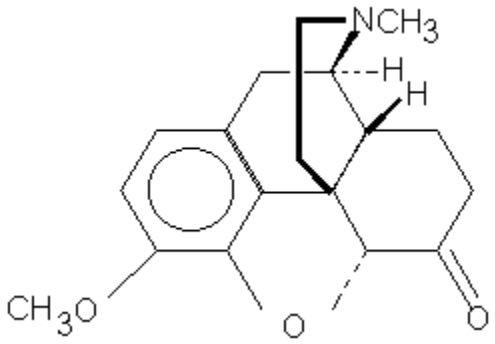
HYDROCODONE

Latest Revision: June 30, 2000



1. SYNONYMS

CFR: Hydrocodone

CAS #: Base: 125-29-1
Hydrochloride: 25968-91-6
Phosphate: 34366-67-1
Tartrate (anhydrous): 143-71-5
Tartrate (hemipentahydrate): 34195-34-1

Stride II: Hydrocodone

Other Names: 6-Deoxy-7,8-dihydro-3-O-methyl-6-oxomorphine
Dihydrocodeinone
Dihydrocodeinone Hydrochloride
Dihydrocodeinone Acid Tartrate
Hydrocodone Acid Tartrate
Hydrocone Bitartrate
Dicodid
Codone
Corutol DH
Hycodan
Hycon
Robidone
Hycomine

2. CHEMICAL AND PHYSICAL DATA

2.1. CHEMICAL DATA

Form	Chemical Formula	Molecular Weight	Melting Point (°C)
Base	$C_{18}H_{21}NO_3$	299.4	198

Hydrochloride	$C_{18}H_{21}NO_3 \cdot HCl \cdot 2.5H_2O$	380.9	158-186
Phosphate	$C_{18}H_{21}NO_3 \cdot 1.5H_3PO_4$	446.4	***
Tartrate	$C_{18}H_{21}NO_3 \cdot C_4H_6O_6 \cdot 2.5H_2O$	494.5	146-148

2.2. SOLUBILITY

Form	A	C	E	H	M	W
Base	***	VS	S	SS	S	I
Hydrochloride	***	***	I	I	***	FS
Phosphate	***	I	I	I	***	VS
Tartrate	SS	I	I	I	PS	S

A = acetone, C = chloroform, E = ether, H = hexane, M = methanol and W = water, VS = very soluble, FS = freely soluble, S = soluble, PS = sparingly soluble, SS = slightly soluble, VSS = very slightly soluble and I = insoluble

3. SCREENING TECHNIQUES

3.1. COLOR TESTS

REAGENT	COLOR PRODUCED
Marquis	Yellow to brown to violet
Mecke's reagent	Yellow to green

3.2. CRYSTAL TESTS

REAGENT	CRYSTALS FORMED
Fulton's iodine reagent C-2	Single rods after 30-60 seconds, the rosettes of needles which grow into rods. The rods then begin to turn into plates which vary in color from orange to orange-red
Platinum bromide in HBr-H_2SO_4	Rosettes of needles yellow in color, forms quickly

3.3. THIN LAYER CHROMATOGRAPHY

Visualization

Acidified iodoplatinate spray

COMPOUND	Relative R_f		
	System TLC 13	**System TLC 14**	**System TLC 15**
acetaminophen	0	0.7	0
aspirin	0	0.1	0
hydrocodone	0.2	0.6	0.2

3.4. GAS CHROMATOGRAPHY

Method HCD-GCS1

Instrument: Gas Chromatograph operated in split mode with FID

Column: 5% phenyl/95% methyl silicone 12 m x 0.2 mm x 0.33 µm film thickness

Carrier gas: Helium at 1.0 mL/min

Temperatures: Injector: 270°C
Detector: 280°C
Oven program:
1) 175°C initial temperature for 1.0 min
2) Ramp to 275°C at 15°C/min
3) Hold final temperature for 3.0 min

Injection Parameters: Split Ratio = 60:1, 1 µL injected

Samples are to be dissolved in 4:1 chloroform: methanol and filtered.

COMPOUND	RRT	COMPOUND	RRT
amphetamine	0.09	diphenhydramine	0.49

methamphetamine	0.10	lidocaine	0.50
aspirin breakdown 1	0.10	theophylline	0.57
aspirin breakdown 2	0.11	aspirin breakdown 5	0.58
nicotinamide	0.13	chlorpheniramine	0.61
ephedrine	0.15	procaine	0.63
phenylpropanolamine	0.15	cocaine	0.79
pseudoephedrine	0.15	triprolidine	0.84
aspirin Breakdown 3	0.18	tetracosane	0.91
3,4-MDMA	0.22	codeine	0.95
aspirin Breakdown 4	0.23	morphine	0.98
benzocaine	0.24	**hydrocodone**	**1.00 (6.46 min)**
guaifenesin	0.30	hydromorphone	1.01
acetaminophen	0.31	oxycodone	1.06
meperidine	0.39	heroin	1.15
caffeine	0.45	quinine	1.27
ketamine	0.48		

4. SEPARATION TECHNIQUES

Dissolve the sample in water and add $NaHCO_3$ until basic. Extract the hydrocodone base from the aqueous layer with chloroform, ether, or hexane. Filter the organic layer through a bed of anhydrous sodium sulfate. Hydrocodone can also be separated from acetaminophen by washing the sample with hexane saturated with NH_4OH. Take the sample to dryness.

