CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65003

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 65-003 SPONSOR : Abbott Laboratories

DRUG AND DOSAGE FORM : Cyclosporine Hard Gelatin Capsules

STRENGTH(S) : 100 mg, 50 mg, and 25 mg

TYPES OF STUDIES : NA

CLINICAL STUDY SITE(S) : NA

ANALYTICAL SITE(S) : NA

STUDY SUMMARY : **Waiver of bioequivalence studies is granted.**

DISSOLUTION : NA

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic NO New facility ___ For cause ____ other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Zakaria Z. Wahba, Ph.D. BRANCH : III

INITIAL : Z.Z.W. DATE : 4/17/2000

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : BMD DATE : 4/17/00

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 4/18/00

(4)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 65-003 – CYCLOSPORINE SPONSOR : Abbott Laboratoreis

DRUG AND DOSAGE FORM : Capsules STRENGTH(S) : 25 mg, 50 mg and 100 mg

TYPES OF STUDIES : In vivo bioequivalence studies under fasting and non-fasting conditions.

CLINICAL STUDY SITE(S

ANALYTICAL SITE(S) :

STUDY SUMMARY : The two studies demonstrated that under fasting and non-fasting conditions, Abbott's Cyclosporine Hard Gelatin Capsule, 100 is bioequivalent to Novartis' Neoral® (Cyclosporine Soft Gelatin Capsule), 100 mg.

DISSOLUTION : The dissolution data for the 100 mg, 50 mg and 25 mg are acceptable.

DSI INSPECTION STATUS

Inspection needed: (YES) / NO	Inspection status:	Inspection results:
First Generic _No__ New facility _Yes (new analytical facility) _ For cause _____ other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Zakaria Z. Wahba, Ph.D. BRANCH : III

INITIAL : /S/ DATE : 5/5/99

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : /S/ DATE : 5/5/99

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : [signature] DATE : 5/28/99

ANDA: #65-003 APPLICANT: Abbott Laboratories

DRUG PRODUCT: Cyclosporine Hard Gelatin Capsules, 100 mg, 50 mg and 25 mg.

The Division of Bioequivalence has completed its review and the following comments for consideration.

1. For your product, Cyclosporine Hard Gelatin Capsules, please follow the method that is published in the Pharmacopeial Forum, 1998, 24 (3):6155-6159, with respect to testing.

   The dissolution approach, Method A should be applied for batch release. If the dissolution testing fails method A during stability evaluation, testing should be conducted.

   Note: Recommendations for testing of hard and soft gelatin capsules have been revised in USP 24 Supplement 1, page #2696, Section <711>. The amount of added to media of pH 6.8 or lower should not exceed activity of Units per mL of media.

2. Your request to change the dissolution media volume from mL to mL, for testing the 25 mg strength is acceptable.

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

BIOEQUIVALENCY DEFICIENCIES

ANDA: #65-003 APPLICANT: Abbott Laboratories

DRUG PRODUCT: Cyclosporine Hard Gelatin Capsules, 100 mg, 50 mg and 25 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. You should provide long term stability data covering the entire period of sample storage from blood collection to analysis. In addition, data on the assay methodology recovery should be included.

2. The bioequivalence study under fasting conditions using Abbott's cyclosporine soft gelatin capsule, 100 mg (lot #27-687-AR-03) is not acceptable since the 90% confidence interval for Cmax is outside the acceptable range of % of the reference listed drug.

3. You should obtain the dissolution data for the 25 mg, 50 mg and 100 mg formulations according to the following specification. The Agency recommends the following dissolution approach:

You are also referred to the Pharmacopial Forum, dated May-June 1998. The comparative dissolution profiles for the test and reference products (in a side-by-side tabular format, if possible) should be submitted with raw dissolution data, the dissolution mean, the range (high, low), and the percentage of coefficient of variation (%C.V.), and date(s) of analysis. Comparative dissolution data for both the test and reference drug products should be

performed simultaneously. In addition, the lot number, lot size (for the test product only), and the manufacturing date for the test product and expiration date for the reference product should be included. The lot number of the dissolution testing should be identical to the one used in the in vivo study.

4. The two bioequivalence studies under fasting and non-fasting conditions used two different reference drug lots, #22265 and 22427, respectively. Please provide the rationale for not using the same reference drug lot number for both the fasting and non-fasting studies.

Sincerely yours,

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

Cyclosporine
100 mg Hard Gelatin Capsule
50 mg Hard Gelatin Capsule
25 mg Hard Gelatin Capsule
ANDA #65-003
Reviewer: Z.Z. Wahba
V:\FIRMSAM\ABBOTT\LRS&REV\65003a3.300

Abbott Laboratories
Abbott Park, IL
Submission Dated:
March 30, 200[illegible]

REVIEW OF AN AMENDMENT

BACKGROUND

- The firm previously submitted two in vivo bioequivalence studies (single-dose under fasting and fed conditions) comparing its test product Cyclosporine Hard Gelatin Capsule, 100 mg, to the reference listed drug Novartis' Neoral® (Cyclosporine Soft Gelatin Capsule), 100 mg. The submission was reviewed and was found acceptable by the Division of Bioequivalence (the submission was dated 5/28/99).

- On May 28, 1999, the firm submitted an amendment requesting a change in the capsule shell formulation of its drug products Cyclosporine Hard Gelatin Capsule, 100 mg, 50 mg, and 25 mg. The change was deletion of the [ ] from the capsule shell composition to meet international requirements. The firm stated that there are no changes to the capsule formulation, and no change in the manufacturing process through encapsulation. The submission was reviewed by the Division of Bioequivalence. Deficiency comments were communicated to the firm.

- The firm intends to market the capsules packaged in foil blisters.

- In this submission, the firm has responded to the deficiency comments and included additional information.

DEFICIENCY COMMENT #1

For all cases where you decided that dissolution testing was necessary, please provide data to support this decision. That is, dissolution data should be presented for samples of the same strength, age, batch, and storage conditions to compare results of testing.

RESPONSE TO DEFICIENCY COMMENT #1

The firm stated that during stability testing of Cyclosporine Capsules, dissolution testing was done only if the sample failed to pass the dissolution specification with the

method. testing was done using capsules from the same stability sample used for testing.

The firm provided comparison of dissolution methods for cyclosporine capsules, 100 mg, 50 mg and 25 mg for the following batches (also see Appendix 1 volume B6.1): 100 mg strength (biobatch #28-687-AR-03, and batches #45-001-AR-03 and #45-5-AR-03, both without the), 50 mg strength (batch #29-719-AR-03, with and batch #45-999-AR-03, without), 25 mg strength (batch #29-686-AR-03, with and batches #45-998-AR-03 and #45-003-AR-03, both without .
The dissolution testing was performed on aged batches 6 to 34 months (see page #18, volume B6.1)

Summary of the above comparison: The dissolution data obtained using dissolution methods showed that the dissolution rate of aged cyclosporine capsules is faster and less variable (lower S.D. values) with the method compared to the method. All samples tested with the method met the dissolution specification, not less than ✓ % (Q) of the labeled amount of the drug (cyclosporine) in the dosage form dissolved in 60 minutes. For samples tested with the method, all samples tested met the dissolution specification (NLT % in 60 minutes), except lot #28-687-AR-03 (100 mg, 34 months old, 25°C/60%RH, packaged in Aclar blisters), and lot #45-998-AR-03 (25 mg, 3, 4 and 6 months old, 40°C/75%RH, packaged in foil/foil blisters). It should noted that the firm provided some dissolution data on the 25 mg strength using volume of ✓ mL. The method requested by the Division of Bioequivalence is published in the Pharmacopeial Forum, 1998, 24 (3):6155-6159 and recommends a 500 mL media volume for testing the 25 mg strength.

DEFICIENCY COMMENT #2

Please compare dissolution profiles for your cyclosporine hard gelatin capsules using the FDA-recommended dissolution media (Tier 1, Pharmacopeial Forum, 1998, 24 (3):6155-6159) versus the identical media with the addition of ✓ . Please provide these comparative profiles for the following batches: 28-687-AR-03, 45-001-AR-03, 29-719-AR-03, 45-999-AR-03, 28-686-AR-03, and 45-998-AR-03. Please specify the amount and activity of added. Please specify the packaging system used for any aged batches of capsules studied, whether HDPE bottles (30 or 100 units per bottle) or blisters (Aclar or foil). If any new batches are tested, please include date of manufacture and method of storage.

RESPONSE TO DEFICIENCY COMMENT #2

The firm conducted dissolution testing (during March 2000) for a total of 14 lots including 6 lots that were manufactured on 11/99 or 12/99. The 14 lots covered 3 different aged lots (34 months

old, 14 months old and 3-4 months old). The information on the lot numbers, date of manufacture, packaging, storage, and date of test are provided in the appendix #2, pages 62-90, volume B6.1.

The dissolution testing data covered the original application lots (approximately 34 months old at the time of testing), the amendment lots (approximately 14 months old at the time of testing), and recently manufactured lots for validation purposes (approximately 3-4 months old at the time of testing). The firm stated that the amount of used was within the limits specified in the USP description of gastric fluid, simulated, and was the amount used in the validated methods for this product. was added to each media at g/L and had a labeled activity of units/mg of protein. The total activity was about Units per mL.

Note: Dissolution testing of the 25 mg capsules was conducted using a 500 mL volume of media as published in the Pharmacopeial Forum and as requested by the Division of Bioequivalence for these experiments. The firm proposes use of mL of dissolution medium for the 25 mg strength.

Summary of the provided dissolution testing data:
(see the attached Tables 1-14 and Figures 1-14)

The dissolution data from with addition of showed that addition of to media increases the rate of dissolution. The dissolution rate of aged cyclosporine capsules is faster and less variable (lower S.D. values at ≥ 30 min) with the media with added compare to dissolution in media without All samples tested with media with added met the dissolution specification not less than of the labeled amount of the drug in the dosage form dissolved in 60 minutes. For samples tested with method, all samples tested met the specification for the drug (NLT 60 minutes) except lot #28-687-AR-03 (100 mg, 34 months old, 25°C/60%RH, packaged in Aclar blisters), and lot #28-686-AR-03 (25 mg, 34 months old, 25°C/60%RH, packaged Aclar blisters). See Tables #1 and #3, and Figures #1 and #3.

The results from 14 month old lots showed that with did increase the rate of dissolution for the 100 mg, and 25 mg capsules (Tables/Figures #4, 5, 7, and 8). Dissolution profiles for the 50 mg capsules tested with and without were similar (Table/Figure #6).

The results from 3-4 month old lots showed that all lots passed the product specification with the method. For the 100 mg capsules and 25 mg, dissolution profiles were similar for capsules tested with and without See the attached Tables

and Figures #9-14. There were no lots provided for the 50 mg strength of this group (3-4 month old lots).

The results of the 25 mg capsules were more variable than for the 100 mg capsules. One lot showed a faster dissolution rate when [redacted] was added to the media (see Table and Figure #13). Another lot showed an apparent decrease in the dissolution rate after 60 minutes using the [redacted] method without [redacted] (see Table and Figure #12). The firm attributed these differences in the level of variability associated with testing the 25 mg capsules to the volume of dissolution medium [redacted] mL). It should be noted that the firm is proposing [redacted] mL for the 25 mg capsules. The firm pointed out that the dissolution rate from 25 mg capsules tested with [redacted] mL of dissolution medium is consistently slower and more variable compared to dissolution rate conducted in [redacted] mL of dissolution medium. Its interpretation for these differences is that the volume of dissolution medium influences [redacted] within the dissolution vessel and the observed differences in the rate of dissolution for the 25 mg capsules may be attributed to the difference in the [redacted] Release profiles for the 25 mg capsules in [redacted] mL of dissolution medium are similar to release profiles for the 50 mg and 100 mg capsules which are tested in [redacted] mL of dissolution medium. Therefore, the firm proposes that the dissolution method using [redacted] mL of dissolution medium be the method used for the 25 mg capsules.

Conclusion: The rate of dissolution decreases with age and the variability of releases increase with age. For aged capsules, the presence of [redacted] in the dissolution medium increases the rate of dissolution and decreases the dissolution rate variability. For freshly manufactured capsules, [redacted] had no significant effect on the rate of dissolution. These observations are consistent with formation of crosslinks in the gelatin capsule shell as the capsules age during storage.

DEFICIENCY COMMENT #3

Using the [redacted] testing method, the dissolution data show that ≥ [redacted] % of the drug is released after 20 minutes of the dissolution testing. Please note that this method may not be adequately discriminatory for routine dissolution testing.

RESPONSE TO DEFICIENCY COMMENT #3

The firm stated that the [redacted] test method was not intended to be used for routine dissolution testing. It was used for testing when a sample fails to meet the dissolution specifications when tested with the [redacted] test method. Capsules from freshly manufactured lots showed rapid release with complete release at 20 minutes using the [redacted] dissolution method. Using the [redacted] dissolution method, the dissolution rate of the test product has

been shown to decrease with time. The testing method has been shown to increase the rate of dissolution for aged capsules, consistent with the expectation for cross-linked gelatin capsules. For fresh lots, the dissolution profiles (Tables and Figures #9-14) are not faster than the initial profiles. This suggests that the did not affect the dissolution of the capsule fill. While the firm did not test the innovator product with the test method, it should be noted that the innovator product demonstrates a dissolution profile faster (generally more than % released at 20 minutes) than the test product when tested with the method.

DEFICIENCY COMMENT #4

Please provide scientific evidence to support the claim that capsule shell cross-linkage causes the variability observed when testing is performed without

RESPONSE TO DEFICIENCY COMMENT #4

Undissolved capsule material (suspected obtained from the dissolution testing of cyclosporine 100 mg capsules lot 28-687-AR-03 was isolated and analyzed using (Capsules were packaged in Aclar blisters and stored for approximately 34 months at 25°C/60% RH prior to dissolution testing.) The purpose was to determine if possible IR absorbances due to cross-linking bonds were present in the material. Samples of the suspected were analyzed and compared with spectra of virgin capsule shells (i.e., capsule shells which were never exposed to capsule fill), cyclosporine and cyclosporine capsule fill. A small absorbance band at about cm^{-1} was observed for the suspected This is consistent with of which are both found in cross-linking products of gelatin.

The firm states that cross-linking of gelatin reduces the solubility of the gelatin. The cross-linked gelatin may form a often described as a thin, water-insoluble film around the capsule contents. Breaking of the film is necessary to release the capsule contents. This film does not disrupt easily under the gentle agitation present in dissolution testing and the variability in the breaking of the film causes increased variability in the dissolution test results. The dissolution data provided in response to items 1 and 2 provide additional evidence that cross-linking of the gelatin capsule shells occurs over time. The addition of to the medium increases the release rate and decreases the variability due to the ability of to digest the cross-lined gelatin.

The firm cited three published reports which demonstrate the decrease in the rate of dissolution and increased variability in dissolution due to conditions expected to be caused by capsule

shell cross-linking which occurred during aging. The articles cited are:
Pharmaceutical Research, Vol. 10, No. 9, 1295-1300, 1993.
Pharmaceutical Technology, March, 72-86, 1989.
Pharmaceutical Technology, June, 76-83, 1993.

GENERAL COMMENTS (NOT TO BE RELEASED UNDER FOI)

All samples tested with with met the dissolution specification not less than (Q) of the labeled amount of the drug in the dosage form dissolved in 60 minutes.

The dissolution data of innovator product demonstrate a dissolution profile faster (generally more than % released at 20 minutes) than the test product when tested with the method.

Data included in this submission support the firm's conclusion that gelatin cross-linking occurs during storage of cyclosporine hard gelatin capsules. The gelatin crosslinking results in slower rates of dissolution as the capsules age.

Various studies have demonstrated that gelatin capsules with a moderate degree of crosslinking are bioequivalent to fresh capsules (Aikman et al., 1998, Pharmacopeial Forum, 24(5):7045-7050; Dey et al., 1993, Pharmaceutical Research, 10(9):1295-1300). Findings also suggest that gelatin capsules with extensive crosslinking are not bioequivalent to fresh capsules and also do not meet dissolution specifications even with the addition of enzyme to the media.

The dissolution method that is published in the Pharmacopeial Forum, 1998, 24 (3):6155-6159, recommends a two tiered dissolution approach:
Method A (Tier 1)
Method B (Tier 2), if the dissolution testing fails method A.

Based on the dissolution data and information provided, the firm conducted the dissolution testing in accordance with the dissolution method that is published in the USP.

Note: Recommendations for testing of hard and soft gelatin capsules have been revised in USP 24 Supplement 1, page #2696, Section <711>. The amount of added to media of pH 6.8 or lower should not exceed activity of Units per mL of media.

The firm's request to change the dissolution media volume from mL to mL, for testing the 25 mg strength is acceptable.

The firm's response to the deficiency comments #1-4 is acceptable.

RECOMMENDATIONS

The information that was submitted by Abbott Laboratories in support of elimination of the from the capsule shell of its Cyclosporine Hard Gelatin is acceptable.

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

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Concur: Date: 7/18/00

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

Attachment #1

Information on Gengraf Capsules Tested

Table No.	Strength	Lot	Description	Package	Mfr. Date
1	100 mg	28-687-AR-03	Registration lot	Aclar Blisters	5/97
2	50 mg	29-719-AR-03	Registration lot	Aclar Blisters	6/97
3	25 mg	28-686-AR-03	Registration lot	Aclar Blisters	6/97
4	100 mg	45-001-AR-03	Amendment lot	Foil blisters	11/98
5	25 mg	45-998-AR-03	Amendment lot	Foil blisters	11/98
6	50 mg	45-999-AR-03	Amendment lot	Foil blisters	11/98
7	100 mg	45-005-AR-03	Supportive lot	Foil blisters	11/98
8	25 mg	45-003-AR-03	Supportive lot	Foil blisters	11/98
9	100 mg	59-479-AF-00	Validation lot	Bulk	11/99
10	100 mg	60-500-AF-00	Validation lot	Bulk	12/99
11	100 mg	60-503-AF-00	Validation lot	Bulk	12/99
12	25 mg	59-478-AF-00	Validation lot	Bulk	11/99
13	25 mg	60-501-AF-00	Validation lot	Bulk	12/99
14	25 mg	60-504-AF-00	Validation lot	Bulk	12/99

Registration and amendment lots were stored in the stated packages at 25°C/60% RH prior to testing. The validation lots were stored in bulk containers (in a inside a foil liner with 6 desiccant packs between the two liners) at 67-77°F (19-25°C), relative humidity not more than 60% prior to testing (per ANDA storage conditions within bulk holding time).

Table 1A. Lot 28-687-AR-03, 100 mg, tested with the LDAO Dissolution Method, Tier 1
Manufactured 5/97, Packaged in Aclar Blisters, Tested on March 6, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	[illegible]	59.8	50.6	60.1	67.6	76.2
SD	13.3	27.0	30.7	30.7	29.1	23.1
Low	0.2	0.2	0.2	0.2	8.4	43.9
High	43.3	79.4	83.9	94.8	97.4	97.5

Table 1B. Lot 28-687-AR-03, 100 mg, tested with the LDAO Dissolution Method, Tier 1 with Pepsin
Manufactured 5/97, Packaged in Aclar Blisters, Tested on March 23, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	22.2	64.0	89.1	99.7	101.8	101.0
SD	12.8	23.3	11.6	2.4	1.3	1.2
Low	1.8	27.9	61.3	95.5	99.9	98.8
High	47.4	97.9	102.4	103.0	103.9	103.5

Figure 1. Lot 28-687-AR-03, 100 mg, Results from Tables 1A and 1B

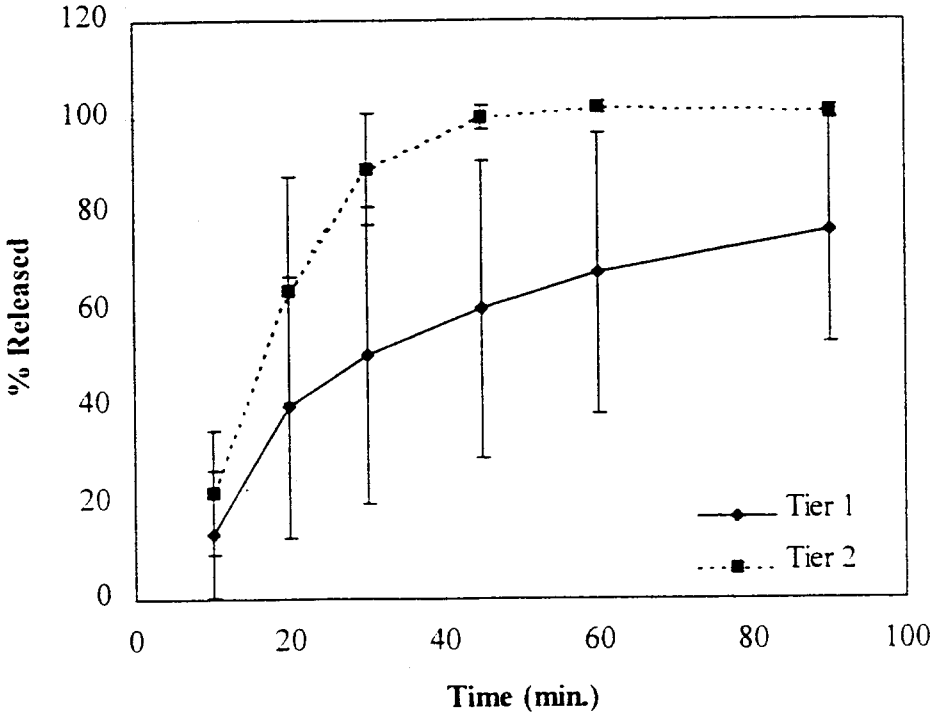


Table 2A. Lot 29-719-AR-03, 50 mg, tested with the LDAO Dissolution Method, Tier 1
Manufactured 6/97, Packaged in Aclar Blisters, Tested on March 20, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	11.1	49.0	65.9	76.5	83.2	91.5
SD	11.8	19.6	21.3	23.2	17.7	15.3
Low	0.4	21.3	28.3	32.9	59.8	68.1
High	32.2	81.3	95.4	110.2	105.5	105.8

Table 2B. Lot 29-719-AR-03, 50 mg, tested with the LDAO Dissolution Method, Tier 1 with Pepsin
Manufactured 6/97, Packaged in Aclar Blisters, Tested on March 22, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	56.1	92.1	100.9	104.3	104.6	104.7
SD	13.9	10.2	5.4	2.2	2.0	1.9
Low	27.9	77.2	87.2	99.5	100.5	102.1
High	75.5	104.3	106.0	107.5	106.8	107.2

Figure 2. Lot 29-719-AR-03, 50 mg, Results from Tables 2A and 2B

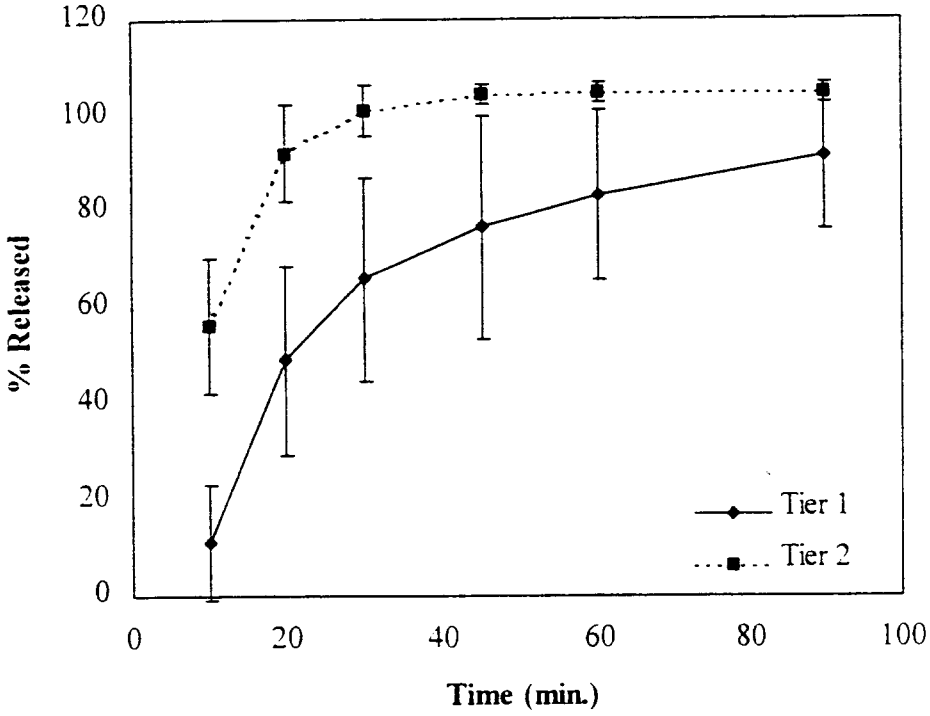


Table 3A. Lot 28-686-AR-03, 25 mg, tested with the LDAO Dissolution Method, Tier 1
Manufactured 6/97, Packaged in Aclar Blisters, Tested on March 23, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	5.6	13.2	23.6	38.6	48.0	59.6
SD	9.9	18.4	21.7	25.9	29.6	28.9
Low	0.3	0.3	0.3	6.7	9.0	15.4
High	34.7	57.8	73.3	84.9	92.6	94.2

Table 3B. Lot 28-686-AR-03, 25 mg, tested with the LDAO Dissolution Method, Tier 1 with Pepsin
Manufactured 6/97, Packaged in Aclar Blisters, Tested on March 22, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	73.7	90.5	95.7	98.3	98.9	99.6
SD	21.0	13.1	11.0	8.1	6.9	3.3
Low	38.5	54.7	63.1	73.3	77.7	90.6
High	96.4	101.3	103.0	103.6	103.2	103.0

Figure 3. Lot 28-686-AR-03. 25 mg, Results from Tables 3A and 3B

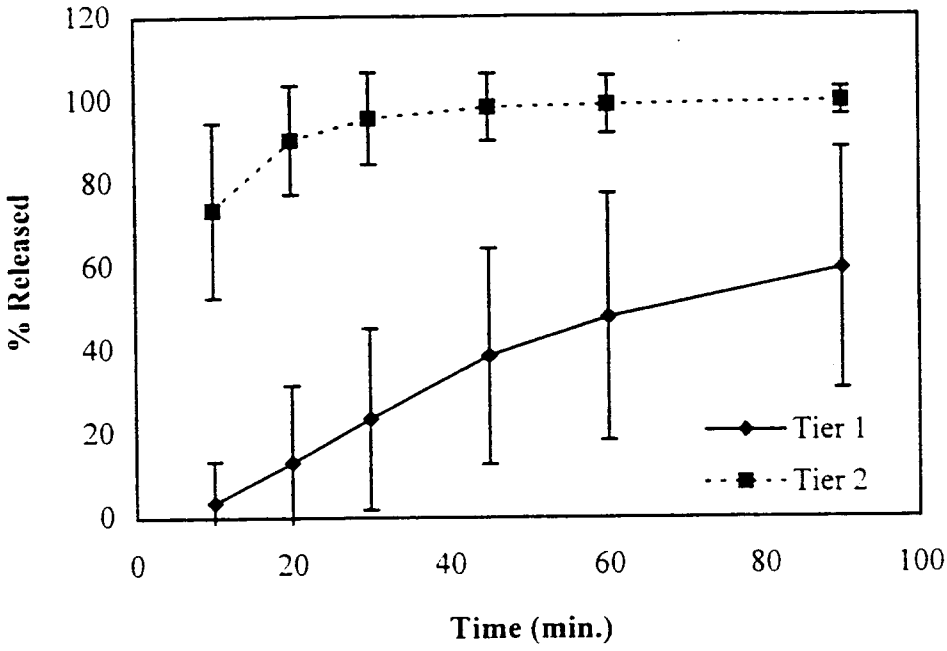


Table 4A. Lot 45-001-AR-03, 100 mg, tested with the LDAO Dissolution Method, Tier 1
Manufactured 11/98, Packaged in Foil Blisters, Tested on March 6, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	38.9	82.3	92.8	98.1	100.0	100.8
SD	15.5	13.7	11.4	7.0	4.6	1.9
Low	17.6	59.2	69.4	81.2	87.5	98.0
High	66.9	103.4	104.0	104.1	103.6	103.7

Table 4B. Lot 45-001-AR-03, 100 mg, tested with the LDAO Dissolution Method, Tier 1 with Pepsin
Manufactured 11/98, Packaged in Foil Blisters, Tested on March 23, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	54.0	92.6	100.5	101.4	101.8	101.5
SD	12.2	7.3	1.6	1.7	0.9	0.9
Low	34.3	80.6	98.0	96.7	100.4	100.0
High	69.3	102.6	102.8	103.3	103.5	102.7

Figure 4. Lot 45-001-AR-03, 100 mg, Results from Tables 4A and 4B

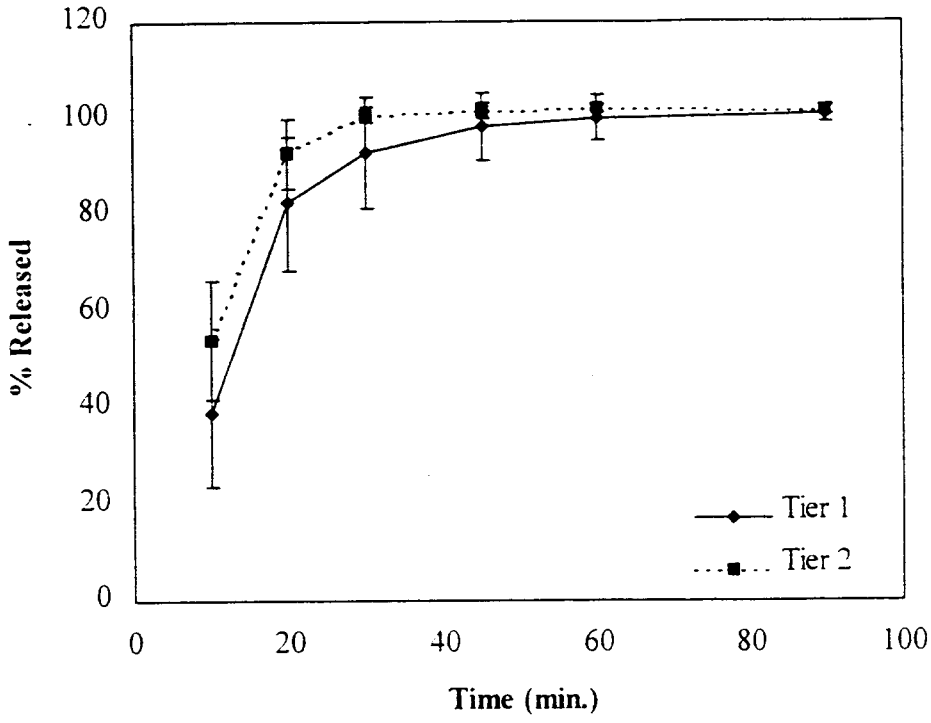


Table 5A. Lot 45-998-AR-03, 25 mg, tested with the LDAO Dissolution Method, Tier 1
Manufactured 11/98, Packaged in Foil Blisters, Tested on March 23, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	37.7	61.9	74.8	82.6	88.1	88.8
SD	25.8	24.1	19.2	17.6	16.0	12.5
Low	0.3	18.9	28.8	36.5	46.0	58.8
High	82.2	98.4	100.1	97.9	100.9	101.9

