A Floating Controlled-Release Drug Delivery System: *In Vitro–in Vivo* Evaluation

Subhash Desai[1,2] and Sanford Bolton[3]

Received September 6, 1992; accepted March 12, 1993

A novel floating controlled-release drug delivery system was formulated in an effort increase the gastric retention time of the dosage form and to control drug release. The buoyancy was attributed to air and oil entrapped in the agar gel network. A floating controlled-release 300-mg theophylline tablet having a density of 0.67 was prepared and compared *in vitro* and *in vivo* to Theo-dur. The *in vitro* release rate of the floating tablet was slower. *In vivo* scintigraphic studies for a floating and a heavy nonfloating tablet, under fasting and nonfasting conditions, showed that the presence of food significantly increased the gastric retention time for both tablets, and tablet density did not appear to make a difference in the gastric retention time. However, the positions of the floating and nonfloating tablets in the stomach were very different. Bioavailability studies in human volunteers under both fasting and nonfasting conditions showed results comparable to those with Theo-dur. The floating controlled-release theophylline tablet maintained constant theophylline levels of about 2 mg/mL for 24 hr, which may be attributable to the release from the agar gel matrix and the buoyancy of the tablet in the stomach.

KEY WORDS: floating; controlled release; theophylline; gastric retention time; bioavailability.

INTRODUCTION

The bioavailability of drugs from pharmaceutical dosage forms is influenced by a variety of factors (1). An important factor in the design of drug delivery systems is the gastric retention time of such systems. Some drugs are well absorbed from all regions of the gastrointestinal tract, while others are poorly absorbed from the intestine or have absorption windows (2). For many drugs, increased or more predictable availability would result if controlled-release systems could be retained in the GI tract for extended periods of time.

Various approaches have been tried to retain the dosage form in the stomach as a way of increasing the overall retention time and include

floating systems (3–13),
high-density pellets (14–16),
bioavailability systems (17–19),
swelling systems (20),
chemical systems (21), and
a shape-based system (22).

For a system to maintain a consistent release rate, it should be able to withstand a variety of physiological variables which may influence gastric emptying such as food, position of body, temperature, and volume of fluid intake. One of the most important factors affecting the GI transit and drug delivery rates of controlled-release systems is the presence or absence of food (23,24). Food-related dose-dumping is a major concern.

The present study describes the formulation of a novel floating controlled-release drug delivery system in the form of a molded tablet. The tablet is prepared with a small amount of a gelling agent (agar) and mineral oil. The density of the final tablet is less than 1, resulting in a system that floats immediately, unlike other systems, which have to imbibe water before flotation. *In vivo* scintigraphic studies were performed to evaluate the position and the gastric retention time of the floating delivery system in the stomach. Studies were performed on the gastric retention time without evaluating the impact on the pharmacokinetic and therapeutic effect. Fasting and nonfasting pharmacokinetic studies were conducted to evaluate the effect of flotation on the release profile of theophylline.

MATERIALS AND METHODS

Tablet Manufacture

The ingredients were weighed as listed in Table I. Theophylline was placed in a glass beaker and a weighed amount of light mineral oil was added. The mixture was stirred with a glass rod to form a homogeneous mixture. Distilled water was added to powdered agar in another glass beaker. The agar suspension was heated to boiling with a bunsen burner with constant stirring. The solution was allowed to cool to about 70°C and then added to the beaker containing the theophylline/light mineral oil mixture. The mixture was stirred vigorously to form a homogeneous suspension and was then poured at 50–55°C into molds. The suspension was allowed to gel for 5 to 10 min and the excess material was scraped off of the molds. The resulting molded tablets were then punched out of the molds and dried overnight at room temperature.

The radiolabeled floating tablets were prepared by adding radiolabeled indium-111 to the hot agar solution. This mixture was added to the drug–oil mixture as described above and a similar procedure was followed. The dried tablets were dip-coated in 10% hydroxypropyl methyl cellulose phthalate (HPMCP-55-S) for 15 sec and dried with hot air. Only the radiolabeled tablets were dip-coated to retain the marker within the tablet. Several formulations were prepared to study the effects of agar concentration, theophylline concentration, moisture content, light mineral oil concentration, and different types of oils.

In Vitro Studies

The dissolution studies for the formulations were performed using U.S.P. Apparatus I, 50 rpm, in 900 mL 0.1 *N* HCl medium (pH 1.2) at 37°C.

