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Confirmation of cannabinoids in meconium using two-dimensional gas chromatography with mass spectrometry detection

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Abstract

Meconium has become the specimen of choice for determining fetal exposure to drugs of abuse, but its physical complexity can cause interferences from matrix effects. A new method to determine 9-carboxy-11-nor-Δ^9-THC (9-THCA) and 11-hydroxy-Δ^9-THC (11-OH-THC) using two-dimensional (2D) GC–MS was developed to reduce interferences and carryover. The method was validated using 70 spiked samples prepared in drug-free meconium and 46 residual patient specimens that were confirmed to contain cannabinoids. Ten patient specimens that failed to confirm due to interferences using the previous GC–MS method were analyzed using the new 2D method and 9-THCA was quantitated in all ten samples. The 2D GC–MS method improved chromatography which significantly reduced interferences and carryover when compared to the previous GC–MS method.

Keywords: Cannabinoids; THC; Meconium; Two-dimensional GC; Mass spectrometry; Deans switch

1. Introduction

Newborns that have been exposed to some drugs of abuse *in utero* may experience withdrawal symptoms consequential to prenatal drug dependence, and may have characteristic physical and mental development problems throughout their lives [1]. It is therefore desirable to diagnose and begin treatment for these individuals as early as possible. State authorities may also consider removing the infant from the biological mother if severe drug abuse and other home conditions indicate that removal is in the best interest of the child. Previously the full history of prenatal drug exposure was dependent upon the mother's willingness to divulge her drug use or upon observations of social workers, however, mothers who disclose the use of drugs while pregnant often minimize the amount of drugs they report using and may not fully disclose the kinds of drugs they have used. Drug testing neonates provides definitive identification of exposure to drugs *in utero*. Specimens available for newborn drug testing include urine, hair, blood, and meconium. Collection of urine and blood from newborns can be difficult, uncomfortable and invasive. In addition, urine taken from the baby shortly after birth only shows the presence of drugs that the mother took within a few days to ca. 2 weeks prior to birth. Collection of hair can be challenging as often very little hair is present. First introduced in the 1980s, meconium is now a widely used specimen to detect drug exposed infants because it gives a longer history of drug exposure than urine. Meconium is the black, tarry stool passed from the rectum by the newborn until the infant begins passing the typical yellow-green stool from formula or breast milk. It begins to form in the intestine between 12 and 16 weeks of gestation and accumulates until birth. Full meconium passage may take as long as 5 days after birth [2]. Drugs and their metabolites collect in meconium beginning at about 5 months gestation, and at term can effectively identify exposure during the last 3–4 months of pregnancy. Meconium has also been shown to be marginally more sensitive than hair for the detection of cocaine and cannabis in newborns [3]. Prenatal *in utero* exposure to marijuana has been recognized as a cause of executive function deficiency and should be diag-

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nosed and prepared for as early as possible in the child's life [4].

Delta-9-tetrahydrocannabinol (THC) is the major pharmacologically active component of the marijuana plant (*Cannabis sativa*). When THC is absorbed (by inhalation of smoke or ingestion in food) it undergoes metabolism to numerous compounds. 9-THCA is a major metabolite of THC [5], and the primary analyte detected in urine by laboratories to determine marijuana use. In meconium, 11-OH-THC is also present, therefore confirmation methods that can detect low concentrations of both 9-THCA and 11-OH-THC will improve identification of THC exposure *in utero*. Indeed, a 6.5% increase in positivity was observed when 11-OH-THC was also used to identify THC in meconium because only the 11-OH-THC is found in some samples [6]. Both metabolites are excreted to a considerable extent as the glucuronide conjugate; it is therefore necessary to hydrolyze the conjugates to improve the sensitivity of the assay and to measure the total amount of each analyte. The method of hydrolysis greatly affects the amount of recovered free metabolite [7].