Table 5B. Lot 45-998-AR-03, 25 mg, tested with the LDAO Dissolution Method, Tier 1 with Pepsin
Manufactured 11/98, Packaged in Foil Blisters, Tested on March 22, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	53.5	77.8	86.3	92.7	96.0	98.9
SD	26.4	24.7	18.6	13.2	11.5	8.9
Low	0.7	27.4	47.5	56.2	62.9	71.1
High	84.5	101.7	101.6	102.1	102.2	103.5

Figure 5. Lot 45-998-AR-03, 25 mg, Results from Tables 5A and 5B

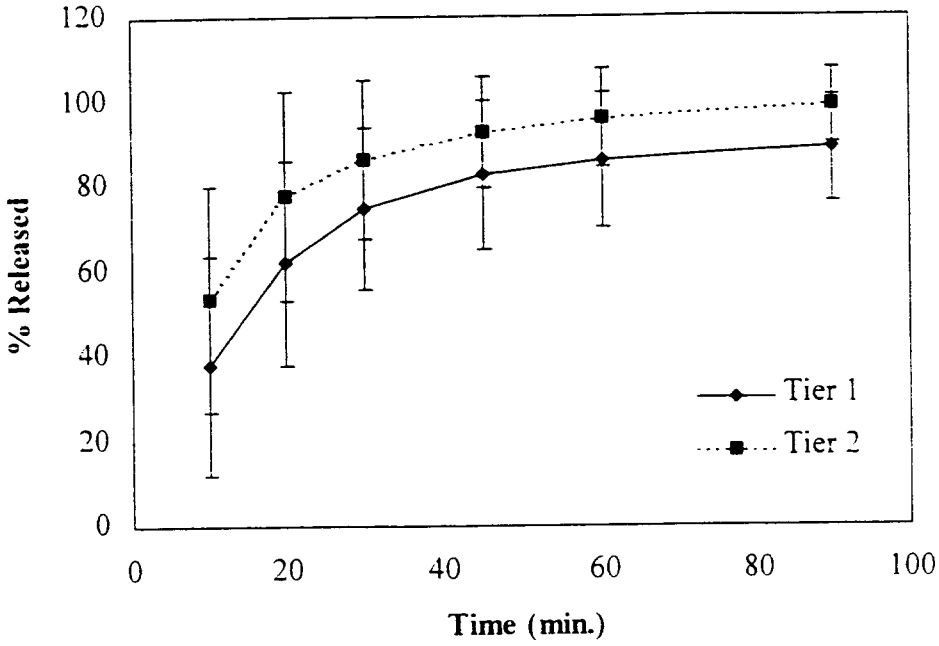


Table 6A. Lot 45-999-AR-03, 50 mg, tested with the LDAO Dissolution Method, Tier 1
Manufactured 11/98, Packaged in Foil Blisters, Tested on March 20, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	65.1	92.8	96.1	98.2	98.1	98.8
SD	19.1	13.7	11.4	10.1	9.1	6.9
Low	34.6	51.5	60.4	66.6	69.7	77.9
High	96.6	102.4	102.5	105.2	103.5	103.9

Table 6B. Lot 45-999-AR-03, 50 mg, tested with the LDAO Dissolution Method, Tier 1 with Pepsin
Manufactured 11/98, Packaged in Foil Blisters, Tested on March 22, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	65.0	92.3	98.0	100.0	100.7	101.8
SD	16.3	8.8	5.6	4.2	3.4	2.4
Low	47.4	76.8	85.8	89.7	94.7	97.9
High	87.3	104.3	104.5	104.6	104.7	104.6

Figure 6. Lot 45-999-AR-03, 50 mg. Results from Tables 6A and 6B

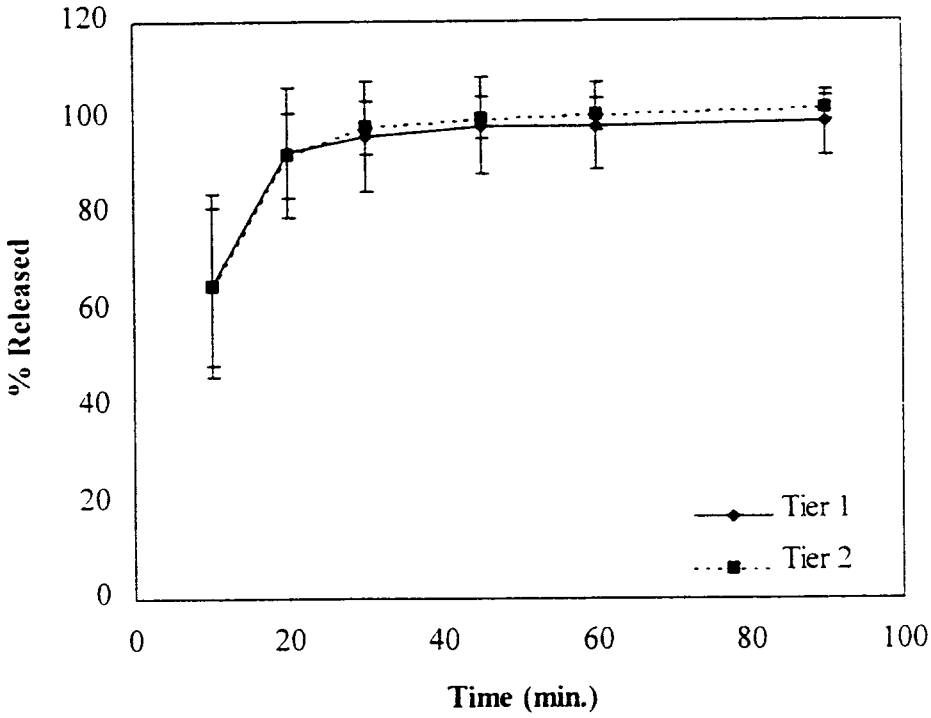


Table 7A. Lot 45-005-AR-03, 100 mg, tested with the LDAO Dissolution Method, Tier 1
Manufactured 11/98, Packaged in Foil Blisters, Tested on March 7, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7	4					
8						
9						
10						
11						
12						
Mean	26.9	66.3	80.7	86.9	89.2	90.1
SD	13.7	20.3	18.5	14.6	13.3	11.3
Low	5.9	29.8	38.2	46.0	49.2	55.0
High	47.6	88.3	98.9	97.2	96.1	98.1

Table 7B. Lot 45-005-AR-03, 100 mg, tested with the LDAO Dissolution Method, Tier 1 with Pepsin
Manufactured 11/98, Packaged in Foil Blisters, Tested on March 23, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	48.3	85.7	97.2	100.0	100.8	100.8
SD	14.9	11.2	6.5	2.9	1.4	0.8
Low	28.4	60.9	77.7	91.0	96.7	99.0
High	83.4	100.5	101.7	101.8	102.0	101.7

Figure 7. Lot 45-005-AR-03, 100 mg, Results from Tables 7A and 7B

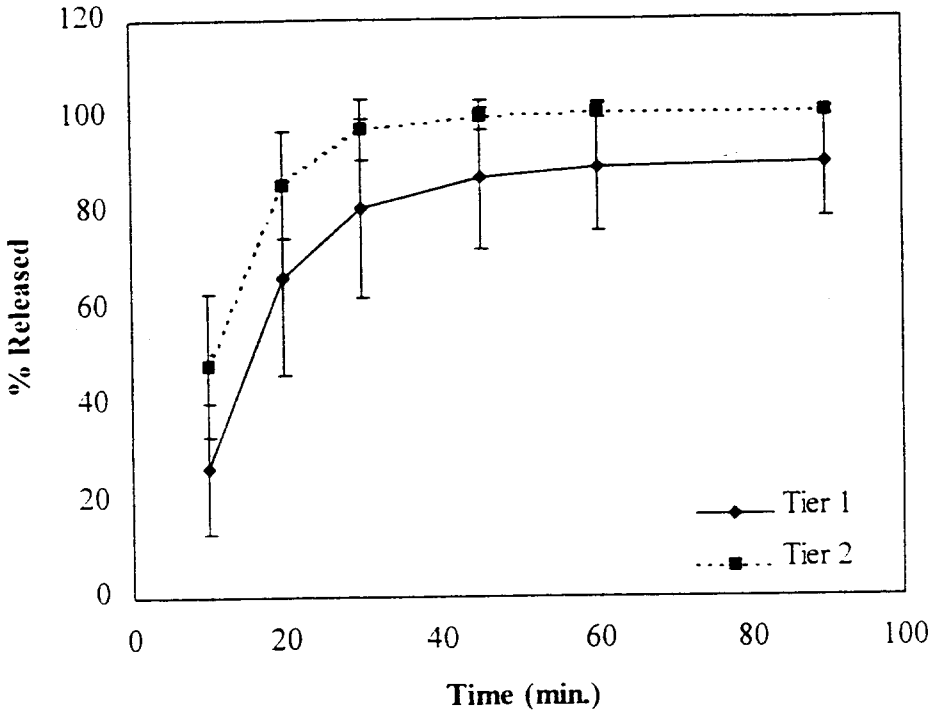


Table 8A. Lot 45-003-AR-03, 25 mg, tested with the LDAO Dissolution Method, Tier 1
Manufactured 11/98, Packaged in Foil Blisters, Tested on March 23, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	47.2	66.2	75.4	82.7	88.3	93.1
SD	35.7	34.2	28.4	23.1	18.5	14.3
Low	4.7	21.1	31.3	38.9	44.7	53.2
High	90.2	100.3	102.9	102.4	103.1	102.9

Table 8B. Lot 45-003-AR-03, 25 mg, tested with the LDAO Dissolution Method, Tier 1 with Pepsin
Manufactured 11/98, Packaged in Foil Blisters, Tested on March 22, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	74.9	86.8	92.4	95.2	97.3	98.7
SD	19.5	16.9	15.4	12.1	8.2	6.1
Low	34.6	47.8	56.9	69.5	73.4	79.7
High	101.8	103.1	103.3	105.2	103.2	102.4

Figure 8. Lot 45-003-AR-03, 25 mg, Results from Tables 8A and 8B

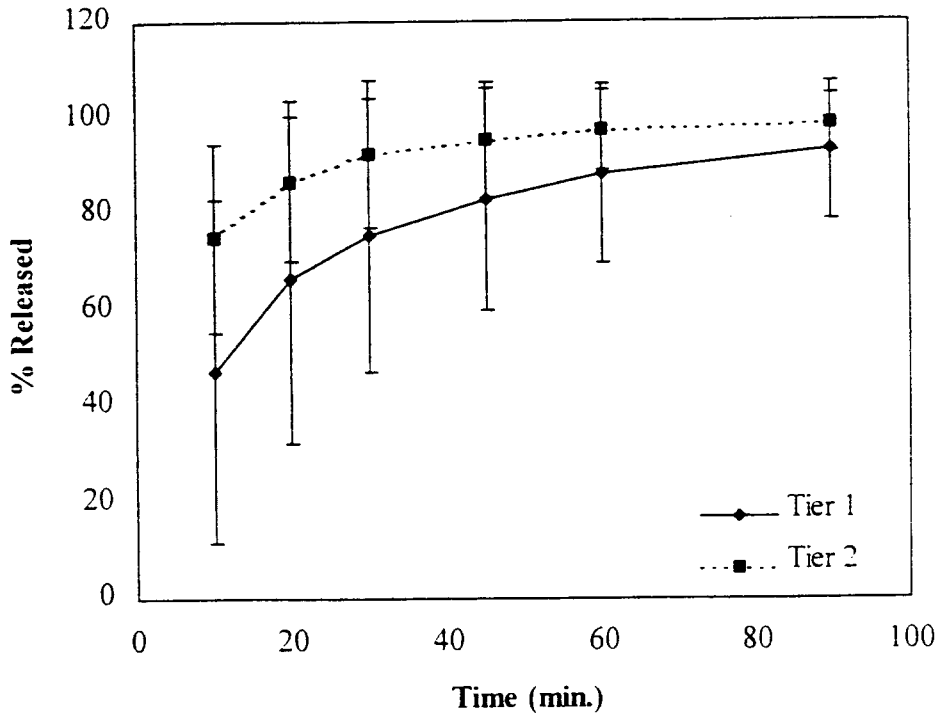


Table 9A. Lot 59-479-AF-00, 100 mg, tested with the LDAO Dissolution Method, Tier 1
Manufactured 11/99, Bulk Container Storage, Tested on March 21, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	52.0	94.0	99.6	100.1	99.6	99.4
SD	13.5	4.3	2.3	1.7	1.6	1.7
Low	31.3	85.6	94.3	96.2	96.7	95.8
High	71.0	100.8	103.1	102.3	102.7	102.2

Table 9B. Lot 59-479-AF-00, 100 mg, tested with the LDAO Dissolution Method, Tier 1 with Pepsin
Manufactured 11/99, Bulk Container Storage, Tested on March 23, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	58.1	96.8	101.7	102.6	102.5	102.4
SD	12.1	4.8	1.1	0.6	0.5	0.6
Low	40.4	85.4	100.0	101.6	101.7	101.3
High	76.0	101.7	103.1	103.5	103.1	103.5

Figure 9. Lot 59-479-AF-00. 100 mg, Results from Tables 9A and 9B

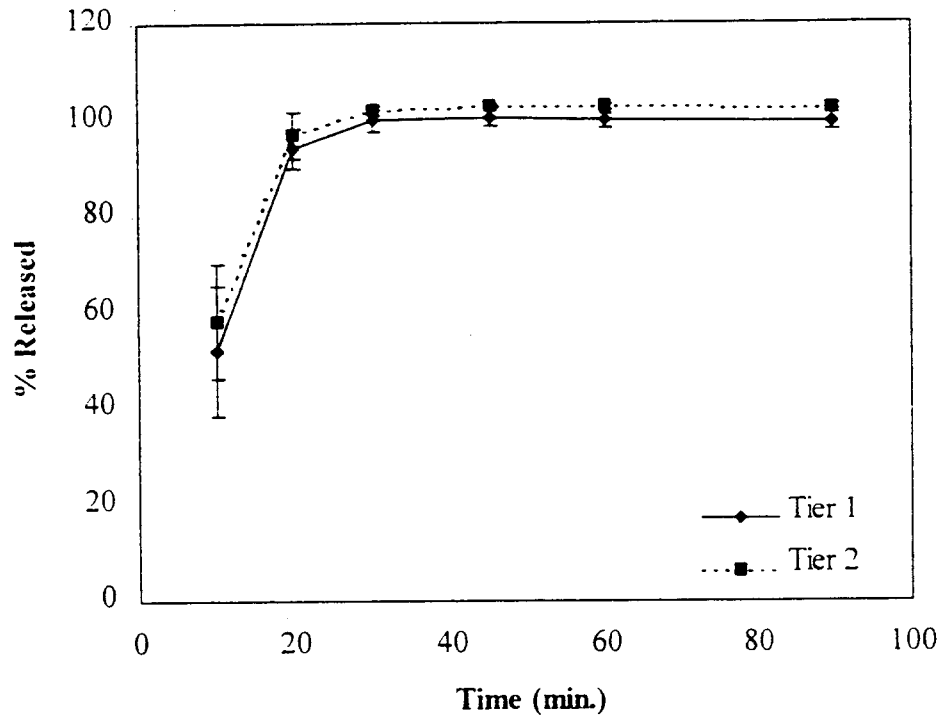


Table 10A. Lot 60-500-AF-00, 100 mg, tested with the LDAO Dissolution Method, Tier 1
Manufactured 12/99, Bulk Container Storage, Tested on March 21, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1				[illegible]2.4		100.4
2				[illegible].8		99.2
3				[illegible]		101.6
4						100.0
5						95.3
6						99.0
7						
8						
9						
10						
11						
12						
Mean	58.4	93.9	99.0	101.0	100.4	98.8
SD	12.0	5.6	2.9	2.0	1.5	1.9
Low	34.9	84.0	94.3	98.9	98.2	95.3
High	74.1	99.5	102.9	105.4	103.0	101.6

Table 10B. Lot 60-500-AF-00, 100 mg, tested with the LDAO Dissolution Method, Tier 1 with Pepsin
Manufactured 12/99, Bulk Container Storage, Tested on March 24, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	51.8	92.6	100.2	102.0	102.5	102.1
SD	9.8	6.4	2.6	0.9	1.3	0.8
Low	31.1	80.8	92.9	100.7	100.3	100.3
High	73.3	101.0	102.3	103.4	105.7	103.1

Figure 10. Lot 60-500-AF-00, 100 mg, Results from Tables 10A and 10B

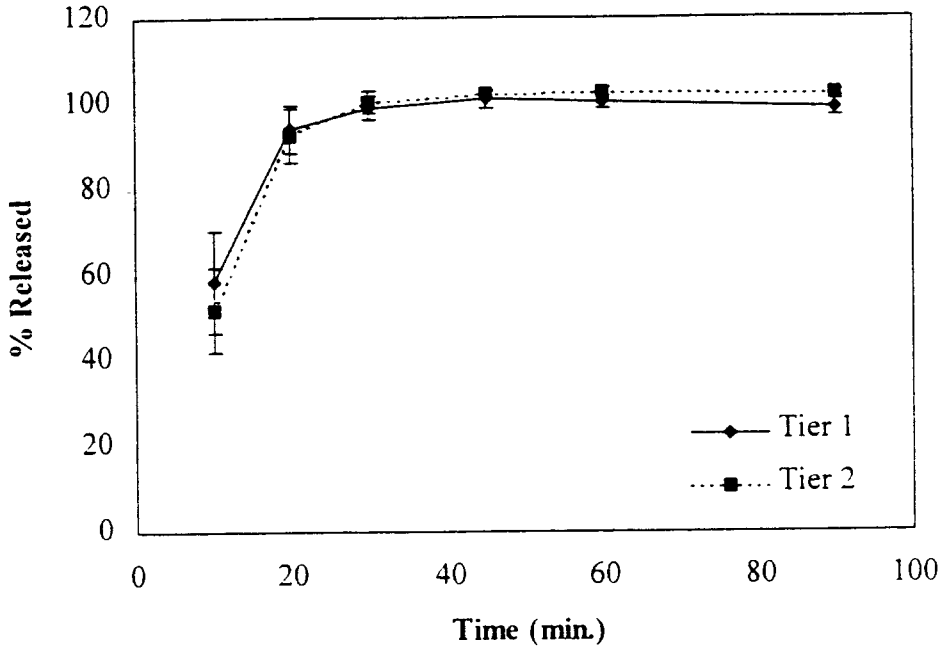


Table 11A. Lot 60-503-AF-00, 100 mg, tested with the LDAO Dissolution Method, Tier 1
Manufactured 12/99, Bulk Container Storage, Tested on March 21, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	63.6	99.4	101.9	102.2	101.6	100.6
SD	9.5	3.0	1.2	1.2	1.5	2.1
Low	48.7	93.2	99.7	100.0	98.6	96.2
High	78.1	103.4	103.1	103.6	103.1	103.1

Table 11B. Lot 60-503-AF-00, 100 mg, tested with the LDAO Dissolution Method, Tier 1 with Pepsin
Manufactured 12/99, Bulk Container Storage, Tested on March 24, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Mean	51.1	92.9	99.2	100.4	100.4	100.4
SD	8.9	4.1	1.7	0.6	0.5	0.6
Low	37.6	84.6	94.8	99.5	99.3	99.3
High	67.9	98.4	100.6	101.3	101.0	101.3

Figure 11. Lot 60-503-AF-00, 100 mg, Results from Tables 11A and 11B

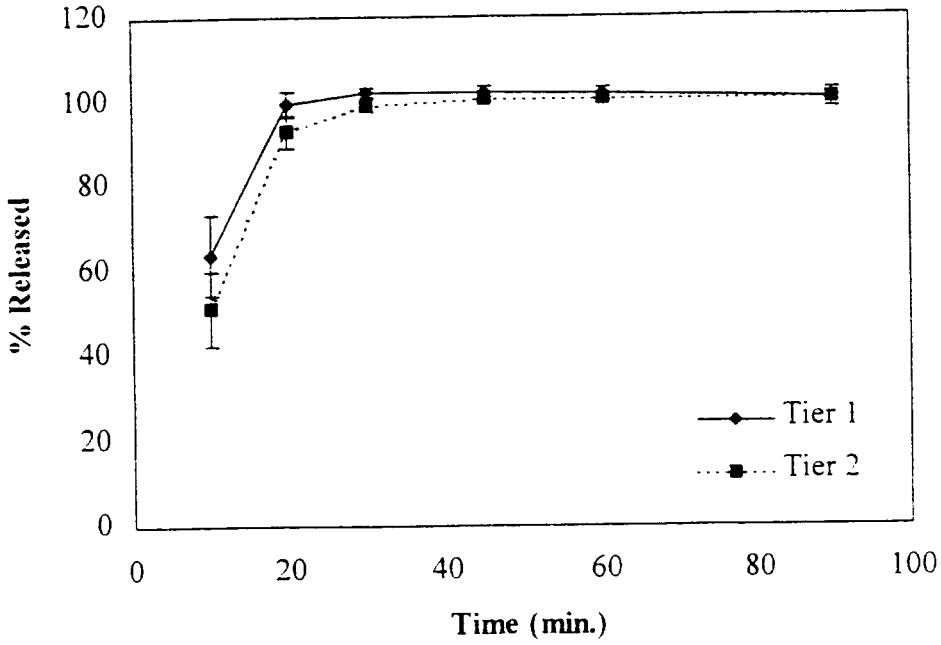


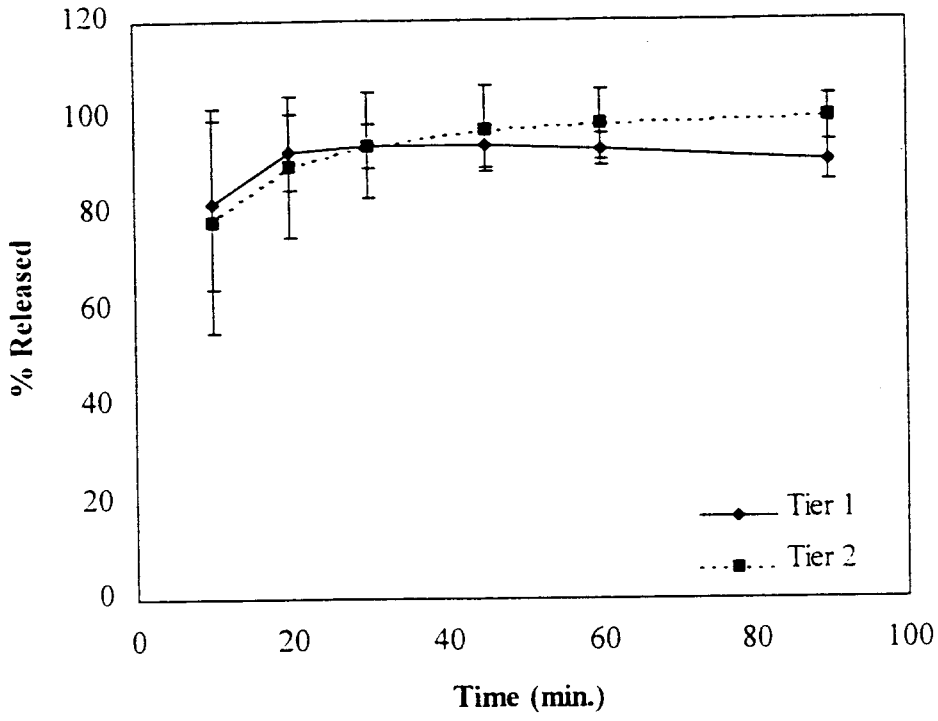
Table 12A. Lot 59-478-AF-00, 25 mg, tested with the LDAO Dissolution Method, Tier 1
Manufactured 11/99, Bulk Container Storage, Tested on March 23, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	81.9	92.9	94.0	93.9	95.1	90.7
SD	17.5	7.8	4.5	4.4	3.2	4.1
Low	53.8	78.3	84.5	86.3	86.3	85.1
High	103.2	103.3	99.9	100.0	98.4	97.9

Table 12B. Lot 59-478-AF-00, 25 mg, tested with the LDAO Dissolution Method, Tier 1 with Pepsin
Manufactured 11/99, Bulk Container Storage, Tested on March 23, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6					99.4	
7						
8						
9						
10						
11						
12						
Mean	78.5	89.8	94.2	97.5	98.4	99.7
SD	23.2	14.6	10.9	9.0	7.2	4.7
Low	35.8	50.1	62.0	70.8	76.2	85.3
High	127.9	103.7	101.5	103.1	103.2	103.6

Figure 12. Lot 59-478-AF-00, 25 mg, Results from Tables 12A and 12B



NOTE: The Tier 1 dissolution data for this lot show a small apparent decrease in the amount released at 90 minutes which is not seen for the Tier 2 data for this lot, or for the Tier 1 or Tier 2 data for the other samples presented. The HPLC chromatograms showed no additional peaks indicating there was no problem with degradation of the samples. The apparent difference between the results at 60 and 90 minutes is not significant, due to the variability associated with this test method (i.e., 500 mL of dissolution medium).

Table 13A. Lot 60-501-AF-00, 25 mg, tested with the LDAO Dissolution Method, Tier 1
Manufactured 12/99, Bulk Container Storage, Tested on March 23, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	59.6	80.0	86.0	89.1	90.0	91.0
SD	23.0	20.9	16.9	13.2	12.0	9.3
Low	20.9	36.3	53.0	65.5	68.3	70.8
High	97.3	100.8	101.6	103.2	103.4	103.2

Table 13B. Lot 60-501-AF-00, 25 mg, tested with the LDAO Dissolution Method, Tier 1 with Pepsin
Manufactured 12/99, Bulk Container Storage, Tested on March 23, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	71.0	91.5	97.6	98.8	99.6	100.3
SD	18.3	9.3	5.1	4.3	3.0	2.0
Low	44.3	76.9	88.0	90.9	92.5	95.0
High	93.6	102.0	102.5	102.6	102.4	102.0

Figure 13. Lot 60-501-AF-00, 25 mg, Results from Tables 13A and 13B

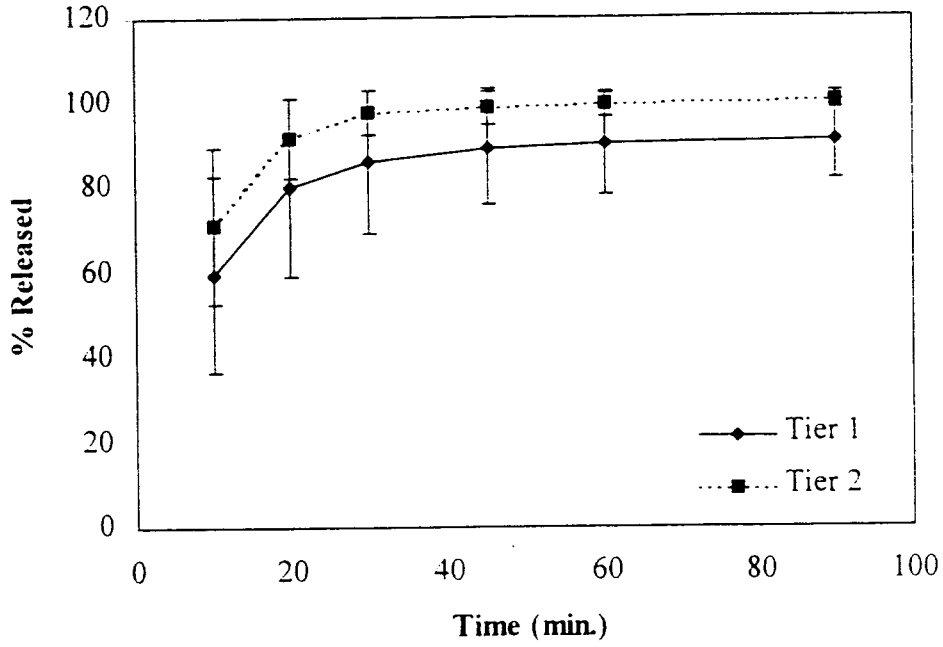


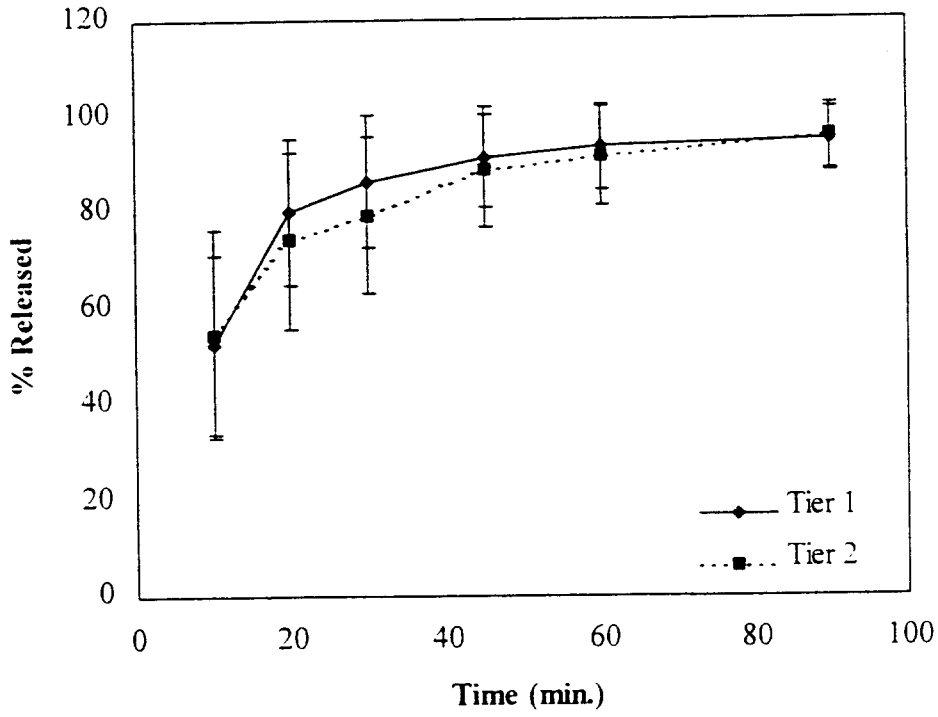
Table 14A. Lot 60-504-AF-00, 25 mg, tested with the LDAO Dissolution Method, Tier 1
Manufactured 12/99, Bulk Container Storage, Tested on March 23, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	52.5	80.0	86.3	91.3	93.5	95.0
SD	18.6	15.3	13.8	10.5	8.8	6.6
Low	12.7	54.4	65.7	70.1	74.1	78.5
High	84.8	99.1	102.1	101.3	101.5	100.4

Table 14B. Lot 60-504-AF-00, 25 mg, tested with the LDAO Dissolution Method, Tier 1 with Pepsin
Manufactured 12/99, Bulk Container Storage, Tested on March 23, 2000

Run #	% Released					
	10 min.	20 min.	30 min.	45 min.	60 min.	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	54.5	74.1	79.2	88.5	91.5	95.6
SD	21.7	18.3	16.3	11.8	10.2	6.8
Low	20.0	44.4	50.4	66.3	71.5	77.7
High	84.7	100.8	99.7	101.0	100.8	102.2

Figure 14. Lot 60-504-AF-00, 25 mg, Results from Tables 14A and 14B



Cyclosporine
100 mg Hard Gelatin Capsule
50 mg Hard Gelatin Capsule
25 mg Hard Gelatin Capsule
ANDA #65-003
Reviewer: Z.Z. Wahba

Abbott Laboratories
Abbott Park, IL
Submission Dated:
May 28, 1999
February 01, 2000
February 10, 2000
February 17, 2000
March 01, 2000

REVIEW OF AN AMENDMENT

BACKGROUND

1. The firm previously submitted two in vivo bioequivalence studies (single-dose under fasting and fed conditions) comparing its test product Cyclosporine Hard Gelatin Capsule, 100 mg, to the reference listed drug Novartis' Neoral® (Cyclosporine Soft Gelatin Capsule), 100 mg. The submission was reviewed and was found acceptable by the Division of Bioequivalence (see reviews dated 10/2/88 and 5/28/99).