5. QUANTITATIVE PROCEDURES

5.1. GAS CHROMATOGRAPHY

Method HCD-GCQ1

Internal Standard Stock Solution:
0.20 mg/mL triprolidine hydrochloride in water.

Standard Solution Preparation:
Accurately weigh and prepare a standard solution of hydrocodone bitartrate at approximately 0.3 mg/mL using the internal standard stock solution. Take 2.0 mL of the standard solution and make the solution basic with

Na_2CO_3 and add 1.0 mL of chloroform. Shake the solution to transfer the internal standard and hydrocodone into the chloroform layer. Discard the aqueous layer and inject the chloroform layer.

Sample Preparation:
Accurately weigh an amount of sample into a volumetric flask and dilute with internal standard stock solution. If necessary dilute the sample so the final concentration approximates the standard concentration or falls within the linear range. Take 2.0 mL of the sample solution and make the solution basic with Na_2CO_3 and add 1.0 mL of chloroform. Shake the solution to transfer the internal standard and hydrocodone into the chloroform layer. Discard the aqueous layer and inject the chloroform layer.

Instrument:	Gas Chromatograph operated in split mode with FID
Column:	5% phenyl/95% methyl silicone 12 m x 0.2 mm x 0.33 µm film thickness
Carrier gas:	Helium at 1.0 mL/min
Temperatures:	Injector: 270°C Detector: 280°C Oven: 250°C
Injection Parameters:	Split Ratio = 60:1, 1µL injected
Typical Retention Time:	Triprolidine: 1.49 min Hydrocodone: 2.37 min
Linear Range:	0.03 to 0.70 mg/mL Hydrocodone Bitartrate
Repeatability:	RSD less than 1.5%
Correlation Coefficient:	0.999
Accuracy:	Error less than 5%

COMPOUND	RRT	COMPOUND	RRT
MDA	<0.23	lidocaine	0.31
MDMA	<0.23	phenobarbital	0.34
acetaminophen	<0.23	procaine	0.39
amphetamine	<0.23	methaqualone	0.53
benzocaine	<0.23	cocaine	0.57
ephedrine	<0.23	tetracaine	0.58
secobarbital	<0.23	triprolidine	0.63
nicotinamide	<0.23	tetracosane	0.71
dimethylsulfone	<0.23	codeine	0.87
methamphetamine	<0.23	morphine	0.98
pentobarbital	<0.23	**hydrocodone**	**1.00 (2.37 min)**

ibuprofen	<0.23	hydromorphone	1.02
phenacetin	0.23	oxycodone	1.20
caffeine	0.30	heroin	1.54
diphenhydramine	0.30	quinine	2.26

5.2. HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

Method HCD-LCQ1

Internal Standard Stock Solution:
0.2 mg/mL strychnine in 85:15 1 N HCl: acetonitrile.

Standard Solution Preparation:
Accurately weigh and prepare a standard solution of hydrocodone bitartrate at approximately 0.2 mg/mL using the internal standard stock solution.

Sample Preparation:
Accurately weigh an amount of sample into a volumetric flask and dilute with internal standard stock solution. If necessary dilute the sample so the final concentration approximates the standard concentration or falls within the linear range. Filter sample with 0.45-micron filter.

Instrument:	High performance liquid chromatograph equipped with diode array
Column:	Waters SymmetryShield RP18, 4.6 mm x 150 mm, 3.5 µm particle size
Detector:	UV, 210 nm
Flow:	1.0 mL/min
Injection Volume:	1µL
Buffer:	20 mM NaH_2PO_4, pH=5.5
Mobile Phase:	Buffer/acetonitrile 85:15
Typical Retention Time:	Hydrocodone Bitartrate: 4.38 min Strychnine: 5.99 min
Linear Range:	0.02 - 0.5 mg/mL Hydrocodone Bitartrate
Repeatability:	RSD less than 1.0%
Correlation Coefficient:	0.9999

Accuracy: Error less than 5%

COMPOUND	RRT	COMPOUND	RRT
morphine	0.44	acetaminophen	0.81
hydromorphone	0.51	oxycodone	0.85
pseudoephedrine	0.67	aspirin	0.90
codeine	0.67	**hydrocodone**	**1.00 (4.38 min)**
ephedrine	0.68	guaifenesin	2.04

6. QUALITATIVE DATA

See spectra on the following pages for FT-IR, Mass Spectrometry, Nuclear Magnetic Resonance, and Vapor Phase IR.

