Dissolution Studies of Some Sustained-Release Theophylline Dosage Forms

KEITH J. SIMONS *x, F. ESTELLE R. SIMONS ‡, KIM D. PLETT *, and CHARLES SCERBO *

Received February 8, 1983, from the **Faculty of Pharmacy, and ‡Department of Pediatrics, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, R3T 2N2 Canada.* Accepted for publication September 19, 1983.

Abstract □ Dissolution studies were carried out with the USP rotating-basket apparatus in both simulated gastric and intestinal fluids. Four different brands of sustained-release theophylline products of different strengths (nine formulations) were studied. The percentage of the dose released in 1 h in gastric fluid ranged from (mean ± *SD*) 6.6 ± 0.9 to 50.1 ± 3.8%. By 6 h, the percentage of the dose released ranged from 10.8 ± 1.8 to 86.5 ± 5.2%. Similar formulations of different strengths released significantly different fractions of their dose at respective sampling times. In intestinal fluid, some formulations released 100% of their dose within 3–4 h, behaving more like enteric-coated preparations. One dosage form appeared to release drug by an apparent zero-order rate. From one brand of theophylline (two strengths), only 48.1 ± 5.6 and 29.9 ± 4.1% of label strength, respectively, dissolved in 25 h in intestinal fluid. Some of these *in vitro* results were rank-correlated to previously reported bioavailability and pharmacokinetic studies.

Keyphrases □ Sustained-release formulations—dissolution, USP rotating-basket apparatus, theophylline □ Theophylline—dissolution, sustained-release formulations, USP rotating-basket apparatus, □ Bioavailability—theophylline, sustained-release formulations, USP rotating-basket apparatus

The importance of using sustained-release theophylline dosage forms for the treatment of respiratory diseases in adults (1–4) and children (5–9) is well established. The absorption characteristics of many sustained-release theophylline products have been defined by several investigators (10, 11), and correlations with *in vitro* dissolution studies have been described (12, 13). However, disintegration and dissolution tests are still the compendial standards of content release and uniformity (14), and only minimal data for theophylline sustained-release products are available. Therefore, dissolution studies were performed on several sustained-release dosage forms, some of which have already been evaluated for bioavailability and pharmacokinetic characteristics (10, 15).

EXPERIMENTAL SECTION

Dosage Forms—Nine commercially available sustained-release theophylline dosage forms were evaluated. Products A[1], B[1], C[2], and D[2] were capsule forms, and products E[3], F[3], G[3], H[4], and J[4] were tablets.

Dissolution Apparatus—The USP rotating-basket dissolution apparatus (14) was used in all experiments. Studies were carried out in simulated gastric or intestinal fluids. Simulated gastric fluid was prepared by dissolving 2 g of NaCl[5] and 3.2 g of pepsin[5] in 7 mL of concentrated HCl[6] and sufficient water to make 1000 mL; the pH of this solution was 1.2. Simulated intestinal fluid was prepared by dissolving 6.8 g of KaH_2PO_4[5] in 250 mL of water. To this were added 190 mL of 0.2 M NaOH[5] and 400 mL of water. The solution was thoroughly mixed, 10 g of pancreatin[5] was added, and the pH was adjusted to 7.5 ± 0.1 with 0.2 M NaOH before the volume was made up to 1000 mL with water.

Procedure—In each study, six dosage forms were tested simultaneously, with one dosage form in each position of the dissolution apparatus. The dosage forms were not added until 900 mL of the solution had reached 37°C in a water bath. This temperature was maintained throughout the study. The baskets were rotated at 100 rpm. All dosage forms were tested in both simulated gastric and intestinal fluids under sink conditions. In simulated gastric fluid studies, 1-mL samples were removed at 0.5- or 1-h intervals for up to 6 h. In simulated intestinal fluid, the sampling times were adjusted so that the rate of release of theophylline from each different dosage form could be optimally evaluated. For dosage forms A, B, E, F, and G, 3-mL samples were removed at 1-h intervals for 12 h and at 25 h. For dosage forms C and D, 3-mL samples were removed every 15 min for a total of 3 h. For dosage forms H and J, 3-mL samples were removed at 10, 20, 30, 40, 50, 60, 75, 90, 105, 120, and 240 min. Samples were not filtered, as no particles were observed, and the volume of sample removed was replaced by fresh dissolution medium at 37°C. All samples were refrigerated until the theophylline content was determined by a spectrophotometric or HPLC procedure (15).

