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Research Article

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Solid Phase Extraction and Analysis of THC and Metabolites from Whole Blood using a Novel Automated Procedure using Liquid Chromatography and Tandem Mass Spectrometry (LC-MS/MS)

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Abstract

In this study, solid phase extraction (SPE) is described using a novel automated procedure to isolate tetrahydrocannabininol and its metabolites from whole blood samples. SPE was performed on an automated system after samples of whole blood were precipitated with acetonitrile. The system was programmed to condition the SPE columns with methylene chloride, methanol, de-ionized (DI) water, and aqueous phosphate buffer (0.1 M pH 7). The samples were loaded by the robot after which the SPE columns were washed with DI water, aqueous phosphate buffer and dried also by the same unit. Each SPE column was eluted with a solvent consisting of ethyl acetate/ hexane (50:50 3 mL) containing 2% glacial acetic acid. The elutes were collected, evaporated to dryness and dissolved in mobile phase (100µL) for analysis by LC-MS/MS in positive/negative MRM mode. Chromatography was performed in gradient mode employing a C_{18} column and a mobile phase consisting of acetonitrile and 0.1% aqueous formic acid. The total run time for each analysis was less than 5 minutes.

The limits of quantitation/detection for this method were determined to be 1.0 ng/mL and 0.5 ng/mL. The method was found to be linear from 1 ng/mL to 100 ng/mL (r^2>0.999). Recoveries of the individual cannabinoids were found to be greater than 95%.

Keywords: Cannabinoids; Solid phase extraction; Automation

Abbreviations: THC: Δ^9-tetrahydrocannabinol; THC-A: 11-nor-9-Carboxy-Δ^9-THC; THC-OH: 11-Hydroxy Δ^9-hydroxytetrahydrocannabinol; GC-MS: Gas Chromatograph coupled to Mass Spectrometer; LC-MS/MS: Liquid Chromatography coupled to Tandem Mass Spectrometer; MRM: Multiple Reaction Monitoring

Introduction

For forensic toxicological laboratories, the confirmation and quantification of THC and its metabolite in whole blood are of the highest on their list of requests from enforcement agencies such as District Attorneys and/ or police departments (be they at city, county or state levels). The ability to efficiently extract, and quickly analyze samples of blood submitted by such agencies is definitely seen as a benefit to the laboratory in question. In this new procedure, the efficient extraction of THC and the metabolites via a novel automated solid phase extraction procedure coupled with fast analysis using tandem mass spectrometry coupled to liquid chromatography offers a new direction for laboratories to embark upon in terms of forensic toxicological analysis especially in the area of drugs and driving cases.

It has been reported recently by Farrell et al. [1], that amongst forensic toxicology laboratories cannabis is one of the most frequently encountered drugs in drugs and driving cases. With regard to the reported analyses of THC, THC-A, and THC-OH (Figures 1-3), previous methods have employed the use of liquid-liquid extraction [2], and solid phase extraction (both polymeric and silica based sorbents) [3,4]. These extractions have been followed in the main with GC-MS analysis [5-7] in which the extracts have been derivatized prior to chromatographic separation/analysis. With the advent of affordable tandem mass spectrometers, LC-MS/MS, methods have been published [8-10] in which the need for derivatization has been eliminated and thus saving valuable time for the analytical process.

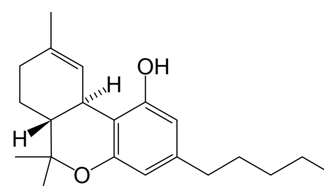

Figure 1: THC Structure.

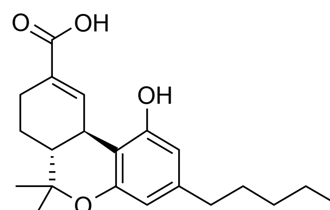

Figure 2: THC-A Structure.

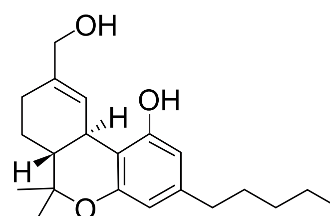

Figure 3: THC-OH Structure.

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In our procedure, we describe the use of an automated system for the extraction of THC and its metabolites from whole blood after off- line acetonitrile precipitation step. This newer automated SPE method coupled with fast LC-MS/MS provides a simple, sensitive, and reproducible quantitative method for the analysis of THC and its metabolites in whole blood. This procedure should be of great assistance to those analysts actively involved with the LC-MS/MS analysis of these drugs in biological matrices as it reduces many of the manual steps involved in the extraction process, thus freeing up valuable analyst time for other activities including overnight operation.

Materials and Methods

Reagents and materials

THC, THC-D3, THC-A, THCA-D3, THC-OH, and THC-OH-D3, respectively were supplied as liquid standards from 1.0 mg/mL solutions (Lipomed, Cambridge MA). Acetonitrile, acetic acid (glacial), ethyl acetate, hexanes (containing >99% n-hexane), methylene chloride and methanol were obtained from Fisher Scientific (Pittsburgh, PA). Phosphate buffer (0.1 M, pH 7) was purchased ready prepared from Fisher Scientific. Formic acid was obtained from Acros Chemicals (via Fisher Scientific) All chemicals were of ACS grade. Solid phase extraction columns (CSTHC (6mL, 200 mg)) were obtained from UCT, Inc., (Bristol PA). Solid phase extraction (SPE) was performed using Janus® Automated Workstation System (Perkin-Elmer, Waltham, Mass.) operated under WinPREP for Janus version 4.8.113 software (supplied by Perkin-Elmer).

Formic acid was made up as a 0.1% (v/v) solution by the addition of 1 mL of the acid to 900 mL of DI water and diluting to 1 L. Acetonitrile containing 0.1% (v/v) was made up by adding 1 mL of formic acid to 900 mL of acetonitrile and diluting to 1 L with the same solvent.

Chromatographic analysis

Analysis was performed using an API 3200 Q-Trap instrument supplied by Applied Biosystems (Foster City CA). The chromatographic system consisted of a Shimadzu CBM 20 A controller, two Shimadzu LC 20 AD pumps including degasser, a Shimadzu SIL 20 AC autosampler, and a Shimadzu CTO AC autosampler compartment (set at 10°C), the instrument was fitted with an Imtakt US-C_{18} column (50 x 2 mm (5 µm)) from Silvertone Sciences (Philadelphia, PA), and was attached to a Unison US- C_{18} guard column (5.0 x 2mm) which was obtained from the same supplier. The liquid chromatography column was maintained at 30°C throughout the analyses. The injection volume was 10 µL. The mobile phase consisted of solvent **A**: DI water containing 0.1% formic acid and solvent **B**: acetonitrile containing 0.1% formic acid, delivered at a flow rate of 0.55 mL/minute. The program was initiated at: 50% acetonitrile rising to 90% in 1.5 minutes. The proportion of acetonitrile was held at 90% for until 1 minute after which it was lowered to 50% in 1 minute and held at this level for a further 2 minutes. The instrument was readied for re-injection after 4.5 minutes.

