NAPHAZOLINE HYDROCHLORIDE

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1. DESCRIPTION

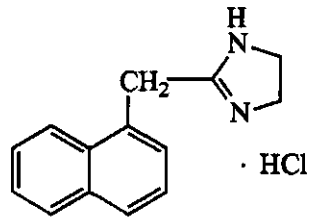
1.1 Name, Formula and Molecular Weight

Naphazoline hydrochloride is an α-adrenergic sympathomimetic agent used in topical nasal or ophthalmic pharmaceutical formulations. Naphazoline has been established as the International Nonproprietary Name (INN) by the World Health Organization for the chemical compound, (2-(1-naphthylmethyl)-2-imidazoline[1,2], which is typically used as either the hydrochloride or nitrate salt. The hydrochloride salt has been given the USAN, naphazoline hydrochloride[1]. Other chemical names include: (a) 1H-imidazole, 4,5-dihydro-2-(1-naphthalenylmethyl)-, monohydrochloride[1], (b) 2-(1-naphthylmethyl)-2-imidazoline monohydrochloride[1], and (c) 4,5-dihydro-2-(1-naphthalenylmethyl)-1H-imidazole, monohydrochloride[3]. The CAS registry number for naphazoline hydrochloride is 550-99-2[1]; the CAS number for the free base is 835-31-4[1].

Empirical Formula[1]: $C_{14}H_{14}N_2 \cdot HCl$

Molecular Weight[1]: 246.74

Structure:



1.2 Appearance, Color and Odor

Naphazoline hydrochloride is a white to almost white, odorless, crystalline powder[4] with a bitter taste[5,6].

1.3 History

An investigation of the vasoconstrictor activity of substituted imidazolines by Fritz Uhlmann at Ciba in Basle, Switzerland during the early 1940's resulted in the introduction of the sympathomimetic drug, naphazoline; its analogs, xylometazoline and oxymetazoline, used as decongestants; and also the α-adrenoceptor antagonist, tolazoline[7,8]. Patents include: U.S Patent 2,161,938 (1939) and Danish Patent 62,889 (1944)[6]. Naphazoline has been marketed under a variety of trade names around the world[2,3,9].

1.4 Pharmacology

Naphazoline is a potent α-adrenergic sympathomimetic agent. It is a vasoconstrictor with a rapid and prolonged action in reducing swelling and congestion when applied to mucous membranes, hence, its use for the symptomatic relief of rhinitis and sinusitis. Rebound congestion and rhinorrhea are common after prolonged use. Nasal drops or spray are used as a 0.05% aqueous solution of the hydrochloride or nitrate, with a usual recommended dosage of 2 drops in each nostril every 3 hours. Aqueous solutions have also been used as ophthalmic conjunctival decongestants[4].

2. SYNTHESIS

Naphazoline hydrochloride has been prepared through a series of synthetic chemical steps beginning with (1-naphthyl)-acetonitrile, I (Figure 1)[3,10]. The starting material, I, is treated with ethanol and hydrochloric acid to obtain the naphthyl-(1)-acetiminoethylether hydrochloride, II[10]. A solution is made of 2.7 parts II and 12 parts absolute alcohol[3]. One part of ethylenediamine is then added and the mixture is heated to gentle boiling with stirring under nitrogen until the evolution of ammonia ceases. The alcohol is then distilled and the residue is dissolved in 40 parts of benzene and 1.8 parts of caustic potash. The benzene is removed and the residue is recrystallized several times from toluene. Reaction with hydrochloric acid gives naphazoline hydrochloride, III[3]. The preparation of radiolabelled naphazoline with ^{14}C in the 2-position of the imidazoline ring has also been reported[11] using α-chloromethylnaphazoline, potassium cyanide-^{14}C, and ethylenediamine.

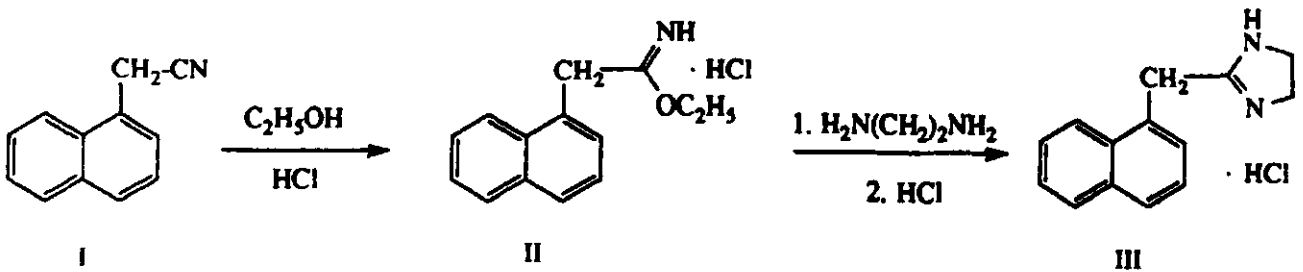


Figure 1. Synthesis of naphazoline hydrochloride.

3. PHYSICAL PROPERTIES

3.1 Spectroscopy

3.1.1 Infrared Spectrum

The infrared spectrum of naphazoline hydrochloride was obtained. A mixture of the drug substance and potassium bromide was pressed into a pellet and analyzed using a Perkin-Elmer Model 1750 FTIR. The spectrum is shown in Figure 2. The major absorption bands for the infrared frequencies and the corresponding assignments are listed in Table I.

3.1.2 Ultraviolet Spectra

The ultraviolet absorption spectra of naphazoline hydrochloride in absolute ethanol, pH 3 buffer (0.05M phosphate), pH 7 buffer (0.05M phosphate) and pH buffer (0.05M borate) were obtained using a Perkin-Elmer 559A UV/VIS spectrophotometer and 1 cm cells. A representative UV spectrum in ethanol is shown in Figure 3. Samples of naphazoline hydrochloride in these solvents were scanned from 200 to 400 nm and the absorption coefficients at wavelengths of maximum absorption were calculated (Table II).

3.1.3 Nuclear Magnetic Resonance Spectra

The ^{1}H-NMR spectrum (100 MHz) of naphazoline hydrochloride has been reported and the chemical shifts have been assigned for the methylene groups[12]. The ^{1}H-NMR spectrum (300 MHz) of naphazoline hydrochloride (143 mgmL DMSO-d_6 at 100°C) was obained using a Varian VXR 300 spectrometer (Figure 4). In order to assign all of the aromatic proton signals, a series of 2-D experiments were carried out: these spectra were not shown but the assignments are listed in Table III.

The ^{13}C-NMR spectrum (22.5 MHz) of naphazoline hydrochloride has been reported and the chemical shifts have been assigned for the methylene and imidazoline carbons[12]. The ^{13}C-NMR spectrum (75 MHz) of naphazoline hydrochloride (143 mg/mL DMSO-d_6 at 100°C) was obtained using a Varian VXR 300 spectrometer (Figure 5) and the assignments are listed in Table III. The Attached Proton Test (APT) (Figure 5) and extensive 2-D studies were performed in order to assign aromatic carbons.

The resonances for the methylene protons were shifted downfield for the HCl salt compared to the base: $\Delta\,\delta$ (ppm) (+ indicates downfield shift compared to base); $\underline{CH_2}CH_2$, +0.44 and aryl-$\underline{CH_2}$, +0.53)[12]. The reso-

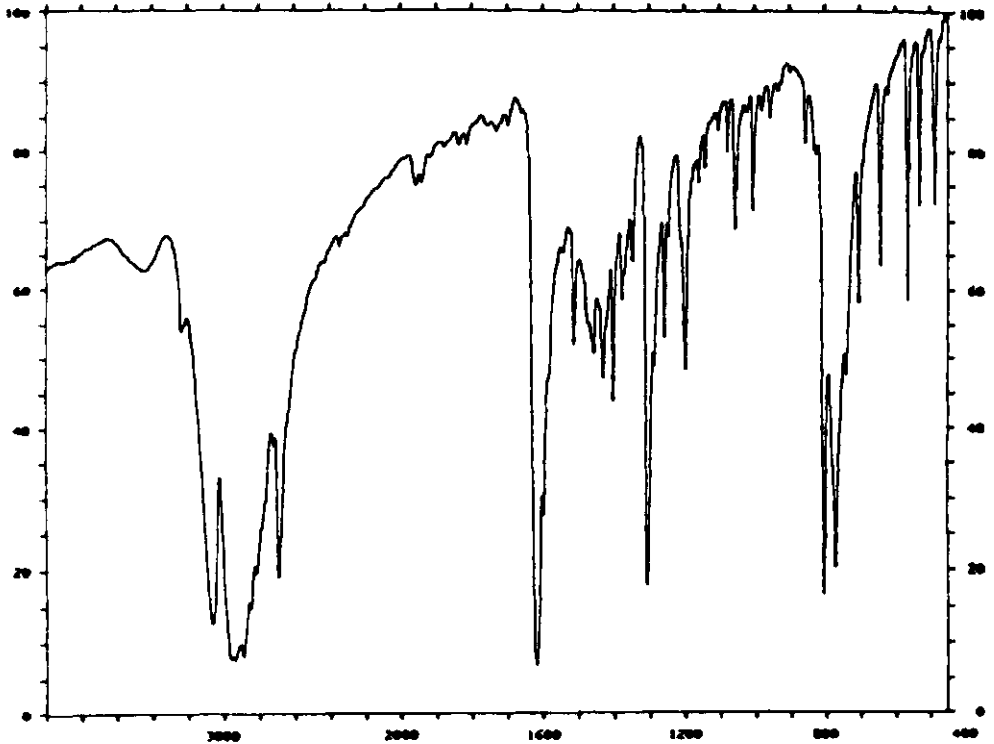


Figure 2. Infrared spectrum (KBr) of naphazoline hydrochloride.

