Preliminary Evaluation of the Correlation between In Vitro Release and In Vivo Bioavailability of Two Aminophylline Slow-Release Tablets

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Abstract □ An in vitro dissolution study has been carried out with a USP rotating paddle apparatus using the stepwise pH change method. The dissolution kinetics of two different matrix-type aminophylline slow-release (SR) tablets were compared. Both aminophylline SR tablets show similar release rates and slow release behavior. The bioavailability of these two aminophylline SR tablets was also evaluated in eight healthy male Chinese volunteers and correlated with in vitro dissolution results by moment analysis. The preliminary results suggest that there is no evidence indicating that the two different matrix types of aminophylline SR tablets are not bioequivalent, and a good in vitro–in vivo correlation for these aminophylline SR tablets may therefore be presumed.

A number of sustained-release aminophylline or theophylline dosage forms for the treatment of asthma in adults and children enjoy a good market.[1–3] Investigating the absorption behavior of such sustained-release products in humans has encountered several complicated practical problems (e.g., volunteer selection, food supply, dosing intervals, blood sampling times, drug analytical methods, side effect risk, and physiological effects). From the economic, technical, and ethical perspectives of bioavailability studies, however, it is necessary to establish an in vitro test method that can predict the progress of drug release and the absorption of products in vivo.

Some sustained-release products demonstrate a relationship between the in vitro dissolution rate of the drugs and their bioavailability in humans.[4–6] Some differences in the in vitro–in vivo correlation have been recognized depending on the physicochemical properties of the drugs and their formulations. We have discovered that theophylline microcapsules exhibit sustained-release behavior in vitro, and this correlates well with their bioavailability in rats and in humans.[7–10] Recently, it was determined that a newly developed hydrophilic matrix aminophylline slow-release (SR) tablet, Anpillin, was bioequivant to the marketed wax matrix aminophylline SR tablet, Phyllocontin, in healthy Chinese volunteers.[11] The present study was undertaken to investigate the dissolution behavior of these two types of aminophylline SR tablets. It also includes data from a pilot bioequivalence study to evaluate the correlation between in vitro dissolution and in vivo bioavailability of these two different matrix-type aminophylline SR tablets.

Experimental Section

Dosage Forms—Two different matrix-type aminophylline slow-release (SR) tablets, each of which consisted of 225 mg of aminophylline, were investigated. The test tablets (Anpillin; Hui Chun Tang Pharm-Works, Taiwan, Republic of China) were hydrophilic matrix-type preparations, and reference tablets (Phyllocontin; Napp Laboratories, U.K.) were wax matrix-type preparations. Both tablet preparations are marketed in Taiwan, Republic of China.

In Vitro Dissolution Studies—The dissolution behavior of 12 aminophylline SR tablets from the lot used in the bioavailability studies was determined at 37 °C using the Apparatus 2 paddle method (50 rpm) specified in the USP XXI dissolution test. The volume of the medium was 900 mL, and the pH was changed from 1.2 to 6.8. During the first 1.5 h, the test was carried out in a pH 1.2 medium as specified in the disintegration test ⟨JP X, General Test⟩, and then the pH was increased to pH 6.8 by addition of ~14.5 g of sodium phosphate tribasic powder. The pH value was monitored by a pH meter. At the prescribed intervals, 5-mL samples were pipetted and filtered through a membrane filter (WCN type, 0.2 μm, 25-mm diameter; Whatman, U.K.). Aliquots of drug-free dissolution medium (same volume and temperature) were added immediately to the dissolution vessel to keep the volume of the dissolution medium in the container constant during the test. The amount of the drug dissolved was determined spectrophotometrically at 271 nm and calculated from the calibration curve ($r = 0.9999$) of a theophylline standard solution (2–12 μg/mL).

