



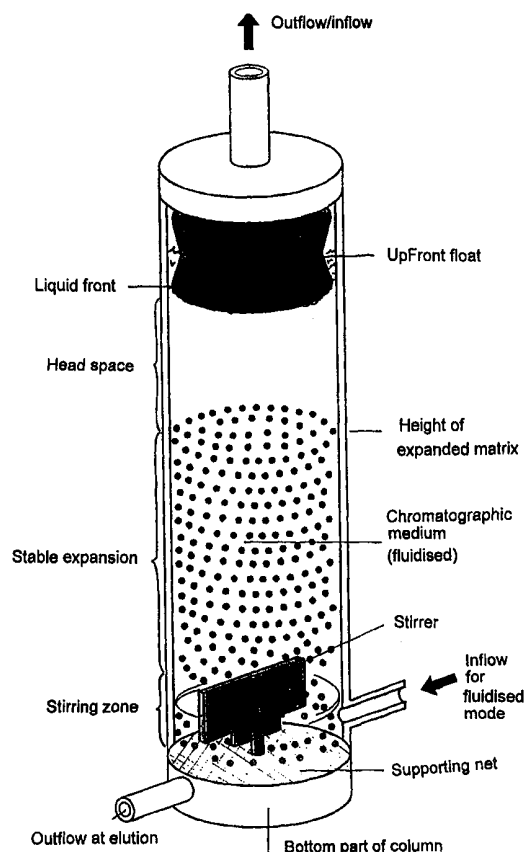
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/DK99/00336 (22) International Filing Date: 18 June 1999 (18.06.99) (30) Priority Data: PA 1998 00828 18 June 1998 (18.06.98) DK (71) Applicant (for all designated States except US): UPFRONT CHROMATOGRAPHY A/S [DK/DK]; Lersø Parkallé 42, DK-2100 Copenhagen Ø (DK). (72) Inventors; and (75) Inventors/Applicants (for US only): OEHLenschLÆGER, René [DK/DK]; Nørre side Allé 3, st. th., DK-2200 Copenhagen N (DK). OLSEN, Brian, A. [DK/DK]; Morbærhaven 5-14, DK-2620 Albertslund (DK). ZAFIRAKOS, Elias [DK/DK]; Bechgaardsgade 15, 2. th., DK-2100 Copenhagen Ø (DK). LIHME, Allan, Otto, Fog [DK/DK]; Furesøbakken 13, DK-3460 Birkerød (DK). (74) Agent: PLOUGMANN, VINGTOFT & PARTNERS A/S; Sankt Annae Plads 11, P.O. Box 3007, DK-1021 Copenhagen K (DK).		(81) Designated States: AE, AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. In English translation (filed in Danish). (88) Date of publication of the international search report: 24 February 2000 (24.02.00)	

(54) Title: EXPANDED BED ADSORPTION SYSTEM

(57) Abstract

The present application describes various improvements and further developments to the Expanded Bed Adsorption (EBA) technology. In particular, the application describes an EBA process where elution is performed in fluidised mode, i.e. in expanded bed mode, the so-called All Expanded Process. This improvement which is based on the use of controlled density particles, e.g. particles having a density of at least 1.3 g/ml, provides valuable advantages with respect to use of reduced amounts of elution buffer. The application also describes the use of magnetic stirring in EBA columns, design of an inlet ring with multiple openings, outlet at the bottom or side an EBA column for the discharge of gel, mobile pipe outlet, floating outlet, temperature regulator at inlet, the use of coloured gel, the use of sensors, processes for the regeneration of buffer in EBA systems, the introduction of baffles, and disposable columns (single use sterile columns).



