

scale filtration process is installed using only small amounts and volumes of the solution and the samples. This is especially important if the components are proteins or the like which are sensitive of damages due to shear forces and other forces existing in large-scale devices. For example biotechnologically produced proteins which have to be concentrated in a solution are extremely costly and on the other side extremely sensitive of damages due to the forces which arises in industrial scale process devices. Therefore, the risk to concentrate such proteins in a solution in industrial scale devices is high. Further, these proteins are often not available in a larger amount.

So, there is a strong demand in the industrial process development for a flow filtration device being able to concentrate a component of a solution preferably by the factor of more than 10 and using a start volume that is at most 20 ml.

Various embodiments seek to provide an optimized TFF-system being able to handle a start volume of a solution of at most 20 ml, preferably at most 10 ml, and to concentrate the components of the solution. The resulting volume of the concentrated solution at the end of the concentration process should preferably be at most 2 ml, particularly preferably at most 1 ml, particularly preferably at most 100 µl. The filtration process should be fast and economical, repeatable and accurate.

The problem is solved with a micro fluidic flow filtration system for increasing the concentration of components contained in a fluid sample with the features as disclosed herein. The problem is also solved with an integrated microfluidic element as disclosed herein.

According to a first aspect, there is provided a microfluidic flow filtration system for increasing the concentration of components contained in a fluid sample having a fluid circuitry-(1),

the fluid circuitry ~~(1)~~ comprising the following elements:

- a tangential flow filtration element ~~(7)~~ having a feed inlet-~~(12)~~, a retentate outlet-~~(13)~~, a permeate outlet ~~(14)~~ and a membrane ~~(15)~~ capable for separating the fluid sample into a retentate stream and a permeate stream upon passage of the fluid sample into the tangential flow filtration element ~~(7)~~ through the feed inlet-~~(12)~~,
- an element for pumping for creating and driving a fluid flow of the fluid sample through the fluid circuitry-~~(1)~~ and the tangential flow filtration element ~~(7)~~,
- at least two elements for obtaining information about the properties of the fluid sample within the fluid circuitry-(1); and

a plurality of conduits (24) connecting the elements to the fluid circuitry (4) through which a fluid stream of the fluid sample is conducted;

wherein

- a minimal working volume of the circuitry (4) being defined by the minimal fluid volume retained in the elements and the conduits (24), such that the fluid can be recirculated in the circuitry (4) without pumping air through the circuitry (4),
- the minimal working volume of the circuitry (4) is at most 5 ml,
- the functionality of at least two elements of the group of elements of the circuitry (4) is integrated in an integrated microfluidic device (20),
- the one integrated microfluidic element (20) defines a volume element having a volume which is at most one fourth of the minimal working volume of the fluid circuitry (4),
- the integrated microfluidic element integrates the functionality of at least two elements for obtaining information about the properties of the fluid sample, and
- one element for obtaining information about the properties is an optical measuring element for determining the concentration of the components contained in the fluid sample and provides the functionality of a cuvette or a capillary channel element for determining the concentration, and
- one element for obtaining information about the properties is a measuring element for determining the viscosity of the fluid sample and provides the functionality of at least two pressure sensor for determining the viscosity.

According to a second aspect, there is provided integrated microfluidic element (20) for a microfluidic flow filtration system for increasing the concentration of components contained in a fluid sample with a fluid circuitry (4) having a minimal working volume of at most 5 ml, preferably for a system (100) according to the first aspect

characterized in that wherein the integrated microfluidic element (20)

defines a volume element having a volume which is at most one fourth of the minimal working volume of the fluid circuitry of the micro flow filtration system, and

provides the functionality of at least two elements of the group of elements of the fluid circuitry (4),

wherein

the group of elements comprises a tangential flow filtration element (7), an element for pumping suitable for creating and driving a fluid flow and at least two elements for obtaining information about the properties of the fluid sample within the circuitry,

wherein the integrated microfluidic element provides the functionality of at least two elements for obtaining information about the properties of the fluid sample,

wherein

one element for obtaining information about the properties of the fluid sample within the circuitry that is an optical measuring element for obtaining information about the concentration of the components contained in the fluid sample, the optical measurement element is a transparent cuvette, and

one element for determining the physical properties of the fluid sample is an element for determining the viscosity of the fluid sample and is a pressure sensor.

