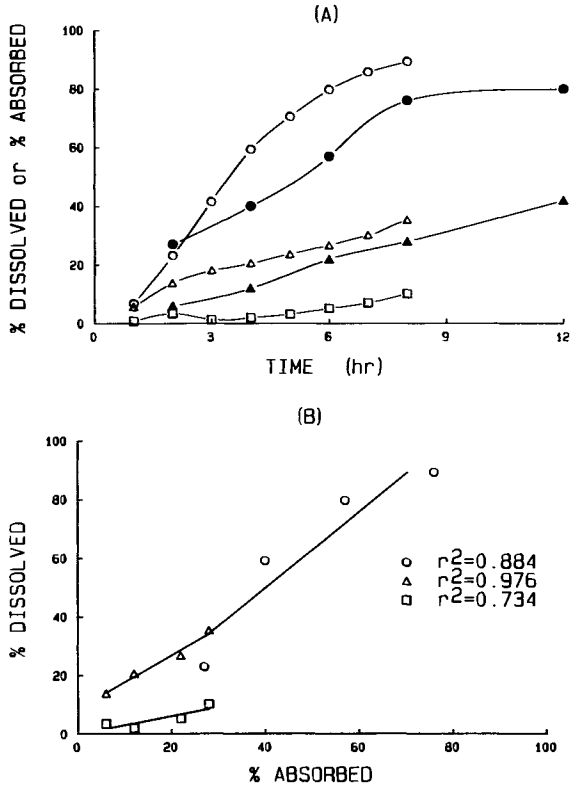

Fig. 6. (A) Profiles of *in vitro* dissolution of product C at pH 7.8 [(○) untreated; (△) treated with premixed oil and bile salts; and (□) treated with oil plus bile salts] as described in the text and *in vivo* absorption under fasting (●) and fed with the dry meal (▲). (B) Relationships between percentage dissolution and percentage absorption. Untreated data were plotted against fasting data (○), while premixed oil and bile salt (△) and oil plus bile salt (□) data were plotted against the "dry meal" data (8), respectively.

In order to support this hypothesis further we repeated the dissolution test under somewhat modified conditions: instead of adding the oil and the bile salt containing buffer into the cell, we mixed them prior to introducing them into the dialysis cell. The *in vitro* data were plotted against the *in vivo* data obtained from Pedersen (Fig. 6B). The effect of the dry meal correlates well with the effect of oil obtained under the modified test conditions. The lowest profile corresponding to the direct exposure of the beads to the oil represents an extreme situation in which the fat/oil ingested with the meal coats the beads preventing wetting—an essential requirement for the dissolution of these beads. This may explain the high interindividual variations observed in the *in vivo* study.

Coadministration of product D with food was reported to lead to an increase in the rate of absorption and to complete absorption after 24 hr, compared to slow and incomplete absorption under fasting conditions (7). Administration with a high-fat meal was found to increase the rate and extent of absorption, whereas administration with a medium- and low-fat meal ingestion did not have a significant effect on the bioavailability of product D (5). One may argue that the medium-fat meal was really not "medium" in fat content, but certainly theophylline bioavailability was not affected when dosed with low-fat meal ingestion.

The present *in vitro* studies did not indicate any effect of the oil on the dissolution of this product under any of the simulated conditions investigated. However, it is clear that the dissolution behavior of product D in alkaline pH media is completely irrespective of the treatment. On the other hand, the dissolution profiles in any of the acidic media remained low with or without treatment with oil (Table I). Ingestion of food generally prolongs retention of the small beads in the GIT, while under fasting conditions beads are more rapidly passed through the GIT. This may explain the incomplete absorption of product D under a fasting condition compared to the higher absorption in the fed state.

At this stage, however, no correlation of the *in vitro* dissolution under the present test conditions with the food-induced change in the extent of absorption was observed for this product.

In conclusion, we have demonstrated that the dissolution profiles of the four CR products of theophylline over a wide range of simulated physiological conditions were

(1) slightly affected by the pH of the medium (products B and C),
(2) moderately affected by the alkaline medium (product A), and
(3) highly affected above a critical pH value of 6.8 (product D).

Treatment with 10% peanut oil under the simulated intestinal (alkaline) conditions within the dialysis cell did not affect the overall dissolution of product A, and this is in accordance with the findings obtained from *in vivo* studies. The oil increased the dissolution of product B when the dissolution medium mimicked the gastric part of the GIT, and this again relates well with the increased absorption due to food observed *in vivo*.

The addition of oil drastically reduced the dissolution

profiles of product C, which was found to correspond to the very significant drop in absorption as a result of a dry meal. This is in support of the hypothesis that wetting of the beads is essential for the dissolution of theophylline and, consequently, for its absorption. We did not find an effect of the simulated food conditions on the dissolution of product D. The increase in bioavailability found *in vivo* could be due to the longer retention of the product in the GIT by food so that the product could be thoroughly absorbed, especially in the intestine. This is clearly demonstrated by the drastic increase in *in vitro* dissolution of product D at higher pH values.

Overall, this *in vitro* rotating dialysis cell method seems to be a useful tool in studying factors which might influence the dissolution and the absorption of CR preparations.

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