CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75706

BIOEQUIVALENCY REVIEW(S)

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-706 SPONSOR : Andrx

DRUG AND DOSAGE FORM : Loratadine and Pseudoephedrine Sulfate ER Tablet

STRENGTH(S) : 10 mg/240 mg

TYPES OF STUDIES : Fasting, Fed, and multiple-dose

CLINICAL STUDY SITE(S) :

ANALYTICAL SITE(S) :

STUDY SUMMARY : The fasting, fed, and multiple-dose studies are acceptable.

DISSOLUTION : The dissolution testing should be conducted in
The test product should meet the following specifications:
Loratadine: NLT % (Q) in 30 minutes
Pseudoephedrine Sulfate:

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _Yes__	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Kuldeep R. Dhariwal BRANCH : II

INITIAL : KRD DATE : 4/26/01

TEAM LEADER : S. Nerurkar BRANCH : II

INITIAL : SN DATE : 4/25/2001

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

INITIAL : DPC DATE : 5/1/01

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 75-706 SPONSOR : Andrx Pharmaceuticals

DRUG AND DOSAGE FORM : Loratadine and Pseudoephedrine Sulfate ER Tablet

STRENGTH(S) : 10 mg/240 mg

TYPES OF STUDIES : N/A

CLINICAL STUDY SITE(S) : N/A

ANALYTICAL SITE(S) : N/A Amendment

STUDY SUMMARY : The firm's request for changes in dissolution medium and specifications is denied. The ANDA was found acceptable on 5/01/01 and remains acceptable with the dissolution conditions approved earlier.

DISSOLUTION : The dissolution testing should be conducted in
The test product should meet the following specifications:

Loratadine: NLT % (Q) in 30 minutes
Pseudoephedrine:

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _Yes__	Inspection requested: (date)	
New facility _____	Inspection completed: (date)	
For cause _____		
Other _____		

PRIMARY REVIEWER : Kuldeep R. Dhariwal, Ph.D. BRANCH : II

INITIAL : KRD DATE : 8/2/01

TEAM LEADER : S. Nerurkar, Ph.D. BRANCH : II

INITIAL : SJN DATE : 8/2/2001

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

INITIAL : DPC DATE : 8/2/01

Loratadine and Pseudoephedrine Sulfate Extended Release Tablets
10 mg/240 mg
ANDA #75-706
Reviewer: Kuldeep R. Dhariwal
File name: 75706SD.D99

Andrx Pharmaceuticals
4001 S.W. 47th Avenue
Ft. Lauderdale
Florida 33314
Submission Date:
December 14, 1999

Review of Fasting, Non-Fasting, and Multiple-dose Studies, and Dissolution Data

First Generic: Yes
Type of Submission: Original ANDA, paper submission.
Contents of Submission: Fasting, non-fasting and multiple-dose studies, and dissolution data.
Indication: For the relief of symptoms of seasonal allergic rhinitis.
RLD: Claritin-D 24 hour ER tablets (Schering).
Pharmacokinetics: Loratadine is rapidly absorbed and extensively metabolized to an active metabolite (descarboethoxy loratadine). The mean elimination half-lives, found in studies in normal adult subjects, were 8.4 hours for loratadine and 28 hours for descarboethoxy loratadine. The bioavailability of loratadine and pseudoephedrine sulfate from Claritin-D 24 hour ER tablets is similar to that achieved with separate administration of the components. Coadministration of loratadine and pseudoephedrine does not significantly affect the bioavailability of either component.
Dosage: Adults and children 12 years of age and over: one tablet daily with a full glass of water.

Bioequivalence Study Under Fasting Conditions:

A. Study Information:

Protocol:	P98-234
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	
Principal Investigator:	
Analytical Facility:	
Analytical Director:	
Statistical Analysis:	

Study Dates:	Period I February 14, 1999 Period II February 28, 1999
Washout Period:	14 days
Analysis Dates:	March 10 to April 28, 1999
Storage Period:	73 days
Study Design:	Randomized, single-dose, two-way crossover.
Randomization Scheme:	AB: 1,4,6,7,8,9,12,15,17,18,19,22, 26,27,29 BA: 2,3,5,10,11,13,14,16,20,21,23, 24,25,28,30

Treatments:

A: Loratadine/Pseudoephedrine sulfate ER tablet, 1x10/240 mg; Oblong, oval, biconvex, straight sides with rounded edges; Andrx; Lot #605R004A; Lot size: tablets; Manufacture Date: not given; Assay: Loratadine: 96.1%, Pseudoephedrine: 98.4%

B: Claritin-D 24 hour ER tablet, 1x10/240 mg; Oval, biconvex, straight sides with rounded edges; Schering; Lot #8-DCS-2008; Expiry Date: 11/99; Assay: Loratadine: 98.0%, Pseudoephedrine: 96.9%

Formulation of test product:	Table 1
Subjects:	30 male, 18-38 years old subjects were enrolled according to the inclusion/exclusion criteria specified in the protocol.
Housing:	From 10 hours pre-dose until 24 hours post-dose. Subjects returned for 36, 48, 72, 96, 120, and 144 h blood draw.
Dosing:	After 10 hour fast, with 240 mL of water.
Sample Collection:	Blood samples (7 mL) were collected in heparinized Vacutainers at pre-dose (0 h) and at following times after dosing: 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours.

B. Study Results:

1. Clinical:

Drop-outs:	Subject #4 dropped prior to period II dosing due to schedule conflict. Subject #25 dropped prior to period II dosing for personal reasons.
Adverse Events:	Headache, pharyngitis, rhinitis and syncope (fainted due to blood draw). None of the events were serious in nature.
Protocol Deviations:	One subject took ibuprofen during the study. There were some sampling time deviations. Actual times were used in pharmacokinetic calculations.

2. Analytical:

Within-Study:

LORATADINE AND DESCARBOETHOXY LORATADINE:

Method:
Internal Standard:

Linearity:

Regression:
QC Samples:

Accuracy:

Precision

Reassays:

PSEUDOEPHEDRINE:

Method:
Internal Standard:
Linearity:

Regression:
QC Samples:
Accuracy:

Precision:

Reassays:

Pre-study Method Validation:

LORATADINE AND DESCARBOETHOXY LORATADINE:

The firm has provided one pre-study validation run for each of the following: loratadine standards, loratadine QC samples, descarboethoxy loratadine standards and descarboethoxy loratadine QC samples (Appendix B, volume 1.6). The firm has not provided method validation data like inter and intra day accuracy, precision, recovery, and stability of loratadine and descarboethoxy loratadine in extracted samples for method

Stability:
a) Loratadine and descarboethoxy loratadine were stable in plasma stored at room temperature for 4 hours prior to extraction.
b) Freeze-thaw: stable over 3 cycles.

Long-term Stability: Stability in plasma at -20^0 C:
Loratadine: 10 months
Descarboethoxy loratadine: 5 months.

PSEUDOEPHEDRINE:

The firm states that this study immediately followed another pseudoephedrine project, therefore a pre-study validation run was not conducted. The firm has provided data from method validation carried out in 1994:

Specificity:

Linearity:

Regression:
QC samples:
Accuracy:

Precision:

Absolute Recovery:

Stability:
a) Pseudoephedrine was stable in plasma stored at room temperature for 4 hours prior to extraction.
b) Pseudoephedrine was stable in extracted samples stored for 24 hours at room temperature.
c) Freeze-thaw: stable over 3 cycles.
d) Long-term: stable for 10 months in samples stored at -20°C.

Comments:

Method validation for pseudoephedrine is acceptable. The firm would be asked to provide method validation data for loratadine and descarboethoxy loratadine.

3. Pharmacokinetics/Statistics:

LORATADINE:

Mean Plasma Concentrations:	Table 2, Figure 1	
Pharmacokinetic Parameters:	Table 2	
90% Confidence Intervals:	$LAUC_{0-t}$	95.07-117.48%
	$LAUC_{0-inf}$	94.73-117.78%
	LC_{max}	89.75-118.58%
Test/Reference Ratios:	AUC_{0-t}	1.11 (0.49-1.80)
	AUC_{0-inf}	1.11 (0.46-1.78)
	C_{max}	1.14 (0.46-3.84)
AUC_{0-t}/AUC_{0-inf} Ratios:	Test	0.95 (0.87-0.99)
	Reference	0.95 (0.89-0.99)
Root MSE:	$LAUC_{0-t}$	0.23215
	$LAUC_{0-inf}$	0.23882
	LC_{max}	0.30557

DESCARBOETHOXY LORATADINE:

Mean Plasma Concentrations:	Table 3, Figure 2	
Pharmacokinetic Parameters:	Table 3	
90% Confidence Intervals:	$LAUC_{0-t}$	93.79-109.24%
	$LAUC_{0-inf}$	93.82-108.98%
	LC_{max}	87.12-109.14%
Test/Reference Ratios:	AUC_{0-t}	1.04 (0.60-1.91)
	AUC_{0-inf}	1.04 (0.61-1.91)
	C_{max}	1.03 (0.43-2.23)
AUC_{0-t}/AUC_{0-inf} Ratios:	Test	0.97 (0.95-0.99)
	Reference	0.97 (0.94-0.99)
Root MSE:	$LAUC_{0-t}$	0.16724
	$LAUC_{0-inf}$	0.16426
	LC_{max}	0.24725

PSEUDOEPHEDRINE:

Mean Plasma Concentrations:	Table 4, Figure 3	
Pharmacokinetic Parameters:	Table 4	
90% Confidence Intervals:	$LAUC_{0-t}$	96.80-106.58%
	$LAUC_{0-inf}$	98.88-108.50%
	LC_{max}	101.16-110.99%
Test/Reference Ratios:	AUC_{0-t}	1.03 (0.73-1.29)
	AUC_{0-inf}	1.05 (0.72-1.32)
	C_{max}	1.07 (0.84-1.48)
AUC_{0-t}/AUC_{0-inf} Ratios:	Test	0.95 (0.79-0.99)
	Reference	0.97 (0.92-0.99)

Root MSE:

$LAUC_{0-t}$	0.10553
$LAUC_{0-inf}$	0.10183
LC_{max}	0.10165

Comments:

1. The reviewer recalculated the pharmacokinetic parameters and 90% confidence intervals. The calculated values are in good agreement with those reported by the firm.
2. Loratadine: There was no statistically significant period, sequence, or treatment effect for any of the pharmacokinetic parameters. The 90% confidence intervals for C_{max} are 87.83%-153.57%, however, the confidence intervals for log-transformed C_{max} are within acceptable limits.
   Descarboethoxy loratadine: A statistically significant sequence effect was observed for $LAUC_{0-t}$ and $LAUC_{0-inf}$.
   Pseudoephedrine: The statistically significant sequence and treatment effects were observed for LC_{max}.
   Statistically significant sequence effect is acceptable because it is a single-dose study in normal healthy subjects, the drug is not an endogenous entity, and the study meets all scientific and statistical criteria outlined in guidance, "Statistical procedures for bioequivalence studies using a standard two-treatment crossover design."
3. The firm should provide the date bio-lot was manufactured.
4. **NOT TO BE RELEASED UNDER FOI:** The amount of hydroxypropyl methylcellulose used in this drug product exceeds the limits. The firm has provided toxicological data to support the use of this ingredient at the proposed level. The Regulatory Support Branch has sent these data for the consult. The report is pending.

   are also used in excess of limits. The firm has provided the composition of these ingredients. All components of these two ingredients are within the limits.
5. Loratadine and descarboethoxy loratadine: The firm has provided bench top stability of these analytes in unextracted samples and freeze-thaw stability data for method on page 5525, vol. 1.13. The firm should provide method validation data like inter and intra day accuracy and precision, recovery, and stability of loratadine and descarboethoxy loratadine in extracted samples for method
6. The firm should provide all SOPs for analytical methods.
7. The fasting study is incomplete.

Bioavailability Study Under Non-Fasting Conditions:

A. Study Information:

Protocol:	P98-246
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	
Principal Investigator:	
Analytical Facility:	
Analytical Director:	
Statistical Analysis:	
Study Dates:	Period I May 08-14, 1999 Period II May 22-28, 1999 Period III June 05-11, 1999
Washout Period:	14 days
Analysis Dates:	June 17 to August 2, 1999
Storage Period:	84 days
Study Design:	Randomized, single-dose, three-way crossover.
Randomization Scheme:	BCA: 1,8,11,13 CBA: 2,10,12,24 BAC: 3,9,17,22 ABC: 4,6,14,18 CAB: 5,7,15,20 ACB: 16,19,21,23

Treatments:

A: Loratadine/Pseudoephedrine sulfate ER tablet, 1x10/240 mg; Oblong, oval, biconvex, straight sides with rounded edges; Andrx; Lot #605R004A; administered after an overnight fast
B: Loratadine/Pseudoephedrine sulfate ER tablet, 1x10/240 mg; Oblong, oval, biconvex, straight sides with rounded edges; Andrx; Lot #605R004A; administered after a standard breakfast
C: Claritin-D 24 hour ER tablet, 1x10/240 mg; Oval, biconvex, straight sides with rounded edges; Schering; Lot #8-DCS-2008; administered after a standard breakfast

Subjects:	24 male, 19-41 years old subjects were enrolled according to the inclusion/exclusion criteria specified in the protocol.
Housing:	From 10 hours pre-dose until 24 hours post-dose. Subjects returned

	for 36, 48, 72, 96, 120, and 144 h blood draw.
Dosing:	Treatment A: Subjects were given a single oral dose of the assigned formulation with 240 mL of water. Treatment B and C: Subjects were given OGD recommended standardized breakfast 30 minutes before dosing after an overnight fast. The dose was given with 240 mL of water.
Sample Collection:	Blood samples (7 mL) were collected in heparinized Vacutainers at pre-dose (0 h) and at following times after dosing: 0.25, 0.50, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours.

B. Study Results:

1. Clinical:

Drop-outs:	Subject #4 dropped prior to period III dosing due to family emergency. Subject #16 dropped prior to period II dosing due to schedule conflict. Subject #21 was dropped prior to period III dosing due to vomiting episodes reported during period I. This subject was inadvertently dosed for period II. Samples from these three subjects were not analyzed.
Adverse Events:	Headache, dizziness, upset stomach, pharyngitis, rhinitis, vomiting, and diarrhea. None of the events were serious in nature.
Protocol Deviations:	One subject took ibuprofen and one subject took aspirin during the study. There were some sampling time deviations. Actual times were used in pharmacokinetic calculations.