Meconium is a complex specimen containing materials from the maternal blood stream and ingested by the fetus *in utero*. The composition includes water, epithelial cells, lanugo, mucus, amniotic fluid, bile acids and salts, fatty material from the vernix caseosa, cholesterol and sterol precursors, blood group substances, enzymes mucopolysaccharides, sugars, lipids, proteins, trace metals, various pancreatic and intestinal secretions, drugs and other compounds ingested or otherwise used by the mother. Consequently, the incidence of matrix interferences is greatly increased in meconium specimens when compared to urine specimens [8]. A GC–MS method for the analysis of cannabinoids in meconium using a liquid–liquid extraction sample preparation was recently reported, however this method had a limit of detection of 7 μg/g and lower limit of quantitation of 20 μg/g, which are on the order of 1000 to 2000 times higher than what we report from our laboratory [9]. Extensive sample preparation techniques like solid phase extraction prior to chromatographic analysis are commonly used to minimize interferences that can hinder quantitation for low-level (ng/g) quantitation of cannabinoids in meconium. Despite solid phase extraction, matrix interferences using our existing GC–MS method resulted in frequent re-extractions of patient specimens. Meconium is only available for approximately 5 days after birth, and the specimen is often of limited quantity, so specimen waste must be minimized. Carryover issues observed commonly with conventional GC–MS analysis created the need to inject a blank between each sample. This work was executed because of a need for a better analytical method that would eliminate interferences, reduce carryover and improve quantitation of cannabinoids in meconium. Two-dimensional gas chromatography-mass spectrometry (2D GC–MS) has been used to improve the analysis of cannabinoids in whole blood [10], hair [11] and oral fluid [12]. Separation is enhanced in 2D GC through "heart-cutting" peaks from one GC column onto a second GC column with a stationary phase of different selectivity using a Deans switch assembly [13]. Co-eluting compounds that interfere with confirmation using only the first column are separated from the analytes of interest on the second column. This technique is very useful for eliminating interferences from co-eluting peaks and separating complex mixtures, however the Deans switch is more complicated to operate than a single column GC–MS. Method development is more involved, and maintenance and trouble-shooting is more complicated because there are more connections with two columns and two detectors. The use of solid phase extraction followed by 2D GC–MS to eliminate interferences and improve chromatography and detection of both 9-THCA and 11-OH-THC in meconium is reported.

2. Experimental

2.1. Specimens

Residual meconium specimens were de-identified to remove personal health information and screened for cannabinoids using EMIT immunoassay reagents with a cutoff of 40 ng/g. Specimens that screened negative for all drug classes ("drug-free") and confirmed negative for THC by GC–MS were pooled and used to prepare calibrators, controls and spiked samples.

2.2. Sample preparation and extraction

Standards of 9-THCA, 11-OH-THC and internal standards 9-THCA-d_9 and 11-OH-THC-d_3 prepared in methanol at 100 μg/mL were obtained from Cerilliant (Round Rock, TX). All analytical reagents and solvents were high purity or HPLC grade and obtained from VWR (West Chester, PA) or Thermo Fisher Scientific (Waltham, MA). Nanopure water was obtained using a Barnstead Nanopure Infinity ultra pure water system (Thermo Fisher Scientific, Waltham, MA). Calibrators and controls (10, 25 and 100 ng/g) were prepared from drug-free meconium spiked with the appropriate concentration of analyte and internal standard, and extracted in the same manner as patient specimens. Meconium (1.00 ± 0.02 g) was weighed into a 5 mL transport tube and 3 mL of methanol were added. A control solution prepared separately from the calibration solution was used to spike a positive control sample at 25 ng/g of each analyte. A negative control spiked only with the internal standards was also prepared. An unextracted control sample prepared in methanol was also analyzed to check instrument function prior to the analysis of each batch of samples. These controls were run with each batch of calibrators and patient specimens. The samples were homogenized using a Fisher Tissuemiser® homogenizer (Thermo Fisher Scientific, Waltham, MA) then centrifuged at $150 \times g$ and 0 °C for 15 min using an ultra high speed centrifuge (Thermo Fisher Scientific, Waltham, MA). The supernatant was transferred to 16 mm × 100 mm glass screw-top vials and evaporated to dryness at 60 °C using a centrifugal vacuum evaporator (Thermo Fisher Scientific, Waltham, MA). After drying (2–3 h), 3.0 mL of 5000 units/mL beta-glucuronidase enzyme solution (Sigma–Aldrich, Milwaukee, WI) were added to each sample and they were incubated at 60 °C overnight for a minimum of 12 h to convert the 9-THCA and 11-OH-THC glucuronides to the free form.