Theophylline Quantitation—Stock solutions of theophylline were prepared in simulated gastric or intestinal fluid at concentrations of 5, 10, 15, 20, and 25 μg/mL. The theophylline content in gastric fluid samples was determined by diluting the samples 2–20 times with gastric fluid and measuring the absorbance at 271 nm[7]. Appropriately diluted simulated gastric fluid samples were used as a reference.

In simulated intestinal fluid samples, the theophylline content had to be extracted before the absorbance could be determined spectrophotometrically. A 0.5-mL aliquot of 2.5 M acetate[5] buffer (pH 6.4) and 6 mL of chloroform–isopropyl alcohol[5] (20:1) were added to 2-mL samples of intestinal fluid.

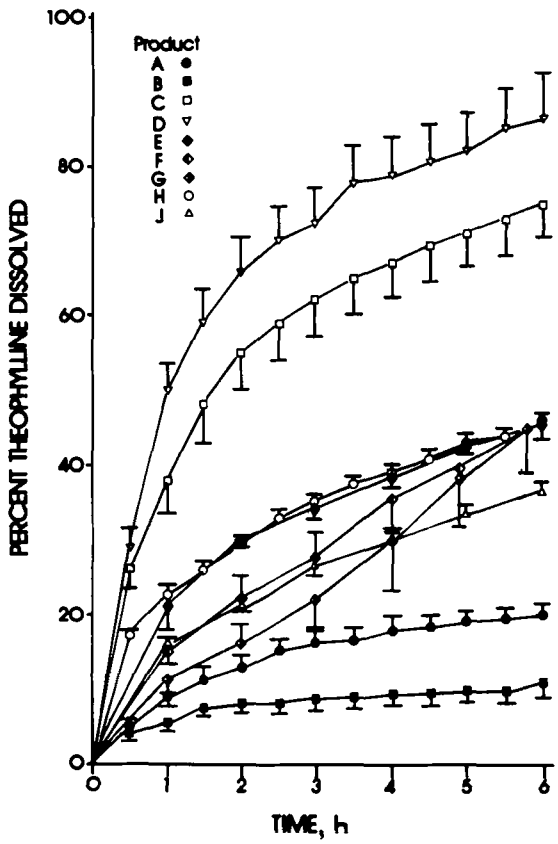

Figure 1—*Percent theophylline dissolved in simulated gastric fluid* versus *time. Results are mean + or − SD; data are from six dosage forms.*

[1] Acrolate 65- and 130-mg capsules; Fleming & Co., Fenton, Mo.
[2] Slo-phyllin 125- and 250-mg Gyrocaps; Dooner Labs, Ft. Washington, Pa.
[3] Theo-Dur 100-, 200-, and 300-mg S-A tablets; Astra Pharmaceuticals, Mississauga, Ontario, Canada L4X 1M4 (Key Pharmaceuticals, Inc., Miami, Fla.)
[4] Theo-Lair 250- and 500-mg SR tablets; Riker Labs., Northridge, Calif.
[5] Fisher Scientific Co., Fair Lawn, N.J.
[6] J. T. Baker Chemical Co., Phillipsburg, N.J.
[7] Acta III Spectrophotometer; Beckman Instruments, Inc., Palo Alto, Calif.

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Table I—Percent Theophylline Dissolved in Simulated Gastric Fluid at Various Times

