

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
21 September 2006 (21.09.2006)

PCT

(10) International Publication Number
WO 2006/097302 A1

(51) International Patent Classification:

G01N 30/56 (2006.01) **B01D 15/22** (2006.01)
G01N 30/60 (2006.01) **B01J 20/281** (2006.01)
B81B 7/04 (2006.01) **B01J 20/32** (2006.01)
B01D 15/20 (2006.01)

(21) International Application Number:

PCT/EP2006/002402

(22) International Filing Date: 15 March 2006 (15.03.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

PCT/EP2005/002868
17 March 2005 (17.03.2005) EP

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

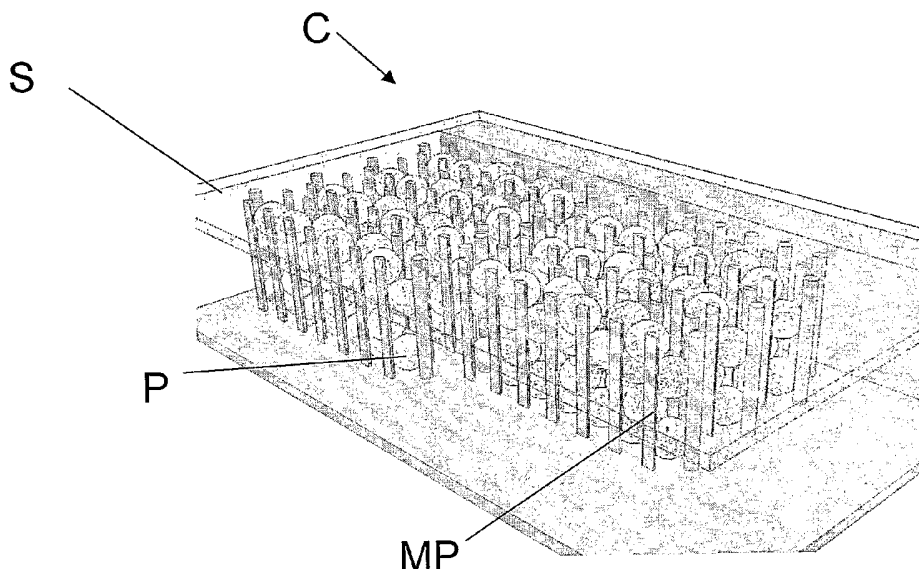
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— of inventorship (Rule 4.17(iv))

[Continued on next page]

(54) Title: METHOD FOR MANUFACTURING PACKED BED COLUMN AND PACKED BED COLUMN OBTAINED THEREWITH



(57) Abstract: The present invention provides a method for manufacturing packed bed columns, characterised in that the method consists of: (1) providing a micro-machined half open-channel filled with an array of suitably positioned and sized micro-pillars and/or micro-porous walls or wall pieces dividing the half-open channel space into regions which are wide enough to accommodate and retain the particles contained in a given particle suspension and regions which are narrow enough to exclude the particles belonging to said suspension during the filling process; (2) completely or partially filling said wide regions by contacting the open surface of the half-open channel with said particle suspension; (3) closing and sealing said half-open channel to form a packed channel with at least one clearly defined inlet and at least one clearly defined outlet.



Published:

— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Method for manufacturing packed bed column and packed bed column obtained therewith**Field of the invention**

The present invention relates to packed bed columns and method for the manufacturing
5 thereof.

Background of the invention

Packed bed columns comprise channels which have been packed with a particulate packing material. The performance of the current generation of packed bed columns used in liquid phase chromatography is known to be deteriorated by the large degree of band
10 broadening stemming from irregularities in the packing density. In addition, packed bed columns yield very large flow resistances, due to the narrow and tortuous structure of their flow paths. In chromatography, these shortcomings of packed bed columns are well known to limit both the speed and the resolution of the separation.

In the art of chemical engineering, it is well known that reducing the axial dispersion (band
15 broadening) and reducing the flow resistance is also beneficial for a wide range of reaction and separation process.

Examples of methods to reduce the flow resistance proposed thus far are the application of perfusion particles, hollow cylinder particles and the use of monolithic ceramic supports. Also the use of structured packings (cf. Sulzer packings) has been proposed. Some of
20 these methods leave the heterogeneity problem unsolved and none of these methods allows the direct use of the commercially available spherical particles developed for use in packed bed columns.

Summary of the invention

The present invention provides a method to improve the order and reduce the flow
25 resistance of packed bed columns filled with any type of commercially or otherwise available spherical particles by first providing a micro-machined half open-channel filled with an array of suitably positioned and sized micro-pillars, and/or micro-porous walls or wall pieces dividing the half-open channel space into regions which are wide enough to accommodate the particles contained in a given particle suspension and regions narrow
30 enough to exclude the particles belonging to said suspension.

The present invention also provides the packed channels and the packed bed columns manufactured according to the present methods.

The present invention concerns packed bed column comprising a channel with at least one clearly defined inlet and at least one clearly defined outlet, characterized in that said channel is filled with an array of suitably positioned and sized micro-pillars and/or micro-porous wall pieces dividing the channel space into wide regions accommodating and
5 retaining particles and narrow regions free of particles.

The present invention also concerns the use of the packed bed columns according to the invention in liquid phase chromatography.

Brief description of the Figures

Figure 1 represents schematic views of a half open-channel comprising an array of
10 suitably positioned hemi-cylindrical micro-pillars (MP) filled with spherical particles (P) according to an embodiment of the present invention: **(a)** partial front view and **(b)** partial birds' eye view.

