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The invention concerns a microreactor with at least one cavity, which is provided with a bottom, a side wall and an opening disposed opposite the bottom, wherein a cross-section intersecting the side wall parallel to the bottom has a shape which differs from a round, square or rectangular shape.

6, 24, 48, 96, 384 or more individual microreactors can for example be realised by means of conventional microreactor arrays (so-called microtitre plates). Much as the number of microreactors varies strongly, the volume of individual reactors can also vary. Whilst we speak of microreactors for any size below 10 ml a further reduction of the volume to below 1ml, below 500 µl, below 100 µl or even below 10 µl can be realised.

A microreactor serves as a reaction vessel for biochemical, chemical or enzymatic reactions as well as microbial fermentation. A reactor array allows the examination of cell cultures with high parallelism at low working volumes, high information gain and the possibility of a simplified automation. Such arrays are in particular suitable for the automation of screening trials under improved mixing and material transfer conditions and they enable an operation that is isolated or sterile compared to the outside, aseptic of monoseptic.

A screening of biological systems is necessary in many areas of biology, chemistry, process technology, pharmacy and in medicine (for example the selection of suitable biological strains, enzymes or suitable culture media and conditions). There is a need for high sample throughputs (parallelisation of trials) and a reduction of sometimes costly starting material.

With the bioreactors used today, such as shake flasks, small fermenters and test tubes one is not able to satisfy this need. The established technologies do not satisfy the requirements for automation, cost minimisation and the necessary high throughput. The need for many parallel trials on a microtitre scale is particular high with biocatalytic systems, as such processes are generally slower and more expensive, especially during the development phase, than comparable chemical processes. There is therefore a need for the development of microbioreactors that will supply a suitable environment for biological cultivation and biocatalytic reactions in the smallest space.

Two criteria can be highlighted as important requirements for suitable operating conditions here: the possibility of carrying out the relevant trials under sterile or monoseptic conditions and the guarantee of a material transfer (fluid-fluid, fluid-gas, solid-fluid, solid-gas) that is suitable and adequate for the biological culture or the biocatalytic reaction system.

Microreactor arrays such as for example microtitre plates offer an ideal platform for realising a high degree of parallelisation. Due to the small reaction volumes (for example >10 µl to <10 µl per chamber), the high degree of parallelisation, (for example 6 to 1536 chambers per plate) and the possibility of automating the cultivation processes (in a form that can be managed by robots) microreactor arrays represent the most cost effective bioreactor with a promising future of all.

The use of non-invasive, optical measuring methods for recording process parameters in this reactor type is already well advanced. The operating conditions of shaken microtitre plates are already well characterised with regard to the material transfer (maximum oxygen transfer capacity, OTRmax)

It has been shown that maximum oxygen transfer capacities OTRmax of just 0.030 mol/l/h can be achieved with air treatment with standard 96-well microtitre plates (round cross-section) (Hermann R., Lehmann M., Büchs J.: Characterization of gas-fluid mass transfer phenomena in microtitre plates. Biotechnol Bioeng, 81(2), 178-186, 2003). This is however very often not sufficient for processing the culture in an oxygen limited way during the culture processing of aerobic, microbial cultures.

The requirements of many microbial cultures often lie above OTR values of 0.05 mol/l/h and in many cases they even reach OTR values of 0.1 mol/l/h in batch processes, and even up to 0.03 mol/l/h on feed batch processes. Higher ITRmax values of 0.1 - 0.15 have been achieved in square and round 96-deep-well plates. These values can however only be achieved with correspondingly small fill volumes of 200 µl. The fluid is almost completely separated from the bottom here and an optical measurement on the bottom is no longer possible. Deep-well plates with an optically transparent bottom do not currently exist either, which makes an optical measurement through the bottom impossible.

Microtitre plates are currently already used for screening biological systems. For this individual reaction chambers are filled, injected and incubated on a rotation shaker. The mostly orbital shaking movement improves the ingress of oxygen into the reaction fluids and mixes the reaction mixture. The microtitre plates are covered with an air permeable membrane (pore size < 0.2 µm) or an air-tight film or a lid construction to keep the system sterile or are cultivated open in a sterile environment.

The microtitre plates used for the described applications are currently offered by various manufacturers in two basic designs: with circular or with rectangular cavities. The first microtitre plates were manufactured by the Hungarian Dr. G. Takatsky in 1951 and had a round cross-section. Microtitre plates with square and rectangular cross-sections were then introduced in the 90s. Microtitre plates are however used in very many areas of chemistry, medicine, biotechnology and biology, so that almost no developments have been targeted at the cultivation of cells in particular.

Patent publication US 5225164 from 1991, in which the possibility of affixing a baffle that projects into the cavity to at least one of the vertical walls of the cavity in a square cavity is described, describes some of the few exceptions. This solution can in principle lead to an improved material transfer, although the baffles can severely limit good mixing and a good material transfer if the fluid circulation in the reactors is extreme.

On the other hand the flow interrupters can lead to a strong drop formation / splashing, which leads to inhomogeneity, increased wall growth and to a wetting and closure of the gas permeable cover of the plates (Büchs J., Introduction to advantages and problems of shaken cultures, Biochem. Eng. J. 7(2), 91-98, 2001). There is also no reference to the realisation and investigation of a microtitre plate with a variation of cavity geometries (outside of the circular and the rectangular cross-section) on the market and in specialist literature.

In practice it is known that the use of microtitre plates with circular cavities in a measuring system like the Bio-Lector-Technologie (WO 2005/098397) sold by company m2p-labs leads to problems with measurement recordings during the shaking process. The permanent shaking movement is necessary to guarantee a continuously good material transfer in the reaction fluid, although it leads to a drastic reduction in the fluid layer until the sensor-equipped bottom of the cavity runs completely free at high shaking speeds, and thus results in problems during measurement value recording (see also: Kensy F., John G.T., Hofmann B., Büchs J., Characterisation of Operation conditions and online monitoring of physiological culture parameters in shaken 24-well microtitre plates; Bioprocess and Biosystems Engineering 28(2), 75-81, 2005).

Various systems for covering such microtitre plates are on the market. Most microtitre plate manufacturers firstly also supply a plastic cover that is placed loosely on the microtitre plate.

Secondly the concept of an adhesive film or membrane has proven itself on the market. Additional equipment (sealers) for the manual or automatic operation are also available from various manufacturers for this use.

Mats made of flexible plastic (for example: silicon) are also sold as a third variant, the nob-like diverticula of which engage every single cavity and close in this way.

Only two systems that press a dimensionally stable lid tightly onto a microtitre plate by means of force are known on the market. The first is a system that is sold as a "sandwich cover plate" by company EnzyScreen.

Secondly a cover that completely encloses a microtitre plate and is held on the microtitre plate in this way is known from patent publication US 6896848. Special devices for application or positioning of the lid are required for both systems. Both systems can therefore not be automated without additional holders or applicators.

Another microtitre plate is known from EP 1 733 793 A2.

The reaction vessels according to prior art described above are not suitable for the majority of applications (in particular chemical reactions with a gaseous phase or cell cultivation). They have the following disadvantages:

- Inadequate gas exchange between the surrounding gaseous phase and the fluid in the cavity
- Inadequate or excessively slow mixing of various components inside the cavity (fluid-fluid mixing or solid-fluid mixing)
- The fluid rises up the wall as the shaking speed increases and reaches the upper edge of the cavity at relatively low shaking speeds. This limits the fill volume that can be used, as the fluid will otherwise spill over the edge of the cavity or cause a blockage of the applied cover membrane.
- Free running of the cavity bottom at increased speeds, which does not permit a

measurement with sensors immobilised or installed at the bottom or optical measurements in the fluid from below the bottom.

- The use of, for example, square cavity cross-sections or cavities with baffles can lead to flow interruptions, which cause the formation of drops and/or aerosols. This can lead to a deposition of solids and reaction components on the walls of the cavity as well as a blocking of the microreactor array cover. Optical measurements can once again be influenced by the formation of drops and/or aerosols.
- Foaming if baffles are too pronounced.

The following disadvantages are considered particularly severe with regard to the various microreactor array cover systems currently known:

- No solid and tight closing of the microtitre plate, in particular during a shaking movement (only loosely positioned standard lids made of plastic).
- Complicated actions, sometimes requiring additional equipment for fixing a cover onto the microtitre plate. No or only complex automation possibilities and costly solutions (adhesive film and plastic mats).
- No or only inadequate/inhomogeneous gas supply and/or undesirably high evaporation of reaction fluid when using established microtitre plate covers (films, lid systems).
- No possibility of sampling or fluid/solids addition/extraction in the microtitre plate without contamination risk for the reaction carried out, as no cover exists that can be reclosed and will guarantee a gas transfer at the same time without additional effort or additional equipment.

It is the task of the invention to overcome the disadvantages of conventional microtitre plates described above and to expand the established concept of a microtitre plate as a vessel, primarily for chemical and biochemical reaction batches, in principle right up to a fully adequate and universally usable reaction and cultivation system in this way in that the following points are preferably fulfilled.

With regard to the microreactor assays these are:

- intensified gas exchange with the fluid within a cavity,
- intensification of mixing a fluid or suspension in a cavity,
- prevention of overspill of the reaction solution from the reaction vessel at the necessary high shaking speeds,

- prevention of free-running of the bottom of a cavity during the shaking process (for example: for guaranteeing an optical or other measurement at the bottom or through the bottom) and realisation of constant contact with possible sensors fitted on the bottom of the cavity,
- avoidance of drip and/or aerosol formations which may affect measurements, cause reaction components and/or biomass deposition on the walls and/or prevent of block material transfer through the gas permeable cover of the microreactor array due to blockages,
- low foam formation thanks to the most homogenous fluid movement possible.

With regard to the cover of the microreactor array these are:

- Firm and tight closure of each individual cavity from neighbouring cavities and the environment through applying a cover that can be arrested on the microreactor array and/or disconnected once more,
- easy handling of the cover with the possibility of automation with conventional grippers of, for example, liquid handling systems,
- reduction of evaporation with simultaneous adequate gas transfer through openings in the lid, by adjusting the size of these openings and/or by using diffusion controlling materials with which these openings are covered,
- possibility of sterile sampling and/or supply and discharge of fluids or solids in individual cavities of a microreactor array.

