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Streamlined Sample Preparation of a Drugs of Abuse Panel in Human Nails Using ISOLUTE® SLE+ Prior to UPLC-MS/MS Analysis

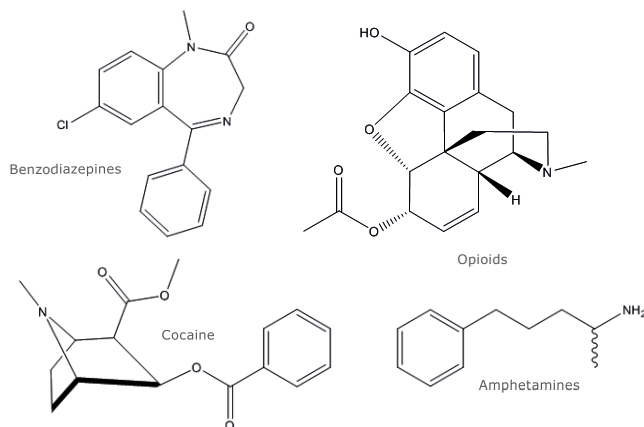


Figure 1. Example structures by class.

Introduction

The testing of alternative matrices in forensic and/or clinical toxicology is gaining popularity, partly due to less invasive means of collection. Matrices such as hair or nail can provide a more rounded picture of abstinence or abuse and associated timeframes. This application note describes the sample pre-treatment and subsequent extraction of 49 drugs of abuse from human nails, prior to LC/MS analysis.

The method utilizes Biotage® Lysera for matrix micropulverization, prior to direct transfer to clean up using ISOLUTE® SLE+ supported liquid extraction products. Elimination of an evaporation step between the micropulverization and supported liquid extraction clean up stages provides a streamlined procedure for nail extraction.

Manual processing protocols were developed using the Biotage® PRESSURE+ 96 (plate format) or 48 (column format) Positive Pressure Manifolds. For automated processing, protocols were developed using Biotage® Extrahera™.

This application note contains procedures optimized for both individual column format and 96-well plate format for higher throughput applications. The methodology delivers clean extracts and analyte recoveries mostly greater than 80% with RSDs lower than 10% for all analytes and LLOQ from 1 pg/mg.

Both manual and automated procedures gave comparable results.

ISOLUTE® SLE+ Supported Liquid Extraction plates and columns offer an efficient alternative to traditional liquid-liquid extraction (LLE) for bioanalytical sample preparation, providing high analyte recoveries, no emulsion formation and significantly reduced preparation time.

Analytes

Amphetamine, Methamphetamine, 3,4-Methylenedioxyamphetamine (MDA), 3,4-Methylenedioxymethamphetamine (MDMA), 3,4-Methylenedioxy-N-ethylamphetamine (MDEA), Hydromorphone, Morphine, Benzoylcegonine (BZE), Oxycodone, Dihydrocodeine, Oxycodone, Mephedrone, Norfentanyl, 7-amino-flunitrazepam, 7-amino-clonazepam, Hydrocodone, Codeine, 6-Monoacetylmorphine (6-MAM), Cocaine, Norketamine, 2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP), Zaleplon, Zopiclone, Norbuprenorphine, Ketamine, Nitrazepam, Flunitrazepam, Clonazepam, α -OH-triazolam, Oxazepam, Estazolam, Temazepam, Zolpidem, Alprazolam, Methadone, Lorazepam, Bromazepam, α -OH-alprazolam, 2-OH-ethyl-flurazepam, Triazolam, Nordiazepam, Diazepam, Midazolam, Fentanyl, Flurazepam, Buprenorphine, Phencyclidine (PCP), Lysergic acid diethylamide (LSD)

Internal standards

Amphetamine-D₅, Morphine-D₃, Benzoylcegonine-D₃ (BZE-D₃), 6-Monoacetylmorphine-D₃ (6-MAM-D₃), Diazepam-D₅

Sample Preparation Procedure

Format

ISOLUTE® SLE+ 400 μ L capacity columns. (p/n 820-0055-B) or

ISOLUTE® SLE+ 400 μ L capacity plates (p/n 820-0400-P01)

Matrix Preparation

Weigh 10 mg of freshly clipped nails into 2 mL Biotage® Lysera tubes (p/n 19-620) containing 5 x 2.4 mm stainless steel beads (p/n 19-640).

