active (trifluoperazine) seems to be the less stable, and as soon as the radical is free and independent in solution, it suffers disproportionation and disappears as that radical.

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Simultaneous Stability-Indicating Determination of Phenylephrine Hydrochloride, Phenylpropanolamine Hydrochloride, and Guaifenesin in Dosage Forms by Reversed-Phase Paired-Ion High-Performance Liquid Chromatography

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Received December 4, 1981, from *Norwich-Eaton Pharmaceuticals, Norwich, NY 13815.* Accepted for publication March 5, 1982.

Abstract □ A method for the quantitative determination of phenylephrine hydrochloride, phenylpropanolamine hydrochloride, and guaifenesin in commercial formulations was developed. A reversed-phase paired-ion high-performance liquid chromatographic technique resolves the active from degradation products, colorings, and flavor and was found applicable to seven commercial dosage forms.

Keyphrases □ Phenylephrine hydrochloride—simultaneous determination with phenylpropanolamine hydrochloride and guaifenesin, reversed-phase paired-ion high-performance liquid chromatography □ Phenylpropanolamine hydrochloride—simultaneous determination with phenylephrine hydrochloride and guaifenesin, reversed-phase paired-ion high-performance liquid chromatography □ Guaifenesin—simultaneous determination with phenylephrine hydrochloride and phenylpropanolamine hydrochloride, reversed-phase paired-ion high-performance liquid chromatography □ High-performance liquid chromatography—reversed-phase paired-ion, simultaneous determination of phenylephrine hydrochloride, phenylpropanolamine hydrochloride, and guaifenesin

The simultaneous determination of the active components in a specific dosage form offers advantages to separate analyses. Simultaneous GLC determinations are typically successful in assaying for phenylpropanolamine hydrochloride and other amines (1–8). At least one GLC assay for guaifenesin (glyceryl guaiacolate) is available in which guaifenesin is extracted and derivatized (9). Simple and reliable procedures for the simultaneous GLC determination of the underivatized phenylephrine hydrochloride and other amines are absent from the chemical literature. Studies are available in which 71 drugs were determined using nitrogen-selective and flame-ionization (FID) detectors (2); 50 amines of pharmaceutical interest (5) and 23 physiologically active amines (8) were determined. None of these methods were responsive to phenylephrine hydrochloride.

To overcome problems arising from the presence of phenylephrine hydrochloride in pharmaceutical formulations, high-performance liquid chromatographic (HPLC) procedures have been developed for simultaneous assay. The desired chromatographic separation involves phenylephrine hydrochloride (I), phenylpropanolamine hydrochloride (II), and guaifenesin (III). The only HPLC method reported in the literature separating I, II, and III with high resolution used a bonded phase cation exchange column (10). A reversed-phase HPLC method employing ion-pairing was preferred, since bonded-phase ion-exchange columns tend to have short lifetimes and poor reproducibility from column to column (11).

Numerous reversed-phase ion-pairing methods have been reported for various combinations of I, II, and III and other drugs. A previous report (12) used a nitrile column

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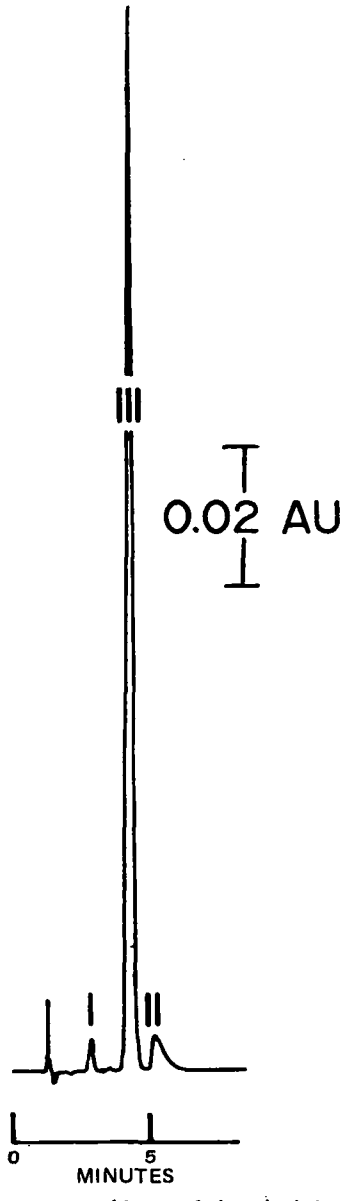

Figure 1—*Chromatogram of 0.8 μg of phenylephrine hydrochloride (I), 8 μg of phenylpropanolamine hydrochloride (II), and 36 μg of guaifenesin (III) with a C_{18} column packed in the lab. See text for chromatographic conditions.*

and an aqueous acetonitrile, acetic acid, heptanesulfonic acid salt ion-pair eluent to barely resolve I and II. Although the hydrophobic C_{18}-bonded phase has not been extensively used for this separation, the more polar phenyl bonded phase has been employed with a methanol, water, acetic acid, heptanesulfonic acid salt ion pair to yield a separation of I, II, and III with k' values of 1.2, 1.9, and 1.4, respectively (13); and to separate II and III at retention times of 15–18 min (14).

Another report (15) separated phenylephrine hydrochloride from other active compounds using a C_{18} column and an aqueous methanol and acetic acid eluent containing heptanesulfonic acid. Determinations involving guaifenesin on C_{18} columns have been characterized by the absence of an ion-pairing agent (16, 17). Phenylephrine hydrochloride and phenylpropanolamine hydrochloride were assayed (18) using a silica gel column with a methylene chloride, methanol, and aqueous ammonia eluent. The purpose of the present work was to improve the separation

Table I—Linearity Area Ratios

Parameter	Phenylephrine hydrochloride	Phenylpropanolamine hydrochloride	Guaifenesin
Correlation coefficient	0.9993	0.99987	0.99988
Standard error of the estimate ($S_{y/x}$)	0.0009	0.001	0.018
Intercept[a], %	−0.5	−0.7	−1.1
Variation[b], %	1.6	0.7	0.7

[a] (y intercept/$\bar{y}$) × 100, where $\bar{y}$ is the average y (22). [b] ($S_{y/x}/\bar{y}$) × 100.

of I, II, and III with a reversed-phase column and ion pairing to yield a method with simplified sample handling (leaching followed by direct injection) and sufficient specificity for stability-indicating analysis.

The specificity requirement dictates knowledge of the known and expected degradation products of I, II, and III. However, II and III have been reported to be stable in dosage form (15, 19) and require extreme conditions for degradation: III can be hydrolyzed to guaiacol with hot

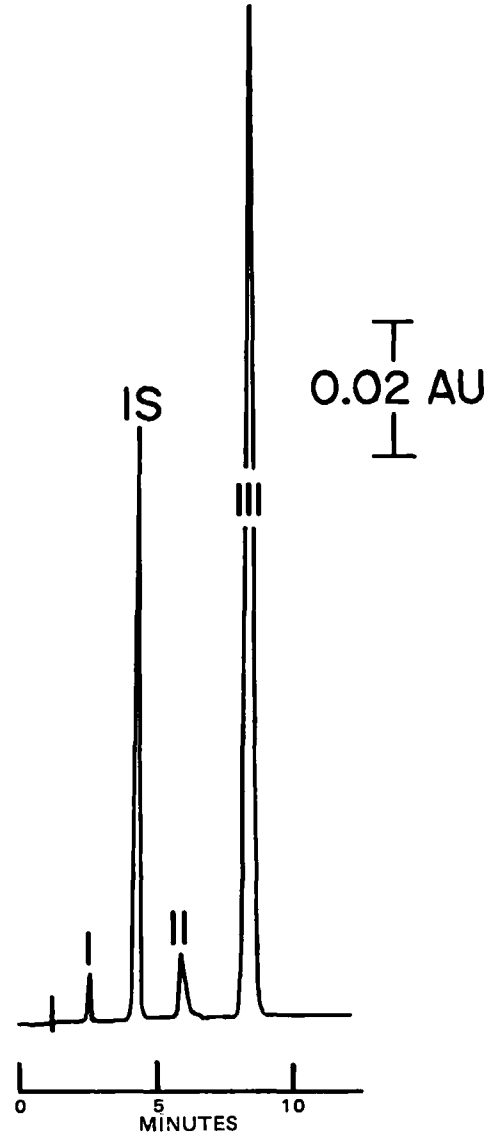

Figure 2—*Chromatogram of 0.8 μg of phenylephrine hydrochloride (I), 8 μg of phenylpropanolamine hydrochloride (II), and 36 μg of guaifenesin (III), and 2,5-dihydroxybenzoic acid internal standard (IS) with a C_8 column. See text for chromatographic conditions.*

Table II—Assay of Thermally Degraded Capsule Samples

Sample	Phenylephrine hydrochloride			Phenylpropanolamine hydrochloride			Guaifenesin		
	mg/g	Label[a], %	Initial, %	mg/g	Label[a], %	Initial, %	mg/g	Label[a], %	Initial, %
Oven at 95°, 9 days	9.42	99.9	97.0	81.5	96.0	97.9	377	100.0	100.5
0.5 *M* HCl RT, 9 days	9.85	104.4	101.4	81.3	95.8	97.6	373	98.8	99.3
0.5 *M* NaOH RT, 9 days	9.31	98.7	95.8	82.5	97.1	99.0	373	98.8	99.3
0.5 *M* NaOH 90°, 3 days	0	0	0	49.3	58.1	59.2	357	94.6	94.8
Initial[b]	9.72	103.0		83.3	98.1		376	99.5	

[a] Label is 9.43 mg/g for phenylephrine hydrochloride, 84.9 mg/g for phenylpropanolamine hydrochloride, and 377 mg/g for guaifenesin. [b] From Table III.

Table III—HPLC Assay of Capsule Sample[a]

Sample Weight, mg	Phenylephrine hydrochloride	Phenylpropanolamine hydrochloride	Guaifenesin
0.6014	9.81	83.8	375
0.6011	9.58	83.4	376
0.6021	9.62	83.3	375
0.8009	9.74	83.3	373
0.8018	9.46	85.8	372
0.8007	9.54	82.0	370
0.9990	10.01	82.2	372
1.0004	9.59	82.9	376
1.0002	9.69	82.6	379
1.2503	10.00	82.3	379
1.2498	9.71	84.4	379
1.2503	9.86	84.3	380
Mean	9.72 mg/g	83.3 mg/g	376 mg/g
RSD (1σ)	1.8%	1.3%	0.9%
Spectrophotometric control assays (average of two)	9.67 mg/g	84.1 mg/g	382 mg/g

[a] Label is 9.43 mg/g for phenylephrine hydrochloride, 84.9 mg/g for phenylpropanolamine hydrochloride, and 377 mg/g for guaifenesin.

concentrated hydrochloric acid (16) and II can be oxidized to benzaldehyde with periodate (20). Analyte I, however, has been reported to readily undergo decomposition in aqueous buffer solutions at 85° to 1,2,3,4-tetrahydro-4,6 (and 4,8)-dihydroxy-2-methylisoquinoline and other minor products with *m*-hydroxybenzaldehyde as an intermediate (21).

EXPERIMENTAL

Reagents and Chemicals—All reagents and chemicals were ACS, USP, or NF quality and were used without further purification. Phenylephrine hydrochloride, phenylpropanolamine hydrochloride, and guaifenesin were used as received[1].

Apparatus—A high-performance liquid chromatograph[2] equipped with a reciprocating pump[3], an absorbance detector at 254 nm[4] (analytical wavelength), and an injector[5] with a 20-μl loop was used. The detector was monitored with a strip-chart recorder and integrator[6]. A variable-wavelength detector[7] set at 270 nm and a fixed-wavelength detector[4] at 280 nm were used for absorbance ratio studies.

Columns—The octadecylsilane columns used were packed[8] in the lab (25 cm × 4-mm i.d.) and commercially packed[8] (30 cm × 4-mm i.d.). The more polar octyl columns examined were a commercially packed column[9] (25 cm × 4.6-mm i.d.) and two columns packed in the lab (25 cm × 4.6-mm i.d. and 30 cm × 4.0-mm i.d.) of the same material[9]. Particle size was 10 μm in all cases.

Chromatographic Conditions—For the C_8 columns, the mobile phase consisted of 300 ml of methanol, 675 ml of water, and 25 ml of pentanesulfonic acid sodium salt in glacial acetic acid[10] to yield an eluent that was 5 m*M* in ion-pairing salt and 1.7% in acetic acid. For the C_{18} columns, the basic mobile phase was 350 ml of methanol, 625 ml of water, and 25 ml of pentanesulfonic acid sodium salt in glacial acetic acid[10]. The methanol concentration had to be adjusted to between 25 and 40% for the different C_{18} columns. Readjusting the eluent for different C_8 columns was not necesary. The flow rate was 2.0 ml/min in all cases.

Standard Solution Preparation—The final method (C_8 column) used a standard solution containing 0.04 mg/ml of I, 0.4 mg/ml of II, 1.8 mg/ml of III, and 0.4 mg/ml of 2,5-dihydroxybenzoic acid internal standard with water as solvent.

Sample Preparation—For the capsule and tablet samples, 1 g of the ground sample was leached with ~250 ml of water containing a controlled amount of 2,5-dihydroxybenzoic acid internal standard (~0.4 mg/ml). The sample was injected directly after a 10-min sonication and 5-min centrifugation at 2500 rpm. For the liquid samples, 4.0–25.0 ml (depending on label claim) was diluted to ~250 ml with water containing the internal standard. The sample was then injected directly.

Thermally Degraded Samples—One-gram samples of a well-mixed capsule material containing I, II, and III as active ingredients were

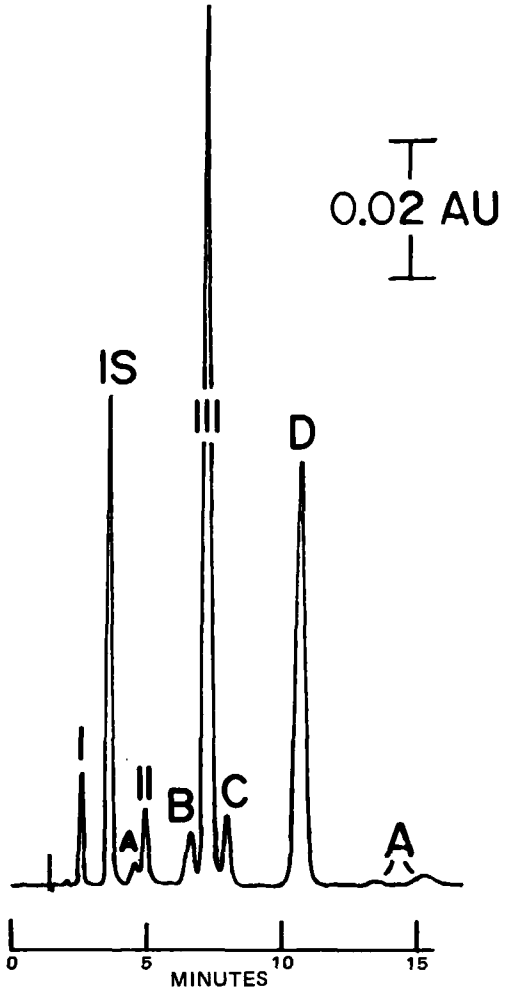

Figure 3—*Chromatogram of phenylephrine hydrochloride (I), phenylpropanolamine hydrochloride (II), and guaifenesin (III), and 2,5-dihydroxybenzoic acid internal standard (IS), and possible degradation products: phenylephrine forced degraded decomposition products (A); m-hydroxybenzaldehyde (B); guaiacol (C); benzaldehyde (D).*

[1] Norwich-Eaton Pharmaceuticals, Norwich, N.Y.
[2] Waters ALC 204, Waters Associates, Milford, Mass.
[3] Waters model 6000A.
[4] Waters model 440.
[5] Rheodyne model 725, Berkeley, Calif.
[6] Hewlett-Packard model 3352B, Avondale, Pa.
[7] Laboratory Data Control model III, Riviera Beach, Fla.
[8] Waters μ-Bondapak C_{18}.
[9] Whatman Partisil-10 C_8.
[10] Waters PIC B-5.

Table IV—HPLC Assay of Various Commercial Dosage Forms

Dosage Form	Sample	Phenylephrine hydrochloride		Phenylpropanolamine hydrochloride		Guaifenesin	
		mg/ml	Label, %	mg/ml	Label, %	mg/ml	Label, %
Syrup	1	—	—	12.3	98.8	99.9	99.9
Syrup	2	—	—	8.3	92.2	31.6	105.2
Syrup	3	—	—	8.7	96.6	97.9	97.9
Syrup	4	—	—	12.5	100.2	95.6	95.6
Eye Drop	5	2.53	101.1	—	—	—	—
Capsule	6[a]	9.72	103.0	83.3	98.1	376	99.7
Tablet	7	—	—	96.0	97.0	518	98.1

[a] From Table III.

weighed into several 500-ml Erlenmeyer flasks. One flask was placed in the oven at 95° for 9 days. Twenty milliliters of 0.5 *M* HCl and 20 ml of 0.5 *M* NaOH were added to two other separate flasks, and both were stored at room temperature for 9 days. In addition, one container was stored in direct sunlight for 13 days, and one container containing sample and 20 ml of 0.5 *M* NaOH was stored at 90° for 3 days. At the end of the required time period, the acidic and basic solutions were neutralized, internal standard added, and all the samples assayed. The analyte and internal standard peaks were also examined for homogeneity by absorbance ratios at 254 and 270 nm, except for the sample stored in 0.5 *M* NaOH at 90°, which was examined at 254 and 280 nm. Analyte I was degraded by the literature method (21) by dissolving 100 mg of standard I in 50 ml of a pH 6.8, 0.04 *M* ammonium acetate buffer and storing the solution in a 95° oven for 13 days.

Calculations—Results for I, II, and III, were calculated from their integrated peak areas and the peak area of the internal standard using the appropriate dilution factors.

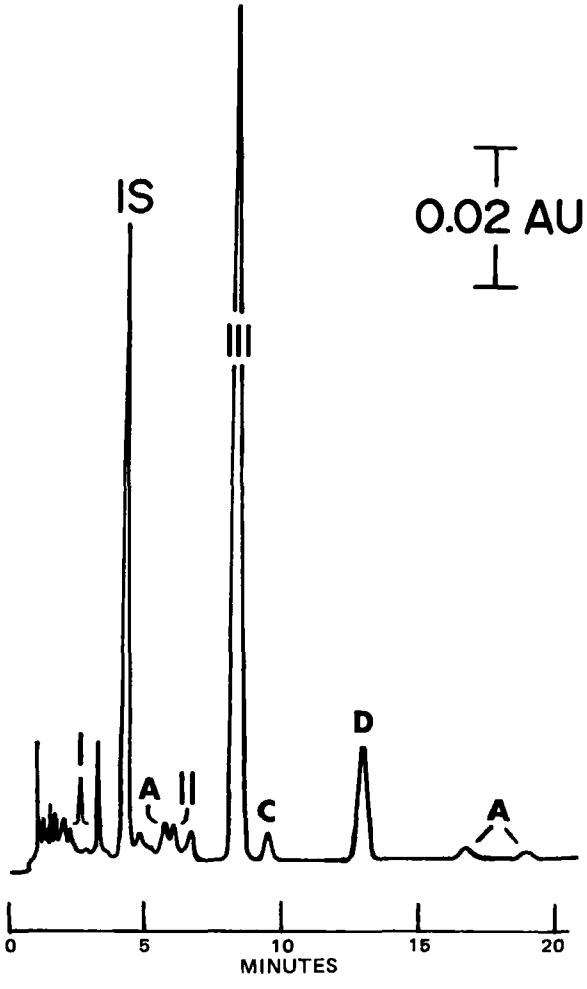

Figure 4—*Chromatogram of forced degraded (0.5 M NaOH at 90°) capsule sample: phenylpropanolamine hydrochloride (II); guaifenesin (III); 2,5-dihydroxybenzoic acid internal standard (IS): phenylephrine hydrochloride degradants (A); guaiacol (B); benzaldehyde (C). The peak for phenylephrine hydrochloride (I), which is totaly degraded, is drawn above the chromatogram.*

RESULTS AND DISCUSSION

Initial attempts to develop a reversed-phase simultaneous determination employed a C_{18} column with a methanol, water, and pentanesulfonic acid eluent yielded an assay that resolved I, II, and III from each other (Fig. 1). The chromatographic system lacked the retention and efficiency to meet the specificity requirement for guaiacol to be resolved from III. Additionally, relative retention appeared to change from column to column, often with packing from the same manufacturer. For example, II eluted after III with column packed in the lab and before III with a commercially packed column.

Exploratory experiments with a more polar octyl column were initiated and good results were obtained. The three analytes were well separated with k' values of 0.9, 2.4, and 3.7 for I, II, and III, respectively (Fig. 2). Identical chromatograms were obtained for a commercially packed column and several columns packed in the lab.

The linearity data for I, II, and III, determined by plotting peak area ratios *versus* standard weight ratios, are presented in Table I. Linearity was observed over the range studied: 0.5–1.5 μg for I; 4.8–14.4 μg for II; and 21–64 μg for III.

Assays of 11 synthetic capsule samples made by spiking placebo with solutions containing known amounts of standard I, II, and III at levels of 50–125% of theoretical yielded average recoveries and relative standard deviations of 100.9 ± 2.1%, 100.3 ± 1.3%, and 100.7 ± 0.8%, respectively.

A chromatogram of a solution containing 2.0 ml of the degraded standard solution of I (after 13 days at 95°), 20 mg of 2,5-dihydroxybenzoic acid, 2 mg of I, 20 mg of II, 89 mg of III, <5 mg of guaiacol (not completely soluble in water), 0.2 mg of *m*-hydroxybenzaldehyde, and <2 mg of benzaldehyde (not completely soluble in water) in 50 ml of water is shown in Fig. 3. All of the actual and postulated degradants were resolved. When the degraded standard solution of I was examined after only one day in the oven, a peak with the same retention time as *m*-hydroxybenzaldehyde was observed. This compound was postulated as an intermediate in a previous report (21), but was not observed.

Assay values for the thermally degraded capsule samples are listed in Table II. Except for the sample stored in 0.5 *M* NaOH at 90°, no extra peaks were noted and no significant degradation was observed. Examination of absorbance ratios indicated homogeneous peaks within experimental error.

A chromatogram (Fig. 4) of the sample solution stored in sodium hydroxide at 90° yielded several additional peaks and low assay values for I, II, and III, as shown in Table II. The difference in retention observed between Figs. 3 and 4 is caused by use of extensively used and freshly packed columns, respectively. Absorbance ratios (254/280 nm) and retention times of pure standards indicated peaks C and D, Fig. 4 were guaiacol and benzaldehyde, respectively. The internal standard and III peaks were also indicated to be homogeneous (II yielded no signal at 280 nm).

α-Aminopropiophenone, a precursor and possible trace impurity in II (23, 24), was found to elute immediately following the II peak. Although not quite baseline resolved, it could be detected down to at least 0.1% of the II concentration. It was not observed in any of the samples.

The assay results for several commercial dosage forms representing liquid, tablet, and capsule preparations are presented in Tables III and IV. None of the excipients in the formulations coeluted with the active ingredients or the internal standard.

The actives I, II, and III in the capsule sample were also determined spectrophotometrically. Analyte I was assayed colorimetrically by the

characteristic reaction of phenols with 4-aminoantipyrine described previously (25). The order of addition of reagents was altered to achieve acceptable precision. With these samples, it was necessary to add the bicarbonate buffer first. Analyte II in an aqueous solution of the sample was quantitatively oxidized to benzaldehyde with alkaline periodate by the procedure described previously (20). The benzaldehyde was then extracted from the solution with chloroform and determined spectrophotometrically. Guaifenesin was extracted from the samples with chloroform and determined by its UV absorbance. As the data in Table III indicate, the spectrophotometric assays are in good agreement with the HPLC assay presented here.

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Kinetics and Mechanism of Degradation of Cefotaxime Sodium in Aqueous Solution

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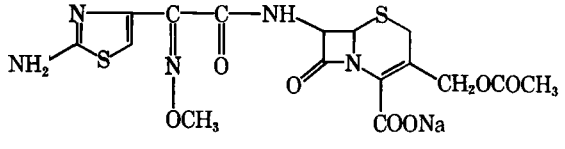
Received January 13, 1982, from the *Pharmaceutical Development Department, Hoechst-Roussel Pharmaceuticals Inc., Somerville, NJ 08876.* Accepted for publication March 15, 1982.

Abstract □ The degradation kinetics and mechanism of a potent new cephalosporin, cefotaxime sodium, in aqueous solution were investigated at pH 0–10 at 25° and an ionic strength of 0.5. The degradation rates were determined by high-pressure liquid chromatography and were observed to follow pseudo first-order kinetics with respect to cefotaxime sodium concentration. The data suggested that the rate of degradation was influenced significantly by solvolytic, hydrogen ion, and hydroxide ion catalysis. No primary salt effects were observed in the acid or neutral regions; however, a positive salt effect was observed at pH 8.94. Buffer catalysis due to the buffer species employed was not seen during the kinetic studies. The pH–rate profile at 25° indicated that the maximum stability of cefotaxime sodium occurred in the pH 4.5–6.5 region. In aqueous solution, cefotaxime was shown to degrade by two parallel reactions: de-esterification at the C-3 position and β-lactam cleavage. Good agreement between the theoretical pH–rate profile and the experimental data support the proposed degradation process.

Keyphrases □ Kinetics—mechanism of degradation of cefotaxime sodium in aqueous solution □ Degradation—kinetics and mechanism, cefotaxime sodium in aqueous solution □ Cefotaxime sodium—kinetics and mechanism of degradation in aqueous solution □ Cephalosporins—cefotaxime sodium, kinetics and mechanism of degradation in aqueous solution

Cefotaxime sodium (I) is a potent new third generation cephalosporin possessing a broad spectrum of activity. Chemically, it is characterized by a 2-amino-4-thiazolyl ring which, in comparison to other cephalosporins, increases antibacterial activity against Gram-negative strains, and by an α-methoximino group which enhances



I

stability to β-lactamases (1–4). Compound I is active against Gram-positive and Gram-negative organisms, especially multiresistant strains, including many aminoglycoside-resistant strains. *In vitro*, its activity against Gram-negative organisms has been shown to be 10–200 times greater than that of the recently developed second generation cephalosporins (5).

The present report describes the stability kinetics of I in aqueous solution. The investigation was initiated to elucidate the mechanism by which I decomposes and to determine those kinetic parameters that will be of value in predicting the stability of the reconstituted antibiotic under a wide range of conditions.

EXPERIMENTAL

Materials—Cefotaxime sodium (I)[1] and desacetylcefotaxime (II)[2] were used without further purification. Desacetylcefotaxime lactone (III) was prepared using a modification of the method for cephalothin de-

[1] Claforan, Hoechst-Roussel Pharmaceuticals Inc., Somerville, N.J.
[2] Hoechst AG, Frankfurt, West Germany.

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