The mass spectrometry performed on an API 3200 QTRAP using both positive/negative MRM modes. The following transitions were monitored in the negative MRM mode (quantification ions underlined): m/z 343.1 → 299.3 and 245.3 for THC-A, and m/z 346.1 → 302.3 and 248.3 for THCA-D3. The following conditions were employed: curtain gas 15, collision gas medium, ion spray voltage -4500V, temperature 650°C, ion source gas(1) 50, ion source gas (2) 50. Positive MRM mode was employed for THC/THC-D3, THC-OH/THC-OH-D3, respectively under the following conditions: curtain gas 15, collision gas medium, ion spray voltage 4500 V, temperature 650°C, ion source gas(1) 50, ion source gas (2) 50. The following transitions were monitored (quantification ions underlined): m/z 315.2 → 193.2 and 123.1 for THC, and m/z 318.2 → 196.2 and 123.1 for THC-D3. THC-OH and THC-OH-D3 were monitored at the following transitions (quantification ions underlined): m/z 331.4 → 193.1 and 201.2 for THC-OH and m/z 334.2 → 196.2 and 133.1 for THC-OH-D3. The data was collected using Analyst Software Version 1.5.2. The mass spectrometric conditions are shown in table 1. Positive confirmation of the cannabinoids was based upon peak retention time and the ratios of the MRM. Retention time had to be within 0.2 minutes of the lowest calibration standard, and ratio of the two transitions had to be less than 25%.

Calibrators and controls

A solution of THC, THC-OH, and THC-A, was prepared at concentrations of 1 µg/mL by the dilution of the stock solution with acetonitrile to 10 mL in a volumetric flask. A solution of THC-D3, THC-A-D3, and THC-OH-D3 were prepared similarly by the dilution of the individual stock solutions to 10 mL with acetonitrile using a separate volumetric flask.

Calibrators were prepared by the addition of 0 µL, 0.5 µL, 1 µL, 5 µL, 10 µL, 25 µL, 50 µL and 100 µL of THC, THC-A, and THC-OH solution (1 µg/mL) to 1 mL samples of drug free whole blood. To the calibrators were added 10 µL of the deuterated internal standards (THC-D3, THC-A-D3, THC-OH-D3 (1 µg/ mL)). Control samples were prepared by the addition of 4 µL and 15 µL of THC, THC-A, and THC-OH solution (1 µg/ mL), respectively to 1 mL of drug free whole blood along with 10 µL of the internal standard solution. All determinations were performed in duplicate. The dynamic range of analytes was set to reflect the typical range of concentrations of the cannabinoids regularly observed at the Massachusetts State Police Crime Laboratory.

In this project 10 case samples (1 mL) were treated in exactly the same fashion as calibrators with respect to the addition of internal standards. All analyses were performed in duplicate.

Sample pretreatment

For preparation of the samples for automated SPE, to each sample

Table 1: Tandem Mass Spectrometric conditions.

Compound	Q1	Q3	DP/ volts	EP /volts	CEP /volts	CE/ volts	CXP /volts
THC (1)	315.2	193.2	46	4	18.8	29	4
THC (2)	315.2	123.1	46	4	18.8	45	4
THC-D3 (1)	318.2	196.2	46	4	18.8	29	4
THC-D3 (2)	318.2	123.2	46	4	18.8	43	4
THC-OH (1)	331.4	193.1	46	4	19.2	35	4
THC-OH (2)	331.4	201.1	46	4	19.2	45	4
THC-OH-D3 (1)	334.2	196.2	46	4	19.3	37	4
THC-OH-D3 (2)	334.2	133.1	46	4	19.3	33	4
THCA (1)	343.1	299.3	-60	-4.5	-18	-28	-20
THCA (2)	343.1	245.3	-60	-4.5	-18	-38	-20
THCA-D3 (1)	346.1	302.3	-65	-4	-18	-28	-20
THCA-D3 (2)	346.1	302.3	-65	-4	-18	-28	-20

Note: Q1 = Precursor Ion; Q3= Product Ion; DP= Declustering Potential; EP= Entrance Potential; CEP= Collision Entrance Potential; CE= Collision Energy; CXP= Collision Exit Potential

of blood (1 mL) was added 2 mL of cold acetonitrile, this was achieved by drop wise addition of the solvent using a disposable pipette whilst the sample was vortex mixed. Following addition of the acetonitrile, the sample was further vortex mixed for approximately 1 minute. Each sample was then centrifuged at 5000 rpm for 10 minutes to separate blood precipitants from the acetonitrile.

Following centrifugation, the acetonitrile phase was transferred manually into individual, clean glass tubes. The solvent was evaporated to approximately 200 µL using a Turbovap® evaporator (Caliper Life Sciences, Framingham MA (now Biotage)) set at 40°C and employing nitrogen as the drying gas. To each tube was added 5 mL of 0.1 M phosphate buffer (pH 7) and the samples were vortex mixed for approximately 0.5 minutes, and then transferred to workstation.

Automated solid phase extraction

At the initiation of the SPE program, the solvent lines of the SPE workstation were purged with 8 mL of methanol. These solvents were aspirated to waste before the conditioning steps were initiated. Each SPE column was conditioned by the sequential addition of : 1 x 3mL of methylene chloride, 1 x 3 mL of methanol, 1 x 3 mL of DI water, and 1 x 1 mL of 0.1 M phosphate buffer (pH 7), respectively. Each liquid was programmed to percolate through the sorbent without the sorbent drying out between additions of the liquids. This was achieved with a slight vacuum applied.

After the phosphate buffer had passed through the SPE column, each sample was loaded on to an individually marked SPE column using an individual disposable tip and aspirated through the sorbent under the program conditions (1 mL/minute). After the final aliquot of sample, the disposable tip was ejected into a bio-hazard container by the automated workstation. The columns were then washed with: 1 x 3 mL of DI water followed by 1 x 3 mL of 0.1 M phosphate buffer (pH 7) and dried under full vacuum for 10 minutes.