The samples were analyzed, after appropriate dilution, using UV spectrophotometer at 273 nm.

[1] G.D. Searle & Co., 5200 Old Orchard Road, Skokie, Illinois 60077.
[2] To whom correspondence should be addressed.
[3] College of Pharmacy and Allied Health Professions, St. John's University, Jamaica, New York 11432.

0724-8741/93/0900-1321$07.00/0

Table I. Percentage of Each Ingredient per Tablet

Ingredient	Percentage
Agar	2
Light mineral oil	19
Water[a]	4
Theophylline	75

[a] Forty percent of the water added in the formulation evaporated during drying.

In Vivo Scintigraphic Studies

The scintigraphic studies using a GE maxicamera were performed at the University of Kentucky, School of Pharmacy. The floating tablets were prepared using acetaminophen as the active ingredient to obtain approval by the Institutional Review Board at the University of Kentucky. They were labeled with indium 111. Heavy, nondisintegrating, nonfloating tablets with a density >1 were labeled with technetium 99m and were prepared by the School of Pharmacy, University of Kentucky, by a proprietary method. Hence, the tablets used for scintigraphy were not the same as the tablets used for *in vivo* absorption studies.

The gastric residence times were monitored after administering both the floating and the nonfloating labeled tablets with 240 mL water to three normal, healthy human volunteers after a 12-hr fast.

The gastric residence times were also monitored under fed conditions. The volunteers were given a meal comprising a cheeseburger, a small portion of french fries, and an apple pie.

Both the floating and the nonfloating tablets were administered immediately after the meal with 240 mL water. The tablets were monitored by placing the volunteers in a sitting position in front of a gamma-camera. The position of the tablets was determined with reference to an external marker. The activity around the tablet was recorded in 1-min intervals and stored on magnetic tape. Each volunteer was scanned for a period of 30 min and then allowed to rest for the next 30 min, after which the scanning cycle was repeated. The tablets were monitored until they left the stomach.

In Vivo Bioavailability Studies

Randomized, two-way bioavailability studies were performed comparing the 300-mg floating theophylline C.R. tablets with 300-mg Theo-Dur tablets (Key Pharmaceuticals) in six healthy human volunteers consisting of five males and one female. Two of the volunteers were smokers. The studies were done under both fasting and fed conditions. In the fasting study, volunteers fasted overnight and were dosed at 8:00 AM with 300 mL of water. The volunteers did not drink any coffee, tea, or cola drinks or eat chocolate or any caffeine-containing products during the study. Food was allowed 4 hr after dosing. Saliva samples were collected in glass jars, after chewing paraffin wax for 2 min, at 0, 1, 2, 3, 4, 6, 8, 12, 15, 24, and 36 hr. The saliva samples were stored at −15°C before analysis.

In the fed study, after an overnight fast, volunteers were dosed immediately after a breakfast consisting of 2 pieces of toast (buttered), 3 sausage links, 2 scrambled eggs, 1 hash brown pattie, and 7 oz of orange juice.

HPLC Analysis of Theophylline in Saliva

Reagents. Reagents were as follows.

(i) Theophylline stock standard: 99.82 mg anhydrous theophylline was dissolved in 1000 mL distilled water.

(ii) Working standards: Std 1, 250 μL stock + 2.250 mL saliva; Std 2, 1:2, 250 μL stock + 2.250 mL saliva; Std 2, 1:4, 250 μL stock + 2.250 mL saliva.

(iii) Internal standard: 12.24 mg of 8-hydroxy ethyl theophylline was dissolved in acetate buffer (0.01 *M*, pH 5.5) and the volume was made up to 1000 mL with acetate buffer.

(iv) Extraction solvent: methanol:chloroform (5:95).

(v) Mobile phase: 6% acetonitrile, filtered, degassed, and prepared fresh.

Procedure. Two hundred fifty microliters of sample or working standard and 250 μL of internal standard were pipetted into four 12 × 75-mm glass tubes and vortexed for 2 sec. Three milliliters of extraction solvent was added to each tube and vortexed for 30 sec. The tubes were centrifuged at 2000 rpm for 5 min and the supernatant was aspirated and discarded from all tubes. The solvent was decanted from the four tubes into one 16 × 20-mm glass tube and evaporated at 50°C in a vacuum over.

