

Patent Claims

1. A system for performing cell culture comprising a bioreactor, a holding tank, a device for producing liquid media for cell cultures and a control system connected to the bioreactor, the holding tank and the device for producing liquid media for cell cultures, whereby the liquid media are produced by dissolving ingredients in water, the device for producing liquid media for cell cultures comprising
- 5 a mixing vessel for holding and mixing a watery formulation;
an agitator for mixing the watery formulation in the mixing vessel;
10 at least one pH meter in the mixing vessel or in fluid connection with the mixing vessel;
- a dosing apparatus connected to the mixing vessel for filling a specific amount of at least one solid ingredient or of at least one mixture of solid ingredients into the mixing vessel;
- 15 a water supply for adding water into the mixing vessel;
a base supply for adding a specific amount of a base or a watery base to the mixing vessel;
- 20 an acid supply for adding a specific amount of an acid or a watery acid to the mixing vessel;
a flow generating apparatus for generating or allowing a flow of the watery formulation from the mixing vessel;
- 25 the control system being connected to the pH meter, such that the measured values of the pH meter are accessible by the control system, the control system being connected to the water supply to control the amount of water being filled into the mixing vessel, the control system being connected to the base supply to control the amount of base or watery base being filled into the mixing vessel, the control system being
- 30 connected to the acid supply to control the amount of acid or watery acid being filled into the mixing vessel, the control system being connected to

- the dosing apparatus to control the amount of the at least one ingredient or the at least one mixture of ingredients being filled into the mixing vessel, whereby the control system is programmed to control the dosing apparatus, the water supply, the base supply, the acid supply, and preferably the flow generating apparatus, depending from the measured values of at least one of the pH meter and whereby the bioreactor and the mixing vessel of the device for producing liquid media for cell cultures are connected via at least a pipeline or tube which is interrupted by at least one holding tank.
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2. A system for performing cell culture according to claim 1 characterized in that at least one sterile filter is arranged in said pipeline or tube.
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3. A system for performing cell culture according to claim 1 or claim 2 characterized in that the system comprises a signal receiving unit which is able to receive a signal from the bioreactor, and the control system is programmed to control the flow of the watery formulation in response to the signal received from the bioreactor via the signal receiving unit.
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4. A system for performing cell culture according to one or more of claims 1 to 3, characterized in that the bioreactor comprises a controller and a signal sending unit which sends a signal to the signal receiving unit if the amount of watery formulation drops below a certain value or fresh watery formulation is needed.
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5. A system for performing cell culture according to one or more of claims 1 to 4, characterized in that the holding tank comprises a controller and a signal sending unit which sends a signal to the signal receiving unit if the amount of watery formulation drops below a certain value or fresh watery formulation is needed and the control system is programmed to control the production of the watery formulation in response to the signal received from the holding tank via the signal receiving unit.
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6. A system for performing cell culture according to one or more of claims 1 to 5, characterized in that the bioreactor is operated in perfusion mode.
- 5 7. A system according to one or more of claims 1 to 6 comprising at least one dissolution sensor for detecting the presence of undissolved ingredients in the watery formulation, whereby the control system is connected to the at least one dissolution sensor, such that the measured values of the at least one dissolution sensor are accessible by the control system.
- 10 8. A system according to one or more of claims 1 to 7 the device comprising at least one sensor for measuring the electrical conductivity of the watery formulation, whereby the at least one sensor for measuring the electrical conductivity of the watery formulation is located in the mixing vessel
- 15 and/or in a pipe for conducting the flow from the mixing vessel, whereby the control system is connected to the at least one sensor for measuring the electrical conductivity of the watery formulation, such that the measured values of the at least one sensor for measuring the electrical conductivity of the watery formulation are accessible by the control
- 20 system and the control system being designed to control at least the flow generating apparatus depending from the measured values of the at least one sensor for measuring the electrical conductivity of the watery formulation, and/or
- 25 a sensor for measuring the osmolarity of the watery formulation, whereby the sensor for measuring the osmolarity of the watery formulation is located in the mixing vessel and/or in a pipe for conducting the flow from the mixing vessel, whereby the control system being connected to the sensor for measuring the osmolarity of the watery formulation, such that the measured values of the sensor for measuring the osmolarity of the
- 30 watery formulation are accessible by the control system and the control system being designed to control at least the flow generating apparatus

depending from the measured values of the sensor for measuring the osmolarity of the watery formulation and/or

5 a sensor for level indication of the watery formulation inside the mixing vessel, whereby the control system being connected to the sensor for level indication, such that the measured values of the sensor for level indication are accessible by the control system and the control system being designed to control at least the flow generating apparatus depending from the measured values of the sensor for level indication and/or

10 a volume sensor and/or a liquid level sensor to measure the volume of watery formulation in the mixing vessel, whereby the control system being connected to the volume sensor and/or the liquid level sensor to control the amount of watery formulation in the mixing vessel and being programmed to fill water and/or the at least one ingredient or the at least

15 one mixture of ingredients into the mixing vessel depending from the measured value of the volume sensor and/or the liquid level sensor and/or at least one weight sensor to measure the weight of content in the mixing vessel and/or the amount of the at least one ingredient or of the at least one mixture of ingredients to be filled into the mixing vessel by the dosing

20 apparatus, whereby the control system being connected to the at least one weight sensor to control the amount of watery formulation in the mixing vessel and being programmed to fill water and/or the at least one ingredient or the at least one mixture of ingredients into the mixing vessel depending from the

25 measured value of the at least one weight sensor and/or the control system being connected to the at least one weight sensor to control the weight of the at least one ingredient or of the at least one mixture of ingredients to be filled into the mixing vessel by the dosing apparatus and being programmed to fill water and/or additional of the at least one

30 ingredient or the at least one mixture of ingredients into the mixing vessel depending from the weight measured by the at least one weight sensor,.