Figure 3. UV spectrum of naphazoline hydrochloride (0.019 mg/mL in ethanol).

Table I. Infrared spectral assignments for naphazoline hydrochloride.

Wavelength (cm^{-1})	Assignment
3150-2500	C-H and N-H stretch
1618	Amine salt N-H
1302, 1198	2° N-H
801, 765	Imidazoline C-H
602, 561, 525, 481	Out of plane ring bend

Table II. Ultraviolet absorption of naphazoline hydrochloride.

	E (1%, 1 cm)				
Solvent	223 nm	270 nm	280 nm	287 nm	291 nm
Ethanol	3622	239	286	196	198
pH 3 Buffer	3214	246	287	198	193
pH 7 Buffer	3246	238	279	193	188
pH 9 Buffer	3294	236	274	191	187

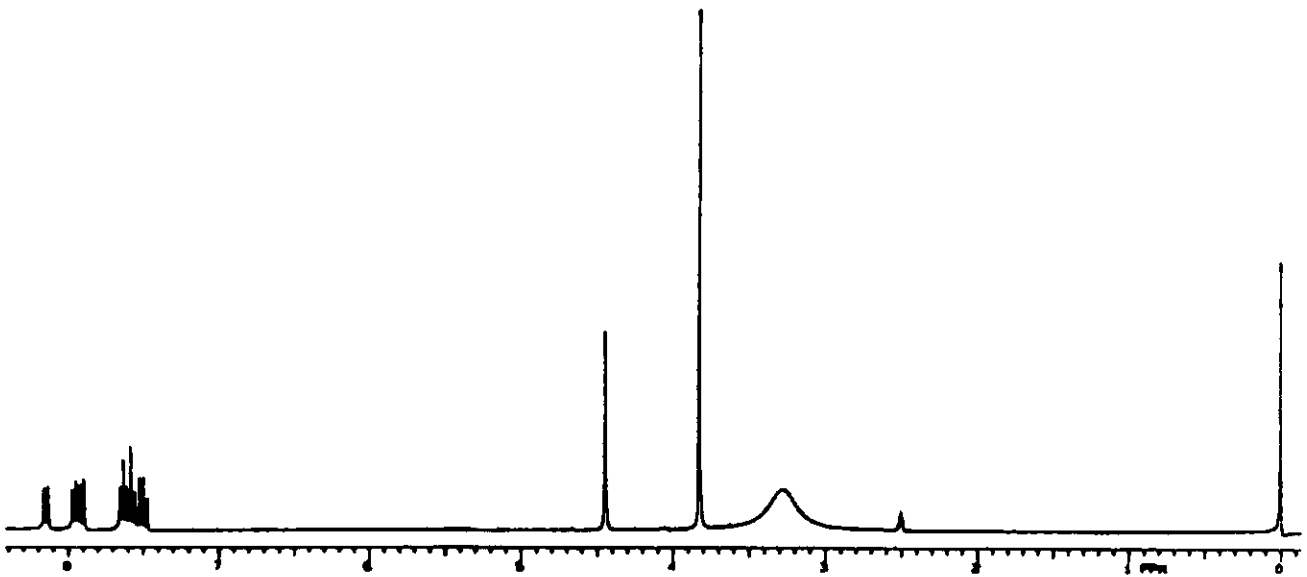


Figure 4. ^{1}H-NMR Spectrum (300 MHz) of naphazoline hydrochloride (143 mg/mL in DMSO-d_6 at 100°C).

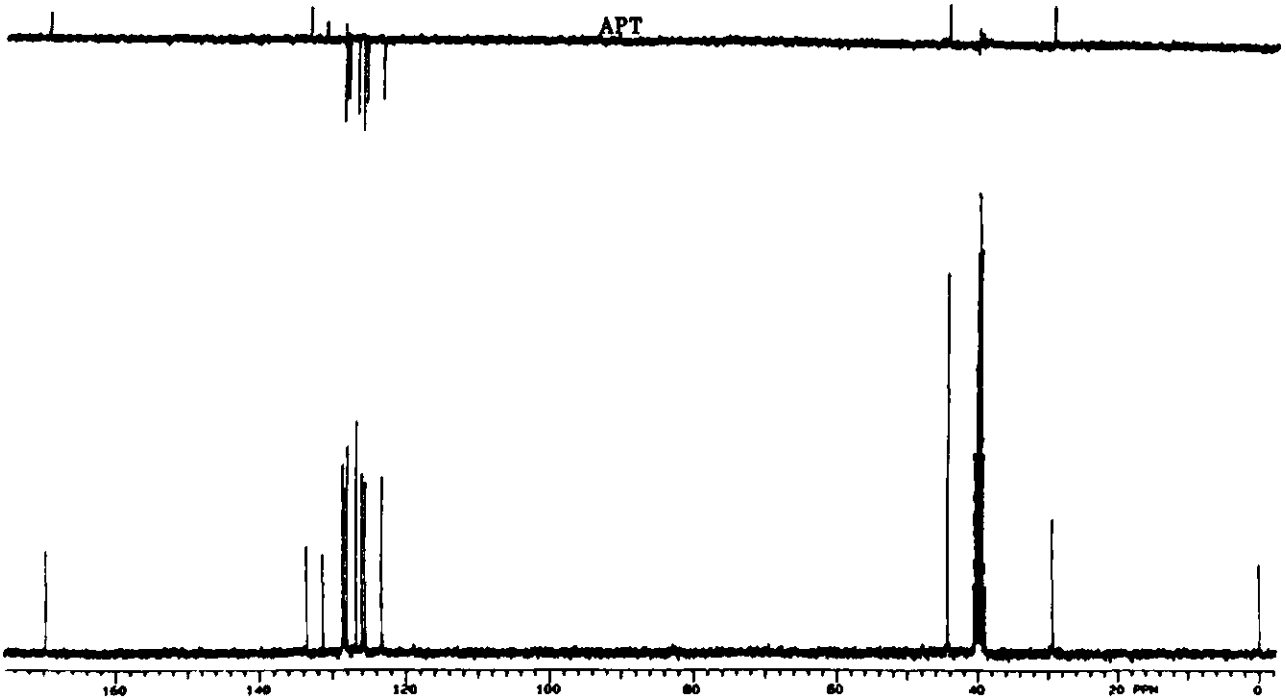
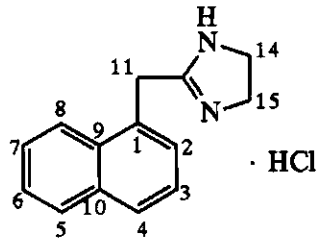


Figure 5. ^{13}*C-NMR Spectrum (75 MHz) of naphazoline hydrochloride (143 mg/mL inDMSO-*d_6 *at 100°C).*

Table III. ^{1}H- (300 MHz) and ^{13}C- (75 MHz) NMR Data for Naphazoline HCl (143 mg/mL in DMSO-d_6 at 100°C).



Assignment	^{1}H δ (ppm)	^{13}C δ (ppm)
1		128.71
2	7.64 (1H,d)	128.09
3	7.49 (1H,m)	125.61
4	7.91 (1H,d)	128.47*
5	7.96 (1H,d)	128.66*
6	7.54 (1H,m)	126.06
7	7.58 (1H,m)	126.83
8	8.15 (1H,d)	123.34
9	-	131.37
10	-	133.57
11	4.45 (2H,s)	29.41
12	-	169.78
14 & 15	3.82 (4H,s)	44.40

* Interchangeable assignments

nances for carbons attached to the imidazoline ring were shifted for the HCl salt compared to the base: $\Delta\ \delta$ (ppm) (- and + indicate upfield and downfield shifts respectively compared to base); $\underline{C}H_2\underline{C}H_2$, -5.09; aryl-$\underline{C}H_2$, -3.63; and N-$\underline{C}$=N, +3.96[11].

3.1.4 Mass Spectra

Mass spectra were obtained for naphazoline hydrochloride using a Finnegan MAT TSQ46 GC/MS/MS unit. A small amount of naphazoline hydrochloride was volatilized by heating at a linear rate of 5 mA/sec from 0 mA to about 500 mA and ionized by either chemical ionization (CI, 0.3 Torr pressure of isobutane) or by electron impact (EI) at 70 eV. The CI and EI mass spectra were presented in Figures 6 and 7 and the interpretation presented in Table IV. The fragmentation pattern was consistent with the chemical structure of naphazoline hydrochloride (Figure 8).