Product	Theophylline Dissolved, %[a]											
	0.5 h	1.0 h	1.5 h	2.0 h	2.5 h	3.0 h	3.5 h	4.0 h	4.5 h	5.0 h	5.5 h	6.0 h
A	4.1 (0.9)	9.1 (1.7)	11.4 (1.6)	13.7 (1.8)	15.0 (1.8)	15.9 (1.8)	16.6 (1.7)	17.7 (1.9)	18.3 (1.5)	19.0 (1.6)	19.5 (1.5)	20.3 (1.5)
B	6.1 (0.8)	6.6 (0.9)	7.3 (0.8)	7.7 (1.1)	8.1 (1.3)	8.6 (1.2)	9.0 (1.3)	9.2 (1.3)	9.5 (1.6)	9.8 (1.5)	10.2 (1.7)	10.8 (1.8)
C	6.1 (2.8)	38.0 (4.6)	48.2 (5.0)	55.1 (4.9)	58.8 (5.0)	61.9 (5.2)	65.0 (4.9)	67.3 (4.8)	69.5 (4.9)	71.2 (4.7)	73.0 (5.1)	75.0 (4.5)
D	9.1 (2.4)	50.1 (3.8)	58.7 (4.8)	66.0 (4.4)	69.8 (4.8)	72.3 (4.3)	77.3 (5.6)	78.9 (5.0)	80.5 (5.2)	82.2 (4.9)	84.9 (5.4)	86.5 (5.2)
E	—[b]	21.2 (3.2)	—	29.6 (0.9)	—	34.0 (1.2)	—	39.4 (1.7)	—	43.5 (1.5)	—	46.1 (2.5)
F	—	14.8 (1.4)	—	21.8 (2.8)	—	26.8 (4.4)	—	35.3 (5.1)	—	39.4 (7.1)	—	45.6 (6.5)
G	—	11.2 (1.9)	—	15.8 (2.5)	—	22.4 (4.4)	—	30.6 (7.0)	—	38.2 (7.0)	—	45.0 (8.3)
H	7.3 (0.5)	22.8 (1.1)	26.2 (0.9)	29.4 (1.1)	33.2 (0.9)	35.3 (0.7)	37.3 (1.0)	38.9 (0.9)	41.1 (1.0)	42.8 (1.3)	44.0 (0.8)	45.9 (0.7)
J	—	15.8 (0.5)	—	21.2 (0.6)	—	26.3 (1.0)	—	30.1 (1.1)	—	33.7 (1.2)	—	36.6 (1.2)

[a] Mean values; *SD* in parentheses. [b] — Samples not collected.

Samples were extracted by shaking on a reciprocating shaker for 5 min and then centrifuging for 5 min. The upper aqueous phase was removed by aspiration, and 5 mL of the organic layer was extracted with 5 mL of 0.1 M NaOH[5] by shaking for 5 min and centrifuging for 10 min. The upper aqueous phase was transferred directly to a spectrophotometric cuvette, and the absorbance was measured at 271 nm[7]. Simulated intestinal fluid samples containing no drug and extracted by the same procedure were used as references.

Calibration curves were constructed by plotting absorbance *versus* theophylline concentration with simulated gastric and intestinal fluid stock solutions. Theophylline concentrations from studies of dosage forms E, F, and G were determined by an HPLC procedure described previously (15). Analytical procedures were compared, and results from both tests were identical.

RESULTS AND DISCUSSION

It is not usually possible to differentiate between structurally related compounds, such as decomposition products or metabolites, by spectrophotometric methods of analysis. However, for dissolution studies of a dosage form containing a single chemical entity, this spectrophotometric procedure had excellent sensitivity and specificity. Since the results from these spectrophotometric assays were identical to those obtained by HPLC analysis, it was assumed that no detectable decomposition occurred during these dissolution studies. In the gastric fluid medium, calibration curves were linear over the concentration range of 0–50 μg/mL, and through a 10-week period they had a maximum coefficient of variation of 9.6%. Nevertheless, calibration curves were determined daily for each set of analyses. Similar results were obtained for the intestinal fluid samples, with a maximum coefficient of variation of 10.6% over a 10-week period. The results from the HPLC procedure had a maximum coefficient of variation of 3.6%. In all individual curves, correlation coefficients were always >0.995.

The maximum dose of theophylline evaluated in these studies was 300 mg, and the volume of sample removed for analysis was replaced by fresh dissolution medium at 37°C, so that the 900-mL initial volume was always maintained. The solubility of theophylline at 25°C is 1 g/120 mL in distilled water (16), so that if the total 300-mg dose dissolved during the study, only 4% of the total solubility of theophylline would be achieved. Therefore, sink conditions were maintained in all studies (17).

