STUDY 21-96-203: (DRUG INTERACTION STUDY WITH OMEPRAZOLE)

A PHARMACOKINETIC STUDY OF THE POTENTIAL INTERACTION BETWEEN CILOSTAZOL AND OMEPRAZOLE IN HEALTHY SUBJECTS

Reference: Volumes 101 to 104
Investigator:
Study Location:
Objective:

To evaluate the effect of concomitant administration of omeprazole on the pharmacokinetics of a single 100 mg dose of cilostazol.

Study design:

This is an open label fixed sequence single-center, multiple dose omeprazole and single dose cilostazol study in 20 healthy male and female volunteers (10 males and 10 females) of age 18 to 55 years. On day 0, subjects received a single 100 mg dose of cilostazol under fasting conditions. On days 7 to 18, subjects received 40 mg omeprazole once daily in the morning. On day 14, they also received another single 100 mg dose of cilostazol in fasted state. Subjects were in the clinic on days 0 to 6 and on days 13 to 18.

Plasma samples for the assay of cilostazol and its metabolites were collected on day 0 and day 14 for 120 hours post cilostazol dosing.

Batch #s: Cilostazol 100 mg tablet: batch # 4K79PA1
Omeprazole 20 mg tablets: batch # D6824

Blood samples were drawn for determination of plasma concentration of cilostazol and its major metabolites (OPC-13015 and OPC-13213) at 0, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 36, 48, 72, 96 and 120 hours after cilostazol dosing on days 0 and 14. Trough blood samples were drawn for determination of omeprazole and 5'-hydroxyomeprazole plasma concentrations on days 7 and 12 to 16.

Analysis of plasma samples for cilostazol and its metabolites, and for omeprazole and 5'-hydroxyomeprazole was carried out using a

Protein binding of cilostazol in plasma samples was determined by of the radioactivity of C-14 cilostazol.

Pharmacokinetic parameters were determined by non-compartmental methods. Descriptive statistics were calculated for PK parameters. The log-transformed PK parameters of cilostazol before and after omeprazole coadministration were compared using a paired t-test. The geometric mean and 95% confidence interval were also calculated for the PK parameters.

Results:

ASSAY PERFORMANCE:

Plasma samples:

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Precision:
Accuracy:

Specificity:

5'-hydroxyomeprazole:

Method used:
Range:
Linearity: Linear within the range.
QC samples:
Precision:
Accuracy:

Specificity:

Assays were found to be acceptable.

No measurable levels of OPC-13217 were observed in the plasma samples.

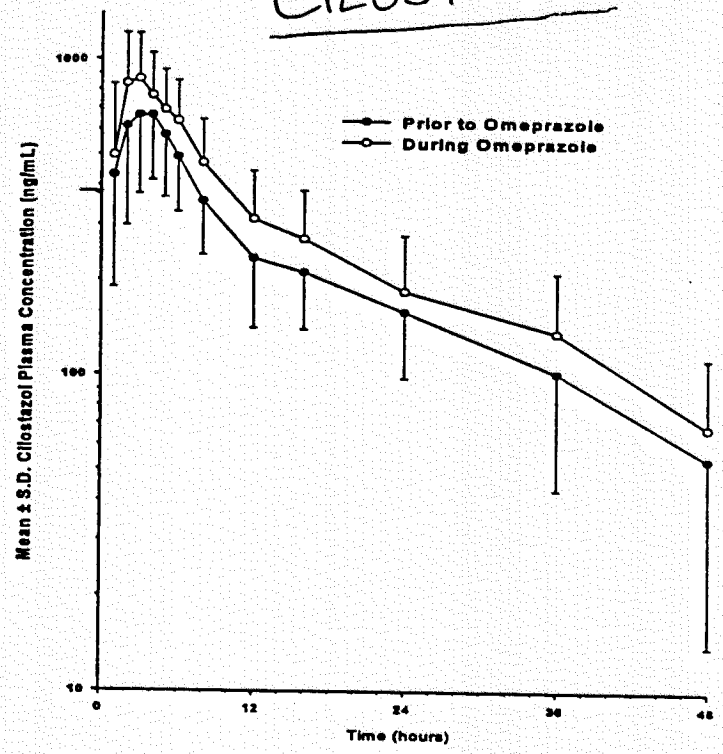
Table below provides a summary of the main pharmacokinetic parameters for cilostazol and its major metabolites given before and after omeprazole.

Parameter	CILOSTAZOL		OPC-13015		OPC-13213	
	Before	After	Before	After	Before	After
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
T_{max} (h)*	3 (1-4)	3 (2-6)	5 (3-36)	8 (4-16)	4 (2-6)	4 (2-12)
C_{max} (ng/mL)	782 ± 281	921 ± 326	142 ± 53	186 ± 65	61 ± 28	48 ± 18
$t_{1/2}$ (h)	18 ± 9	16 ± 7	-	-	-	-
AUC_T (hr·ng/mL)	10287 ± 2186	13033 ± 4169	2716 ± 991	4554 ± 1826	566 ± 197	361 ± 121
$AUC_{0-\infty}$ (hr·ng/mL)	11801 ± 2936	14436 ± 3969	-	-	-	-
CL/F (L/hr/kg)	0.13 ± 0.03	0.11 ± 0.03	-	-	-	-
f_a (%)	2.29 ± 0.56	2.33 ± 0.23	-	-	-	-