In Vivo Bioavailability Studies—The bioavailability study of aminophylline SR test and reference tablets in eight healthy male Chinese volunteers was performed using a randomized, two-way crossover and single-dose study design. Volunteers were required to fast for at least 12 h before and for 4 h after administration of the separate tablets. After an overnight fast, each volunteer received one tablet together with 150 mL of water. Blood samples were collected from a catheter in a forearm vein at prescribed intervals. The centrifuged serum was used to determine the theophylline concentration using an FPIA kit method (Abbott Laboratory, IL).[12] The sensitivity of the assay was 0.5 μg/mL, and the coefficient of variation (CV) of the assay in our laboratory was <5%. The detailed schedule was described in a previous study.[11] A 1-week washout period was allowed between administration of each tablet.

Data Analysis—Moment analysis was used to describe the time courses of dissolution and absorption. The mean in vitro dissolution time (MDT), describing the first moment of the dissolution rate–time curve, is defined as follows:[13,14]

$$\mathrm{MDT} = \int_0^\infty t(\mathrm{d}m/\mathrm{d}t)\mathrm{d}t \Big/ \int_0^\infty (\mathrm{d}m/\mathrm{d}t)\mathrm{d}t \qquad (1)$$

where $\mathrm{d}m/\mathrm{d}t$ is the dissolution rate at time t.

The mean residence time in vivo (MRT) of the serum concentration–time profile is calculated in a similar manner:[13,14]

$$\mathrm{MRT} = \int_0^\infty tC_p\mathrm{d}t \Big/ \int_0^\infty C_p\mathrm{d}t \qquad (2)$$

where C_p is the serum concentration at time t.

The pharmacokinetic parameters after single oral administration of these two types of aminophylline SR tablets were determined, using a Estrip program to obtain initial estimates followed by a

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MULTI program,[15,16] according to a one-compartment model with first-order absorption.[17]

Statistical Analysis—The pharmacokinetic parameters of both formulations were compared statistically by an analysis of variance (ANOVA) test. A p value of <0.05 was considered statistically significant. Results are expressed as the mean ± standard deviation (SD).

Results and Discussion

The mean percentage of theophylline released from 12 dosage units of aminophylline SR test and reference tablets (Tables I and II), sampled at various times in the dissolution medium by using the stepwise pH change method to simulate pH variation in the GI tract, versus time (h) is shown in Figure 1. Both dissolution profiles exhibited slow-release behavior and a similar release profile. The data (Tables I and II) also showed less product variability, with small coefficients of variation (CV). However, these curves were significantly different at several sampling times (e.g., 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5, 12.0, and 15.0 h, $p < 0.05$). This indicates that the release rate of the aminophylline SR test tablets was slower than that of the reference tablets. The correlation of MDT for aminophylline SR test and reference tablets is shown in Figure 2. A linear relationship ($y = 0.8651x + 0.1734$, $r = 0.9959$, $n = 5$) was obtained. This indicates that release rate and release amount from both products were nearly equal. We also found no statistically significant difference between the MDT values of each group. This suggests that the dissolution behavior was similar.

The release rate of these two different matrix-type aminophylline SR products may be fitted to the following equation:[18,19]

$$\frac{M_t}{M_\infty} = Kt^n \tag{3}$$

where M_t/M_∞ is the fraction of drug released at the release time t, K is a constant incorporating structural and geometric characteristics of the controlled-release dosage form, and n is constant belonging to the mechanism of drug release. The value of n was obtained by log–log plots of the results. When $n = 1$ belonged to Case II transport, zero-order release rate kinetics are indicated; $n = 0.5$ corresponded to Fickian diffusion controlled-release kinetics; and $0.5 < n < 1.0$ corresponded to non-Fickian transport.

The mean values of n for aminophylline SR test and reference tablets in this study are 0.647 ± 0.073 ($r = 0.9903$) and 0.664 ± 0.043 ($r = 0.9910$), respectively. The mean values of K for aminophylline SR test and reference tablets are 2.663 ± 0.102 and 2.691 ± 0.146 h^{-n}, respectively. The value is within the range $0.5 < n < 1.0$. This indicates that the release mechanisms of both aminophylline SR tablets belong to non-Fickian transport, regardless of matrix type. The relax-

Table I—Percent of Aminophylline Dissolved from Twelve Aminophylline Slow-Release Reference Tablets

