CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 74-845

BIOEQUIVALENCE REVIEW(S)

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-845 APPLICANT: Biovail Corporation International

DRUG PRODUCT: Diltiazem Hydrochloride Extended Release Capsules
60 mg, 90 mg, and 120 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 6.5, at 37° C using USP 23 apparatus 1 (basket) at 100 rpm. The test products should meet the following interim specifications:

Not more than 10% at 1 hour, 10-30% at 6 hours, 34-60% at 9 hours, and not less than 80% at 24 hours, of the labeled amount of diltiazem are dissolved.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Diltiazem Hydrochloride
Extended Release Capsules
60, 90, 120 mg
ANDA # 74-845
Reviewer: Lin-Whei Chuang

Biovail Corp. International
Toronto, Ontario, Canada

Submission Date:
March 26, 1998

Review of the Third Amendment to Five Bioequivalence Studies, Dissolution Data, and Waiver Request

The original submission consisted of results for 5 bioequivalence studies, dissolution data (using apparatus III, 20 dpm, gradient pH) and waiver request (submitted on 1/31/96). The submission was found to be incomplete due to 2 deficiencies (review of 3/4/97).

The first amendment (submitted on 4/7/97) adequately addressed the deficiency concerning study data. Therefore 4 of the 5 studies (except for the 4-way pharmacokinetic study which was not required for approval) were found to be acceptable. The firm also proposed a new dissolution method (paddle, 100 rpm, phosphate buffer at a constant pH of 6.75) which was found to be incomplete (review of 10/23/97).

In the second amendment (submitted on 12/30/97 and 2/12/98), the firm proposed another dissolution method (basket, 100 rpm, phosphate buffer at pH 6.5). Two deficiencies were found (review of 3/3/98) and the firm's responses are discussed in this review:

1. The specification proposed by the firm for the 6-hour time

For 60 mg Capsules:

For 90 mg and 120 mg Capsules:

2. Please submit dissolution data for the 60 mg and 90 mg strengths of the test products using the proposed isocratic pH method (pH 6.5 phosphate buffer). The dissolution test should be conducted on 12 capsules of the test product versus 12 capsules of the reference product. The percent of label claim dissolved at each specified testing interval should be reported for each individual capsule. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

Firm's Response: The firm conducted the dissolution testing on all 3 strengths and the data are presented in the table below and in Figures 1-3:

***In Vitro* Dissolution Testing**			
Drug (Generic Name):	Diltiazem HCL		
Dosage Form:	Extended Release Capsule		
Dose Strength:	60, 90 and 120 mg		
ANDA No.:	74-845		
Firm:	Biovail Corporation International		
Submission Date:	04/07/97		
I. Conditions for Dissolution Testing:			
USP XXIII Apparatus:	I (Basket)	RPM: 100	
No. Units Tested:	12		
Medium:	Phosphate buffer -pH 6.5	Volume: 900 mL	
Tolerance (proposed):			
		or	
Reference Drug:	Cardizem® SR capsule (Marion Merrell Dow)		
Assay Methodology:			
II. Results of In Vitro Dissolution Testing:			

Sampling Times (Hours)	Test Product Lot # 95D007 Strength (mg): 120			Reference Product Lot # P20223 Strength (mg): 120		
	Mean % dissolved	Range (%)	RSD (%)	Mean % dissolved	Range (%)	RSD (%)
1	0.21		523	5.87		10.05
6	21.61		9.41	54.95		4.36
9	45.93		6.77	78.48		2.88
20	77.48		2.16	109.58		1.65
22				110.85		1.57
24	82.74		2.64			

Sampling Times (Hours)	Test Product Lot # 95D006 Strength (mg): 90			Reference Product Lot # P1-279 Strength (mg): 90		
	Mean % dissolved	Range (%)	RSD (%)	Mean % dissolved	Range (%)	RSD (%)
1	1.28		17.11	5.46		9.24
6	22.47		3.60	59.89		3.40
9	49.62		3.07	82.21		3.51
20	85.72		3.36	113.98		2.26
24	91.34		3.37	117.29		2.29

Sampling Times (Hours)	Test Product Lot # 95D005 Strength (mg): 60			Reference Product Lot # ED1426 Strength (mg): 60		
	Mean % dissolved	Range (%)	RSD (%)	Mean % dissolved	Range (%)	RSD (%)
1	1.52		21.79	4.43		12.53
6	27.30		5.43	52.15		4.09
9	55.72		4.63	79.99		2.80
20	86.79		4.80	114.67		3.60
24	94.89		5.35	118.78		2.69

Reviewer's Comments:

1. The Division of Bioequivalence would recommend the following dissolution specifications for all 3 strengths of the test products (60 mg, 90 mg, and 120 mg strengths):

Rationale of electing above specifications for all 3 strengths are:

a. The dissolution profiles of all 3 strengths are considered similar since the f2 values were >50 (53.3 for 60 mg vs. 120 mg, and 62.3 for 90 mg vs. 120 mg).

b. Selecting different dissolution specifications for different strengths of the same product would indicate that they have different dissolution profiles.

c. The results presented by the firm in the dissolution table fall within the recommended specifications for all 3 strengths of the test product.

d. The additional sampling time point of 6 hours is added for better quality control of the test product.

e. The last time point should be the time point where at least 80% or drug has dissolved as recommended in the recently published *Guidance for Industry on "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations", Chapter VII, Section B1.*

Recommendation:

1. The single-dose, fasted bioequivalence study, and multiple-dose fasted bioequivalence study, conducted by Biovail Corporation International on its Diltiazem Hydrochloride Extended Release 120 mg capsule, lot #C3/95A1A21-MTC3, comparing it to Cardizem® SR 120 mg capsule, lot #P20223,

have been previously (03/04/97) found acceptable by the Division of Bioequivalence.

2. The single-dose, fed and fasted bioequivalence study, conducted by Biovail Corporation International on its Diltiazem Hydrochloride Extended Release 120 mg capsule, lot #C3/95A1A21-MTC3, comparing it to Cardizem^{R} SR 120 mg capsule, lot #P20223, has also been previously (10/28/97) found acceptable by the Division of Bioequivalence.

3. The dissolution testings conducted by Biovail Corporation International on its Diltiazem Hydrochloride Extended Release 60 mg, 90 mg, and 120 mg capsules, lot #95D005, #95D006, and #95D007, comparing it to Cardizem^{R} SR 60 mg, 90 mg, and 120 mg capsule, lot #ED1426, #P10279, and #P20223, have now been found acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program and conducted in 900 mL of phosphate buffer, pH 6.5, at 37° C using USP 23 apparatus 1 (basket) at 100 rpm. The test products should meet the following interim specifications:

4. The waiver of bioequivalence requirement for the 60 mg and 90 mg strengths of the test product are granted.

/S/ 6/3/98

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

/S/

RD INITIALED YHUANG 6/3/98
FT INITIALED YHUANG

Concur Date: 6/8/98

/S/
Dale Conner, Pharm.D.
Director, Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 74-845 APPLICANT: Biovail Corporation International

DRUG PRODUCT: Diltiazem Hydrochloride Extended Release Capsules
60 mg, 90 mg, and 120 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 6.5, at 37° C using USP 23 apparatus 1 (basket) at 100 rpm. The test products should meet the following interim specifications:

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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26 March, 1998

Bioequivalency Amendment

BIOAVAILABILITY
ORIG AMENDMENT
N/A

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773
USA

Attention: Dr. Dale P. Conner
Director, Division of Bioequivalence

Dear Dr. Conner,

Re: ANDA # 74-845
Diltiazem Hydrochloride Extended-Release Capsules USP, 60, 90, 120 mg
Response to FDA fax dated March 3, 1998

In accordance with 21 CFR 314.96, we enclose our response to the comments listed on your fax of March 3, 1998. All deficiencies have been addressed. We trust that this response is complete and satisfactory for filing and review by the Office of Generic Drugs.

We enclose a signed and dated FDA form 356h in this amendment, which is being submitted in triplicate (original and 2 copies).

Should you have any questions or comments, please contact the undersigned directly at (416) 285-6000 ext. 212, or by fax at (905) 608-1616.

RECEIVED
MAR 30 1998
GENERIC DRUGS

Sincerely yours,
BIOVAIL CORPORATION INTERNATIONAL

George E. Markus, M.Sc.
Manager, Regulatory Affairs

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MAR 3 [illegible]

BIOEQUIVALENCY DEFICIENCIES

ANDA: 74-845 APPLICANT: Biovail Corp. International

DRUG PRODUCT: Diltiazem HCl ER Capsules, 60, 90, 120 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. The specification proposed by you for the 6-hour time point

2. Please submit dissolution data for the 60 mg and 90 mg strengths of the test products using the proposed isocratic pH method (pH 6.5 phosphate buffer). The dissolution test should be conducted on 12 capsules of the test product versus 12 capsules of the reference product. The percent of label claim dissolved at each specified testing interval should be reported for each individual capsule. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

Sincerely yours,

/S/

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Diltiazem Hydrochloride
Extended Release Capsules
60, 90, 120 mg
ANDA # 74-845
Reviewer: L. Chuang

Biovail Corp. International
Toronto, Ontario, Canada

Submission Date:
December 30, 1997
February 12, 1998

Review of a Second Amendment to Five Bioequivalence Studies, Dissolution Data, and Waiver Request

The firm conducted 5 bioequivalence studies, including 2 single-dose fasted studies, 1 single-dose fed and fasted study, 1 multiple-dose fasted study, and a pilot 4-way pharmacokinetic study (submitted on 1/31/96). They were found to be incomplete due to 2 deficiencies (review of 3/4/97).

An amendment (submitted on 4/7/97) adequately addressed the deficiency concerning study data. Therefore 4 of the 5 studies (except for the 4-way pharmacokinetic study which was not required for approval) were found to be acceptable (review of 10/23/97). However, the other deficiency concerning the dissolution data was still incomplete due to the following 5 comments:

1. Because it's the firm's intention that the gradient pH method will be phased out and replaced by the single pH method, the Division of Bioequivalence would not make further comments on the gradient pH method. However, the firm still needs to explain why the dissolution of the 60 mg strength is faster than the 90 mg and 120 mg strengths using the gradient pH method. The fact that isocratic method yielded comparative dissolution results for all 3 strengths may indicate that this isocratic pH method does not have the differentiating power.

   Firm's Response:

   The firm hypothesized that the faster dissolution rate of the 60 mg strength, using the gradient pH method (USP apparatus 3), may be due to its smaller fill weight. The smaller fill permits impingement of individual pellets on the bottom wire mesh of the reciprocating cylinders during dissolution testing.

This hypothesis was tested in the dissolution testing of 3 strengths of test product using the single pH method (pH = 6.5) but with USP apparatus 1, opposed to apparatus 2 which was previously proposed by the firm. During the testing, beads from the 60 mg strength (fill weight of 199 mg) covered only half of the bottom wire mesh of the basket while beads from the 120 mg strength (383 mg fill weight) covered the entire bottom with double layers of beads covering half the area. Furthermore, the dissolution profile and release rate of 2x60 mg were identical as those of 1x120 mg. The results are presented below in Table 1:

Table 1: Dissolution of Diltiazem HCL ER Capsules (Biovail) PH = 6.5, USP apparatus 1, 100 RPM

Time (Hour)	Percent Dissolved			
Strength	60 mg	90 mg	120 mg	2x60 mg
0	0	0	0	0
1	0.61	0	0	0.35
2	2.15	1.28	0	1.12
3	6.25	4.11	3.3	3.76
4	12.42	8.83	8.46	8.46
5	20.21	14.91	15.11	14.35
6	29.50	22.15	23.15	21.34
7	39.77	30.53	32.09	29.19
8	50.06	39.55	40.98	37.44
9	59.08	48.07	48.54	44.99
10	66.62	55.29	54.40	51.31
11	73.11	60.66	59.10	56.42
12	77.95	64.72	62.68	60.54
13	81.78	68.05	65.71	63.96
14	84.82	70.99	68.24	66.65
15	87.46	73.54	70.25	69.00
16	89.82	75.84	71.93	71.09
17	91.88	77.82	73.35	73.01

18	93.58	79.56	74.97	74.87
19	95.07	81.24	76.26	76.44
20	96.34	82.70	77.47	

Reviewer's Comment: The firm's explanation for the faster dissolution rate of the 60 mg strength is acceptable.

2. The validation report for the isocratic pH dissolution method indicated that the dissolution of the test product is very sensitive to pH changes, i.e. the dissolution profile changed from pH 6.70 to pH 6.75 and to pH 6.8.

The firm has expressed intention to reduce this variation by tight pH control of the pH medium. However, this would be difficult to accomplish since, as shown in its validation report, **a change of 0.05 unit of pH** could cause a **variation as wide as 25%** of the amount dissolved.

Firm's Response:

The firm developed another isocratic pH (6.5) dissolution method using USP apparatus 1 (basket). The method was validated for accuracy and precision (for 5%, 50% and 100% of label claim), selectivity (negligible interference from capsule shell and excipients), and reproducibility (between two systems). The basket speed (50, 75 & 100 rpm) had no significant effect on the amount released. The influence of pH is presented below in Table 2:

Table 2: Comparative Dissolution of Diltiazem HCl ER 120 mg Capsules (Biovail) At Various pH, USP apparatus 1, 100 RPM

Time (Hour)	Percent Dissolved (CV%, n=6)		
Strength	pH = 6.45	pH = 6.50	pH = 6.55
0	0	0	0
1	0	0	0.48 (37)
2	0.56 (186)	0	1.45 (16)
3	4.03 (46)	3.30 (33)	4.67 (5)
4	8.55 (23)	8.46 (14)	9.99 (3)

5	14.30 (15)	15.11 (9)	17.08 (2)
6	21.00 (10)	23.15 (7)	25.82 (2)
7	28.55 (8)	32.09 (5)	35.58 (2)
8	36.62 (6)	40.98 (4)	45.13 (2)
9	44.14 (5)	48.54 (3)	53.19 (1)
10	50.43 (4)	54.40 (3)	59.94 (1)
11	55.49 (3)	59.10 (3)	64.18 (1)
12	59.60 (3)	62.68 (2)	67.83 (1)
13	62.82 (3)	65.71 (2)	70.70 (1)
14	65.46 (2)	68.24 (2)	73.18 (1)
15	67.64 (2)	70.25 (2)	75.29 (1)
16	69.61 (2)	71.93 (2)	77.13 (1)
17	71.36 (2)	73.35 (2)	78.78 (1)
18	72.91 (2)	74.97 (2)	80.25 (1)
19	74.33 (2)	76.26 (2)	81.63 (1)
20	75.65 (2)	77.47 (2)	82.84 (1)
21	76.90 (2)	78.55 (2)	
22		79.55 (2)	
23		80.48 (2)	
24		81.39 (2)	

Reviewer's Comment:

Among the 3 slightly different pH used in the validation of this new dissolution method, the dissolution rate was highest and the variation was the lowest at pH 6.55.

3. For the *in vitro* dissolution testing of extended release drug products, the Office recommends USP apparatus 1 for capsules and aqueous media of various pH (see *"Guidance: Oral Extended (Controlled) Release Dosage Forms: In Vivo Bioequivalence and In Vitro Dissolution Testing", 09/03/93)*. The purpose is to select a pH with enough discriminating power for the final testing method. This is especially important for the test product due to its pH sensitive nature.

Firm's Response: A dissolution method was developed by the firm using USP apparatus 1, phosphate buffer pH 6.5, and testing time over 20 hours.

Reviewer's Comment: The dissolution method is the same as described below in #4. See reviewer's comments of #4.

4. The dissolution data submitted by the firm using the single pH method are incomplete. The dissolution test should be conducted in 12 capsules of the test product versus 12 capsules of the reference product. The percent of label claim dissolved at each specified testing interval should be reported for each individual capsule. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

Firm's Response: The firm conducted the following dissolution testing:

Table 5 - In Vitro Dissolution Testing

Drug (Generic Name): Diltiazem HCL
Dosage Form: Extended Release Capsule
Dose Strength: 60, 90 and 120 mg
ANDA No.: 74-845
Firm: Biovail Corporation International
Submission Date: 04/07/97

I. Conditions for Dissolution Testing:

USP XXIII Apparatus: I (Basket) RPM: 100
No. Units Tested: 12
Medium: Phosphate buffer -pH 6.5 Volume: 900 mL
Tolerance:

Reference Drug: Cardizem® SR capsule (Marion Merrell Dow)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # 95D007 Strength (mg): 120			Reference Product Lot # P20223 Strength (mg): 120		
	Mean % dissolved	Range (%)	RSD(%)	Mean % dissolved	Range (%)	RSD (%)

1	0.21			523	5.87	5			10
2	0.76			130	15.60	1			7
3	3.54			23	26.02	2			6
4	8.20			11	36.10	3			6
5	14.25		4	10	45.81	4			5
6	21.61		5	9	54.95	5			4
7	29.93		2	9	63.47	5			4
8	38.41		8	8	71.36	6			3
9	45.93		5	7	78.48	7			3
10	51.98		5	6	85.02	8			2
11	56.86		5	5	90.73	8			2
12	60.69		)	4	95.42	9			2
13	63.91		9	4	99.06	9		3	2
14	66.61		1	3	110.85	9		5	2
15	68.83		1	3	103.96	1		3	2
16	70.79		9	3	105.61	1		5	1
17	72.63		9	2	106.89	1		75	2
18	74.35		9	2	107.93	1		57	2
19	75.95			2	108.84	1		12	2
20	77.48		9	2	109.58	1		)4	2
21	78.91			2	110.26	1		76	2
22	80.28			2	110.85	1		52	2
23	81.53			2					
24	82.74			3					

Reviewer's Comments:

a. The format of the dissolution submitted by the firm is acceptable.

b. The mean amount dissolved at 6 hours was 21.61% (18.56-24.85%), which was outside the range of 34-56% specified in the tolerance proposed by the firm.

c. Although the firm did not conduct isocratic pH dissolution testing using lower pH, this should not be a concern for dose-dumping in the stomach because:

(1) Earlier dissolution data submitted by the firm using gradient pH method indicated that at pH 1.5 and 4.5, the mean percent dissolved was only 1-2%.

(2) The mean Tmax of diltiazem obtained in the bioequivalence studies was 7-8 hours, a time period long enough for the drug to pass through the stomach.

5. To set the dissolution specification for an extended release oral dosage form without an *IVIVC*, such as the test product, the firm is advised to consult with the recently published *Guidance for Industry on "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations", Chapter VII, Section B1.*

Firm's Response: The firm has proposed, in its submission of 12/30/97 and again per telephone amendment of 2/12/98, the following dissolution specification:

1 hour
6 hours
20 hours

Reviewer's Comment: The specification proposed by the firm for the 6-hour time point does not match the observed dissolution data (20.35-23.77%).

Deficiencies:

1. The specification proposed by the firm for the 6-hour time point does not match with the mean dissolution profile obtained from the bioavailability lot (20.35-23.77%).

2. Please submit dissolution data for the 60 mg and 90 mg strengths of the test products using the proposed isocratic pH method (pH 6.5 phosphate buffer). The dissolution test should be conducted on 12 capsules of the test product versus 12 capsules of the reference product. The percent of label

claim dissolved at each specified testing interval should be reported for each individual capsule. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

Recommendations:

1. The dissolution testing conducted by Biovail on its diltiazem hydrochloride capsules, 60 mg, 90 mg and 120 mg have been found incomplete due to two deficiencies.

2. The waiver request for the 60 mg and 90 mg strengths of the test drugs can not be granted pending the acceptance of the dissolution tests for all three strengths of the test product.

The firm should be informed of the Deficiencies and Recommendations.

Lin-Whei Chuang 3/2/98

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG
FT INITIALED YHUANG 3/3/98

Concur Dale Conner Date: 3/3/98
Dale Conner, Pharm.D.
Director, Division of Bioequivalence

cc: ANDA
HFD

BIOEQUIVALENCY DEFICIENCIES

ANDA: 74-845 APPLICANT: Biovail Corp. International

DRUG PRODUCT: Diltiazem HCl ER Capsules, 60, 90, 120 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet. The following deficiencies have been identified:

1. The specification proposed by you for the 6-hour time point does not match with the mean dissolution profile obtained from the bioavailability lot (20.35-23.77%).

2. Please submit dissolution data for the 60 mg and 90 mg strengths of the test products using the proposed isocratic pH method (pH 6.5 phosphate buffer). The dissolution test should be conducted on 12 capsules of the test product versus 12 capsules of the reference product. The percent of label claim dissolved at each specified testing interval should be reported for each individual capsule. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 74-845 SPONSOR : Biovail Corp. International
DRUG & DOSAGE FORM : Diltiazem HCl Extended Release Capsules
STRENGTHS : 60 mg, 90 mg, 120 mg
TYPES OF STUDIES: Two Fasting BE study (2-way)
One Food study (3-way)
One Multiple Dose study (2-way)
One Pilot PK study (4-way)
Dissolution testings on all strengths
Waiver request for the 60 mg and 90 mg strengths

CLINICAL STUDY SITE: Biovail Corporation International, Toronto, Canada
ANALYTICAL SITE : Same as Clinical study site.

RESULTS:

First Fasting BE study (2-way): Non-Pivotal
Second Fasting BE study (2-way): Acceptable
Food study (3-way): Acceptable
Multiple Dose study (2-way): Acceptable
Pilot PK study (4-way): Non-Pivotal

Dissolution testings: Acceptable with interim specifications

Waiver request for the 60 mg and 90 mg strengths: Granted

PRIMARY REVIEWER :Lin-Whei Chuang BRANCH : I

INITIAL :_____ DATE : 6/3/98

BRANCH CHIEF : Yih-Chain Huang, Ph.D. BRANCH : I

INITIAL : _____ DATE : 6/3/98

DIRECTOR

DIVISION OF BIOEQUIVALENCE : Dale Conner, Pharm.D.

INITIAL :__ _____ DATE : 6/8/98

NOV 1 2 1997

BIOEQUIVALENCY DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA/AADA: 74-845 APPLICANT: Biovail Corporation

DRUG PRODUCT: Diltiazem HCl Extended Release Capsules, USP 60, 90, and 120 mg.

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified.

1. Because it is your intention that the gradient pH method will be phased out and replaced by the single pH method, the Division of Bioequivalence will not make further comments on the gradient pH method. However, you still need to explain why the dissolution of the 60 mg strength is faster than the 90 mg and 120 mg strengths using the gradient pH method. The fact that the isocratic method yielded comparative dissolution results for all 3 strengths may indicate that this isocratic pH method does not have the differentiating power.

2. The validation report for the isocratic pH dissolution method indicated that the dissolution of the test product is very sensitive to pH changes, i.e. the dissolution profile changed from pH 6.70 to pH 6.75 and to pH 6.8.

   Biovail has expressed the intention to reduce this variation by tight control of the pH medium. However, this would be difficult to accomplish since, as shown in the validation report, **a change of 0.05 unit of pH** could cause a **variation as wide as 25%** of the amount dissolved.

3. For the *in vitro* dissolution testing of extended release drug products, the Office recommends USP apparatus 1 for capsules and aqueous media of various pH ((see *"Guidance: Oral Extended (Controlled) Release Dosage Forms: In Vivo Bioequivalence and In Vitro Dissolution Testing", 09/03/93)*. The purpose is to select a pH with enough discriminating power for the final testing method. This is especially important for the test product due to its pH sensitive nature.

4. The dissolution data submitted using the single pH method are incomplete. The dissolution test should be conducted in 12 capsules of the test product versus 12 capsules of the reference product. The percent of label claim dissolved at each specified testing interval should be reported for each individual capsule. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

5. To set the dissolution specification for an extended release oral dosage form without an IVIVC, such as the test product, you are advised to consult the recently published Guidance for Industry on "Extended Release Oral Dosage Forms: Development, Evaluation and Application of In Vitro/In Vivo Correlations", chapter VII, section B1.

Sincerely yours,

/S/

Rabindra N. Patnaik, Ph.D.
Acting Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

NOV 1 2 1997

BIOEQUIVALENCY AMENDMENT

ANDA/AADA: 74-545

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: Biovail Corporation
ATTN: Mimi Brennan

PHONE:(416) 285-6000 X 418
FAX: ~~(416) 285-6499~~ (905) 608-1616

FROM: Lizzie Sanchez, Project Manager (301-827-5847)

Dear Madam:

This is in reference to the bioequivalency data submitted on April 7, 1997, pursuant to Section 505(j)/~~507~~ of the Federal Food, Drug, and Cosmetic Act for Diltiazem HCl Extended-Release Capsules, USP 60, 90 and 120 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached 2 pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

Diltiazem Hydrochloride
Extended Release Capsules, 60, 90, 120 mg
ANDA # 74-845
Reviewer: L. Chuang

Biovail Corporation International
Toronto, Ontario, Canada
Submission Date:
April 7, 1997

Review of an Amendment to Five Bioequivalence Studies, Dissolution Data, and Waiver Request

The 5 bioequivalence studies conducted by the firm included 2 single-dose fasted studies , 1 single-dose fed and fasted study, 1 multiple-dose fasted study, and a pilot 4-way pharmacokinetic study. Two deficiencies were found in the review of 03/04/97. The firm's response in this amendment are discussed below:

Deficiency #1: For the fed and fasted study, the firm should provide a summary table of all samples selected for re-assay due to "inconsistency with other analysis values". The table should include all assayed values and the rationale of selecting the reported value.

Firm's Response: The firm's SOP does not contain information of the number of sample allowed to be re-assayed due to pharmacokinetic anomaly. In this fed and fasted study, among the 137 samples selected for re-assay, the number of samples selected for re-assay due to *"profile is questionable"* are 52 for diltiazem, 62 for deacetyldiltiazem (DAD), and 55 for N-monodemethyldiltiazem (NMD). The reason for the reported value of each re-assayed sample was also described in the firm's SOP.

Reviewer's Comments:

a. Out of the total of 1071 study samples, the percentages of samples selected for re-assay due to *"profile is questionable"* were 5.0% for diltiazem, 5.8% for DAD and 5.1% for NMD.

b. Firm's response is adequate.

Deficiency #2: The dissolution tests conducted by the firm were incomplete for the following reasons:

a. The proposed dissolution specification is not appropriate due to the following reasons:

(1)

Firm's Response: Since a level A (1:1) correlation was not achieved in the *in vivo/in vitro*

correlation study, the dissolution specifications were based only on the data generated from the biobatch. The firm submitted additional dissolution data from all 3 strengths of test products as presented in Table 1:

Table 1: *In* Vitro dissolution Data of Test Products – Gradient pH Method

	60 mg Capsule, Lot #95D005		90 mg Capsules, Lot #96D006		120 mg Capsules, Lot #95D007	
Time Point (Proposed Spec.)	Mean % (n=6)	Range (%)	Mean % (n=6)	Range (%)	Mean % (n=6)	Range (%)
2 hrs	1		1		1	
4 hrs	37		27		27	
6 hrs	87		80		75	

The range of dissolution results for all 3 product strengths is at 4-hour and at 6-hour which is closer to the specification of at 4 hours and at 6 hours.

Based on these data, the firm proposes the following amended dissolution specification using the gradient pH method as described in the original ANDA:

2 hr:
4 hr:
8 hr:

In addition, in its submission of 02/11/97, which was in response to Chemistry's letter of 11/27/96, the firm submitted a single pH method to be used as an alternative method to the pH gradient method. This isocratic pH dissolution method has the following parameter:

Medium: **900 mL of Phosphate buffer pH 6.75**
Apparatus: **USP Apparatus 2**
Paddle speed: **100 rpm**
Specification:
1 hr:
6 hr:
12 hr:

Reviewer's Comments:

* It appears that the firm's specification at 4 hours, using the gradient pH method, was chosen to accommodate the results from the 60 mg capsule.

* The firm's proposal for a new specification of gradient pH method has no meaning at all, because the gradient pH method will be phased out.

* The firm did not submit any actual dissolution data using this isocratic pH method.

(2) The results of the pilot 4-way single-dose study (#1602) indicated that neither the slow-releasing nor the fast-releasing batch is bioequivalent to the biobatch (medium-releasing batch), and yet the proposed specifications covered the dissolution results from all 3 batches. This is inconsistent with the principle of *in vitro-in vivo* correlation.

