

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO	
RAD: 13-239171- -11	FECHA: 2016-06-27 10:29:22
DEP: 2020 DIRECCION DE NUEVAS CREACIONES	EVE: 378 FASE NACIONAL INCLUIDO CAPITULO I
TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II	FOLIOS: 12
ACT: 519 TRASLADOINFORME	

DIRECCIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado(a)/Señor(a)
CARLOS R. OLARTE GARCIA

Asunto: Radicación: 13-239171- -11
Trámite: 11
Evento: 378
Actuación: 519
Oficio: 8330
Folios: 12

Patente de Invención	X			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	X	Capítulo I	X	Capítulo II	
No. Solicitud Internacional	PCT/EP2012/054180				
Fecha de Presentación Internacional	09/03/2012				

Como resultado del examen de fondo realizado, con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Rad. N° 13-239171-00000-0000	08/octubre/2013
	Rad. N° 13-239171-00000-0000	08/octubre/2013
Reivindicaciones:	Rad. N° 13-239171-00008-0000	18/agosto/2015
	Rad. N° 13-239171-00009-0000	04/septiembre/2015
Dibujos:	Rad. N° 13-239171-00000-0000	08/octubre/2013
Prioridades:	EP 11157564.3	09/marzo/2011
	US 61/450.993	09/marzo/2011

2. Análisis de la Prioridad

Se acepta la reivindicación de prioridad porque ésta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

De acuerdo con lo establecido en el numeral 1.2.2.2 del Capítulo Primero del Título X de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa

pagada por el solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las cubiertas por la tasa pagada. Por lo tanto, se estudiarán las reivindicaciones 1 a 22 presentes en las páginas 2 a 4 del radicado N° 13-239171-00009-0000.

Título de la solicitud: “Un dispositivo portátil para tomar muestras y un método para tomar muestras de sustancias de fármacos a partir de la respiración exhalado” (Pág. 1 del radicado 13-239171-00000-0000).

El problema planteado en esta solicitud consiste en la necesidad de diseñar un dispositivo portátil que permita detectar sustancias ilícitas en una persona y su proceso de fabricación.

Para resolver este problema técnico, la solicitud en estudio proporciona un dispositivo portátil para tomar una prueba de fármaco, para recoger manualmente una muestra de respiración exhalada de un sujeto para su análisis posterior basado en sensor. El dispositivo portátil para la prueba de fármaco comprende: un alojamiento que comprende por lo menos una entrada y por lo menos una salida para que la respiración exhalada salga a través de ella, y una membrana recolectora de muestra, dispuesta en el alojamiento; un elemento tubular que tiene una sección de boquilla para que el sujeto exhale en ella, y una sección de trampa selectiva en comunicación de fluido con la boquilla y con la entrada del alojamiento, que tiene una trayectoria de flujo de gas no recta para dejar pasar los aerosoles a través del elemento tubular; adicionalmente el proceso fabricación comprende los pasos de calentar una primera parte de un alojamiento de plástico, a fin de alargar la circunferencia de la primera parte. El proceso comprende también asentar una membrana recolectora de muestra muy próxima a una abertura que no sea una abertura de salida ni una de entrada, de la primera parte. Además, el proceso comprende emplear el calor de la primera parte para fundir la membrana recolectora de muestras en un borde. El proceso incluye adicionalmente utilizar el borde fundido para sujetar la membrana recolectora de muestras al alojamiento. También el proceso incluye deslizar una fracción de una segunda parte del alojamiento, que tiene una temperatura menor que la primera parte, dentro de la primera parte. La primera parte, cuando se enfríe, encogerá y se obtendrá un ajuste hermético alrededor de la fracción de la segunda parte y, al mismo tiempo, el alojamiento encapsulará la membrana recolectora de muestras.

El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): G 01 N 33/497; A 61 B 5/00.

4. De la solicitud de patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

- Se sugiere al solicitante incluir entre paréntesis () los números de referencia de cada uno de los elementos que hacen parte de la invención de acuerdo con la numeración empleada en los dibujos, tanto en el capítulo reivindicatorio como descriptivo, los cuales deben ser coincidentes. Lo anterior, con el fin de hacer más fácil y sencilla la comprensión de la materia reivindicada.
- En las reivindicaciones 1, 3 a 5, 10, 13, 14, 18 y 19 se reconocen resultado a obtener donde mencionan: reivindicación 1 “(...) *configurada para actuar como un prefiltro para filtrar la saliva o moco o partículas grandes o agregados de dicho aire exhalado*”, “(...) *configurada para determinar que un volumen previamente definido de la trayectoria exhalada ha pasado a través de la membrana recolectora de muestra*”, reivindicación 3 “(...) *para medir un volumen proporcional al volumen previamente definido de la respiración exhalada*”, reivindicaciones 4 y 5 “(...) *adaptado para extraer una porción definida de la respiración exhalada hacia la unidad medidora de volumen*”; reivindicación 10 “(...) *una caída de presión de 36 Pa a 9.5 m/min de velocidad*”

media"; reivindicación 13; "(...) para denegar a la respiración exhalada una trayectoria recta a través del lumen del conducto; creando de esa manera la sección de trampa selectiva, que permite primeramente que los aerosoles de la respiración exhalada pasen a través de ella"; reivindicación 14 "(...) que tienen un tamaño que permite únicamente que los aerosoles pasen a través de ellos"; reivindicación 18 "(...) de manera que la primera parte, cuando se enfríe, encoja y se obtenga un ajuste hermético alrededor de la segunda parte (...)"; reivindicación 19 "(...) una unidad censora para analizar una muestra recolectada de la respiración exhalada de un sujeto por medio de dicho dispositivo", puesto que las reivindicaciones incluirían no sólo las soluciones propuestas por el solicitante, sino todas las alternativas presentes o futuras que lleguen a esos resultados. Se sugiere reemplazarlos por las características esenciales, estructurales o funcionales, que contribuyen a la obtención de esos efectos.

- En la reivindicación 1, hay funcionalidades donde divulgan: "(...) para que salga a través de ellas la respiración exhalada", "(...) para que el sujeto exhale en ella", "(...) para recolectar los aerosoles de la respiración exhalada"; las cuales no son características técnicas de la invención, puesto que las funcionalidades (funciones realizadas) sirven para entender la relación que hay entre los diferentes elementos estructurales, pero son solo los elementos estructurales los que definen la invención haciendo a las funcionalidades opcionales y, por lo tanto, las funcionalidades no le pueden dar novedad y/o nivel inventivo a un aparato. Adicionalmente se indica a la solicitante que los aparatos se deben describir con los elementos estructurales físicos que hacen posible la realización de las funciones en vez de describirlo por medio de sus funciones. En conclusión, las funcionalidades no permiten definir una diferencia entre dos aparatos porque un mismo aparato puede realizar dos funciones diferentes y seguir siendo el mismo aparato.
- La reivindicación 1 no es clara donde menciona "(...) una sección de trampa selectiva", puesto que no se hace referencia en que consiste la trampa ni tampoco se especifica de qué manera es selectiva. Adicionalmente tampoco es clara donde divulga "(...) una trayectoria de gas no recta para permitir que pasen los aerosoles a través del elemento", ya que no se hace referencia a que tipo de gas ni a qué tipo de aerosol son los que permite pasar a través del elemento tubular. Se le sugiere caracterizar la invención por sus componentes técnicos estructurales que cumplen con el mismo efecto técnico.
- En las reivindicaciones 1, 8, 9, 12, 13, 15, 16 y 19 el término "(...) por lo menos" es relativo por lo cual no permite distinguir la invención del estado de la técnica, porque indica el rango inferior pero no el superior. Se sugiere reemplazar el término incluyendo el rango que tenga sustento en la descripción.
- El termino: "(...) aproximadamente" en la reivindicación 10 es impreciso, por lo cual no permite distinguir la invención del estado de la técnica. Se sugiere sustituirlo por un término preciso o un rango concreto.
- La expresión: "(...) fibras acrílicas y fibras de polipropileno" en la reivindicación 11, que si bien son conocidos, son términos generales que sugieren de forma imprecisa que la protección se extiende a otras posibles variaciones o modificaciones.
- La materia objeto de la reivindicación 19 divulga un sistema haciendo referencia al dispositivo de las reivindicaciones 1 a 17, lo cual no es permitido porque se trata de una falsa dependencia. Se sugiere hacer la corrección necesaria.

- La expresión: “(...) *un volumen previamente definido*” en las reivindicaciones 3 y 5 es impreciso. por lo cual no permite distinguir la invención del estado de la técnica. Se sugiere sustituirlo por un término preciso o un rango concreto.
- En las reivindicaciones 15 y 16 se mencionan las características técnicas de un elemento ajeno a los componentes técnicos estructurales del dispositivo portátil tomador de muestras de fármaco así: reivindicación 15 “(...) *en el que los aerosoles comprenden compuestos no volátiles de por lo menos una sustancia de fármaco en la respiración exhalada (...)*”; reivindicación 16: “(...) *en el que los aerosoles comprenden compuestos no volátiles de por lo menos una sustancia de fármaco en la respiración exhalada; y donde la sustancia de fármaco está comprendida en la lista que comprende: anfetaminas, éxtasis, cannabis, THC y cannabinoides, opiatos, heroína, morfina, 6-AM, cocaína, benzodiacepinas, propoxifeno, metadona, buprenorfina, tramadol, LSD, fármacos de diseñador/internet, Kathinon, 20 GHB, meprobamat, fármacos Z, triptaminas o esteroides anabólicos*”. Adicionalmente, estas reivindicaciones fallan en ser claras, puesto que no indican específicamente donde se encuentran los aerosoles en el dispositivo.
- La materia objeto de la reivindicación 18 divulga un proceso haciendo referencia a las reivindicaciones 1 a 17 de dispositivo, lo cual no es permitido ya que se trata de una falsa dependencia. Se sugiere hacer la corrección necesaria.
- En la reivindicación 9, se reconocen los siguientes errores de traducción: “*portador aglutinado por hilad*”, “*peso de gasa*”. Se sugiere hacer la corrección necesaria.
- La reivindicación 9 presenta el siguiente error de digitación “(...) *hilad*”. Se sugiere hacer la corrección correspondiente
- El término “(...) *igual a*” en la reivindicación 13 es relativo por lo cual no permite distinguir la invención del estado de la técnica. Se sugiere sustituirlo por un término o rango concreto.

5. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad: marzo 09 de 2011, y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación*
D3	US 5'465,728	“Breath collection”	14/noviembre/1995
D4	Artículo 1*	“Method for determination of methadone in exhaled breath collected from subjects undergoing methadone maintenance treatment”	03/julio/2010

*BECK O ET AL: “[Method for determination of methadone in exhaled breath collected from subjects undergoing methadone maintenance treatment](#)”, JOURNAL OF CHROMATOGRAPHY B: BIOMEDICAL SCIENCES & APPLICATIONS, ELSEVIER, AMSTERDAM, NL, vol. 878, no. 24, 15 August 2010 (2010-08-15), pages 2255 - 2259, XP027193279, ISSN: 1570-0232, [retrieved on 20100703]

El documento D3¹ divulga un aparato que es altamente portátil se utiliza para recoger el aliento de los mamíferos para el análisis químico y como una herramienta de diagnóstico para el médico. El aparato comprende un recipiente de depósito de fluido que tiene primero y segundo extremos y un cuerpo que se extiende entre estos extremos a fin de definir una cámara interior; un portal de entrada aliento; un portal de salida aliento; un portal de muestreo; una chaqueta para mantener la temperatura de la cámara; un contenedor de muestras para la realización de muestras de aire espirado; y medios de bomba para mover

¹<http://jat.oxfordjournals.org/content/34/5/233.abstract>

muestras seleccionadas de aliento desde el recipiente de reserva en el recipiente de la muestra (resumen).

El documento D4² divulga un método para la determinación de la metadona en el aliento exhalado de los pacientes en tratamiento de mantenimiento con metadona (resumen). Dispositivo de muestreo utilizado para recoger muestras de aliento exhalado en un disco Empore C18 (Pág. 2, Fig. 1).

6 . Examen de Patentabilidad (Art 14 D486)

Nivel inventivo (Art18 D486)

La reivindicación 1 consiste en: “*Un dispositivo portátil tomador de muestra de sustancias de fármaco, para tomar una muestra de la respiración exhalada de un sujeto para su posterior análisis basado en sensor, que comprende: (...)*.” (Ver página 2 del radicado N° 13-239171-00009-0000).

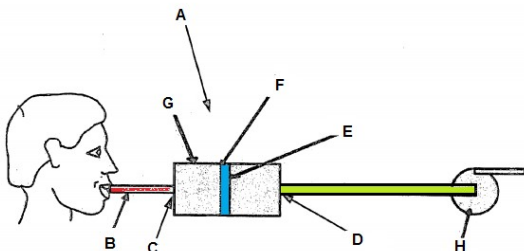
Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características esenciales	D3	D4
Un dispositivo portátil tomador de muestra de sustancias de fármaco.	Un aparato que es altamente portátil e incluso de mano se utiliza para recoger el aliento de los mamíferos para el análisis químico y como una herramienta de diagnóstico para el médico (Resumen).	Un dispositivo de muestreo utilizado para recoger muestras de aliento exhalado en un disco Empore C18 (Fig. 1).
Un alojamiento que comprende por lo menos una entrada y por lo menos una salida.	Cámara (18) (Fig. 4).	Colector de muestreo (G) (Fig. 1).
Una membrana recolectora de muestras dispuesta en el alojamiento.	No menciona.	Disco de Empore C18 (F) (Fig. 1).
Un elemento tubular que tiene una sección de boquilla para que el sujeto exhale en ella.	Una boquilla (40) puede ser una parte moldeada integralmente del tubo (38), para la inserción en la boca de un paciente humano, sellada por los labios (Col. 4, líneas 45 a 47).	Boquilla (B) (Fig. 1).
Una sección de trampa selectiva en comunicación de fluido con la boquilla y la entrada del alojamiento.	Atrapamiento Adsorbente: La respiración alveolar se extrae a través de una trampa (Col. 5, líneas 66 y 67). En la figura 5 se muestra la trampa (213) (Fig. 5).	No menciona.
La sección de trampa selectiva tiene una trayectoria de flujo de gas no recta configurada para actuar como un prefiltro para filtrar la saliva o moco o partículas grandes de dicho aire exhalado.	El extremo (14) del aparato (10) lleva un acoplador (36) para el acoplamiento sellado con un tubo de respiración (38) (que se muestra fragmentado) adaptada para recoger el aliento de la vía aérea pulmonar de un sujeto. Por ejemplo, como se muestra en la figura. 1 una boquilla (40) puede ser una parte moldeada integralmente del tubo (38), para la inserción en la boca de un paciente humano, sellada por los labios (Col. 4, líneas 43 a 50). En la figura 4 se muestra que el tubo (38) tiene la boquilla (40) por la cual el usuario exhalara y el recorrido del flujo no es lineal debido a las nervaduras (38') y el flujo no será recto porque el tubo	No menciona.

2 <http://www.sciencedirect.com/science/article/pii/S1570023210004277>

	(38) vertical se une a la cámara horizontal (18) (Fig. 4).	
Una unidad medidora de volumen para determinar que un volumen previamente definido de la trayectoria exhalada ha pasado a través de la membrana recolectora de muestra.	Unidad de medición respirometro ³ (58) (Fig. 4).	No menciona.

***Empore C18 <http://pubs.acs.org/doi/abs/10.1021/ac034278w>



(Figura 1 documento D4)

Los documentos D3 y D4 se consideran el estado de la técnica cercano a la invención definida en la reivindicación 1 porque divulgan un dispositivo portátil tomador de muestra de sustancias de fármaco.

La diferencia entre la invención, definida en la reivindicación 1 y el aparato para recoger el aliento exhalado de un usuario de D3 consiste en que no hace referencia a una membrana recolectora de muestras dispuesta en el alojamiento.

El efecto que logra el incluir una membrana recolectora de muestras dispuesta en el alojamiento, es que permite una recolección adecuada de los aerosoles de la respiración exhalada del usuario y a su vez reduce las pérdidas de presión durante la exhalación.