* median (range)

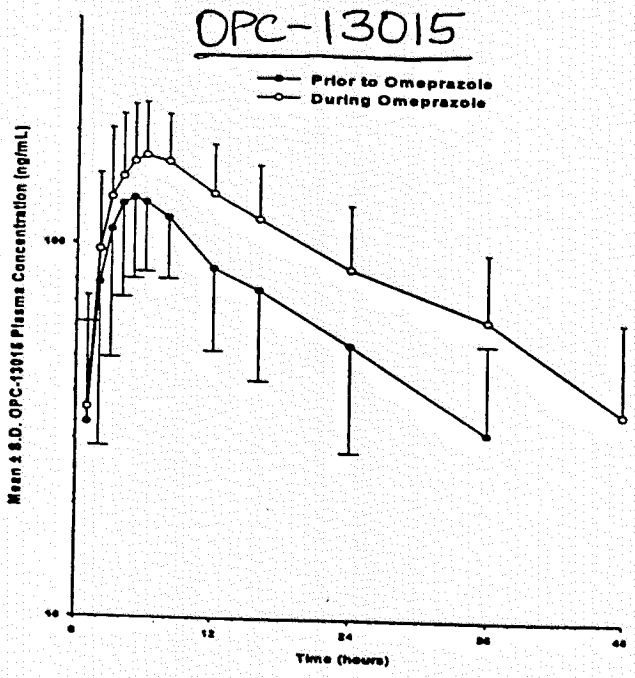
Plot of mean concentration profiles for cilostazol before and after omeprazole treatment are given in the figure below.

CILOSTAZOL

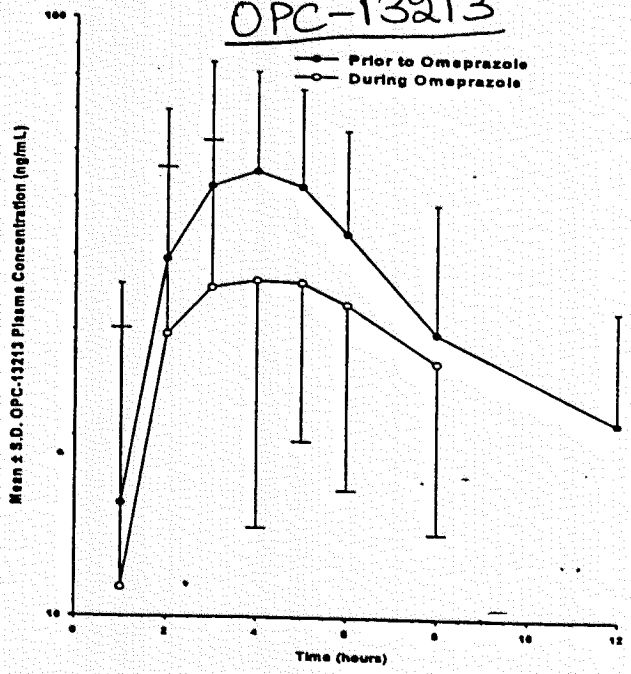


Plots of mean concentration profiles for OPC-13015 and OPC-13213 after administration of cilostazol before and after omeprazole treatment are given in the figures below.

OPC-13015



OPC-13213



The following table shows the geometric mean ratio (using parameter without omeprazole as reference) and 95% confidence interval on Cmax and AUC_T of cilostazol and its active metabolites.

Moiety	Geometric mean ratio of Cmax	95% confidence interval	Geometric mean ratio of AUC_T	95% confidence interval
Cilostazol	1.14	0.96 - 1.31	1.24	1.13 - 1.35
OPC-13015	1.26	1.11 - 1.41	1.64	1.43 - 1.85
OPC-13213	0.75	0.65 - 0.85	0.63	0.50 - 0.76

Following omeprazole coadministration, cilostazol Cmax increased by 18% and AUCT by 26%. The increase in AUCT was statistically significant ($p<0.001$). The OPC-13015 Cmax increased by 29% and AUCT by 69%. These increases were statistically significant. The mean Cmax and AUCT of OPC-13213 decreased significantly by 22% and 31%. There is no statistically significant difference in cilostazol free fraction after administration of omeprazole. Only about 2% of cilostazol is unbound in plasma. A 20% reduction in unbound clearance of cilostazol after omeprazole treatment was observed.

No measurable trough omeprazole plasma concentrations were observed in plasma. This can be expected to be due to the very short half-life of omeprazole (<1 hour).

Conclusions:

Coadministration of omeprazole with cilostazol resulted in a small but significant increase in cilostazol plasma concentrations, a significant increase in the metabolite OPC-13015 concentrations and a decrease in OPC-13213 plasma concentrations. According to the sponsor, precautions should be taken when coadministering cilostazol with inhibitors of CYP2C subfamily.

Comments:

Results of this study indicate that coadministration of potent CYP2C19 inhibitors with cilostazol can result in small but significant drug interactions. Hence caution is recommended for coadministration of these drugs with cilostazol.