3.2 Thermal Properties

3.2.1 Melting Range

The melting point of naphazoline hydrochloride has been reported as 257°C[13] with a range of 255-60 (decomposition)[5,6]; the melting point for the base has been reported as 115-120°C[13].

3.2.2 Differential Thermal Analysis

A 2-mg sample of naphazoline hydrochloride drug substance was heated from 40°C to 300°C at a linear rate of 20°C/min using a Perkin-Elmer DSC-4. One single, sharp endotherm was observed with an onset of 259°C and a maximum of 261°C, corresponding to the melting range, after which decomposition occurred (Figure 9).

3.2.3 Thermogravimetric Analysis

A 7-mg sample of naphazoline hydrochloride was heated using a Perkin-Elmer System 4 Thermogravimetric Analyzer from 40°C to 298°C at a linear rate of 20°C/min. The drug substance exhibited a gradual weight loss near the melting range (Figure 10).

3.3 X-Ray Crystallography and Powder Diffractometry

Naphazoline hydrochloride exists as a crystalline powder[4]. Podder *et al.*[15] described the crystal structure: M_r = 246.73, monoclinic, $P2_1/c$, a = 11.895 (3), b = 9.228 (2), c = 12.820 (3) Å, β = 117.18 (2)°, V = 1252 Å^3, Z = 4, D_m = 1.30, D_x = 1.29 Mg m^{-3}, λ (Cukα) = 1.5418 Å, μ = 2.48 mm^{-1}, F(000) = 524, T = 277 (1) K. Final R = 0.040 for 1291 observed reflec-

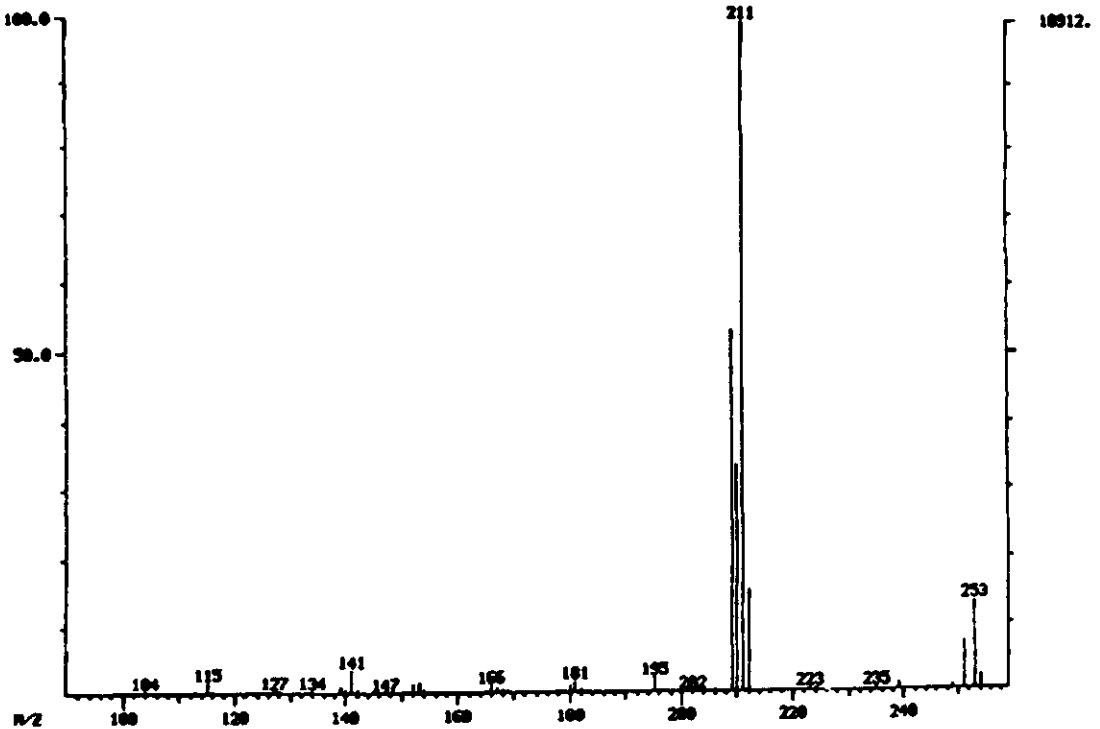


Figure 6. CI Mass spectrum of naphazoline hydrochloride.

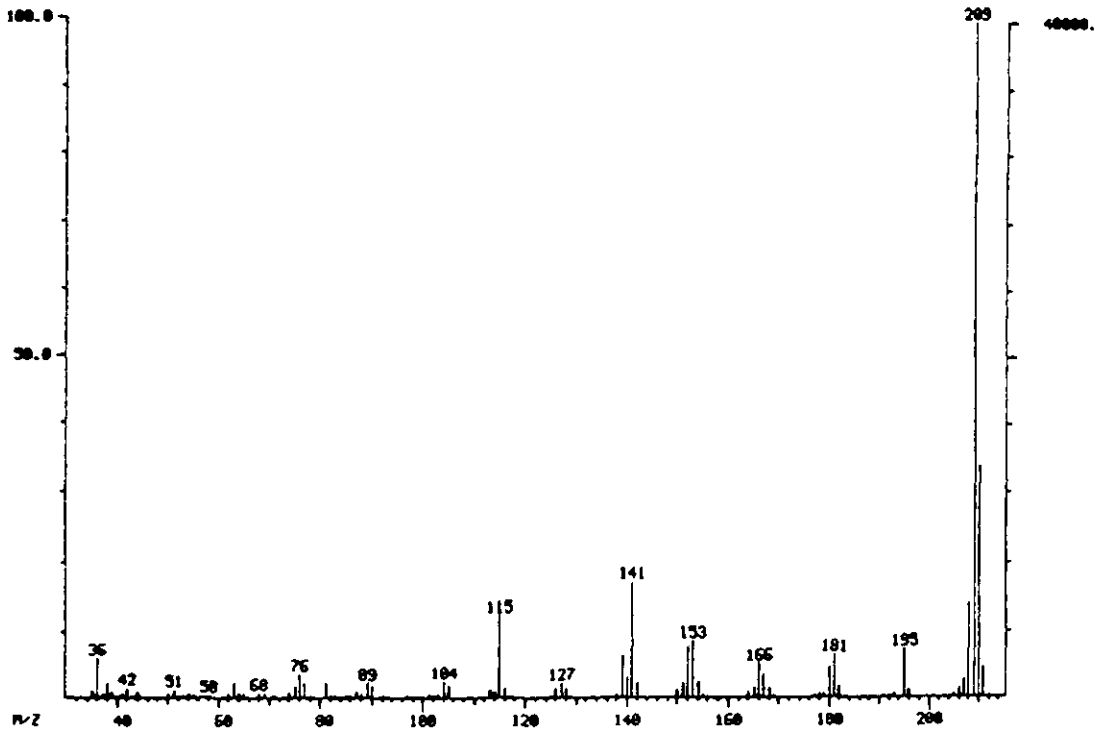


Figure 7. EI Mass spectrum of naphazoline hydrochloride.

Table IV. EI and CI Mass spectral Assignments for naphazoline hydrochloride

EI (m/e)	Rel. Abun. (%)	Assignment	Rel. Abun. (%)	CI (m/e)
		$[M + C_3H_7]^+$	13	253
211	4	$[M+H]^+$	100	211
209	100	$[M-H]^+$	53	209
195	7	$[M-NH]^+$		
181	6	$[M-NHCH_2]^+$		
153	9	$[M-C_2H_5N_2]^+$		
141	9	$[M-C_3H_5N_2]^+$		
115	12	$[M-C_5H_7N_2]^+$		

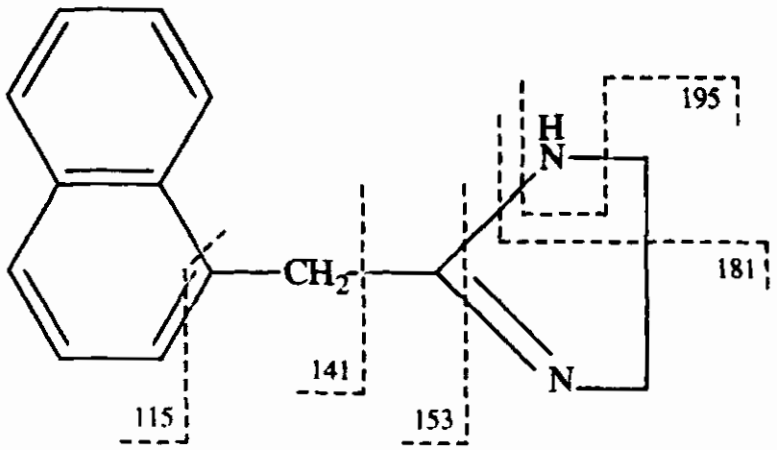


Figure 8. Mass spectral fragmentation pattern for naphazoline hydrochloride.