Prior to elution, the solvent lines of the automated work station were washed with 8 mL of methanol, then 8 mL of the elution solvent (hexane/ethyl acetate solvent mixture (50: 50 (v/v) containing 2% acetic acid)) and diverted to waste. The SPE columns were then eluted with 3 mL of this elution solvent. After the elution step, the solvent lines on the automated SPE work station were flushed with 8 mL of methanol. The steps for the automated SPE are shown in table 2.

The eluent from each SPE column was evaporated to dryness using a gentle stream of nitrogen at 40°C, after which the samples were dissolved in 100 µL of a solution consisting of 95% mobile phase solvent A and 5% mobile phase solvent B for analysis by LC-MS/MS, representative chromatograms of the negative control and blood containing the cannabinoids and internal standards are shown in figures 4-5.

Selectivity

In the analysis of whole blood samples via SPE and LC-MS/MS it is essential to ensure that the interfering effects of other drug compounds can be eliminated. In this procedure, whole blood (1 mL) was spiked with a mixed drug "cocktail" at a concentration of 500 ng/mL: (bupropion, lidocaine, methadone, amitriptyline, nortriptyline, thioridazine, trazodone, mesoridazine, pethidine, diphenhydramine, phenyltoloxamine, imipramine, desipramine, benztropine, trimethoprim, diltiazem, haloperidol, strychnine, morphine,

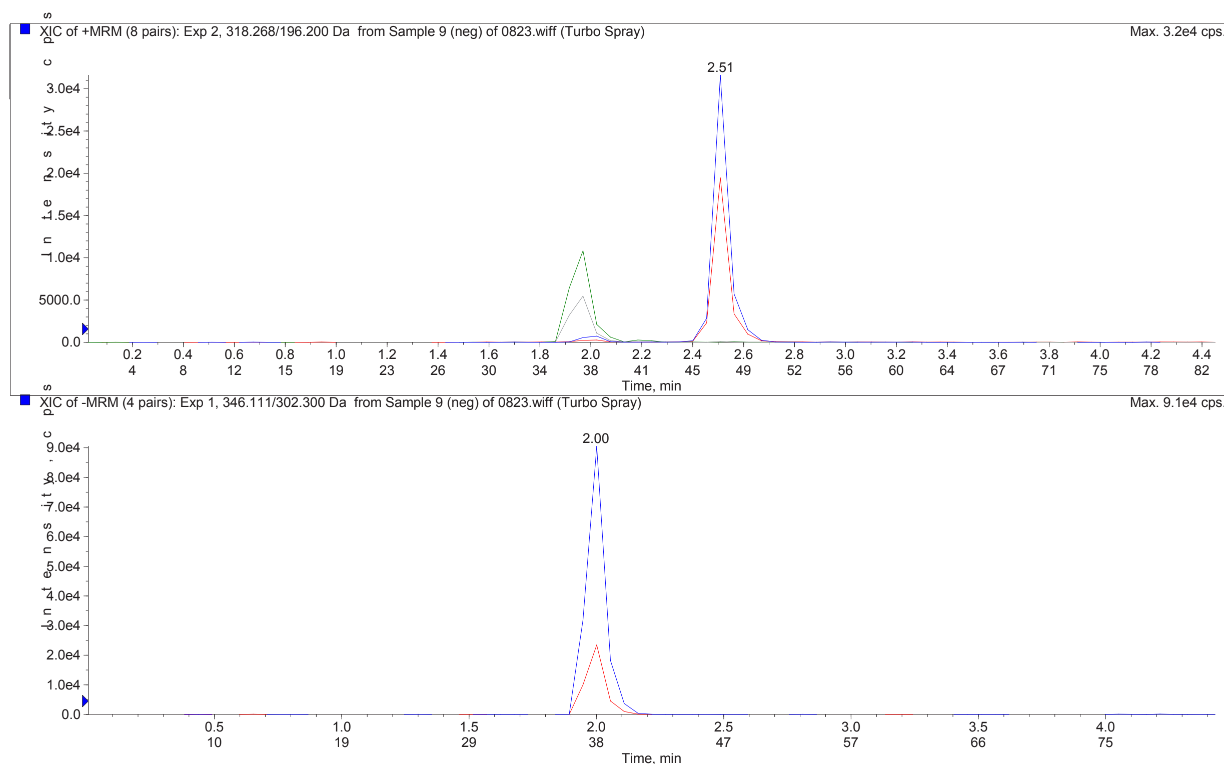

Figure 4: Chromatogram of SPE extract of whole blood (Negative Control). Upper Trace: THC-OH-D3, THC-D3. Lower Trace: THC-A-D3.