2. The firm has submitted a supplement requesting a change in the capsule shell formulation of its drug products Cyclosporine Hard Gelatin Capsule, 100 mg, 50 mg, and 25 mg. The change was deletion of the from the capsule shell composition to meet international requirements. The firm stated that there are no changes to the capsule formulation, and no change in the manufacturing process through encapsulation (pp. 273, 377 and 378, vol. A3.1).

3. The dissolution data that was provided by the firm does not contain dissolution data on the fresh biobatch. The firm provided dissolution data for aged capsules packaged in bottles and blisters.

4. The firm intends to market the capsules packaged in foil blisters.

II. FORMULATION COMPOSITION
(SHOULD NOT BE RELEASED UNDER FOI)

Abbott's formulation for its Cyclosporine Hard Gelatin Capsule, 100 mg, 50 mg, and 25 mg, is included in this report (Attachment #1).

Note: No change in the formulation except the elimination of the from the capsule shell.

III. **DISSOULTION DATA**
(ALL DATA AND FIGURES SHOULD NOT BE RELEASED UNDER FOI)

1. The firm submitted the following data according to Method A (i.e. Tier 1) which was published in the Pharmacopeial Forum, May-June 1998.

The dissolution testing for the strengths 25 mg, 50 mg and 100 mg is summarized below:

Method A:	FDA method (also refer to The Pharmacopial Forum, dated May-June 1998)
Apparatus:	Apparatus II (Paddle) at 75 rpm
Medium:	0.1N HCl containing 0.2% LDAO (lauryldimethylamine-N-oxide) for 25 and 50 mg capsules; 0.1N HCl containing 0.4% LDAO for 100 mg capsules.
Volume:	500 mL for 25 mg strength and 1000 mL for 50 mg and 100 mg strengths (Per the Pharmacopeial Forum, dated May-June 1998).

Number of Units: 12 Capsules

Test products:

Abbott's Cyclosporine Hard Gelatin Capsules, 25 mg (lot #45-998-AR-03), 50 mg (lot #45-999-AR-03), and 100 mg (lot #45-001-AR-03).

Reference products:

Novartis' Neoral® (Cyclosporine Soft Gelatin Capsules), 25 mg (lot #300429), 50 mg (lot #238), and 100 mg (lot #22265). In addition, Abbott's Cyclosporine Hard Gelatin Capsules, 100 mg (bio-lot #28-687-AR-03).

Note: It is recommended in the monograph published in USP Pharmacopeial Forum 24 (3) that if this test fails, Method B should be performed. Method B is summarized below.

Method B (Tier 2):

	FDA method (also refer to The Pharmacopial Forum, dated May-June 1998)
Apparatus:	Apparatus II (Paddle) at 75 rpm
Medium:	Gastric fluid TS containing 0.2% LDAO for 25 and 50 mg capsules; gastric fluid TS containing 0.4% LDAO for 100 mg capsules.
Volume:	500 mL for 25 mg strength and 1000 mL for 50 mg and 100 mg strengths (Per the Pharmacopeial Forum, dated May-June 1998).

Number of Units: 12 Capsules

The preparation of Test Solutions is as follows:
(Reported on pages 2235 and 2241, USP 24)

Gastric Fluid, Stimulated, TS: Dissolve 2.0 g of sodium chloride and 3.2 g of purified pepsin, that is derived from porcine stomach mucosa, with an activity of 800 to 2500 units per mg of protein, in 7.0 mL of hydrochloric acid and sufficient water to make 1000 mL. This test solution has a pH of about 1.2.

Hydrochloric Acid, Normal (0.1 N): Dilute 8.5 mL of hydrochloric acid with water to 1000 mL. Standardize the solution as follows. Accurately weigh 0.5 g of tromethamine, previously dried at 105° for 3 hours. Dissolve in 50 mL of water, and add 2 drops of bromocresol green TS. Titrate with 0.1 N hydrochloric acid to a pale yellow endpoint. Calculate the normality. Each 12.114 mg of tromethamine is equivalent to 1 mL of 0.1 N hydrochloric acid.

Note: The normality of simulated gastric fluid (SGF), at 0.08 N, is slightly lower than that of 0.1 N HCl.

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): Cyclosporine Hard Gelatin Capsules, 100 mg
ANDA No.: 65-003
Firm: Abbott Laboratories
Submission Date: 5/28/99

I. Conditions for Dissolution Testing:

Method:	FDA method (also refer to The Pharmacopeial Forum, dated May-June 1998)
Apparatus:	USP Apparatus II (Paddle) at 75 rpm
Medium:	1000 mL of 0.1N HCl containing 0.4% LDAO
Test product:	Abbott's Cyclosporine Hard Gelatin Capsules, 100 mg (lot #45-001-AR-03)
Reference product:	Novartis' Neoral® Capsules, 100 mg (lot #22265)
Specification:	

II. Results of In Vitro Dissolution Testing:

Sampling Time (minutes)	Test Product: Abbott's Cyclosporine Hard Gelatin Capsules (without yellow color) Lot # 45-001-AR-03 Strength(mg) 100 mg			Reference Product: Abbott's Cyclosporine Hard Gelatin Capsules (BIO-LOT, with yellow color) Lot # 28-687-AR-03 Strength(mg) 100 mg		
	Mean %	Range	% CV	Mean %	Range	%CV
10	77.4		13.2	31.6		61.8
20	102.3		3.8	68.2		30.7
30	104.3		0.9	84.2		21.6
45	104.5		0.9	93.7		15.3
60	104.2		0.9	97.5		10.8
90	103.9		1.0	99.4		9.2

Table 2. In Vitro Dissolution Testing						
II. Results of In Vitro Dissolution Testing:						
Sampling Time (minutes)	Test Product: Abbott's Cyclosporine Hard Gelatin Capsules (without yellow color) Lot # 45-001-AR-03 Strength(mg) 100 mg			Reference Product: Novartis' Neoral® Capsules Lot # 22265 Strength(mg) 100 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	77.4		13.2	81.5		17.7
20	102.3		3.8	97.1		2.9
30	104.3		0.9	98.6		2.0
45	104.5		0.9	98.9		1.3
60	104.2		0.9	98.6		1.6
90	103.9		1.0	98.3		1.6

Table 3. In Vitro Dissolution Testing						
Drug (Generic Name): Cyclosporine Hard Gelatin Capsules, 50 mg ANDA No.: 65-003 Firm: Abbott Laboratories Submission Date: 5/28/99						
I. Conditions for Dissolution Testing:						
Method: FDA method (also refer to The Pharmacopeial Forum, dated May-June 1998) Apparatus: USP Apparatus II (Paddle) at 75 rpm Medium: 1000 mL of 0.1N HCl containing 0.2% LDAO Test product: Abbott's Cyclosporine Hard Gelatin Capsules, 50 mg (lot #45-999-AR-03) Reference product: Novartis' Neoral® Capsules, 50 mg (lot #238) Specification:						
II. Results of In Vitro Dissolution Testing:						
Sampling Time (minutes)	Test Product: Abbott's Cyclosporine Hard Gelatin Capsules (without yellow color) Lot # 45-999-AR-03 Strength(mg) 50 mg			Reference Product: Novartis' Neoral® Capsules Lot #238 Strength(mg) 50 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	84.1		11.4	93.2		5.1
20	100		1.6	100.1		1.0
30	100.4		1.4	100.6		0.8
45	100.3		1.1	100		0.7
60	100.2		1.2	100.2		1.0
90	99.5		1.4	100.3		0.9

Table 4. In Vitro Dissolution Testing						
Drug (Generic Name): Cyclosporine Hard Gelatin Capsules, 25 mg ANDA No.: 65-003 Firm: Abbott Laboratories Submission Date: 5/28/99						
I. Conditions for Dissolution Testing:						
Method:	FDA method **(also refer to The Pharmacopeial Forum, dated May-June 1998)**					
Apparatus:	USP Apparatus II (Paddle) at 75 rpm					
Medium:	500 mL of 0.1N HCl containing 0.2% LDAO					
Test product:	Abbott's Cyclosporine Hard Gelatin Capsules, 25 mg (lot #45-998-AR-03)					
Reference product:	Novartis' Neoral® Capsules, 25 mg (lot #300429)					
Specification:						
II. Results of In Vitro Dissolution Testing:						
Sampling Time (minutes)	Test Product: Abbott's Cyclosporine Hard Gelatin Capsules (without yellow color) Lot # 45-998-AR-03 Strength(mg) 25 mg			Reference Product: Novartis' Neoral® Capsules Lot #300429 Strength(mg) 25 mg		
	Mean %	Range	% CV	Mean %	Range	% CV
10	71.7		23.1	83.2		12.9
20	86.1		14.7	96.4		4.6
30	92.2		12.1	98.7		2.0
45	95.5		10.1	99.8		0.9
60	97.5		8.3	98.7		1.1
90	98.9		5.8	99.4		1.2

Content Uniformity and Assay Potency:
(from study amendment dated 2/1/200)

Test product	Content Uniformity (Mean %)	Assay (Average)
100 mg strength	102%	100.8
50 mg strength	100.8%	99.8
25 mg strength	101.2%	101.2

Comments on dissolution data:

As shown in Table 1 above, the reviewer compared the dissolution profile of the biobatch to that of the new batch without yellow color. Batch 45-001-AR-03, without yellow color, was fresh at the time of dissolution testing. The dissolution profiles generated using the biobatch #28-687-AR-03, which was aged 18 months at the time of initial dissolution testing, differ from the dissolution profiles of fresh batch #45-001-AR-03. A similar situation was observed for the dissolution data from the 25 mg and 50 mg strengths.

2. On 2/10/2000, in response to a request from the Agency, the firm submitted an amendment which includes dissolution data on two lots (with and without the yellow dye) for the 100 mg strength (lot #28-687-AR-03 and lot #45-001-AR-03). Lot #45-001-AR-03 was manufactured under low humidity conditions to minimize the product water content in response to physical stability issues seen at about 6 month time point for lot #28-687-AR-03. Dissolution data from lot #45-001-AR-03 (without yellow color), aged 12 months, were submitted. As previously stated, lot #28-687-AR-03 was aged 17/18 months at the time of initial dissolution testing. The firm stated that drug release using the LDOA (Tier 1) method was highly variable for 18 month (lot #28-687-AR-03) stability samples. The firm moved to Tier 2 to meet dissolution specifications for capsules packaged in Aclar

lity
the

Comment: The submission of 2/10/2000 did not contain dissolution data on the 25 and 50 mg strengths. The submitted dissolution profiles suggest that

However, because the normality and pH of simulated gastric fluid differs slightly from the Tier 1 dissolution media, this cannot be concluded with certainty.

3. On 2/17/2000, in response to a request from the Agency, the firm submitted dissolution data on 25 mg, 50 mg and 100 mg after 12 months and 24 months, applying the dissolution testing methods, Tier 1 and Tier 2. Again, the firm emphasized using the Tier 2 dissolution testing method as a more appropriate dissolution method for this product. The firm claims that the use of

Comment: No further scientific evidence was presented to support the firm's claim regarding the issue of formation of capsule shell cross-linkage.

4. In the 3/1/2000 amendment, the firm provided a number of dissolution profile figures for the 100 mg strength, Lot #28-687-AR-03 (test product Bio-lot, with yellow dye), lot #45-001-AR-03 (test product, without yellow dye), Lot #22265 (reference product bio-lot, used in the bioequivalence study under fasting conditions) and Lot #22427 (reference product bio-lot, used in the bioequivalence study under non-fasting conditions). The firm presented dissolution profiles using different testing methods (1) SDS test method, (2) Tier 1 method, and (3) Tier 2 mthod. All the figures are provided in Attachment #4. Note that dissolution data on freshly manufactured Lot #28-687-AR-03 obtained using the SDS method was originally submitted to ANDA 65-003 in March of 1998.

Comment:
(a) The Division of Bioequivalence previously commented on the SDS method and found it unacceptable for dissolution testing of Abbott's cyclosporine capsules.
(b) The Tier 1 testing method shows significant reduction in the rate of drug release with capsule aging. Also, the rate of drug release appears to vary with the type of storage. Stability appears better with blisters than in bottles of 30 or 100.
(c) The Tier 2 testing method shows a significant increase in the rate of drug release at early dissolution time points. The amount of drug released at 20 minutes exceeds 80%.

DEFICIENCIES

The following deficiencies have been identified:

1. For all cases where the firm decided that Tier 2 dissolution testing was necessary, data to support this decision were not provided. The firm should present dissolution data for samples of the same strength, age, batch, and storage conditions to compare results of Tier 1 versus Tier 2 testing.

2. The firm should compare dissolution profiles for their test product cyclosporine hard gelatin capsules using the FDA-recommended dissolution media (Tier 1, Pharmacopeial Forum, 1998, 24 (3):6155-6159) versus the identical media with the addition of The comparative dissolution profiles for the following batches: 28-687-AR-03, 45-001-AR-03, 29-719-AR-03, 45-999-AR-03, 28-686-AR-03, and 45-998-AR-03 should be provided. Information on the amount and activity of added should be submitted. In addition, the packaging system used for any aged batches of capsules studied, whether ottles (30 or 100 units per bottle) or blisters (Aclar or foil) should be specified. If any new batches are tested, the firm should include date of manufacture and method of storage.

3. Using the Tier 2 testing method, the dissolution data show that ≥ 80% of the drug is released after 20 minutes of the dissolution testing. This method may not be adequately discriminatory for routine dissolution testing.

4. The firm should provide scientific evidence to support the

RECOMMENDATIONS

The information that was submitted by Abbott Laboratories in support of elimination of the yellow dye from the capsule shell of its Cyclosporine Hard Gelatin is not complete due to the deficiencies cited above.

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT 3/3/00
FT INITIALLED BDAVIT 3/9/00

Concur: _____ Date: 3/13/00
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY DEFICIENCIES

ANDA: #65-003 APPLICANT: Abbott Laboratories

DRUG PRODUCT: Cyclosporine Hard Gelatin Capsules, 100 mg, 50 mg and 25 mg.

The Division of Bioequivalence has completed its review and has no further questions at this time. The following deficiencies have been identified:

1. For all cases where you decided that dissolution testing was necessary, please provide data to support this decision. That is, dissolution data should be presented for samples of the same strength, age, batch, and storage conditions to compare results of Tier 1 versus Tier 2 testing.

2. Please compare dissolution profiles for your cyclosporine hard gelatin capsules using the FDA-recommended dissolution media (Tier 1, Pharmacopeial Forum, 1998, 24 (3):6155-6159) versus the identical media with the addition of Please provide these comparative profiles for the following batches: 28-687-AR-03, 45-001-AR-03, 29-719-AR-03, 45-999-AR-03, 28-686-AR-03, and 45-998-AR-03. Please specify the amount and activity of added. Please specify the packaging system used for any aged batches of capsules studied, whether HDPE bottles (30 or 100 units per bottle) or blisters (Aclar or foil). If any new batches are tested, please include date of manufacture and method of storage.

3. Using the testing method, the dissolution data show that % of the drug is released after 20 minutes of the dissolution testing. Please note that this method may not be adequately discriminatory for routine dissolution testing.

4.

Sincerely yours,

/S/

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

Attachment #1

Section VII. Components and Composition Statements (continued)

Attachment #2

Figure 1. Gengraf Capsules, 100 mg Dissolution Profiles
Fresh Tier 1 and 18 month Tier 2

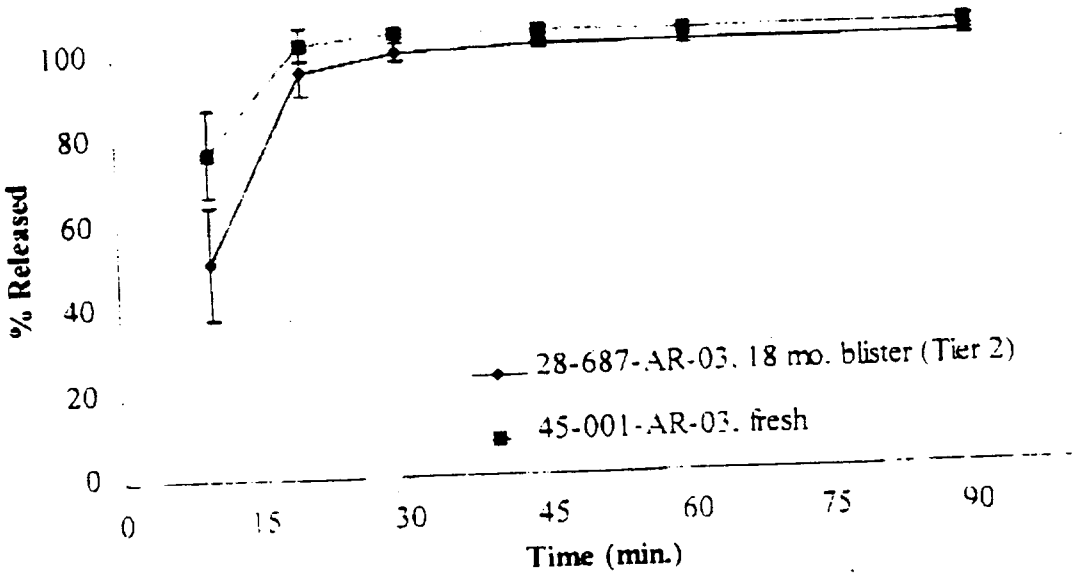
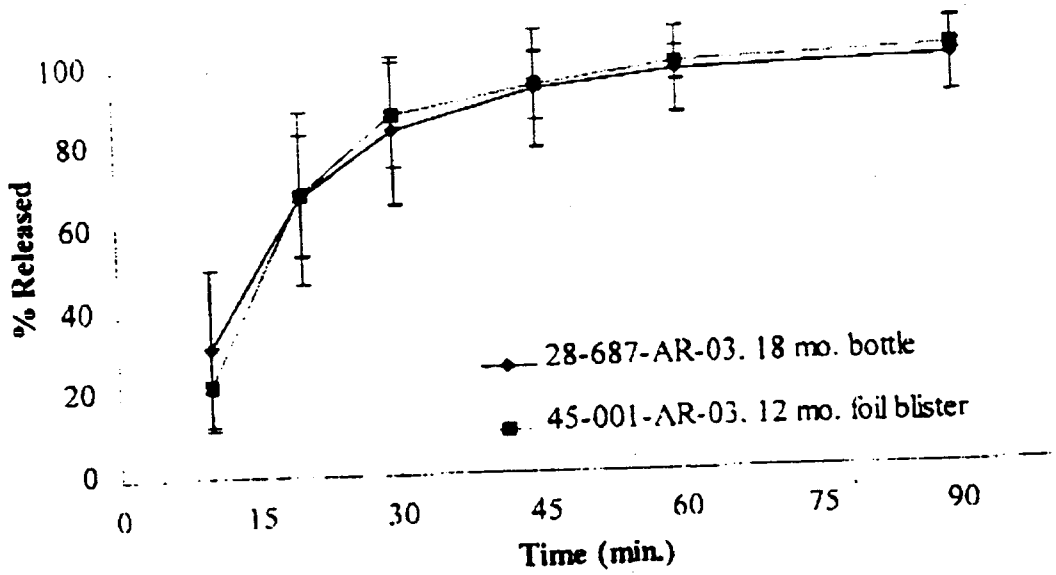


Figure 2. Gengraf Capsules, 100 mg Dissolution Profiles -12 and 18 month Tier 1



Attachment #2
(Continued)

Table 1: Dissolution Data for Cyclosporine Capsules [MODIFIED], 100 mg

Product	Testing		% Released						Ref.
			10	20	30	45	60	90 min	
Gengraf 28-687-AR-03 18 month HDPE Bottle	LDAO Tier 1 n=24	Mean	31.6	68.2	84.2	93.7	97.5	99.4	1
		%CV	61.8	30.7	21.6	15.3	10.8	9.2	
Gengraf 28-687-AR-03 18 mo. Aclar Blister	LDAO Tier 1 n=6	Mean	20.2	53.0	68.5	76.2	81.8	93.9	2
		%CV	44.9	40.0	44.0	35.5	30.7	10.6	
Gengraf 28-687-AR-03 18 mo. Aclar Blister	LDAO Tier 2 n=6	Mean	51.5	95.9	100.1	101.1	101.3	101.2	2
		%CV	25.9	5.8	2.2	0.9	0.9	0.7	
Gengraf 45-001-AR-03 Fresh capsules	LDAO Tier 1 n=12	Mean	77.4	102.3	104.3	104.5	104.2	103.9	3
		%CV	13.2	3.8	0.9	0.9	0.9	1.0	
Gengraf 45-001-AR-03 12 mo. Foil Blister	LDAO Tier 1 n=6	Mean	22.7	68.5	87.9	94.4	99.2	101.6	4
		%CV	42.8	21.8	14.8	9.6	4.1	1.4	
Neoral 22265	LDAO Tier 1 n=12	Mean	81.5	97.1	98.6	98.9	98.6	98.3	1
		%CV	17.7	2.9	2.0	1.3	1.6	1.6	
Neoral 22427	LDAO Tier 1 n=12	Mean	93.7	98.9	99.2	99.4	99.4	99.1	1
		%CV	3.1	0.7	0.7	0.6	0.5	0.5	

References

[1] Response to 10/9 deficiency letter submitted March 31, 1999

[2] DL99-31 submitted May 28, 1999 volume 7, p. 2279 (lot number was incorrectly identified as 28-697-AR-03)

[3] Data from R&D/99/053 LDAO method validation report submitted May 28, 1999 volume 2, p 376

[4] Individual capsule data are attached in Table 2.

Attachment #2
(Continued)

Table 2. Dissolution Data for Cyclosporine Capsules, 100 mg, Lot 45-001-AR-03 Capsules tested after storage in foil blisters at 25°C 60% RH for 12 months.

	% Released					
Run #	**10**	**20**	**30**	**45**	**60**	**90 min**
1	15.9	60.3	88.9	98.0	102.8	103.9
2	20.1	63.7	83.4	89.9	91.2	102.3
3	41.7	89.3	98.9	100.6	100.6	100.7
4	22.7	54.4	64.2	77.7	99.4	101.8
5	19.9	85.2	95.8	99.3	99.7	99.8
6	15.8	57.9	96.3	100.6	101.2	101.2
Mean	**22.7**	**68.5**	**87.9**	**94.4**	**99.2**	**101.6**
% CV	42.8	21.8	14.8	9.6	4.1	1.4

Attachment # 3

Table 1
Dissolution data on original lots of Gengraf Capsules after 24 months at 25°C/60%RH

Sample		% Released 10	20	30	45	60	90 min.
25mg Lot 28-686-AR-03							
Aclar Blister	Mean	45.9	82.4	87.0	94.7	97.6	98.1
	sd	27.6	29.5	13.3	8.2	5.5	3.3
HDPE Bottles of 30	Mean	48.4	77.9	87.8	98.8	101.1	99.7
	sd	31.8	31.7	22.2	3.6	3.7	2.3
HDPE Bottles of 100	Mean	61.2	85.7	87.9	94.3	100.1	101.5
	sd	46.0	32.6	29.8	17.6	3.8	1.7
50 mg Lot Lot 29-719-AR-03							
Aclar Blisters (Tier 2)	Mean	48.3	82.8	96.0	101.3	102.8	104.3
	sd	24.0	19.5	10.6	7.1	5.7	4.1
HDPE Bottles of 30	Mean	44.9	83.4	94.6	97.5	99.9	98.9
	sd	15.9	13.6	10.0	5.2	1.4	2.1
HDPE Bottles of 100	Mean	38.8	84.5	93.0	98.8	101.2	100.9
	sd	24.7	18.0	10.2	4.3	0.5	0.7
100 mg Lot Lot 28-687-AR-03							
Aclar Blisters (Tier 2)	Mean	23.4	83.1	98.2	102.8	104.1	104.2
	sd	5.5	10.2	3.1	1.6	0.8	0.6
HDPE Bottles of 30	Mean	16.0	47.6	69.5	92.9	99.8	101.7
	sd	7.3	16.9	14.1	12.3	5.3	4.2
HDPE Bottles of 100	Mean	14.2	35.1	56.0	90.2	95.6	100.2
	sd	5.7	13.8	19.3	10.5	9.3	4.0

Table 2
Dissolution data on modified lots of Gengraf Capsules after 12 months at 25°C/60%RH

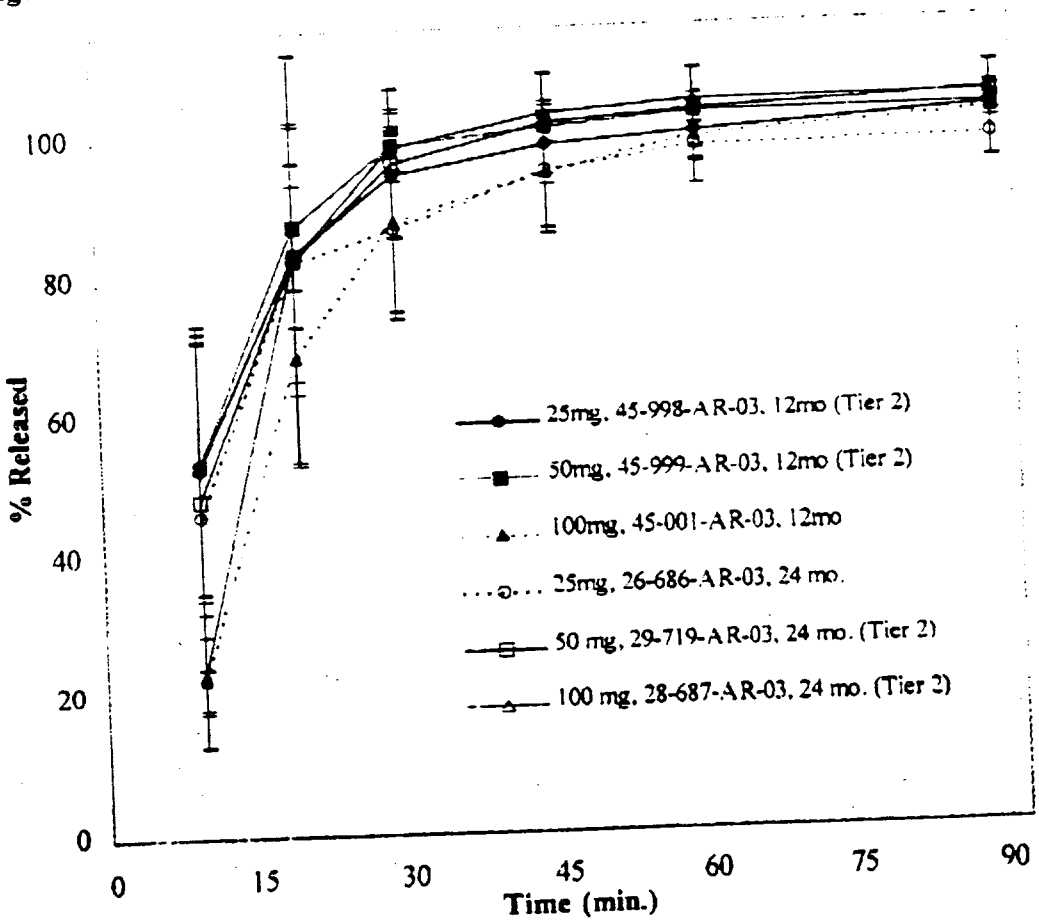
Sample		% Released 10	20	30	45	60	90 min.
25mg. 45-998-AR-03 (Tier 2)	Mean	52.6	83.4	94.5	98.3	99.8	102.2
	sd	18.3	18.3	8.8	5.7	4.2	1.2
50mg. 45-999-AR-03 (Tier 2)	Mean	53.3	87.4	98.7	100.7	102.5	102.5
	sd	18.1	9	5.2	2	1.7	1.2
100mg. 45-001-AR-03	Mean	22.7	68.5	87.9	94.4	99.2	101.6
	sd	9.7	14.9	13.0	8.6	4.1	1.4

Attachment #3
(continued)

Table 3
Tier 1 and Tier 2 dissolution data for Gengraf Capsules, 100 mg, Lot 45-001-AR-03

		% Released					
		10	20	30	45	60	90 min.
Tier 1	Mean	28.9	72.7	87.3	95.3	97.4	99.6
	sd	13.3	17.1	14.4	10.4	7.8	2.4
Tier 2	Mean	49.6	91.3	100.8	102.8	102.8	102.9
	sd	10.6	5.5	2.4	1.6	1.3	1.1