HPLC Conditions. HPLC conditions were as follows: column—C18, 3 μm, 5-cm i.d., Altex; mobile phase—6% acetonitrile in distilled water; flow rate—3 mL/min; wavelength—254 mm; pressure—22 psi; injection—auto injector, with 5-sec flush time and 20-μL sample volume.

RESULTS AND DISCUSSIONS

Mechanism of Buoyancy

In the formulation shown in Table I, the amounts of agar, light mineral oil, and water are the optimum amounts needed for the given amount of theophylline to achieve a floating tablet. The amount of agar needed to form the floating tablet is remarkably low (2%).

Table II shows the effect of the evaporating moisture (25°C) on the density of the tablet. This is a unique characteristic of this formulation. The water content after drying also is very low and should not pose stability concerns. The light mineral is uniformly distributed throughout the tablet

Table II. Moisture Content and Effect on Density at 25°C

	Time (hr)							
	0	1	2	3	5	8	12	24
% moisture content (per tablet)	73	47	26	17	12	10	8	4
density	1.18	1.00	0.86	0.80	0.76	0.75	0.70	0.67

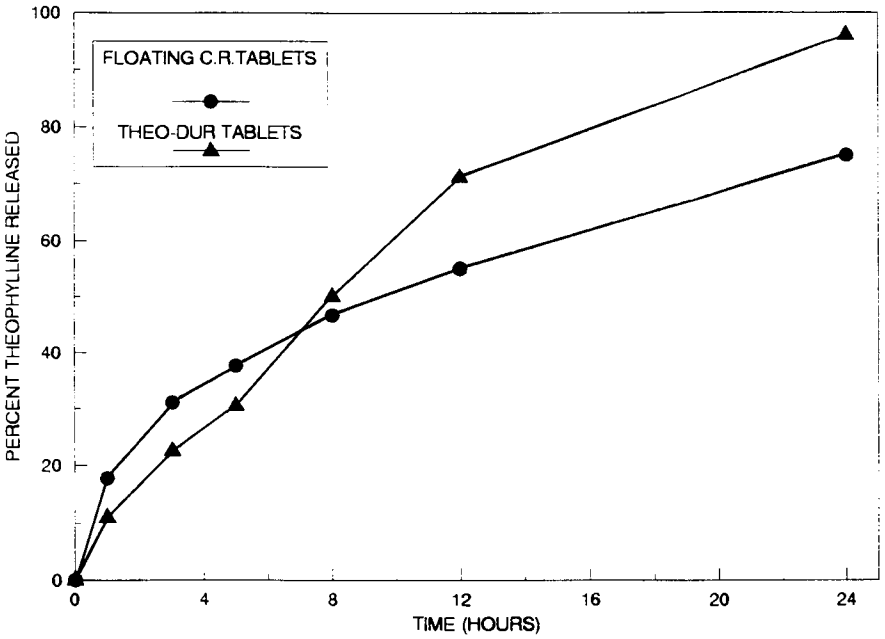

Fig. 1. Comparative dissolution profile of 300-mg floating theophylline C.R. tablets and 300-mg Theo-dur tablets using U.S.P. Apparatus I at 50 rpm and 900 mL 0.1 *N* HCl (pH 1.2).

and is essential for the floating property of the tablet when relatively high amounts of drug are used. Table II shows an initial tablet density of 1.18. After 2 hr of drying at room temperature, the density drops to 0.86 and the tablets start to float. After 24 hr, the moisture content has reached equilibrium (4%) and tablet density is 0.67.

Although the density of the tablets after 2 hr of drying is less than 1, the tablets float only for a short time when placed in gastric fluid, since the lost water is easily imbibed. After 24 hr of drying, the tablets float continuously. The water that evaporates gets replaced by air, which is entrapped in the agar gel network.

Although the mechanism is not clear, the light mineral oil in the formulation may prevent the air entrapped in the gel matrix from escaping when placed in gastric fluid due to its inherent hydrophobicity. The air trapped in the tablet gel network reduces the density and is a large factor in the buoyancy of the tablet.

The gel network also binds the tablet together and gives it the desired hardness and friability properties. In addition, the agar gel network controls the drug release characteristics. Thus, the ingredients in this simple and unique formulation are important in the formation of a floating, controlled-release drug delivery system.