The absolute bioavailability of orally administered theophylline in aqueous solutions was calculated to be 100%; absorption was rapid, with peak serum concentrations occurring at 1 h after dose administration (18). The rate and extent of theophylline absorption after administration of sustained-release products would, therefore, be controlled by the rate and extent of drug release from the dosage form. Also, since these dosage forms may contain larger doses of drug than conventional preparations, the rate and completeness of drug release from the matrix must be uniform and well controlled. Fluctuations in serum theophylline concentrations will then be minimal, and efficacy will be achieved without toxicity.

The efficacy and safety of most sustained-release theophylline dosage forms has been well documented (1–9). However, variability and incompleteness

Table II—Percent Theophylline Dissolved in Simulated Intestinal Fluid at Various Times

Product	Theophylline Dissolved, %[a]												
	1.0 h	2.0 h	3.0 h	4.0 h	5.0 h	6.0 h	7.0 h	8.0 h	9.0 h	10.0 h	11.0 h	12.0 h	25.0 h
A	3.0 (2.5)	6.4 (2.3)	11.5 (2.0)	14.2 (2.5)	18.4 (4.4)	19.5 (4.7)	21.6 (5.3)	24.4 (4.9)	26.2 (5.2)	28.8 (5.7)	32.1 (4.7)	37.1 (5.3)	48.1 (5.6)
B	7.1 (0.8)	11.2 (3.2)	14.7 (2.5)	17.8 (2.8)	19.9 (2.8)	22.3 (3.3)	22.3 (3.8)	23.5 (3.8)	23.3 (4.3)	24.7 (3.6)	24.5 (3.1)	24.0 (3.2)	29.5 (4.1)
E	29.1 (2.3)	37.2 (3.8)	43.1 (4.7)	47.2 (4.9)	52.3 (5.5)	56.0 (6.4)	61.0 (6.6)	64.5 (6.9)	67.7 (7.5)	72.0 (7.2)	75.2 (8.6)	78.4 (7.9)	95.1 (7.6)
F	14.0 (1.9)	21.8 (2.8)	26.8 (4.4)	35.3 (5.1)	39.4 (7.1)	45.6 (6.5)	50.1 (7.4)	54.5 (8.4)	58.9 (8.5)	61.6 (6.0)	62.2 (7.4)	66.6 (7.1)	87.6 (10.5)
G	11.2 (1.9) 0.25[b]	15.8 (2.5) 0.5[b]	22.4 (4.4) 0.75[b]	30.6 (7.0) 1.0[b]	38.2 (7.0) 1.25[b]	45.0 (8.3) 1.5[b]	53.9 (9.4) 1.75[b]	56.6 (9.6) 2.0[b]	68.0 (3.9) 2.25[b]	71.6 (2.0) 2.5[b]	75.9 (4.4) 2.75[b]	72.9 (10.9) 3.0[b]	89.4 (4.1)
C	18.4 (4.2)	39.4 (3.8)	50.7 (3.1)	60.2 (4.2)	70.1 (3.5)	79.4 (8.1)	87.7 (10.7)	94.9 (10.8)	95.5 (5.4)	95.5 (6.0)	94.9 (5.0)	93.9 (2.8)	
D	18.5 (3.4) 10[c]	40.0 (5.8) 20[c]	55.7 (5.8) 30[c]	65.7 (7.9) 40[c]	73.2 (5.6) 50[c]	78.5 (4.2) 60[c]	86.3 (3.6) 75[c]	90.5 (6.1) 90[c]	91.4 (3.3) 105[c]	96.4 (4.7) 120[c]	94.3 (1.8) 240[c]	95.7 (5.1)	
H	7.7 (1.8)	14.3 (3.9)	21.7 (4.7)	26.6 (5.6)	32.4 (7.2)	36.0 (7.2)	41.7 (9.3)	52.9 (14.3)	56.7 (12.7)	63.3 (13.7)	88.5 (18.5)		
J	3.3 (1.1)	8.4 (2.0)	13.5 (2.4)	18.4 (2.7)	22.0 (3.0)	24.9 (3.6)	30.6 (3.8)	38.8 (4.6)	43.6 (5.0)	48.8 (4.8)	77.0 (5.7)		

[a] Mean values; *SD* in parentheses. [b] Adjusted time intervals (h). [c] Adjusted time intervals (min).