Sampling Interval, h	Aminophylline, %												Mean, %	SD[a]	CV, %[b]
	1	2	3	4	5	6	7	8	9	10	11	12			
0.5	9.90	8.54	8.29	7.90	7.70	7.09	9.47	9.69	8.97	9.88	8.93	8.65	8.75	0.90	10.29
1.0	14.12	13.43	12.74	12.01	11.49	11.91	14.21	14.31	11.29	13.22	11.67	12.38	12.73	1.11	8.72
1.5	17.19	17.63	16.94	15.62	15.66	16.93	16.39	16.68	17.39	17.38	16.66	17.01	16.79	0.64	3.81
2.0	24.62	28.13	23.86	23.06	23.69	24.36	23.41	22.38	23.16	24.26	28.31	27.02	24.69	2.00	8.10
3.0	35.36	40.83	31.98	36.11	32.47	33.51	33.78	36.40	38.38	32.38	33.59	36.10	35.07	2.66	7.59
4.5	45.79	55.20	43.29	46.48	42.19	43.42	47.23	48.93	43.48	43.42	46.38	50.79	46.38	3.79	8.17
6.0	54.72	64.98	52.59	54.16	50.97	51.60	55.78	53.19	52.87	53.19	56.78	55.67	54.71	3.67	6.71
7.5	62.43	70.66	60.85	61.78	59.69	58.49	63.66	62.19	59.36	60.71	58.69	59.49	61.50	3.30	5.37
9.0	70.08	75.11	68.16	67.31	66.40	65.15	70.01	72.38	66.39	70.23	65.48	63.76	68.37	3.30	4.83
10.5	76.87	78.68	75.42	73.05	72.78	72.02	73.89	74.19	72.86	73.17	74.19	75.27	74.53	1.88	2.52
12.0	78.69	81.01	78.76	76.42	76.42	75.11	77.33	76.87	78.92	80.16	77.34	78.03	77.92	1.68	2.16
15.0	83.79	85.77	83.90	80.95	80.78	79.46	79.79	80.88	83.09	82.39	82.01	82.56	82.11	1.85	2.25
18.0	87.19	88.58	88.26	83.91	86.42	82.23	85.17	82.39	86.07	88.27	86.39	87.67	86.05	2.21	2.57
21.0	89.14	91.40	91.47	87.15	87.97	85.81	91.76	91.73	90.80	90.78	89.01	91.31	89.86	2.00	2.23
24.0	92.29	94.32	94.07	91.73	92.47	92.24	93.93	94.02	94.78	93.42	93.17	94.56	93.42	1.02	1.09

[a] Standard deviation ($n = 12$). [b] Coefficient of variation.

Table II—Percent of Aminophylline Dissolved from Twelve Aminophylline Slow-Release Test Tablets

Sampling Interval, h	Aminophylline, %												Mean, %	SD[a]	CV, %[b]
	1	2	3	4	5	6	7	8	9	10	11	12			
0.5	10.72	10.20	10.70	7.31	7.97	14.04	7.73	9.38	9.12	9.48	10.48	11.82	9.91	1.87	10.09
1.0	13.49	14.59	13.44	11.08	11.30	11.81	12.31	13.59	13.47	12.38	13.22	12.38	12.76	1.05	8.22
1.5	15.92	17.61	16.95	14.34	14.92	14.99	16.40	17.01	17.16	15.78	17.89	16.07	16.25	1.12	6.89
2.0	21.28	22.81	24.33	21.26	21.57	23.58	22.18	21.47	23.14	25.18	22.38	20.19	22.45	1.43	6.37
3.0	29.23	29.56	31.73	29.02	29.36	30.21	28.76	29.07	28.79	29.88	30.10	29.88	29.63	0.82	2.78
4.5	37.93	42.09	38.77	38.95	40.19	38.88	39.43	40.78	38.59	40.91	39.82	37.17	39.46	1.38	3.50
6.0	47.93	51.13	56.25	47.59	49.16	47.77	50.13	51.36	47.86	52.38	49.76	47.88	49.93	2.87	5.15
7.5	55.41	59.99	60.08	55.21	56.69	56.07	56.71	56.66	57.87	59.68	58.31	60.76	57.79	1.95	3.37
9.0	66.57	67.68	64.49	63.85	65.83	58.27	65.33	66.38	63.58	65.38	67.68	66.17	65.10	2.52	3.87
10.5	66.58	69.65	69.12	68.87	70.97	70.56	67.85	70.01	66.15	68.38	69.17	70.72	69.00	1.55	2.17
12.0	71.54	74.01	73.57	72.68	74.77	74.47	72.10	73.84	71.38	71.41	72.86	74.74	73.11	1.29	1.77
15.0	77.98	81.34	81.89	79.62	81.96	81.75	78.41	80.11	78.93	82.39	79.88	81.69	80.50	1.53	1.90
18.0	81.87	86.91	86.56	84.36	85.89	84.66	82.30	84.57	86.38	84.36	86.17	83.54	84.80	1.05	1.24
21.0	92.37	91.71	92.02	89.57	90.86	93.47	89.89	91.81	90.19	89.38	91.19	91.41	91.16	1.23	1.35
24.0	95.76	95.13	95.57	93.28	94.37	93.47	95.43	93.67	93.17	93.08	93.82	93.27	94.17	1.03	1.09