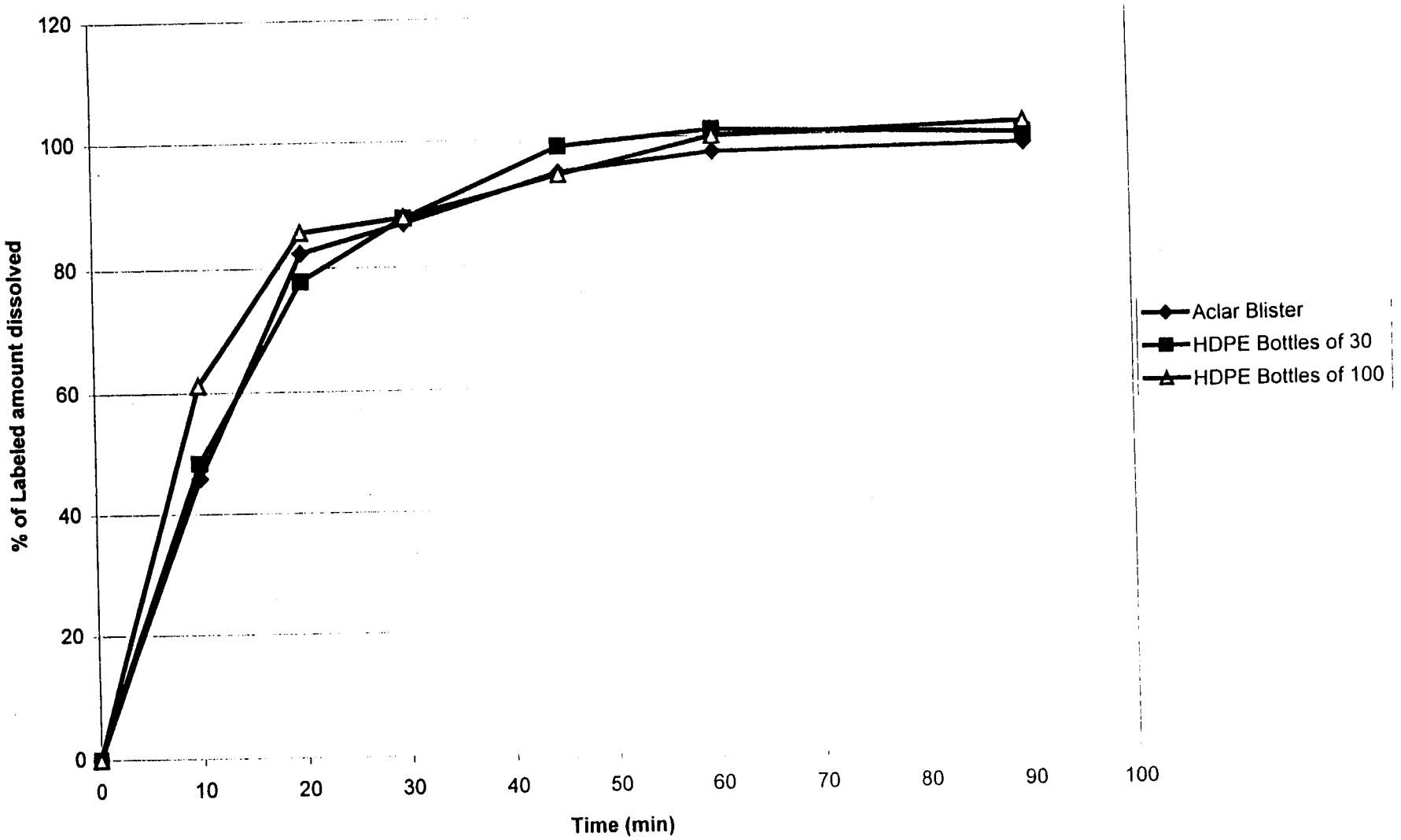
Figure 1. Gengraf Capsule Dissolution Profiles for Product Stored at 25°C/60%RH



Attachment #3
(Continued)

From Table #1 2/17/00

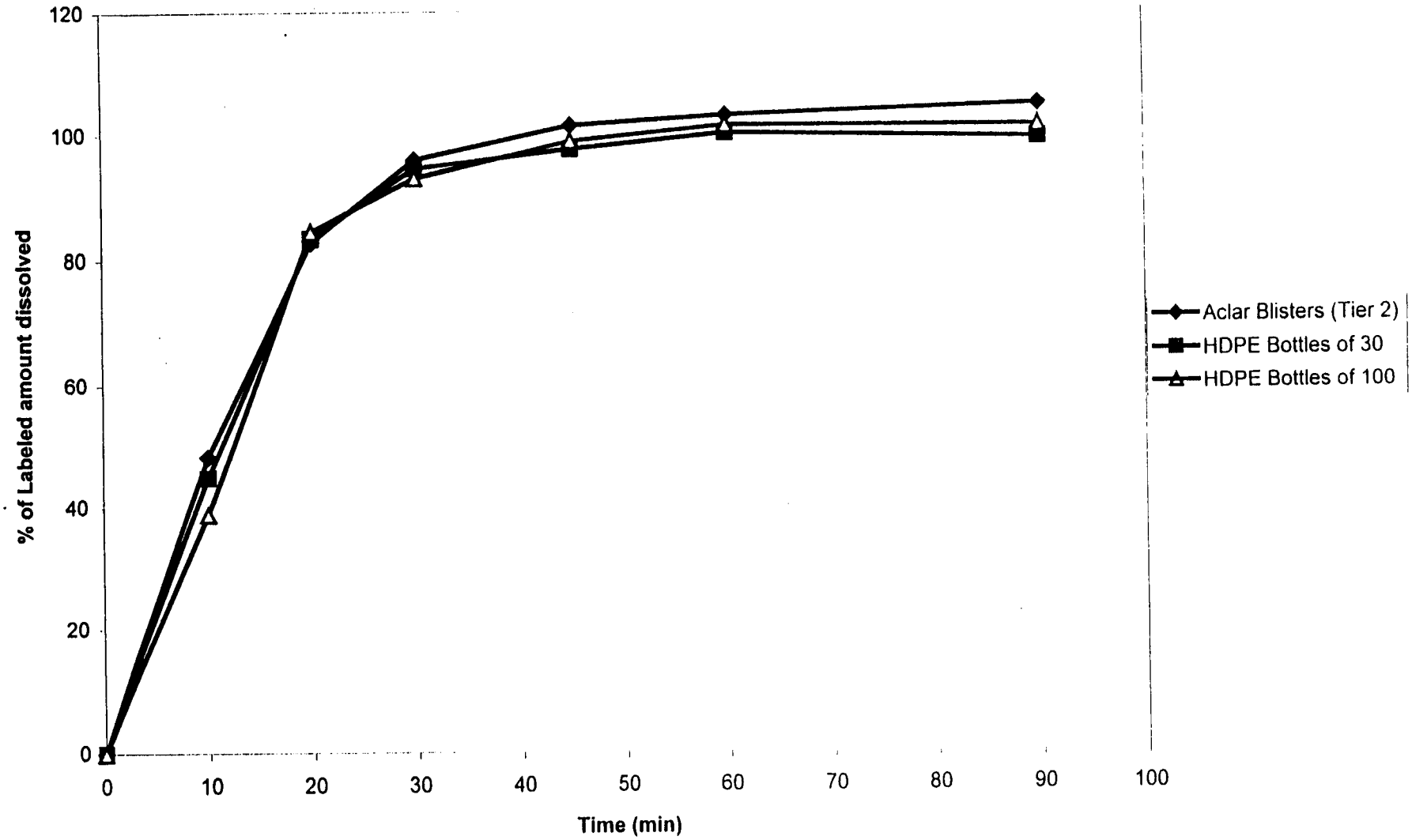
Dissolution Data, 24 months, 25 mg Lot 28-686-AR-03



Attachment #3
(Continued)

From
Table #1
2/17/00

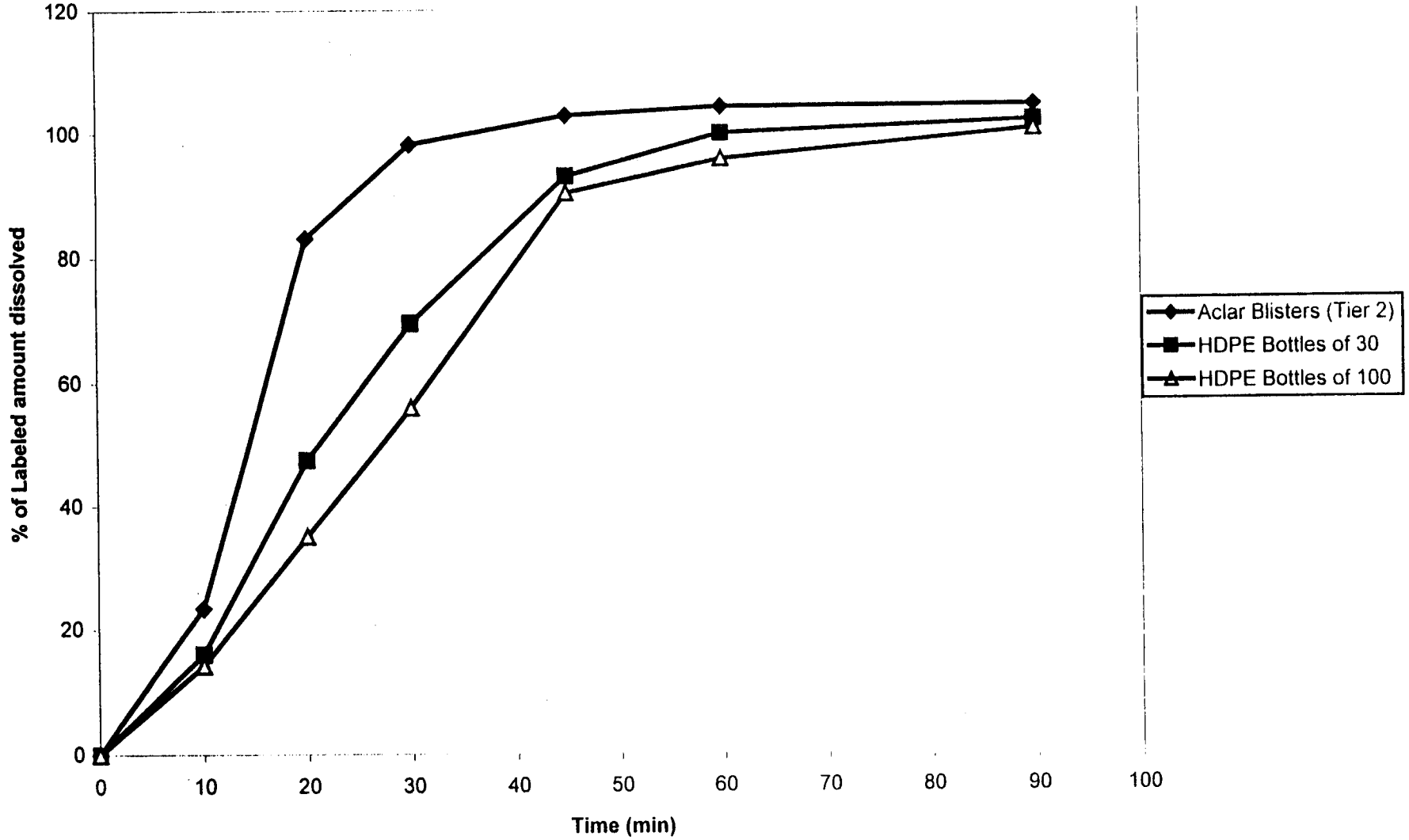
Dissolution Data, 24 months, 50 mg Lot 29-719-AR-03



attachment #3
(Continued)

from
Table #1
2/17/00

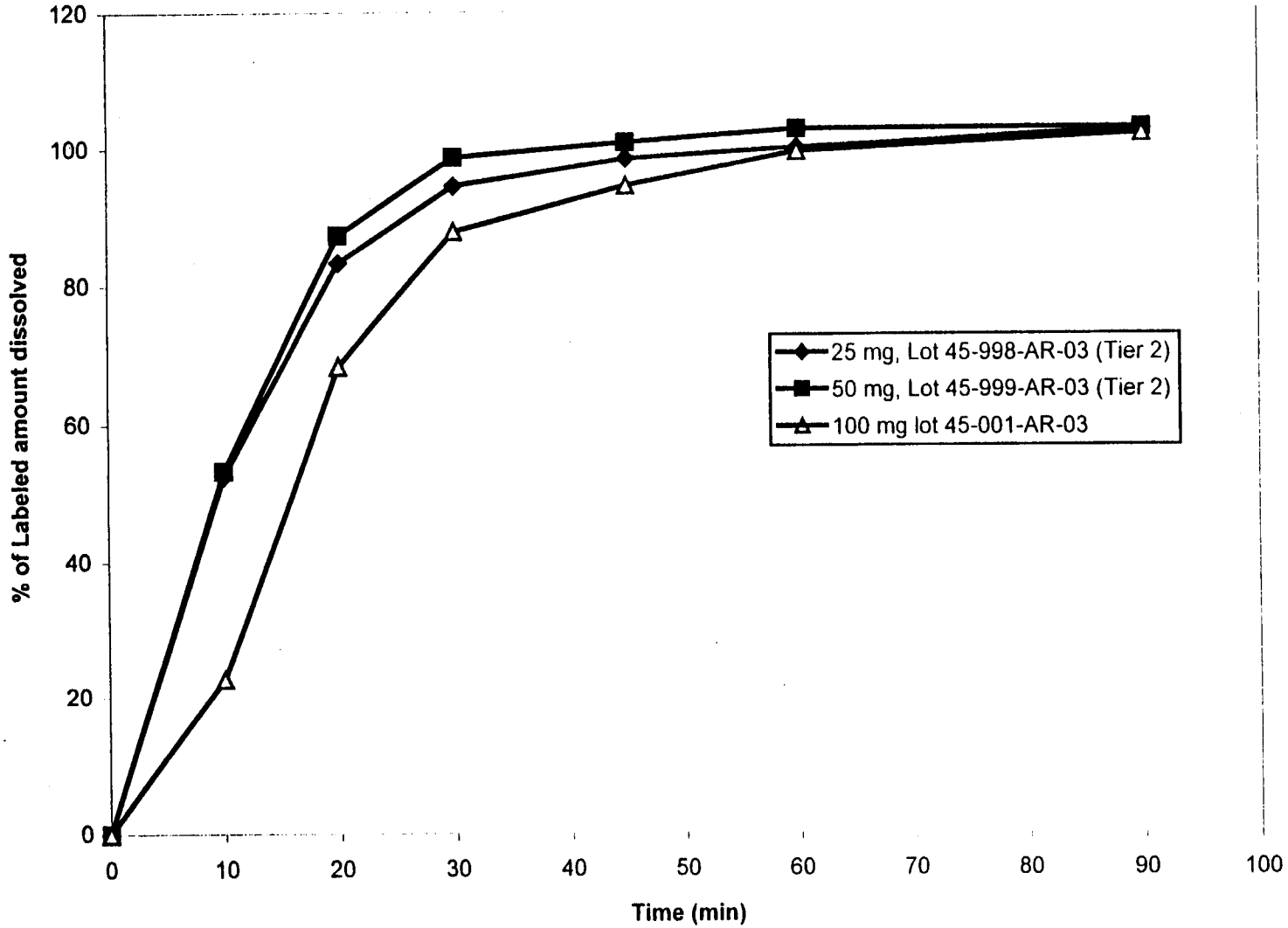
Dissolution Data, 24 months, 100 mg Lot 28-687-AR-03



Attachment #3
(Continued)

from Table #2 2/17/00

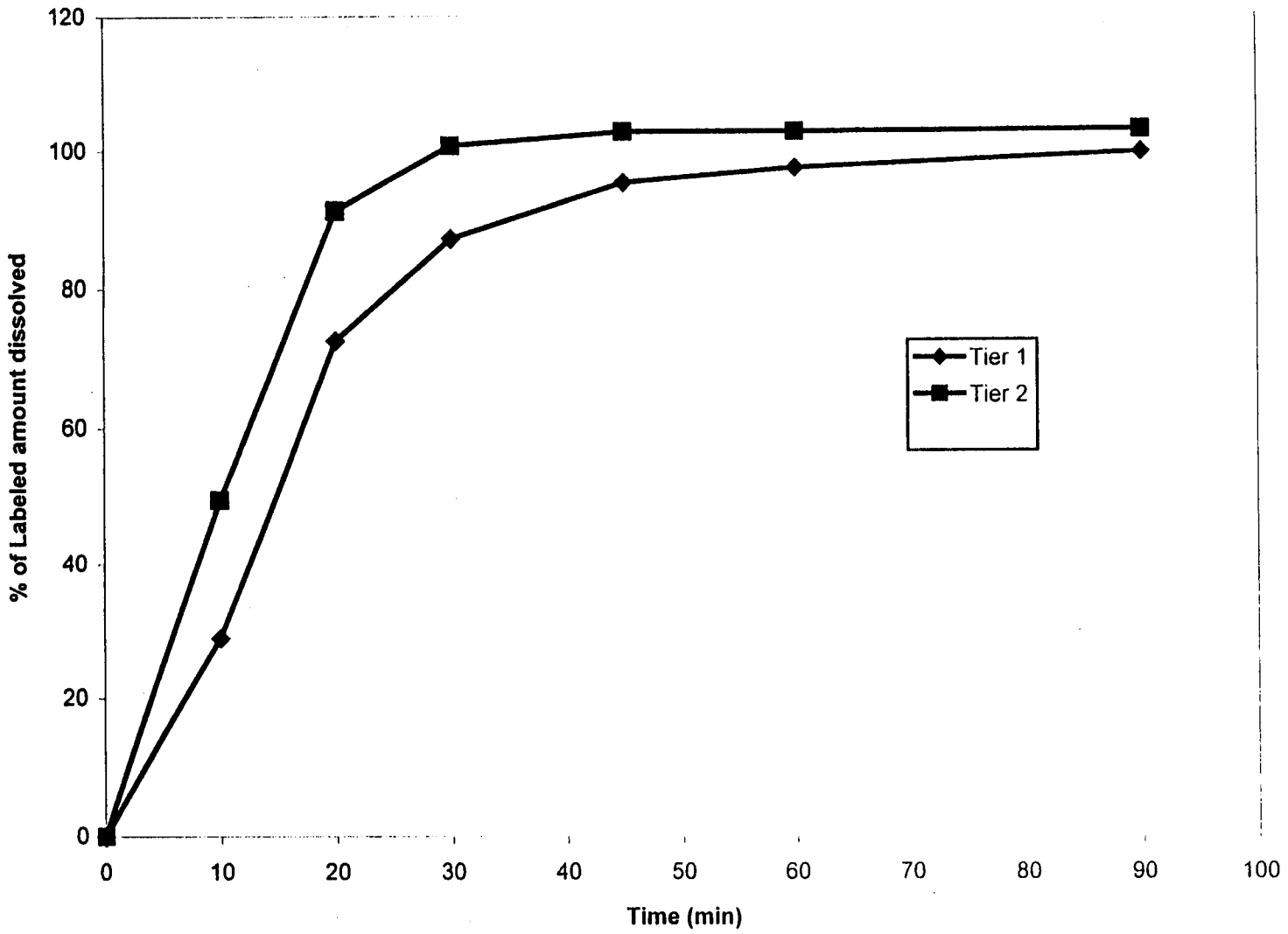
Dissolution Data, 12 months



Attachment #3
(Continued)

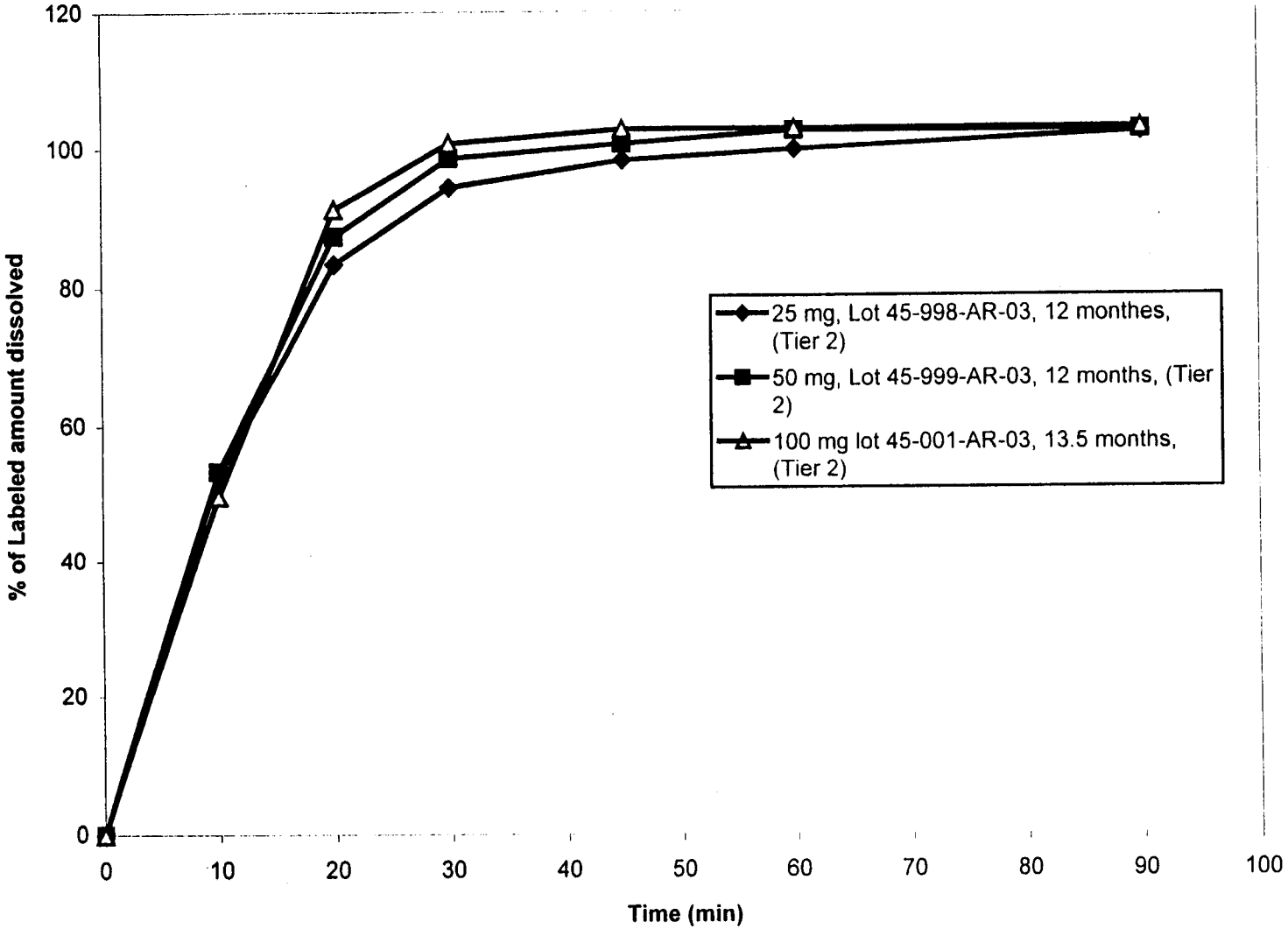
from table #3
2/17/00

Dissolution Data, 100 mg, Lot 45-001-AR-03



Attachment #3
(Continued)

Dissolution Data (using Tier 2 method)



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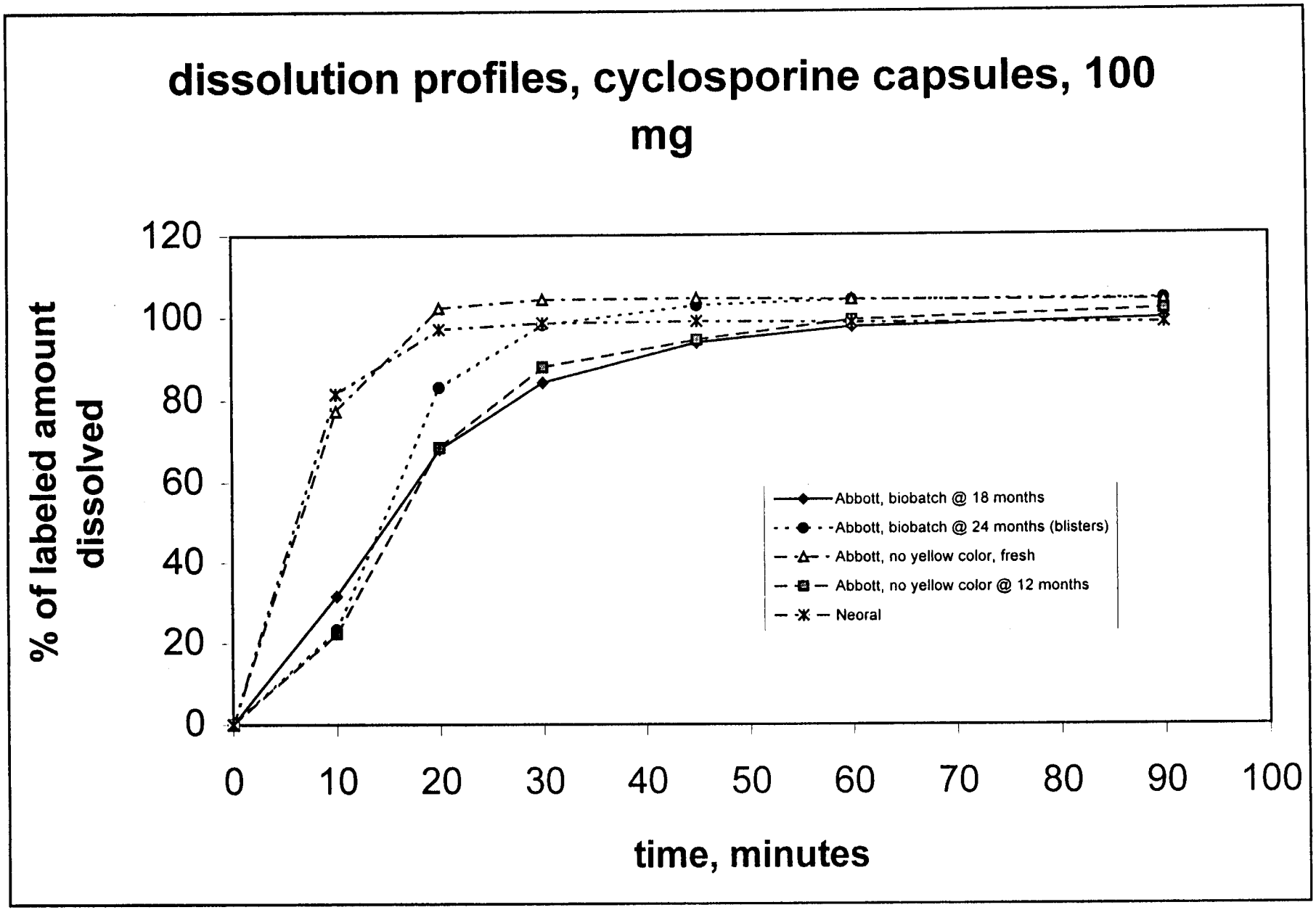
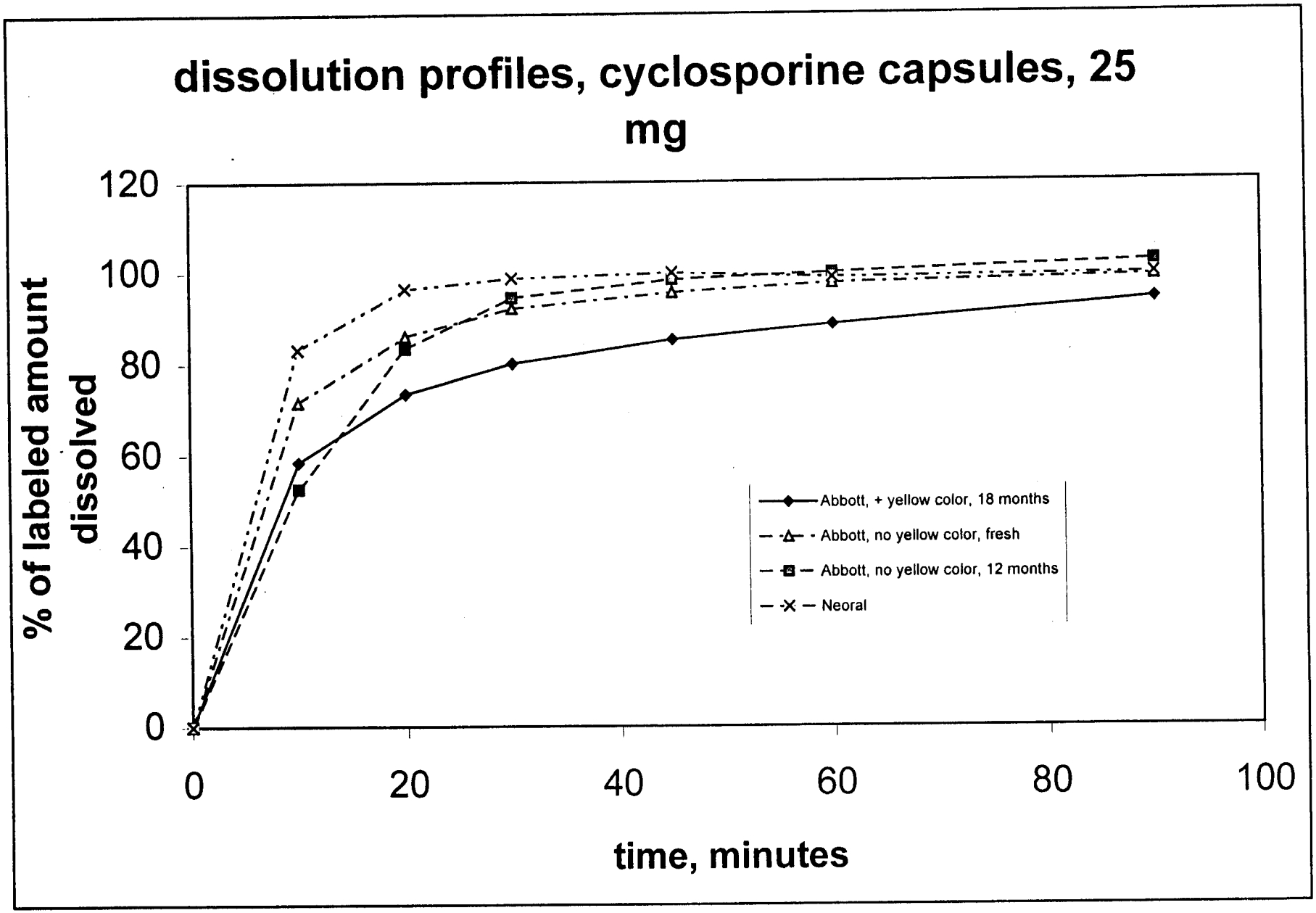
(continued)



Attach exhibit #3
(continued)



