supplied from the outside to an interior of the container bag and sprayed onto a foam which has formed on a surface of the liquid phase in the container bag in order to at least partially destroy the foam.

Document [11] describes a container which has flexible walls surrounding a container interior. At least one electrical sensor is installed into the container interior and has at least one or two electrically conductive plates for determining the conductivity or impedance of a medium that surrounds the plates. The plates are connected via connecting lines to a control and regulating unit outside the container interior. The sensor formed from at least two plates may be designed for detection of fluid and/or foam.

Document [12] is directed to systems for liquid level and foam monitoring and regulation in a vessel, such as a bioreactor. The systems use infrared devices, such as cameras and sensors, to detect foaming and automated control of defoaming is performed by using defoaming agents.

It is therefore an object of the present invention to overcome the deficiencies of prior art and to provide a foam destruction device which allows foam destruction or foam control in a method during which foam formation takes place, without the use of anti-foaming additives and dispensing with mechanical means driven by motor, particularly mechanically-electronically or electronically operated components to destroy the foam. The device shall be applicable from laboratory up to industrial scale. Furthermore, it is a further object to provide a process to destroy or control the foaming in a foam-producing method which allows foam destruction or foam control without the use of anti-foaming additives and dispensing with mechanical means driven by motor, particularly mechanically-electronically or electronically operated components to destroy the foam. The process should be feasible on a laboratory or industrial scale.

SUMMARY

Surprisingly, it was found that the disadvantages known from prior art can be overcome by using a tube for foam control or foam destruction, which, by passing compressed fluid through it, performs chaotic and thus uncontrollable movements and thereby at least partially destroys the foam.

The disclosure therefore relates to a foam destruction device for destroying foam and/or controlling the foam height H_F in a reactor in which a foam-generating method is carried out, comprising:

- a reactor which is to be filled or is filled with a liquid medium having a liquid level;
- a flexible tube having a first end, a second end, a selected length L_T and a selected inner and outer diameter;
- a rigid fluid line located above the liquid level of the liquid medium to be filled into the reactor or with which the reactor is filled;
- a fluid connection that is connected to the rigid fluid line;

whereby

- the first end of the tube is attached to the fluid line to allow compressed fluid to pass through the tube;

- the second end of the tube is not fixed but is free to move so as to be able to create a chaotic pattern of movement of the second end of the tube by the compressed fluid flowing through the tube; and
- the length L_T of the tube is chosen such that the second end of the tube comes into contact with the liquid level of the liquid medium to be filled into the reactor or with which the reactor is filled, for the case of the maximum filling volume. Alternatively, the length L_T of the tube is chosen such that the second end of the tube does not come into contact with the liquid level of the liquid medium to be filled into the reactor or with which the reactor is filled.

In one aspect, the present disclosure provides a foam destruction device for destroying foam and/or controlling the foam height H_F in a reactor in which a foam-generating method is carried out, comprising:
- a reactor, which is to be filled or is filled with a liquid medium having a liquid level;
- a flexible tube having a first end, a second end, a selected length L_T and a selected inner and outer diameter;
- a rigid fluid line located above the liquid level of the liquid medium to be filled into the reactor or with which the reactor is filled;
- a fluid connection that is connected to the rigid fluid line;

whereby
- the first end of the tube is attached to the fluid line to allow compressed fluid to pass through the tube;
- the second end of the tube is not fixed but is free to move so as to be able to create a chaotic pattern of movement of the second end of the tube by the compressed fluid flowing through the tube; and
- the length L_T of the tube is chosen such that the second end of the tube comes into contact with the liquid level of the liquid medium to be filled into the reactor or with which the reactor is filled or does not come into contact with the liquid level of the liquid medium to be filled into the reactor or with which the reactor is filled.

Also a subject-matter of the present disclosure is to provide a process for destroying foam and/or controlling the foam height H_F in a reactor in which a foam-generating method is to be carried out, comprising the steps of:
- providing a reactor in which a method is to be carried out in which foaming occurs comprising a liquid medium having a liquid level;
- providing a flexible tube having a first end, a second end, a selected length L_T and a selected inner and outer diameter,

- providing a rigid fluid line that is placed above the liquid level of the liquid medium in the reactor;
- providing a fluid connection that is connected to the rigid fluid line;
- attaching a first end of the tube to the fluid line connected to the gas connection, the second end of the tube not being fixed and remaining free to move;
- allowing the tube to hang loosely downwards from the point of attachment with the fluid line into the reactor, the length L_T of the tube being chosen such that the second end of the tube comes into contact with the liquid level of the liquid medium in the reactor, for the case of the maximum filling volume, or the length L_T of the tube being chosen such that the second end of the tube does not come into contact with the liquid level of the liquid medium;
- as soon as foam forms in the foam-generating method, adjusting the fluid flow through the tube so that the second end of the tube performs a chaotic pattern of movement in the reactor; and
- destroying the formed foam and/or controlling the foam height H_F of the formed foam by contact of the tube with the foam and by the compressed fluid exiting from the tube.