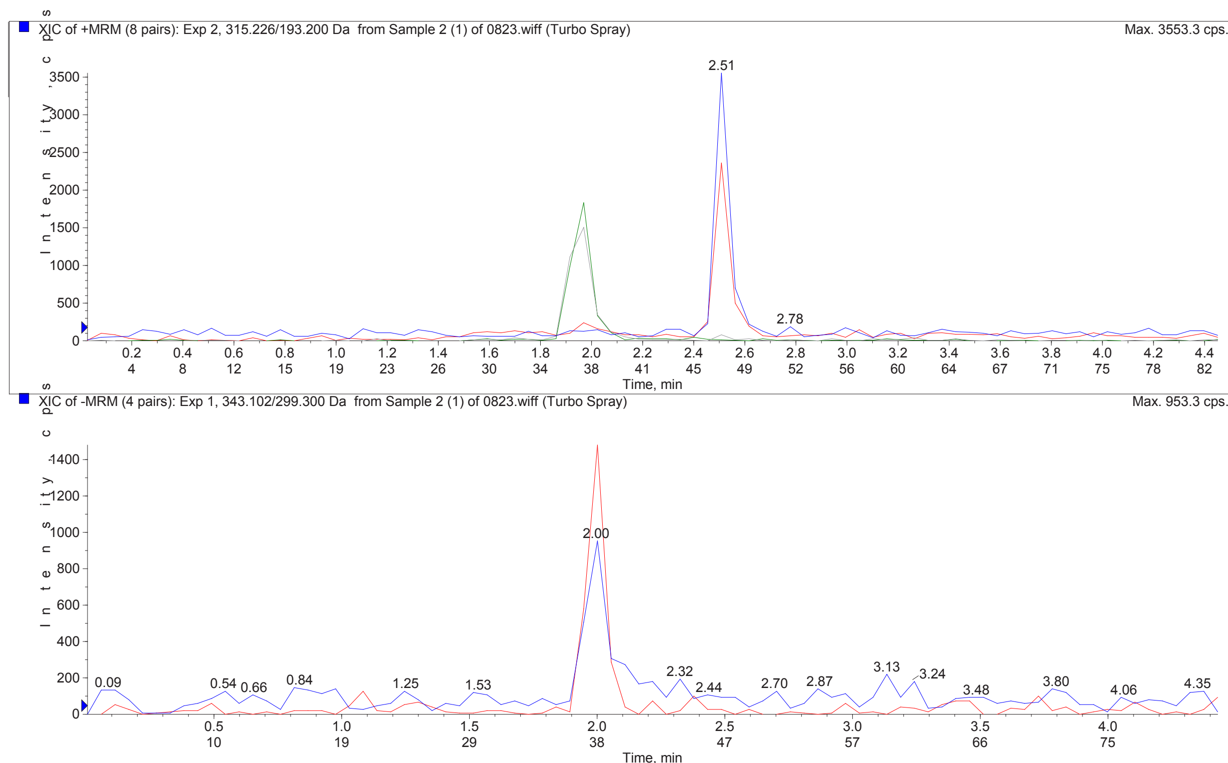

Figure 5: Chromatogram of THC/ THCA/THC-OH at LOQ (1 ng/ mL). Upper Trace: THC-OH, THC. Lower Trace: THC-A.

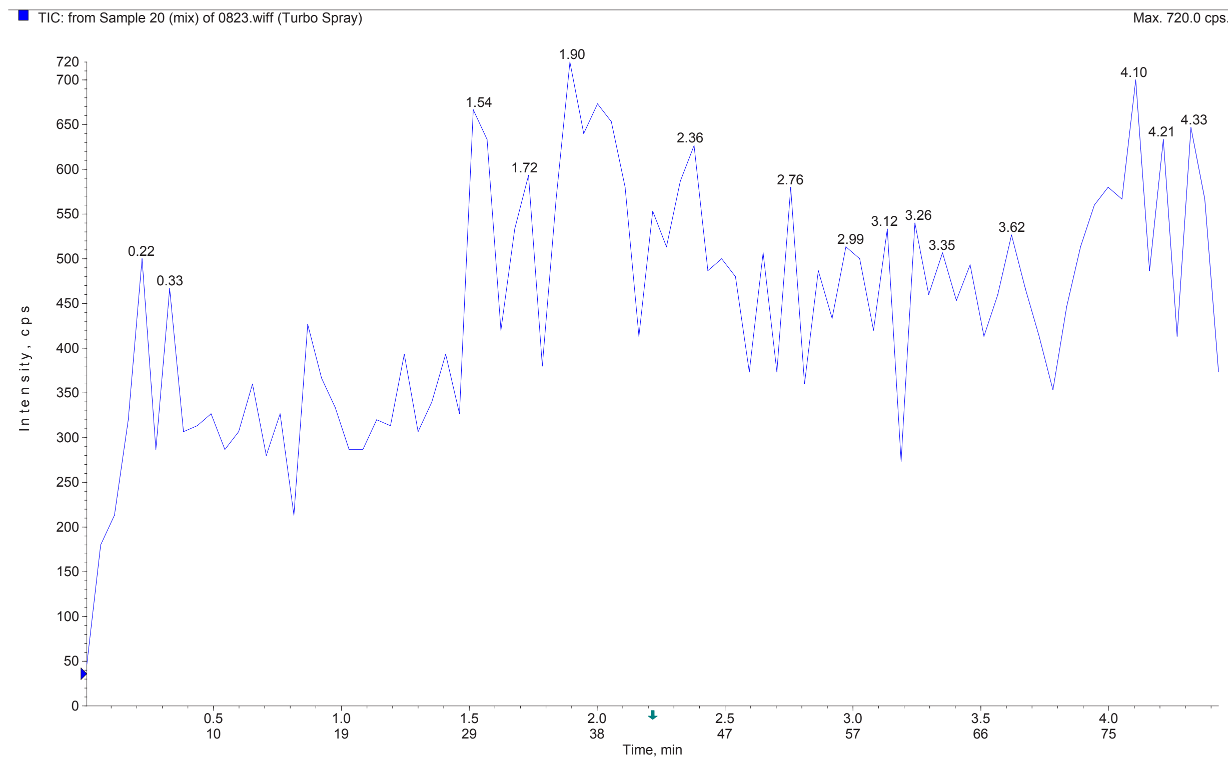

Figure 6: Chromatogram of whole blood spiked with cocktail of drugs run at cannabinoid MRM's.

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Table 2: Results of 10 re-analyzed cases.

Case	THC/ (ng/ mL)	THC-OH (ng/ mL)	THCA/ (ng/mL)
1	0	0	11
2	1.3	1.5	8.3
3	<LOQ	<LOQ	11
4	0	0	5.1
5	1.1	1.2	11
6	0	0	55
7	1.3	1.7	33
8	1.9	2.5	22
9	2.3	2.9	23
10	1.5	1.9	30

codeine, 6-acetylmorphine, oxycodone, oxymorphone, hydrocodone, noroxycodone, hydromorphone, diazepam, nordiazepam, oxazepam, temazepam, alprazolam, α-hydroxyalprazolam, lorazepam, triazolam, α-hydroxytriazolam, flunitrazepam, 7 amino-flunitrazepam, chlordiazepoxide, midazolam, α-hydroxymidazolam, flurazepam, desalkyl-flurazepam, cocaine, ecgonine methyl ester, ecgonine ethyl ester, benzoylecgonine, cocaethylene, clonazepam, 7 amino-clonazepam, gamma butyrolactone (GBL), 1, 4 butane diol (1,4, BD), and gamma valerolactone (GVL)) and extracted according to the SPE method. It was observed that the interfering effect of these compounds was not found to be significant (Figure 6).

Matrix effects

Studies into the matrix effects were performed according to a previously published procedure [11]. In this part of the study, aliquots of a solution containing THC, THC-A, and THC-OH (covering the linear range) were evaporated to dryness, dissolved in mobile phase and analyzed by LC-MS/MS (**A**). Concurrently, a set of drug free blood samples were subjected to the SPE process noted, after elution of the SPE columns, the elution solvent was spiked with a solution containing THC, THC-A, and THC-OH and evaporated to dryness. The residues were dissolved in mobile phase for analysis by LC-MS/MS. (**B**). A second set of blood samples samples were spiked with a solution containing THC, THC-A, and THC-OH and processed via the SPE method. After elution these samples were analyzed by LC-MS/MS(**C**). The data (peak areas) for A, B, and C were collected by Analyst 1.5.2. By comparing the peak areas of B with those of A an assessment of matrix effects was made. These data are shown later. The comparison of peak areas for C with B provided data for the recoveries (shown later).