After hydrolysis was complete, the samples were cooled, and 200 μL of 6 M NaOH was added to each sample to optimize absorption of the cannabinoids onto the SPE column [7]. Samples were centrifuged at 150 × g and 0 °C for 15 min. The supernatant from each sample was loaded onto individual 35 mg/3 mL CEREX Polycrom THC SPE columns (SPEware Inc., San Pedro, CA) which had been placed in a CEREX 48 place positive pressure manifold (SPEware Inc., San Pedro, CA). The Polycrom THC sorbent consisted of a polymeric dual-mode anion exchanger. The columns were conditioned prior to use with 2 mL of methanol. The samples were loaded onto the columns at 1 drop per 4 s. The samples were washed with 2 mL of 85:15:1 water:acetonitrile:NH_4OH at 1 drop per second, then dried under nitrogen at 172 kPa and room temperature for 15 min. Next, the samples were washed with 25:75 ethyl acetate:hexane at a rate of 1 drop per second. The analytes and internal standards were eluted from the columns at 1 drop per 4 s into Max-recovery autosampler vials (Waters Corporation, Milton, MA) using 1.5 mL of 74:25:1 hexane:ethyl acetate:acetic acid. The samples were evaporated to dryness using a CEREX Sample Concentrator (SPEware Inc., San Pedro, CA) and derivatized with 10 μL of *N*-methyl-*N*-trimethylsilyltrifluoroacetamide (MSTFA) (United Chemical Technologies, Inc., Bristol, PA) and 10 μL of acetonitrile prior to instrumental analysis by 2D GC–MS.

2.3. Instrumentation

An Agilent 6890 gas chromatograph was equipped with a flame ionization detector, a 5973 mass spectrum detector (MSD), a Deans switch assembly and a cryo trap (Agilent Technologies, Palo Alto, CA, USA). The cryo trap was installed in the oven compartment after the Deans switch at the inlet of column two and cooled with house air at 413 kPa. Helium was the GC carrier gas. Pulsed splitless injection was used, and the injection volume was 1 μL. The injection port temperature was 250 °C. Ions were generated by electron impact. Selective ion monitoring was used. The ions monitored were 473 (quantitative), 488 and 474 (qualitative) for 9-THCA, 371 (quantitative), 474 and 459 (qualitative) for 11-OH-THC, 380 (quantitative) and 479 (qualitative) for 9-THCA-d_9, and 374 (quantitative) and 477 (qualitative) for 11-OH-THC-d_3. The dwell time was 50 ms with a span of 0.3 amu and low resolution mode was selected. The transfer line temperature was at 280 °C. The MS QUAD was at 150 °C, and the source was set to 230 °C. The EM offset was 400 V and the resulting EM voltage was 2211.8 V. The Deans switch was turned on as the peaks containing the analytes of interest were eluted from column one, re-routing them to the cryo trap for additional separation on column two. Column one was an Agilent DB-5 MS (15 m, 0.25 mm ID, 0.25 μm), and column two was an Agilent DB-17 MS (15 m, 0.25 mm ID, 0.25 μm). The oven temperature program was 200 °C for 0.2 min, ramp to 280 °C at 15 °C/min, hold for 3.8 min. This was the oven ramp for the separation on column one. Deans switch cut times were 7.55 to 7.85 min for 11-OH-THC and 11-OH-THC-d9, and 8.80 to 9.26 min for 9-THCA and 9-THCA-d3. The cryo trap temperature was maintained at 100 °C during the first oven ramp to capture the analytes from column one. The oven was then cooled back to 200 °C, held there for 0.2 min, and ramped to 250 °C at 10 °C/min and held for 1.0 min. This was the oven profile for the separation on column two. The cryo trap temperature was rapidly increased to 320 °C after the 0.2 min hold, which released the sample onto column two right before the second oven ramp was initiated.

The pressures were determined using the Deans switch calculator (accessory software provided by Agilent) to provide a flow rate of 1.0 mL/min through column one and a flow rate of 2.0 mL/min through column two. The Deans switch calculator determined a column one (inlet) pressure of 169.6 kPa, and a column two pressure of 124.8 kPa. The inlet pressure was maintained for 10.5 min until the 9-THCA, 11-OH-THC and internal standards had eluted from column one. The inlet pressure was then reduced to 6.9 kPa for the remainder of the run which created a backflush of column one. The pressure on column two was maintained until the end of the run. At this point, a 4 min post run was performed where the pressure on column two was increased to 414 kPa while the oven was ramped to 320 °C to initiate a forward flush cleaning step for column two. During this time, the pressure on column one was left at 6.9 kPa at 320 °C to continue the backflush cleaning step for column one. Fig. 1 summarizes operation of the 2D Deans switch GC–MS system, showing the pressure on both columns, the oven profile and the cryo trap temperature during the course of a run.

