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(54) CONNECTOR DEVICE FOR MICROFLUIDIC CIRCUITS

(57) The present invention relates to a connector device (1) for use with a microfluidic circuit (2), the device (1) comprising at least one coupling (5) between an external microfluidic component and an inlet (3) or outlet (4) of the microfluidic circuit (2). Advantageously, the coupling (5) is designed to house a connection means between the external component and the connector device (1) and which additionally comprises an exhaust opening (6) configured as a means for evacuating gas during the connection of said external component to the inlet (3) or outlet (4) of the microfluidic circuit (2). The main advantage of the device (1) is that it allows the elimination of air and bubbles during the connection of the system, such that the use of encapsulations or complex coupling methods is not required.

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Description

FIELD OF THE INVENTION

[0001] The present invention is comprised in the microfluidic device sector, and generally in the technical field relating to microfluidics for *in vitro* cell culture and analysis. More specifically, the object of the invention relates to a connector for microfluidic devices which allows preventing the entry of bubbles present in the working fluids during the connection of the components of a fluidic circuit to said microfluidic devices.

BACKGROUND OF THE INVENTION

[0002] *In vitro* cell culture is a widely used technique which allows observing the behavior, morphology, and physical condition of the cells or performing biochemical analyses and assays under given biological conditions. Moreover, microfluidics is the science that studies the behavior of microfluids, which is a very important discipline in the study of biological processes on a microscale and on a mesoscale in which devices referred to as microfluidic devices or microfluidics devices are used for such purpose.

[0003] In microfluidics devices for cell culture and biological analysis, the fluid in which the cells are immersed is circulated for the purpose of simulating biomimetic environments in cultures, thereby obtaining *in vitro* results which can be extrapolated to *in vivo* situations to a greater or lesser extent, depending on the reproducibility in the assay of the conditions that the cell would experience in a living organism. It is, therefore, of vital importance to have devices which allow optimum circulation of the working fluids and prevent problems derived from the features of said devices, for the purpose of improving the reproducibility of processes in a living organism.

[0004] It is known in the state of the art that one of the main problems relating to the use of microfluidics devices both for performing cell cultures and in applications of another type is the accidental occurrence of air bubbles in the fluid. Said bubbles occur particularly in given regions of the devices, such as the connections with fluid circulation channels or the inlets and outlets of the microfluidic chips in which the culture is housed. This problem entails serious limitations in practice, so in recent years various systems for removing bubbles from the fluid as it passes through the microfluidic device have been developed, either by confining said bubbles in a region located of said device or by preventing their presence therein by using bubble traps, like the system used in European patent EP 1792655 B1. In this context, there are microfluidics devices with different systems for removing bubbles on the market which can be integrated into the device itself or placed at the inlet thereof, such that the incoming fluid no longer contains air bubbles.

[0005] Another solution existing on the market, which is less complex and proposed as an improvement of the solutions mentioned above, is the use of encapsulation parts or systems like the device of international patent application WO 2014/053678 A1. Nevertheless, these systems have limitations derived from the connections between the encapsulation and the device such as, for example, the possibility of contamination with unwanted flows or contaminants coming from other fluid circulation channels. Additionally, the use of encapsulation parts or systems entails a risk of the occurrence of connection errors due to manufacturing tolerances and involves the need to use elastic parts in the joints to assure that said connections are sealed.

[0006] The main drawback of systems for removing bubbles available today is that the bubbles that are removed from the fluid are trapped inside the traps or channels of the device, which involves the need to empty said channels every so often, which adds risks and problems derived from said operation. Another drawback is the complexity added to microfluidic systems in which these systems are integrated, whether they are integrated internally or externally with respect to the microfluidics devices.

[0007] Therefore, it has become necessary to have on the market simpler alternatives for removing bubbles in microfluidics devices which do not require the use of encapsulations or other more complex methods, since they involve the use of membranes or the generation of a vacuum in the device, and which additionally conduct the bubbles removed from the fluid out of the device, such that they are not trapped inside same, making it necessary to cyclically empty or clean the microfluidic channels.