Por lo tanto, el problema técnico objetivo que pretende resolver esta invención se puede formular así: ¿Cómo garantizar la idoneidad de la muestra recolectada en un dispositivo de muestreo de aire exhalado?

Sin embargo, la utilización de una membrana que permite una recolección adecuada de los aerosoles de la respiración exhalada del usuario ya se encuentra divulgada en el documento D4 que se refiere a un disco de empore C₁₈ (F) (Fig. 4), el cual es una membrana para la toma de muestras en muy bajas concentraciones de compuestos nitroaromáticos sin degradación o pérdida de los mismos.⁴

En consecuencia, la persona del oficio normalmente versada en la materia, incluiría la membrana recolectora en forma de disco de empore C₁₈ del documento D4 en el aparato para recoger el aliento divulgado en el documento D3 para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual se considera obvia.

Asimismo, el documento D3 divulga las características de las reivindicaciones dependientes así:

- Reivindicación 2: El extremo (14) del aparato (10) lleva un acoplador (36) para el acoplamiento sellado con un tubo de respiración (38) (Col. 4, líneas 43 a 46).
- Reivindicación 3: Después de un minuto de la derivación, el grifo (62) se ajusta de

3 http://www.coleparmer.com/assets/Catalog_pdfs/PDF_CP/JZ_1035.pdf

4 <http://pubs.acs.org/doi/abs/10.1021/ac034278w>

modo que la respiración alveolar pasa a través de la trampa adsorbente (66). En la práctica, una muestra utilizable (101) puede ser recogida utilizando una velocidad de flujo de 2,0 l / min durante 5,0 minutos. Sin embargo, las muestras más pequeñas o más grandes pueden recogerse lo desear (Col. 7, líneas 1 a 5).

- Reivindicación 4: Un portal de muestreo (22) perfora el recipiente (12) del cuerpo en un punto proximal al extremo (14) y proporciona comunicación de fluido entre la cámara (18) y el exterior del recipiente (12). Una válvula (24) controla la comunicación de modo que las muestras de gas dentro de la cámara (18) pueden ser retirados de la cámara (18) o se seleccionan para la recogida en el recipiente 26 montado en el portal de muestreo (22), tal como se describirá más adelante. Una válvula de charnela acción de resorte (28) está montado en la salida de ventilación (20) con la suficiente fuerza de resorte para mantener la rejilla de ventilación 20 cerrado excepto cuando el sujeto está exhalando dentro de la cámara (18) (Col. 4, líneas 20 a 25).
- Reivindicación 5: Puede incluir disposiciones sobre métodos alternativos de recogida de muestras de aliento, además de la captura de adsorción: es decir, atrapamiento criogénico, captura química, colecciones de contenedores evacuados, y las colecciones de bolsas (Col. 2, líneas 60 a 63).
- Reivindicación 6: en la figura. 2, el aliento recogido se puede evacuar por bombeo en una bolsa, para el ensayo y / o posterior concentración en el laboratorio (Col. 6, líneas 16 a 20).
- Reivindicación 12: El orificio de ventilación (20) incluye un filtro (56) y un microorganismo respirómetro (58). La salida del portal (22) se ha extendido a través del conducto (60) dentro del manguito de calentamiento (30') y está conectado al interior de camión (2). El recipiente (26') se encuentra en camión (2) y recibe aliento recogido cuando se selecciona a través del grifo de (3) vías (62) conectado al conducto 60 a través de una manguera flexible (64) (Col. 6, líneas 45 a 53).

De igual forma, el documento D4 divulga las características de las reivindicaciones dependientes así:

- Reivindicación 7 y 11: donde la membrana de recolección es el disco de Empore C18 (F) (Fig. 1).
- Reivindicación 15 y 16: Un método para la determinación de la metadona en el aliento exhalado de los pacientes en tratamiento de mantenimiento con metadona (resumen).
- Reivindicación 19: Un método para la determinación de la metadona en el aliento exhalado de los pacientes en tratamiento de mantenimiento con metadona. Aliento exhalado se obtuvo de 13 pacientes después de la ingesta de la dosis diaria de metadona. Los compuestos fueron atrapados por filtrar el aire a través de una superficie de sílice C18 modificada. Después de la elución de cualquier metadona atrapada el extracto se analizó mediante un método de espectrometría de masas en tándem de cromatografía líquida combinada (resumen).

De igual manera, las reivindicaciones 1, 3 a 5, 10, 13, 14, 18 y 19 no mencionan características técnicas tangibles adicionales que puedan brindarle nivel inventivo al objeto de las reivindicaciones 1 y 18 puesto que estas se encuentran redactadas en términos de resultados a alcanzar, efectos o ventajas y usos.

7. Conclusión

Los requisitos de patentabilidad de la presente solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D3	US 5'465,728	1 a 6 y 12	Nivel Inventivo
D4	Articulo 1*	1, 7, 11, 15, 16 y 19	Nivel inventivo
---	----	1, 3 a 5, 10, 13, 14, 18 y 19	Art. 30

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Si como respuesta a este requerimiento el solicitante llegara a modificar: i) el capítulo reivindicatorio, ii) la descripción de la invención a proteger, iii) o presente un nuevo capítulo reivindicatorio, y desee que se realice un nuevo examen de patentabilidad a esta modificación, no deberá pagar la tasa de modificación voluntaria pero sí la correspondiente a la tasa de examen de patentabilidad. En todo caso, el número de requerimientos por no patentabilidad estará supeditado a que el término del estudio de patentabilidad no sea superior a 18 meses, contados desde la publicación de la solicitud de patente de invención. Adicionalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones deberá pagar la tasa por reivindicación adicional.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 2016-06-28

Elaboró: Harold Snehdyer Vega Russi

Revisó: Rosa Patricia Tellez Chavarro

Search history

- Search 1: device and membrane and chamber and sampling and exhaled breath (Results 3)
- Search 2: Breath and apparatus and test (Results 352)
- Search 3: portable sampling and device and exhaled breath (Results 2)
- Search 4: Device recover component fractions from exhaled air (Results 0)
- Search 5: Apparatus to recover component fractions from exhaled air (Results 1)
- Search 6: nozzle and trap and chamber and membrane (Results 70)
- Search 7: PN=(US4292978 OR US5465728 OR US5834626 OR WO0184112 OR WO09030957 OR EP2781917 OR WO13132085 OR WO14147015 OR DE19718924 OR EP2518499) (Results 9)
- Search 8: PN=(US4292978 OR US5465728 OR US5834626 OR WO0184112 OR WO09030957 OR EP2781917 OR WO13132085 OR WO14147015) (Results 7)
- Search 9: 7 and 2 (Results 0)
- Search 10: PN=(WO 2012/120140) (Results 100000)
- Search 11: PN=(WO2012120140) (Results 1)
- Search 12: [SP]: 1. a portable drug sampling device for handheldly collecting a sample from exhaled breath of a subject for further sensor based analysis, comprising: a housing comprising at least one inlet and at least one outlet for said exhaled breath to exit through, and a sampling membrane arranged in said housing and a tubular element having a mouthpiece section for said subject to exhale into, wherein said sampling membrane is arranged to collect said aerosols from said exhaled breath and wherein said tubular element has a selective trap section in fluid communication with said mouthpiece and said inlet of said housing, said selective trap section having a non-straight gas flow path for letting aerosols pass through and for substantially preventing big particles and/or aggregates and/or saliva to be collected by said sampling membrane. 2. the device according to claim 1, wherein said tubular element is detachable from said housing or wherein said tubular element is an integrated part of said housing. 3. the device according to claim 1, wherein said volume measure unit is configured to measure a volume proportional to said pre-defined volume of said exhaled breath. 4. the device according to claim 3, wherein a port is arranged downstream said mouthpiece and upstream said sampling membrane and wherein said port is adapted to extract a defined portion of said exhaled breath into said volume measure unit. 5. the device according to claim 1, said volume measure unit comprising a gas volume collecting element, such as a bag, having a volume and wherein a port is arranged downstream said mouthpiece and upstream said sampling membrane and wherein said port is adapted to extract a defined portion of said exhaled breath into said volume measure unit and wherein said volume of said gas volume collecting element is proportional to said pre-defined volume of said exhaled breath. 6. the device according to claim 5, wherein said volume collecting element is a non-elastic bag with a predetermined volume. 7. the device according to claim 1, wherein said sampling membrane is a filter membrane. 8. the device according to claim 7, wherein said filter membrane comprises at least one layer of non-woven filtration media with a specific weight in the range of 23 g/m³ to 500 g/m³. 9. the device according to claim 8, wherein said filter membrane comprises at least one further layer being a spunbonded carrier with a scrim weight of 10 to 20 g/m³. 10. the device according to claim 8, wherein said filter membrane has a filter surface to be passed by exhaled gas of approximately 800 mm² and a pressure drop of 36 pa at 9.5 m/min media velocity. 11. the device according to claim 7, wherein said filter membrane is made of a blend of acrylic fibers and polypropylene fibers. 12. the device according to claim 1, wherein said housing includes at least two outlets. 13. the device according to claim 1, wherein said tubular element further comprises: an inlet, and an outlet in connection with a lumen at least two baffles, each having a height of at least a length of a radius of the lumen and wherein said baffles are arranged on different sides of the lumen to deny an exhaled breath a straight path through said lumen of said tubular element, thereby creating said selective trap section, which primarily said aerosols in said exhaled breath are permitted to pass through. 14. the device according to claim 13, wherein each baffle comprises orifices with a size that only permit said aerosols to pass through. 15. the device according to claim 1, wherein said aerosols comprise non-volatile compounds of at least one drug substance in said exhaled breath. 16. the device according to claim 15, wherein said drug substance is comprised in the list comprising amphetamine, ecstasy, cannabis, thc and cannabinoids, opiates, heroin, morphine, 6-am, cocaine, benzodiazepines, propoxyphene, methadone, buprenorphine, tramadol, lsd, designer/internet drugs, kathinon, ghb, meprobramat, z-drugs, tryptamines, or anabolic steroids. 17. (canceled) 18. a process to manufacture a portable sampling device, comprising: heating a first part of a plastic housing, thereby enlarging said first part's circumference seating a sampling membrane in close proximity to an opening, said opening not being an outlet or an inlet, of said first part employing said heat from said first part for melting said sampling membrane at an edge utilizing said melted edge for fastening said sampling membrane to said housing sliding a fraction of a second part of said housing, having a temperature lower than said first part, inside of said first part, whereby the first part when cooling down will shrink and obtaining a tight fit around said fraction of said second part and at the same time said housing will encapsulating said sampling membrane. 19. the device according to claim 1, further comprising in combination a sensor unit for analyzing a sample collected from exhaled breath of a subject by means of said device, the combination forming a system for detecting the presence and/or determining the quantitative amount of at least one drug compound in said exhaled breath. 20. a method of screening a person for drugs, comprising collecting a sample from exhaled breath of a subject for sensor based analysis of said sample, said collecting comprising said subject exhaling into a device, collecting aerosols from said exhaled breath in a sampling membrane of said device, and passing said exhaled breath through a tubular element having a non-straight gas flow path for letting aerosols pass through and for substantially preventing big particles and/or aggregates and/or saliva to be collected by said sampling membrane extracting a content from said sampling membrane and employing a sensor unit for detecting traces of said drugs in said content, and analyzing a presence of said drugs based on a result obtained from said sensor unit. 21. the method according to claim 20, further comprising providing a portable drug substance sampling device for collecting said sample from exhaled breath of a subject, said portable sampling device comprising a housing including at least one inlet and at least one outlet for said exhaled breath to exit through and a sampling membrane arranged in said housing to collect aerosols from said exhaled breath, a tubular element having a mouthpiece section for said subject to exhale into and a selective trap section in fluid communication with said mouthpiece and said inlet of said housing, said selective trap section having a non-straight gas flow path for letting aerosols pass through said tubular element, and a volume measure unit for determining that a pre-defined volume of said exhaled breath has passed through said sampling membrane. 22. (canceled) 23. the device according to claim 1, further comprising a volume measure unit for determining that a pre-defined volume of said exhaled breath has passed through said sampling membrane. 24. the device according to claim 7, wherein said filter membrane is an electrostatic filter membrane. 25. the method according to claim 20, further comprising measuring a pre-defined fraction of said exhaled breath volume for determining a specific total volume of said exhaled breath passing through said sampling membrane, and when said specific total volume is determined as having passed through said sampling membrane terminating said exhalation and sealing off said device. (Results 9)
- Search 13: [SP]: field of the invention [0001] this invention pertains in general to the field of portable handheld devices, sampling systems and methods for collecting a sample from exhaled breath of a subject, and for detecting the presence (i.e. qualitative) or determining the quantitative amount of at least one illicit drug substance or compound in exhaled breath. more particularly the invention relates to such portable handheld devices. background of the invention [0002] it is known that exhaled breath is commonly used in alcohol testing and today's technology makes it possible to perform on-site breath testing with legally defensible results using infrared spectroscopy.[0003] testing for other illicit drugs of abuse traditionally requires blood or urine samples. alternatively specimens comprising hair, sweat or oral fluid could be used. blood sampling is invasive and requires medically trained personnel, whereby test subject often have to be transported to a hospital for sampling. these procedures are time and effort consuming. with long lead times the test result will be too old. urine sampling may also be considered intruding on personal integrity. even other issues related to samples and specimens taken from a subject to be tested arise. for instance, blood samples, and especially urine samples are at risk of the subject exchanging the samples or using clean samples from another subject to avoid being discovered with traces of illicit drugs.[0004] thus, there is a need to provide a non-invasive, not-specimen based apparatus, system and/or method for detecting the presence (i.e. qualitative) or determining the quantitative amount of at least one drug substance in a subject. particularly a device and method which should be easy to use with no or little training, especially a device and method for directly, at the site/on-site, screening a person for illicit drugs and obtaining results that could be approved by court.[0005] hence, an improved apparatus, system and/or method for at site/on site sampling of a subject for drug substances are desired. such a device, system and/or method for sampling the subject for illicit drugs of abuse and/or medical drugs would be desired. the apparatus, system and/or method should be efficient, non-bulky, user friendly both for operators and the subject. it should further be not intruding and not invasive.[0006] another application would be to take samples from exhaled breath for sampling aerosols which may transport biomarkers. the samples could then be analyzed and detected biomarkers may be used for diagnosis of medical conditions of the tested subject. measuring biomarkers in exhaled air would be non-invasive and enables repeated sampling which can be useful for early detection of disease as well as monitoring of disease progression and therapy response.[0007] a known method for sampling biomarkers in exhaled breath condensate (ebc) i.e. exhaled water vapor that is condensed by the means of low temperature. both volatile and non-volatile compounds have been identified using ebc. the non-volatiles found in ebc are believed to originate from particles formed within the airways. the collection of exhaled breath condensate (ebc) is connected with a number of serious methodological difficulties such as dilution with water resulting in very low concentrations of the substances of interest, high contamination with substances originating from the oral cavity, high intraindividual coefficient of variation and a very inefficient way to sample, especially, non-volatiles compounds[0008] hence, a method solving the short come of methods for easy monitoring of the airways that also allows frequent sampling would be advantageously. particularly if the method may be performed risk free. thus, there is a need to provide a non-invasive based apparatus, system and/or method for detecting the presence (i.e. qualitative) or determining the quantitative amount of at least one biomarker for medical diagnosis of a subject. particularly, a device and method being easy to use with no or little training, especially a device and method to be used directly, at the site/on-site, for sampling and/or testing a subject for a medical diseases or illnesses would be advantageously. the device and method should have a sensitive for biomarkers high enough to obtain results of a standard that could be used for diagnosis of medical conditions.[0009] hence, an improved apparatus, system and/or method for at site/on site sampling of biomarkers from a subject is desired. the apparatus, system and/or method should be efficient, non-bulky, user friendly both for

