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APPLICATION NUMBER:

74910

BIOEQUIVALENCY REVIEW(S)

ORG.

MAY - 5 1997

Diltiazem Hydrochloride ER Capsules	Mylan
60, 90 and 120 mg Capsules	Morgantown, WV
ANDA #74-910	Submission Date:
Reviewer: Moo Park	June 12, 1996
	September 12, 1996

Addendum to
Review of Two *In Vivo* Bioequivalence Studies, Dissolution Data and Two Waiver Requests

I. Objectives

Addendum was prepared to the original review dated October 28, 1996 to clarify the followings with regard to the steady-state study results:

1. Are the data in hard copy identical to the data in the submitted diskette?

2. Discrepancies found in the submission and reviewer's data summary recalculated by reviewer.

3. Subject #4 showed multiple missing plasma data points. If the subject is dropped from the statistical analyses, would the study still pass the 90% confidence intervals?

II. Summary of Findings

1. The data in the hard copy was found to be identical to the data in the diskette.

2. For the discrepancies found in the submission and reviewer's data summary recalculated by reviewer, Mylan used wrong algorithm in determining CMAX. The CMAX was chosen from 96-180 hours instead of 168-180 hours interval, which was the last dosing interval in the steady-state study. As a result, the TMAX and Fluctuation also became wrong since the algorithm for the TMAX and Fluctuation involved CMAX. Reviewer's summary in the original review corrected all the wrong parameters. The insignificant discrepancies found in the mean plasma levels

in the submission and the reviewer's calculation is due to the missing values for subject #4. Reviewer calculated the mean plasma levels based on the interpolated data for missing values. The interpolation on linear scale for missing data may be used in AUC calculation. Mylan used the interpolation for AUC calculation. However, Mylan dropped the missing values in the calculation of mean plasma levels. Either way did not make any difference in the determination of bioequivalence.

3. The data analyses performed without the data for Subject #4 indicated that all the 90% confidence intervals for log trasformed AUCT, CMAX, CMIN and CAVG, calculated for diltiazem, desacetyl diltiazem and desmethyl diltiazem under steady-state conditions were within the acceptable range of 80-125%. Details of data analyses are given in Section IV.

IV. Results of Data Analyses without Subject #4

Plasma levels and pharmacokinetic parameters for diltiazem (parent drug), and two metabolites, desacetyl diltiazem and desmethyl diltiazem, were summarized below:

1. Diltiazem

a. Plasma levels of diltiazem under SS conditions

Table d1. MEAN PLASMA DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	89.58	26.68	97.45	31.20	0.92
1	86.13	35.18	88.23	27.07	0.98
2	82.14	32.80	84.68	26.93	0.97
3	88.41	38.64	87.10	27.01	1.02
4	103.84	51.03	94.87	29.41	1.09
5	123.15	53.23	113.72	34.63	1.08
6	155.16	57.18	149.64	40.14	1.04
7	160.66	54.65	161.17	38.27	1.00
8	154.48	46.80	160.10	37.55	0.96
9	136.04	45.30	146.87	32.65	0.93
10	120.08	40.04	130.13	34.58	0.92
11	104.56	42.43	112.31	31.31	0.93
12	93.16	39.20	99.16	32.58	0.94

b. PK parameters of diltiazem under SS conditions

Table d2. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCT	1406.00	482.50	1427.11	355.09	0.99
CAVG	117.17	40.21	118.93	29.59	0.99
CMAX	170.17	52.85	171.22	36.84	0.99
CMIN	77.13	29.38	82.44	25.76	0.94
FLUC1	0.81	0.27	0.77	0.25	1.05
FLUC2	1.32	0.67	1.18	0.54	1.12
LAUCT	1340.60	0.31	1386.85	0.24	0.97
LCAVG	111.72	0.31	115.57	0.24	0.97
LCMAX	162.53	0.31	167.21	0.23	0.97
LCMIN	72.60	0.35	78.86	0.31	0.92
LFLUC1	0.77	0.34	0.74	0.31	1.04
LFLUC2	1.18	0.48	1.08	0.42	1.09

Table d3. LSMEANS AND RATIOS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	RLSM12
PARAMETER			
AUCT	1406.00	1427.11	0.99
CAVG	117.17	118.93	0.99
CMAX	170.17	171.22	0.99
CMIN	77.13	82.44	0.94
FLUC1	0.81	0.77	1.05
FLUC2	1.32	1.18	1.12
LAUCT	1340.60	1386.85	0.97
LCAVG	111.72	115.57	0.97
LCMAX	162.53	167.21	0.97
LCMIN	72.60	78.86	0.92
LFLUC1	0.77	0.74	1.04
LFLUC2	1.18	1.08	1.09

Table d4. LSMEANS AND 90% CONFIDENCE INTERVALS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	LSM1	LSM2	LOWCI12	UPPCI12
AUCT	1406.00	1427.11	91.99	105.05
CAVG	117.17	118.93	91.99	105.05
CMAX	170.17	171.22	92.31	106.46
CMIN	77.13	82.44	86.92	100.18
FLUC1	0.81	0.77	94.90	115.26
FLUC2	1.32	1.18	96.71	127.66
LAUCT	1340.60	1386.85	90.78	102.94
LCAVG	111.72	115.57	90.78	102.94
LCMAX	162.53	167.21	90.26	104.68
LCMIN	72.60	78.86	85.80	98.78
LFLUC1	0.77	0.74	94.25	115.33
LFLUC2	1.18	1.08	94.85	126.34

2. Desacetyl diltiazem

a. Plasma levels of desacetyl diltiazem under SS conditions

Table dad1. MEAN PLASMA DESACETYL DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
0	14.94	15.27	17.49	18.59	0.85
1	14.96	15.89	17.19	19.29	0.87
2	14.73	14.38	16.95	19.22	0.87
3	15.12	16.04	16.90	19.90	0.89
4	15.75	17.79	17.24	20.26	0.91
5	16.65	17.41	17.64	19.48	0.94
6	17.93	19.22	18.51	20.52	0.97
7	19.24	20.65	20.03	22.65	0.96
8	19.38	20.81	20.98	23.62	0.92
9	19,23	19.16	21.49	23.75	0.89
10	18.83	20.70	20.62	23.63	0.91
11	17.22	19.52	20.02	25.87	0.86
12	16.96	19.89	18.90	24.36	0.90

b. PK parameters of desacetyl diltiazem under SS conditions

Table dad2. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANI-LOG

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCT	205.00	218.54	225.79	259.34	0.91
CAVG	17.08	18.21	18.82	21.61	0.91
CMAX	20.33	21.09	22.30	25.21	0.91
CMIN	13.48	14.48	15.98	18.68	0.84
FLUC1	0.42	0.12	0.35	0.12	1.18
FLUC2	0.54	0.19	0.43	0.17	1.26
LAUCT	161.63	0.58	172.06	0.61	0.94
LCAVG	13.47	0.58	14.34	0.61	0.94
LCMAX	16.22	0.57	17.12	0.60	0.95
LCMIN	10.58	0.59	12.04	0.63	0.88
LFLUC1	0.40	0.31	0.33	0.37	1.20
LFLUC2	0.51	0.38	0.40	0.42	1.28

Table dad3. LSMEANS AND RATIOS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	RLSM12
PARAMETER			
AUCT	205.00	225.79	0.91
CAVG	17.08	18.82	0.91
CMAX	20.33	22.30	0.91
CMIN	13.48	15.98	0.84
FLUC1	0.42	0.35	1.18
FLUC2	0.54	0.43	1.26
LAUCT	161.63	172.06	0.94
LCAVG	13.47	14.34	0.94
LCMAX	16.22	17.12	0.95
LCMIN	10.58	12.04	0.88
LFLUC1	0.40	0.33	1.20
LFLUC2	0.51	0.40	1.28

Table dad4. LSMEANS AND 90% CONFIDENCE INTERVALS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCT	205.00	225.79	82.65	98.93
CAVG	17.08	18.82	82.65	98.93
CMAX	20.33	22.30	82.56	99.78
CMIN	13.48	15.98	73.59	95.13
FLUC1	0.42	0.35	105.53	130.56
FLUC2	0.54	0.43	111.14	141.78
LAUCT	161.63	172.06	89.00	99.16
LCAVG	13.47	14.34	89.00	99.16
LCMAX	16.22	17.12	89.34	100.48
LCMIN	10.58	12.04	83.05	92.85
LFLUC1	0.40	0.33	105.35	136.66
LFLUC2	0.51	0.40	110.14	149.60

3. Desmethyl diltiazem

a. Plasma levels of desmethyl diltiazem under SS conditions

Table dmd1. MEAN PLASMA DESMETHYL DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	30.66	5.66	33.24	6.70	0.92
1	29.41	5.26	30.99	6.15	0.95
2	28.47	5.36	29.84	5.92	0.95
3	28.63	5.33	29.91	5.99	0.96
4	30.10	6.47	30.34	5.94	0.99
5	33.65	7.23	32.76	6.78	1.03
6	36.73	8.31	36.49	7.47	1.01
7	39.71	8.09	40.43	7.19	0.98
8	41.50	8.15	42.25	7.75	0.98
9	39.50	7.78	41.23	7.11	0.96
10	38.15	7.54	40.07	7.48	0.95
11	35.77	7.79	38.13	6.97	0.94
12	34.58	8.04	36.61	7.15	0.94

b. PK parameters of desmethyl diltiazem under SS conditions

Table dmd2. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANI-LOG

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	414.24	76.96	427.37	77.07	0.97
CAVG	34.52	6.41	35.61	6.42	0.97
CMAX	42.37	7.92	43.38	7.43	0.98
CMIN	26.91	5.25	29.09	5.65	0.93
FLUC1	0.45	0.10	0.40	0.10	1.11
FLUC2	0.58	0.17	0.50	0.16	1.16
LAUCT	407.25	0.19	420.72	0.18	0.97
LCAVG	33.94	0.19	35.06	0.18	0.97
LCMAX	41.65	0.19	42.74	0.18	0.97
LCMIN	26.43	0.20	28.59	0.19	0.92
LFLUC1	0.44	0.24	0.39	0.26	1.11
LFLUC2	0.56	0.31	0.48	0.31	1.17

Table dmd3. LSMEANS AND RATIOS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	LSM1	LSM2	RLSM12
AUCT	414.24	427.37	0.97
CAVG	34.52	35.61	0.97
CMAX	42.37	43.38	0.98
CMIN	26.91	29.09	0.93
FLUC1	0.45	0.40	1.11
FLUC2	0.58	0.50	1.16
LAUCT	407.25	420.72	0.97
LCAVG	33.94	35.06	0.97
LCMAX	41.65	42.74	0.97
LCMIN	26.43	28.59	0.92
LFLUC1	0.44	0.39	1.11
LFLUC2	0.56	0.48	1.17

Table dmd4. LSMEANS AND 90% CONFIDENCE INTERVALS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCT	414.24	427.37	93.76	100.09
CAVG	34.52	35.61	93.76	100.09
CMAX	42.37	43.38	94.34	100.99
CMIN	26.91	29.09	88.51	96.52
FLUC1	0.45	0.40	101.02	120.73
FLUC2	0.58	0.50	103.81	128.86
LAUCT	407.25	420.72	93.64	100.07
LCAVG	33.94	35.06	93.64	100.07
LCMAX	41.65	42.74	93.75	101.32
LCMIN	26.43	28.59	88.66	96.40
LFLUC1	0.44	0.39	101.03	122.77
LFLUC2	0.56	0.48	103.42	131.49

V. Conclusion

This addendum clarified the data discrepancies between the submitted data and reviewer's calculation. The 90% confidence intervals for log trasformed AUCT, CMAX, CMIN and CAVG, calculated for the data without Subject #4 for diltiazem, desacetyl diltiazem and desmethyl diltiazem are within the acceptable range of 80-125%. This fully supports the conclusion made by reviewer in the original review dated October 28, 1996.

/S/

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/S/ 5/2/1997

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Concur: _____ Date: 5/2/97

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cc: ANDA #74-910 (original, duplicate), Park, Drug File, Division File

OCT 28 1996

Diltiazem Hydrochloride ER Capsules	Mylan
60, 90 and 120 mg Capsules	Morgantown, WV
ANDA #74-910	Submission Date:
Reviewer: Moo Park	June 12, 1996
	September 12, 1996

Review of Two *In Vivo* Bioequivalence Studies, Dissolution Data and Two Waiver Requests

I. Objectives

Review of:

- An open-label randomized, two-way crossover bioequivalence study to compare the relative bioavailability of diltiazem extended release (ER) 120 mg capsules manufactured by MYLAN to that achieved by Cardizem^{R} SR, Hoechst Marion Roussel, 120 mg capsules under fasting and steady-state conditions. Fasting and steady-state studies were combined into one 8-day study.