2.4. Method validation

The method was validated for accuracy, precision, linearity, analytical measurement range, specificity, and carryover using

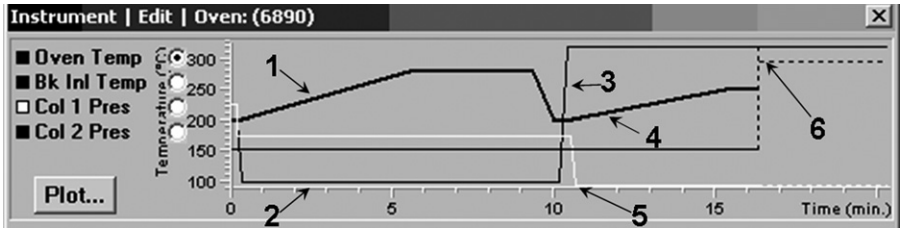

Fig. 1. Screen shot from Chemstation® showing operation of Agilent 6890 GC with Deans switch assembly, cryo trap and two temperature programs. (1) Oven profile for separation on column 1. (2) Cryo trap (back inlet) temperature (maintained at 100 °C during separation on column 1). (3) The cryo trap temperature is rapidly increased to release the sample onto column 2. (4) Oven profile for separation on column 2. (5) After Deans switch is turned off, the pressure on column 1 is lowered to backflush late eluting compounds from column 1. (6) After separation on column 2, the oven temperature is increased to 320 °C, and the pressure on column 2 is increased to flush late eluting compounds from column 2. Column 1 also continues to be backflushed until the next injection.

46 positive patient specimens and 70 spiked samples. Linearity, accuracy, total precision, within-run precision, between-run precision and the analytical measurement range were determined by analyzing spiked samples in triplicate on three different days. Forty-six patient specimens were analyzed by the previous GC–MS method and the 2D method and the results compared. Carryover was evaluated by analyzing a blank injected after running a spiked sample. Spiked samples at 100 to 2500 ng/g were used to determine carryover.

3. Results and discussion

Several changes were made to the extraction method [6] to improve recovery and reduce sample preparation time. The elution solvent was changed from 90:10:1 hexane:ethyl acetate:acetic acid to 74:25:1 hexane:ethyl acetate:acetic acid to improve recovery of 11-OH-THC. Originally, 3 mL of elution solvent were used to elute the samples from the SPE columns into screw-capped vials. The elution solvent was evaporated and MTBSTFA was added. The samples were incubated for 25 min, after which they were dried and reconstituted in 1-chlorobutane, then transferred to autosampler vials for injection. The volume of elution solvent was changed to 1.5 mL, and the derivatizing reagent was changed to MSTFA. Reducing the volume of elution solvent permitted elution directly into autosampler vials. Using MSTFA to derivatize the samples eliminated the incubation step prior to injection. This reduced the preparation time for each batch of samples by 40 min.

The primary goal of this work was to eliminate carryover and chromatographic interferences in the analysis of cannabinoids in meconium by employing the Deans switch assembly. Fig. 2a and b compares the total ion chromatograms (TIC) of a sample spiked at the cutoff concentration using the original GC–MS method and the Deans switch method (second column). The peaks of interest were not well separated from other components in the single column chromatogram. Both analytes were well-resolved from other components in the Deans switch TIC. Co-eluting interferences were often present in blank samples, spiked samples and patient specimens analyzed by the single column GC method, but no relevant peaks co-eluted with 9-THCA or 11-OH-THC in the Deans switch chromatograms, permitting accurate identification and quantitation of the analytes. 9-THCA and its internal standard co-elute in the GC–MS TIC, but are almost baseline resolved in the Deans switch TIC. It is clear that the Deans switch method provided better resolution 9-THCA, 11-OH-THC and the internal standards from other compounds in the sample matrix. The limit of detection (LOD) for the Deans switch method was 5 ng/g. LOD was the lowest concentration for which the analyte met all qualitative criteria for correct identification (retention time ±2%, all monitored ions present with acceptable ion ratios) and the peak of interest had a signal to noise ratio that exceeded 3:1. The lower limit of quantitation (LLOQ) was 10 ng/g. LLOQ was defined as the lowest concentration which could be identified and quantitated, all qualitative criteria were met, and the peak of interest had a signal to noise ratio greater than 5:1. The upper limit of quantitation (ULOQ) was 500 ng/g for 11-OH-THC, and 1000 ng/g for 9-THCA. Table 1 summarizes validation data for the Deans switch method. Analytical measurement range, linearity and accuracy required all concentrations were within ±15% of target concentration and all qualitative criteria were met. The slope for linear regression data was between 0.85 and 1.15, the y intercept was less than the LLOQ, and the R^2 was greater than 0.95. Results for precision were determined from three separate batches of samples extracted and analyzed in triplicate on three different days. Average within-run CVs were determined from the average of the standard deviations for each day at each target concentration. Between-run CVs were reported as the standard deviation of the average concentrations for each day at each target concentration. Total CV was the square root of the sum of the squares of

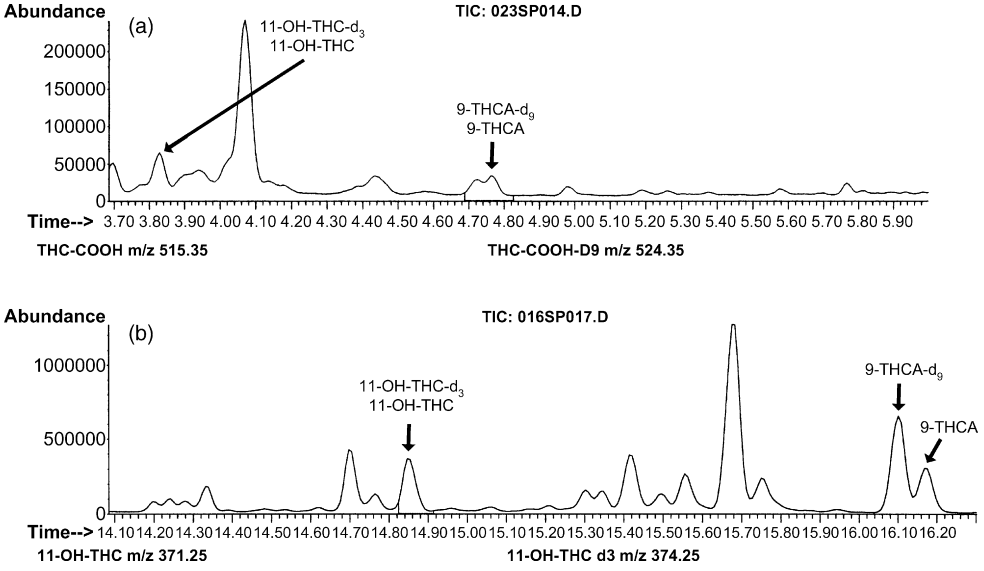

Fig. 2. (a and b) Total ion chromatogram (TIC) comparing the separation of 9-THCA and 11-OH-THC in a sample spiked at the cutoff (10 ng/g) using the single column GC–MS method (a) and the 2D Deans switch method (b).

Table 1
Accuracy and precision data for Deans switch 2D GC–MS method

	Average recovery (%)	Average imprecision		
		Within-run CV (%)	Between-run CV (%)	Total CV (%)
11-OH-THC (ng/g)				
10	106.0	6.9	7.9	10.5
100	102.2	8.4	4.0	9.3
500	87.0	2.5	4.0	4.7
9-THCA (ng/g)				
10	111.1	6.5	8.0	10.3
100	97.9	10.5	0.4	10.5
500	90.2	4.8	0.3	4.8
1000	99.9	8.0	1.6	8.1

the CVs for within-run and between-run precision at each target concentration. Precision also required CVs within ±15%, and concentrations within ±15% of the target concentration.