operators and the subject. summary of the invention [0010] accordingly, embodiments of the present invention preferably seek to mitigate, alleviate or eliminate one or more deficiencies, disadvantages or issues in the art, such as the above-identified, singly or in any combination by providing a system and a method, according to the appended patent claims.[0011] according to one aspect of the invention, a portable drug substance sampling device is provided for collecting a sample from exhaled breath of a subject for further sensor based analysis. the device comprising a housing comprising at least one inlet and at least one outlet for the exhaled breath to exit through and a sampling membrane arranged in the housing.[0012] the device further comprising a tubular element having a mouthpiece section for the subject to exhale into. the tubular element is a selective trap section in fluid communication with the mouthpiece and the inlet of the housing and the selective trap section is having a non-straight gas flow path for letting aerosols pass through said tubular element.[0013] the sampling membrane is arranged to collect the aerosols from the exhaled breath. further the device comprising a volume measure unit for determining that a pre-defined volume of the exhaled breath has passed through the sampling membrane.[0014] the exhaled breath volume is not stored in a volume for analysis of the chemical contents of the entire breath volume. rather, traces of the drug substance are attached to a sampling membrane. analysis is not made online of the breath volume, but of the traces in the sampling membrane. the portable drug testing device may be sealed and sent further for the analysis, such as in a laboratory. collection of the traces is made quickly, by exhaling a predetermined volume of breath through the sampling membrane. the obtain results when using the device are reliable and have a proven robustness. using the invented drug testing device is far more convenient, quicker and cheaper than any previous breath sample collection methods.[0015] compounds exhaled in expired air may originate from blood by a mechanism of producing a gas phase in the alveoli. alternatively, compounds may originate from other parts of the airways. non-volatile compounds are transferred from the lungs carried by an aerosol. here the non-volatile are drug substances or compounds and could be either medical drugs or legal or illegal narcotic substances or markers thereof. the drug substances are collected on-site using a portable system comprising a sampling membrane. the collected samples are to be sent to a laboratory for further analysis. alternatively, compact on-site analysis equipment may be used to perform the analysis. the analysis is performed using a suitable analyzing method like spectroscopy or preferably mass-spectroscopy or surface enhanced raman spectroscopy (sers). other similar sensitive methods known to the skilled person may be used.[0016] since the portable drug testing device is small and designed to be easy to handle it may be used by any personnel anywhere on-site. thus the drug testing device is adapted to be used instead of more intrusive tests, like tests based on the much common urine or blood samples.[0017] the housing could be made of any material like, plastic, metal or glass as long as it is possibly to either clean or preferable be aseptic but could also be used sterile. the housing could alternatively or in addition be made of a disposable material. in this way the housing may, after being used for sampling and after the analysis of the collected compounds has been performed, be discarded.[0018] the tubular section is used to improve the quality of the test by preventing big particles and/or aggregates and/or saliva to be collected by the sampling membrane. this may be done by having a selective trap section in the tubular section which has baffles to force the exhaled breath to pass a non-straight gas flow path.[0019] in some embodiments of the invention, the tubular element is detachable from the housing or the tubular element is an integrated part of the housing.[0020] in some embodiments of the invention, the volume measure unit is configured to measure a volume proportional to the pre-defined volume of the exhaled breath.[0021] in some embodiments of the invention, a port is arranged downstream the mouthpiece and upstream the sampling membrane. the port is adapted to extract a defined portion of the exhaled breath into the volume measure unit.[0022] in some embodiments of the invention, the volume measure unit comprising a gas volume collecting element, such as a bag, having a volume and wherein a port is arranged downstream the mouthpiece and upstream the sampling membrane and wherein the port is adapted to extract a defined portion of the exhaled breath into the volume measure unit.[0023] this is an easy and effective way of determining when a pre-defined volume of exhaled breath has passed through the sampling membrane. the bag is blown up by utilizing the back pressure due to air flow resistance of the sampling membrane. the volume of the gas volume collecting element is proportional to the pre-defined volume of the exhaled breath.[0024] in some embodiments of the invention, the volume collecting element is a non-elastic bag with a predetermined volume and/or size.[0025] an elastic bag could be used but a non-elastic bag with a specific volume is easier to blow up and can only hold that specific volume.[0026] in some embodiments of the invention, the sampling membrane is a filter membrane, preferably an electrostatic filter membrane.[0027] in some embodiments of the invention, the filter membrane comprising at least one layer of non-woven filtration media with a specific weight in the range of 23 g/m³ to 500 g/m³, preferably in the range of 150 up to 300 g/m³, and even more preferably in the range of 200 up to 280 g/m³. [0028] in some embodiments of the invention, the filter membrane comprising at least on further layer being a spunbonded carrier with a scrim weight of 10 to 20 g/m³. [0029] one important parameter of a sampling device that is fulfilled by using a filter membrane made of fibers is the low pressure drop. to be able to collect exhaled breath samples from most subjects the pressure drop through the system has to be as low as possible. the flow rate of a subject's exhalation depends on some parameters for example the subject's age, mental state (mr, alzheimer's), medical condition (sepsis, parkinson's) or other medications like benzodiazepines, opiates, neuroleptics, local anesthetics or intoxicants etc. many people with a history of drug abuse have a very low flow rate.[0030] in some embodiments of the invention, the filter membrane has a filter surface to be passed by exhaled gas of approximately 800 mm² and a pressure drop of 36 pa at 9.5 m/min media velocity.[0031] in some embodiments of the invention, the filter membrane is made of a blend of acrylic fibers and polypropylene fibers.[0032] the acrylic fibers have electrostatic properties while the polypropylene fibers will make the filter structure stronger, for example make the polypropylene fibers give the filter membrane enough support so that requires sizes and shapes can be punched out from the material.[0033] in some embodiments of the invention, the housing may have at least two outlets.[0034] two outlet will help to prevent a subject to be tested from stopping the air from flowing out of the outlet and thereby preventing enough exhaled breath from passing through the sampling element.[0035] in some embodiments of the invention, the tubular element further comprises an inlet, an outlet in connection with a lumen, at least two baffles, each having a height of at least a length of a radius of the lumen. the baffles are arranged on different sides of the lumen to deny an exhaled breath a straight path through the lumen of the conduit, thereby creating the selective trap section, which primarily the aerosols in the exhaled breath are permitted to pass through.[0036] in some embodiments of the invention, each baffle may comprise orifices with a size that only permit the aerosols to pass through.[0037] in some embodiments of the invention, the aerosols comprise non-volatile compounds of at least one drug substance in the exhaled breath. the drug substance is comprised in the list comprising amphetamine, ecstasy, cannabis, thc and cannabinoids, opiates, heroin, morphine, 6-am, cocaine, benzodiazepines, propoxyphene, methadone, buprenorphine, tramadol, lsd, designer/internet drugs, katinon, ghb, meprobamat, z-drugs, tryptamines, or anabolic steroids but are not limited to these since other illicit drugs (drugs of abuse) not included in the list may also be detectable due to similar interchanges with the human body as the above mentioned illicit drug substances.[0038] according to another aspect of the invention, the portable drug testing device may be used for non-intrusive breath testing a subject for illicit drug substances, preferably as a substitute for testing the subject for the drug substance by sampling blood or urine.[0039] the compositions of the exhaled particles are believed to reflect the airway's mucus layer and/or respiratory tract lining fluid, which probably reflects the blood content of the drug. the drug substances or compounds are believed by the inventors to most likely to come from the central part of the airway system. the non-volatile drug substances or compounds are carried by liquid droplets (aerosol) that are formed during normal breathing, for example, by the turbulent airflow causing the airway-lining fluid to nebulize. the aerosols are possible to collect as exhaled breath condensates. the theory comes from anesthetic studies that have showed that anesthetic potency correlates with lipid solubility. holds true across species and implies when a specific hydrophobic region is occupied the more soluble the anesthetic agent is in blood the faster the drug goes into the body.[0040] according to yet another aspect of the invention, a system is provided for detecting the presence and/or determining the quantitative amount of at least one drug compound in said exhaled breath. the system comprising a portable drug testing device and a sensor unit for analyzing a sample collected from exhaled breath of a subject by means of said device.[0041] the mass-spectroscopy or sers are the preferred analyzing methods, since this technology has a very high selectivity and sensibility of bioanalysis especially with regards to trace analytes in biological samples. the preferable interface for the mass spectroscopy is liquid chromatography.[0042] the sampling membrane may be emptied from collected particles and analyzed by dissolving the collected particles from the exhaled breath in a solvent. the solvent could than be analyzed by the sensor unit. another method could be to evaporate the content of the sampling membrane onto a sers surface.[0043] in a further aspect of the invention, a process to manufacture the portable drug testing device is provided, the process comprising: heating a first part of a plastic housing, thereby enlarging the first part's circumference. the process further comprises seating a sampling membrane in close proximity to an opening, not being an outlet or an inlet, of the first part. moreover, the process comprises employing the heat from the first part for melting the sampling membrane at an edge. the process further includes utilizing the melted edge for fastening the sampling membrane to the housing. further, the process includes sliding a fraction of a second part of the housing, having a temperature lower than the first part, inside of the first part. the first part when cooling down will shrink and a tight fit is obtained around the fraction of the second part and at the same time the housing will encapsulating the sampling membrane.[0044] in a further aspect of the invention, a system for detecting the presence or determining the quantitative amount of at least one drug compound in the exhaled breath is provided. the system comprising a device for drug testing, and a sensor unit for analyzing a sample collected from exhaled breath of a subject by means of said device.[0045] the system may be used to determining the presence of a drug substance in the exhaled breath either quantitative and/or qualitative.[0046] in yet another aspect of the invention, a method of screening a person for drugs is provided. the method comprising, collecting a sample from exhaled breath of a subject, such as by using the herein disclosed device for drug sampling, and sensor based analysis of the sample. the method comprising, the subject exhaling into the device. collecting aerosols from the exhaled breath in a sampling membrane of the device. measuring a pre-defined fraction of the exhaled breath volume for determining a specific total volume of the exhaled breath passing through the sampling membrane. when the specific total volume is determined as having passed through the sampling membrane terminating the exhalation and sealing the device off. the method further comprises extracting content from the sampling membrane. employing a sensor unit for detecting traces of the drugs in the content, and analyzing a presence of the drugs based on a result obtained from the sensor unit.[0047] further embodiments of the invention are defined in the dependent claims, wherein features for the second and subsequent aspects of the invention are as for the first aspect mutatis mutandis.[0048] alternative and/or additional, embodiments of the invention, provides for a portable sampling device for collecting aerosols comprising biomarkers from exhaled breath of a subject for further sensor based analysis. by sampling biomarkers from exhaled breath the device may help providing vital information for early detection and/or diagnosis of diseases or illnesses as well as monitoring of disease progression and/or therapy response.[0049] devices, systems and methods for sampling non-volatile biomarkers are in accordance with the devices, systems and methods for sampling of drug substances and/or compounds herein described.[0050] some known non-volatile biomarker that may be transported by aerosols in exhaled breath is comprised in the list comprising lipids, peptides, nucleotides, prostanoids, proteins, dna or rna.[0051] these biomarkers may be used for diagnosis of diseases or illnesses, such as cancer (such as lung cancer), asthma, inflammation, infection (such as tuberculosis) and/or oxidative stress or other medical conditions.[0052] it should be emphasized that the term "comprises/comprising" when used in this specification is taken to specify the presence of stated features, integers, steps or components but does not preclude the presence or addition of one or more other features, integers, steps, components or groups thereof. brief description of the drawings [0053] these and other aspects, features and advantages of which embodiments of the invention are capable of will be apparent and elucidated from the following description of embodiments of the present invention, reference being made to the accompanying drawings, in which[0054] fig. 1a-c are schematic illustrations showing an embodiment of a tubular element with a mouthpiece section, and a selective trap section designed to mainly permit aerosols from exhaled breath from a subject to pass through[0055] fig. 2 is a schematic illustration illustrating an embodiment of a portable device configured to collect a sample from exhaled breath of a subject[0056] fig. 3 is an embodiment of a portable sampling device showing a housing with a sampling element being a filter membrane[0057] fig. 4a is depicting a tubular section[0058] figs. 4b and c are depicting a portable sampling device at different stages of use[0059] fig. 5 is showing a flow-chart illustrating a method for using a portable device configured to collect a sample from exhaled breath of a subject and[0060] fig. 6 illustrates a system for detecting the presence or determining the quantitative amount of at least one drug compound in exhaled breath. description of embodiments [0061] specific embodiments of the invention will now be described with reference to the accompanying drawings. this invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art. the terminology used in the detailed description of the embodiments illustrated in the accompanying drawings is not intended to be limiting of the invention. in the drawings, like numbers refer to like elements.[0062] in an embodiment of the invention according to fig. 1a-c a tubular element with a mouthpiece section and a selective trap section is depicted. the selective trap section of the tubular element is designed to permit primarily aerosols to pass through. hence denying saliva and/or mucus and/or larger particles and/or aggregated to enter the housing and thereby avoiding the sampling membrane to be clogged.[0063] the tubular element is a conduit with a coaxial lumen having transversal baffles. the cross-section of the lumen could have any shape but is preferably circular or oval. in fig. 1a two complementary cross-section views 10, 11 along the length of a tubular element with a mouthpiece section are shown. the shape of the two parts are close to two half-pipes, wherein both parts comprising open ends 101, 102 which will form an inlet, being a mouthpiece section, and an outlet, when put together. the section between the inlet 101 and outlet 102 is a selective trap section 111 (see fig. 1b). in fig. 1a, part 10 comprises two transversal baffles 103 and part 11 one. hence the total number of baffles 103 seated in the lumen 104 in the illustrated embodiment of the tubular element is three. in reality any suitable number of baffles needed to obtain the needed effect could be seated in the lumen of the tubular element. the section of the tubular element with the baffles 103 forms the selective trap section 111[0064] the transversal baffles 103 may be perpendicular to the inner wall 105 of the lumen 104 (as depicted in fig. 1a). alternatively and/or additionally, in some embodiments the transversal baffles 103 may have any suitable angle relative the inner wall 105 of the lumen 104.[0065] in fig. 1b a cross-section of the tubular element is depicted from a different view, showing the height of the transversal baffles and the path the exhaled breath must travel from the inlet 101 to the outlet 102. in the upper cross-section view the height 106 of the baffles 103 are shown related to the radius 107 of the lumen. the baffles 103 protrude into the lumen 104 at least a distance being the same as the radius 107. preferably the height 106 of the baffles 103 should be taller than the length of the radius 107 of the lumen 104. the baffles 103 are in fig. 2b

depicted as perpendicular to the inner wall 105 of the lumen 104. in reality each baffle 103 could have any suitable angle relative the inner wall 105 of the lumen 104 as long as they extend into the lumen the same distance as the radius 107 or longer.[0066] the baffles 103 in the selective trap section 111 should be spaced to optimizing passing of aerosols and at the same time minimizing the amount of saliva and/or mucus and/or particles and/or aggregates 108 permitted through the tubular element to the outlet 102. alternatively and/or additionally, in some embodiments the spacing is depending on the height and/or the angle of the baffles 103.[0067] further in fig. 1b, the arrows in the lower cross-section show the non-straight travel of exhaled breath and of the aerosols through selective trap section 111 of the tubular element. the aerosols will easily travel from the inlet 101 to the outlet 102 while the heavier or larger in size particles or aggregates 108 that may clog a sampling membrane will be denied by the baffles 103. the selective trap section 111 of tubular element may therefore act as a pre-filter.

[0068] alternatively and/or additionally, in some embodiments of the invention the baffles 103 include orifices sized to mainly permit aerosols to pass through the orifices.[0069] in fig. 1c the mouthpiece section 12 is depict. the inlet 109 could have any shape but one that has shown to be particularly suitable and comfortable is an oval shape. 110 depict the contours of the tubular section previously described in figs. 4 a and b.[0070] in fig. 2 is a schematic illustration showing an embodiment of a portable system configured to collect a sample from exhaled breath of a subject. sampling system 20 is configured to collect a sample from exhaled breath of a subject 201. the subject will exhale through a mouthpiece and a tubular element 202 being in flow communication with a housing 204 via at least one inlet 203. the mouthpiece and tubular element 202 may be of same size or type as a conventional used for alcohol-test. preferably the mouthpiece and tubular element 202 is configured to mainly permit aerosols to pass through. even more preferably configured according to the previously described invention.