The micro flow filtration system according to the disclosure for increasing the concentration of components contained in a fluid sample has a fluid circuitry in form of a loop in which the fluid sample or solution is recirculated. The fluid circuitry comprises a tangential flow filtration element (TFF-element), an element for pumping which is suitable for increasing and driving a fluid flow of the fluid sample through the fluid circuitry and through the tangential flow filtration

element, at least one element for obtaining information about the properties of the fluid sample within the circuitry, and a plurality of conduits connecting the elements to the fluid circuitry through which the fluid stream of the fluid sample is conducted. Optionally, the fluid circuitry comprises also a regulator element for regulation the pressure and/ or the flow in the circuitry.

The fluid circuitry has a minimal working volume which is also called minimal recirculation volume. This volume is the amount of fluid which has to be retained in the fluid circuitry such that the fluid can be recirculated in the circuitry without pumping air through the circuitry. In other words, the elements of the fluid circuitry and the conduits connecting these elements have to be filled with a fluid in such a manner that a continuous fluid flow in the circuitry can be arranged. The minimal working volume depends on the elements used in the circuitry. For example, if tubings for transporting the fluid are installed in the circuitry, these tubings have also a non-negligible contribution to the minimal working volume. The minimal working volume of the circuitry of the micro fluid filtration system according to the ~~disclosure~~ disclosure is at most 5 ml. Preferably, the minimal working volume of the circuitry is even smaller, e.g. preferably at most 2ml, further preferably at most 1ml, particularly preferably at most 100 μ l.

According to the disclosure the fluid circuitry contains also an integrated microfluidic device in which the functionality of at least two elements of the group of elements of the circuitry is integrated. So, the integrated micro fluidic device is an element or a component of the circuitry in which the function of at least two of the above mentioned elements of the circuitry is implemented. So, instead of the two separate elements, which are substituted, only one integrated micro fluidic element is arranged in the circuitry. Preferably, the integrated microfluidic element is arranged in the retentate circuitry of the fluid circuitry and not in the permeate circuitry. Especially in a concentration mode such positioning of the microfluidic element is advantageous because the functionality of two elements of the circuitry is provided in only one element and the working volume of the system is decreased or reduced.

and

5 - one element for obtaining information about the properties is an optical measuring element for determining the concentration of the components contained in the fluid sample and provides the functionality of a cuvette or a capillary channel element for determining the concentration, and

10 - one element for obtaining information about the properties is a measuring element for determining the viscosity of the fluid sample and provides the functionality of at least two pressure sensor for determining the viscosity.

15 2. Microfluidic flow filtration system according to claim 1, wherein ~~the optical measuring element for determining the concentration is a cuvette and/or the measuring element for determining the viscosity is at least one element for determining pressure preferably in combination with a capillary channel element.~~

3. Microfluidic flow filtration system according to claim 1, wherein ~~the integrated microfluidic element provides the functionality~~

 - ~~of a the cuvette or a the capillary channel element for determining the concentration, preferably in form of is a transparent capillary, and,~~

~~—of at least one pressure sensor, preferably of at least two pressure
sensors, for determining the viscosity.~~

- 5 4. Microfluidic flow filtration system according to claim 1, wherein the integrated microfluidic element provides the functionality of at least one element for determining pressure, preferably a pressure sensor, and the tangential flow filtration element.
- 10 5. Microfluidic flow filtration system according to any of the preceding claims, wherein the integrated microfluidic element having a housing and the tangential flow filtration element having a TFF-housing which is part of the housing of the microfluidic element,

the one element for obtaining information about the properties of the fluid sample within the circuitry that is an optical measuring element for obtaining information about the concentration of the components contained in the fluid sample, the optical measurement element is a transparent cuvette, and or an

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one element for determining the physical properties of the fluid sample is an element for determining the viscosity of the fluid sample and is a pressure sensor.

~~12. Integrated microfluidic element according to the preceding claim wherein the at least two elements for obtaining information about the properties of the fluid sample within the circuitry are~~

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~~—an optical measuring element for obtaining information about the concentration of the components contained in the fluid sample and~~

~~—an element for determining the physical properties of the fluid sample, preferably for determining the viscosity of the fluid sample.~~

5 ~~13. Integrated microfluidic element according to claims 11 or 12, wherein the optical measurement element is a transparent cuvette and the two elements for obtaining information about the properties of the fluid sample are preferably pressure sensors.~~

10 ~~14.12.~~ Integrated microfluidic element according to claims 11 to ~~13~~ wherein it comprises the functionality of the tangential flow filtration element and of two elements for obtaining information about the properties of the fluid sample, which are preferably pressure sensors, and preferably but not mandatory in addition the functionality of the pressure regulator element.

15 ~~15.13.~~ Integrated microfluidic element according to claims 11 to ~~14.12~~ wherein it comprises the functionality of a capillary or capillary channel and of two elements for obtaining information about the properties of the fluid sample, which are preferably pressure sensors.

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