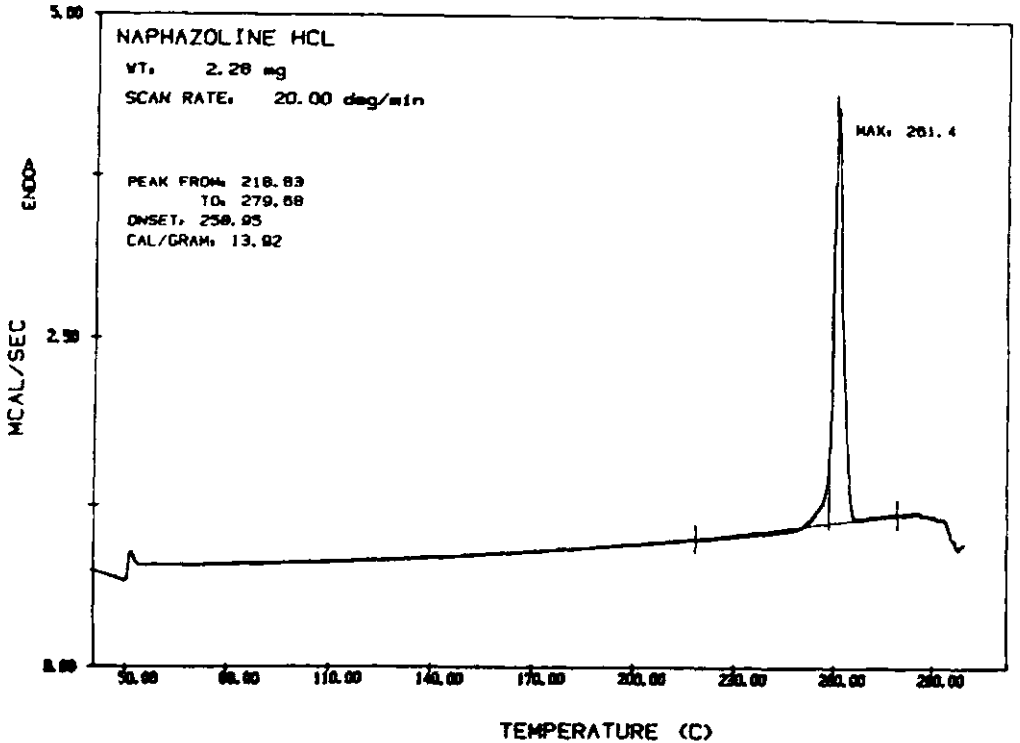


Figure 9. DSC of naphazoline hydrochloride.

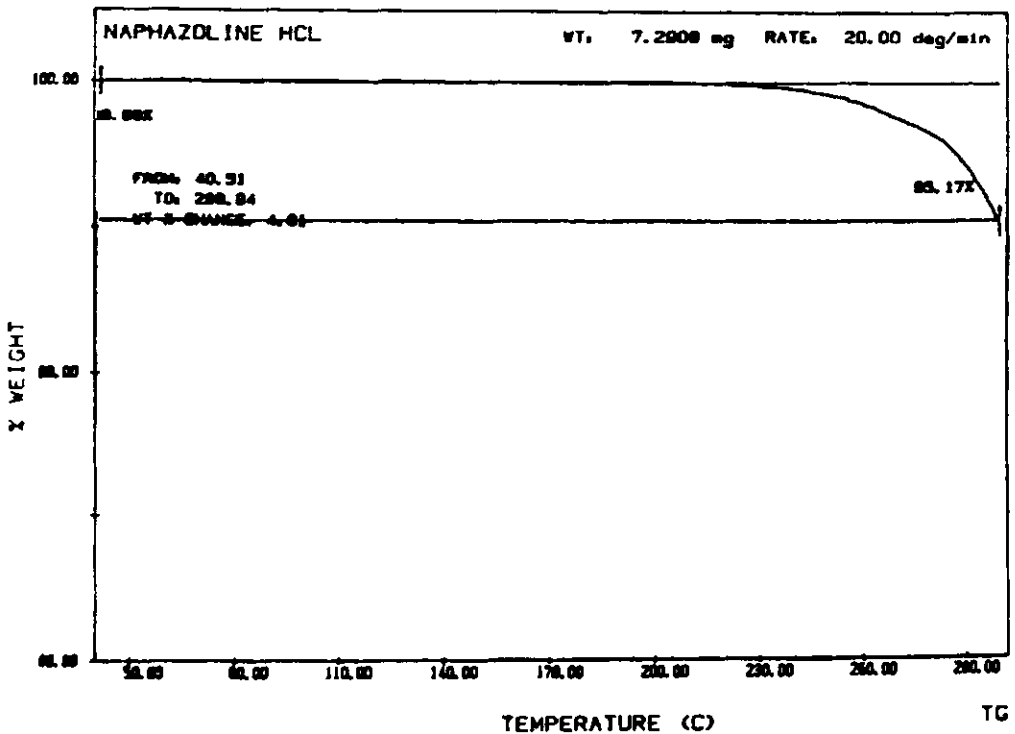


Figure 10. TGA of naphazoline hydrochloride.

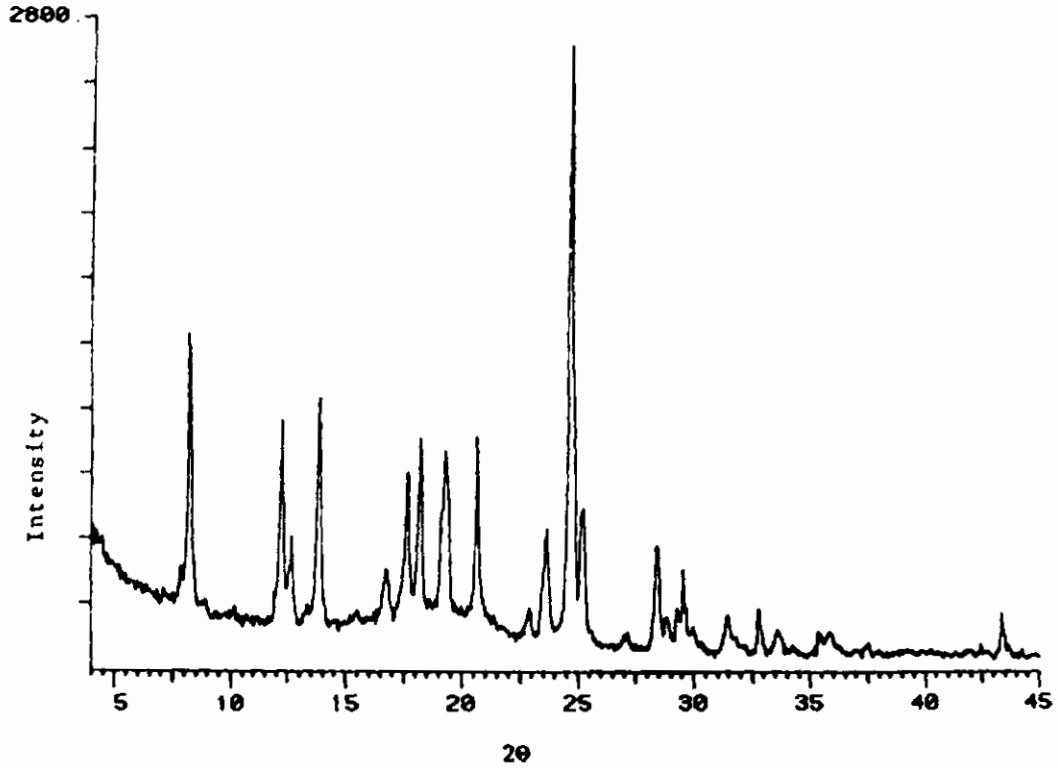


Figure 11. X-Ray powder diffraction pattern of naphazoline hydrochloride.

Table V. X-Ray powder diffraction data for naphazoline hydrochloride obtained using CuKα radiation and indexed on the basis of a monoclinic cell: $P2_1/c$, a = 11.895 (3), b = 9.228 (2), c = 12.820 (3) Å, β = 117.18 (2)°.

h	*k*	*l*	d	Intensity	*h*	*k*	*l*	d	Intensity
1	0	0	10.7	47	2	1	1	3.760	18
0	1	1	7.21	29	1	2	1		
1	1	0	6.97	13	-2	1	3		
-1	1	1			-1	2	2		
-1	0	2	6.38	41	-3	1	1	3.598	100
0	0	2	5.71	3	-3	1	2		
2	0	0	5.28	8	0	2	2		
1	1	1			3	0	0	3.529	23
-2	0	-2			0	1	3		
-2	1	1	5.01	25	3	1	0	3.300	4
0	1	2	4.87	29	-1	0	4	3.135	18
0	2	0	4.60	27	1	2	2		
2	1	0			2	2	1	3.091	6
0	2	1	4.29	30	2	1	2	3.042	8
1	0	2			-2	1	4	3.016	14
-3	0	2	3.881	6					
1	1	2							

tions. The bond lengths of the N-C-N group of the imidazoline ring were short and indicative of double bond character. One nitrogen atom was protonated and both nitrogen atoms participated in hydrogen bonding. Each chlorine atom was involved in two intermolecular hydrogen bonds of the form N1-H···Cl···H-N2, that linked the molecules into continuous parallel chains[15].

