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DEVELOPMENTS IN LEGAL CHEMISTRY. SIBUTRAMINE EFFECTS THE BOUNDARY BETWEEN LEGAL AND ILLEGAL CONSUMPTION

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Abstract

In the present paper we determined the presence of sibutramine in urine using the GC-MS/MS system. The determination of sibutramine was studied in relation to slimming health foods[1]. Prolonged or excessive consumption of unauthorized pharmaceuticals may cause serious adverse consequences on health. In this study, samples were extracted with the help of methanol and acetonitryl and the sibutramine concentrations were found in the range of 0,5 g/l.

Keywords: *sibutramine, GC-MS/MS, methanol and acetonitryl, HPLC-MS*

Introduction

Amphetamines are psychostimulant drugs that produce increased wakefulness, decreased fatigue and appetite.

The pressor effect of amphetamine was first described by Piness and associates (1933). In 1933, it was noted that it is a bronchodilator, a respiratory stimulant with analeptic action and was compared to epinephrine. Amphetamines described as methamphetamine and dextroamphetamine belongs to the group of drugs that potentially increase the levels of norepinephrine, serotonin and dopamine, euphoria-inducing drugs absorbed at cellular level.

From a medical perspective, amphetamines are sympathomimetic substances, related to derivatives of adrenaline (epinephrine) in which central excitatory effects prevail. Amphetamine is a stimulant of the nervous system due to its weak and long-term pressor action (approximately ten times longer than that of adrenaline).

Amphetamine was first synthesized in 1887 by the Romanian Lazar Edeleanu in Berlin, Germany. The name derives from phenylisopropylamine. It was one of a series of compounds obtained from plants ephedrine was derived from, that had been isolated by Ma Huang together with Nagayoshi Nagai.

Adrenaline and noradrenaline are hormones secreted by the adrenal glands, located in the upper pole of the kidney, and more specifically, the renal medulla. Both hormones exert similar effects of sympathetic stimulation, but while norepinephrine has more intense vascular actions, adrenaline activates especially the energy metabolism.

Amphetamine activity at the brain level is specific; certain receptors that respond to amphetamine in several brain regions do not conduct the impulse to other regions, although they exert effects on behaviour by carrying neurotransmitters in the brain, including

[11] Yamamoto S-Shokuhin Eiseigaku Zasshi, 369, 2011.

dopamine, serotonin and norepinephrine. So dopamine D_2 receptors in the hippocampus – the brain region associated with memory formation – appear not to be affected by the presence of amphetamines.

I.1. CHEMICHAL STRUCTURE

In terms of illicit production, alongside amphetamine, the following are obtained:

- Specific chemical (the chemical used as green material, precursor, reagent or solvent in illegal processes or substance control).

- Precursor (chemicals which in clandestine processes are incorporated, in full or in part, in the final production of the molecule of the substance under international control).

-Reagent (chemical that reacts or participates in the reaction, but does not become part of the final product).

- Solvent (is the liquid substance that dissolves another solid substance without changing the chemical composition, and does not become part of the final product).

- Impurities (natural constituents originating from plant materials or from materials obtained through the processing of those remaining in the final product after complete process conversion).

- Adulterants (pharmacologically active substances remaining or added after the conversion of the final product).

- Diluent (pharmacologically inactive substance added to the final product to increase volume).

Amphetamines belong to the class of phenylalkylamines and classify into:

Amphetamines (found under the following names: 1-phenylpropan-2-amine,

□ methyl-benzeneethanamine

□ methylphenethylamine)

Methamphetamine (found under the following names:

2-(methylamino)-1-phenyl-1-propanone

N,□dimethylaminobenzene

N,□ dimethylphenethyl-benzene

N-methyl-amphethamine

Phenylisopropylmethylamine)

Sibutramine (found under the following names: Meridia, Ectiva, Reductil,

1-[1-(4-chlorophenyl) cyclo-butyl]-NH,3-trimethyl-butane-1-amine)

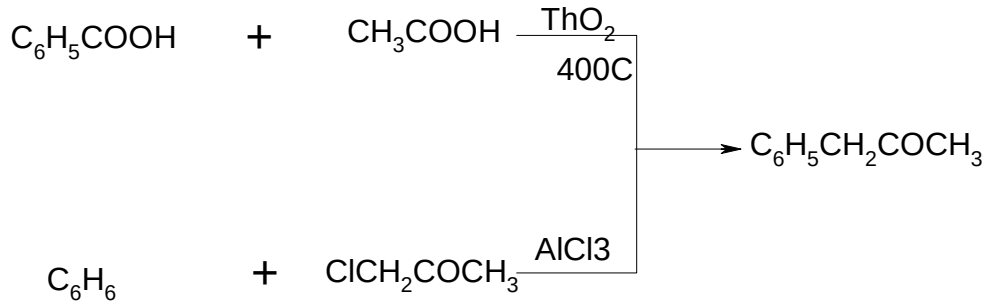
Methylphenidate (found under the following names: centedrin, ritalin)

Amfepramone (found under the name: Diethylpropion amphetamine)

Fenfluramine (found under the name: fenfluramine)

I.2. SYNTHESIS

Amphetamine is prepared from benzyl-methyl-ketone, by using several methods commonly used to convert the carbonyl group into the group – CH_2NH_2 (reduction of the nitrogen functional derivatives of carbonyl compounds). Benzyl-methyl-ketone is obtained by heating a mixture of phenylacetic acid and acetic acid at 400 C, in the presence of thorium dioxide or through the Friedel – Crafts reaction between benzene and chloroacetone, in the presence of aluminum chloride.



I.3. FORMULATION

Amphetamine-products generally come in the form of sulfates or phosphates. They are available on the international market in the form of tablets, capsules, syrups and elixirs. The vast majority of amphetamines appear as hydrochlorides or sulfates.

In terms of solubility, amphetamines are insoluble in water. As free bases they are soluble in organic solvents such as ethanol, diethyl ether, and chloroform. Hydrochlorides are soluble in water and ethanol, slightly soluble in chloroform and insoluble in diethyl ether. Sulphates and phosphates are soluble in water, slightly soluble in ethanol and insoluble in diethyl ether and chloroform. Trimethylamphetamine have boiling points ranging between 118 C - 220 C.

Amphetamine has two optical isomers:

- Dextroamphetamine – dextrorotatory stereoisomer
- Levoamphetamine – levorotary stereoisomer

Dexamphetamine is 2-4 times more active than the racemic compound as a psychomotor stimulant and less active as sympathomimetic. Also the dextrorotatory isomer is 24 times more active than its levorotary enantiomer.

Methamphetamine has amphetamine-like properties but its sympathomimetic effects are weak in normal doses.

Methylphenidate is a chemical related to amphetamines, having weaker psychomotor stimulant properties and weak peripheral actions. The effect is fast and relatively short in duration, corresponding to a half-life of 1-2 hours, which is an advantage over amphetamine.

Fenfluramine is a halogenated amphetamine derivative. Amphetamines may react with H_3PO_4 and H_2SO_4 forming amphetamine sulphate and phosphate. Amphetamine derivatives are:

A. Dimethoxy-amphetamines -2.5-dimethoxy-amphetamine (DMA)
-4bromo-2.5- dimethoxy-amphetamine (DOB)
- 2.5-dimethoxy-4-methylamphetamine (STP, DOM)
- 3.4 - methylenedioxyamphetamine
- 1-methoxy-4-amphetamine
- dimethoxy-2, 5-ethyl-4-amphetamine
- methoxy-3-methylenedioxy-4,5-amphetamine

B. Trimethoxy-amphetamines - 3,4,5-trimethoxyamphetamine (TMA 1)
- 2,4,5-trimethoxyamphetamine (TMA 2)
- 2,3,4-trimethoxyamphetamine (TMA 3)
- 2,3,5-trimethoxyamphetamine (TMA 4)
- 2,3,4-trimethoxyphenyl-propan-2-amine
- 2,3,6-trimethoxyamphetamine (TMA 5)
- 2,4,6- trimethoxyphenyl-propane (TMA 6)

I.4 CHEMICHAL DETERMINATION

The most common methods for the determination of amphetamines in biological products are spectrophotometric, immunologic fluorescence - FPIA (Fluorescence Polarisation Imunoassay), immunochromatographic, gas or liquid chromatography. These include:

I.5.1. *The spectrophotometric method* – in this case, amphetamine engage, in alkaline medium, with diazotized p-nitroaniline resulting in a calorimetric red azo-derivative.

I.5.2. *The immunofluorescence method* – is used in screening tests for testing a group of subjects suspected of amphetamine or methamphetamine consumption, using urine as a bioassay. For an amount of urine of 150 µl/ determination, results are obtained in a period of 12 to 14 minutes. Results are given as present or absent, because of the methods implemented using a six point-calibration curve, rather than a 1-point calibration for the FPIA assay system – the cut-off value being used for the determination of xenobiotic substances in the urine by reading the light polarization vector in polarization milliunits. A positive result will be necessarily confirmed by the GC-MS method.

I.5.3. *Immunochromatographic method* – is the appearance of a coloured band on a solid support (one to check, another to validate the presence or absence of amphetamines or methamphetamines in the urine, saliva or sweat, the type of biological fluids depending on the manufacturer of the immunochromatographic test). It also uses urine to detect: opiates, cocaine, phencyclidine, cannabis, barbiturates, benzodiazepines, tricyclic antidepressants. A positive result will be necessarily confirmed by the GC-MS method.

I.5.4. *The gas-chromatographic method coupled with the GC-MS mass spectrophotometer*

I.5.5. The HPLC-MS – DAD method

II. EXPERIMENTAL

II.1 Materials

To determine the amphetamines- sibutramine in this case the following materials were used:

- Spectrophotometer Cary 5 - Varian
- FPIA AXSYM - Abbot system
- GC-MS/MS Saturn 2000 - Varian system
- HPLC-MS/MS-DAD system - Varian
- Eppendorf centrifuge 5616
- Analytical balance - Precisa 40SM-200A
- Magnetic stirrer - HP 240
- Ultrasonic bath - Branson 2210
- Thermostat - Memmert
- Accessories and reagents specific to an analytical toxicology laboratory
- Sibutramine (10 mg amphetamine - Zentiva)

Sibutramine (trade name Meridia in the U.S. and Canada, Ectiva in South Africa, Reductil in Europe and most other countries), is an orally administered agent for the treatment of obesity as an appetite suppressant. It has virtually no potential for abuse because of the lack of dopaminergic effects. It is used as an anorexic, which is the only reason for its classification as a controlled drug, as in the mid-20th century it resulted in a number of cases of abuse or addiction.

II.2. METHODS

II.2.1. Gas chromatography method coupled with the GC-MS mass spectrometer

It consists of three submethods for each device that is part of the GC-MS system. Thus there will be a method for autosampler 8200, one for gas chromatograph 3800 and one for mass spectrometer Saturn 2000.

Autosampler 8200

Number of containers – 48; Volume injection syringe – 10 μl

Number of liquids for washing injection syringe – 2

Time for washing injection syringe with a washer fluid – 20 s

Time of taking over the injection matrix – between air plugs

Injection volume – 1 μl; Depth of penetration of the needle into the bottle – 80%

Fluid intake speed – 1 μl/ s; Heating time for the needle in the injector– 6 s

Injection speed – 10 μl / s; Time of the needle remaining in the injector after injection– 6 s

Gas chromatography 3800

Injector type 1079; Injection temperature – 300^0C

Split rate 5% constant for the duration of the analysis; Constant flow – 1.2 ml/min

Oven temperature program, T_0 – 180^0C waiting time 1.1 min

Growth in T1 - 290^0C with 5^0C/min speed; T1 – 290^0C waiting time – 13.9 min

Saturn 2000

Filament off – 0 – 3min, AGC field "full scan" – 50 – 400 amu; Time 3 – 35 min

Scan duration – 1s/scan; Filament current – 10 μA; Maximum number of ions 25,000 Ionization maximum duration 25 ms; Prescan duration 100 μs

Mass to lower fund – 45 amu

III. RESULTS

In the conditions mentioned, sibutramine extracted by two methods from a capsule of 10 mg Amphetamine – Zentiva was highlighted.

The extraction was performed from 7.5 mg excipient in methanol and acetonytril 1: 1 and 7.5 mg excipient in dichloroethane, dichloromethane and chloroform 1: 1: 1. The solutions were ultrasonated for one hour and centrifuged for 10 minutes. The supernatant was the injection matrix for both the gas chromatographic and the HPLC methods. Fig. 1 shows the resulting total ion chromatogram following the injection of sibutramine solution with a concentration of 0.5 mg/l.

Chromatogram Plot

File: \\saturn2000\hdd saturn2\saturn\data\prb24664.ms
Sample: URINA 6/16/09 1:19 PM
Sample Notes: SIBUTRAMINE (EXTRACTIE IN TEI SOLVENTI)
Operator: MIHAI Scan Range: 1 - 3000 Time Range: 0.01 - 50.00 min.

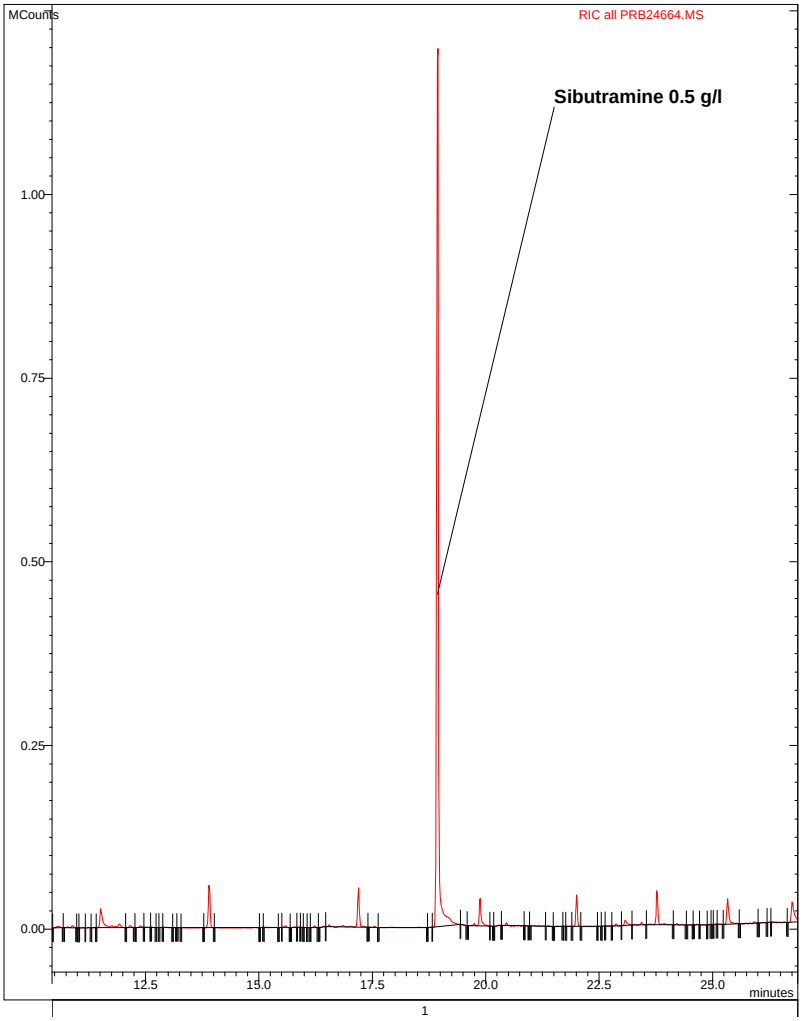


Fig. 1. Total ion chromatogram of sibutramine at a concentration of 0.5 g/l.

Saturn Purity Search Hit List

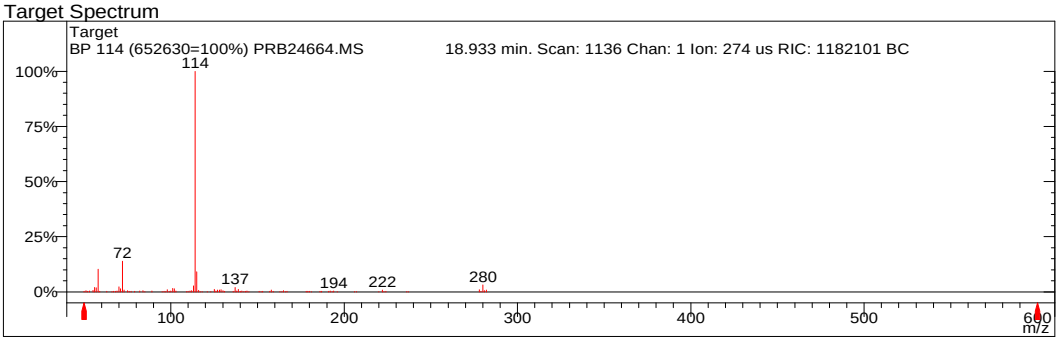
Saturn Purity Search Results

Hits Found:	25
Pre-Search Hits Found:	765

Saturn Purity Search Parameters

Threshold:	100
Target Ion Range:	50 - 600
Library MW Range:	50 - 600
Library Ion Range:	All of Library Entry
Local Normalization:	Off
Requested Pre-Search:	250
Requested Final Search:	25
Search 7 Libraries:	A. c:\saturnws\satlib\nist98m.lbr B. c:\saturnws\satlib\nist98r.lbr C. c:\saturnws\satlib\pmw.lbr D. c:\saturnws\satlib\libr_tr.lbr E. c:\saturnws\satlib\libr_tx.lbr F. c:\saturnws\satlib\libr_gp.lbr G. c:\program files\wiley\wiley6.lbr

Target Spectrum

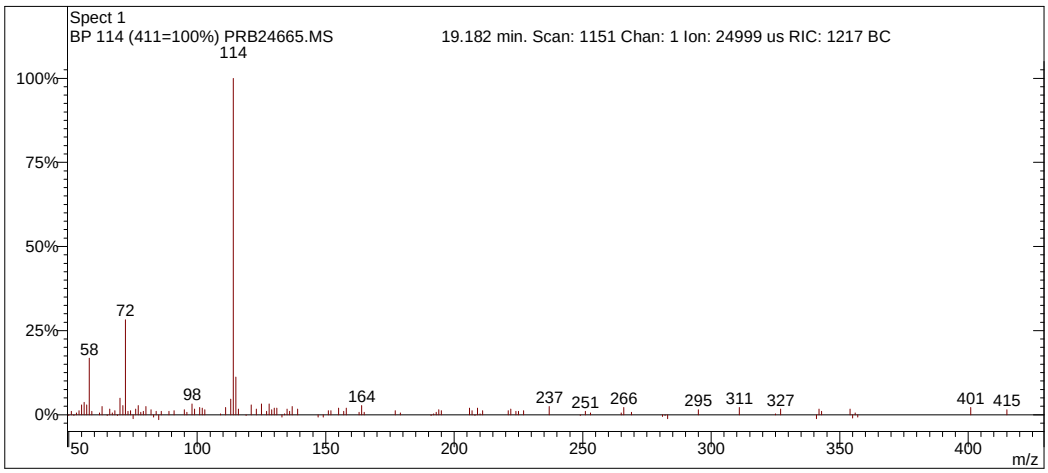


Spectrum from \\Saturn2000\hdd saturn2\Saturn\DATA\PRB24664.MS
Scan No: 1136, Time: 18.933 minutes
No averaging. Background corrected.
Comment: 18.933 min. Scan: 1136 Chan: 1 Ion: 274 us RIC: 1182101 BC
Pair Count: 99 MW: 0 Formula: None CAS No: None Acquired Range: 50 - 282

	Purity	Fit	RFit	Entry #	MW.	Formula, CAS No., Name
1	925	965	938	8741 C	280	C17H26ClN, 106650-56-0, Sibutramine
2.	698	890	754	51423 A	380	C18H40N2S3, None, Ethane, 1-[(2-diisopropylamino)ethyl
3	663	850	763	51413 A	517	C27H30Cl3N3O, None, 1-[[2-[Butylamino]butyl]imino]-7-chl
4.	632	844	702	51422 A	114	C4H6N2S, 60-56-0, Methimazole
5.	631	829	701	9084 G	114	C4H6N2S, 60-56-0, 2H-Imidazole-2-thione, 1,3-dihydro-1
6.	629	761	766	2305 C	375	None, None,
7.	628	855	665	34872 G	159	C8H17NO2, None, N,N-dimethyl leucine $$
8	625	734	744	51559 A	295	C21H29N, 5966-41-6, Benzenepropanamine, N,N-bis(1-methyl
9	611	793	708	51416 A	157	C10H23N, 4458-33-7, Ethyl di-N-butylamine
10	611	758	673	12442 B	129	C7H15NO, 13444-24-1, 3-Piperidinol, 1-ethyl-
11.	603	841	659	51369 A	143	C8H17NO, None, Oxazolidine, 2,2-diethyl-3-methyl-
12	602	850	631	121870 G	267	C11H26NO2PS, 71840-25-0, Phosphonothioic acid, methyl-,
13	601	849	630	12428 B	267	C11H26NO2PS, 71840-25-0, Phosphonothioic acid, methyl-,
14.	598	800	660	51419 A	233	C11H27NSSi, None, 2-Diisopropylaminoethanethiol, TMS d
15	580	776	600	12432 B	129	C8H19N, 7087-68-5, Diisopropylethylamine
16	580	775	692	51365 A	129	C8H19N, 16486-74-1, N-Butyl-tert-butylamine
17.	579	798	666	9085 G	114	C4H6N2S, 60-56-0, 2H-Imidazole-2-thione, 1,3-dihydro-1
18.	577	717	779	2304 C	375	None, None,
19	576	751	703	51409 A	129	C7H15NO, 57817-78-4, Oxazolidine, 3-ethyl-2,2-dimethyl-
20.	573	770	697	51404 A	228	C14H32N2, None, 1,2-Bis-(2-diisopropylaminoethyl) et
21	572	713	631	18936 A	204	C10H24N2O2, 26549-21-3, 1,4-Butanediamine, 2,3-dimethoxy
22	569	740	663	51428 A	267	C11H26NO2PS, 50782-69-9, VX
23	563	732	751	51414 A	533	C28H31ClF3N3O2, None, 1-[[2-[Butylamino]butyl]imino]-7-c

Fig. 2. Sibutramine mass spectrum and the result of search in the mass spectra libraries.

Scan 1151 from \\Saturn2000\hdd saturn2\Saturn\DATA\PRB24665.MS



Spectrum from \\Saturn2000\hdd saturn2\Saturn\DATA\PRB24665.MS
Scan No: 1151, Time: 19.182 minutes
No averaging. Background corrected.
Comment: 19.182 min. Scan: 1151 Chan: 1 Ion: 24999 us RIC: 1217 BC
Pair Count: 114 MW: 0 Formula: None CAS No: None Acquired Range: 50 - 429

Ion	Int	%BP	Ion	Int	%BP	Ion	Int	%BP	Ion	Int	%BP
51	4	1	84	4	1	131	8	2	210	1	0
53	2	0	86	4	1	134	1	0	211	5	1
54	5	1	89	4	1	135	7	2	221	5	1
55	12	3	91	5	1	136	4	1	222	7	2
56	15	4	95	6	1	137	10	2	224	4	1
57	12	3	96	3	1	139	7	2	225	4	1
58	69	17	98	13	3	151	5	1	227	5	1
59	4	1	99	7	2	152	5	1	237	10	2
62	2	0	101	9	2	155	8	2	251	4	1
63	10	2	102	8	2	157	4	1	253	2	0
66	7	2	103	6	1	158	8	2	265	2	0
67	2	0	109	1	0	163	3	1	266	9	2
68	5	1	111	9	2	164	11	3	269	3	1
70	20	5	113	19	5	165	3	1	295	6	1
71	11	3	114	411	100	177	5	1	311	9	2
72	116	28	115	46	11	179	2	0	325	1	0
73	4	1	116	7	2	192	1	0	327	7	2
74	5	1	121	12	3	193	3	1	342	7	2
76	7	2	123	7	2	194	6	1	343	4	1
77	11	3	125	13	3	195	5	1	354	7	2
78	3	1	127	4	1	206	8	2	356	2	0
79	4	1	128	13	3	207	5	1	401	9	2
80	10	2	129	6	1	209	8	2	415	6	1
82	6	1	130	8	2						

Fig. 3. Sibutramine mass spectrum at a concentration of 5 mg/l.

II.2.2 HPLC-DAD-MS Methods

II.2.2.1 HPLC-MS Method

It is presented as a method for determining sibutramine in the injection matrices whose obtaining was described in paragraph 5.2.4.

Program duration: 30 min.

ProStar solvent pumps

Constant flow 500 µl/min of solvent B

ProStar 410 Autosampler

Number of containers – 84 of 2 ml; 3 of 10 ml

Injection syringe volume – 250 µl

Injection loop volume – 100 µl

Volume hose connecting the needle for collecting the sample – 15 µl
Syringe speed – 1µl/ s
Flush volume – 30 µl
Temperature of carousel with samples 40^0C
Use of sample bottle pressure
ProStar 500 column oven
Number of columns – four
Work Column 1 (C8-3)
Column temperature – 35^0C
Stabilization time 0.1 min
Delays after transition 0.1 min
1200L mass spectrometer
ESI ionization type
Ionization type - positive
Scan speed 1 scan/s
Detector voltage – 1480 V
Peak width of the first quadrupole – 0.7 amu
Peak width of the third quadrupole – 0.9 amu
Scan range 50 – 350 amu
Detector ProStar with diode area 335
Acquisition range – 200 to 400 nm
Slit width – 2 nm
Minimum purity level – 220 nm
Maximum purity level – 360 nm
Absorption spectrum acquisition: for each nm from the acquisition field
Display of absorption variation by two wavelenghts: 254 and 280 nm
Noise monitoring by 26 points.

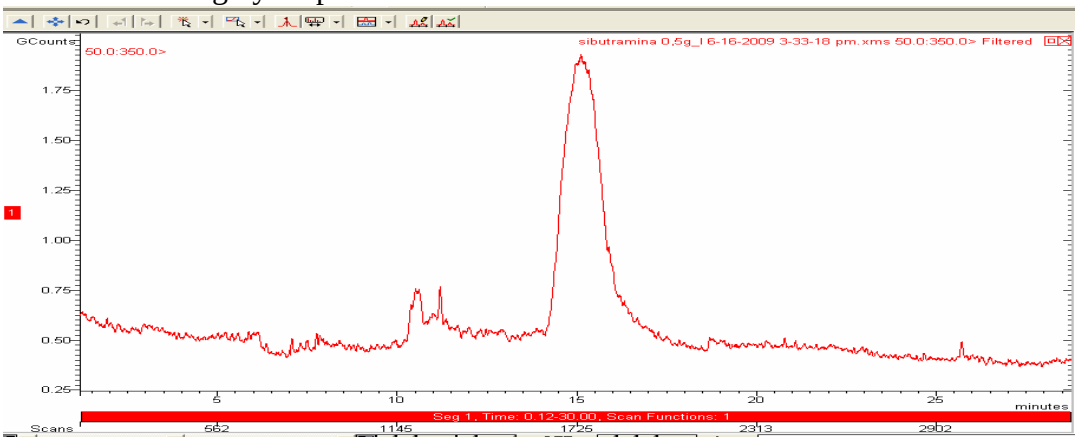


Fig. 4, Total ion chromatogram of sibutramine at 0.5 g/l.

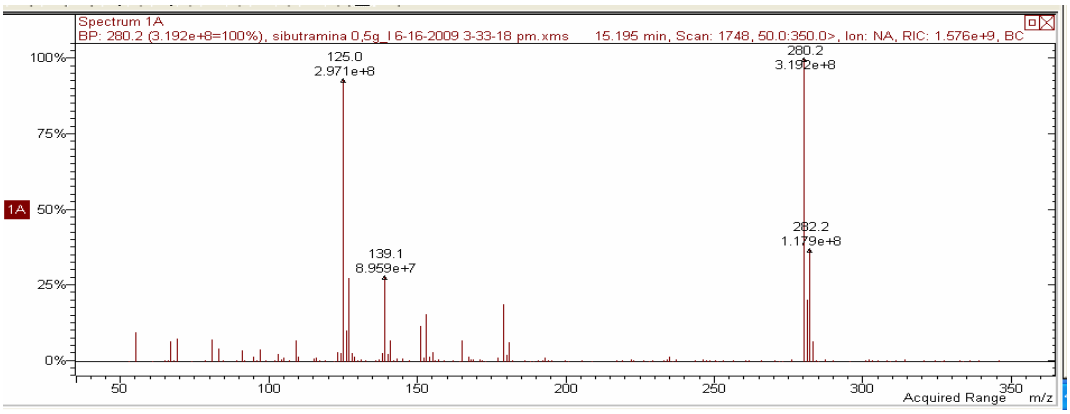


Fig. 5. Sibutramine mass spectrum at 0.5 g/l.

Fig. 6. Mass sibutramine spectrum at 0.5 g/l as compared with that found in the MI spectra library of the HPLC-MS system.

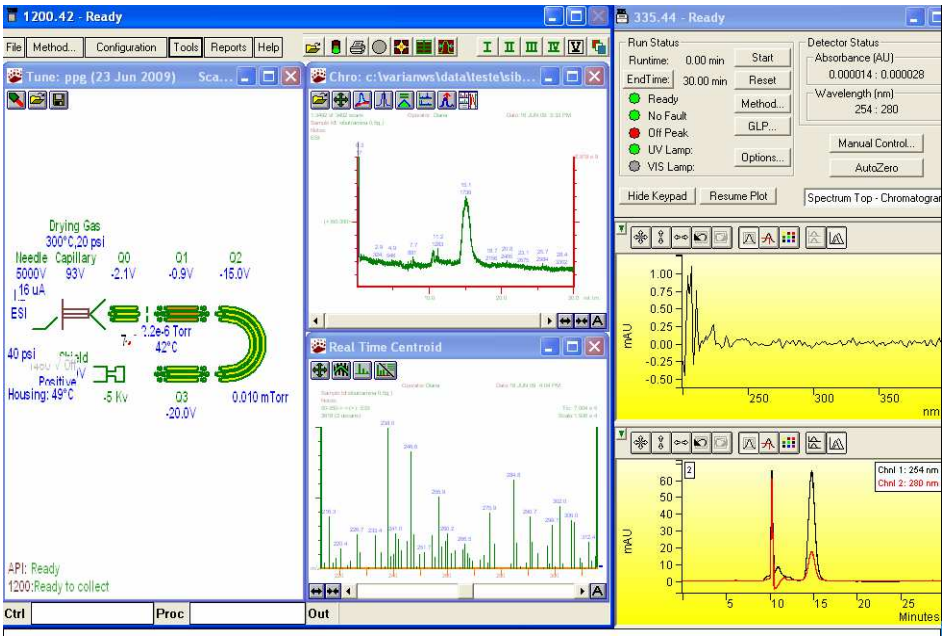


Fig. 7. Total ion chromatogram of sibutramine in a matrix of three solvents compared to a liquid chromatogram obtained at 254 nm (black) and 280 nm (red).

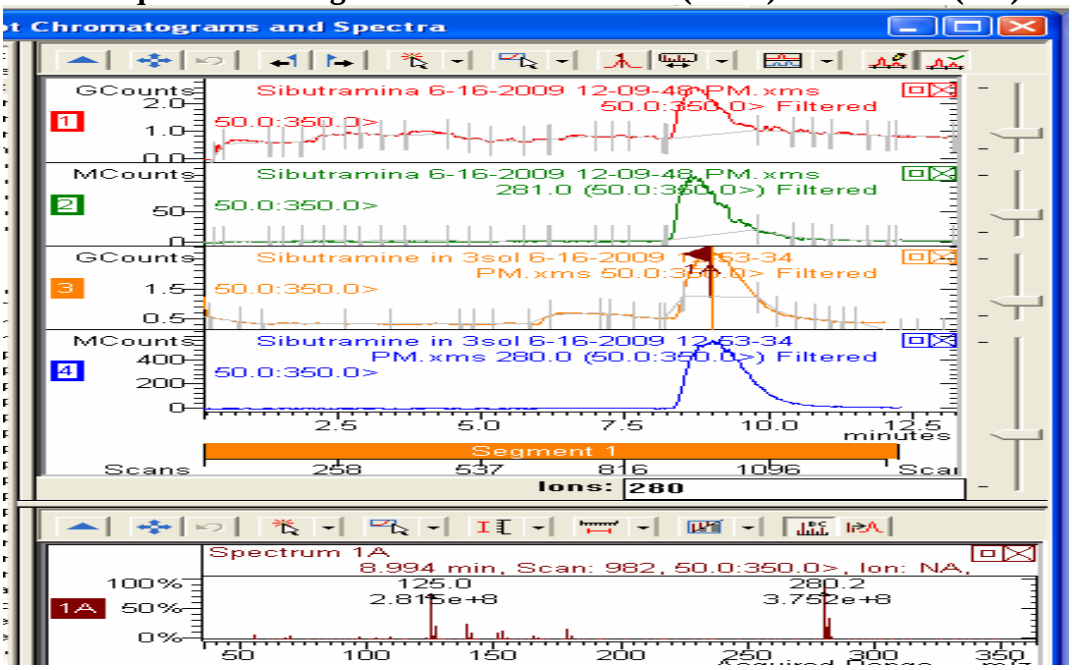


Fig. 8. Total ion chromatograms (tracks 1 and 3) and ion chromatograms 281 (routes 2 and 4) of sibutramine at 0.5 g/l in methanol + acetonitrile matrix (tracks 1 and 2) and three solvent matrix (tracks 3 and 4).

II, 2.2. HPLC MS/MS Method

It is presented as a method for determining sibutramine through the MS/MS technique.

Program duration: 30 min.
ProStar solvent pumps
Constant flow 500 µl/min of solvent B
ProStar 410 Autosampler
Number of containers – 84 of 2 ml; 3 of 10 ml
Injection syringe volume – 250 µl
Injection loop volume – 100 µl
Volume hose connecting the needle for collecting the sample – 15 µl
Syringe speed – 1µl/ s
Flush volume – 30 µl
Temperature of carousel with samples 40^0C
Use of sample bottle pressure
ProStar 500 column oven
Number of columns – four
Work Column 1 (C8-3)
Column temperature – 35^0C
Stabilization time 0.1 min
Delays after transition 0.1 min
1200L mass spectrometer
ESI ionization type
Ionization type - positive

Scan speed 1 scan/s
Detector voltage – 1480 V
Peak width of the first quadrupole – given by calibration
Peak width of the third quadrupole – given by calibration
Step 1 Q_1 -280 amu; Q_3 – 97 amu; with collision voltage: – 10.0 V
Step 2 Q_1 -280 amu; Q_3 – 139 amu; with collision voltage: – 11.5 V
Step 3 Q_1 -280 amu; Q_3 – 153 amu; with collision voltage: – 11.0 V.
Detector ProStar with diode area 335
Acquisition range – 200 to 400 nm
Slit width – 2 nm
Minimum purity level – 220 nm
Maximum purity level – 360 nm
Absorption spectrum acquisition: every 2 nm
Display of absorption variation by two wavelenghts: 254 and 280 nm
Noise monitoring by 27 points.

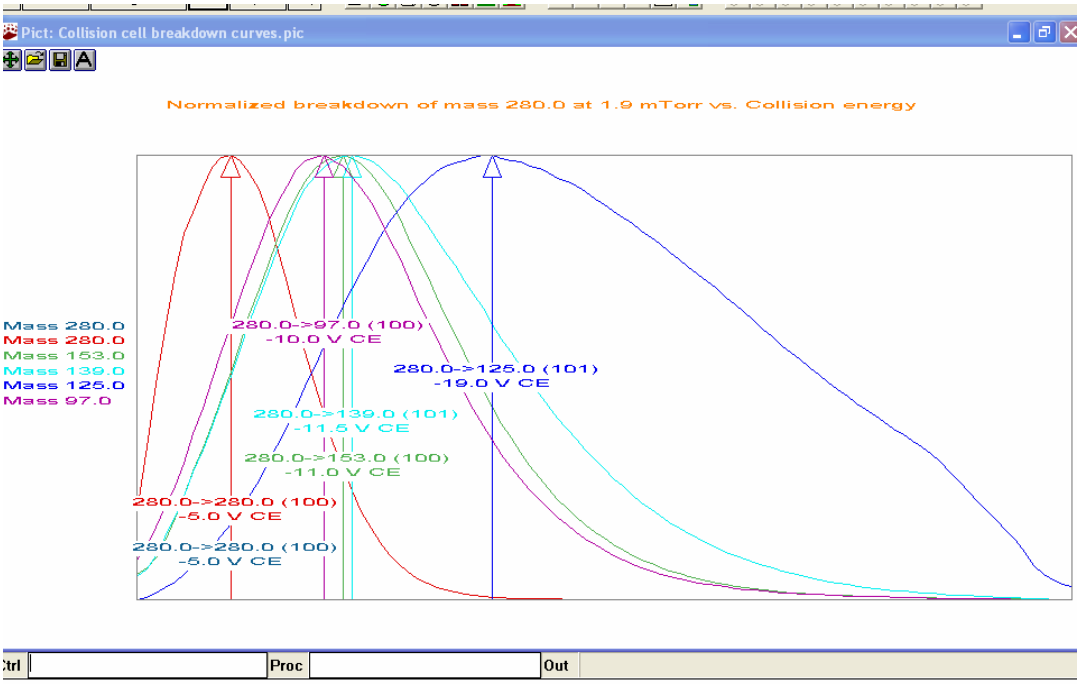


Fig. 9. Result of ion 280 dissociation selected from the mass spectrum of sibutramine.

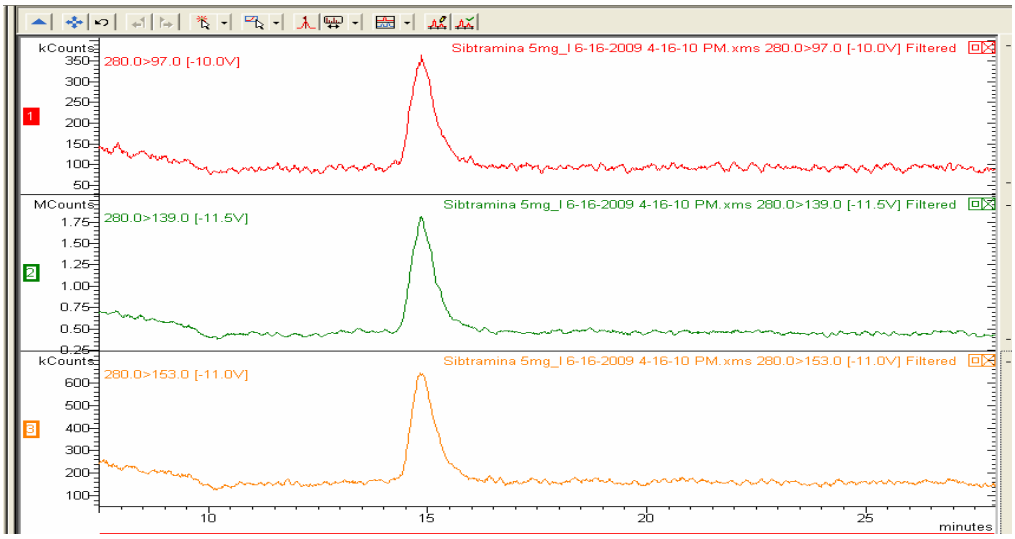


Fig. 10. The MS/MS spectrum of sibutramine in a concentration of 5 mg/l.

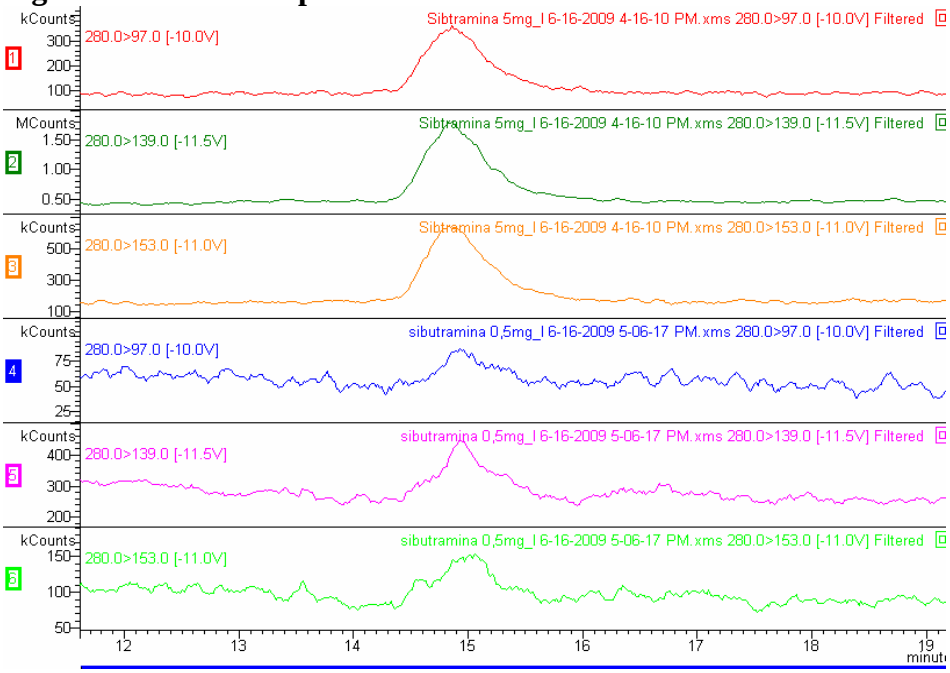


Fig. 11. Comparison between the MS/MS spectrum of sibutramine in concentration of 5 mg/l (tracks 1-3) and that obtained at a concentration of 0.5 mg/l.

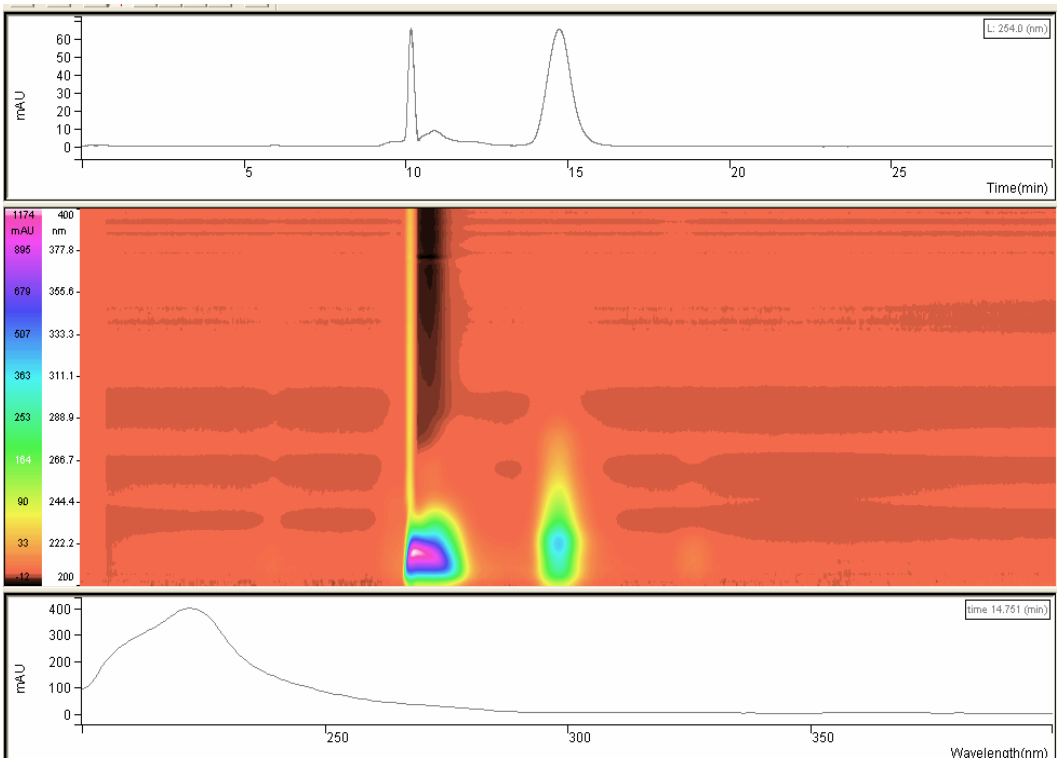


Fig. 12. Liquid chromatocartogram of sibutramine in concentration of 0.5 g/l.

IV. DISCUSSION

IV.1. Pharmacology

IV.1.1. Pharmacological effects

Another characteristic effect of sibutramine is its anorexigenic nature. Amphetamine decreases appetite and facilitates compliance with hypocaloric diet by the obese, helping weight loss.

The effects on the central nervous system are due to their interference at the level of catecholaminergic synapses. Amphetamine releases catecholamines from presynaptic terminals, reduces their uptake in these endings and inhibits their intraneuronal inactivation by monoamine oxidase. Psychomotor stimulation corresponds to an increase in the activity of the ascending reticular activating system, favouring the attentiveness process. Thus, wakeness reactions are amplified and there is a state of alertness in connection with the elective action on noradrenergic neurons, with the release of noradrenaline, with certain central synapses. The anorexigenic effect is due to the hypothalamic feeding center and corresponds to a local release of noradrenaline and dopamine. Stimulation of motility and motor stereotypes, arising from high doses, are assigned to dopamine release in the striated muscle. Psychotic phenomena produced by toxic doses are due to the release of dopamine in the mesolimbic system and to the release of serotonin.

Sibutramine also has sympathomimetic effects, i.e. there is an increase in blood pressure, weak bronchodilation, sphincter contraction and relaxation of the bladder fundus, increase of fatty acid concentration in the plasma.

In patients with narcolepsy sibutramine allows sleep seizure control without changing the state of catalepsy. Its therapeutic benefit lies in delaying in the development of fast sleep.

In the case of hyperkinetic syndrome in children (ADHD), sibutramine is effective especially in school children. The drug produces a decrease in the state of anxiety, motor agitation. The capacity for attention also increases without diminishing the learning process and mitigatess at least in part impulsiveness and behavioural disturbances.

In Parkinson's, the therapeutic benefits consist in reducing rigidity, oculogyric crisis prevention, improved mood and better sleep.

In epilepsy, it has a certain special efficacy regarding Petit Mall crises and antagonizes central depressant unwanted effects.

Amphetamine is readily absorbed in the intestine, being effective if taken orally. It has a half-life of 7-14 hours. It is eliminated through urine, and its metabolism is via the liver. In acidic urine a large quantity of amphetamine is released, as the pH decrease – increases the proportion of the dissociated form.

IV.1.2. Dose administration

Amphetamine use is limited due to its aggressive neuro-central effects. Its psychomotor stimulant effect recommands it for use only in special circumstances that require mandatory increased psychomotor performance and the removal of the feeling of fatigue.

Its dosage is in amounts of 3-6 mg/day 2-3 times a day, the last dose being administered before 4 p.m., to avoid insomnia at night. The usual dose in humans causes mental excitation phenomena with feelings of freshness, fun, initiative, increased concentration, the need to talk, the appearance of fatigue being delayed.

Thus, this “state of well-being” leads to developing tolerance, to phenomena of chronic intoxication, psychiatric disorders and a state of addiction, involving a change from the condition of taking a medicine to that of drug consumer, a background that favours the consumption of other substances with high toxicity as well.

IV.2 Toxicology

Tolerance initially concerns peripheral, sympathomimetic effects, which quickly become progressively weaker and which include a number of effects on nerves + psychomotor stimulation, euphoria, anorexia – and the lethal effect (a person may survive doses of 500 mg to 1 gram, when exitus occurs). Development of tolerance requires progressively higher doses that produce chronic neurotoxic and psychotoxic phenomena - hyperactivity, irritability, tremors, motor stereotypes, mental disorder with delusions and hallucinations similar to those in paranoid schizophrenia.

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