[a] Standard deviation ($n = 12$). [b] Coefficient of variation.

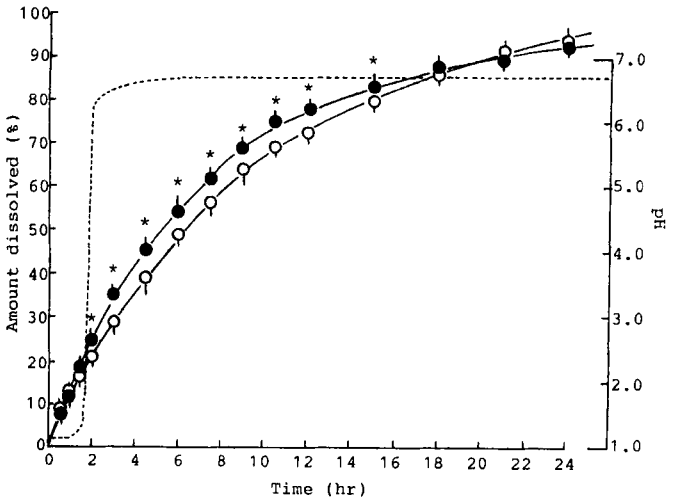

Figure 1—Dissolution profiles of aminophylline slow-release tablets using the pH change dissolution method (paddle method at 50 rpm). Key: (○) test tablets; (●) reference tablets; (*) $p < 0.05$; (- - -) results of pH change; (—) results of dissolution. The vertical bars represent the standard deviation of the mean (n = 12).

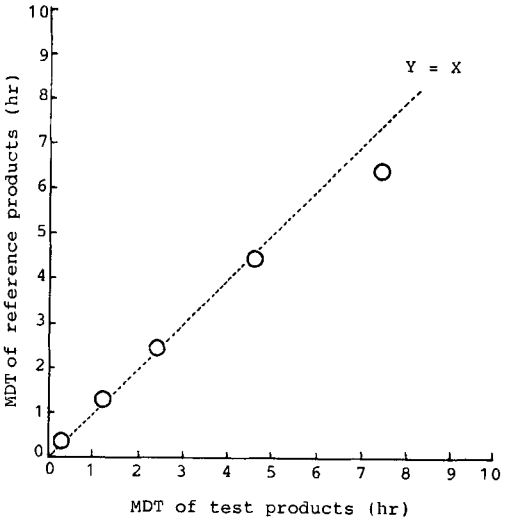

Figure 2—Correlation of MDT for aminophylline slow-release test and reference tablets. The data was taken at timed intervals of 1.0, 3.0, 6.0, 12.0, and 24.0 h. Each point represents the mean of 12 experiments. The dotted line represents the linear regression with slope = 1 and intercept = 0.

ation-dependent swelling phenomenon might be used to interpret this release mechanism for aminophylline released from both aminophylline SR tablets.[18,19] The n and K values are almost equal, indicating that there is no evidence to indicate that they are not similar.