STUDY 21-95-301: (DRUG INTERACTION STUDY WITH ASPIRIN)

A RANDOMIZED DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTIPLE DOSE CROSSOVER STUDY TO INVESTIGATE THE SAFETY AND POTENTIAL INTERACTION OF THE CO-ADMINISTRATION OF CILOSTAZOL AND ACETYLSALICYLIC ACID (ASA) IN HEALTHY SUBJECTS

Reference: Volume 84-87
Investigator:
Study Location:
Objective:

1. To determine and compare the safety and tolerability of multiple oral doses of cilostazol alone and cilostazol coadministered with aspirin in normal healthy male volunteers.
2. To study the effect of multiple dosing of cilostazol with aspirin on the pharmacokinetics of cilostazol and its metabolites (limited PK), platelet aggregation and bleeding times in normal healthy male subjects.

Study design:

This is a double-blind, single-center, randomized, placebo-controlled, multiple dose design crossover study in 12 healthy male volunteers (11 subjects completed the study) of age 18-35 years. The participants received placebo or cilostazol 100 mg twice daily for 10 days plus 325 mg aspirin once daily on days 6 to 10 only. This was followed by a 14 day washout period. Then subjects received the alternate treatment in the second period of the study. Plasma samples were collected on days 1, 4, 6, 9, 25, 28, 30 and 33, at 0 and 3 hours post-dose and at 0, 3, 8 and 12 hours post-dose on days 5 and 29 and at 0, 3, 8, 12 and 24 hours post-dose on days 10 and 34 for determination of plasma cilostazol and its metabolite concentrations. Additional plasma samples were also drawn at selected time points to determine plasma salicylate concentrations (24 hours after dosing). ADP and arachidonic acid induced platelet aggregation (AUC), bleeding time, prothrombin time (PT) and activated partial thromboplastin time (APTT) were assessed at various time points in this study.

Batch #s: Cilostazol 100 mg tablet: batch # 4K79PA1
Matching placebo, batch # 4L75P100
ASA (acetylsalicylic acid) 325 mg tablet: batch#s 4FA673 and 4KA689

Pharmacokinetic parameters were determined using non-compartmental methods. Summary statistics for Cmax, AUC0-t and trough plasma concentrations were generated. Statistical comparisons of PK parameters for day 5 versus day 10 were performed using paired t-tests to see the effect of multiple dosing of aspirin on steady state PK of cilostazol. Statistical comparisons of PD parameters were performed, using descriptive measures for day 5 (29) versus day 10 (34) for both cilostazol and placebo treatments to summarize change within subject. For between subject comparison across treatments (placebo vs. cilostazol and placebo + aspirin vs. cilostazol + aspirin) two-sided tests (alpha = 0.05) were performed.

Results:

ASSAY PERFORMANCE:

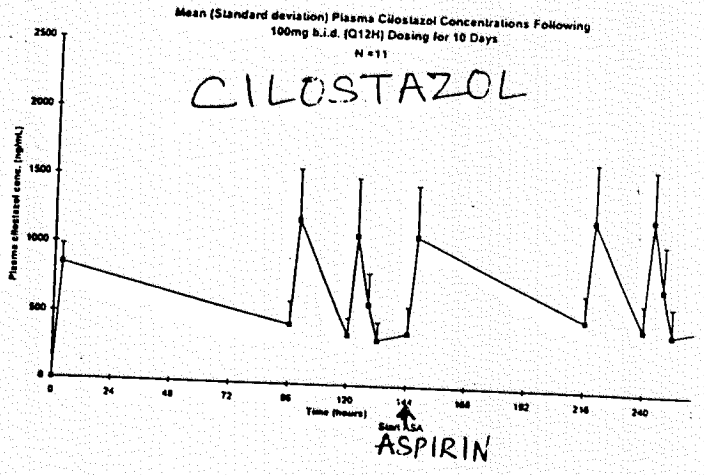
Plasma samples: For cilostazol and its metabolites OPC-13015 and OPC-13213

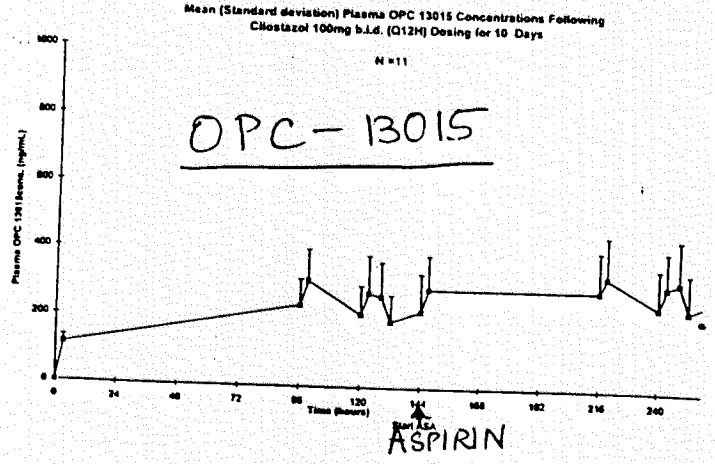
Method used:
Range:
Linearity:
Precision:

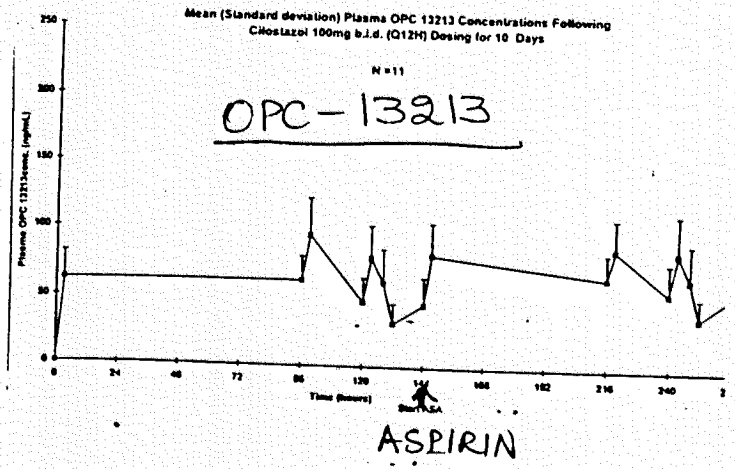
Accuracy:

Sensitivity:
Specificity:

No plasma salicylate concentrations were detected in the 24 hour samples drawn. Plots of mean concentration profiles for cilostazol and its metabolites OPC-13015 and OPC-13213 after cilostazol administration with and without the administration of aspirin are shown in the following three figures while the corresponding pk parameters are summarized in the tables below.







Part I Comparison of cilostazol C_{max} on Days 5 and 10 of dosing

Treatment (n=11)	Day 5 (ng/mL)	Day 10 (ng/mL)	Mean Diff (ng/mL)	SE	T value	Power	P-value
Cilostazol	1109.17	1264.54	155.37	3.6163	1.50	0.0854	0.1647

Part II Comparison of cilostazol trough levels on Day 5 and Day 10 of dosing

Treatment (n=11)	Day 5 (ng/mL)	Day 10 (ng/mL)	Mean Diff (ng/mL)	SE	T value	Power	P-value
Cilostazol	370.64	467.99	97.36	34.50	2.8212	0.1424	0.0181

Part III Comparison of plasma cilostazol AUC_{0-t} on Days 5 and 10 of dosing

(N=11)	Day 5	Day 10	Mean Diff	T-value	P-value
	(ng/mL.h	(ng/mL.h)	(ng/mL.h)		
11	8314.7	10101	1786.3	2.22	0.023

Part IV Comparison of plasma OPC 13213 AUC_{0-t} on Days 5 and 10 of dosing

(n=10)	Day 5 (ng/mL.h)	Day 10 (ng/mL.h)	Mean Diff (ng/mL.h)	T value	P-value
	783.92	881.22	97.3	2.26	0.027

Part V Comparison of plasma OPC 13213 Cmax on Days 5 and 10 of dosing

(n=11)	Day 5 (ng/mL.)	Day 10 (ng/mL.)	Mean Diff (ng/mL.)	T value	P-value
	85.53	87.56	2.03	2.23	0.63

Part VI Comparison of plasma OPC 13015 AUC_{0-t} on Days 5 and 10 of dosing

(n=11)	Day 5 (ng/mL.h)	Day 10 (ng/mL.h)	Mean Diff (ng/mL.h)	T value	P-value
	3019.12	3521.26	502.14	2.23	0.01

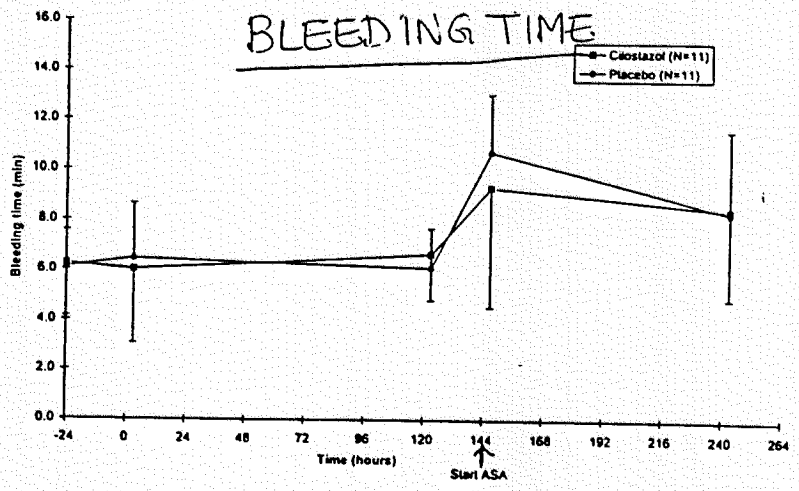
Part VII Comparison of plasma OPC 13015 Cmax on Days 5 and 10 of dosing

(n=11)	Day 5 (ng/mL.)	Day 10 (ng/mL)	Mean Diff (ng/mL)	T value	P-value
	293.12	335.62	42.5	2.23	0.006

While the data should be interpreted with caution since very few samples were taken to assess AUC, examination of data indicates that 1) for cilostazol, statistically significant increases in AUC0-t and trough plasma concentrations following concomitant administration of cilostazol and aspirin were observed. Further, a 14% increase in Cmax of cilostazol was observed upon concomitant administration; 2) for OPC-13015, statistically significant increases were observed in AUC0-t and Cmax following cilostazol + aspirin compared to cilostazol alone; and 3) for OPC-13213, the AUC0-t was significantly higher after cilostazol and aspirin compared to cilostazol alone.