Ion ratios were within ±40%. Although it is standard practice to have ion ratios within ±20%, the nature of the meconium matrix makes this difficult. Meconium is a very complex matrix. Thus, imprecision is higher in meconium-based tests than that observed with other biological matrices such as urine or plasma. We have achieved very low (ng/g) limits of detection and quantitation in this very challenging matrix. Meconium is also a specimen in limited supply. Because of the limited supply and the fact that the actual concentration of the drugs is of limited clinical utility (i.e., the correlation between concentrations and details of drug use and exposure is not well defined), it is clinically important to provide evidence of drug exposure to health care providers as soon as possible. As such, the choice to be less stringent in acceptable ion mass ratios in our view, translates to less repeat testing and better clinical service.

Carryover was defined as being present if the analyte was quantitated at a concentration above the LOD and all qualitative criteria were met. No carryover was observed for 11-OH-THC. 9-THCA was measured at 5.9 ng/g (slightly above the LOD of 5 ng/g) in a blank preceded by a sample spiked at 500 ng/g. 9-THCA was present at 2.9 ng/g (less than the LOD) in a blank preceded by a sample spiked at 250 ng/g. Samples greater than 250 ng/g are rarely seen in our laboratory, therefore based on these results, the decision was made to evaluate samples preceded by a sample greater than 250 ng/g for carryover.

Fig. 3a and b show the comparison of spiked samples prepared with drug-free meconium that was known to cause interferences with the GC–MS method analyzed by both methods for 9-THCA and 11-OH-THC, respectively. Spike concentrations were 5, 10, 50 and 200 ng/g. The recovery of 9-THCA using the GC–MS method was poor, but was excellent using the Deans switch method. The recovery of 11-OH-THC was good using the previous method, but improved using the Deans switch 2D GC–MS method. Moreover, the ion mass ratios for both analytes were outside of the acceptance criteria (±40%) when analyzed by the GC–MS method, so even though total recovery for 11-OH-THC appears acceptable, results could not be reported. Interferences that prevented identification and quantitation of cannabinoids occurred about 20% of the time using the GC–MS method. Forty-six patient specimens that contained no interferences and could be confirmed using the GC–MS method were compared to results obtained using the 2D method. Linear regression data for 9-THCA was $n = 29$, standard error = 12.93%, $y = 0.9105x + 2.3849$, $R^2 = 0.9722$. The linear regression analysis for 11-OH-THC was $n = 7$, standard error = 1.35%, $y = 1.0979x - 1.2784$, $R^2 = 0.9989$. The correlation was very good for 11-OH-THC, but was not as linear for the 9-THCA data. A Bland-Altman test was also performed on the patient specimen data [14]. Bland-Altman plots are shown in Fig. 4a and b. These plots show that the best agreement for 9-THCA was achieved between 10 and 150 ng/g, and all except two data points were within two standard deviations (2SD) of the mean. The 11-OH-THC data also showed good agreement, with one point (the highest concentration) being just slightly outside the 2SD window. The correlation for 9-THCA was acceptable considering the complex nature of the meconium matrix, and the known interferences in the GC–MS method. The results from the analysis of the spiked samples and patient specimens indicate that matrix interferences in the GC–MS method had a significant negative impact on the quantitation of 9-THCA, but the effect was not as pronounced for 11-OH-THC. Differences in the concentrations of 9-THCA determined between the two methods were attributed

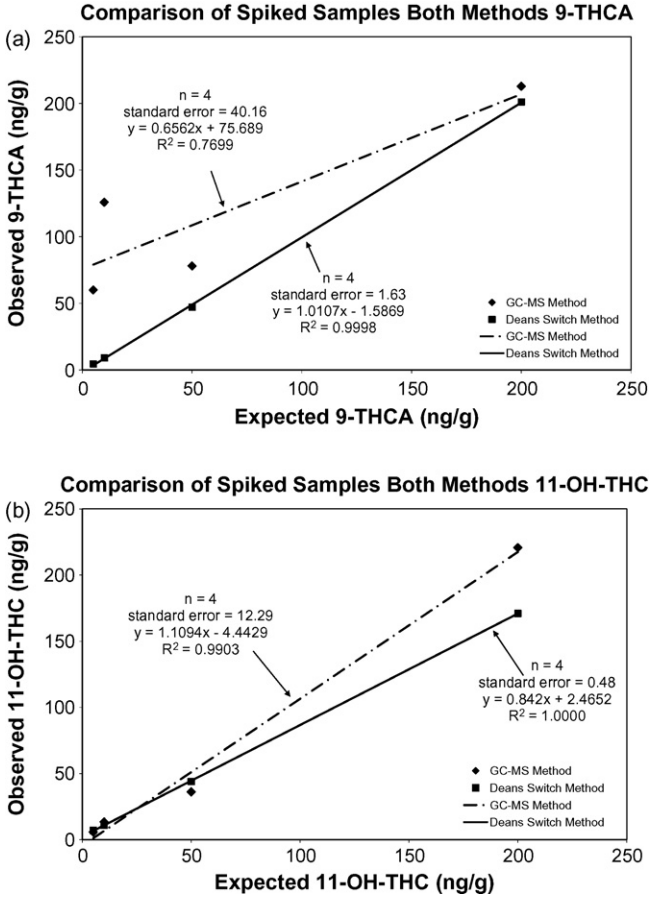

Fig. 3. (a and b) Comparison of samples spiked with 9-THCA (a) and 11-OH-THC (b) analyzed using both methods.

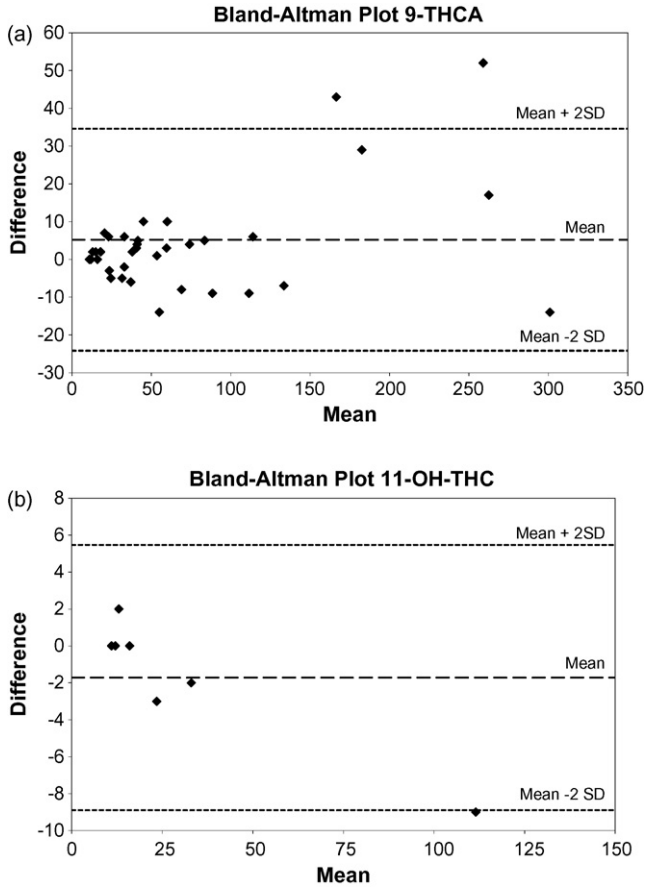

Fig. 4. (a and b) Bland-Altman plots comparing results for 9-THCA and 11-OH-THC analyzed by both methods.

to the non-homogeneity and non-uniform composition of the meconium matrix. Ten samples that failed to confirm due to interferences using the previous single column GC–MS method were analyzed using the Deans switch method and 9-THCA was quantitated in all ten samples with no interfering peaks observed. The total run time for the Deans switch method was 20 min, because the method performs two complete separations on two different columns with one injection. The run time for the GC–MS method was 9 min, but a blank had to be injected between each patient sample, so injection-to-injection time was comparable for the two methods. The Deans switch method provided superior chromatography and a significant reduction in carryover.

4. Conclusions

Modifying the elution solvent and switching the derivatizing reagent from MTBSTFA to MSTFA resulted in a reduction in sample preparation time without sacrificing sensitivity, selectivity, accuracy or precision. The new 2D GC–MS method eliminated matrix interferences when compared to the existing GC–MS method. A longer run time resulted from the new method, but total injection-to-injection time was comparable because carryover was reduced, eliminating the need to inject a blank between each sample. The 2D GC–MS method using the cryo trap and Deans switch assembly improved chromatography and provided a better, more robust method for the analysis of cannabinoids in meconium.

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