The individual serum theophylline concentrations of these

Table III—Individual Serum Theophylline Concentrations after Single Oral Administration of 225-mg Aminophylline Slow-Release Reference Tablets in Eight Volunteers

Time, h	Serum Theophylline, μg/mL								Mean, μg/mL[a]	SD[b]	CV, %[c]
	1	2	3	4	5	6	7	8			
0.5	0.93	1.74	0.93	1.10	1.88	1.18	1.04	1.71	1.266	0.362	28.59
1	1.25	2.34	1.17	1.69	2.60	0.90	2.12	2.57	1.760	0.608	34.55
2	5.46	2.95	2.19	1.89	3.26	1.12	2.37	2.74	2.780	1.285	46.22
3	5.57	3.83	2.91	2.96	3.42	1.51	2.76	3.31	3.309	1.150	34.75
4	4.62	4.40	3.00	2.47	3.92	1.95	3.35	3.11	3.549	1.025	28.88
5	4.62	4.26	2.95	4.11	3.76	2.83	3.21	3.26	3.819	0.757	19.82
6	5.81	3.46	3.59	4.41	3.41	2.47	3.42	3.39	3.855	0.988	25.63
7	4.06	3.18	3.47	4.82	3.31	2.31	3.51	3.01	3.601	0.751	20.86
8	3.64	2.93	3.19	4.35	3.49	2.51	2.89	2.94	3.396	0.641	18.88
10	3.43	3.04	3.25	3.69	3.31	2.16	2.69	2.56	3.134	0.497	15.86
12	3.13	2.56	3.30	3.01	2.81	1.83	2.03	2.65	2.620	0.534	20.38
16	1.94	1.70	3.30	2.61	1.98	1.40	1.71	1.78	2.095	0.603	28.78
24	1.44	1.16	1.80	1.76	1.05	1.63	1.00	1.31	1.364	0.334	24.49

[a] These data are plotted in Figure 3. [b] Standard deviation (n = 8). [c] Coefficient of variation.

Table IV—Individual Serum Theophylline Concentrations after Single Oral Administration of 225-mg Aminophylline Slow-Release Test Tablets in Eight Volunteers

Time, h	Serum Theophylline, μg/mL								Mean, μg/mL[a]	SD[b]	CV, %[c]
	1	2	3	4	5	6	7	8			
0.5	0.58	1.06	0.86	1.89	1.85	0.95	1.01	1.71	1.239	0.502	40.52
1	1.16	1.63	1.09	2.09	2.23	1.12	2.17	2.57	1.758	0.584	33.22
2	1.94	1.86	1.53	3.04	3.39	2.00	1.85	2.74	2.294	0.669	29.16
3	3.42	3.02	2.38	3.37	4.02	3.61	2.55	3.31	3.210	0.542	16.88
4	3.48	3.36	2.94	4.10	4.31	2.87	2.56	3.11	3.341	0.607	18.17
5	3.83	3.34	3.19	4.14	4.25	3.25	3.09	3.26	3.544	0.459	12.95
6	3.14	3.57	3.01	4.41	3.99	3.16	3.08	3.39	3.469	0.498	14.36
7	3.03	2.44	3.40	4.90	3.82	3.39	2.48	3.01	3.311	0.793	23.95
8	3.36	2.87	2.89	5.10	3.80	2.89	2.57	2.94	3.302	0.817	24.74
10	3.04	3.00	3.46	4.56	3.70	2.56	2.83	2.56	3.214	0.675	21.00
12	2.36	2.27	2.84	3.77	2.76	2.07	2.49	2.65	2.651	0.520	19.62
16	2.68	1.70	2.10	3.05	1.75	2.19	2.06	1.78	2.164	0.478	22.09
24	1.36	0.66	1.27	2.14	0.60	1.44	0.79	1.31	1.196	0.508	42.47

[a] These data are plotted in Figure 3. [b] Standard deviation (n = 8). [c] Coefficient of variation.