A solution containing THC, THC-OH, and THC-A (concentration: 50ng/mL, and 500 ng/mL) was infused into the tandem mass spectrometer using the onboard syringe pump (controlled by Analyst 1.5.2 software) via a Hamilton syringe (model# 1001TTL, volume =1 mL) (supplied by Fisher Scientific) at a flowrate of 5 μL/minute. At the same time as the solution of THC/THC-A/THC-OH was flowing into the mass spectrometer, a 10 μL aliquot of the SPE extracted blood in mobile phase (100 μL) was injected using the autosampler syringe on the Shimadzu liquid chromatograph. The liquid chromatograph and mass spectrometer were arranged so that samples from the liquid chromatograph were mixed into the flow of THC/THC-A/THC-OH solution in a 3 port "T" section before the total flow entered the mass spectrometer. Any suppression/enhancement effects could be monitored at the MRMS's for THC/THC-A/THC-OH and the deuterated analogues. Chromatograms of the results are shown in figures 7 and 8.

Results

Recovery

It was found that for samples spiked at 4 ng/mL and 15 ng/mL, levels of 4.1 ± 0.3 ng/mL (THC-OH), and 4.2 ± 0.4 ng/mL (THC), 3.9 ± 0.4 ng/mL (THC-A) , 15.3 ± 1.9 ng/mL (THC-OH), and 15.1 ± 1.9 ng/mL (THC), and 14.8 ± 1.5 ng/mL were obtained. This indicates a recovery of 96 ± 2%, (THC), 97 ± 3 %,(THC-A), and 96 ± 3%,(THC-OH) i.e. greater than 95% overall.

Precision

Intra and inter-day imprecision was less than 6 % and 11%, respectively for THC and less than 4% and 9%, respectively for THC-A and 6%and 10%, respectively for THC-OH. This method was found to be linear (r^2>0.999) over the dynamic range 0 to 100 ng/mL for THC, THC-A, and THC-OH, respectively (Figures 9-11).

Matrix effects

It was found that the matrix effects were not observed to be significant (<6% for all 3 types of cannabinoids). Ion suppression was also not found to be significant (<5%).

LOD/LOQ

The limit of detection (LOD) of a particular method can be defined as the level at which the signal to noise ratio for the particular analyte is greater or equal than 3:1. The limit quantification (LOQ) for the method is the level at which the signal to noise ratio for a particular analyte is greater than or equal to 10:1. In this project, LOD and LOQ were determined empirically by extracting analytes via SPE at decreasing concentrations until an LOD and LOQ were obtained, these values were 0.5 and 1.0 ng/mL, respectively (Figure 5).

Tandem mass spectrometry

This project was aimed at introducing a more efficient methodology to the forensic community involved in toxicological analyses. With this in mind, sensitivity i.e. the ability to detect low levels of analytes is highly important, it was found that although THC-A can be detected using the tandem mass spectrometer in positive MRM mode, sensitivity is increased by altering the mode from positive into negative mode. As the THC-A is eluted just before THC-OH on the analytical LC column, which is well separated from the THC (Figures 5 and 12), the system was programmed to run in both negative and positive MRM mode simultaneously, thus all 3 cannabinoids and their deuterated internal standards could be determined and measured.

SPE

Currently, there is no adapter to perform the acetonitrile precipitation step on the workstation and this must be performed manually. For each sample, a period of 2 minutes is required. Sample centrifugation and evaporation takes less than 10 minutes, but all samples are treated concurrently. The samples are loaded onto the Janus® Automated Workstation after dilution has been performed and are placed in pre-programmed positions. Although up to 40 samples are able to be processed in one session, this project looked at 10 positive cases as an example of the coupling of an automated SPE system with LC-MS/MS for the analysis of THC and metabolites.

The Janus® automated workstation contains all the conditioning, wash and elution solvents required for solid phase extraction, thus

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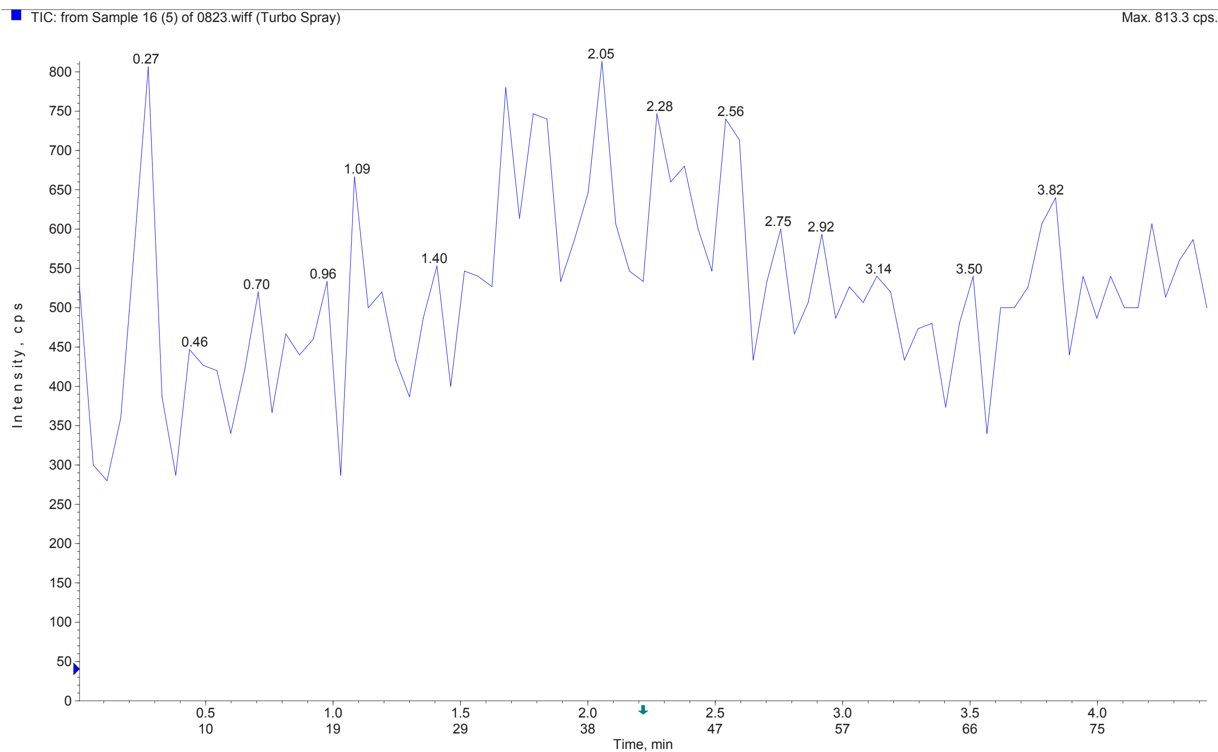

Figure 7: Chromatogram of matrix ion suppression/ enhancement effects at 50 ng/mL.