In Vitro Dissolution Studies

Various formulation parameters were modified to study their effect on the dissolution of theophylline. Changes in agar concentration (from 1 to 6%), oil concentration, and oil type (olive oil, peanut oil, cottonseed oil, castor oil) did not have any appreciable effect on the release of theophylline. However, the floating and hardness properties of the tablets were modified.

The comparative dissolution profiles of the floating 300-mg theophylline C.R. 300 tablet and 300-mg Theo-dur tablet are shown in Fig. 1. The release rate of Theo-dur is slower initially but increases later, whereas the floating tablet has a comparatively faster initial release rate, with a slower rate after 8 hr. Theo-dur releases theophylline mainly through an erosion process, while the floating tablet releases theophylline through a diffusion process with a square root of time relationship proposed by Higuchi. The combination of slow release and flotation properties was therefore achieved *in vitro*.

In Vivo Scintigraphic Studies

The scintigraphic studies were done both under fasted and fed conditions using the floating tablet and a nonfloating control tablet with a weight and density approximately twice those of the floating tablet. Both dosage forms were nondisintegrating units.

The initial location of the tablets after simultaneous administration showed that, in all but one case, the floating tablet initially landed high in the stomach and the nonfloating tablet landed low in the stomach, near the pylorus.

Under fasting conditions, for example, the floating tablet remained floating in the upper part of the stomach 90 min

Table III. Gastric Retention Time of Floating and Nonfloating Tablets in Healthy Male Volunteers Under Fasting and Nonfasting Conditions

	Fasting (min)		Nonfasting (min)	
Volunteer	Nonfloating	Floating	Nonfloating	Floating
GAG	19	20	390	357
SRD	162	163	>480	>480
SMB	>237	100	—	—
AFP	—	—	487	450

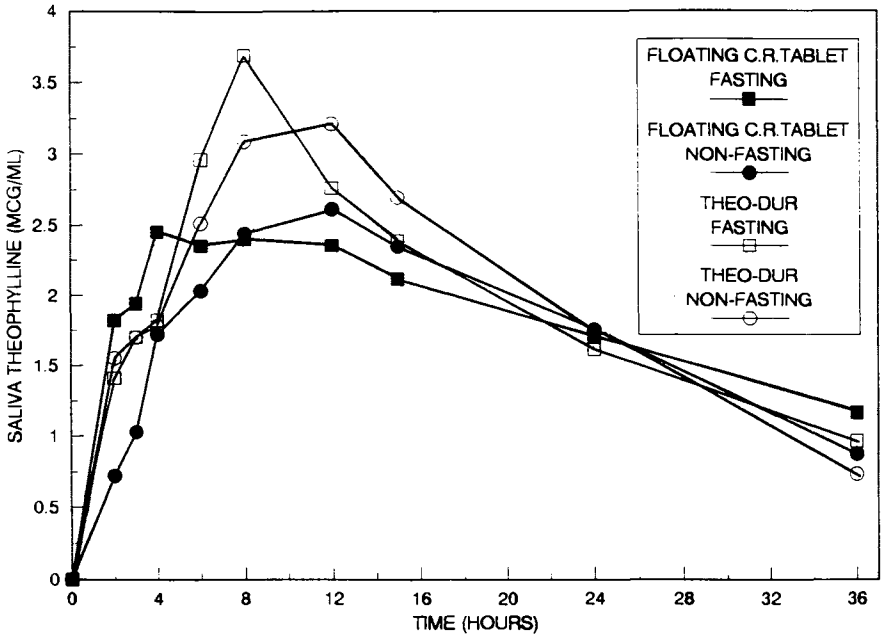

Fig. 2. Average theophylline saliva levels of 300-mg floating theophylline C.R. tablets and Theo-dur under fasting and nonfasting conditions, in six healthy human volunteers.

after dosing and, after about 161 min, settled near the pylorus and was subsequently ejected from the stomach. Hence the onset of the migrating myoelectric complex starts the descent of the floating tablet. Under fed conditions, the floating tablet remains floating for 270 min after dosing and, 335 min into the study, settles near the pylorus. However, the ejection from the stomach is delayed until between 392 and 452 min, unlike the fasting condition.