[0071] the housing 204 could be made of any suitably material or combinations thereof such as, metal, plastic, glass or ceramics[0072] the housing 204 comprises a sampling membrane 205 for collecting the non-volatile drug substances from the exhaled breath. the exhaled breath exits the housing through at least one outlet 206. the portable system is sealed after being used and sent to a laboratory 207 to be analyzed. analysis of the amount of illicit drugs could be performed using a range of methods but preferably methods are surface enhanced raman spectroscopy (sers) or mass-spectroscopy, for example liquid-chromatography mass-spectroscopy (lcms).[0073] alternatively and/or additionally, in some embodiments the portable sampling system is made to be a disposable product. when designed to be a disposable product the housing as well as the mouthpiece is preferably made of a plastic material.[0074] the sampling system and elements for collecting drug substances should be kept clean and preferable be aseptic but could also be used sterile.[0075] alternatively and/or additionally, in some embodiments of the invention a volume measure unit 208 may be used for detecting the amount of exhaled breath from the tested subject. preferably the volume measure unit 208 comprising a port arranged downstream the mouthpiece section and upstream the sampling membrane 205. preferably the port is attached to the tubular element. a pre-defined fraction or portion of the exhaled breath will be extracted through the port and used for calculating the amount of exhaled breath passed through the sampling membrane 205. preferably the volume measure unit 208 is further comprising a gas volume collecting element, preferably a bag, in communication with the port. the gas volume collecting element has a predefined volume when expanded. the volume of exhaled breath through passed through the sampling membrane 205 may be proportional to the volume of the bag when full.[0076] alternatively to a gas volume collecting element, such as a bag, a flow meter could be used with an indicator, such as indicators changing colour, may be used to indicate when a pre-determined volume has passed through the sampling membrane.[0077] in fig. 3 is an embodiment of a portable sampling system 30 is depicted comprising a housing 301, with a sampling membrane 302, a tubular element 303 with a mouthpiece section 308 and a selective trap section, and a volume measure unit comprising a port 307 and a gas volume collecting element 304. the volume measure unit is used for calculating the volume of exhaled breath passing through the sampling membrane 302.[0078] the sampling membrane could be placed anywhere in the housing 301. preferably the sampling membrane is fastened to the inner walls of the housing 301. the housing 301 is preferably constructed out of two or more parts, a first part with an inlet 305 and one part with at least one outlet 306.[0079] the mouthpiece section 308 and tubular element 303 is detachable and in fluid communication with the housing 301 via the inlet 305. the tubular element 303 is acting as a pre-filter for filtering out saliva and/or mucus and/or large particles and/or aggregates from the exhaled breath, according to what has previously been described. thus a cleaner sampling membrane, such as a filter membrane, to be analyzed is obtained which may result in better and more accurate analysis. other advantages with using a tubular element 303 is the prevention of contamination between subjects and sample[0080] alternatively and/or additionally, in some embodiments the mouthpiece section 308 and tubular element 303 is not detachable but integrated with the first part of the housing 301.[0081] connected either to the tubular element 303 or between the mouthpiece section 308 and the inlet 305 is a port 307 for extracting a portion or fraction of the exhaled breath from the subject. the extracted exhaled breath is used to blow up a gas volume measuring element 304, such as non-elastic bag or an elastic balloon. in this embodiment a non-elastic bag made of plastic is used since it requires less force to be blown up and will automatically stop when full.[0082] when the bag is full the exhaled breath passing through the sampling membrane can be calculated since it will be proportional to volume of the bag. for example, by extracting a tenth of the volume exhaled by the subject, a full two liter bag means that 18 liter has passed through the sampling membrane (20 liter exhaled in total).[0083] additionally, in some embodiments the port may comprise a one-way valve so that the extracted breath will only enter the bag but not leave.[0084] alternatively and/or additionally, in some embodiments the port utilizes the back pressure created by the sampling membrane to extract the exhaled breathe through the port 307.[0085] alternatively, in some embodiments, a flow meter could be used with an indicator, such as indicators changing colour, may be used to indicate when a pre-determined volume has passed through the sampling membrane.[0086] the extracted portion or fraction of the exhaled breath being measured is proportional to the predefined volume of exhaled breath passing through the sampling membrane. thus by measuring this fraction or portion and by knowing the ratio of air being extracted and air passing through the sampling membrane the total amount of exhaled breath passing through the sampling membrane may be determined.[0087] the exhaled breathe will, after flowing through the tubular element 303, travel into the housing 301 and be brought into contact with the sampling membrane, preferably a filter membrane.[0088] the drug substances being non-volatile compounds conveyed by aerosols in the exhaled breath is collected by the sampling membrane, such as preferably a filter membrane, as the exhaled breath is permeated through the sampling membrane.[0089] it should be noted that the sampling membrane 302 which being a filter membrane is not to be confused with an electronic or chemical sampling units and/or traps. the sampling element 302 is a physical entity on which the drug substance is collected. collection may in different embodiments be based on various principles, singly or in combination, comprising depositing, catching, fastening, condensing of non-volatile constituents on the sampling element 302.[0090] using a filter membrane allows for a low pressure drop through the portable system 30 making it easy and comfortable to exhale through it. this is important since many drug addicts experience problems with their lungs.[0091] in the embodiment depicted in fig. 3, the filter membrane is placed to block the path for the exhaled breath through the portable system 30. in other embodiments the filter could be placed along the side of any of the walls of the housing 301.[0092] there are many possibilities for fastening the filter membrane is needed, either by using a separate support structure retaining the filter, which may be an element that is either fastened to the inside walls of the housing 301 or a segment being slide onto a first part of the housing during the assembly before the second part of the housing is mounted.[0093] alternatively and/or additionally, in some embodiments the filter membrane is fastened direct onto the inside walls of the housing 301, either by glue or by heat and thereby melting a small part of the edge of the filter membrane.[0094] the second part of the housing is either screwed or slid onto the first part of the housing. the second part comprises at least one outlet 306. alternatively and/or additionally, in some embodiment the housing 301 comprises at least two outlets 306. this will aid to avoid a subject being tested to block the outlet and thereby blowing up the measuring element 304 with minimum exhaled breath being permeated through the filter membrane[0095] in an embodiment of the portable device 30 the sampling element 302 is a filter membrane made of synthetic and/or half-synthetic fibers for the exhaled breath to diffuse through.[0096] the filter membrane will have a structure that catches the aerosols and thereby collects the drug substances being exhaled while letting gas pass through. the aerosol particles comprise the non-volatile drug compounds. preferably the filter membrane is operable to collect the aerosols from the air with a high volumetric capacity while maintaining a low pressure drop across the filter substrate.[0097] alternatively and/or additionally, in some embodiments the filter membrane may be an electrostatic filter made of fibers.[0098] alternatively and/or additionally, in some embodiments the filter membrane may be of a non-woven polymeric fibrous that may be an electret.[0099] alternatively and/or additionally, in some embodiments the filter membrane is an electrostatic filter being preferably a non-woven filter membrane comprising a blend of acrylic fibers and polypropylene fibers. the filter membrane could have a density (sometimes called grade or weight) in the range 23 up to 500 grams per square metre. but it has been shown that the range 130 up to 300 grams per square metre is preferred. even more preferably is the range 200 up to 280 grams per square metre.[0100] alternatively and/or additionally, in some embodiments the non-woven layer could be attached to at least further layer. further layers could be used to enhance a filter membrane's physical properties or improve filtration performance. the extra layer could be a carrier, preferably a polypropylene spunbonded carrier. the spunbond carrier may have a scrim weight in the range 10 up to 20 grams per square metre, preferably 15 grams per square metre.[0101] for example a three layered filter membrane comprising one non-woven layer with a density of 250 grams per square metre and two layers being carriers each with a scrim weight of 15 grams per square metre will have a air flow resistance of about 36 pa at 9.5 m/min media velocity.[0102] alternatively and/or additionally, in some embodiments, the filter membrane may be corrugated to enhance the filtering area within a given housing volume.[0103] the portable system is configured and adapted to have a sensitive for illicit drugs high enough to obtain results of a standard that could be used as prof in court. other advantages are that the test may be performed anywhere at a low cost and short lead time before obtaining a result. since no specially trained personnel are needed and the test is does not need to be performed at, for example, a hospital.[0104] other advantages are that the invented portable sampling system is neither invasive, e.g. blood sampling, nor intruding on personal integrity, e.g. urine sampling. even known issues with methods used today, related to samples and specimens taken from a subject to be tested are avoided. for instance for blood samples, and especially for urine samples are a risk of the subject exchanging the samples or using clean samples from another subject to avoid being discovered with traces of illicit drugs. the suspected subject can also be tested immediately and does not need to be transported to have the test done later. hence a more accurate result of the level of an illicit drug at the time of for example an arrest can be obtained.[0105] in fig. 4a-c one embodiment of the invention is illustrated at different stages. fig. 4a depicts a tubular element 40 before being assembled and mounted. 401 shows the mouthpiece section with an inlet, 402 shows the selective trap section of the tubular element, 403 shows the outlet, 404 the port for extracting a portion of the exhaled breath and 405 shows the baffles used to obtain the non-straight gas flow path.[0106] fig. 4b illustrates the device 41 when being ready to be used: 401 shows the mouthpiece section 402 the tubular section comprising the baffles 407 is the inlet to the housing 406 408 shows the outlet from the housing 406 404 is the port for extracting a portion of the exhaled breath for determining the volume of exhaled breath passing the sampling membrane. the illustration does not show the volume measure unit (i.e. the bag) attached to the extraction port 404.[0107] fig. 4c is illustrating a used sampling device 42. the mouthpiece section and tubular element is detached and plugs 409, 410 are mounted to the inlet 407 and the outlet 408 of the housing 406. this will seal off the housing 406 and the sampling membrane comprised inside. at this stage the portable sampling device 42 is ready to be sent to a laboratory, for example by post. in fig. 4c it is shown that the housing 406 is made of two parts 411 and 412 mounted together[0108] the process of manufacturing a portable device according to the embodiments described herewithin when the housing is made in plastic could be formed the following way (reference to the parts shown in fig. 4a-c): a first part, for example, 412 of a housing is heated and thereby enlarging the circumference of the first part 412. when seating a filter membrane in close proximity to the large opening being approximately the middle of the device, at least one compound in the filter membrane will melt at the edge of the filter membrane. this will stick or fastening the filter membrane to the inner wall of the first part 412. the first part of the housing 412 could then be slid or screwed or snapped onto the second part 411. thus a tight fit may be obtained when the first part 412 cools off and its circumference decreases.[0109] fig. 5 is a flow-chart illustrating a method 50 for using a portable system configured to collecting a sample 502 from exhaled breath from a subject. briefly, fig. 5 illustrates detecting the presence and/or determining the quantitative amount 503 of at least one illicit drug substance or compound in a collected sample. the illicit drug compounds will be collected as aerosols, being non-volatile particles and/or compounds, from the exhaled breath. the method comprising of: a subject exhaling 501 into the invented portable system a sampling unit will collect a sample 502 comprises drug substances or compounds the collected sample will be extracted from the sampling membrane and analyzed 503 using mass-spectroscopy or sers.[0110] with reference to fig. 5, a subject will exhale 501 in and out preferably the subject will exhale into the portable system until a specific volume of exhaled breath has been passed through the sampling membrane, such as preferably a filter membrane.[0111] alternatively and/or additionally, in some embodiments the subject has to exhale either for a certain time or for a fixed number of times such as 1 to 10 times into a portable system. when breathing a fixed number of times each exhale could be set to last for a fixed time.[0112] to measure a specific volume, one preferred method is to use a port between either located on the mouthpiece or between the mouthpiece and the inlet of the housing. a portion of the exhaled breath will be extracted 504 through the port and blow up an element such as a non-elastic bag. hence when the bag is full, the volume of said bag will be proportional to the volume passed through the sampling membrane.[0113] alternatively and/or additionally, in some embodiments a bag with elastic properties can be used.[0114] a deep breath is preferred to reach exhaled breath from deep lying lung portions such as the central or the peripheral lung regions.[0115] the exhaled breath will then be collected 502 by the sampling element, i.e. an easy to breathe through filter membrane, suitably for collecting drug substances before it exits the system. the filter membrane is preferably made of synthetics and/or half synthetics fibers preferably the filter membrane has electrostatic-properties. using a filter membrane will create a small, light weighted and easy to use method that can be used everywhere by anyone to detect if a subject is under influence of an illicit drug. the sampling method is of such high quality that the obtained results are of a court approved standard. these results are obtain using a method that is neither invasive, e.g. blood sampling, nor intruding on personal integrity, e.g. urine sampling. hence the known drawbacks with these methods are prevented.[0116] after being used, the housing of the sampling system will sealed off by sealing the inlet and the outlet and be sent to a laboratory, whereby the collected compounds in the filter are removed and analyzed 503 using an appropriate analyzing method such as mass-spectroscopy or sers.[0117] fig. 6 illustrates a system 60 for detecting the presence or determining the quantitative amount of at least one drug compound in exhaled breath. the system comprising a portable drug testing device 602 for handheldly collecting a sample from exhaled breathe from a subject 601. the device 602 could be according to any

embodiment described herein. further, the system 60 comprises a sensor unit 603 for analyzing the collected compounds in the testing device 602. the sensor could be any know type of sensor but preferably mass spectroscopy or sers. to be able to analyze the collected sample the content of the filter membrane in the device 602 is extracted. this could be done for example by using a solvent to be analyzed using the sensor unit 603. another method is heating the filter and thereby evaporating the content of the filter for example onto a sers surface.[0118] in the following further examples of implementations of the invention and how an analysis may be performed is demonstrated. these original observations demonstrate drug testing based on sampling of expired air.example 1 sampling of drugs of abuse from exhaled human breath using filter membrane [0119] table 1 shows sampling of methadone from exhaled breath using a filter membrane comprising one layer being a non-woven electrostatic filter with a blend of acrylic fibers and polypropylene fibers with a density of 250 grams per square metre and two carriers each with a scrim weight of 15 grams per square metre. the tests where performed at 4 different occasions. the first column shows the diameter of the used filter, the second the sampling time the third the amount of methadone collected per minute the fourth the obtained range of methadone among the tested subjects and the fifth column the number of subjects tested.table 1diametersamplingmethadoneof filtertimepg/minmmminmean plus or minus sdrangen47386 plus or minus 5218-1686323112 plus or minus 89 47-266532392 plus or minus 6228-1996321204 plus or minus 11621-3266[0120] table 2 shows sampling of methadone in breath from a pre-study when using variable densities of the electrostatic filter membrane. type is the density of the non-woven layer at each test, the other headlines are the same as for table 1.table 2methadonetyppeg/min(grams per square metre)mean plus or minus sdrangen15074.4 plus or minus 80.424-216525071.0 plus or minus 90.119-231530091.8 plus or minus 110 20-2875[0121] table 3 shows sampling of methadone in exhaled breath using two different thicknesses of the electrostatic filter membrane inserted in a sampling device. the subject exhales through the tubular section comprising baffles to trapping large particles and saliva. the tables show that the aerosols will not be trapped by the baffles in the tubular element.table 3constructed samplerfiltermethadone pg/minthicknessmean plus or minus sdrangen140 plus or minus 2712-855242 plus or minus 2817-905 biomarkers [0122] additionally and/or alternatively, some embodiments of the invention, provides for a portable sampling device for collecting aerosols comprising biomarkers from exhaled breath of a subject for further sensor based analysis. by sampling biomarkers from exhaled breath the device may help providing vital information for early detection and/or diagnosis of diseases or illnesses as well as monitoring of disease progression and/or therapy response.[0123] devices, systems and methods for sampling non-volatile biomarkers are in accordance with the devices, systems and methods for sampling of drug substances and/or compounds herein described.[0124] some known non-volatile biomarker that may be transported by aerosols in exhaled breath is comprised in the list comprising lipids, peptides, nucleotides, prostanoids, proteins, dna or rna. these biomarkers may be used for diagnosis of diseases or illnesses, such as cancer (such as lung cancer), asthma, inflammation, infection (such as tuberculosis) and/or oxidative stress or other medical conditions.[0125] in conjunction with the hereinabove described embodiments for sampling drug substances or compounds, which being equally suitable to be used as a portable sampling device for collecting aerosols comprising biomarkers from exhaled breath of a subject for further sensor based analysis, some preferred aspects of the invention provides for a portable sampling device for collecting aerosols comprising biomarkers from exhaled breath of a subject for further sensor based analysis. the portable sampling device comprising a housing comprising at least one inlet and at least one outlet for the exhaled breath to exit through, and a sampling membrane arranged in the housing. the sampling membrane is arranged to collect the aerosols from said exhaled breath.[0126] additionally, some embodiments further comprising a tubular element having a mouthpiece section for the subject to exhale into, and a selective trap section in fluid communication with the mouthpiece and the inlet of the housing. the selective trap section has a non-straight gas flow path for letting primarily aerosols pass through said tubular element.[0127] additionally, some embodiments, further comprising a volume measure unit for determining that a pre-defined volume of said exhaled breath has passed through said sampling membrane.[0128] additionally, some embodiments, wherein said tubular element is detachable from said housing or wherein said tubular element is an integrated part of the housing.[0129] additionally and/or alternatively, in some embodiments the volume measure unit is configured to measure a volume proportional to the pre-defined volume of the exhaled breath.[0130] additionally and/or alternatively, in some embodiments a port is arranged downstream the mouthpiece and upstream the sampling membrane and wherein the port is adapted to extract a defined portion of the exhaled breath into the volume measure unit.[0131] additionally and/or alternatively, in some embodiments, the volume measure unit comprising a gas volume collecting element, such as a bag, having a volume and wherein a port is arranged downstream the mouthpiece and upstream the sampling membrane and wherein the port is adapted to extract a defined portion of the exhaled breath into the volume measure unit. the volume of said gas volume collecting element is proportional to the pre-defined volume of the exhaled breath.[0132] additionally and/or alternatively, in some embodiments the volume collecting element is a non-elastic bag with a predetermined volume. [0133] additionally and/or alternatively, in some embodiments the sampling membrane is a filter membrane, preferably an electrostatic filter membrane.[0134] the device according to the invention provides for method to sample aerosols comprise non-volatile biomarkers in exhaled breath. the aerosols comprise non-volatile compounds of at least one biomarker in the exhaled breath and wherein the biomarker is comprised in the list comprising lipids, peptides, nucleotides, prostanoids, proteins, dna or rna.[0135] a further aspect of the invention is a use of the device, for non-invasive sampling of exhaled breath detection of biomarkers which may be used for diagnosis of diseases or illnesses, such as cancer, inflammation, infection and/or oxidative stress.[0136] a yet further aspect provides for a method of diagnosis a medical condition of a subject, comprising collecting a sample from exhaled breath of a subject, such as by using the disclosed device, for sensor based analysis of the sample. the method comprising the step of having the subject exhaling into said device collecting aerosols from the exhaled breath in a sampling membrane of the device sealing the device off extracting a content from the sampling membrane and employing a sensor unit, such as off-site or on-site, for detecting traces of biomarkers in the content, and diagnosing said subject based on a result obtained from the sensor unit.[0137] additionally, some embodiments of this aspect further comprising measuring a pre-defined fraction of the exhaled breath volume for determining a specific total volume of the exhaled breath passing through the sampling membrane. when the specific total volume is determined as having passed through the sampling membrane terminating the exhalation. the present invention has been described above with reference to specific embodiments. however, other alternatively and/or additionally embodiments than the above described are equally possible within the scope of the invention. different method steps than those described above, performing the method by hardware or software, may be provided within the scope of the invention. the different features and steps of the invention may be combined in other combinations than those described. the scope of the invention is only limited by the appended patent claims. (Results 11)

Search
14: Respiratory filters (Results 33)

Search
15: Breathtest device (Results 0)

Search
16: filter and Breathtest device and chamber (Results 0)

Title: Breath test mouthpiece

Abstract: Source: US4292978A A breath-test mouthpiece of the type used to remove solids, saliva and water vapor from the breath of a subject being tested to determine a breath constituent, typically breath alcohol, including axially-aligned mouth and tube pipes with a hollow central collector having a lip-engaging edge to either side of the mouth pipe and an enlarged cross section multi-path interior baffle forcing the breath to flow along a serpentine-shaped path as it moves from the mouth pipe to the tube pipe.

Classifications:

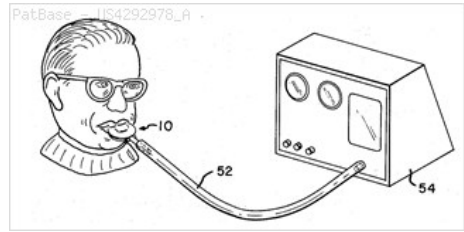
International (IPC 8-9): A61B5/097 G01N1/22 G01N33/497 (Advanced/Invention); A61B5/08 G01N33/483 (Core/Invention)

International (IPC 1-7): A61B10/00 G01N1/22

CPC: A61B5/097 G01N33/4972

European: A61B5/097 G01N33/497A

US: 128/730 422/84 55/440 600/532 600/543



Family:

Publication number	Publication date	Application number	Application date
CA1148383 A1	19830621	CA19800360947	19800924
US4292978 A	19811006	US19790107429	19791226

Priority:

US19790107429 19791226 CA19800360947 19800924

Assignee(s): (std): GUTH RICHARD U

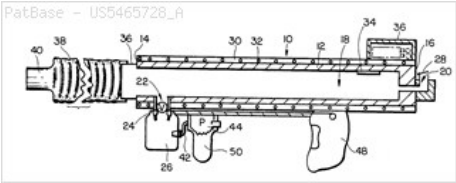
Inventor(s): (std): GUTH RICHARD U

Title: BREATH COLLECTION

Abstract: Source: US5465728A Apparatus which is highly portable and even hand-held is used to collect mammalian breath for chemical analysis and as a diagnostic tool for the physician. The apparatus comprises a fluid reservoir container having first and second ends and a body extending between these ends so as to define an interior chamber; a breath entry portal; a breath exit portal; a sampling portal; a jacket to maintain the temperature of the chamber; a sample container for holding samples of exhaled breath; and pump means for moving selected samples of breath from the reservoir container into the sample container.

Classifications:

International (IPC 8-9): A61B5/08 A61B5/083 A61B5/097 G01N1/24 G01N33/497 (Advanced/Invention); A61B5/08 G01N33/497 (Advanced/Non-invention); A61B5/08 G01N1/24 (Core/Invention); G01N33/483 (Core/Non-invention)
International (IPC 1-7): A61B5/08 A61B5/083 A61B5/097
CPC: A61B5/097 G01N1/24 G01N33/497 G01N2001/248 Y10S977/904
European: A61B5/097 G01N1/24 S01N1/24V S01N33/497
US: 128/204.17 128/730 600/543 977/904



Family:

Publication number	Publication date	Application number	Application date
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DE69533661 T2	20060223	DE19956033661T	19950106
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WO9518566 A1	19950713	WO1995US00172	19950106

Priority:

US19940179918 19940111 WO1995US00172 19950106

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Assignee(s): MICHAEL PHILLIPS

Inventor(s): (std): PHILLIPS MICHAEL

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Designated states: AT AU BE BR CA CH DE DK ES FR GB GR IE IT JP LI LU MC NL PT SE

Title: Apparatus to recover component fractions from exhaled air

Abstract: Source: DE19718924A1 The appts. to recover component fractions from exhaled air has a mouthpiece (2) with an inhaling (3) and exhaling (4) valve in front of the filter holder unit (5) with a fibre nonwoven (6). The matter is deposited on the nonwoven or porous material as an aerosol. The components of the exhaled air are condensed on the cool surface together or are separated by centrifugal action, vacuum, gas pressure or decanting. They are analysed by ELISA, RIA or high performance liquid chromatography (HPLC) techniques.

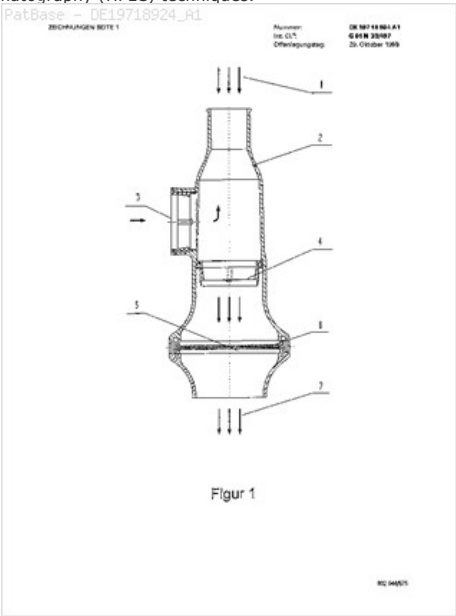
Classifications:

International (IPC 8-9): G01N33/497 G01N33/53 G01N33/543 G01N33/68 (Advanced/Invention); G01N1/40 (Advanced/Non-invention); G01N33/483 G01N33/53 G01N33/543 G01N33/68 (Core/Invention); G01N1/40 (Core/Non-invention)

International (IPC 1-7): A61B5/8 C12Q1/28 C12Q1/42 C12Q1/46 G01N1/22 G01N1/42 G01N31/22 G01N33/497 G01N33/535 G01N33/543 G01N33/577

CPC: G01N33/497 G01N33/543 G01N33/53 G01N33/6893 G01N2001/4088

European: G01N33/497 G01N33/53 G01N33/543 G01N33/68V S01N1/40A S01N1/40V3



Family:

Publication number	Publication date	Application number	Application date
DE19718924 A1	19981029	DE19971018924	19970428
DE19742331 A1	19990325	DE19971042331	19970919

Priority:
DE19971018924 19970428 DE19971042331 19970919

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Assignee(s): MEDIUM SENSOR GMBH 12681 BERLIN DE

Inventor(s): (std): WINSEL KLAUS DIPL CHEM DR RER ; ADLER FRANK DIPL PHYS

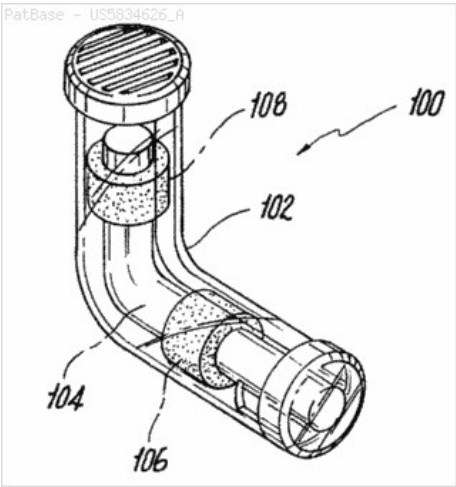
Inventor(s): ADLER FRANK DIPL PHYS 13053 BERLIN DE ; WINSEL KLAUS DIPL CHEM DR RER NAT DR SC NAT 10243 ; WINSEL KLAUS DIPL CHEM DR RER NAT DR SC NAT

Title: Colorimetric indicators for breath, air, gas and vapor analyses and method of manufacture

Abstract: Source: US5834626A Colorimetric indicators for breath, air, gas, and vapor analyses that can be thrown away after a single use, are easy to use, low cost, small, and simple to manufacture for indicating at least volume passed through the colorimetric indicators and may also be used to indicate concentration of an analyte within breath, air, gas, and vapor passed through the colorimetric indicators. The present invention is directed to colorimetric indicators for breath, air, gas, and vapor analyses. The colorimetric indicators may have a housing with an entrance port, an outlet, a volume indicator, and an analyte indicating reagent. The volume indicator may be a breath volume reagent. Different analytes may be measured, the analyte indicating reagent depending upon the particular analyte being monitored. The breath volume indicator is colorimetric, and changes color when a predetermined volume of air is passed through the colorimetric indicators for breath, air, gas, and vapor analyses. The analyte indicator reagent is also colorimetric, and changes color when a predetermined amount of chemical concentration of the analyte is exposed to the analyte indicator reagent. A process for manufacturing a colorimetric indicator for breath, air, gas, and vapor analyses, comprises at least the following steps: immobilizing a reagent, such color change inducing reagent being composed of at least one constant concentration component.

Classifications:

International (IPC 8-9): G01N21/78 G01N31/22 G01N33/497
G01N33/98 (Advanced/Invention);
G01N21/77 G01N31/22 G01N33/483 G01N33/98 (Core/Invention)
International (IPC 1-7): G01N1/22 G01N27/62
CPC: G01N21/783 G01N31/22 G01N33/4972 G01N33/98 G01N2800/307
European: G01N21/78B G01N31/22 G01N33/497A G01N33/98 S01N800/30G
US: 422/83 422/85 422/86 73/23.3 73/233 73/25.04 73/29.01 73/31.03



Family:

Publication number	Publication date	Application number	Application date
US5834626 A	19981110	US19960758557	19961129

Priority:

US19960758557 19961129

Assignee(s): (std): DE CASTRO EMORY S ; MALAT DOUGLAS R

Inventor(s): (std): DE CASTRO EMORY S ; MALAT DOUGLAS R

Title: Method and device for collecting and analyzing exhaled breath

Abstract: Source: US2003208132A A method and device for collecting, storing, shipping, preparing and analyzing condensate derived from the exhaled breath of a user. Using the mouthpiece (15) of the device (10), a human subject inhales drawing air through a check valve (30).

Classifications:

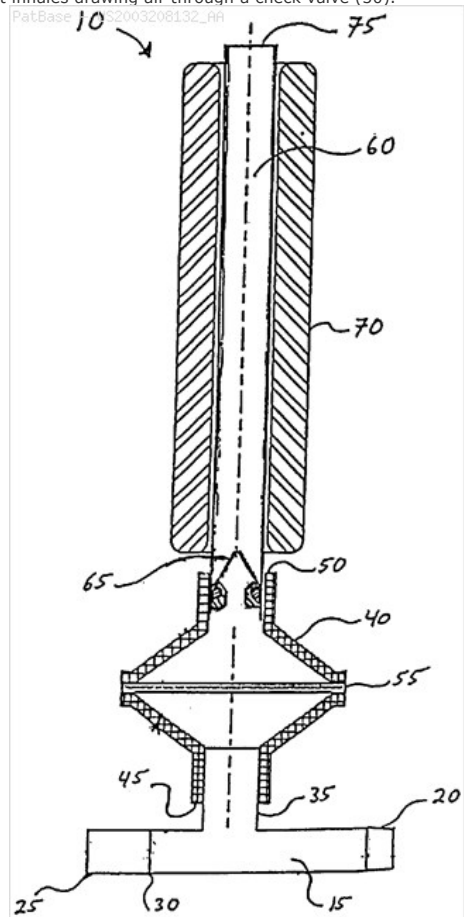
International (IPC 8-9): A61B5/08 A61B5/097 B65D81/00 G01N1/22 G01N33/497 (Advanced/Invention); A61B5/02 B32B27/04 B32B27/12 B32B5/02 G01N1/22 G01N31/00 G01N33/00 G01N33/49 G01N33/497 (Advanced/Non-invention); B65D81/00 G01N1/22 G01N33/483 (Core/Invention); A61B5/02 B32B27/04 B32B27/12 B32B5/02 G01N1/22 G01N31/00 G01N33/00 G01N33/48 G01N33/483 (Core/Non-invention)

International (IPC 1-7): A61B5/08 G01N1/22

CPC: A61B5/097 G01N1/22 G01N33/0014 G01N33/497 A61B5/08

European: A61B5/08 A61B5/097 G01N1/22 G01N33/497 S01N33/00D2A2 S01N33/497

US: 600/532 600/532S 600/543 600/543P



Family:

Publication number	Publication date	Application number	Application date
AU2001261091 AA	20011112	AU20010261091	20010430
EP1409985 A1	20040421	EP20010934950	20010430
EP1409985 A4	20090107	EP20010934950	20010430
US2003208132 AA	20031106	US20020257912	20021017
US2007232952 AA	20071004	US20060467255	20060825
US7118537 BB	20061010	US20010257912	20010430
WO0184112 A1	20011108	WO2001US13895	20010430

Priority:

US20000200979P 20000501 WO2001US13895 20010430 US20010257912 20010430
US20060467255 20060825 US20020257912 20021017

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Inventor(s): (std): BADDOUR ALFRED R

Inventor(s): ALFRED R BADDOUR ; BADDOUR ALFRED

Agent(s): WOODS ROGERS PLC; PETER E

Designated states: AE AG AL AM AT AU AZ BA BB BE BF BG BJ BR BY BZ CA CF CG CH CI CM CN CO CR CU CY CZ DE DK DM DZ EE ES FI FR GA GB GD GE GH GM GN GR GW HR HU ID IE IL IN IS IT JP KE KG KP KR KZ LC LI LK LR LS LT LU LV MA MC MD MG MK ML MN MR MW MX MZ NE NL NO NZ PL PT RO RU SD SE SG SI SK SL SN SZ TD TG TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

Title: APPARATUS AND METHOD

Abstract: Source: US2011208081A A breath testing apparatus having a sampling device (10) and a sensor (50), wherein said sampling device is detachable. A method of analysing the breath of a patient is also provided.