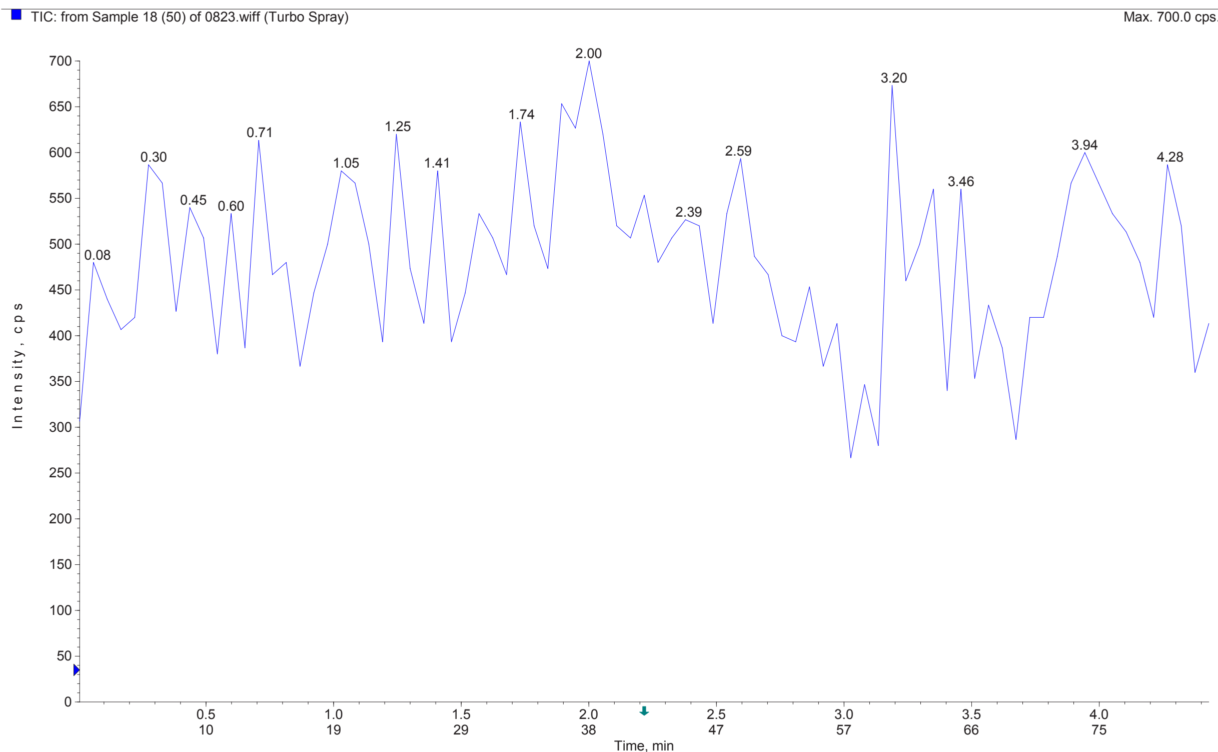

Figure 8: Chromatogram of matrix ion suppression/enhancement effects at 500 ng/mL.

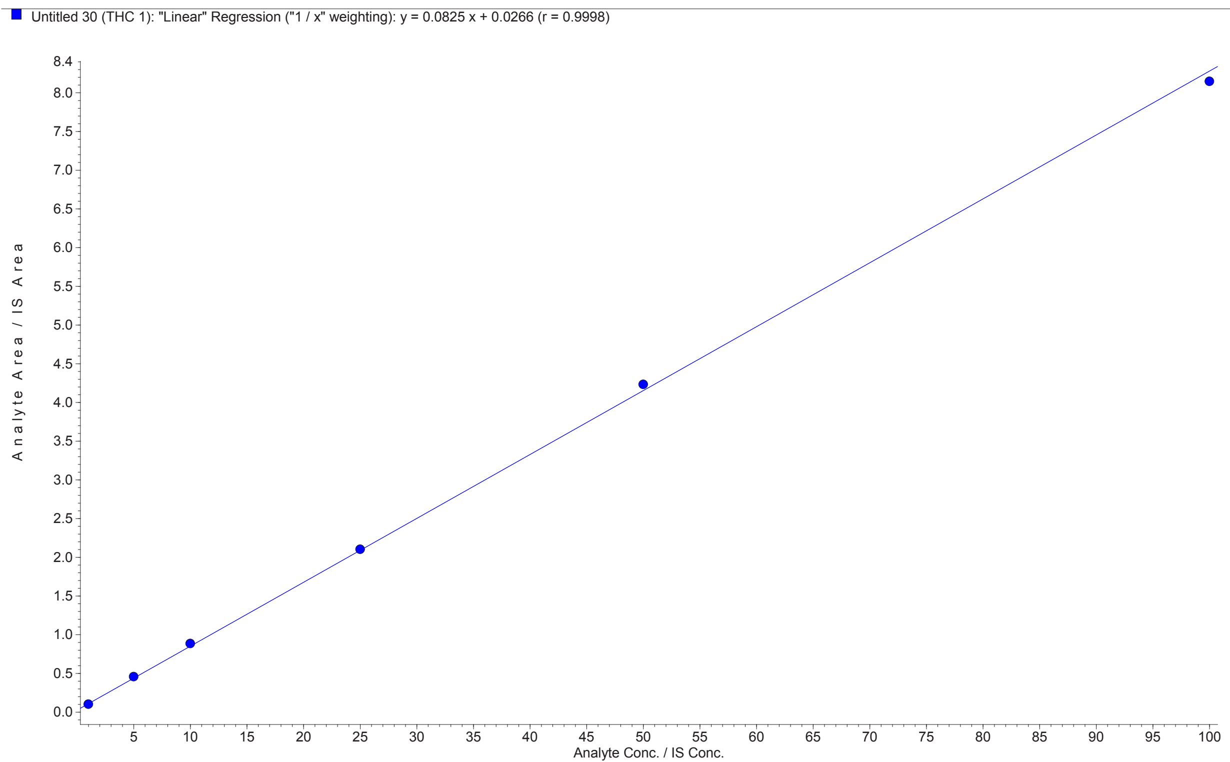

Figure 9: Graph of THC over the calibration range (1 to 100 ng/mL).