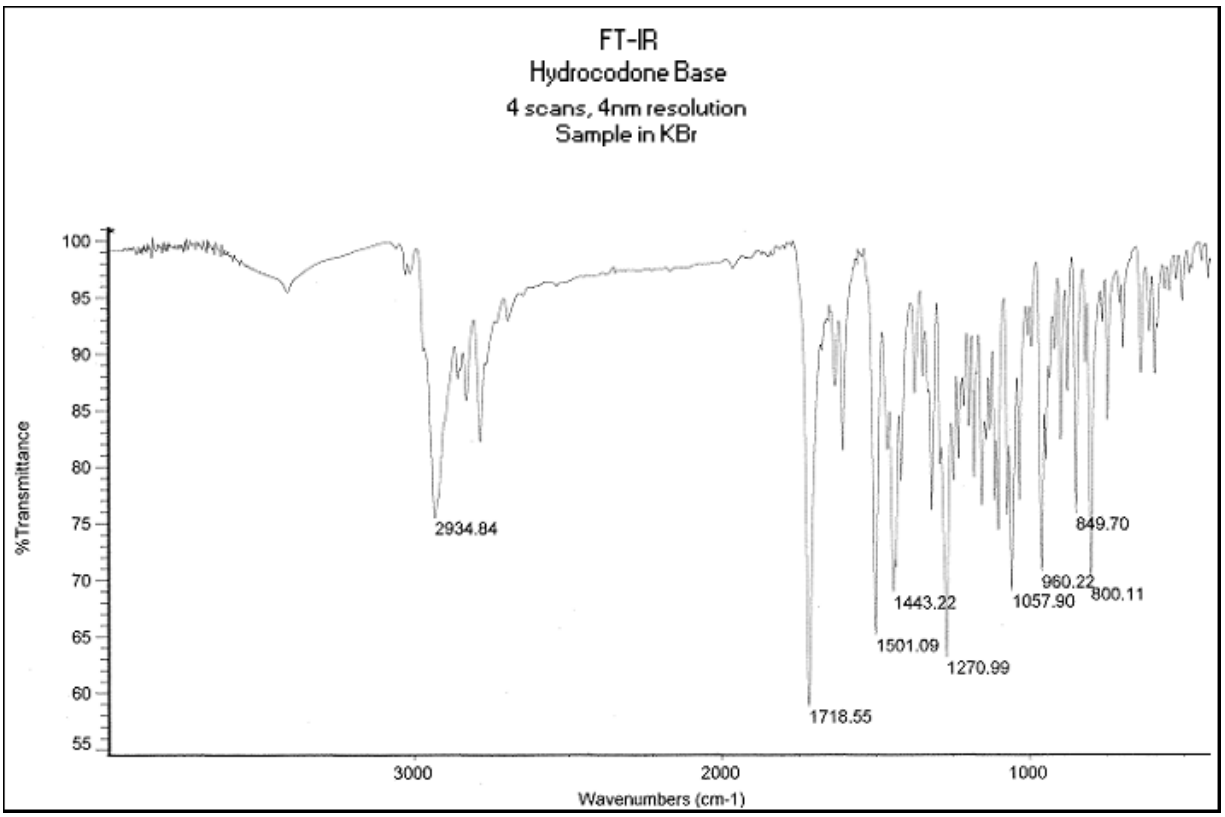
It should be noted that hydrocodone bitartrate undergoes some decomposition in D_2O. The NMR spectra may have minor peaks present. A basic extraction into $CDCI_3$ provides improved spectra.