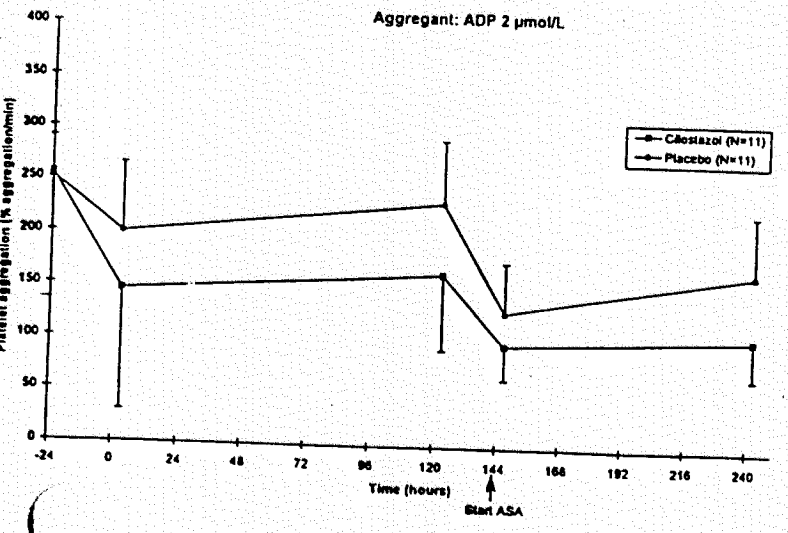
The following three figures show the effect of concomitant administration of cilostazol and aspirin on bleeding time and platelet aggregation (with ADP and arachidonic acid).

Mean (Standard deviation) Bleeding Time (min)



Mean (Standard deviation) Platelet Aggregation: AUC (% aggregation/min)

Aggregant: ADP 2 µmol/L



Mean (Standard deviation) Platelet Aggregation: AUC (% aggregation/min)

Aggregant: Arachidonic acid 500 µg/mL

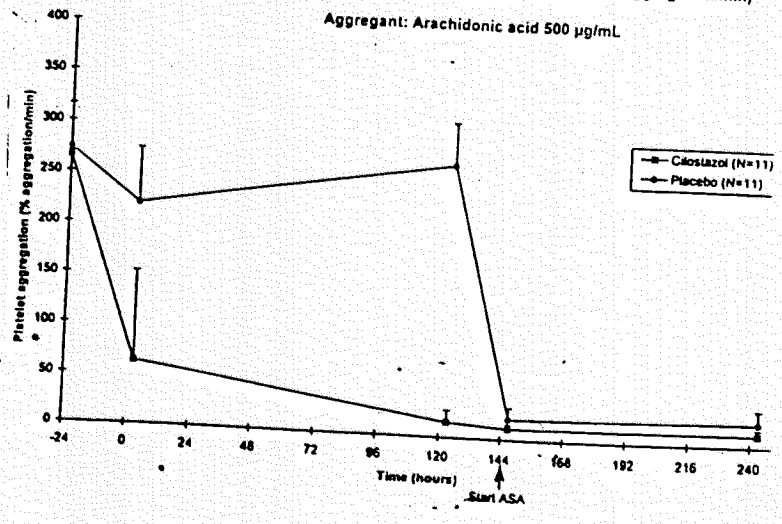


Table below shows the statistical comparison of PT for cilostazol vs. Placebo and cilostazol + aspirin vs. placebo + aspirin.

Comparison	Day	Mean (Sec) Cilostazol	Mean (Seconds) Placebo	P-Value
Cilostazol vs. Placebo	Baseline	12.07	12.15	.766
Cilostazol vs. Placebo	5	12.23	12.21	.934
Cilostazol + ASA vs. Placebo + ASA	10	12.33	12.41	.797

Table below shows the statistical comparison of APTT for cilostazol vs. Placebo and cilostazol + aspirin vs. placebo + aspirin.

Comparison	Day	Mean Cilostazol	Mean Placebo	P-Value
Cilostazol vs. Placebo	Baseline	33.29	32.86	.625
Cilostazol vs. Placebo	5	33.31	32.06	.231
Cilostazol + ASA vs. Placebo + ASA	10	32.29	31.85	.544

Table below shows the statistical comparison of bleeding time for cilostazol vs. Placebo and cilostazol + aspirin vs. placebo + aspirin.

Comparison	Day	Mean Cilostazol	Mean Placebo	P-Value
Cilostazol vs. Placebo	Baseline	6.23	5.94	.700
Cilostazol vs. Placebo	5	6.54	6.19	.617
Cilostazol + ASA vs. Placebo + ASA	10	8.41	8.15	.855

Table below shows the statistical comparison of platelet aggregation for cilostazol vs. Placebo and cilostazol + aspirin vs. placebo + aspirin.