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INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 99/00336

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 B01D15/02

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)

IPC 6 B01D

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HJORTH R: "Expanded-bed adsorption in industrial bioprocessing: recent developments" TRENDS IN BIOTECHNOLOGY, vol. 15, no. 6, 1 June 1997 (1997-06-01), page 230-235 XP004064512 ISSN: 0167-7799 page 232, column 2, paragraph 2 --- -/--	1

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in 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 such 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

5 October 1999

Date of mailing of the international search report

10. 12. 99

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Zinngrebe, U

INTERNATIONAL SEARCH REPORT

International Application No

PCT/DK 99/00336

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THOMMES J ET AL: "Isolation of monoclonal antibodies from cell containing hybridoma broth using a protein A coated adsorbent in expanded beds" JOURNAL OF CHROMATOGRAPHY A, vol. 752, no. 1-2, 1 November 1996 (1996-11-01), page 111-122 XP004071206 ISSN: 0021-9673 page 114, column 2, paragraph 2	1
A	BJORKLUND M ET AL: "Characterisation of silica-based heparin-affinity adsorbents through column chromatography of plasma fractions containing thrombin<1" JOURNAL OF CHROMATOGRAPHY A, vol. 743, no. 1, 30 August 1996 (1996-08-30), page 145-162 XP004020279 ISSN: 0021-9673	2
X	page 150, column 1, paragraph 2; figure 1	9
A	KAUFMANN M: "Unstable proteins: how to subject them to chromatographic separations for purification procedures" JOURNAL OF CHROMATOGRAPHY B: BIOMEDICAL SCIENCES & APPLICATIONS, vol. 699, no. 1-2, 10 October 1997 (1997-10-10), page 347-369 XP004095003 ISSN: 0378-4347 figure 5 -----	2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 99/ 00336

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. CLAIM : 2	5. CLAIM : 8	9. CLAIM : 16	13. CLAIM : 24
2. CLAIMS : 3, 10, 19	6. CLAIM : 11	10. CLAIM : 17	14. CLAIMS : 25-26
3. CLAIM : 6	7. CLAIM : 12	11. CLAIM : 18	
4. CLAIM : 7	8. CLAIM : 14	12. CLAIMS : 20-23	

FOR FURTHER INFORMATION PLEASE SEE FORM PCT/ISA/206 MAILED 15.10.99.

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

2

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INVITATION TO PAY ADDITIONAL FEES

International application No.

PCT/DK 99/00336

This International Searching Authority considers that there are 14.. (number of) inventions claimed in the international application, covered by the following groups of claims:
(independent claims only; dependent claims belong to the groups where they refer back to the independent claims;
claims anticipated by the partial search not mentioned, belonging to group one.)

1. claim 2 EBA elution in expanded bed mode using exactly one inlet and one outlet.
addresses the problem Separate elution outflow increases production costs
2. claims 3,10,19 Use of a magnetic stirrer in the EBA inlet stream inside the column
addresses the problem Stirring shaft needs a hole in column bottom and is difficult to sanitise
3. claim 6 EBA elution in expanded bed mode at a flow rate of 0.1-100 cm/min
addresses the problem EBA elution in expanded bed mode flow rates are not optimal.
4. claim 7 EBA elution in expanded bed mode at an expansion ratio of 1-5.
addresses the problem EBA elution in expanded bed mode expansion ratios are not optimal.
5. claim 8 EBA elution in expanded bed mode using a medium density of 1.2g/ml.
addresses the problem EBA elution in expanded bed mode medium density is not optimal.
6. claim 11 EBA using inlet ring comprising multiple outlet openings.
addresses the problem Large conventional columns require excessive inlet flow rates.
7. claim 12 EBA using coloured gel.
addresses the problem Opaque raw materials hinder visual control of matrix expansion.
8. claim 14 EBA column with length/diameter ratio of 2-100.
addresses the problem EBA columns do not have an optimal length/diameter ratio.
9. claim 16 EBA column with end parts made in one piece.
addresses the problem EBA columns with multiple piece end parts are expensive to manufacture.
10. claim 17 EBA column closed by seals before in operation.
addresses the problem Unsealed columns do not allow plug-&-use, because they cannot be delivered sterile.
11. claim 18 EBA column where the matrix material is sterile.
addresses the problem Unsealed columns cannot be kept sterile.
12. claim 20-23 EBA column where the matrix occupies 1/5 to 1/1.2 of the column volume.
addresses the problem EBA columns do not have an optimal filling ratio.
13. claim 24 EBA column filled with storage buffer.
addresses the problem EBA column headspace filled with gas during storage.
14. claim 25-26 Packed Column Chromatography using sphere-in-sphere matrix particles.
addresses the problem Column chromatography packings are not particularly pressure stable.