[0008] In view of the aforementioned technical problems, the connector object of the present invention is intended for meeting said need by means of a connector which allows effectively preventing the presence of bubbles in microfluidics devices, does not require needing ancillary, and has a simple design. The invention therefore allows removing bubbles during the connection of a fluidic circuit to one or more microfluid devices, as well as purging said fluidic circuit before its connection to the devices *in situ.*

BRIEF DESCRIPTION OF THE INVENTION

[0009] Therefore, an object of the present invention is to provide a solution for preventing the presence of bubbles in microfluidic devices as an alternative to the solutions existing in the state of the art. To that end, a connector for microfluidic

devices comprising a coupling for one or more fluid circulation channels, designed for the entry or exit of said fluid to/from the microfluidic device through the connector, is proposed.

[0010] More specifically, the object of the invention is a connector device suitable for use with a microfluidic circuit, said device comprising at least one coupling between an external microfluidic component and an inlet or outlet of said microfluidic circuit. Advantageously, said coupling is designed to house a connection means between the external component and the connector device; and additionally comprising an exhaust opening configured as a means for evacuating gas (for example, air) during the connection of said external component to the inlet or outlet of the microfluidic circuit.

[0011] This achieves preventing the presence of bubbles in the device, removing them during the connection and the passage of fluid from the microfluidic circuit to the microfluidic device, through the coupling object of the invention and its associated exhaust opening. The fluid entering the microfluidic device is therefore bubble-free without needing to use other more complex systems, such as encapsulation systems.

[0012] In a preferred embodiment of the invention, the connector device comprises at least one discharge well for fluid coming from the exhaust opening, the origin of which is either the microfluidic circuit itself or the external components to be connected to the device. The preceding description allows eliminating the periodic emptying and cleaning of the connector during the purge phase prior to the connection. The removal of the air that enters the circuit due to changes in pressure thereof, suction, or accidental entrainment of air into the circuit is thereby facilitated, allowing a safe and bubble-free connection. The isolation of the fluid with bubbles discarded from the fluidic circuit is also achieved.

[0013] In an embodiment of the invention based on the use of a discharge well, the connector device comprises at least two couplings arranged on one and the same discharge well. In an alternative or complementary manner, the device comprises a discharge well arranged such that it collects the fluid coming from a single coupling through the corresponding exhaust opening thereof. The discharge well allows collecting the excess fluid and purging the fluidic circuit, such that there is no uncontrolled transfer of fluid into the microfluid device, and constitutes a benefit to hygiene while the fluid is collected. This translates into easier handling by the end user and a lower probability of contamination.

[0014] In another preferred embodiment of the invention, the microfluidic circuit comprises one or more of the following elements, alone or in combination: circulation channels or microchannels, biological sample housing chambers or microchambers, microfluidic chips. This achieves an enormous versatility which makes the device suitable for a wide range of biological and microfluidic applications.

[0015] In another preferred embodiment of the invention, the device comprises couplings to at least an inlet and an outlet of the microfluidic circuit. It is thereby assured that the fluid that reaches and leaves the microfluidic circuit does so free of air bubbles.

[0016] In another preferred embodiment of the invention, the coupling is based on a threaded connection means. Nevertheless, said coupling can be based on other means, such as a pressure or clip connection means, for example.

[0017] In another preferred embodiment of the invention, the inlet or the outlet of the microfluidic circuit is equipped with a leak-tight connection means. More preferably, said connection comprises one or more O-rings, eliminating the need for other internal connection means and preventing the problems derived from their own tolerances.

[0018] In another preferred embodiment of the invention, one or more of the elements forming the connector device are manufactured with a biocompatible material. More preferably, said material comprises methacrylate (PMMA), polycarbonate (PC), cyclic olefin polymers or copolymers, polymer photoresists, or similar materials.

[0019] In another preferred embodiment of the invention, one or more of the elements forming the connector device are manufactured with an optically transparent or radio transparent material.