With regard to a microreactor the task is solved in that a cross-section intersecting the side wall parallel to the bottom has a shape that differs from a round, square or rectangular shape. Shape is here meant as the basic shape, wherein this basic shape is not changed by smaller flow interrupters.

The solution of the described task is realised by a change in the geometry of a cavity away from the established geometries of a circular cylinder shape or a rectangular cross-section.

The task is solved in that the round or square cavities known from prior art are changed in such a way that the positive characteristics of a flow interruption through inserting projections or indentations in the cavity as well as the positive characteristics of a round cavity, and thus the most undisturbed flow possible, ideally complement each other for the application described.

The newly suggested cavity shapes interrupt the rotary flow movement only moderately when an orbital shaking movement is applied.

The interference with or hindering of a consistent wall flow forms a turbulent flow profile, which has a positive influence on the mixing as well as the material transfer from the gaseous phase into the liquid phase and vice versa. The formation of the projections or indentations should be adapted in such a way here that a drop or aerosol formation cannot take place, which could result in a blocking of an overlaying cover (for example a membrane) or the accumulation/precipitation of fluid or solids (for example biomass) on the reactor walls. Adapting the flow interrupting effect can also realise that the fluid continuously wets the bottom and therefore enables optical or other measurements on the cavity bottom. An adaptation of the flow interrupting effect also means that the possible fill volume, before an overspill of the fluid at a corresponding shaking frequency occurs, can be increased.

The task can be solved by realising various cavity geometries:

The first variation approach for the base surface of the cavities arises from an extreme of a square base surface and approaches the other extreme of a round base surface by increasing the number of corners. It is therefore suggested that the cross-section has more than four corners.

The construction relevant length of the base side of a polygon can also be calculated by constructing a triangle between a base side and two neighbouring radii of the polygon for a given area of 112.16 mm^2. It is therefore alternatively suggested that the cross-section has fewer than four corners here.

In the second variation approach the transition to the circular base surface was, once again based on a square, realised by constructing circles with increasing radii in the corners of the square. The sizes of the radius of the corner arc as well as the remaining straight of the starting square are construction relevant.

It is of advantage if the cavity differs from the shape of a polygon.

The shape can be described in that a cross-section intersecting parallel to the bottom of the side walls has at least one concave and/or convex circle segment that projects into the cross-section with a radius or projects from the same, wherein this radius is between 0.067 and 0.49 times the diagonal of the cross-section.

One example envisages that the basic shape of the cross-section is any polygon or a circle which as several concave or convex circle segments.

The cross-section can have an arc that forms a circle segment of more than 90°, or the cross-section can have more than 3, preferably more than 4 arcs, which each form a circle segment of more than 90°.

In the third variation approach a pentagon was selected as the starting shape and transformed into a circle in stages by rounding the edges.

With regard to the second and the third variation approach it is suggested according to the invention that the cross-section has corners with a radius of more than 0.5 mm.

A fourth approach of adapting the originally circular basic shape of the cavity consists of inserting baffles of various shapes and sizes. The basic shape created cannot be easily calculated in many cases. To reach the stipulated 112.16 mm^2 here the surface was measured and then scaled accordingly after drawing it with the software AutoCAD, Ver. 14.01 from company Autodesk Inc.

This results in a shape where the cross-section has an area that projects into the cavity. One alternative envisages that the cross-section has an area that projects from the cavity. It is of advantage for many embodiments if the area is arranged in one corner.

It is further suggested that several of such areas with different dimensions are envisaged or that several of such areas border each other.

In the simplest case rectangular or semi-circular chicanes were installed on the walls of the cavity across its entire height.

It is therefore suggested that the area is a rectangle or a circle section.

The respective cross-section of the geometry of the cavity used can further widen in an upward direction, for example to guarantee better demoulding following injection moulding, or narrows in height direction, for example to be able to increase the fill volume further at a corresponding shaking frequency without an overspill of the fluid occurring.

The above mentioned cavity geometries, which then transform into another cavity geometry in height direction either upwards or downwards, can be used as a further solution of the task. The transition can be realised between one of the cavity geometries described here for this, or into a round, square or rectangular cavity geometry. In the same way a transition between a round, square or rectangular cavity geometry can occur.

As an example it is therefore suggested that a further cross-section intersecting the side wall parallel to the bottom has a round, square or rectangular shape.

For certain applications it can also be of advantage if at least one component changing the cross-section is inserted through the bottom or a lid into the cavity.

It is suggested that the bottom is designed from an optically transparent material to enable measurements through the bottom.

It is of advantage if the microreactor has several cavities, which are particularly preferably arranged in the form of an array.

Irrespective of the embodiments described previously and the advantages that can be realised with the same it is of advantage and crucial to the invention if a microreactor - in particular a microreactor described previously - has a special lid.

This cover preferably has a gas permeable surface, in particular for sealing each individual cavity against solids and liquids in the environment in particular with an array. At the same time it is of advantage if an opening is arranged above each cavity, the shape and size of which and the material closing the same is designed in such a way that the evaporation of reaction fluid is severely reduced and a material transfer from the surrounding gaseous phase into the liquid phase in the cavity and vice versa is not affected.

It is also suggested that the lid has a resealable area. It is particularly preferred if the lid is designed as a single piece with the wall and/or the bottom with the exception of a gas permeable and/or resealable area.

It is of advantage if the lid has a sandwich material made from a solid, a flexible and/or a gas permeable material. One embodiment envisages that the lid has a robust frame with a seal.

The lid can be attached to the wall under pre-tension and it can be fitted to the wall according to the Luer principle. It is preferred here that the male part of the Luer closure is fitted to the lid and the wall forms the female counterpart.

One variant envisages that the lid is connected with the wall via slanted surfaces that can be displaced in reaction to each other. This can for example be realised in that a wedge can be inserted into a gap to disconnect the lid from the wall in order to separate the lid from the wall.

To lift the lid it is suggested that holes are arranged in said lid for disconnecting the lid, which can be engaged by a gripper. It is of particular advantage here if the grippers have an arrangement for applying a mechanical or pneumatic counterpressure for disconnecting the lid. Holes can for example be envisaged in openings for disconnecting an anchored lid, through which pins or hollow needles of a gripper arm apply mechanical or pneumatic pressure to the cavity for disconnecting the cover from the reaction vessel arrangement.

It is suggested for fitting the lid that said lid is glued to the wall. The lid can also be arrested on the wall or it can have a means for generating underpressure in the cavity.

It is of advantage if the lid enables a supply and discharge of reactants as well as sampling without interrupting the shaking process.

One embodiment example envisages that the microreactor forms part of a microreactor assay with several similar cavities and preferably has a shaking device.

The drawing shows measurement results and embodiment variants of microreactors, reactor arrays and various covers for reactors and reactor arrays.

Shown are:

Figure 1 variations of the number of corners of a cavity,

Figure 2 variations of the design of corners in a square cavity,

Figure 3 variations of the design of corners of a pentagonal cavity,

Figure 4 schematic illustrations of cavities with rectangular and semi-circular baffles,

Figure 5 schematic construction of a pentagonal base surface with asymmetric semi-circular chicanes,

Figure 6 schematic pentagonal and hexagonal base surfaces with asymmetric semi-circular chicanes,

Figure 7 schematic square, pentagonal and hexagonal base surfaces with rounded corner and tip chicanes,

Figure 8 a photograph of various microreactor geometries arranged as arrays,

Figure 9 a photograph of the prototypes of the cover according to the Luer principle for microreactor arrays,

Figure 10 schematic illustrations explaining the Luer principle,

Figure 11 schematic arrangement for holding the lid on a microreactor array by means of underpressure,

Figure 12 schematic illustration of hooks for holding the lid on a microreactor array,

Figure 13 schematic possibilities of disconnecting the lid from a microreactor array,

Figure 14 schematic multi-functional lid positioned on a microreactor array,

Figure 15 graphic illustrations of measurement results for the maximum oxygen transfer rate in various example geometries,

Figure 16 graphic illustrations of measurement results for the maximum oxygen transfer rate in further example geometries realised,

Figure 17 graphically illustrated measurement results for the maximum oxygen transfer rate of example geometries with chicanes,

Figure 18 measurement results for the maximum fill volume in example geometries realised, and

Figure 19 measurement results for the measurable fill height in a cavity in example geometries realised during an orbital shaking movement.

Figure 1 shows how the construction relevant length of the base side of a polygon can be calculated if the area is given - in the present example it is 112.16 mm^2 - by constructing a triangle between a base side and two neighbouring radii of the polygon.

The variation approach shown in Figure 2 assumed a square where the transition to a circular base surface is realised by constructing circles with increasing radii in the corners of the square. The sizes of the radius of the corner circle as well as the remaining straight of the starting square are of relevance for the construction.

Figure 3 shows the same approach with the example of a pentagon as the starting shape.

Figure 4 shows how an originally circular base shape of a cavity can be amended in that baffles of various shapes and sizes are inserted. The base surface created in this way cannot be easily calculated for many surfaces. To realise the stipulation of 112.16 mm^2 the surface was measured and then scaled after drawing the same with a CAD system. For this square and semi-circular chicanes were installed as examples across the entire height of the walls of the cavities. These are however mere examples and the shape of the chicane as well as their expansion across the height of the cavity can vary in different embodiment examples.

Figures 5 to 7 base surface geometries resulting from theoretic considerations for a meaningful conversion into the most varied geometric shapes. Circles of a defined size, the radius of which was changed in 1mm increments, were inserted with all of these base shapes. The selection of geometries resulting from the same was made on the basis of a purely theoretical evaluation of their influence on the flow in the cavity. Shapes with extremely strongly or very weakly pronounced baffles were thus excluded from consideration.

Illustrations 6 and 7 show baffle base surfaces originating from a pentagonal or hexagonal base surface. Its construction is illustrated by way of examples in illustrations 6 and 7. The corner of this base surface was rounded, wherein one or two millimetres were used as a radius for the corner circles. A semi-circular chicane with a radius of 1 mm is applied at each corner. This construction stipulates a rotation direction for shaking for the cavities due to an absence of symmetry.

Further base shapes of cavities are illustrated in Figure 7. Based on square, pentagonal, hexagonal or heptagonal base shapes the corners are once again rounded, wherein the surface between these corners is not flat in this case, but has tips reaching inwards. These tips form the chicanes in these cavities.