- 5 9. A system according to one or more of claims 1 to 8, whereby the flow generating apparatus is or comprises a pumping device for pumping the formulation from the mixing vessel to the holding tank and/or from the holding tank into the bioreactor and thereby generating the flow of the formulation from the mixing vessel and/or the flow generating apparatus is or comprises a controllable valve for controlling the flow of the formulation from the mixing vessel to the holding tank and/or from the holding tank into the bioreactor, whereby preferably the flow of the formulation is driven by gravity and/or the pumping device.
- 10 10. A system according to one or more of claims 1 to 9, whereby the control system comprises one or more of the following programming:
- 15 - the control system is programmed to control the agitator depending from the measured values of at least one of the pH meter and/or, if present, of the dissolution sensor, and/or of the at least one sensor for measuring the electrical conductivity of the watery formulation and/or of the sensor for measuring the osmolarity of the watery formulation and/or a time information given by the timing element;
- 20 - the control system is programmed to produce at least two different types of liquid media for the growth of at least two different cell cultures or different process phases of the same cell culture process;
- 25 - the control system is programmed to start the production of a new batch of liquid media triggered via a signal or a request to the control system via at least one interface.
- 30 11. A system according to any one of claims 1 to 10, whereby all pipes and containers coming in contact with the watery formulation of the system are single-use parts.

12. A system according to one or more of claims 1 to 11, whereby the flow of the watery formulation from the mixing vessel generated or allowed by the flow generating apparatus flows into the holding tank and/or into the bioreactor, whereby the control system is connected to a signal receiving unit, which is able to receive a signal from the bioreactor and/or the holding tank, and the control system is programmed to control the flow of the watery formulation in response to the signal received from the bioreactor and/or the holding tank via the signal receiving unit.

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13. A process for performing cell culture comprising the following method steps:

- Providing a system for performing cell culture comprising a bioreactor, a holding tank and a device for producing liquid media for cell cultures according to one or more of claims 1 to 12
- Performing cell culture in a bioreactor
- Continuously or one or several times during the cell culture performing a process for producing liquid media for cell culture using a device for producing liquid media for cell culture
- Continuously or one or several times during the cell culture flowing watery formulation, which typically is liquid medium for cell culture produced in the device for producing liquid media for cell culture from the mixing vessel of the device to the holding tank and/or from the holding tank to the bioreactor,

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whereby the process for producing liquid media for cell culture comprises the steps of

- A) Filling water and a specific amount of at least one ingredient or at least one mixture of ingredients into the mixing vessel and mixing them therein to a watery formulation;

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- 5 B) Once or repeatedly measuring pH of the watery formulation in the mixing vessel by the at least one pH meter and optionally detecting the presence of undissolved ingredients in the watery formulation in the mixing vessel at least one dissolution sensor by means of the control system;
- C) Automatically filling at least once a specific amount of water, base, watery base, acid, watery acid and/or one or more buffer solutions into the mixing vessel depending on the measured pH value and/or the presence of undissolved ingredients by means of the control system;
- 10 D) After all of the required at least one ingredient or the at least one mixture of ingredients have been filled into the mixing vessel and mixed to a final watery formulation, providing a volume flow of the final watery formulation from the mixing vessel controlled by the control system.
- 15 14. A process according to claim 13, whereby the process for producing media further comprises the method step
- C2) Automatically filling a specific amount of one or more selected from an additional ingredient, an additional mixture of ingredients, water, a base, a watery base, one or more buffer solutions, an acid and a watery acid, into the mixing vessel controlled by the control system before method step D).
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- 25 15. A process for cell culture, comprising a process according to one or more of claims 13 to 14, further comprising culturing cells in a bioreactor with liquid media inlet and a harvest outlet, comprising the method steps of
- i. continuously or one or several times during the cell culture process inserting fresh liquid media from the device into the bioreactor via the liquid media inlet; and
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- ii. continuously or one or several times during the cell culture process removing harvest from the bioreactor via the harvest outlet;
and wherein preferably the process steps i and ii are regulated such that the volume of the cell culture in the bioreactor is kept at a constant level, and
a sensor for measuring the liquid level in the bioreactor automatically sends a signal to the control system if the level of liquid media drops below a predefined value or if harvest is removed from the bioreactor, whereby the control system starts preparation of fresh liquid medium according to a process according to one or more of claims 13 to 14 upon receiving the signal.