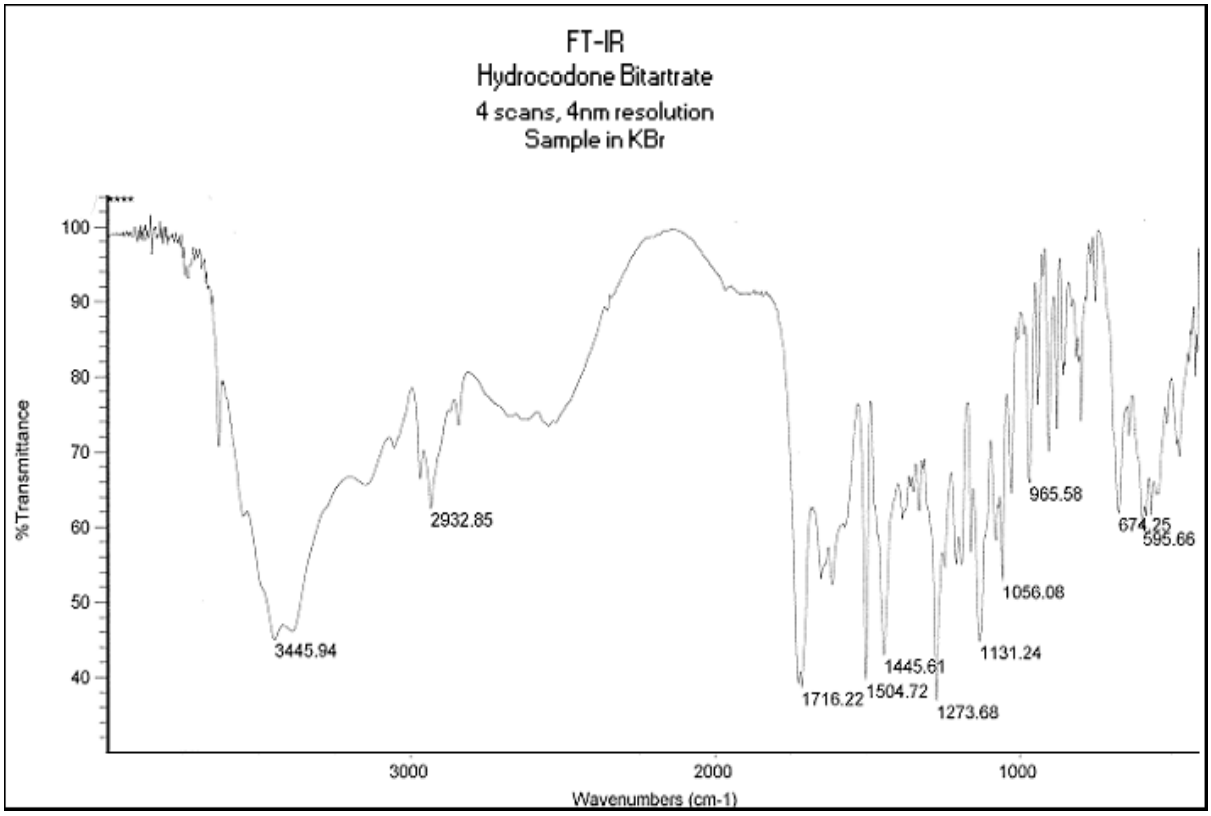
7. REFERENCES

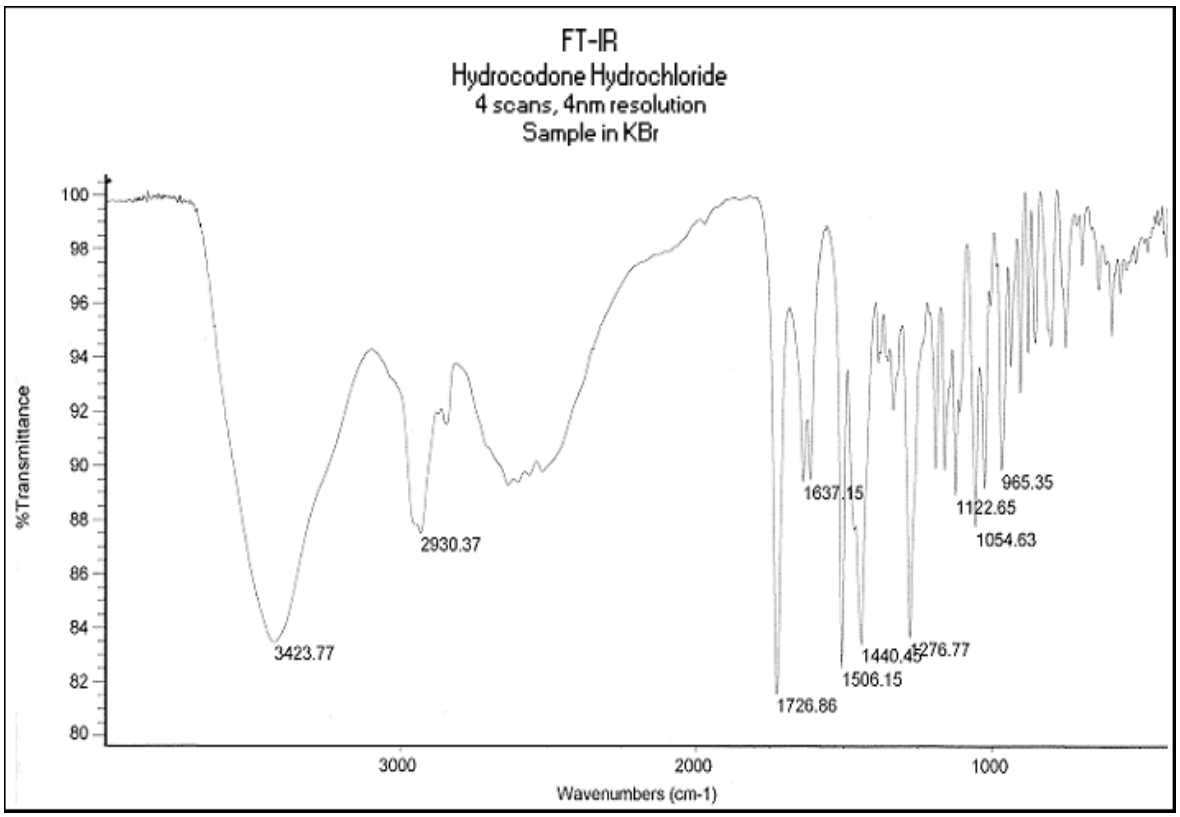
Clarke, E.G.C., *Isolation and Identification of Drugs, 2nd Edition*, The Pharmaceutical Press, 1986.