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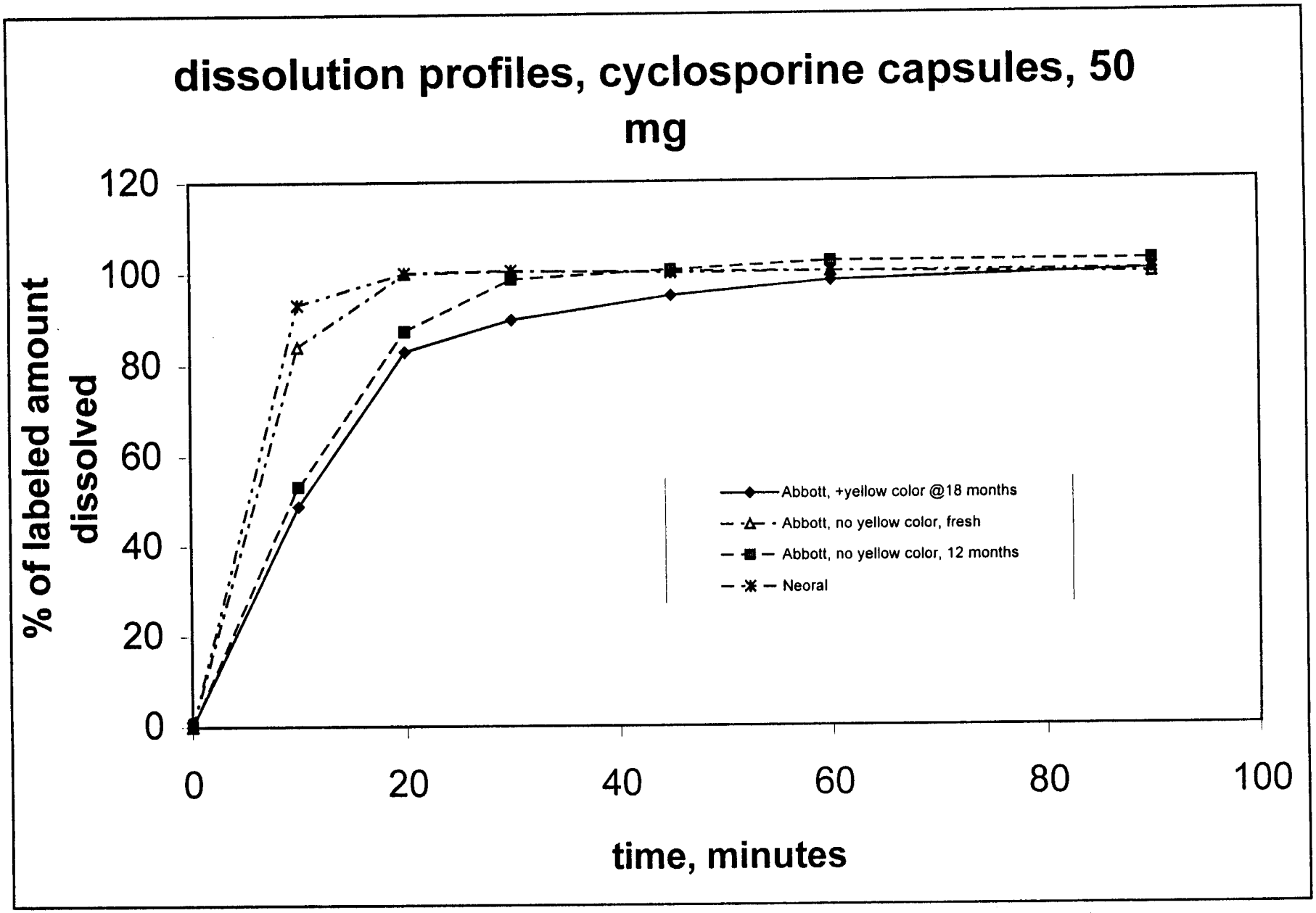

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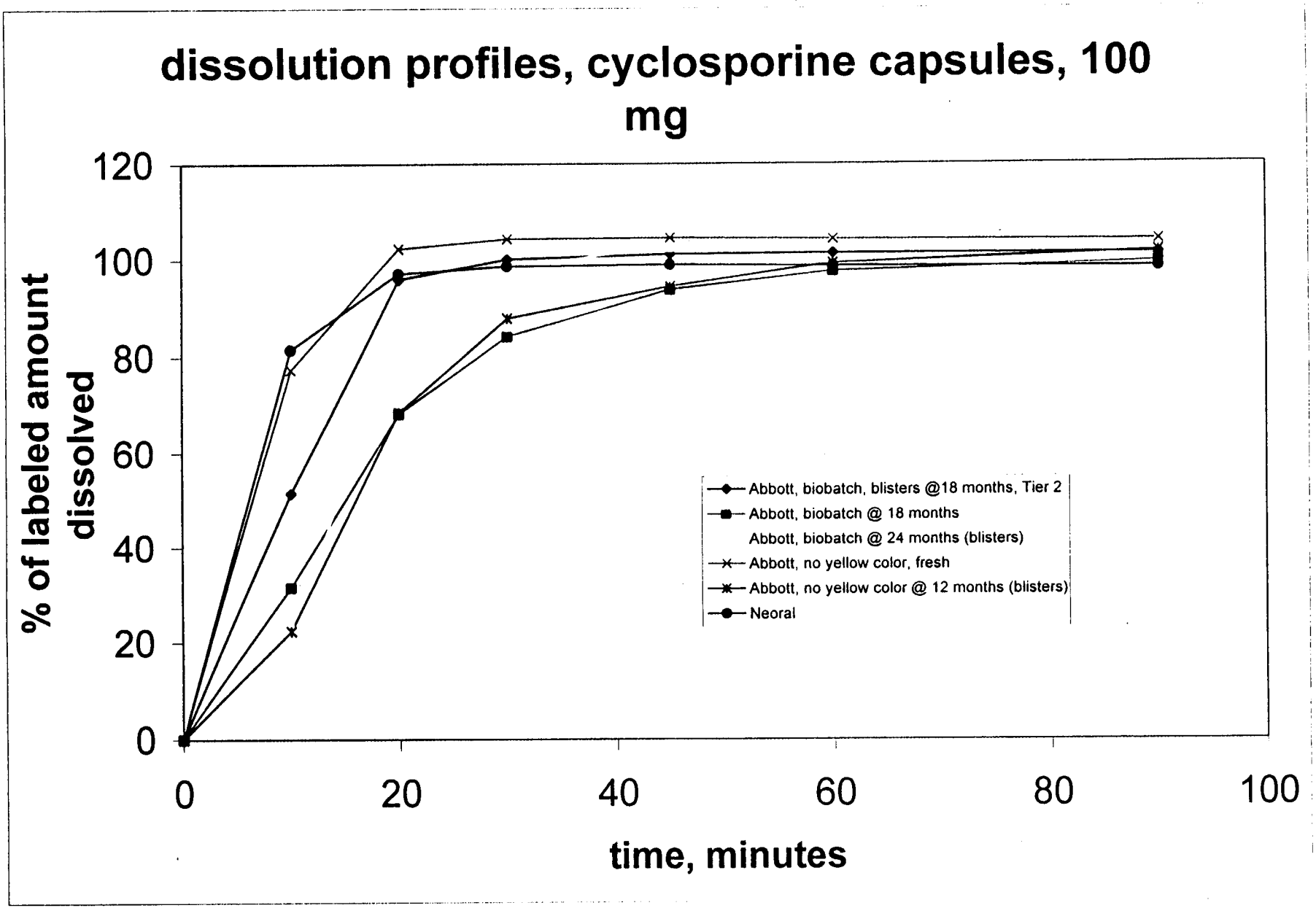
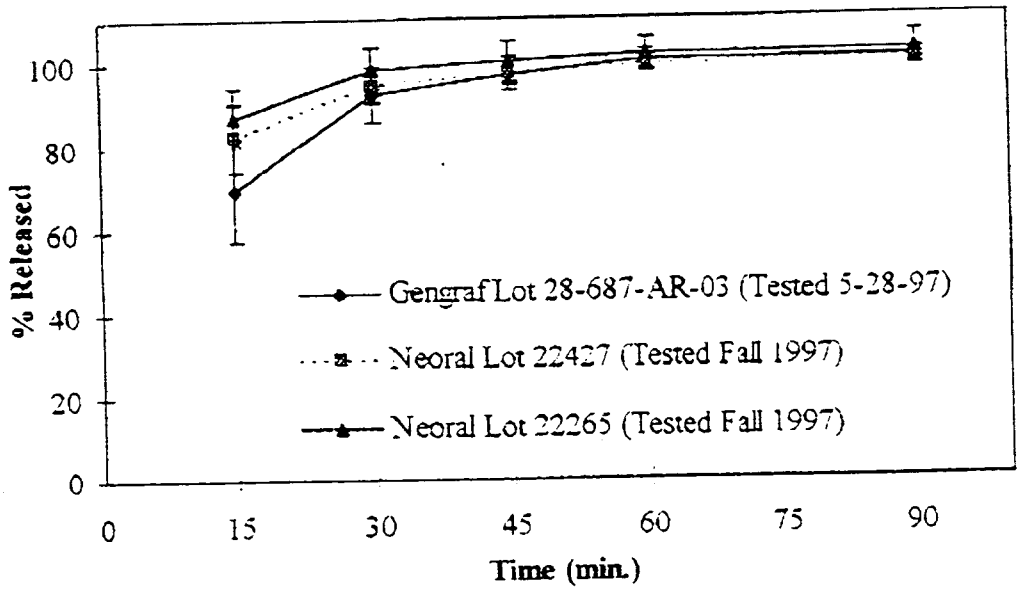
(Continued)



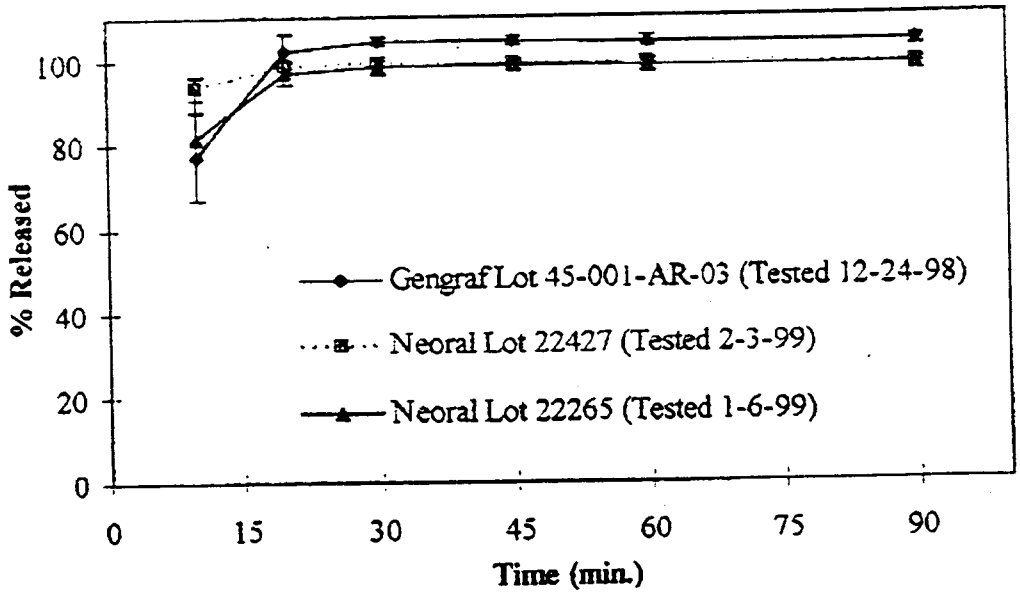
Attachment # 4

Table 2. **Comparison of Gengraf and Neoral Dissolution Profiles**

SDS Test Method: USP App. 2, 50 rpm, 900 mL 0.2% SDS



LDAO Test Method: USP App. 2, 75 rpm, 1000 mL 0.1N HCl with 0.4% LDAO



Neoral Expiration: Lot 22427 11/98, Lot 22265 10/98

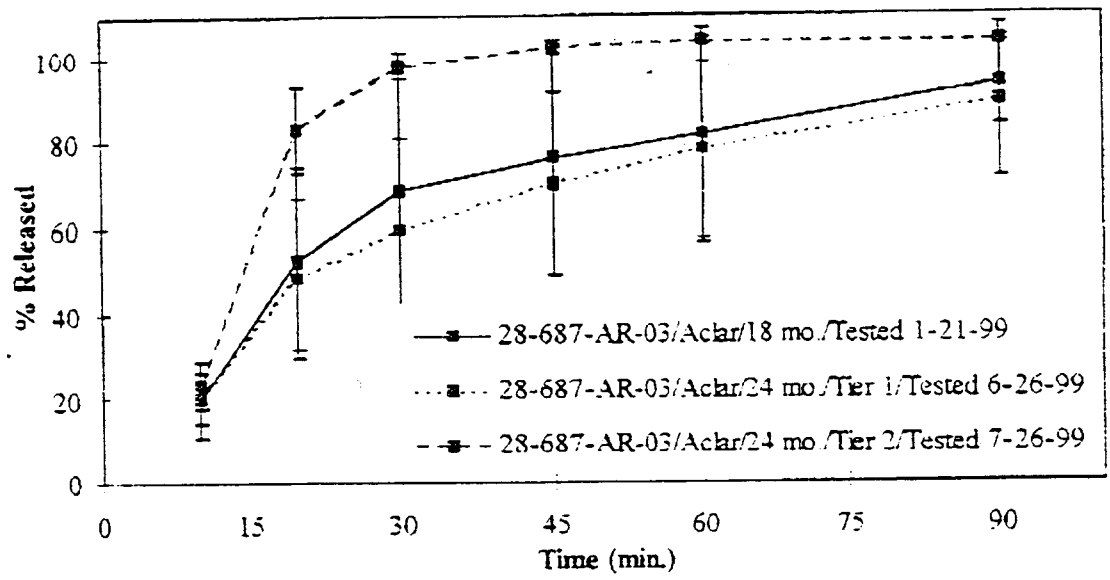
Comments

Dissolution of Neoral is consistently faster than or similar to Gengraf with either dissolution method.

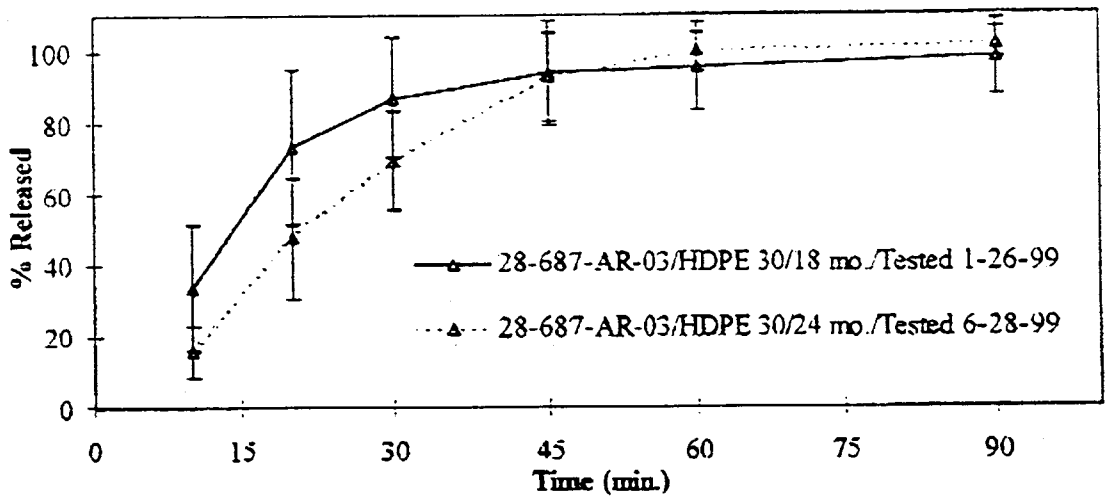
attachment #4
(continued)

Table 3. Original Lot (28-687-AR-03) Tested with LDAO Dissolution Method

Aclar Blisters



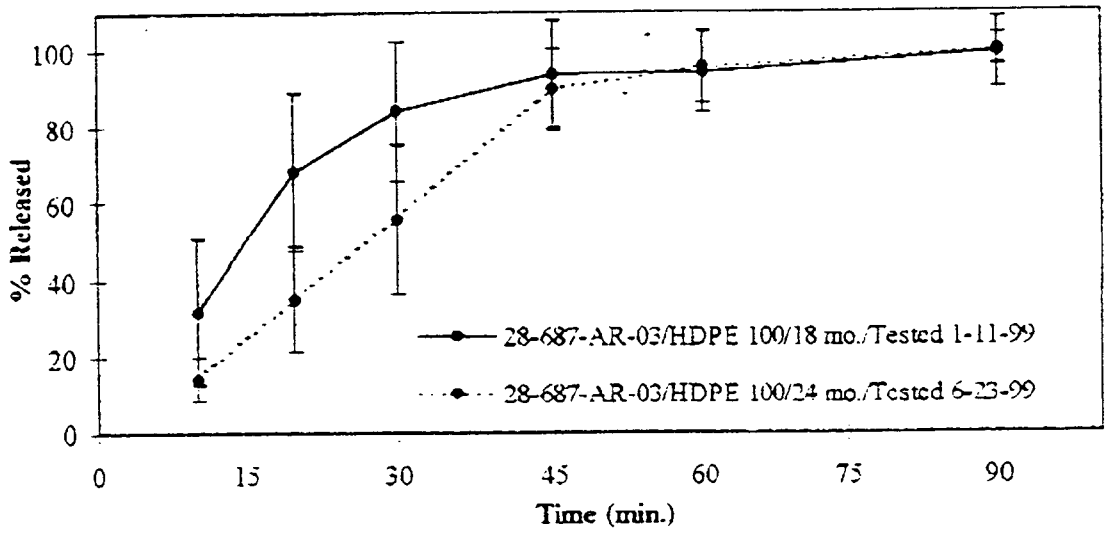
HDPE Bottles of 30



Attachment #4
(Continued)

Table 3. Original Lot (28-687-AR-03) Tested with LDAO Dissolution Method (continued)

HDPE Bottles of 100

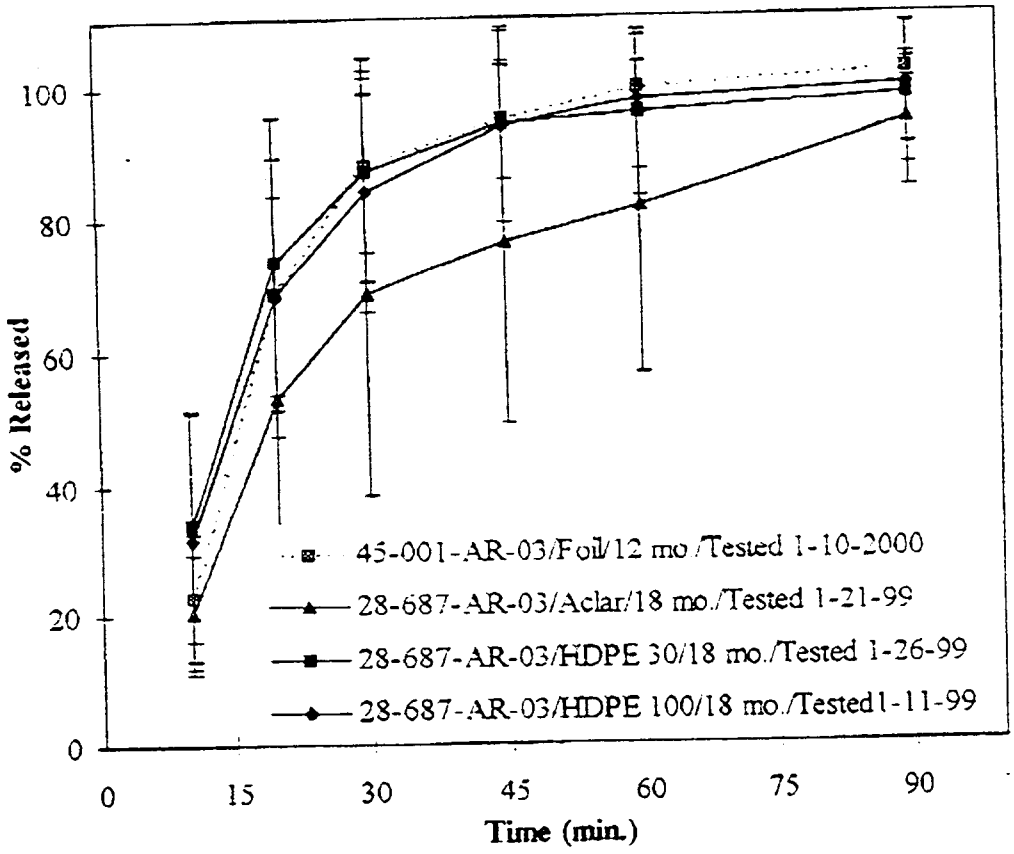


Comments

Dissolution was highly variable and appeared to decrease from 18 months (solid lines) to 24 months (dotted lines). Only capsules packaged in Aclar blisters required Tier 2 testing at 24 months (dashed line).

Attachment #4
(Continued)

Table 4. Original and Amendment Lots Tested with LDAO Dissolution Method



Comments

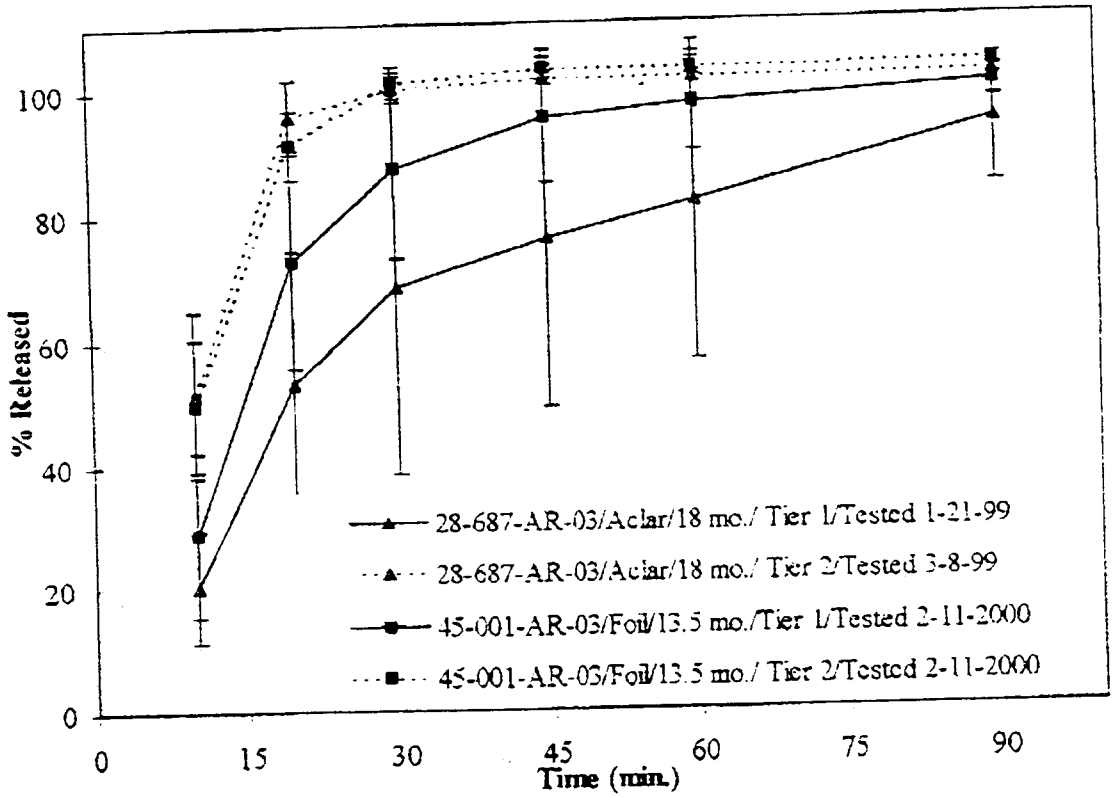
Due to the apparent aging effect on dissolution, the most valid comparisons are for capsules which are similar in age. The original lot was first tested with the LDAO method at 18 months. The latest stability interval for the amendment lot is 12 months. The profile for the amendment lot at 12 months (dotted line) is similar to the profiles for the original lot in bottles of 30 and 100 capsules at 18 months. Capsules stored in Aclar blisters are slower at 18 months.

f2 values for comparison with 45-001-AR-03

aclar blister 41.4
bottles of 30 63.4
bottles of 100 68.7

Attachment #4
(Continued)

Table 5. **Original Lot (18 months) and Amendment Lot (13.5 months) Tested with Tier 1 and 2 LDAO Dissolution Methods**



Comments

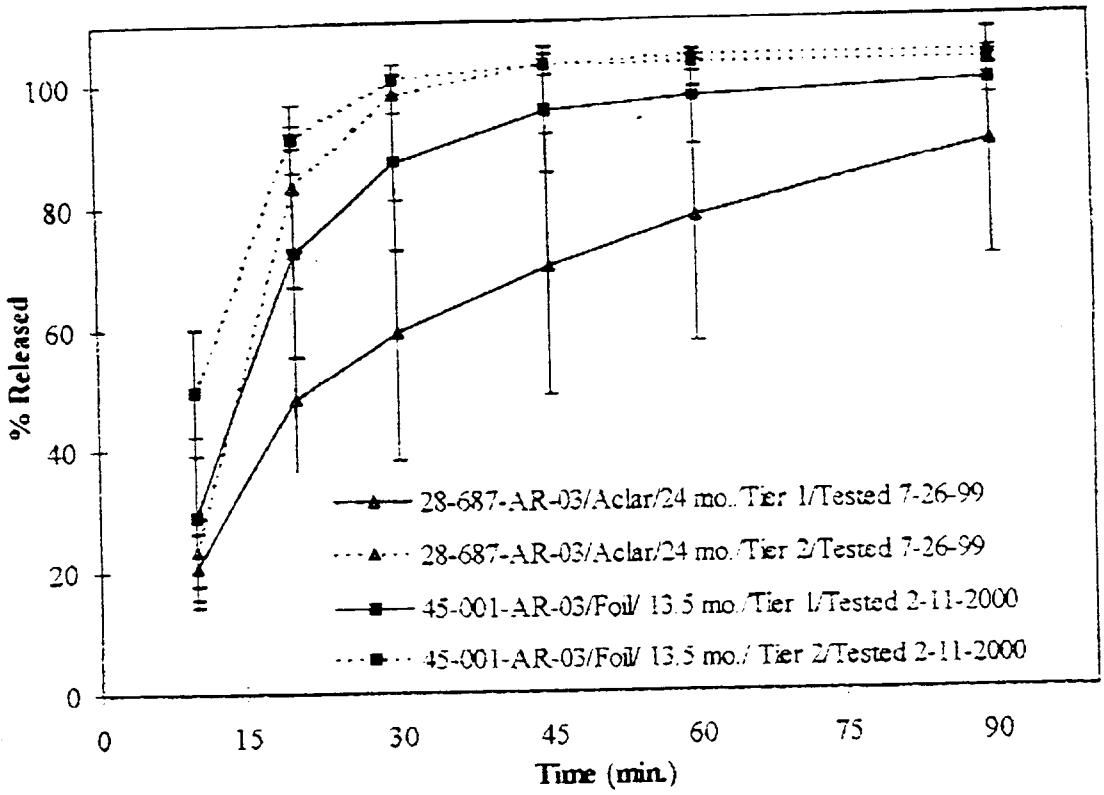
Tier 2 profiles were faster and less variable than Tier 1 profiles.

f2 value for Tier 1 testing 40.3

f2 value for Tier 2 testing 79.6

Attachment #4
(continued)

Table 6. **Original Lot (24 months) and Amendment Lot (13.5 months) Tested with Tier 1 and 2 LDAO Dissolution Methods**



Comments

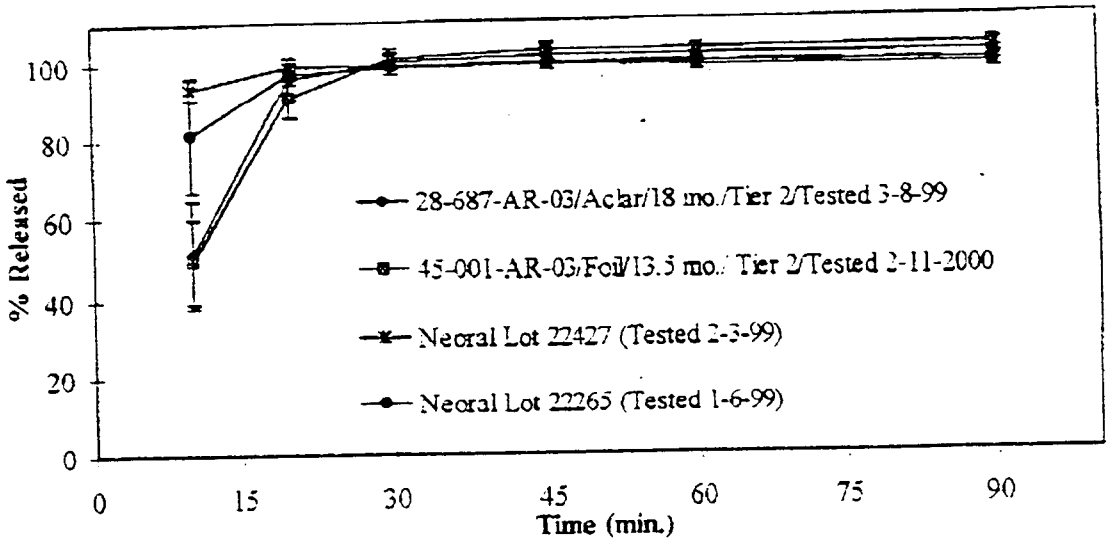
Tier 2 profiles were faster and less variable than Tier 1 profiles.