Firm's Response: The firm's stated that since a 1:1 correlation was not achieved during the *IVIVC* study, this supporting study will not be the determining factor in the setting of the specification.

Reviewer's Comment: Firm's response is adequate.

(3) Comparison between the observed dissolution results and the proposed specification at each time point shows that the proposed range is much wider than the actual data observed, as demonstrated below in Table 2.

Table 2: Comparison of Actual Dissolution Data and the Proposed Specification

Time point (hour)	Actual Result	Proposed Specification
1		
2		
4		
6		
8		
12	100.7 - [illegible]	

Firm's Response: The actual results presented in the above table only pertain to the 120 mg strength. When the data of all 3 strengths are considered, the range is wider and more closely represents the proposed specification.

Reviewer's Comment: It appears that the firm's specification at 4 hours, using the gradient pH method, was chosen to accommodate the results from the 60 mg capsule.

b. The firm chose to use gradient pH of dissolution media and USP 3 dissolution apparatus with the speed of 20 DPM. Since the proposed dissolution specifications were not fully supported by the observed data, the firm should either revise the specifications or submit additional data for review. The firm should also consider other dissolution testing methods, such as those described in the Guidance for Oral Extended Release Dosage Forms.

Firm's Response: As described in its response to deficiency #2a(1), the firm had submitted a single pH method to be used as an alternative method to the pH gradient method. Both

methods will be employed , but the gradient pH method will be phased out and replaced by the single pH method. This isocratic pH dissolution method has the following parameter:

Medium: **900 mL of Phosphate buffer pH 6.75**
Apparatus: **USP Apparatus 2**
Paddle speed: **100 rpm**
Specification: **1 hr:**
6 hr:
12 hr:

Dissolution tests were performed with the 120 mg strength (lot #95D007) using single pH medium and employing USP apparatus 2 at 100 rpm; and USP apparatus 3 at 20 dpm which was the apparatus used in the gradient pH method. The results are presented below in Table 3:

Table 3: Comparison of dissolution profiles of 120 mg strength - Single pH Method

Time (hr)	USP apparatus 3	USP apparatus 2
	Amount Dissolved (%)	
0		
1		
2		
4		
6		
12		
16		9

The firm concluded that results from both methods are comparable. The single pH method will be employed in the future for quality control release and stability of the test products.

A validation report for the isocratic pH dissolution test method for diltiazem HCl ER bid USP capsules was also provided by the firm.

Reviewer's Comments:

* The firm did not provide any detailed information of the results in Table 3, i.e., number of capsules tested, range of results, CV%.

* The validation report for the isocratic pH dissolution method indicated that the dissolution of the test product is very sensitive to pH changes, i.e. the dissolution profile changed from pH 6.70 to pH 6.75 and to pH 6.8.

The firm has expressed concerns that the pH of the dissolution medium may cause a variation in the dissolution results. It intends to reduce this variation by tight pH control of the pH medium. However, this would be difficult to accomplish since, as shown in its validation report, **a change of 0.05 unit of pH** could cause a **variation as wide as 25%** of the amount dissolved.

c. For the dissolution method and specification for diltiazem HCl extended-release capsules, the firm is also advised to refer to USP 23, Supplement 5, p.2919-2920.

Firm's Response: The firm referred to the response to deficiency 2b and stated that the single pH method follows the requirements of USP dissolution testing.

Reviewer's Comments:

* For diltiazem hydrochloride ER capsules which are labeled for dosing every 12 hours, the USP (USP 23, Supplement 5, p.2919-2920) recommends either one of the following three dissolution tests:

Test 1:
Medium: water; 900 mL
Apparatus 2: 100 rpm
Times: 3 hours, 9 hours; 12 hours
Tolerance: 3 hours -
9 hours -
12 hours -

Test 4:
Medium: water; 900 mL
Apparatus 2: 100 rpm
Times: 4 hours, 8 hours; 12 hours, and 24 hours
Tolerance: 4 hours -
8 hours -
12 hours -
24 hours -

Test 5:
Medium: 0.05 M phosphate buffer, pH 7.2, 900 mL
Apparatus 2: 50 rpm
Times: 1 hour, 3 hours; 8 hours
Tolerance: 1 hours -
3 hours -
12 hours -

The firm's dissolution method and specification do not follow any of the above 3 tests.

* For the *in vitro* dissolution testing of extended release drug products, the Office recommends USP apparatus 1 for capsules and aqueous media of various pH ((see *"Guidance: Oral Extended (Controlled) Release Dosage Forms: In Vivo Bioequivalence and In Vitro Dissolution Testing", 09/03/93).* The purpose is to select a pH with enough discriminating power for the final testing method. This is especially important for the test product due to its pH sensitive nature.

d. The dissolution rates for the 60 mg strength product were faster than those for the 90 mg and 120 mg strengths and were similar to those observed for the fast-releasing formulation of the 120 mg strength,. The firm should provide explanation for such observation,

Firm's Response: The biobatches for all 3 strengths were produced using the same population of beads (IR lot A1A2) encapsulated into different sizes of capsules. The firm conducted dissolution tests, in two different laboratories, Biovail R&D Laboratories and Biovail Stenbach Laboratory (the production site), on all 3 strengths using the single pH method as described in its responses to 2a(1) and 2b. The results are presented below in Table 4:

Table 4: Dissolution data obtained from two laboratories – Single pH Method

	Biobail R&D laboratory			Biovail Stenbach (production) lab.		
	Cumulative amount released (%)			Cumulative amount released (%)		
	60 mg	90 mg	120 mg	60 mg	90 mg	120 mg
Time (hr)						
1						
2						
4						
6						
10						

The firm concluded that the dissolution profiles are comparable among the 3 strengths using the single pH method.

Reviewer's Comments:

* The firm did not provide any detailed information of the results in Table 4, i.e., number of capsules tested, range of results, CV%.

* The firm still needs to explain why the dissolution of the 60 mg strength is faster than the 90 mg and 120 mg strengths using the gradient pH method. The fact that isocratic

method yielded comparative dissolution results for all 3 strengths may indicate that this isocratic pH method does not have the differentiating power.

e. The dissolution tests were conducted in 2 batches of 6 capsules each. The dissolution test should be conducted in 12 capsules of the test product versus 12 capsules of the reference product. The percent of label claim dissolved at each specified testing interval should be reported for each individual capsule. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should also be reported.

Firm's Response: The firm submitted the requested information as presented below in Table 5:

Table 5 - In Vitro Dissolution Testing

Drug (Generic Name): Diltiazem HCl
Dosage Form: Extended Release Capsule
Dose Strength: 60, 90 and 120 mg
ANDA No.: 74-845
Firm: Biovail Corporation International
Submission Date: 04/07/97

I. Conditions for Dissolution Testing:

USP XXIII Apparatus: III (Bio-Dias) DPM: 20
No. Units Tested: 6+6
Medium: Phosphate buffer -pH 1.5 at 0-1 hour Volume: 250 mL
pH 4.5 at 1-2 hour
pH 6.9 at 2-6 hour
pH 7.2 at 6-12 hour

Tolerance:

Reference Drug: Cardizem[R] SR capsule (Marion Merrell Dow)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # C3/95 A1A21MTC3 (Pkg. 95D007) Strength (mg): 120			Reference Product Lot # P20223 Strength (mg): 120		
	Mean % dissolved	Range (%)	RSD(%)	Mean % dissolved	Range (%)	RSD (%)
1	1		12.79	5		9.02
2	1		14.71	11		6.58
4	21	[illegible]	9.65	32		3.25

6	72		2.98	66		2.66
8	100		1.69	92		2.03
12	104		1.73	109		1.78
Sampling Times (Hours)	Test Product Lot # C3/95A1A22-MTC2 (Pkg. 95D006) Strength (mg): 90			Reference Product Lot # P10279 Strength (mg): 90		
	Mean % dissolved	Range (%)	RSD (%)	Mean % dissolved	Range (%)	RSD (%)
1	1		19.35	5		8.78
2	1		19.07	11		6.31
4	23		6.36	33		5.34
6	78		3.57	69		3.78
8	104		3.62	96		2.19
12	106		3.69	112	109 - .	1.29
Sampling Times (Hours)	Test Product Lot # C3/95A1A21-MTC1 (Pkg. 95D005) Strength (mg): 60			Reference Product Lot # E01426 Strength (mg): 60		
	Mean % dissolved	Range (%)	RSD (%)	Mean % dissolved	Range (%)	RSD (%)
1	1		17.95	5		9.83
2	1		16.72	10		8.34
4	41		7.51	32		4.51
6	93		3.26	71		7.87
8	106		3.60	96		3.55
12	107		3.61	112		1.97

Reviewer's Comment: The data in Table 5 comply with the Division's request in deficiency 2e.

f. The batch numbers were not reported for the test products used in the dissolution test presented in Table 3 of the report for project Dil-B12.

Firm's Response: The firm provided the batch numbers for the slow, medium and fast batches which were identical to those presented in Table 2 of the same report.

General Comments:

1. Because it's the firm's intention that the gradient pH method will be phased out and replaced by the single pH method, the Division of Bioequivalence would not make further comments on the gradient pH method. However, the firm still needs to explain why the dissolution of the 60 mg strength is faster than the 90 mg and 120 mg strengths using the gradient pH method. The fact that isocratic method yielded comparative dissolution results for all 3 strengths may indicate that this isocratic pH method does not have the differentiating power.

2. The validation report for the isocratic pH dissolution method indicated that the dissolution of the test product is very sensitive to pH changes, i.e. the dissolution profile changed from pH 6.70 to pH 6.75 and to pH 6.8.

   The firm has expressed intention to reduce this variation by tight pH control of the pH medium. However, this would be difficult to accomplish since, as shown in its validation report, **a change of 0.05 unit of pH** could cause a **variation as wide as 25%** of the amount dissolved.

3. For the *in vitro* dissolution testing of extended release drug products, the Office recommends USP apparatus 1 for capsules and aqueous media of various pH ((see *"Guidance: Oral Extended (Controlled) Release Dosage Forms: In Vivo Bioequivalence and In Vitro Dissolution Testing", 09/03/93).* The purpose is to select a pH with enough discriminating power for the final testing method. This is especially important for the test product due to its pH sensitive nature.

4. The dissolution data submitted by the firm using the single pH method are incomplete. The dissolution test should be conducted in 12 capsules of the test product versus 12 capsules of the reference product. The percent of label claim dissolved at each specified testing interval should be reported for each individual capsule. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

5. To set the dissolution specification for an extended release oral dosage form without an *IVIVC*, such as the test product, the firm is advised to consult with the recently published *Guidance for Industry on "Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations", Chapter VII, Section B1.*

Deficiency:

The dissolution test conducted by the firm has been found to be incomplete due to General Comments #1-5.

nendation:

The single-dose, fasted bioequivalence study, and multiple-dose fasted bioequivalence study, conducted by Biovail Corporation International on its Diltiazem Hydrochloride Extended Release 120 mg capsule, lot ##C3/95A1A21-MTC3, comparing it to Cardizem^{R} SR 120 mg capsule, lot #P20223, have been previously (03/04/97) found acceptable by the Division of Bioequivalence.

2. The single-dose, fed and fasted bioequivalence study, conducted by Biovail Corporation International on its Diltiazem Hydrochloride Extended Release 120 mg capsule, lot #C3/95A1A21-MTC3, comparing it to Cardizem^{R} SR 120 mg capsule, lot #P20223, is now found to be acceptable by the Division of Bioequivalence.

3. The dissolution testings conducted by Biovail Corporation International on its Diltiazem Hydrochloride Extended Release 60 mg, 90 mg and 120 mg capsules have been found incomplete due to the deficiency.

4. The waiver request for the 60 mg and 90 mg strengths of the test drugs can not be granted pending the acceptance of the dissolution tests.

The firm should be informed of the General Comments, Deficiency and Recommendations.

/S/ 10/23/97

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG /S/ 10/24/97
FT INITIALED YHUANG

Concur /S/ Date: 10/29/97
Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

cc:

45a.497

ANDA 74-845

MAR 13 1997

Biovail Corporation International
Attention: Robert Burford
U. S. Representative
200 Hurlbutt Street
Wilton, CT 06897-7299

Dear Sir:

Reference is made to the bioequivalence data submitted on January 31, 1996 in support of Diltiazem Hydrochloride Extended Release Capsules, 60 mg, 90 mg and 120 mg.

The Office of Generic Drugs has reviewed the submitted bioequivalence data and the following comments are provided for your consideration:

1. The Division has no further questions about either the single-dose, or the multiple-dose fasted bioequivalence studies, conducted on Diltiazem Hydrochloride Extended Release 120 mg capsule, (Biovail) lot #C3/95A1A21-MTC3, comparing it with Cardizem^{R} SR 120 mg capsule, lot #P20223 (Marion Labs).

2. The single-dose, food challenge study, conducted on Diltiazem Hydrochloride Extended Release capsules, 120 mg, lot #C3/95A1A21-MTC3, comparing it with Cardizem^{R} SR capsules, 120 mg, lot #P20223, has been found incomplete. For study #1533-1, please provide a summary of all samples selected for re-assay due to "inconsistency with other analysis values". The table (preferred format) should include the original assay value, reason for re-assay, re-assayed value, value selected for the final report, and the rationale for choosing the selected value.

3. The dissolution tests have been found incomplete for the following reasons:

   a. The tentative or the proposed dissolution specification is not appropriate for the following reasons:

      1) [redacted] at 4 hours

specification for the 6-hour time point. There is no differentiation between the test product with fast-, medium-, or slow-releasing characteristics using the proposed specification.

2) The results of the pilot 4-way single-dose study (#1602) indicated that neither the slow-releasing nor the fast-releasing batch is bioequivalent to the biobatch (medium-releasing batch), and yet the proposed specifications cover the dissolution results from all 3 batches. This is inconsistent with the principle of *in vitro-in vivo* correlation.

3) Comparison between the observed dissolution results and the proposed specification at each time point shows that the proposed range is much wider than the actual data observed, as demonstrated in the table below.

Comparison of Actual Dissolution Data and the Proposed Specification		
Time point (hour)	Actual Result	Proposed Specification
1		
2		
4		
6		
8		
12		

b. The firm chose to use gradient pH of dissolution media and USP dissolution apparatus 3 with the speed of 20 DPM. Since the proposed dissolution specifications were not fully supported by the observed data, the firm should either revise the specifications or submit additional data for review. The firm should also consider other dissolution testing methods, such as those described in the Guidance for Oral Extended Release Dosage Forms.

c. For the dissolution method and specification for diltiazem hydrochloride extended-release capsules, the firm is also advised to refer to USP 23, Supplement 5, p.2919-2920.

d. The dissolution rates for the 60 mg strength product were faster than those for the 90 mg and 120 mg strengths and were similar to those observed for the fast-releasing formulation of the 120 mg strength. Provide an explanation for this observation.

e. The dissolution tests were conducted in 2 batches of 6 capsules each. The dissolution test should be conducted in 12 capsules of the test product versus 12 capsules of the reference product. The percent of label claim dissolved at each specified testing interval should be reported for each individual capsule. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should also be reported.

f. The batch numbers were not reported for the test products used in the dissolution test presented in Table 3 of the report for project Dil-B12.

4. The request for waiver of the bioequivalence requirements for the 60 mg and 90 mg strengths of the test drugs can not be granted pending the acceptance of all the required bioequivalence studies on the 120 mg strength and the comparative dissolution tests on each strength.

As described under 21 CFR 314.96 an action which will amend this application is required. The amendment will be required to address all of the comments presented in this letter. Should you have any questions, please call Lizzie Sanchez, Pharm.D., Project Manager, at (301) 594-2290. In future correspondence regarding this issue, please include a copy of this letter.

Sincerely yours,

Nicholas Fleischer, Ph.D.
Director,
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MAR - 4 1997

Diltiazem Hydrochloride
Extended Release Capsules, 60, 90, 120 mg
ANDA # 74-845
Reviewer: L. Chuang

Biovail Corporation International
Toronto, Ontario, Canada
Submission Date:
January 31, 1996

Review of Five Bioequivalence Studies, Dissolution Data, and Waiver Request

Diltiazem HCl is a calcium ion influx inhibitor. It produces antihypertensive effect primarily by relaxation of vascular smooth muscle and the resultant decrease in peripheral vascular resistance. It is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive medications, such as diuretics.

Diltiazem is well absorbed from the GI tract and is subject to an extensive first-pass effect and undergoes extensive metabolism and results in two known active metabolites, desacetyldiltiazem (DAD) and N-monodemethyldiltiazem (NMD). Plasma elimination half-life is about 3-4.5 hours and is slightly increased with dose. When the innovator product was coadministered with a high fat content breakfast, the extent of diltiazem absorption was not affected. Dose-dumping does not occur.

Marion Laboratories is the innovator and markets this drug under the brand name i) Cardizem^{R} in 30 mg, 60 mg, 90 mg and 120 mg strength (immediate release) tablets; ii) Cardizem^{R} SR in 60 mg, 90 mg, and 120 mg strength extended-release capsules; and iii) Cardizem^{R} CD in 180 mg, 240 mg, and 300 mg strength extended-release capsules.

The submission contains reports of the following 5 bioequivalence studies:

1. 2-way single-dose fasted study (#1532-1) in 24 subjects
2. 2-way single-dose fasted repeat study (#1659) in 38 subjects
3. 3-way single-dose food effect study (#1533-1) in 21 subjects
4. 2-way multiple-dose study (#1534-2) in 24 subjects
5. Pilot 4-way single-dose pharmacokinetic study (#1602) in 12 subjects

Bioequivalence Study #1532-1 -- 2-Way, Single Dose, Fasted

The objective of this study was to compare the rate and extent of absorption of the firm's Diltiazem HCl 120 mg sustained-released capsules to Cardizem^{R} SR 120 mg capsules under fasted condition.

The clinical study was conducted at Biovail Corporation International in Toronto, Ontario, Canada during 07/14-17/95 and 07/ 21-24/95 with as the principal investigator. The analytical study was conducted at Biovail Corporation International in Toronto, Ontario, Canada during 07/26-09/18/95 by analysts

The design of the study was a single-dose, 2-way crossover in non-smoking male volunteers under fasted condition. The protocol was approved by Institutional Review Board of Biovail Corporation International (chaired by on 05/10/95.

Twenty-six (26) non-smoking male volunteers, 18-42 years old, were enrolled who had their preclinical laboratory test data reviewed by the physician which included biochemical profile, hematology, urinalysis and drugs of abuse screen. The inclusion criteria were:

1. male, 18-45 years old, non-smoking, and body weight within ±10% of ideal weight
2. availability for the entire study period and willingness to sign the informed consent form
3. normal vital signs and ECG, blood pressure > 100/60 mm/Hg, pulse rate > 50 bpm
4. Clinical laboratory values within ±10% of normal range unless considered clinically insignificant by the investigator
5. negative for drugs of abuse

The exclusion criteria were:

1. history or presence of hypersensitivity to Diltiazem or related drugs
2. history or presence of disease of any organs or condition known to interfere with the absorption, distribution, metabolism or excretion of drugs
3. significant illness during the 4 weeks prior to entry into this study
4. history of frequent headache
5. any physical abnormality
6. requirement of drug maintenance therapy, history of drug dependency, of psychological disease
7. Alcohol abuse or participation in a clinical trial within 30 days preceding this study, including MAO inhibitors
8. use of enzyme-inducing or enzyme-inhibiting drugs within 30 days prior to entry into this study
9. Administration of any medication within 14 days preceding entry to this study
10. blood donation within the previous 60 days

After an overnight fast of 10 hr, on the morning of 07/15/95, each subject received one of the following treatments with 240 mL of water:

Treatment A - Test Drug: Diltiazem HCl ER capsule, 1 x 120 mg, Biovail Corporation International, lot #C3/95A1A21-MTC3, potency 100.6%, manufacturing date , lot size of psules.

Treatment B - Reference Drug: Cardizem^{R} SR capsule, 1 x 120 mg, Marion Merrell Dow Inc., lot #P20223, expired 12/95, potency 100.2%.

Water was allowed ad libitum 1 hour post dose. After a 7-day washout, on 07/22/95, each subject was crossed over to the alternative treatment. Subjects remained fasted for 4.5 hours post dose and ambulatory for 4 hours post dose. They were confined to the clinical facility at 9 PM the evening before dosing until after the 48-hours blood draw. Blood pressure, heart rate and ECG were monitored at 0, 2, 4, 8 and 12 hours post-dose during each period. Physical examination and laboratory tests were repeated at the completion of the study.

Blood samples (10 mL each) were collected in Vacutainers containing EDTA at 0, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, 24, 28, 36, and 48 hours post-dose. Plasma samples were prepared, frozen, and stored at -70°C until transferred to the analytical site and assayed for Diltiazem, DAD, and NMD.

Analytical Method -- **Not for Release through FOI**:

Diltiazem, plus metabolites and internal standard (propranolol) were extracted into an organic solvent from 1 mL of basified plasma. The analytes were back extracted into an acid solution and injected onto .

The maximal duration of plasma samples storage was 65 days which was shorter than the period covered by the validated long-term stability study (25 weeks, see below).

Method Validation

The results of pre-study validation were reported as following:

Calibration Range: Diltiazem: 3.1-804.4 ng/mL (correlation coefficient of 0.9988, n=6)
DAD: 1.0-262.3 ng/mL (correlation coefficient of 0.9996. n=6)
NMD: 3.1-794.8 ng/mL (correlation coefficient of 0.9995, n=6)

Limit of Quantitation: Diltiazem: 3.1 ng/mL (precision 5.9% CV, accuracy 96.8%, n=5)
DAD: 1.0 ng/mL (precision 8.1% CV, accuracy 110%, n=6)
NMD: 3.1 ng/mL (precision 3.5% CV, accuracy 96.8%, n=6)

Specificity: Lack of interferences from endogenous plasma components.

Precision and Accuracy are presented below in Table 1:

Table 1: Precision and Accuracy

Analyte (assay range)	Intra-Assay (n=5)		Inter-Assay (n=5)	
	Precision (% CV)	Accuracy (%)	Precision (% CV)	Accuracy (%)
Diltiazem (4.4-567.8 ng/mL)	1.1 - 4.7	97.7 - 110.7	2.0 - 5.4	93.2 - 104.2

DAD (1.5-193.7 ng/mL)	1.0 - 9.7	106.0 - 113.2	1.5 - 13.5	93.3 - 105.7
NMD (4.5-580.8 ng/mL)	1.7 - 4.4	93.9 - 106.7	2.1 - 10.2	102.1 - 111.1

The stability of 3 analytes under different conditions are presented below in Table 2.

Table 2: Stability Data

Condition	Diltiazem	DAD	NMD
whole blood in ice bath for 30 minutes	97.9%	100.5%	92.8%
whole blood at room temperature for 30 min.	97.5%	100.4%	93.6%
plasma with buffer for 15, 30, 45, and 60 minutes	97.4-102%	97.4-100.0%	99.1-105.0%
extracted samples (in 3 concentrations) in acid solution for 21 hours	96.6-102.0%	104.3-105.2%	99.0-101.4%
3 freeze-thaw cycles as compared to 1 freeze-thaw cycle	103.3%	100.0%	100.3%
25-week in plasma (with 3 concentrations) at -70°C	108.6-118.5%	100.1-113.4%	99.5-103.3%

The recoveries of diltiazem, DAD and NMD over the concentration range of their respective calibration curve range were 89.2-110.5%, 94.4-142.9% and 97.5-121.4%, respectively. The recovery of internal standard was 99.5%.

The assay method was further validated during the analysis of the study samples when 18 standard curves, each curve contained a 6-point calibration and duplicates of 4 levels of QC samples, for every of the 3 analytes were conducted. The correlation coefficients of the curves were 0.9982, 0.9961 and 0.9973 or larger for diltiazem, DAD and NMD, respectively. The accuracy and precision of these standard and QC samples are presented below in Table 3:

Table 3: During-Study Validation Data – Single Dose – Fasting – #1532-1

	Accuracy (%)		Precision (% CV)	
Analyte	Standard	QC Sample	Standard	QC Sample
Diltiazem	93.3 - 104.2	91.1 - 110.0	2.5 - 10.5	7.2 - 11.2
DAD	100.0 - 102.5	96.6 - 108.8	2.7 - 8.5	7.1 - 11.8
NMD	98.2 - 103.3	91.1 - 102.1	2.5 - 6.2	10.2 - 13.6

Results:

Of the 26 subjects enrolled, 2 subjects did not complete the study. Subject #6 was dismissed from the study during period 1 (treatment B) because of an 2° AV block type 1, and subject #24 did not report for period 2 dosing.

There were no other protocol deviation. Twenty-five (25) adverse events were reported by 14 subjects, 6 during treatment A and 19 during treatment B. The adverse effects were sinus bradycardia, headache, 2° AV block type 1, SR non-specific T-wave changes (and inversion in V2 to V6), SR non-specific ST changes, weakness, diarrhea, dizziness, diaphoresis, and pallor.

No clinically significant abnormalities were reported during the physical examination and laboratory tests at the completion of the study.

The plasma samples from 24 subjects (excluding subjects #6 and #24, both were in the sequence of BA) were assayed for diltiazem, DAD and NMD. Reassays conducted due to the anomaly of the first value included 14 samples for diltiazem, 14 samples for DAD and 17 samples for NMD. Each was repeated at least twice, and the average of the repeated results were reported.

The mean plasma concentrations of diltiazem, DAD and NMD at each sampling point after both treatments and the mean pharmacokinetic parameters are presented below in Figures 1-3 and Tables 4-6. The calculation of K_d was based on the most linear portion of the terminal elimination phase in the semi-log plot of individual subject data.

Table 4: Mean (C.V.%) Plasma Diltiazem Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 24 - 1 x 120 mg ER Capsule - Fasting Study - Single Dose)

Time (hour)	Biovail (Treatment A)	Marion Merrell Dow (Treatment B)
0	0	0
1	0	0
2	0	2.40 (140)
3	0.76 (490)	9.30 (84)
4	9.11 (137)	26.22 (96)
5	47.45 (72)	58.84 (63)
6	76.43 (53)	79.56 (52)
7	87.36 (38)	81.20 (37)
8	86.05 (34)	86.26 (36)
10	65.15 (37)	71.09 (45)

12	52.49 (37)	57.61 (40)
16	31.97 (46)	34.72 (46)
20	19.78 (54)	22.00 (46)
24	15.19 (66)	16.69 (73)
28	12.18 (66)	11.39 (76)
36	5.10 (124)	4.02 (76)
48	0.69 (407)	0.48 (367)
AUC_{0-t} (ng*hr/mL)	1007.09 (36)	1080.54 (42)
AUC_{0-inf} (ng*hr/mL)	1076.32 (36)	1144.72 (40)
C_{max} (ng/mL)	98.23 (36)	95.40 (43)
$LNAUC_{0-t}$	947.63[a]	994.22[a]
$LNAUC_{0-inf}$	1015.29[a]	1061.48[a]
LNC_{max}	93.16[a]	87.92[a]
T_{max} (hour)	7.38 (28)	7.83 (19)
$T_{1/2}$ (hour)	7.94 (31)	7.41 (34)

a = geometric mean

Table 5: Mean (C.V.%) Plasma DAD Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 24 - 1 x 120 mg ER Capsule - Fasting Study - Single Dose)

Time (hour)	Biovail (Treatment A)	Marion Merrell Dow (Treatment B)
0	0	0
1	0	0
2	0.07 (490)	0
3	0.04 (490)	0.27 (233)
4	0.05 (490)	0.65 (174)
5	1.13 (131)	1.48 (108)
6	2.83 (77)	3.17 (63)
7	4.31 (60)	3.89 (48)
8	5.37 (65)	4.99 (48)
10	6.08 (68)	5.89 (62)

12	6.13 (67)	6.27 (69)
16	4.99 (75)	5.13 (70)
20	3.95 (64)	4.55 (75)
24	3.34 (71)	3.52 (77)
28	2.72 (72)	2.87 (108)
36	1.34 (99)	1.38 (129)
48	0.52 (151)	0.51 (205)
AUC_{0-t} (ng*hr/mL)	125.26 (70)	129.75 (17)
AUC_{0-inf} (ng*hr/mL)	166.13 (53)	166.45 (67)
C_{max} (ng/mL)	6.81 (63)	6.86 (62)
$LNAUC_{0-t}$	100.59[a]	98.13[a]
$LNAUC_{0-inf}$	147.58[a]	140.16[a]
LNC_{max}	5.82[a]	5.86[a]
T_{max} (hour)	11.21 (35)	11.42 (34)
$T_{1/2}$ (hour)	16.75 (76)	13.57 (51)

a = geometric mean

Table 6 Mean (C.V.%) Plasma NMD Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 24 - 1 x 120 mg ER Capsule - Fasting Study - Single Dose)

Time (hour)	Biovail (Treatment A)	Marion Merrell Dow (Treatment B)
0	0	0
1	0	0
2	0	0
3	0	0.75 (237)
4	1.28 (193)	4.68 (96)
5	7.21 (86)	10.75 (60)
6	13.21 (54)	15.30 (52)
7	17.78 (39)	17.35 (33)
8	19.66 (35)	20.33 (33)
10	20.01 (33)	20.50 (37)
12	18.09 (34)	18.76 (30)

16	13.97 (33)	14.88 (29)
20	10.38 (34)	11.57 (33)
24	8.57 (43)	8.47 (36)
28	7.17 (40)	6.91 (39)
36	3.39 (76)	2.90 (83)
48	0.42 (271)	0.44 (277)
AUC_{0-t} (ng*hr/mL)	353.38 (34)	369.92 (33)
AUC_{0-inf} (ng*hr/mL)	434.75 (28)	454.69 (26)
C_{max} (ng/mL)	22.04 (30)	22.58 (36)
$LNAUC_{0-t}$	334.21[a]	350.77[a]
$LNAUC_{0-inf}$	419.04[a]	440.59[a]
LNC_{max}	20.85[a]	21.33[a]
T_{max} (hour)	9.38 (24)	9.96 (29)
$T_{1/2}$ (hour)	12.33 (37)	12.31 (63)

a = geometric mean

Analysis of Variance was performed on the log-transformed data of AUC_{0-t}, AUC_{0-inf}, and C_{max}, using SAS GLM procedure. The model included sequence, subject within sequence, treatment and period as factors. The sequence effect was tested using the subjects within sequence effect as the error term. The treatment and period effect were tested against the residual mean square error.