Comparison of platelet aggregation (AUC) for cilostazol versus placebo and cilostazol + ASA versus placebo + ASA Part I: 2 μmol/L ADP

Comparison	Day	Mean Cilostazol	Mean Placebo	P-Value
Cilostazol vs. Placebo	-1	258.9	247.5	.559
Cilostazol vs. Placebo	5	170.7	231.6	.032
Cilostazol + ASA vs. Placebo + ASA	10	106.3	168.3	.004

Part II: 4 μmol/L ADP

Comparison	Day	Mean Cilostazol	Mean Placebo	P-Value
Cilostazol vs. Placebo	-1	284.1	283.5	.980
Cilostazol vs. Placebo	5	272.4	283.6	.596
Cilostazol + ASA vs. Placebo + ASA	10	207.2	266.4	.009

Part III: 500 μg/mL Arachidonic Acid

Comparison	Day	Mean Cilostazol	Mean Placebo	P-Value
Cilostazol vs. Placebo	-1	271.6	265.5	.767
Cilostazol vs. Placebo	5	14.2	266.3.	.000
Cilostazol + ASA vs. Placebo + ASA	10	11.5	22.9	.012

These results indicate that cilostazol did not change the PT, APTT and bleeding time. With 2 μmol/l ADP as aggregant, platelet aggregation was 73% of that of placebo when cilostazol was administered alone and 63% that of placebo + aspirin when cilostazol was concomitantly administered with aspirin. With 4 μmol/l ADP as aggregant, platelet aggregation was 96.1% of that of placebo when cilostazol was administered alone and 77.8% that of placebo + aspirin when cilostazol was concomitantly administered with aspirin. With 500 μg/ml arachidonic acid as aggregant, cilostazol produced a marked inhibition of platelet aggregation (50.3% reduction in platelet aggregation) which was unaffected by coadministration with aspirin.

Conclusions:

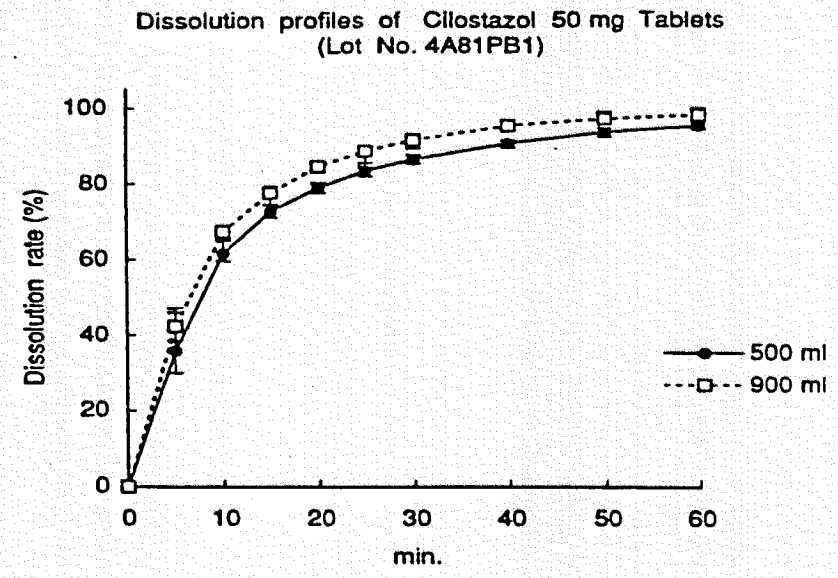
Coadministration of cilostazol and aspirin resulted in small increases in plasma levels of cilostazol and two of its active metabolites. No clinically significant interactions between cilostazol and aspirin were noted with respect to PT, APTT and bleeding time. Significant differences in ADP induced platelet aggregation (AUC) were observed upon concomitant administration of cilostazol and aspirin. Clinical relevance of these differences is unknown.

DISSOLUTION:

A. DISSOLUTION TESTING METHOD DEVELOPMENT:

The sponsor provided solubility data for the drug substance at various pH values. Cilostazol is very poorly soluble in aqueous media without surfactants. The dissolution method development has been reviewed previously and the dissolution medium selected has been found to be acceptable (see review by Dr.Alfreda Burnett, date April 23, 1997). The sponsor has also provided data to show the effect of paddle speed on dissolution of cilostazol. The selected dissolution conditions are:

In the original submission, the sponsor was using 500 ml of dissolution medium for the 50 mg tablet as compared to 900 ml for the 100 mg tablet. In this submission, based on FDA's recommendation, the sponsor has provided data to compare the dissolution profiles of the 50 mg tablet using 500 and 900 ml of medium (dissolution profiles shown in the figure below). The dissolution profiles are comparable.



CONCLUSION: The sponsor proposed dissolution method and specifications are shown below:

(1) Dosage Form: **Tablet**

(2) Strength(s):

(3) Apparatus Type:

(4) Media:

(5) Volume:

(6) Speed of Rotation: (Rate of Flow for Flow-through Apparatus):