2. Analytical:

LORATADINE AND DESCARBOETHOXY LORATADINE:

Within-Study:

Method:
Internal Standard:

Linearity:

Regression:
QC Samples:

Accuracy:

Precision

Reassays:

Pre-study Method Validation:

The firm has provided following pre-study method validation data for method:

Linearity:

Regression:
QC Samples:

Accuracy:

Precision

Relative Recovery:

Stability:

a) This assay was originally validated as method A modification was made to the extraction procedure, which required revalidation of the method. The freeze-thaw stability and room temperature stability were demonstrated using method and were not repeated during validation of method. The stability data provided using method are acceptable.
b) Loratadine and descarboethoxy loratadine were stable in extracted samples for 3 days.
c) Long-term: stable for 6 weeks in samples stored at -20°C. During the fasting study sample analyses, the firm

demonstrated the stability of loratadine for 10 months and for descarboethoxy loratadine for 5 months in frozen samples.

PSEUDOEPHEDRINE:

Method:
Internal Standard:
Linearity:

Regression:
QC Samples:
Accuracy:

Precision:

Reassays:

3. Pharmacokinetics/Statistics:

LORATADINE:

Mean Plasma Concentrations:	Table 5, Figure 4		
Pharmacokinetic Parameters:	Table 6		
AUC_{0-t}/AUC_{0-inf} Ratios:	Test fasting	0.95	(0.86-0.99)
	Test non-fasting	0.95	(0.86-0.98)
	Ref non-fasting	0.95	(0.89-0.99)

DESCARBOETHOXY LORATADINE:

Mean Plasma Concentrations:	Table 7, Figure 5		
Pharmacokinetic Parameters:	Table 8		
AUC_{0-t}/AUC_{0-inf} Ratios:	Test fasting	0.97	(0.96-0.99)
	Test non-fasting	0.97	(0.95-0.99)
	Ref non-fasting	0.97	(0.94-0.99)

PSEUDOEPHEDRINE:

Mean Plasma Concentrations:	Table 9, Figure 6		
Pharmacokinetic Parameters:	Table 10		
AUC_{0-t}/AUC_{0-inf} Ratios:	Test fasting	0.96	(0.89-0.99)
	Test non-fasting	0.95	(0.75-0.98)
	Ref non-fasting	0.97	(0.91-0.99)

Comments:

1. The pharmacokinetic parameters and ratios of means recalculated by the reviewer are in good agreement with those reported by the firm.
2. Subject #1 experienced diarrhea 4 days after period III dosing. Subject #6 experienced diarrhea 10 days after period II dosing. Subject #22 vomited 2 days after period II dosing. These subjects were not excluded from the analyses.
3. Subject #13 had measurable descarboethoxy loratadine levels at 0 h in period II (reference non-fasting) and period III (test fasting). In both the instances, the 0 h drug level was more than 5% of its C_{max} for this subject. This subject was excluded from the analyses for descarboethoxy loratadine. The data presented in Tables 7 and 8 are derived from such analyses. The ratios of means for AUC_{0-t}, AUC_{0-inf}, and C_{max} between test non-fasting and reference non-fasting remained within acceptable limits.
4. Loratadine: The terminal elimination half-life and therefore AUC_{0-inf} could not be calculated for subject numbers 3 and 6 (test non-fasting). Reviewer agrees with this observation.
5. The firm needs to provide manufacture date of the bio-lot.
6. The relative recovery of loratadine ranges from % to % and that of descarboethoxy loratadine ranges from % to %. The firm should explain the variation in the recovery at three different concentrations. Were the three concentrations used in the recovery experiments close to low, medium, and high QC samples? How was the relative recovery calculated? Is this the response measured from the matrix (plasma) as a percentage of that measured from pure solvent? The firm should provide the absolute recovery of loratadine, descarboethoxy loratadine and their internal standards. Recovery experiments should be performed by comparing the analytical results for extracted samples at three concentrations with unextracted standards that represent 100% recovery.
7. The non-fasting study is incomplete due to comments 5 and 6.

Bioequivalence Study Under Multi-dose Conditions:

A. Study Information:

Protocol#:	P98-259
IRB Approval:	Yes
Consent Form Signed:	Yes
Clinical Site:	
Principal Investigator:	
Analytical Facility:	
Analytical Director:	
Statistical Analysis:	
Study Dates:	Period I June 21-30, 1999 Period II July 19-28, 1999
Analysis Dates:	August 4 to August 27, 1999
Storage Period:	66 days
Study Design:	Randomized, multi-dose, two-way crossover with a wash-out period of 20 days between dose 9 of period I and dose I of period II.
Randomization scheme:	AB: 2,3,4,6,8,9,10,12,13,14,16,17,22, 24,29 BA: 1,5,7,11,15,18,19,20,21,23,25,26, 27,28

Treatments:

A: Loratadine/Pseudoephedrine Sulfate ER tablets, 1x10/240 mg; Oblong, oval, biconvex, straight sides with rounded edges; Andrx Pharmaceuticals; Lot #605R004A

B: Claritin-D 24 hour ER tablets, 1x10/240 mg; Oval, biconvex, straight sides with rounded edges; Schering; Lot #8-DCS-2008

Subjects:	29 healthy male, 18-44 years old subjects were enrolled according to the inclusion/exclusion criteria specified in the protocol.
Housing:	Approximately 10 hours prior to dose 1 and until at least 24 hours after dose 9 each period.
Dosing:	Every 24 hours for 9 consecutive days with 240 mL of water.
Sample Collection:	Blood samples (7 mL) were collected in heparinized containers within one hour prior to dose 1, dose 7, dose 8, dose 9

and after dose 9 at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours.

B. Study results:

1. Clinical:

Drop-outs: Subject numbers 3 and 18 withdrew prior to period II dosing due to schedule conflict. Subject #24 withdrew prior to dose 2 in period I due to personal reasons.

Adverse Events: Leg cramps, headache, dry lips, upset stomach, achy, dry mouth, nausea, sore throat, dry nose, runny nose, sweaty and vomiting. The events were comparable on test and reference drugs.

Protocol Deviations: There were 5 sampling time deviations of less than 4 minutes. Some subjects took ibuprofen, aspirin, and cough drops during the study.

2. Analytical:

Within-Study:

LORATADINE AND DESCARBOETHOXY LORATADINE:

Method:
Internal Standard:

Linearity:

Regression:
QC Samples:

Accuracy:

Precision

Reassays:

PSEUDOEPHEDRINE:

Method:
Internal Standard:
Linearity:

Regression:
QC Samples:
Accuracy:

Precision:

Reassays:

3. Pharmacokinetics/Statistics:

LORATADINE:

Mean Plasma Concentrations:	Table 11, Figure 7	
Pharmacokinetic Parameters:	Table 11	
90% Confidence Intervals:	$LAUC_{192-216}$	88.96-103.83%
	LC_{max}	**78.96**-104.42%
	LC_{avg}	88.96-103.83%
	LC_{min}	86.73-105.78%

DESCARBOETHOXY LORATADINE:

Mean Plasma Concentrations:	Table 12, Figure 8	
Pharmacokinetic Parameters:	Table 12	
90% Confidence Intervals:	$LAUC_{192-216}$	98.32-107.96%
	LC_{max}	89.79-105.18%
	LC_{avg}	98.32-107.96%
	LC_{min}	100.01-110.98%

PSEUDOEPHEDRINE:

Mean Plasma Concentrations:	Table 13, Figure 9	
Pharmacokinetic Parameters:	Table 13	
90% Confidence Intervals:	$LAUC_{192-216}$	96.34-106.37%
	LC_{max}	98.69-109.03%
	LC_{avg}	96.34-106.37%
	LC_{min}	80.59-104.88%

Comments:

1. Loratadine:
   a) Subject #28 had extremely high plasma loratadine levels for both periods when compared to other subjects. The firm has submitted the results of the statistical analyses with and without this subject. Following 90% CI are obtained for LC_{max}:
   Including subject #28: %
   Excluding subject #28: %

   However, a subject can not be dropped from data analysis solely on this basis. The pharmacokinetic data in Table 11 are based on reviewer's calculation including subject #28. The 90% confidence intervals for LC_{max} are outside the acceptable limits.
   Note: In fasting study subject #26 showed extremely high plasma loratadine levels in both periods compared to other subjects. The subject was not omitted from the analysis.
   b) Subject #6, 8 and 16 had no measurable loratadine concentrations at 144, 168, and 192 hours on test product. Subject # 16 and 20 had no measurable loratadine concentrations at these time points on reference product. Subject #26 had no measurable loratadine concentrations at 144 and 168 hours on reference product. Therefore it is not clear if these subjects attained steady state. The half-life of loratadine is about 15 hours and that of its metabolite is 23 hours. The firm used 144, 168 and 192 hours as steady state period. The first point (144 hours is about 9 half-lives of loratadine and therefore, theoretically, subjects should have reached the steady state. The reviewer however repeated statistical analyses after dropping these subjects. The 90% CI for LC_{max} remains outside the acceptable limits.

All subjects (n=26)	**78.96**-104.42%
Excluding subjects 6,8,16,20 (n=22)	**79.48**-110.21%
Excluding subjects 6,8,16,20,26 (n=21)	**78.89**-111.18%

2. Descarboethoxy loratadine:
   a) The 90%_confidence intervals for $LAUC_{192-216}$, LC_{max}, LC_{avg}, and LC_{min} are within acceptable limits.
   b) Subject_#13 had measurable drug concentration (more than % of C_{max}) at 0 h in period II (reference drug). The 90% confidence intervals remained within acceptable limits after dropping this subject from analysis.
3. Pseudoephedrine:
   a) The 90% confidence intervals for $LAUC_{192-216}$, LC_{max}, LC_{avg}, and LC_{min} are within acceptable limits.
   b) Subject #25 had measurable drug concentration (less than % of C_{max}) at 0 h in period II (test drug). The 90% confidence intervals remains within acceptable limits after dropping this subject from analysis.
4. Subject #12 and 28 vomited during the study. Since both the episodes of vomiting were several days after the dosing, these subjects were not dropped from the analysis.
5. On February 19, 1999 Andrx requested waivers for analyses of loratadine and descarboethoxy loratadine in plasma samples obtained from non-fasting and multiple-dose studies. This was based on the fact that the loratadine component of this product is formulated for immediate release and, food and multiple-dose studies are not required for the immediate release drug products. In response, the Agency requested to analyze loratadine and descarboethoxy loratadine in plasma samples from all three bioequivalence studies. The Agency's basis for requesting these analyses was the long half-lives of the components and the potential for accumulation of both the parent compound and the metabolite.

   The firm in this submission states that loratadine data in multiple-dose study should be disregarded for following reasons:

   a) Draft BA/BE guidance states "Because a single-dose study is considered more sensitive in assessing the primary question in a BE study (release of the drug substance from the drug product into the system circulation), a multiple-dose study is not generally recommended, even in instances where nonlinear kinetics are present."

   b) Loratadine is extensively metabolized and therefore its absorption is highly variable. Multiple-dose studies appear to contribute additional variability.

c) Subject #28 in this study showed unusually high plasma levels of loratadine for both test and reference products. When the study results are reanalyzed without subject #28, the loratadine C_{max} value meet the statistical requirements for this parameter.

d) No accumulation of loratadine was observed in our multiple-dose study. In fact, the profiles of loratadine in our multiple-dose study were lower than the profiles in our single-dose study. It is generally believed that if the ratio of AUC_{0-24}/AUC_{0-inf} from a single-dose study is larger than there will be no accumulation in a multiple-dose study for a once-a-day product. The ratio of AUC_{0-24}/AUC_{0-inf} from our single-dose study was

6. The Division of Bioequivalence currently requests measurement of loratadine and descarboethoxy loratadine in all three bioequivalence studies. The 90% confidence intervals for loratadine LC_{max} in this study are outside the acceptable limits and therefore the multiple-dose study is not acceptable.

In Vitro Dissolution Testing:

The dissolution profiles were generated using apparatus I (basket) at 100 rpm in the following 5 media:
% Tween 80/simulated gastric fluid
simulated gastric fluid
pH 4.2 acetate buffer
pH 6.5 phosphate buffer and
pH 7.5 phosphate buffer

The results show that loratadine dissolves very poorly at pH 6.5 and 7.5 % in 30 minutes) but the dissolution of pseudoephedrine is not affected by pH. The firm is proposing following dissolution method and specifications:

The guidance 'Oral extended (controlled) release dosage forms: *In Vivo* Bioequivalence and *In Vitro* Dissolution Testing' recommends dissolution testing using apparatus II (paddle) at 50 and 75 rpm for tablets. The firm did not conduct the dissolution testing using apparatus II (paddle). Based on the innovator's method, results provided by the firm, and discussion with the Division of Bioequivalence dissolution specialist Nhan Tran, the following suggestion will be made to the firm:

Deficiencies:

Recommendations:

1. The bioequivalence study conducted under fasting conditions by Andrx Pharmaceuticals on its loratadine/pseudoephedrine sulfate 10/240 mg ER tablet, lot #605R004A comparing it to Claritin-D 24 hour ER tablet, lot #8-DCS-2008 manufactured by Schering has been found incomplete by the Division of Bioequivalence.
2. The bioequivalence study conducted under non-fasting conditions by Andrx Pharmaceuticals on its loratadine/ pseudoephedrine sulfate 10/240 mg ER tablet, lot #605R004A comparing it to Claritin-D 24 hour ER tablet, lot #8-DCS-2008 manufactured by Schering has been found incomplete by the Division of Bioequivalence.
3. The multiple-dose bioequivalence study conducted by Andrx Pharmaceuticals on its loratadine/pseudoephedrine sulfate 10/240 mg ER tablet, lot #605R004A comparing it to Claritin-D 24 hour ER tablet, lot #8-DCS-2008 manufactured by Schering has been found unacceptable by the Division of Bioequivalence.
4. The dissolution testing conducted by the firm on its loratadine/pseudoephedrine sulfate 10/240 mg ER tablet is incomplete.
5. From the bioequivalence point of view, the firm has not met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is incomplete.