No significant sequence, period, or treatment effects were detected for any of the parameters.

The LS means of the non-transformed and log-transformed pharmacokinetic parameters, ratios of these means and the 90% confidence intervals of test product versus reference product are presented in Tables 7-9.

Table 7: Statistical Analysis of Diltiazem Data -- Fasting Study -- Single Dose (n=24)

Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
AUC_{0-t}	1008.27	1075.33	0.94	(0.848; 1.019)
$LNAUC_{0-t}$	6.8560 (949.60[a])	6.8990 (991.28[a])	0.96[b]	(0.884; 1.038)
AUC_{0-inf}	1076.42	1139.49	0.94	(0.865; 1.018)

$LNAUC_{0-inf}$	6.9238[a] (1016.20[a])	6.9646 (1058.52[a])	0.96[b]	(0.890; 1.035)
C_{max}	98.00	94.91	1.03	(0.862; 1.201)
LNC_{max}	4.5335 (93.08[a])	4.4734 (87.66[a])	1.06[b]	(0.897; 1.257)

a = Geometric Mean
b = Ratio of Geometric Means

Table 8: Statistical Analysis of DAD Data – Fasting Study – Single Dose (n=24)

Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
AUC_{0-t}	124.33	128.22	0.97	(0.863; 1.077)
$LNAUC_{0-t}$	4.6018 (99.67[a])	4.5700 (96.55[a])	1.03[b]	(0.919; 1.159)
AUC_{0-inf}	165.49	164.65	1.01	(0.865; 1.145)
$LNAUC_{0-inf}$	4.9942[a] (147.55[a])	4.9293 (138.28[a])	1.07[b]	(0.921; 1.237)
C_{max}	6.72	6.81	0.99	(0.862; 1.114)
LNC_{max}	1.7499 (5.75[a])	1.7577 (5.80[a])	0.99[b]	(0.885; 1.112)

a = Geometric Mean
b = Ratio of Geometric Means

Table 9: Statistical Analysis of NMD Data – Fasting Study – Single Dose (n=24)

Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
AUC_{0-t}	352.18	368.09	0.96	(0.893; 1.021)
$LNAUC_{0-t}$	5.8089 (333.24[a])	5.8559 (349.28[a])	0.95[b]	(0.889; 1.024)
AUC_{0-inf}	433.41	452.55	0.96	(0.880; 1.035)
$LNAUC_{0-inf}$	6.0353[a] (417.93[a])	6.0846 (439.05[a])	0.95[b]	(0.883; 1.026)
C_{max}	21.87	22.50	0.979	(0.854; 1.090)
LNC_{max}	3.0300 (20.70[a])	3.0562 (21.25[a])	0.97[b]	(0.870; 1.091)

a = Geometric Mean

b = Ratio of Geometric Means

Comments:

1. The validation report of the analytical methodology for the 3 analytes is acceptable.

2. The ratios of AUC_{0-t}/AUC_{0-inf} for DAD and NMD of some subjects were below 0.8. This was due to the nature of the extended release dosage form of the drug products and the limit of blood collection time period (48 hours).

3. The 90% confidence intervals of $LNAUC_{0-t}$, $LNAUC_{0-inf}$, and LNC_{max} for all 3 analytes were all within 80-125% except that of LNC_{max} for diltiazem was 89.7-125.7%. This could be the reason the firm repeated this single dose fasted study in more subjects.

4. The calculation of all pharmacokinetic parameters, their LS means, and the 90% confidence intervals submitted by the sponsor have been confirmed by the reviewer's own calculation.

Bioequivalence Study #1659 -- *Repeated*, 2-Way, Single Dose, Fasted

The objective of this repeated study was to compare the bioavailability of a single dose of the firm's diltiazem HCl 1x120 mg sustained-released capsule to Cardizem^{R} SR 1x120 mg capsule under fasted condition.

The clinical study was conducted at Biovail Corporation International in Toronto, Ontario, Canada during 10/20-30/95 (group 1, n=32) and 10/27-11/06/95 (group 2, n=6) to ensure at least 32 subjects completed the study with as the principal investigator. The analytical study was conducted at Biovail Corporation International in Toronto, Ontario, Canada during 10/31-12/01/95 by analyst

The design of the study was a single-dose, 2-way crossover in non-smoking male volunteers under fasted condition. The protocol was approved by Institutional Review Board of Biovail Corporation International (chaired by on 10/04/95.

Thirty-eight (38) non-smoking male volunteers, 18-41 years old, were enrolled who had their preclinical laboratory test data reviewed by the physician which included biochemical profile, hematology, urinalysis and drugs of abuse screen. The inclusion and exclusion criteria were the same as those stated in the previous study (#1532-1).

After an overnight fast of 10 hr, on the morning of 10/21/95 for group 1 (n=32) and 10/28/95 for group 2 (n=6), each subject received one of the following treatments with 240 mL of water:

Treatment A - Test Drug: Diltiazem HCl ER capsule, 1 x 120 mg, Biovail Corporation International, lot #C3/95A1A21-MTC3, potency 100.6%,

manufacturing date , lot size of apsules.

Treatment B - Reference Drug: Cardizem[R] SR capsule, 1 x 120 mg, Marion Merrell Dow Inc., lot #P20223, expired 12/95, potency 100.2%.

After a 7-day washout, on the morning of 10/28/95 for group 1 (n=32) and 11/04/95 for group 2 (n=6), each subject was crossed over to the alternative treatment. The study procedures, including blood sampling schedule, were the same as in the previous study #1532-1.

Analytical Method -- **Not for Release through FOI:**

The same validated analytical methods were conducted for the analysis of plasma diltiazem, DAD and NMD of this study. The maximal duration of plasma samples storage was 41 days which was shorter than the period covered by the validated long-term stability study (25 weeks).

The assay method was further validated during the analysis of the study samples when 22 standard curves, each curve contained a 6-point calibration and duplicates of 4 levels of QC samples, for every of the 3 analytes were conducted. The correlation coefficients of the curves were 0.9983, 0.9982 and 0.9988 or larger for diltiazem, DAD and NMD, respectively. The accuracy and precision of these standard and QC samples are presented below in Table 10:

Table 10: During-Study Validation Data – *Repeated* – Single Dose – Fasting – #1659

	Accuracy (%)		Precision (% CV)	
Analyte	Standard	QC Sample	Standard	QC Sample
Diltiazem	97.2 - 100.6	100.2 - 112.4	2.5 - 10.8	5.6 - 10.6
DAD	91.6 - 110.0	98.9 - 108.2	2.0 - 10.5	5.8 - 12.3
NMD	94.0 - 109.2	97.4 - 109.5	2.0 - 5.9	7.0 - 10.3

Results:

All 38 subjects completed the study. There were no protocol deviation except that the post-study electrolytes of 4 subjects were not analyzed. Forty-seven (47) adverse events were reported by 26 subjects, 27 during treatment A and 20 during treatment B. The adverse effects were sinus bradycardia, headache, borderline 1° AV block, lightheaded, diaphoresis, pallor, weakness, and tightness in chest.

No clinically significant abnormalities were reported during the physical examination and laboratory tests at the completion of the study.

The plasma samples from 38 subjects were assayed for diltiazem, DAD and NMD. Reassays conducted due to the anomaly of the first value included 11 samples for diltiazem, 5 samples for DAD and 9 samples for NMD. Each was repeated at least twice, and the average of the repeated results was reported.

The mean plasma concentrations of diltiazem, DAD and NMD at each sampling point after both treatments and the mean pharmacokinetic parameters are presented below in Figures 4-6 and Tables 11-13. The calculation of K_{el} was based on the most linear portion of the terminal elimination phase in the semi-log plot of individual subject data.

Table 11: Mean (C.V.%) Plasma Diltiazem Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 38 - 1 x 120 mg ER Capsule - *Repeated* Fasting Study - Single Dose)

Time (hour)	Biovail (Treatment A)	Marion Merrell Dow (Treatment B)
0	0	0
1	0	0
2	0	1.26 (165)
3	0.28 (351)	5.68 (73)
4	5.99 (197)	13.07 (78)
5	30.12 (92)	37.07 (69)
6	59.62 (59)	59.17 (61)
7	78.64 (39)	74.35 (54)
8	84.27 (39)	81.21 (46)
10	66.41 (37)	66.03 (40)
12	49.72 (37)	51.55 (41)
16	30.35 (42)	31.28 (50)
20	18.67 (44)	18.65 (46)
24	14.04 (51)	13.06 (48)
28	10.73 (58)	9.91 (62)
36	4.01 (98)	3.53 (110)
48	0.69 (304)	0.26 (347)
AUC_{0-t} (ng*hr/mL)	920.15 (38)	920.71 (44)
AUC_{0-inf} (ng*hr/mL)	986.62 (36)	983.17 (43)
C_{max} (ng/mL)	91.27 (35)	86.22 (43)

$LNAUC_{0-t}$	857.67[a]	848.39[a]
$LNAUC_{0-inf}$	926.48[a]	909.36[a]
LNC_{max}	86.15[a]	79.34[a]
T_{max} (hour)	7.58 (17)	8.11 (23)
$T_{1/2}$ (hour)	8.16 (40)	7.40 (31)

a = geometric mean

Table 12: Mean (C.V.%) Plasma DAD Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 38 - 1 x 120 mg ER Capsule - *Repeated* Fasting Study - Single Dose)

Time (hour)	Biovail (Treatment A)	Marion Merrell Dow (Treatment B)
0	0	0
1	0	0.06 (430)
2	0.04 (616)	0.03 (616)
3	0	0.03 (616)
4	0.07 (430)	0.16 (358)
5	0.65 (141)	0.95 (176)
6	2.02 (96)	2.27 (103)
7	3.34 (67)	3.52 (81)
8	4.64 (62)	4.81 (67)
10	5.73 (71)	5.46 (71)
12	5.98 (78)	6.03 (74)
16	5.37 (95)	5.30 (95)
20	4.42 (95)	4.17 (103)
24	3.91 (112)	3.63 (111)
28	3.22 (140)	3.04 (141)
36	1.55 (200)	1.58 (192)
48	0.56 (304)	0.50 (305)
AUC_{0-t} (ng*hr/mL)	130.01 (113)	127.20 (115)
AUC_{0-inf} (ng*hr/mL)	164.69 (106)	162.57 (106)
C_{max} (ng/mL)	6.56 (79)	6.48 (77)
$LNAUC_{0-t}$	93.59[a]	91.29[a]

$LNAUC_{0-inf}$	125.49[a]	120.99[a]
LNC_{max}	5.45[a]	5.40[a]
T_{max} (hour)	11.26 (32)	11.37 (19)
$T_{1/2}$ (hour)	12.12 (41)	12.04 (52)

a = geometric mean

Table 13 Mean (C.V.%) Plasma NMD Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 38 - 1 x 120 mg ER Capsule - *Repeated* Fasting Study - Single Dose)

Time (hour)	Biovail (Treatment A)	Marion Merrell Dow (Treatment B)
0	0	0
1	0	0
2	0.16 (616)	0
3	0	0.36 (298)
4	1.05 (240)	3.14 (89)
5	5.20 (95)	8.14 (50)
6	10.92 (58)	12.54 (40)
7	15.74 (27)	16.74 (38)
8	18.44 (24)	19.14 (28)
10	19.34 (23)	19.70 (23)
12	17.46 (23)	18.17 (22)
16	14.20 (26)	14.77 (31)
20	10.50 (26)	10.86 (30)
24	8.82 (30)	8.87 (31)
28	7.18 (33)	7.33 (38)
36	4.08 (76)	3.75 (65)
48	0.64 (215)	0.38 (296)
AUC_{0-t} (ng*hr/mL)	352.77 (29)	363.50 (30)
AUC_{0-inf} (ng*hr/mL)	435.55 (29)	442.03 (32)
C_{max} (ng/mL)	20.51 (23)	21.29 (24)
$LNAUC_{0-t}$	338.71[a]	349.89[a]
$LNAUC_{0-inf}$	420.73[a]	423.34[a]

LNC_{max}	19.98[a]		20.68[a]	
T_{max} (hour)	9.61	(22)	9.76	(25)
$T_{1/2}$ (hour)	12.06	(29)	11.57	(39)

a = geometric mean

Analysis of Variance was performed on the log-transformed data of AUC_{0-t}, AUC_{0-inf}, and C_{max}, using SAS GLM procedure. The model included sequence, subject within sequence, treatment and period as factors. The sequence effect was tested using the subjects within sequence effect as the error term. The treatment and period effect were tested against the residual mean square error.

No significant sequence, period, or treatment effects were detected for any of the parameters.

The LS means of the log-transformed pharmacokinetic parameters, ratios of these means and the 90% confidence intervals of test product versus reference product are presented in Table 14.

Table 14: Statistical Analysis - *Repeated* Fasting Single Dose Study - (n=38)

Parameter	Analyte	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
$LNAUC_{0-t}$	Diltiazem	6.7542 (857.67[a])	6.7433 (848.39[a])	1.01[b]	(0.952; 1.073)
$LNAUC_{0-inf}$		6.8314 (926.48[a])	6.8127 (909.36[a])	1.02[b]	(0.964; 1.077)
LNC_{max}		4.4561 (86.15[a])	4.3737 (79.34[a])	1.09[b]	(0.974; 1.210)
$LNAUC_{0-t}$	DAD	4.5389 (93.58 [a])	4.5140 (91.29[a])	1.02[b]	(0.952; 1.104)
$LNAUC_{0-inf}$		4.8323 (125.49[a])	4.7957 (120.99[a])	1.04[b]	(0.958; 1.123)
LNC_{max}		1.6953 (5.45[a])	1.6857 (5.40[a])	1.01[b]	(0.926; 1.110)
$LNAUC_{0-t}$	NMD	5.8251 (338.71 [a])	5.8576 (349.88[a])	0.97[b]	(0.921; 1.018)
$LNAUC_{0-inf}$		6.0420 (420.73[a])	6.0482 (423.34[a])	0.99[b]	(0.929; 1.064)
LNC_{max}		2.9947 (19.98[a])	3.0289 (20.67[a])	0.97[b]	(0.896; 1.043)

a = Geometric Mean
b = Ratio of Geometric Means

Comments:

The ANOVA conducted by the firm contained only 2 periods. However, the study was conducted in three (3) different time periods as following:

Subject #	Date of Period 1	Date of Period 2
# 1-32	10/21-23/95	10/28-30/95
# 33-38	10/28-30/95	11/4-6/95

The reviewer repeated the ANOVA on both the untransformed and log-transformed data, using 3 periods, defining the period as:

Period 1: 10/21-23/95
Period 2: 10/28-30/95
Period 3: 11/4-6/95

The results are presented in Tables 15-17.

Table 15: Statistical Analysis of Diltiazem Data- *Repeated* Fasting Single Dose Study - (n = 38) – (Period = 3)

Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
AUC_{0-t}	946.58	947.14	1.00	(0.944; 1.055)
$LNAUC_{0-t}$	6.7895 (888.45[a])	6.7786 (878.83[a])	1.01[b]	(0.952; 1.073)
AUC_{0-inf}	1017.20	1013.75	1.00	(0.948; 1.059)
$LNAUC_{0-inf}$	6.8715 (964.45[a])	6.8529 (946.62[a])	1.02[b]	(0.965; 1.076)
C_{max}	92.91	87.86	1.06	(0.949; 1.166)
LNC_{max}	4.4850 (88.66[a])	4.4026 (81.66[a])	1.09[b]	(0.973; 1.212)

a = Geometric Mean
b = Ratio of Geometric Means

Table 16: Statistical Analysis of DAD Data- *Repeated* Fasting Single Dose Study - (n = 38) – (Period = 3)

Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
AUC_{0-t}	134.73	131.92	1.02	(0.964; 1.079)

$LNAUC_{0-t}$	4.5984 (99.33[a])	4.5736 (96.89[a])	1.02[b]	(0.955; 1.100)
AUC_{0-inf}	169.81	167.69	1.01	(0.940; 1.086)
$LNAUC_{0-inf}$	4.8947 (133.59[a])	4.8582 (128.80[a])	1.04[b]	(0.964; 1.116)
C_{max}	6.66	6.58	1.01	(0.926; 1.097)
LNC_{max}	1.7154 (5.56[a])	1.7059 (5.51[a])	1.01[b]	(0.925; 1.102)

a = Geometric Mean
b = Ratio of Geometric Means

Table 17: Statistical Analysis of NMD Data- *Repeated* Fasting Single Dose Study - (n = 38) -- (Period = 3)

Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
AUC_{0-t}	360.00	370.73	0.97	(0.925; 1.017)
$LNAUC_{0-t}$	5.8449 (345.47[a])	5.8774 (356.87[a])	0.97[b]	(0.921; 1.018)
AUC_{0-inf}	425.19	431.66	0.98	(0.899; 1.071)
$LNAUC_{0-inf}$	6.0321 (416.58[a])	6.0382 (419.16[a])	0.99[b]	(0.928; 1.065)
C_{max}	20.26	21.04	0.96	(0.887; 1.039)
LNC_{max}	2.9871 (19.83[a])	3.0213 (20.52[a])	0.97[b]	(0.895; 1.044)

a = Geometric Mean
b = Ratio of Geometric Means

Comments:

1. The ratios of AUC_{0-t}/AUC_{0-inf} for DAD and NMD of some subjects were below 0.8. This was due to the nature of the extended release dosage form of the drug products.

2. The 90% confidence intervals of $LNAUC_{0-t}$, $LNAUC_{0-inf}$, and LNC_{max} for all 3 analytes were all within 80-125%.

3. The results of this single-dose study in fasted subjects are acceptable.

Bioequivalence Study #1533-1-- 3-Way, Single Dose, Fed and Fasted

The objective of this study was to compare the rate and extent of the absorption of the firm's diltiazem HCl 120 mg extended-released capsules under fed and fasted conditions and Cardizem^{R} SR 120 mg capsules under fed condition.

The clinical study was conducted at Biovail Corporation International in Toronto, Ontario, Canada during 06/09-06/26/95 with as the principal investigator. The analytical study was conducted at Biovail Corporation International in Toronto, Ontario, Canada during 06/27-08/24/95 by analysts

The design of the study was a single-dose, 3-way crossover in non-smoking male volunteers under fed and fasted condition. The protocol was approved by Institutional Review Board of Biovail Corporation International (chaired by on 05/10/95.

Twenty-two (22) non-smoking male volunteers, 18-41 years old, were enrolled who had their preclinical laboratory test data reviewed by the physician which included biochemical profile, hematology, urinalysis and drugs of abuse screen. The inclusion and exclusion criteria were the same as those stated in the previous study (#1532-1).

After an overnight fast of 10 hr, on the morning of 06/10/95, each subject received one of the following treatments with 240 mL of water:

Treatment A - Test Drug: Diltiazem HCl ER capsule, 1 x 120 mg, Biovail Corporation International, lot #C3/95A1A21-MTC3, potency 100.6%, manufacturing date , lot size of apsules, 5 minutes after complete ingestion of a standard high-fat breakfast*.

Treatment B - Reference Drug: Cardizem^{R} SR capsule, 1 x 120 mg, Marion Merrell Dow Inc., lot #P20223, expired 12/95, potency 100.2%, 5 minutes after complete ingestion of a standard high-fat breakfast*.

Treatment C - Test Drug: Diltiazem HCl ER capsule, 1 x 120 mg, Biovail Corporation International, lot #C3/95A1A21-MTC3, potency 100.6%, manufacturing date , lot size of apsules, under fasted condition.

* = 1 fried egg, 1 slice American cheese, 1 slice Canadian bacon, 1 buttered English muffin, 1 serving of hash brown potatoes, 240 mL whole milk, and 180 mL orange juice.

With a 7-day washout period, on the mornings of 06/17/95 and 06/24/95, each subject was crossed over to one of the other treatments according to the sequence assigned randomly (ABC, BAC, BCA, CBA, ACB or CAB). The study procedures, including blood sampling schedule, were the same as

in the previous study #1532-1.

Analytical Method -- **Not for Release through FOI**:
The same validated analytical methods were conducted for the analysis of plasma diltiazem, DAD and NMD of this study. The maximal duration of plasma samples storage was 75 days which was shorter than the period covered by the validated long-term stability study (25 weeks).

The assay method was further validated during the analysis of the study samples when 22, 24, and 25 standard curves, each curve contained a 6-point calibration and duplicates of 4 levels of QC samples, for diltiazem, DAD and NMD, respectively, were conducted. The correlation coefficients of the curves were 0.9978, 0.9972 and 0.9982 or larger for diltiazem, DAD and NMD, respectively. The accuracy and precision of these standard and QC samples are presented below in Table 18:

Table 18: During-Study Validation Data -- Single Dose. Fed and Fasted #1533-1

	Accuracy (%)		Precision (% CV)	
Analyte	Standard	QC Sample	Standard	QC Sample
Diltiazem	96.7 - 102.1	103.0 - 109.5	2.2 - 9.5	4.4 - 12.0
DAD	97.5 - 100.0	93.3 - 100.0	2.5 - 11.4	7.2 - 14.1
NMD	94.2 - 110.0	97.8 - 100.0	1.7 - 8.5	9.9 - 14.7

Results:

Of the 22 subjects enrolled, subject # 20 was dismissed prior to period 1 dosing due to abnormal pre-dose ECG. There were no protocol deviation. Seventeen (17) adverse events were reported by 9 subjects, 5 during treatment A, 7 during treatment B and 5 during treatment C. The adverse effects were sinus bradycardia, headache, and borderline 1° AV block.

No clinically significant abnormalities were reported during the physical examination and laboratory tests at the completion of the study.

The plasma samples from 21 subjects (1071 samples) were assayed for diltiazem, DAD and NMD. Reassays conducted due to the anomaly of the first value included 114 samples for diltiazem, 118 samples for DAD and 121 samples for NMD.

The mean plasma concentrations of diltiazem, DAD and NMD at each sampling point after all 3 treatments and the mean pharmacokinetic parameters are presented below in Figures 7-9 and Tables 19-21. The calculation of K_d was based on the most linear portion of the terminal elimination phase in the semi-log plot of individual subject data.

Table 19: Mean (C.V.%) Plasma Diltiazem Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 21 - 1 x 120 mg ER Capsule - Fed and Fasted Study - Single Dose)

Time (hour)	Biovail – Fed (Treatment A)	Marion Merrell Dow – Fed (Treatment B)	Biovail – Fasted (Treatment C)
0	0	0	0
1	0	0.75 (329)	0
2	0.15 (458)	3.16 (146)	0.32 (458)
3	3.82 (268)	8.89 (65)	1.13 (398)
4	7.04 (215)	17.01 (62)	3.80 (269)
5	20.47 (193)	34.76 (41)	26.57 (88)
6	34.27 (155)	47.44 (37)	62.72 (54)
7	68.78 (85)	79.30 (50)	95.91 (48)
8	91.54 (60)	105.99 (45)	99.78 (48)
10	88.39 (57)	92.21 (32)	78.84 (41)
12	71.46 (69)	69.70 (35)	63.00 (45)
16	45.47 (65)	40.49 (48)	35.42 (46)
20	31.63 (67)	25.06 (48)	22.46 (46)
24	23.84 (95)	15.48 (54)	15.44 (51)
28	18.12 (93)	11.10 (56)	11.54 (52)
36	6.47 (124)	3.70 (113)	4.53 (84)
48	1.48 (248)	0.42 (318)	0.80 (280)
AUC_{0-t} (ng*hr/mL)	1227.38 (47)	1146.03 (37)	1075.87 (41)
AUC_{0-inf} (ng*hr/mL)	1306.13 (43)	1210.53 (36)	1136.59 (41)
C_{max} (ng/mL)	126.14 (40)	112.80 (37)	112.42 (41)
$LNAUC_{0-t}$	1146.61[a]	1076.92[a]	995.24[a]
$LNAUC_{0-inf}$	1235.11[a]	1140.86[a]	1055.08[a]
LNC_{max}	116.22[a]	105.26[a]	103.54[a]
T_{max} (hour)	10.43 (47)	8.86 (15)	7.76 (18)
$T_{1/2}$ (hour)	7.41 (37)	6.89 (30)	7.53 (22)

a = geometric mean

Table 20: Mean (C.V.%) Plasma DAD Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 21 - 1 x 120 mg ER Capsule - Fed and Fasted Study - Single Dose)

Time (hour)	Biovail – Fed (Treatment A)	Marion Merrell Dow – Fed (Treatment B)	Biovail – Fasted (Treatment C)
0	0	0	0
1	0	0.15 (458)	0
2	0	0.15 (318)	0.05 (458)
3	0	0.18 (458)	0
4	0.19 (341)	0.10 (316)	0.10 (316)
5	0.75 (217)	0.72 (119)	0.40 (200)
6	1.04 (217)	1.81 (93)	1.60 (88)
7	2.52 (131)	3.25 (76)	3.62 (56)
8	4.22 (100)	5.72 (86)	5.29 (62)
10	8.02 (87)	8.02 (87)	6.81 (62)
12	6.68 (76)	7.97 (84)	7.17 (62)
16	5.76 (79)	6.78 (96)	6.20 (75)
20	5.43 (83)	5.70 (88)	5.28 (82)
24	4.64 (85)	4.49 (101)	4.24 (82)
28	3.75 (104)	3.82 (126)	3.52 (110)
36	2.04 (142)	1.83 (159)	1.78 (165)
48	0.62 (250)	0.62 (252)	0.65 (218)
AUC_{0-t} (ng*hr/mL)	147.56 (90)	162.05 (106)	148.99 (92)
AUC_{0-inf} (ng*hr/mL)	186.90 (80)	204.33 (95)	183.62 (82)
C_{max} (ng/mL)	7.89 (59)	8.89 (75)	7.63 (63)
$LNAUC_{0-t}$	116.57[a]	114.11[a]	109.16[a]
$LNAUC_{0-inf}$	155.15[a]	153.80[a]	148.18[a]
LNC_{max}	6.88[a]	7.28[a]	6.44[a]
T_{max} (hour)	13.05 (47)	11.81 (24)	7.76 (18)
$T_{1/2}$ (hour)	12.21 (42)	12.87 (59)	7.53 (22)

a = geometric mean

Table 21: Mean (C.V.%) Plasma NMD Concentrations (ng/mL) at Each Sampling Time Point and

Mean Pharmacokinetic Parameters (n = 21 - 1 x 120 mg ER Capsule - Fed and Fasted Study - Single Dose)

Time (hour)	Biovail -- Fed (Treatment A)	Marion Merrell Dow -- Fed (Treatment B)	Biovail -- Fasted (Treatment C)
0	0	0	0
1	0	0.15 (458)	0
2	0	0.43 (322)	0
3	0.53 (316)	1.39 (134)	0.42 (325)
4	1.70 (225)	4.14 (60)	0.63 (350)
5	3.28 (171)	8.88 (37)	4.09 (108)
6	6.80 (140)	12.12 (28)	10.38 (48)
7	13.99 (88)	18.17 (38)	17.37 (39)
8	18.98 (63)	23.52 (35)	19.97 (37)
10	22.64 (48)	25.26 (30)	21.68 (38)
12	21.46 (43)	23.70 (30)	20.60 (37)
16	17.44 (38)	17.53 (32)	15.66 (33)
20	14.27 (36)	13.76 (34)	12.17 (35)
24	10.81 (35)	9.88 (34)	9.37 (34)
28	9.59 (42)	8.08 (34)	7.66 (48)
36	4.16 (81)	3.79 (59)	3.65 (72)
48	0.77 (281)	0.70 (266)	0.49 (251)
AUC_{0-t} (ng*hr/mL)	417.16 (28)	437.08 (30)	381.59 (34)
AUC_{0-inf} (ng*hr/mL)	511.54 (25)	503.61 (30)	449.34 (33)
C_{max} (ng/mL)	27.80 (32)	27.20 (28)	23.36 (36)
$LNAUC_{0-t}$	402.50[a]	418.00[a]	357.87[a]
$LNAUC_{0-inf}$	496.62[a]	483.69[a]	424.97[a]
LNC_{max}	26.41[a]	26.22[a]	21.90[a]
T_{max} (hour)	11.57 (47)	10.48 (22)	9.19 (19)
$T_{1/2}$ (hour)	11.09 (34)	10.22 (26)	10.50 (21)

a = geometric mean

Analysis of Variance was performed on the log-transformed data of AUC_{0-t}, AUC_{0-inf}, and C_{max}, using SAS GLM procedure. The model included sequence, subject within sequence, treatment and period as factors. The sequence effect was tested using the subjects within sequence effect as the error term. The treatment and period effect were tested against the residual mean square error.