Figure 2a-d represents top views of some of the many possible micro-pillar (MP) and micro-porous wall pieces (MWP) and micro-wall (MW) arrangements according to
15 embodiments of the present invention which can be used to contain particles (P) in wide regions and to exclude them from the narrow regions forming a continuous flow through space guiding a flow with direction F.

Figure 3 represents top views of some of the many possible configurations according to embodiments of the method of the present invention wherein a mixture of influenceable
20 particles (IP) is loaded in the narrow flow-through channels **(a)** or in the regions where the different narrow flow-through channels intersect **(b)** and where they can create a lateral mixing (LM).

Detailed description

In particular the present invention provides a method for manufacturing packed bed
25 columns, characterised in that the method consists of

1) providing a micro-machined half open-channel filled with an array of suitably positioned and sized micro-pillars and/or micro-porous walls or wall pieces dividing the half-open channel space into regions which are wide enough to accommodate and retain the particles contained in a given particle suspension and regions which are narrow enough to
30 exclude the particles belonging to said suspension during the filling process

2) completely or partially filling said wide regions by contacting the open surface of the half-open channel with said particle suspension

3) closing and sealing said half-open channel to form a packed channel with at least one clearly defined inlet and at least one clearly defined outlet.

As used in the specification and the appended claims, the singular forms "a", "an," and "the" include plural referents unless the context clearly dictates otherwise. By way of
5 example, "a method" means one method or more than one method.

The recitation of numerical ranges by endpoints includes all numbers and fractions subsumed within that range (e.g. 1 to 5 includes 1, 1.5, 2, 2.75, 3, 3.80, 4, and 5).

The pillars surrounding the wide regions are positioned sufficiently close to each other such that the particles fitting into the wide regions are retained there during the operation
10 of the column. (Fig.1 and Fig.2a). As used herein the term "wide region" refers to a region having an internal width substantially equal or larger to the size of a given particle such as to allow the accommodation of at least one particle. As used herein "width substantially equal" refers to a width sufficient to allow the accommodation of a particle of a given size. As used herein the term "narrow region" refers to a region having an internal width smaller
15 than the size of said given particle.

Preferably, said narrow regions form a continuous flow-through space. Even more preferably, said flow-through space consists of regularly intersecting parallel flow-through channels exhibiting an identical flow resistance (Fig. 2).

Using micromachining techniques allowing to etch micro-porous materials, it is also
20 possible that said micro-pillars are micro-porous themselves, or are replaced by micro-machined permeable micro-porous wall pieces forming a fully closed container (Fig. 2b) Non-limiting examples of highly suitable micro-porous starting materials known in the art to produce such micro-porous micro-pillars or micro-containers are aerogels, xerogels and porous silicon for example. Fig. 2b shows a configuration wherein said pillars are
25 completely replaced by micro-porous walls. Fig. 2c shows a case wherein a closed container is formed by a combination of micro-pillars and micro-porous wall pieces. In an alternative embodiment, it is also possible that the micro-pillars in the embodiment shown in Fig. 2c are obviated and that said wide regions are surrounded by a number of micro-porous wall pieces (Fig. 2d) positioned sufficiently close to each other such that the
30 particles fitting into the wide regions are retained there during the operation of the column.

After complete or partial filling of the wide channel regions, the top surface of said half-open channel containing the micro-pillar array can be closed and sealed with any method known in the art, including anodic wafer bonding and polymer film gluing, to form a closed channel with at least one clearly defined inlet and at least one clearly defined outlet.

A process to machine the desired arrays of micro-pillars or micro-porous wall pieces or closed micro-porous wall containers with the highest possible height over width ratio is the Bosch process which is one of the recent Deep Reactive Ion Etching (DRIE) methods known in the art for the etching of silicon and characterised therein that it consists of a
5 sequence of dry plasma etching steps, intermitted by a sidewall passivation step. Fine tuning of both the passivation and the etch step in terms of timing, etch gas composition and RF-power, will allow to make the pillars for use in the present invention with large (i.e., larger than 10) height over width aspect-ratio's. The larger the height over width ratio, the deeper the channels can be made, and the larger the mass loadability to the channels will
10 be. The latter is of great importance to maximize the detection sensitivity of the fabricated channels. For some separation applications involving small sample quantities, such as in single cell analysis for example, it would however suffice to fabricate columns with a single layer of beads.

Using the current state-of-the-art micromachining techniques, micro-pillars with a circular,
15 hemi-circular, diamond-like, triangular, square, rectangular, ellipsoidal or any other suitable cross-sectional shape can be conceived. In some preferred embodiments all pillars will have the same cross-sectional shape, whereas in other preferred embodiments two or more different pillar geometries could be used.

Preferably, the particle suspensions used to fill the wide channel regions are mono-modal.

20 To promote the filling of said wide channel regions, said filling step can be assisted using any suitable convection generation device or brushing device known in the art. Non-limiting examples of applicable convection generation devices are ultra-sound mixers and rotating disk devices.

To either at least partially inactivate the participation of the pillar or micro-porous wall
25 surface in the separation or reaction process or to let the pillar or micro-porous wall surface at least partially contribute in the separation or reaction process, said micro-pillars or said micro-porous walls can be coated with any desirable chemical substance or materials layer.

In an advanced approach, said wide regions are only partially filled leaving room to
30 subject the particles to an alternating influence such as an oscillating displacement in a direction running substantially parallel with the axis of said micro-machined pillars. The additional mixing generated by said oscillating displacement can be used to promote the mass transfer processes in the fluid phase. The desired oscillating displacement can for

example be generated using an oscillating gravitational (e.g., based on the use of a piezo-crystal), an electrical or a magnetic force.