The array shown in Figure 8 consists of different cavities and serves for examining the performance function of various geometries.

The cover of a microreactor array realised as a prototype shown in Figure 9 closes each individual cavity tightly against its surroundings and has an opening above each cavity that is designed in such a way that the evaporation of the reaction fluid is severely reduced and a material transfer from the surrounding gaseous phase into the fluid in the cavity and in the opposite direction is not affected.

Individual or all reactors of a microreactor array are designed as Luer sleeves opposite the lids designed with Luer cores here. The design of all cavities as Luer sleeves to realise the simultaneous sealing of all cavities against the surroundings is an advantage.

The Luer principle shown in Figure 10 has proven to be very advantageous with this prototype. It is capable of closing individual reaction chambers off from their surroundings tightly and sealing them. For this the cavity 1 is closed with a lid 2 which serves as a cover. The lid 2 has conical pass elements 3 that lie against the cavity wall and seal the lid 2 against the cavity 1. The lid 2 has a gas permeable film 4 at its top, which can be glued onto the lid or welded to the same. This film ensures the necessary gas exchange, a reduced evaporation and monoseptic operation. It is envisaged to pre-sterilise the microreactor array and the fitted lid components with a final gas permeable film and provide these to the user.

Another embodiment is illustrated in Figure 10B. A flexible sealing layer 7 is envisaged on the cavities 5, 6 here, on which a gas permeable film 8 lies.

The microreactor array has a conical cavity in its body, which serves as a female Luer sleeve 9. A cover 10 for the microreactor array has a Luer core 11 that cooperates with the sleeve 9 as a male part and holds the cover on the array.

The flexible layer 7 is affixed above the cavities. It seals by means of a corresponding contact pressure of the lid, which is held by the Luer connection and seals all wells. The Luer sleeves can for example be fitted between individual wells and on the frame of the microreactor array. One possible arrangement is shown in illustration 10C. The possible positions for Luer sleeves are shown here as fitting points 12 on the microreactor array 13 for sealing the cavities 14.

Figure 10D shows how the Luer principle can be applied across the entirety of the microreactor array. At least two opposing sides of the array frame 15 are sloped for this. They therefore serve as a Luer core for the lid 16, which either forms a circumferential Luer sleeve or is pulled over the sides of the array frame 15 only on the opposing sides. The array lid 16 is therefore designed as a Luer sleeve and enters into a positive connection with the array frame 15. A gas permeable film 17 and a flexible cover layer 18 are in turn envisaged between the lid 16 and the microreactor array frame.

To guarantee an even or adequate contact pressure of the lid 19 onto the flexible layer 20 at every point of the microreactor array 21 it is of advantage if the lid 19 bulges towards the inside, a is shown in Figure 10E. This ensures an even tension distribution.

Figure 11 shows an embodiment variant where the lid 22 is aspirated onto microreactor array 23 with a vacuum or underpressure. For this, vacuum is aspirated through a bore 24 in the body of the microreactor array 23 and underpressure generated in this way, and the lid is pulled to the microreactor assay 23 by a suction cup or a similar intermediate piece 25. This presses the flexible layer 26 with the gas permeable film 27 lying on the same onto the cavities to seal the same. Compression and sealing remains active for as long as the vacuum is pulled or underpressure is generated. This connection is therefore very easy to disconnect. The suction buttons 25 and the bores 24 can be distributed on the array as desired depending on the application.

Figure 12A illustrates how the lid 30 is fitted on the plate geometry with a barbed hook 31. In the embodiment the barbed hook 31 hooks up to a bridge 32. The only thing necessary here is that the lid 30 is pushed onto the microreactor array 33 from the top or from the side with its barbed hook 31. In the closed condition the lid 30 is held so close to the microreactor array 33 that it presses the flexible layer 34 onto the cavities (not shown) and thus seals the same.

Figure 12B shows a variant where the barbed hook 35 hooks up to a groove 36 in the microreactor array 37.

In order to loosen the lid 30 again later it is of advantage to guide the barbed hook 35 of the lid 30 in a guide groove 38. In the end position of the guide groove 38 the barbed hook 35 is held by the spring tension of the flexible layer 39. An external force that slightly exceeds the spring tension of the flexible layer 38 must be applied to the lid 30 by means of the gripper arm of a pipetting robot or applied manually in order to arrest or disconnect it in the end position.

Figure 12D shows an alternative solution for fitting the lid 40 to the microreactor array 41 by applying a spring tension to the barbed hook 43 by means of the spring 42. Only by applying an external force 44 by means of a gripper arm of a pipetting robot or in a manual way can the tension of the spring 42 be counteracted and the barbed hook 43 spread open. The lid 40 can be affixed and the barbed hook arrest on the side bridge 45 by displacing the lid 40 towards and a subsequent relaxing of the spring 42.

With some applications it may be necessary that the lid is disconnected from the microreactor array once more. This possibility is also to be solved with simple means without large additional equipment in addition to a simple liquid handling system with grippers (standard pipetting robot). One possibility for this is shown in Figure 13. It is firstly possible to disconnect the Luer connection by means of overpressure inside the Luer sleeve as shown in Figure 13A. The overpressure can be applied with a compressed air line attached to a gripper arm of a pipetting robot through the bore in the Luer core. For this a compressed air line 51 must be routed to each Luer core 50.

Figure 13B shows how pins 53 are fitted on a plate 52, which press the Luer cores 54 loose from the bottom. As soon as the plate is simply positioned on the pins 53, the pins 53 will be guided through bores 55 in the microreactor array base body 56 and press the lid 57 on the Luer cores 54 upwards.

If several Luer connections or other force connections are used above the microreactor array for fitting the lid it is of advantage if force does not need to be applied in a targeted way to every individual connection. The construction illustrated in Figure 13C shows one solution for this. The force 60 is applied only to the outer frame 61 of the lid 62 here, into which bevelled shoes 63 are driven horizontally under the lid 62 as fingers of a gripper arm. A deflection of the force 60 into the vertical occurs on the diagonal wall 64 of the microreactor array 65 here in that the shoe 63 drives under lid 62 and lifts the same. The movement of the shoe 63 forces a relative movement of the microreactor array 65 towards the lid 62 and disconnects it in this way.

Figure 13D shows a slight variation of this principle. The shoe 66 is here chamfered in an upward direction. The lid 67 drives upwards via a slope 68, wherein the microreactor array 69 remains in its fixed position.

A further disconnection mechanism is illustrated in Figure 13E. This disconnection mechanism manages without a special sloped shoe on the fingers of a gripping arm. By realising two mirror-image slopes 70 and 71 on the microreactor array 72 and the cover 73 a deflection of a horizontal force 74 applied to cover designed flexible in part on this side surface directs this force 74 upwards on the vertical according to the principle described above.

It becomes increasingly necessary to obtain not just online information from the reactor batches of a microreactor array through corresponding use of sensors in or on the reactors, but also to verify time-related changes in reaction conditions with further offline analytics or to obtain further insights. It is therefore also important to acquire sample material from individual reactors as part of the reaction management and to subsequently maintain such reactions in an uninfluenced way. It may also be necessary to supply or discharge liquid of solid substances to or from the reaction mixture. It is therefore necessary to obtain reversible access to the reaction vessel. For this reason an opening for sampling and/or the supply or discharge of substrates/reactants should be realised in addition to the opening in the lid for the gas permeable layer.

The use of a septa material made of silicon or another flexible polymer, which recloses independently thanks to its material characteristics, is envisaged for this. The septa should lastly be perforatable with a cannula 80, a pipette or a pipette tip in order to pipette sample material 81 into or out of the cavity interior. Following withdrawal of the cannula 80 and reclosure of the septa the reaction should continue uninfluenced. Sterile sampling is extremely important in particular with cellular applications in order not to allow contamination of the usually monoseptic culture processing.

It is of advantage in particular with very rapid reactions and fermentations to carry out sampling or interfere with the process without interrupting the shaking process in order not to limit material transport. It is envisaged for this to carry out the shaking process with a diameter small enough to allow penetration of the reaction chamber through a septa during said shaking process and the taking of a sample or the supply or discharge of substrates. Shaking diameters of 1 to 5 mm are of advantage here. It should also be ensured that the cannula for sampling is deformed at most within the flexible area or is flexibly mounted during the shaking process.

The arrangement shown in Figure 14 has a cannula 80 that is guided through an opening 82 in a rigid lid back 83, through a gas permeable film 84 and a flexible cover layer 84 into a cavity 86 in order to withdraw reaction fluid from the cavity 86 or introduce the same into the cavity. Bores 87 aligned with the openings 88 in the rigid cover back 83 are envisaged in the flexible cover layer 85 for a material transport between the inside and outside.

The enormous advantages of an amended geometry of the cavities of a microreactor array have been proven with extensive trials with several prototypes. It has firstly been shown that an enormous increase of the oxygen transfer rate into the reaction fluid, the size of which represents a limiting factor in particular for microbial fermentations in microtitre plates according to prior art, can be realised. It has further been shown that the cavity geometries used in available microtitre plates or deep-well plates according to prior art (circular or square) do not constitute the optimum for oxygen entry in any way. Maximum material transfer rates (here oxygen transfer rate, OTR (Oxygen Transfer Rate)) for various geometries and shaking speeds as well as different working volumes (shaking diameter 3 mm orbit each) are illustrated in Figures 15 to 17. It can also be deduced from this measurement data that the cavity shapes described in patent publication US 5225164 cannot be optimal either, as a maximum oxygen entry cannot be expected from the combination of the square base shape with angular baffles, although a strong drop formation has been observed.

During a second trial series the overspilling or the formation of drops during an orbital shaking movement was investigated. It was examined for each embodiment realised how high the maximum fill volume is at a shaking speed of 1,000 rpm and a shaking diameter of 3 mm in a 200 mm high prototype microtitre plate (Figure 18).

It can be shown that an advantageous conduct of the fluid occurs when the projections or invaginations acting as flow interrupters are only small or have moderate increases.

Apart from these two advantages of the invention, an increased material transfer at a simultaneously low tendency to form drops or overspill the reaction fluid, a further substantial advantage of the invention lies in the prevention of the free running of the bottom of the cavity.

To investigate this characteristic a back calculation was carried out via the fluorescence intensity of a fluoroescein solution to the layer thickness of fluid located at the bottom of a well during the rotation of the shaker. The results described in Figure 19 show that the stronger the corners and edges are pronounced, the more the fluid is prevented from expanding across the cavity walls and thus escape from the bottom.