- An open-label randomized, three-way crossover bioequivalence study to compare the relative bioavailability of diltiazem extended release (ER) 120 mg capsules manufactured by MYLAN to that achieved by Cardizem^{R} SR, Hoechst Marion Roussel, 120 mg capsules under nonfasting conditions.

- Dissolution data for the 60 mg, 90 mg and 120 mg Capsules of the test and reference products.

- A waiver request for the 60 mg and 90 mg capsules of the test product.

II. Background

Diltiazem hydrochloride is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). The therapeutic effects of diltiazem are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of the cardiac and vascular smooth muscle.

Diltiazem is well absorbed from the gastrointestinal tract and is subject to an extensive first-pass effect, giving an absolute bioavailability of about 40%. Diltiazem undergoes extensive

metabolism, in which 2-4% of the unchanged drug appears in the urine. *In vitro* binding studies show that diltiazem is 70-80% bound to plasma proteins. The plasma elimination half-life following single or multiple drug administration is about 3-4.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10-20% of the parent drug and is 25-50% as potent a coronary vasodilator as diltiazem. Minimum therapeutic plasma levels of diltiazem appear to bc in the range of 50-200 ng/mL. There is departure from linearity when dose strengths are increased; the half-life is slightly increased with dose. Hepatic impairment delays elimination and increases half-life and bioavailability.

Diltiazem is absorbed from Cardizem^{R} SR dosage form to about 92% of a reference solution during steady-state dosing. A single 120 mg dose of the capsule results in detectable plasma levels within 2-3 hours and peak plasma levels at 6-11 hours. The apparent elimination half-life after single or multiple dosing is 5-7 hours. The departure from linearity similar to that observed with the conventional tablet is observed. As the dose of Cardizem^{R} SR is increased from 60 mg twice daily (BID) to 120 mg BID, there is an increase in the area under the plasma concentration-time curve (AUC) of 2.6 times. When the dose is increased from 240 to 360 mg daily, there is an increase in AUC of 1.8 times. The average plasma levels of the capsule dosed twice daily at steady-state are equivalent to the tablet dosed four times daily when the same total daily dose is administered.

Cardizem^{R} SR is indicated for the treatment of hypertension, at daily doses ranging from 120-360 mg/day. Doses of 60-120 mg BID are usual starting doses, while the usual optimum dosage range is 120-180 mg BID.

III. Study Details

Protocols of the two *in vivo* bioequivalence studies are summarized below:

A. Fasting Single and Multiple Dose Study

1. Protocol #9559

2. Applicant: Mylan, Morgantown, WV

3. Study sites:

Clinical study:	Clinical and Pharmacologic Research Morgantown, WV
Analytical:	Mylan Pharmaceuticals Morgantown, WV

4. Investigators:

Principal investigator: Thomas S. Clark, MD

5. Clinical study dates: 11/15-12/21/95

   Assay dates: 1/3-3/13/96

6. Study design: Open-label, randomized, two-way crossover design.

7. Subjects: Twenty-eight healthy male volunteers from the Morgantown, West Virginia area were accepted for entry into the clinical phase of the study. In accordance with the criteria noted in the protocol #9559, subjects were determined to be in good health prior to entry into the study on the basis of interview, physical examination, complete blood count, differential, clinical chemistries, and urinalysis. Four subjects were withdrawn during phase 1. Twenty-four subjects successfully completed both phases of the clinical portion of the study.

8. Product information:

   Treatment 1: Test product
   Diltiazem HCl ER Capsules, 120 mg
   Mylan Pharmaceuticals, Inc.
   Lot # 2B005L
   Manufacture Date: 10/25/95
   Production Lot:

   Treatment 2: Reference product
   Cardizem^{R} SR Capsules, 120 mg
   Hoechst Marion Roussel, Inc.
   Lot # P20228 - EXP. 2/96

9. Dosing: Each treatment consisted of the administration of a single 120 mg dose of extended release diltiazem HCl (1 x 120 mg capsules) on day 1, then a 120 mg dose every twelve hours for day 3 through day 7 and a single dose on the morning of day 8. Subjects engaged in normal activity for the first 12 hours following the morning dose, avoiding vigorous exertion and complete rest.

10. Food and fluid intake: Each dose was administered with 240 mL of water. Subjects were required to fast overnight and for five hours after each dose on study days 1 and 8. Standard meals were provided at five and ten hours after each dose. On days 3 through 7 subjects were given a standard breakfast one hour after dosing. Snacks were provided during the evening of each day. Water was not allowed from 2 hours before until 2 hours after the morning dosing but was allowed at all other

times. During housing, meal plans were identical for both periods.

11. Housing: Subjects were housed at the clinical site from 11 hours before the first dose until 24 hours after the first dose. For the dosing throughout days 3-8, volunteers entered the study site no later than 9:00 pm on the day prior to dosing and remain at the clinical site until 12 hours after dosing on day 8.

12. Washout period: 21 days.

13. Blood samples: Serial blood samples were collected for 48 hours after the first dose, and 12 hours after the last dose on day 8. Trough Cmin samples were taken prior to the morning dose on days 6, 7, and 8.

    Blood samples for single dose study: On day 1, a single-dose was administered and no other doses were given for 48 hours. Single-dose blood samples were taken pre-dose and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 24, 36, and 48 hours post dose.

    Blood samples for mulltiple dose study: Doses during the steady-state portion of the study were given at 12 hours on day 3 through day 7 and once in the morning on day 8. On days 5, 6, and 7, Cmin blood samples were collected at 96, 120, and 144 hours, respectively. On day 8 blood samples were collected at 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, and 180 hours after the first dose administered on day 1.

14. Monitoring of subjects: Vital signs (including blood pressure, pulse rates and a Lead 11 ECG) were measured pre-dose and hourly for the first 12 hours and then at 24, 36 and 48 hours post-dose during the single dose study. During steady-state attainment vital signs were measured before the morning dose at 96, 120, 144 and 168 hours, following the first dose of drug administration on day 1.

15. IRB and informed consent: Concurrence obtained.

16. Pharmacokinetic and statistical analysis: S A S - G L M procedures were used on AUCT, AUCI, CMAX, KE, THALF, CAVG, CMIN, TMAX, FLUC1, FLUC2 and blood levels at each sampling points. The 90% confidence intervals (CI) were calculated for AUCT, AUCI, CMAX, CAVG, CMIN, FLUC1, AND FLUC2. An analysis of steady-state attainment was performed using concentration data from the 120, 144 and 168 hour plasma samples.

B. Bioequivalence Study under Nonfasting Conditions

1. Protocol #9572

2. Applicant: Mylan, Morgantown, WV

3. Study sites:

Clinical study: Clinical and Pharmacologic Research
Morgantown, WV

Analytical: Mylan Pharmaceuticals
Morgantown, WV

4. Investigators:

Principal investigator: Thomas S. Clark, MD

5. Clinical study dates: 1/14-2/13/96

Assay dates: 2/14-3/7/96

6. Study design: Open-label, randomized, three-way crossover design.

7. Subjects: Twenty-three healthy male volunteers from the Morgantown, West Virginia area were accepted for entry into the clinical phase of the study. In accordance with the criteria noted in the protocol #9572, subjects were determined to be in good health prior to entry into the study on the basis of interview, physical examination, complete blood count, differential, clinical chemistries, and urinalysis.

Twenty volunteers were present on the first day of dosing. Subjects #8 and #6 failed to report for personal reasons prior to phase 2 and 3. Subject #17 was withdrawn due to treatment for bronchitis and Subject #20 was discontinued due to pharyngitis prior to phase 2 and 3, respectively. Sixteen subjects successfully completed all three phases of the clinical portion of the study.

8. Product information:

Treatment 1:
Diltiazem HCl ER Capsules, 120 mg
Mylan Pharmaceuticals Inc.
1 x 120 ms, Administered with Food
Lot #2B005L
Production Lot - Units
Manufacturing date - 10/25/95

Treatment 2:
Cardizem^{R} SR Capsules, 120 mg
Marion Merrell Dow
1 x 120 mg, Administered with food
Lot #P20228, Exp. 2/96

Treatment 3:
Diltiazem HCl ER Capsules, 120 mg
Mylan Pharmaceuticals Inc.
1 x 120 mg, Fasting Administration
Lot #2B005L, Exp. To Be Determined
Production Lot - Units
Manufacturing Date- 10/25/95

9. Dosing: Each treatment consisted of the administration of 120 mg of the extended release diltiazem HCl (1 x 120 mg capsule) with 240 mL of water.

10. Food and fluid intake: Subjects receiving treatments 1 and 2 (fed) were required to fast overnight until 15 minutes prior to dosing, when they were given a standard breakfast. Breakfast consisted of 1 buttered English muffin, 1 fried egg, 1 slice of Canadian bacon, 1 slice of American cheese, 1 serving of hashed brown potatoes, 6 ounces of orange juice, and 8 ounces of whole milk. Standard meals (lunch and dinner) were provided at approximately 5 and 10 hours after dosing, and at appropriate times thereafter. Water was not permitted from two hours before until two hours after dosing, but was allowed at all other times.

11. Housing: From evening on the day prior to dosing until 24 hours after dosing.

12. Washout period: 14 days.

13. Blood samples: Serial blood samples were collected predose, and then post dose at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 18, 24, 30, 36 and 48 hours.

14. Monitoring of subjects: Volunteers engaged in normal activity for the first 12 hours after drug administration. Vital signs (including blood pressure, and pulse rate) were measured predose and hourly for the first 12 hours and then at 16, 24, 36 and 48 hours after dosing. A lead 11 ECG was recorded prior to dosing and hourly for the first 12 hours then at 24, 36 and 48 hours after dosing.

15. IRB and informed consent: Concurrence obtained.

16. Pharmacokinetic and statistical analysis: S A S - G L M procedures were used on AUCT, AUCI, CMAX, KE, THALF, TMAX, and blood levels at each sampling points. Test/Reference ratios were calculated for AUCT, AUCI, and CMAX.

IV. <u>Validation of Assay Method for Plasma Samples</u>

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V. In Vivo Results with Statistical Analysis

A. Single Dose Study under Fasting Conditions and Multiple Dose Study under Steady-State Conditions (#9559)

Twenty-eight healthy male volunteers were accepted for entry into the clinical phase of the study. Four subjects were withdrawn during phase 1. Subject #28 was withdrawn due to adverse events assessed as probably drug related. Subjects #3 and #27 were withdrawn due to protocol violations. Subject #8 elected to withdraw from the study for personal reasons not related to the study. Twenty-four subjects successfully completed both phases of the clinical portion of the study. Subject #13 was removed from the statistical portion of the study due to a protocol violation. This individual took an over-the-counter medication during the washout phase of the study. Therefore, the pharmacokinetic and statistical analyses were performed on the data for 23 subjects.

Vital signs were analyzed for statistical differences; these include systolic and diastolic blood pressure, heart rate and percent change from baseline of the ECG PR interval. There were no clinically significant differences in the parameters evaluated.

There were eight adverse events (7 subjects) reported during the eight day study. There were seven reports of headache and one

experience of dizziness, which were all assessed as probably drug related. There were no serious or life-threatening medical events reported for this study.

A-1. Single Dose Study Results under Fasting Conditions

Plasma levels and pharmacokinetic parameters for diltiazem (parent drug), and two metabolites, desacetyl diltiazem and desmethyl diltiazem, were summarized below:

1. Diltiazem

a. Plasma levels of diltiazem under fasting conditions

Mean plasma level-time profiles for the test and reference products were similar to each other as shown in Fig. 1 and Table 10. Peak mean diltiazem levels for the test and reference products were 81 ng/mL at 7 hours and 83 ng/mL at 7 hours, respectively. The peak diltiazem levels are approximately 12-13 times higher than those of desacetyl diltiazem and 4 times higher than those of desmethyl diltiazem.

The plasma data show that there is an apparent time lag of two hours in absorption process after the dose is administered under fasting conditions.

Table 10. MEAN PLASMA DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
MEAN1=TEST(LOT #2B005L); MEAN2=REFERENCE(LOT#P20228)
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.00	0.00	0.10	0.50	0.00
2	1.42	2.26	2.52	1.78	0.56
3	9.76	9.53	7.36	3.38	1.33
4	22.91	26.57	16.98	12.94	1.35
5	43.35	34.90	36.09	23.34	1.20
6	74.35	38.42	76.26	31.87	0.98
7	81.19	36.12	82.57	22.50	0.98
8	77.95	29.41	82.05	18.46	0.95
9	72.68	26.22	79.13	18.04	0.92
10	63.86	20.73	68.18	14.99	0.94
11	57.29	17.21	60.30	13.54	0.95
12	49.77	15.63	51.28	11.78	0.97
16	28.57	10.45	28.01	8.24	1.02
24	11.70	4.87	11.48	4.46	1.02
36	1.81	1.74	2.03	2.20	0.89
48	0.10	0.46	0.09	0.43	1.07

b. PK parameters of diltiazem under fasting conditions

Arithmetic and geometric means are summarized in Table 11 and least-squares means are shown in Table 12. The test/reference ratios of the least-squares means for the log-transformed PK

parameters, LAUCT, LAUCI, and LCMAX, are within range.