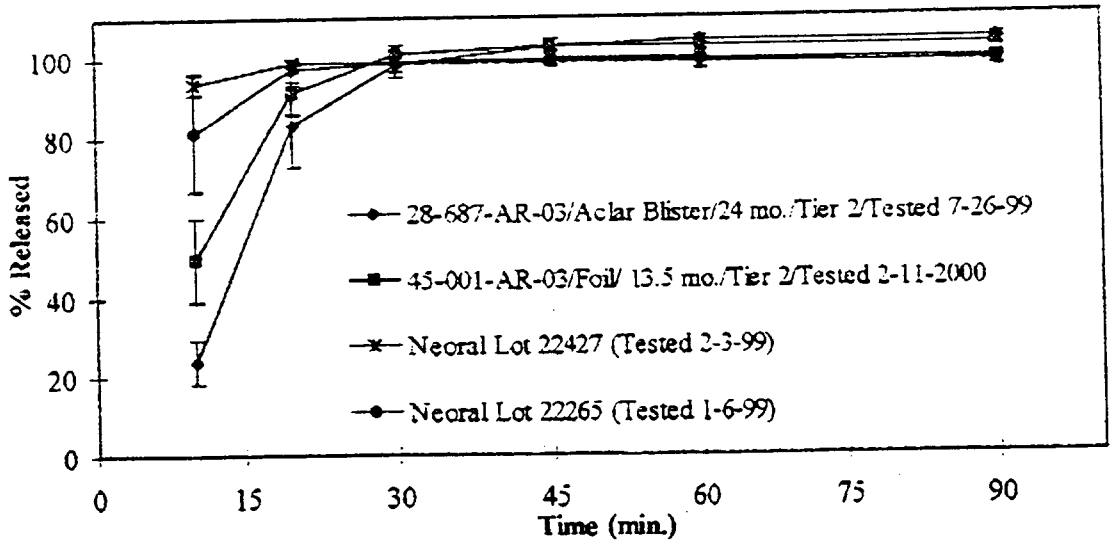
f2 value for Tier 1 testing 34.4

f2 value for Tier 2 testing 47.3

Attachment #4
(Continued)

Table 7. Comparison of Tier 2 Gengraf Dissolution with Neoral (Tier 1)



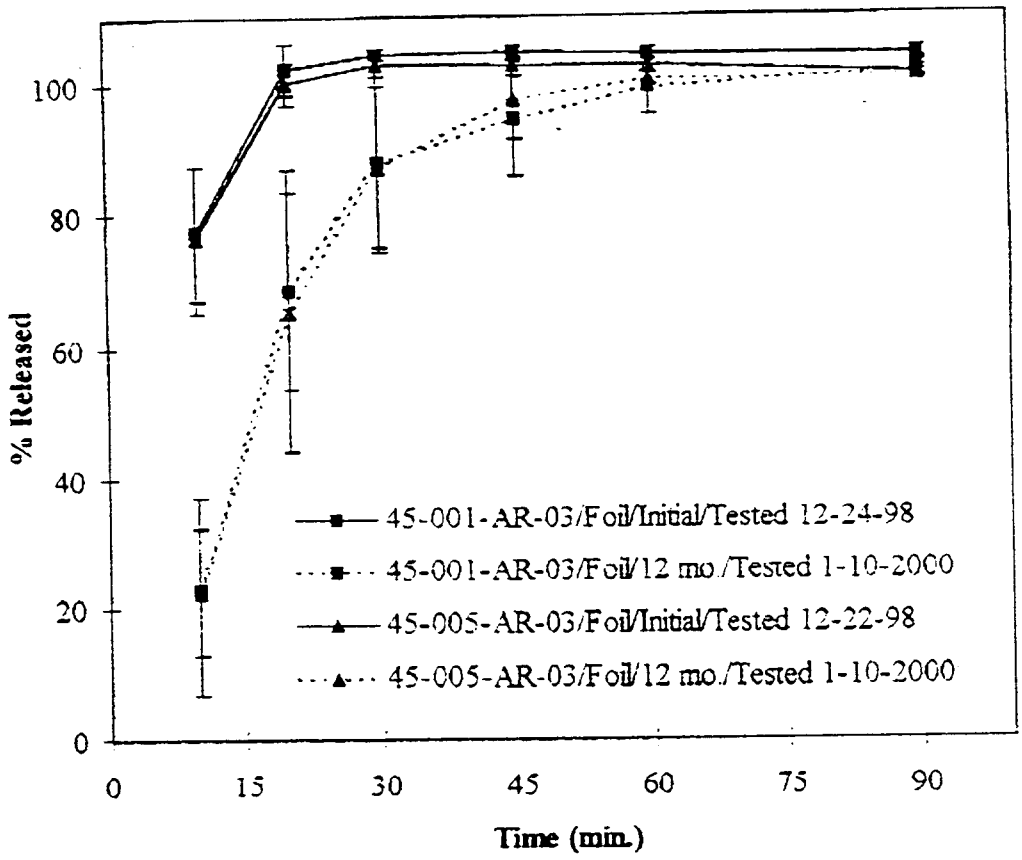


Comments

Due to the observed slowing in the dissolution of Gengraf Capsules, Tier 2 data may be more appropriate for comparison with Neoral. Release from Gengraf Capsules is lower at the 10 minute time point, similar at 20 minutes and complete from both products by 30 minutes.

Attachment #4
(Continued)

Table 8. Comparison of Lots 45-001-AR-03 and 45-005-AR-03 With LDAO Dissolution Method



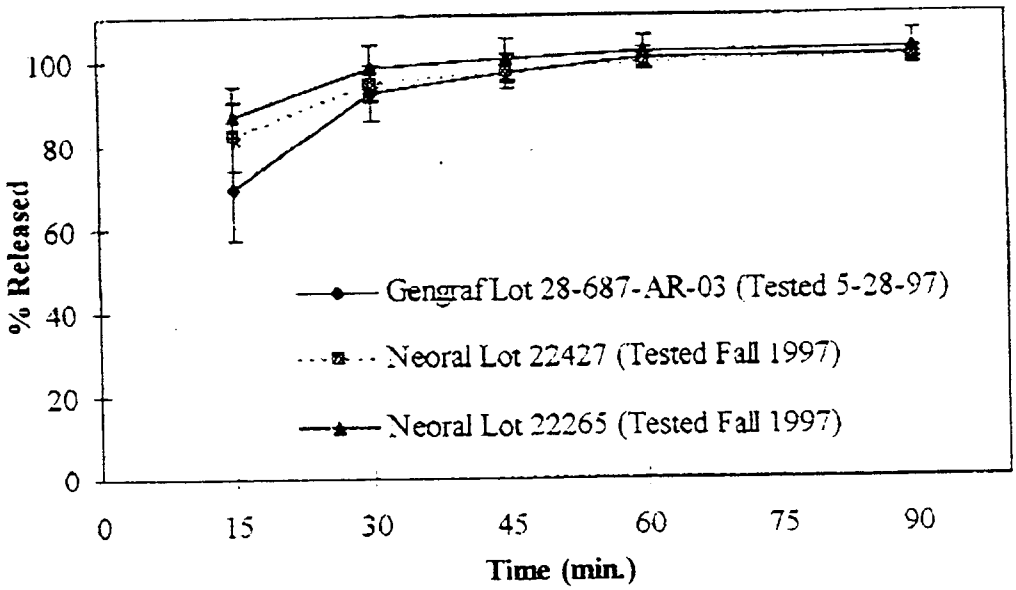
Both lots show slower dissolution at 12 months vs. Initial. Profiles for the two lots are superimposable at the initial and 12 month stability intervals.

Table 1. Information on Gengraf Capsules, 100 mg

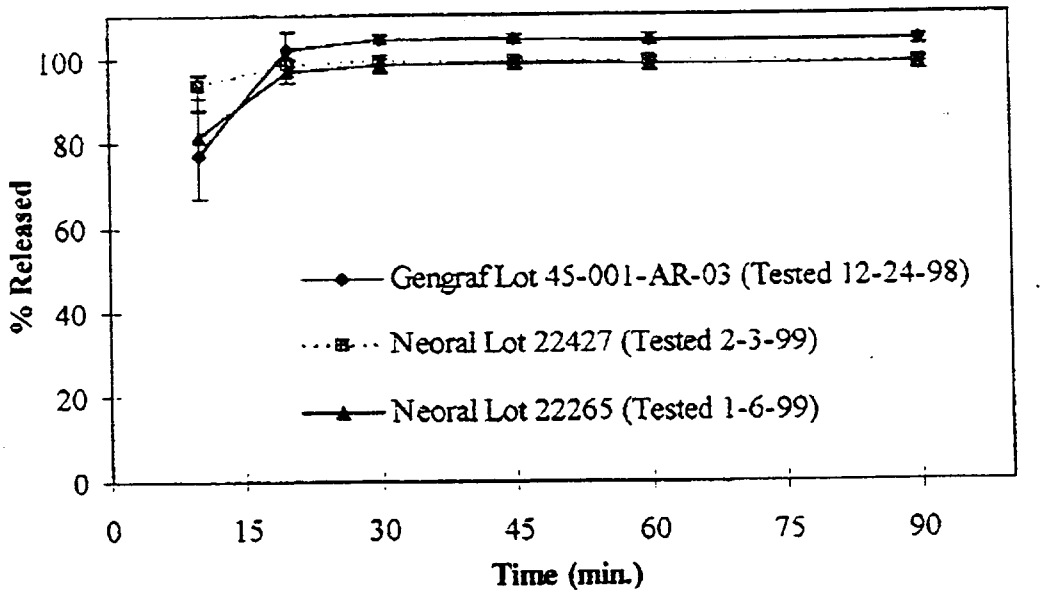
	Original Application	Amendment
Premix	Lot 28-685-AR-03 161.7 kg	Lot 45-001-AR-03 98.6 L
100 mg Capsules	Lot 28-687-AR-03	Lot 45-001-AR-03
Manufacture Date	5/97	11/98
Dissolution Method at Release	USP App. 2, 50 rpm	USP App. 2, 75 rpm ıth indicated
Capsule Color	With yellow dye	Yellow dye removed
Packaging Types	[illegible]	Foil Blisters
Label Storage (Data provided were generated for capsules stored at the label storage condition)	25°C/60%RH	25°C/60%RH

Table 2. Comparison of Gengraf and Neoral Dissolution Profiles

SDS Test Method: USP App. 2, 50 rpm, 900 mL 0.2% SDS



LDAO Test Method: USP App. 2, 75 rpm, 1000 mL 0.1N HCl with 0.4% LDAO



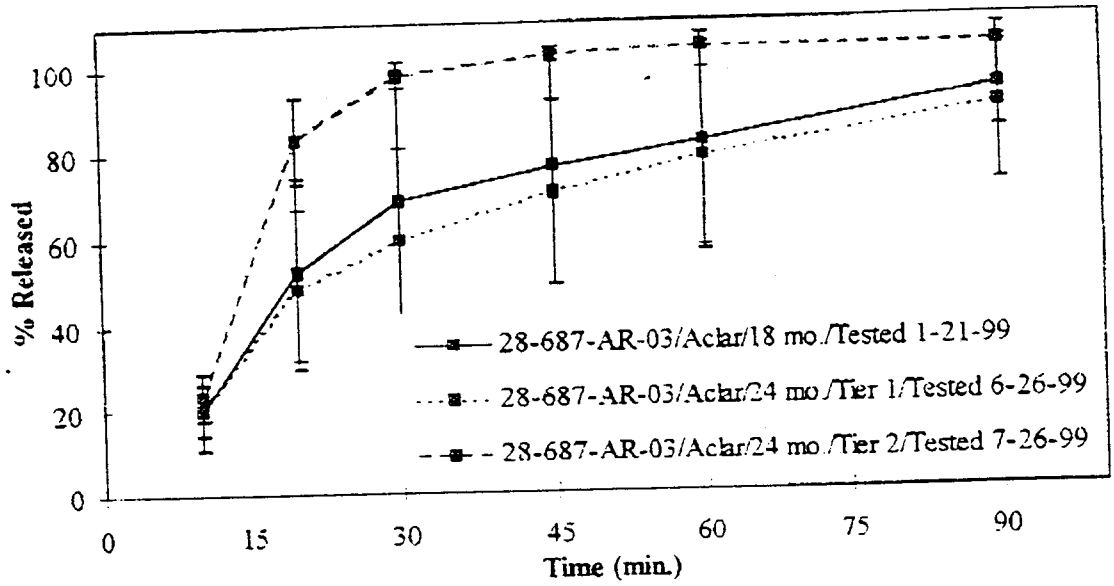
Neoral Expiration: Lot 22427 11/98, Lot 22265 10/98

Comments

Dissolution of Neoral is consistently faster than or similar to Gengraf with either dissolution method.

Table 3. Original Lot (28-687-AR-03) Tested with LDAO Dissolution Method

Aclar Blisters



HDPE Bottles of 30

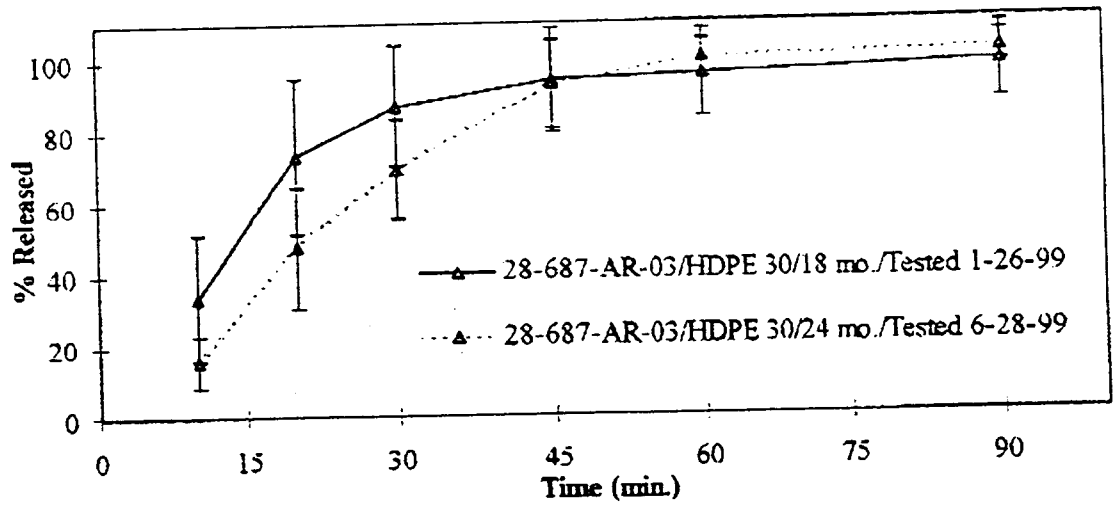
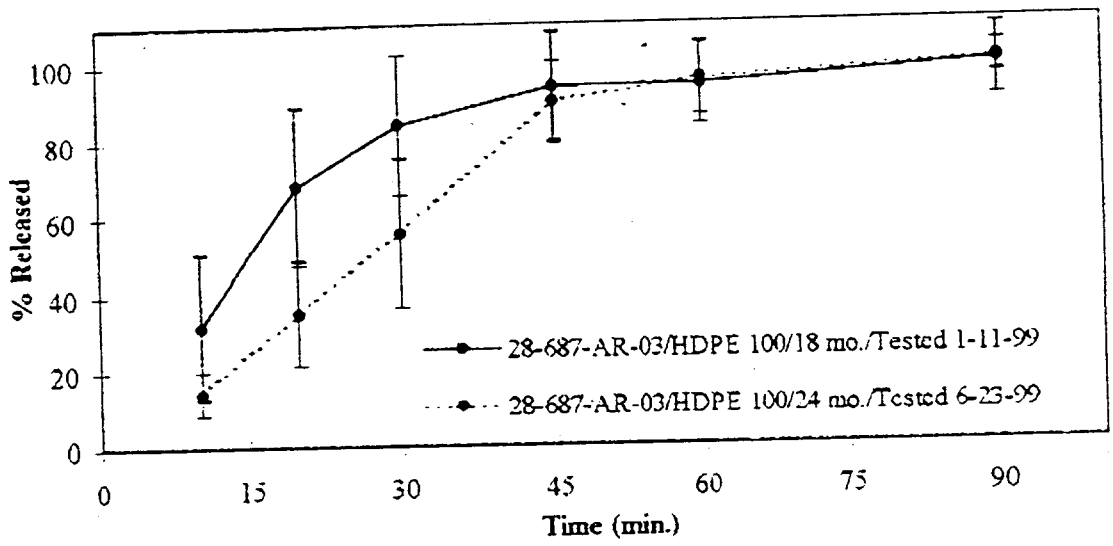


Table 3. Original Lot (28-687-AR-03) Tested with LDAO Dissolution Method (continued)

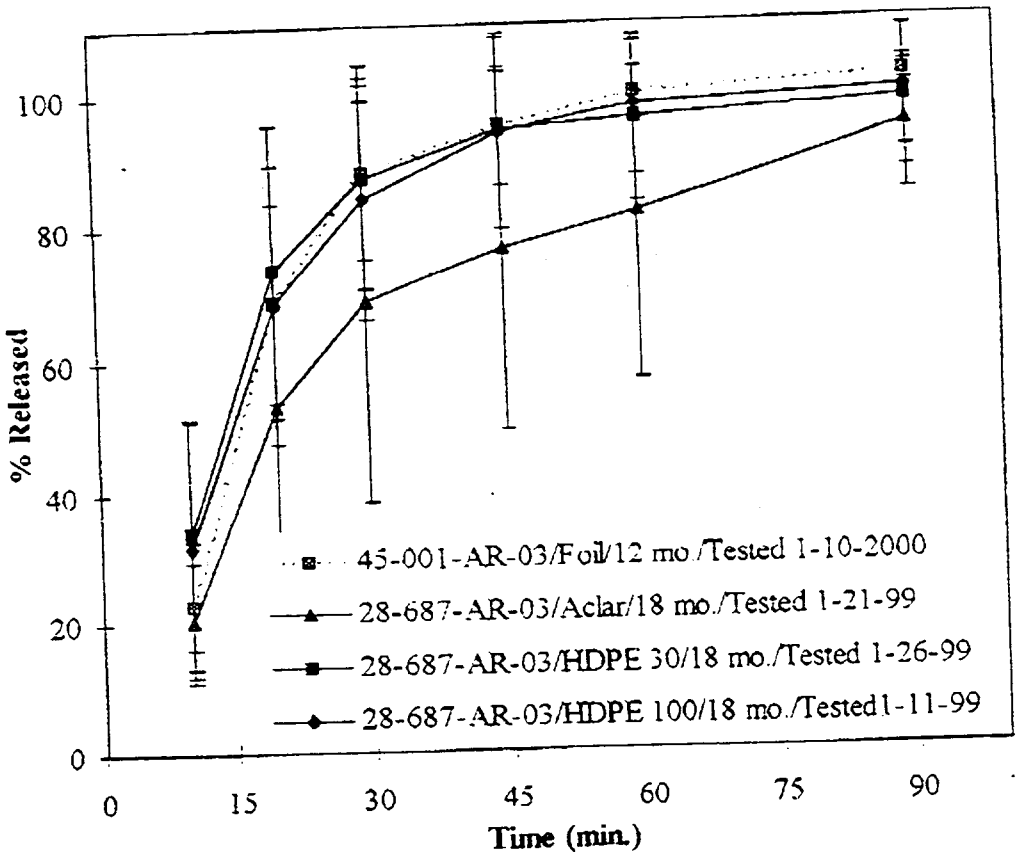
HDPE Bottles of 100



Comments

Dissolution was highly variable and appeared to decrease from 18 months (solid lines) to 24 months (dotted lines). Only capsules packaged in Aclar blisters required Tier 2 testing at 24 months (dashed line).

Table 4. **Original and Amendment Lots Tested with LDAO Dissolution Method**



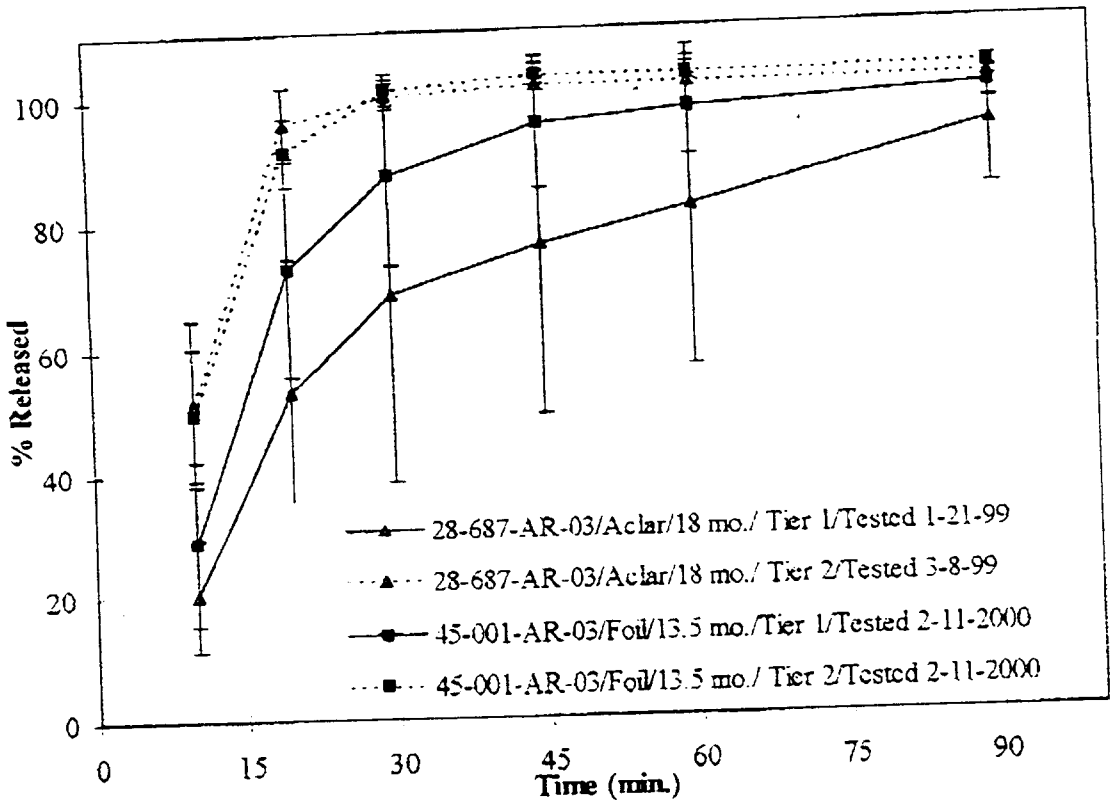
Comments

Due to the apparent aging effect on dissolution, the most valid comparisons are for capsules which are similar in age. The original lot was first tested with the LDAO method at 18 months. The latest stability interval for the amendment lot is 12 months. The profile for the amendment lot at 12 months (dotted line) is similar to the profiles for the original lot in bottles of 30 and 100 capsules at 18 months. Capsules stored in Aclar blisters are slower at 18 months.

f2 values for comparison with 45-001-AR-03

aclar blister 41.4
bottles of 30 63.4
bottles of 100 68.7

Table 5. **Original Lot (18 months) and Amendment Lot (13.5 months) Tested with Tier 1 and 2 LDAO Dissolution Methods**



Comments

Tier 2 profiles were faster and less variable than Tier 1 profiles.

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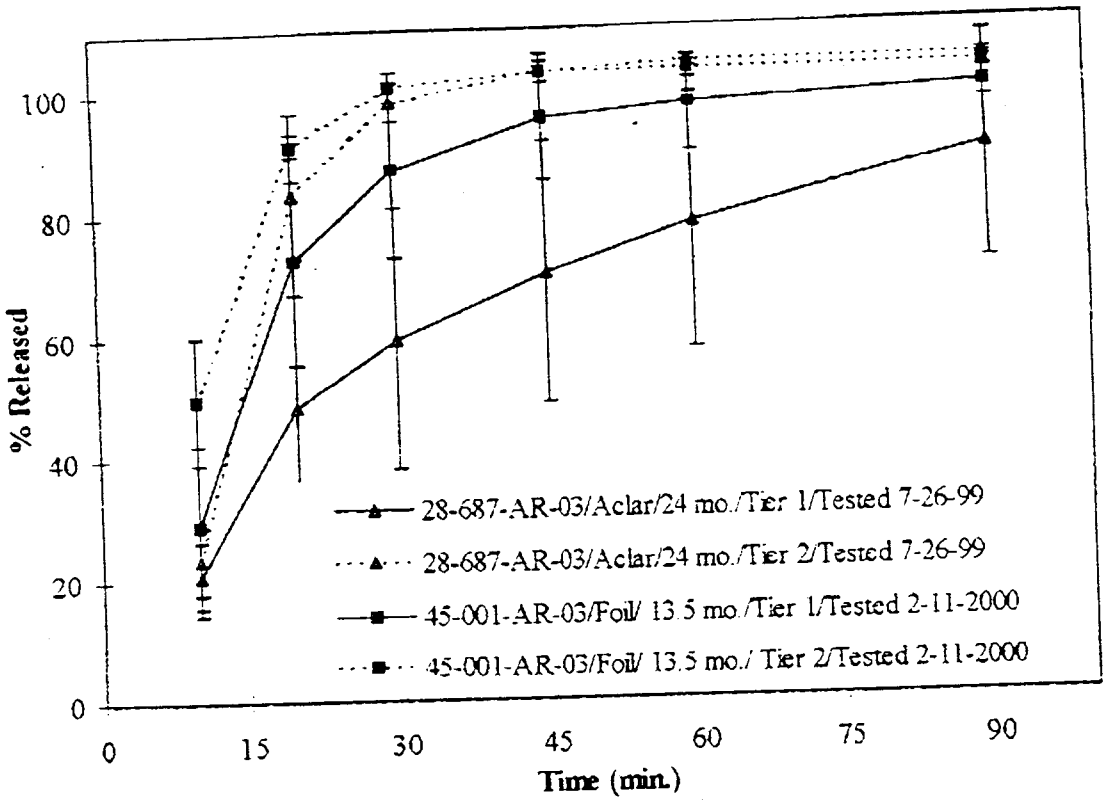
f2 value for Tier 2 testing 79.6

Table 6. **Original Lot (24 months) and Amendment Lot (13.5 months) Tested with Tier 1 and 2 LDAO Dissolution Methods**



Comments

Tier 2 profiles were faster and less variable than Tier 1 profiles.

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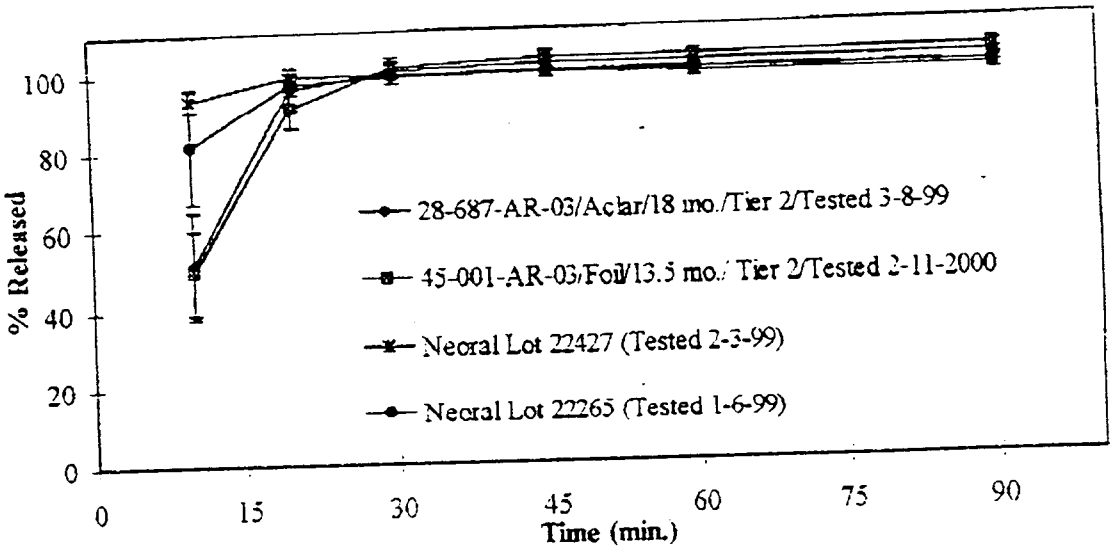
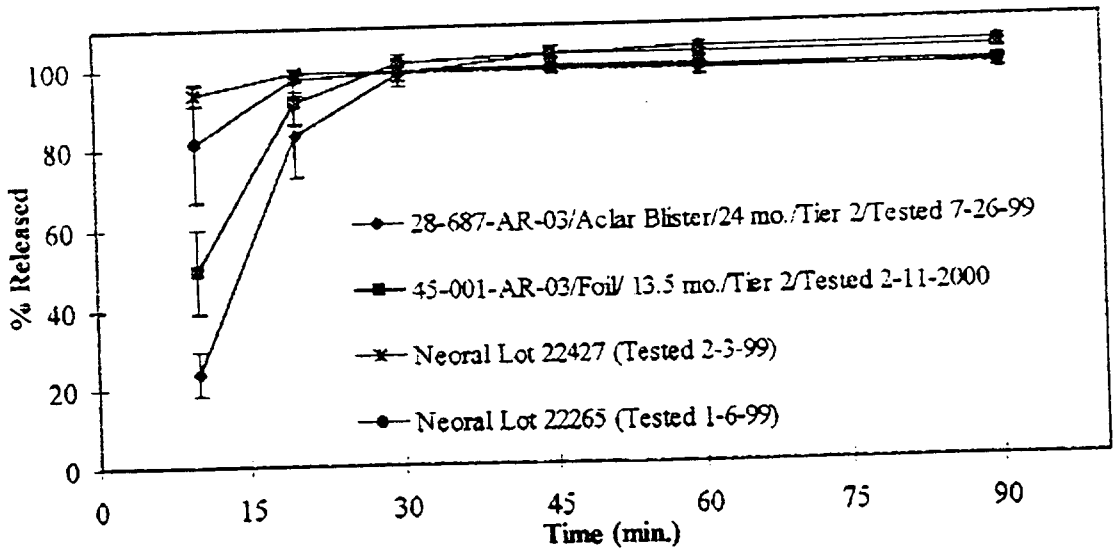
f2 value for Tier 2 testing 47.3

Table 7. Comparison of Tier 2 Gengraf Dissolution with Neoral (Tier 1)

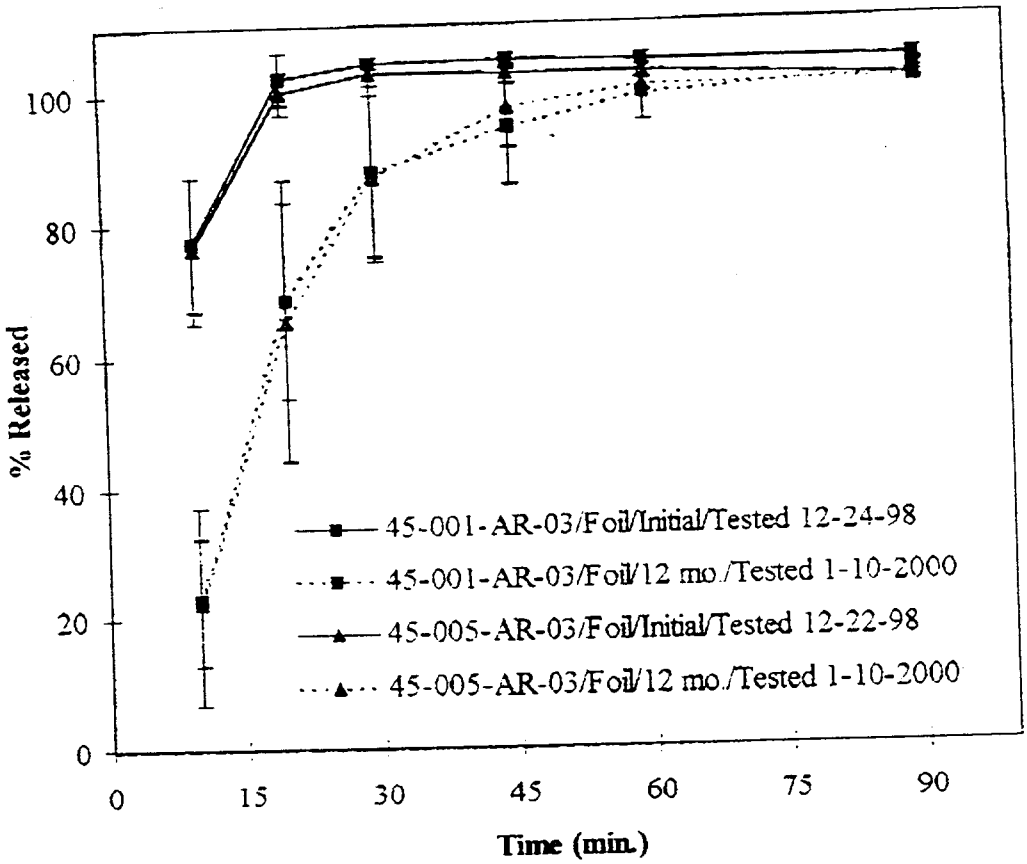




Comments

Due to the observed slowing in the dissolution of Gengraf Capsules, Tier 2 data may be more appropriate for comparison with Neoral. Release from Gengraf Capsules is lower at the 10 minute time point, similar at 20 minutes and complete from both products by 30 minutes.