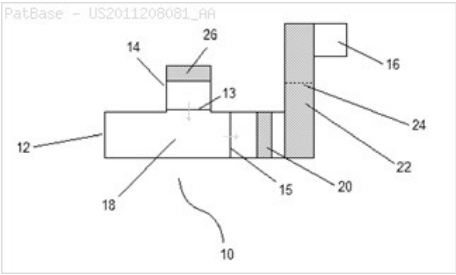
Classifications:

International (IPC 8-9): A61B5/08 G01N33/497 (Advanced/Invention); G01N33/483 (Core/Invention)

CPC: G01N33/0037 G01N33/497

European: G01N33/497 S01N33/00D2D4A

US: 600/532 600/532P



Family:

Publication number	Publication date	Application number	Application date
EP2185928 A1	20100519	EP20080788764	20080908
GB200717433 A0	20071017	GB20070017433	20070907
US2011208081 AA	20110825	US20080674776	20080908
WO09030957 A1	20090312	WO2008GB50794	20080908

Priority:
GB20070017433 20070907 WO2008GB50794 20080908

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Title: PORTABLE SAMPLING DEVICE AND METHOD FOR SAMPLING DRUG SUBSTANCES FROM EXHALED BREATH

Abstract: Source: US2014366609A A portable drug sampling device for handheldly collecting a sample from exhaled breath of a subject for further sensor based analysis. The device comprising: a housing (406) comprising at least one inlet (407) and at least one outlet (408) for the exhaled breath to exit through, and a sampling membrane (302) arranged in the housing. A tubular element (40) having a mouthpiece section (401) for the subject to exhale into, and a saliva trap section comprising baffles (103) to create a non-straight gas flow path for letting aerosols pass through the tubular element. The sampling membrane (302) is arranged to collect the aerosols from the exhaled breath. The portable drug testing device further comprises a volume collecting element (208).

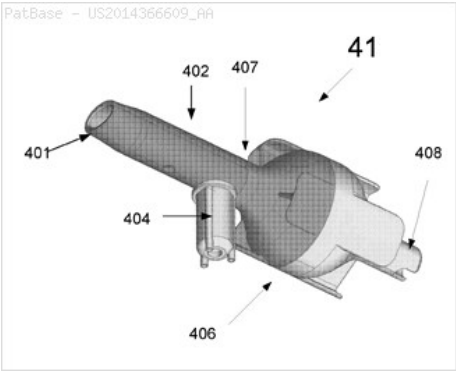
Classifications:

International (IPC 8-9): A61B5/08 A61B5/097 B29C65/46 B29C65/66 G01N1/02 G01N33/497 (Advanced/Invention)

CPC: G01N33/18 G01N33/1826 A61B5/091 A61B5/4845 B29C65/46 B29C65/665 G01N2033/4975 B29K2023/10 G01N33/497 A61B5/082 A61B5/097 B29K2033/04 B29K2105/256 B29K2105/258

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Family:

Publication number	Publication date	Application number	Application date
CN103814294 A	20140521	CN201280022314	20120309
CO6870013 A2	20140220	CO20130239171	20131008
EA201391293 A1	20141128	EA20130091293	20120309
EP2518499 A1	20121031	EP20110157564	20110309
EP2684043 A1	20140115	EP20120709832	20120309
JP2014510914 T2	20140501	JP20130557129T	20120309
MX2013010242 A1	20140501	MX20130010242	20130906
US2014366609 AA	20141218	US20120003915	20120309
WO12120140 A1	20120913	WO2012EP54180	20120309

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EP20110157564 20110309 US20110450993P 20110309 WO2012EP54180 20120309
EP20120709832 20120309 US20120003915 20120309

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Title: PORTABLE SAMPLING DEVICE AND METHOD FOR DETECTION OF BIOMARKERS IN EXHALED BREATH

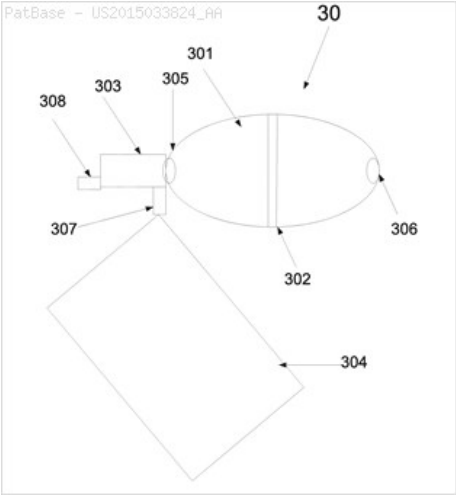
Abstract: Source: US2015033824A A portable method and sampling device for collecting aerosols comprising biomarkers from exhaled breath of a subject for further sensor based analysis. The sampling device (41) comprising a housing (406) comprising at least one inlet (407) and at least one outlet (408) for the exhaled breath to exit through, and a sampling membrane arranged in the housing. The sampling membrane is arranged to collect the aerosols from said exhaled breath.

Classifications:

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CPC: G01N33/497 A61B5/082

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Publication number	Publication date	Application number	Application date
EP2823300 A1	20150114	EP20130713094	20130308
US2015033824 AA	20150205	US20130383846	20130308
WO13132085 A1	20130912	WO2013EP54789	20130308

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US20120608326P 20120308 WO2013EP54789 20130308 US20130383846 20130308

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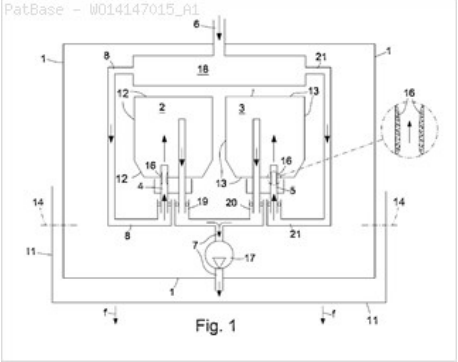
Title: APPARATUS AND METHOD FOR SAMPLING AND ANALYZING BREATH

Abstract: A portable apparatus (10, BACT) to be used to sample and analyze volatile organic compounds (VOCS) in breath air, comprising: - a box (1) that is divided at the inside in two internal sections (2, 3) each housing a sample collecting tube or filter (4, 5) in turn containing a stationary phase (16) suitable for retaining determined analytes, as drugs and/or respective metabolites, having specific chemical physical properties, contained in breath air; - a breath pre-accumulation chamber (18) for receiving the breath air from the outside through a breath entrance connection (6) and for feeding the received breath air to the sample collecting filters (4, 5) housed in said two internal sections (2, 3), with these two sample collecting filters (4, 5) being connected in parallel to said chamber (18); and - a tool application kit (15, 22, 23) for removing the two sample collecting filters (4, 5) from the respective sections (2, 3) in the box (1) of the apparatus (10), in a way that avoids any contamination of them, and for extracting the analytes that are retained by the stationary phase (16) on the same two sample collecting filters (4, 5), wherein, in the event of a positive detection of drug in a first filter (4), of said two sample collecting tubes or filters (4, 5), analyzed by using said tool application kit (15, 23), also the second filter (5) of said sample collecting filters (4, 5) is analyzed, in particular by using a gas chromatography-mass spectrometer (GC-MS) or a liquid chromatography-mass spectrometer (LC-MS), in order to confirm the results of the analysis performed on the first sample collecting filter (4). The sampling and analyzing apparatus of the invention is particularly suitable for executing road drug tests, in compliance with the requirements and the needs of the procedure of the police that has to perform these drug tests.

Classifications:

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EP2781917 A1	20140924	EP20130159744	20130318
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WO14147015 A8	20141106	WO2014EP55277	20140317

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Method for determination of methadone in exhaled breath collected from subjects undergoing methadone maintenance treatment

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ABSTRACT

At present drugs of abuse testing using exhaled breath as specimen is only possible for alcohol. However, we recently discovered that using modern liquid chromatography–mass spectrometry technique amphetamine and methamphetamine is detectable in exhaled breath following intake in drug addicts. We therefore undertook to develop a method for determination of methadone in exhaled breath from patients undergoing methadone maintenance treatment. Exhaled breath was collected from 13 patients after intake of the daily methadone dose. The compounds were trapped by filtering the air through a C18 modified silica surface. After elution of any trapped methadone the extract was analysed by a combined liquid chromatography–tandem mass spectrometry method. Recovery of trapped methadone from the filter surface was 96%, no significant matrix effect was observed, and the quantification using methadone-d3 as an internal standard was accurate (<10% bias) and precise (coefficient of variation 1.6–2.0%). Methadone was indisputably identified by means of the mass spectrometry technique in exhaled breath samples from all 13 patients. Identification was based on monitoring two product ions in selected reaction monitoring mode with correct relative ratio ($\pm 20\%$) and correct retention time. Excretion rates ranged from 0.39 to 78 ng/min. No methadone was detected in 10 control subjects. This finding confirms that breath testing is a new possibility for drugs of abuse testing. Collection of exhaled breath specimen is likely to be more convenient and safe as compared to other matrices presently in use.

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1. Introduction

Exhaled breath is commonly being used in alcohol testing and today's technology makes it even possible to perform on-site breath testing with legally defensible results using infrared spectroscopy and to apply it for alcohollocks [1,2]. Testing for other drugs of abuse traditionally requires other specimens. In traffic medicine a blood sample is needed for documenting driving under the influence, while in other testing urine is the most common specimen. Alternative specimens comprise hair, sweat and oral fluid [3,4]. In recent time oral fluid testing has been in focus both for laboratory and on-site testing [5]. This interest in oral fluid testing has demonstrated the true need for specimen alternative to blood and urine in drugs of abuse testing. While blood is invasive and need medically trained personnel and facilities, urine sampling is considered intruding on personal integrity and is not free from risk of adulteration [6].

Methadone is used in the treatment of heroin addiction and for pain control [7,8]. In methadone maintenance treatment a fixed dose is administered over long time to provide stable blood concen-

trations with through levels being above 250 ng/mL [9]. Compliance to the prescribed dose regimen is controlled by frequent analyses of urine and blood samples. Because of inter-individual variation in the disposition of methadone each patient receives an individual dose [9]. Blood sampling is often problematic in this patient group because of previous chronic intravenous injections and urine samples might be adulterated after relapse into side abuse [6].

Human exhaled breath is known to contain a great number of substances including non-volatile compounds [10,11]. Over 3000 analytes have been detected in human breath [12]. The anaesthetic drug propofol, which is administrated during surgery, can be measured in exhaled breath by mass spectrometry techniques with breath and blood concentrations being correlated during steady-state conditions [13]. We recently were able to demonstrate that amphetamine and methamphetamine are detectable in exhaled breath from drug addicts recovering from acute intoxications [14]. The collection of breath sample was done by passing breath air through a solid-phase extraction cartridge and subsequent analysis by liquid chromatography–tandem mass spectrometry in selected reaction monitoring (SRM) mode.

The possibility of using exhaled breath for drugs of abuse testing is attractive as it would overcome the problem of sampling difficulties and produce a sample with less risk for adulteration or

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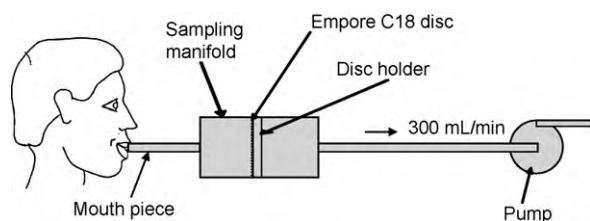


Fig. 1. Outline of the sampling device used to collect exhaled breath samples on an Empore C18 disc. The subjects were asked to breathe more deeply than normal during the 10 min sampling time.

alternate explanations. For these reasons we undertook to further investigate whether exhaled breath can be a specimen for drugs of abuse testing by investigation the possible presence of methadone in exhaled breath from patients undergoing methadone maintenance treatment.

2. Materials and methods

2.1. Chemicals and materials

Methadone and methadone-d3 (both 1.0 mg/mL) were obtained as ampouled methanol solutions from Cerilliant Corporation (Round Rock, TX). Methanol, acetonitrile and ethyl acetate of HPLC grade were from JT Baker (Mallinckrodt Baker BV, Deventer, Holland). Formic acid and 2-propanol of HPLC grade was from Merck GmbH (Darmstadt, Germany). The Milli-Q water was of ultra-pure quality (>18 MΩ/cm) and prepared in-house. The analytical column Aquity UPLC BEH C18 (1.7 μm 1.0 mm × 100 mm) was from Waters Corporation (Milford, MA). The 47 mm C18 Empore disc was from Varian Inc. (Palo Alto, CA).

2.2. Preparation of methadone solutions

The ampouled methadone and methadone-d3 solutions were diluted to 100 μg/mL using methanol. These solutions were further diluted to suitable concentrations in 0.1% formic acid and stored at −18 °C for a maximum of 1 year.

2.3. Patients and control subjects

Thirteen patients undergoing methadone maintenance treatment (12 males, 1 female, ages 31–58) were recruited from the methadone program in Stockholm (Beroendecentrum Stockholm). The patients were in steady-state and received supervised daily doses of methadone between 70 and 155 mg. The patients were subjected to constant control of compliance to treatment by urine drug testing. As a control group ten drug-free healthy volunteers (4 males, 6 females, ages 29–66) were recruited. Ethical approval was obtained from the Stockholm Regional Ethics Committee (no. 2008/1347-31).

2.4. Sampling of exhaled breath

Compounds present in the exhaled breath were collected for 10 min by suction through a 47 mm Empore C18 disc using a membrane pump to assist the flow (about 300 mL/min). The subjects were asked to breathe more deeply than normal into a mouth piece (no. 4091148, Palmenco AB, Stockholm, Sweden) mounted in the sampling device holding the Empore disc (Fig. 1). It was estimated that all the exhaled breath was collected through the filter during the sampling period. Following sampling the Empore disc was dismantled using a tweezers and stored at −80 °C. The sampling device was carefully cleaned between uses, which takes about 15 min.

2.5. Sample preparation

Following storage the Empore disc was cut into 5 mm × 5 mm pieces using a scalpel and transferred to a 10 mL glass test-tube. A volume of 100 μL of 100 ng/mL methadone-d3 was added and mixed using a Vortex mixer, 300 μL of 2-propanol was added (to wet the surface), mixed and finally 5 mL of 20% methanol in ethyl acetate was added. This mixture was shaken for one hour in a thermostatic bath at 37 °C. Thereafter, the test-tube was centrifuged for 15 min at 3000 × g at 10 °C, the supernatant transferred to a new 10 mL glass test-tube, and the extraction procedure repeated using 1 mL of 20% methanol in ethyl acetate. Finally the two supernatants were combined, 10 μL of 10% aqueous formic acid added and evaporated to dryness under a stream of nitrogen at a temperature of 40 °C. The dry residue was dissolved in 100 μL of 50% methanol in ethyl acetate.