The simultaneous examination of the three test series described (oxygen entry, maximum fill volume, running free from the bottom) would suggest that the invention improves the concept of the microtitre plate in principle compared to prior art, in particular when used as a cell cultivation system. The fact that a clearly higher oxygen entry can be achieved at simultaneous adequate homogeneous hydrodynamics without drop and splash formation means that unlimited fermentation of microorganisms and higher cells (plant, animal and human cells) is possible across wide areas. The prevention of a running free from the bottom of the cavity means that a sufficiently high fluid column remains at the bottom of the cavity even at high shaking speeds. The fluid of a measurement at the bottom of the cavity is made clearly more accessible in this way. Sensors attached here are no longer at risk of losing contact with the reaction mixture.

The novel design of the cover of the microtitre plate overcomes a grave disadvantage that normally occurs during cultivation in microtitre plates. The fluid loss from the cavity that normally occurs in particular at higher cultivation temperatures is clearly reduced. At the same time an adequate gas exchange between the surroundings and the reaction volume is made possible. Each cavity remains accessible for sampling through a septum. The construction of the cover from a dimensionally stable part and a flexible material for sealing as well as possibility of an easy disconnecting of the cover means that the invention offers the possibility of integrating the system into automated systems (pipetting robot, gripper arm) without additional large equipment of special applicators.

Patentkrav

1. Mikroreaktor med mindst én kavitet, der har en bund, en sidevæg og en åbning modsat bunden, hvor et tværsnit, der skærer sidevæggen parallelt med bunden, har en form, der afviger fra en rund, kvadratisk eller rektangulær form, *kendetegnet ved, at* tværsnittet har en vilkårlig polygonal grundform, der har mindst én eller flere konkave eller konvekse cirkelsegmenter, hvor cirklerne med en radius på mere end 0,5 mm er konstrueret ved hjørnerne af polygonen.

2. Mikroreaktor ifølge krav 1, *kendetegnet ved, at* tværsnittet har mere end 3, fortrinsvis mere end 4 buer, der henholdsvis danner et segment af en cirkel på mere end 90°.

3. Mikroreaktor ifølge et hvilket som helst af de foregående krav, *kendetegnet ved, at* tværsnittet har et område, der rager ind i eller ud af kaviteten, og en flerhed af områderne har forskellige dimensioner.

4. Mikroreaktor ifølge et hvilket som helst af de foregående krav, *kendetegnet ved, at* et yderligere tværsnit, der skærer sidevæggen parallelt med bunden, har en rund, kvadratisk eller rektangulær form.

5. Mikroreaktor ifølge et hvilket som helst af de foregående krav, *kendetegnet ved, at* mindst én komponent, der ændrer tværsnittet, er indført i kaviteten gennem bunden eller gennem et dæksel.

6. Mikroreaktor ifølge et hvilket som helst af de foregående krav, *kendetegnet ved, at* bunden er fremstillet af et optisk transparent materiale, der muliggør målinger gennem bunden.

7. Mikroreaktor ifølge et hvilket som helst af de foregående krav, *kendetegnet ved, at* den har en flerhed af kaviteter.

8. Mikroreaktor ifølge et hvilket som helst af de foregående krav, *kendetegnet ved, at* den har et dæksel.

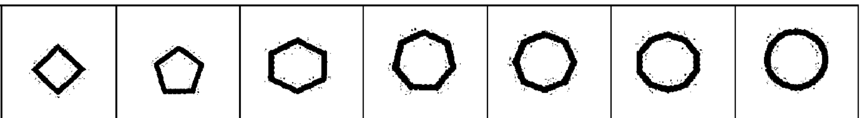
9. Mikroreaktor ifølge krav 8, *kendetegnet ved, at* dækslet har en gasgennemtrængelig flade.

10. Mikroreaktor ifølge krav 8 eller krav 9, *kendetegnet ved, at* dækslet har en flade, der kan lukkes igen.

11. Mikroreaktor ifølge et hvilket som helst af de foregående krav, *kendetegnet ved, at* den danner en del af en mikroreaktoropstilling med en flerhed af identiske kaviteter.

12. Mikroreaktor ifølge et hvilket som helst af de foregående krav, *kendetegnet ved, at* den er forsynet med en rysteanordning.

13. Mikroreaktor ifølge et hvilket som helst af de foregående krav, *kendetegnet ved, at* den muliggør tilførsel og fjernelse af reagenser og prøvetagning uden afbrydelse af rysteprocessen.



Antal kanter	4	5	6	7	8	10	∞
Sidelængde [mm]	10,59	8,07	6,57	5,56	4,82	3,82	0

FIG. 1

Radius hjørne cirkel [mm]	0	1	2	3	4	5	5,975
Sidelængde grundkvadrat [mm]	10,59	10,63	10,75	10,95	11,22	11,56	11,95
Resterende lige linje kvadrat [mm]	10,59	8,63	6,75	4,95	3,22	1,56	0

FIG. 2

Radius hjørne cirkel [mm]	0	1	2	3	4	5	5,975
Sidelængde grundpentagon [mm]	8,07	8,09	8,14	8,23	8,35	8;5	8,68
Resterende lige linje pentagon [mm]	8,07	6,64	5,24	3,87	2,54	1,24	0

FIG. 3

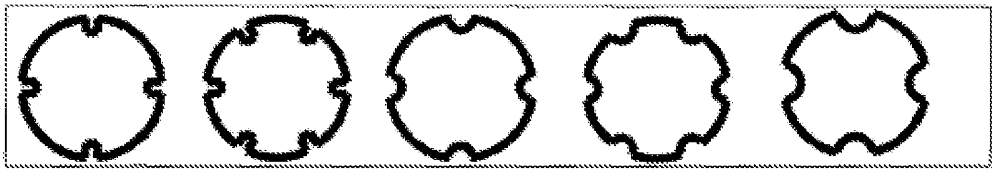


FIG. 4

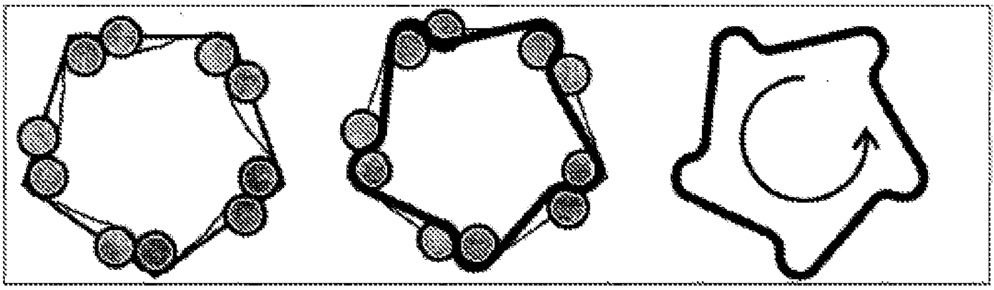


FIG. 5

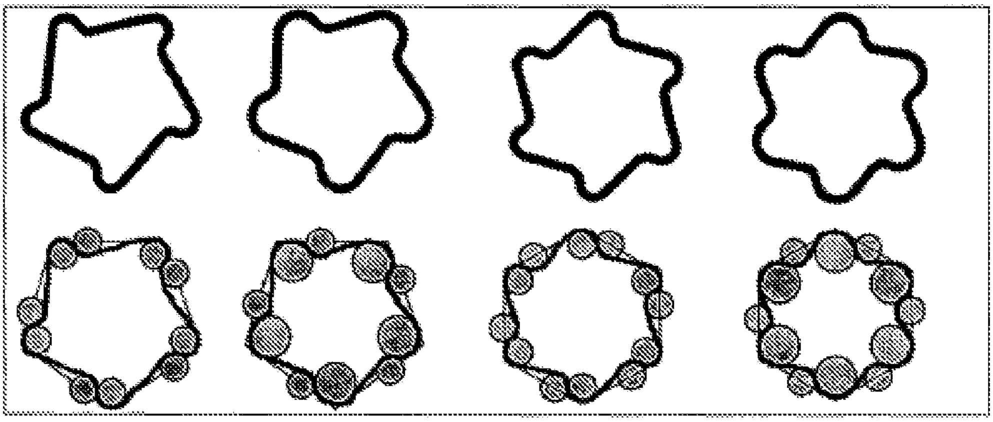


FIG. 6

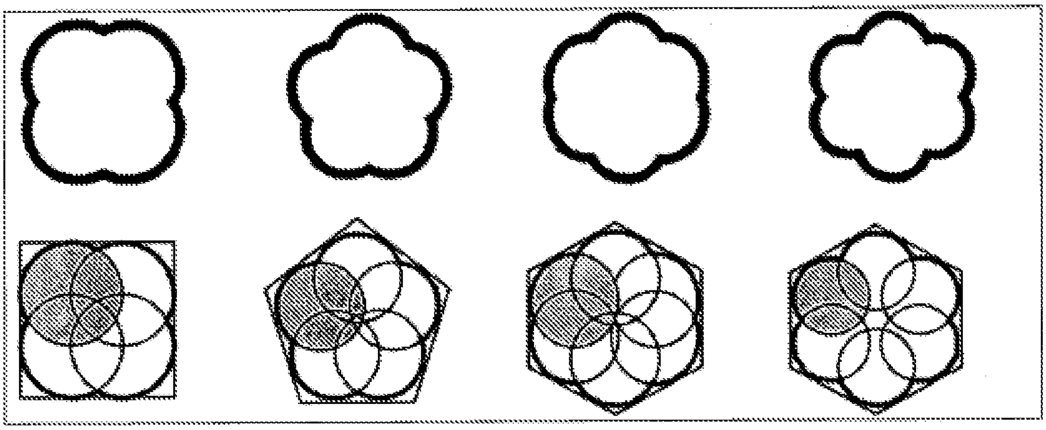


FIG. 7

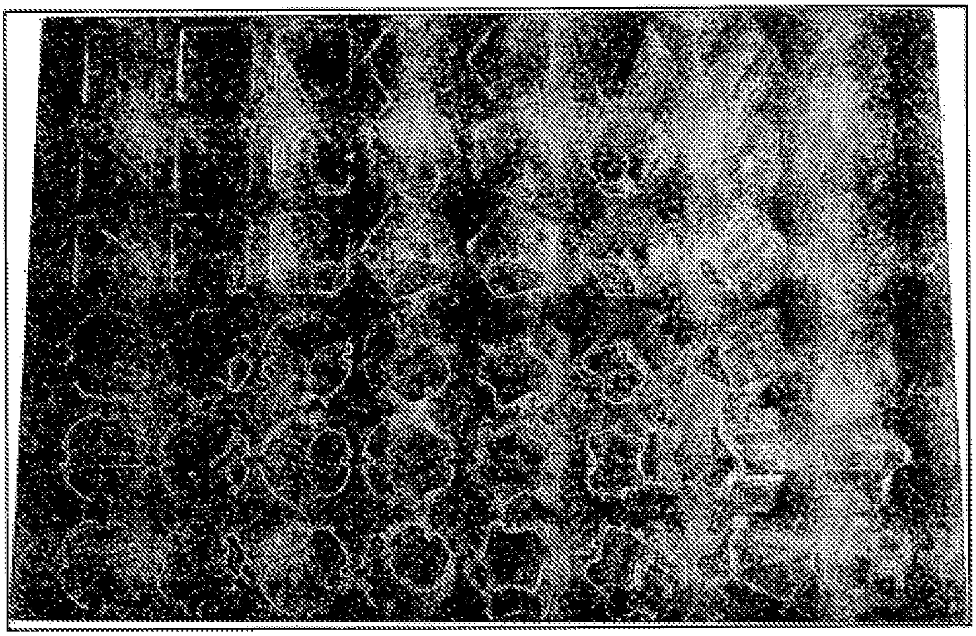


FIG. 8

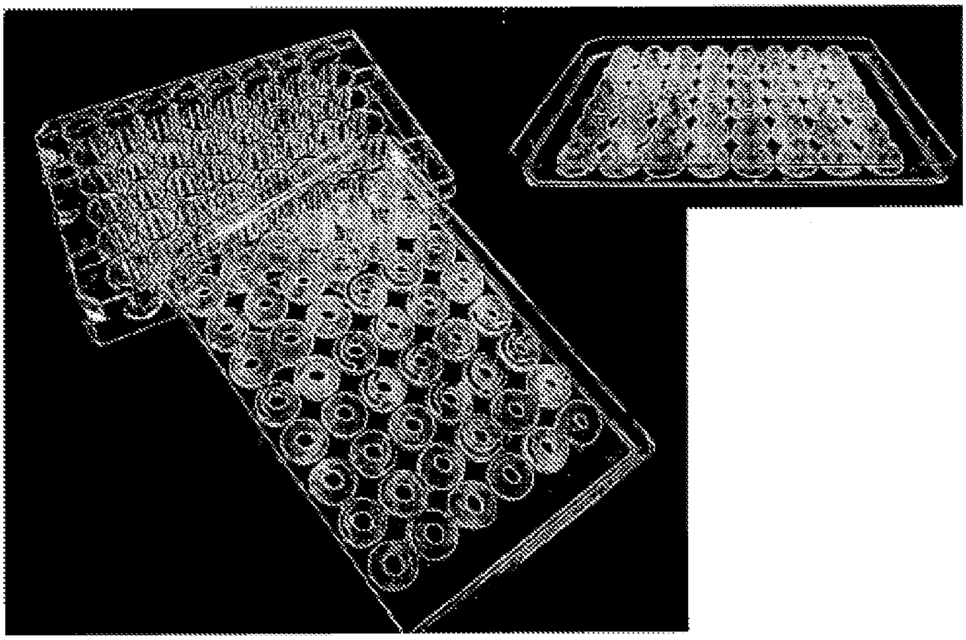


FIG.9

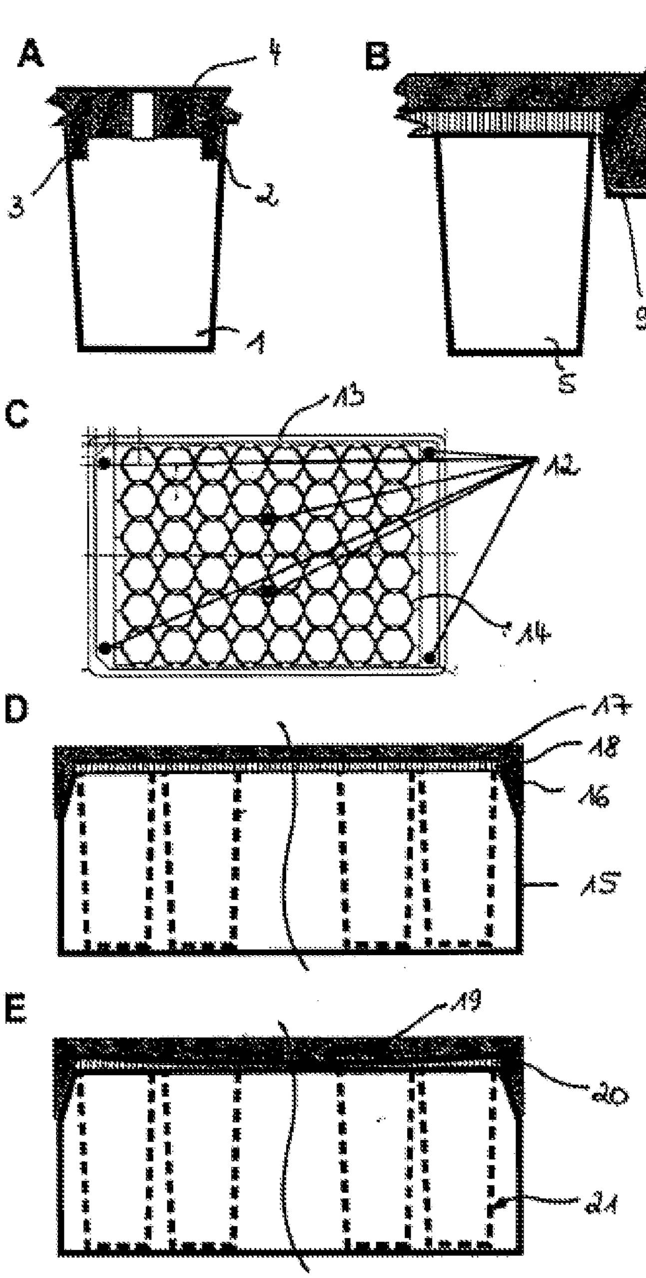


FIG. 10

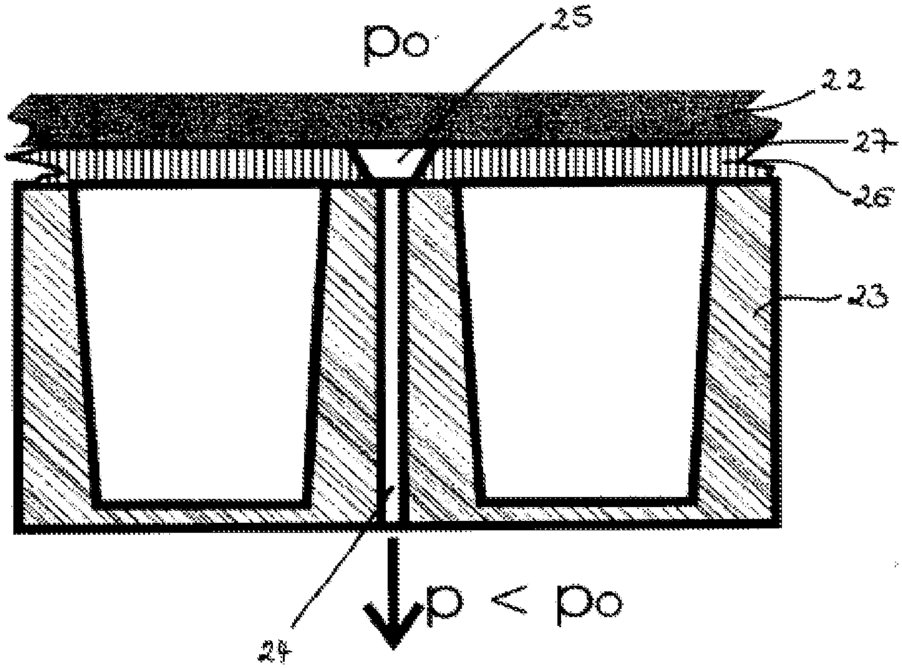


FIG. 11

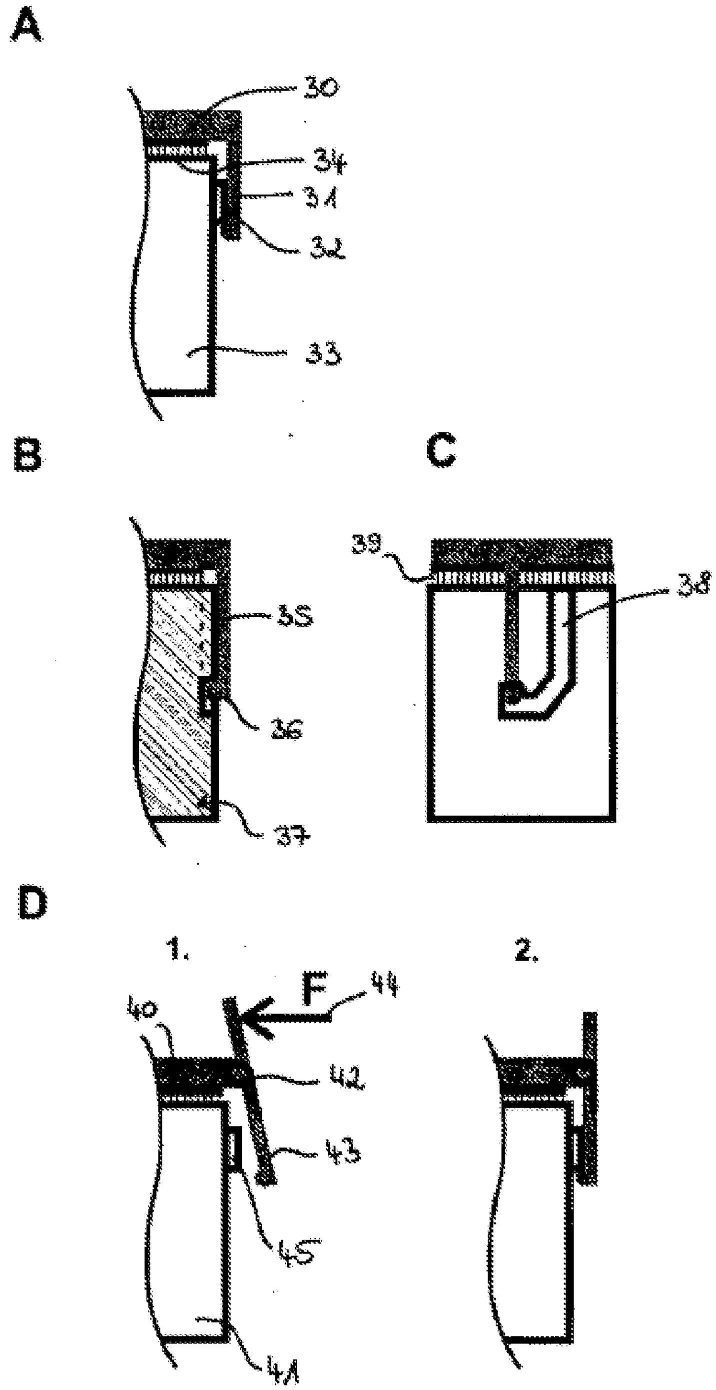


FIG. 12

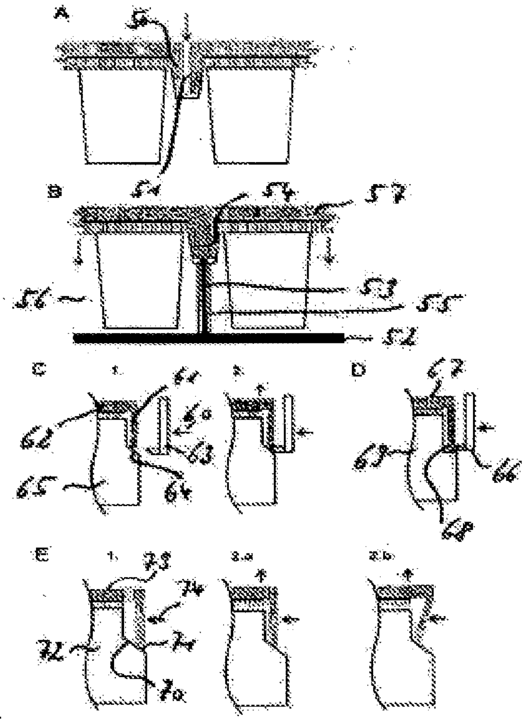


Fig. 13

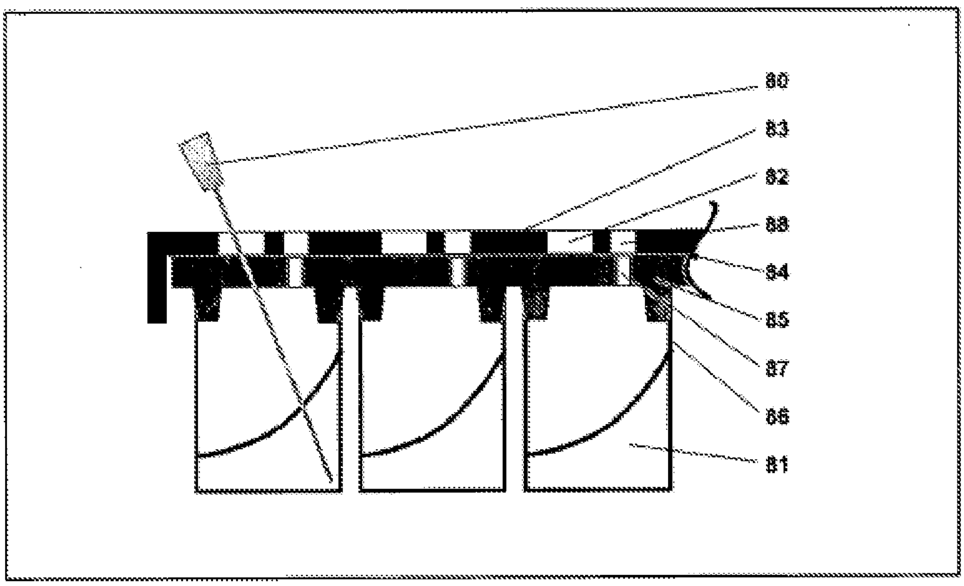


FIG. 14

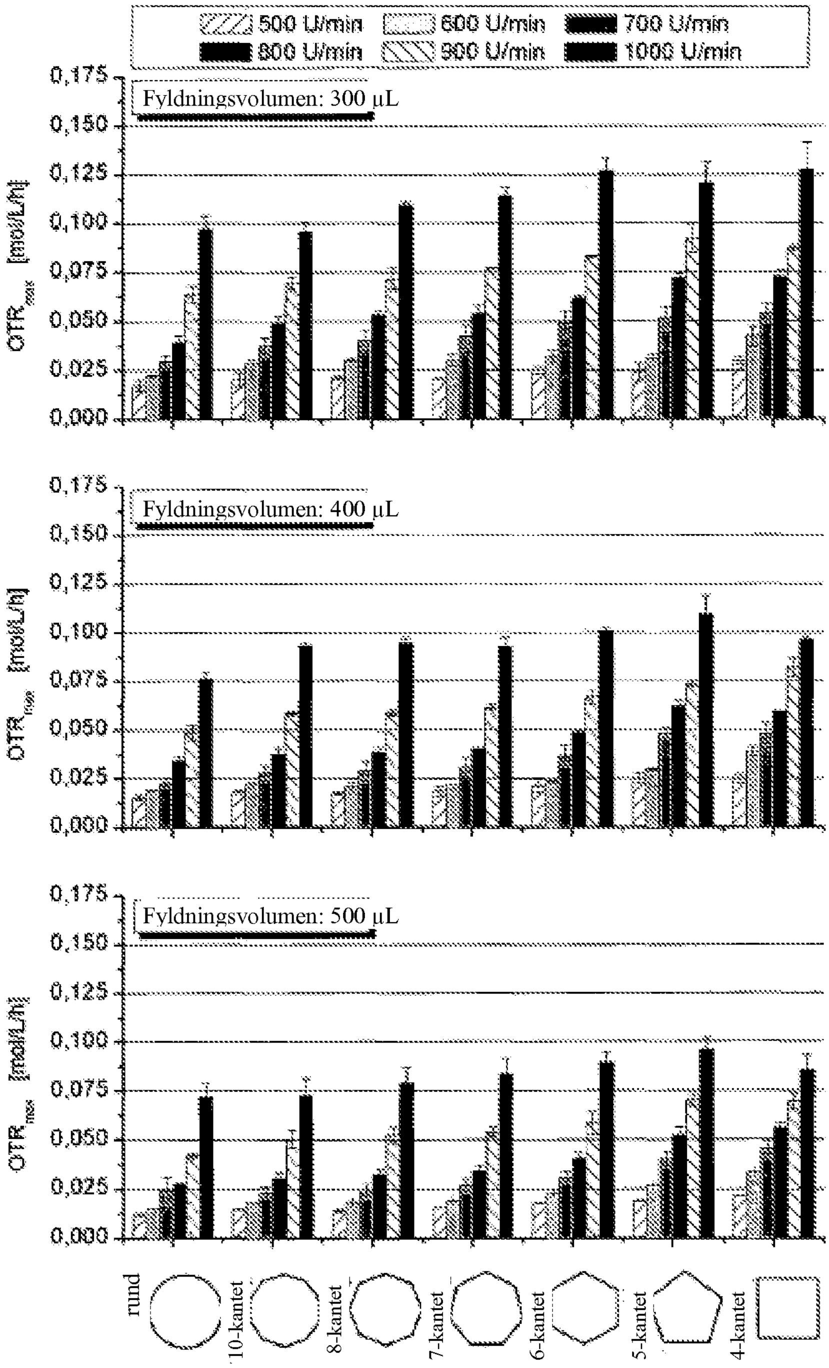

500 U/min
600 U/min
700 U/min
800 U/min
900 U/min
1000 U/min
Fyldningsvolumen: 300 µL
Fyldningsvolumen: 400 µL
Fyldningsvolumen: 500 µL
OTRmax [mol/L/h]
0,000
0,025
0,050
0,075
0,100
0,125
0,150
0,175
rund
10-kantet
8-kantet
7-kantet
6-kantet
5-kantet
4-kantet

FIG. 15

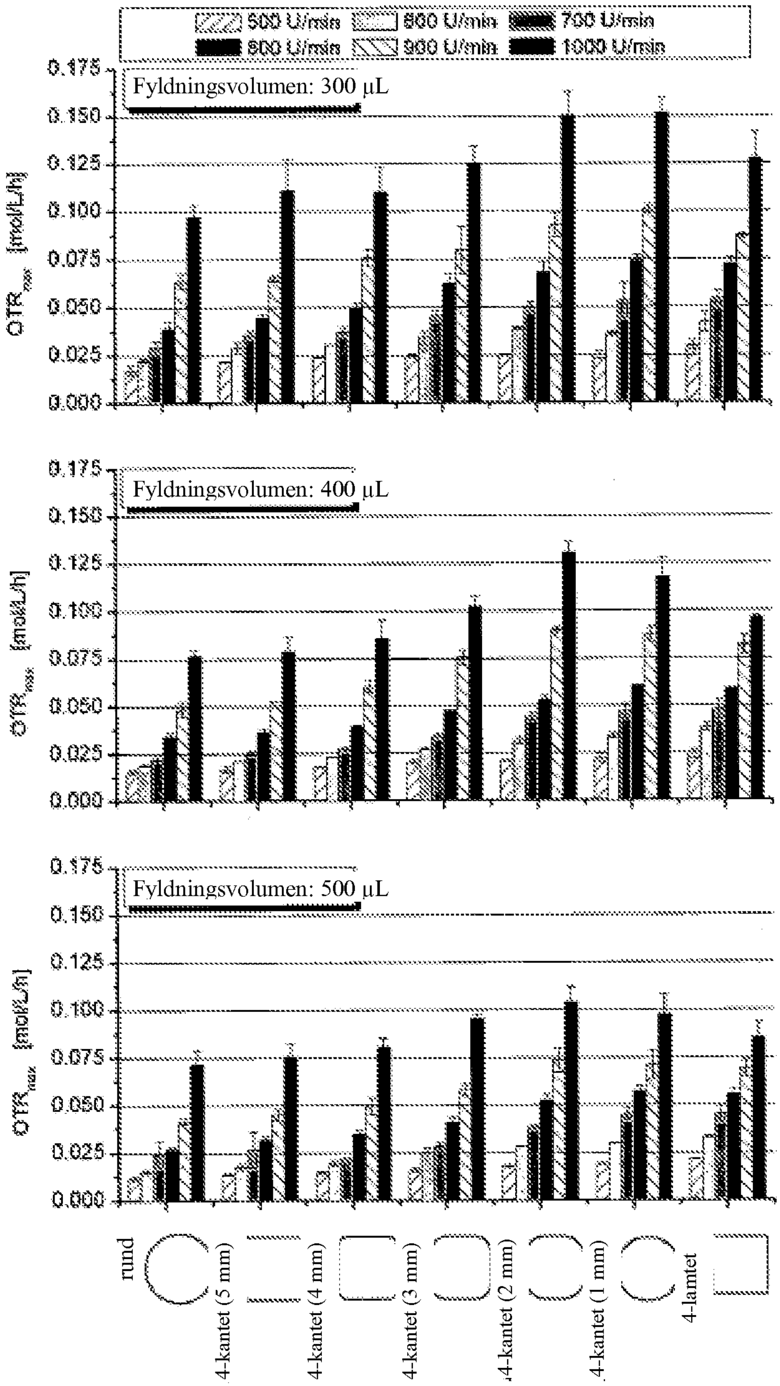

500 U/min
600 U/min
700 U/min
800 U/min
900 U/min
1000 U/min
Fyldningsvolumen: 300 µL
Fyldningsvolumen: 400 µL
Fyldningsvolumen: 500 µL
OTR max [mol/L/h]
0.175
0.150
0.125
0.100
0.075
0.050
0.025
0.000
rund
4-kantet (5 mm)
4-kantet (4 mm)
4-kantet (3 mm)
4-kantet (2 mm)
4-kantet (1 mm)
4-lamtet

FIG. 16

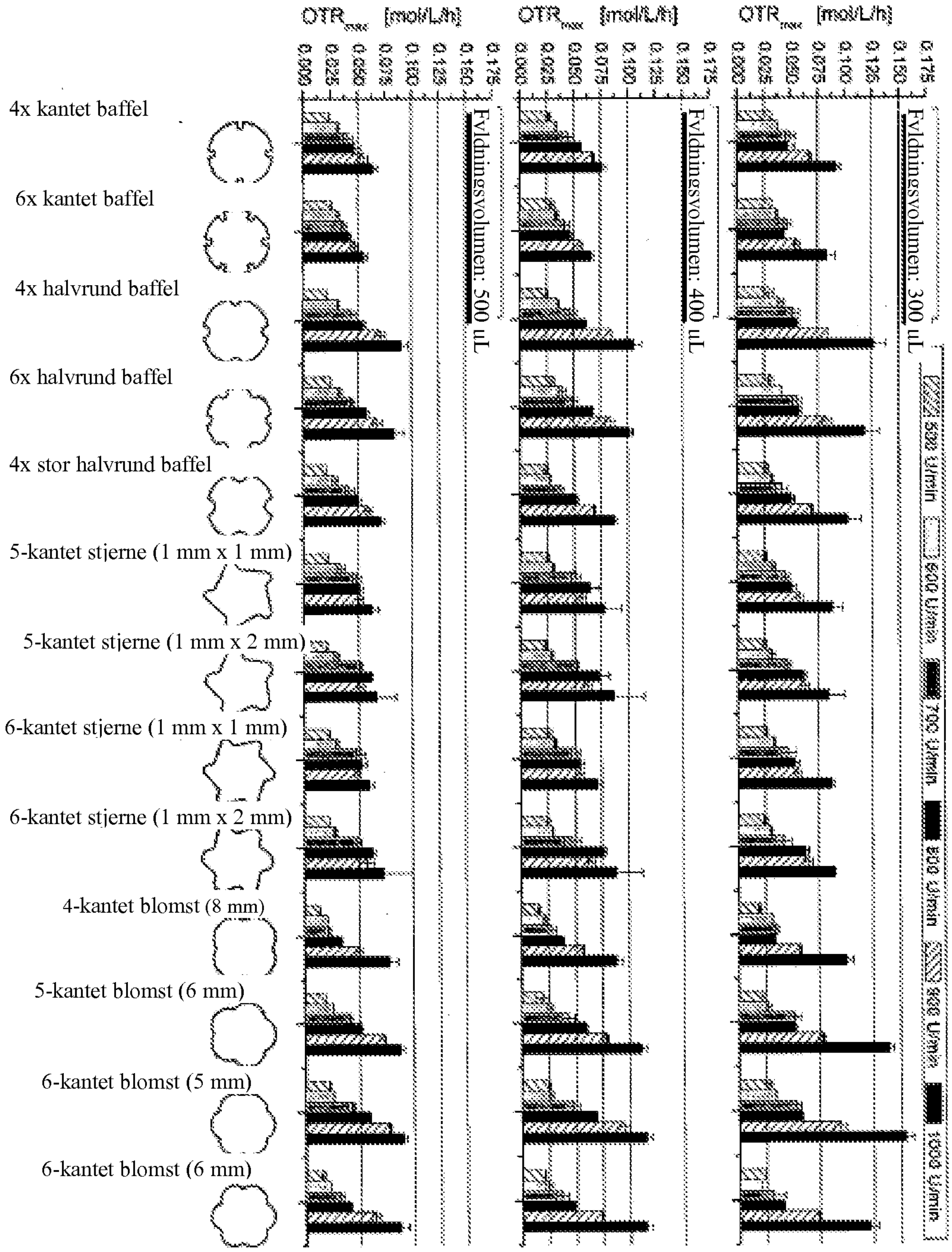

4x kantet baffel
6x kantet baffel
4x halvrund baffel
6x halvrund baffel
4x stor halvrund baffel
5-kantet stjerne (1 mm x 1 mm)
5-kantet stjerne (1 mm x 2 mm)
6-kantet stjerne (1 mm x 1 mm)
6-kantet stjerne (1 mm x 2 mm)
4-kantet blomst (8 mm)
5-kantet blomst (6 mm)
6-kantet blomst (5 mm)
6-kantet blomst (6 mm)
OTR max [mol/L/h]
Fyldningsvolumen: 500 uL
Fyldningsvolumen: 400 uL
Fyldningsvolumen: 300 uL
500 U/min
600 U/min
700 U/min
800 U/min
900 U/min
1000 U/min

FIG. 17

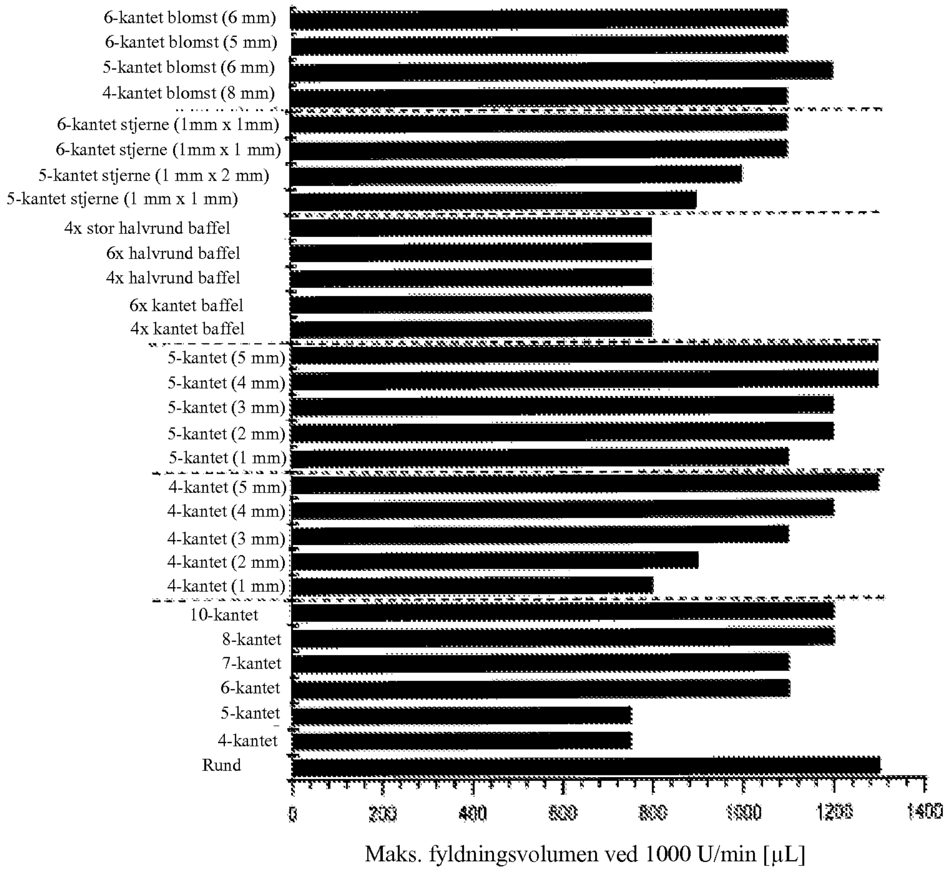
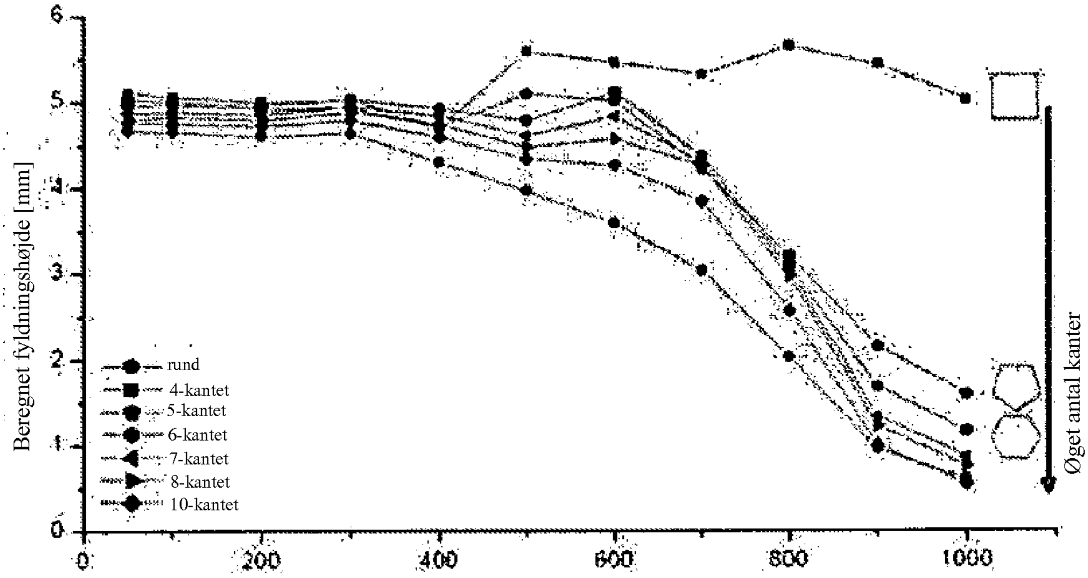
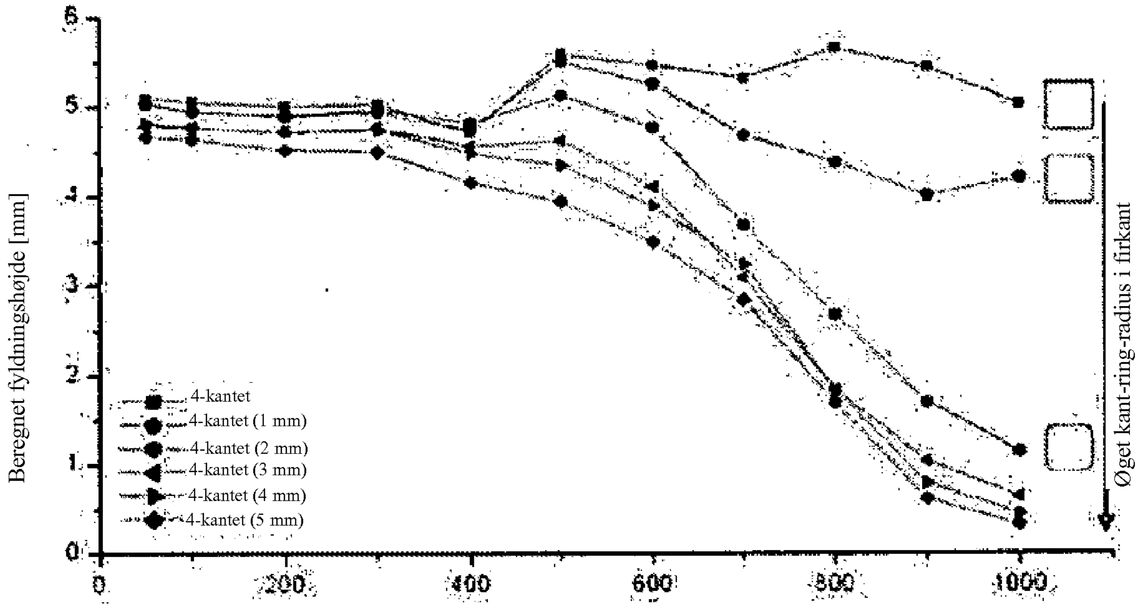
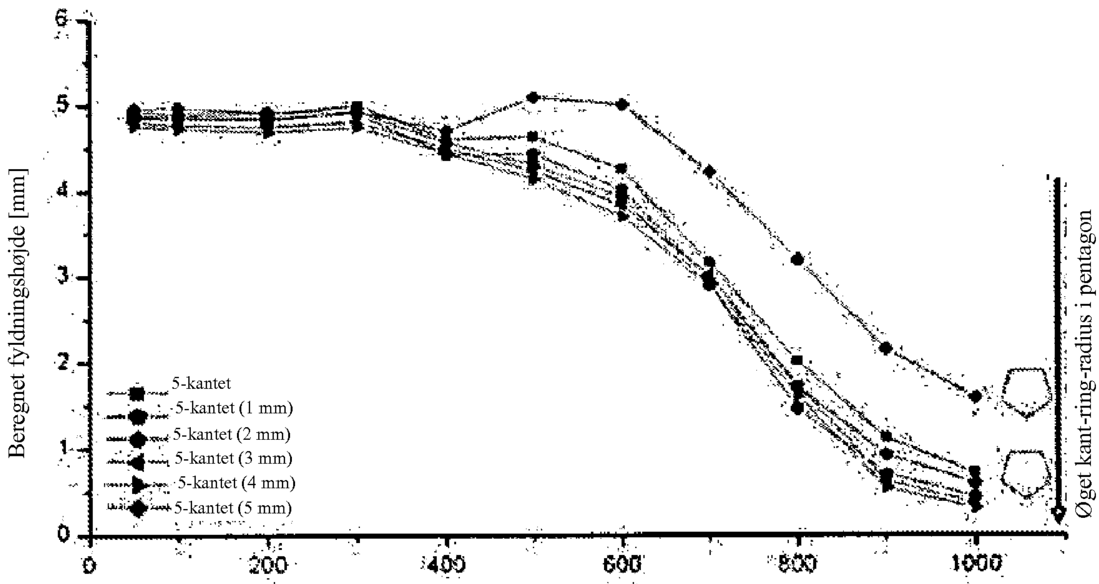

6-kantet blomst (6 mm)
6-kantet blomst (5 mm)
5-kantet blomst (6 mm)
4-kantet blomst (8 mm)
6-kantet stjerne (1mm x 1mm)
6-kantet stjerne (1mm x 1 mm)
5-kantet stjerne (1 mm x 2 mm)
5-kantet stjerne (1 mm x 1 mm)
4x stor halvrund baffel
6x halvrund baffel
4x halvrund baffel
6x kantet baffel
4x kantet baffel
5-kantet (5 mm)
5-kantet (4 mm)
5-kantet (3 mm)
5-kantet (2 mm)
5-kantet (1 mm)
4-kantet (5 mm)
4-kantet (4 mm)
4-kantet (3 mm)
4-kantet (2 mm)
4-kantet (1 mm)
10-kantet
8-kantet
7-kantet
6-kantet
5-kantet
4-kantet
Rund
0
200
400
600
800
1000
1200
1400
Maks. fyldningsvolumen ved 1000 U/min [µL]

FIG. 18


Beregnet fyldningshøjde [mm]
rund
4-kantet
5-kantet
6-kantet
7-kantet
8-kantet
10-kantet
Øget antal kanter
0
1
2
3
4
5
6
200
400
600
800
1000


Beregnet fyldningshøjde [mm]
4-kantet
4-kantet (1 mm)
4-kantet (2 mm)
4-kantet (3 mm)
4-kantet (4 mm)
4-kantet (5 mm)
Øget kant-ring-radius i firkant
0
1
2
3
4
5
6
200
400
600
800
1000


Beregnet fyldningshøjde [mm]
5-kantet
5-kantet (1 mm)
5-kantet (2 mm)
5-kantet (3 mm)
5-kantet (4 mm)
5-kantet (5 mm)
Øget kant-ring-radius i pentagon
0
1
2
3
4
5
6
200
400
600
800
1000

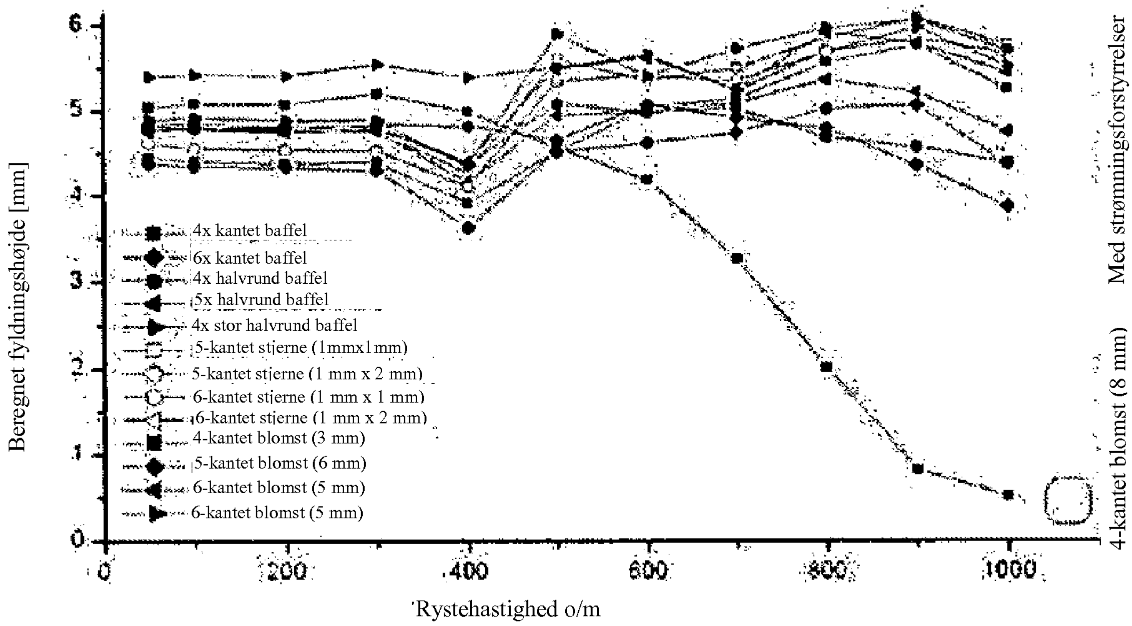

Beregnet fyldningshøjde [mm]
Rystehastighed o/m
4x kantet baffel
6x kantet baffel
4x halvrund baffel
5x halvrund baffel
4x stor halvrund baffel
5-kantet stjerne (1mmx1mm)
5-kantet stjerne (1 mm x 2 mm)
6-kantet stjerne (1 mm x 1 mm)
6-kantet stjerne (1 mm x 2 mm)
4-kantet blomst (3 mm)
5-kantet blomst (6 mm)
6-kantet blomst (5 mm)
6-kantet blomst (5 mm)
Med strømningsforstyrrelser
4-kantet blomst (8 mm)
0
1
2
3
4
5
6
0
200
400
600
800
1000

FIG. 19