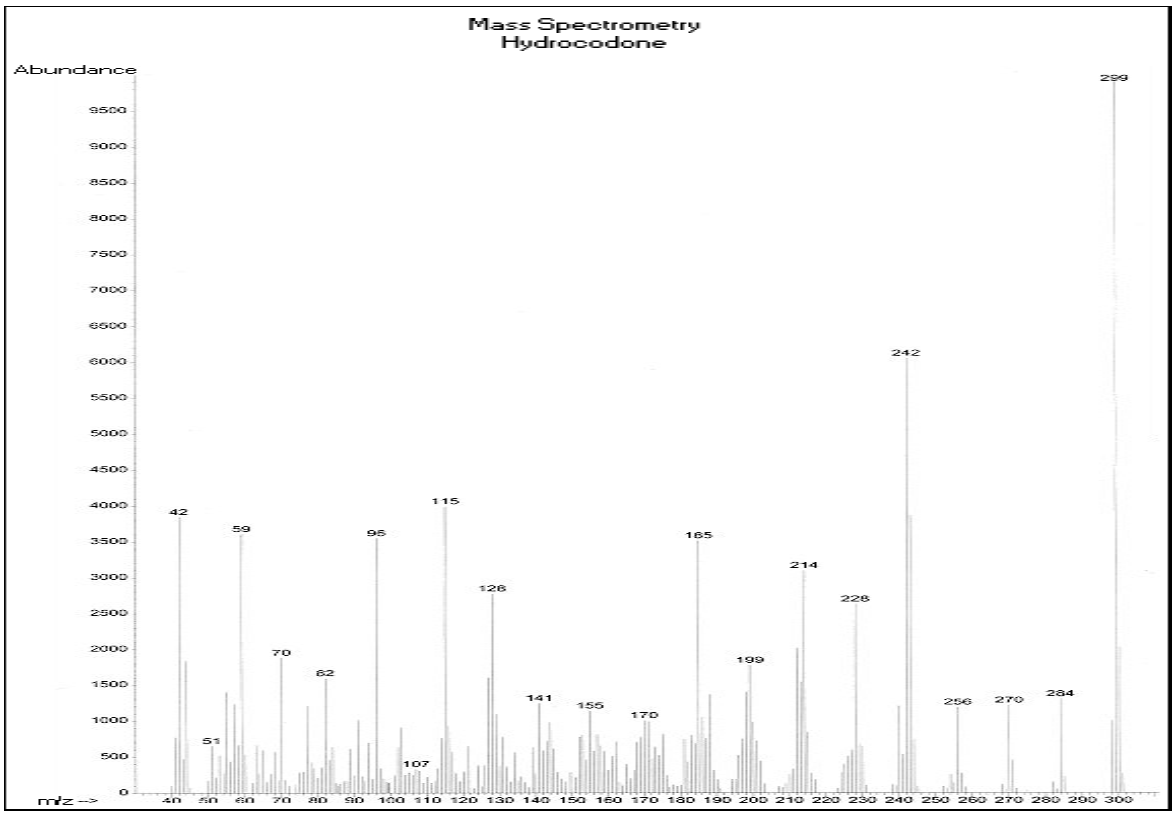
Budavari, S., *The Merck Index, 12th Edition*, Merck and Co., Inc., 1996.

Butler, W. P., *Methods of Analysis for Alkaloids, Opiates, Marihuana, Barbiturates and Miscellaneous Drugs*, The Internal Revenue Service, pp 50-51.


FT-IR
Hydrocodone Base
4 scans, 4nm resolution
Sample in KBr
% Transmittance
Wavenumbers (cm-1)
2934.84
1718.55
1501.09
1443.22
1270.99
1057.90
960.22
849.70
800.11

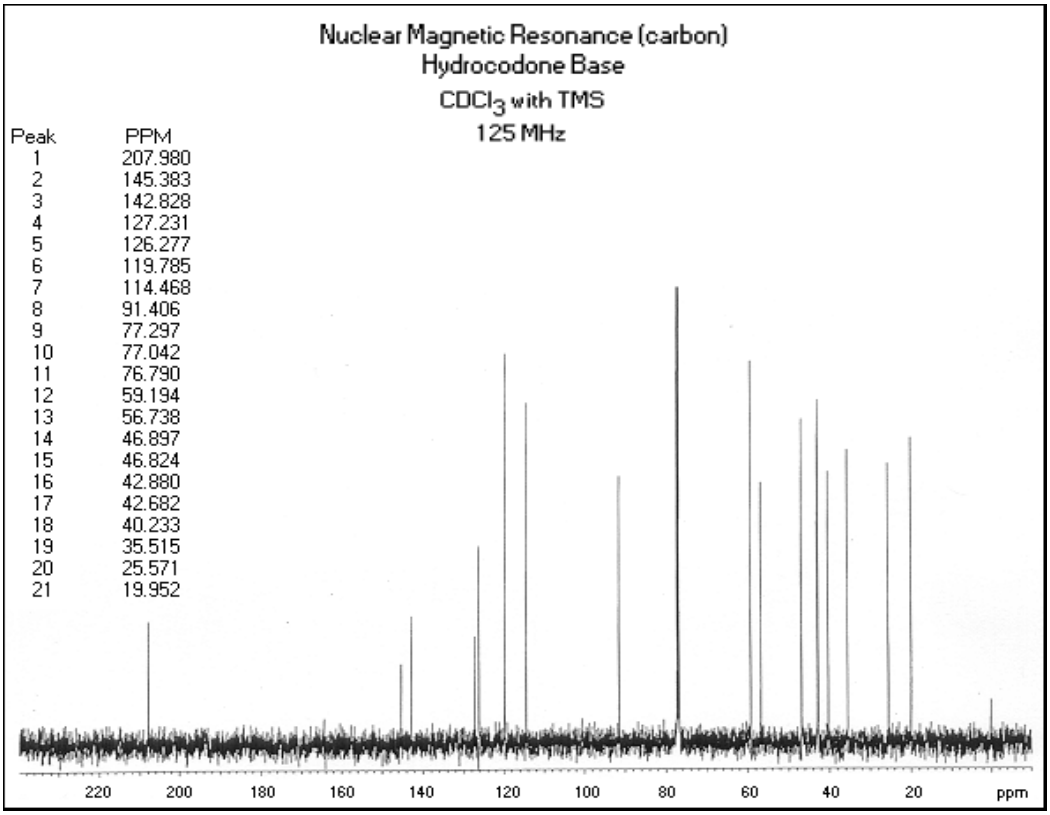

FT-IR
Hydrocodone Bitartrate
4 scans, 4nm resolution
Sample in KBr
% Transmittance
Wavenumbers (cm-1)
3445.94
2932.85
1716.22
1504.72
1445.61
1273.68
1131.24
1056.08
965.58
674.25
595.66


FT-IR
Hydrocodone Hydrochloride
4 scans, 4nm resolution
Sample in KBr
%Transmittance
100
98
96
94
92
90
88
86
84
82
80
3423.77
2930.37
1726.86
1637.15
1506.15
1440.45
1276.77
1122.65
1054.63
965.35
3000
2000
1000
Wavenumbers (cm-1)


Mass Spectrometry
Hydrocodone
Abundance
m/z -->

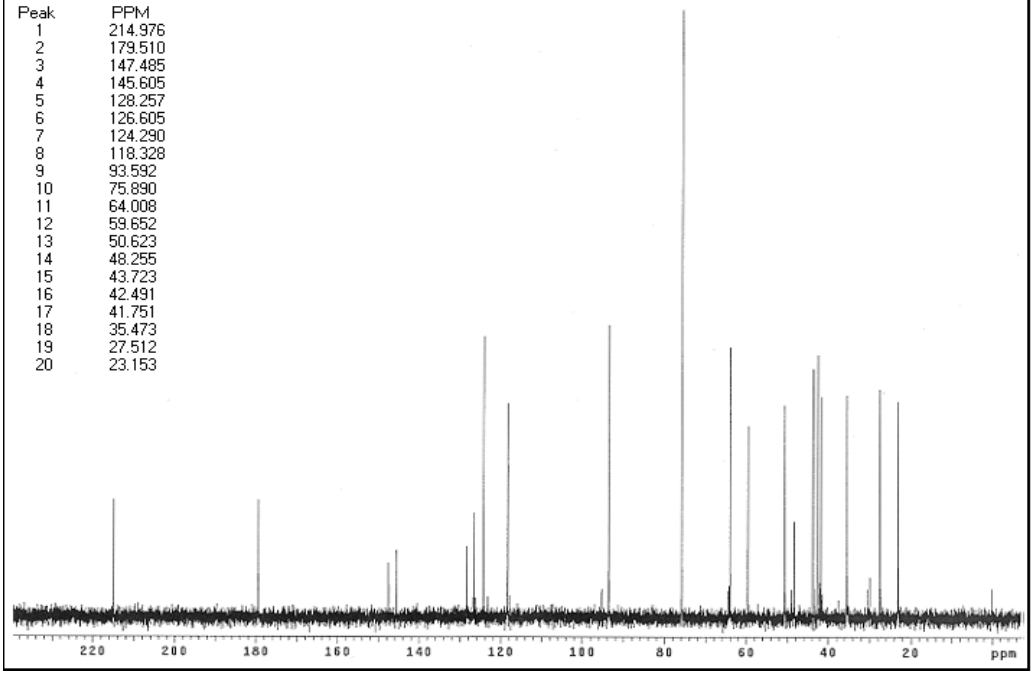
Nuclear Magnetic Resonance (carbon)
Hydrocodone Base
$CDCl_3$ with TMS
125 MHz

Peak	PPM
1	207.980
2	145.383
3	142.828
4	127.231
5	126.277
6	119.785
7	114.468
8	91.406
9	77.297
10	77.042
11	76.790
12	59.194
13	56.738
14	46.897
15	46.824
16	42.880
17	42.682
18	40.233
19	35.515
20	25.571
21	19.952



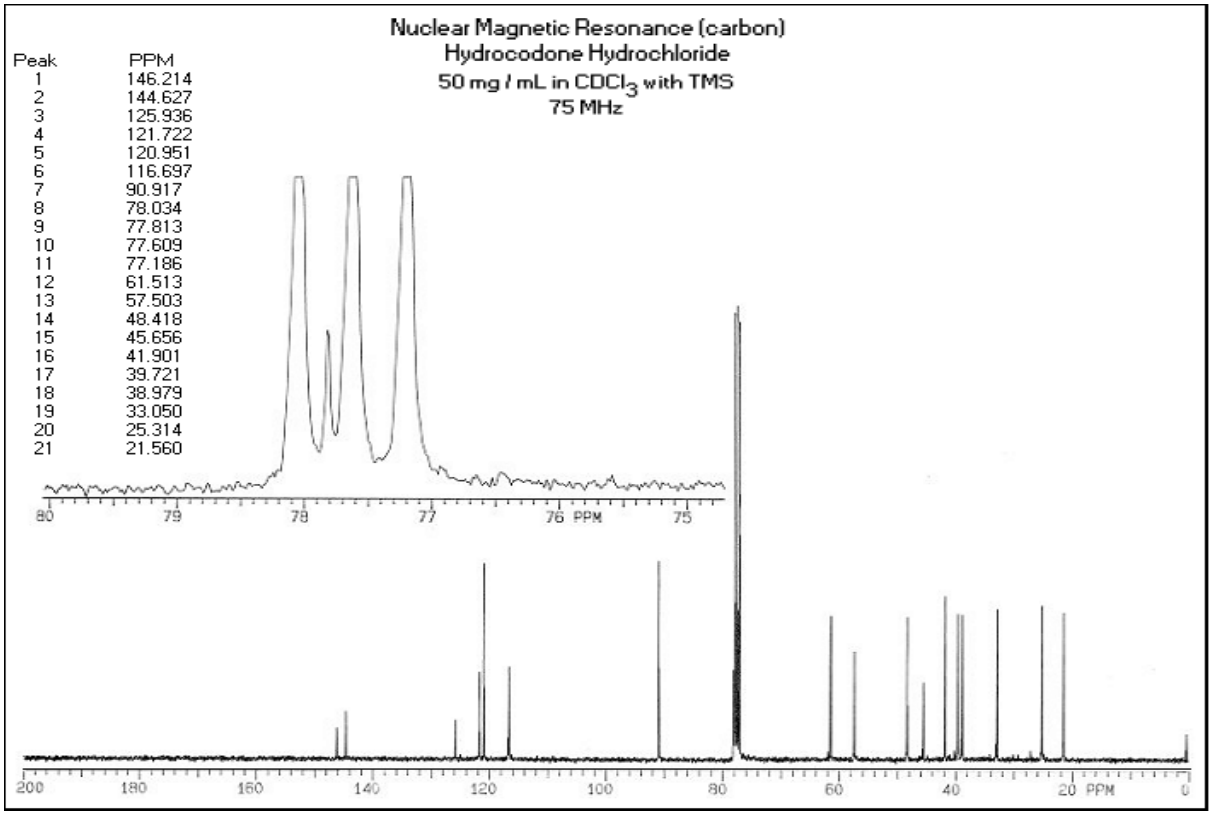
Nuclear Magnetic Resonance (carbon)
Hydrocodone Bitartrate
D_2O with TSP
125 MHz

Peak	PPM
1	214.976
2	179.510
3	147.485
4	145.605
5	128.257
6	126.605
7	124.290
8	118.328
9	93.592
10	75.890
11	64.008
12	59.652
13	50.623
14	48.255
15	43.723
16	42.491
17	41.751
18	35.473
19	27.512
20	23.153