and that the international application does not comply with the requirements of unity of invention (rules 13.1, 13.2 and 13.3),
for the reasons indicated below.

INVITATION TO PAY ADDITIONAL FEES

International application No.

PCT/DK 99/00336

(A) Considerations a priori (before consultation of the state of the art)

Even without consultation of the prior art there is no Unity of Invention between any two of claims (1,9),10,11,12. Claims 1,9 describe elution in expanded bed mode, claims 10-12 are unrelated to the elution mode and relate to EBA in general, eg. using state-of-the-art elution.

The a priori feature of claim 1 is to elute in fluidised mode (p.10,1.21; p.31,1.12).

The a priori feature of claim 10 is use of a magnetic stirrer.

The a priori feature of claim 11 is use of an inlet ring.

The a priori feature of claim 12 is use of coloured gel.

All these features are different from one another.

The problem addressed by claim 1 is to correct the technical prejudice that elution in fluidised mode is impossible (p.11,1.1).

The problems addressed by claims 10,11,12 are mentioned above.

All the problems are different from one another, therefore the features are not corresponding.

There is no technical relationship between any two of the claims (1,9), 10,11,12, which implies that they do not belong to one single inventive concept.

The man skilled in the art knows EBA and packed bed chromatography. He knows that adsorption columns usually are hollow cylinders with openings in the ends, and that they often are assembled from a plastic cylinder mantle and two end parts. He knows that the active medium often consists of particulate material and is usually located inside the column.

Claims 13,15 do not contribute over this knowledge and therefore do not involve inventive activity.

This means that for the purpose of Unity of Invention the formerly dependent claims 14,16-21,24 are treated as independent claims².

The a priori feature of claim 14 is a length/diameter ratio of 2-100.

The a priori feature of claim 16 is end pieces made in one piece.

The a priori feature of claim 17 is a seal over the top and bottom openings which needs to be broken before use.

The a priori feature of claim 18 is sterile matrix material.

The a priori feature of claim 19 is use of a magnetic stirrer.

The a priori feature of claim 20 is a filling ratio of 1/5 ... 1/1.2 .

The a priori feature of claim 21 is a float adapter.

The a priori feature of claim 24 is a storage buffer.

Claim 19 has the same feature as claim 10 and therefore belongs to the same inventive concept as claim 10.

According to the description (p.24,1.16-18) the feature of claim 17 (seals) is a requirement for a sterile matrix of claim 18. This creates technical link between claims 17 and 18, both claims therefore belong to the same inventive concept.

Claims 1,9 describe elution in expanded bed mode, claims 14,16,(17,18),19,20,21,24 are unrelated to elution, but relate to EBA in general, eg. using state-of-the-art elution. Moreover, both problems and features of claims (1,9),(10,19),11,12,14,16,(17,18),19,20,21,24 are different from one another, which means that the features are not corresponding.

There is no technical relationship between any two of the claims (1,9),(10,19),11,12,14,16,(17,18),19,20,21,24 which implies that they do not belong to one single inventive concept.

²Note: in the following, three rectifications to remove supposed clerical errors from the text of the claims are assumed:

a) page 33, line 1: read 1/1.2 instead of 1.2

b) page 32, line 32: read 13 instead of 12

c) page 33, line 8: read 21 instead of 13

page 33, line 11: read 21 instead of 13

Attention is drawn to rule 6.4 PCT stipulating that multiple dependent claims may not form the basis of other multiple dependent claims.