/S/

Kuldeep R. Dhariwal, Ph.D.
Review Branch_II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR

/S/ Date 3/27/2000

Concur: /S/ Date 5/8/00

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

Table 1

Quantitative Composition of Loratadine/Pseudoephedrine Sulfate, 10/240 mg ER Tablets

Ingredient	mg/tablet
Loratadine (micronized)	
Pseudoephedrine sulfate	
Hydroxypropyl methylcellulose	
Lactose monohydrate,	
Sodium lauryl sulfate	
Glyceryl monostearate	
Talc	
Magnesium stearate	
Colloidal silicon dioxide	
Candelilla wax powder	
Imprinting Ink Opacode WB (NS-78-17715, black)	
Total Tablet Weight	922.89

Test: Oblong, oval, biconvex, straight sides with rounded edges.
Ref: Oval, biconvex, straight sides with rounded edges.

Table 2

MEAN PLASMA LORATADINE LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS, n=28

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	0.01	0.02	0.06	0.09	0.17
0.5	0.41	0.76	0.56	0.90	0.73
0.75	1.41	2.62	1.57	2.28	0.90
1	2.27	4.65	2.26	3.82	1.00
1.5	2.98	6.63	2.36	4.20	1.26
2	2.23	3.81	2.08	4.17	1.07
3	1.57	3.04	1.46	3.41	1.07
4	0.90	1.58	0.98	2.51	0.92
6	0.42	0.91	0.40	1.11	1.04
8	0.20	0.41	0.24	0.75	0.82
12	0.10	0.27	0.11	0.35	0.94
16	0.07	0.17	0.07	0.22	0.91
24	0.04	0.10	0.04	0.14	0.87
36	0.03	0.08	0.03	0.11	0.95
48	0.02	0.07	0.02	0.08	0.90
72	0.01	0.04	0.01	0.04	1.21
96	0.01	0.02	0.00	0.02	1.22
120	0.00	0.01	0.00	0.02	0.82
144	0.00	0.01	0.00	0.01	1.41

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	11.57	24.86	11.44	27.97	1.01
AUCT	11.19	24.34	11.06	27.60	1.01
CMAX	3.11	6.62	2.58	4.27	1.21
KE	0.12	0.13	0.11	0.13	1.09
LAUCI	4.94	1.18	4.68	1.17	1.06
LAUCT	4.70	1.19	4.44	1.18	1.06
LCMAX	1.38	1.13	1.34	1.09	1.03
THALF	14.68	11.22	15.88	12.90	0.92
TMAX	1.53	0.48	1.36	0.50	1.12

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	11.57	11.44	1.01	89.15	113.02
AUCT	11.19	11.06	1.01	88.46	113.91
CMAX	3.11	2.58	1.21	87.83	153.57
LAUCI	4.94	4.68	1.06	94.73	117.78
LAUCT	4.70	4.44	1.06	95.07	117.48
LCMAX	1.38	1.34	1.03	89.75	118.58

Table 3

MEAN PLASMA DESCARBOETHOXY LORATADINE LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS IN FASTING STUDY, N=28

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	0.01	0.03	0.09	0.12	0.12
0.5	0.53	0.51	1.06	0.91	0.49
0.75	1.74	1.10	2.65	1.86	0.66
1	2.54	1.41	3.36	1.99	0.76
1.5	3.44	2.39	3.63	1.77	0.95
2	3.19	1.45	3.26	1.43	0.98
3	2.90	1.30	2.79	1.15	1.04
4	2.39	0.98	2.33	0.86	1.03
6	2.37	1.10	2.16	0.81	1.10
8	1.80	0.81	1.88	0.99	0.96
12	1.25	0.57	1.19	0.49	1.06
16	0.88	0.43	0.83	0.35	1.06
24	0.62	0.29	0.60	0.29	1.03
36	0.44	0.25	0.39	0.20	1.11
48	0.25	0.14	0.23	0.12	1.09
72	0.12	0.07	0.10	0.06	1.15
96	0.05	0.04	0.06	0.04	0.96
120	0.03	0.03	0.02	0.02	1.27
144	0.01	0.02	0.01	0.01	1.33

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	54.38	24.38	52.75	21.53	1.03
AUCT	53.16	24.21	51.51	21.39	1.03
CMAX	3.87	2.32	3.89	1.89	0.99
KE	0.03	0.01	0.03	0.01	1.00
LAUCI	48.85	0.50	48.31	0.44	1.01
LAUCT	47.59	0.50	47.01	0.45	1.01
LCMAX	3.38	0.52	3.46	0.51	0.98
THALF	22.85	5.61	23.03	6.03	0.99
TMAX	2.05	1.02	2.02	1.56	1.02

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	54.38	52.75	1.03	96.06	110.10
AUCT	53.16	51.51	1.03	96.05	110.34
CMAX	3.87	3.89	0.99	83.66	115.07
LAUCI	48.85	48.31	1.01	93.82	108.98
LAUCT	47.59	47.01	1.01	93.79	109.24
LCMAX	3.38	3.46	0.98	87.12	109.14

Table 4

MEAN PLASMA PSEUDOEPHEDRINE LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS IN FASTING STUDY, N=28

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.25	0.00	0.00	1.46	4.32	0.00
0.5	11.31	12.07	23.34	16.79	0.48
0.75	47.19	19.28	60.73	25.35	0.78
1	80.47	25.04	89.85	28.36	0.90
1.5	130.90	28.42	141.39	40.27	0.93
2	175.61	34.77	179.96	42.28	0.98
3	256.00	43.38	243.00	44.56	1.05
4	308.86	49.30	271.61	50.61	1.14
6	344.68	56.15	324.79	65.63	1.06
8	319.36	64.78	316.79	75.31	1.01
12	253.89	58.12	259.25	70.90	0.98
16	197.37	52.91	213.29	58.64	0.93
24	104.74	36.83	103.51	30.46	1.01
36	31.20	16.78	26.21	13.92	1.19
48	9.46	32.10	1.64	4.04	5.78
72	0.00	0.00	0.00	0.00	.

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	6504.36	1443.20	6274.61	1408.45	1.04
AUCT	6172.64	1369.49	6071.61	1397.87	1.02
CMAX	351.36	56.18	334.18	68.35	1.05
KE	0.10	0.02	0.11	0.02	0.89
LAUCI	6353.47	0.22	6134.04	0.21	1.04
LAUCT	6024.56	0.23	5931.46	0.22	1.02
LCMAX	347.04	0.16	327.52	0.21	1.06
THALF	7.37	1.56	6.49	1.12	1.14
TMAX	6.07	1.68	6.46	1.75	0.94

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	6504.36	6274.61	1.04	99.08	108.24
AUCT	6172.64	6071.61	1.02	97.07	106.25
CMAX	351.36	334.18	1.05	100.45	109.83
LAUCI	6353.47	6134.04	1.04	98.88	108.50
LAUCT	6024.56	5931.46	1.02	96.80	106.58
LCMAX	347.04	327.52	1.06	101.16	110.99

Table 5

MEAN PLASMA LORATADINE LEVELS FOR TEST AND REFERENCE PRODUCTS IN NON-FASTING STUDY, N=21

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.25	0.04	0.06	0.01	0.01	0.04	0.11	6.68
0.5	0.56	0.85	0.37	0.51	0.33	0.47	1.50
0.75	1.38	2.02	1.14	1.35	0.88	0.87	1.22
1	1.87	2.75	1.75	2.01	1.53	1.36	1.07
1.5	2.27	4.19	2.13	2.08	2.55	2.07	1.07
2	1.80	3.08	2.09	1.95	2.64	2.24	0.86
3	1.13	1.45	1.85	1.80	2.23	2.20	0.61
4	0.76	0.92	1.28	1.30	1.47	1.49	0.59
6	0.35	0.43	0.69	0.96	0.70	0.59	0.51
8	0.15	0.20	0.33	0.39	0.30	0.24	0.45
12	0.06	0.09	0.15	0.16	0.13	0.11	0.42
16	0.04	0.07	0.10	0.12	0.08	0.07	0.41
24	0.02	0.05	0.05	0.05	0.05	0.04	0.49
36	0.01	0.03	0.03	0.03	0.03	0.03	0.48
48	0.01	0.03	0.02	0.03	0.02	0.02	0.52
72	0.01	0.02	0.01	0.02	0.01	0.02	0.69
96	0.00	0.02	0.01	0.02	0.01	0.01	0.71
120	0.00	0.01	0.00	0.01	0.00	0.01	0.85
144	0.00	0.01	0.00	0.01	0.00	0.01	1.12

(CONTINUED)

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
MEAN PLASMA LORATADINE LEVELS FOR TEST AND REFERENCE PRODUCTS

	RMEAN13	RMEAN23
TIME HR		
0	.	.
0.25	0.89	0.13
0.5	1.70	1.14
0.75	1.56	1.29
1	1.22	1.14
1.5	0.89	0.84
2	0.68	0.79
3	0.51	0.83
4	0.52	0.87
6	0.50	0.98
8	0.50	1.09
12	0.48	1.14
16	0.51	1.24
24	0.50	1.02
36	0.42	0.88
48	0.63	1.20
72	0.77	1.11
96	0.71	1.01
120	0.77	0.90
144	1.78	1.60

1= Test fasting
2= Test non-fasting
3= Ref non-fasting

Table 6

LORATADINE ARITHMETIC MEANS, LS MEANS AND RATIOS IN NON-FASTING STUDY, N=21

ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	9.04	13.97	13.35	13.26	14.22	12.23	0.68
AUCT	8.55	13.30	12.71	12.32	13.51	11.51	0.67
CMAX	2.52	4.23	2.98	2.20	3.10	2.33	0.84
KE	0.17	0.16	0.04	0.02	0.05	0.07	4.21
LAUCI	4.89	1.07	9.83	0.76	10.50	0.81	0.50
LAUCT	4.63	1.07	9.47	0.74	9.98	0.81	0.49
LCMAX	1.33	1.04	2.29	0.76	2.36	0.79	0.58
THALF	18.22	25.52	25.67	16.43	25.51	16.87	0.71
TMAX	1.93	1.28	2.01	1.00	2.20	1.39	0.96

(CONTINUED)

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

	RMEAN13	RMEAN23
PARAMETER		
AUCI	0.64	0.94
AUCT	0.63	0.94
CMAX	0.81	0.96
KE	3.19	0.76
LAUCI	0.47	0.94
LAUCT	0.46	0.95
LCMAX	0.56	0.97
THALF	0.71	1.01
TMAX	0.88	0.91

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

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	8.22	12.63	13.45	0.65	0.61	0.94
AUCT	7.76	12.02	12.77	0.65	0.61	0.94
CMAX	2.31	2.81	2.95	0.82	0.78	0.95
LAUCI	4.49	9.64	9.93	0.47	0.45	0.97
LAUCT	4.25	8.96	9.42	0.47	0.45	0.95
LCMAX	1.20	2.16	2.24	0.55	0.54	0.97

1= Test Fasting
2= Test Non-fasting
3= Ref Non-fasting

Table 7

MEAN PLASMA DESCARBOETHOXY LORATADINE LEVELS (ng/mL) FOR TEST AND REFERENCE PRODUCTS IN NON-FASTING STUDY, N=20

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.25	0.05	0.07	0.00	0.01	0.02	0.05	11.86
0.5	1.04	1.12	0.41	0.59	0.45	0.60	2.55
0.75	2.47	2.22	1.48	1.62	1.16	1.05	1.67
1	3.04	2.17	2.13	2.06	2.02	1.59	1.43
1.5	3.61	2.07	2.69	1.89	3.48	2.36	1.34
2	3.52	1.89	2.89	1.46	3.58	2.27	1.22
3	3.03	1.46	2.85	1.22	3.47	2.26	1.06
4	2.42	1.01	2.56	0.95	3.02	1.62	0.94
6	2.23	0.98	2.20	1.11	2.68	1.24	1.01
8	1.61	0.78	1.66	0.80	1.94	0.95	0.97
12	1.03	0.56	1.10	0.45	1.30	0.74	0.93
16	0.70	0.40	0.78	0.37	0.90	0.51	0.90
24	0.53	0.38	0.58	0.38	0.67	0.42	0.92
36	0.35	0.27	0.39	0.35	0.45	0.34	0.88
48	0.23	0.24	0.25	0.21	0.28	0.27	0.95
72	0.08	0.04	0.12	0.13	0.14	0.14	0.70
96	0.06	0.10	0.06	0.10	0.07	0.10	0.95
120	0.02	0.05	0.02	0.05	0.03	0.06	0.99
144	0.01	0.03	0.01	0.04	0.01	0.04	1.09

(CONTINUED)

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

	RMEAN13	RMEAN23
TIME HR		
0	.	.
0.25	2.17	0.18
0.5	2.34	0.92
0.75	2.13	1.28
1	1.51	1.06
1.5	1.04	0.77
2	0.98	0.81
3	0.87	0.82
4	0.80	0.85
6	0.83	0.82
8	0.83	0.86
12	0.79	0.84
16	0.78	0.87
24	0.80	0.86
36	0.76	0.87
48	0.82	0.86
72	0.62	0.88
96	0.90	0.95
120	0.88	0.89
144	0.82	0.75

1= Test Fasting
2= Test Non-Fasting
3= Ref Non-Fasting

Table 8

DESCARBOETHOXY LORATADINE ARITHMETIC MEANS, LS MEANS AND RATIOS IN NON-FASTING STUDY, N=20

ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	50.44	35.17	50.97	31.06	59.30	39.40	0.99
AUCT	49.11	34.15	49.46	29.67	57.67	37.98	0.99
CMAX	3.98	1.98	3.82	1.42	4.24	2.27	1.04
KE	0.03	0.01	0.03	0.01	0.03	0.01	1.00
LAUCI	44.61	0.44	46.45	0.38	52.67	0.44	0.96
LAUCT	43.40	0.45	45.16	0.38	51.23	0.44	0.96
LCMAX	3.62	0.42	3.58	0.38	3.82	0.45	1.01
THALF	21.27	4.46	21.13	4.24	21.14	4.45	1.01
TMAX	1.91	1.13	2.71	1.82	2.53	1.34	0.71