To obtain an x-ray powder diffraction pattern, a sample of the drug substance was irradiated using a Philips powder diffractometer equipped with a diffracted beam graphite monochronometer. CuKα (l = 1.5405 Å) radiation was used for obtaining the powder pattern (Figure 11). All of the diffraction lines could be assigned *hkl* indicies on the basis of the unit cell parameters proving that the material was single-phase (Table V).

3.4 Partition Coefficients

Partition coefficients were determined for naphazoline hydrochloride between pH 3 buffer (0.05 M phosphate), pH 7.0 buffer (0.05 M phosphate) and pH 9 buffer (0.05 M borate) versus 1-octanol. All solutions were prepared using octanol-saturated buffers and buffer-saturated octanol. Tubes containing 100 mg of naphazoline hydrochloride, 10 ml of buffer and 10 ml of octanol were agitated for 2 hours at 23°C and allowed to partition overnight. Analysis (HPLC) of the aqueous phases of each mixture revealed the following partition coefficients: pH 3.0 = 0; pH 7.0 = 0; pH 9.0 = 7.4.

3.5 Ionization Constant, pKa

The pKa of naphazoline HCl has been reported as 10.9 at 20°C[4], 10.35 ± 0.02 at 25°C[16], 10.13 ± 0.02 at 35°C[16], and 9.92 ± 0.03 at 45°C[16].

3.6 Solubility

The solubility of naphazoline hydrochloride in various solvents at room temperature is presented in Table VI.

Table VI. Solubility of Naphazoline Hydrochloride

Solvent	Solubility	Reference
Water	1 in 6	13
Ethanol	1 in 15	13
Chloroform	Very slightly soluble	4
Diethyl Ether	Practically insoluble	4

3.7 Solution Color, Clarity and pH

An aqueous solution (1 in 100) of naphazoline hydrochloride in carbon dioxide-free water is clear, colorless and exhibits a pH value between 5.0 and 6.6[17].

4. TYPICAL METHODS OF ANALYSIS

4.1 Identity

4.1.1 Infrared Spectrophotometry

The identity of naphazoline hydrochloride may be determined by comparison of its infrared spectrum (KBr) (see Figure 2) to an authentic reference standard[17].

4.1.2 Ultraviolet Spectrophotometry

The identity of naphazoline hydrochloride may be confirmed by comparison of its ultraviolet spectrum (1 in 50,000) to that of an authentic standard and the observation of a maximum at 280 nm[17].

4.1.3 Chloride Identity Test

An aqueous solution of naphazoline hydrochloride (1 in 100) is treated with 6N ammonium hydroxide to precipitate naphazoline base. The filtrate then yields a white, curdy precipitate upon the addition of 0.1N silver nitrate. The precipitate is insoluble in nitric acid but is soluble in a slight excess of 6N ammonium hydroxide[5,17].

4.1.4 Reaction with Bromine

A 10-mL aliquot of an aqueous solution of naphazoline hydrochloride (1 in 100) when mixed with 5 mL of bromine-saturated water yields a yellow precipitate. Upon boiling, a deep purple color is produced[5].

4.2 Colorimetry

Naphazoline has been analyzed by colorimetry using reagents such as sodium nitroprusside[18], ceric sulfate[19], chloranil[19], bromocresol green[20], bromophenol blue[20], bromothymol blue[20], methyl orange[20], cobaltous acetate in chloroform-methanol[21], iodine in chloroform[22-25], and 2,6-dichlorophenol-indophenol in $CHCl_3$[26].

4.3 Elemental Analysis

Elemental analysis of a sample of naphazoline hydrochloride was performed: Anal. ($C_{14}H_{14}N_2$·HCl) C (calcd 68.14; found, 68.52), H (calcd, 6.14; found, 6.28), N (calcd, 11.36; found, 11.48), Cl (calcd, 14.37; found, 14.54).

4.4 Titrimetry

Naphazoline hydrochloride drug substance may be titrimetrically assayed as described in the USP monograph[17]. The hydrochloride salt is dissolved in glacial acetic acid with mercuric acetate and titrated with dilute perchloric acid using crystal violet as the indicator. Also, nonaqueous titration of naphazoline hydrochloride in acetic anhydride/glacial acetic acid with dilute perchloric acid and potentiometric detection has been described as an official method in the Japanese Pharmacopoeia[5]. In addition, nonaqueous titration with dioctylsulfosuccinate sodium salt using 3'3"5'5"-tetrabromophenolphthalein as the indicator has also been reported[25].

4.5 Chromatography

4.5.1 Thin-Layer Chromatography

The USP describes a TLC method for ordinary impurities in naphazoline hydrochloride drug substance[17]. A sample of the drug substance dissolved in methanol (10 mg/mL) is spotted on a silica gel TLC plate, eluted with a mobile phase of methanol-glacial acetic acid-water (8:1:1, v/v/v), and visualized with iodoplatinate spray.

4.5.2 High-Pressure Liquid Chromatography

Naphazoline has been analyzed in ophthalmic preparations by HPLC using a 10 μm octadecylsilane column (3.9 X 300 mm), a mobile phase of 0.08 M $HClO_4$ (pH 2.2)-methanol (7/3, v/v), a flow rate of 2 mL/min and UV detection at 265 nm[28]; in ear and eye drops using a 10 μm octadecylsilane column (4 X 250 mm), a mobile phase of methanol-water (40/60, v/v), a flow rate of 2 mL/min and UV detection at 279 nm[29]; in ophthalmic formulations or raw material using a 5 μm cyano column (4.6 X 150 mm), a mobile phase of dilute phosphate solution (pH 3)/-acetonitrile (60:40, v/v), a flow rate of 2.0 mL/min and UV detection at 225 nm[30] or a 5μm octylsilane column (4.6 X 250 mm), a mobile phase of 0.05 M phosphate solution (pH 5.6)-acetonitrile (4:1, v/v) containing 0.07 M triethylamine, a flow rate of 1.5 mL/min and UV detection at 270 nm[30]; in tablets and capsules using a 10 μm phenyl column (4 X 300 mm), a mobile phase of water-methanol-glacial acetic acid (55:44:1, v/v/v) containing 0.005 M heptane sulfonic acid sodium salt, at a flow rate of 2.0 mL/min and UV detection at 254 nm[31].

4.5.3 Gas Chromatography

Naphazoline has been analyzed by gas chromatography using various stationary phases including OV-1 3%, OV-3 3%, OV-7 3%, OV-17 2%, and QF-1 5%[32].

5. STABILITY-DEGRADATION

5.1 Potential Routes of Degradation

Naphazoline has been shown to be relatively stable in acidic or neutral solutions but readily prone to hydrolysis in basic solution. The first step in the hydrolytic reaction[33] results in the formation of 1-naphthylacetylethylenediamine which upon vigorous treatment[34], undergoes further cleavage to form 1-naphthylacetic acid and ethylenediamine (Figure 12). The kinetics of this reaction have been described[16]. The major degradation products of naphazoline, 1-naphthylacetylethylenediamine and 1-naphthylacetic acid, have been prepared[33] and investigated[30,33,34].

5.1.1 Characterization of 1-Naphthylacetylethylenediamine Hydrochloride

5.1.1.1 Thin-Layer Chromatography of 1-Naphthylacetylethylenediamine

An adaptation of the USP TLC procedure[17] for the determination of ordinary impurities in naphazoline hydrochloride allowed for the detection of 1-naphthylacetylethylenediamine in the presence of naphazoline. Using silica gel 60 high-performance TLC plates (20 X 20 cm) and a mobile phase of methanol-glacial acetic acid-purified water (8:1:1, v/v/v), spots were visible after spraying with ninhydrin: naphazoline $R_f = 0.54$; 1-naphthylacetylethylenediamine $R_f = 0.63$[30]. A similar method has been described in the European Pharmacopoeia for 1-naphthylacetylethylenediamine in naphazoline nitrate[35].

5.1.1.2 Liquid Chromatography of 1-Naphthylacetylethylenediamine

1-Naphthylacetylethylenediamine has been quantitated in the presence of naphazoline and 1-naphthylacetic acid using column chromatography followed by UV assay[33,34]. A modern HPLC procedure has been developed for the analysis of 1-naphthylacetylethylenediamine in the presence of naphazoline by HPLC using a 5 μm cyano column (4.6 X 150 mm), a mobile phase of 0.025 M Na_2HPO_4 buffer (pH 7.4)-acetonitrile (35:65, v/v), a flow rate of 2.0 mL/min and UV detection at 270 nm[30]. Retention times were: naphazoline, 6.3 min; 1-naphthylacetylethylenediamine, 3.1 min (Figure 13).