INVITATION TO PAY ADDITIONAL FEES

International application No.

PCT/DK 99/00336

Claim 25 does not relate to EBA, but to the much broader field of Packed Chromatography, suggesting improvements for a régime claim 1 expressly avoids.

The feature of claim 25 is the use of sphere-in-sphere matrix particles.

The problem addressed by claim 25 is that chromatography packings are not particularly pressure stable.

Both problem and feature of this claim are different from the preceding ones.

Therefore the feature of claim 25 does not correspond to any preceding feature.

The sphere-in-sphere matrix of claim 25 has no technical link to any other prior claim and therefore does not form part of a single inventive concept with any of them.

There is no technical relationship between any two of the claims (1,9),(10,19),11,12,14,16,(17,18),19,20,21,24,25. Any two of them do not belong to one single inventive concept, which implies that there is no Unity of Invention between them.

(B) Considerations a posteriori (after consultation of the state of the art)

The international search authority has by the attribution of categories to the documents cited in the search report expressed a preliminary assessment of the inventive activity with respect to the claims in group one.

It follows first an explanation of the relevance of the closest state of the art (XP4064512) with respect to the claims of group one and then an analysis of the unity of invention between the remaining independent claims.

Analysis of claim 1 leads to the following list of features:

claim / Feature

- | | | |
|---|---|---|
| 1 | 1 | establishing an Expanded Bed Adsorption Column |
| | 2 | with particulate matrix |
| | 3 | rinsing the column to remove impurities |
| | 4 | eluting the target molecules in expanded bed mode |

XP4064512 teaches

a) on page 232 in Table 1 that the media are particulates

b) on page 232 in Col. 2, par 2 that unbound material is washed out and that elution may be carried out in expanded-bed mode.

All features of claim 1 are already taught by XP4064512.

The prior art located during the search, as represented by the document XP4064512, reveals that the subject matter of claim 1 is not new for the skilled person.

For the purpose of Unity of Invention this claim is disregarded as it does not contribute over the state of the art.

This means that for the purpose of Unity of Invention the formerly dependent claims 2-8 are treated as independent claims.

The invention to be searched is the one first mentioned in the claims.

Claim 2 introduces as additional feature that the column has exactly one inlet and exactly one outlet.

This is not disclosed by XP4064512 in the context of elution in expanded bed mode, therefore it represented the subject of the search.

The features of claims 4,5 are disclosed in the abstract of XP4064512 and are therefore not inventive.

INVITATION TO PAY ADDITIONAL FEES

International application No.

PCT/DK 99/00336

The feature of claim 2 is to have exactly one inlet and one outlet.
The feature of claim 3 is to have a means for magnetic stirring.
The feature of claim 6 is a flow rate of 1-100 cm³/min.
The feature of claim 7 is an expansion ratio of 1-5.
The feature of claim 8 is a matrix density of at least 1.2g/ml.

The feature of claim 3 comprises the feature of claim 10, therefore both claims share the same inventive concept and address the same problem.

The problems of the other claims are given above.

Both problem and feature of claims 2,3,6,7,8 are different from one another, which makes implies the features are not corresponding and that any two of these claims do not belong to one single inventive concept.

The search authority considered whether the description (p.11;p.12,par.2;fig A1) established a link between the process parameters of claims 6,7,8.

The description teaches that only two of the three parameters flow rate, expansion ratio and medium density can be arbitrarily chosen, the third one is then given from figure A1.

Claims 6,7,8 each specify only one of the three process parameters. Therefore it is not possible to deduce from the feature in one of claims 6,7,8 the feature(s) of the other(s) of claims 6,7,8.

This shows that the process parameters are not corresponding.

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No claim of any group has a special technical feature in common with or corresponding to a claim of any other group.

It follows that the international application relates to various inventions, between some of which there is no technical relationship, and the requirements of Rule 13.2 PCT are therefore not fulfilled. Hence there is no single inventive concept linking all the inventions, which implies that Rule 13.1 PCT is not satisfied.