The gastric retention times for both the floating and the nonfloating tablets under fasted and fed conditions are given in Table III. There does not appear to be a significant difference between the gastric retention time of the floating and that of the nonfloating tablet. The emptying depends on the onset of the migrating myoelectric complex. Gastric retention time was significantly increased under fed conditions, since the onset of migrating myoelectric complex is delayed. It was not possible to determine the floating characteristics of the dosage form after it left the stomach due to leaching of the radiolabeled markers.

In Vivo Bioavailability Studies

Although serum is generally preferred for the determination of drug concentration in bioavailability studies, saliva, if obtained frequently and in sufficient quantities, can reliably provide the rate and extent of absorption of many drugs, including theophylline (25).

Figure 2 shows the mean saliva theophylline levels of the floating 300-mg theophylline C.R. tablet and Theo-dur in the six volunteers under both fasting and nonfasting conditions.

Table IV shows the comparison of AUC, C_{max}, and T_{max} of the volunteers under both fasting and nonfasting conditions. ANOVA results show no significant differences be-

Table IV. Comparison of AUC, C_{max}, and T_{max} of 300-mg Floating Theophylline C.R. Tablet and 300-mg Theo-dur Tablet Under Fasting and Nonfasting Conditions

	Fasting						Nonfasting					
	Floating tablet			Theo-dur			Floating tablet			Theo-dur		
Subject	AUC	C_{max}	T_{max}	AUC	C_{max}	T_{max}	AUC	C_{max}	T_{max}	AUC	C_{max}	T_{max}
SB	113.61	4.03	12	57.71	3.90	8	189.28	3.22	8	108.75	3.90	8
SD	132.85	2.45	24	103.46	3.74	8	87.90	3.00	24	90.18	3.55	12
SG	181.66	2.91	15	165.21	5.04	8	81.20	4.05	12	98.83	3.36	12
JB	118.91	3.91	6	110.85	4.77	8	77.51	3.25	15	83.71	4.07	12
PI	29.14	2.82	4	31.04	1.48	8	41.40	1.85	8	51.73	1.94	6
SA	58.42	2.12	4	84.89	3.23	8	54.68	3.69	8	64.10	3.32	8
Mean	105.77	3.04	10.83	92.19	3.69	8.0	88.66	3.18	12.50	82.05	3.36	9.67
sd	54.48	0.77	7.86	46.45	1.28	0.0	52.33	0.75	6.32	20.79	0.75	2.66
cv%	51.51	25.33	72.58	50.39	34.69	0.0	59.02	23.58	50.56	25.34	22.32	27.51

tween the two formulations for all three parameters, under fasting and nonfasting conditions.

The coefficients of variation for AUC and C_{max} for the floating tablet remain similar under fasting and nonfasting conditions. From Fig. 2, it is apparent that food does not dramatically affect the saliva level resulting from the floating tablet, although the rate of release is slower, compared to Theo-dur. The floating tablet maintains constant theophylline levels of about 2 μg/mL for 24 hr. Since the *in vitro* release profile indicated a square root of time release characteristic, the dynamics of drug release *in vivo* appear to differ from that observed *in vitro*.

In conclusion, a unique floating sustained-release dosage form of theophylline was formulated using a simple, inexpensive gel matrix. *In vitro* dissolution studies show that the molded tablets release the drug in a reproducible manner via a diffusion mechanism. The tablets remain intact and float throughout the dissolution process. *In vivo* scintigraphic studies, using a prototype formulation containing acetaminophen, suggested that the tablet indeed floats in the stomach. However, gastric retention time was not different from that of a heavy noneroding control tablet.

The floating theophylline tablet and a commercial product were compared in fasted and fed volunteers. Although no statistically significant differences were observed between formulations, the floating tablet showed a more gradual release of the drug. The theophylline saliva profiles for the fed and fasted state were similar.

Acknowledgments

We would like to thank George Digenis and Alan Parr for conducting the scintigraphic studies at the University of Kentucky; Forest Laboratories, New York; and the State of New York for their financial support.

U.S. patent 4,814,179 (March 21, 1989) for this delivery system has been assigned to St. John's University and licensed to Forest Laboratories, New York.