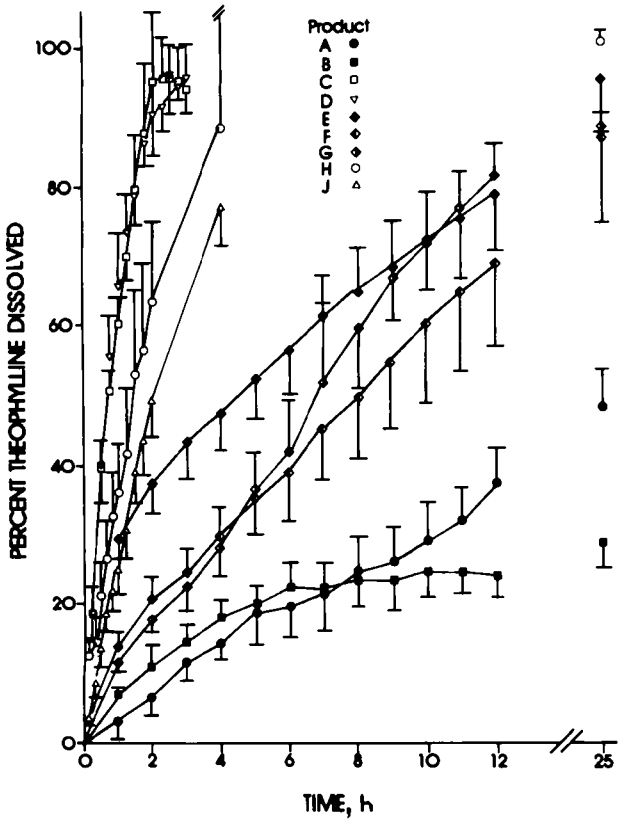

Figure 2—*Percent theophylline dissolved in simulated intestinal fluid* versus *time. Results are mean + or − SD; data are from six dosage forms.*

of theophylline release from some sustained-release preparations after single-dose administration to asthmatic patients has been demonstrated (10). Similar results have been found in the present dissolution studies with the rotating-basket dissolution apparatus (14) and by evaluating the products in both simulated gastric and intestinal fluids.

The percentages of theophylline dissolved at various times from the simulated gastric fluid studies are presented in Table I, and the percent dissolved *versus* time plot is shown in Fig. 1. The dosage forms studied released 6.6 ± 0.9 to 50.1 ± 3.8% of their drug content within 1 h in simulated gastric fluid. Although no simple correlation exists, the values obtained for the percentage of the dose released in 1 h *in vitro* from these products exhibit the same rank order as the values obtained at 1 h *in vivo* with some of these same products (10).

After the initial release of drug through the first 0.5–1.0 h, all of the products displayed some type of sustained-release characteristics (Fig. 1). However, the variability between products clearly demonstrates that these products are not readily interchangeable. Since the mean gastric residence time has been reported to be 3.61 ± 1.47 h (19), the dissolution studies in simulated gastric fluid were terminated after 6 h. At that time, the mean percentage of the dose released ranged from 10.8 ± 1.8 to 86.5 ± 5.2% (Table I).

Of greater concern is the differences in the rate of release of drug from similar preparations of different strength. Both at 3 and 6 h, products A and B, C and D, and H and J all released significantly different amounts of drug ($p \leq 0.005$). Product E released significantly more drug than F and G at 3 h ($p \leq 0.005$), but not at 6 h. Products F and G released similar amounts of drug at 3 and 6 h ($p = 0.005$). Theophylline doses are often individualized by using a combination of different strengths of the same brand of product (4). However, different strengths of the same brand cannot be arbitrarily assumed to release drug at similar rates. A more rational approach may be to adjust the dose by taking one-half of the higher strength dosage form to individualize the dosages. No significant difference was detected *in vivo* when this approach was used for product E (15). In addition, these *in vitro* studies may not reflect the *in vivo* situation. The *in vivo* results for products E and G were not significantly different (10).

Since these products were all sustained-release dosage forms, the dissolution studies in simulated intestinal fluid provide additional information. The percentage of theophylline dissolved at various times in simulated intestinal fluid is shown in Table II, and percent dissolved *versus* time plots for all dosage forms are presented in Fig. 2. The results from these studies show even greater product variability.

