Methylenedioxypyrovalerone: History, Pharmacology, and Analytical Methods

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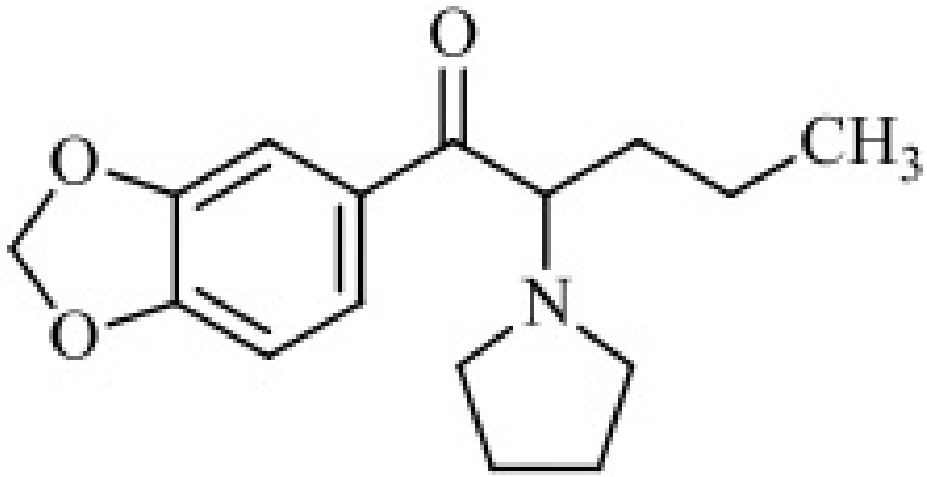
Overview

- MDPV – A synthetic drug of abuse
- History – Short, but definitely not sweet
  - Emergency Scheduling
  - Eventual permanent ban
  - Analogs causing problems
- Pharmacology – A laundry list of physical and psychological effects
  - Are they truly caused by MDPV?
- Analytical Methods
  - GCMS
  - MS/MS
  - HPLC

MDPV Structure



“Bath Salts” – MDPV is Common Component

A Brief History

- MDPV emerged in approximately 2010
- Structurally similar to cathinone, an alkaloid derived from the khat plant native to East Africa and the Arabian Peninsula
- MDPV has no approved medical use in the United States
- On October 21, 2011 MDPV and all its salts, isomers, and salts of isomers were placed under temporary control as Schedule 1 drugs.
- On July 9, 2012, this control became permanent due to the passage of the Synthetic Drug Abuse Prevention Act of 2012.

Circumventing the Laws

- Head Shops, Gas Stations, and Convenience stores still sell these “bath salts” that often contain MDPV
- They are referred to as plant foods, insecticides, research chemicals, and stain removers
- Often labeled as "not for human consumption" in an effort to get around the law.

The Analog Problem

- MDPV is only one of many “bath salt” type drugs
- As soon as one drug (like MDPV) is scheduled, the chemists who manufacture these drugs tweak the structure
- Now a new drug with essentially the same effect as the old, but a slightly different structure, is available that is not scheduled
- Analog laws are not always effective in accounting for these

Pharmacology – How it Operates in the Body

- MDPV is structurally similar to compounds with known pharmacology such as amphetamine and MDMA
- Reuptake Inhibition – increases the levels of extracellular monoamine neurotransmitters like Dopamine and Norepinephrine
- Studies have been performed with rats to determine pharmacological details

Pharmacology Continued

- MDPV belongs to a group of α-pyrrolidinophenone compounds researched in the 1960's and shown to have central stimulant properties.
- Studied in 1971 as a possible treatment for chronic fatigue syndrome
- Never reached market due to their high potential for abuse

Physical Effects

- Tachycardia
- Hypertension
- Vasoconstriction
- Acral Cyanosis
- Arrhythmia
- Palpitations
- Hyperthermia
- Sweating
- Pupil dilations
- Epistaxis
- Muscle Tremor and Spasms
- Hyper-Reflexia
- Rhabdomyolysis
- Seizures
- Respiratory Distress
- Myocardial Infarction
- Cardiovascular Collapse
- Stroke
- Cerebral Edema
- Coma
- **Death**