REFERENCES

1. W. I. Higuchi, F. H. Ho, Norman, and H. P. Merkle. Design of oral drug delivery systems past, present and future. *Drug Dev. Ind. Pharm.* 9(7):1227–1239 (1983).
2. A. F. Hofman, J. H. Pressman, C. F. Code, and Witztum. Controlled entry of orally administered drugs: Physiological considerations. *Drug Dev. Ind. Pharm.* 9(7):1077–1109 (1983).
3. D. W. Davis. U.S. patent 3,418,999 (Dec. 31, 1968).
4. A. S. Michaels. U.S. patent 3,786,813 (Jan. 22, 1974).
5. A. S. Michaels, J. D. Bashwa, and A. Zaffaroni. U.S. patent 3,901,232 (Aug. 26, 1975).
6. R. M. Harrigan. U.S. patent 4,055,178 (Oct. 24, 1977).
7. S. Watanabe, M. Kayano, Y. Ishimo, and K. Miyos. U.S. patent 3,976,764 (Aug. 24, 1976).
8. H. Umezawa. U.S. patent 4,101,650 (July 18, 1978).
9. P. R. Sheth and J. L. Tossounian. U.S. patent 4,167,558 (Sept. 11, 1979).
10. P. R. Sheth and J. L. Tossounian. U.S. patent 4,140,755 (Feb. 20, 1979).
11. P. R. Sheth and J. L. Tossounian. U.S. patent 4,126,672 (Nov. 21, 1978).
12. S. S. Davis, A. F. Stockwell, and S. E. Walker. The design and evaluation of controlled release systems for the gastrointestinal tract. *J. Control. Release* 2:27–38 (1985).
13. S. Desai. *A Novel Floating Controlled Release Drug Delivery System: In-Vitro–in-Vivo Characterization,* Doctoral thesis, St. John's University, Jamaica, NY, 1986.
14. A. Rednick and S. Tucker. U.S. patent 3,507,952 (Apr. 21, 1970).
15. H. Bechgaard and K. Ladefoged. Distribution of pellets in the gastrointestinal tract. The influence on transit time exerted by the density or diameter of pellets. *J. Pharm. Pharmacol.* 30:690–692 (1978).
16. J. Sjogren and C. Bogentoft. How useful is enteric coating to improve drug delivery? In H. Bundgaard, A. B. Hansen, and H. Kofod (eds.), *Optimization of Drug Delivery,* Alfred Benzon Symposium 17, Munksgaard, Copenhagen, 1982.
17. K. Park and J. R. Robinson. Bioadhesive polymers as platforms for oral-controlled drug delivery: Method to study bioadhesion. *Int. J. Pharm.* 19:107–127 (1984).
18. H. S. Ching, H. Park, P. Kelley, and J. R. Robinson. Bioadhesive polymers as platforms for oral controlled drug delivery II: Synthesis and evaluation of some swelling, water-insoluble bioadhesive polymers. *J. Pharm. Sci.* 74(7):399–405 (1985).
19. M. A. Longer, H. S. Ching, and J. R. Robinson. Bioadhesive polymers as platforms for oral controlled drug delivery III: Oral delivery of chlorothiazide using a bioadhesive polymer. *J. Pharm. Sci.* 74(4):406–411 (1985).
20. J. Urquahart and F. Thewues. U.S. patent 4,434,153 (Feb. 28, 1984).
21. R. Groning and G. Heun. Oral dosage forms with controlled gastrointestinal transit. *Drug Dev. Ind. Pharm.* 10(4):527–539 (1984).
22. R. Cargill, L. J. Coldwell, K. Engle, J. A. Fix, P. A. Porter, and C. R. Gardner. Controlled gastric emptying. 1. Effects of physical properties on gastric residence times of nondisintegrating geometric shapes in beagle dogs. *Pharm Res.* 5(8):533–536 (1988).
23. S. S. Davis, J. G. Hardy, M. J. Taylor, D. R. Whalley, and C. G. Wilson. The effect of food on the gastrointestinal transit of pellets and an osmotic device (Osmet). *Int. J. Pharm.* 21:331–340 (1984).
24. S. O'Reilly, C. G. Wilson, and J. G. Hardy. The influence of food on the gastric emptying of multiparticulate dosage forms. *Int. J. Pharm.* 34:213–216 (1987).
25. A. P. Sips, P. M. Edelbrook, S. Kulstadt, *et al.* Food does not effect in bioavailability of theophylline from theolin Retard. *Eur. J. Clin. Pharmacol.* 26:405–407 (1984).