Micropulverization Procedure

Grind to a fine powder using Biotage® Lysera: 8 x 6.95 m/sec for 45 seconds with a 45s dwell.

Add 1 mL methanolic 0.1% (v/v) NH₄OH to each nail sample after micropulverization. Also add 10 μ L of a 100 pg/mL ISTD solution giving a 100 pg/mg spike.Mix.

Centrifuge tubes for 10 minutes at 13,300 rpm (Heraeus Pico 17 Microcentrifuge (Thermo Scientific) with 24 position, 2 mL rotor).

Post Micropulverisation

Transfer an aliquot of supernatant directly to the appropriate ISOLUTE SLE+ product for clean up as described below.

Supported Liquid Extraction Conditions

	ISOLUTE® SLE+ 400 µL Columns Part Number 820-0055-B	ISOLUTE® SLE+ 400 µL Plate Part number 820-0400-P01
Sample loading	Load up to 400 µL of supernatant directly to ISOLUTE®SLE+ sorbent. Note: A pulse of pressure is not needed to initiate flow with methanolic loads. Allow the sample to absorb for 5 minutes.	Load up to 400 µL of supernatant directly to ISOLUTE®SLE+ sorbent. Note: A pulse of pressure is not required to initiate flow with methanolic loads. Allow the sample to absorb for 5 minutes.
Analyte Extraction	Apply DCM/IPA (95/5, v/v, 600 µL) and allow to flow under gravity for 5 minutes. Apply a further aliquot of MTBE (600 µL) and allow to flow under gravity for 5 minutes. To complete solvent removal apply a pulse of positive pressure at 10 psi (10–20 seconds).	Apply DCM/IPA (95/5, v/v, 600 µL) allow to flow under gravity for 5 minutes. Apply a further aliquot of MTBE (600 µL) and allow to flow under gravity for 5 minutes. To complete solvent removal apply a pulse of positive pressure at 10 psi (10-20 seconds).
Collection vessels	Collect extract in 12x75 mm glass tubes	Collect extract in 96-well collection plates.
Post elution	Evaporate extracts at 40 °C, in the presence of 100 µL of 50 mM HCl in MeOH per tube in order to avoid evaporative losses of amphetamines, for 30 mins at a flow rate of 1.5 L/min using a TurboVap® LV.	Evaporate extracts at 40 °C, in the presence of 100 µL of 50 mM HCl in MeOH per well in order to avoid evaporative losses of amphetamines, for 30 mins at a flow rate of 20-40 L/min using the Biotage® SPE Dry-96.
Reconstitute	Reconstitute extracts in a mix of mobile phase A/mobile phase B (80:20, v/v, 200 µL). Vortex mix, transfer into a 96-well format plate and cover with a sealing mat prior to injection.	Reconstitute extracts in a mix of mobile phase A/mobile phase B (80:20, v/v, 200 µL). Vortex mix. Cover plate with a sealing mat prior to injection.

UHPLC Conditions

Instrument

Shimadzu Nexera X2 UHPLC

Column

Restek Raptor™ Biphenyl 2.7 µm (100 x 2.1 mm) with a Restek EXP holder and Biphenyl guard column

Mobile Phase

A: 2 mM Ammonium formate (aq) with 0.1% formic acid

B: 2 mM Ammonium formate in methanol with 0.1% formic acid

Flow Rate

0.4 mL/min

Injection Volume

5 µL

Column Temperature

30 °C

Table 1. UHPLC Gradient.

Time (min)	%A	%B
0	80	20
2.00	80	20
7.50	40	60
11.25	40	60
12.75	0	100
13.50	0	100
13.51	80	20
15.00	80	20

Mass Spectrometry Conditions

Instrument

Shimadzu 8060 Triple Quadrupole MS using ES interface

Nebulizing Gas Flow

3 L/min

Drying Gas Flow

3 L/min

Heating Gas Flow

17 L/min

Interface Temperature

400 °C

DL Temperature

250 °C

Heat Block Temperature

300 °C

CID Gas Flow

270 kPa

Table 2. MS conditions for target analytes in positive mode.

Analytes	MRM Transition	Collision Energy
Morphine-D ₃	289.0>201.1	-26.0
	289.0>152.1	-50.0
Morphine	286.0>152.1	-50.0
	286.0>201.1	-25.0
Oxymorphone	302.00>227.1	-30.0
	302.00>198.1	-45.0
Hydromorphone	286.0>185.0	-30.0
	286.0>157.0	-40.0
Amphetamine-D ₅	141.0>93.0	-15.0
	141.0>124.15	-20.0
Amphetamine	136>91.05	-15.0
	136>119.1	-14.0
Methamphetamine	150.0>90.95	-20.0
	150>119.1	-14.0
MDA	180>105	-20.0
	180>77	-40.0
Dihydrocodeine	302>119.05	-35.0
	302>171	-45.0
Codeine	300.0>215.1	-25.0
	300.0>165	-40.0
6-MAM-D ₃	331.0>165.1	-40.0
	331.0>211.1	-25.0
6-MAM	328.0>165.1	40.0
	328.0>211.1	-25.0
MDMA	194.0>163.1	-15.0
	194.0>105.0	-25.0
Oxycodone	316.2>241.2	-20.0
	178.00>145.05	-20.0
Mephedrone	178.00>144.00	-30.0
	300.0>199.05	-30.0
Hydrocodone	300.0>171.1	-40.0
MDEA	208>163.05	-15.0
	208>105.05	-25.0
Nor-Ketamine	223.9>125	-20.0
	223.9>179.05	-15.0

Analytes	MRM Transition	Collision Energy
Nor-Fentanyl	233.0>84.05	-20.0
	233.0>56.05	-26.0
BZE-D ₃	293.00>171.05	-20.0
	293.00>77.00	-50.0
BZE	289.90>168.05	-20.0
	289.90>105.00	-30.0
Ketamine	237.90>125.00	-30.0
	237.90>207.05	-14.0
7-Aminoclonazepam	285.90>222.10	-25.0
	285.90>121.10	-29.0
Cocaine	304.00>182.05	-20.0
	304.00>82.05	-30.0
Zopiclone	388.90>245.05	-15.0
	388.90>217.00	-35.0
Norbuprenorphine	414.00>101.25	-39.0
	414.00>187.20	-38.0
LSD	323.50>208.10	-29.0
	323.50>223.25	-23.0
7-Aminoflunitrazepam	283.90>135.05	-30.0
	283.90>227.05	-26.0
Zolpidem	308.00>235.10	-35.0
	308.00>263.10	-25.0
Buprenorphine	468.10>396.25	-40.0
	468.10>414.30	-35.0
Fentanyl	337.00>188.10	-20.0
	337.00>105.00	-40.0
Flurazepam	388.00>315.00	-20.0
	388.00>288.00	-26.0
PCP	244.00>91.05	-35.0
	244.00>159.15	-14.0
Midazolam	325.90>249.10	-35.0
	325.90>223.00	-40.0
Bromazepam	315.80>182.10	-31.0
	315.80>209.10	-27.0

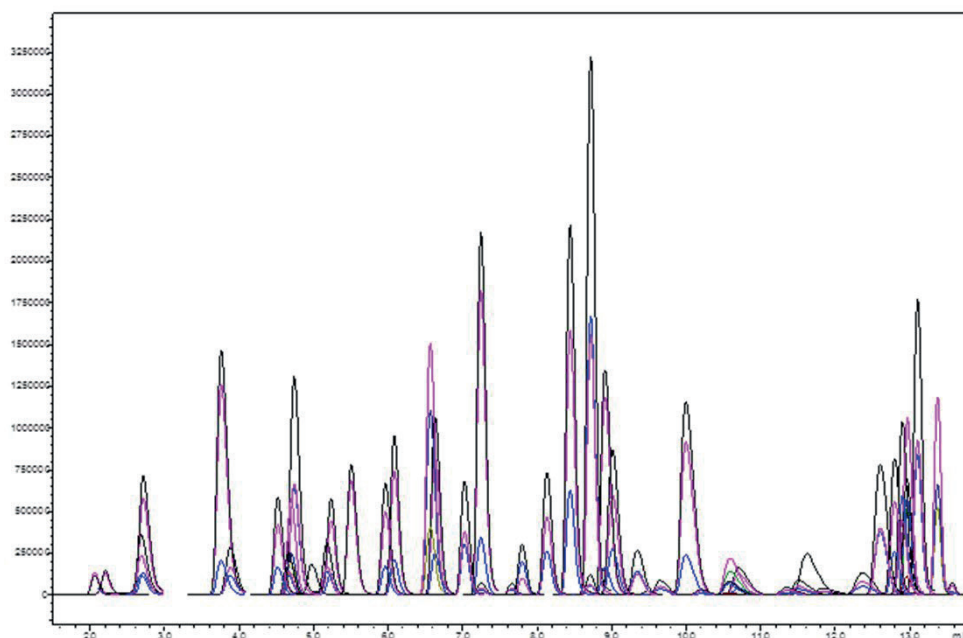


Figure 3. Representative chromatography for application analytes spiked at 1 ng/mL.

Linearity was investigated for human nails spiked between 1–1000 pg/mg. Good linearity was observed for all analytes delivering r^2 values greater than 0.99. Table 3. details linearity performance and associated LOQ for each analyte, using the

400 μ L capacity column format, p/n 820-0055-B. Similar results were obtained from both columns and plate formats, with either manual or automated processing.

Table 3. Analyte calibration curve r^2 and LOQ performance.

Analytes	400 μ L Load r^2	400 μ L Load LLOQ (pg/mL)
Morphine	0.999	1
Oxymorphone	0.999	< 1
Hydromorphone	0.999	< 1
Amphetamine	0.994	1
Methamphetamine	0.999	< 1
MDA	0.997	5
Dihydrocodeine	0.999	< 1
Codeine	0.999	< 1
6-MAM	0.999	< 1
MDMA	0.999	< 1
Oxycodone	0.997	< 1
Mephedrone	0.999	< 1
Hydrocodone	0.999	< 1
MDEA	0.999	< 1
Nor-Ketamine	0.998	< 1
Nor-Fentanyl	0.999	< 1
BZE	0.993	< 1
Ketamine	0.999	< 1
7-Aminoclonazepam	0.996	< 1
Cocaine	0.995	< 1
Zopiclone	0.999	1
Norbuprenorphine	0.999	5
LSD	0.996	5
7-Aminoflunitrazepam	0.997	1

Analytes	400 μ L Load r^2	400 μ L Load LLOQ (pg/mL)
Zolpidem	0.999	< 1
Buprenorphine	0.999	< 1
Fentanyl	0.997	< 1
Flurazepam	0.999	< 1
PCP	0.999	< 5
Midazolam	0.998	< 1
Bromazepam	0.999	< 5
EDDP	0.998	< 1
Lorazepam	0.997	10
Oxazepam	0.997	5
Nitrazepam	0.998	1
Clonazepam	0.998	1
a-OH-Triazolam	0.999	< 5
2-OH-et-flurazepam	0.999	1
Methadrone	0.997	5
a-OH-Alprazolam	0.999	5
Nordiazepam	0.999	1
Zaleplon	0.999	< 1
Flunitrazepam	0.999	1
Estazolam	0.999	1
Temazepam	0.998	1
Triazolam	0.999	< 1
Alprazolam	0.999	5
Diazepam	0.998	1

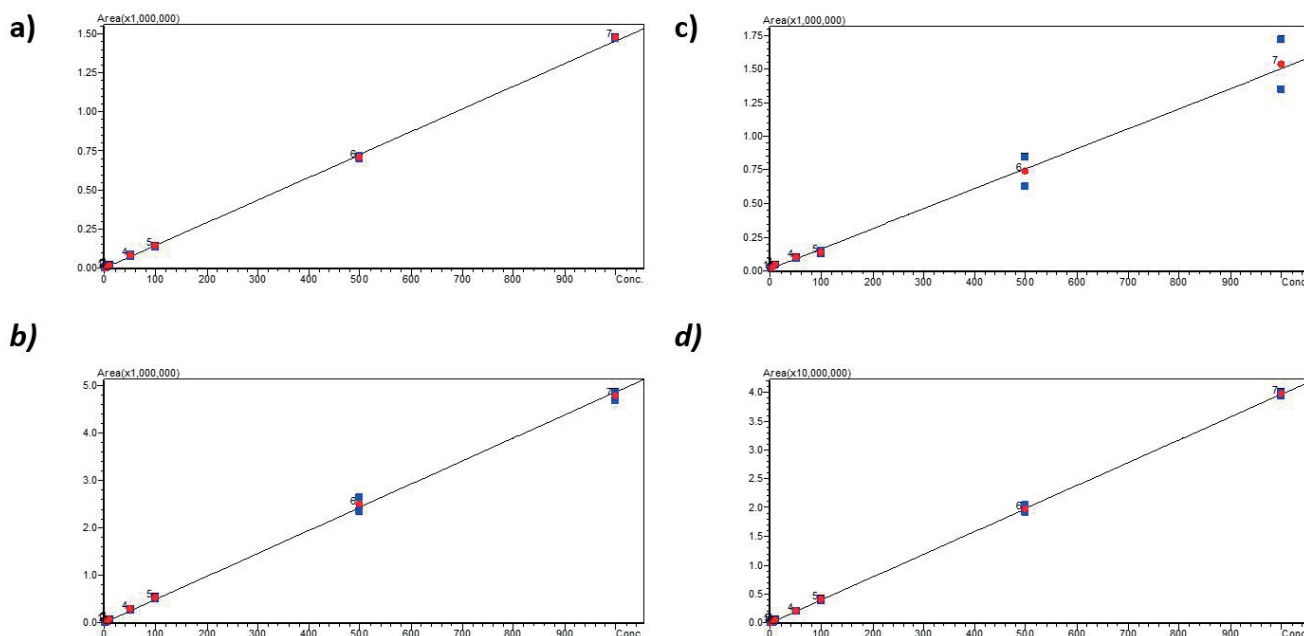


Figure 4. Calibration curves for Buprenorphine (a), 6-MAM (b), BZE (c) and Methamphetamine (d) extracted from human nails using the 400 μ L capacity column format loading 400 μ L of extract (manual processing). Similar results were achieved for the 400 μ L capacity plate formats, and for automated processing procedures.