Behavioral and Mental Status Effects

- Panic Attacks
- Anxiety
- Agitation
- Paranoia
- Hallucinations
- Psychosis
- Aggressive Behavior
- Violent Behavior
- Excited Delirium
- Self-Destructive Behavior
- Self-Mutilation
- Suicidal Ideation
- Memory Loss
- Insomnia
- Anorexia
- Depression

Introduction to the Body

- Administered via snorting, smoking, and intravenous or intramuscular injection
- The average high lasts approximately 6-8 hours with a peak at 90 minutes.
- The average dose is 5-20 mg. (MDMA is 100-150 mg)
- The "come-down" from the drug is described as so unpleasant that users either cease abuse completely or *combine the drug with benzodiazepines or alcohol*

The Problem with MDPV Symptoms

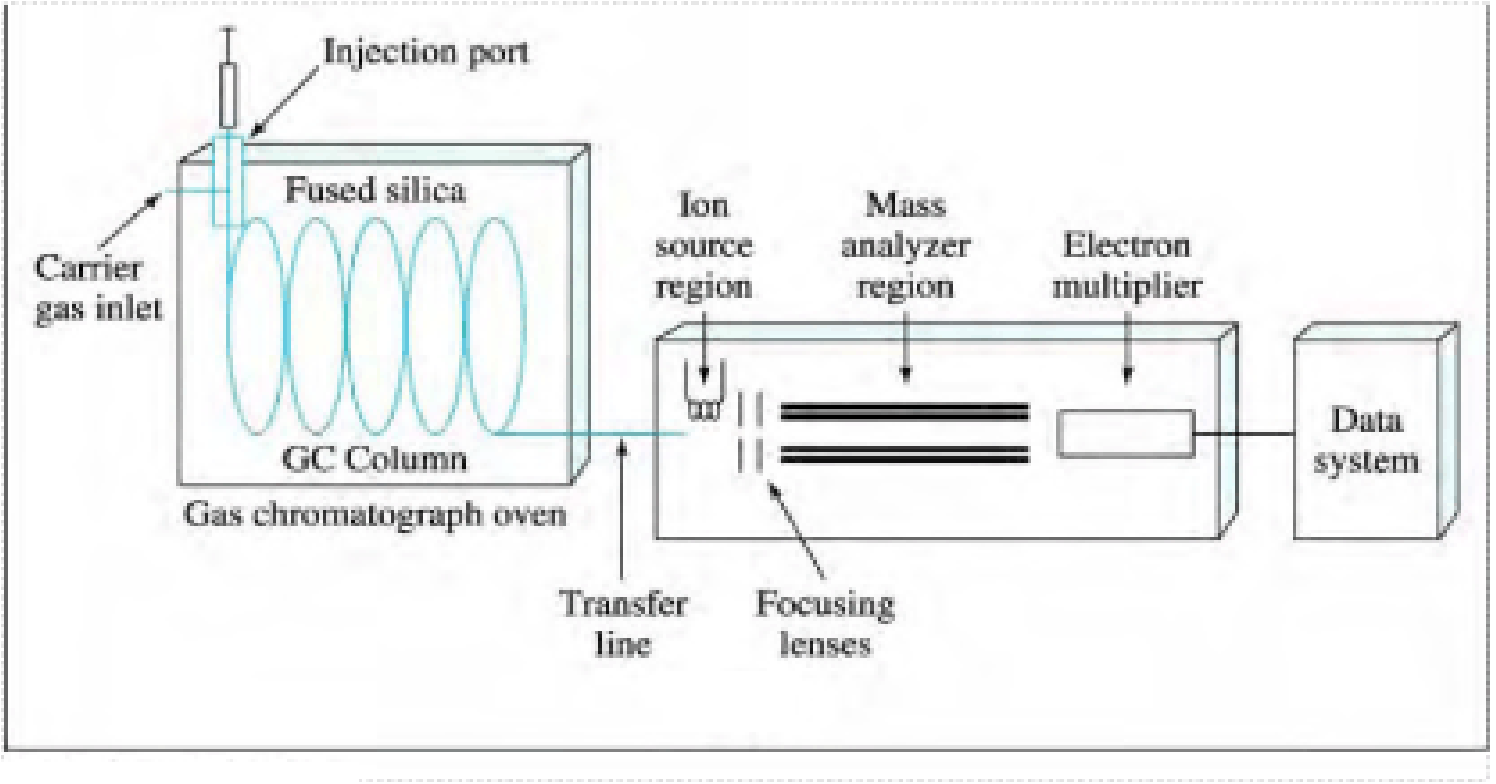
- When MDPV is proposed as the means of an overdose, the abuser had often been taking other drugs or drinking alcohol
  - are the symptoms from the MDPV or the additional drugs/alcohol?
- Further research needed to establish symptoms from only MDPV
- Ethical implications – research cannot really go beyond the anecdotal