In a preferred embodiment, the side of said wide regions facing the incoming fluid flow is sufficiently closed to prevent the incoming fluid flow to enter said wide region. This will
5 prevent the enclosed particles to be subjected to a net displacement in the direction of the fluid flow during their oscillating motion. Preferably the shape of said side should be well-streamlined so as to yield a minimal flow resistance.

In a more advanced approach, it is also possible to also partially fill at least all of said narrow regions or all of said wide regions with a second suspension of particles which can
10 be subjected to an alternating influence. For example, it is also possible to partially fill said narrow regions with a second suspension of particles after said wide regions are filled with said first suspension. If the particles of said second dimension are influenceable by an oscillating gravitational (e.g., based on the use of a piezo-crystal), an electrical or a magnetic force, they can be subjected to an alternating displacement motion so as to
15 promote the radial and transversal mixing in said narrow regions. If the particles of said second suspension precisely fit between the pillar openings in said narrow region, they will not be carried along with the main flow and will remain in their compartment (Fig. 3a). If said wide regions are only partially filled, said influenceable particles can also be added to said wide regions to promote the mixing in said wide regions.

20 In an alternative embodiment according to the present invention, it would also be possible to design the flow-through channel intersection spaces such that these spaces can retain particles of a second or third suspension which can be subjected to an alternating influence so as to promote the transversal mixing in said flow-through channel intersection spaces (Fig. 3b).

25 In another embodiment, the micro-pillars and the permeable micro-walls or wall pieces have an effective diameter ranging from 0.1 micrometer to 10 micrometer and have a height over width aspect ratio preferably ranging between 0.5 and at least 50, and preferably even more.

In another embodiment, the narrow regions are preferably between 0.1 micrometer and 50
30 micrometer wide and said wide regions are preferably between 0.5 micrometer and 500 micrometer wide.

Embodiments of the present invention are described with reference to Figures 1-3.

Referring to Figure 1, schematic views of a packed channel (C) are shown. Figure 1a represents a partial front view of packed channel (C) and Figure 1b a partial bird's eye

view thereof. The packed channel is comprised of an array of suitably positioned hemi-cylindrical micro-pillars (MP) filled with spherical particles (P) according to an embodiment of the present invention. The arrangement of the micro-pillars is such as to define wide regions (WR) and narrow regions (NR). The half open channel (C) is shown partially
5 sealed with a seal (S). The micro-pillars (MP) surrounding the wide regions (WR) are positioned sufficiently close to each other such that the particles fitting into the wide regions (WR) are retained there during the operation of the column. Preferably, said narrow regions (NR) form a continuous flow-through space.

Referring to Figure 2a-d, schematic top views of some of the many possible micro-pillar
10 (MP) and micro-porous wall pieces (MWP) and micro-wall (W) arrangements are shown. Figure 2a represents the top view of micro-pillar arrangement containing particles (P) in wide regions (WR), wherein said particles (P) are excluded from the narrow regions (NR), said narrow regions (NR) forming a continuous flow through space guiding a flow having a direction F. In an embodiment said flow-through space comprises regularly intersecting
15 parallel flow-through channels exhibiting an identical flow resistance. In an embodiment, said micro-pillars are micro-porous.

Figure 2b represents the top view of micro-wall (W) arrangements forming fully closed containers delimiting wide regions (WR) containing particles (P), wherein narrow regions (NR) form a continuous flow through-space guiding a flow having a direction F. The micro-
20 walls are preferably permeable and micro-porous

Figure 2c shows a configuration wherein closed containers delimiting the wide regions (WR) are formed by a combination of micro-pillars (MP) and micro-porous wall pieces (MWP). The particles (P) fit in the wide regions (WR) and the narrow regions (NR) form a flow through space. In an alternative embodiment illustrated in Figure 2d, the micro-pillars
25 in the embodiment shown in Figure 2c are obviated and the said wide regions (WR) are surrounded by a number of micro-porous wall pieces (MWP) positioned sufficiently close to each other such that the particles (P) fitting into the wide regions are retained there during the operation of the column.

In an embodiment illustrated under Figure 3, after the wide regions (WR) delimited by the
30 micro-pillar are filled with a first suspension of particles (P), the narrow regions (NR) can be filled with a second suspension of particles (IP) of smaller dimension. If the particles of said second suspension are influenceable by an oscillating gravitational (e.g., based on the use of a piezo-crystal), an electrical or a magnetic force, they can be subjected to an alternating displacement motion so as to promote the radial and transversal mixing in said
35 narrow regions. Referring to Figure 3, top views of arrangements of micro-pillars (MP)

delimiting wide regions (WR) and narrow regions (NR), said wide regions being loaded with particles (P) and said narrow regions (NR) being loaded with a mixture of smaller influenceable particles (IP). The mixture of influenceable particles (IP) is loaded in the narrow flow-through channels (Figure 3a) or in the regions where the different narrow
5 flow-through channels intersect (Figure 3b) and where they can create a lateral mixing (LM). If the particles (IP) of said second suspension precisely fit between the pillar (MP) openings in said narrow region (NR), they will not be carried along with the main flow and will remain in their compartment (Figure 3a). In the alternative embodiment shown in Figure 3b, the flow-through channel intersection spaces is designed such that these
10 spaces can retain particles (IP) of a second or third suspension which can be subjected to an alternating influence so as to promote the transversal mixing in said flow-through channel intersection spaces.

In a further embodiment not shown, the wide regions (WR) can be only partially filled, and influenceable particles (IP) can also be added to said wide regions to promote the mixing
15 in said wide regions.

The present invention also encompasses the packed channels and the packed bed columns manufactured according to the present methods. These packed bed columns are particularly suitable for use in liquid phase chromatography.