(CONTINUED)

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

	RMEAN13	RMEAN23
PARAMETER		
AUCI	0.85	0.86
AUCT	0.85	0.86
CMAX	0.94	0.90
KE	0.99	1.00
LAUCI	0.85	0.88
LAUCT	0.85	0.88
LCMAX	0.95	0.94
THALF	1.01	1.00
TMAX	0.76	1.07

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

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	48.45	49.50	58.13	0.98	0.83	0.85
AUCT	47.17	48.04	56.55	0.98	0.83	0.85
CMAX	3.83	3.73	4.18	1.02	0.92	0.89
LAUCI	43.27	45.57	52.06	0.95	0.83	0.88
LAUCT	42.07	44.30	50.63	0.95	0.83	0.87
LCMAX	3.50	3.50	3.77	1.00	0.93	0.93

1= Test Fasting
2= Test Non-fasting
3= Ref Non-fasting

Table 9

MEAN PLASMA PSEUDOEPHEDRINE LEVELS (ng/mL) FOR TEST AND REFERENCE PRODUCTS
IN NON-FASTING STUDY, N=21

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
TIME HR							
0	0.00	0.00	0.00	0.00	0.00	0.00	.
0.25	0.89	4.06	0.00	0.00	0.00	0.00	.
0.5	17.26	16.66	17.27	22.67	9.60	13.84	1.00
0.75	49.80	24.32	45.60	49.91	38.05	30.14	1.09
1	79.59	26.44	76.57	65.07	67.57	41.32	1.04
1.5	143.49	40.69	131.43	69.12	134.53	62.27	1.09
2	188.57	41.65	175.06	67.11	180.38	69.33	1.08
3	260.14	39.42	252.67	54.03	249.65	65.27	1.03
4	291.05	37.07	307.00	59.07	300.81	50.50	0.95
6	339.10	57.91	339.57	56.08	367.57	68.97	1.00
8	329.76	58.69	332.10	62.21	360.33	86.06	0.99
12	271.14	60.09	271.62	65.72	291.00	73.56	1.00
16	223.19	66.47	214.43	64.53	217.76	62.04	1.04
24	117.62	41.52	108.67	48.72	95.82	39.66	1.08
36	34.39	24.15	27.11	21.09	23.94	16.53	1.27
48	5.54	11.61	3.69	8.77	2.19	5.78	1.50
72	0.54	2.36	0.00	0.00	0.00	0.00	.

(CONTINUED)

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
MEAN PLASMA PSEUDOEPHEDRINE LEVELS FOR TEST AND REFERENCE PRODUCTS

	RMEAN13	RMEAN23
TIME HR		
0	.	.
0.25	.	.
0.5	1.80	1.80
0.75	1.31	1.20
1	1.18	1.13
1.5	1.07	0.98
2	1.05	0.97
3	1.04	1.01
4	0.97	1.02
6	0.92	0.92
8	0.92	0.92
12	0.93	0.93
16	1.02	0.98
24	1.23	1.13
36	1.44	1.13
48	2.54	1.69
72	.	.

1= Test Fasting
2= Test Non-fasting
3= Ref Non-fasting

Table 10

PSEUDOEPHEDRINE ARITHMETIC MEANS, LS MEANS, AND RATIOS IN NON-FASTING STUDY, N=21

ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3	RMEAN12
PARAMETER							
AUCI	6852.48	1715.61	6592.24	1544.14	6596.19	1532.90	1.04
AUCT	6589.71	1731.90	6274.67	1554.95	6399.14	1475.01	1.05
CMAX	351.52	53.64	357.86	57.58	385.19	62.05	0.98
KE	0.10	0.02	0.10	0.02	0.11	0.02	0.94
LAUCI	6670.36	0.23	6441.57	0.21	6425.14	0.24	1.04
LAUCT	6396.46	0.25	6112.84	0.23	6234.27	0.24	1.05
LCMAX	347.69	0.15	353.24	0.17	380.32	0.16	0.98
THALF	7.50	1.42	7.03	1.36	6.26	1.13	1.07
TMAX	6.20	1.40	6.19	1.89	6.81	1.83	1.00

(CONTINUED)

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

	RMEAN13	RMEAN23
PARAMETER		
AUCI	1.04	1.00
AUCT	1.03	0.98
CMAX	0.91	0.93
KE	0.84	0.90
LAUCI	1.04	1.00
LAUCT	1.03	0.98
LCMAX	0.91	0.93
THALF	1.20	1.12
TMAX	0.91	0.91

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

	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
PARAMETER						
AUCI	6824.89	6617.15	6632.98	1.03	1.03	1.00
AUCT	6572.06	6302.67	6436.43	1.04	1.02	0.98
CMAX	349.86	358.02	384.97	0.98	0.91	0.93
LAUCI	6656.42	6475.76	6472.72	1.03	1.03	1.00
LAUCT	6393.86	6149.65	6282.12	1.04	1.02	0.98
LCMAX	346.59	353.61	380.38	0.98	0.91	0.93

1= Test fasting
2= Test non-fasting
3= Ref non-fasting

Table 11

MEAN PLASMA LORATADINE LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS IN MULTIPLE-DOSE STUDY, N=26

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0		0		
144	0.06	0.11	0.063	0.11	1.0
168	0.07	0.10	0.07	0.11	1.00
192	0.07	0.11	0.07	0.10	1.01
192.25	0.08	0.11	0.13	0.15	0.66
192.5	0.49	0.58	0.94	1.41	0.52
192.75	1.22	1.30	1.89	2.78	0.64
193	1.83	2.00	2.49	4.26	0.74
193.5	2.04	2.74	2.75	4.77	0.74
194	1.88	2.93	2.11	3.49	0.89
195	1.35	2.15	1.34	2.10	1.01
196	0.92	1.30	0.79	1.20	1.16
198	0.37	0.59	0.35	0.57	1.07
200	0.22	0.34	0.22	0.38	0.99
204	0.12	0.21	0.12	0.23	0.98
208	0.08	0.15	0.10	0.18	0.83
216	0.07	0.12	0.07	0.12	0.97

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCT	9.00	12.90	9.88	15.94	0.91
CAVG	0.37	0.54	0.41	0.66	0.91
CMAX	2.38	2.96	3.06	4.88	0.78
CMIN	0.06	0.10	0.06	0.10	0.96
FLUC1	6.79	1.38	7.23	1.71	0.94
LAUCT	5.45	0.99	5.67	1.00	0.96
LCAVG	0.23	0.99	0.24	1.00	0.96
LCMAX	1.54	0.95	1.69	1.03	0.91
LCMIN	0.05	0.82	0.05	0.89	1.03
LFLUC1	6.64	0.22	7.02	0.25	0.95
LTMAX	193.51	0.00	193.32	0.00	1.00
TMAX	193.51	0.79	193.32	0.51	1.00

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCT	9.00	9.88	78.44	103.70
CAVG	0.37	0.41	78.44	103.70
CMAX	2.38	3.06	54.27	101.25
CMIN	0.06	0.06	89.84	101.36
FLUC1	6.79	7.23	84.32	103.48
LAUCT	5.45	5.67	88.96	103.83
LCAVG	0.23	0.24	88.96	103.83
LCMAX	1.54	1.69	78.96	104.42
LCMIN	0.05	0.05	86.73	105.78
LFLUC1	6.64	7.02	84.88	105.31

Table 12

MEAN PLASMA DESCARBOETHOXYLORATADINE LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS IN MULTIPLE-DOSE STUDY, N= 26

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0		0.03		
144	1.20	1.55	1.22	1.58	0.98
168	1.19	1.53	1.22	2.00	0.98
192	1.16	1.46	1.21	2.19	0.96
192.25	1.25	1.72	1.37	2.27	0.91
192.5	2.20	2.03	2.87	2.51	0.77
192.75	3.39	2.23	4.18	2.62	0.81
193	4.39	2.26	4.86	2.43	0.90
193.5	4.62	2.33	5.05	2.27	0.91
194	4.54	2.32	4.47	2.05	1.01
195	4.09	2.12	3.94	2.16	1.04
196	3.79	2.51	3.31	1.88	1.15
198	3.29	2.28	3.05	1.91	1.08
200	2.70	2.24	2.53	2.16	1.07
204	1.98	2.21	1.78	1.59	1.11
208	1.52	2.00	1.57	2.19	0.97
216	1.17	1.71	1.22	2.18	0.95

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCT	55.81	48.54	53.96	47.68	1.03
CAVG	2.33	2.02	2.25	1.99	1.03
CMAX	5.24	2.46	5.36	2.38	0.98
CMIN	1.09	1.45	1.06	1.61	1.03
FLUC1	2.12	0.61	2.29	0.64	0.93
LAUCT	46.51	0.55	45.15	0.53	1.03
LCAVG	1.94	0.55	1.88	0.53	1.03
LCMAX	4.80	0.42	4.93	0.40	0.97
LCMIN	0.79	0.70	0.75	0.67	1.05
LFLUC1	2.01	0.37	2.15	0.43	0.94
LTMAX	193.82	0.01	193.39	0.00	1.00
TMAX	193.83	1.05	193.39	0.60	1.00

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCT	55.81	53.96	98.26	108.59
CAVG	2.33	2.25	98.26	108.59
CMAX	5.24	5.36	89.57	106.18
CMIN	1.09	1.06	95.85	109.66
FLUC1	2.12	2.29	85.81	99.59
LAUCT	46.51	45.15	98.32	107.96
LCAVG	1.94	1.88	98.32	107.96
LCMAX	4.80	4.93	89.79	105.18
LCMIN	0.79	0.75	100.01	110.98
LFLUC1	2.01	2.15	86.95	100.96

Table 13

MEAN PLASMA PSEUDOEPHEDRINE LEVELS (ng/mL) FOR TEST (1) AND REFERENCE (2) PRODUCTS IN MULTIPLE-DOSE STUDY, N=26

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.727	3.71	0.0		
144	146.26	56.88	141.99	56.46	1.03
168	133.38	47.01	142.35	51.44	0.94
192	136.56	63.00	138.47	50.38	0.99
192.25	129.37	63.50	132.61	46.44	0.98
192.5	136.99	55.72	156.32	44.35	0.88
192.75	169.07	64.78	177.54	46.52	0.95
193	204.29	71.27	206.04	48.36	0.99
193.5	261.50	83.08	256.62	53.26	1.02
194	291.31	90.24	292.23	55.49	1.00
195	366.46	85.62	362.31	73.14	1.01
196	417.31	80.83	405.65	66.31	1.03
198	464.62	92.51	441.38	84.88	1.05
200	443.08	100.65	427.23	71.99	1.04
204	356.77	94.24	358.15	85.25	1.00
208	287.40	99.60	282.19	82.13	1.02
216	137.14	57.22	129.10	49.65	1.06

UNIT: PLASMA LEVEL=NG/ML TIME=HRS
ARITHMETIC MEANS AND RATIOS

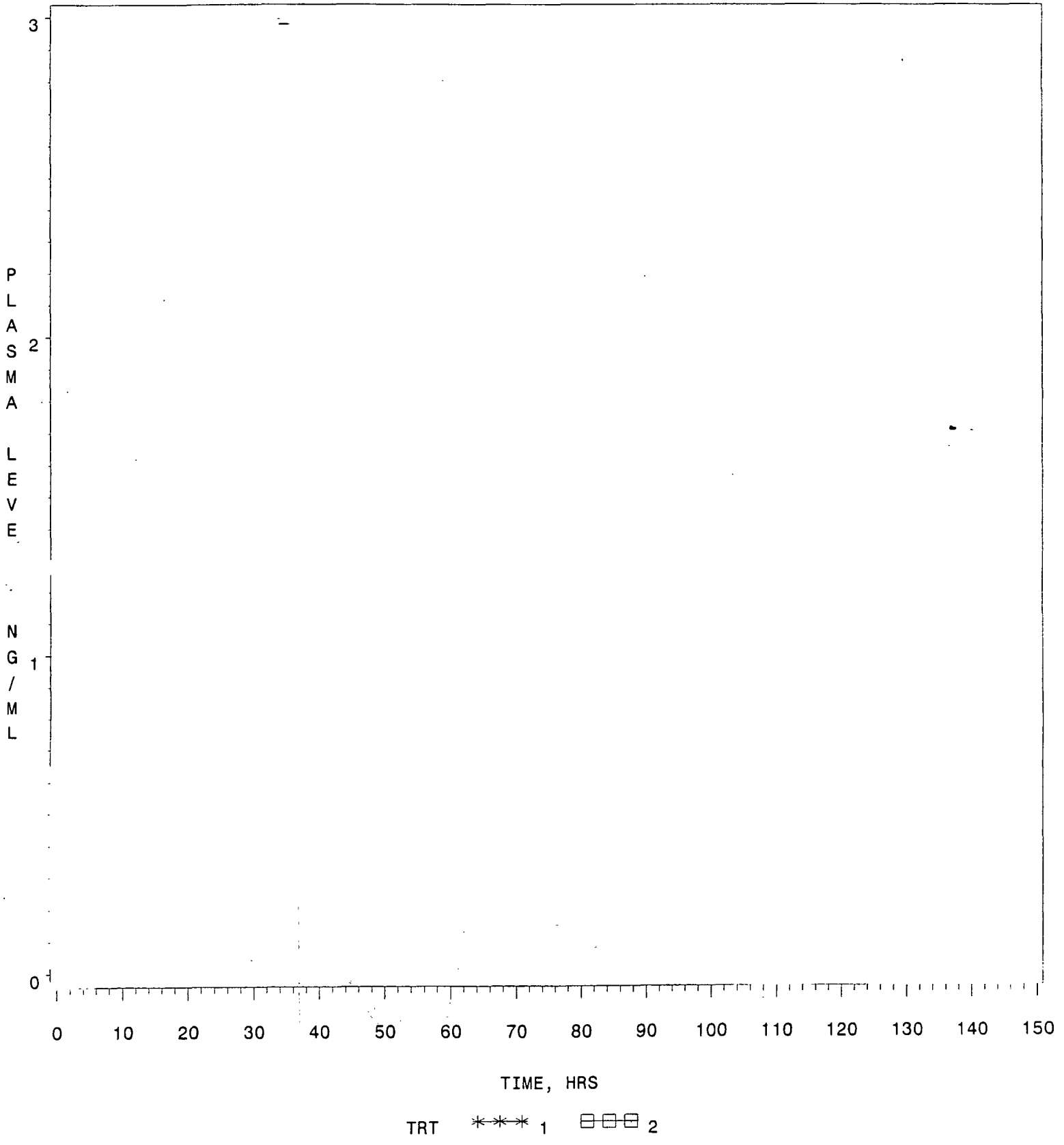
	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCT	7509.53	1885.32	7336.11	1424.59	1.02
CAVG	312.90	78.55	305.67	59.36	1.02
CMAX	473.77	93.11	454.04	76.20	1.04
CMIN	116.20	56.15	116.51	41.62	1.00
FLUC1	1.18	0.24	1.12	0.23	1.05
LAUCT	7293.36	0.25	7204.72	0.19	1.01
LCAVG	303.89	0.25	300.20	0.19	1.01
LCMAX	464.55	0.21	447.84	0.17	1.04
LCMIN	101.11	0.59	109.98	0.35	0.92
LFLUC1	1.16	0.21	1.10	0.21	1.05
LTMAX	197.96	0.01	199.06	0.01	0.99
TMAX	197.96	1.34	199.08	2.42	0.99