The 90% confidence intervals for the log-transformed PK parameters, LAUCT, LAUCI, and LCMAX, are within the acceptable range of 80-125 as shown in Table 13.

Table 11. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCI	950.99	349.26	954.35	215.36	1.00
AUCT	909.53	356.72	910.99	221.50	1.00
CMAX	88.53	33.01	93.14	26.64	0.95
KE	0.12	0.02	0.13	0.02	0.98
LAUCI	891.99	0.37	928.76	0.25	0.96
LAUCT	845.03	0.40	883.06	0.26	0.96
LCMAX	82.70	0.38	89.89	0.27	0.92
THALF	5.69	0.92	5.54	0.78	1.03
TMAX	7.52	1.68	7.48	1.41	1.01

Table 12. LSMEANS AND RATIOS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	LSM1	LSM2	RLSM12
AUCI	947.58	953.24	0.99
AUCT	906.33	910.61	1.00
CMAX	88.23	92.89	0.95
LAUCI	888.78	927.18	0.96
LAUCT	842.04	882.13	0.95
LCMAX	82.41	89.55	0.92

Table 13. LSMEANS AND 90% CONFIDENCE INTERVALS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	LSM1	LSM2	LOWCI12	UPPCI12
AUCI	947.58	953.24	90.46	108.35
AUCT	906.33	910.61	89.72	109.35
CMAX	88.23	92.89	82.53	107.44
LAUCI	888.78	927.18	87.08	105.53
LAUCT	842.04	882.13	85.74	106.28
LCMAX	82.41	89.55	81.29	104.17

2. Desacetyl diltiazem

a. Plasma levels of desacetyl diltiazem under fasting conditions

Mean plasma level-time profiles for the test and reference products were similar to each other as shown in Fig. 2 and Table 14. Peak mean desacetyl diltiazem levels for the test and reference products were 6.2 ng/mL at 10 hours and 6.8 ng/mL at 10 hours, respectively.

Table 14. MEAN PLASMA DESACETYL DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.00	0.00	0.00	0.00	.
2	0.00	0.00	0.00	0.00	.
3	0.05	0.23	0.00	0.00	.
4	0.78	1.96	0.29	0.69	2.73
5	1.74	1.42	1.50	1.52	1.15
6	3.61	1.66	3.97	2.21	0.91
7	4.61	1.85	5.25	2.46	0.88
8	5.54	2.30	6.18	2.75	0.90
9	5.97	2.54	6.67	3.09	0.89
10	6.19	2.92	6.83	3.48	0.91
11	6.15	3.26	6.79	3.99	0.91
12	5.86	3.44	6.35	3.84	0.92
16	5.02	4.06	5.30	4.11	0.95
24	3.03	3.79	3.06	2.71	0.99
36	0.88	2.62	0.63	1.50	1.41
48	0.33	1.13	0.20	0.66	1.68

b. PK parameters of desacetyl diltiazem under fasting conditions

Arithmetic and geometric means are summarized in Table 15 and least-squares means are shown in Table 16. The test/reference ratios of the least-squares means for the log-transformed PK parameters, LAUCT, LAUCI, and LCMAX, are within range.

The 90% confidence intervals for the log-transformed PK parameters, LAUCT, LAUCI, and LCMAX, are within the acceptable range of 80-125 as shown in Table 17.

Table 15. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCI	147.79	134.40	147.03	105.15	1.01
AUCT	111.03	117.88	112.44	100.87	0.99
CMAX	7.13	3.89	7.39	3.95	0.97
KE	0.07	0.02	0.07	0.02	1.03
LAUCI	117.79	0.62	127.21	0.49	0.93
LAUCT	82.68	0.70	92.23	0.56	0.90
LCMAX	6.38	0.46	6.72	0.42	0.95
THALF	10.40	2.86	10.49	2.39	0.99
TMAX	9.74	2.20	9.83	1.40	0.99

Table 16. LSMEANS AND RATIOS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	LSM1	LSM2	RLSM12
AUCI	149.22	148.16	1.01
AUCT	112.47	113.71	0.99
CMAX	7.17	7.42	0.97
LAUCI	118.16	127.74	0.93
LAUCT	83.11	92.75	0.90
LCMAX	6.40	6.72	0.95

Table 17. LSMEANS AND 90% CONFIDENCE INTERVALS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	LSM1	LSM2	LOWCI12	UPPCI12
AUCI	149.22	148.16	88.99	112.43
AUCT	112.47	113.71	88.32	109.50
CMAX	7.17	7.42	87.40	106.02
LAUCI	118.16	127.74	82.78	103.36
LAUCT	83.11	92.75	80.14	100.20
LCMAX	6.40	6.72	87.22	103.95

3. Desmethyl diltiazem

a. Plasma levels of desmethyl diltiazem under fasting conditions

Mean plasma level-time profiles for the test and reference products

were similar to each other as shown in Fig. 3 and Table 18. Peak mean desmethyl diltiazem levels for the test and reference products were 19.8 ng/mL at 9 hours and 21.5 ng/mL at 9 hours, respectively.

Table 18. MEAN PLASMA DESMETHYL DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
1	0.00	0.00	0.00	0.00	.
2	0.00	0.00	0.09	0.44	0.00
3	1.45	1.78	1.40	1.44	1.03
4	4.90	3.09	4.60	2.56	1.06
5	9.69	4.39	8.95	4.95	1.08
6	15.40	5.11	16.00	6.15	0.96
7	18.58	5.65	19.44	5.24	0.96
8	19.62	5.06	20.72	3.89	0.95
9	19.75	4.61	21.52	4.09	0.92
10	19.26	4.26	20.91	3.63	0.92
11	18.92	4.02	19.99	3.29	0.95
12	17.97	3.85	18.84	3.22	0.95
16	13.65	3.41	13.96	2.80	0.98
24	7.57	2.34	7.65	1.90	0.99
36	2.26	1.73	2.23	1.76	1.01
48	0.11	0.53	0.09	0.44	1.20

b. <u>PK parameters of desmethyl diltiazem under fasting conditions</u>

Arithmetic and geometric means are summarized in Table 19 and least-squares means are shown in Table 20. The test/reference ratios of the least-squares means for the log-transformed PK parameters, LAUCT, LAUCI, and LCMAX, are within range.

The 90% confidence intervals for the log-transformed PK parameters, LAUCT, LAUCI, and LCMAX, are within the acceptable range of 80-125 as shown in Table 21.

Table 19. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCI	383.35	92.77	394.57	75.02	0.97
AUCT	335.96	94.43	345.41	76.31	0.97
CMAX	21.38	4.46	22.75	4.54	0.94
KE	0.08	0.01	0.08	0.01	0.98
LAUCI	372.49	0.25	387.22	0.20	0.96
LAUCT	323.15	0.29	336.79	0.24	0.96
LCMAX	20.96	0.20	22.32	0.20	0.94
THALF	8.74	1.10	8.71	1.63	1.00
TMAX	9.09	1.83	8.70	1.46	1.05

Table 20. LSMEANS AND RATIOS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	LSM1	LSM2	RLSM12
AUCI	382.58	394.39	0.97
AUCT	335.46	345.46	0.97
CMAX	21.32	22.70	0.94
LAUCI	371.52	386.85	0.96
LAUCT	322.46	336.71	0.96
LCMAX	20.90	22.27	0.94

Table 21. LSMEANS AND 90% CONFIDENCE INTERVALS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	LSM1	LSM2	LOWCI12	UPPCI12
AUCI	382.58	394.39	91.40	102.61
AUCT	335.46	345.46	89.96	104.25
CMAX	21.32	22.70	87.30	100.54
LAUCI	371.52	386.85	90.26	102.19
LAUCT	322.46	336.71	88.70	103.41
LCMAX	20.90	22.27	87.89	100.28

A-2. Study Results under Steady-State (SS) Conditions

The applicant showed by regression analysis and t-test that steady-state was achieved within 5 days of dosing. The applicant also showed that no statistically significant differences in mean slopes between treatments exist for diltiazem, desacetyl diltiazem or N-desmethyl diltiazem.

Plasma levels and pharmacokinetic parameters for diltiazem (parent drug), and two metabolites, desacetyl diltiazem and desmethyl diltiazem, were summarized below:

1. Diltiazem

a. Plasma levels of diltiazem under SS conditions

Mean plasma level-time profiles for the test and reference products under steady-state conditions were similar to each other as shown in Fig. 4 and Table 22. Peak mean diltiazem levels for the test and reference products were 157 ng/mL at 7 hours and 159 ng/mL at 7 hours, respectively. The peak diltiazem levels are approximately 8 times higher than those of desacetyl diltiazem and 4 times higher than those of desmethyl diltiazem.

The plasma data show that there is an apparent lag time of two hours in absorption process after the dose is administered under steady-state conditions. During this two-hour period the plasma levels actually decreased.

Table 22. MEAN PLASMA DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

TIME HR	MEAN1	SD1	MEAN2	SD2	RMEAN12
0	88.43	26.65	95.36	32.09	0.93
1	84.54	35.21	86.22	28.15	0.98
2	80.67	32.81	82.51	28.29	0.98
3	86.64	38.69	85.04	28.17	1.02
4	101.37	51.24	92.70	30.56	1.09
5	119.82	54.41	111.53	35.42	1.07
6	150.93	59.42	146.69	41.69	1.03
7	156.69	56.69	158.53	39.49	0.99
8	151.27	48.24	158.52	37.46	0.95
9	134.13	45.20	144.93	33.23	0.93
10	117.53	40.99	128.07	35.19	0.92
11	101.35	44.22	110.18	32.25	0.92
12	89.11	42.94	94.85	37.96	0.94

b. PK parameters of diltiazem under SS conditions

Arithmetic and geometric means are summarized in Table 23 and least-squares means are shown in Table 24. The test/reference

ratios of the least-squares means for the log-transformed PK parameters, LAUCT, LCAVG, LCMAX, LCMIN and LFLUC1 are within 0.92-1.04 range.

The 90% confidence intervals for the log-transformed PK parameters, LAUCT, LCAVG, LCMAX, LCMIN and LFLUC1 are within the acceptable range of 80-125 as shown in Table 25.

Table 23. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	1367.69	505.94	1398.65	372.81	0.98
CAVG	113.97	42.16	116.55	31.07	0.98
CMAX	166.77	54.14	169.16	37.34	0.99
CMIN	73.78	32.90	78.86	30.48	0.94
FLUC1	0.87	0.38	0.82	0.34	1.06
FLUC2	1.32	0.67	1.18	0.54	1.12
LAUCT	1287.05	0.36	1352.01	0.27	0.95
LCAVG	107.25	0.36	112.67	0.27	0.95
LCMAX	158.57	0.33	165.03	0.23	0.96
LCMIN	72.60	0.35	78.86	0.31	0.92
LFLUC1	0.80	0.40	0.77	0.37	1.04
LFLUC2	1.18	0.48	1.08	0.42	1.09

Table 24. LSMEANS AND RATIOS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	LSM1	LSM2	RLSM12
AUCT	1363.27	1396.96	0.98
CAVG	113.61	116.41	0.98
CMAX	166.35	168.72	0.99
CMIN	73.60	78.79	0.93
FLUC1	0.86	0.82	1.06
FLUC2	1.32	1.18	1.12
LAUCT	1284.82	1351.40	0.95
LCAVG	107.07	112.62	0.95
LCMAX	158.23	164.61	0.96
LCMIN	72.60	78.86	0.92
LFLUC1	0.80	0.76	1.05
LFLUC2	1.18	1.08	1.09

Table 25. LSMEANS AND 90% CONFIDENCE INTERVALS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCT	1363.27	1396.96	91.03	104.15
CAVG	113.61	116.41	91.03	104.15
CMAX	166.35	168.72	91.61	105.58
CMIN	73.60	78.79	86.80	100.03
FLUC1	0.86	0.82	96.50	115.22
FLUC2	1.32	1.18	96.71	127.66
LAUCT	1284.82	1351.40	88.92	101.66
LCAVG	107.07	112.62	88.92	101.66
LCMAX	158.23	164.61	89.32	103.45
LCMIN	72.60	78.86	85.80	98.78
LFLUC1	0.80	0.76	95.05	115.28
LFLUC2	1.18	1.08	94.85	126.34

2. Desacetyl diltiazem

a. Plasma levels of desacetyl diltiazem under SS conditions

Mean plasma level-time profiles for the test and reference products under steady-state conditions were similar to each other as shown in Fig. 5 and Table 26. Peak mean desacetyl diltiazem levels for the test and reference products were 18.9 ng/mL at 8 hours and 21.1 ng/mL at 9 hours, respectively.