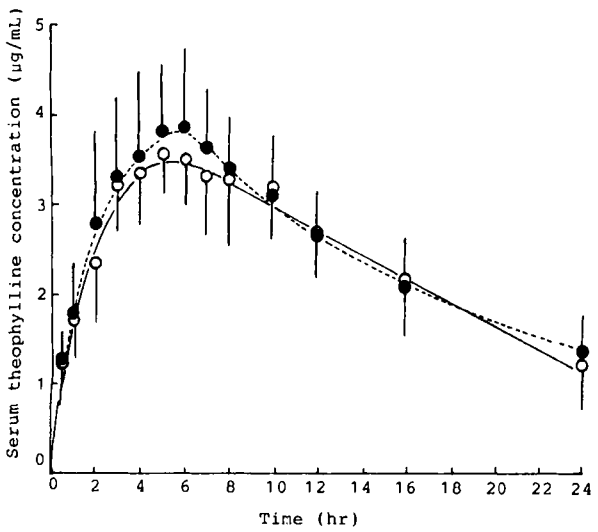

Figure 3—Mean serum theophylline concentrations in eight volunteers after single oral administration of aminophylline slow-release tablets. Key: (○) test tablets; (●) reference tablets. The vertical bars represent the standard deviation of the mean (n = 8).

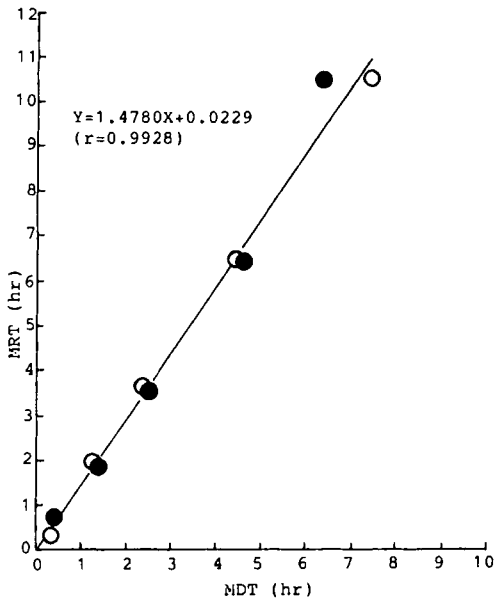

Figure 4—Correlation between MRT and MDT for aminophylline slow-release tablets. Key: (○) test tablets; (●) reference tablets. The data were taken at timed intervals of 1.0, 3.0, 6.0, 12.0, and 24.0 h. Each point represents the mean of eight experiments for MRT and of 12 experiments for MDT.

two types of aminophylline SR tablets are listed in Tables III and IV. The pharmacokinetic parameters calculated and observed from the mean serum theophylline concentration–time curve (Figure 3) are given in Table V. Both aminophylline SR tablets gave similar bioavailability and pharmacokinetic values; the ANOVA confirmed no statistically significant difference ($p > 0.05$) at each point for these two types of aminophylline SR tablets due to the wide interindividual variability in the serum theophylline concentrations. This suggests that both types of aminophylline SR tablets showed similar bioequivalence. The relationship between MRT and MDT for aminophylline SR test and reference tablets is shown in Figure 4. The mean regression line was calculated to be $y = 1.479x + 0.0179$ ($r = 0.9938$, $n = 10$). A good in vitro–in vivo correlation is characterized by a high coefficient of determination ($r > 0.99$). This pilot study suggests that the in vivo bioavailability of aminophylline SR tablets can be predicted by the in vitro dissolution profile of the dosage form.

Moment analysis has been claimed to be useful in studies of quantitative in vitro–in vivo correlations related to drug

Table V—Pharmacokinetic Parameters of Theophylline after Single Oral Administration of 225-mg Aminophylline Slow-Release Tablets

Tablet	Subject	C_{max}, μg/mL[a]	C_{max}, μg/mL[b]	t_{max}, h[a]	t_{max}, h[b]	$AUC_{0\to\infty}$, μg · h/mL	K_e, h^{-1}	$K_e t_{1/2}$, h	K_a, h^{-1}	$K_a t_{1/2}$, h	Vd, L/kg	Cl, mL/min/kg
Reference	1	5.81	5.27	6	3.60	83.02	0.082	8.47	0.80	0.87	0.45	0.61
	2	4.40	3.90	4	4.05	70.45	0.076	9.07	0.54	1.29	0.57	0.72
	3	3.59	3.48	6	8.04	110.22	0.047	14.89	0.25	2.82	0.54	0.42
	4	4.82	3.78	7	7.24	83.40	0.086	8.08	0.20	3.49	0.40	0.57
	5	3.92	3.74	4	4.78	75.68	0.074	9.31	0.35	1.97	0.55	0.68
	6	2.83	2.30	5	7.40	71.84	0.046	15.08	0.27	2.58	0.89	0.68
	7	3.51	3.30	7	5.10	60.76	0.086	8.02	0.34	2.03	0.58	0.84
	8	4.81	4.41	5	5.13	70.17	0.113	6.16	0.31	2.27	0.41	0.78
Mean		4.22	3.77	5.50	5.67	78.19	0.076	9.89	0.38	2.17	0.55	0.66
SD		0.93	0.86	1.20	1.66	14.89	0.022	3.29	0.20	0.83	0.16	0.13
Test	1	3.83	3.45	5	5.42	87.16	0.024	13.51	0.49	1.40	0.68	0.58
	2	3.57	3.23	6	5.51	55.64	0.108	6.45	0.27	2.61	0.51	0.92
	3	3.40	3.11	7	7.28	66.73	0.092	7.55	0.19	3.64	0.45	0.69
	4	5.10	4.59	8	7.43	105.23	0.094	7.38	0.16	4.49	0.29	0.45
	5	4.31	4.26	4	5.02	65.70	0.139	4.99	0.23	3.01	0.33	0.77
	6	3.39	3.19	7	5.11	78.46	0.053	13.10	0.51	1.37	0.71	0.63
	7	3.09	2.69	5	6.46	57.09	0.102	6.82	0.16	4.24	0.52	0.88
	8	3.39	3.29	6	4.28	78.29	0.054	12.78	0.51	1.37	0.77	0.69
Mean		3.76	3.48	6.00	5.81	74.29	0.083	9.07	0.32	2.77	0.53	0.70
SD		0.66	0.63	1.31	1.13	16.61	0.037	3.45	0.16	1.30	0.18	0.16
F ratio		1.242	0.620	0.636	0.042	0.245	0.213	0.232	0.567	1.218	0.038	0.328
ANOVA test		NS[c]	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS

[a] Value directly observed from the individual serum concentration–time curve. [b] Value computed from the individual simulated serum concentration–time curve. [c] Not significant ($p < 0.05$).

release.[13,14] This correlation can be advantageous during the formulation design of solid dosage forms. It can provide quantifiable information of biopharmaceutical predictions due to changes in in vitro dissolution properties which can result from formulation variables such as the types of excipients used, excipient ratio, surfactants, blending time, etc. As shown in Figure 4, the separate regression line calculated for aminophylline SR test tablets was MRT = 1.3925MDT + 0.1126 (r = 0.9998), and the separate regression line calculated for aminophylline SR reference tablets was MRT = 1.6002MDT − 0.1498 (r = 0.9953). The intercepts, 0.2204 and 0.2264 h, can be interpreted as the MRT for an oral aqueous solution, although of opposite sign value. Although the value of the correlation coefficient (r) was somewhat different for aminophylline SR test and reference tablets, there was no significant difference. The slopes of both the linear regression lines are also >1, indicating that the dissolution of both aminophylline SR tablets is faster in vivo than in vitro. This may be due to the more complicated physiological effects prevailing in the GI tract which cannot be mimicked in the dissolution medium.

The data from this pilot study suggest that the bioavailability of aminophylline SR test tablets developed in Taiwan, Republic of China, are similar to the aminophylline SR reference tablets. The in vitro dissolution profiles of these aminophylline SR tablets may be a predictor of the in vivo bioavailability of these products. Clinical studies using at least 24 normal volunteers are required for definitive evaluation of this possibility.

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Acknowledgments

The authors are grateful to Hui-Chun Tang Pharma-Works Company, Ltd., Taiwan, Republic of China, for the supply of Anpillin slow-release tablets.