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	LOWCI12	UPPCI12
PARAMETER				
AUCT	7509.53	7336.11	96.66	108.07
CAVG	312.90	305.67	96.66	108.07
CMAX	473.77	454.04	98.77	109.93
CMIN	116.20	116.51	89.87	109.60
FLUC1	1.18	1.12	100.32	110.01
LAUCT	7293.36	7204.72	96.34	106.37
LCAVG	303.89	300.20	96.34	106.37
LCMAX	464.55	447.84	98.69	109.03
LCMIN	101.11	109.98	80.59	104.88
LFLUC1	1.16	1.10	100.19	110.51

FIG 1. PLASMA LORATADINE LEVELS

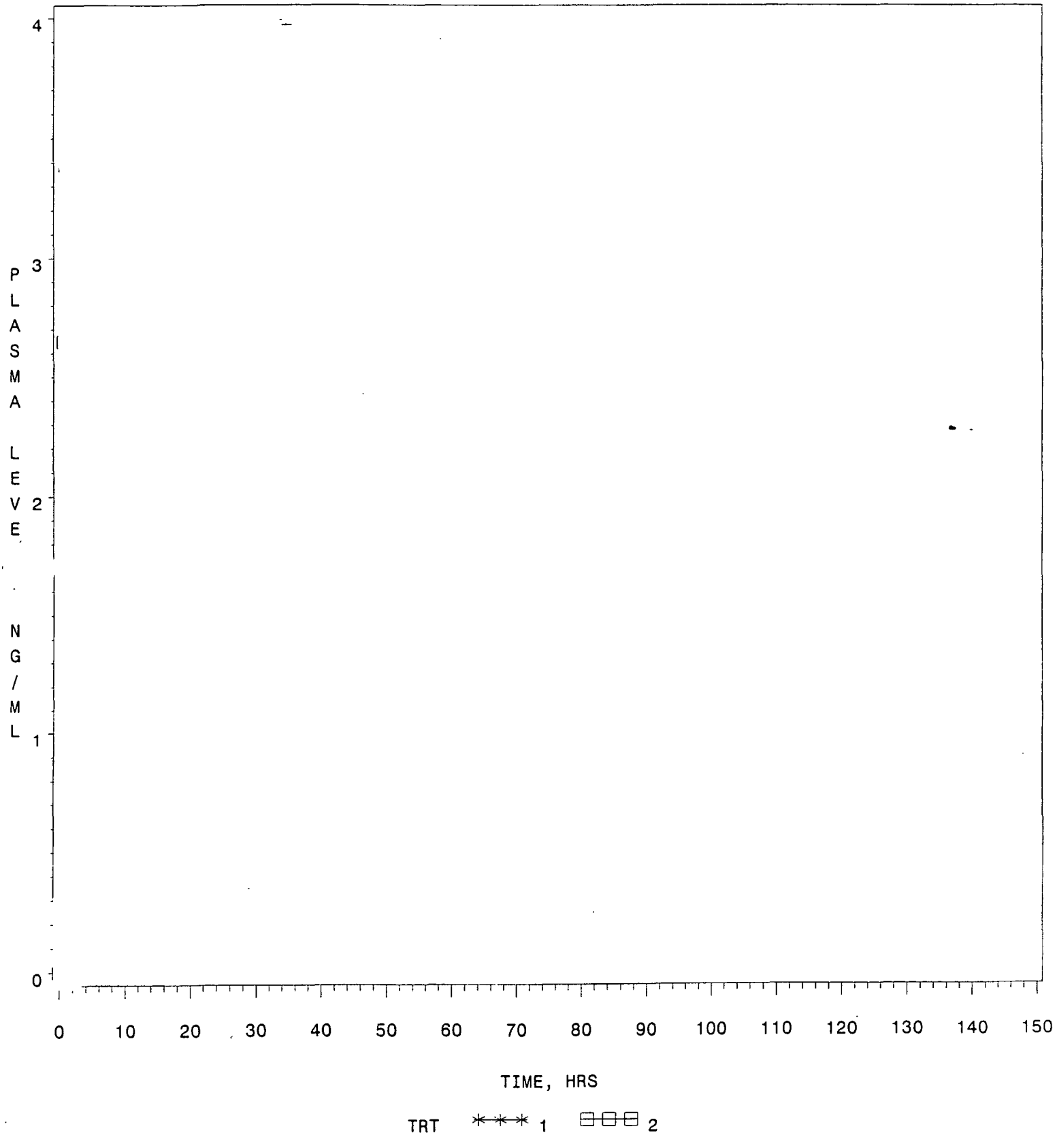
LORATADINE/PSEUDOEPHEDRINE TABLETS, 10/240 MG, ANDA #75-706
UNDER FASTING CONDITIONS
DOSE=1 X 10/240 MG



1=TEST(ANDRX) 2=REF(SCHERING)

FIG 2. PLASMA DESCARBOETHOXYLORATADINE LEVELS

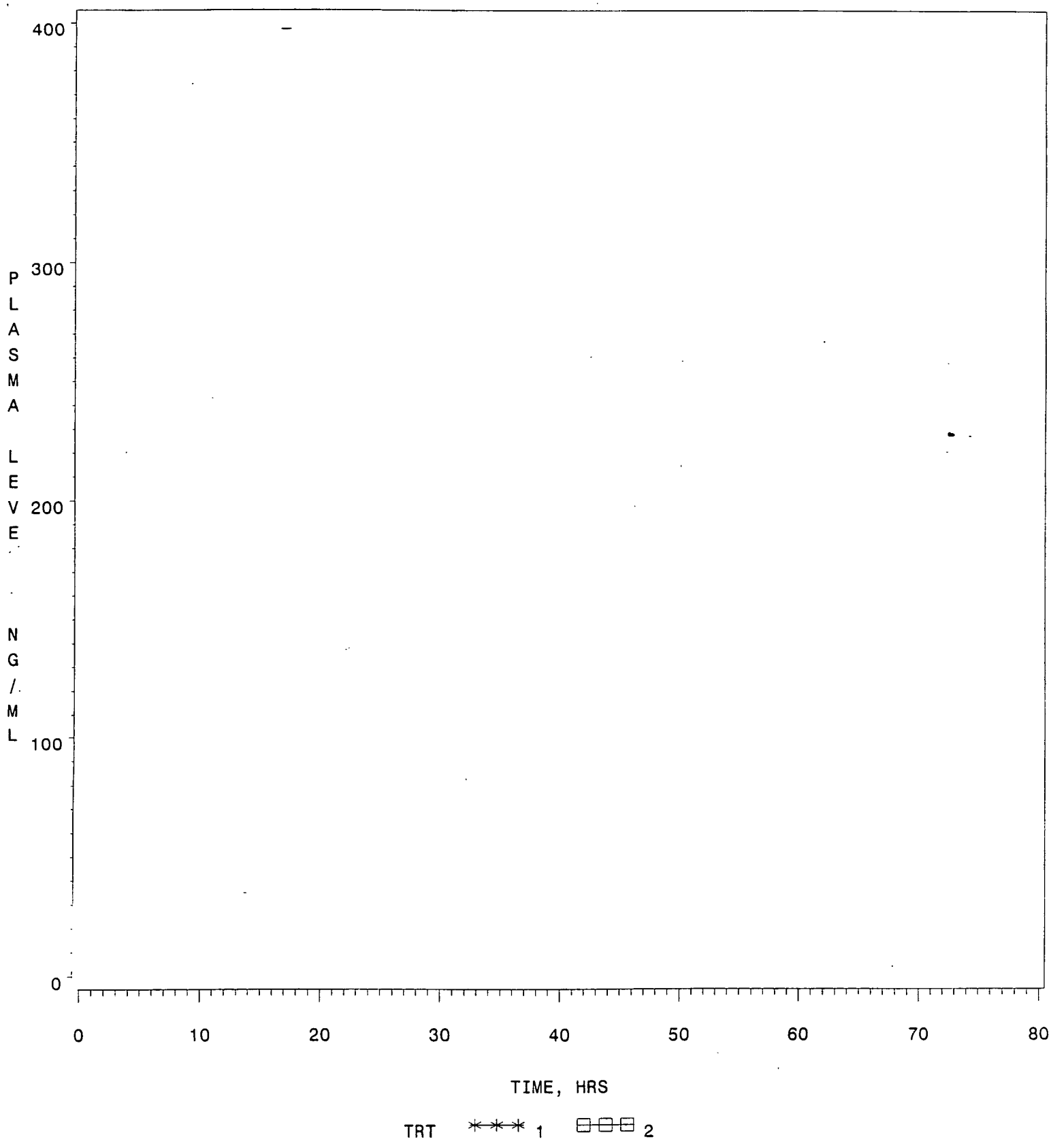
LORATADINE/PSEUDOEPHEDRINE TABLETS, 10/240 MG, ANDA #75-706
UNDER FASTING CONDITIONS
DOSE=1 X 10/240 MG



1=TEST(ANDRX) 2=REF(SCHERING)

FIG 3. PLASMA PSEUDOEPHEDRINE LEVELS

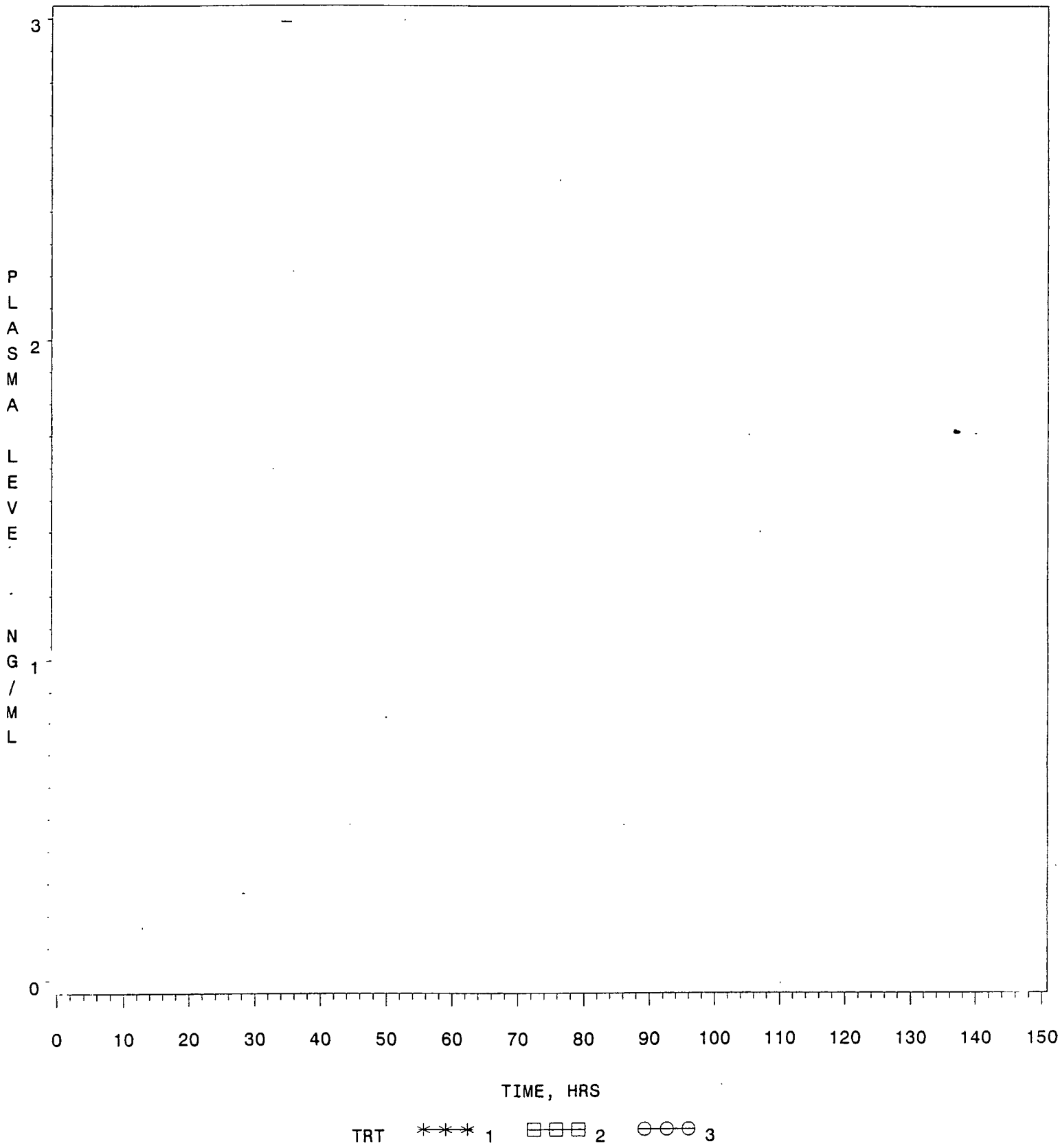
LORATADINE/PSEUDOEPHEDRINE TABLETS, 10/240 MG, ANDA #75-706
UNDER FASTING CONDITIONS
DOSE=1 X 10/240 MG



1=TEST(ANDRX) 2=REF(SCHERING)

FIG 4. PLASMA LORATADINE LEVELS

LORATADINE/PSEUDOEPHEDRINE, 10/240 MG, ANDA #75-706
UNDER FASTING/NONFASTING CONDITIONS
DOSE=1 X 10/240 MG



1=TEST(FAST) 2=TEST(FED) 3=REF(FED)

FIG 5. PLASMA DESCARBOETHOXY LORATADINE LEVELS

LORATADINE/PSEUDOEPHEDRINE, 10/240 MG, ANDA #75-706
UNDER FASTING/NONFASTING CONDITIONS
DOSE=1 X 10/240 MG

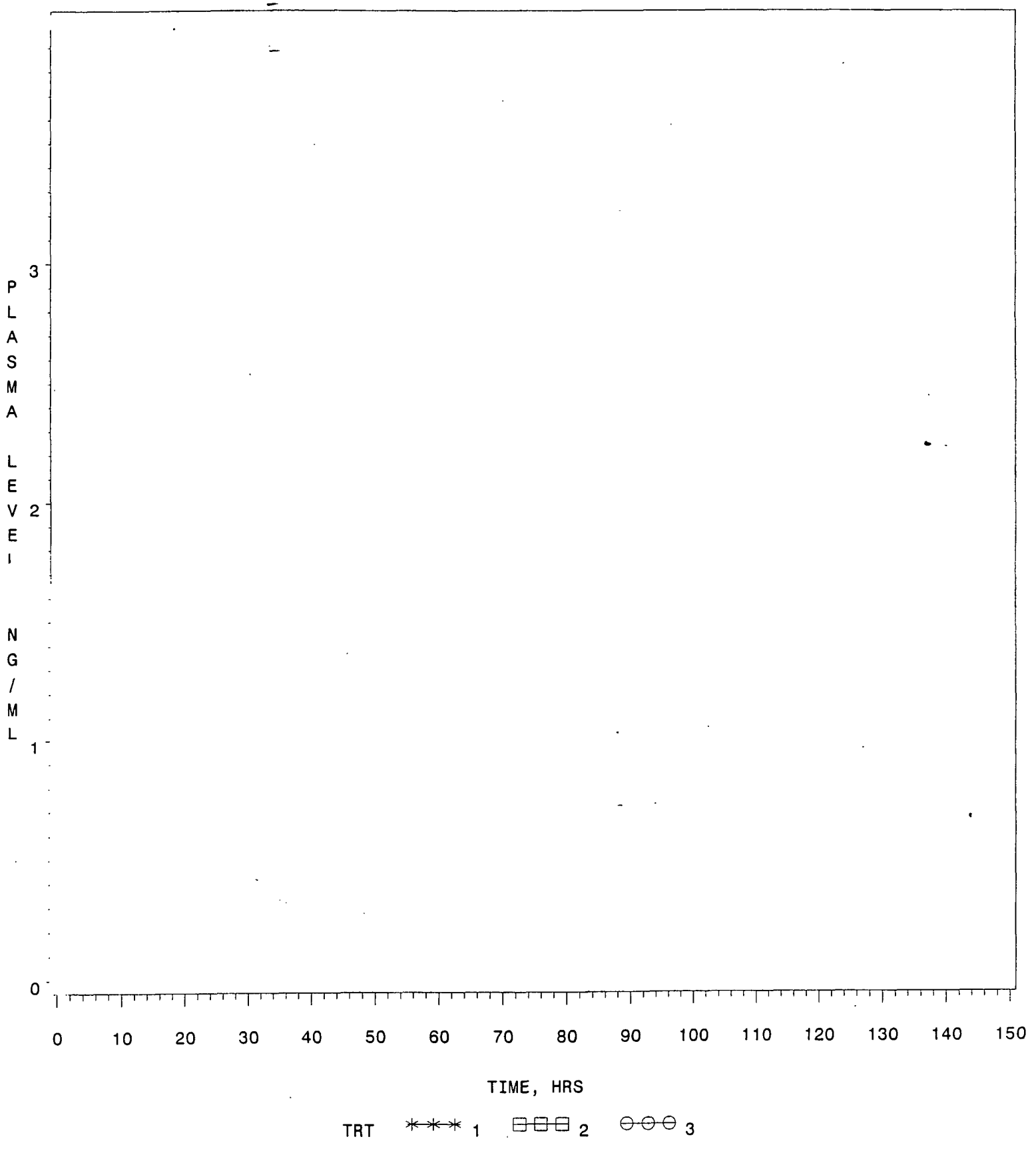


FIG 6. PLASMA PSEUDOEPHEDRINE LEVELS

LORATADINE/PSEUDOEPHEDRINE, 10/240 MG, ANDA #75-706
UNDER FASTING/NONFASTING CONDITIONS
DOSE=1 X 10/240 MG

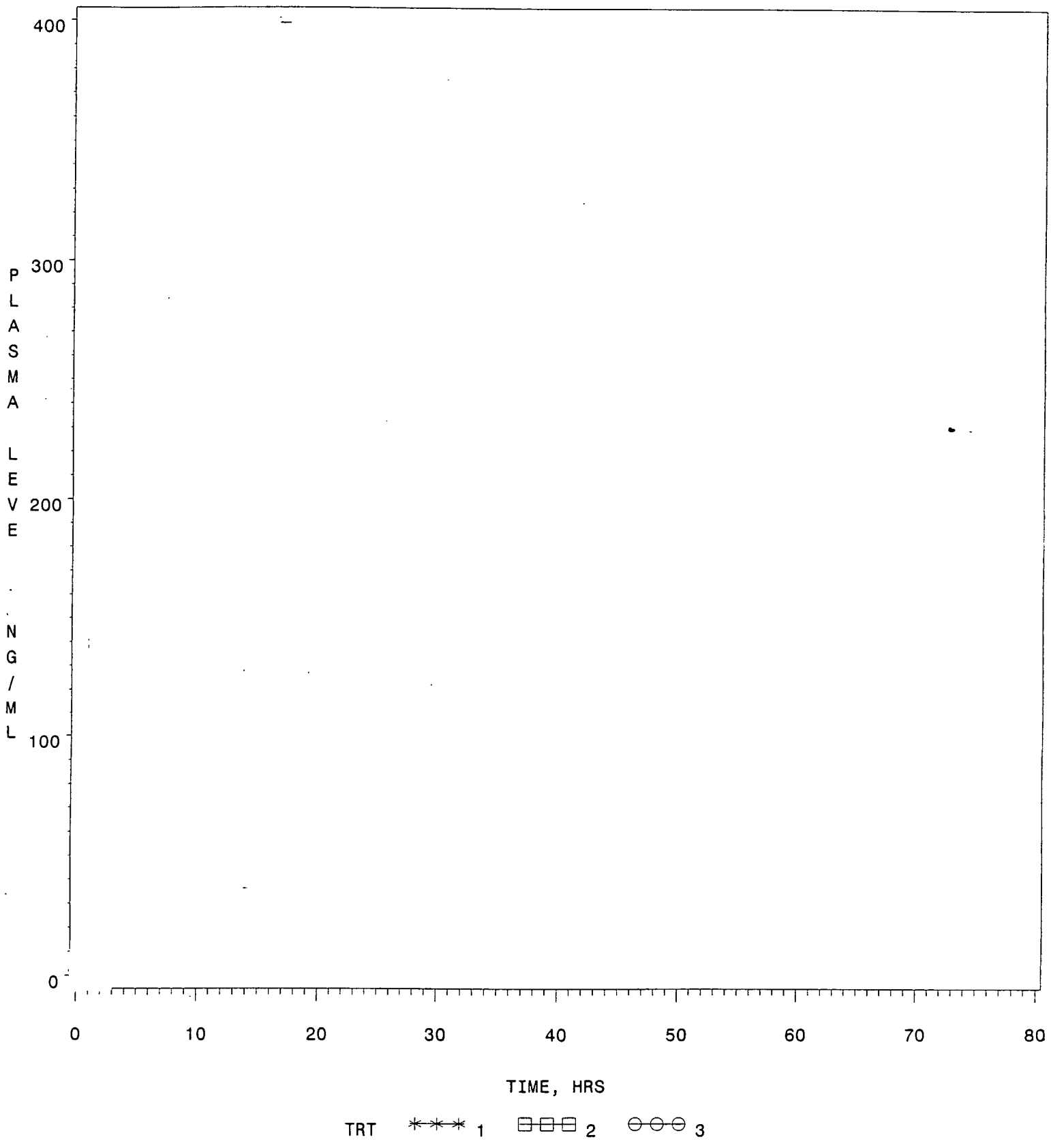
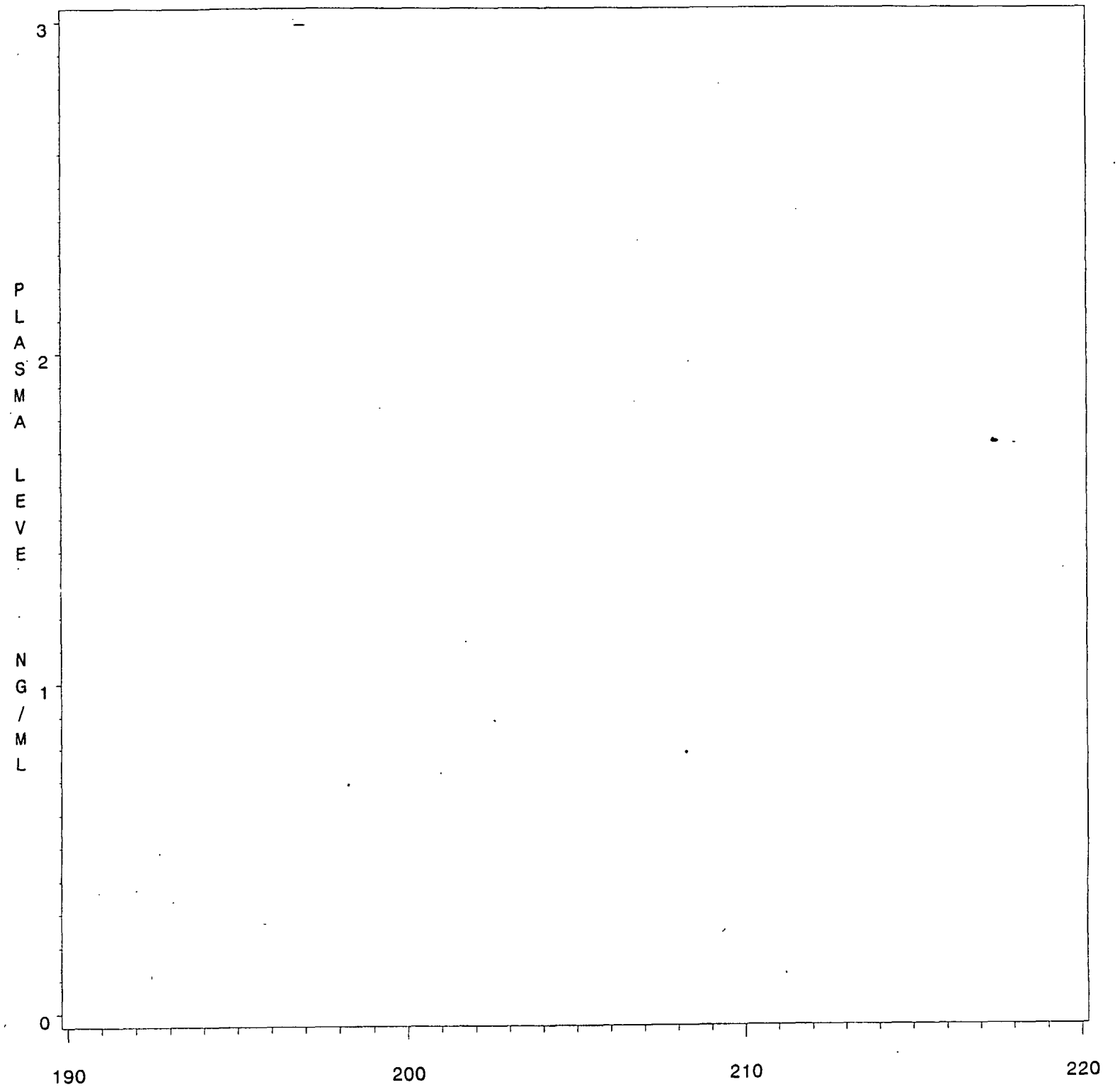