Chemicals and Reagents

- » Methanol (LC-MS grade), Ultra-Pure Methanol (Gradient MS), dichloromethane (99.8%), isopropanol (99.9%), MTBE (99%) and formic acid (98%) were purchased from Honeywell Research Chemicals (Bucharest, Romania).
- » All analyte standards and deuterated internal standards, hydrochloric acid (37%) and ammonium formate (LC-MS grade) were purchased from Sigma- Aldrich Company Ltd. (Gillingham, UK).
- » Ammonium hydroxide (28–30%) was purchased from Merck.
- » Water used was 18.2 MOhm-cm, drawn daily from a Direct-Q5 water purifier.
- » 0.1% NH_4OH was prepared by adding 100 μ L of ammonium hydroxide to 99.9 mL of methanol
- » 50mM HCl in MeOH was prepared by adding 50 μ L of hydrochloric acid to 1 to 12 mL of methanol.
- » DCM: IPA (95:5, v/v) was prepared by adding 5 mL of isopropanol to 95 mL of DCM and mixing.
- » Mobile phase A (2 mM ammonium formate (aq), 0.1 % formic acid) was prepared by adding 126 mg of ammonium formate to 500 mL of purified water, adding 1 mL of concentrated formic acid and making up to 1 L with purified water.
- » Mobile phase B (2 mM ammonium formate (methanol), 0.1 % formic acid) was prepared by adding 126 mg of ammonium formate to 500 mL of HPLC grade methanol, adding 1 mL of concentrated formic acid and making up to 1 L with HPLC grade methanol.
- » Internal standards(100 pg/ μ L) were prepared from a 10 ng/ μ L stock solution by adding 10 μ L of each of to 950 μ L of MeOH. 10 μ L of this solution was then added to each calibration.

Additional Information

- » All data shown in this application note was generated using freshly clipped nails provided by healthy human volunteers.
- » Biotage® Lysera hints and tips.
 - » A minimum of four tubes must be loaded in the tube carriage to ensure balance during processing.
 - » Ensure vial caps are firmly tightened and Lysera locking mechanism is fully engaged.
 - » To minimize sample transfer and manipulation steps, 2 mL Lysera tubes were placed directly into the centrifuge (Heraeus Pico 17 Microcentrifuge (Thermo Scientific) with 24 position, 2 mL rotor).

Ordering Information

Part Number	Description	Quantity
19-060	Biotage® Lysera	1
19-649	2 mL Reinforced Tubes with screw caps (Bulk pack)	1000
19-640	2.4 mm Metal Beads - 500 grams	1
820-0055-B	ISOLUTE® SLE+ 400 µL sample volume columns	50
820-0400-P01	ISOLUTE® SLE+ 400 µL Capacity Plate	1
PPM-96	Biotage® PRESSURE+ 96 Positive Pressure Manifold	1
PPM-48	Biotage® PRESSURE+ 48 Positive Pressure Manifold	1
415000	TurboVap® LV	1
SD-9600-DHS-EU	Biotage® SPE Dry 96 Sample Evaporator 220/240 V	1
SD-9600-DHS-NA	Biotage® SPE Dry 96 Sample Evaporator 100/120 V	1
121-5203	Collection Plate, 2 mL Square	50
121-5204	Piercable Sealing Mat	50
C44651	Test Tubes (12 x 75 mm, Uncapped)	1000
414001	Biotage® Extrahera™	1

Biotage® Extrahera™ Settings

The method described in this application note was automated on the Biotage® Extrahera™ using ISOLUTE® SLE+ 400 µL capacity columns and 96-well plates. This appendix contains the software settings required to configure Extrahera to run

the column format method. As described in the main body of the application note, analyte recoveries, %RSDs, linearities and LOQs were comparable for both manually processed and automated methods, for both extraction formats.

Sample Name:	DoA Nails – Direct Method
Sample Plate/Rack:	12 x 75 mm Test Tubes, 24
Extraction Media:	ISOLUTE SLE+ 400 µL columns

Settings

"Sample" Tab

Sample Type:

Methanolic Sample

Starting Sample Volume (μL):

420

Method Comment:

Screenshot

< Cancel	Edit SLE Method - DoA Nails - Direct Method	Save >
----------	--	--------

Method name

DoA Nails - Direct Method

Sample plate/rack

12 x 75 mm Test Tubes,...
>

Extraction media

ISOLUTE SLE+ 400 µL C...
>

Pretreatment

☐ Off

Load

On

☐

Elution

On

☐

Sample	Pretreatment	Load	Elution (2)
<p>Sample type</p> <div style="border: 1px solid #ccc; padding: 2px; display: flex; justify-content: space-between;"> <div style="background-color: #2e7d32; color: white; padding: 2px 5px;">MeOH</div> > </div> <p>Starting sample volume in plate/rack (µL)</p> <div style="border: 1px solid #ccc; padding: 2px;">420</div> <p>Reuse sample tips?</p> <div style="border: 1px solid #ccc; padding: 2px; display: flex; justify-content: space-between;"> <input type="checkbox"/> No </div>			
<p>Method comment</p> <div style="border: 1px solid #ccc; min-height: 140px;"></div>			

Pre-treatment	
No. of steps	0
Pause after last step	No
Dispose tips after last step	No

Solvent
1
2
3
4

	1	2	3	4
Volume (μL)				
Wait Time (min)				



Edit SLE Method - DoA Nails - Direct Method

Method name: DoA Nails - Direct Method

Sample plate/rack: 12 x 75 mm Test Tubes,...

Extraction media: ISOLUTE SLE+ 400 µL C...

Pretreatment: ☐ Off

Load: ☒ On

Elution: ☒ On

Volume (µL): 400

Air push time (s): 0

Advanced pressure settings: Edit...

Premix? ☒ Yes

Number of times: 4

Wait time (min): 5

Pause after each load? ☐ No

Collect in position: D (Wa...)

Load

Pressure (Bar)	0
Pause after each load	No
Volume	400
Collect in position	D
Positive pressure time	0
Premix	Yes
Number of times	4
Wait time (min)	5

'Advanced Settings'

Edit SLE Method - DoA Nails - Direct Method

Method name: DoA Nails - Direct Method

Sample plate/rack: 12 x 75 mm Test Tubes,...

Extraction media: ISOLUTE SLE+ 400 µL C...

Pretreatment: ☐ Off

Load: ☒ On

Elution: ☒ On

Number of steps: 2

Air push after last elution? ☐ No

Air push time (s): 0

Dispose solvent tips after each step? ☐ No

Solvent 1: DCM:IPA (95:5)

Volume (µL): 600

Collect in position: A

Wait time (min): 5

Advanced pressure settings: Edit...

Repeat (number of times): 1

Pause after this step? ☐ No

Solvent 2: MTBE

Volume (µL): 600

Collect in position: A

Wait time (min): 5

Advanced pressure settings: Edit...

Repeat (number of times): 1

Pause after this step? ☐ No

Elution**Activated**

No. of steps	2
Pressure (Bar)	
Plate Dry	No
Dry time	0
Pause	5

Solvent

- 1 DCM:IPA (95:5)
- 2 MTBE
- 3
- 4

	1	2	3	4
Volume	600	600		
Position	A	A		
Pressure time	0	Advanced Pressure		
Repeat	1	1		
Pause	No	No		

'Advanced Settings'

Advanced Pressure:

2 Steps; 1.0 Bar for 30 seconds; 2.0 bar for 10 seconds

Edit Advanced Pressure Settings

Use advanced pressure settings? ☒ Yes

Number of steps: 2

1. Pressure (bar): 1.0

Positive pressure time (s): 30

2. Pressure (bar): 2.0

Positive pressure time (s): 10

Air Push? ☐ No

Air push time (s): 0

Solvent Properties

Solvent Description	
1	DCM:IPA (95:5)
2	MTBE
3	
4	
5	
6	
7	
8	
9	
10	



Solvent	1	2	3	4	5	6	7	8	9	10
Reservoir Type	Refillable		Non Refillable							
Capacity										
Aspiration flow rate (mL/min)	10	10								
Dispense flow rate (mL/min)	10	10								
Lower air gap flow rate (mL/min)	10	10								
Lower air gap volume (µL)	5	5								
Upper air gap flow rate (mL/min)	120	120								
Upper air gap volume (µL)	100	100								
Upper air gap dispense pause	300	300								
Conditioning?	Yes	Yes								
Conditioning number of times	2	2								
Conditioning flow rate (mL/min)	10	10								
Chlorinated	Yes	No								
Serial dispense	No	No								

< Cancel

Edit Sample - MeOH Sample

Save >

Sample
Sample name
MeOH Sample
Sample description
MeOH
Aspiration flow rate (mL/min)
10
Dispense flow rate (mL/min)
20

Air Gap
Lower air gap flow rate (mL/min)
20
Lower air gap volume (µL)
20
Upper air gap flow rate (mL/min)
120
Upper air gap volume (µL)
100
Upper air gap dispense pause (ms)
300

Aspirate
Aspirate post dispense?
Yes ☒

"Sample" Screen

Sample name	MeOH sample
Sample description	Default settings for MeOH
Aspiration flow rate	10
Dispense flow rate	20
Lower air gap flow rate	20
Lower air gap volume	20
Upper air gap flow rate	120
Upper air gap volume	100
Upper air gap dispense pause	300

< Cancel Edit Extraction Media - ISOLUTE SLE+ 400 µL C... Save >

Extraction Media	Pipetting Height
Name ISOLUTE SLE+ 400 µL Column	Solvent dispensation height (mm) -119.0
Manufacturer Biotage	Sample dispensation height (mm) -124.0
Part number 820-0055-B	Aspiration height (mm) -124.0
Capacity volume (µL) 0	Tune Pipetting Heights...
Format 24	
Comment <div></div>	

"Extraction Media" Screen

Name	ISOLUTE [®] SLE+ 400 µL Column
Manufacturer	Biotage
Part number	820-0055-B
Capacity volume	400
Format	96
Comment	
Solvent dispensation height	-119
Sample dispensation height	-124
Aspiration height	-124

< Cancel Edit Sample Plate/Rack - 12 x 75 mm Test Tub... Save >

Sample Plate/Rack	Pipetting Height
Name 12 x 75 mm Test Tubes, 24	Aspiration height (mm) -191.0
Capacity volume (µL) 5000	Pretreatment dispensation height (mm) -120.0
Format 24	Tune Pipetting Heights...

"Sample Plate/Rack" Screen

Name	12 x 75 mm Test Tubes, 24
Capacity volume	5000
Format	24
Aspiration height	-191
Pretreatment dispensation height	-120

< Cancel	Edit Pipette Tip - 1000 µL Biotage tip	Save >
<div>Pipette Tip</div> <div>Name</div> <div>1000 µL Biotage tip</div> <div>Manufacturer</div> <div>Biotage</div> <div>Part number</div> <div>414141</div> <div>Capacity (µL)</div> <div>1000</div> <div>Length (mm)</div> <div>95</div>		

"Pipette tip" Screen

Name	1000 µL Biotage Tip
Manufacturer	Biotage
Part number	414141
Capacity (µL)	1000
Length (mm)	95

EUROPE

Main Office: +46 18 565900
Toll Free: +800 18 565710
Fax: +46 18 591922
Order Tel: +46 18 565710
Order Fax: +46 18 565705
order@biotage.com
Support Tel: +46 18 56 59 11
Support Fax: + 46 18 56 57 11
eu-1-pointsupport@biotage.com

NORTH & LATIN AMERICA

Main Office: +1 704 654 4900
Toll Free: +1 800 446 4752
Fax: +1 704 654 4917
Order Tel: +1 704 654 4900
Order Fax: +1 434 296 8217
ordermailbox@biotage.com
Support Tel: +1 800 446 4752
Outside US: +1 704 654 4900
us-1-pointsupport@biotage.com

JAPAN

Tel: +81 3 5627 3123
Fax: +81 3 5627 3121
jp_order@biotage.com
jp-1-pointsupport@biotage.com

CHINA

Tel: +86 21 68162810
Fax: +86 21 68162829
cn_order@biotage.com
cn-1-pointsupport@biotage.com

KOREA

Tel: + 82 31 706 8500
Fax: + 82 31 706 8510
korea_info@biotage.com
kr-1-pointsupport@biotage.com

INDIA

Tel: +91 22 4005 3712
india@biotage.com

Distributors in other regions
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