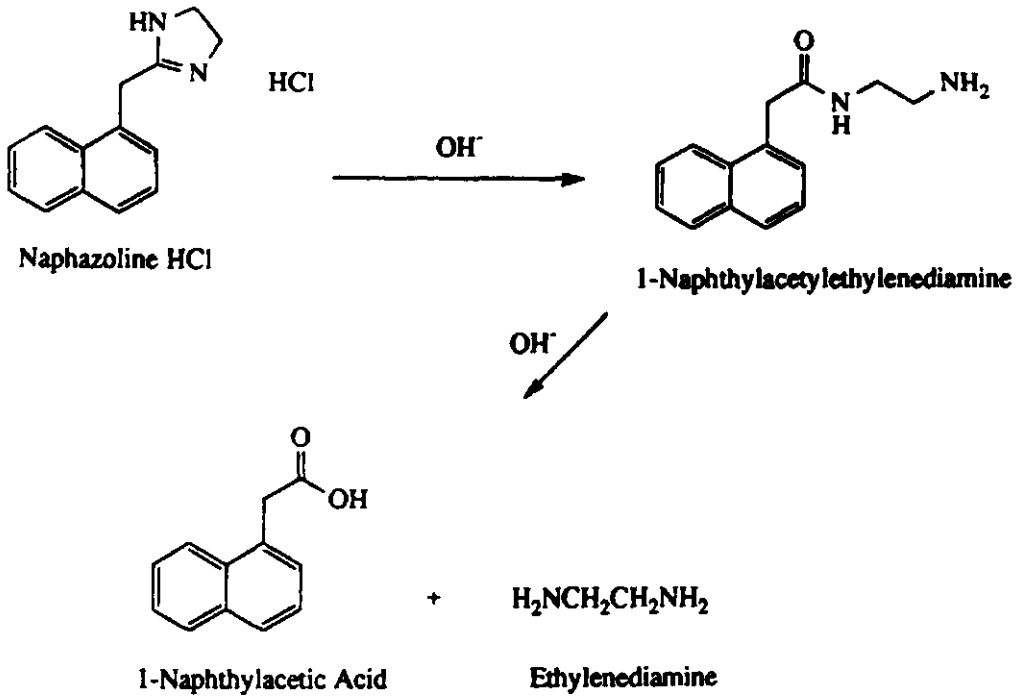


Figure 12. Degradation products of naphazoline hydrochloride under alkaline conditions.

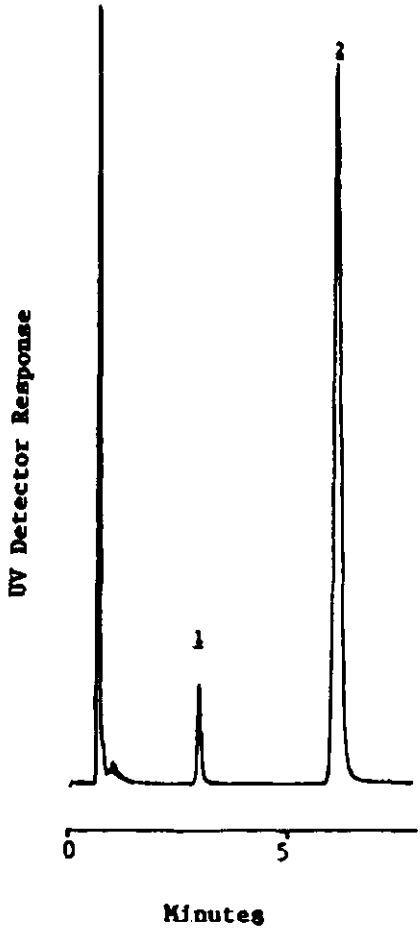


Figure 13. HPLC of 1-naphthylacetylethylenediamine HCl (0.2 µg), 1, and naphazoline HCl (1.2 µg), 2 [5 µm cyano column, 4.6 X 150 mm, 0.025 M phosphate buffer (pH 7.4)-acetonitrile (35:65, v/v), 2.0 mL/min, UV 270].

5.1.1.3. Synthesis of 1-Naphthylacetylethylenediamine Hydrochloride

The synthesis of 1-naphthylacetylethylenediamine was described by Schwartz *et al.*[33] using a modification of previous work by Miescher *et al*[36]. Five grams of naphazoline hydrochloride were refluxed with 100 ml of 0.5N NaOH for 30 minutes. The mixture was then cooled, made alkaline, and extracted with $CHCl_3$. The $CHCl_3$ extract was evaporated, leaving a yellowish oil which solidified upon chilling to give the base as an off-white solid recrystallized from $CHCl_3$-petroleum ether (1:1) mp 93-95°C. The base in chloroform was treated with HCl gas to obtain the HCl salt as an off-white solid mp 142-8°C.

5.1.1.4. Physical/Chemical Properties of 1-Naphthylacetylethylenediamine Hydrochloride

A sample of 1-naphthylacetylethylenediamine hydrochloride was prepared and evaluated[30]. The substance appeared as off-white powder with a melting point of 153.8-154.2°C. The material was not hygroscopic. The IR spectrum (Table VII, Figure 14), UV spectrum (Figure 15), ^{1}H-NMR spectrum (Table VIII, Figure 16), ^{13}C-NMR and APT spectra (Table VIII, Figure 17), and mass spectrum (Table IX, Figure 18) were consistent with the proposed chemical structure. The DSC (Figure 19) of 1-naphthylacetylethylenediamine hydrochloride was consistent with the metling range.

Table VII. Infrared spectral assignments for 1-naphthylacetylethylenediamine HCl.

Wavelength (cm^{-1})	Assignment
3392	1° amide N-H stretch
3220-2400	C-H and N-H stretch
1641	amide C=O
1599,1482,1438	aryl C-C stretch
1520	2° amide N-H
802,795,779	substituted aromatic

5.1.2. Synthesis and Analysis of 1-Naphthylacetic acid

The synthesis of another naphazoline degradation product, 1-naphthylacetic acid, was described by Schwartz *et al*[33]. Five grams of naphazoline HCl were refluxed with 50 ml of 1N NaOH for 2 hours. The mixture was cooled

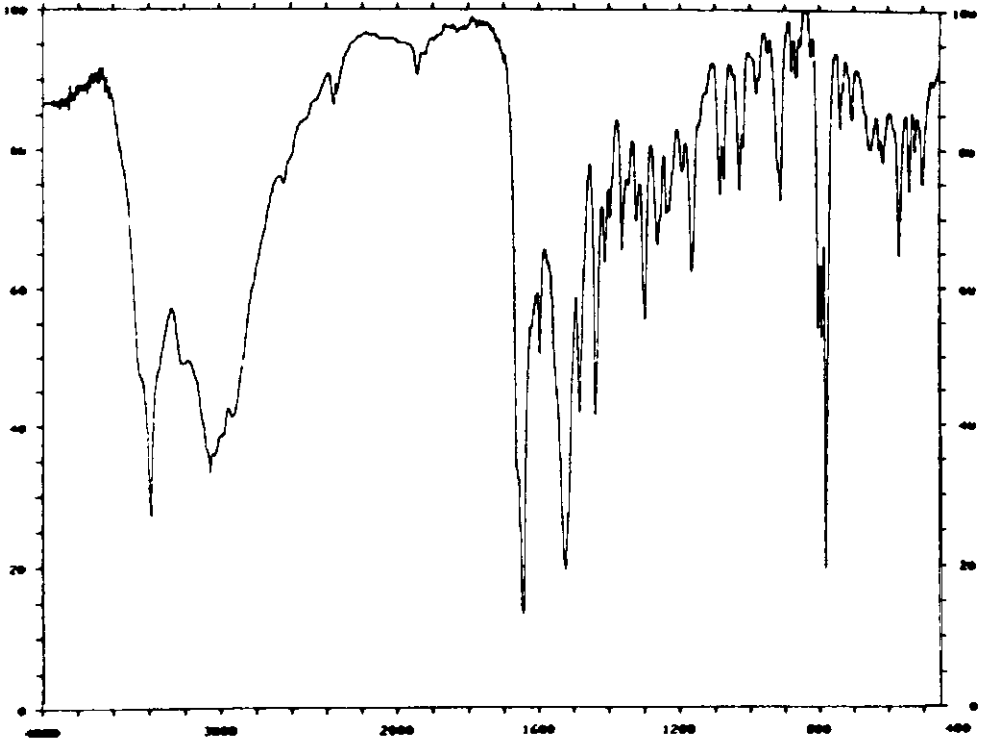


Figure 14. Infrared spectrum (KBr) of 1-naphthylacetylethylenediamine HCl.