Table 8. Comparison of Lots 45-001-AR-03 and 45-005-AR-03 With LDAO Dissolution Method



Both lots show slower dissolution at 12 months vs. Initial. Profiles for the two lots are superimposable at the initial and 12 month stability intervals.

BIOEQUIVALENCY DEFICIENCIES

ANDA: #65-003 APPLICANT: Abbott Laboratories

DRUG PRODUCT: Cyclosporine Hard Gelatin Capsules, 100 mg, 50 mg and 25 mg.

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

The dissolution testing should be incorporated into your stability and quality control programs:

> The dissolution testing should be conducted as follows: 0.1N HCl containing 0.2% LDAO (lauryldimethylamine-N-oxide) for 25 and 50 mg capsules; 0.1N HCl containing 0.4% for 100 mg capsules, using USP 23 apparatus II (Paddle) at 75 rpm. Volume of the dissolution medium as follows: 500 mL for 25 mg strength and 1000 mL for 50 mg and 100 mg strengths (Per the Pharmacopial Forum, dated May-June 1998). The test product should meet the following specifications:
>
> > Not less than % (Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes.

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/

for 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 # : 65-003 – CYCLOSPORINE SPONSOR : Abbott Laboratoreis

DRUG AND DOSAGE FORM : Capsules STRENGTH(S) : 25 mg, 50 mg and 100 mg

TYPES OF STUDIES : In vivo bioequivalence studies under fasting and non-fasting conditions.

CLINICAL STUDY SITE(S

ANALYTICAL SITE(S) :

STUDY SUMMARY : The two studies demonstrated that under fasting and non-fasting conditions, Abbott's Cyclosporine Hard Gelatin Capsule, 100 is bioequivalent to Novartis' Neoral® (Cyclosporine Soft Gelatin Capsule), 100 mg.

DISSOLUTION : The dissolution data for the 100 mg, 50 mg and 25 mg are acceptable.

DSI INSPECTION STATUS

Inspection needed: (YES) / NO	Inspection status:	Inspection results:
First Generic _No__ New facility _Yes (new analytical facility) _ For cause _____ other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Zakaria Z. Wahba, Ph.D. BRANCH : III

INITIAL : /S/ DATE : 5/5/99

TEAM LEADER : Barbara M. Davit, Ph.D. BRANCH : III

INITIAL : /S/ DATE : 5/5/99

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : [signature] DATE : 5/20/99

Cyclosporine
100 mg Hard Gelatin Capsule
50 mg Hard Gelatin Capsule
25 mg Hard Gelatin Capsule
ANDA #65-003
Reviewer: Z.Z. Wahba
V:\FIRMSAM\ABBOTT\LRS&REV\65003a.399

Abbott Laboratories
Abbott Park, IL
Submission Dated:
March 31, 1999
April 23, 1999

REVIEW OF AN AMENDMENT

BACKGROUND

1. The firm previously submitted two in vivo bioequivalence studies (single-dose under fasting and fed conditions) comparing its test product Cyclosporine Hard Gelatin Capsule, 100 mg, to the reference listed drug Novartis' Neoral® (Cyclosporine Soft Gelatin Capsule), 100 mg. The submission was reviewed and was found incomplete by the Division of Bioequivalence (the submission was dated October 02, 1998).

2. In this submission, the firm has responded to the deficiency comments and included additional information in the current submission.

DEFICIENCY COMMENT #1

The firm was asked to provide information in support of long term stability data covering the entire period of sample storage from blood collection to analysis.

RESPONSE TO DEFICIENCY COMMENT #1

Cyclosporine was stable for at least 60 days in human whole blood samples at -20°C. The %CV for the quality control samples was 3.4%, 4.7% and 3.2% for 2.70, 270.0 and 771.0 ng/mL, respectively. Accuracy was 100.4, 88.7, and 93.0%, respectively.

The firm's response to comment #1 is acceptable.

DEFICIENCY COMMENT #2

The bioequivalence study under fasting conditions using Abbott's cyclosporine **soft** gelatin capsule, 100 mg is not acceptable since the 90% confidence interval for Cmax is outside the acceptable range of 80-125% of the reference listed drug.

RESPONSE TO DEFICIENCY COMMENT #2

The sponsor agrees that the bioequivalence study of Abbott's **soft** cyclosporine soft gelatin capsule, 100 mg is not acceptable. The firm stated that the soft gelatin capsule formulation is not being pursued for commercial use. The application (ANDA 65003) requests approval of the **hard** gelatin capsule formulation which meets bioequivalence criteria.

The firm's response to comment #2 is acceptable.

DEFICIENCY COMMENT #3

The firm was asked to obtain the dissolution data for the 25 mg, 50 mg and 100 mg formulations according to the following method and specification. The Agency recommends the following dissolution approach:

Tier 1: 0.1N HCl containing 0.2% LDAO (lauryldimethylamine-N-oxide) for 25 and 50 mg capsules; 0.1N HCl containing 0.4% for 100 mg capsules. Apparatus: Paddle 75 rpm.

Tier 2: If not passing at Tier 1: SGF with containing 0.2% LDAO for 25 and 50 mg capsules; SGF with containing 0.4% for 100 mg capsules. Apparatus: Paddle 75 rpm.

RESPONSE TO DEFICIENCY COMMENT #3

The dissolution testing for the strengths 25 mg, 50 mg and 100 mg is summarized below:

Method:	FDA method (also refer to The Pharmacopial Forum, dated May-June 1998)
Apparatus:	Apparatus II (Paddle) at 75 rpm
Medium:	0.1N HCl containing 0.2% LDAO (lauryldimethylamine-N-oxide) for 25 and 50 mg capsules; 0.1N HCl containing 0.4% for 100 mg capsules.
Volume:	500 mL for 25 mg strength and 1000 mL for 50 mg and 100 mg strengths (Per the Pharmacopial Forum, dated May-June 1998).
Number of Units:	12 Tablets
Test products:	Abbott's Cyclosporine Hard Gelatin Capsules, 25 mg (lot #28-686-AR-03), 50 mg (lot #29-719-AR-03), and 100 mg (lot #28-687-AR-03).
Reference products:	Novartis' Neoral® (Cyclosporine Soft Gelatin Capsules), 25 mg (lot #300429), 50 mg (lot #238), and 100 mg (lot #22265, for fasting study; lot #22427, for fed study).

Results:

1. Copies of the dissolution data statements are included in this report (Attachments #1-7). The dissolution data are reported in volume B2.1, Bioequivalency Deficiencies Responses dated 03/31/99 and 04/23/99.

2. The dissolution comparison profiles (for all strengths) using the similarity factor (F2), are included in this report (Attachment #8-16).

Conclusion:
All dissolution data meet the dissolution specifications (Not less than % (Q) of the labeled amount of the drug in the dosage form is dissolved in 60 minutes). The dissolution data for the test products are acceptable.

Comments on the dissolution data: (NOT TO BE RELEASED UNDER FOI)

The F2 values (similarity factor) for the 100 mg, 50 mg and 25 mg strengths of the test product are as follows:

F2 Factor		
Strengths	**Test**	**Reference**
50 mg vs 100 mg (bio-study)	48.72	62.19
25 mg vs 100 mg (bio-study)	42.94	92.03

100 mg Test bio-lot vs Ref. Bio-lot (fast study)	F2=28.66
100 mg Test bio-lot vs Ref. Bio-lot (fed study)	F2=24.86
50 mg Test vs 50 mg Ref.	F2=32.99
25 mg Test vs 25 mg Ref.	F2=35.89

DEFICIENCY COMMENT #4

The two bioequivalence studies under fasting and non-fasting conditions used two different reference drug lots, #22265 and 22427, respectively. Please provide the rationale for not using the same reference drug lot number for both the fasting and non-fasting studies.

RESPONSE TO DEFICIENCY COMMENT #4

The sponsor was unable to buy enough supplies of one lot of the reference product to conduct the two studies and to have enough drug reserve as per policy. However, the two different reference drug lots were almost identical with regard to potency and dissolution characteristics and had expiration dates one month apart.

The firm's response to comment #4 is acceptable.

Attachment #1

Table III. Dissolution Data for Cyclosporine Capsules, 100 mg, Lot 28-687-AR-03.

Test date Jan. 5, 1999.

	% Released					
Run #	10	20	30	45	60	90 min
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
Mean	31.6	68.2	84.2	93.7	97.5	99.4
% CV	61.8	30.7	21.6	15.3	10.8	9.2
Low						
High						

Attachment #2

Table IV. Dissolution Data for Neoral, 100 mg, Lot 22265.

Test Date Jan. 6, 1999.

	% Released					
Run #	10	20	30	45	60	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	81.5	97.1	98.6	98.9	98.6	98.3
% CV	17.7	2.9	2.0	1.3	1.6	1.6
Low						
High						

Attachment #3

Table V. Dissolution Data for Neoral, 100 mg, Lot 22427.

Test Date Feb. 3, 1999.

Run #	% Released					
	10	20	30	45	60	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	93.7	98.9	99.2	99.4	99.4	99.1
% CV	3.1	0.7	0.7	0.6	0.5	0.5
Low						
High						

Attachment # 4

Table VI. Dissolution data for Cyclosporine Capsules, 50 mg, Lot 29-719-AR-03.

Test Date Jan. 5, 1999.

	% Released					
Run #	**10**	**20**	**30**	**45**	**60**	**90 min.**
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	49.0	83.0	89.9	95.0	98.2	100.2
% CV	45.7	26.1	17.8	11.8	8.4	3.5
Low						
High						

Attachment #5

Table 8. Dissolution Data for Optoral Capsules, 50 mg, Lot 238

Test Date April 19, 1999

Method A

	% Released					
Run	10	20	30	45	60	90 min.
5						
6						
7						
8						
9						
10						
11						
12						
Mean	93.2	100.1	100.6	100.0	100.2	100.3
SD	4.7	1.0	0.8	0.7	1.0	0.9
%CV	5.1	1.0	0.8	0.7	1.0	0.9
Low						
High						

Attachment #6

Table VII. Dissolution Data for Cyclosporine Capsules, 25 mg, Lot 28-686-AR-03, using 500 mL of 2 mg/mL LDAO in 0.1N HCl as the dissolution medium.

Test Date Jan. 5, 1999.

Run #	% Released					
	10	20	30	45	60	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	58.5	73.5	80.1	85.2	88.4	94.0
% CV	35.7	23.3	20.3	17.4	14.1	8.9
Low						
High						

Attachment #7

Table 7. Dissolution Data for Neoral Capsules, 25 mg, Lot 300429 using 500 mL of 2 mg/mL LDAO in 0.1N HCl

Test Date April 19, 1999

Method A

	% Released					
Run	10	20	30	45	60	90 min.
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Mean	83.2	96.4	98.7	99.8	98.7	99.4
SD	10.8	4.5	1.9	0.9	1.1	1.2
%CV	12.9	4.6	2.0	0.9	1.1	1.2
Low						
High						

Attachment #8

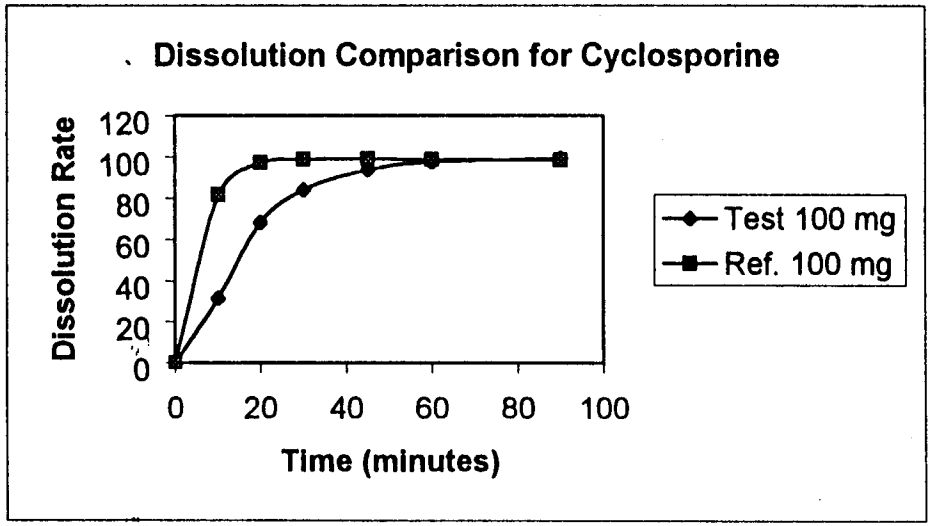
ANDA 65-003, Cyclosporine Hard Gelatin Capsules
Dissolution Comparison - Profile using the similarity factor F2

Test - 100 mg Lot #28-687-AR-03, bio-lot
Reference - 100 mg Lot #22265, bio-lot (fasting study)

time	Test 100 mg	Ref. 100 mg	Difference	(Diff)sq	sum of sq	ss/n	1+ss/n	to -.5 pwr	times 100	log	times 50
10	31.6	81.5	-49.9	2490	3562.04	712	713.4	0.03744	3.743958	0.57333	28.66655
20	68.2	97.1	-28.9	835.21							
30	84.2	98.6	-14.4	207.36		**F2=28.66**					
45	93.7	98.9	-5.2	27.04							
60	97.5	98.6	-1.1	1.21							
90	99.4	98.3	1.1	1.21							

dissolution comparison

time	Test 100 mg	Ref. 100 mg
0	0	0
10	31.6	81.5
20	68.2	97.1
30	84.2	98.6
45	93.7	98.9
60	97.5	98.6
90	99.4	98.3



Attachment #10

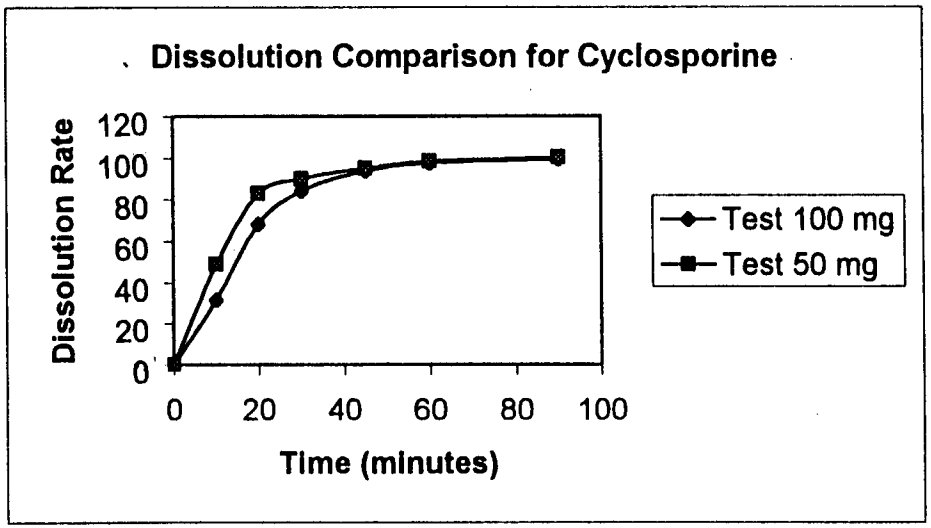
ANDA 65-003, Cyclosporine Hard Gelatin Capsules
Dissolution Comparison - Profile using the similarity factor F2

Test - 100 mg Lot #28-687-AR-03, bio-lot
Test - 50 mg Lot #29-719-AR-03

time	Test 100 mg	Test 50 mg	Difference	(Diff)sq	sum of sq	ss/n	1+ss/n	to -.5 pwr	times 100	log	times 50
10	31.6	49	-17.4	302.76	557.11	111	112.4	0.094314	9.431361	0.97457	48.72872
20	68.2	83	-14.8	219.04							
30	84.2	89.9	-5.7	32.49		**F2=48.72**					
45	93.7	95	-1.3	1.69							
60	97.5	98.2	-0.7	0.49							
90	99.4	100.2	-0.8	0.64							

dissolution comparison

time	Test 100 mg	Test 50 mg
0	0	0
10	31.6	49
20	68.2	83
30	84.2	89.9
45	93.7	95
60	97.5	98.2
90	99.4	100.2



Attachment #9

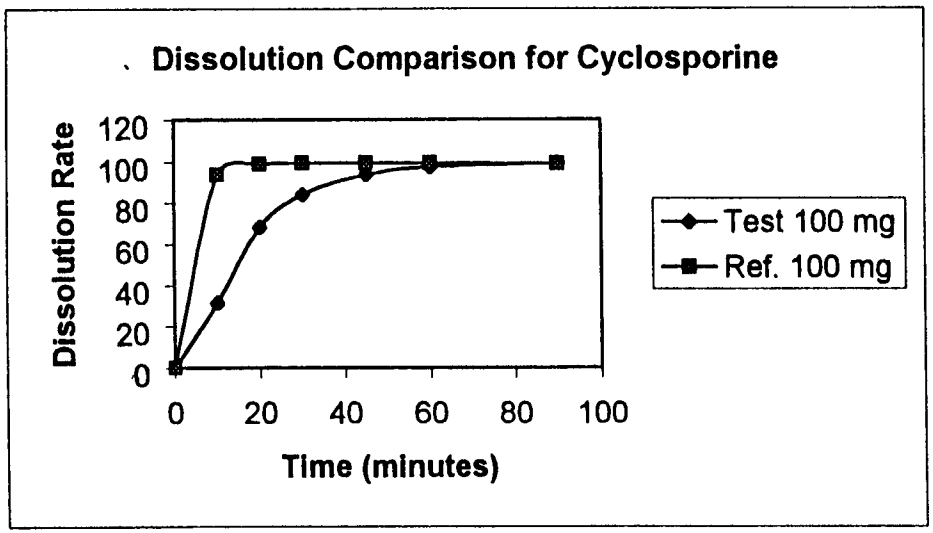
ANDA 65-003, Cyclosporine Hard Gelatin Capsules
Dissolution Comparison - Profile using the similarity factor F2

Test - 100 mg Lot #28-687-AR-03, bio-lot
Reference - 100 mg Lot #22427, bio-lot (Fed Study)

time	Test 100 mg	Ref. 100 mg	Difference	(Diff)sq	sum of sq	ss/n	1+ss/n	to -.5 pwr	times 100	log	times 50
10	31.6	93.7	-62.1	3856.4	5060.09	1012	1013	0.031419	3.141893	0.49719	24.85957
20	68.2	98.9	-30.7	942.49							
30	84.2	99.2	-15	225		**F2=24.86**					
45	93.7	99.4	-5.7	32.49							
60	97.5	99.4	-1.9	3.61							
90	99.4	99.1	0.3	0.09							

dissolution comparison

time	Test 100 mg	Ref. 100 mg	
0	0	0	
10	31.6	93.7	
20	68.2	98.9	
30	84.2	99.2	
45	93.7	99.4	
60	97.5	99.4	
90	99.4	99.1	



Attachment # 11

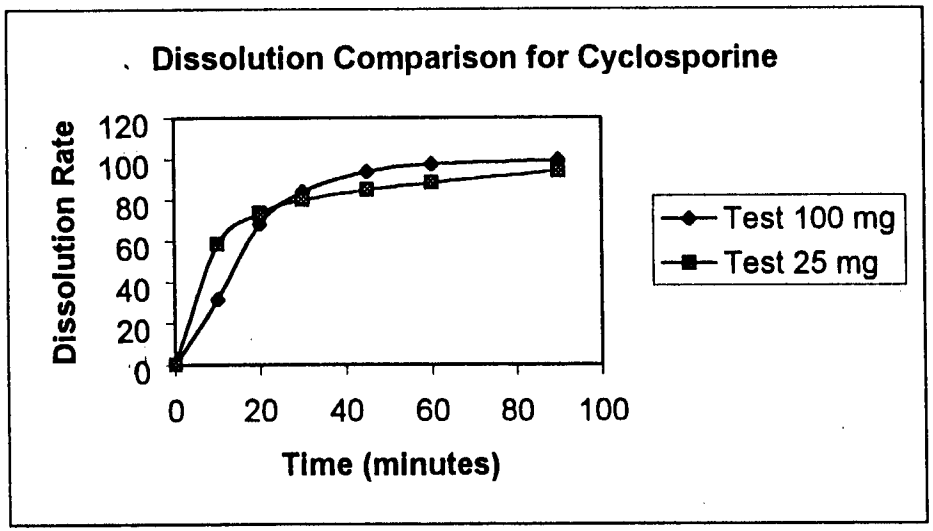
ANDA 65-003, Cyclosporine Hard Gelatin Capsules
Dissolution Comparison - Profile using the similarity factor F2

Test - 100 mg Lot #28-687-AR-03, bio-lot
Test - 25 mg Lot #28-686-AR-03

time	Test 100 mg	Test 25 mg	Difference	(Diff)sq	sum of sq	ss/n	1+ss/n	to -.5 pwr	times 100	log	times 50
10	31.6	58.5	-26.9	723.61	952.73	191	191.5	0.072254	7.225426	0.85886	42.94317
20	68.2	73.5	-5.3	28.09							
30	84.2	80.1	4.1	16.81		**F2=42.94**					
45	93.7	85.2	8.5	72.25							
60	97.5	88.4	9.1	82.81							
90	99.4	94	5.4	29.16							

dissolution comparison

time	Test 100 mg	Test 25 mg	
0	0	0	
10	31.6	58.5	
20	68.2	73.5	
30	84.2	80.1	
45	93.7	85.2	
60	97.5	88.4	
90	99.4	94	



Attachment #12

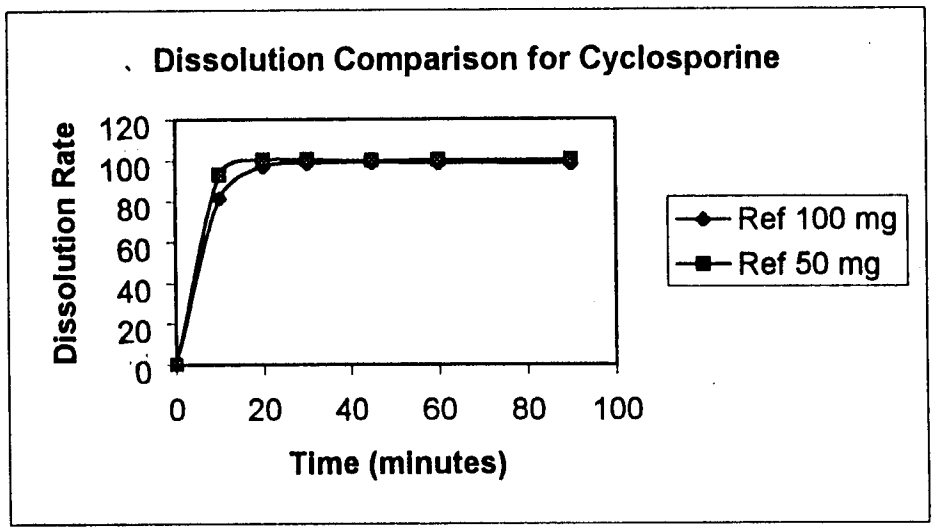
ANDA 65-003, Cyclosporine Hard Gelatin Capsules
Dissolution Comparison - Profile using the similarity factor F2

Reference - 100 mg Lot #22265, bio-lot
Reference - 50 mg Lot #238

time	Ref 100 mg	Ref 50 mg	Difference	(Diff)sq	sum of sq	ss/n	1+ss/n	to -.5 pwr	times 100	log	times 50
10	81.5	93.2	-11.7	136.89	157.66	31.5	32.53	0.175325	17.53253	1.24384	62.19223
20	97.1	100.1	-3	9							
30	98.6	100.6	-2	4		**F2=62.19**					
45	98.9	100	-1.1	1.21							
60	98.6	100.2	-1.6	2.56							
90	98.3	100.3	-2	4							

dissolution comparison

time	Ref 100 mg	Ref 50 mg	
0	0	0	
10	81.5	93.2	
20	97.1	100.1	
30	98.6	100.6	
45	98.9	100	
60	98.6	100.2	
90	98.3	100.3	



Attachment #13

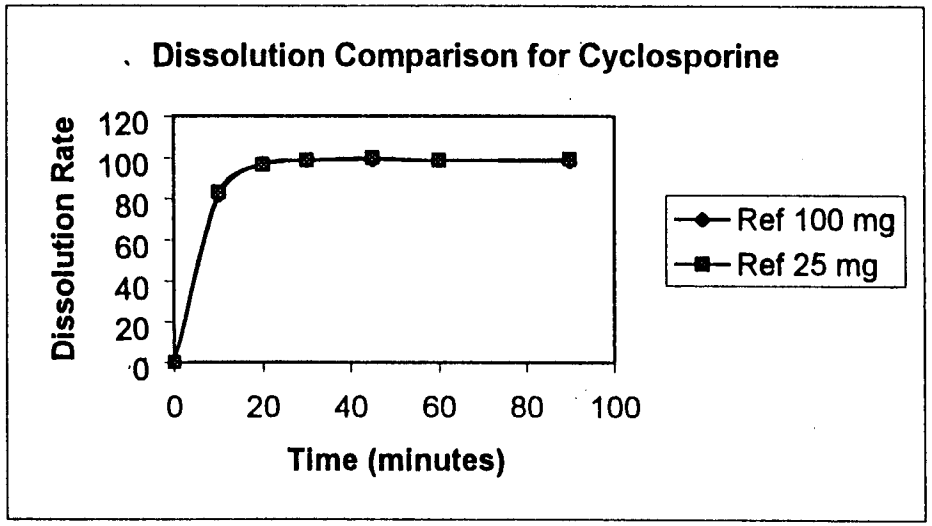
ANDA 65-003, Cyclosporine Hard Gelatin Capsules
Dissolution Comparison - Profile using the similarity factor F2

Reference - 100 mg Lot #22265, bio-lot
Reference - 25 mg Lot #300429

time	Ref 100 mg	Ref 25 mg	Difference	(Diff)sq	sum of sq	ss/n	1+ss/n	to -.5 pwr	times 100	log	times 50
10	81.5	83.2	-1.7	2.89	5.42	1.08	2.084	0.692709	69.27095	1.84055	92.02756
20	97.1	96.4	0.7	0.49							
30	98.6	98.7	-0.1	0.01		**F2=92.03**					
45	98.9	99.8	-0.9	0.81							
60	98.6	98.7	-0.1	0.01							
90	98.3	99.4	-1.1	1.21							

dissolution comparison

time	Ref 100 mg	Ref 25 mg	
0	0	0	
10	81.5	83.2	
20	97.1	96.4	
30	98.6	98.7	
45	98.9	99.8	
60	98.6	98.7	
90	98.3	99.4	



Attachment #14

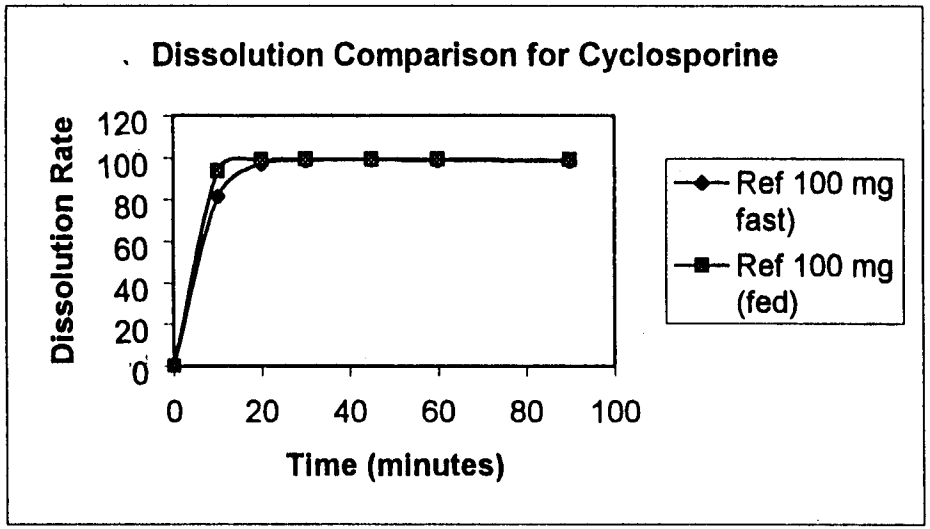
ANDA 65-003, Cyclosporine Hard Gelatin Capsules
Dissolution Comparison - Profile using the similarity factor F2

Reference - 100 mg Lot #22265, bio-lot (fast study)
Reference - 100 mg Lot #22427, bio-lot (fed study)

time	Ref 100 mg (fast)	Ref 100 mg (fed)	Difference	(Diff)sq	sum of sq	ss/n	1+ss/n	to -.5 pwr	times 100	log	times 50
10	81.5	93.7	-12.2	148.84	153.97	30.8	31.79	0.177348	17.73485	1.24883	62.44137
20	97.1	98.9	-1.8	3.24							
30	98.6	99.2	-0.6	0.36		**F2=62.44**					
45	98.9	99.4	-0.5	0.25							
60	98.6	99.4	-0.8	0.64							
90	98.3	99.1	-0.8	0.64							

dissolution comparison

time	Ref 100 mg fast)	Ref 100 mg (fed)
0	0	0
10	81.5	93.7
20	97.1	98.9
30	98.6	99.2
45	98.9	99.4
60	98.6	99.4
90	98.3	99.1