The LS means of the log-transformed pharmacokinetic parameters and ratios of these means are presented in Tables 22-24.

Table 22: Ratios of Least-Square Means of Pharmacokinetic Parameters of Diltiazem Fed and Fasted Study (n=21)

Parameter	LS Means: Biovail – Fed (Treatment A)	LS Means: MMDow – Fed (Treatment B)	LS Means: Biovail – Fasted (Treatment C)	A/B	A/C
AUC_{0-t}	1215.29	1134.14	1064.19	1.07	1.14
$LNAUC_{0-t}$	7.0405 (1141.94[a])	6.9776 (1072.38[a])	6.8986 (990.90[a])	1.06[b]	1.15[b]
AUC_{0-inf}	1292.83	1198.73	1126.30	1.08	1.15
$LNAUC_{0-inf}$	7.1134 (1228.31[a])	7.0354 (1136.10[a])	6.9585 (1052.10[a])	1.08[b]	1.17[b]
C_{max}	126.40	112.31	111.17	1.12	1.14
LNC_{max}	4.7602 (116.77[a])	4.6556 (105.18[a])	4.6337 (102.90[a])	1.11[b]	1.13[b]
T_{max}	10.35	8.84	7.81	1.17	1.32
$T_{1/2}$	7.32	6.84	7.53	1.07	0.97

a = Geometric Mean
b = Ratio of Geometric Means

Table 23: Ratios of Least-Square Means of Pharmacokinetic Parameters of DAD Fed and Fasted Study (n=21)

Parameter	LS Means: Biovail – Fed (Treatment A)	LS Means: MMDow – Fed (Treatment B)	LS Means: Biovail – Fasted (Treatment C)	A/B	A/C
AUC_{0-t}	142.42	157.28	144.59	0.90	0.98
$LNAUC_{0-t}$	4.7463 (115.16[a])	4.7280 (113.07[a])	4.6867 (108.50[a])	1.02[b]	1.15[b]
AUC_{0-inf}	179.50	198.14	178.62	0.91	1.00
$LNAUC_{0-inf}$	5.0189 (151.25[a])	5.0186 (151.21[a])	4.9763 (144.93[a])	1.00[b]	1.04[b]

C_{max}	7.75	8.74	7.48	0.89	1.04
LNC_{max}	1.9202 (6.86[a])	1.9802 (7.24[a])	1.8563 (6.40[a])	0.95[b]	1.07[b]
T_{max}	12.94	11.78	11.75	1.10	1.10
$T_{1/2}$	11.76	12.60	11.83	0.93	0.99

a = Geometric Mean
b = Ratio of Geometric Means

Table 24: Ratios of Least-Square Means of Pharmacokinetic Parameters of NMD Fed and Fasted Study (n=21)

Parameter	LS Means: Biovail – Fed (Treatment A)	LS Means: MMDow – Fed (Treatment B)	LS Means: Biovail – Fasted (Treatment C)	A/B	A/C
AUC_{0-t}	420.19	439.34	383.09	0.96	1.10
$LNAUC_{0-t}$	6.0075 (406.47[a])	6.0439 (421.52[a])	5.8871 (360.38[a])	0.96[b]	1.13[b]
AUC_{0-inf}	513.53	505.55	451.23	1.02	1.14
$LNAUC_{0-inf}$	6.2133 (499.34[a])	6.1874 (486.57[a])	6.0584 (427.71[a])	1.03[b]	1.17[b]
C_{max}	28.18	27.45	23.49	1.03	1.17
LNC_{max}	3.2895 (26.83[a])	3.2772 (26.50[a])	3.0920 (22.02[a])	1.01[b]	1.22[b]
T_{max}	11.50	10.45	9.21	1.10	1.25
$T_{1/2}$	10.96	10.17	10.53	1.08	0.97

a = Geometric Mean
b = Ratio of Geometric Means

Comments:

1. The number of plasma samples selected for re-assay due to the anomaly of the first value was larger than 10% for each analyte, i.e., out of a total of 1071 plasma samples, 114 were repeated for diltiazem, 118 for DAD and 121 for NMD, all due to anomalies of the first assay values.

2. The calculation of all pharmacokinetic parameters, their LS means, and the 90% confidence intervals submitted by the sponsor have been confirmed by the reviewer's own calculation.

3. The ratios of least-square geometric means of AUC_{0-t}, AUC_{0-inf} and C_{max} are all within 0.8-

1.25 for diltiazem, DAD and NMD.

4. When comparing post-prandial to fasting administration of the test drug, the mean C_{max} of diltiazem, DAD and NMD were 1.07-1.22 times; the mean AUCs were 1.04-1.17 times; and the mean T_{max} were changed by -0.2 to +1.2 hours.

Deficiency:

The firm should provide a summary table of all samples selected for re-assay due to "inconsistence with other analysis values". The table should include all assayed values and the rationale of selecting the reported value.

Bioequivalence Study #1534-2 -- Multiple Dose -- Fasted -- 2-Way Crossover

The objective of this study was to compare the steady state bioavailability of Biovail and Marion Merrell Dow (Cardizem^R SR) diltiazem HCl 120 mg SR capsules under fasted condition.

The clinical study was conducted at Biovail Corporation International in Toronto, Ontario, Canada during 07/27-08/17/95 (group 1, n=25) and 08/10-31/95 (group 2, n=6) with as the principal investigator. The analytical study was conducted at Biovail Corporation International in Toronto, Ontario, Canada during 09/05-10/19/95 by analyst

The design of the study was a multiple-dose (1x120 mg at 7 AM and 7 PM for 6 days and at 7 AM on the 7th day), 2-way crossover in non-smoking male volunteers under fasted condition (fasted for 10 hours before the 7 AM dose and 2 hours before the 7 PM dose). The protocol was approved by Institutional Review Board of Biovail Corporation International (chaired by on 06/14/95.

Twenty-five (25) and 6 non-smoking male volunteers (for group 1 and group 2 respectively), 18-43 years old, were enrolled who had their preclinical laboratory test data reviewed by the physician which included biochemical profile, hematology, urinalysis and drugs of abuse screen. The inclusion and exclusion criteria were the same as those stated in the previous study (#1532-1).

After an overnight fast of 10 hr, starting on the morning of 07/28/95 for group 1 and 08/11/95 for group 2, each subject received one of the following treatments:

Treatment A - Test Drug: Diltiazem HCl ER capsule, 1 x 120 mg, twice daily at 7 AM and 7 PM for 6 days and once at 7 AM on the 7th day, Biovail Corporation International, lot #C3/95A1A21-MTC3, potency 100.6%, manufacturing date , lot size of psules.

Treatment B - Reference Drug: Cardizem^R SR capsule, 1 x 120 mg, twice daily at 7 AM and 7 PM for 6 days and once at 7 AM on the 7th

day, Marion Merrell Dow Inc., lot #P20223, expired 12/95, potency 100.2%.

Each dose was taken with 240 mL of water. Blood samples (10 mL each) were collected in Vacutainers containing EDTA at 0 hour of days 1, 4, 5 and 6; and at 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours of day 7, post-dose. Plasma samples were prepared, frozen, and stored at -70°C until transferred to the analytical site and assayed for diltiazem, DAD, and NMD.

With a 7-day washout period, on the mornings of 08/11/95 for group 1 and 08/24/95 for group 2, each subject was crossed over to the other treatment.

On days 1-6 of each period, subjects were fasted daily for 10 hours prior to the 7 AM dosing, and for 2 hours prior to the 7 PM dosing. They were fasted for 4.5 hours after every dosing. Blood pressure, heart rate and ECG were monitored on days 1-6 at 0, 2, 4, 8, 12, and 16 hours post-dose, and on day 7 at 0, 2, 4, 8, and hours post-dose, during each period. Physical examination and laboratory tests were repeated at the completion of the study.

Analytical Method -- **Not for Release through FOI**:

The same validated analytical methods were conducted for the analysis of plasma diltiazem, DAD and NMD of this study. The maximal duration of plasma samples storage was 83 days which was shorter than the period covered by the validated long-term stability study (25 weeks).

The assay method was further validated during the analysis of the study samples when 15 standard curves, each curve contained a 6-point calibration and duplicates of 4 levels of QC samples, for diltiazem, DAD and NMD, respectively, were conducted. The correlation coefficients of the curves were 0.9972, 0.9968 and 0.9956 or larger for diltiazem, DAD and NMD, respectively. The accuracy and precision of these standard and QC samples are presented below in Table 25:

Table 25: During-Study Validation Data -- Multiple Dose. Fasted Study, #1534-2

	Accuracy (%)		Precision (% CV)	
Analyte	Standard	QC Sample	Standard	QC Sample
Diltiazem				
DAD				
NMD				

Results:

Of the 25 subjects enrolled for group 1 (subjects #1-25), 21 subjects completed the study. Subject # 11 was dismissed prior to period 1 dosing and #2 prior to period 2 (treatment A) dosing, both due to abnormal pre-dose ECG. Subject #14 was dismissed after period 1 (treatment B) dosing, and #23

after period 2 (treatment B) dosing, both due to low blood pressure.

Out of the 6 subjects enrolled for group 2 (subjects #27-32), 4 subjects completed the study. Subjects #27 was dismissed after period 1 (treatment B) dosing due to a skin rash and #28 withdrew prior to period 2 (treatment B) dosing for personal reason.

Therefore, a total of 25 subjects completed the study, 21 from group 1 and 4 from group 2. There were no significant protocol deviation.

A total of 184 cases of sinus bradycardia were reported, 85 during treatment A by 16 subjects and 99 during treatment B by 21 subjects. Three (3) cases of borderline 1° AV block were reported by 3 different subjects (all during treatment B). One case each of 1° AV block , borderline 2° AV block type II (reported by the same subject during treatment A), nausea, sore throat, general malaise and hives (all during treatment B) were reported. The symptom of hives reported by #27 was treated with 1x25 mg of Benadryl tablet. Subject # 27 was subsequently dismissed from the study.

No clinically significant abnormalities were reported during the physical examination and laboratory tests at the completion of the study.

The plasma samples from 25 subjects (850 samples) were assayed for diltiazem, DAD and NMD. Reassays conducted without explanation in 5 samples for DAD and 2 samples for NMD.

The mean plasma concentrations of diltiazem, DAD and NMD at each sampling point after both treatments and the mean pharmacokinetic parameters are presented below in Figures 10-12 and Tables 26-28. The pharmacokinetic parameters included the following:

- AUC_{0-12} (derived using trapezoidal rule for area of time-concentration on day 7)
- C_{max} (maximum concentration on day 7),
- C_{min} (minimum concentration on day 7),
- T_{max} (time of C_{max} after the last dose),
- degree of fluctuation (Flux) calculated as $(C_{max}-C_{min})/(AUC_{0-12}/12)$

Table 26: Mean (C.V.%) Plasma Diltiazem Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 25 - 1 x 120 mg ER Capsule - Multiple Dose)

Time	Biovail (Treatment A)	Marion Merrell Dow (Treatment B)
Day 1	0	0
Day 4	85.74 (33)	98.19 (35)
Day 5	99.42 (35)	98.57 (39)
Day 6	88.19 (36)	101.32 (35)
Day 7, 0 Hour	91.37 (38)	93.92 (32)

Day 7, 1 Hour	88.67	(36)	92.10	(54)
Day 7, 2 Hour	82.50	(34)	80.95	(33)
Day 7, 3 Hour	79.03	(45)	77.90	(34)
Day 7, 4 Hour	84.84	(43)	86.85	(43)
Day 7, 5 Hour	119.75	(57)	114.15	(39)
Day 7, 6 Hour	145.55	(38)	134.70	(30)
Day 7, 7 Hour	167.39	(33)	145.68	(27)
Day 7, 8 Hour	157.34	(29)	138.18	(23)
Day 7, 9 Hour	133.24	(33)	115.55	(20)
Day 7, 10 Hour	104.53	(37)	98.52	(25)
Day 7, 11 Hour	89.16	(32)	89.92	(34)
Day 7, 12 Hour	79.74	(30)	77.71	(42)
AUC_{0-12} (ng*hr/mL)	1337.52	(30)	1260.33	(26)
C_{max} (ng/mL)	181.52	(33)	163.83	(29)
$LNAUC_{0-t}$	1270.41[a]		1213.10[a]	
LNC_{max}	171.10[a]		157.41[a]	
T_{max} (hour)	7.08	(16)	6.68	(24)
C_{min} (ng/mL)	65.29	(37)	69.78	(30)
Flux (%)	104.93	(24)	91.33	(33)

a = geometric mean

Table 27: Mean (C.V.%) Plasma DAD Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 25 - 1 x 120 mg ER Capsule - Multiple Dose)

Time	Biovail (Treatment A)		Marion Merrell Dow (Treatment B)	
Day 1	0		0	
Day 4	10.71	(43)	11.01	(42)
Day 5	12.42	(51)	11.23	(51)
Day 6	9.76	(42)	10.97	(52)
Day 7, 0 Hour	11.26	(49)	10.87	(48)
Day 7, 1 Hour	10.42	(40)	10.81	(52)
Day 7, 2 Hour	10.63	(42)	10.25	(42)

Day 7, 3 Hour	10.33	(47)	9.89	(45)
Day 7, 4 Hour	10.10	(46)	10.12	(47)
Day 7, 5 Hour	10.53	(52)	10.03	(46)
Day 7, 6 Hour	11.47	(54)	10.55	(45)
Day 7, 7 Hour	12.86	(52)	11.72	(40)
Day 7, 8 Hour	13.48	(54)	12.16	(44)
Day 7, 9 Hour	13.10	(56)	11.62	(46)
Day 7, 10 Hour	12.02	(56)	10.84	(50)
Day 7, 11 Hour	10.80	(54)	10.36	(50)
Day 7, 12 Hour	10.40	(52)	9.68	(55)
AUC_{0-12} (ng*hr/mL)	136.56	(48)	128.63	(45)
C_{max} (ng/mL)	14.93	(57)	13.56	(43)
$LNAUC_{0-t}$	123.17[a]		118.01[a]	
LNC_{max}	13.17[a]		12.50[a]	
T_{max} (hour)	6.88	(36)	6.84	(37)
C_{min} (ng/mL)	8.90	(47)	8.39	(52)
Flux (%)	50.94	(34)	50.54	(38)

a = geometric mean

Table 28: Mean (C.V.%) Plasma NMD Concentrations (ng/mL) at Each Sampling Time Point and Mean Pharmacokinetic Parameters (n = 25 - 1 x 120 mg ER Capsule - Multiple Dose)

Time	Biovail (Treatment A)		Marion Merrell Dow (Treatment B)	
Day 1	0		0	
Day 4	32.57	(26)	35.58	(28)
Day 5	35.42	(31)	35.50	(33)
Day 6	30.95	(27)	36.48	(31)
Day 7, 0 Hour	34.49	(26)	36.60	(31)
Day 7, 1 Hour	33.42	(25)	35.46	(35)
Day 7, 2 Hour	32.43	(25)	33.76	(25)
Day 7, 3 Hour	31.37	(33)	31.99	(27)
Day 7, 4 Hour	30.86	(28)	33.54	(32)

Day 7, 5 Hour	33.05	(33)	35.20	(30)
Day 7, 6 Hour	38.86	(27)	40.02	(27)
Day 7, 7 Hour	44.76	(25)	43.57	(26)
Day 7, 8 Hour	44.64	(25)	43.50	(20)
Day 7, 9 Hour	43.05	(27)	41.09	(20)
Day 7, 10 Hour	39.84	(27)	38.58	(22)
Day 7, 11 Hour	36.55	(28)	37.02	(24)
Day 7, 12 Hour	35.34	(27)	34.27	(27)
AUC_{0-12} (ng*hr/mL)	443.75	(24)	449.17	(24)
C_{max} (ng/mL)	48.81	(25)	47.71	(26)
$LNAUC_{0-t}$	430.49[a]		437.38[a]	
LNC_{max}	47.21[a]		46.23[a]	
T_{max} (hour)	7.80	(16)	7.12	(28)
C_{min} (ng/mL)	27.96	(27)	30.14	(25)
Flux (%)	57.90	494)	46.83	(37)

a = geometric mean

Analysis of Variance was performed on the log-transformed data of AUC_{0-12}, and C_{max}, using SAS GLM procedure. The model included sequence, subject within sequence, treatment and period as factors. The sequence effect was tested using the subjects within sequence effect as the error term. The treatment and period effect were tested against the residual mean square error.

Significant period effects were detected for LNC_{max} of diltiazem, and $LNAUC_{0-12}$ of NMD (p=0.032 and 0.022 respectively).

The LS means of the non-transformed and log-transformed pharmacokinetic parameters, ratios of these means and the 90% confidence intervals of test product versus reference product are presented in Tables 29.

Table 29: Statistical Analysis of Diltiazem, DAD and NMD Data
– Multiple Dose Study - (n=25) –

Analyte	Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
Diltiazem	$LNAUC_{0-t}$	7.1433 (1265.65[a])	7.1000 (1211.82[a])	1.04[b]	(0.986; 1.106)

Diltiazem	LNC_{max}	5.1392 (170.58[a])	5.0607 (157.71[a])	1.08[b]	(0.987; 1.186)
DAD	$LNAUC_{0-t}$	4.8099 (122.73[a])	4.7690 (117.81[a])	1.04[b]	(1.002; 1.083)
DAD	LNC_{max}	2.5739 (13.12[a])	2.5253 (12.49[a])	1.04[b]	(0.977; 1.128)
NMD	$LNAUC_{0-t}$	6.0630 (429.69[a])	6.0810 (437.48[a])	0.98[b]	(0.947; 1.019)
NMD	LNC_{max}	3.8522 (47.10[a])	3.8346 (46.28[a])	1.02[b]	(0.940; 1.102)

a = Geometric Mean
b = Ratio of Geometric Means

Comments:

The ANOVA conducted by the firm contained only 2 periods. However, the study was conducted in three (3) different time periods as following:

Subject #	Date of Period 1	Date of Period 2
# 1-25	07/28-08/04/95	08/11-17/95
# 27-32	08/11-17/95	08/24-31/95

The reviewer repeated the ANOVA on both untransformed and log-transformed data, using 3 periods, defining the period as:

Period 1: 07/28-0804/95
Period 2: 08/11-17/95
Period 3: 08/24-31/95

The results are presented in Table 30.

Table 30: Statistical Analysis of Diltiazem, DAD and NMD Data – Multiple Dose Study - (n=25) – Period = 3

Analyte	Parameter	LS Means (Test)	LS Means (Reference)	T/R	90% Confidence Interval
Diltiazem	AUC_{0-t}	1273.60	1198.26	1.06	(1.001; 1.125)
Diltiazem	C_{max}	166.87	149.54	1.12	(1.017; 1.214)
Diltiazem	$LNAUC_{0-t}$	7.0855 (1194.58[a])	7.0409 (1142.47[a])	1.05[b]	(0.991; 1.104)

Diltiazem	LNC_{max}	5.0328 (153.37[a])	4.9522 (141.49[a])	1.08[b]	(0.998; 1.177)
DAD	AUC_{0-t}	130.88	123.02	1.06	(1.027; 1.101)
DAD	C_{max}	13.48	12.10	1.11	(1.006; 1.222)
DAD	$LNAUC_{0-t}$	4.7627 (117.06[a])	4.7207 (112.25[a])	1.04[b]	(1.009; 1.078)
DAD	LNC_{max}	2.4855 (12.01[a])	2.4349 (11.41[a])	1.05[b]	(0.990; 1.118)
NMD	AUC_{0-t}	430.07	436.17	0.99	(0.946; 1.026)
NMD	C_{max}	45.69	44.66	1.02	(0.939; 1.106)
NMD	$LNAUC_{0-t}$	6.0240 (413.24[a])	6.0413 (420.44[a])	0.98[b]	(0.946; 1.098)
NMD	LNC_{max}	3.7763 (43.65[a])	3.7572 (42.83[a])	1.02[b]	(0.946; 1.098)

a = Geometric Mean
b = Ratio of Geometric Means

Comments:

1. The 90% confidence intervals of $LNAUC_{0-t}$, $LNAUC_{0-inf}$, and LNC_{max} for all 3 analytes were all within 80-125%..

2. The results of this multiple dose study are acceptable.

Pilot 4-Way Single-Dose Study #1602

The objective of this study was to determine the rate and extent of absorption of 3 sustained-release diltiazem 120 mg capsules formulations relative to diltiazem HCl oral solution in healthy volunteers under fasting condition. The results of this study was used as the justification of the firm's proposed *in vitro* dissolution specification.

The 4 formulations used were:

1) Formulation A: fast-releasing fraction, lot #C3/95A1A21-FTC
2) Formulation B: medium-releasing fraction, #C3/95A1A21-MTC3 (same lot used in all 4 previous bioequivalence studies
3) Formulation C: slow-releasing fraction, lot #C3/95A1A21-STC
4) Formulation D: diltiazem HCl solution, 120 mg/50 mL, lot #01000295

The clinical study was conducted at Biovail Corporation International in Toronto, Ontario, Canada during 09/06-09/30/95 with as the principal investigator. The analytical study was conducted at Biovail Corporation International in Toronto, Ontario, Canada during 10/06-11/22/95 by analyst

The design of the study was a single-dose, 4-way crossover in non-smoking male volunteers under fasted condition. The protocol was approved by Institutional Review Board of Biovail Corporation International (chaired by on 08/31/95.

Sixteen (16) non-smoking male volunteers, 19-44 years old, were enrolled who had their preclinical laboratory test data reviewed by the physician which included biochemical profile, hematology, urinalysis and drugs of abuse screen. The inclusion and exclusion criteria were the same as those stated in the previous study (#1532-1). Plasma samples from subjects #1-12 were analyzed.

Since the results of this study won't have any impact on the bioequivalence of the test and reference drugs, details of the study, i.e. adverse reactions, assay details, etc., were not reviewed. The mean plasma concentration of the 3 analytes are presented in Figures 13-15. The mean pharmacokinetic parameters of all 3 analytes are summarized below in Table 31:

Table 31: Mean Pharmacokinetic Parameters -- Single-Dose, 4-Way Crossover Study #1602

Pharmacokinetic Parameter	Formulation / Analyte	A (Fast-Releasing Capsule)	B (Medium-Releasing Capsule)	C (Slow-Releasing Capsule)	D (Solution)
AUC_{0-t}	Diltiazem	865.85	803.98	695.72	916.90
AUC_{0-inf}		910.70	855.63	778.37	950.67
C_{max}		110.98	103.24	72.84	225.08
T_{max} (hr)		6.58	7.75	9.50	0.76
$T_{1/2}$ (hr)		5.37	5.79	6.36	4.36
AUC_{0-t}	DAD	64.49	65.53	61.38	55.99
AUC_{0-inf}		90.60	86.92	93.43	71.66
C_{max}		4.80	4.93	4.24	5.12
T_{max} (hr)		9.83	10.50	12.33	3.35
$T_{1/2}$ (hr)		11.34	10.76	13.12	7.85
AUC_{0-t}	NMD	319.10	322.35	269.98	367.26
AUC_{0-inf}		388.97	392.65	352.20	420.81
C_{max}		24.48	23.77	19.03	47.39

T_{max} (hr)		8.25	8.17	11.50	0.85
$T_{1/2}$		9.23	9.92	10.58	8.81

ANOVA was performed on the log-transformed data of AUC and C_{max} parameters. The 90% confidence intervals and the ratios of LS means of these log-transformed parameters of diltiazem for treatments A versus B and treatment C versus B (treatment B was the medium-releasing fraction, which is the same lot used in all 4 previous bioequivalence studies) are presented below in Table 32:

Table 32: Statistical Analysis of Diltiazem Data

	Parameter	A vs. B	C vs. B
Ratio of LS Means	$LNAUC_{0-t}$	1.049	0.8857
	$LNAUC_{0-inf}$	1.043	0.9241
	LNC_{max}	1.066	0.7332
90% Conf. Interval	$LNAUC_{0-t}$	0.925-1.190	0.781-1.005
	$LNAUC_{0-inf}$	0.927-1.174	0.821-1.040
	LNC_{max}	0.838-1.355	0.577-0.932

Comment:

Assessing bioequivalence with the standard 90% confidence interval of 80-125%, neither the fasting-releasing capsule (treatment A) nor the slow-releasing capsule (treatment C) is bioequivalent to the medium-releasing capsule (treatment B).