Almost all of the theophylline content, 93.9 ± 2.8 and 95.7 ± 5.1% from products C and D, respectively, was released in 3 h in simulated intestinal fluid. This means that the rate of release of drug from these dosage forms may be very dependent on gastric emptying time. These two products also yielded the fastest rate of drug release in simulated gastric fluid (Table I, Fig. 1) and displayed the characteristics of enteric-coated formulations rather than sustained-release dosage forms. These products also exhibited similar characteristics *in vivo* (10), as virtually 100% of the dose was absorbed in 6 h from these formulations. The results obtained from the two different strengths of this dosage form in simulated intestinal fluid were not significantly different at any time ($p = 0.005$).

Although the results from products E, F, G, and H were not significantly different in gastric fluid at 6 h ($p = 0.005$), the results obtained in intestinal fluid were different ($p \leq 0.005$). Products H and J released 88.5 ± 18.5 and 77.0 ± 5.7%, respectively, of their drug content within 4 h, whereas products E, F, and G released only 47.2 ± 4.9, 35.3 ± 5.1, and 30.6 ± 7.0%, respectively. Unfortunately, products H and J were not studied *in vivo* previously (10).

One interesting aspect of products E, F, and G is that the percent theophylline released *versus* time plots are linear after 3 h (Fig. 2). These results indicate that an approximation to zero-order release from these dosage forms was achieved. These findings have also been reported in previous studies *in vivo* (15). Despite the delayed release, virtually all of the dose was released from these products between 12 and 25 h. These results confirm the earlier *in vivo* studies (10) in which 100% of the dose appeared to be absorbed by 16 h.

Products A and B demonstrate very poor drug availability both in simulated gastric and intestinal fluids. At 25 h, only 48.1 ± 5.6 and 29.5 ± 4.1% of the dose was released, respectively, for products A and B. These results mirrored the earlier *in vivo* findings in which only 70% of the dose appeared to be absorbed by 20 h. Again, the results from the two dosage forms of different strengths were significantly different ($p \leq 0.005$).

All results were also analyzed by plotting the log percentage of the labeled dose remaining to be dissolved *versus* time. In some instances these plots were linear. However, the fact that these relationships may be simply artifacts of the systems has been thoroughly examined and discussed previously (20). Therefore, these results are not presented.

In conclusion, the *in vitro* dissolution results in this study were obtained with the rotating-basket dissolution apparatus and independent trials in both simulated gastric and intestinal fluids (14). The pattern of drug release from these sustained-release products obtained *in vitro* mirrored the *in vivo* absorption results obtained with some of these products (10, 15). These rank-order comparisons provide additional information as to the usefulness of dissolution studies as compendial methods for determining product content, uniformity, and rate and extent of drug release.

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Dosage Form Design for Improvement of Bioavailability of Levodopa VI: Formulation of Effervescent Enteric-Coated Tablets

KENJI NISHIMURA, KUNIHIRO SASAHARA ˣ, MIKIO ARAI, TAKASHI NITANAI, YOSHIHIKO IKEGAMI, TADASHI MORIOKA, and EIICHI NAKAJIMA

Received March 4, 1983, from the *Product Development Laboratories, Sankyo Company, Ltd., 1-chome, 2-58, Hiromachi, Shinagawa, Tokyo, Japan.* Accepted for publication July 1, 1983.

Abstract □ A new dosage form of levodopa, which has the characteristics of loading high concentrations of levodopa at the upper part of the intestine, has been developed to improve its bioavailability. It is shown that an effervescent tablet formulation, coated with hydroxypropyl methylcellulose phthalate (carboxybenzoyl radical content: 20–24%) as the enteric material, is suitable for the purpose of dissolution. This was confirmed from animal experiments, which showed that tablets of this composition disintegrate instantly on reaching the upper part of the intestine. This tablet was considered appropriate for the bioavailability tests described in this paper.

Keyphrases □ Levodopa—effervescent enteric-coated tablet, intestinal absorption, dissolution □ Effervescent enteric-coated tablet—levodopa, intestinal absorption, lag time of dissolution and absorption, effect of size and shape □ Film material—hydroxypropyl methylcellulose phthalate, effervescent enteric-coated tablet, levodopa

It has been shown in previous work in this series (1, 2) that the bioavailability of levodopa could be improved by loading high concentrations of the drug at the upper part of the intestine, the optimum site of absorption, and then inducing temporary saturation of levodopa decarboxylase. The present work describes the preparation of an oral solid dosage form of levodopa with improved bioavailability. The *in vitro* dissolution and *in vivo* disintegration behavior also are reported.