[0020] Definitions of some of the main terms used in the present description and their scope of interpretation in light of the invention herein claimed are provided below:

A connector device must be interpreted to mean a connection means of a microfluidic circuit housed in said device with one or more external microfluidic components with respect to said device.

[0021] A microfluidic circuit must be interpreted to mean any microfluidic elements housed in the connector device, such as channels or microchannels, housing or culture chambers or microchambers, microfluidic chips, or similar elements used in the scope of microfluidics or lab-on-a-chip system technologies.

[0022] An inlet into the microfluidic circuit must be interpreted to mean any means of passage whereby fluid is introduced into said circuit, and where said inlet is configured for connection thereof with an external microfluidic component with respect to the connector device.

[0023] An outlet of the microfluidic circuit must be interpreted to mean any means of passage whereby fluid is extracted from said circuit, and where said outlet is configured for connection thereof with an external microfluidic component with respect to the connector device.

[0024] A coupling of external microfluidic components with respect to the connector device must be interpreted to mean any means configured for connecting an inlet or an outlet of the microfluidic circuit with a circulation channel connected to an external microfluidic component with respect to the connector device.

[0025] An external microfluidic component must be interpreted to mean any element configured with fluid circulating or housing means in a microfluidic system, such as additional external circuits, circulation pumps, fluid infeed sources, etc.

[0026] An exhaust opening must be interpreted to mean an opening made in the actual coupling of the connector device, arranged such that it allows the exit or expulsion of gases during the purge or pre-connection process of an external microfluidic component to an inlet or outlet of the connector device. As an example, in a threaded coupling, the opening can be arranged parallel to the axis of the threading and on its outer longitudinal perimeter, such that a portion of said opening is always free for the exhaust of air until completing the closure path of said threading.

[0027] A discharge well must be interpreted to mean any means of receiving and/or housing the fluid coming from the exhaust opening during the method for the connection of an external microfluidic component to an inlet or outlet of the connector device for the purposes of storing or discarding said fluid, isolating it from the fluidic connection region and channels of the device.

[0028] The expression "comprises" must be interpreted to mean, when it is applied to the relationship between a main element with respect to other secondary elements, that said main element includes or contains said secondary elements but without excluding other additional elements.

DESCRIPTION OF THE DRAWINGS

[0029] To complete the description of the invention and for the purpose of helping to better understand its technical features, a set of drawings is attached hereto in which the following is depicted with an illustrative and non-limiting character:

Figure 1 shows a top perspective view of the connector object of the invention according to a preferred embodiment thereof.

Figure 2 shows two views, a plan view and an elevational view, of the connector object of the invention according to another preferred embodiment thereof.

Figure 3 shows an external isometric perspective view of the connector object of the invention according to the preferred embodiment thereof according to Figure 2.

REFERENCE NUMBERS USED IN THE DRAWINGS

[0030]

(1)	Connector device
(2)	Microfluidic circuit
(3)	Inlets into the microfluidic circuit
(4)	Outlets of the microfluidic circuit
(5)	Coupling of external microfluidic components with respect to the connector device
(6)	Exhaust opening
(7)	Discharge well

DETAILED DESCRIPTION OF THE INVENTION

[0031] A detailed description of the invention in reference to a preferred embodiment thereof is provided below based on Figures 1 to 3 of the present document.

[0032] As shown in Figure 1, the present invention relates to a connector device (1) for use with a microfluidic circuit (2), said circuit (2) being able to comprise one or more fluid circulating or housing means, such as circulation channels, housing chambers or microchambers, microfluidic chips, or the like. Therefore, the connector device (1) of the invention is preferably proposed a connection means between one or more inlets (3) and/or outlets (4) of the microfluidic circuit (2) and one or more external microfluidic components, where the design and the elements forming the connector device (1) assure that the fluid circulating through said microfluidic circuit (2) reaches or leaves same, preventing the presence of bubbles in the purge and connection phase.