The plasma data show that there is an apparent lag time of two hours in absorption process after the dose is administered under steady-state conditions. During this two-hour period the plasma levels actually decreased.

Table 26. MEAN PLASMA DESACETYL DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	14.66	14.98	17.16	18.23	0.85
1	14.63	15.60	16.84	18.92	0.87
2	14.40	14.14	16.53	18.88	0.87
3	14.75	15.77	16.49	19.54	0.89
4	15.33	17.50	16.81	19.90	0.91
5	16.17	17.17	17.24	19.14	0.94
6	17.42	18.93	18.10	20.14	0.96
7	18.70	20.34	19.60	22.23	0.95
8	18.86	20.49	20.54	23.17	0.92
9	18.75	18.86	21.09	23.29	0.89
10	18.25	20.41	20.06	23.25	0.91
11	16.59	19.31	19.28	25.53	0.86
12	16.23	19.76	18.07	24.13	0.90

b. PK parameters of desacetyl diltiazem under SS conditions

Arithmetic and geometric means are summarized in Table 27 and least-squares means are shown in Table 28. The test/reference ratios of the least-squares means for the log-transformed PK parameters, LAUCT, LCAVG, LCMAX, LCMIN and LFLUC1 are within 0.88-1.19 range.

The 90% confidence intervals for the log-transformed PK parameters, LAUCT, LCAVG, LCMAX, and LCMIN are within the acceptable range of 80-125 as shown in Table 29. The 90% confidence interval for LFLUC1 was

Table 27. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	MEAN1	SD1	MEAN2	SD2	RMEAN12
AUCT	199.23	215.30	220.14	254.82	0.91
CAVG	16.60	17.94	18.34	21.24	0.91
CMAX	19.82	20.75	21.87	24.72	0.91
CMIN	12.89	14.42	15.28	18.55	0.84
FLUC1	0.46	0.24	0.41	0.27	1.14
FLUC2	0.54	0.19	0.43	0.17	1.26
LAUCT	156.08	0.59	167.74	0.61	0.93
LCAVG	13.01	0.59	13.98	0.61	0.93
LCMAX	15.77	0.57	16.87	0.59	0.93
LCMIN	10.58	0.59	12.04	0.63	0.88
LFLUC1	0.42	0.40	0.36	0.48	1.19
LFLUC2	0.51	0.38	0.40	0.42	1.28

Table 28. LSMEANS AND RATIOS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

PARAMETER	LSM1	LSM2	RLSM12
AUCT	201.91	223.32	0.90
CAVG	16.83	18.61	0.90
CMAX	20.07	22.16	0.91
CMIN	13.09	15.53	0.84
FLUC1	0.46	0.40	1.14
FLUC2	0.54	0.43	1.26
LAUCT	157.19	168.90	0.93
LCAVG	13.10	14.08	0.93
LCMAX	15.88	16.96	0.94
LCMIN	10.58	12.04	0.88
LFLUC1	0.42	0.35	1.19
LFLUC2	0.51	0.40	1.28

Table 29. LSMEANS AND 90% CONFIDENCE INTERVALS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCT	201.91	223.32	82.55	98.27
CAVG	16.83	18.61	82.55	98.27
CMAX	20.07	22.16	82.30	98.92
CMIN	13.09	15.53	73.69	94.85
FLUC1	0.46	0.40	103.43	125.26
FLUC2	0.54	0.43	111.14	141.78
LAUCT	157.19	168.90	88.16	98.25
LCAVG	13.10	14.08	88.16	98.25
LCMAX	15.88	16.96	88.16	99.41
LCMIN	10.58	12.04	83.05	92.85
LFLUC1	0.42	0.35	105.29	135.06
LFLUC2	0.51	0.40	110.14	149.60

3. Desmethyl diltiazem

a. Plasma levels of desmethyl diltiazem under SS conditions

Mean plasma level-time profiles for the test and reference products under steady-state conditions were similar to each other as shown in Fig. 6 and Table 30. Peak mean desmethyl diltiazem levels for the test and reference products were 40.7 ng/mL at 8 hours and 42.0 ng/mL at 8 hours, respectively.

The plasma data show that there is an apparent lag time of two hours in absorption process after the dose is administered under steady-state conditions. During this two-hour period the plasma levels actually decreased.

Table 30. MEAN PLASMA DESMETHYL DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	30.47	5.61	32.89	6.76	0.93
1	28.96	5.59	30.61	6.28	0.95
2	28.06	5.58	29.31	6.31	0.96
3	28.18	5.65	29.42	6.30	0.96
4	29.53	6.88	29.87	6.21	0.99
5	32.88	7.97	32.34	6.93	1.02
6	35.92	9.00	36.06	7.59	1.00
7	38.86	8.88	39.98	7.36	0.97
8	40.67	8.90	42.03	7.64	0.97
9	38.85	8.22	40.88	7.16	0.95
10	37.21	8.65	39.57	7.69	0.94
11	34.57	9.54	37.52	7.42	0.92
12	33.07	10.66	35.02	10.34	0.94

b. PK parameters of desmethyl diltiazem under SS conditions

Arithmetic and geometric means are summarized in Table 31 and least-squares means are shown in Table 32. The test/reference ratios of the least-squares means for the log-transformed PK parameters, LAUCT, LCAVG, LCMAX, LCMIN and LFLUC1 are within range.

The 90% confidence intervals for the log-transformed PK parameters, LAUCT, LCAVG, LCMAX, and LCMIN are within the acceptable range of 80-125 as shown in Table 33.

Table 31. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCT	403.86	90.17	421.01	81.23	0.96
CAVG	33.66	7.51	35.08	6.77	0.96
CMAX	41.83	8.17	43.26	7.28	0.97
CMIN	25.74	7.60	27.83	8.20	0.93
FLUC1	0.52	0.35	0.46	0.27	1.12
FLUC2	0.58	0.17	0.51	0.16	1.15
LAUCT	392.62	0.26	413.41	0.20	0.95
LCAVG	32.72	0.26	34.45	0.20	0.95
LCMAX	41.05	0.20	42.64	0.18	0.96
LCMIN	26.43	0.20	28.59	0.19	0.92
LFLUC1	0.47	0.40	0.42	0.39	1.11
LFLUC2	0.56	0.31	0.49	0.31	1.15

Table 32. LSMEANS AND RATIOS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	RLSM12
PARAMETER			
AUCT	403.33	420.72	0.96
CAVG	33.61	35.06	0.96
CMAX	41.75	43.20	0.97
CMIN	25.75	27.85	0.92
FLUC1	0.51	0.46	1.12
FLUC2	0.58	0.51	1.15
LAUCT	392.23	413.08	0.95
LCAVG	32.69	34.42	0.95
LCMAX	40.97	42.58	0.96
LCMIN	26.43	28.59	0.92
LFLUC1	0.46	0.42	1.11
LFLUC2	0.56	0.49	1.15

Table 33. LSMEANS AND 90% CONFIDENCE INTERVALS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCT	403.33	420.72	92.30	99.43
CAVG	33.61	35.06	92.30	99.43
CMAX	41.75	43.20	93.26	100.00
CMIN	25.75	27.85	88.45	96.48
LAUCT	392.23	413.08	90.59	99.52
LCAVG	32.69	34.42	90.59	99.52
LCMAX	40.97	42.58	92.47	100.13
LCMIN	26.43	28.59	88.66	96.40

B. Study under Nonfasting Conditions (#9572)

Twenty-three healthy male volunteers were accepted for entry into the clinical phase of the study. Twenty volunteers were present on the first day of dosing. Subjects #8 and #6 failed to report for personal reasons which were not study related prior to phase 2 and 3, respectively. Subject #17 was withdrawn due to treatment for bronchitis and Subject #20 was discontinued due to pharyngitis prior to phase 2 and 3, respectively. Sixteen subjects successfully completed all three phases of the clinical portion of the study.

Vital signs (including blood pressure, and pulse rate) were measured predose and hourly for the first 12 hours and then at 16, 24, 36 and 48 hours after dosing. A lead 11 ECG was recorded prior to dosing and hourly for the first 12 hours then at 24, 36 and 48 hours after dosing. There were no clinically significant differences in the vital signs for the fed treatments (1 and 2).

There were twelve adverse events reported for this study. Of the twelve reported, eleven were assessed as drug-related. There were ten reports of a headache and one report of blurred vision. Prior to phase 3 subject #20 was discontinued due to pharyngitis. There were no serious or life threatening adverse events reported for this study.

Plasma levels and pharmacokinetic parameters for diltiazem (parent drug), and two metabolites, desacetyl diltiazem and desmethyl diltiazem, were summarized below:

1. Diltiazem

a. Plasma levels of diltiazem under nonfasting conditions

Mean plasma level-time profiles for the test and reference products

under nonfasting conditions were similar to each other as shown in Fig. 7 and Table 34. Mean plasma level-time profile for the test product under fasting conditions was similar to the results obtained under nonfasting conditions. No obvious food effect is shown in the data obtained. Peak mean diltiazem levels for the test-fed, reference-fed, and test-fast were 81.6 ng/mL at 8 hours, 80.6 ng/mL at 8 hours, and 83.3 ng/mL at 7 hours, respectively.

The plasma data show that there is an apparent lag time of two hours in absorption process after the dose is administered under fasting and nonfasting conditions.

Table 34. MEAN PLASMA DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
MEAN1=TEST-FED; MEAN2=REFERENCE-FED; MEAN3=TEST-FAST
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	0.00	0.00	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.00	0.00	0.00
2	0.71	2.10	2.17	2.84	1.70	1.88
3	5.27	5.40	7.46	5.29	7.52	5.88
4	16.18	10.08	14.78	10.96	20.44	15.79
5	27.40	21.10	21.66	15.26	41.38	33.04
6	55.25	31.96	46.52	20.06	79.73	44.96
7	69.61	31.34	63.57	22.95	83.31	38.75
8	81.58	33.64	80.59	34.77	81.11	40.85
9	76.93	29.25	76.11	29.54	75.06	40.28
10	69.53	27.17	73.28	30.56	66.42	37.78
11	57.58	23.93	66.73	29.75	54.84	28.93
12	49.23	23.39	57.75	26.13	46.48	25.13
14	36.46	17.89	43.92	21.85	36.12	18.80
16	27.42	14.63	32.03	18.14	26.74	14.37
18	21.74	13.17	22.70	11.90	20.41	11.98
24	11.87	8.54	12.64	7.32	11.22	6.92
30	6.10	5.06	6.33	4.91	5.69	4.65
36	2.80	3.41	2.57	2.64	2.60	2.35
48	0.39	1.08	0.88	1.38	0.48	1.03

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	.	.
1	.	.	.
2	0.33	0.42	1.28
3	0.71	0.70	0.99
4	1.09	0.79	0.72
5	1.26	0.66	0.52
6	1.19	0.69	0.58
7	1.10	0.84	0.76
8	1.01	1.01	0.99
9	1.01	1.02	1.01
10	0.95	1.05	1.10
11	0.86	1.05	1.22
12	0.85	1.06	1.24
14	0.83	1.01	1.22
16	0.86	1.03	1.20
18	0.96	1.06	1.11
24	0.94	1.06	1.13
30	0.96	1.07	1.11
36	1.09	1.08	0.99
48	0.45	0.82	1.83

b. <u>PK parameters of diltiazem under nonfasting conditions</u>

Arithmetic and geometric means are summarized in Table 35 and least-squares means are shown in Table 36. The test/reference ratios of the least-squares means under nonfasting conditions for the log-transformed PK parameters, LAUCT, LAUCI, and LCMAX, are within range.

Table 35. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
PARAMETER						
AUCI	902.02	389.59	949.24	429.26	931.91	490.88
AUCT	869.53	389.00	913.30	430.48	903.22	490.27
CMAX	92.31	30.41	88.66	35.01	90.98	44.80
KE	0.12	0.03	0.11	0.03	0.11	0.02
LAUCI	826.43	0.43	873.67	0.41	808.06	0.57
LAUCT	791.47	0.45	833.98	0.43	775.15	0.59
LCMAX	88.31	0.30	83.43	0.35	79.64	0.56
THALF	6.22	1.51	7.01	2.54	6.29	1.28
TMAX	8.13	1.67	9.25	1.44	7.38	1.02

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
PARAMETER			
AUCI	0.95	0.97	1.02
AUCT	0.95	0.96	1.01
CMAX	1.04	1.01	0.97
KE	1.09	1.04	0.95
LAUCI	0.95	1.02	1.08
LAUCT	0.95	1.02	1.08
LCMAX	1.06	1.11	1.05
THALF	0.89	0.99	1.11
TMAX	0.88	1.10	1.25

Table 36. LSMEANS AND RATIOS
FOR DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	922.64	964.77	952.53	0.96	0.97	1.01
AUCT	890.24	928.21	923.94	0.96	0.96	1.00
CMAX	93.14	88.03	91.82	1.06	1.01	0.96
LAUCI	838.64	882.67	819.99	0.95	1.02	1.08
LAUCT	803.78	842.49	787.21	0.95	1.02	1.07
LCMAX	88.90	82.90	80.18	1.07	1.11	1.03

2. Desacetyl Diltiazem

a. Plasma levels of desacetyl diltiazem under nonfasting conditions

Mean plasma level-time profiles for the test and reference products under nonfasting conditions were similar to each other as shown in Fig. 8 and Table 37. Mean plasma level-time profile for the test

product under fasting conditions was similar to the results obtained under nonfasting conditions. No obvious food effect is shown in the data obtained. Peak mean desacetyl diltiazem levels for the test-fed, reference-fed, and test-fast were 6.9 ng/mL at 10 hours, 6.4 ng/mL at 12 hours, and 6.5 ng/mL at 9 hours, respectively.

Table 37. MEAN PLASMA DESACETYL DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	0.00	0.00	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.00	0.00	0.00
2	0.00	0.00	0.00	0.00	0.00	0.00
3	0.00	0.00	0.00	0.00	0.00	0.00
4	0.31	0.56	0.22	0.62	0.44	0.80
5	1.00	1.20	0.65	1.05	1.52	1.81
6	2.69	1.83	2.18	1.24	3.81	2.62
7	4.20	2.59	3.52	1.74	5.04	2.47
8	5.47	2.89	4.97	2.13	5.65	2.85
9	6.61	3.32	5.98	2.70	6.49	3.25
10	6.85	3.64	6.21	2.83	6.34	3.83
11	6.58	3.75	6.35	3.30	6.41	3.58
12	6.51	3.72	6.38	3.42	6.14	3.73
14	5.91	3.33	6.03	3.41	5.81	3.37
16	5.34	3.01	5.50	3.44	5.15	2.99
18	4.51	2.84	4.62	2.80	4.27	2.71
24	3.25	2.39	3.27	2.28	3.07	2.11
30	1.84	1.86	1.77	1.98	1.60	1.80
36	0.71	1.38	0.77	1.17	0.74	1.09
48	0.21	0.60	0.18	0.49	0.15	0.42

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	.	.
1	.	.	.
2	.	.	.
3	.	.	.
4	1.41	0.71	0.51
5	1.54	0.66	0.43
6	1.24	0.71	0.57
7	1.20	0.83	0.70
8	1.10	0.97	0.88
9	1.11	1.02	0.92
10	1.10	1.08	0.98
11	1.04	1.03	0.99
12	1.02	1.06	1.04
14	0.98	1.02	1.04
16	0.97	1.04	1.07
18	0.98	1.06	1.08
24	0.99	1.06	1.06
30	1.04	1.15	1.11
36	0.92	0.95	1.03
48	1.17	1.35	1.16

b. PK parameters of desacetyl diltiazem under nonfasting conditions

Arithmetic and geometric means are summarized in Table 38 and least-squares means are shown in Table 39. The test/reference ratios of the least-squares means under nonfasting conditions for the log-transformed PK parameters, LAUCT, LAUCI, and LCMAX, are within range.

Table 38. ARITHMETIC AND GEOMETRIC MEANS AND RATIOS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
PARAMETER						
AUCI	162.22	103.64	140.45	82.43	148.46	82.40
AUCT	117.65	84.82	114.15	79.55	114.47	79.86
CMAX	7.40	3.80	7.08	3.34	6.95	3.64
KE	0.06	0.04	0.06	0.02	0.06	0.03
LAUCI	133.42	0.67	121.41	0.55	128.79	0.56
LAUCT	92.85	0.73	93.01	0.66	89.77	0.77
LCMAX	6.56	0.51	6.46	0.43	6.11	0.54
THALF	15.15	15.28	11.75	3.24	12.03	5.76
TMAX	10.19	2.07	10.81	1.76	10.13	1.96

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
PARAMETER			
AUCI	1.16	1.09	0.95
AUCT	1.03	1.03	1.00
CMAX	1.05	1.06	1.02
KE	1.01	1.02	1.01
LAUCI	1.10	1.04	0.94
LAUCT	1.00	1.03	1.04
LCMAX	1.01	1.07	1.06
THALF	1.29	1.26	0.98
TMAX	0.94	1.01	1.07

Table 39. LSMEANS AND RATIOS
FOR DESACETYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	161.40	144.71	145.85	1.12	1.11	0.99
AUCT	119.18	117.17	116.00	1.02	1.03	1.01
CMAX	7.41	7.18	6.96	1.03	1.06	1.03
LAUCI	131.03	124.13	125.11	1.06	1.05	0.99
LAUCT	92.61	94.50	89.53	0.98	1.03	1.06
LCMAX	6.51	6.53	6.07	1.00	1.07	1.08

3. Desmethyl diltiazem

a. Plasma levels of desmethyl diltiazem under nonfasting conditions

Mean plasma level-time profiles for the test and reference products under nonfasting conditions were similar to each other as shown in Fig. 9 and Table 40. Mean plasma level-time profile for the test product under fasting conditions was similar to the results obtained under nonfasting conditions. No obvious food effect is shown in the data obtained. Peak mean desmethyl diltiazem levels for the test-fed, reference-fed, and test-fast were 21.9 ng/mL at 9 hours, 21.3 ng/mL at 10 hours, and 19.8 ng/mL at 9 hours, respectively.

Table 40. MEAN PLASMA DESMETHYL DILTIAZEM LEVELS FOR TEST AND REFERENCE PRODUCTS
UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
TIME HR						
0	0.00	0.00	0.00	0.00	0.00	0.00
1	0.00	0.00	0.00	0.00	0.00	0.00
2	0.00	0.00	0.00	0.00	0.00	0.00
3	0.35	1.00	0.58	1.30	1.08	1.47
4	3.77	2.76	3.38	1.85	4.08	2.60
5	6.97	4.07	5.61	2.08	8.36	4.67
6	14.20	5.95	12.54	3.27	15.80	5.93
7	18.03	6.32	16.82	3.29	18.85	5.81
8	21.66	5.33	20.41	3.97	19.81	5.99
9	21.87	4.50	20.84	4.46	19.83	6.42
10	21.51	4.35	21.32	5.44	19.17	6.20
11	19.78	4.50	20.70	5.44	18.07	5.86
12	18.72	4.73	19.49	5.39	16.59	5.72
14	15.71	4.23	17.29	5.07	15.03	4.80
16	13.35	3.95	14.56	4.99	12.65	4.11
18	11.37	3.93	11.90	3.90	10.53	3.74
24	7.41	3.17	7.69	3.09	6.90	3.09
30	4.72	2.91	5.21	2.54	4.26	2.84
36	2.29	2.14	2.33	2.15	2.00	2.00
48	0.32	0.89	0.32	0.89	0.27	0.74

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
TIME HR			
0	.	.	.
1	.	.	.
2	.	.	.
3	0.61	0.33	0.54
4	1.11	0.93	0.83
5	1.24	0.83	0.67
6	1.13	0.90	0.79
7	1.07	0.96	0.89
8	1.06	1.09	1.03
9	1.05	1.10	1.05
10	1.01	1.12	1.11
11	0.96	1.09	1.15
12	0.96	1.13	1.17
14	0.91	1.05	1.15
16	0.92	1.06	1.15
18	0.96	1.08	1.13
24	0.96	1.07	1.12
30	0.91	1.11	1.22
36	0.98	1.14	1.16
48	0.99	1.18	1.19

b. PK parameters of desmethyl diltiazem under nonfasting conditions

Arithmetic and geometric means are summarized in Table 41 and least-squares means are shown in Table 42. The test/reference ratios of the least-squares means under nonfasting conditions for the log-transformed PK parameters, LAUCT, LAUCI, and LCMAX, are within range.

Table 41. ARITHMETIC MEANS AND RATIOS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
PARAMETER						
AUCI	377.32	114.56	387.30	120.10	357.15	128.32
AUCT	342.54	110.55	350.29	116.94	321.45	127.27
CMAX	23.68	4.11	23.15	5.22	21.17	6.64
KE	0.09	0.01	0.08	0.01	0.09	0.01
LAUCI	360.60	0.32	370.38	0.31	335.17	0.37
LAUCT	325.40	0.34	332.91	0.33	297.28	0.42
LCMAX	23.34	0.18	22.64	0.22	20.20	0.32
THALF	8.10	1.21	8.53	1.34	8.29	1.20
TMAX	8.69	1.45	9.31	1.35	8.19	1.17

(CONTINUED)

	RMEAN12	RMEAN13	RMEAN23
PARAMETER			
AUCI	0.97	1.06	1.08
AUCT	0.98	1.07	1.09
CMAX	1.02	1.12	1.09
KE	1.05	1.02	0.97
LAUCI	0.97	1.08	1.11
LAUCT	0.98	1.09	1.12
LCMAX	1.03	1.16	1.12
THALF	0.95	0.98	1.03
TMAX	0.93	1.06	1.14

Table 42. LSMEANS AND RATIOS
FOR DESMETHYL DILTIAZEM
UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	382.42	390.39	362.25	0.98	1.06	1.08
AUCT	348.12	354.11	327.02	0.98	1.06	1.08
CMAX	23.63	22.91	21.13	1.03	1.12	1.08
LAUCI	363.78	371.59	338.13	0.98	1.08	1.10
LAUCT	328.97	334.77	300.54	0.98	1.09	1.11
LCMAX	23.28	22.38	20.15	1.04	1.16	1.11

C. Summary of Sequence Effects from PROC GLM

Significant sequence effects at the significance level of 0.1 were identified throughout the three studies only with LFLUC1 and LFLUC2 of desacetyl diltiazem under steady-state conditions.

VI. Product Information

1. Formulation

Test formulation for the 120 mg strength capsule is shown in Table 43. Granules are produced from the ingredients and these same granules are used to produce the 60 mg, 90 mg and 120 mg capsules. Inactive ingredients of the reference product consist of fumaric acid, povidone, starch, sucrose, talc, titanium dioxide, coloring agents and other ingredients.

Table 43. Test Formulation for 120 mg Strength

Ingredient	Content mg/tablet	w/w %
Diltiazem Hydrochloride, USP	120	
Povidone, NF		
Silicon Dioxide, NF		
Sugar Spheres, NF		
Methacrylic Acid Copolymer, NF		
Diethyl Phthalate, NF		
Total	256.4	100

2. Assay and content uniformity

VII. Dissolution

Test and reference products met USP dissolution specifications as shown in Table 46. USP dissolution specifications are shown in Table 45:

Table 45. Dissolution Method

USP Method for Dissolution Testing USP Drug Release Test 4	
Medium and Volume	water; 900 mL
Apparatus and rpm	2 (paddle); 100 rpm
Time	4, 8, 12 and 24 hours
Tolerances	4 hrs % 8 hrs % 12 hrs % 24 hrs NLT %
Assay Method	

VIII. Waiver Request

The applicant requested a waiver for the 60 mg and 90 mg capsules. Based on the acceptable *in vivo* and *in vitro* dissolution data and proportionality of formulations, the waivers for the 60 mg and 90 mg capsules are granted.

IX. Comments

1. Study under Single Dose Fasting and Multiple Dose Steady-State Conditions (#9559): Twenty-eight healthy male volunteers were accepted for entry into the clinical phase of the study. Twenty-four subjects successfully completed both phases of the clinical portion of the study. Pharmacokinetic and statistical analyses were performed on the data for 23 subjects.

   Study under Nonfasting Conditions (#9572): Twenty-three healthy male volunteers were accepted for entry into the clinical phase of the study. Sixteen subjects successfully completed all three phases of the clinical portion of the study.

2. Study under single dose fasting conditions: The 90% confidence intervals of LAUCT, LAUCI and LCMAX for diltiazem, desacetyl diltiazem and desmethyl diltiazem were all within the

acceptable range of 80-125.

3. Study under steady-state conditions: The 90% confidence intervals of LAUCT, LCAVG, LCMAX, and LCMIN for diltiazem, desacetyl diltiazem and desmethyl diltiazem were all within the acceptable range of 80-125.

4. Study under nonfasting conditions: The test/reference ratios of LAUCT, LAUCI and LCMAX under nonfasting conditions for diltiazem, desacetyl diltiazem and desmethyl diltiazem were all within the acceptable range of 0.8-1.25.

5. Assay method validation data are acceptable.

6. Test products (60 mg, 90 mg and 120 mg strengths) met USP dissolution specifications.

7. Formulation: Three test formulations, 60 mg, 90 mg and 120 mg strengths, are proportional in active and inactive ingredients. The same granules were used to manufacture the 60 mg, 90 mg and 120 capsules.

8. There was no severe medical event which required a clinical action.

9. The batch size of the bio-batch (120 mg strength; lot #2B005L) was capsules.

10. Waivers are granted for the 60 mg and 90 mg capsules.

X. Deficiency

None.

XI. Recommendations

1. The *in vivo* bioequivalence studies conducted under fasting, steady-state and nonfasting conditions by Mylan on its Diltiazem Hydrochloride ER Capsules, 120 mg strength, lot #2B005L, comparing it to Hoechst Marion Roussel's Cardizem^{R} SR, 120 mg capsules, lot #P20228, have been found acceptable. The studies demonstrate that Mylan's Diltiazem Hydrochloride ER Capsules, 120 mg strength, is bioequivalent to the reference product, Hoechst Marion Roussel's Cardizem^{R} SR, 120 mg capsules.

2. The USP dissolution testing conducted by Mylan on its Diltiazem Hydrochloride ER Capsules, 120 mg strength, lot #2B005L, 90 mg strength, lot #2B004L, and 60 mg strength, lot #2B003L, is acceptable. The formulations for the 60 mg and 90 mg capsules are proportional to the 120 mg strength capsules of the test product which underwent an acceptable bioequivalence studies (submission date: 6/12/96). The waivers of *in vivo* bioequivalence study requirements for the 60 mg and 90 mg strength capsules of the test product are granted. The 60 mg and 90 mg strength capsules of the test product are ,therefore, deemed bioequivalent to the 60 mg and 90 mg strength capsules of Hoechst Marion Roussel's Cardizem^{R} SR.

3. The USP dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 Apparatus 2 (Paddle) at 100 rpm. The test product should meet the following specifications:

4 hrs		%
8 hrs		%
12 hrs		%
24 hrs	NLT	%

4. From the bioequivalence point of view, the firm met the *in vivo* bioequivalence studies and *in vitro* dissolution testing requirements and the application is approvable.

The firm should be informed of the recommendations.

/S/

Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE

/S/ 10/1/96

Ramakant M. Mhatre, Ph.D.
Team Leader, Review Branch III
Division of Bioequivalence

Concur: /S/ Date: 10/28/96

for Keith K. Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA #74-910 (original, duplicate), Park, Drug File, Division File

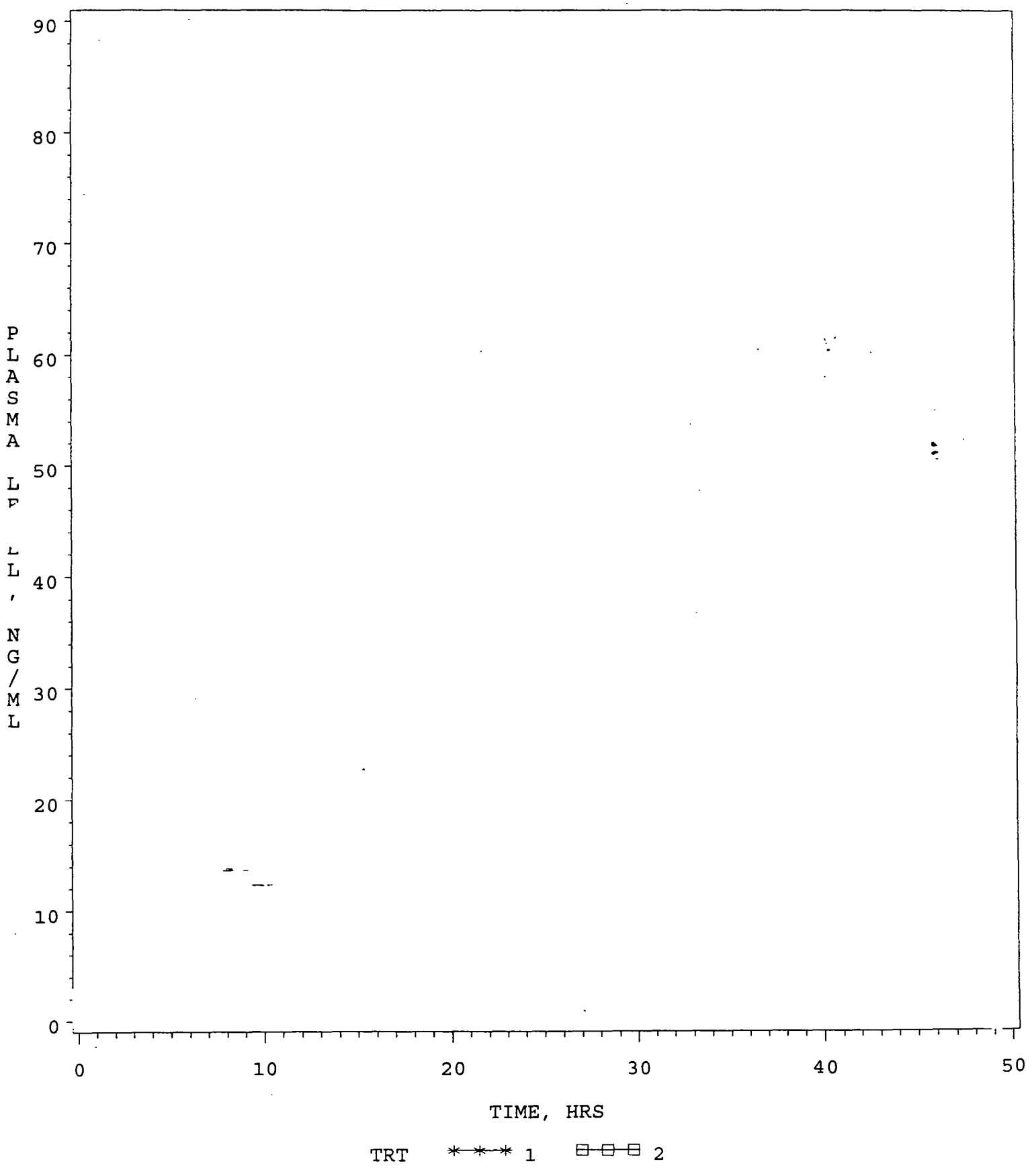
Table 46. *In Vitro* Dissolution Testing Data						
I. General Information						
Drug Product (Generic Name)	Diltiazem Hydrochloride ER Capsules					
Strength	60, 90, and 120 mg Capsules					
ANDA Number	74-910					
Applicant	Mylan					
Reference Drug Product	Cardizem^{R} SR Capsules, 60, 90 and 120 mg					
II. USP Method for Dissolution Testing USP Drug Release Test 4						
Medium and Volume	water; 900 mL					
Apparatus and rpm	2 (paddle); 100 rpm					
Time	4, 8, 12 and 24 hours					
Tolerances	4 hrs % 8 hrs % 12 hrs % 24 hrs NLT %					
Assay Method						
III. Dissolution Data (%)						
Time	Test Product Lot No: 2B003L Strength: 60 mg No of Units: 12			Reference Product Lot No: E01526 Strength: 60 mg No of Units: 12		
hrs	Mean	Range	%CV	Mean	Range	%CV
4	18		7.4	33		7.3
8	47		3.5	67		7.5
12	68		2.8	95		3.6
24	95		2.6	114		4.1

Time	Test Product Lot No: 2B004L Strength: 90 mg No of Units: 12			Reference Product Lot No: P10286 Strength: 90 mg No of Units: 12		
hrs	Mean	Range	%CV	Mean	Range	%CV
4	18		12.3	34		6.5
8	51		3.7	73		8.0
12	71		3.0	107		6.4
24	98		2.2	127		2.0

Time	Test Product Lot No: 2B005L Strength: 120 mg No of Units: 12			Reference Product Lot No: P20228 Strength: 120 mg No of Units: 12		
hrs	Mean	Range	%CV	Mean	Range	%CV
4	18		6.2	24		5.2
8	50		4.7	65		6.7
12	73		3.5	84		3.4
24	96		2.7	101		1.8

FIG P-1. PLASMA DILTIAZEM LEVELS

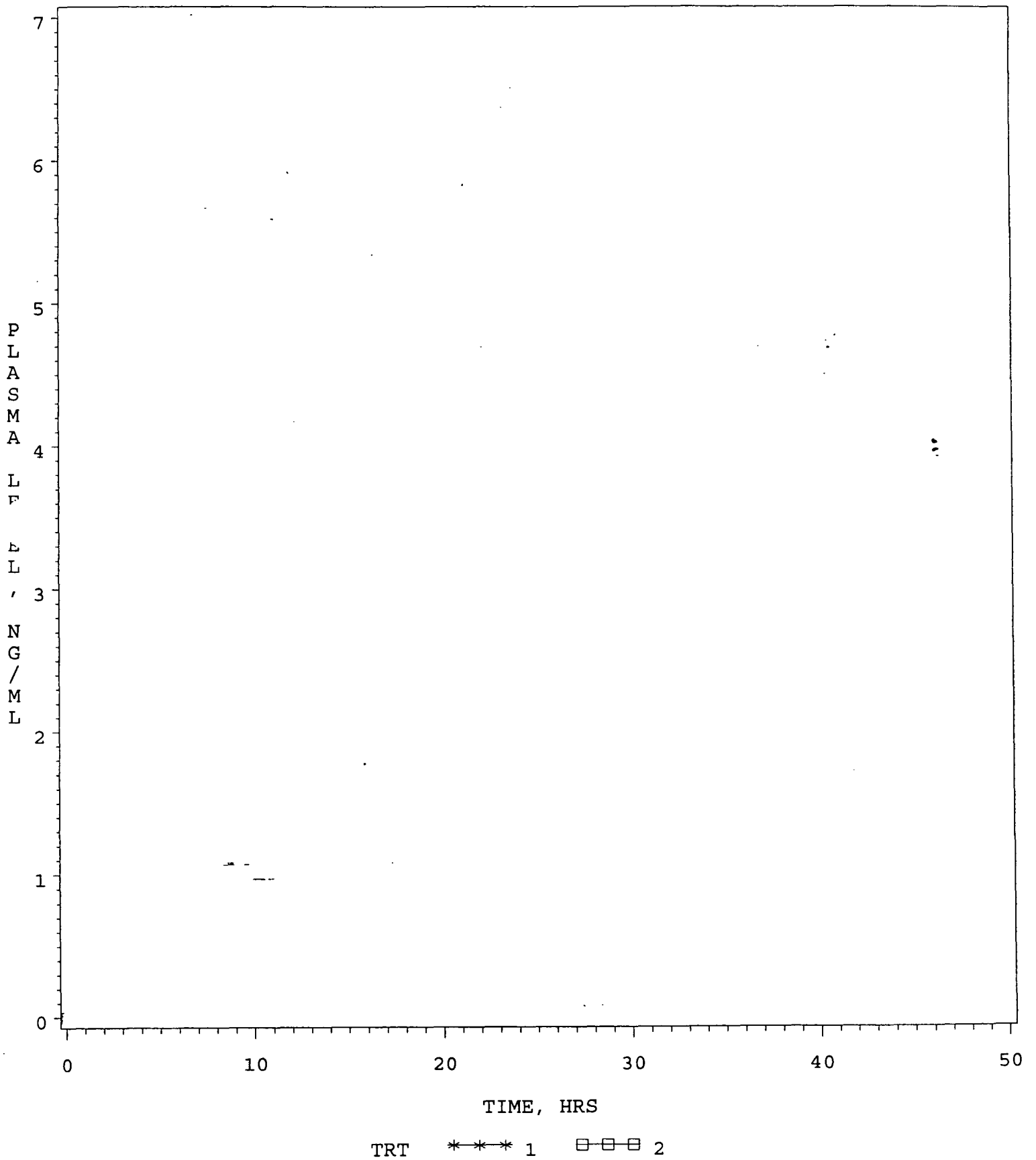
DILTIAZEM HYDROCHLORIDE ER CAPSULES, 120 MG, ANDA #74-910
UNDER FASTING CONDITIONS
DOSE=1 X 120 MG



1=TEST PRODUCT(MYLAN) 2=REFERENCE PRODUCT(HMR)

FIG P-2. PLASMA DESACETYL DILTIAZEM LEVELS

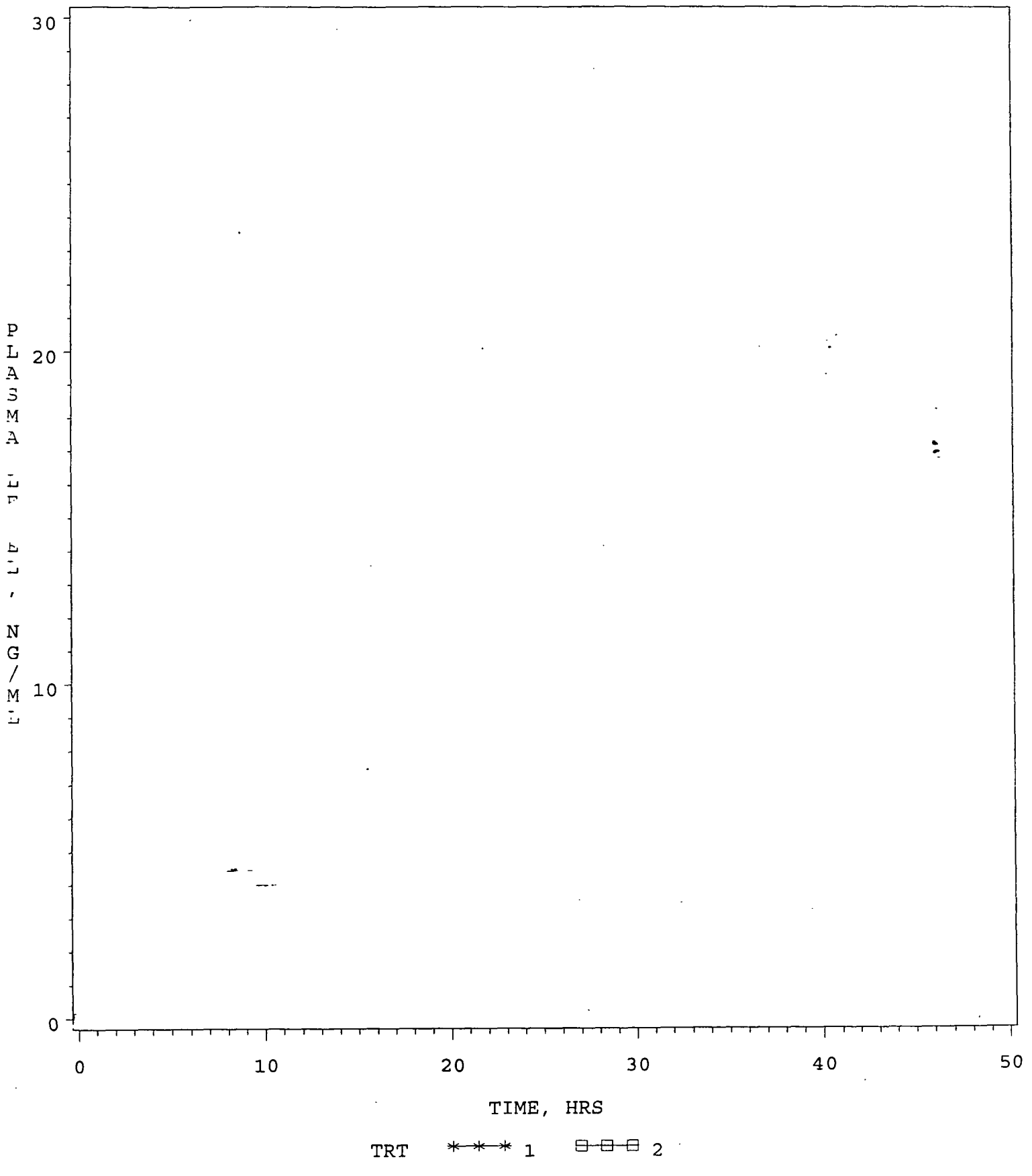
DILTIAZEM HYDROCHLORIDE ER CAPSULES, 120 MG, ANDA #74-910
UNDER FASTING CONDITIONS
DOSE=1 X 120 MG



1=TEST PRODUCT(MYLAN) 2=REFERENCE PRODUCT(HMR)

FIG P-3. PLASMA DESMETHYL DILTIAZEM LEVELS

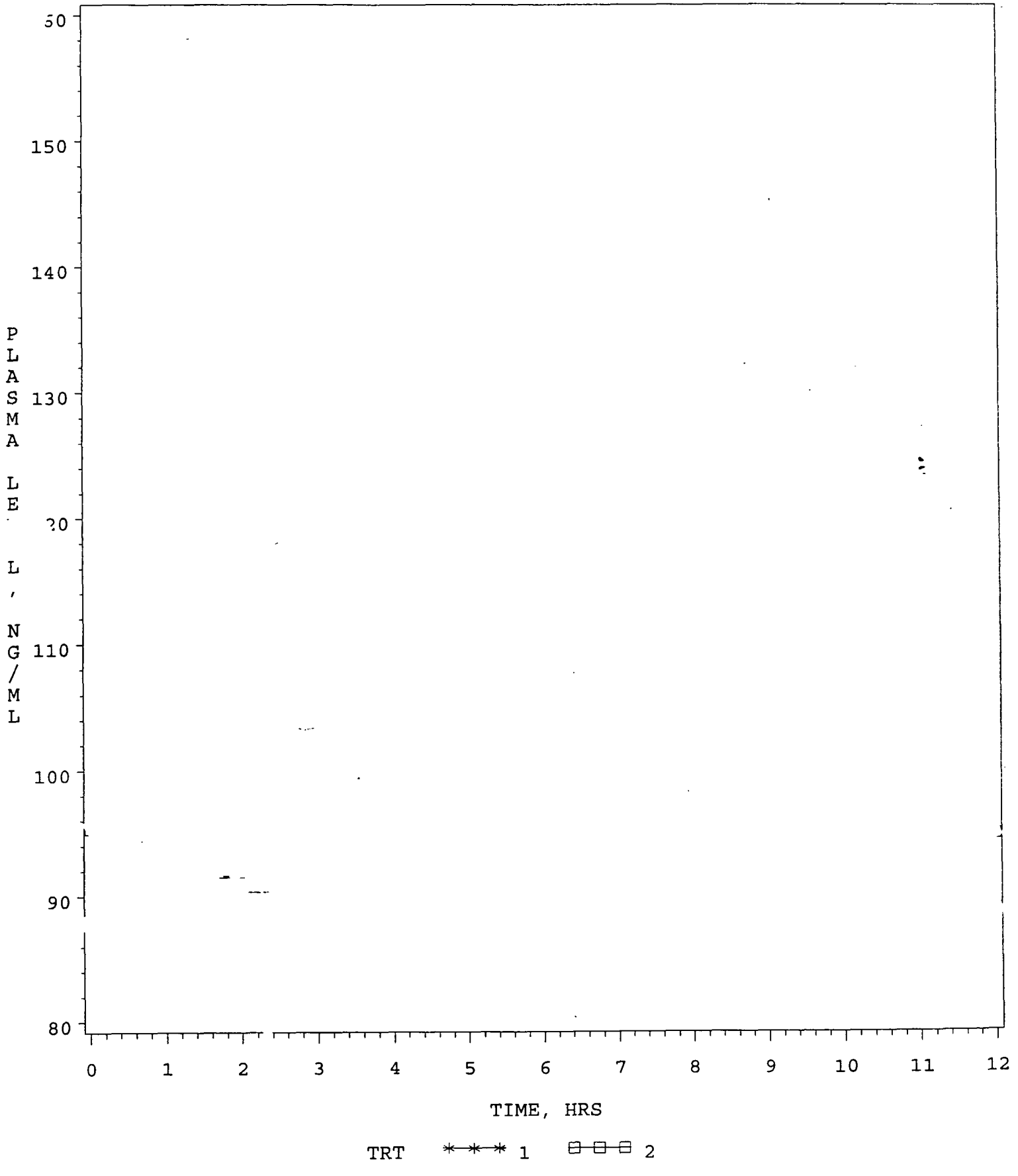
DILTIAZEM HYDROCHLORIDE ER CAPSULES, 120 MG, ANDA #74-910
UNDER FASTING CONDITIONS
DOSE=1 X 120 MG



1=TEST PRODUCT(MYLAN) 2=REFERENCE PRODUCT(HMR)

FIG P-4. PLASMA DILTIAZEM LEVELS IN THE LAST DOSING INTERVAL

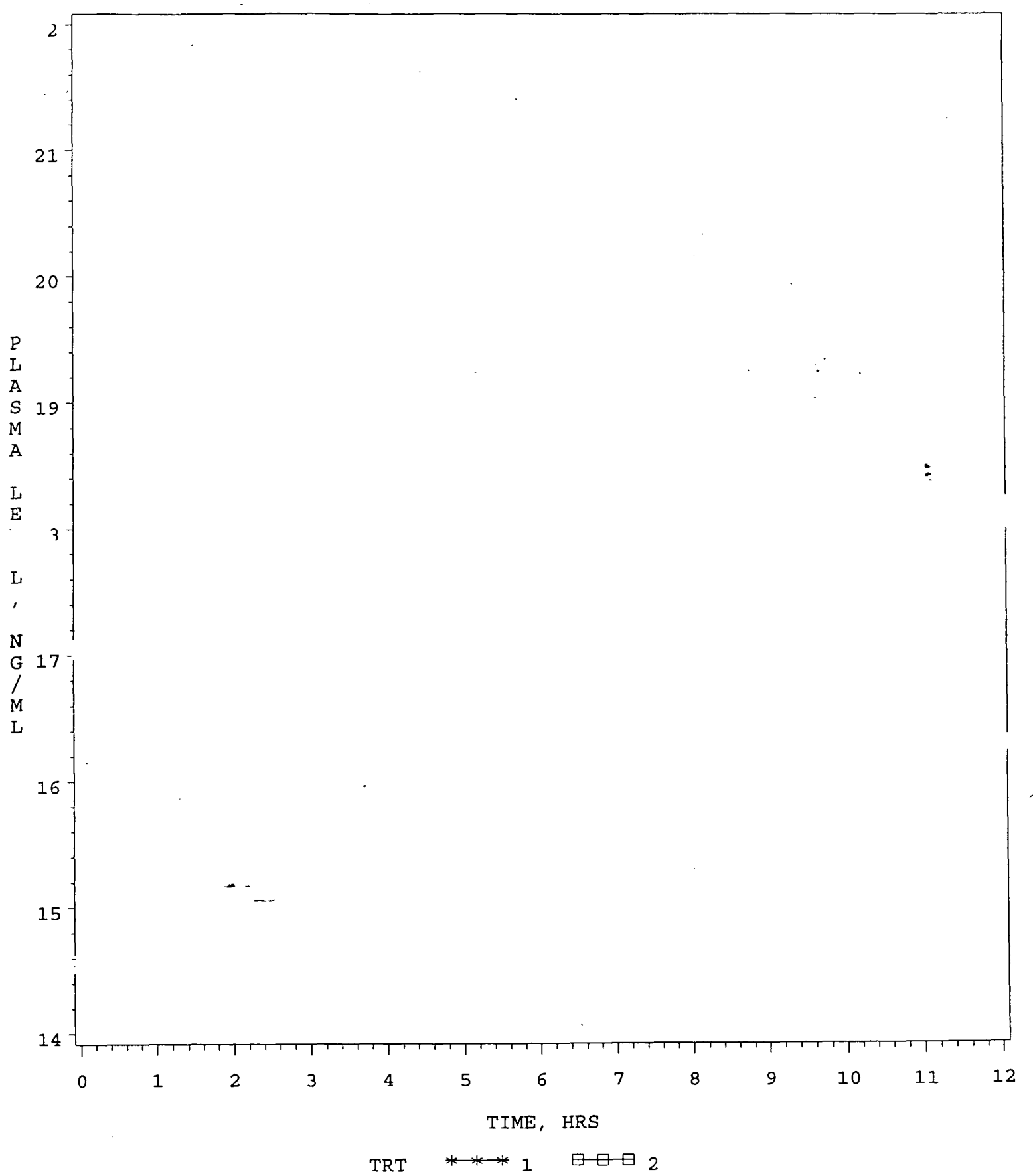
DILTIAZEM HYDROCHLORIDE ER CAPSULES, 120 MG, ANDA #74-910
UNDER MULTIPLE-DOSE STEADY-STATE CONDITIONS
DOSE=1 X 120 MG, DOSING INTERVAL(TAU)=12 HOURS DURING 3-8 DAYS



1=TEST PRODUCT(MYLAN) 2=REFERENCE PRODUCT(HMR)

FIG P-5. PLASMA DESACETYL DILTIAZEM LEVELS IN THE LAST DOSING INTERVAL

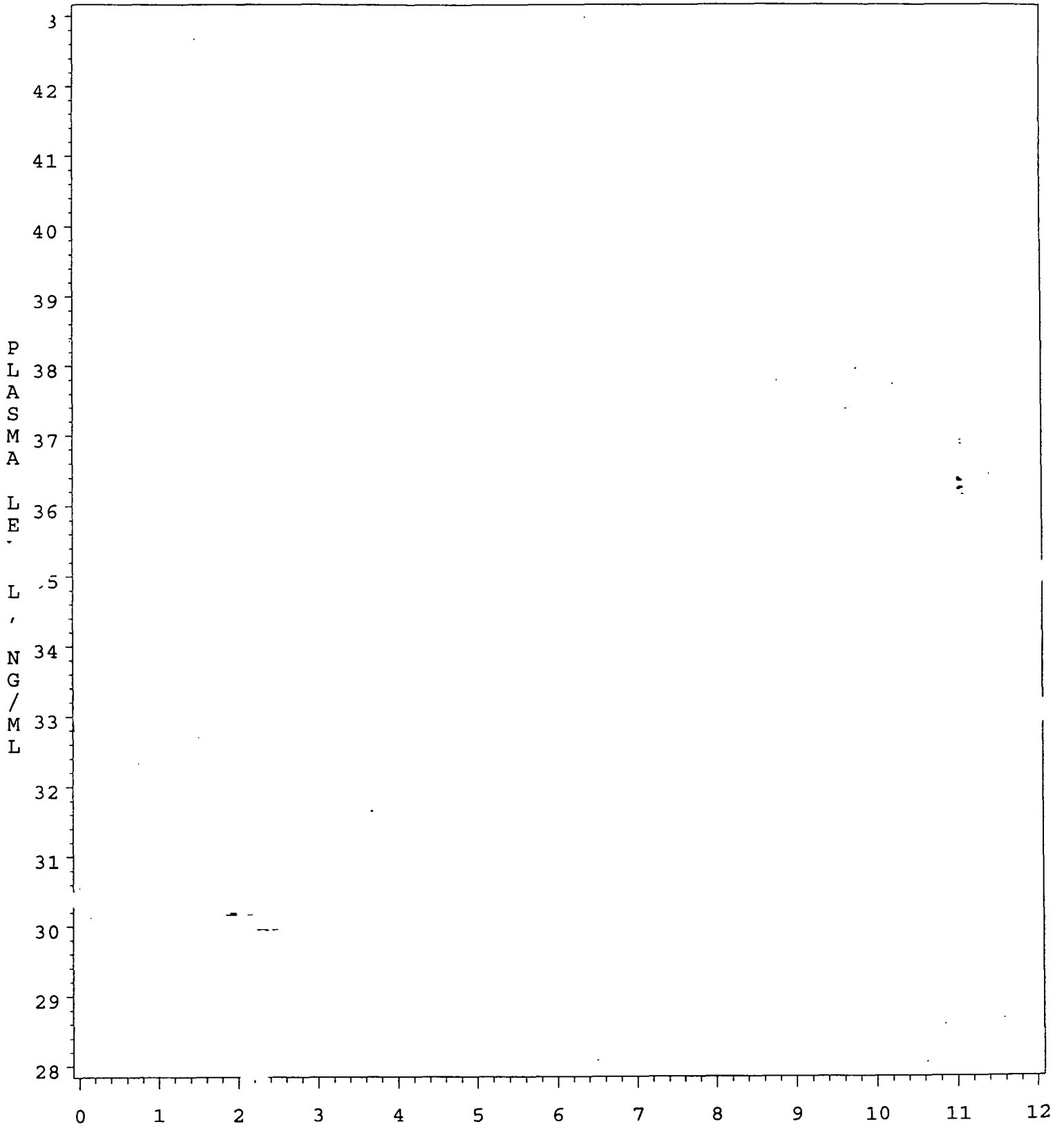
DILTIAZEM HYDROCHLORIDE ER CAPSULES, 120 MG, ANDA #74-910
UNDER MULTIPLE-DOSE STEADY-STATE CONDITIONS
DOSE=1 X 120 MG, DOSING INTERVAL(TAU)=12 HOURS DURING 3-8 DAYS



1=TEST PRODUCT(MYLAN) 2=REFERENCE PRODUCT(HMR)

FIG P-6. PLASMA DESMETHYL DILTIAZEM LEVELS IN THE LAST DOSING INTERVAL

DILTIAZEM HYDROCHLORIDE ER CAPSULES, 120 MG, ANDA #74-910
UNDER MULTIPLE-DOSE STEADY-STATE CONDITIONS
DOSE=1 X 120 MG, DOSING INTERVAL(TAU)=12 HOURS DURING 3-8 DAYS



1=TEST PRODUCT(MYLAN) 2=REFERENCE PRODUCT(HMR)

FIG P-7. PLASMA DILTIAZEM LEVELS

DILTIAZEM HYDROCHLORIDE ER CAPSULES, 120 MG, ANDA #74-910
UNDER NONFASTING CONDITIONS
DOSE=1 X 120 MG

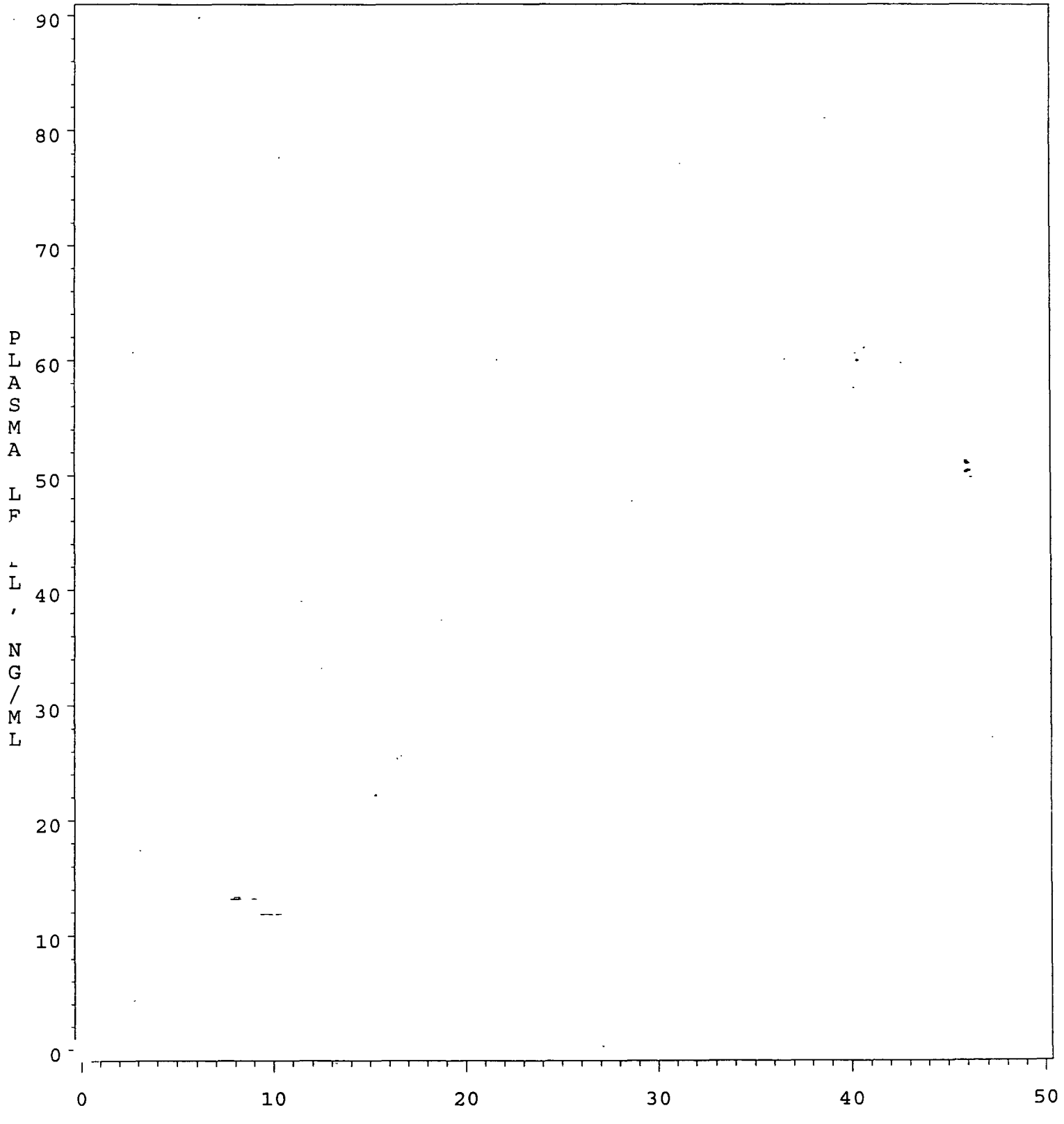


FIG P-8. PLASMA DESACETYL DILTIAZEM LEVELS

DILTIAZEM HYDROCHLORIDE ER CAPSULES, 120 MG, ANDA #74-910
UNDER NONFASTING CONDITIONS
DOSE=1 X 120 MG

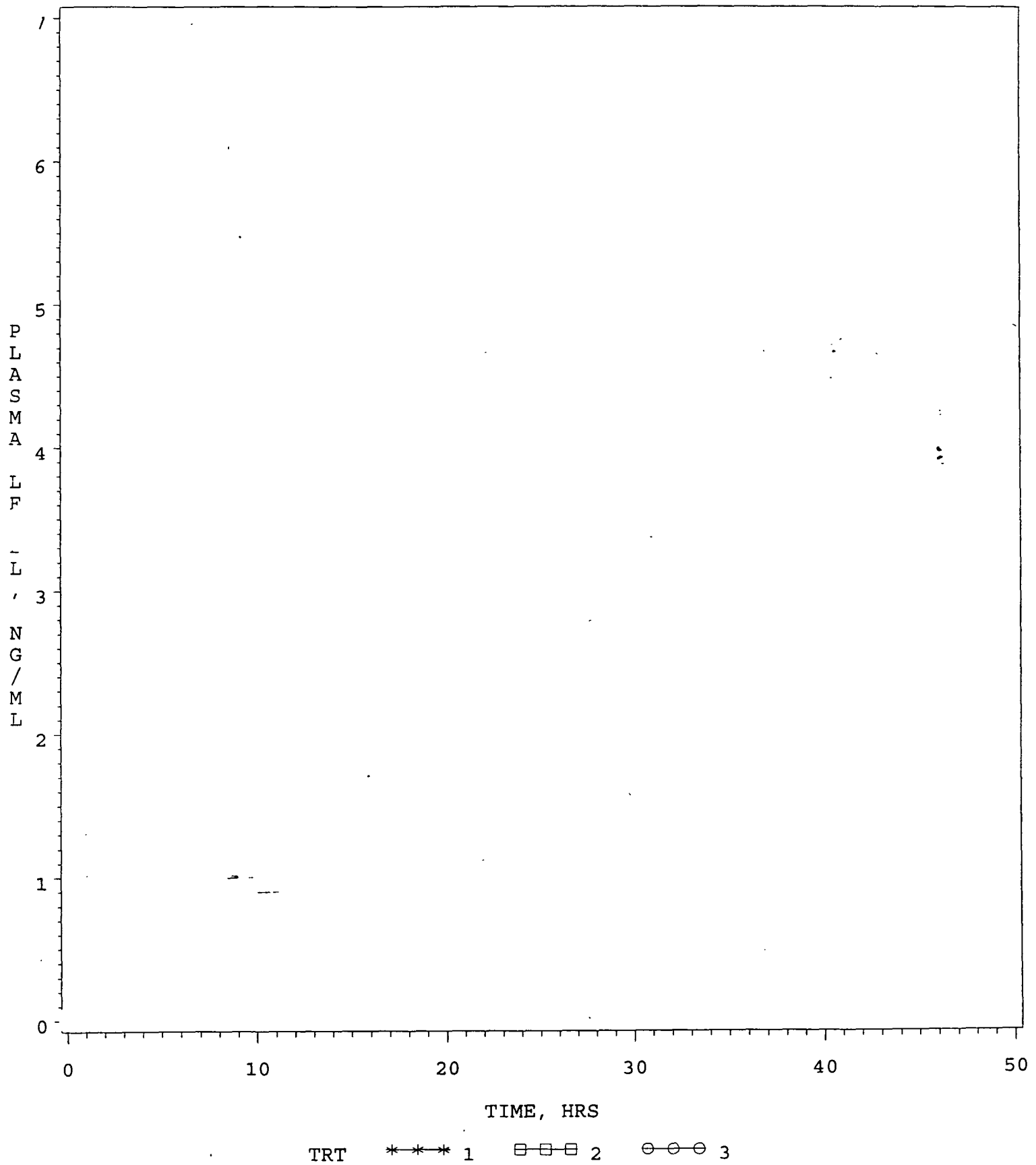


FIG P-9. PLASMA DESMETHYL DILTIAZEM LEVELS

DILTIAZEM HYDROCHLORIDE ER CAPSULES, 120 MG, ANDA #74-910
UNDER NONFASTING CONDITIONS
DOSE=1 X 120 MG