EXPERIMENTAL SECTION

Preparation of Effervescent Enteric-Coated Tablets of Levodopa [I]—A granular mixture of levodopa USP and carboxymethylcellulose[1] was prepared by the wet granulation method using an aqueous solution of hydroxypropyl cellulose[2] as a binder. All other diluents, effervescent agents, lubricants, and/or coloring agents were mixed with the dried granulation, and the mixture was compressed into tablets. These tablets were coated successively with hydroxypropyl methylcellulose USP (II) (5% w/w) and then with hydroxypropyl methylcellulose phthalate (III)[3] (10% w/w) in methylene dichloride–ethanol (1:1, w/w) solution[4] to obtain enteric-coated tablets. All the coating agents that were used here are accepted for drug use by the FDA.

Dissolution Tests—A modified disintegration test apparatus was used in the dissolution tests of levodopa and/or dyes (3). The frequency rate of the basket-rack assembly was set between 5 and 20 cpm. Ten-mesh stainless steel cloth was fitted over the top of the basket-rack assembly to prevent the tablet from floating out of the tube of the assembly during dissolution.

Dissolution media (900 mL) at various pH values, prepared by mixing test solutions 1 and 2 (JP IX), were heated to 37 ± 0.5°C and placed in the dissolution apparatus. One tablet was placed in the basket. The solution was drawn from the flask through the flow cell (length 5 mm) by a pump[5] and returned to the flask at a flow rate of ~25 mL/min. The differences in absorbance between λ_1 (258.5 nm) and λ_2 (281 nm) for levodopa, λ_1 (620 nm) and λ_2 (662 nm) for methylene blue, and λ_1 (600 nm) and λ_2 (522 nm) for erythromycin were measured with a dual-wavelength spectrophotometer[6] and

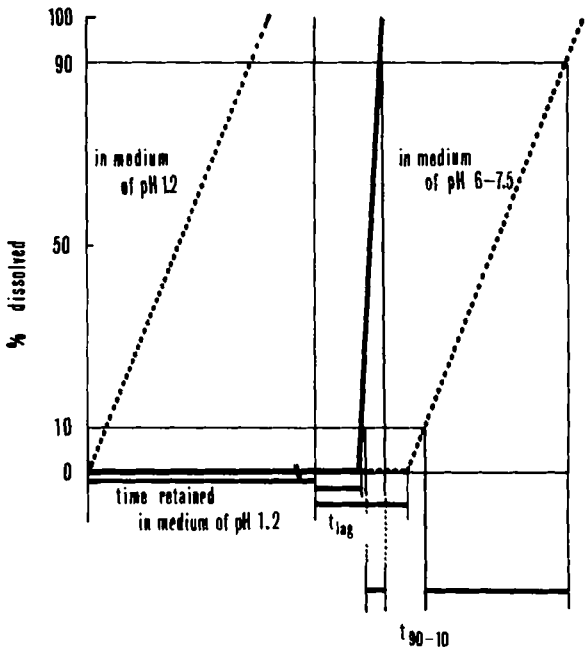

Figure 1—*Dissolution patterns of levodopa. The solid line shows the desired pattern; the dotted lines show conventional dosage forms.*

[1] Marketed as NS300, Gotoku Yakuhin, Tokyo, Japan; acid form of sodium carboxymethylcellulose USP.
[2] Nippon Soda Co., Ltd., Oiso-machi, Kanagawa, Japan; F.C.C. III P280.
[3] Shinetsu Chemicals Co., Ltd., Tokyo, Japan; Biddle Sawyer Corporation, 2, Penn-Plaza, New York, N.Y. 10121, U.S.A.; Master File No. DMF-2151.
[4] A substitute solution is acetone–ethanol solution (1:1, w/w) or acetone–isopropyl alcohol (1:1, w/w).
[5] Type MBP-100, Iwaki Co., Ltd., Japan.
[6] Hitachi-156 Spectrophotometer; Hitachi Co., Ltd., Tokyo, Japan.

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