Attachment # 15

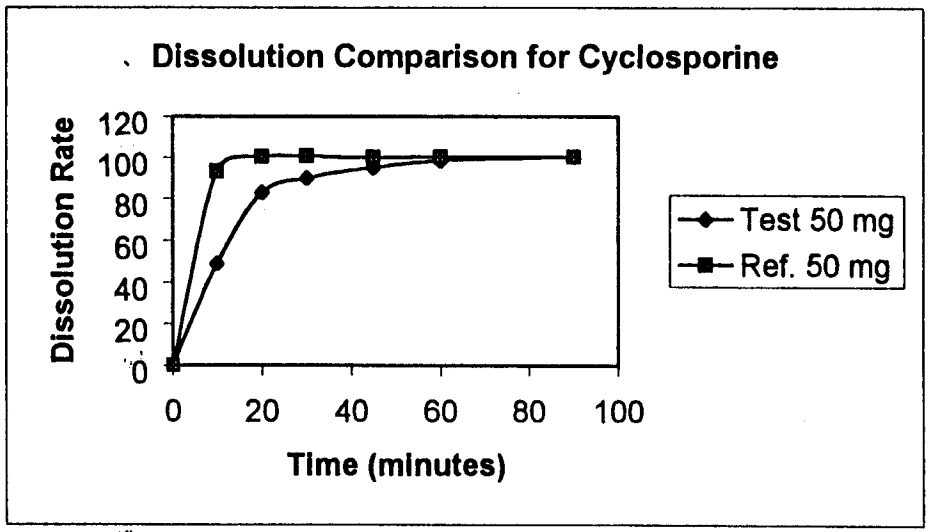
ANDA 65-003, Cyclosporine Hard Gelatin Capsules
Dissolution Comparison - Profile using the similarity factor F2

Test - 50 mg Lot #29-719-AR-03
Reference - 50 mg Lot #238

time	Test 50 mg	Ref. 50 mg	Difference	(Diff)sq	sum of sq	ss/n	1+ss/n	to -.5 pwr	times 100	log	times 50
10	49	93.2	-44.2	1953.6	2389.55	478	478.9	0.045695	4.569546	0.65987	32.99365
20	83	100.1	-17.1	292.41							
30	89.9	100.6	-10.7	114.49		**F2=32.99**					
45	95	100	-5	25							
60	98.2	100.2	-2	4							
90	100.2	100.3	-0.1	0.01							

dissolution comparison

time	Test 50 mg	Ref. 50 mg	
0	0	0	
10	49	93.2	
20	83	100.1	
30	89.9	100.6	
45	95	100	
60	98.2	100.2	
90	100.2	100.3	



Attachment #16

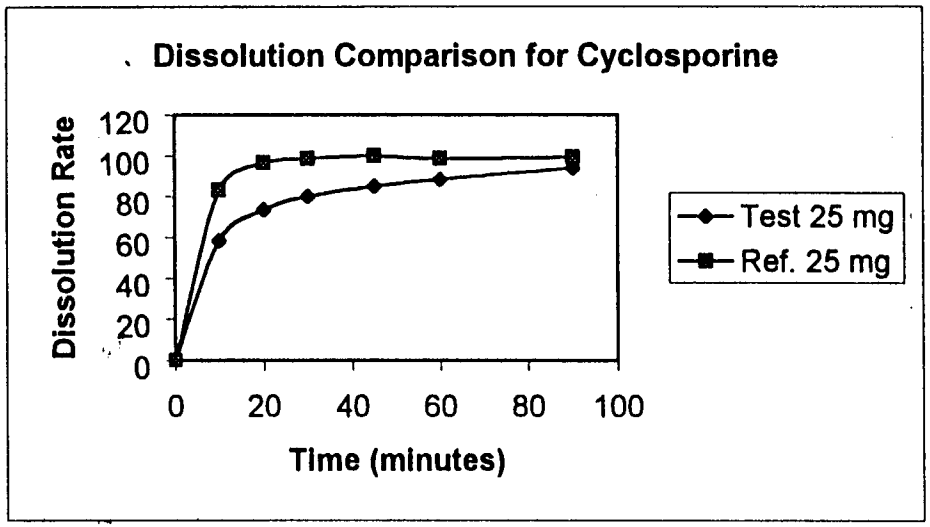
ANDA 65-003, Cyclosporine Hard Gelatin Capsules
Dissolution Comparison - Profile using the similarity factor F2

Test - 25 mg Lot #28-686-AR-03
Reference - 25 mg Lot #300429

time	Test 25 mg	Ref. 25 mg	Difference	(Diff)sq	sum of sq	ss/n	1+ss/n	to -.5 pwr	times 100	log	times 50
10	58.5	83.2	-24.7	610.09	1828.87	366	366.8	0.052216	5.221565	0.7178	35.89004
20	73.5	96.4	-22.9	524.41							
30	80.1	98.7	-18.6	345.96		**F2=35.89**					
45	85.2	99.8	-14.6	213.16							
60	88.4	98.7	-10.3	106.09							
90	94	99.4	-5.4	29.16							

dissolution comparison

time	Test 25 mg	Ref. 25 mg
0	0	0
10	58.5	83.2
20	73.5	96.4
30	80.1	98.7
45	85.2	99.8
60	88.4	98.7
90	94	99.4



Cyclosporine
100 mg Hard Gelatin Capsule
50 mg Hard Gelatin Capsule
25 mg Hard Gelatin Capsule
ANDA #65-003
Reviewer: Z.Z. Wahba
File #65003sdw.d97

Abbott Laboratories
Abbott Park, IL
Submission Dated:
March 3, 1998
July 20, 1998
August 5, 1998

REVIEW OF TWO BIOEQUIVALENCE STUDIES AND IN VITRO DISSOLUTION TESTING DATA

I. OBJECTIVE:

Review the following:

1. Abbott's in vivo bioequivalence studies under fasting and non-fasting conditions comparing its drug product Cyclosporine Hard Gelatin Capsule, 100 mg, to the reference listed drug Novartis' Neoral® (Cyclosporine Soft Gelatin Capsule), 100 mg.

2. Dissolution data for 25 mg, 50 mg and 100 mg strengths of the test and reference drug products.

3. Waiver requests for the 25 mg and 50 mg strengths capsules.

II. INTRODUCTION:

Cyclosporine is a potent immunosuppressive agent. It is indicated for the prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants. The exact mechanism of action of cyclosporine is still unclear.

The immunosuppressive activity of cyclosporine is primarily due to the parent drug. The extent of absorption of cyclosporine is dependent on the individual patient, the patient population, and the formulation. Cyclosporine is distributed largely outside the blood volume. In blood, the distribution is concentration dependent. Approximately % is in plasma, % in lymphocytes, % in granulocytes and % in erythrocytes. At higher concentrations, the uptake by leukocytes and erythrocytes becomes saturated. Elimination of cyclosporine is primarily biliary with only 6% of the drug excreted in urine.

Following oral administration of cyclosporine, the time to peak blood cyclosporine concentrations (Tmax) ranged from 1.5 to 2.0 hours. The administration of food with Neoral® decreases the cyclosporine AUC and Cmax.

RLD: Neoral® Soft Gelatin Capsules, 100 mg (Novartis pharmaceuticals).

Recommended dose: depending on the transplanted organ and other immunosuppressive agents included in the immunosuppressive protocol.

III. SINGLE DOSE BIOEQUIVALENCE STUDY, UNDER FASTING FASTING CONDITIONS (Study Protocol #M97-685)

A. Sponsor:
Abbott Laboratories
100 Abbott Park Road
Abbott Park, IL 60064-3500

Study Site:
Clinical Facility

Principal Investigator:

Analytical Facility

B. Study design:
Single dose, randomized, three-period, six-sequence, three-treatment, two-group, crossover study under fasting conditions.

Clinical Study Dates:

Group-1 (subjects #1-33):	July 21, 1997, July 28, 1997 and August 04, 1997.
Group-2 (subjects #34-66):	July 24, 1997, July 31, 1997 and August 09, 1997.

Sample Analysis Dates:
August 08, 1997 to September 02, 1997.

C. **Subjects**:
Sixty-six (66) healthy male and female subjects participated and 65 subjects were enrolled in the study. Sixty-three (63) subjects (males=34, females=29) completed all three periods of the study. Subjects #29 was terminated from the study prior to dosing in the second period due to conjunctivitis. Subject #21 was terminated from the study prior to dosing in the third period due to an urinary tract infection. The subjects were within 18 to 45 years of age, and their body weights were within ± 10% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

D. **Treatment Plan**:
Treatment A: Under fasting conditions, 3 X 100 mg Abbott's Cyclosporine **Hard** Gelatin Capsule (with designation SF-21), Bulk Product Lot #28-687-AR-03/7428N, Batch size: capsules, potency: 101.1%, content uniformity: 101.2%, manufacturing date: 05/21/97.

Treatment B: Under fasting conditions, 3 X 100 mg Abbott's Cyclosporine **Soft** Gelatin Capsule (with designation P-9P), Bulk Product Lot #27-655-AR-CC/7408N, Batch size: capsules, potency: 100.7%, content uniformity: (not given), manufacturing date: 05/28/97.

Treatment C: Under fasting conditions, 3 X 100 mg Novartis' Neoral® (Cyclosporine Soft Gelatin), Lot #22265, potency: 99.4%, content uniformity: (not given), expiration date: 10/01/98.

Washout period: 7 days.

E. **Food and Fluid Intake**:
Subjects fasted overnight for at least 10 hours before dosing and 4 hours after dosing. The drug products were administered with 180 mL of orange juice at room temperature. No food or beverage, except for water to quench thirst, was allowed. The subjects received their

medication according to a randomized dosing schedule. Standard meals were provided at appropriate times thereafter.

F. **Blood Sampling**:

Blood samples were collected in vacutainers tubes containing EDTA, before dosing (0 hour) and at 0.25, 0.50, 0.75, 1.00, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10, 12, 15, 18, 24, 30, 36, and 48 hours post-dosing. The blood samples were stored frozen at -10°C until analysis.

G. **Assay Methodology**: (Not to be released under FOI)

H. IN VIVO BE STUDY & STATISTICAL ANALYSIS:

Adverse events: one-hundred-four adverse events were reported by 46 subjects during the course of the study. The number of adverse events reported in the three regiments A, B, and C were relatively equally tolerated (57, 60 and 57, respectively). The most frequently reported adverse events (reported by 8 or more subjects) associated with Formulation A were vasodilation and asthenia, and with Formulation B and C, vasodilation and headache. All of the adverse events were rated as mild in severity and all the 63 subjects completed the clinical study.

The blood concentration and pharmacokinetic parameters of cyclosporine were analyzed using SAS-GLM procedure for analysis of variance. The Reviewer recalculated all the pharmacokinetic parameters and statistics including group effect in the model and the results of the recalculation are in agreement with the sponsor's submission. Blood concentrations and pharmacokinetic parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are presented below:

Table #1
Mean Cyclosporine Concentrations (ng/mL) in Whole Blood in 63 Subjects Following a Single Oral Dose of 3X100 mg Cyclosporine Capsules Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12	RMEAN13	RMEAN23
TIME HR									
0.25	2.65	6.33	4.87	4.91	5.82	7.85	0.54	0.45	0.84
0.5	127.00	110.99	100.80	84.29	191.97	159.65	1.26	0.66	0.53
0.75	467.65	234.54	337.18	210.60	601.61	312.10	1.39	0.78	0.56
1	782.89	291.28	573.46	298.85	938.49	357.10	1.37	0.83	0.61
1.5	1016.83	270.59	875.94	300.71	1178.13	380.28	1.16	0.86	0.74
2	994.49	246.51	985.91	260.19	1179.27	312.69	1.01	0.84	0.84
2.5	893.44	235.03	970.65	257.99	1058.09	281.29	0.92	0.84	0.92
3	770.60	222.43	878.86	260.55	895.18	251.57	0.88	0.86	0.98
4	554.68	181.63	639.29	225.84	636.95	197.46	0.87	0.87	1.00
6	291.49	88.41	319.53	111.80	332.68	94.85	0.91	0.88	0.96
8	183.56	54.60	194.99	64.27	212.57	59.39	0.94	0.86	0.92
10	129.03	35.62	135.69	43.59	149.31	43.28	0.95	0.86	0.91
12	90.65	24.72	94.29	31.01	103.04	28.79	0.96	0.88	0.92
15	61.60	16.34	64.05	20.13	70.37	18.29	0.96	0.88	0.91
18	47.71	12.36	49.40	15.80	54.77	14.93	0.97	0.87	0.90
24	30.90	8.56	31.76	10.74	34.51	9.98	0.97	0.90	0.92
30	20.69	6.15	21.63	8.32	23.30	7.13	0.96	0.89	0.93
36	16.02	5.22	16.57	6.60	18.29	5.68	0.97	0.88	0.91
48	11.75	4.47	12.15	5.59	13.51	4.93	0.97	0.87	0.90

MEAN1=Test-Hard Gel Cap. MEAN2=Test-Soft-Gel Cap.
MEAN3=Ref.-product

Table #2
Mean Pharmacokinetic Parameters (Arithmetic) for Cyclosporine in 63 Subjects Following a Single Oral Dose of 3X100 Cyclosporine Capsules, Under Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12	RMEAN13	RMEAN23
PARAMETER									
AUCI	5987.18	1479.26	6189.83	1828.56	6964.84	1694.21	0.97	0.86	0.89
AUCT	5664.02	1355.67	5853.33	1649.19	6583.25	1573.79	0.97	0.86	0.89
CMAX	1098.35	245.29	1058.17	258.63	1299.84	317.90	1.04	0.84	0.81
KE	0.04	0.01	0.04	0.01	0.04	0.01	1.00	1.04	1.04
*LAUCI	5823.44	0.23	5935.61	0.29	6771.37	0.24	0.98	0.86	0.88
*LAUCT	5517.81	0.23	5628.26	0.29	6404.66	0.24	0.98	0.86	0.88
*LCMAX	1072.11	0.22	1027.40	0.25	1266.61	0.23	1.04	0.85	0.81
THALF	18.09	4.07	18.09	3.90	18.82	3.98	1.00	0.96	0.96
TMAX	1.83	0.59	2.22	0.55	1.92	0.69	0.83	0.96	1.16

MEAN1=Test-Hard Gel Cap. MEAN2=Test-Soft Gel Cap.
MEAN3=Ref.-product
UNIT: AUC=NG.HR/ML CMAX=NG/ML
* The values represent the geometric mean (antilog of the means of the logs).

Table #3
Mean Pharmacokinetic Parameters (LSMean) for Cyclosporine in 63 Subjects Following a Single Oral Dose of 3X100 Cyclosporine Capsules, Under Fasting Conditions

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
LAUCI	5817.00	5923.59	6760.77	0.98	0.86	0.88
LAUCT	5513.29	5619.00	6396.77	0.98	0.86	0.88
LCMAX	1069.97	1025.29	1264.05	1.04	0.85	0.81

MEAN1=Test-Hard Gel Cap. MEAN2=Test-Soft Gel Cap.
MEAN3=Ref.-product

Table #4
LSMeans And The 90% Confidence Intervals in 63 Subjects Following a Single Oral Dose of 3X100 Cyclosporine Capsules, Under Fasting Conditions

	LSM1	LSM2	LSM3	LOWCI12	UPPCI12	LOWCI13	UPPCI13	LOWCI23	UPPCI23
LAUCI	5817.00	5923.59	6760.77	94.88	101.64	83.13	89.06	84.65	90.69
LAUCT	5513.29	5619.00	6396.77	94.86	101.48	83.33	89.15	84.93	90.85
LCMAX	1069.97	1025.29	1264.05	100.46	108.40	81.49	87.93	78.08	84.26

MEAN1=Test-Hard Gel Cap. MEAN2=Test-Soft Gel Cap.

MEAN3=Ref.-product
UNIT: AUC=NG HR/ML CMAX=NG/ML

Comment on the fasting study:

1. For treatment A (Abbott's cyclosporine hard gelatin capsule), the 90% confidence intervals (LOWCI13-UPPCI13) for the LSMeans log-transformed AUCt, AUCi and Cmax were within the acceptable range of % (Table #4). Therefore, formulation A is acceptable.

2.

3. **Only Abbott's cyclosporine hard gelatin capsule, 100 mg (lot #28-687-AR-03) has been found to be bioequivalent to the reference listed product, Novartis' Neoral® (Cyclosporine Soft Gelatin).**

Note: Two subjects in this study experienced emesis within two hours of dosing. Subject #26 in Period-2 (Treatment C) and subject #31 in Period-1 (Treatment C) vomited 41 and 66 minutes after dosing, respectively. The subjects exhibited normal blood cyclosporine concentration-time profiles and drug absorption appears to be complete. However, an additional analysis of variance (ANOVA) was performed by the reviewer for all subjects excluding subjects #26 and 31 and the results are presented below.

Table #5
LSMeans And The 90% Confidence Intervals in 61 Subjects Following a Single Oral Dose of 3X100 Cyclosporine Capsules, Under Fasting Conditions

	LSM1	LSM2	LSM3	LOWCI12	UPPCI12	LOWCI13	UPPCI13	LOWCI23	UPPCI23
LAUCI	5801.74	5908.05	6821.27	95.09	101.42	82.36	87.84	83.87	89.45
LAUCT	5499.67	5610.02	6454.15	94.99	101.18	82.56	87.95	84.22	89.71
LCMAX	1072.74	1025.84	1268.18	100.57	108.74	81.35	87.96	77.79	84.11

MEAN1=Test-Hard Gel Cap. MEAN2=Test-Soft Gel Cap.
MEAN3=Ref.-product
UNIT: AUC=NG.HR/ML CMAX=NG/ML

Results and Conclusion: Tables #4 and # 5 were obtained from the statistical analysis of all subjects (63 subjects) and the 61 subjects (excluding subjects 26 and 31), respectively, show that there is no significant difference in the outcome of the 90% confidence intervals if the two subjects (#26 and 31) were either included or excluded from the statistical analysis.

IV. SINGLE DOSE BIOEQUIVALENCE STUDY, UNDER NON-FASTING CONDITIONS (Study Protocol #M97-686)

A. Sponsor:
Abbott Laboratories
100 Abbott Park Road
Abbott Park, IL 60064-3500

Study Site:
Clinical Facility

Analytical Facility

B. Study design:
Single dose, randomized, three-period, six-sequence, three-

treatment, crossover study under fasting and non-fasting conditions.

Clinical Study Dates:
September 22, 1997; September 29, 1997 and October 06, 1997.

Sample Analysis Dates:
September 22, 1997 to October 21, 1997.

C. **Subjects**:
Forty-eight (48) healthy male (n=26) and female (n=22) subjects were recruited and 45 subjects (23 males and 22 females) completed the study. Subject #19 withdrew from the study due to personal reasons (after dosing and completing the study procedures for Period-2). Subject #26 and 39 were terminated from the study due to positive drug screens for marijuana metabolites and benzodiazepines, respectively on study Day-1 of Period-2. The subjects were within 18 to 45 years of age, and their body weights were within ± 10% of the ideal weight as defined by the Metropolitan Life Insurance Chart.

D. **Treatment Plan**:

Treatment A: Under fasting conditions, 3 X 100 mg Abbott's Cyclosporine Hard Gelatin Capsule, Bulk Product Lot #28-687-AR-03/7428N, Batch size: capsules, potency: 101.1%, content uniformity: 101.2%, manufacturing date: 05/21/97.

Treatment B: Under non-fasting conditions, 3 X 100 mg Abbott's Cyclosporine Hard Gelatin Capsule, Bulk Product Lot #28-687-AR-03/7428N, Batch size: capsules, potency: 101.1%, content uniformity: 101.2%, manufacturing date: 05/21/97.

Treatment C: Under non-fasting conditions, 3 X 100 mg Novartis' Neoral® (Cyclosporine Soft Gelatin), Lot #22427, potency: 100.0%, content uniformity: (not given), expiration date: 11/01/98.

Washout period: 7 days.

E. **Food and Fluid Intake**:
Subjects who received treatment A, fasted overnight for 10 hours before dosing and for 4 hours after each drug administration. Subjects who received treatments B and C, fasted overnight for 9.5 hours before they were fed a standard high fat breakfast, which was consumed in its entirety 30 minutes before drug administration. Each dose was followed by 180 mL of orange juice at room temperature according to randomized dosing schedule. Standard meals were provided at appropriate times thereafter.

F. **Blood Sampling**:
Blood samples were collected in vacutainer tubes containing EDTA, before dosing (0 hour) and at 0.25, 0.50, 0.75, 1.00, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10, 12, 15, 18, 24, 30, 36, and 48 hours post-dosing. The blood samples were stored frozen at -10°C until analysis.

G. **Assay Methodology**:
The same as protocol #M97-685, under fasting conditions.

H. **IN VIVO BE STUDY & STATISTICAL ANALYSIS**:

Adverse events: Fifty-one adverse events were reported by 24 subjects during the course of the study. The number of adverse events reported in the three regiments A, B, and C were well tolerated (17, 15 and 19, respectively). The most frequent reported adverse event was vasodilation occurring in all three regiments (N=6, 13%, N=8, 17.8% and N=7, 14.6% for regimens A, B and C, respectively).

The blood concentration and pharmacokinetic parameters of cyclosporine were analyzed using SAS-GLM procedure for analysis of variance. The Reviewer recalculated all the pharmacokinetic parameters and statistics and the results of the recalculation are in agreement with the sponsor's submission. Blood concentrations and pharmacokinetic parameters, AUCt, AUCi, Cmax, Tmax, Kel, T1/2 are presented below:

Table #6
Mean Cyclosporine Concentrations (ng/mL) in Whole Blood in 45 Subjects Following a Single Oral Dose of 3X100 mg Cyclosporine Capsules Under Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12	RMEAN13	RMEAN23
TIME HR									
0.25	3.14	4.72	1.80	1.75	2.66	2.65	1.74	1.18	0.68
0.5	141.74	108.42	11.98	30.16	144.99	136.47	11.83	0.98	0.08
0.75	619.74	244.92	94.59	136.67	596.38	435.47	6.55	1.04	0.16
1	1043.92	303.14	306.03	277.16	1020.58	515.73	3.41	1.02	0.30
1.5	1283.62	230.06	846.08	456.87	1367.96	355.47	1.52	0.94	0.62
2	1200.48	210.95	1123.47	364.81	1289.90	302.14	1.07	0.93	0.87
2.5	1063.25	255.67	1182.85	252.36	1146.29	281.95	0.90	0.93	1.03
3	897.91	267.55	1098.93	224.81	953.58	257.14	0.82	0.94	1.15
4	630.87	199.88	858.35	218.54	716.23	204.50	0.73	0.88	1.20
6	318.25	86.96	500.03	164.05	415.45	140.19	0.64	0.77	1.20
8	207.70	59.26	292.54	96.97	246.15	77.21	0.71	0.84	1.19
10	139.65	41.19	208.94	74.81	167.95	51.44	0.67	0.83	1.24
12	99.30	30.16	146.62	52.03	123.98	43.11	0.68	0.80	1.18
15	67.14	19.13	90.85	29.80	78.13	24.16	0.74	0.86	1.16
18	48.35	13.97	63.84	19.35	56.90	17.15	0.76	0.85	1.12
24	30.73	11.11	40.81	26.20	34.86	12.42	0.75	0.88	1.17
30	20.97	6.38	25.62	9.00	23.55	7.55	0.82	0.89	1.09
36	15.87	4.46	20.44	7.29	18.94	6.09	0.78	0.84	1.08
48	11.93	3.89	14.81	5.53	13.87	4.97	0.81	0.86	1.07

MEAN1=Test-Fast MEAN2=Test-Fed MEAN3=Ref.-Fed

Table #7
Mean Pharmacokinetic Parameters (Arithmetic) for Cyclosporine in 45 Subjects Following a Single Oral Dose of 3X100 Cyclosporine Capsules, Under Non-Fasting Conditions

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12	RMEAN13	RMEAN23
AUCI	6840.69	1417.63	7860.99	1797.91	7733.14	1911.24	0.87	0.88	1.02
AUCT	6499.38	1349.58	7430.83	1630.70	7324.16	1781.64	0.87	0.89	1.01
CMAX	1347.36	226.20	1277.89	268.46	1449.50	324.49	1.05	0.93	0.88
KE	0.04	0.01	0.04	0.01	0.04	0.01	0.96	1.04	1.09
*LAUCI	6693.46	0.21	7664.56	0.23	7455.65	0.29	0.87	0.90	1.03
*LAUCT	6362.17	0.21	7260.54	0.22	7064.45	0.29	0.88	0.90	1.03
*LCMAX	1328.62	0.17	1251.93	0.20	1409.75	0.25	1.06	0.94	0.89
THALF	19.38	5.46	19.01	6.36	20.23	5.72	1.02	0.96	0.94
TMAX	1.58	0.43	2.36	0.56	1.68	0.44	0.67	0.94	1.40

MEAN1=Test-Fast MEAN2=Test-Fed MEAN3=Ref.-Fed

UNIT: AUC=NG.HR/ML CMAX=NG/ML

RMEAN23=T/R ratio under non-fasting conditions

* The values represent the geometric mean (antilog of the means of the logs).

Table #8

Mean Pharmacokinetic Parameters (LSMean) for Cyclosporine in 45 Subjects Following a Single Oral Dose of 3X100 Cyclosporine Capsules, Under Non-Fasting Conditions

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
LAUCI	6696.80	7694.65	7433.91	0.87	0.90	1.04
LAUCT	6363.40	7286.37	7042.14	0.87	0.90	1.03
LCMAX	1330.35	1257.38	1407.30	1.06	0.95	0.89

MEAN1=Test-Fast MEAN2=Test-Fed MEAN3=Ref.-Fed
UNIT: AUC=NG.HR/ML CMAX=NG/ML
RMEAN23=T/R ratio under non-fasting conditions

Comment on the non-fasting study:
Under non-fasting conditions, the T/R mean ratios (RLSM23) for log-transformed AUCt, AUCi and Cmax were within the acceptable range of 0.80 to 1.25 (Table #8).

Note: Two subjects in this study experienced emesis within two hours of dosing. Subject #11 in Period 3 (Treatment C) and subject #47 in Period 3 (Treatment A) vomited 104 and 62 minutes after dosing, respectively. An analysis of variance (ANOVA) was performed by the reviewer for all subjects excluding subjects #11 and 47 and the results are presented below.

Table 9

Mean Pharmacokinetic Parameters (LSMean) for Cyclosporine in 43 Subjects Following a Single Oral Dose of 3X100 Cyclosporine Capsules, Under Non-Fasting Conditions

PARAMETER	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
AUCI	6827.67	7860.52	7941.02	0.87	0.86	0.99
AUCT	6487.90	7436.17	7525.89	0.87	0.86	0.99
CMAX	1355.85	1282.91	1475.11	1.06	0.92	0.87
LAUCI	6674.55	7666.53	7754.96	0.87	0.86	0.99
LAUCT	6344.73	7265.84	7358.27	0.87	0.86	0.99
LCMAX	1336.58	1255.83	1440.82	1.06	0.93	0.87

MEAN1=Test-Fast MEAN2=Test-Fed MEAN3=Ref.-Fed
UNIT: AUC=NG.HR/ML CMAX=NG/ML
RMEAN23=T/R ratio under non-fasting conditions

Results and Conclusion: Tables #8 and #9 obtained from the statistical analysis of all subject (45 subjects) and the 43

subjects (excluding subjects 11 and 47), respectively, show that there is no significant difference in the outcome of the T/R ratios if the two subjects (#11 and 47) were either included or excluded from the statistical analysis.

V. FORMULATION COMPARISON

Abbott comparative formulations for its test products, cyclosporine hard gelatin capsules, 25 mg, 50 mg and 100 mg are reported on page #21, volume C1.1. A copy of the formulation statement is included in this report (Attachment #1).

VI. DISSOLUTION

The dissolution data that were submitted did not meet the dissolution specifications set by the Agency. Please see the deficiency comment section.

VII. DEFICIENCIES

1. The firm should provide long term stability data covering the entire period of sample storage from blood collection to analysis. In addition, data on the assay methodology recovery should be included.

2. The bioequivalence study under fasting conditions using Abbott's cyclosporine soft gelatin capsule, 100 mg (lot #27-687-AR-03) is not acceptable since the 90% confidence interval for Cmax is outside the acceptable range of 80-125% of the reference listed drug.

3. The firm should obtain the dissolution data for the 25 mg, 50 mg and 100 mg formulations according to the following specification. The Agency recommends the following dissolution approach:

   Tier 1: 0.1N HCl containing 0.2% LDAO (lauryldimethylamine-N-oxide) for 25 and 50 mg capsules; 0.1N HCl containing 0.4% for 100 mg capsules. Apparatus: Paddle 75 rpm.

   Tier 2: If not passing at Tier 1: SGF with containing 0.2% LDAO for 25 and 50 mg capsules; SGF with containing 0.4% for 100 mg capsules. Paddle 75 rpm, The

suggested time points are 10, 20, 30, 45, 60 and 90 minutes.

The firm is also referred to the Pharmacopial Forum, dated May-June 1998. The comparative dissolution profiles for the test and reference products (in a side-by-side tabular format, if possible) should be submitted with raw dissolution data, the dissolution mean, the range (high, low), and the percentage of coefficient of variation (%C.V.), and date(s) of analysis. Comparative dissolution data for both the test and reference drug products should be performed simultaneously. In addition, the lot number, lot size (for the test product only), and the manufacturing date for the test product and expiration date for the reference product should be included. The lot number of the dissolution testing should be identical to the one used in the in vivo study.

4. The two bioequivalence studies under fasting and non-fasting conditions used two different reference drug lots, #22265 and 22427, respectively. Please provide the rationale for not using the same reference drug lot number for both the fasting and non-fasting studies.

VIII. RECOMMENDATIONS:

The in vivo bioequivalence study conducted under fasting and non-fasting conditions by Abbott Laboratories on its Cyclosporine Hard Gelatin Capsules, 100 mg (lot #28-687-AR-03), comparing it to the reference listed drug Novartis's Neoral® (Cyclosporine Soft Gelatin Capsule), 100 mg, has been found incomplete due to the deficiencies #1-4.

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALLED BDAVIT 9/22/98
FT INITIALLED BDAVIT

9/23/98

Concur: _____ Date: 10/2/98

for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence