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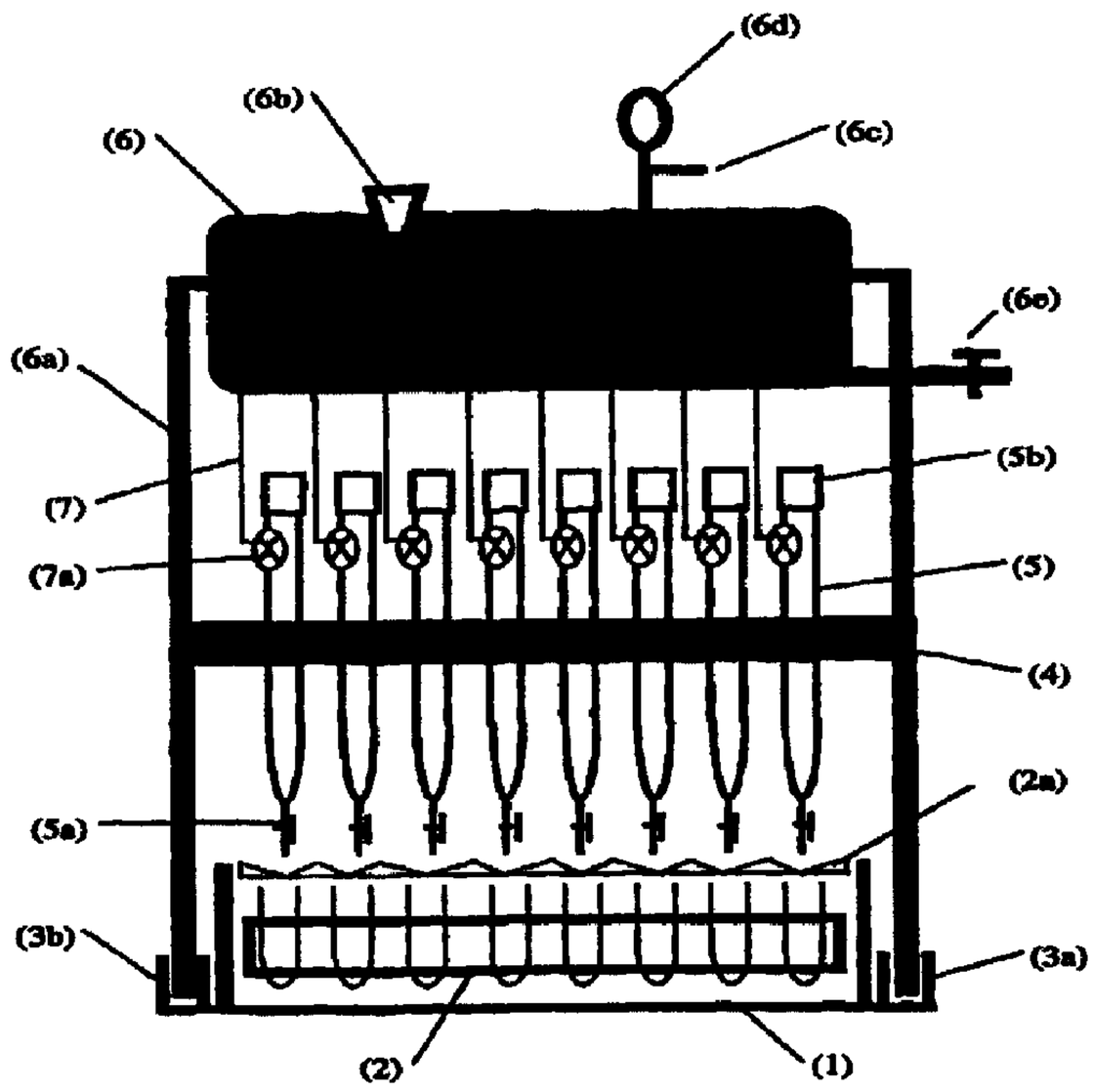
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(54) **DISPOSITIF ET PROCEDE POUR CHROMATOGRAPHIE EN PARALLELE**

(54) **METHOD AND DEVICE FOR PARALLEL CHROMATOGRAPHY**



(57) L'invention concerne un dispositif ou appareil, ainsi qu'un procédé permettant de faire fonctionner plusieurs colonnes de chromatographie montées en parallèle, en vue d'effectuer un fractionnement simultané. L'appareil et le procédé sont utilisés avantageusement, en particulier pour la recherche dans le domaine de la synthèse organique, en vue d'effectuer simultanément et en parallèle, la séparation, l'isolement et la purification de plusieurs composés chimiques, par exemple, de nouvelles matières actives d'emploi potentiel pour médicaments, y compris et en particulier à l'échelle de semi-préparations.

(57) The invention relates to a device or equipment as well as to a method for the simultaneous, fractionating operation of a plurality of parallel chromatographic columns. It is particularly advantageous to apply this equipment and method in research, in the framework of organic synthesis for simultaneous, parallel separation, isolation and purification of a plurality of chemical compounds, e.g. of potential new active ingredients for medicaments, particularly also on the semi-preparative scale.

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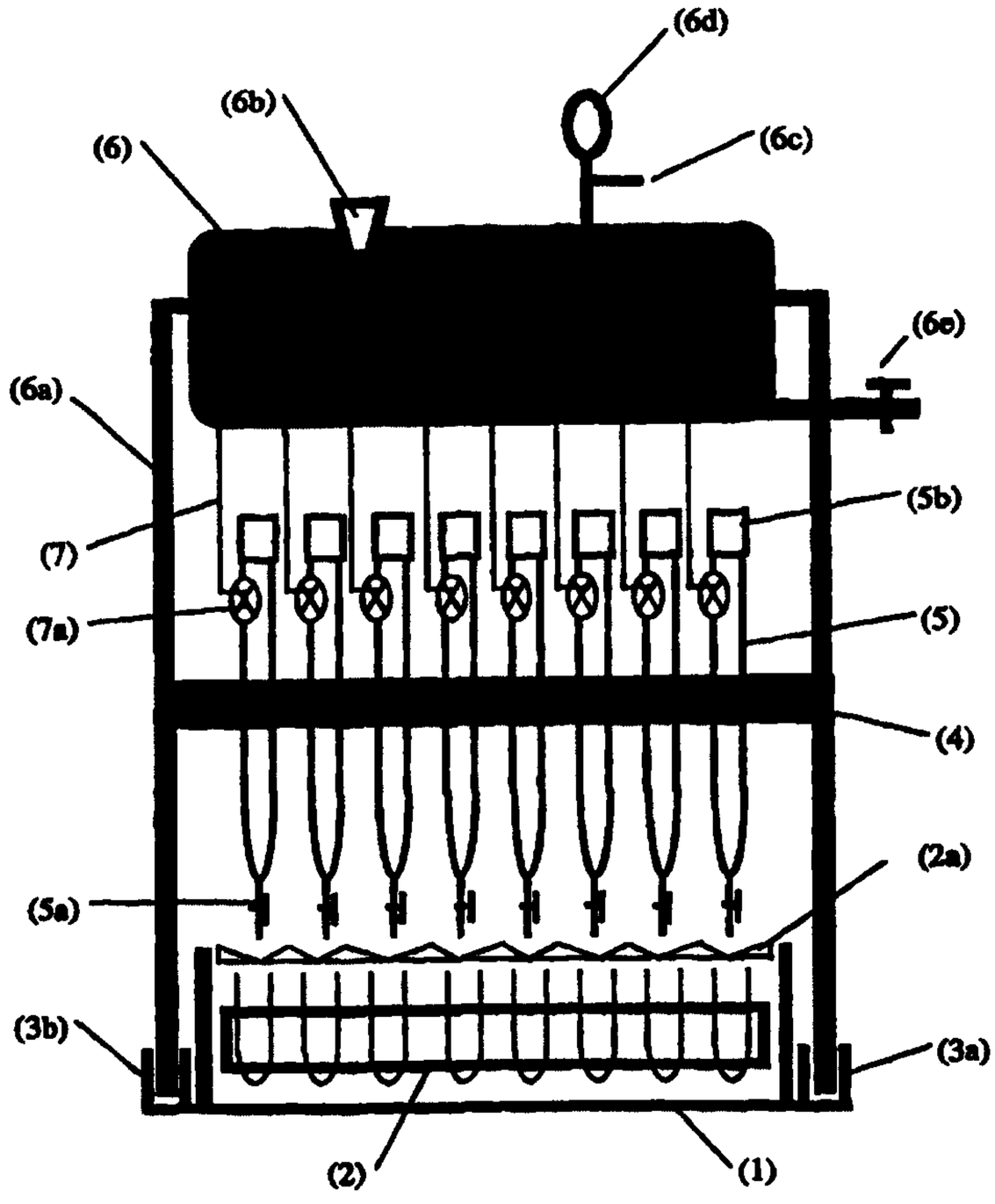
(54) Bezeichnung: VORRICHTUNG UND VERFAHREN ZUR PARALLEL–CHROMATOGRAPHIE

(57) Abstract

The invention relates to a device or equipment as well as to a method for the simultaneous, fractionating operation of a plurality of parallel chromatographic columns. It is particularly advantageous to apply this equipment and method in research, in the framework of organic synthesis for simultaneous, parallel separation, isolation and purification of a plurality of chemical compounds, e.g. of potential new active ingredients for medicaments, particularly also on the semi–preparative scale.

(57) Zusammenfassung

Die Erfindung betrifft eine Vorrichtung bzw. Apparatur sowie ein Verfahren zum gleichzeitigen, fraktionierenden Betrieb mehrerer parallel angeordneter Chromatographiesäulen. Die Apparatur und das Verfahren lassen sich insbesondere in der Forschung im Rahmen der organischen Synthese für die gleichzeitige, parallele Abtrennung, Isolierung und Aufreinigung mehrerer chemischer Verbindungen, z.B. potentieller neuer Arzneimittelwirkstoffe, insbesondere auch im semipräparativen Maßstab, vorteilhaft einsetzen.



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METHOD AND DEVICE FOR PARALLEL CHROMATOGRAPHY

Description

The invention relates to a device or equipment as well as to a method for the simultaneous, fractionating operation of several parallel chromatography columns. The equipment and the method can be utilized in a particularly advantageous manner in research, within the context of organic synthesis for simultaneous, parallel separation, isolation, and purification of many chemical compounds, such as new active ingredients for medicaments, and especially on the semi-preparative scale.

Column chromatography is a typical method for separating substance mixtures within the context of organic synthesis, especially in the form of a liquid-solid chromatography. Pharmaceutical research today, therefore, would be unthinkable without column chromatography as a method for isolating and subsequently identifying synthesized organic substances. Since the identification a new type of active ingredient continues to be a difficult and expensive enterprise which necessitates the synthesis of a large number of chemical compounds, the need for innovations with respect to equipment and method still persists. The role of so-called multi-component synthesis is becoming increasingly important for both the search for as well as the optimization of **chemical leads**, in order to produce chemical compounds within smaller and smaller periods of time. To the extent that systematic molecular variation by way of multi-component synthesis results in a plurality of different compounds extremely quickly, other methods applied within the context of searching for active ingredients--for example methods for separating substance mixtures or for isolating and purifying individual substances--must also stay apace with the heightened synthesis capacity. For example, although it still was sufficient for classical synthesis procedures to subject the synthesized compounds to a chromatography individually and, if necessary, sequentially, modern synthesis methods with a higher capacity as well as multi-component chemistry also require a heightened output capacity during the separation of substance mixtures or during the isolation and purification of synthesized compounds, and especially on a semi-preparative scale.

The task thus was to make a simple and efficient device for the simultaneous parallel execution of column chromatographies, especially for the semi-preparative scale.

The task is solved by means of the device or equipment which are stated in the claims as well as by means of the method for column chromatography described.

Accordingly, the invention particularly concerns a device for the simultaneous parallel execution of a particular number n of column chromatographies, in which the device is characterized by

a) a plate mounting, preferably in the form of a **bottom vat**
--which serves to accommodate one or several removable test tube racks (fraction collectors), wherein these test tube racks are adapted in their measurements, either individually or collectively, to the internal dimensions of the plate mounting, preferably the bottom vat, such that an arrangement of m rows lying at a distance from one another with n test tubes standing at a distance in juxtaposition can be effected,

--wherein the plate mounting, preferably the bottom vat, can have yet another solvent drain arranged on one or both of the **ends** (in "position 0" and/or "end-position") to this end, if necessary;

b) a slide rail which is arranged parallel to each longitudinal side of the plate mounting, preferably the bottom vat, with a motor-driven, steerable cradle;

c) a mobile bridge which is arranged on the cradle --by means of which said bridge can be moved across the plate mounting at a distance--, and which serves as a support for the fixed or, if necessary, interchangeable accommodation of several chromatographic columns ("column support bridge");

d) a number n of chromatographic columns which are arranged in rows on the column support bridge parallel to the end of the plate mounting, preferably the bottom vat, in such a way that the line of position of the chromatographic columns' **dropper tips** to be traversed is coordinated with the position of the test tubes in the individual rows, in the process of which the chromatographic columns can be designed for working under pressure;

e) a solvent container for accommodating an eluting agent or, if necessary, several solvent containers for accommodating various eluting agents, in which the solvent container or containers also can be designed as pressure containers, if need be, and in

which the solvent container or containers also can be arranged to be connected to the column support bridge above the chromatographic columns;

f) fixed or flexible supply tubes for introducing the eluting agent or agents from the solvent container or containers into the chromatography columns;

g) a motor drive for moving the cradle with the column support bridge on the slide rails and an electronic control device for automatic control, in particular of the time interval, the rate of feed, and the position of the column support bridge along the plate mounting, preferably along the bottom vat;

in which the number n refers to the chromatographic columns arranged on the column support bridge and represents a number larger than 5;

and in which the number m refers to the possible test tube rows which can be traversed by the column support bridge.

The particular dimensions of the device or the individual components, as well as the exact arrangement of the components can be embodied in accordance with the needs and desires of the respective user. In this way, the structural design and production of the inventive device can be accomplished thus without particular difficulty. Aside from the components described above, more components can be provided which are tailored to further user requirements or to other requirements (such as safety regulations) can be provided, if desired. For example, the plate mounting, designed as a bottom vat, can be fitted with a suctioning device for suctioning the solvent vapors from the plate mounting or vat area and its surroundings. Moreover, if desired, the entire device can also be equipped with a shrouding cover or an **object suctioner**, to the extent that the dimensioning of the device prohibits working with **conventional laboratory equipment,**. The plate mounting itself comprises two parallel longitudinal walls as well as two perpendicular lateral walls (ends, or a top and a bottom), as well as a floor plate connected tightly to the lateral walls in the embodiment of a bottom vat. The plate mounting or vat is securely connected to the slide rails which are arranged parallel to the longitudinal walls of the plate mounting or vat. In this way, the cradle moving inside can be moved precisely to a particular position along the plate mounting or vat. The test tube racks (fraction collectors) which can be placed into the plate mounting or vat are designed in the usual manner and are suited for accommodating of test tubes with various diameters which are

commercially available. If desired, the test tube rack can be fitted with a suitable covering which serves as a funnel and splash guard. Furthermore, a test tube rack which prevents the transposition of test tubes is advantageous because the processing of the samples can be facilitated in the future. The chromatographic columns are likewise columns having the desired dimensions which comprise standard commercial sizes, such as glass pipes with a thread which can be sealed at the top by means of screw plugs or in some other suitable manner so as to be compression-proof. The actuator for moving the cradle on the slide rails and the electronic control device are constructed in the conventional manner or in the manner typical for the market. The electronic control device serves to regulate automatically the time interval, the rate of feed, and the position of the column support bridge above the test tubes as well as to shut down the device automatically after the previously-indicated fraction count has been attained (corresponds to the number of test tube rows) or after the end position has been reached. A solvent drain as a device for drop collection can be advantageous in the end position (that is at the **bottom** of the plate or vat.

Conventional solvent containers can be used to introduce the eluting agent or agents into the chromatographic columns. While the column chromatography is being executed, the eluting agents can be pumped out via the supply lines to the ends of the chromatographic columns under normal pressure by means of one or several pumps, e.g. hose pumps.

Generally, it is prudent to operate more than 5 columns simultaneously, in order to fully utilize the advantages of the inventive device for parallel chromatography. For this reason, generally speaking, a number of chromatographic columns from N = 6 to 15, preferably a number from N = 6 to 10, can be arranged on the column support bridge. If necessary, more chromatographic columns also can be mounted next to one another on the column support bridge, whereby this is not advisable due to the increased construction expense associated with it.

In another variation of the invention, performing the parallel column chromatography under excess pressure is planned. The inventive device distinguishes itself here in that the components of the device --especially the chromatographic columns, the solvent container or containers, the supply lines, the connecting elements, and the sealing elements-- have been structurally designed for working under pressure, preferably for working with excess pressures of up to 10 bar, as necessary.

In another, advantageous variation of the invention, arranging the solvent container or containers of the inventive device is planned such that the solvent container or containers is or are tightly connected to the column support bridge above the chromatographic columns.

The solvent container can hereby be constructed with sub-divisions in the interior for the application of various eluting agents, or even without sub-divisions, to the degree that the parallel chromatographies are to be executed predominantly with only one homogenous eluting agent. Furthermore, it is also possible to arrange several separate solvent containers next to one another above the chromatographic columns on the column support bridge. In any event, it is advisable to design the solvent container or containers in this variation of the invention for working under excess pressure. The solvent container or containers therefore generally consist of a compression-proof metal hollow chamber which either can be fashioned itself to be resistant to the solvent or which can be fitted with a solvent-resistant coating. Moreover, the solvent container or containers have a feed opening for the solvent which can be sealed in a pressure-resistant manner as well as an inlet for the pressure gas (for example nitrogen or a noble gas) for measuring and regulating the pressure which is appropriately connected to a manometer. For safety-related reasons, the closure of the inlet opening can be designed as a rupture disk and can have a pressure-relieving profile. In order to drain the solvent, the solvent container or containers generally possess another suitable escape valve on their bottom side.

The invention also concerns a method for the simultaneous parallel execution of a particular number n of fractionating column chromatographies by means of the inventive device. The device according to the invention distinguishes itself in that n chromatographic columns are fed and conditioned in the conventional manner with solid phase and solvent to begin with; thereafter, the samples are released onto the column ends, and, if necessary, the column tops are sealed; thereafter, the actual fractionating column chromatographies are initiated over the first row of test tubes in position with the chromatographic columns (that is, in position 1 or the starting position), in which the introduction of the solvent into the ends of the chromatographic columns is begun, after which one moves the individual test tube rows into the pre-set positioning and time intervals while adhering to a pre-determined holding time over each test tube, if necessary under excess pressure, in accordance with the program of the electronic control device, beginning with row 1 through to row m, and collects the individual fractions in the test tubes. If necessary, filling and conditioning the

chromatographic columns as well as the sampling task can be performed via a solvent drain which is arranged parallel to the column end (in "position 0") in this connection before the parallel chromatographic columns are moved into the first test tube row (in "position 1" or the "starting position") to begin the parallel fractionating column chromatography.

If a test tube glass rack is used with the covering plate described above, the column support bridge, the column support bridge **the test tubes** also can be traversed in perpetual motion over the test tubes at an according rate of feed.. The distribution of the fractions over the individual test tubes then ensues by means of the corresponding, funnel-shaped constructions on the covering plate over the individual test tubes; the holding time which is stated above within the scope of the inventive method then hereby corresponds to the time interval which is indicated for traversing a **funnel ball**.

The inventive device as well as the inventive method have a number of advantages with respect to conventional devices and methods for column chromatography. For example, the invention enables the simultaneous operation of a certain number of chromatographic columns parallel in an automated operating sequence. While the conventional operation of individual columns in juxtaposition or sequentially requires a larger amount of equipment (for example several fraction collectors, pumps, etc.) and also means higher expense with respect to time, operation, and sampling for the laboratory personnel when preparing for and performing the individual chromatographies, the inventive method with the inventive device, in contrast, can be executed in an efficient, automated operational sequence while significantly decreasing operating time. Within the framework of the automated operational sequence with the inventive method, the individual steps of a column chromatography can be efficiently executed in a parallel manner: first, all the columns of the parallel chromatography are fed and conditioned with solid phase and solvent; in the next operational step, all the columns of the parallel chromatography are loaded with the samples; in addition, especially with the variation with only one solvent container connected to the column support bridge, the introduction of eluting agents and also the generation and regulation of pressure works very efficiently for the laboratory personnel. In addition, the device which is suggested in accordance with the invention and the method for parallel chromatography facilitate a heightened output capacity in comparison to conventionally-operated column chromatographies.

Further structural embodiments and advantages of the invention can be found in figures 1 through 3, by means of which examples the invention is further iterated without limiting them in their scope.

Explanations to the Figures

Figure 1:
A schematic depiction of an inventive parallel column chromatography system (cross-sectional perspective, seen from the top or bottom; a compression-proof solvent container, connected to the column support bridge; parallel operation of 8 chromatographic columns. The referential numbers in figure 1 hereby refer to the following:

(1) = bottom vat
(2) = test tube rack with m rows, each with 8 test tubes in a row
(2a) = plate (covering) as a splash guard and a feed device (funnel)
(3a), (3b) = slide rails on the longitudinal side walls of the bottom vat
(4) = column support bridge for either the fixed or interchangeable accommodation of chromatographic columns; in this case, 8 chromatographic columns
(5) = chromatographic columns
(5a) = dropper tips of the chromatographic columns with or without a valve (such as cone plugs or solenoid valves)
(5b) = column **seal/closure**; for example, a screw plug with or without a septum
(6) = solvent container; in this case, a one-piece form designed to withstand pressure
(6a) = support for the solvent container arrangement and for the connection to the column support bridge
(6b) = solvent inlet with a rupture disk and a pressure-release valve which can be sealed
(6c) = inlet for pressure gas (for example nitrogen, a noble gas, associated here with a manometer (6b) for measuring pressure and, if necessary, a valve for pressure regulation or as an escape valve
(6d) = manometer

(6e) = emergency drain tap for solvent

(7) = solvent supply lines for supplying the eluting agent from the solvent containers to the column top end, with a supply valve (7a); the supply valves (7a) can be embodied as cone plugs (for example as a two-way or three-way tap) or as solenoid valves.

Figure 2:

A parallel chromatography system viewed schematically in longitudinal view. The components and referential numbers given in Fig. 2 correspond to the following, to the extent that they have not been indicated in Fig. 1 already:

(8) = a motor-driven cradle and column support bridge

(9) = fraction collector = test tube rack with test tubes = (2)

(10) = plate (covering) as a splash guard and feeder device = (2a)

Figure 3:

Columns for a parallel chromatography system, viewed schematically. The components and referential numbers given in Fig. 3 refer to the following here:

(5b) = screw plug

(7) = nitrogen and solvent inlet

(7a) = three-way tap

(11) = sampling chamber, in this example about 2 ml

(12) = Teflon bond with seals for bonding column and cap

(13) = Teflon cap with seals and a glass frit as a column drain (instead of 5a)

Patent Claims

1. A device for the simultaneous, parallel execution of a particular number n of fractionating column chromatographies, characterized in that
a) a plate mounting, preferably in the form of a bottom vat,
--which serves to accommodate one or several removable test tube racks, whereby these test tube racks are adapted in their dimensions, either individually or collectively, to the interior dimensions of the plate mounting, preferably bottom vat, such that an arrangement of m rows lying at a distance from one another with n test tubes standing next to one another at a distance can be effected parallel to the top of the plate mounting;

--in which the plate mounting, preferably the bottom vat, can have yet another solvent drain arranged parallel to this (in "position 0" and/or "end position") at one or both of the ends, if necessary;

b) a slide rail with a motor-driven, steerable cradle, each of which is arranged parallel with each longitudinal side of the plate mounting, preferably bottom vat;

c) a mobile bridge which is arranged on the cradle and which can be moved by means of said cradle at a certain distance lengthwise over the plate mounting, preferably over the bottom vat, said cradle serving as a support for the fixed or, if necessary, interchangeable accommodation of several chromatographic columns ("column support bridge");

d) a number n of chromatographic columns which are arranged in rows parallel to the end of the plate mounting, preferably bottom vat, on the column support bridge in such a manner that the line of position of the dropper tips of the chromatographic columns to be traversed is coordinated with the position of the test tubes in the individual rows, in which the chromatographic columns can be designed to work under pressure, if necessary;

e) a solvent container for accommodating an eluting agent or, if need be, several solvent containers for accommodating various eluting agents, in which the solvent container or containers can also be designed as pressure containers, if necessary, and in which the solvent container or containers also can be connected to the column support bridge over the chromatographic columns, if needed;

f) supply lines which are designed to be fixed or flexible as pressure lines, as necessary, for the introduction of the eluting agent or agents from the solvent container or containers into the chromatographic columns;

g) a motor drive for moving the cradle with the column support bridge on the slide rails and an electronic control device for automatic control, especially of the timing and positioning of the column support bridge along the plate mounting, preferably along the bottom vat;

wherein the number n refers to the chromatographic columns arranged on the column support bridge and represents a whole number larger than 5, and wherein the number m refers to the possible number of test tube rows which can be traversed by the column support bridge.

2. A device in accordance with claim 1, characterized in that the number n of chromatographic columns amounts to 6 to 15, and preferably 6 to 10.

3. A device in accordance with claim 1, characterized in that the components of the device, insofar as it is necessary--in particular the chromatographic columns, the solvent container or containers, the supply lines, the connecting elements, and the sealing elements--are structurally designed to work under excess pressures of up to 10 bar.

4. A device in accordance with claim 1, characterized in that the solvent container or containers is or are connected securely to the column support bridge above the chromatographic columns.

5. A method for the simultaneous, parallel execution of a particular number n of fractionating column chromatographies by means of a device in accordance with claim 1, characterized in that n chromatographic columns first are fed and conditioned in the conventional manner with solid phase and solvent; thereafter, the samples are loaded onto the column tops and the column tops are closed, if necessary; then the actual fractionating chromatographies are begun over the first row of test tubes in position with the chromatographic columns ("position 1" or "starting position") by initiating the introduction of the solvent into the top ends of the chromatographic columns, after which one moves the individual test tube rows corresponding with the pre-determined positioning and time interval in accordance with the program of the electronic control

device, if necessary under the previously noted excess pressure, while adhering to a pre-determined holding time over each test tube row, beginning with row 1 through row m, and collects the individual fractions in the tubes; characterized in that the filling and conditioning of the chromatographic columns, if necessary the sampling procedure as well, can be executed over a solvent drain which is arranged parallel on the top end (in "position 0") before the parallel chromatographic columns is over the first row of test tubes ("position 1" or "starting position") moved to begin the parallel, fractionating column chromatography.

Fig. 1:

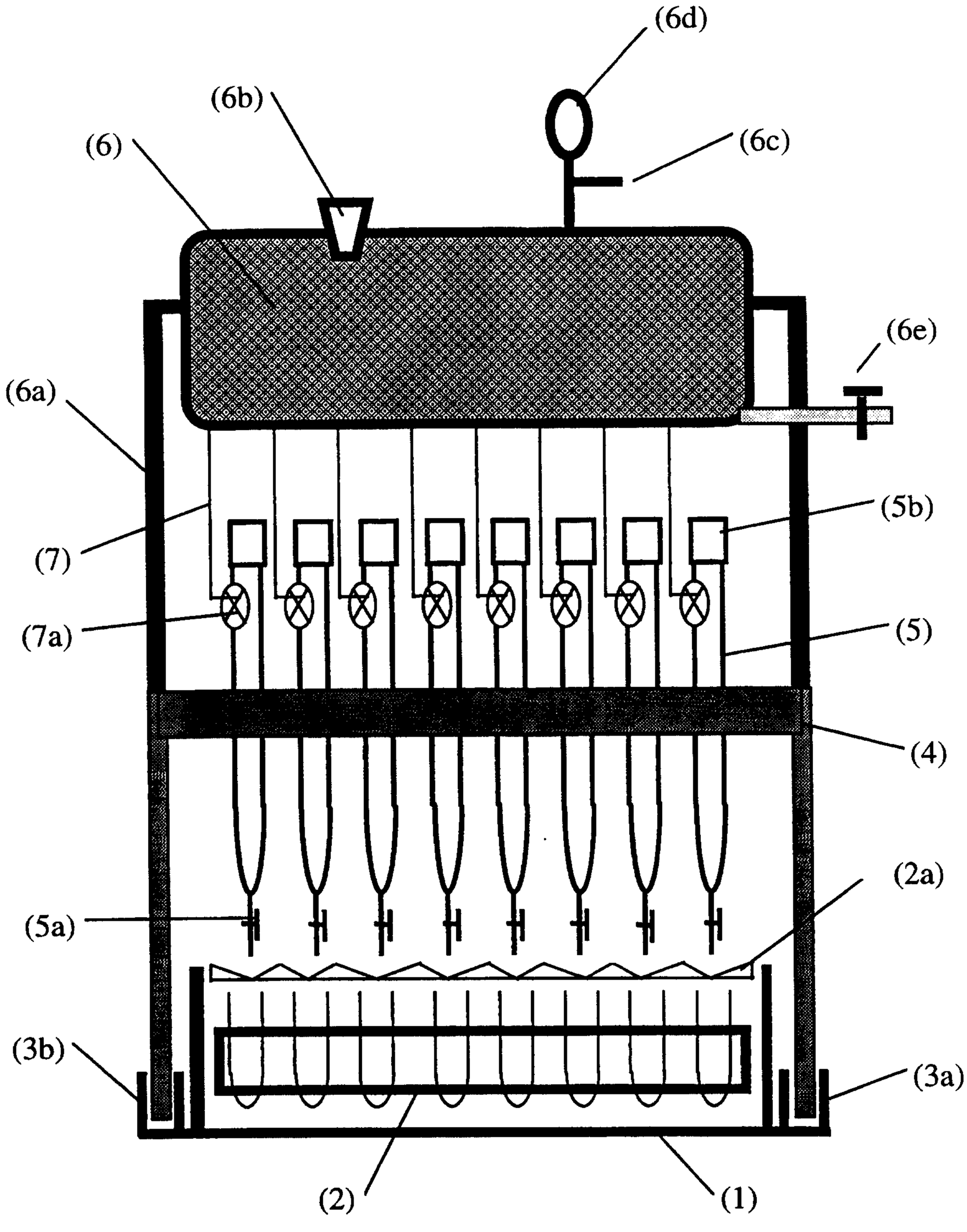


Fig. 2:

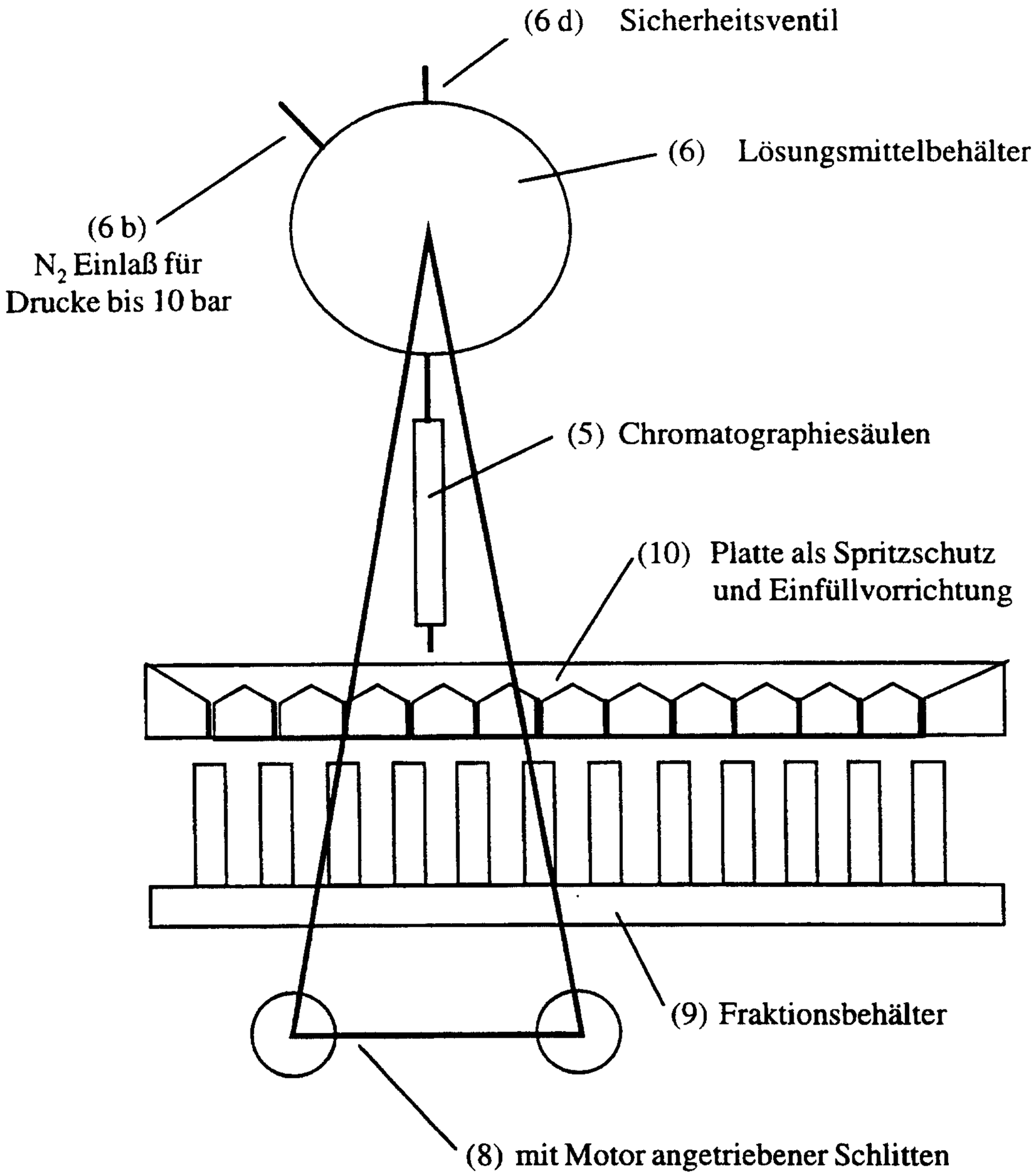

(6 d) Sicherheitsventil
(6) Lösungsmittelbehälter
(6 b)
N_2 Einlaß für
Drucke bis 10 bar
(5) Chromatographiesäulen
(10) Platte als Spritzschutz
und Einfüllvorrichtung
(9) Fraktionsbehälter
(8) mit Motor angetriebener Schlitten

Fig. 3:

Säule für Parallelchromatographiesystem

