

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50-786

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Dissolution medium: Water at 37°C
Volume: 900 mL
Paddle speed: 75 rpm
Analytical method: Atomic absorption spectroscopy
Specification: Q = [redacted] (NLT [redacted] at 20 min)

Metronidazole

Apparatus: USP apparatus II (paddle)
Dissolution medium: 0.1N HCl at 37°C
Volume: 900 mL
Paddle speed: 75 rpm
Analytical method: HPLC with UV detection
Specification: Q = [redacted] (NLT [redacted] at 30 min)

Tetracycline HCl

Apparatus: USP apparatus II (paddle)
Dissolution medium: 0.1N HCl at 37°C
Volume: 900 mL
Paddle speed: 75 rpm
Analytical method: HPLC
Specification: Q = [redacted] (NLT [redacted] at 20 min)

III. Labeling Comments

Labeling comments from the OCPB reviewer are incorporated into the final label (version 09/15/03) in Appendix 1.

Seong H. Jang, Ph.D.
Reviewer
Clinical Pharmacology and Biopharmaceutics

DPEIII/OCPB

Concurrence _____
Phil Colangelo, Pharm.D., Ph.D.
Team Leader
Clinical Pharmacology and Biopharmaceutics

DPEIII/OCPB

Dissolution of Helizide[®] Capsule

According to the Division's requests, dated on May 22, 2003, the sponsor submitted additional dissolution data which were obtained from testing 12 capsules of three different Helizide[®] lots (9E520, 9E521 and 9E522) at paddle speeds of 50, 75 and 100 rpm. The dissolution profiles of three components, i.e., biscalcitrates, metronidazole, and tetracycline HCl, are shown in Figures 1 to 3. The relevant raw data are attached in Appendix 2 at the end of this review.

Figure 1: Influence of mixing speed on dissolution profiles of Biscalcitrates from Helicide (n= 3 lots, 12 capsules from each lot)

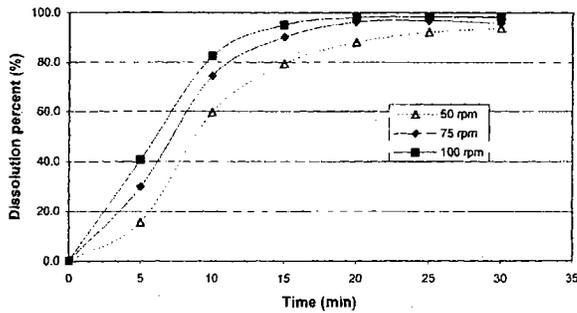


Figure 2: Influence of mixing speed on dissolution profiles of metronidazole from Helicide (n= 3 lots, 12 capsules from each lot)

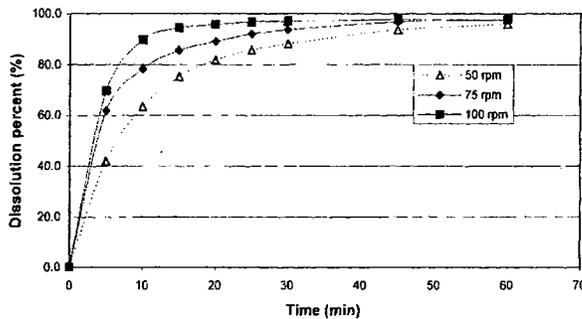
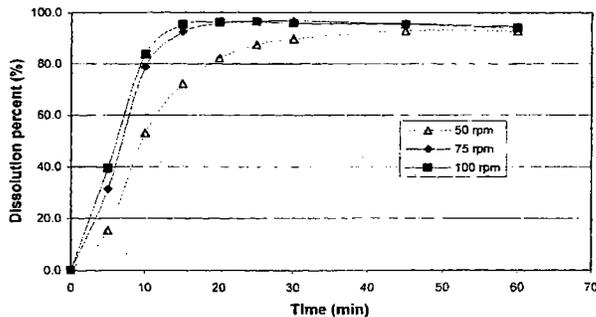


Figure 3: Influence of mixing speed on dissolution profiles of tetracycline HCl from Helicide (n= 3 lots, 12 capsules from each lot)



Apparatus: USP apparatus II (paddle)
Dissolution medium: 0.1N HCl at 37°C
Volume: 900 mL
Paddle speed: 100 rpm
Analytical method: HPLC
Specification: NLT $\geq 75\%$ in 60 minutes

3. Recommendation

The proposed dissolution method is acceptable with decreases in paddle speeds from 100 rpm to 75 rpm. We recommend the sponsor use the following as final dissolution methods and specifications for each component of Helizide[®] capsule.

Biscaltrate Potassium

Apparatus: USP apparatus II (paddle)
Dissolution medium: Water at 37°C
Volume: 900 mL
Paddle speed: 75 rpm
Analytical method: Atomic absorption spectroscopy
Specification: $Q = \geq 75\%$ (NLT $\geq 75\%$ at 20 min)

Metronidazole

Apparatus: USP apparatus II (paddle)
Dissolution medium: 0.1N HCl at 37°C
Volume: 900 mL
Paddle speed: 75 rpm
Analytical method: HPLC with UV detection
Specification: $Q = \geq 75\%$ (NLT $\geq 75\%$ at 30 min)

Tetracycline HCl

Apparatus: USP apparatus II (paddle)
Dissolution medium: 0.1N HCl at 37°C
Volume: 900 mL
Paddle speed: 75 rpm
Analytical method: HPLC
Specification: $Q = \geq 75\%$ (NLT $\geq 75\%$) at 20 min

Appendix 1

Proposed Labeling with OCPB Reviewer Revision

NDA-50-786: Helizide[®]

(Biskalcitrate Potassium, Metronidazole, Tetracycline)

Version: September 15, 2003

19 Page(s) Withheld

 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Appendix 2:

**Raw data For Biskalcitrate, metronidazole, and tetracycline HCl
dissolution profiles from Helicide Lot 9E520, 9E521, and 9E522 at 50,
75 and 100 rpm**

Dissolution profiles of Biscalcitrato (expressed as bismuth oxide) in Helicide caps

Speed: 100 rpm

NCA: A33-030526-041

Lot: 9E520

Time	1	2	3	4	5	6	7	8	9	10	11	12	Avr.	SD
After 5 min													41,0	12,5
After 10 min													86,2	13,2
After 15 min													96,4	8,9
After 20 min													99,8	3,6
After 25 min													100,9	2,2
After 30 min													101,3	2,1

Speed: 75 rpm

NCA: A33-030526-042

Lot: 9E520

Time	1	2	3	4	5	6	7	8	9	10	11	12	Avr.	SD
After 5 min													26,6	17,4
After 10 min													76,7	16,0
After 15 min													92,1	7,5
After 20 min													96,4	2,9
After 25 min													97,2	2,4
After 30 min													96,1	3,2

Speed: 50 rpm

NCA: A33-030526-043

Lot: 9E520

Time	1	2	3	4	5	6	7	8	9	10	11	12	Avr.	SD
After 5 min													15,7	9,7
After 10 min													62,0	11,4
After 15 min													83,0	6,8
After 20 min													93,1	5,5
After 25 min													96,1	3,6
After 30 min													97,6	2,3

Dissolution profiles of Biskalcitrate (expressed as bismuth oxide) in Helicide caps

Speed: 100 rpm

NCA: A33-030526-044

Lot: 9E521

Time	1	2	3	4	5	6	7	8	9	10	11	12	Avr.	SD
After 5 min													54,6	18,2
After 10 min													90,5	8,3
After 15 min													96,7	5,2
After 20 min													97,9	4,0
After 25 min													97,9	3,4
After 30 min													96,9	2,5

Speed: 75 rpm

NCA: A33-030526-045

Lot: 9E521

Time	1	2	3	4	5	6	7	8	9	10	11	12	Avr.	SD
After 5 min													49,5	8,9
After 10 min													86,3	8,8
After 15 min													93,7	6,3
After 20 min													96,7	3,9
After 25 min													97,5	3,1
After 30 min													96,1	2,6

Speed: 50 rpm

NCA: A33-030526-046

Lot: 9E521

Time	1	2	3	4	5	6	7	8	9	10	11	12	Avr.	SD
After 5 min													23,4	14,8
After 10 min													74,9	9,3
After 15 min													87,7	6,4
After 20 min													92,8	5,6
After 25 min													95,9	4,1
After 30 min													96,8	3,2

Dissolution profiles of Biscalcitrato (expressed as bismuth oxide) in Helicide caps

Speed: 100 rpm

NCA: A33-030526-047

Lot: 9E522

Time	1	2	3	4	5	6	7	8	9	10	11	12	Avr.	SD
After 5 min													26,5	23,5
After 10 min													71,0	18,0
After 15 min													92,1	9,4
After 20 min													96,7	4,6
After 25 min													96,6	2,7
After 30 min													96,7	3,2

Speed: 75 rpm

NCA: A33-030526-048

Lot: 9E522

Time	1	2	3	4	5	6	7	8	9	10	11	12	Avr.	SD
After 5 min													13,5	15,5
After 10 min													60,6	25,1
After 15 min													84,7	10,9
After 20 min													95,6	2,7
After 25 min													95,7	2,3
After 30 min													94,9	2,7

Speed: 50 rpm

NCA: A33-030526-049

Lot: 9E522

Time	1	2	3	4	5	6	7	8	9	10	11	12	Avr.	SD
After 5 min													7,7	14,1
After 10 min													42,3	24,8
After 15 min													67,6	26,7
After 20 min													78,5	21,5
After 25 min													84,6	15,1
After 30 min													86,7	12,4

Helicide Capsule
 Lot #: 9E520
 A33-030526-041
 Metronidazole 100rpm

	1	2	3	4	5	6	7	8	9	10	11	12	Avr.	SD
5 min													76,6	16,2
10 min													95,4	7,0
15 min													99,0	5,5
20 min													99,4	4,3
25 min													100,3	2,7
30 min													100,1	2,5
45 min													99,7	2,4
60 min													99,1	2,3

Helicide Capsule
 Lot: 9E520
 A33-030526-042
 Metronidazole 75 rpm

	1	2	3	4	5	6	7	8	9	10	11	12	Avr.	SD
5 min													67,7	14,0
10 min													83,1	11,3
15 min													91,3	9,5
20 min													95,2	7,5
25 min													96,8	6,3
30 min													97,5	5,2
45 min													99,1	3,4
60 min													99,6	3,5

Helicide Capsule
 Lot: 9E520
 A33-030526-043
 Metronidazole 50rpm

	1	2	3	4	5	6	7	8	9	10	11	12	Avr.	SD
5 min													47,5	22,1
10 min													71,7	18,1
15 min													81,5	15,5
20 min													86,7	13,1
25 min													89,4	11,1
30 min													91,2	9,6
45 min													94,5	7,0
60 min													96,4	5,7

Helicide Capsule
 Lot: 9E521
 A33-030526-044
 Metronidazole 100 rpm

	1	2	3	4	5	6	7	8	9	10	11	12	Average	SD
5 min													76,0	14,3
10 min													94,9	8,2
15 min													98,5	3,4
20 min													98,8	3,1
25 min													98,8	3,0
30 min													98,2	3,0
45 min													97,8	2,9
60 min													97,3	3,0

Helicide Capsule
 Lot: 9E521
 A33-030526-045
 Metronidazole - 75 rpm

	1	2	3	4	5	6	7	8	9	10	11	12	Average	SD
5 min													73,2	12,8
10 min													88,0	9,1
15 min													92,3	5,4
20 min													94,1	3,1
25 min													95,3	2,9
30 min													95,1	2,8
45 min													95,7	3,0
60 min													95,4	2,9

Helicide Capsule
 Lot: 9E521
 A33-030526-046
 Metronidazole - 50 rpm

	1	2	3	4	5	6	7	8	9	10	11	12	Average	SD
5 min													41,3	12,2
10 min													62,4	11,6
15 min													77,6	14,3
20 min													84,4	13,3
25 min													87,9	11,6
30 min													89,2	9,4
45 min													93,3	5,7
60 min													94,0	4,2

Helicide Capsule
 Lot: 9E522
 A33-030526-047
 Metronidazole 100rpm

	1	2	3	4	5	6	7	8	9	10	11	12	Average	SD
5 min													56,5	18,7
10 min													78,6	11,4
15 min													85,6	9,4
20min													89,3	7,3
25 min													91,3	5,9
30 min													92,8	4,9
45 min													95,7	3,4
60 min													96,6	3,2

Helicide Capsule
 Lot: 9E522
 A33-030526-048
 Metronidazole 75 rpm

	1	2	3	4	5	6	7	8	9	10	11	12	Average	SD
5 min													44,6	24,9
10 min													64,2	26,9
15 min													73,3	23,7
20min													77,7	19,0
25 min													83,9	16,7
30 min													88,3	13,1
45 min													95,3	8,5
60 min													97,8	5,7

Helicide Capsule
 Lot: 9E522
 A33-030526-049
 Metronidazole 50 rpm

	1	2	3	4	5	6	7	8	9	10	11	12	Average	SD
5 min													37,2	18,6
10 min													56,1	16,5
15 min													67,0	15,0
20min													74,7	13,2
25 min													80,1	10,9
30 min													84,2	9,7
45 min													93,1	7,6
60 min													97,4	4,7

Helicide Capsule
 Lot #: 9E520
 A33-030526-041
 Tetracycline 100rpm

	1	2	3	4	5	6	7	8	9	10	11	12	Avr.	SD
5 min													29,4	21,3
10 min													78,9	23,9
15 min													91,8	15,1
20min													94,5	10,5
25 min													96,3	6,8
30 min													96,3	4,8
45 min													96,7	2,2
60 min													95,8	1,9

Helicide Capsule
 Lot: 9E520
 A33-030526-042
 Tetracycline 75 rpm

	1	2	3	4	5	6	7	8	9	10	11	12	Avr.	SD
5 min													19,8	13,0
10 min													68,6	18,8
15 min													88,1	14,7
20min													96,3	8,4
25 min													99,3	2,3
30 min													99,5	1,8
45 min													98,5	1,8
60 min													97,3	1,9

Helicide Capsule
 Lot: 9E520
 A33-030526-043
 Tetracycline 50rpm

	1	2	3	4	5	6	7	8	9	10	11	12	Avr.	SD
5 min													10,4	10,3
10 min													41,4	30,6
15 min													59,9	34,6
20min													70,2	35,1
25 min													75,7	34,7
30 min													79,8	34,4
45 min													87,5	34,5
60 min													88,7	32,2

Helicide Capsule
 Lot: 9E521
 A33-030526-044
 Tetracycline HCl - 100 rpm

	1	2	3	4	5	6	7	8	9	10	11	12	Average	SD
5 min													30,6	17,4
10 min													80,7	15,0
15 min													97,1	4,5
20 min													97,8	2,2
25 min													97,2	1,8
30 min													96,7	1,6
45 min													95,6	1,6
60 min													94,0	1,3

Helicide Capsule
 Lot: 9E521
 A33-030526-045
 Tetracycline HCl - 75rpm

	1	2	3	4	5	6	7	8	9	10	11	12	Average	SD
5 min													21,7	11,5
10 min													75,9	16,5
15 min													92,7	6,6
20 min													95,5	2,8
25 min													95,7	1,8
30 min													95,6	1,6
45 min													94,8	1,8
60 min													93,9	1,8

Helicide Capsule
 Lot: 9E521
 A33-030526-046
 Tetracycline HCl - 50 rpm

	1	2	3	4	5	6	7	8	9	10	11	12	Average	SD
5 min													7,7	6,5
10 min													39,2	19,8
15 min													63,4	19,5
20 min													81,3	13,8
25 min													90,6	8,8
30 min													93,5	5,4
45 min													95,9	1,6
60 min													95,0	1,5

Helicide Capsule
 Lot: 9E522
 A33-030526-047
 Tetracycline HCl 100rpm

	1	2	3	4	5	6	7	8	9	10	11	12	Average	SD
5 min													58,8	22,3
10 min													94,5	6,8
15 min													97,0	1,9
20 min													96,4	1,7
25 min													95,7	1,7
30 min													94,9	1,7
45 min													93,8	1,7
60 min													92,7	1,7

Helicide Capsule
 Lot: 9E522
 A33-030526-048
 Tetracycline HCl 75 rpm

	1	2	3	4	5	6	7	8	9	10	11	12	Average	SD
5 min													52,7	23,7
10 min													91,9	7,9
15 min													96,3	1,7
20 min													95,8	1,4
25 min													95,3	1,6
30 min													94,9	1,6
45 min													93,8	2,1
60 min													92,8	2,1

Helicide Capsule
 Lot: 9E522
 A33-030526-049
 Tetracycline HCl 50 rpm

	1	2	3	4	5	6	7	8	9	10	11	12	Average	SD
5 min													27,9	16,4
10 min													78,4	18,2
15 min													93,5	9,0
20 min													95,4	3,2
25 min													96,3	1,7
30 min													96,0	1,5
45 min													95,4	1,1
60 min													94,6	1,0

Submitted on October, 30, 2003

Aztreonam dissolution

BE522-75 RPM

	1	2	3	4	5	6	7	8	9	10	11	12	Average	STD	RSD
10 min													84.4	8.8	10.4%
20 min													93.2	5.0	5.4%
30 min													95.5	3.3	3.4%
40 min													96.7	2.5	2.5%
50 min													96.9	2.2	2.3%
60 min													96.9	2.2	2.3%
70 min													96.5	2.0	2.1%
80 min													96.0	1.9	2.0%

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/s/

Seong Jang
10/1/03 09:48:03 AM
BIOPHARMACEUTICS

Phil Colangelo
10/1/03 03:39:25 PM
BIOPHARMACEUTICS

Clinical Pharmacology and Biopharmaceutics Comments
NDA 50-786; Helizide capsules

Submission Date: October 30, 2002

The information contained in NDA 50-786, dated on October 30, 2002, has been reviewed. The dissolution data from one batch of Helizide capsules at paddle speed of 75 rpm is not adequate to evaluate the dissolution of this product. Dissolution-time profiles from at least three batches are needed to appropriately determine the dissolution acceptance criteria. In addition, dissolution at a lower paddle speed, e.g., 50 rpm, is also recommended. Therefore, the following additional dissolution data is to be submitted prior to the approval:

1. Dissolution-time profiles of each ingredient of Helizide from at least three capsule batches at paddle speed of **75 and 50 rpm**. Testing 12 capsules per batch is acceptable.
2. All raw dissolution data, including % dissolution of each capsule at each time point.
3. For the purpose of comparison, please re-submit dissolution data at 100 rpm, together with the additional data at 75 and 50 rpm.

Seong H. Jang, Ph.D.
Reviewer
Clinical Pharmacology and Biopharmaceutics

DPEIII/OCPB

Concurrence

Phil Colangelo, Pharm.D., Ph.D.
Team Leader
Clinical Pharmacology and Biopharmaceutics

DPEIII/OCPB

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Seong Jang
5/22/03 09:18:13 AM
BIOPHARMACEUTICS

Phil Colangelo
7/31/03 04:26:37 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY / BIOPHARMACEUTICS REVIEW

NDA: 50-786

Submission Dates: 9/28/01; 1/28/02; 4/18/02

Brand Name: Helicide® capsules in combination with Prilosec® (Omeprazole)

Generic Name: Biskalcitrate Potassium + Metronidazole + Tetracycline

Reviewer: Joette M. Meyer, Pharm.D.

Team Leader: Barbara Davit, Ph.D.

OCPB Division: Division of Pharmaceutical Evaluation III

OND Division: Division of Special Pathogen and Immunologic Drug Products

Applicant: Axcan Scandipharm Inc.
Birmingham, AL

Relevant IND(s): _____

Type of Submission: New NDA, NME

Formulation: oral capsule

Strength: 140 mg Biskalcitrate Potassium + 125 mg Metronidazole +
125 mg Tetracycline Hydrochloride

Indication:

Helicide® capsules, in combination with omeprazole, are indicated for the eradication of *H. pylori* in patients with *H. pylori* infection and duodenal ulcer disease (active or by history). The eradication of *H. pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence in patients with active duodenal ulcer disease.

1 EXECUTIVE SUMMARY

The NDA for this product is filed under Section 505(b)(2) of the FD&C Act, with reference to the approved Helidac® product (bismuth subsalicylate, metronidazole, and tetracycline as separate capsules and packaged together in blister packs).

The individual pharmacokinetics of bismuth salts, metronidazole, and tetracycline have all been previously reported in the scientific literature. The applicant was requested by the Division to perform three clinical pharmacology studies with Helicide:

- (1) a comparison of the bioavailability following a single clinical dose of bismuth citrate potassium, plus metronidazole, plus tetracycline hydrochloride formulated as Helicide capsules versus the three drugs given as separate tablets/capsules
- (2) a food effect study
- (3) a drug interaction study to compare the bioavailability of bismuth following multiple dose administration of Helicide capsules administered with and without omeprazole.

The results of the bioavailability study comparing administration of bismuth citrate potassium, metronidazole, and tetracycline hydrochloride formulated as Helicide capsules compared to administration as separate tablets/capsules containing the individual drug product demonstrate low and variable plasma concentrations of tetracycline and bismuth following administration of Helicide capsules compared to the individual tablets/capsules.

The results of the food effect study demonstrate decreased systemic exposure of bismuth, metronidazole, and tetracycline when administered as Helicide capsules with food as compared to fasting.

Despite lower exposure to one or more of the components of the Helicide capsule when administered in the Helicide dosage form or with food, clinical response (i.e., bacterial eradication) was achieved with the Helicide regimen in the clinical development program. The formulation of Helicide used in the pivotal Phase III trial was the same as used in these studies and patients were instructed to take the medication with food. In the Phase III trial the eradication rate in the Helicide treatment regimen demonstrated high eradication rates and statistical non-inferiority when compared to the active comparator regimen comprised of omeprazole, amoxicillin, and clarithromycin (87.7% versus 83.2%; point estimate 4.5%, 95% CI -3.9; 12.8). Therefore, local (topical) exposure, and not systemic exposure, may be important for *H. pylori* eradication.

In contrast, exposure to bismuth is increased when Helicide is administered in combination with omeprazole compared to administration of Helicide alone. Although bismuth peak concentrations (C_{max}) were elevated with the combination, they did not exceed the alarm level for causing neurotoxicity. There is no clinical evidence in the literature to suggest that transient high peak concentrations (i.e., C_{max}) are related to toxicity. Rather, it is only sustained steady state concentrations obtained with chronic dosing that have been associated with neurotoxicity. Steady state concentrations of bismuth are obtained after 4 to 5 weeks of chronic dosing whereas the duration of dosing in this study was only 6 days. The recommended treatment regimen of Helicide and omeprazole is indicated for a total of 10 days. Therefore, it is unlikely that patients receiving treatment will achieve steady state concentrations of bismuth. Finally, this study was performed under fasting conditions and food decreases systemic absorption of bismuth, as discussed above. In clinical practice, patients will be instructed to take Helicide following meals. There are no data available on steady-state concentrations of bismuth following multiple doses of Helicide and omeprazole when dosed with food. However, the adverse events reported in the clinical trial do not suggest that patients experienced neurotoxicity during therapy.

In summary, alterations in the bioavailability of bismuth, metronidazole, and/or tetracycline after administration of Helicide capsules with food or omeprazole are of limited clinical significance, as supported by the efficacy and safety data obtained with the regimen in the Phase III clinical trial.

1.1 RECOMMENDATION

The information contained in Item 6: Human Pharmacokinetics and Bioavailability of NDA 21-362 for Helicide capsules in combination with omeprazole has been reviewed and was found to be acceptable and adequate to support approval. The dissolution method is acceptable. However, the applicant is requested to submit additional dissolution data at lower paddle speeds (i.e., 25 and 50 rpm) to set the specification prior to approval.

Of Note: The Office of Compliance is recommending non-approval of this product due to a failed Prior Approval Inspection (PAI) for the biscalcitrates component.

1.2 PHASE IV COMMITMENTS

There are no Phase IV commitments recommended at this time.

Joette M. Meyer, Pharm.D.
Senior Clinical Pharmacology Reviewer
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

Barbara Davit, Ph.D.
Clinical Pharmacology Team Leader
Office of Clinical Pharmacology/Biopharmaceutics
Division of Pharmaceutical Evaluation III

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2 CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS SYNOPSIS

The NDA for this product is filed under Section 505(b)(2) of the FD&C Act, with reference to the approved Helidac® product (bismuth subsalicylate, metronidazole, and tetracycline as separate capsules and packaged together in blister packs). Helidac® was developed by Procter & Gamble (NDA 50-719) and subsequently sold to Prometheus Laboratories Inc.

The individual pharmacokinetics of bismuth salts, metronidazole, and tetracycline have all been previously reported in the scientific literature. The applicant was requested by the Division to perform three clinical pharmacology studies with Helicide:

- (1) a comparison of the bioavailability following a single clinical dose of biscalcitrates potassium, plus metronidazole, plus tetracycline hydrochloride formulated as Helicide capsules versus the three drugs given as separate tablets/capsules
- (2) a food effect study
- (3) a drug interaction study to compare the bioavailability of bismuth following multiple dose administration of Helicide® capsules administered with and without omeprazole.

3 QUESTION BASED REVIEW (QBR)

3.1 GENERAL ATTRIBUTES

Chemical Name

Biscalcitrates potassium

Metronidazole

2-methyl-5-nitroimidazole-1-ethanol

Tetracycline

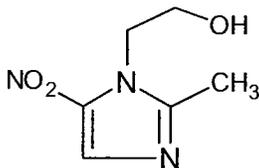
(4S,4aS,5aS,6S,12aS)-4-(dimethylamino)-1,4,4a,5,5a,6,11,12a-octahydro-3,6,10,12,12a-penta-hydroxy-6-methyl-1,11-dioxo-2-naphthacene-carboxamide monohydrochloride

Chemical Structure

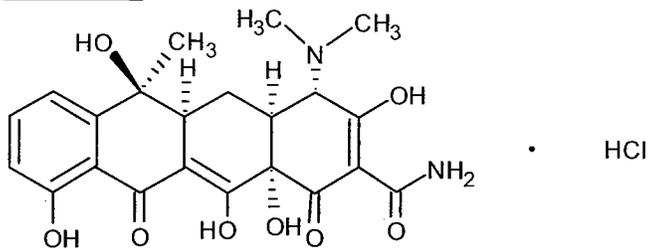
Biscalcitrates potassium

Biscalcitrates is

Metronidazole



Tetracycline



Molecular Formula/ Molecular Weight

Biskalcitrate potassium

or

Metronidazole 711.15

Tetracycline 480.90

Formulation

Helicide capsules are a combination antimicrobial product, containing biskalcitrate potassium, metronidazole, and tetracycline hydrochloride. The final product is a hard gelatin capsule, size 0, which contains the following components:

- biskalcitrate potassium, 140 mg (equivalent to 40 mg bismuth oxide)
- metronidazole, 125 mg
- a smaller capsule (size 3) containing tetracycline hydrochloride, 125 mg

Component	Use	[mg/capsule]
Tetracycline Capsules		
Tetracycline HCl	/	
Lactose monohydrate, S.D.		
Magnesium stearate		
Talc		
Total blend weight		
Hard gelatin capsule, size 3	Unit dose form	1 unit
Total capsule weight		
Metronidazole – Biscalcitrates Blend		
biscalcitrates potassium salt	/	140.0 (equivalent to of Bi ₂ O ₃)
Metronidazole		
Talc		
Magnesium stearate		
Total blend weight		
Final Product Unit Dose Form		
Hard gelatin capsule, size 0 elongated	Unit dose form	1 unit
Total fill weight		
Total capsule weight		

— tetracycline hydrochloride overage is used

Reviewer's Comment: _____ is manufacturing the inner tetracycline capsule. The applicant is using DMF _____ as a reference. The reason for the — overage is unclear and the applicant has been asked to provide the rationale.

3.1.1 What is the proposed indication?

Helicide capsules (biscalcitrates potassium, metronidazole, and tetracycline hydrochloride), in combination with omeprazole are indicated for the eradication of *H. pylori* in patients with *H. pylori* infection and duodenal ulcer disease (active or by history). The eradication of *H. pylori* has been demonstrated to reduce the risk of duodenal ulcer recurrence in patients with active duodenal ulcer disease.

3.1.2 What is the proposed dosing regimen for Helicide?

Helicide should be given as three (3) capsules four times a day, after meals and at bedtime, in conjunction with omeprazole 20 mg twice a day, for 10 days.

3.2 GENERAL CLINICAL PHARMACOLOGY

3.2.1 What are the basic pharmacokinetic characteristics of metronidazole, tetracycline, and bismuth when administered as Helicide?

The arithmetic mean plasma pharmacokinetic parameters for metronidazole, tetracycline, and bismuth following single-dose administration of three Helicide capsules (i.e., the clinical dose) in the fasted state are shown in Tables 1-3.

TABLE 1
Metronidazole Arithmetic Mean (%CV) Pharmacokinetic Parameters
When Administered as a Single-Dose of 3 x Helicide Capsules [N=18]

PARAMETER	Metronidazole (375 mg) in 3 Helicide Capsules	
	MEAN [Range]	% C.V.
C _{max} (ng/mL)	8666.26 [5249.11 – 12570.54]	21.9
T _{max} * (hours)	0.75 [0.50 – 3.50]	N/A
AUC _T (ng h/mL)	83018.45 [61439.34 – 115392.35]	17.0
AUC _∞ (ng h/mL)	84413.59 [62370.29 – 118088.47]	17.2
AUC _{T/∞} (%)	98.38 [97.14 – 99.14]	0.6
K _{el} (hour ⁻¹)	0.0911 [0.0599 – 0.1314]	18.9
T _{1/2el} (hours)	7.85 [5.57 – 11.88]	18.4

* For T_{max} the median is presented.

TABLE 2
Tetracycline Arithmetic Mean (%CV) Pharmacokinetic Parameters
When Administered as a Single Dose of 3 x Helicide Capsules [N=18]

PARAMETER	Tetracycline (375 mg) in 3 Helicide Capsules	
	MEAN [Range]	% C.V.
C _{max} (ng/mL)	773.82 [197.52 – 1222.84]	46.9
T _{max} * (hours)	3.25 [1.33 – 5.00]	N/A
AUC _T (ng h/mL)	9674.02 [1891.04 – 15607.26]	49.9
AUC _∞ (ng h/mL)	9986.66 [2120.98 – 16090.10]	49.0
AUC _{T/∞} (%)	95.86 [89.16 – 98.81]	2.9
K _{el} (hour ⁻¹)	0.0611 [0.0330 – 0.0770]	19.8
T _{1/2el} (hours)	11.89 [9.00 – 21.01]	25.4

* For T_{max} the median is presented.

TABLE 3
Bismuth Arithmetic Mean (%CV) Pharmacokinetic Parameters
When Administered as a Single Dose of 3 x Helicide Capsules

PARAMETER	Bismuth (420 mg) in 3 Helicide Capsules	
	MEAN [Range]	% C.V.
C _{max} (pg/mL)	16702.1 [1513.2 – 147143.5]	202.2
T _{max} * (hour)	0.59 [0.50 – 1.67]	N/A
AUC _T (pg h/mL)	42529.6 [4451.4 – 353568.7]	190.6
AUC _∞ (pg h/mL)	56507.9 [5842.0 – 383003.0]	177.6
AUC _{T/∞} (%)	83.5 [55.5 – 90.7]	15.0
K _{el} (hour ⁻¹)	0.1189 [0.0094 – 0.2300]	64.2
T _{1/2el} (hour)	19.59 [3.01 – 74.50]	142.2

* For T_{max}, the median is presented.

3.3 GENERAL BIOPHARMACEUTICS

3.3.1 What effect does administration of biscalcitrates potassium, metronidazole, and tetracycline hydrochloride formulated as Helicide capsules have on bioavailability of each of the drugs as compared to administration as separate tablets/capsules containing the individual drug product?

The bioavailability of metronidazole is not significantly different between the combined formulation (i.e., Helicide) and metronidazole capsules. The 90% confidence intervals of the geometric mean ratios of C_{max} and AUC for metronidazole in Helicide versus metronidazole capsules administered alone are within the range of 0.80 to 1.25.

The bioavailability of tetracycline is lower when tetracycline is administered as Helicide versus tetracycline capsules alone. The geometric mean point estimates of the ratio of tetracycline when administered as Helicide versus tetracycline capsules alone are between 0.90 and 1.0 for C_{max}, AUC_T and AUC_∞. However, the lower bounds of the 90% confidence intervals for the ratios of C_{max}, AUC_T and AUC_∞ are below 0.80. The intrasubject variability is estimated as 38%, 47%, and 44.9% for C_{max}, AUC_T and AUC_∞, respectively. Due to the relatively high intrasubject variability, this study was likely underpowered to maintain the 90% confidence intervals of tetracycline within the range of 0.80 to 1.25.

Exposure to bismuth, in terms of both C_{max} and AUC, is highly variable. The lower bounds of the 90% confidence intervals of the geometric mean ratios of C_{max}, AUC_T and AUC_∞ for bismuth in Helicide versus bismuth capsules administered alone are below 0.80. Yet, for AUC_T and AUC_∞, the upper bounds of the 90% confidence intervals are

above 1.25. The intrasubject variability is estimated as 114%, 121%, and 108% for C_{max} , AUC_T and AUC_{∞} , respectively. Although the variability is high, in this case, increasing the number of subjects will probably not change the outcome because the point estimates for all three parameters are at or below 0.85.

Reviewer's Comment: It is important to note that this is not a replicate design study. Therefore, the estimates of intra-subject variability may reflect actual differences in the formulation rather than purely differences within an individual.

To summarize the bioavailability of Helicide versus administration of each drug separately:

Metronidazole

- Mean C_{max} ratio 0.95 (90% confidence interval; 0.89 to 1.03)
- Mean AUC_T ratio 1.03 (90% confidence interval; 1.00 to 1.06)
- Mean AUC_{∞} ratio 1.03 (90% confidence interval; 1.00 to 1.06)

Tetracycline

- Mean C_{max} ratio 0.94 (90% confidence interval; 0.76 to 1.16)
- Mean AUC_T ratio 0.93 (90% confidence interval; 0.72 to 1.19)
- Mean AUC_{∞} ratio 0.93 (90% confidence interval; 0.73 to 1.19)

Bismuth

- Mean C_{max} ratio 0.65 (90% confidence interval; 0.39 to 1.10)
- Mean AUC_T ratio 0.85 (90% confidence interval; 0.50 to 1.46)
- Mean AUC_{∞} ratio 0.73 (90% confidence interval; 0.41 to 1.33)

The formulation of Helicide used in the pivotal Phase III trial was the same as used in this bioavailability study. In the Phase III trial the eradication rate in the Helicide treatment regimen demonstrated high eradication rates and statistical non-inferiority when compared to the active comparator regimen comprised of omeprazole, amoxicillin, and clarithromycin (87.7% versus 83.2%; point estimate 4.5%, 95% CI -3.9; 12.8).

Although the plasma concentrations of tetracycline and bismuth are low and variable following administration of Helicide capsules, clinical response (i.e., eradication) was achieved with the Helicide regimen in the Phase III clinical trial. Therefore, local (topical) exposure, and not systemic exposure, may be important for *H. pylori* eradication.

3.3.2 What effect does co-administration of Helicide capsules with omeprazole have on the bioavailability of bismuth?

Exposure to bismuth is significantly increased when Helicide is administered in combination with omeprazole as compared to administration of Helicide alone. The geometric mean ratio of C_{max} is 3.10 (90% confidence interval; 2.07 to 4.66) and AUC is 2.73 (90% confidence interval 2.20 to 3.37).

Elevated steady-state blood concentrations of bismuth are known to be associated with neurotoxicity (i.e., myoclonic jerks, trembling, memory disturbances, confusion and problems of physical coordination). Concentrations of > 50 ng/mL and > 100 ng/mL have been suggested in the literature as "safety" and "alarm" levels, respectively, for

bismuth toxicity. One subject in this study had a bismuth concentration of > 50 ng/mL, but it did not exceed 100 ng/mL (i.e., 73.2 ng/mL). This high concentration was observed at T_{max} obtained following multiple dosing and was transient. There is no clinical evidence in the literature to suggest that transient high peak concentrations are related to toxicity. In addition, steady state concentrations of bismuth are obtained only after 4 to 5 weeks of chronic dosing and the duration of dosing in this study was 6 days. The recommended treatment regimen of Helicide and omeprazole is indicated for a total of 10 days. It is unlikely that patients receiving treatment will achieve steady state concentrations of bismuth. Finally, this study was performed under fasting conditions and food decreases systemic absorption of bismuth (see Question 4.3.3 below). In clinical practice, patients will be instructed to take Helicide following a meal. There are no data available on steady-state concentrations of bismuth following multiple doses of Helicide and omeprazole when dosed with food. However, the adverse events reported in the clinical trial do not suggest that patients experienced neurotoxicity during therapy.

Reviewer's Comment: One additional subject achieved elevated systemic concentrations of bismuth. The subject was enrolled in the bioavailability study of Helicide versus the individual drugs alone and achieved a bismuth C_{max} of 147 ng/mL following administration of a single dose of 3 Helicide capsules. For the reasons cited above, it is unlikely that this high transient concentration was harmful to the subject.

3.3.3 What is the effect of food on the bioavailability of Helicide capsules and what dosing recommendations should be made regarding administration in relation to meals?

Food delays absorption of metronidazole (mean T_{max} of 3.0 hours fed versus 0.75 hours fasting) and bismuth (i.e., a mean T_{max} of 3.5 hours fed versus 0.59 hours fasted) from Helicide capsules.

Food significantly decreases exposure to metronidazole, tetracycline, and bismuth when administered as Helicide. The geometric mean ratio of C_{max} for metronidazole is reduced under fed versus fasting conditions, although the 90% confidence intervals for AUC_T and AUC_{∞} are within the range of 0.80 to 1.25. The 90% confidence intervals for the geometric mean ratios of C_{max} , AUC_T and AUC_{∞} under fed versus fasting conditions are not within the range of 0.80 to 1.25 for tetracycline and bismuth.

To summarize Helicide administered under fed versus fasted conditions:

Metronidazole

- Mean C_{max} ratio 0.80 (90% confidence interval; 0.74 to 0.86)
- Mean AUC_T ratio 0.94 (90% confidence interval; 0.91 to 0.96)
- Mean AUC_{∞} ratio 0.94 (90% confidence interval; 0.91 to 0.96)

Tetracycline

- Mean C_{max} ratio 0.73 (90% confidence interval; 0.59 to 0.90)
- Mean AUC_T ratio 0.66 (90% confidence interval; 0.51 to 0.85)
- Mean AUC_{∞} ratio 0.66 (90% confidence interval; 0.52 to 0.85)

Bismuth

- Mean C_{max} ratio 0.19 (90% confidence interval; 0.12 to 0.33)
- Mean AUC_T ratio 0.41 (90% confidence interval; 0.24 to 0.70)
- Mean AUC_{∞} ratio 0.45 (90% confidence interval; 0.25 to 0.81)

The dosing regimen used in the pivotal Phase III trial was three Helicide capsules after meals and at bedtime given with omeprazole 20 mg twice daily after breakfast and supper. The eradication rate in the Helicide treatment regimen demonstrated high eradication rates and statistical non-inferiority when compared to the active comparator regimen comprised of omeprazole, amoxicillin, and clarithromycin (87.7% versus 83.2%; point estimate 4.5%, 95% CI -3.9; 12.8).

*Reviewer's Comment: The applicant originally proposed administering the Helicide treatment regimen in the Phase III trials on an empty stomach (i.e., before meals). The Division questioned the applicant as to the rationale for dosing on an empty stomach, since medications in the Helidac® regimen are indicated to be taken with meals. In addition, it has been shown that administration of ranitidine bismuth citrate (Tritec®) with food increases eradication rates compared to administration on an empty stomach (Webb, et al. Am J Gastroenterol 1995;90:1273-7). In response, the applicant modified the dosing to after meals based on the rationale that a prolonged gastric residence time of the drug, induced by the fed state, increases the duration of contact between *H. pylori* and the active medication leading to improved eradication rates.*

Although food decreases the systemic exposure of bismuth, metronidazole, and tetracycline when administered as Helicide capsules, clinical response (i.e., bacterial eradication) was achieved with the Helicide regimen in the Phase III clinical trial. Therefore, local (topical) exposure, and not systemic exposure, may be important for *H. pylori* eradication.

3.3.4 Has the applicant developed an appropriate dissolution method and specification that will assure *in vivo* performance and quality of the product?

The applicant proposes the following methods and specifications. Dissolution profiles for metronidazole, tetracycline, and biscalcitrates can be found in Appendix 1. The initial dissolution method and specification is for the inner tetracycline (size 3) capsule.

Proposed Dissolution Method and Specification for Tetracycline Capsules

Dosage Form	Capsule
Strength	125 mg
Apparatus	USP Apparatus II (paddle)
Dissolution Medium	0.1 N HCl
Volume	900 mL
Paddle Speed	100 rpm
Sampling Time	0, 10, 20, 30, 40, 50, 60, 70, 80 min
Analytical Method	HPLC
Specification	NLT  in 60 minutes

Metronidazole

	Applicant	USP
Apparatus	USP Apparatus 2 (paddle)	USP Apparatus 1 (basket)
Dissolution Medium	0.1 N HCl at 37°C	0.1 N HCl at 37°C
Volume	900 mL	900 mL
Paddle Speed	100 rpm	100 rpm
Specification	NLT (Q)  at 60 minutes	NLT (Q)  at 60 minutes

The following comments on the applicant's choice of paddle speed were prepared by the reviewer prior to NDA submission, but were inadvertently not sent.

Please note that a paddle speed of 100 rpm with Apparatus 2 is usually discouraged, because it is often difficult to obtain discriminatory data with this speed

For an adequate evaluation of your proposed dissolution method for Helicide, please include data collected from the investigation of lower paddle speeds (i.e. 50 and 75 rpm) in the NDA submission.

Since the Office of Compliance is recommending non-approval of the product, the request to provide this data will be included in the action letter.

3.4 ANALYTICAL

3.4.1 Were the analytical procedures used to determine drug concentrations in this NDA acceptable?

The full validation and performance reports of the assays for metronidazole, tetracycline, and bismuth in plasma were submitted. The usual lower limits of quantification (LLQ) and calibration ranges for the assay are shown below.

Substance	Method	Matrix	LLQ	Calibration Range
Metronidazole	HPLC/UV	Plasma	49.95 ng/mL	49.95 to 19979.96 ng/mL
Tetracycline	HPLC/MS	Plasma	9.98 ng/mL	9.98 to 1996.28 ng/mL
Bismuth	ICP/MS	Plasma	200 pg/mL	200 to 40000 pg/mL

The performance of the assay during study sample analysis was acceptable as evidenced by QC sample precision and accuracy within $\pm 15\%$.

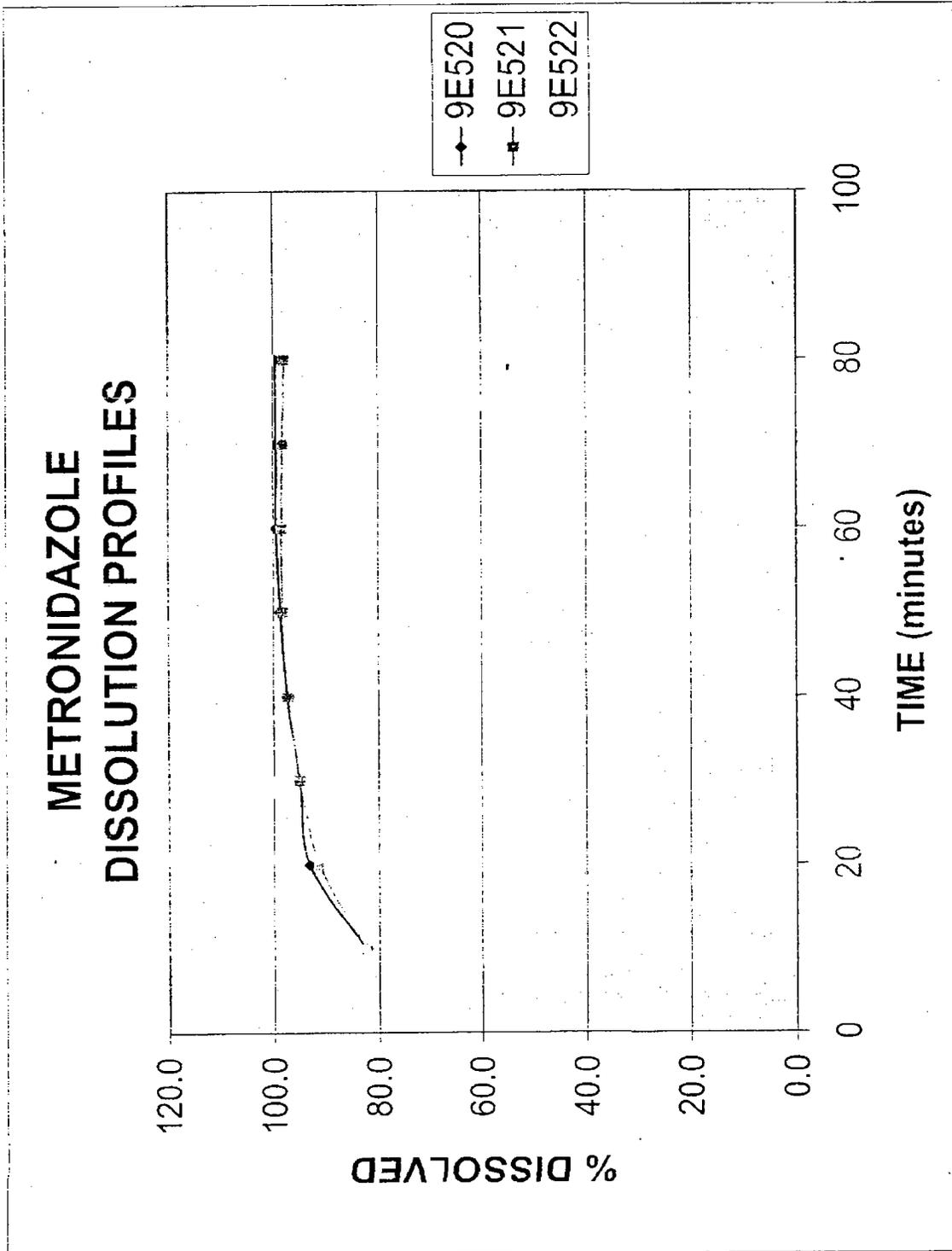
4 LABELING

The Office of Compliance is recommending non-approval of this product due to a failed Prior Approval Inspection (PAI) for the biscalcitrates component. The final label will be negotiated at the time of resubmission. The applicant's proposed label can be found in Appendix 3 (Section 5.3).

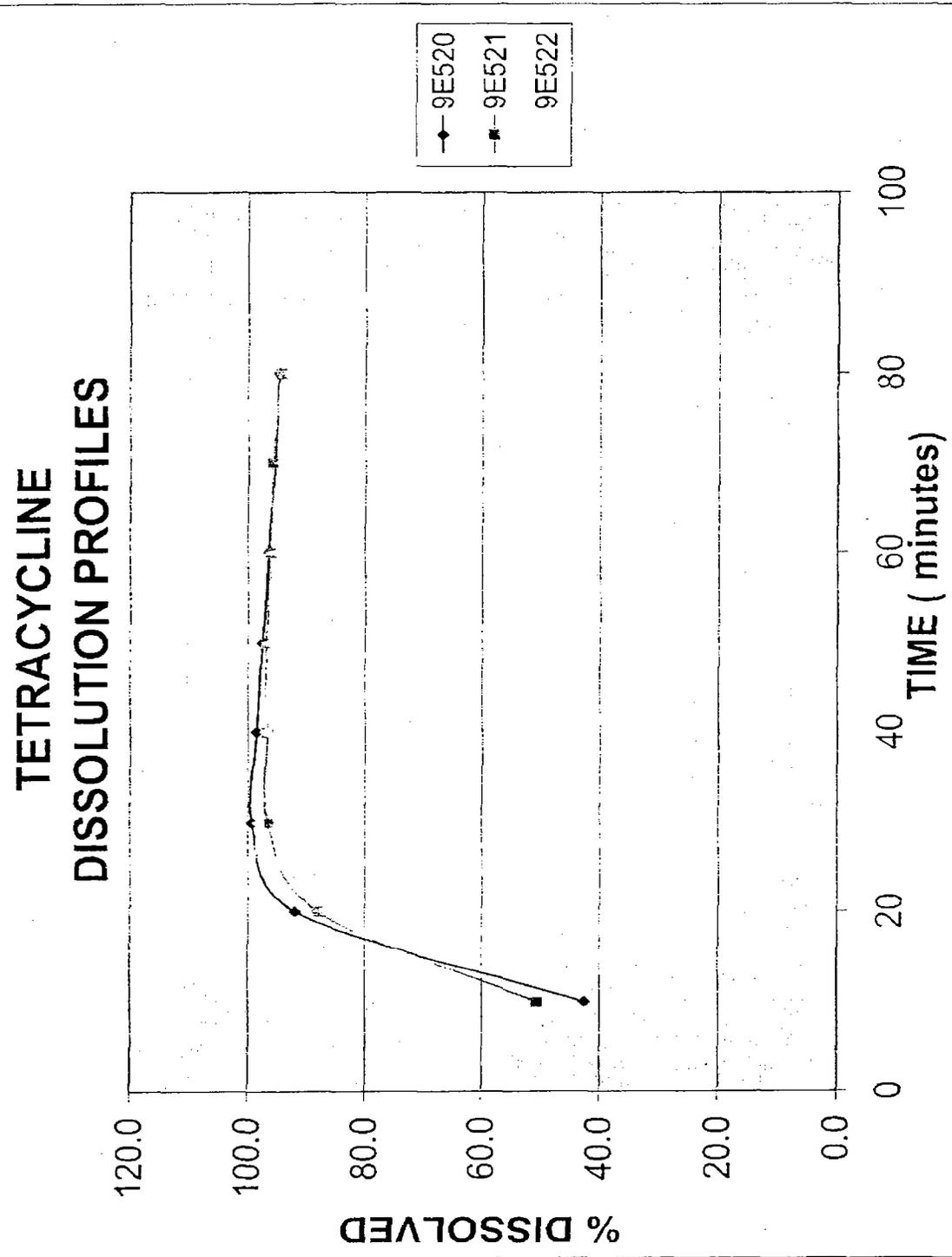
5 APPENDICES

5.1 APPENDIX 1 – DISSOLUTION PROFILES FOR METRONIDIAZOLE, TETRACYCLINE, AND BISMUTH

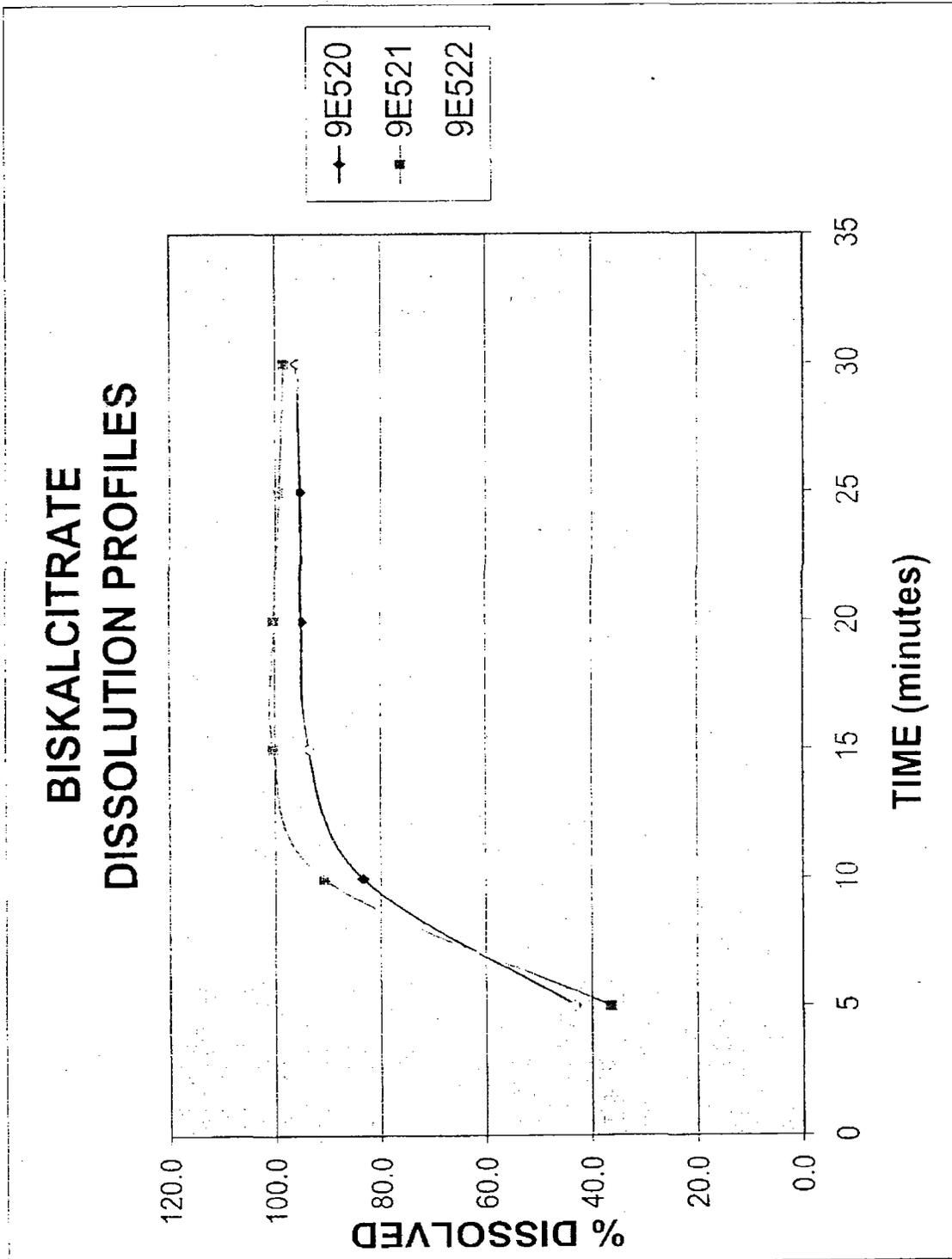
APPENDIX 1
Dissolution Profile for Metronidazole



APPENDIX 1 (continued)
Dissolution Profiles for Tetracycline



APPENDIX 1 (continued)
Dissolution Profiles for Biscalcitrates



5.2 APPENDIX 2 – INDIVIDUAL STUDY REPORTS

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5.3 APPENDIX 3 – APPLICANT’S PROPOSED LABEL

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19 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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/s/

Joette Meyer
7/26/02 04:16:02 PM
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Barbara Davit
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