[0033] In different embodiments of the invention, the connector device (1) can hold elements intended for *in vitro* analysis (including, for example, housing chambers or culture chips as part of the microfluidic circuit (2)) or can be considered as a means for removing bubbles between several external components (including, for example, connection

or distribution microchannels as elements of the circuit (2), as shown in Figure 1), where same are connected to the inlets (3) and/or to the outlets (4) of the device (1).

[0034] Additionally, in an embodiment of the invention illustrated in Figure 2 the connector device (1) can comprise as many inlets (3) as outlets (4) arranged at different points of connection to the microfluidic circuit (2). By means of said embodiment, the absence of bubbles both upon reaching and upon leaving the circuit (2) is assured.

[0035] For the connection of the inlets (3) and/or the outlets (4) of the device (1) to the external components (for example, additional external fluidic circuits, circulation pumps, fluid infeed sources, etc.), the use of corresponding couplings (5) (Figures 1 to 3) is considered, where each of said couplings (5) is designed to house a connection channel between the external component and the connector device (1) of the invention. Preferably, the couplings (5) are based on threaded connection means, although other mechanisms such as pressure or clip connection means are also possible in the scope of the invention.

[0036] To prevent bubble formation upon connecting the external fluidic components to the coupling (5) and its respective inlet (3) or outlet (4), said coupling (5) is equipped with an exhaust opening (6) configured as a means for evacuating air during the purge phase prior to the connection of said external component. Therefore, any bubble coming from the component to be connected will be evacuated through the exhaust opening (6). This furthermore prevents having to use other systems that are more complex or involve the need to empty said channels every so often, which adds risks of contamination and problems derived from said operation. In the embodiment of Figures 1 to 3 based on threaded couplings (5), all the air bubbles produced during the connection process (that is, when screwing the external connection channel to the coupling (5)) are removed through the exhaust opening (6) existing in said threaded couplings (5).

[0037] As an additional advantage of the connector device (1) object of the invention, the existence of an exhaust opening (6) allows excess fluid to exit during the process of closing the microfluidic device (2), thereby preventing overpressures inside the microfluidic circuit (2).

[0038] Likewise, in a preferred embodiment of the invention the connector device (1) object of the invention comprises at least one discharge well (7) for fluid coming from the exhaust opening (6), the origin of which is either the microfluidic circuit (2) itself or the external components to be connected to the device (1). The discharge well (7) provides additional advantages to the invention, since it allows collecting the discard fluid lost during connection, storing it for analysis or subsequent removal, at the desired time. Preferably, the discharge well (7) is an open well to facilitate access to its contents for purposes of analysis or removal.

[0039] In different embodiments of the invention, each exhaust opening (6) can be connected to a single discharge well (7), or one and the same well (7) can be arranged for collecting the fluid coming from several openings (6). The first case is advantageous in analysis applications, since it allows keeping each fluid isolated by each external component connected to the device (1). In turn, the use of a common discharge well (7) may be suitable in applications for removing fluid.

[0040] In different embodiments of the invention, it is possible to configure the couplings (5), the inlets (3), or the outlets (4) of the microfluidic circuit (2) with leak-tight connection means, such as O-rings, which constitutes an additional measure for assuring suitable coupling of the connector device (1) of the invention with the external microfluidic components.

[0041] Likewise, the elements forming the connector device (1) of the invention are preferably manufactured with biocompatible materials (i.e., with one or more pharmacologically inert compounds that do not negatively interfere with the biological materials or cultures housed in the microfluidic circuit), such as methacrylate (PMMA), polycarbonate (PC), polymer photoresists such as SU-8, cyclic olefin polymers or copolymers, etc.

[0042] For those applications of the invention intended for biological analysis by means of optical instruments, one or more of the elements forming the connector device (1) can be optically transparent or radio transparent to facilitate access of said instruments to the biological material.

Claims

1. A connector device (1) for use with a microfluidic circuit (2), the device (1) comprising at least one coupling (5) between an external microfluidic component and an inlet (3) or outlet (4) of said microfluidic circuit (2),
characterized in that said coupling (5) is designed to house a connection means between the external component and the connector device (1) and which additionally comprises an exhaust opening (6) configured as a means for evacuating gas during the connection of said external component to the inlet (3) or outlet (4) of the microfluidic circuit (2).

2. The connector device (1) according to the preceding claim, wherein the microfluidic circuit (2) comprises one or more of the following elements, alone or in combination: circulation channels or microchannels, biological sample

housing chambers or microchambers, microfluidic chips.

3. The connector device (1) according to any of the preceding claims, the device comprising couplings (5) to at least an inlet (3) and an outlet (4) of the microfluidic circuit (2).

4. The connector device (1) according to any of the preceding claims, wherein the coupling (5) comprises a threaded connection means.

5. The connector device (1) according to any of the preceding claims, wherein the coupling (5) comprises a pressure or clip connection means.

6. The connector device (1) according to any of the preceding claims, comprising at least one discharge well (7) for fluid coming from the exhaust opening (6), the origin of which is either the microfluidic circuit (2) itself or the external components to be connected to the device (1).

7. The connector device (1) according to the preceding claim, comprising at least two couplings (5) arranged on one and the same discharge well (7).

8. The connector device (1) according to any of claims 6 to 7, comprising a discharge well (7) arranged such that it collects the fluid coming from a single coupling (5) through the corresponding exhaust opening (7) thereof.

9. The connector device (1) according to any of claims 6 to 7, wherein the discharge well (7) is an open well.

10. The connector device (1) according to any of the preceding claims, wherein the coupling (5), the inlet (3), or the outlet (4) of the microfluidic circuit (2) is equipped with leak-tight connection means.

11. The connector device (1) according to the preceding claim, wherein the leak-tight connection means comprise one or more O-rings.

12. The connector device (1) according to any of the preceding claims, wherein one or more of the elements forming said device (1) are manufactured with a biocompatible material.

13. The connector device (1) according to the preceding claim, wherein the biocompatible material comprises methacrylate (PMMA), polycarbonate (PC), cyclic olefin polymers or copolymers, or polymer photoresists.

14. The connector device (1) according to any of the preceding claims, wherein one or more of the elements forming said device (1) are manufactured with an optically transparent or radio transparent material.

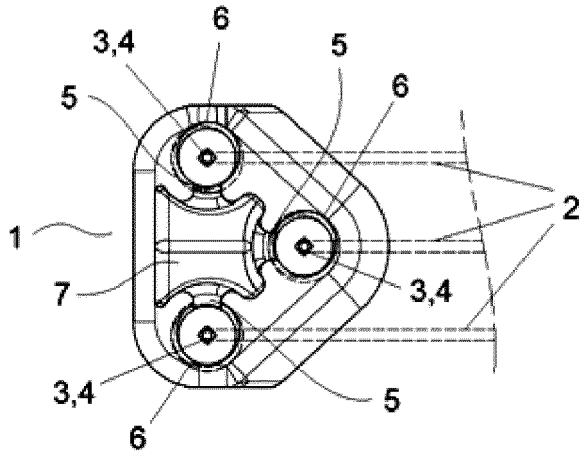

FIG. 1

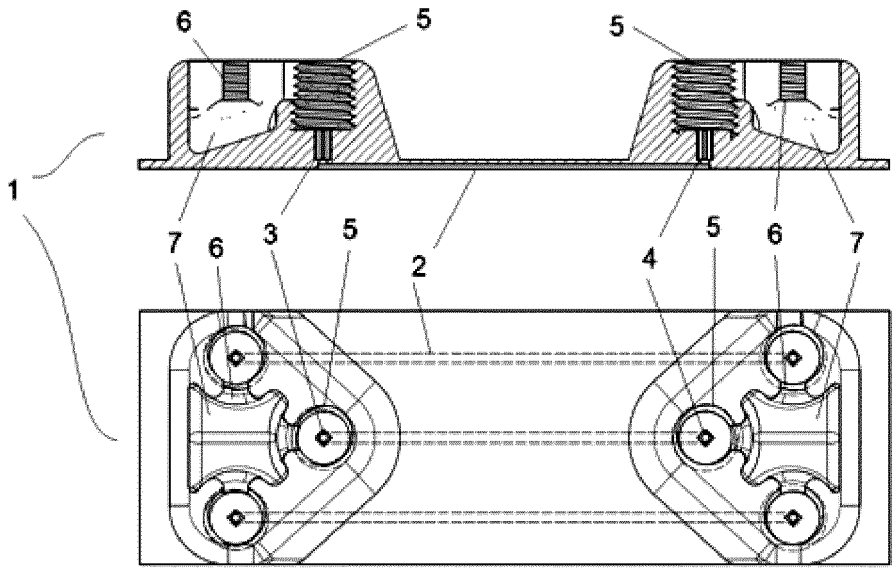

FIG. 2

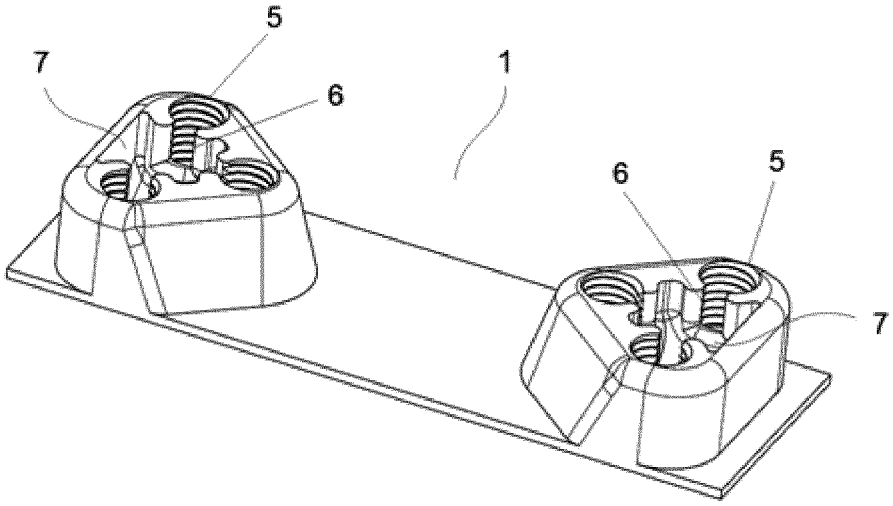

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/ES2017/070643

A. CLASSIFICATION OF SUBJECT MATTER

B01L3/00 (2006.01)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
B01L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPODOC, INVENES, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2014210364 A2 (HARVARD COLLEGE) 31/12/2014, paragraphs[0036 - 0080]; figures.	1
A	US 2015204763 A1 (STELZLE MARTIN ET AL.) 23/07/2015, paragraphs[0138 - 0251]; figures.	1
A	US 2005000364 A1 (KRAEMER PETER ET AL.) 06/01/2005, paragraphs[0032 - 0040]; figures.	1
A	US 2004228764 A1 (STEPHENS DALE ET AL.) 18/11/2004, paragraphs[0043 - 0059]; figures.	1
A	US 2008085219 A1 (BEEBE DAVID J ET AL.) 10/04/2008, paragraphs[0030 - 0062]; figures.	1

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance.
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure use, exhibition, or other means.
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other documents , such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
01/12/2017	**(05/12/2017)**
Name and mailing address of the ISA/ OFICINA ESPAÑOLA DE PATENTES Y MARCAS Paseo de la Castellana, 75 - 28071 Madrid (España) Facsimile No.: 91 349 53 04	Authorized officer R. Reyes Lizcano Telephone No. 91 3495527

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/ES2017/070643

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Form PCT/ISA/210 (patent family annex) (January 2015)

REFERENCES CITED IN THE DESCRIPTION

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- EP 1792655 B1 **[0004]**
- WO 2014053678 A1 **[0005]**