(7) Sampling Time(s): **Pretest, 5, 10, 15, 20, 25, 30, 40, 50 and 60 minutes**

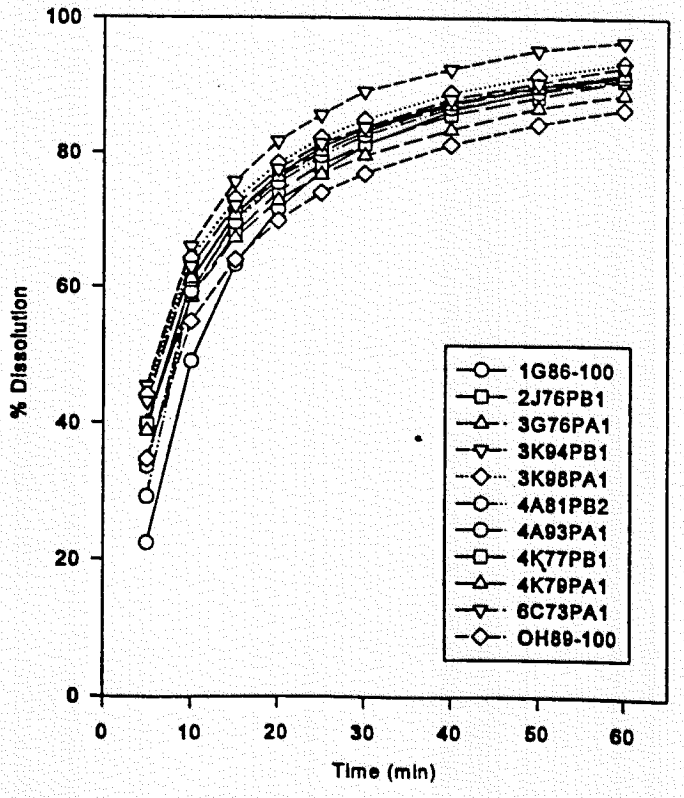
(8) Brief Description of Dissolution Analytical Method:

(9) Recommended Dissolution Specification:

The selected dissolution method is acceptable.

B. DISSOLUTION SPECIFICATIONS:

Dissolution data on 6 units from eleven cilostazol batches (both 50 and 100 mg strengths) that were either used in phase III clinical trials, pivotal biostudies or stability studies has been submitted. The mean % dissolved vs. time for these batches in shown in the following figure:



The mean % dissolved for these 11 batches is shown in the following tables:

Time in minutes	Mean % (% CV) cilostazol dissolved					
	1G86-100, 100 mg tab	2J76PB1 50 mg tab	3G76PA1 100 mg tab	3K94PB1 50 mg tab	3K98PA1 100 mg tab	4A81PB2 50 mg tab
5	22.4 (18.8)	39.7 (9.3)	40.0 (7.8)	45.4 (6.2)	44.1 (13.2)	33.6 (7.9)
10	49.1 (15.7)	58.7 (4.1)	58.5 (2.1)	65.9 (2.0)	64.2 (3.6)	59.2 (2.6)
15	63.3 (9.0)	67.9 (2.4)	67.2 (1.3)	75.6 (0.7)	73.0 (2.1)	69.9 (1.6)
20	71.5 (5.45)	74.1 (2.6)	72.8 (1.7)	81.7 (0.5)	78.4 (1.9)	76.1 (1.6)
25	77.2 (3.0)	78.2 (1.8)	76.7 (1.2)	85.6 (0.9)	82.2 (1.7)	80.0 (1.3)
30	81.1 (1.9)	81.3 (2.1)	79.6 (1.0)	89.1 (1.0)	84.9 (1.7)	83.3 (1.2)
40	86.3 (0.9)	85.7 (1.5)	83.5 (1.0)	92.4 (1.0)	88.9 (1.5)	87.5 (1.2)
50	89.3 (0.8)	88.3 (1.5)	86.7 (1.2)	95.2 (0.8)	91.4 (1.6)	90.0 (1.1)
60	91.4 (0.9)	90.8 (1.9)	88.7 (1.0)	96.5 (1.0)	93.3 (1.7)	91.7 (1.4)

Time in minutes	Mean % (% CV) cilostazol dissolved				
	4A93PA1 100 mg tab	4K77PB1 50 mg tab	4K79PA1 100 mg tab	6C73PA1 100 mg tab	OH89-100 100 mg tab
5	29.2 (8.9)	39.8 (7.2)	38.8 (15.0)	43.1 (7.4)	34.7 (10.1)
10	59.3 (2.6)	61.0 (2.3)	61.2 (3.1)	63.0 (3.0)	54.9 (2.7)
15	69.5 (1.9)	70.8 (1.2)	70.6 (1.4)	72.0 (2.8)	64.0 (1.3)
20	75.4 (1.8)	76.7 (0.9)	76.3 (1.0)	77.5 (2.6)	69.8 (1.0)
25	79.5 (1.9)	80.8 (0.9)	80.2 (0.8)	81.4 (2.1)	74.0 (0.8)
30	82.6 (1.8)	83.6 (0.9)	83.1 (0.8)	83.8 (2.2)	76.9 (0.8)
40	86.7 (1.6)	87.4 (0.9)	87.1 (0.7)	88.0 (2.2)	81.3 (0.7)
50	89.0 (1.9)	89.8 (0.9)	89.7 (0.8)	90.4 (1.9)	84.3 (0.6)
60	91.0 (1.8)	91.4 (0.8)	91.6 (0.8)	92.8 (2.3)	86.5 (0.6)

CONCLUSION:

Based on this data, the sponsor selected dissolution method is acceptable. The sponsor should change the dissolution specification to The final FDA selected method and dissolution specification for cilostazol tablets is:

COMMENTS: All the dissolution data provided is based on 6 tablets per batch. In future, the sponsor should provide dissolution data on 12 tablets per lot. For this NDA, this data is acceptable for setting specifications, since additional data on 12 tablets per lot for the 50 mg tablet strength has been provided (as shown below) to request for waiver of change in shape of tablet. This data is comparable to the above dissolution data.

C. WAIVER FOR A BIOEQUIVALENCE STUDY BETWEEN THE 50 MG TABLET (CLINICAL FORMULATION) AND THE 50 MG TABLET (TO-BE MARKETED FORMULATION):

The formulation of the clinical and to-be marketed formulation are identical. The only of the 50 mg tablet This is a minor change and hence in vitro dissolution comparison is adequate for justification of this change. No biostudy is required. The sponsor has provided dissolution data on 12 units per lot. The appropriate description of batches and f2 values are shown below:

In order to compare the dissolution rates of 50 mg tablets (lot Nos. 6J79PBT1, 6J79PBT2 and 6J79PBT3) recently manufactured, round 50 mg tablets (lot Nos. 4A81PB1, 4A81PB2 and 4A81PB3) used for the primary NDA stability studies, and round 50 mg tablets (6J79PB1, 6J79PB2 and 6J79PB3) manufactured using the used for the manufacture of the 50 mg tablets (lot Nos. 6J79PBT1, 6J79PBT2 and 6J79PBT3), dissolution test using the test method specified in the "Proposed Regulatory Specifications of Cilostazol 50 mg Tablets" was carried out. The test results are shown in the following figures. The f_2 values for these tablets were calculated according to the formula in SUPAC-IR Guideline, and the equivalence between the tablets and the tablets was evaluated.

As shown in the following table, the lowest dissolution rate among the three lots of the triangular 50 mg tablets recently manufactured was compared with the highest rate among the three lots of the round 50 mg tablets used for the primary NDA stability studies (No.1). Furthermore, in the case of the triangular and round 50 mg tablets manufactured using the same lot of the dissolution rates of 50 mg and 50 mg were compared to each other on a lot-to-lot basis (No.2). As shown below, the f_2 values are over 60, so that the tablets and the tablets are considered to be equivalent.

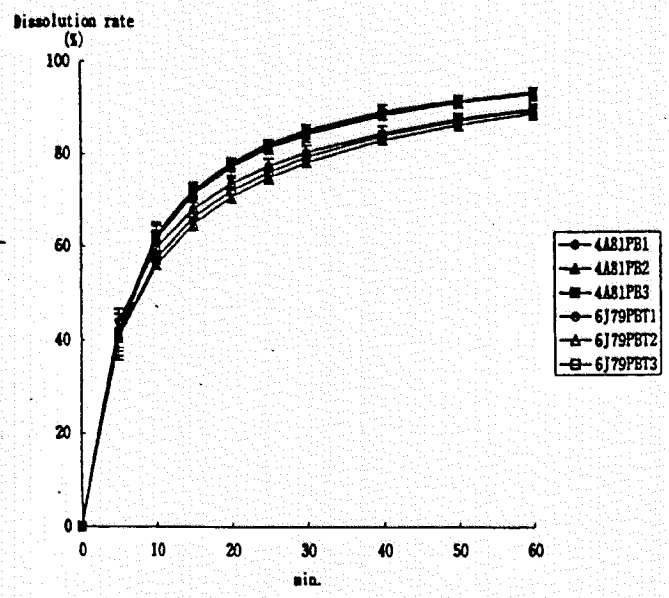
Comparison of Dissolution (f_2 value) Between 50-mg Tablets and 50-mg Tablets

			f_2 value*
(No. 1)	Lot No. 6J79PBT2	Lot No. 4A81PB1	60.2
(No.2)	Lot No. 6J79PBT1	Lot No.6J79PB1	94.8
	Lot No. 6J79PBT2	Lot No. 6J79PB2	94.4
	Lot No. 6J79PBT3	Lot No. 6J79PB3	81.1

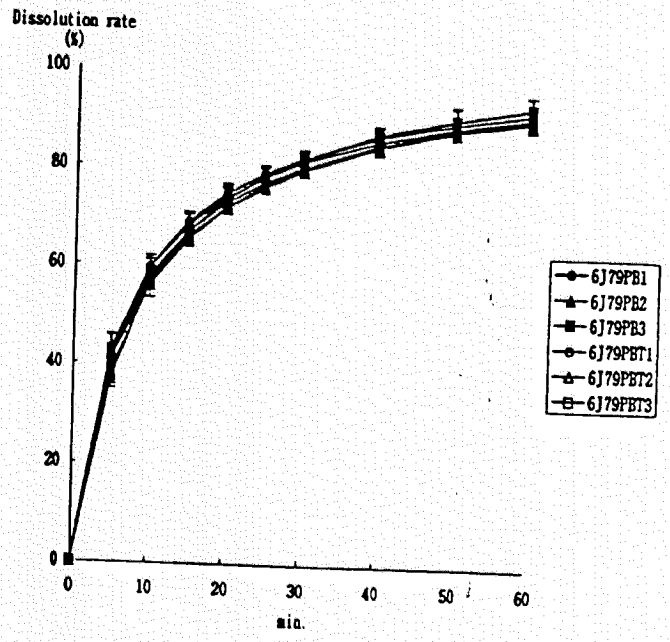
*Calculated from the dissolution values at 5, 10, 15, 20, 25, 30, 40, 50 and 60 min.

The corresponding dissolution profiles are shown in the following two figures:

Dissolution Profiles of Cilostazol 50 mg Tablets



Dissolution Profiles of Cilostazol 50 mg Tablets



CONCLUSION: The dissolution profiles for the to-be marketed formulation are comparable to the clinical trial formulation. Hence, a biowaiver can be granted.