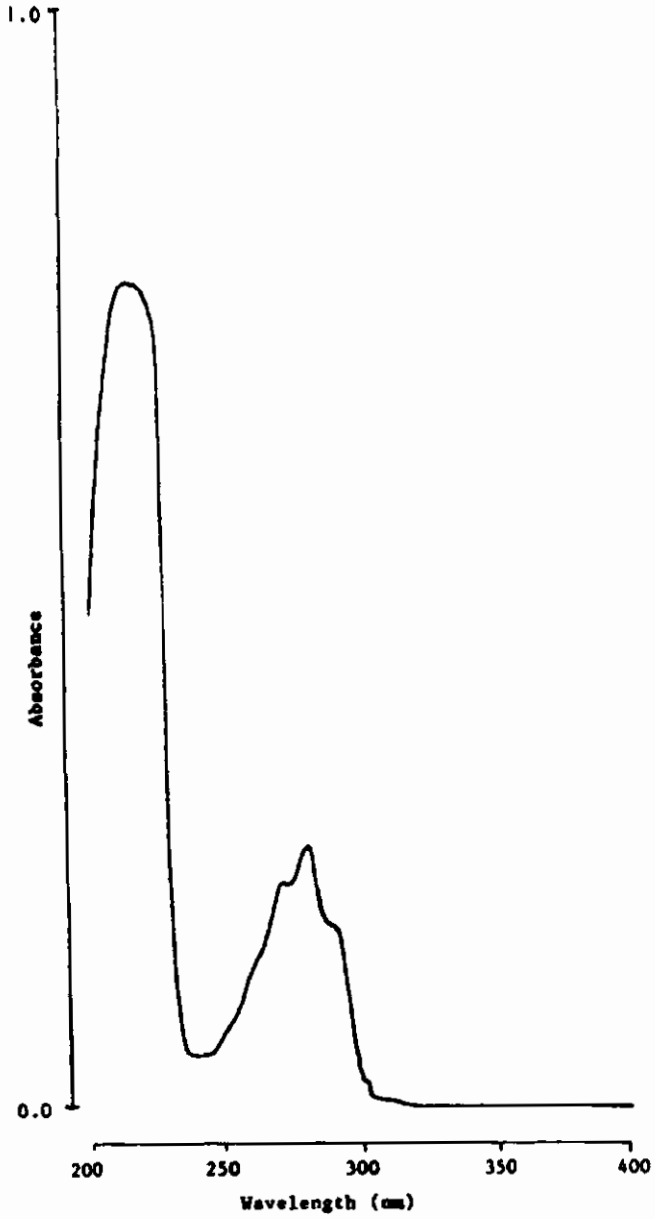


Figure 15. UV Spectrum of 1-naphthylacetylethylenediamine HCl (0.02 mg/mL in ethanol).

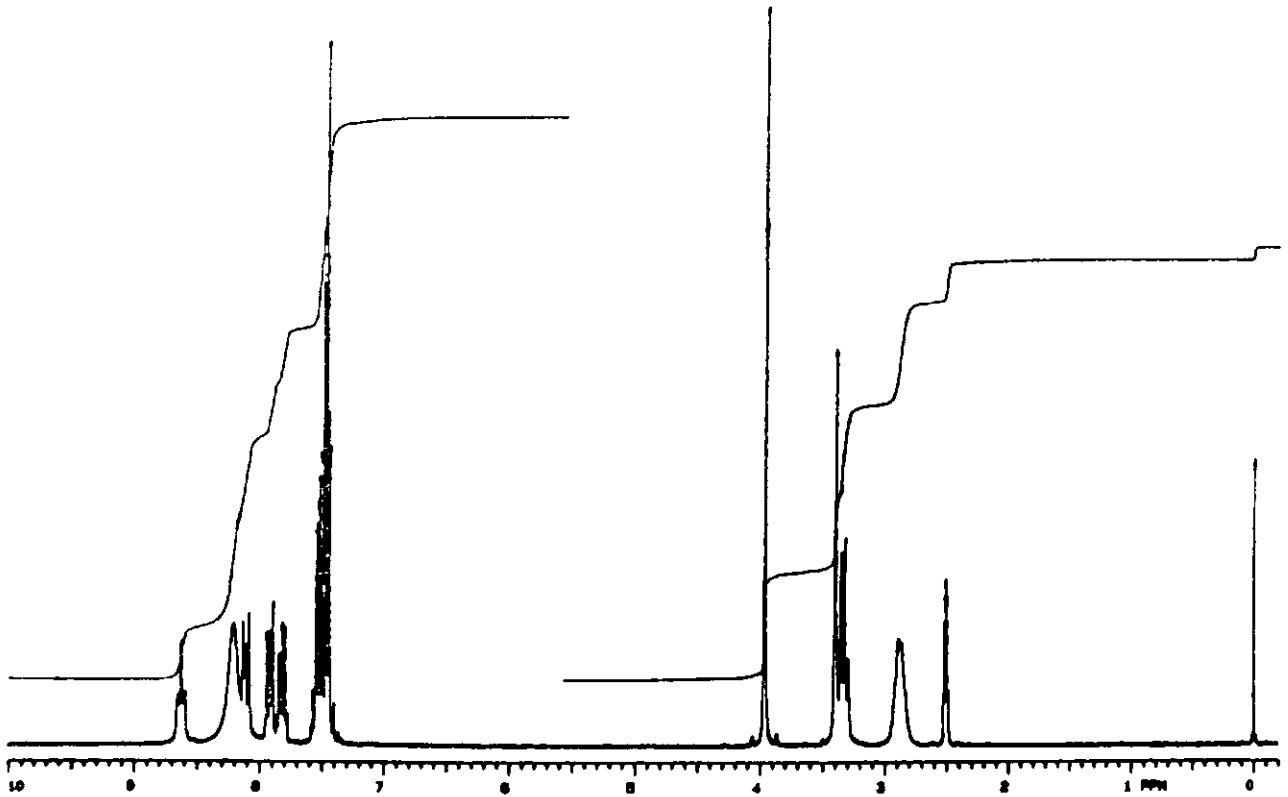


Figure 16. ^{1}H-NMR (200 MHz) of 1-naphthylacetylethylenediamine HCl (20 mg in DMSO-d_6).

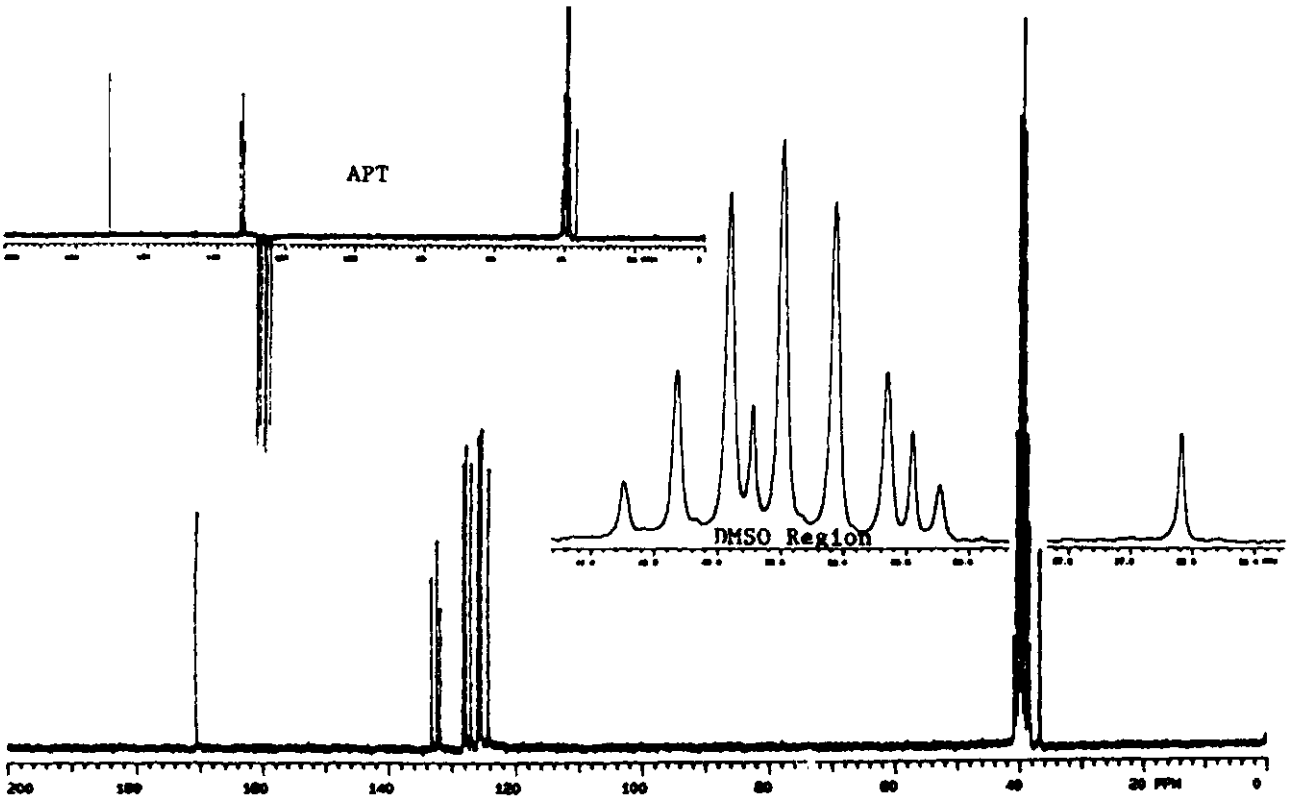
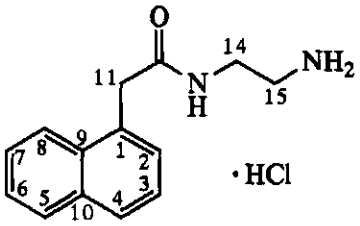


Figure 17. ^{13}C-NMR (50 MHz) of 1-naphthylacetylethylenediamine HCl (20 mg in DMSO-d_6).

Table VIII. NMR assignments for 1-naphthylacetylethylenediamne HCl (20 mg in DMSO-d_6).



Assignment	^{1}H δ (ppm)	^{13}C δ (ppm)
1		132.49 or 131.98
2	7.44-8.60	
3	7.44-8.60	
4	7.44-8.60	124.34,125.47,
5	7.44-8.60	125.59,125.96,
6	7.44-8.60	127.08,127.88,
7	7.44-8.60	128.31
8	7.44-8.60	
9		132.49 or 131.98
10		133.29
11	3.96 (2H,s)	36.59
12		170.68
13	3.40 (1H, s, exch. D_2O)	
14	3.32 (2H, m)	38.23 or 39.72
15	2.89 (2H, br d)	38.23 or 39.72
16	8.21 (2H, br s, exch. D_2O)	

and acidified with HCl, producing a flocculent white precipitate. The precipitate was filtered, washed with cold H_2O and recrystallized from hot H_2O mp 133-134°C; UV spectrum, λ max 283 μm, E (1%, 1 cm in $CHCl_3$) = 360. 1-Naphthylacetic acid has been quantitated in the presence of naphazoline and 1-naphthylacetylethylenediamine using column chromatography followed by UV assay[33,34].

Table IX. EI Mass spectrum of 1-naphthylacetylethylenediamine HCl.

EI (m/e)	Relative Abundance (%)	Assignment
228	4	$[M]^+$
199	14	$[M\text{-}NHCH_2]^+$
185	73	$[M\text{-}NHCH_2CH_2]^+$
141	100	$[M\text{-}C_3H_7N_2O]^+$
128	14	$[M\text{-}C_4H_8N_2O]^+$

5.2 Solid-State Stability

Naphazoline hydrochloride drug substance has been shown to be stable for at least 6 months under the conditions of room temperature, 4°C, 35°C, 40°C at 75% relative humidity, 50°C and exposure to light (1000 foot-candles) at room temperature. The drug substance was found not to be hygroscopic.

An investigation was performed to determine if naphazoline hydrochloride would exhibit polymorphism. Samples of the drug substance were treated with (a) heat at 100°C for 4 hours or (b) vigorously ground with a mortar and pestle. Analytical data from IR, DSC, and x-ray powder diffractometry showed no changes compared to a control sample, suggesting no evidence of polymorphism for naphazoline hydrochloride[30].

5.3 Solution Stability

The stability of naphazoline hydrochloride in aqueous buffers (pH 4.5, 7.0, 9.0) and oxygen-saturated water was evaluated under the conditions room temperature, 35°C, 55°C, and light exposure[30]. The drug was relatively stable under all conditions at acidic and neutral pH and in oxygen-saturated water for at least 26 weeks. The alkaline solutions, however, turned a range of dark colors and showed severe degradation after only 4 weeks.

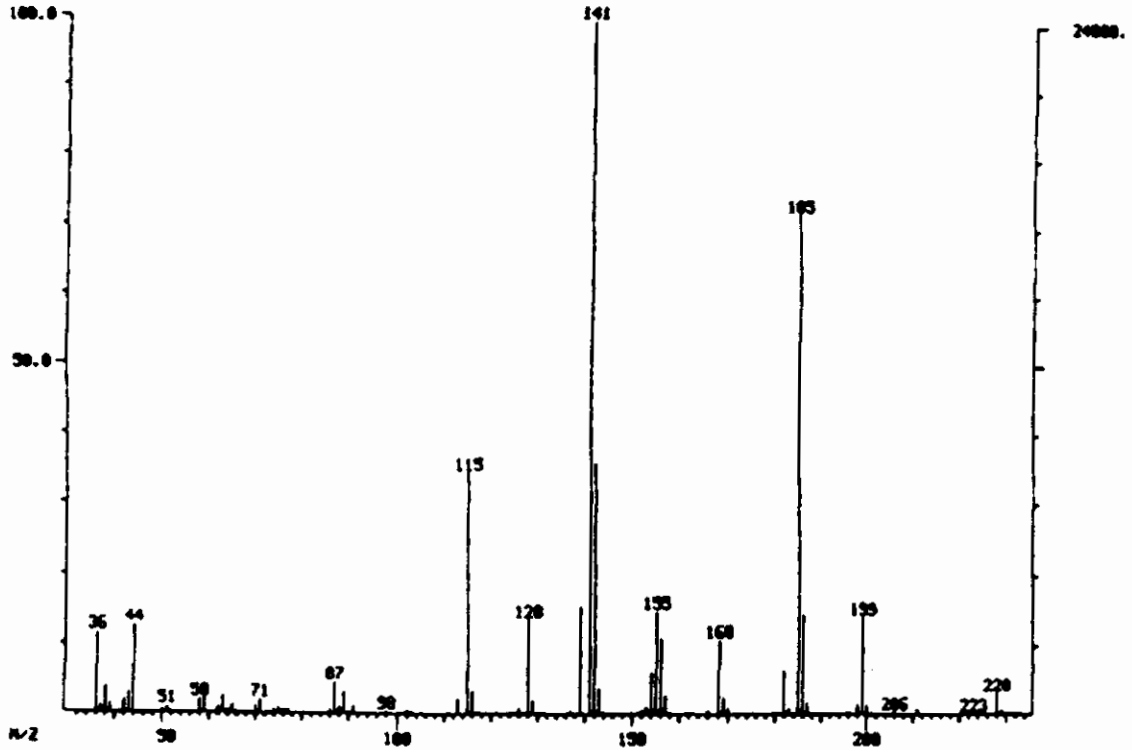


Figure 18. EI Mass spectrum of 1-naphthylacetylethylenediamine HCl.

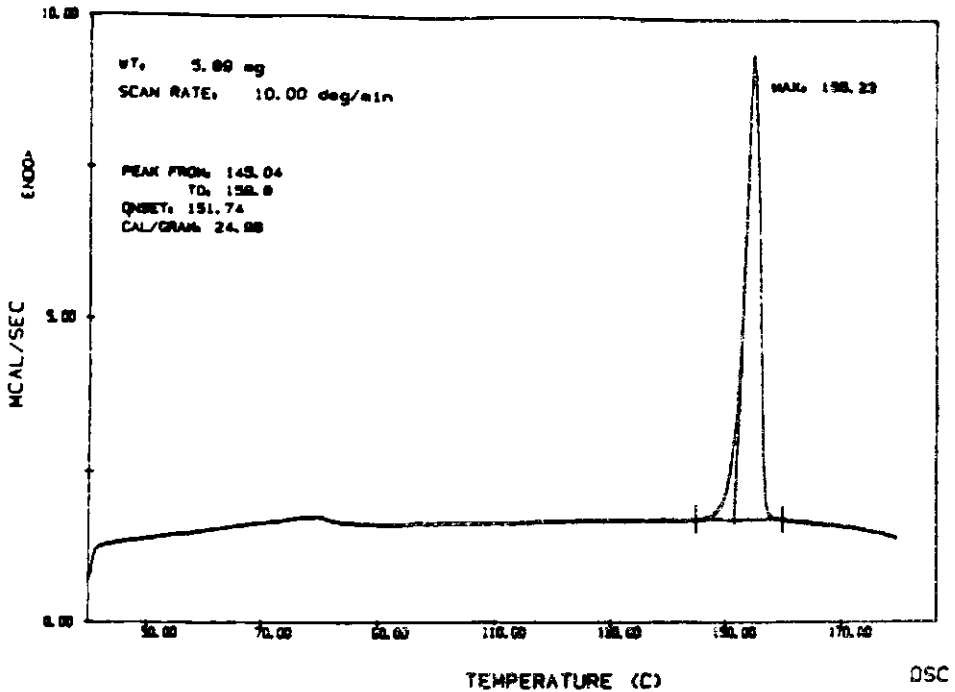


Figure 19. DSC of 1-naphthylacetylethylenediamine HCl.

6. DISPOSITION AND TOXICITY

Naphazoline hydrochloride is commercially available in concentrations of 0.01 to 0.1% as a nasal or ocular decongestant. Local effects are obtained after topical administration to the eye and nasal passages. Metabolic studies could not be found in the literature, despite the report of the synthesis of ^{14}C-labelled drug substance intended for that purpose[11]. Dittgen *et al.*[37] studied the elimination of naphazoline from the isolated pig eye after topical application. Reports of systemic effects of poisoning with naphazoline have been scarce[38]. The LD_{50} s.c. in rats has been reported as 385 mg/kg[6].

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