2.6. Mass spectrometry analysis

An aliquot of 3 μL was subjected to analysis by UPLC–MS/MS (Waters Quattro Premier XE). The chromatographic system was a Aquity UPLC BEH C18 column, 100 mm × 1.0 mm, particle size 1.7 μm, with a gradient system consisting of A=0.1% formic acid and B=acetonitrile. The mobile phase was 95% A for 1.2 min, followed by a linear gradient from 5% B to 65% B to 3.0 min. The equilibration time between injections was 4.0 min (95% A). The flow rate was 0.20 mL/min.

Two product ions from the protonated molecules were monitored for methadone (m/z 310 → 265; 310 → 105) and one for methadone-d3 (m/z 313 → 268). This was done by SRM in the positive electrospray mode, with 75 ms dwell time for each channel. Other instrumental settings are provided in Table 1. The minimum detectable amount (signal to noise 3) injected on column was about ~0.2 pg.

2.7. Quantification

Standards for quantification were prepared from fortified blank Empore discs.

These were prepared by adding 10, 25, 50, 100 and 200 μL (corresponds to 3.0, 7.5, 15, 30 and 60 ng on the surface) of a solution containing 300 ng/mL of methadone. After drying the discs were prepared for analysis as described above. Calibration curves were constructed using linear regression analysis, with weighting factor 1/x.

2.8. Method validation

Five replications of the calibration curve were analysed on different occasions. Limit of detection (LOD) and lower limit of quantification (LLOQ) was assessed by applying 10 pg of methadone onto a blank Empore disc and subject it for analysis. Imprecision and accuracy were estimated by analysis of six replicates of methadone applied on blank Empore discs at three levels (3.0, 15, 45 ng/disc). Recovery of extracting methadone from the Empore disc was estimated by comparison with a reference sample prepared directly in the final extract solvent. Matrix effects were estimated by extracting blank filter and filter from healthy volunteer and fortify with methadone in the final extract. This was compared with a reference sample without matrix. In addition, an infusion experiment was performed where injection of a control breath extract was injected while infusing methadone post-column and compared with injection of mobile phase A. The infusion rate was 10 μL/min and the infused methadone solution was 0.5 μg/mL in 0.1% formic acid in 50% methanol.

Table 1

Instrumental settings of the mass spectrometer.

Analyte	Precursor ion (<i>m/z</i>)	Product ion (<i>m/z</i>)	Cone voltage (V)	Collision energy (eV)
Methadone	310	265	25	16
Methadone	310	105	25	30
Methadone-d3	313	268	24	14

Source block temperature, 130 °C; desolvation gas temperature, 350 °C; desolvation gas flow, 950 L/h; cone gas flow, 50 L/h; capillary voltage, 2.0 kV; collision gas flow, 0.30 mL/min; multiplier voltage, 700 V.

Table 2

Summary of data obtained for methadone sampled in exhaled breath from 13 methadone maintenance patients.

Case no.	Methadone dose (mg/d)	Number of breaths	Sampling time after dose intake (min)	Mouth wash prior to sampling	Methadone excretion (ng/min)
1	90	41	13	No	1.0
2	100	59	44	Yes	0.39
3	100	127	27	No	1.9
4	140	91	10	Yes	5.8
5	80	94	25	Yes	1.2
6	155	45	10	Yes	0.87
7	100	42	60	Yes	3.5
8	100	56	13	Yes	1.5
9	120	35	>10 ^a	No	1.4
10	70	46	12	Yes	0.90
11	100	66	13	Yes	0.93
12	100	90	18	Yes	>6.0 ^b
13	120	59	8	Yes	2.6

^a Not noted.

^b Extrapolated value from 180 ng/disc standard was 78.

3. Results

3.1. Method validation

The peak area ratio of methadone to methadone-d3 was linear between 3 and 60 ng per sample corresponding to 0.3 and 6.0 ng methadone exhaled in breath per min. The correlation coefficients (r^2) of the calibration curves were between 0.991 and 0.999 (mean 0.996, $n=5$). LOD (signal to noise 3) was estimated to 4 pg/sample (~0.4 pg in breath/min) and LLOQ (signal to noise 10) was estimated to 15 pg/sample, while the calibrated measuring range was 3.0–60 ng/sample.

Imprecision (coefficient of variation, CV) was estimated within-series to 1.6%, 1.9% and 2.0% at levels 3.0, 15, and 45 ng/sample ($n=6$). The accuracy was 104%, 109% and 104%, respectively. The extraction recovery of methadone from the Empore disc surface was measured in duplicate using samples at the 15 ng/sample level and was 96.6% ($n=4$). Matrix effects were estimated by addition of methadone (15 ng/sample) to extracts prepared from blank Empore discs and from Empore discs used for collection of exhaled breath from a healthy volunteer. The methadone peak area was compared with the reference sample containing no matrix. The matrix effect for blank Empore discs was 109% (SD 9, $n=8$) and for breath sample discs 108% (SD 40, $n=8$). The response of infused methadone following injection of matrix is shown graphically in Fig. 2. Although a drop in response was seen shortly following the void volume no matrix effect was observed at the retention time of methadone. The increase in response followed the increasing acetonitrile content.

3.2. Application of the method

Methadone was detected in the sampled exhaled breath from all 13 studied patients, which was in accordance with the daily observed dose intake of methadone (Fig. 3(a), Table 2). In all cases this was also supported by compliance to treatment as controlled by routine analysis of urine and by supervised dose intake. None of the 10 control subjects had detectable levels of methadone (<0.005 ng/min) in the exhaled breath samples (Fig. 3(b)). The

detection level was set by the contribution of methadone-d3 to the two methadone channels.

Identification of detected methadone was based on a correct relative (to methadone-d3) retention time ($\pm 0.5\%$) and correct ($< \pm 20\%$) relative ion intensity ratio between the two product ions (see Fig. 3(a) and (c)). The amount of methadone collected from breath was high enough to produce strong analytical response. This makes the identification secure and methadone was identified according to these criteria in samples from all methadone patients. The amount of methadone ranged >15-fold from 0.39 to >6.0 (78) ng/min. The highest value obtained was outside the measuring range and appeared to be an outlier. Table 2 summarizes the results and collected data for the 13 patient samples. No difference in results could be observed between subjects sampled with or without mouth wash prior to sampling (Table 2). No significant correlation of excretion rate with methadone dose was observed.

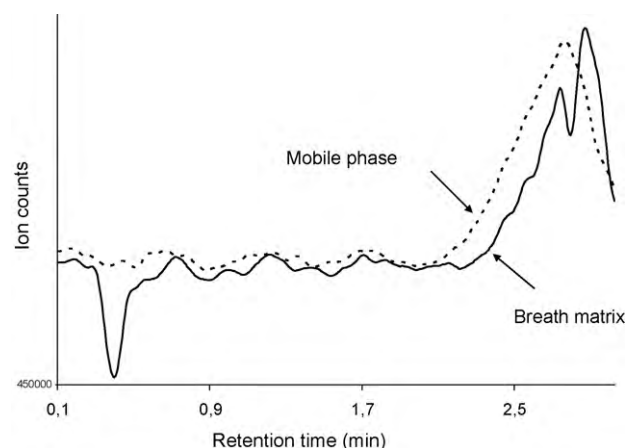


Fig. 2. The matrix effect on methadone ionisation was studied at the *m/z* 310/265 transition. Methadone was infused post-column (infusion rate 10 μ L/min of a methadone solution containing 0.5 μ g/mL in 0.1% formic acid in 50% methanol) and a control breath extract was injected (breath matrix trace). For comparison, control mobile phase A was injected.

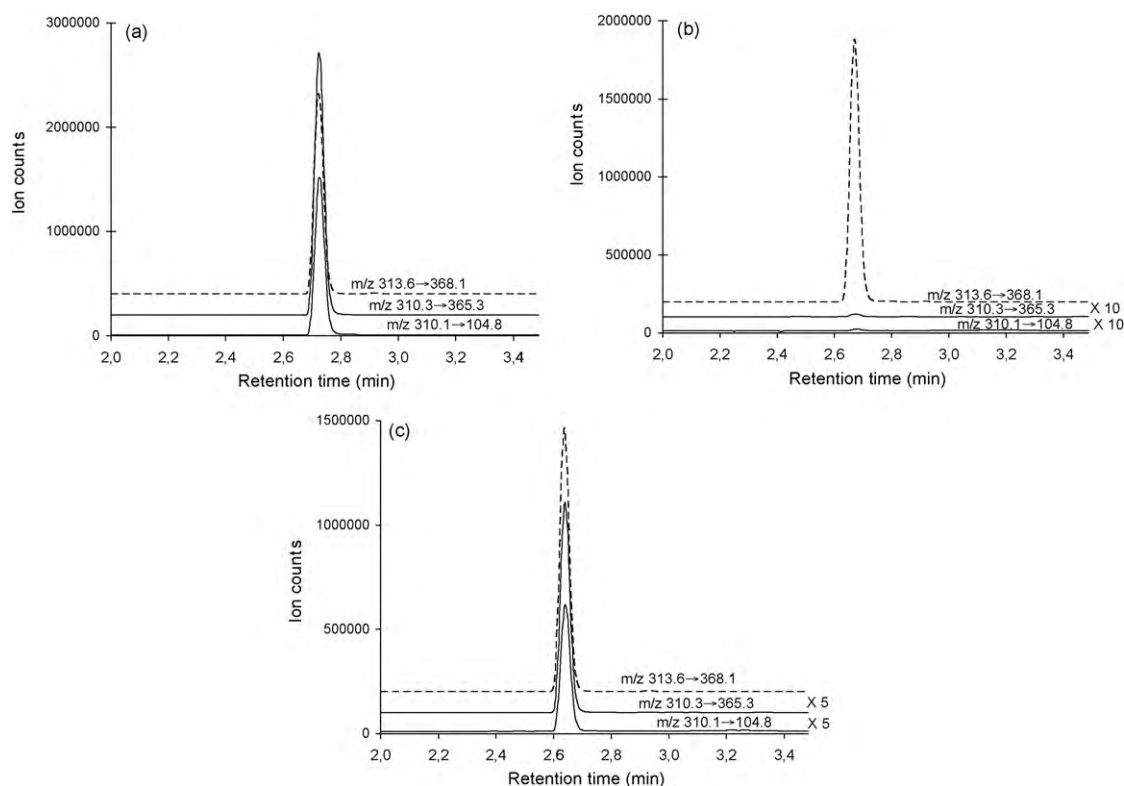


Fig. 3. Chromatograms from the identification of methadone in exhaled breath from (a) a methadone patient (subject 11 of Table 2), (b) a control subject with no detectable methadone, and (c) a standard prepared from a blank filter with added methadone (3.0 ng). Identification using LC–MS/MS was based on the presence of compound with correct retention time and with correct relative abundance of the two product ions. The markings $\times 10$ and $\times 5$ in the figure means that the response was multiplied this much relative to the internal standard channel.

Each subject was breathing at own chosen pace. The number of breaths during the 10 min sampling time was therefore recorded (Table 2). Table 2 also reports the actual sampling time after dose intake. Due to practical reasons this time interval could not be the same for all subjects but varied between 8 and 60 min.

4. Discussion

This study reports the original observation that methadone can be detected in exhaled breath collected from patients undergoing methadone maintenance treatment. This observation opens up a new possible specimen for monitoring compliance in methadone treatment.

The identification of methadone by mass spectrometry followed commonly accepted criteria being successfully applied in urine drug testing [15]. The fact that all 13 patients and no control subject had methadone detectable in breath makes the results convincing. This was also the case with our previous finding on amphetamine and methamphetamine [14]. The excretion rate of methadone (0.39–78 ng/min) was much higher than was seen before for amphetamine and methamphetamine (0.2–139 pg/min). This might be caused by several reasons one being that the methadone patients were in steady-state while the amphetamine intoxication cases were in recovery phase. Other pharmacokinetic features might also differ between compounds possibly making methadone more available for breath transport. However, blood levels of amphetamine and methamphetamine measured in these patients at the time of breath sampling were in the range of methadone under steady-state conditions. Nevertheless, the sampling of methadone patients was performed following the daily dose intake of methadone. Another reason for different measured excretion rates might be that the sampling procedure was differ-

ent in the two experiments. In the present study we used a wider sampling disc providing more optimal flow rate [16], and there was also a shorter distance between the subject and the filter. In three subjects no mouth wash was performed before sampling indicating that material present in mouth did not contribute to the measured methadone as the results were similar as for the other subjects.

Propofol was measured in the gas phase with calibrators prepared using a gas generator [13]. Apart from the gas phase human breath also contains components carried in particles and droplets, which can be collected as exhaled breath condensate [17]. It was shown that this fraction derives mainly from the central airways in addition to the airway lining fluid [17]. The mechanism for excretion of methadone in exhaled breath remains to be determined.

In conclusion, this observation of methadone being present and measurable in exhaled breath demonstrates that drug testing using breath is feasible and deserves further investigation. Exhaled breath might be developed into a much more easily accessible and safer specimen than other matrices presently used for drug testing. Our results so far demonstrate that current bio-analytical technology enables the measurement of methadone, amphetamine and methamphetamine and possibly other drugs of abuse in exhaled breath. Since methadone is chronically administered in methadone maintenance therapy it might be used as a study analyte for more detailed studies on the excretion mechanism and development of sampling techniques. One practical limitation at the moment is the relatively long sampling time of 10 min.

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Amphetamines Detected in Exhaled Breath from Drug Addicts: A New Possible Method for Drugs-of-Abuse Testing

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Abstract

Testing for drugs of abuse in sample matrices alternative to urine such as blood, sweat, and saliva have received increasing attention and is needed, for example, in traffic medicine. Human breath is known to contain a large number of substances including non-volatile molecules. We explore whether intake of amphetamines could be detected by analytical investigation of exhaled breath from drug addicts. Exhaled breath was collected from 12 drug addict patients after recovering from acute intoxication. Self-reported intake of "amphetamine" was confirmed by analysis of urine and plasma. The compounds were trapped by filtering the air through a modified silica surface and subsequently analyzed by a combined liquid chromatography–tandem mass spectrometry method. As a control, exhaled breath was collected in the same way from eight healthy volunteers. Here we report for the first time that amphetamine and methamphetamine are present in exhaled breath following ingestion of these compounds by drug addicts. Both amphetamine and methamphetamine were indisputably identified by means of the mass spectrometry technique in exhaled breath samples from all 12 patients. Identifications were based on monitoring two product ions in selected reaction monitoring mode and having correct relative ratios ($\pm 20\%$). Excretion rates ranged from 0.2 to 139 pg/min. No amphetamine or methamphetamine was detected in the control subjects. This finding, using a yet non-validated sampling procedure, opens a new possibility for drugs-of-abuse testing. Collection of exhaled breath is likely to be more convenient and safe as compared to matrices presently in use.

Introduction

Combating drug abuse is of primary concern in societies all over the world. Testing for drugs of abuse is a common practice effective in detecting drug users and is an integral part of clinical treatment programs. Furthermore, drug testing is used in workplaces and has important forensic applications. Testing is usually performed by laboratory investigation on collected urine samples, but the use of on-site testing and

sample matrices alternative to urine such as blood, sweat, and saliva have received increasing attention and is needed, for example, in traffic medicine (1–3). The ongoing interest and application of saliva testing in traffic medicine has demonstrated a true need for tests based on simpler and safer sampling procedures (4,5) and with immediately available results.

Testing for alcohol is readily available using portable instruments for breath analysis. Apart from alcohol, exhaled breath has so far not been developed for testing of any other drugs of abuse. However, exhaled breath is known to contain a great number of substances including non-volatile compounds. It is known that non-volatile compounds can be detected in expired breath air, possibly carried as an aerosol (6,7). Altogether over 3000 analytes have been detected in human breath (8). Apart from alcohol testing, breath analysis is established for the diagnosis of *H. pylori* infection and for nitric oxide measurement in asthma monitoring, and its potential for use in other areas is evident (6,8).

The possibility of using exhaled breath for drugs-of-abuse testing is attractive as it would overcome the problem of sampling difficulties and produce a sample devoid of any complicated risk for adulteration or alternate explanations. Recent technological advances in mass spectrometry (MS) have enabled the combination of increased selectivity and sensitivity of bioanalysis. The interfacing of liquid chromatography (LC) with tandem MS has provided a new means for toxicology analysis and for analysis of trace analytes in biological samples in general (9). For these reasons, we investigate whether amphetamine and methamphetamine could be detected in exhaled breath from active drug users by employing a most sensitive and selective bioanalytical technology ultra-performance LC–MS–MS in selected reaction monitoring (SRM) mode.