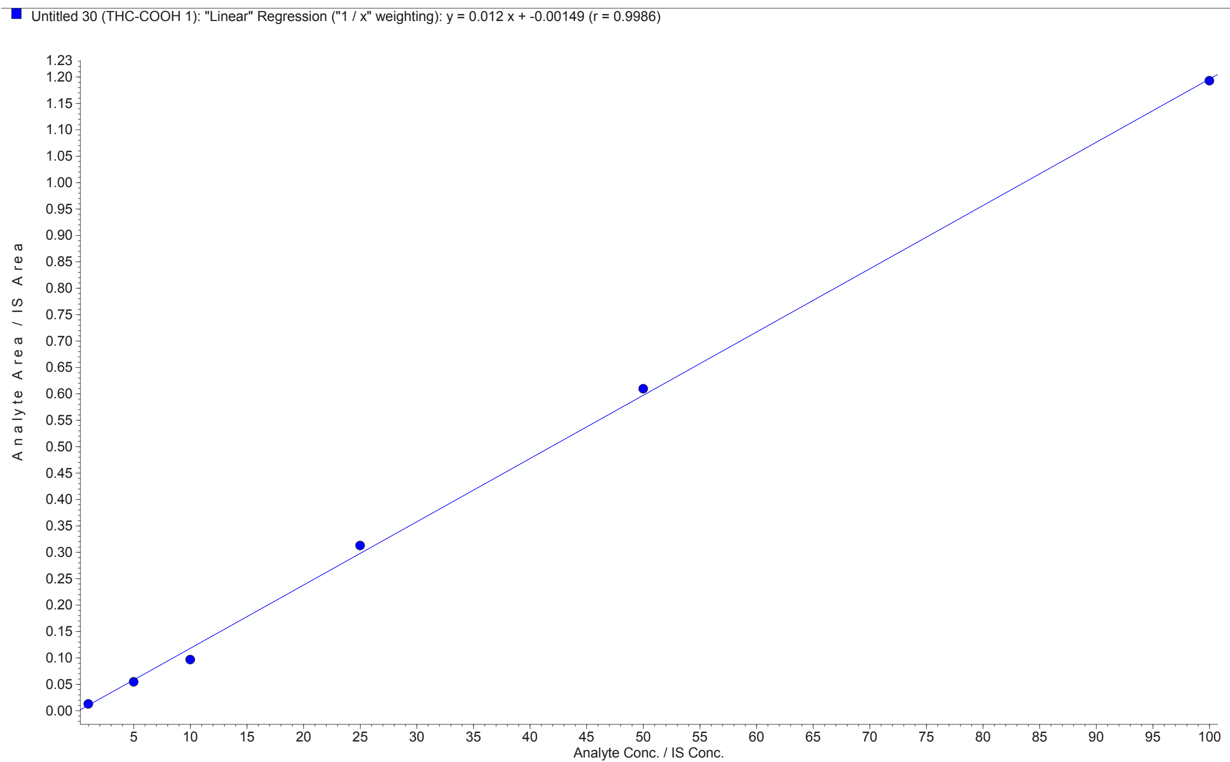

Figure 10: Graph of THCA over the calibration range (1 to 100 ng/mL).

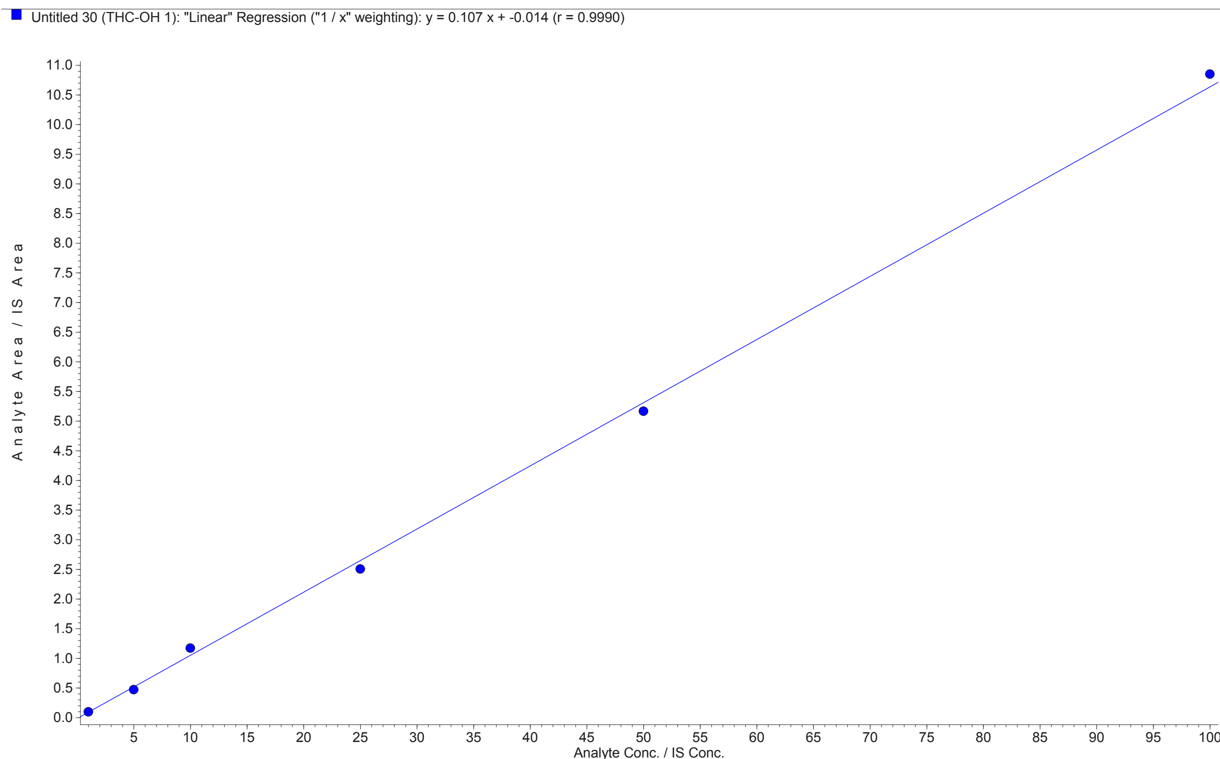

Figure 11: Graph of THC-OH over the calibration range (1 to 100 ng/mL).