The present invention also provides a packed bed column comprising a channel with at
20 least one clearly defined inlet and at least one clearly defined outlet, characterized in that said channel is filled with an array of suitably positioned and sized micro-pillars and/or micro-porous wall pieces dividing the channel space into wide regions accommodating and retaining particles and narrow regions free of particles. Preferably, said narrow regions form a continuous flow-through space. Even more preferably, said flow-through
25 space consists of regularly intersecting parallel flow-through channels exhibiting an identical flow resistance.

As described above, the micro-pillars can have a circular, hemi-circular, diamond-like, triangular, square, rectangular, ellipsoidal or any other suitable cross-sectional shape. In some preferred embodiments all pillars will have the same cross-sectional shape,
30 whereas in other preferred embodiments two or more different pillar geometries could be used.

As previously described above, said wide regions can be also only partially filled with said particles. In a further embodiment, said narrow regions or all of said wide regions are partially filled with a second suspension of particles.

In addition, the side of said wide regions facing the incoming fluid flow can be further covered with a pillar having a well-streamlined shape and acting so as to prevent the incoming fluid flow to enter said wide regions.

In an embodiment, said micro-pillars or said micro-porous walls can be coated to either at least partially inactivate the participation of the pillar or micro-porous wall surface in the separation or reaction process or to let the pillar or micro-porous wall surface at least partially contribute in the separation or reaction process. Said coating can be any desirable chemical substance or materials layer suitable to impart the above mentioned properties to the pillar or walls.

10 In an embodiment said micro-pillars and said permeable micro-walls or wall pieces have an effective diameter ranging from 0.1 micrometer to 10 micrometer and have a height over width aspect ratio preferably ranging between 0.5 and at least 50. Preferably, the narrow regions are between 0.1 micrometer and 50 micrometer wide and the wide regions are between 0.5 micrometer and 500 micrometer wide.

15 The packing particles used may be particles of a variety of shapes, such as spherical, hemispherical, "irregular" spheres, rods with aspect ratios of $<5:1$, fractured "chips" (i.e., shapes associated with finely ground materials), precipitated crystallites (tiny cubes, prisms, dodecahedral, etc.) or powders. Spherical or nearly spherical shapes are preferred, however, since such shapes allow for the most uniform and dense packing. The
20 packing materials may be solid, hollow or porous such as, for example, solid, hollow or porous spheres. Preferred packing materials are ceramic, metallic or polymeric. The ceramic materials which can be used include, for example, soda-lime glass, borosilicate glass, porous silica (silica gel) and non-porous silica. The metals which can be used include, for example, colloidal gold, colloidal silver, nickel and stainless steel. The
25 polymeric materials which can be used include, for example, polyacrylates, polyacrylamides, polymethacrylates, polystyrene/divinylbenzene copolymers (PS/DVB); and natural based polymers such as celluloses. Particularly preferred materials are borosilicate glass, silica (both porous silica and non-porous silica) and PS/DVB copolymer.

30 The packed channels and the packed bed columns can be used for performing separations or for participating in chemical reactions.

The present invention provides a method for performing a separation of components in a sample. The method comprises contacting the sample with the packed channels or the

packed bed columns according of the invention. In one embodiment, the sample is passed through a chromatographic column containing the packed channels of the invention.

The invention provides a separation device comprising the chromatographic material of the invention.

5 In particular, the present invention encompasses the use of the packed channels and the packed bed columns according to the invention in liquid phase chromatography, including but not limited to reversed-phase, normal-phase, adsorption, size-exclusion, affinity, and ion chromatography.

The invention and its advantages are readily understood from the foregoing description. It
10 is apparent that various changes can be made in the method without departing from the spirit and scope of the invention.

Claims

1. A method for manufacturing packed bed columns, characterised in that the method consists of
 - 5 1) providing a micro-machined half open-channel filled with an array of suitably positioned and sized micro-pillars and/or micro-porous walls or wall pieces dividing the half-open channel space into regions which are wide enough to accommodate and retain the particles contained in a given particle suspension and regions which are narrow enough to exclude the particles belonging to said suspension during the filling process
 - 10 2) completely or partially filling said wide regions by contacting the open surface of the half-open channel with said particle suspension
 - 3) closing and sealing said half-open channel to form a packed channel with at least one clearly defined inlet and at least one clearly defined outlet.
2. A method according to claim 1, wherein said narrow regions form a continuous flow-
15 through space.
3. A method according to claim 2, wherein said flow-through space consists of regularly intersecting parallel flow-through channels exhibiting an identical flow resistance.
4. A method according to any of claims 1-3 wherein said micro-pillars have a circular, hemi-circular, diamond-like, triangular, square, rectangular, ellipsoidal or any other
20 suitable cross-sectional shape.
5. A method according to claims 4 wherein said micro-pillars have different cross-sectional shapes.
6. A method according to any of claims 1-5 wherein said filling step is assisted using a convection generation device or a brushing device.
- 25 7. A method according to any of claims 1-6 wherein said particle suspension is mono-modal in size.
8. A method according to any of claims 1-7 wherein said wide regions are only partially filled.
9. A method according to any of claims 1-8, wherein the side of said wide regions facing
30 the incoming fluid flow is covered with a pillar having a well-streamlined shape and acting so as to prevent the incoming fluid flow to enter said wide regions.

10. A method according to claim 8 wherein the particles filling said wide regions are subjected to an alternating influence acting in a direction running substantially parallel with the axis of said *micro-machined pillars*.
11. A method according to any of claims 8-10, wherein at least all of said narrow regions
5 or all of said wide regions are partially filled with a second suspension of particles which can be subjected to an alternating influence.
12. A method according to claims 10 or 11 wherein said influence is a gravitational, an electrical or a magnetic force.
13. A method according to any of claims 1-12, wherein said micro-pillars or said micro-
10 porous walls are coated.
14. A method according to any of claims 1-13, wherein said micro-pillars and said permeable micro-walls or wall pieces preferably have an effective diameter ranging from 0.1 micrometer to 10 micrometer and have a height over width aspect ratio preferably ranging between 0.5 and at least 50 .
- 15 15. A method according to any of claims 1-13, wherein said narrow regions are between 0.1 micrometer and 50 micrometer wide and wherein said wide regions are between 0.5 micrometer and 500 micrometer wide.
16. A packed bed column comprising a channel with at least one clearly defined inlet and at least one clearly defined outlet, characterized in that said channel is filled with an
20 array of suitably positioned and sized micro-pillars and/or micro-porous wall pieces dividing the channel space into wide regions comprising packing particles and narrow regions free of packing particles .
17. A packed bed column according to claim 16, wherein said narrow regions form a continuous flow-through space.
- 25 18. A packed bed column according to claim 17, wherein said flow-through space consists of *regularly intersecting parallel flow-through channels* exhibiting an identical flow resistance.
19. A packed bed column according to any of claims 16-18, wherein said micro-pillars have a circular, hemi-circular, diamond-like, triangular, square, rectangular, ellipsoidal
30 or any other suitable cross-sectional shape.
20. A packed bed column according to claim 19 wherein said micro-pillars have different cross-sectional shapes.

21. A packed bed column according to any of claims 16-20 wherein said particle is mono-modal in size.
22. A packed bed column according to any of claims 16-21 wherein said wide regions are only partially filled with said particles.
- 5 23. A packed bed column according to any of claims 16-22, wherein the side of said wide regions facing the incoming fluid flow is covered with a pillar having a well-streamlined shape and acting so as to prevent the incoming fluid flow to enter said wide regions.
24. A packed bed column according to any of claims 16-23, wherein at least all of said narrow regions or all of said wide regions are partially filled with a second suspension
10 of particles.
25. A packed bed column according to any of claims 16-24, wherein said micro-pillars or said micro-porous walls are coated.
26. A packed bed column according to any of claims 16-25, wherein said micro-pillars and said permeable micro-walls or wall pieces have an effective diameter ranging from 0.1
15 micrometer to 10 micrometer and have a height over width aspect ratio preferably ranging between 0.5 and at least 50.
27. A packed bed column according to any of claims 16-26, wherein said narrow regions are between 0.1 micrometer and 50 micrometer wide and wherein said wide regions are between 0.5 micrometer and 500 micrometer wide.
- 20 28. Use of a packed bed column according to any of claims 16-26 in liquid phase chromatography.

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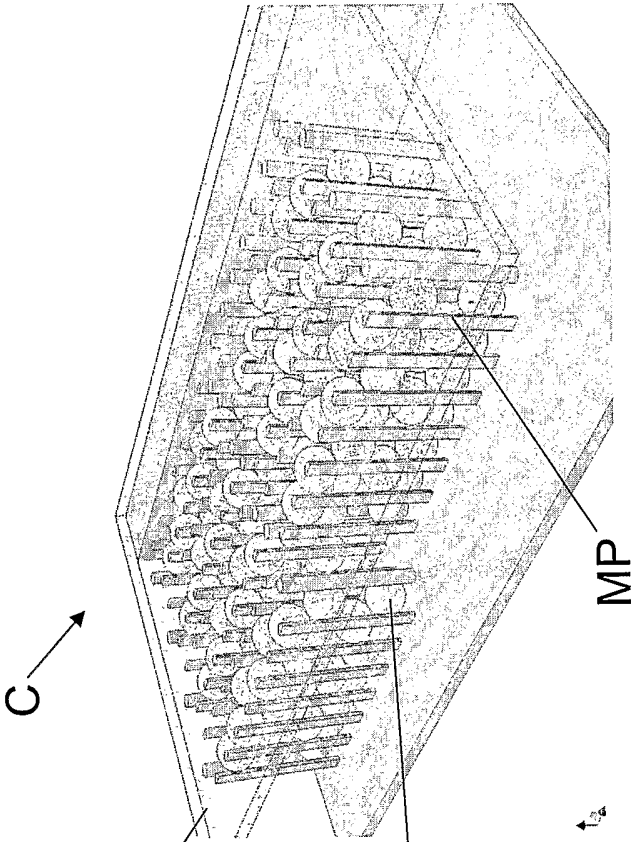


FIG. 1b

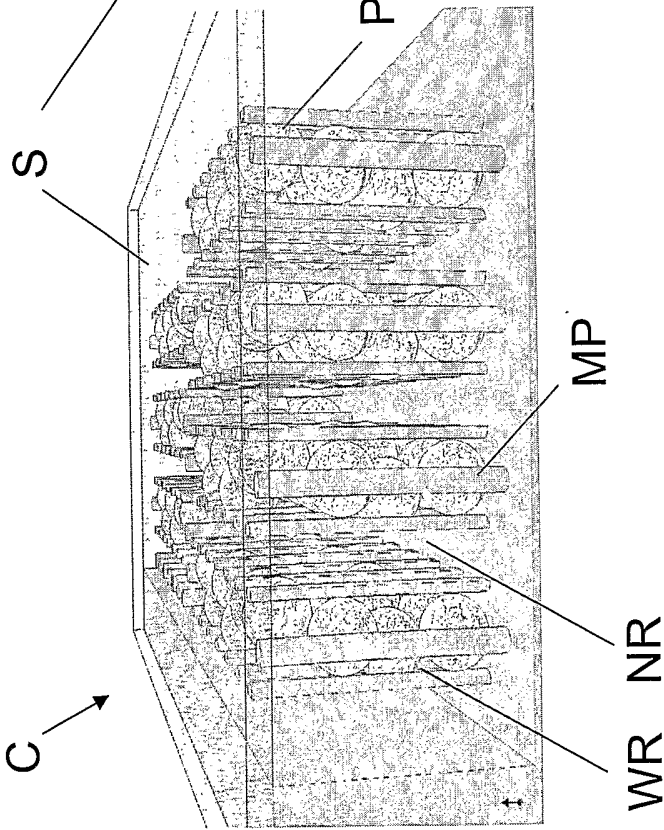


FIG. 1a

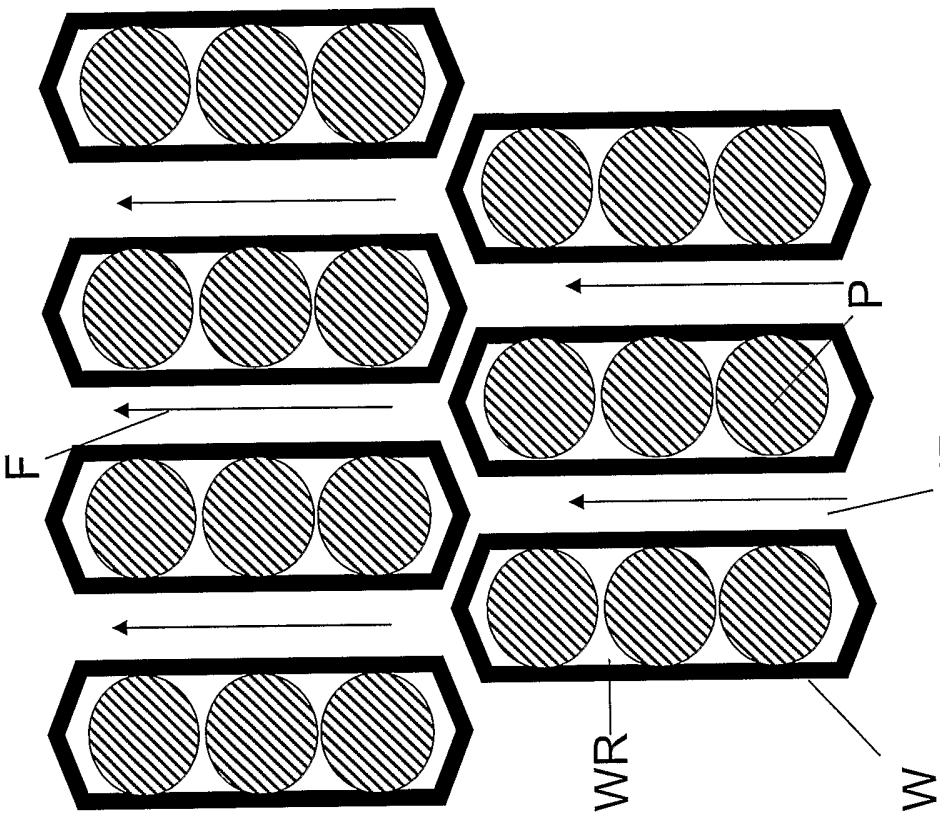


FIG. 2b

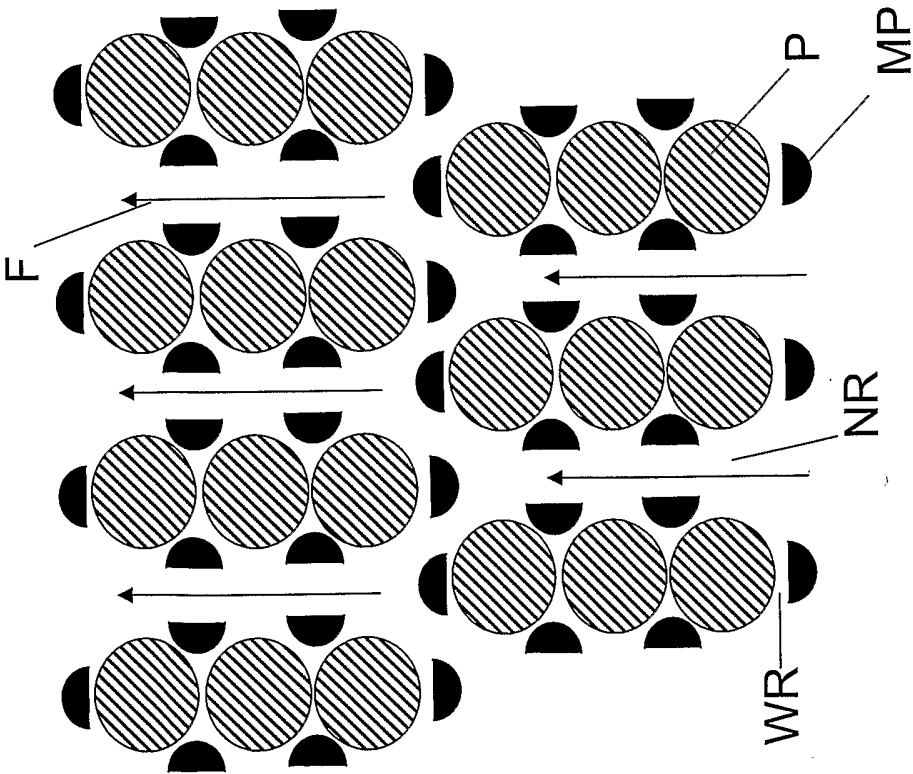


FIG. 2a

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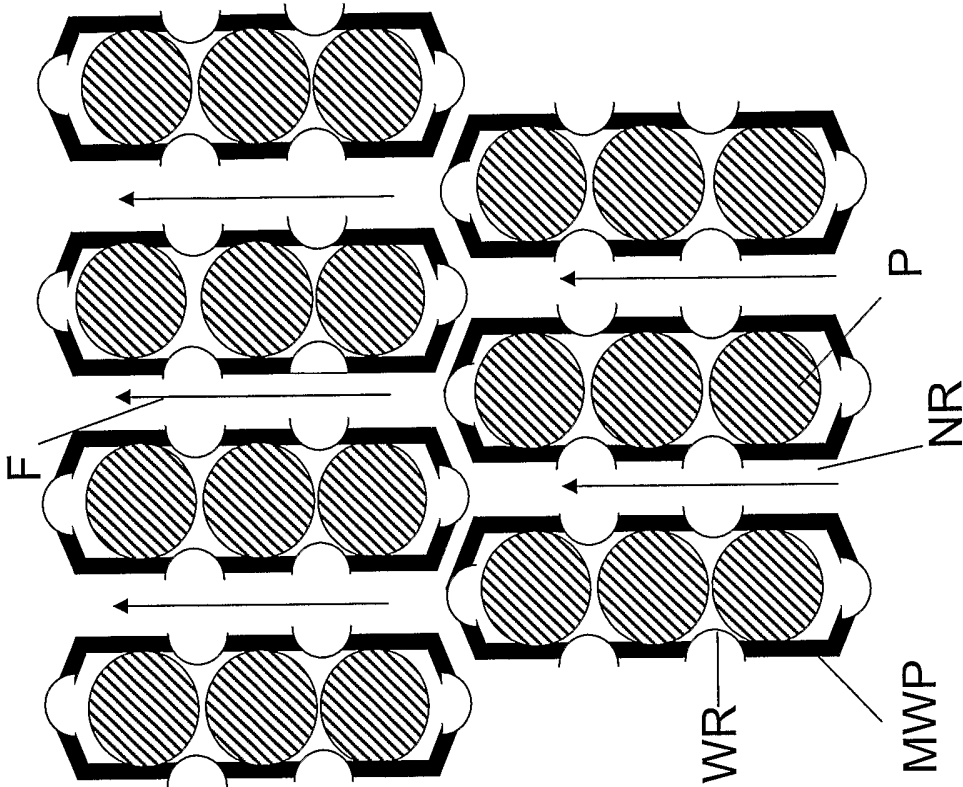


FIG. 2d

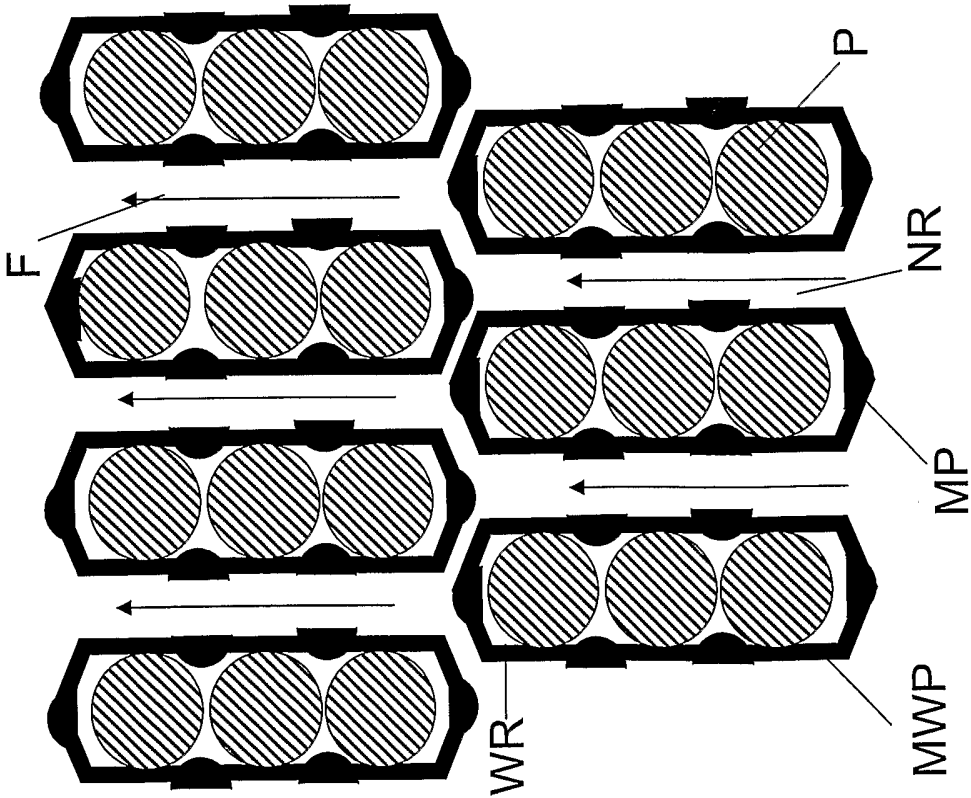


FIG. 2c

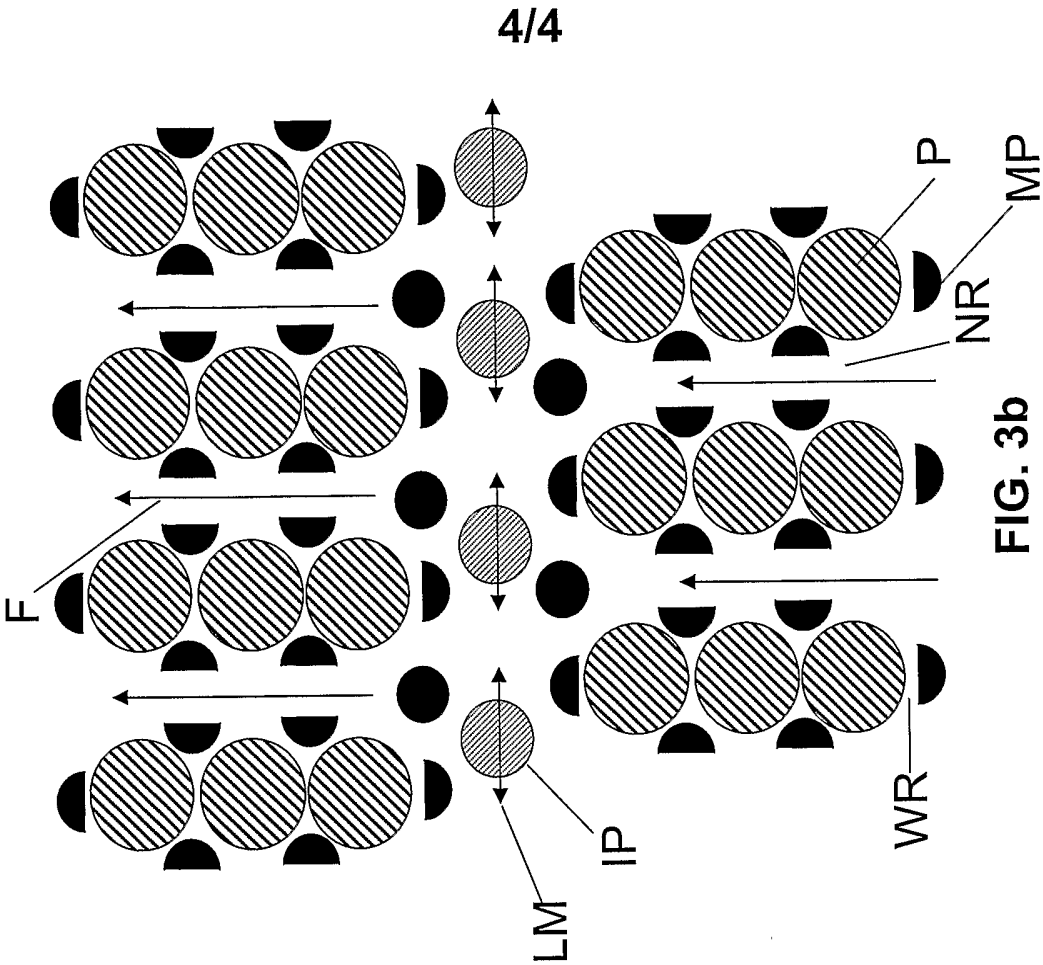


FIG. 3b

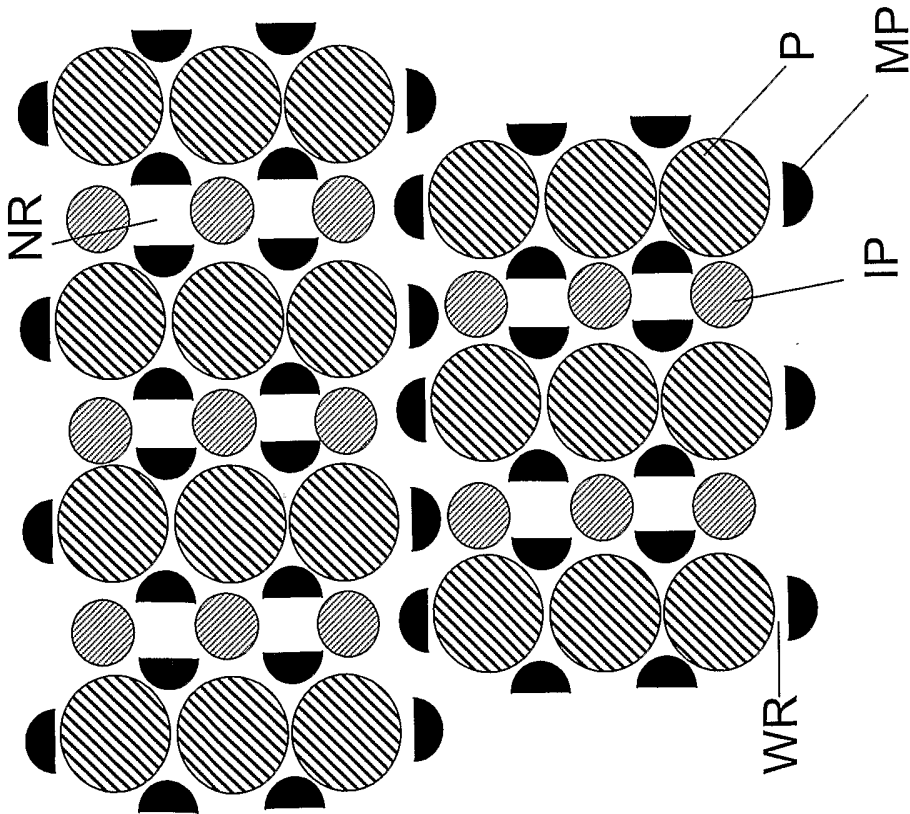


FIG. 3a

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/002402

A. CLASSIFICATION OF SUBJECT MATTER

INV. G01N30/56 G01N30/60 B81B7/04 B01D15/20 B01D15/22
ADD. B01J20/281 B01J20/32

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)

B81B B01D B01L G01N B01J

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 practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/046020 A (COMMISSARIAT A L'ENERGIE ATOMIQUE; COMBETTE, PHILIPPE; MITTLER, FREDER) 3 June 2004 (2004-06-03)	1-4,6-8, 10-19, 21,22, 24-28
Y	the whole document	5,9,20, 23
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