Treatment for MDPV Overdose

- Treatment is currently not evidence-based
- Poison control centers often recommend benzodiazepines to treat the sympathetic overstimulation.
- However, since many abusers often mix MDPV with benzodiazepines, this may be ineffective depending on what was taken.
- Benzodiazepines are also recommended due to concern of seizures as a symptom of an OD

Analytical Methods – GCMS

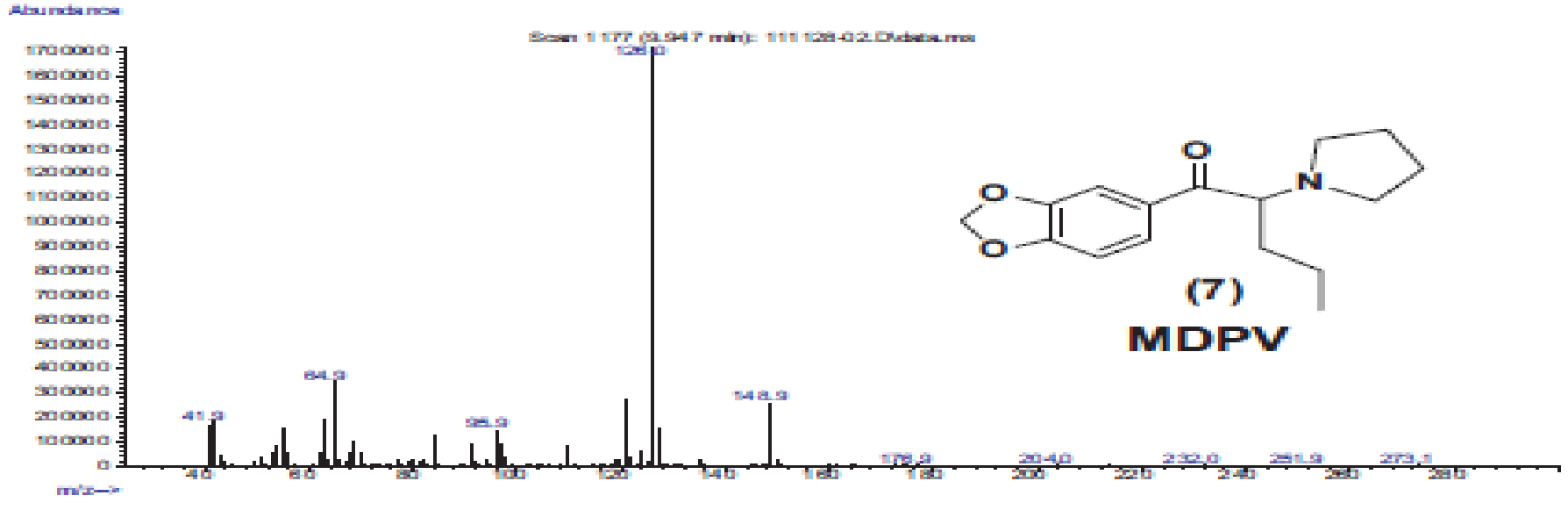
- Gas Chromatography – Mass Spectrometry
- Usually available in most laboratories



The Problem with GCMS

- GCMS has trouble differentiating between compounds with comparable structures (They "break apart" the same way)
- MDPV and other bath salts have many analogs with incredibly similar structures
- As bath salt street samples are often combinations of different drugs, GCMS may not be able to establish which drug is present
- This is a problem as some drugs are illegal while others have yet to be scheduled

GCMS Spectrum – MDPV and Analog



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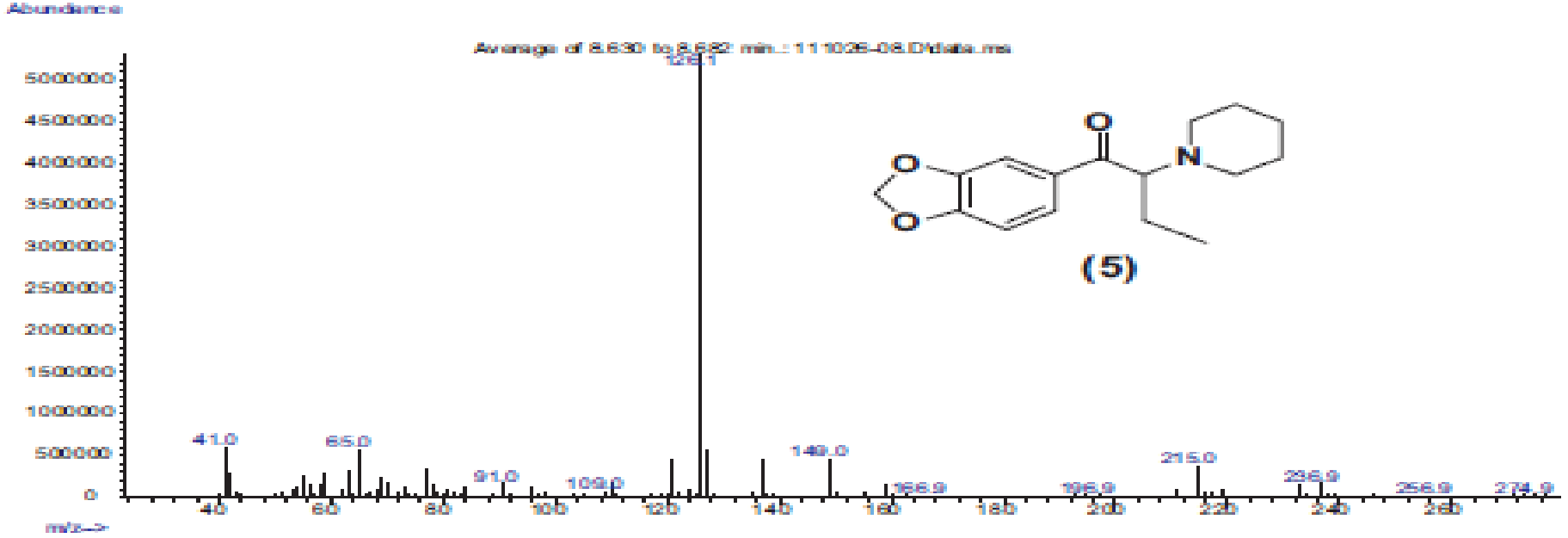
MDPV



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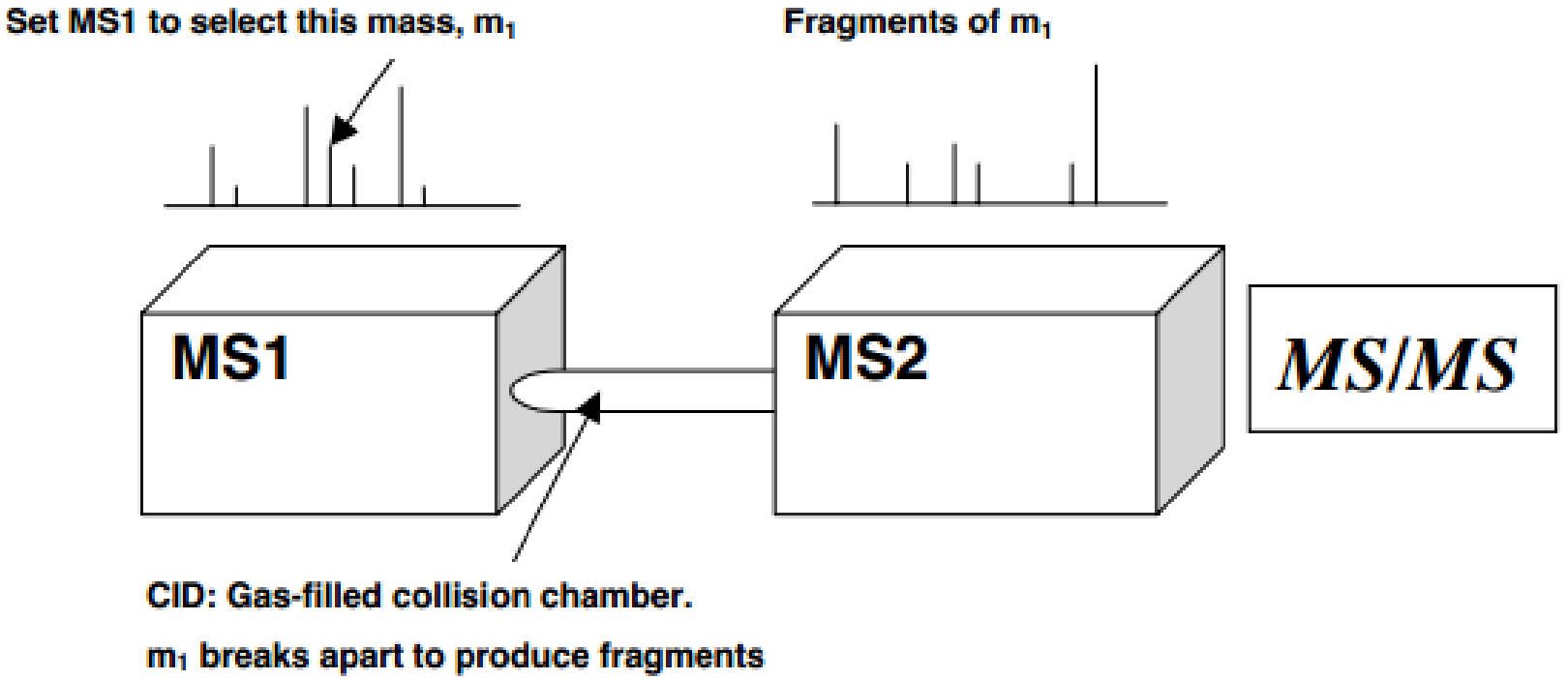
One Potential Solution – Derivatization

- Derivatization allows for differentiation between analogous drug samples
- Derivatization agents usually target one specific functional group on a compound
- This functional group is then converted to a derivate with differing solubility, boiling point, etc from the original
- Since the chemical properties are now different, GCMS will be able to more easily identify analogous compounds

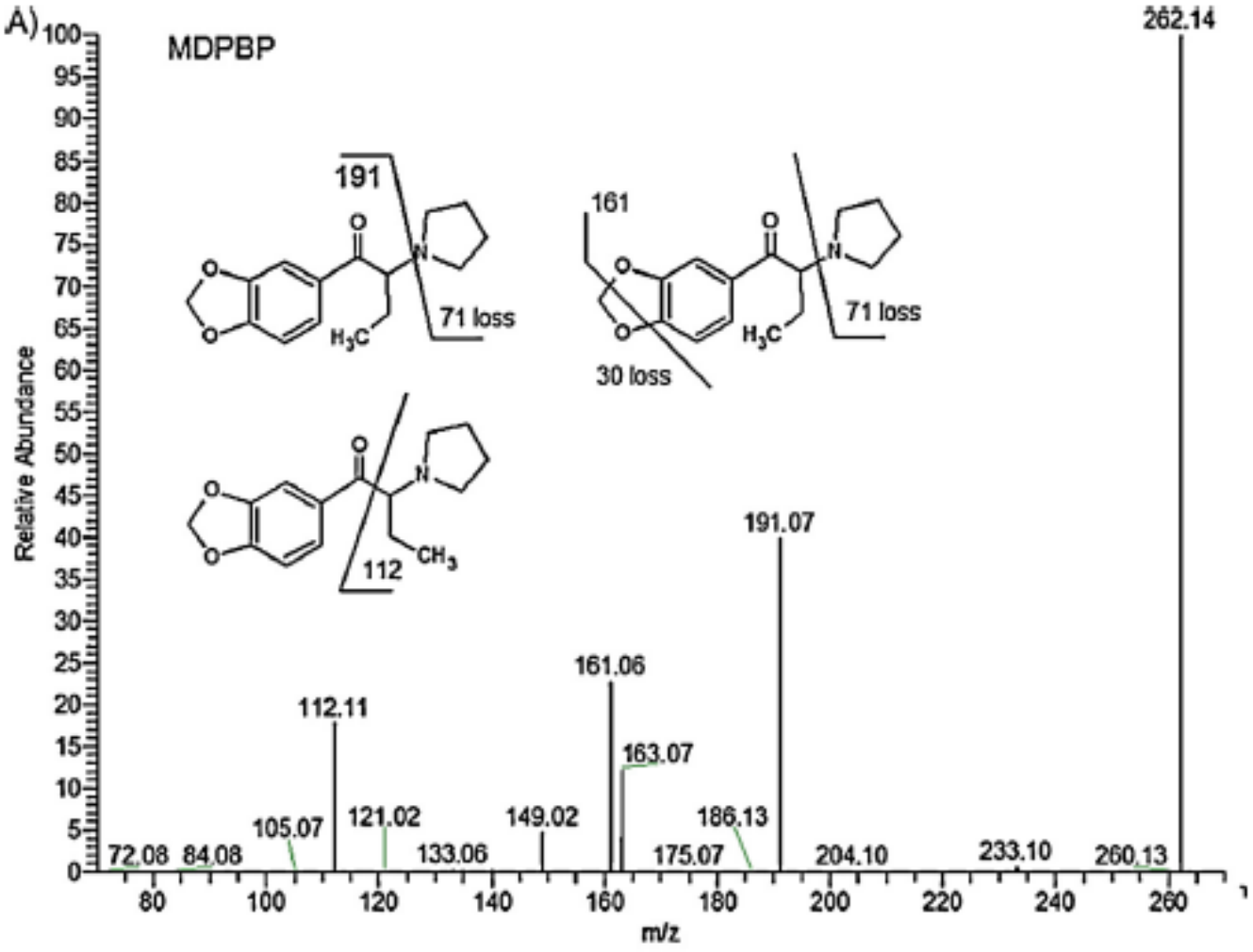
Analytical Methods – MS/MS

- Tandem Mass Spectrometry
- Mass spectrometers are usually combined with separation devices like GC or LC.
- In MS/MS, the separation device is another mass spectrometer
- MS/MS is used for the structural studies of complex molecules

MS/MS Diagram



MS/MS Spectrum



What can be established by MS/MS

- Accurate masses of compounds (depending on resolution, high resolution is needed)
- How the compounds fragment (Product Ions)
- If the masses are accurate enough to establish tentative chemical structures, comparison to a library of known structures can be done to ascertain compound identity