Materials and Methods

Chemicals and materials

Amphetamine, methamphetamine, and amphetamine- d_5 was obtained as ampouled methanol solutions from Cerilliant

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(Round Rock, TX). Ammonia (25%) solution was obtained from VWR International (Darmstadt, Germany); methanol and acetonitrile of HPLC grade was from JT Baker (Mallinckrodt Baker BV, Deventer, Holland); ethyl acetate and formic acid of HPLC grade were from Merck (Darmstadt, Germany). The water was of ultra-pure quality ($> 18 \text{ M}\Omega/\text{cm}$) and prepared in-house. The AQUITY UPLC BEH C_{18} column was from Waters (Milford, MA), and the 30 mg SPEC DAS solid-phase extraction (SPE) cartridges were from Varian (Palo Alto, CA).

Patients and control subjects

Twelve patients reporting recent use of amphetamine (7 male, 5 female, ages 22–51) were recruited from two addiction treatment clinics in Stockholm (Beroendecentrum Stockholm) after recovering from acute intoxication. History of drug use was assessed by interviewing and by using two structured questionnaires, AUDIT (for alcohol) and DUDIT (for illicit drugs) (10–12). The patients scored a median of 2.5 (range 0–34) in the AUDIT and 34.5 (range 12–43) in the DUDIT questionnaires. In the AUDIT questionnaire, the limit for harmful use is 8 (max 40), and for DUDIT, the limit was 6 (max 44). The low average AUDIT score and high DUDIT score reflect the limited use of alcohol and the heavy use of illicit drugs (e.g., amphetamine), respectively, in the studied patients.

Recent drug intake was further investigated by analysis of plasma and urine samples. In three of the cases, blood sampling was not possible because of clinical factors. The urine and EDTA plasma samples were collected following the exhaled breath sampling and stored at -80°C . As a control group, 8 drug-free healthy volunteers (3 male, 5 female, ages 29–67) were recruited. Ethical approval was obtained from the Stockholm Regional Ethics Committee (No 2008/1347-31).

Sampling of exhaled breath

Compounds in exhaled breath were collected for 10 min by suction through a SPEC DAS cartridge. The patients were asked to breathe normally in a face mask (no. 1516, Intersurgical, Berkshire, U.K.), and a three-way coupling was used to withdraw breath air (Figure 1). It was estimated that about half of the exhaled breath was collected through the SPEC DAS cartridge via a 3-m long plastic tubing. Following sampling, the cartridge was stored at -80°C .

MS analysis

Following storage, the SPE cartridge was subsequently eluted with 2% ammonia (25%) in a mixture of methanol and ethyl acetate (20:80, v/v) at the time of analysis. The eluate was evaporated to dryness under nitrogen gas after adding of formic acid (10 μL of 10% formic acid in MeOH), and the residue was redissolved in 30 μL of 0.1% formic acid containing internal standard (5.94 ng amphetamine- d_5). An aliquot of 3 μL was subjected to analysis by SRM UPLC–MS–MS (Waters Quattro Premier XE). The chromatographic system was an ACQUITY UPLC BEH C_{18} column (100 mm $\times$ 1.0 mm, particle size 1.7 μm) with a gradient system that consisted of A = 0.1% formic acid and B = acetonitrile. The linear gradient started at 100% A and ended at 70% A after 1.7 min. Thereafter, 100% was pumped for 0.49 min before returning to 100% A.

Two product ions from the protonated molecules were monitored for amphetamine (m/z 136 $\rightarrow$ 119; 136 $\rightarrow$ 91), two for methamphetamine (m/z 150 $\rightarrow$ 119; 150 $\rightarrow$ 91) and one for amphetamine- d_5 (m/z 141 $\rightarrow$ 124). This was done by SRM in the positive electrospray mode with 25 ms dwell time for each channel. Other instrumental settings are provided in Table I. The minimum detectable amount (signal-to-noise ratio = 3) injected on column was about 0.1 pg.

Methods used for plasma and urine analysis were in routine use in the laboratory and based on published LC–MS procedures (13,14).

Quantitation

Standards for quantitation were prepared by using the matrix from blank SPE cartridges.

Results

In all 12 studied patients, amphetamine and/or methamphetamine were detected in the exhaled breath sample, which was in accordance with self-reported drug intake (Table II). In

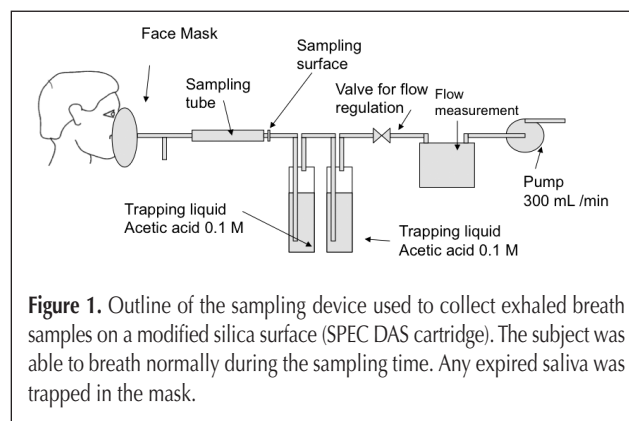


Figure 1. Outline of the sampling device used to collect exhaled breath samples on a modified silica surface (SPEC DAS cartridge). The subject was able to breathe normally during the sampling time. Any expired saliva was trapped in the mask.

Table I. Instrumental Settings of the Mass Spectrometer

Analyte	Precursor Ion m/z	Product Ion m/z	Cone Voltage (V)	Collision Energy (eV)
Amphetamine	135.96	91.01	17	14
Amphetamine	135.96	119.02	17	8
Methamphetamine	150.03	90.99	21	18
Methamphetamine	150.03	119.00	21	10
Amphetamine- d_5	140.96	124.00	17	14
Source block temperature			150 $^\circ\text{C}$	
Desolvation gas temperature			350 $^\circ\text{C}$	
Desolvation gas flow, N_2			900 L/h	
Capillary voltage			1.0 kV	
Collision gas flow, N_2			30 L/h	
Multiplier voltage			700 V	

all cases, the self-reported intake was supported by analysis of plasma and urine. The presence and relative levels of amphetamine and methamphetamine indicated mixed drug use of both compounds, which is in accordance with a recent trend in Sweden observed in the clinical urine drug testing. None of the patients specifically reported the use of methamphetamine.

Identification of detected analytes was based on a correct relative (to amphetamine- d_5) retention time ($\pm 0.5\%$) and correct ($< \pm 20\%$) relative ion intensity ratio between the two product ions (Figure 2). Because levels were generally low, background signal resulted in failure to fulfill identification criteria in some of the samples, despite the fact that signal was actually present at the correct retention times (Figure 3). The amount of substance collected from exhaled breath ranged from 0.2 to 103 pg/min for amphetamine and < 0.3 to 139 pg/min for methamphetamine (Table II). In the eight healthy controls, no amphetamine or methamphetamine were detected (Figure 4).

When comparing response for internal standard between standards and samples, no indication of ion suppression from matrix was evident. No amphetamine or methamphetamine

was detected in the trapping liquid (Figure 1).

Discussion

This study reports the original observation that self-administered amphetamine and methamphetamine can be detected in exhaled breath collected from drug addicts. The identification of amphetamine and methamphetamine followed commonly accepted criteria. These criteria for identification are in accordance with scientific standards and are being successfully applied in urine drug testing (15). No correlation between plasma and exhaled breath levels was evident from the results indicating that the exhaled breath sample might represent another compartment than blood. However, the sampling technique employed could not be validated for extraction efficiency, but a similar application has been used and validated for collection of airborne aromatics (16). The collection cartridge material used in the present study is normally used for extraction of analytes from aqueous solutions. It is, therefore,

Table II. Summary of Data Obtained for Plasma, Urine, and Exhaled Breath*

Case No.	Self-Reported Recent Drug Use	AUDIT Score	DUDIT Score	Plasma [†] (ng/mL)	Urine [†] (µg/mL)	U-Creatinine (mmol/L)	Breath [†] (pg/min)
1	Amphetamine, diazepam	1	14	A = 166 M = 1.9	A = 107 M = 0.69	32.0	A = 0.7 M < 0.3 [‡]
2	Amphetamine, diazepam	3	26	A = 62.4 M = 0.6	A = 14 M = 0.08	15.2	A = 0.2 M < 0.3 [‡]
3	Amphetamine	4	19	A = 282 M = 2.1	A = 30 M = 0.12	12.6	A = 0.5 M < 0.3 [‡]
4	Amphetamine, methylphenidate	2	12	A = 110 M = 27	A = 63 M = 5.4	27.2	A = 19 M = 1.2
5	Amphetamine, zopiclone	5	37	A = 53 M = 52	A = 30 M = 19	21.2	A = 0.4 M = 0.4
6	Amphetamine, alprazolam, buprenorphine, flunitrazepam, morphine, zopiclone	0	32	No sample	A = 5.3 M = 62	7.9	A = 102 M = 139
7	Amphetamine	3	30	A = 4.3 M = 3.2	A = 0.94 M = 0.40	8.1	A < 0.6 [‡] M = 0.5
8	Amphetamine, diazepam, heroin, methadone	0	41	No sample	A = 20 M = 119	31.6	A < 0.3 [†] M = 0.6
9	Amphetamine, alprazolam, diazepam, methylphenidate	0	40	No sample	A = 6.7 M = 0.02	15.0	A = 0.4 M < 0.3 [‡]
10	Amphetamine, flunitrazepam, methadone	10	43	A = 535 M = 64	A = 229 M = 15	33.3	A = 0.7 M < 0.3 [‡]
11	Amphetamine, cannabis, clonazepam, methadone	0	40	A = 504 M = 274	A = 163 M = 51	22.1	A = 5.2 M = 1.3
12	Amphetamine, benzodiazepine, cannabis, heroin	34	40	A = 2.0	A = 1.3	19.0	A = 1.4

* Sampled from 12 drugs addicts after recovery from acute intoxication.

[†] A, amphetamine and M, methamphetamine.

[‡] LOD was estimated for each chromatogram individually and was limited when observed peaks did not meet identification criteria.

unknown to what degree the amphetamines are trapped from exhaled breath and the reproducibility of the extraction efficiency, which may have contributed to the variability in detected amounts in the exhaled breath samples. It was not possible to validate the accuracy and precision in quantitation in the present study, but this will be the topic for further work. Firm conclusions regarding a possible correlation of exhaled breath excretion rate with blood levels can, therefore, not be made at this point.

The majority of the patients were sampled after hospitalization and recovery following acute drug intoxication. The urine and plasma data indicated that in most cases sampling was performed close to "amphetamine" intake (< 24 h), whereas in other cases low levels (< ~5 µg/mL) in urine indicated longer

times since intake (Table I). Analytes were, however, still detected in the exhaled breath. The relative proportion of amphetamine and methamphetamine in the exhaled breath agreed well from a qualitative perspective with plasma results, which further support the validity of the findings. In cases 1, 2, and 3, there was a clear predominance of amphetamine in plasma, which was reflected in the breath sample; in cases 4, 5, and 11, a higher proportion of methamphetamine was reflected in both specimens.

Apart from alcohol, exhaled breath has so far not been considered for testing of any other drugs of abuse since earlier studies in the 1970s and 1980s on tetrahydrocannabinol in breath following cannabis smoking (17). However, exhaled breath is known to contain a great number of substances including non-volatile compounds (6–8). It is, therefore, reasonable to assume that also abused drugs can be excreted this way. Compounds exhaled in exhaled breath may originate from blood by a mechanism of producing a gas phase in the alveoli (18,19). Alternatively, compounds may originate from other parts of the airways (18,19). The importance and role of the aerosol fraction for the excretion of drugs of abuse in exhaled breath needs to be addressed in future work.

This original observation demonstrates that drug testing using exhaled breath is feasible and deserves further investigation. Exhaled breath sampling is more accessible and safer than other matrices presently used for drug testing. Our results demonstrate that current bioanalytical technology enables the use of exhaled breath for detecting and measuring drugs of abuse. A better and validated sampling technique is needed to extend these findings to other drugs of abuse in exhaled breath. The possible development of a miniaturized detector that would enable field testing for drugs of abuse in general is intriguing and would be expected to significantly contribute to the area of drug testing in, for example, traffic medicine.

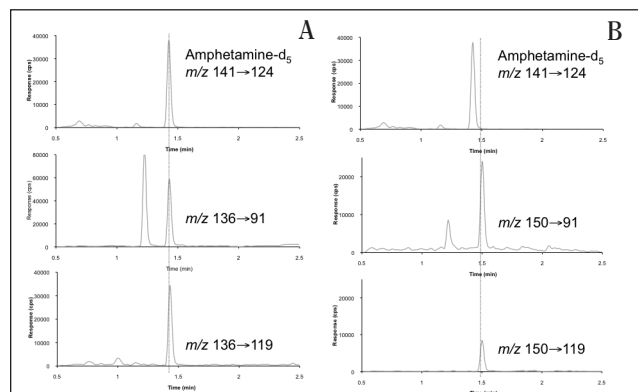


Figure 2. Chromatograms from the identification of amphetamine (A) and methamphetamine (B) in exhaled breath from one patient (case 11 of Table II) after intake of "amphetamine". The urine and plasma data suggest possible intake of methamphetamine with amphetamine. Identification using LC–MS–MS was based on the presence of compounds with correct retention time and with correct relative abundance of two product ions.

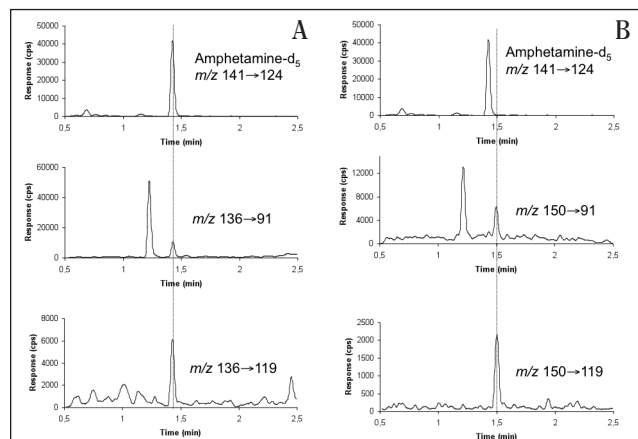


Figure 3. Chromatograms from the identification of amphetamine (A) and failure to identify methamphetamine (B) in exhaled breath from one patient (case 10 of Table II) after intake of "amphetamine". The urine and plasma data suggest intake of amphetamine with methamphetamine. Identification using LC–MS–MS was based on the presence of compounds with correct retention time and with correct relative abundance of two product ions. For methamphetamine, the product ion ratio (0.55) was outside the acceptance criterion $0.41 \pm 20\%$.

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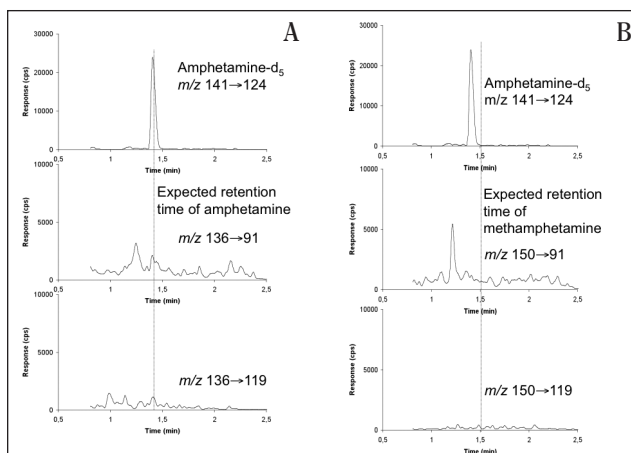


Figure 4. Chromatograms from the analysis of amphetamine (A) and methamphetamine (B) in an exhaled breath extract from a control subject.

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