FIG P-7. PLASMA LORATADINE LEVELS

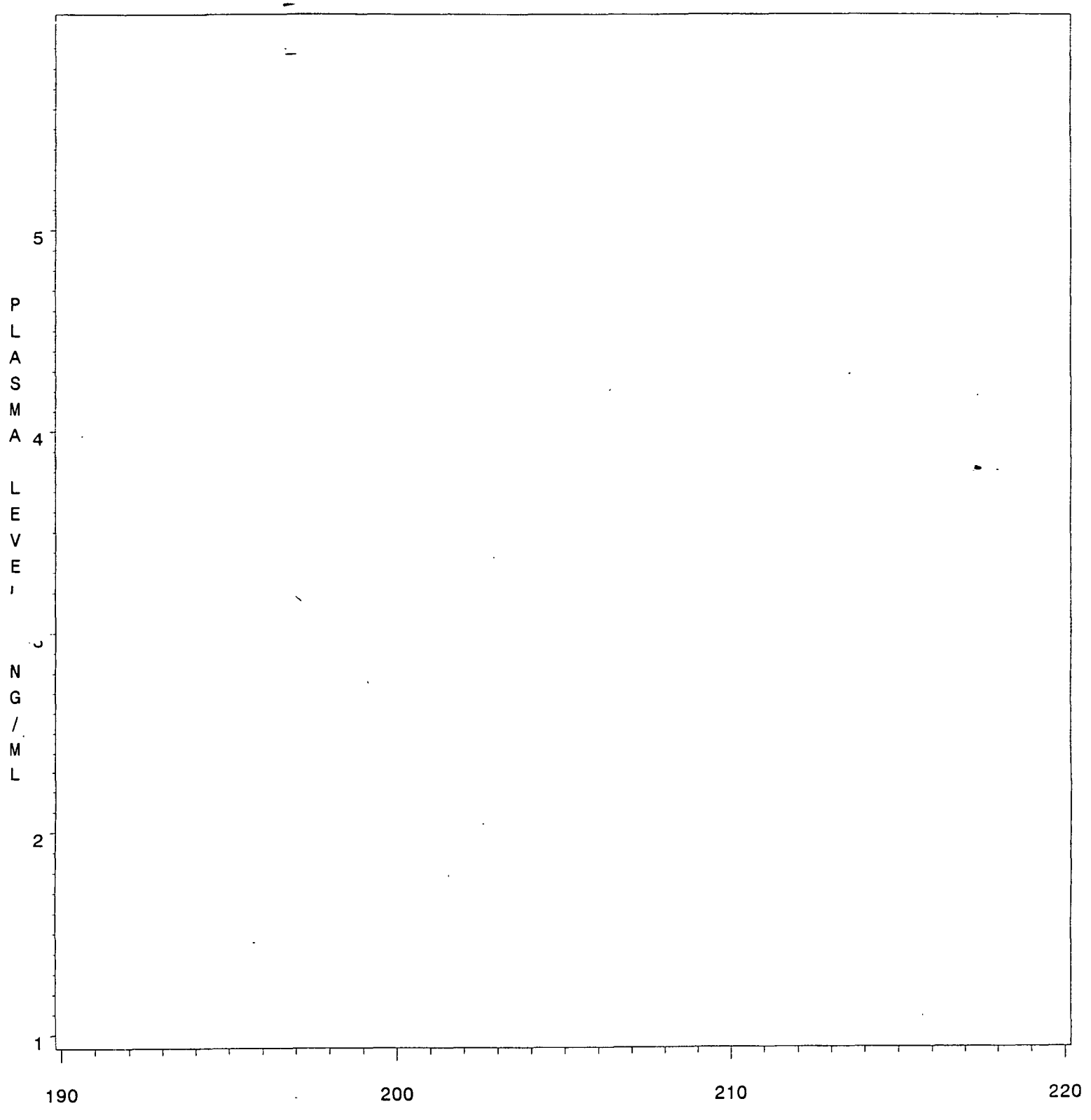
LORATADINE/PSEUDOEPHEDRINE ER TABLETS, 10/240 MG, ANDA #75-706
UNDER STEADY-STATE CONDITIONS
DOSE=1Q/240 MG ONE TIME/DAY FOR 8 DAYS AND ONCE PER 9TH DAY



1=TEST PRODUCT(ANDRX) 2=REFERENCE PRODUCT(SCHERING)

FIG P-8. PLASMA DESCARBOETHOXYLORATADINE LEVELS

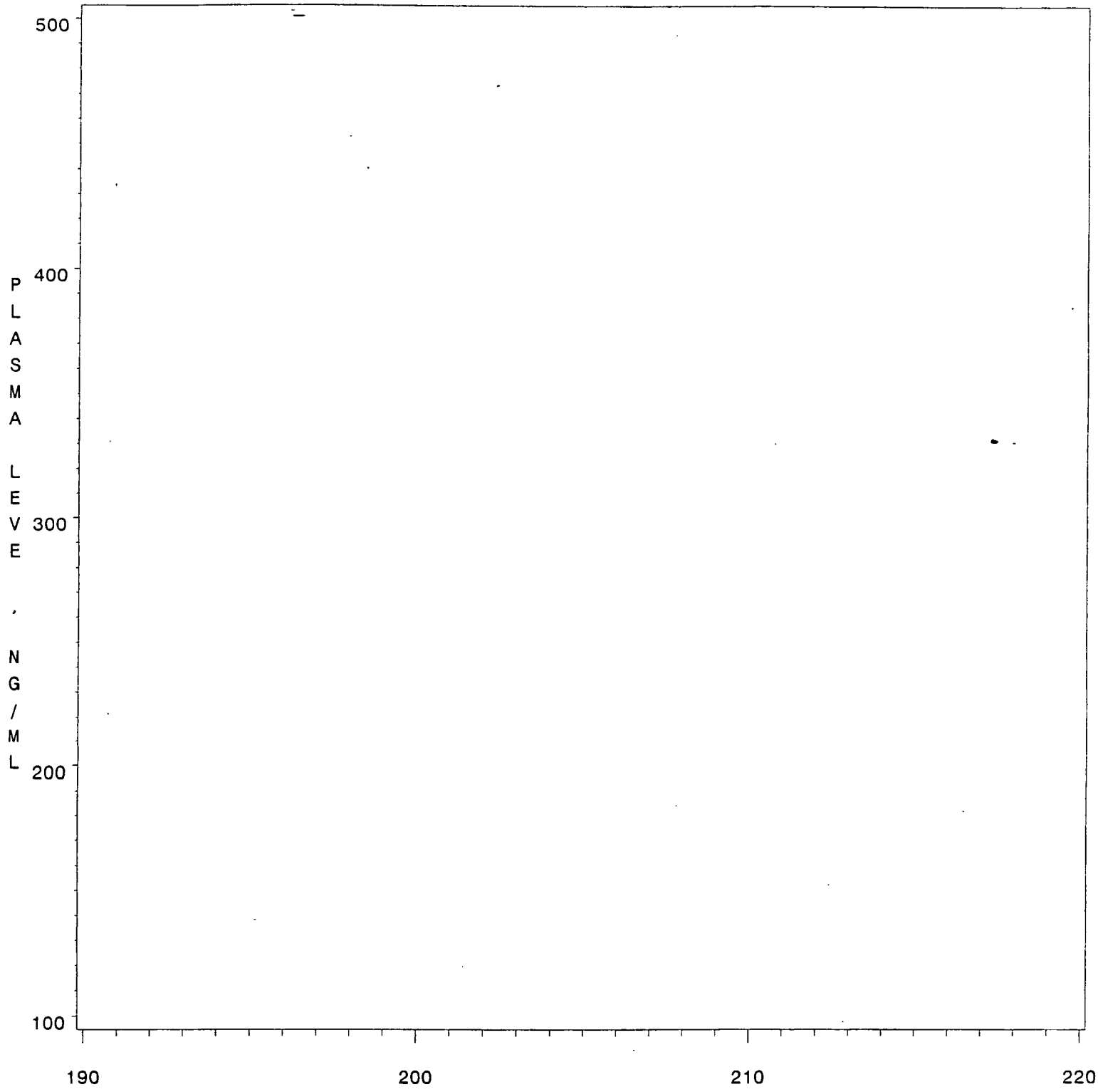
LORATADINE/PSEUDOEPHEDRINE ER TABLETS, 10/240 MG, ANDA #75-706
UNDER STEADY-STATE CONDITIONS
DOSE=10/240 MG ONE TIME/DAY FOR 8 DAYS AND ONCE PER 9TH DAY



1=TEST PRODUCT(ANDRX) 2=REFERENCE PRODUCT(SCHERING)

FIG P-9. PLASMA PSEUDOEPHEDRINE LEVELS

LORATADINE/PSEUDOEPHEDRINE ER TABLETS, 10/240 MG, ANDA #75-706
UNDER STEADY-STATE CONDITIONS
DOSE=10/240 MG ONE TIME/DAY FOR 8 DAYS AND ONCE PER 9TH DAY



1=TEST PRODUCT(ANDRX) 2=REFERENCE PRODUCT(SCHERING)

Table 1. *In Vitro* Dissolution Testing

Drug (Generic Name): Loratadine and Pseudoephedrine Sulfate Extended-release (ER) Tablets, 10 mg/240 mg
Dose Strength: 10 mg Loratadine
240 mg Pseudoephedrine Sulfate
Firm: Andrx Pharmaceuticals, Inc.

I. Conditions for Dissolution/Release Testing:

Method Ref.:
USP 23 Apparatus: Basket — Medium:
RPM: 100 — Volume: 900 mL
No. Units Tested: 12 — Tolerance (Q): N/A
Reference Drug: Claritin-D®24Hour (10 mg loratadine/240 mg pseudoephedrine sulfate) ER Tablets
Assay Method:

II. Results of *In Vitro* Dissolution/Release Testing:

Sampling Times	Test Product: Loratadine and PsdoSO_4* ER Tablets, 10 mg/240 mg Lot #: 605R004 Exp. Date:2 years Strength: 10 mg Loratadine 240 mg Psdo SO_4*			Refe. Product: Claritin-D®24Hour ER Tablets Lot #: 8-DCS-2008 Exp. Date: 2 years Strength: 10 mg Loratadine 240 mg Psdo SO_4*		
Loratadine (min)	Mean(%)	Range(%)	RSD(%)	Mean(%)	Range(%)	RSD(%)
5	8		21.4	53		4.2
15	68		8.8	88		4.8
30	91		7.8	94		5.4
60	94		7.3	96		5.7
120	94		7.1	98		5.7
	Assay: 96.1% LC Content Uniformity: Average(%LC): 94.6 Range(%LC): %RSD(n=10): 3.3			Assay: 98.0%LC Content Uniformity: Average(%LC): 99.4 Range(%LC): %RSD(n=10): 4.7		
Psdo SO_4* (hour)	Mean(%)	Range(%)	RSD(%)	Mean(%)	Range(%)	RSD(%)
0.083	0		346.4	0		346.4
0.25	5		50.0	8		4.4
0.5	12		12.0	14		2.5
1	22		7.0	22		1.7
2	34		5.4	35		1.2
4	50		4.5	52		1.3
8	73		3.4	76		1.1
12	85		1.9	89		1.4
16	94		1.9	95		1.1
20	98		1.9	99		0.8
	Assay: 98.4%LC Content Uniformity: Average(%LC): 98.9 Range(%LC): %RSD(n=10): 2.0			Assay: 96.9%LC Content Uniformity: Average(%LC): 97.0 Range(%LC): %RSD(n=10): 0.8		

* Psdo SO_4: Pseudoephedrine Sulfate.

Table 2. Dissolution Profile of Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/ 240 mg

›ratadine

Method: USP Apparatus I, 100 rpm, n=12

Test Product: Andrx Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/240 mg, Lot# 605R004

Amount Dissolved (%)

Time (min)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0														0	0
5														8	21.4
15														68	8.8
30														91	7.8
60														94	7.3
120														94	7.1

Reference Product: Claritin-D 24 Hour ER Tablets, Lot# 8-DCS-2008

Amount Dissolved (%)

Time (min)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0														0	0
5														53	4.2
15														88	4.8
30														94	5.4
60														98	5.7
120														98	5.7

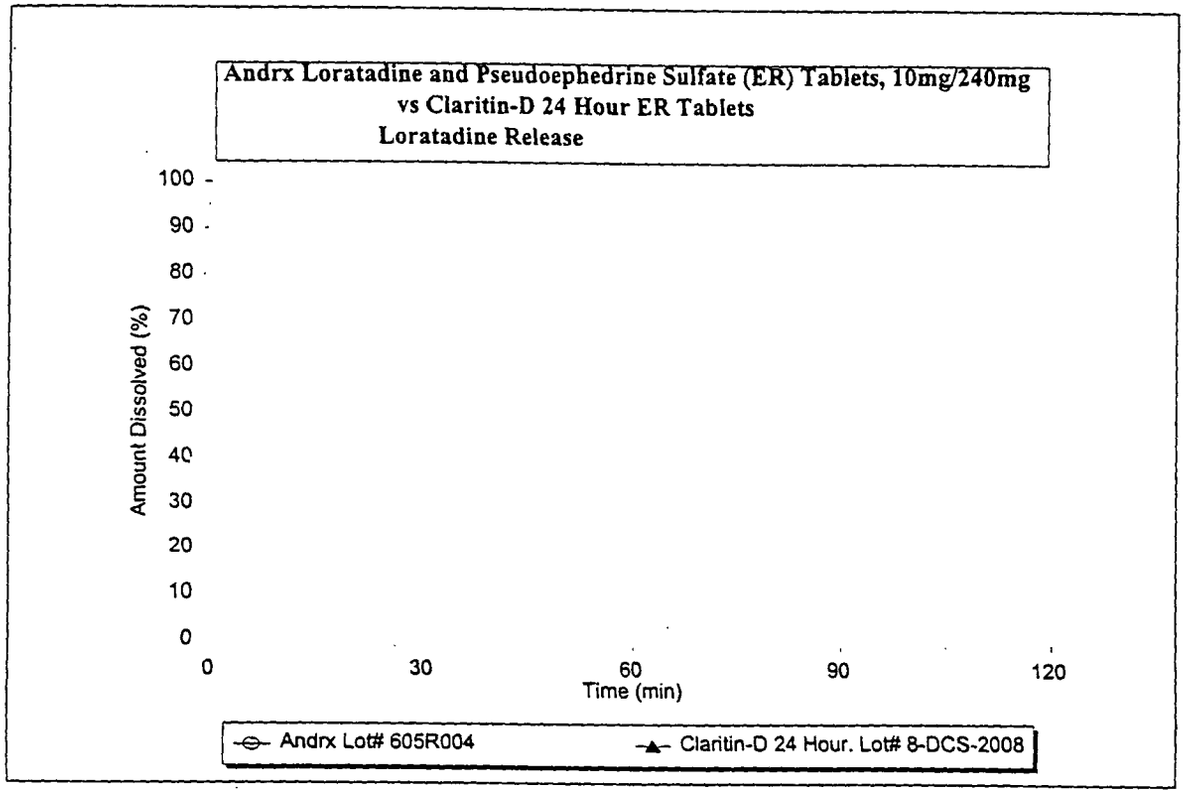


Table 3. Dissolution Profile of Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/ 240 mg

ıdoephedrine Sulfate

ıd: USP Apparatus I, 100 rpm, n=12

Test Product: Andrx Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/240 mg, Lot# 605R004

Amount Dissolved (%)

Time (Hr)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0														0	0
0.0833														0	346.4
0.25														5	50.0
0.5														12	12.0
1														22	7.0
2														34	5.4
4														50	4.5
8														73	3.4
12														85	1.9
16														94	1.9
20														98	1.9

Reference Product: Claritin-D 24 Hour ER Tablets, Lot# 8-DCS-2008

Amount Dissolved (%)