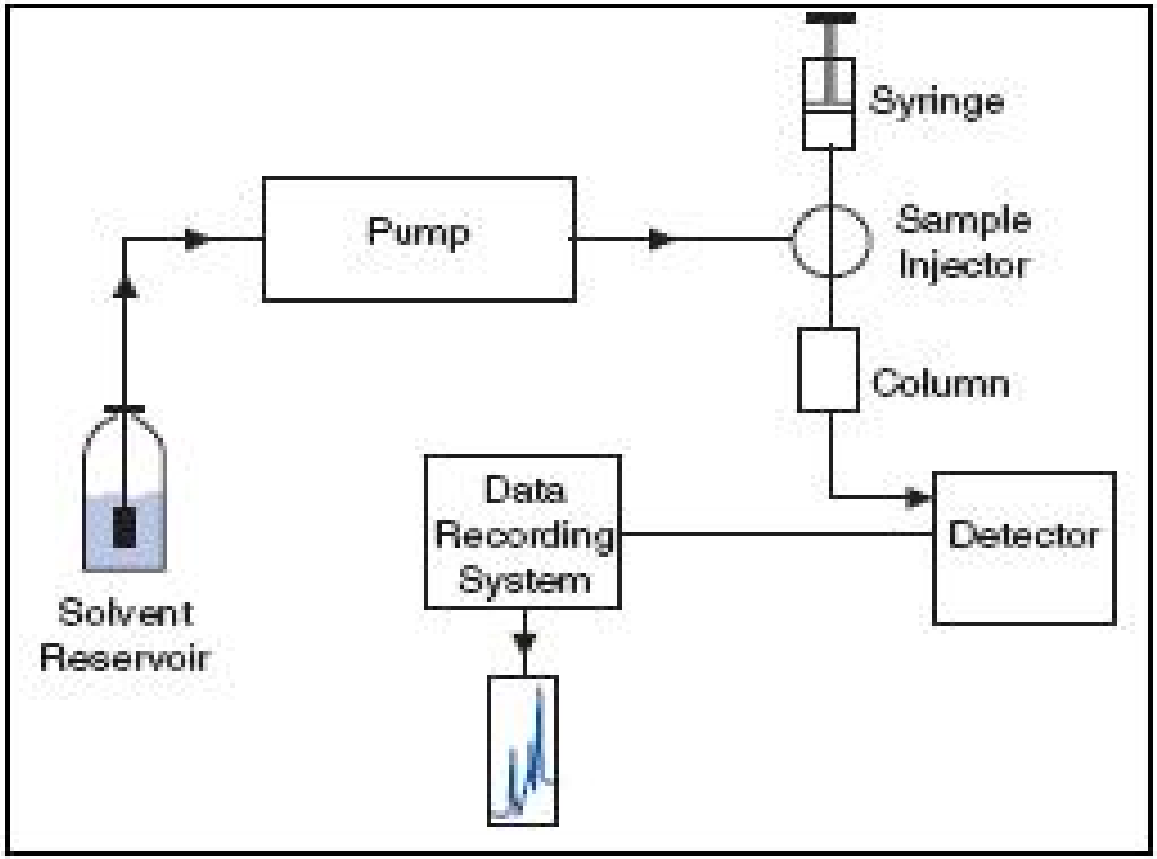
Compound	Measured mass [M+H] (amu)	Theoretical mass [M+H] (amu)	Error (ppm)	Precursor ion [M+H]	Product ion 1	Product ion 2	Product ion 3	Product ion 4
Butylone	N/A	N/A	N/A	222	204	191	174	72
Mephedrone	178.1223	178.1226	1.7	178	160	147	N/A	N/A
Ethcathinone	178.1222	178.1226	2.2	178	160	132	105	N/A
4-FMC	182.0971	182.0976	2.7	182	164	N/A	N/A	N/A
4-MEC	192.1379	192.1383	2.1	192	174	146	119	98
Unknown saccharide	217.0681	217.0680	0.5	217	195	182	165	138
α-PVP	232.1690	232.1696	2.6	232	161	126	105	91
D2PM	238.1584	N/A	N/A	238	221	143	129	117
MDPBP	262.1428	262.1438	3.8	262	191	161	112	72
β-Naphyrone	282.1844	282.1852	2.8	282	211	183	141	126
4-MPPP	218.1533	218.1539	2.8	218	147	119	98	72

The Problem with MS/MS

- MS/MS is only accurate for single-compound samples (pure MDPV, etc)
- Again, bath salt street samples are often mixtures of different drugs
- Running a mixed sample with MS/MS will result in inconclusive data
- Is there a solution?

The Solution – HPLC

- High Performance Liquid Chromatography



Building a GCMS Library

- By combining MS/MS with HPLC, individual components of mixtures can be identified
- If available, standards of these drugs can be purchase and analyzed on GCMS
- An in-house library can be developed that will allow for differentiation in GCMS for future bath salt samples
- Of course, this will be tedious to maintain as new drug analogs are consistently being released

Conclusions

- MDPV has decreased in popularity but remains dangerous nonetheless
- Clandestine labs release unscheduled analogs faster than the law can schedule them
- Treatment is limited and usually based on anecdotal evidence unsupported by research
- GCMS is widely available in labs, but may have difficulty differentiating between drug analogs of MDPV
- MS/MS combined with HPLC has more success but is not as common in labs

Acknowledgements

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