Dissolution Testing:

Two dissolution runs of 6 capsules each were performed on the test and reference drug, 120 mg, 90 mg and 60 mg. The results are presented below in Table 33. **The tentative specification included in this table was derived from the dissolution data generated during the initial development of the formulation.**

Table 33 - In Vitro Dissolution Testing

Drug (Generic Name): Diltiazem HCl
Dosage Form: Extended Release Capsule
Dose Strength: 60, 90 and 120 mg
ANDA No.: 74-845
Firm: Biovail Corporation International
Submission Date: 1/31/96

I. Conditions for Dissolution Testing:

USP XXIII Apparatus: III (Bio-Diss) DPM: 20
No. Units Tested: 6+6
Medium: Phosphate buffer -pH 1.5 at 0-1 hour Volume: 250 mL
pH 4.5 at 1-2 hour
pH 6.9 at 2-6 hour
pH 7.2 at 6-12 hour

Tolerance:

Reference Drug: Cardizem SR capsule (Marion Merrell Dow)
Assay Methodology:

II. Results of In Vitro Dissolution Testing:

Sampling Times (Hours)	Test Product Lot # C3/95 A1A21MTC3 Strength (mg): 120			Reference Product Lot # P20223 Strength (mg): 120		
	Mean % dissolved (first 6 capsules)	Range (%)	RSD (%)	Mean % dissolved (first 6 capsules)	Range (%)	RSD (%)
1	1.05		13.13	5.13	–	–
2	1.20		14.91	11.37	–	–
4	19.85		6.51	32.42		
6	70.60		2.78	65.53		
8	100.40		1.91	92.15		
12	104.20		1.90	109.33		
	Mean % dissolved (second 6 capsules)		RSD (%)	Mean % dissolved (second 6 capsules)	Range (%)	RSD (%)
1	0.96		11.04	4.85		
2	1.03		9.99	10.78		
4	22.76		7.05	32.3		
6	73.23		2.01	65.97		
8	100.28		1.62	92.17		
12	103.43		1.62	109		

Sampling Times (Hours)	Test Product Lot # 95D006 Strength (mg): 90			Reference Product Strength (mg): 90		
	Mean % dissolved (first 6 capsules)	Range (%)	RSD (%)	Mean % dissolved Lot # P10279	Range (%)	RSD (%)
1	1.27		19.76	5	–	–
2	1.38		20.15	11	–	–
4	23.17		6.96	33		
6	77.20		3.83	69		
8	102.72		4.06	96		
12	105.52		4.09	112		
	Mean % dissolved (second 6 capsules)		RSD (%)	Mean % dissolved Lot #P10277	Range (%)	RSD (%)
1	1.20		20.41	5		
2	1.30		18.84	11		
4	23.03		6.36	35		
6	77.88		3.59	74		
8	104.32		3.31	99		
12	107.35		3.39	115		

Sampling Times (Hours)	Test Product Lot # 95D005 Strength (mg): 60		Reference Product Strength (mg): 60		
	Mean % dissolved (first 6 capsules)	RSD (%)	Mean % dissolved Lot #E01379	Range (%)	RSD (%)
1	1.32	13.06	5	–	–
2	1.47	11.13	10	–	–
4	42.50	6.68	30		
6	94.00	2.47	68		
8	105.87	2.48	95		
12	106.93	2.53	111		
	Mean % dissolved (second 6 capsules)	RSD (%)	Mean % dissolved Lot #E01426	Range	RSD (%)
1	1.33	23.08	5		

2	1.50
4	40.48
6	92.80
8	105.67
12	106.70

21.91	10		
8.16	32		
4.06	71		
4.74	96		
4.72	112		

Additional Dissolution Data Analysis:

The mean dissolution data of the 3 formulations of capsules (fast, medium, and slow release) in study of #1602 were fitted to the Sigmoid E_{max} model using WinNonlin version 1.0:

$$D_T = (D_{max} * T^{\gamma}) / (T^{\gamma} + T_{50}^{\gamma})$$

where D_T = % diltiazem dissolved in time T
D_{max} = maximum % of label claim dissolved
T_{50} = time at which 50% of D_{max} is dissolved
γ = power function

The dissolution data set of each formulation fitted into the above model had a correlation coefficient of 0.99 or greater. The mean T_{50} were found to be 4.366, 5.20, and 5.516 hours for formulation A, B, and C, respectively.

Predicted values obtained from the above equation and the actual dissolution result are compared in Table 34:

Table 34: Mean Dissolution Data and Predicted Dissolution Values

Time (hr)	Percent Dissolved					
	Fast-Releasing Batch		Medium-Releasing Batch (Bio-Batch)		Slow-Releasing Batch	
	Observed	Predicted	Observed	Predicted	Observed	Predicted
1	1 (1.2-1.5)	0.177	1	0	1 (0.9-1.1)	0
2	3 (2.4-3.2)	3.45	1	0.545	1 (0.9-1.1)	0.15
4	43 (35-45)	42.5	21	20.3	13 (12-14)	11.9
6	82 (77-84)	83.5	72	73.3	66 (63-69)	67.3
8	100 (96-103)	97.5	100	97.5	100 (97-104)	97.5
12	102 (97-105)	103	104	106	104 (101-109)	106

Dissolution Apparatus:	USP III (Bio-Diss)
Medium:	Phosphate Buffer (sequential pHs: 1.5, 4.5, 6.9, 7.2)
DPM:	20

The tentative *in vitro* dissolution specification in Table 33 was challenged with the *in vivo* data generated in the pilot 4-way single-dose study (#1602) presented previously.

Linear regression analysis were performed between T_{50} and each of the mean pharmacokinetic parameters of the 3 formulations. Linear correlation was found for AUC_{0-t} and for MRT and to a less degree for C_{max} (see Figures 16-18).

Based on these linear correlations, the pharmacokinetic parameters were estimated for the tentative lower and upper dissolution limits of:

The pharmacokinetic parameter range calculated based on these limits, expressed as % of target value (from *in vivo* study), were:

AUC_{0-t}	:	98.2 - 110.9 %	
MRT	:	102.4 - 88.2 %	(MRT is inversely related to the rate of dissolution)
C_{max}	:	96.0 - 120.2 %	

The firm concluded that these limits could be further lowered without compromising bioavailability **since they are well within 80-120%** (except C_{max}). The firm proposes to lower the dissolution specification at 4 hours and 6 hours, each by 5%. The pharmacokinetic range calculated based on these new limits, expressed as % of target value (from *in vivo* study), were:

AUC_{0-t}	:	93.6 - 110.9 %	
MRT	:	107.0 - 88.2 %	(MRT is inversely related to the rate of dissolution)
C_{max}	:	88.3 - 120.2 %	

The final proposed dissolution specification is:

For QC purposes, the following sampling time-points and specification are proposed:

Comments:

1. The tentative or the proposed dissolution specification is not appropriate due to the following reasons:

   a.

   b. The results of the pilot 4-way single-dose study (#1602) indicated that neither the slow-releasing nor the fast-releasing batch is bioequivalent to the biobatch (medium-releasing batch), and yet the proposed specifications covered the dissolution results from all 3 batches. This is inconsistent with the principle of *in vitro-in vivo* correlation.

   c. Comparison between the observed dissolution results and the proposed specification at each time point shows that the proposed range is much wider than the actual data observed, as demonstrated below in Table 35.

Table 35: Comparison of Actual Dissolution Data and the Proposed Specification

Time point (hour)	Actual Result	Proposed Specification
1		
2		
4		
6		
8		
12		

2. The firm chose to use gradient pH of dissolution media and USP 3 dissolution apparatus with the speed of 20 DPM. Since the proposed dissolution specifications were not fully supported by the observed data, the firm should either revise the specifications or submit additional data

for review. The firm should also consider other dissolution testing methods, such as those described in the Guidance for Oral Extended Release Dosage Forms.

3. For the dissolution method and specification for diltiazem HCl extended-release capsules, the firm is also advised to refer to USP 23, Supplement 3, p.2919-2920.

4. The dissolution rates for the 60 mg strength product were faster than those for the 90 mg and 120 mg strengths and were similar to those observed for the fast-releasing formulation of the 120 mg strength,. The firm should provide explanation for such observation.

5. The dissolution tests were conducted in 2 batches of 6 capsules each. The dissolution test should be conducted in 12 capsules of the test product versus 12 capsules of the reference product. The percent of label claim dissolved at each specified testing interval should be reported for each individual capsule. The mean percent dissolved, the range (highest, lowest) of dissolution, and the coefficient of variation (relative standard deviation) should be reported.

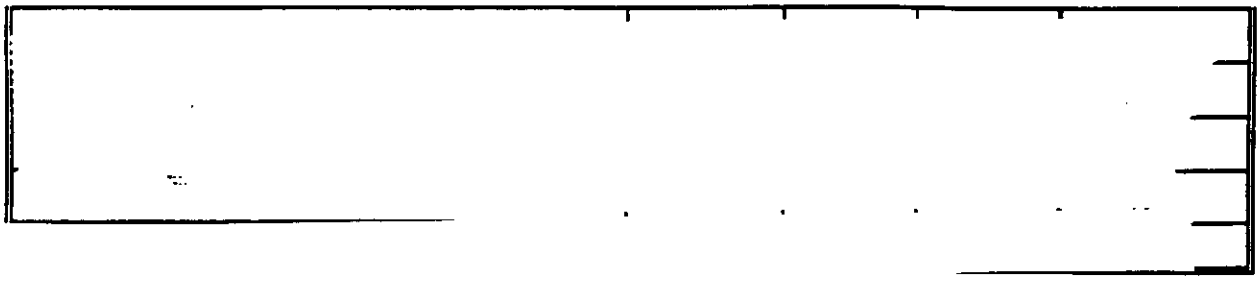
6. The batch numbers were not reported for the test products used in the dissolution test presented in Table 3 of the report for project Dil-B12.

The composition of diltiazem HCl extended-release capsules, 60 mg, 90 mg, and 120 mg, manufactured by the Biovail Corporate International, are presented below in Table 36:

Table 36: Composition of Diltiazem HCl Extended-Release Capsules, 60 mg, 90 mg, and 120 mg, by Biovail
(--Not Releasable through FOI--)

	% W/W	60 mg	90 mg	120 mg
Components	mg/Capsule			

see package insert



Waiver Request:

The 60, 90, and 120 mg capsules were manufactured using the same batch of extended-release beads. The only difference in these capsules is the difference in capsule filled weights.

The firm is requesting waivers of bioequivalence studies for the 60 mg and 90 mg capsules.

Deficiencies:

1. For the fed and fasted study, #1533-1, the firm should provide a summary table of all samples selected for re-assay due to "inconsistence with other analysis values". The table should include all assayed values and the rationale of selecting the reported value.

2. The dissolution tests conducted by the firm were incomplete. Comments #1-6 in the dissolution testing section should be forwarded to the firm.

Recommendation:

1. The single-dose, fasted bioequivalence study, and multiple-dose fasted bioequivalence study, conducted by Biovail Corporation International on its Diltiazem Hydrochloride Extended Release 120 mg capsule, lot #C3/95A1A21-MTC3, comparing it to Cardizem^{R} SR 120 mg capsule, lot #P20223, have been found acceptable by the Division of Bioequivalence.

2. The single-dose, fed and fasted bioequivalence study, conducted by Biovail Corporation International on its Diltiazem Hydrochloride Extended Release 120 mg capsule, lot #C3/95A1A21-MTC3, comparing it to Cardizem^{R} SR 120 mg capsule, lot #P20223, have been found incomplete by the Division of Bioequivalence due to deficiency #1.

3. The dissolution testings conducted by Biovail Corporation International on its Diltiazem Hydrochloride Extended Release 60 mg, 90 mg and 120 mg capsules have been found incomplete due to deficiency #2.

4. The waiver request for the 60 mg and 90 mg strengths of the test drugs can not be granted pending the acceptance of the bioequivalence study of the 120 mg strength and the dissolution tests.

The firm should be informed of the Deficiencies and Recommendations.

/S/ 2/6/97

Lin-Whei Chuang
Division of Bioequivalence
Review Branch I

RD INITIALED YHUANG /S/
FT INITIALED YHUANG 2/7/97

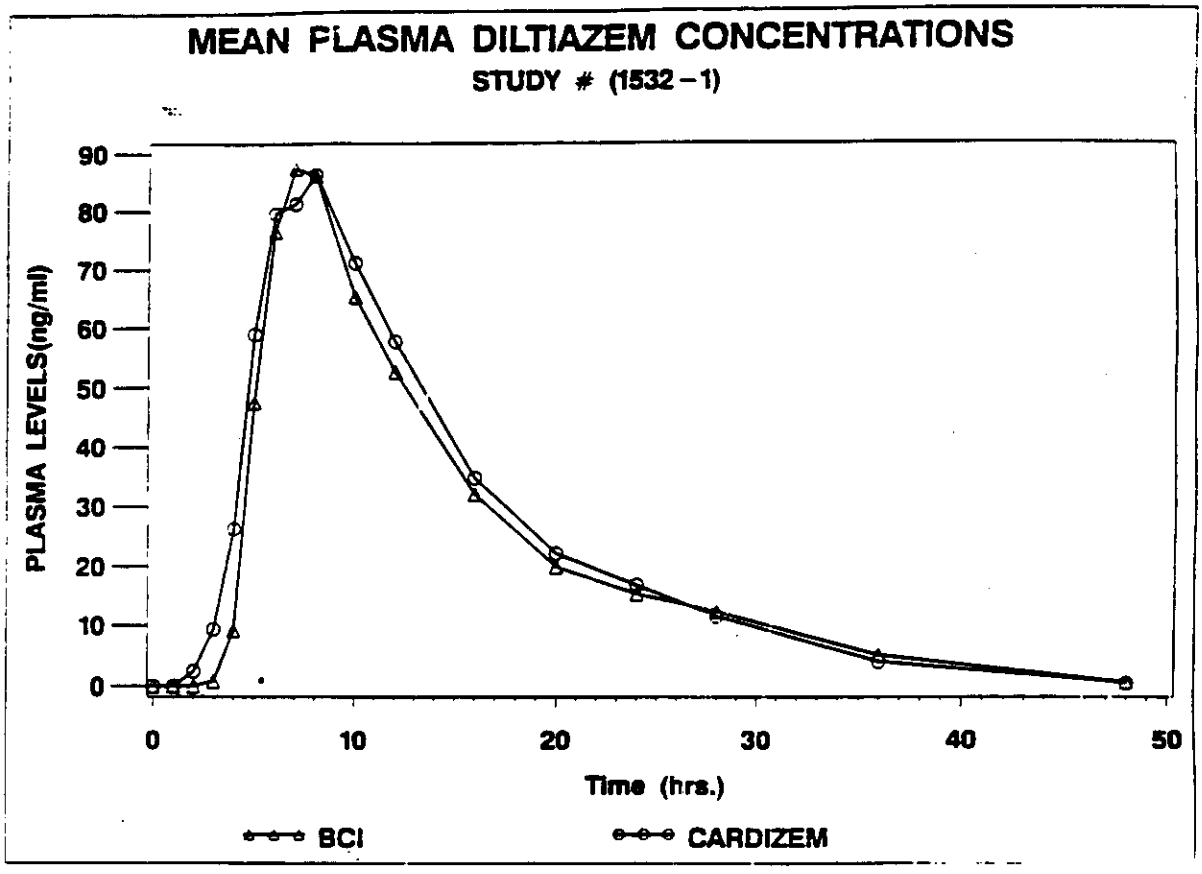
Concur /S/ Date: 2/28/97

Rabindra Patnaik, Ph.D.
Acting Director, Division of Bioequivalence

Figure 1

BIOVAIL CORPORATION INTERNATIONAL
STUDY #1532-1 (B95-261PK-B12)

DILTIAZEM



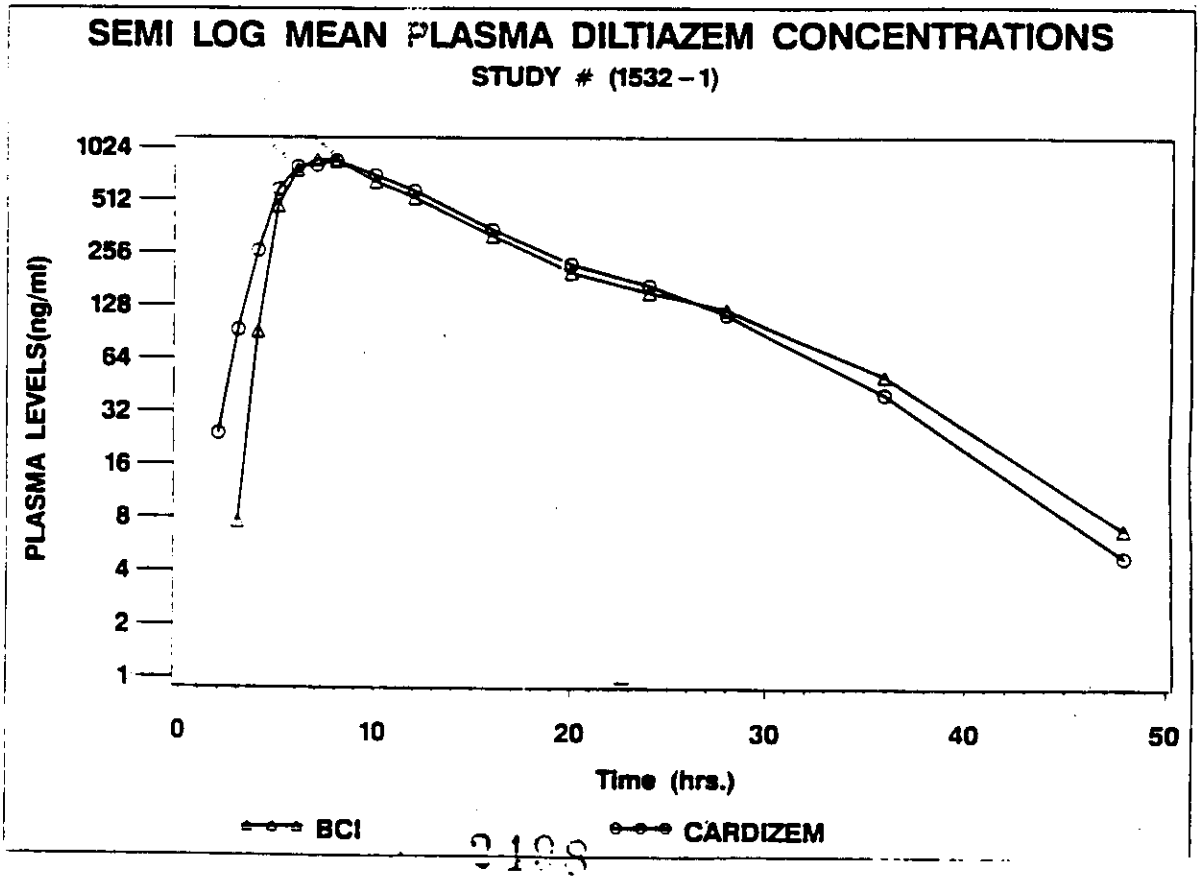


Figure 2

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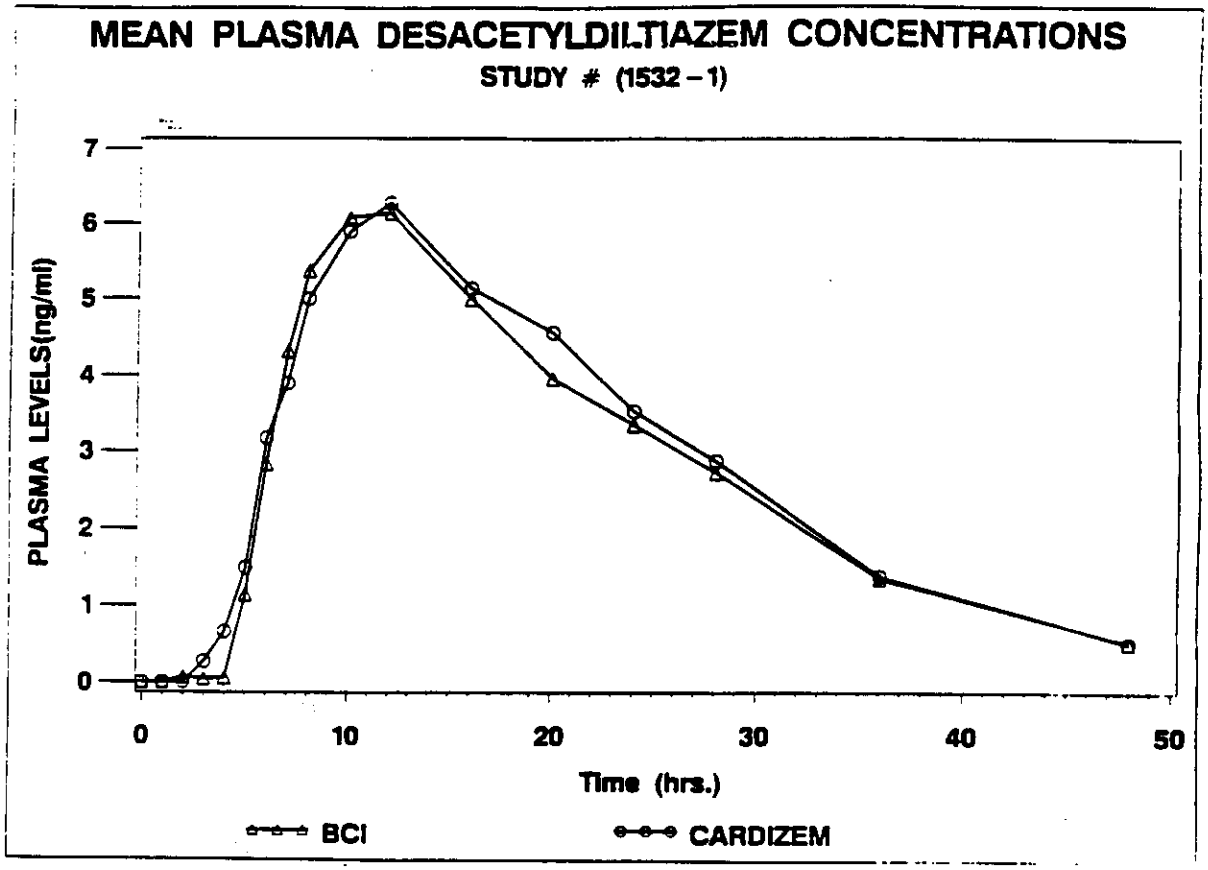
BIOVAIL CORPORATION INTERNATIONAL
STUDY #1532-1 (B95-261PK-B12)

DILTIAZEM



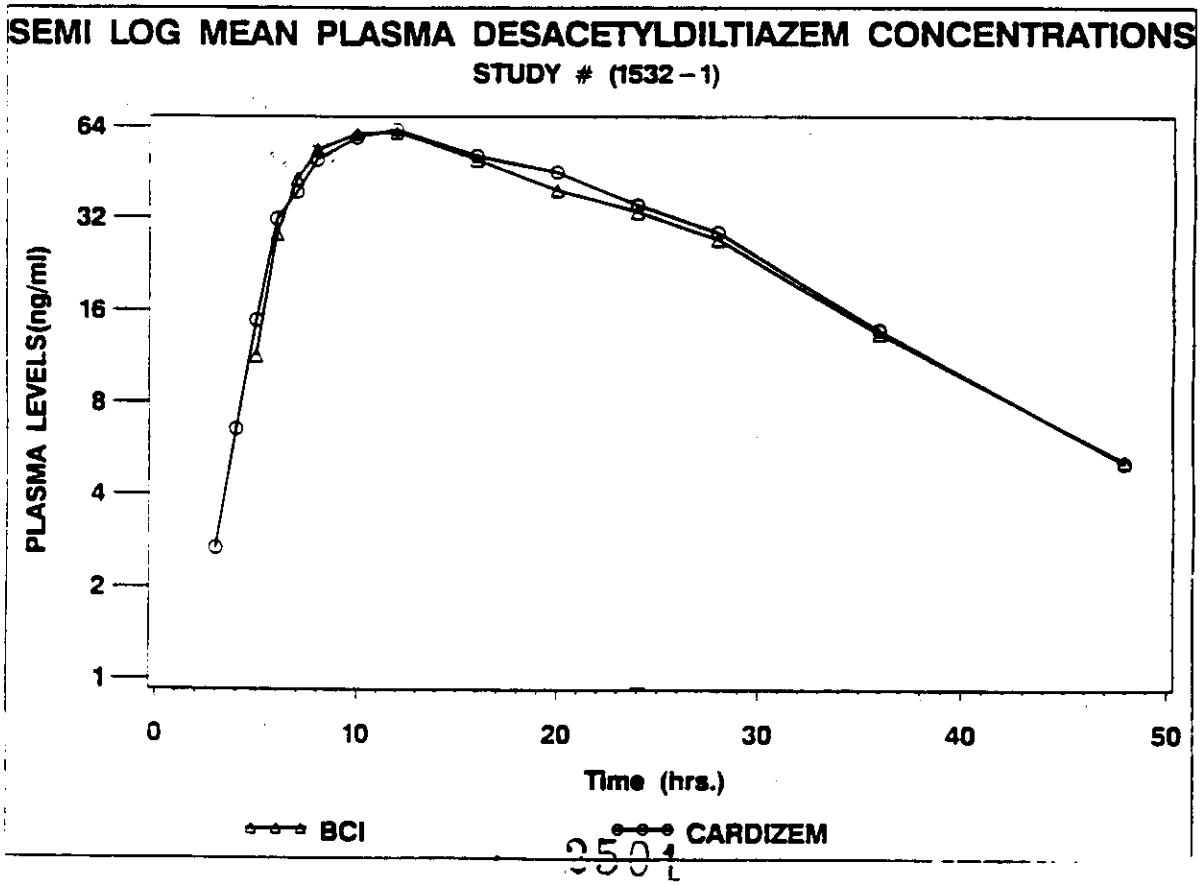


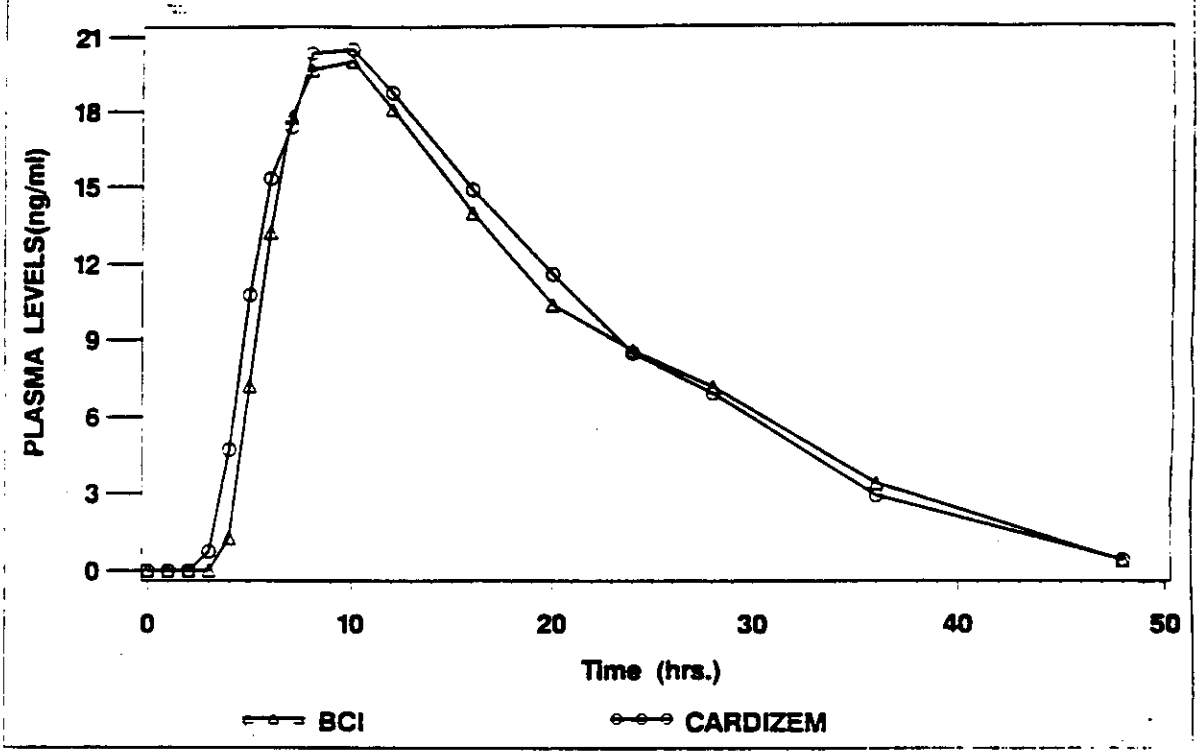
Figure 3

BIOVAIL CORPORATION INTERNATIONAL
STUDY #1532-1 (B95-261PK-B12)

DILTIAZEM

MEAN PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS

STUDY # (1532-1)



SEMI LOG MEAN PLASMA N-DESMETHYLDILTIAZEM CONCENTRATIONS

STUDY # (1532-1)

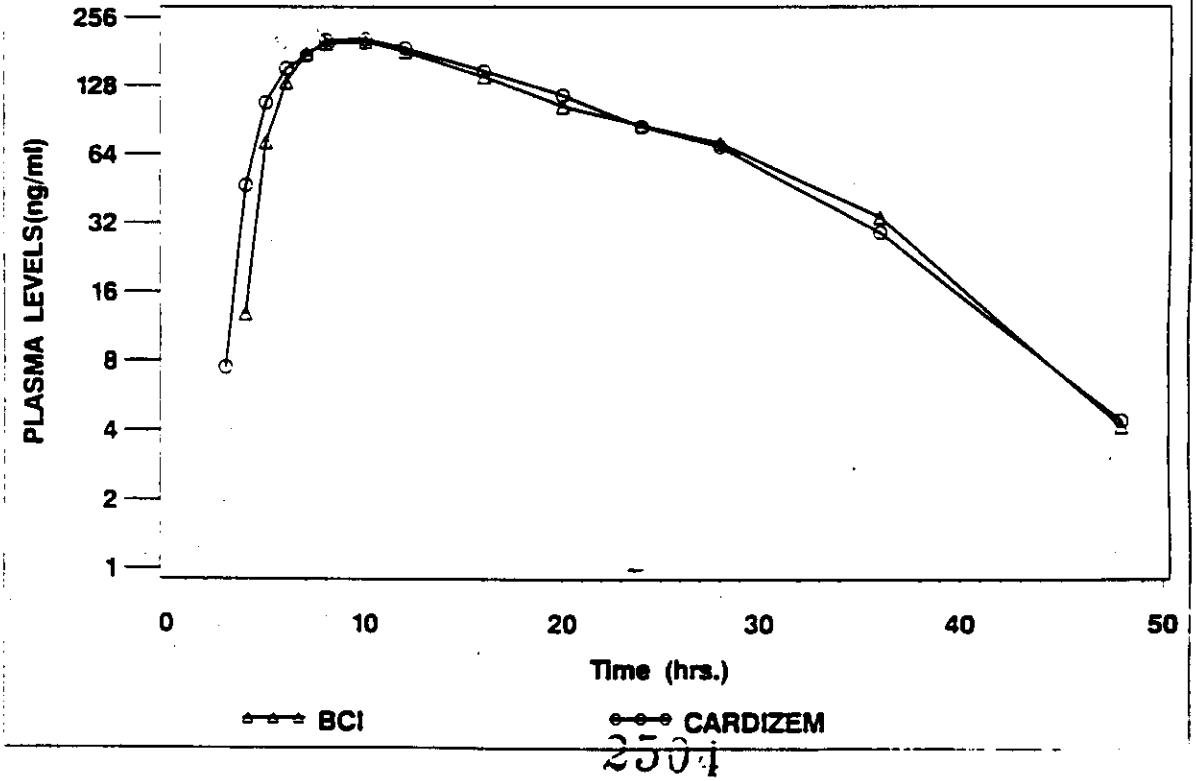
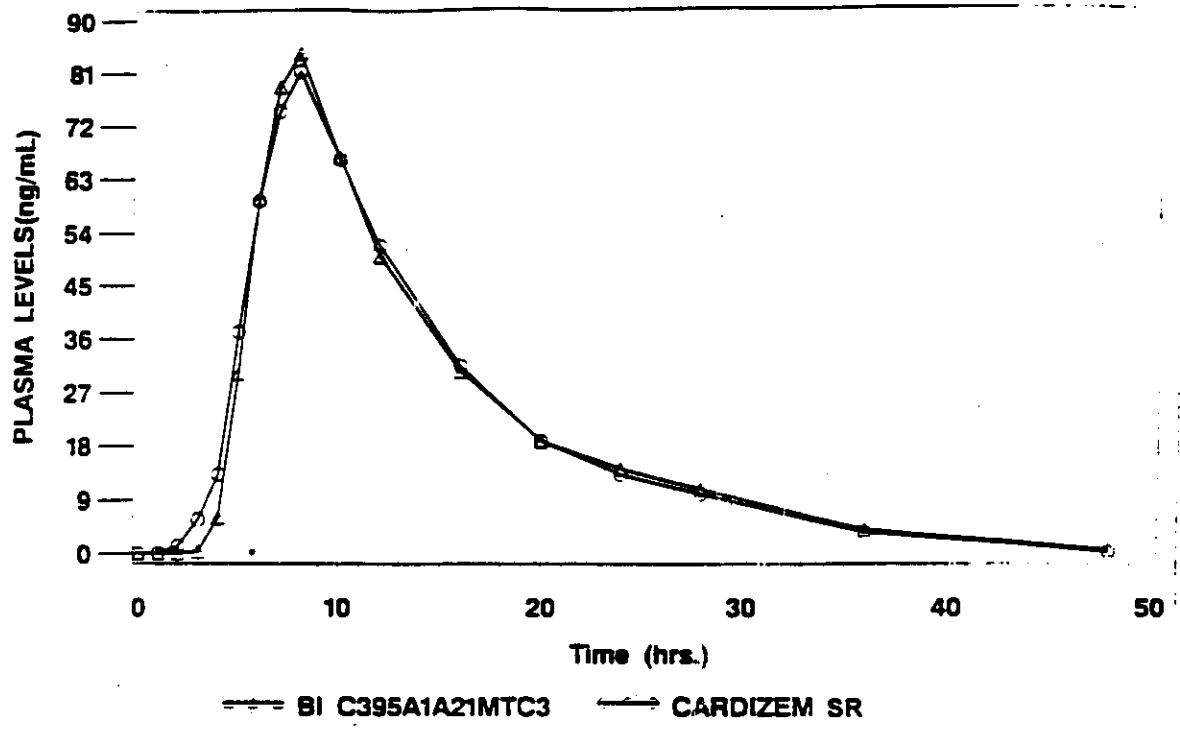


Figure 4

BIOVAIL CORPORATION INTERNATIONAL
STUDY #1659 (B95-279PK-B12)

MEAN PLASMA DILTIAZEM CONCENTRATIONS
(STUDY # 1659)



SEMI LOG MEAN PLASMA DILTIAZEM CONCENTRATIONS
(STUDY # 1659)

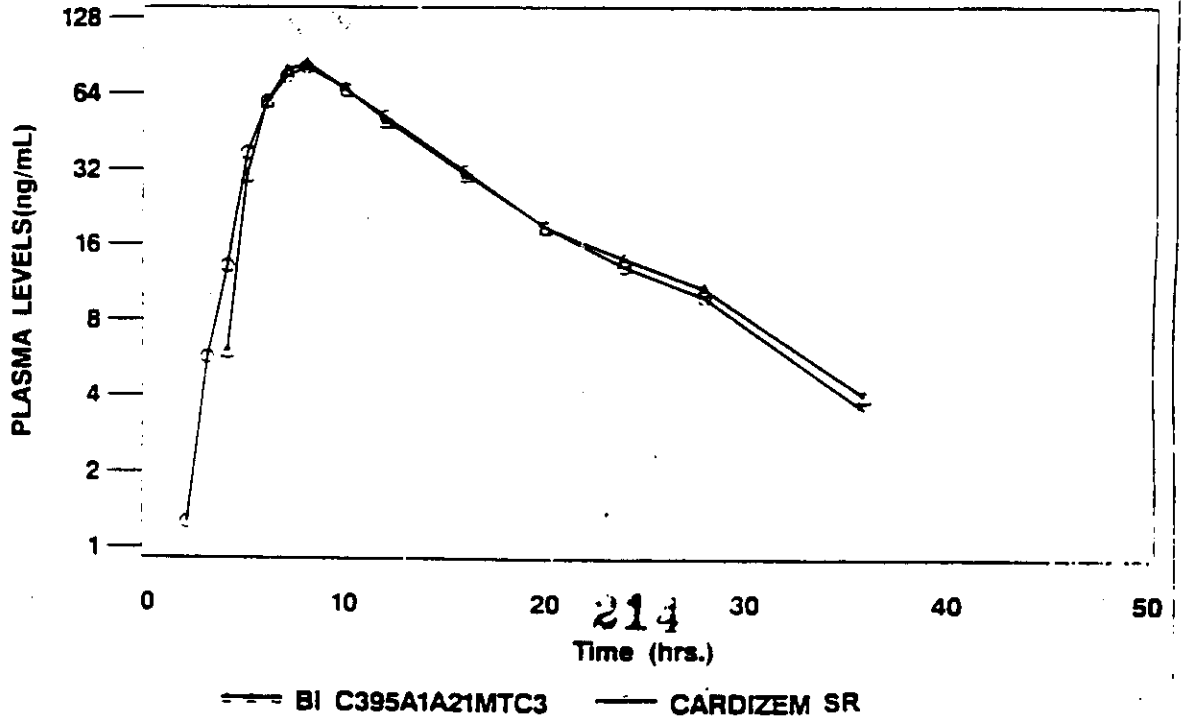
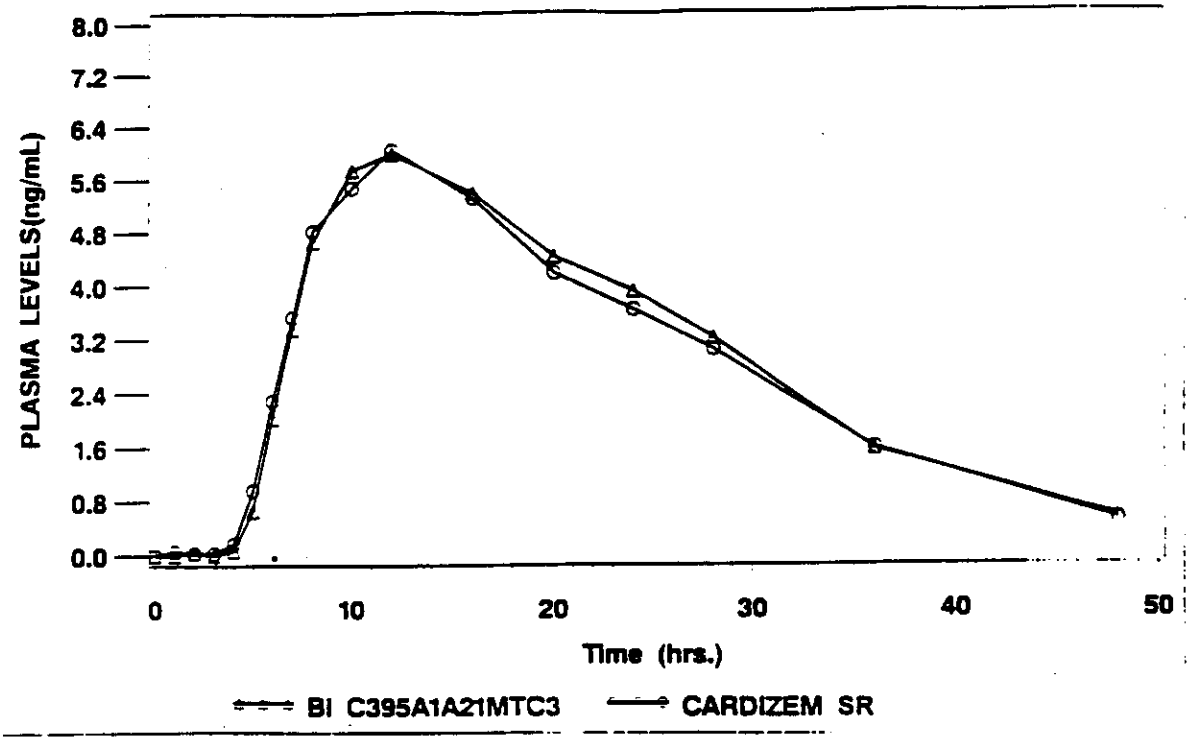


Figure 5

BIOVAIL CORPORATION INTERNATIONAL
STUDY #1659 (895-279PK-B12)

MEAN PLASMA DESACETYLDILTIAZEM CONCENTRATIONS
(STUDY # 1659)



SEMI LOG MEAN PLASMA DESACETYLDILTIAZEM CONCENTRATIONS
(STUDY # 1659)

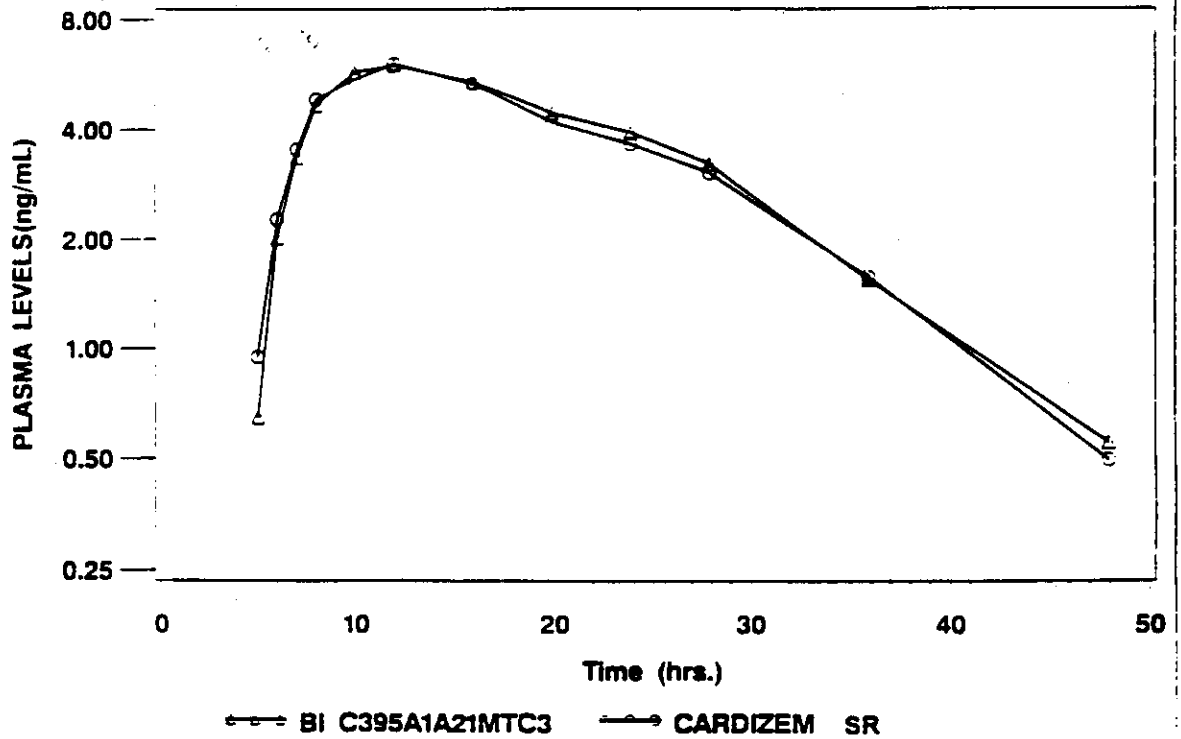
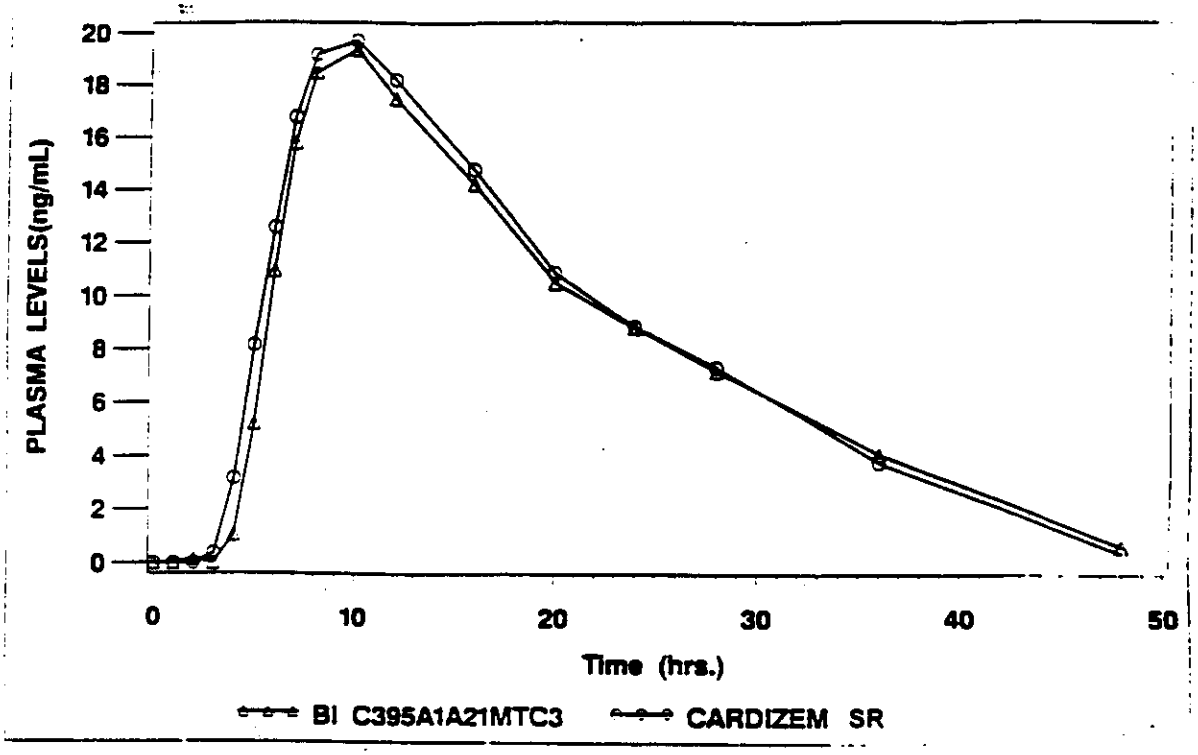


Figure 6

011

BIOVAIL CORPORATION INTERNATIONAL
STUDY #1659 (B95-279PK-B121

MEAN PLASMA DESMETHYLDILTIAZEM CONCENTRATIONS
(STUDY # 1659)



SEMI LOG MEAN PLASMA DESMETHYLDILTIAZEM CONCENTRATIONS
(STUDY # 1659)

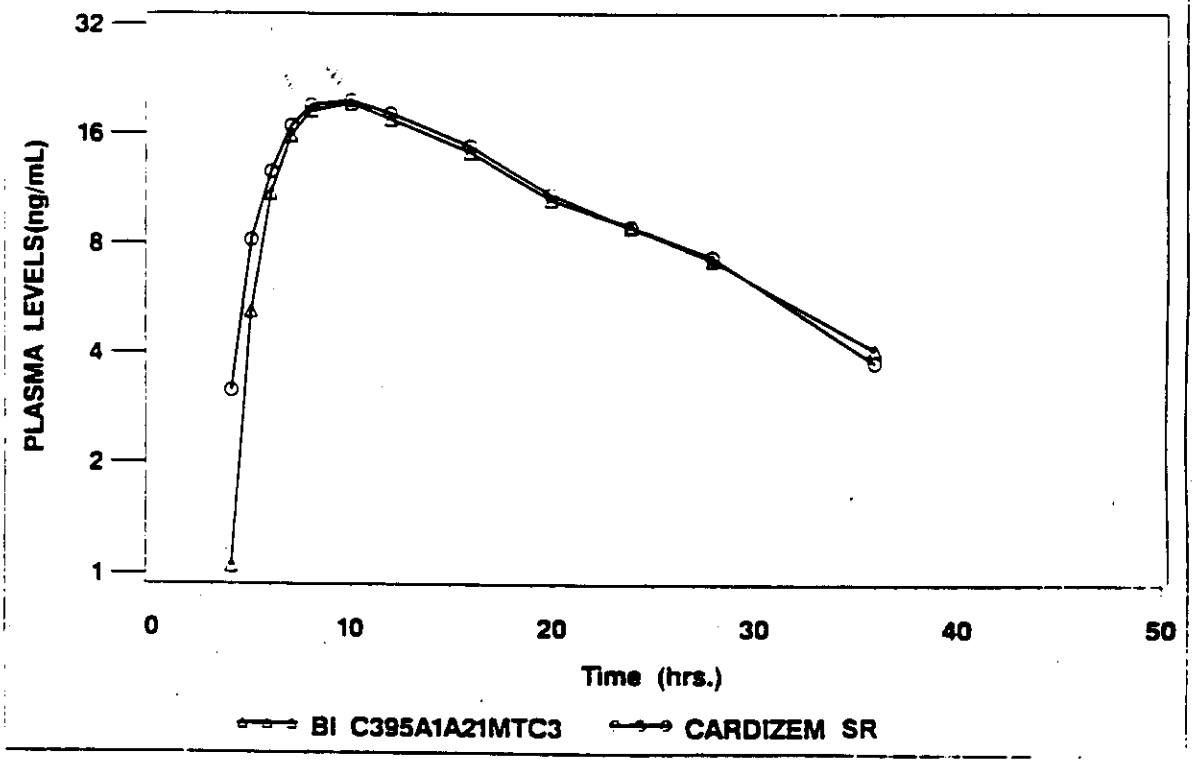
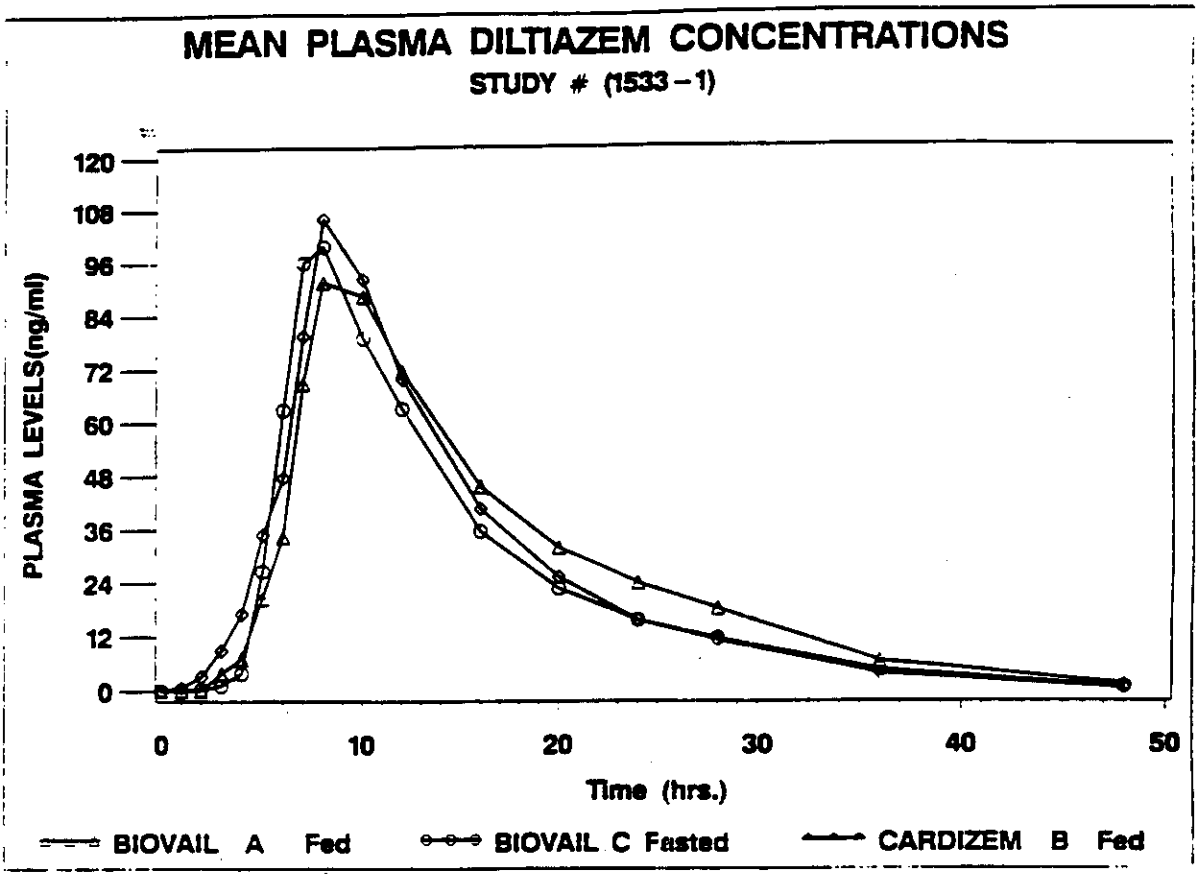


Figure 1

BIOVAIL CORPORATION INTERNATIONAL
STUDY # 1533-1 (B95-262PK-B12)

DILTIAZEM



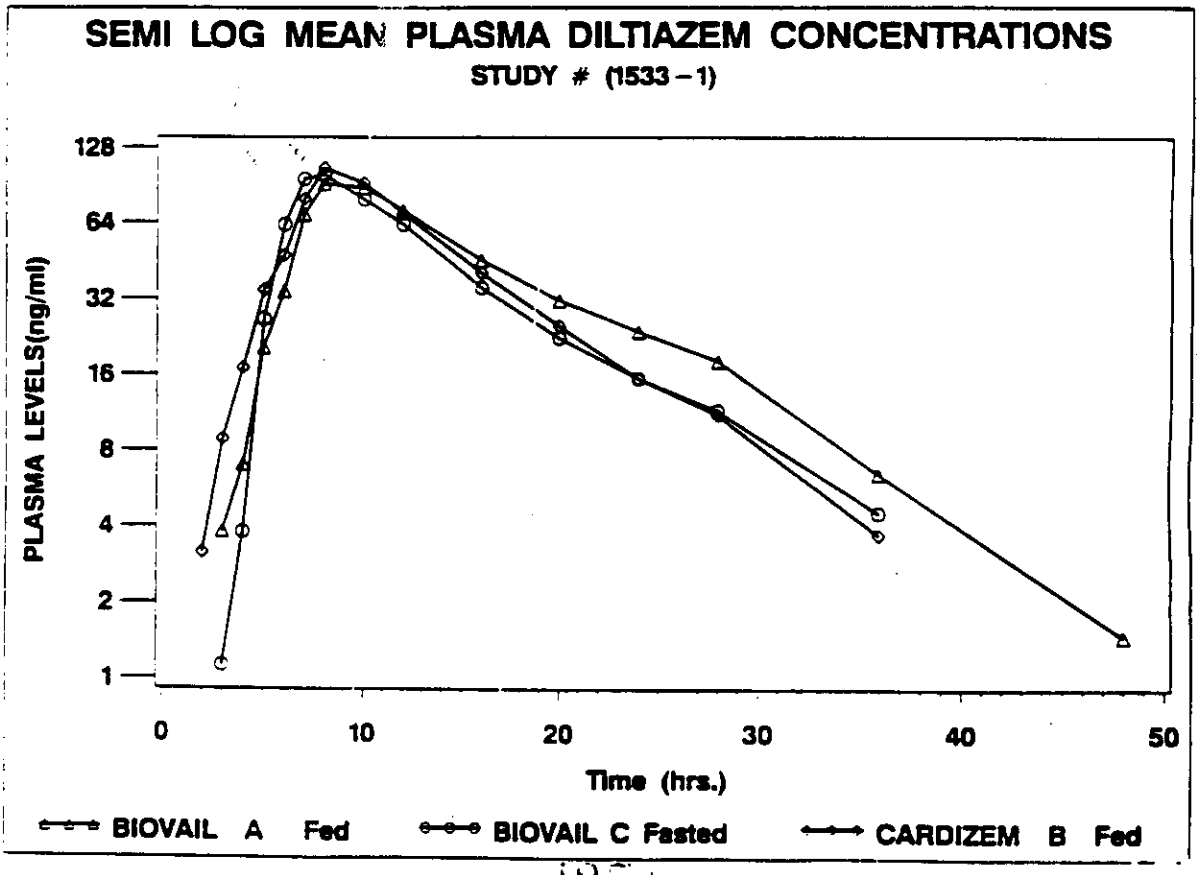
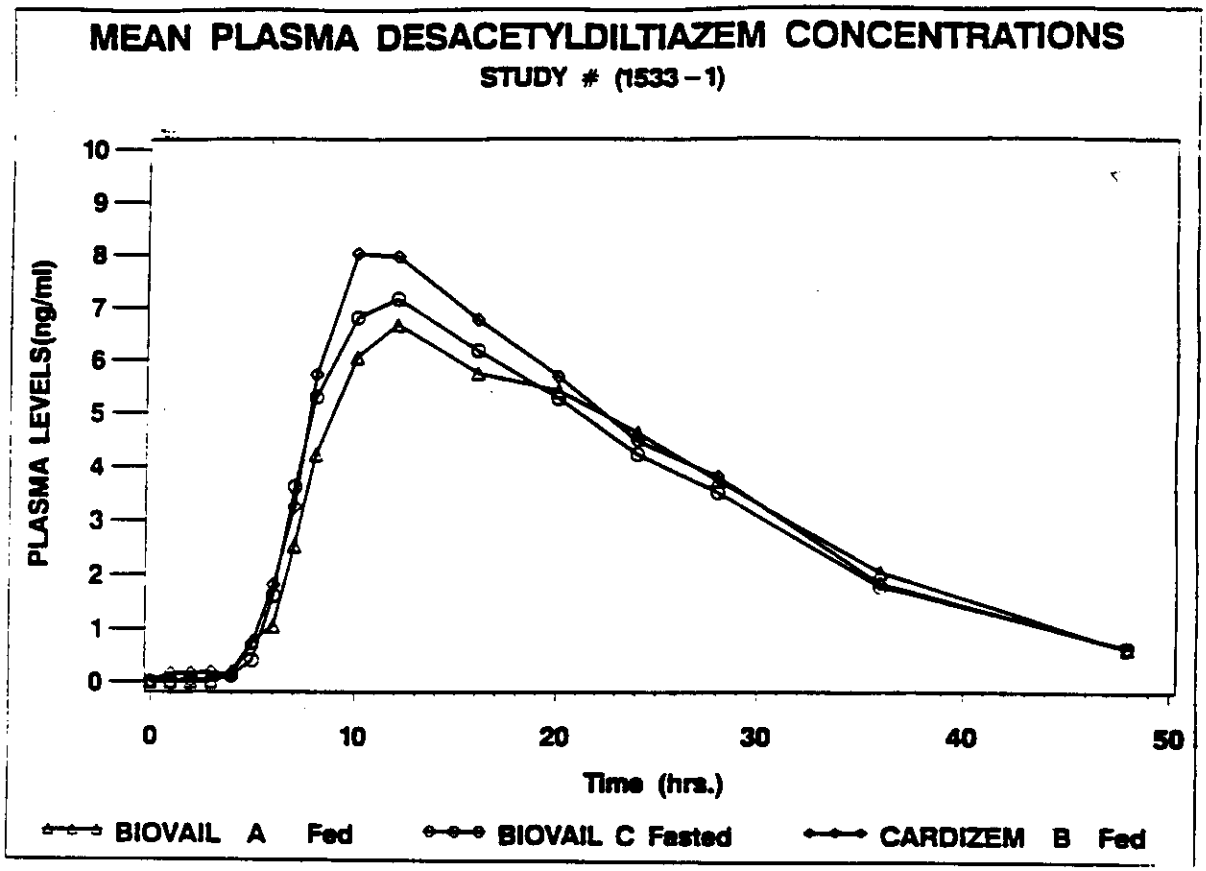
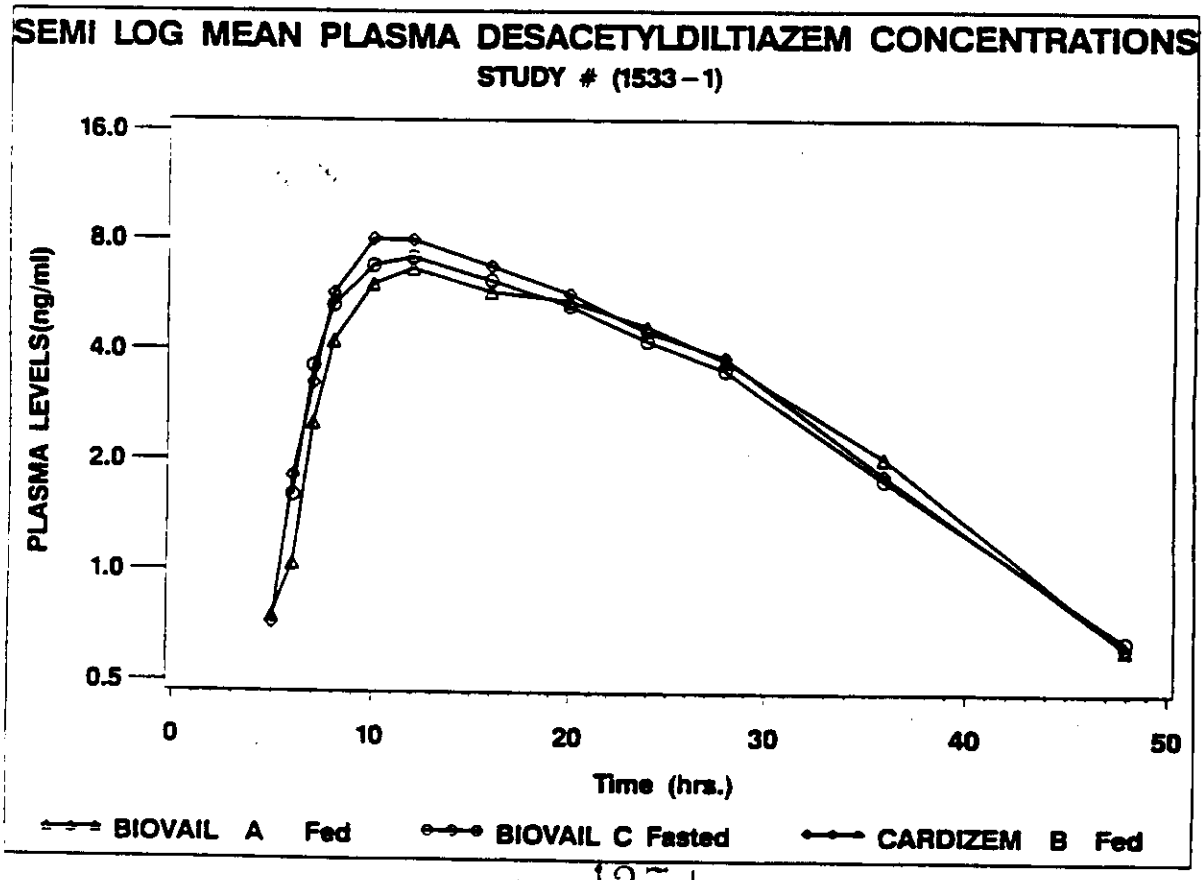


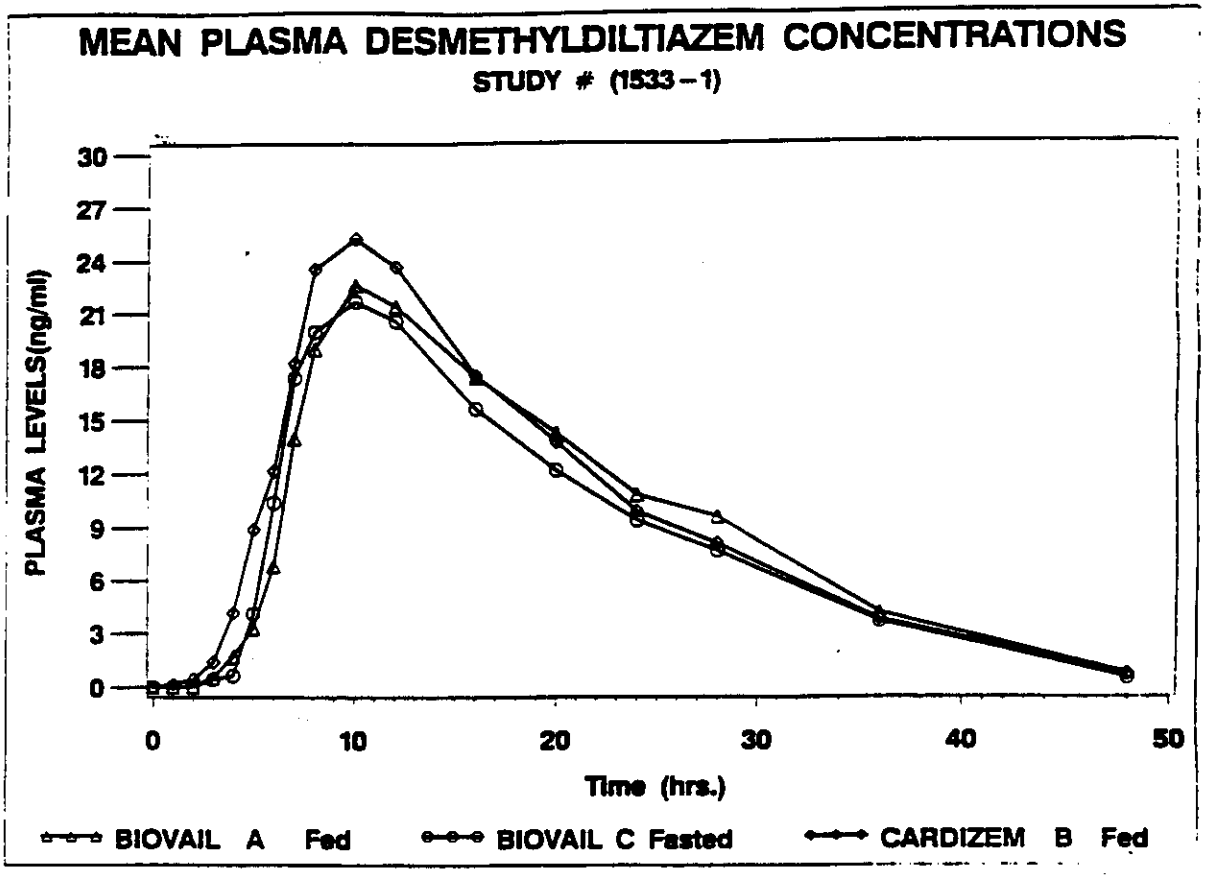
Figure 8

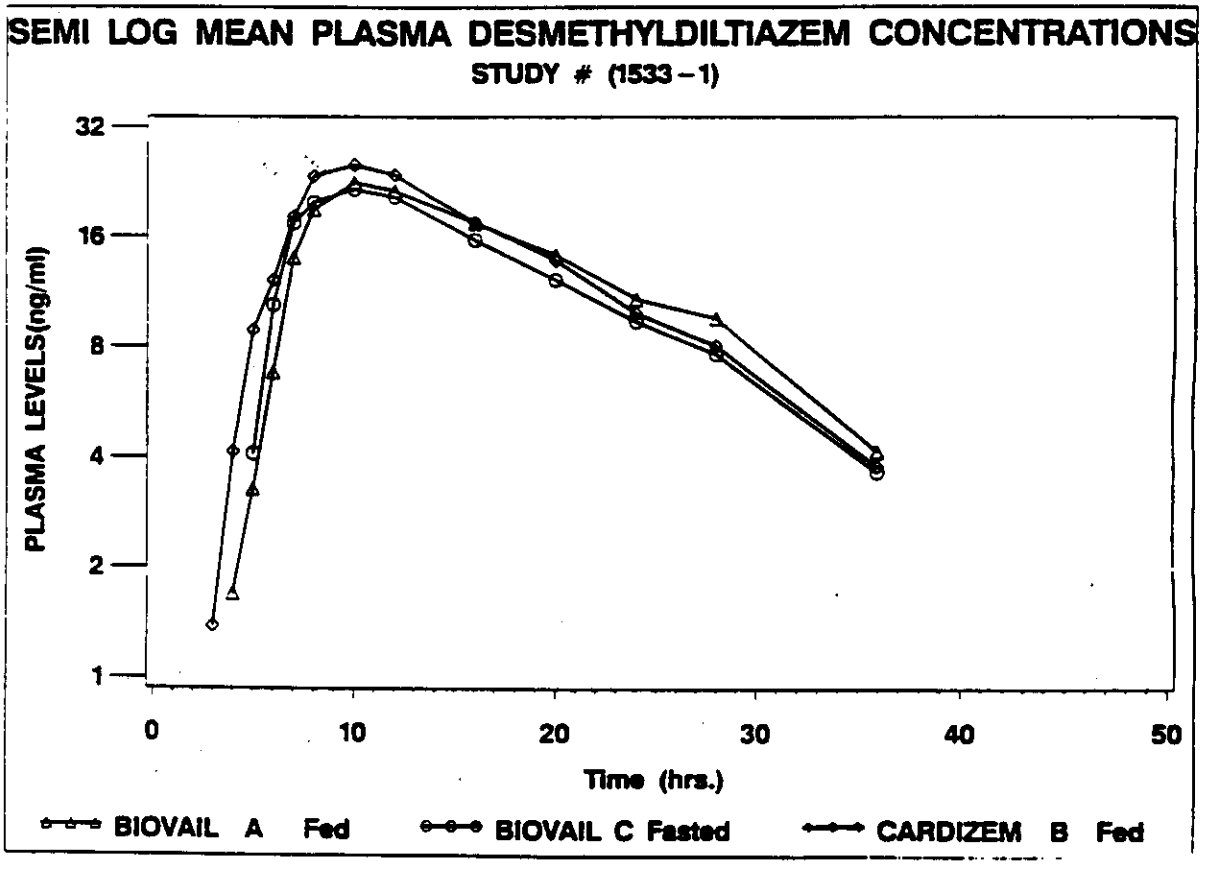
BIOVAIL CORPORATION INTERNATIONAL
STUDY # 1533-1 (B95-262PK-B12)

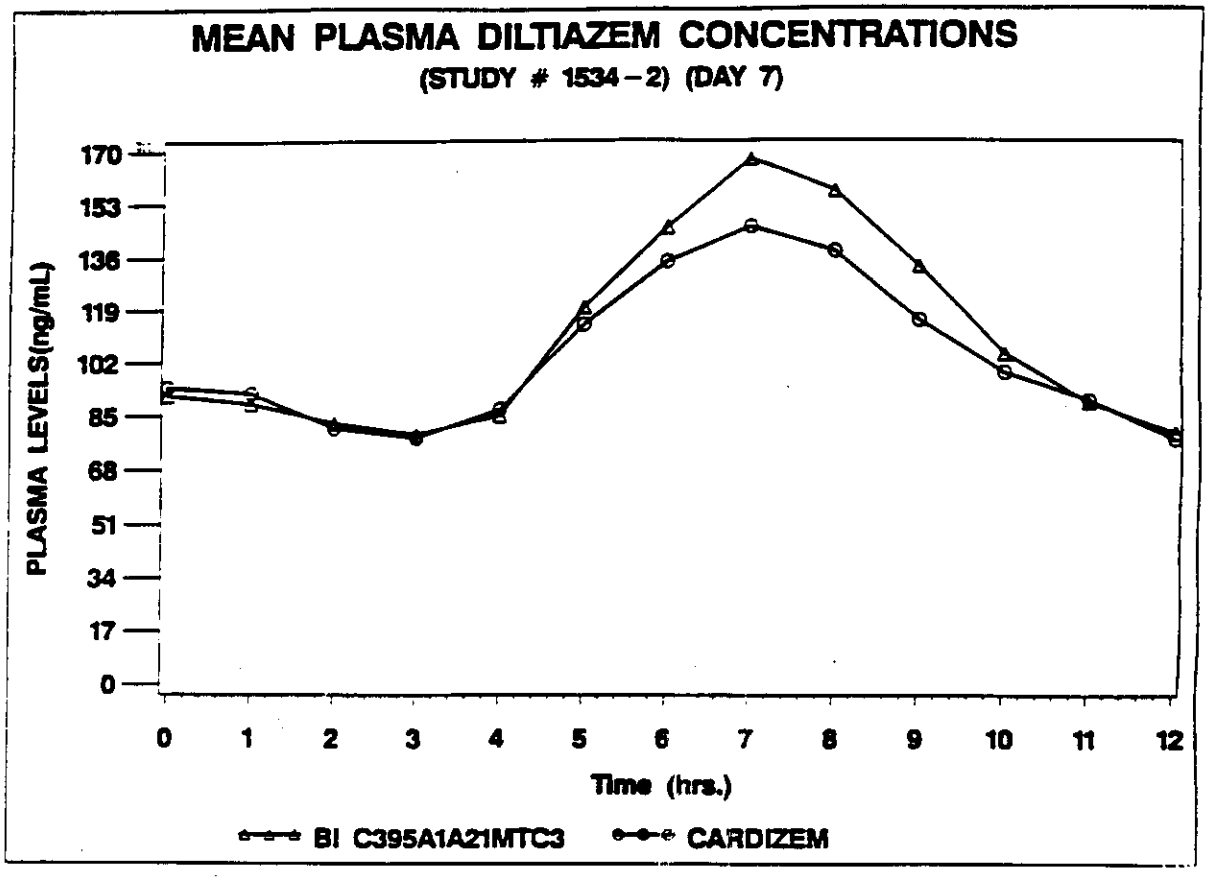
DILTIAZEM






MEAN PLASMA DESMETHYLDILTIAZEM CONCENTRATIONS
STUDY # (1533-1)
PLASMA LEVELS(ng/ml)
30
27
24
21
18
15
12
9
6
3
0
0
10
20
30
40
50
Time (hrs.)
BIOVAIL A Fed
BIOVAIL C Fasted
CARDIZEM B Fed


SEMI LOG MEAN PLASMA DESMETHYLDILTIAZEM CONCENTRATIONS
STUDY # (1533-1)
PLASMA LEVELS(ng/ml)
32
16
8
4
2
1
0
10
20
30
40
50
Time (hrs.)
BIOVAIL A Fed
BIOVAIL C Fasted
CARDIZEM B Fed


MEAN PLASMA DILTIAZEM CONCENTRATIONS
(STUDY # 1534 – 2) (DAY 7)
PLASMA LEVELS(ng/mL)
170
153
136
119
102
85
68
51
34
17
0
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (hrs.)
BI C395A1A21MTC3
CARDIZEM

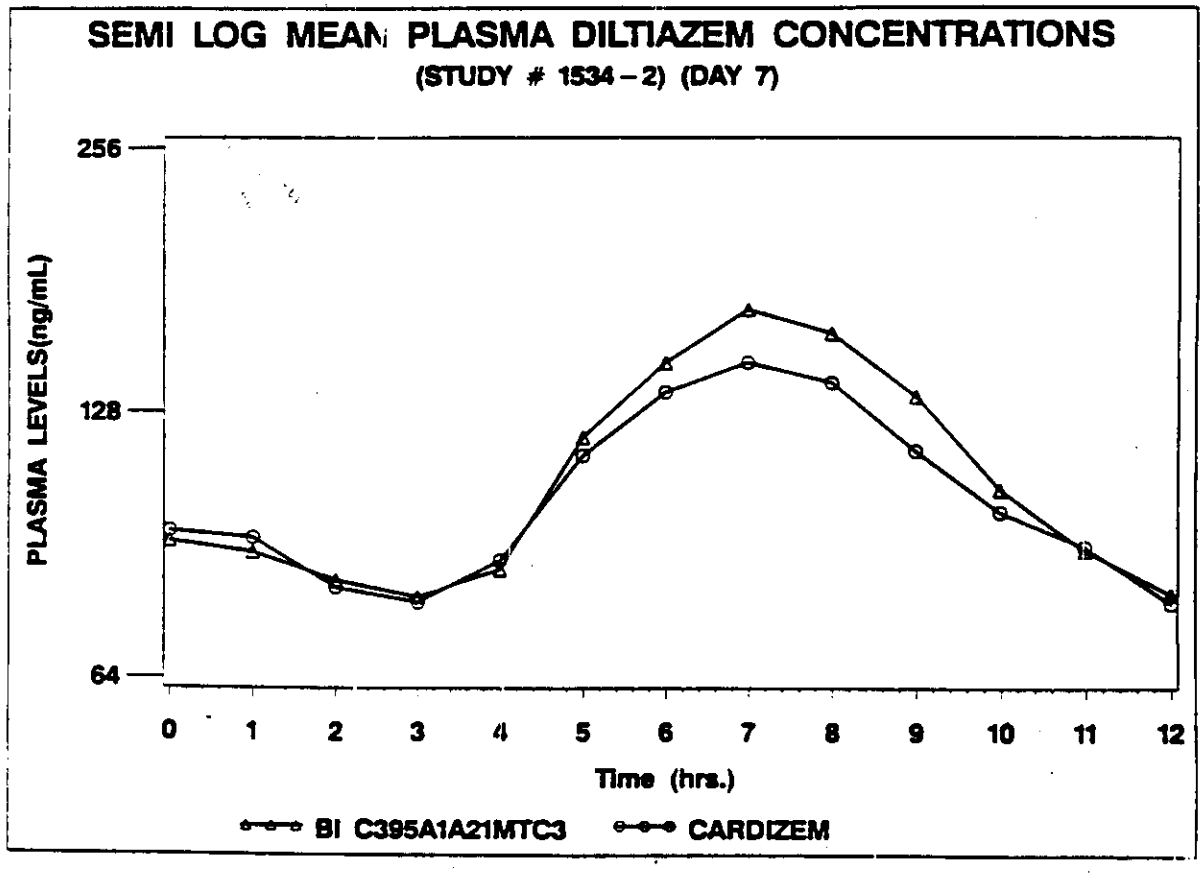
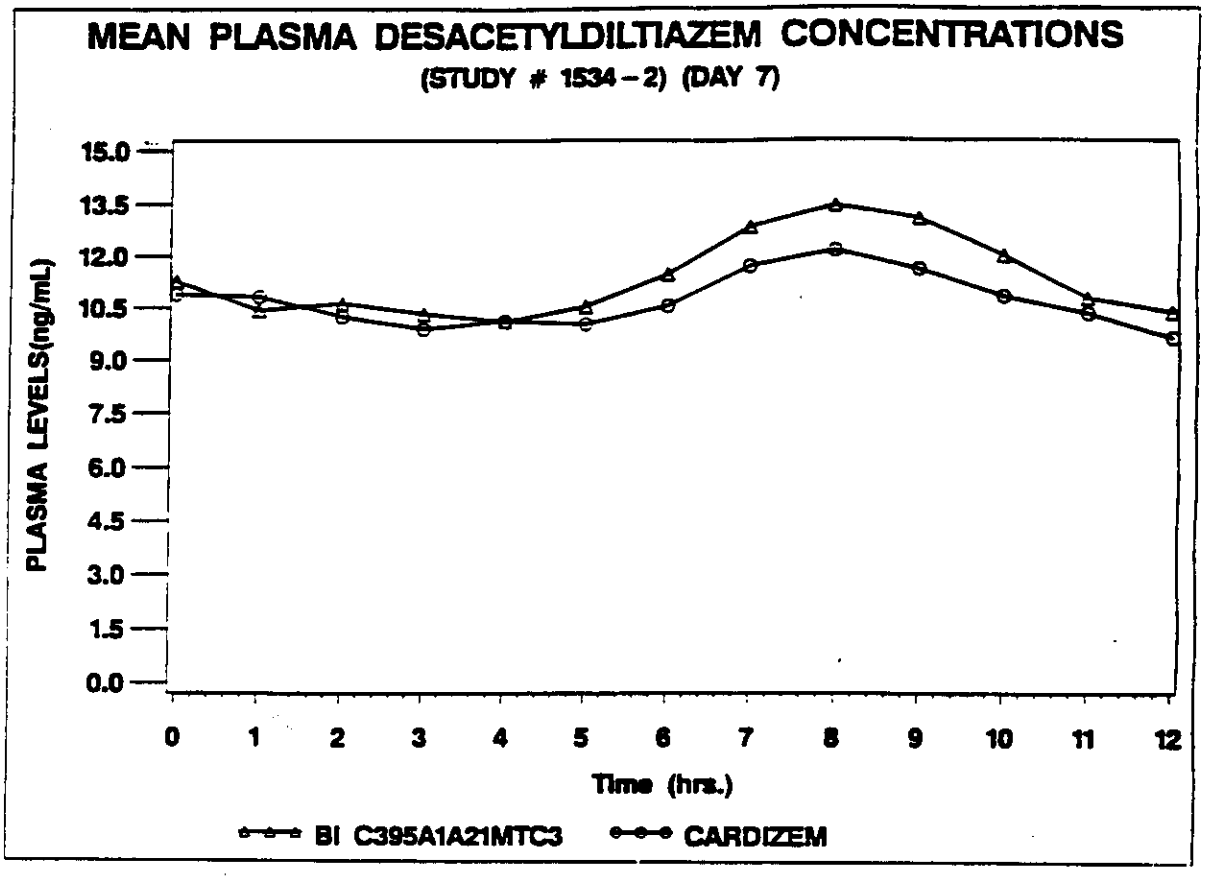
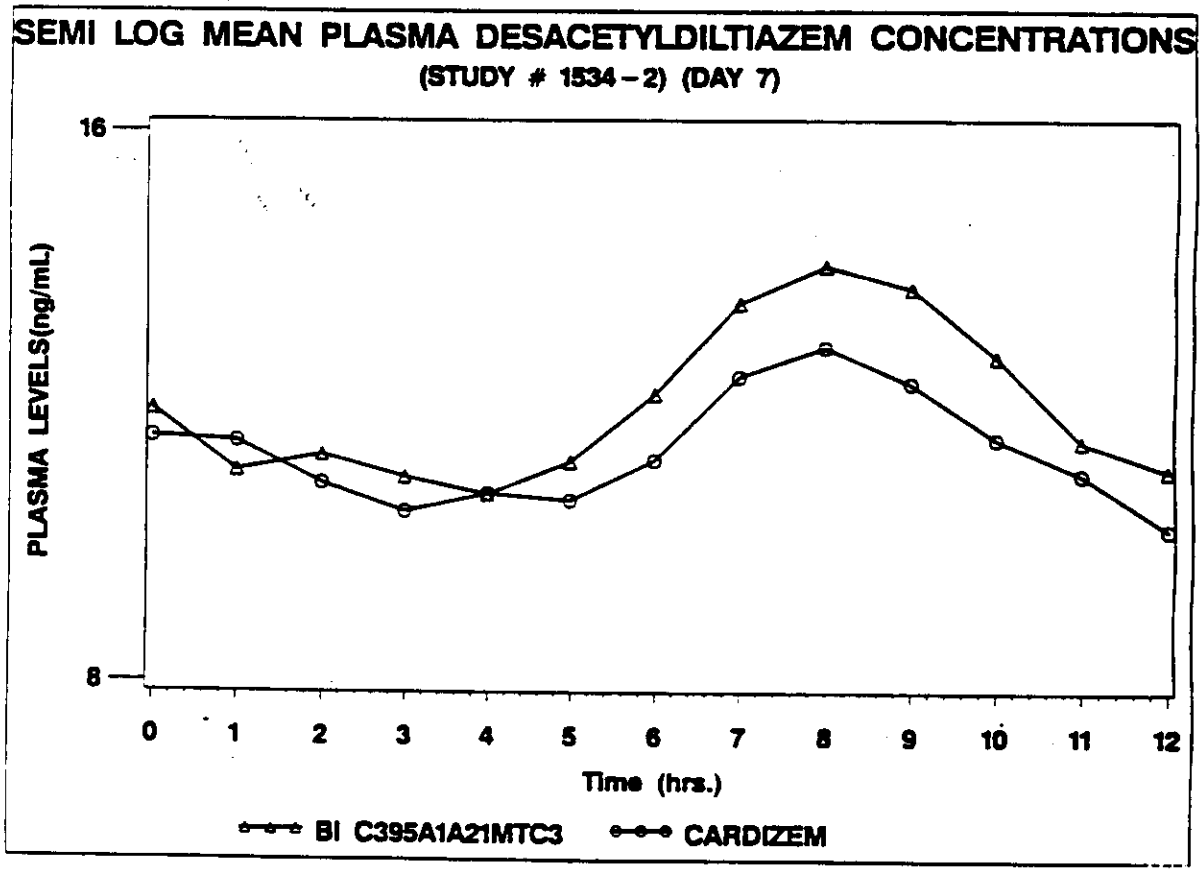
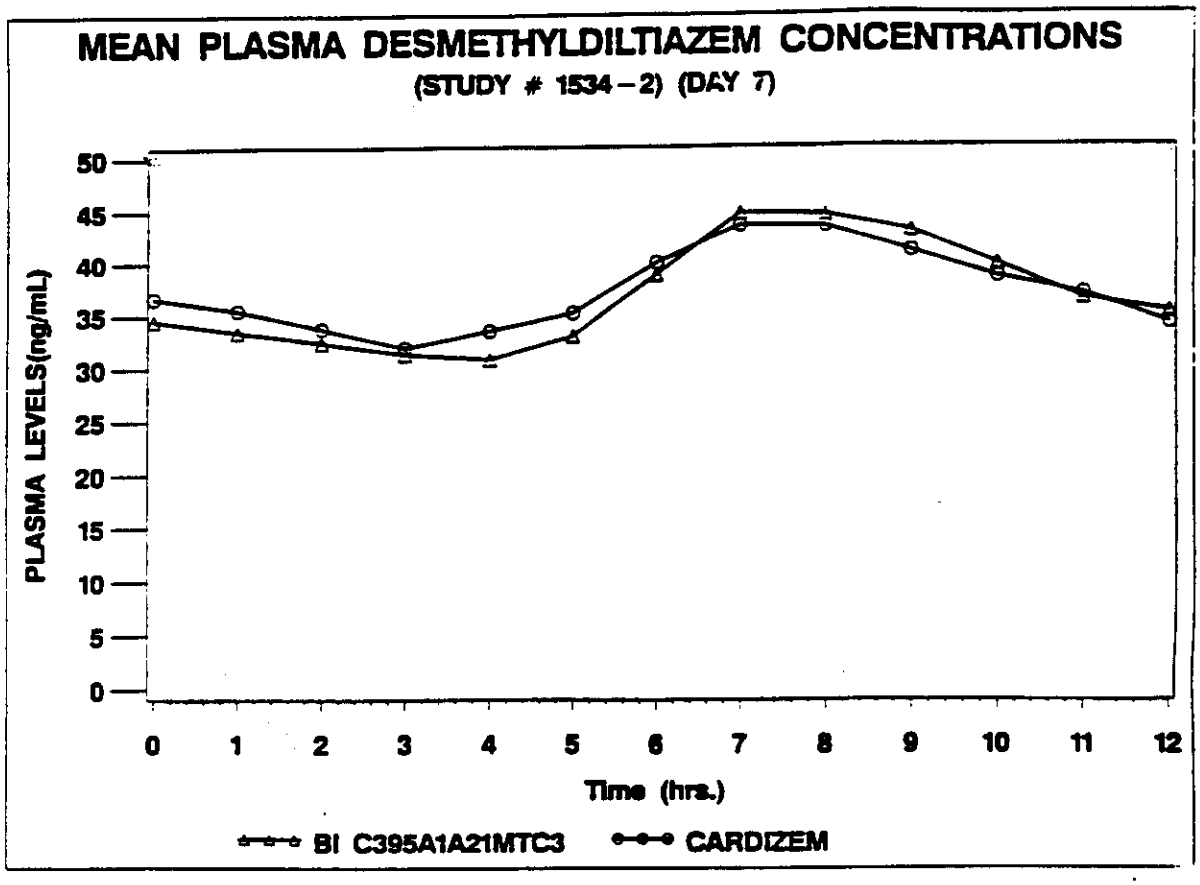