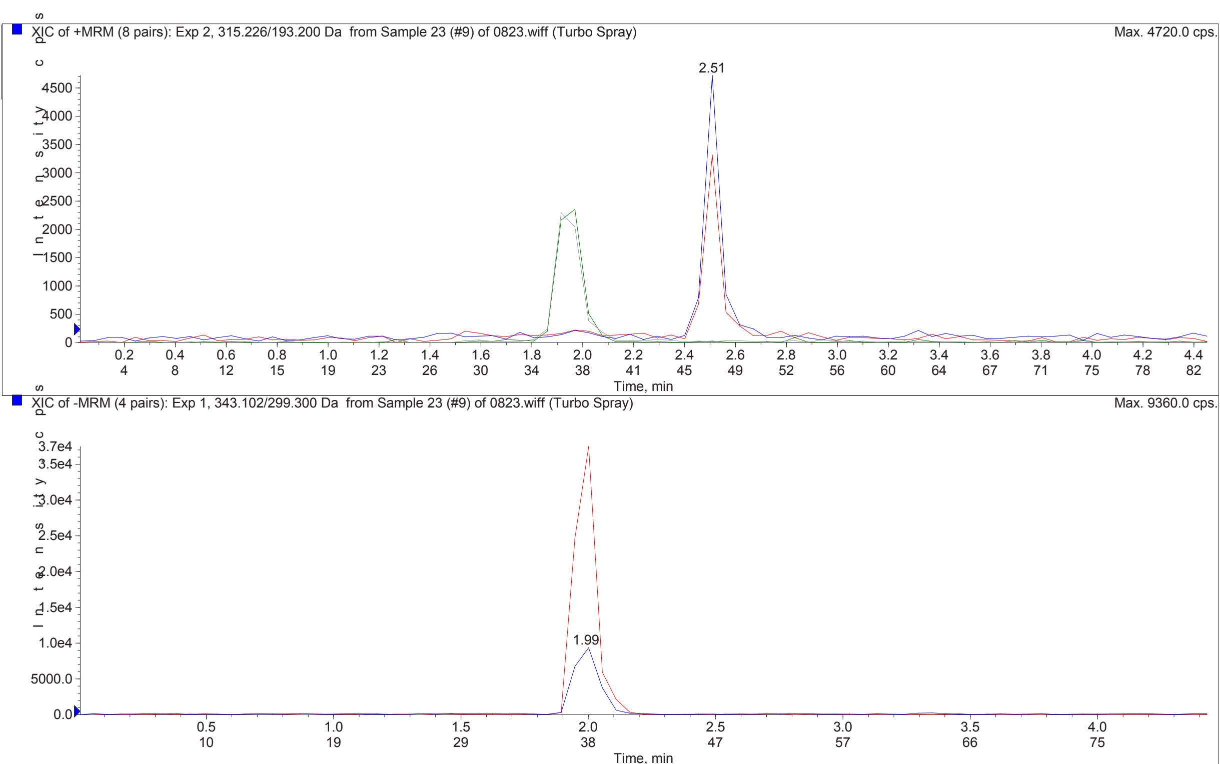

Figure 12: Case Sample #9 (showing THC-OH, THC, and THC-A (lower)): Concentration of THC-OH= 2.3 ng/mL. Concentration of THC=2.9 ng/mL. Concentration of THC-A= 23 ng/mL.

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Figure 13: Automated SPE program.

Case	THC/ (ng/ mL)	THC-OH (ng/ mL)	THCA/ (ng/mL)
1	0	0	11
2	1.3	1.5	8.3
3	<LOQ	<LOQ	11
4	0	0	5.1
5	1.1	1.2	11
6	0	0	55
7	1.3	1.7	33
8	1.9	2.5	22
9	2.3	2.9	23
10	1.5	1.9	30

Table 2: Results of 10 re-analyzed cases.

needs no manual intervention after the program is started. After the conditioning, loading, and washing steps are complete, the SPE tubes are dried under full vacuum, after which the marked elution collection tubes are placed into their allocated positions, and programmed elution is performed.

This automated part of procedure takes approximately 30 minutes and requires no manual input apart from the re-placing of the collection rack. After completion of the process, the samples are removed and placed in an evaporator. This step takes less than 10 minutes, after which the samples are dissolved in mobile phase for analysis. A screen snapshot of the procedure is shown in figure 13.

Sample stability

After extraction, the samples were allowed to sit in the autosampler compartment for a period of 5 days. Injections were made on day 1, day 3 and day 5, post extraction. The results were compared with the initial extraction injection. It was found that there was no degradation in the samples, and the peak areas were within 5% of the initial results.

Case samples

In this project, 10 samples from closed out cases were subjected to analysis using SPE and fast LC-MS/MS. The values obtained from the original analyses ranged from 0 ng/mL to 2.2 ng/mL (THC), 5.1 ng/mL to 57 (THCA).

The details of the re-analysis of ten cases are shown in table 2.

The values obtained by this new methodology were found to be consistent with the original test values. In the previous tests, the concentrations of THC-OH were not determined. A chromatogram obtained from case # 9 is shown in figure 12.

Conclusion

The application of an automated solid phase extraction system coupled to LC-MS/MS has be shown to be not only advantageous in terms of analytical performance but also in time saved, thus increasing productivity. Although certain parts of the operation i.e. solvent deproteination and evaporation still require manual assistance, the rest of the SPE procedure can be productively left for the automated workstation to process. This leaves busy analysts in the laboratory to attend to other activities. In these days of laboratories being request to perform more analyses in less and less time, the coupling of these two analytical aspects i.e. automated SPE and fast LC-MS/MS is a distinct benefit for analysts in the area of medico- judicial drug testing in biological samples.

Acknowledgement

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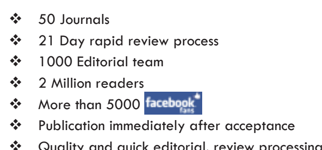
- More than 5000 
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