Time (Hr)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0														0	0
0.0833														0	346.4
0.25														8	4.4
0.5														14	2.5
1														22	1.7
2														35	1.2
4														52	1.3
8														76	1.1
12														89	1.4
16														95	1.1
20														99	0.8

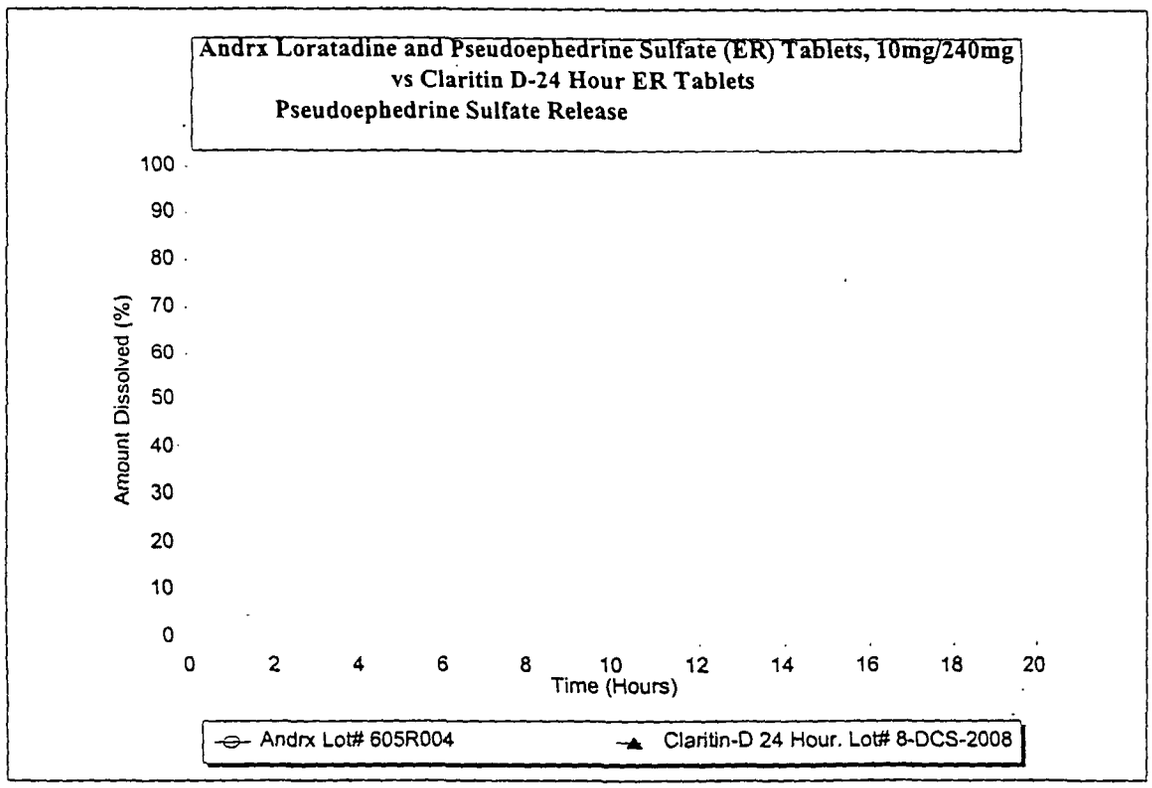


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Table 4. Dissolution Profile of Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/ 240 mg

oratadine

Method: USP Apparatus I, 100 rpm, n=12

Test Product: Andrx Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/240 mg, Lot# 605R004

Amount Dissolved (%)

Time (min)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0														0	0
5														6	14.4
15														56	6.7
30														78	5.1
60														82	4.7
120														82	4.7

Reference Product: Claritin-D 24 Hour ER Tablets, Lot# 8-DCS-2008

Amount Dissolved (%)

Time (min)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0														0	0
5														53	7.7
15														89	7.4
30														95	7.9
60														97	8.2
120														99	8.4

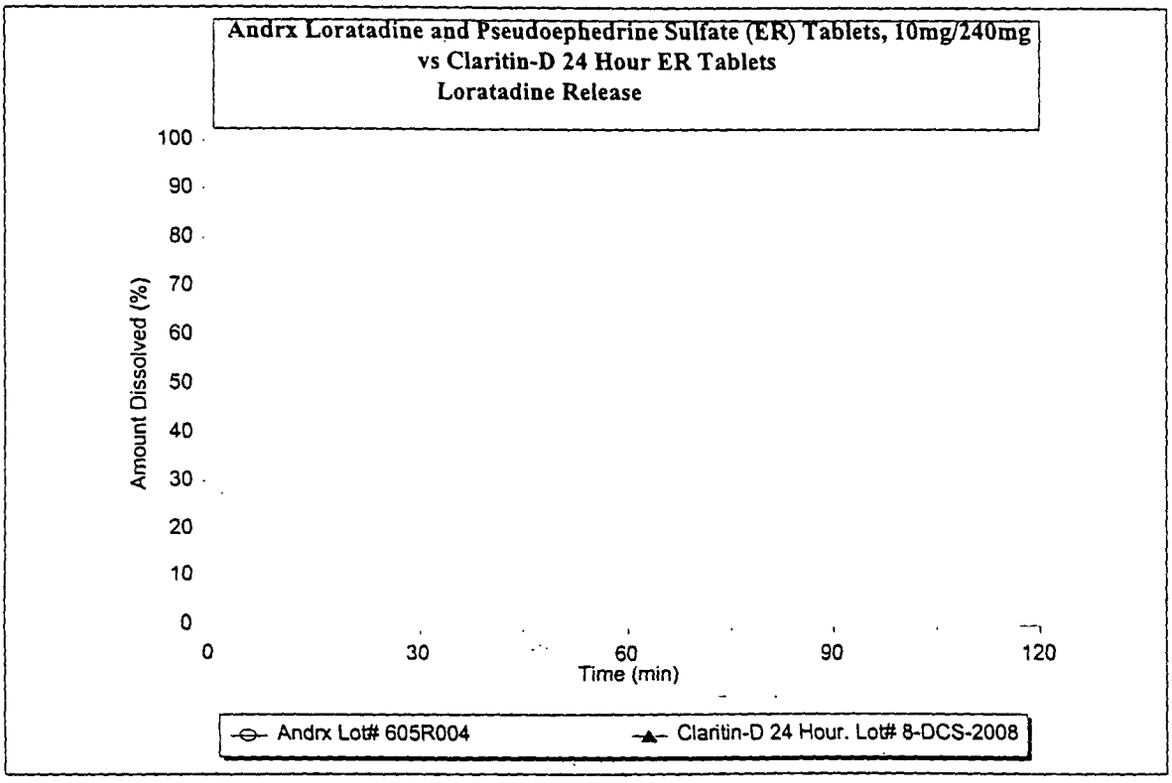


Table 5. Dissolution Profile of Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/ 240 mg

udoephedrine Sulfate

ethod: USP Apparatus I, 100 rpm, n=12

Test Product: Andrx Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/240 mg, Lot# 605R004

Amount Dissolved (%)

Time (Hr)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0														0	0
0.0833														0	ERR
0.25														1	66.4
0.5														10	6.3
1														19	5.3
2														33	3.7
4														51	3.1
8														75	3.4
12														88	3.4
16														96	4.5
20														101	4.7

Reference Product: Claritin-D 24 Hour ER Tablets, Lot# 8-DCS-2008

Amount Dissolved (%)

Time (Hr)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0														0	0
0.0833														0	ERR
0.25														4	76.0
0.5														11	10.0
1														19	7.1
2														31	4.1
4														49	3.8
8														73	3.2
12														86	2.2
16														91	2.5
20														97	1.5

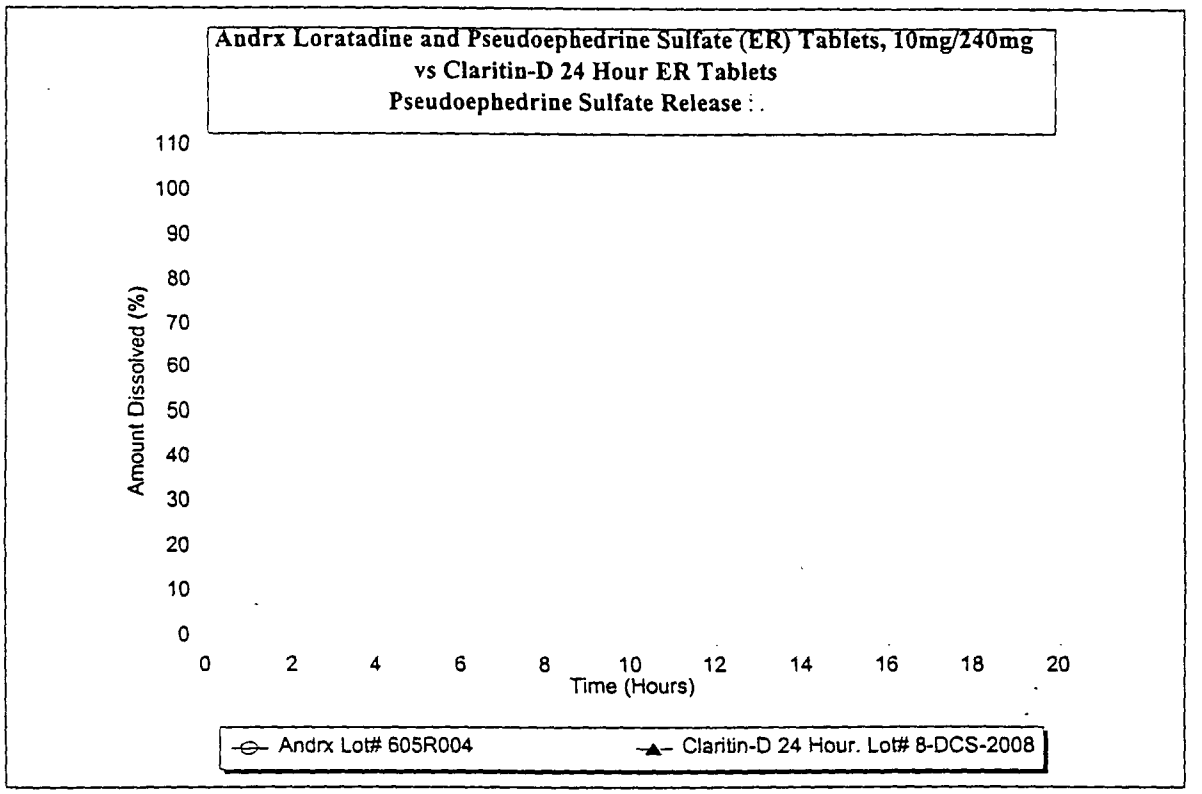


Table 6. Dissolution Profile of Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/ 240 mg in pH 4.2 Acetate Buffer

tadine

od: USP Apparatus I, 100 rpm, n=12

Test Product: Andrx Loratadine and Pseudoephedrine Sulfate (ER) Tablets, 10mg/240 mg, Lot# 605R004

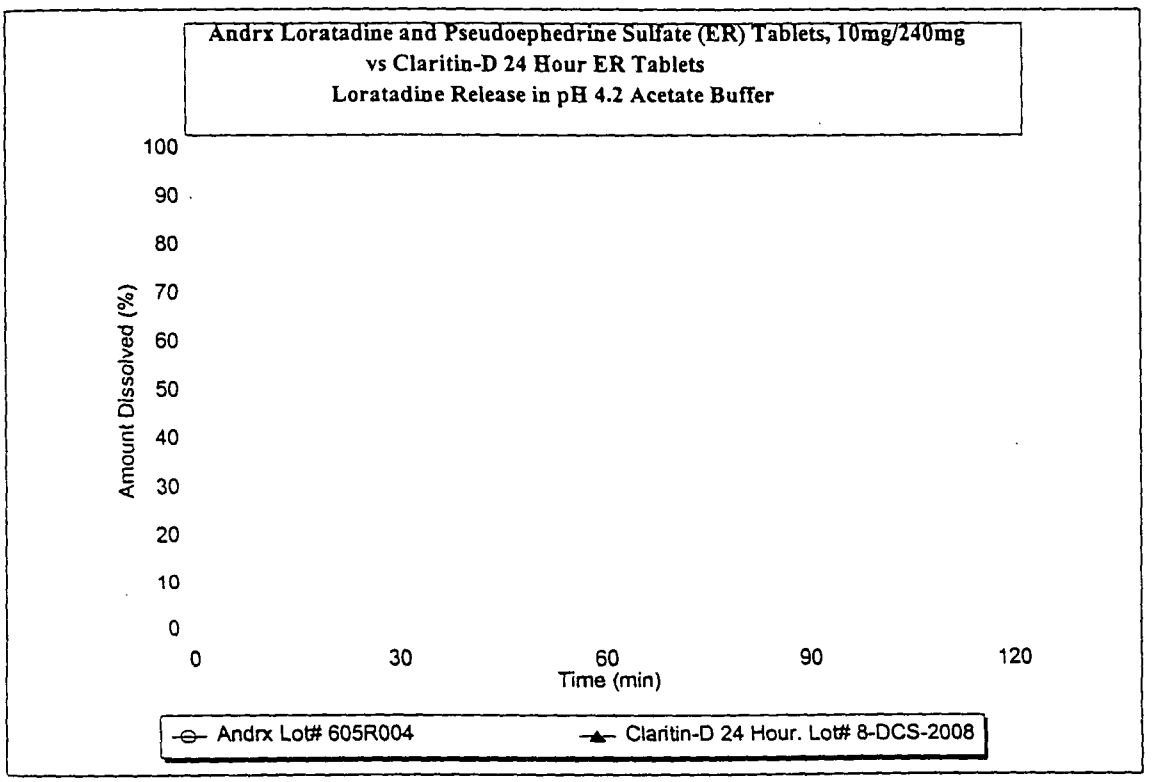
Amount Dissolved (%)

Time (min)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0														0	0
5														19	7.6
15														49	2.9
30														71	3.0
60														78	1.6
120														78	4.1

Reference Product: Claritin-D 24 Hour ER Tablets, Lot# 8-DCS-2008

Amount Dissolved (%)

Time (min)	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Range	Avg	%RSD
0														0	0
5														7	26.4
15														42	18.0
30														64	13.9
60														76	12.1
120														84	8.9



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