SEMI LOG MEAN PLASMA DILTIAZEM CONCENTRATIONS
(STUDY # 1534 – 2) (DAY 7)
PLASMA LEVELS(ng/mL)
256
128
64
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (hrs.)
BI C395A1A21MTC3
CARDIZEM

Figure 11

BIOVAIL CORPORATION INTERNATIONAL
STUDY # 1534-2 (B95-263PK-B12)






MEAN PLASMA DESMETHYLDILTIAZEM CONCENTRATIONS
(STUDY # 1534-2) (DAY 7)
PLASMA LEVELS(ng/mL)
50
45
40
35
30
25
20
15
10
5
0
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (hrs.)
BI C395A1A21MTC3
CARDIZEM

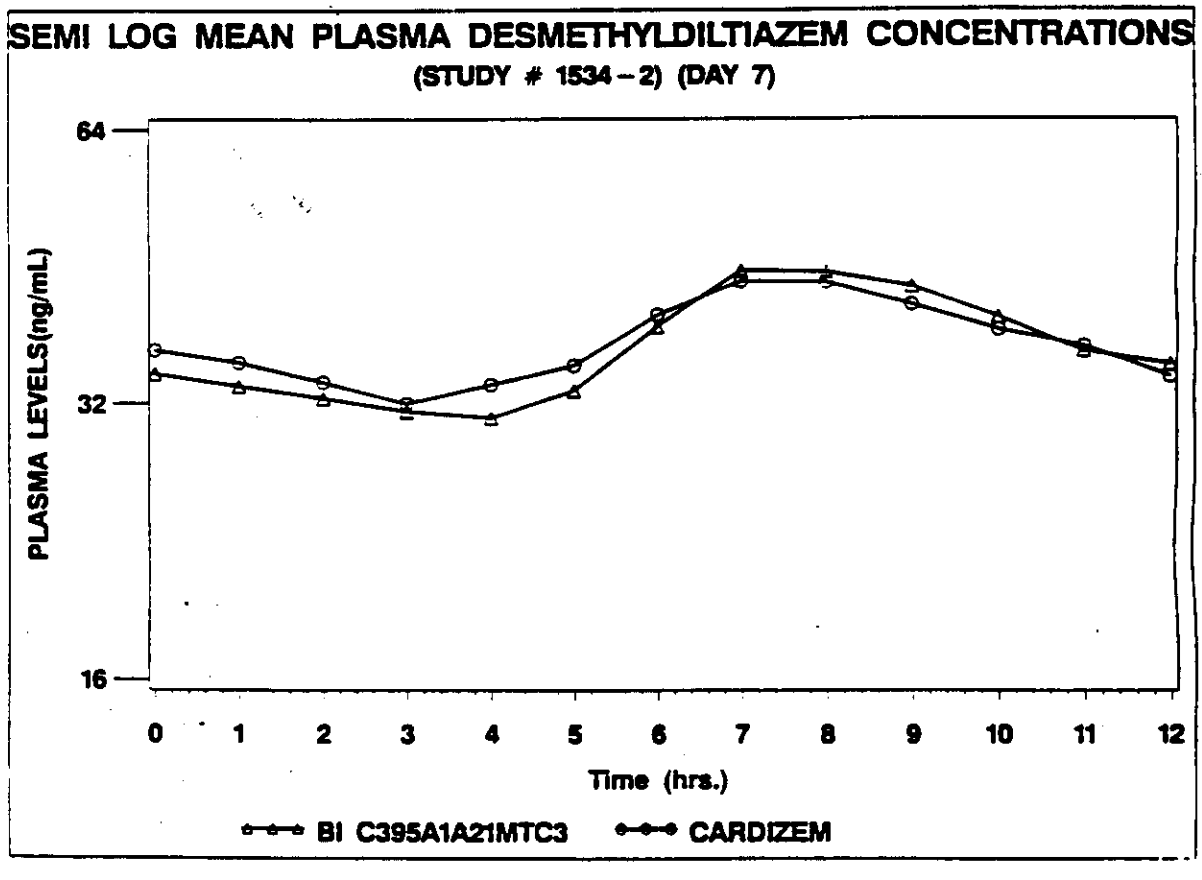

SEMI LOG MEAN PLASMA DESMETHYLDILTIAZEM CONCENTRATIONS
(STUDY # 1534-2) (DAY 7)
PLASMA LEVELS(ng/mL)
64
32
16
0 1 2 3 4 5 6 7 8 9 10 11 12
Time (hrs.)
BI C395A1A21MTC3
CARDIZEM

Figure 13

007

BIOVAIL CORPORATION INTERNATIONAL
STUDY # 1602 (B95-269PK-B12)

MEAN PLASMA DILTIAZEM CONCENTRATIONS
(STUDY # 1602)

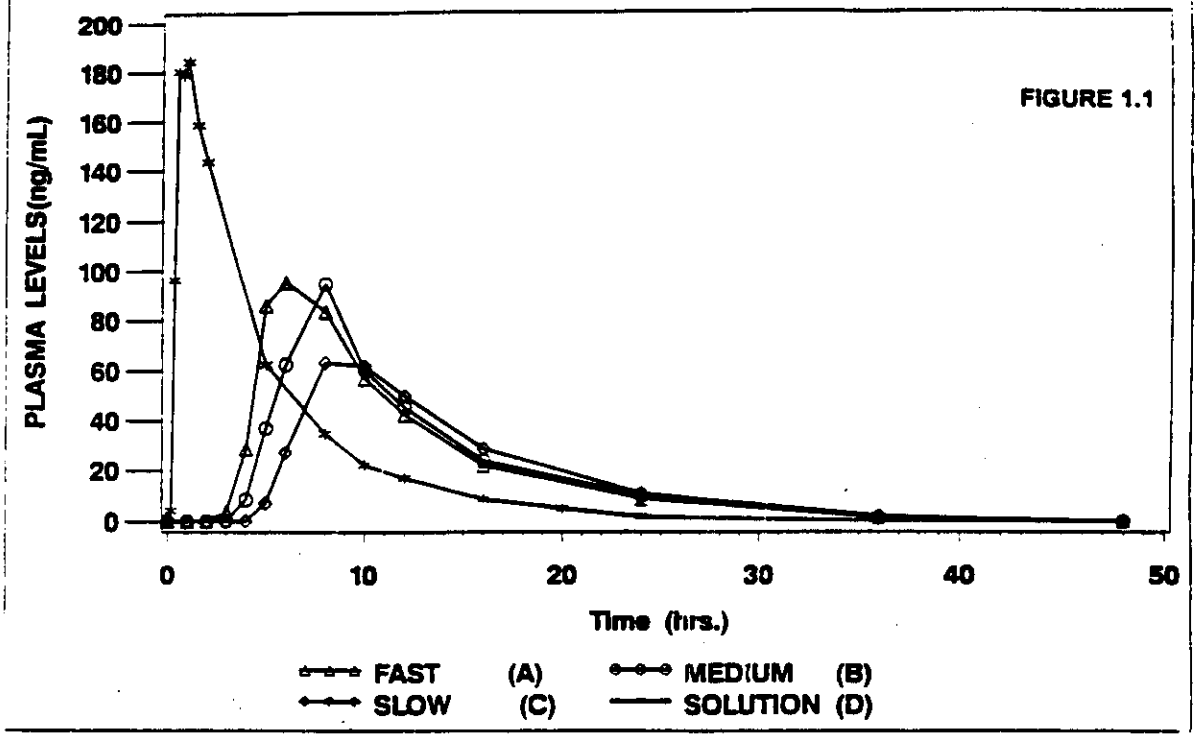


FIGURE 1.1

SEMI LOG MEAN PLASMA DILTIAZEM CONCENTRATIONS
(STUDY # 1602)

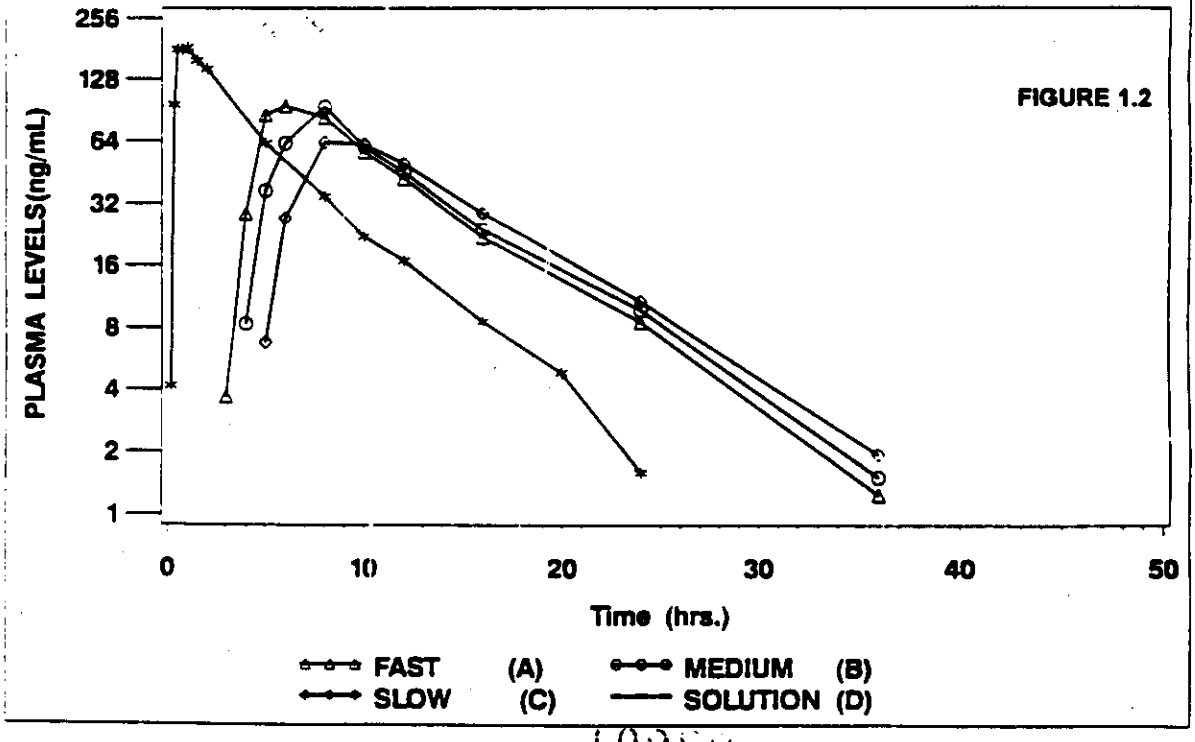


FIGURE 1.2

Figure 14

MEAN PLASMA DESACETYLDILTIAZEM CONCENTRATIONS
(STUDY # 1602)

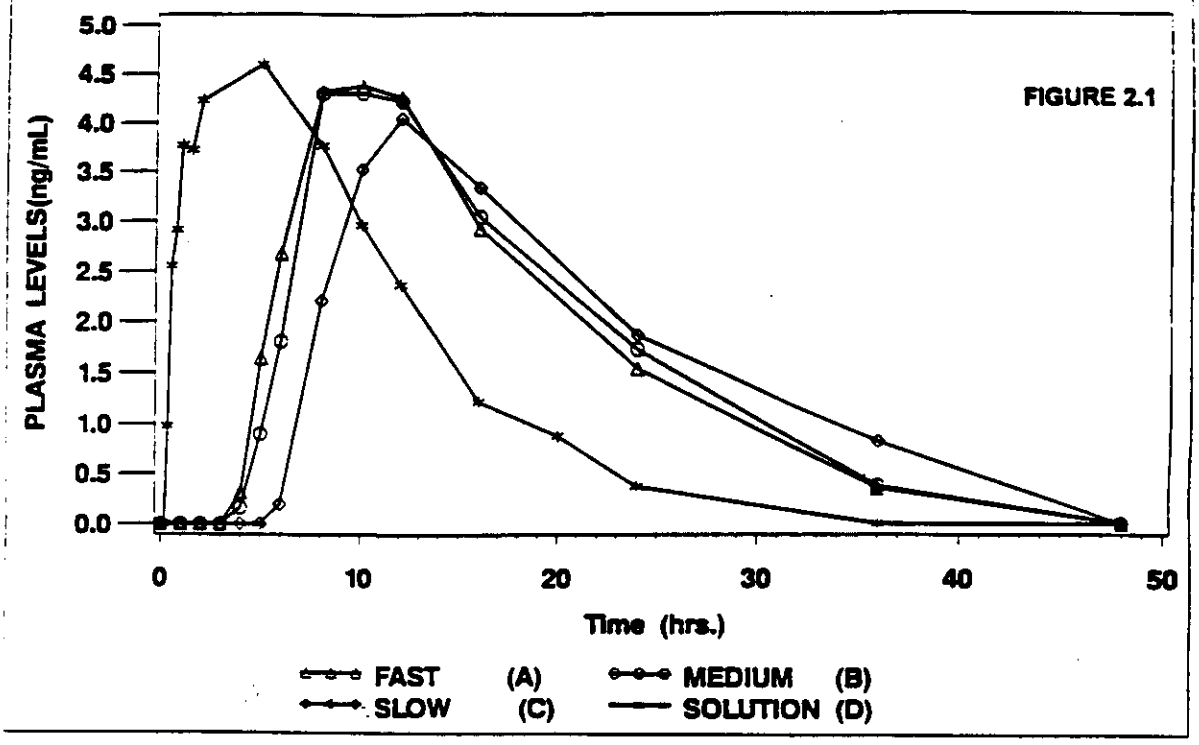


FIGURE 2.1

SEMI LOG MEAN PLASMA DESACETYLDILTIAZEM CONCENTRATIONS
(STUDY # 1602)

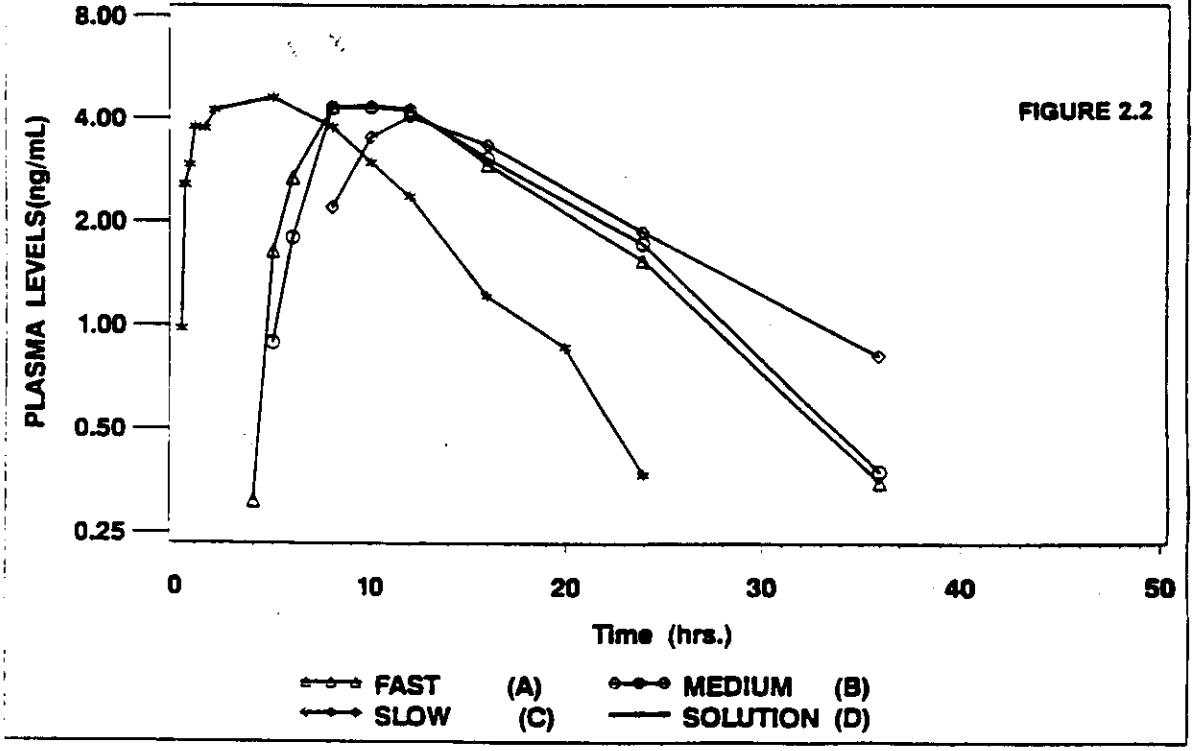


FIGURE 2.2

Figure 15

MEAN PLASMA DESMETHYLDILTIAZEM CONCENTRATIONS
(STUDY # 1602)

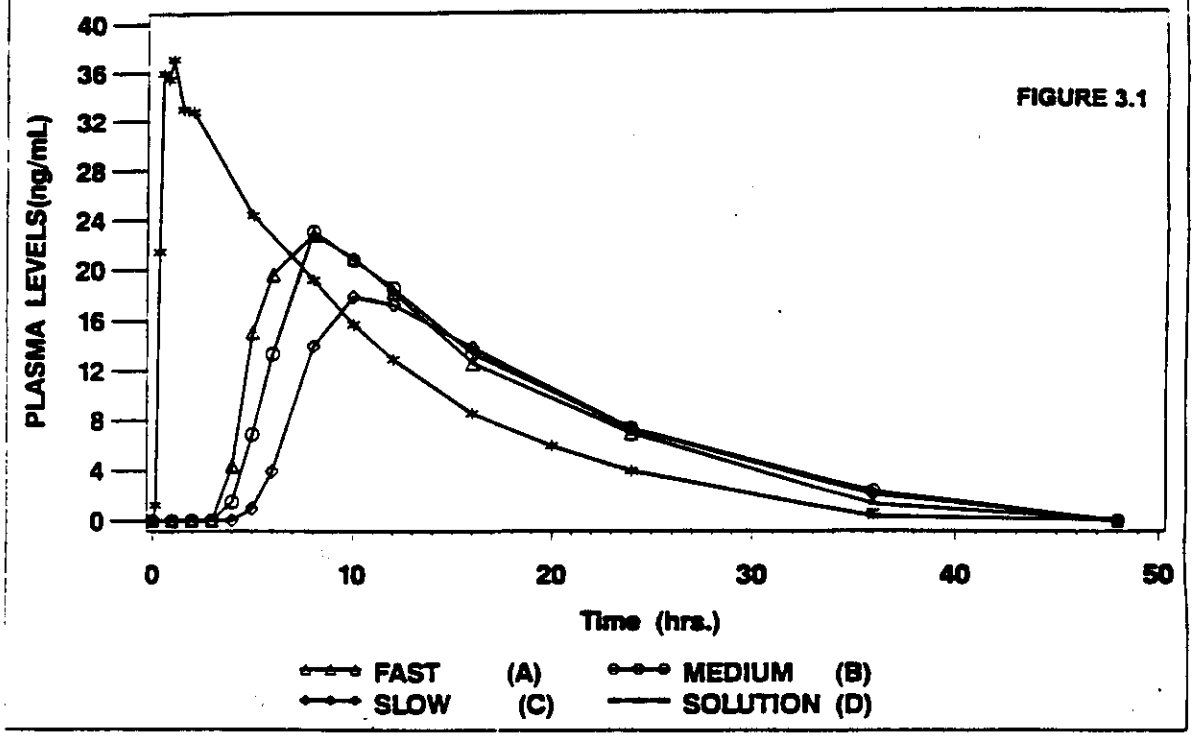


FIGURE 3.1

SEMI LOG MEAN PLASMA DESMETHYLDILTIAZEM CONCENTRATIONS
(STUDY # 1602)

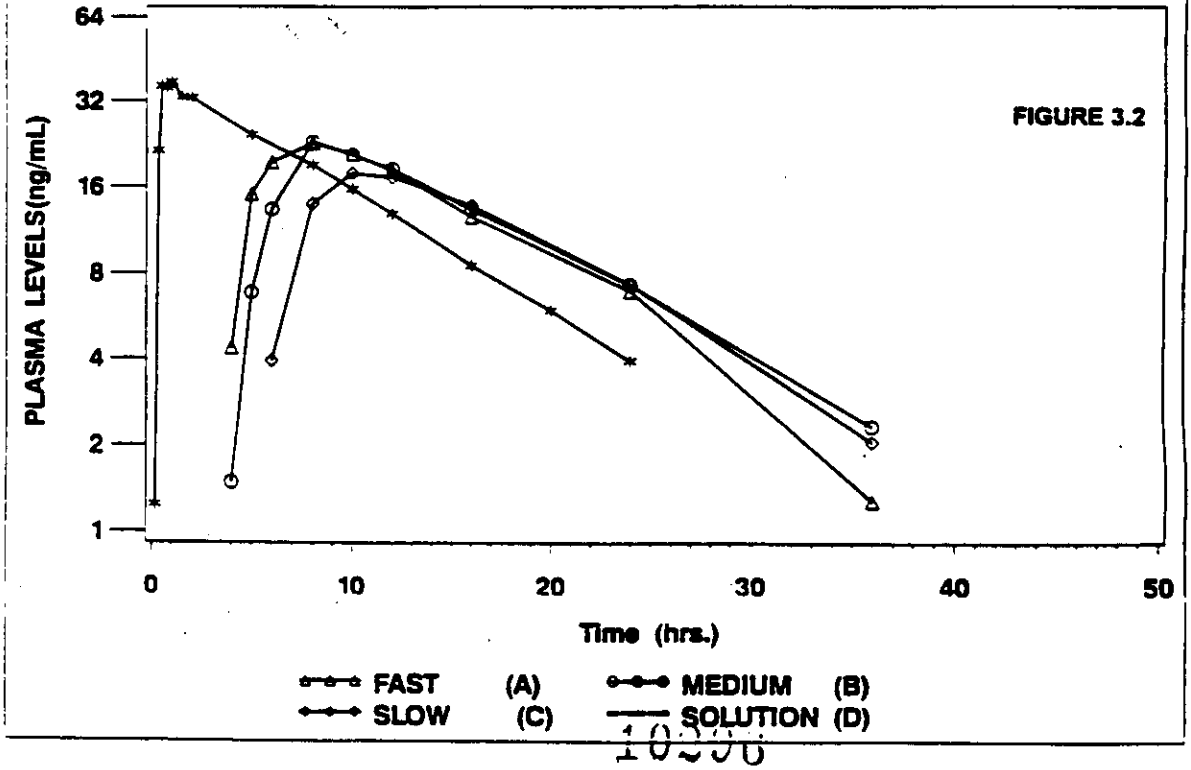


FIGURE 3.2

Regression Equation	Y=1457-132.96X	Y=1.667+2.014X	Y=238.02-28..327X
Correlation Coefficient (r)	0.918	0.959	0.835

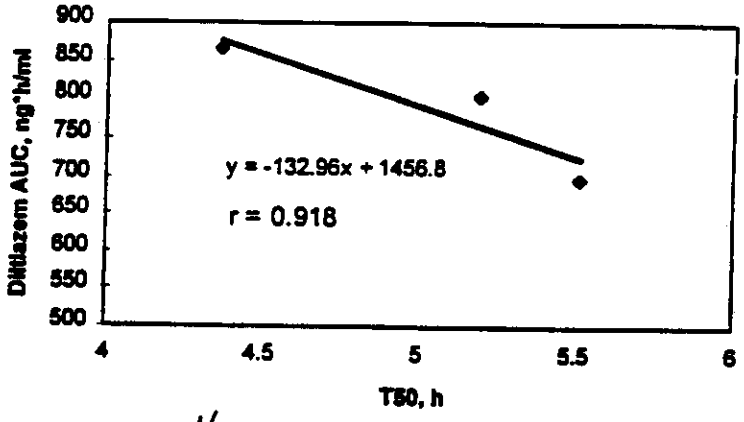


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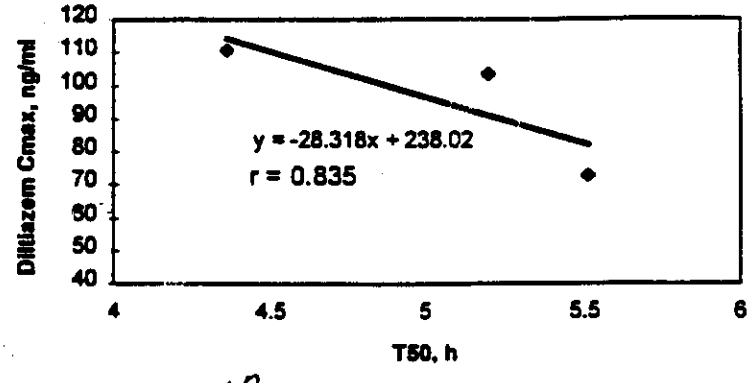
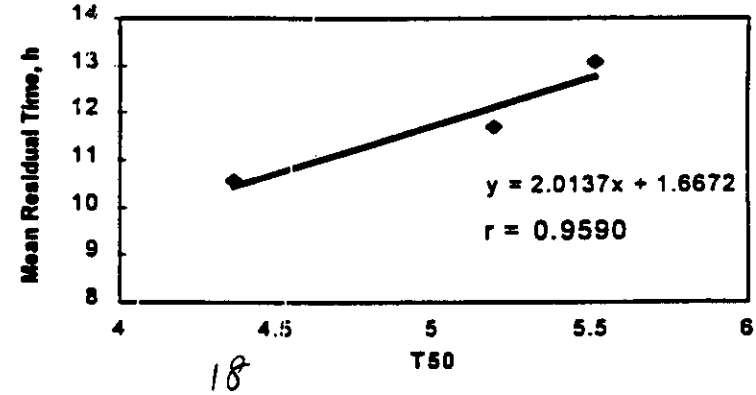
Figure 3: Correlation of AUC_{0-t} and T_{50}.



17

Figure 4: Correlation of C_{max} and T_{50}.



18

Figure 5: Correlation of MRT and T_{50}.