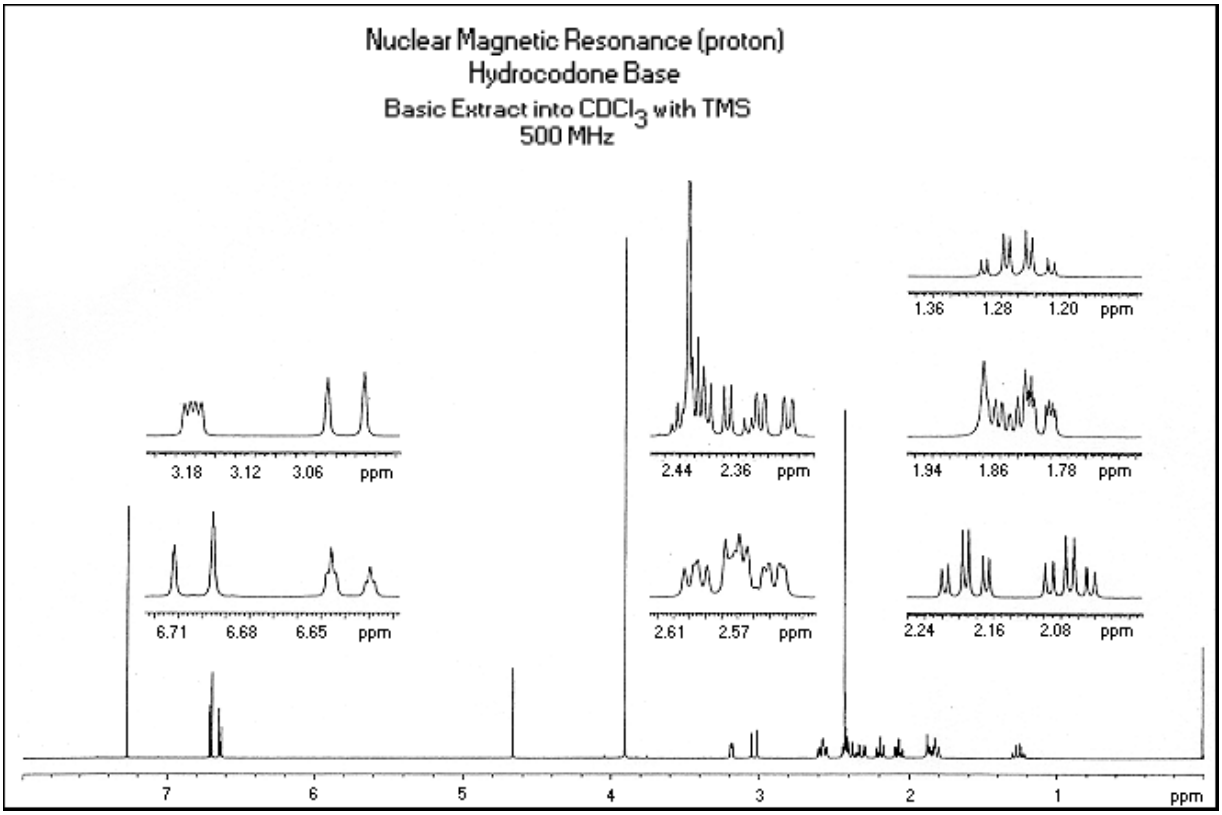


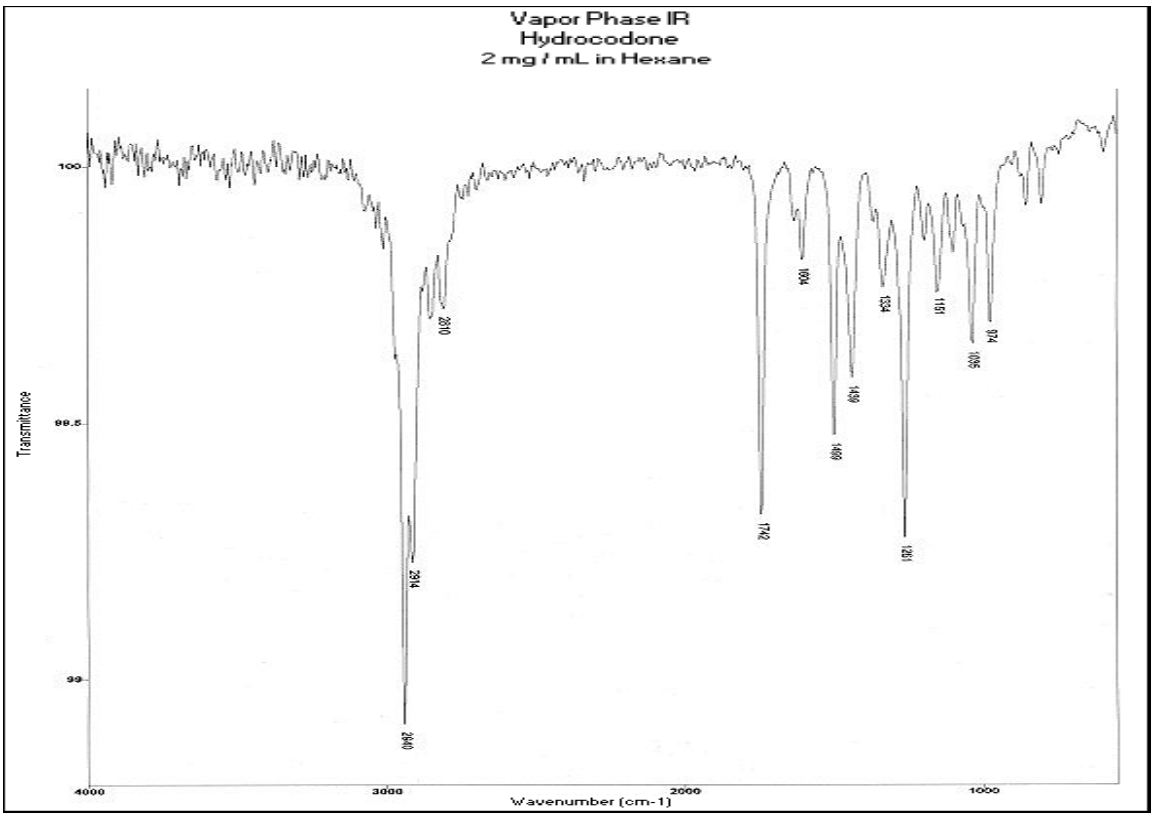
Nuclear Magnetic Resonance (carbon)
Hydrocodone Hydrochloride
50 mg / mL in $CDCl_3$ with TMS
75 MHz

Peak	PPM
1	146.214
2	144.627
3	125.936
4	121.722
5	120.951
6	116.697
7	90.917
8	78.034
9	77.813
10	77.609
11	77.186
12	61.513
13	57.503
14	48.418
15	45.656
16	41.901
17	39.721
18	38.979
19	33.050
20	25.314
21	21.560



Nuclear Magnetic Resonance (proton)
Hydrocodone Base
Basic Extract into $CDCl_3$ with TMS
500 MHz




Vapor Phase IR
Hydrocodone
2 mg / mL in Hexane
Transmittance
100
99.5
99
2940
2914
2860
1742
1604
1469
1459
1334
1261
1151
1095
974
4000
3000
2000
1000
Wavenumber (cm-1)