In another aspect, the present disclosure provides a process for destroying foam and/or controlling the foam height H_F in a reactor in which a foam-generating method is to be carried out, comprising the steps of:

- providing a reactor in which a method is to be carried out in which foaming occurs comprising a liquid medium having a liquid level;
- providing a flexible tube having a first end, a second end, a selected length L_T and a selected inner and outer diameter;
- providing a rigid fluid line that is placed above the liquid level of the liquid medium in the reactor;
- providing a fluid connection that is connected to the rigid fluid line;
- attaching a first end of the tube to the fluid line connected to the fluid connection, the second end of the tube not being fixed and remaining free to move;
- allowing the tube to hang loosely downwards from the point of attachment with the fluid line into the reactor, the length L_T of the tube being chosen such that the second end of the tube comes into contact with the liquid level of the liquid medium in the reactor or does not come into contact with the liquid level of the liquid medium;
- as soon as foam forms in the foam-generating method, adjusting the fluid flow through the tube so that the second end of the tube performs a chaotic pattern of movement in the reactor; and
- destroying the formed foam and/or controlling the foam height H_F of the formed foam by contact of the tube with the foam and by the compressed fluid exiting from the tube.

The disclosure is also directed to a method (foam-generating method) for culturing prokaryotic or eukaryotic cells in liquid cell culture in a bioreactor, wherein foam is generated during the method, wherein a foam destroying device according to the present disclosure is used in the bioreactor performing a process for destroying foam and/or controlling the foam height H_F in the reactor according to the present disclosure.

In another aspect, the present disclosure provides a method for culturing prokaryotic or eukaryotic cells in liquid cell culture in a bioreactor, wherein foam is generated during the method, wherein a foam destroying device as described herein is used in the bioreactor performing a process for destroying foam and/or controlling the foam height H_F in the reactor as described herein.

It is also disclosed a method (foam-generating method) for producing a recombinant protein, the method comprising the steps of:

step a) culturing prokaryotic or eukaryotic cells expressing a recombinant protein in cell culture in a bioreactor, wherein foam is generated during culturing of the cells;

step b) harvesting the recombinant protein;

step c) purifying the recombinant protein;

wherein in step (a) a foam destroying device according to the present disclosure is used in the bioreactor performing a process for destroying foam and/or controlling foam height H_F in the reactor according to the present disclosure.

In another aspect, the present disclosure provides a method for producing a recombinant protein, the method comprising the steps of:

step a) culturing prokaryotic or eukaryotic cells expressing a recombinant protein in cell culture in a bioreactor, wherein foam is generated during culturing of the cells;

step b) harvesting the recombinant protein;

step c) purifying the recombinant protein;

wherein in step (a) a foam destroying device as described herein is used in the bioreactor performing a process for destroying foam and/or controlling foam height H_F in the reactor as described herein.

The disclosure is therefore based on the concept of active foam destruction or control, in which a flexible tube fastened to a fluid line at only one end above the liquid level in a reactor and by compressed fluid flowing through it is set in chaotic motion, whereby the chaotic motion of the tube and the compressed fluid flowing out of the tube destroys or controls the foam formed.

According to the disclosure, it is thus possible to destroy or control the foam without the addition of chemical additives, such as anti-foaming agents, or recourse to electronically or mechanically-electronically driven components.

BRIEF DESCRIPTION OF THE DRAWINGS

Embodiments of the prior art and of the present invention will be described by way of example with reference to the accompanying figures, which are schematic and are not intended to be drawn to scale so that no assumption of precise geometric values can be made regarding the original size. The figures of the present disclosure are incorporated in and constitute a part of the specification, also illustrating embodiments of the invention without limitation to the specific embodiments described. The drawings together with the summary and detailed description serve to explain the principles of the present disclosure. The same features are denoted by the same reference signs throughout the figures. In the figures show:

Figure 1a	a schematic three-dimensional representation of an embodiment of a tube used according to the invention;
Figure 1b	a top view of the second end of the tube of Fig. 1a;
Figure 2a, 2b, 2c	schematically illustrate examples of 3 movement patterns of a tube in a reactor by means of a top view of the movement of the second free end of a tube;
Figures 3a and 3b	simplified schematic sectional views of bioreactors with a device for foam destruction and/or control, each comprising one flexible tube according to an embodiment of the invention;
Figure 3c to 3f	simplified schematic sectional views of reactors with a device for foam destruction and/or control, each comprising 2 flexible tubes according to an embodiment of the invention;

Claims

1. A foam destruction device for destroying foam and/or controlling the foam height H_F in a reactor in which a foam-generating method is carried out, comprising:
- a reactor, which is to be filled or is filled with a liquid medium having a liquid level;
- a flexible tube having a first end, a second end, a selected length L_T and a selected inner and outer diameter;
- a rigid fluid line located above the liquid level of the liquid medium to be filled into the reactor or with which the reactor is filled;
- a fluid connection that is connected to the rigid fluid line;

whereby
- the first end of the tube is attached to the fluid line to allow compressed fluid to pass through the tube;
- the second end of the tube is not fixed but is free to move so as to be able to create a chaotic pattern of movement of the second end of the tube by the compressed fluid flowing through the tube; and
- the length L_T of the tube is chosen such that the second end of the tube comes into contact with the liquid level of the liquid medium to be filled into the reactor or with which the reactor is filled or does not come into contact with the liquid level of the liquid medium to be filled into the reactor or with which the reactor is filled.

2. The foam destruction device according to claim 1,
characterized in that
the reactor is selected from a bioreactor or chemical reactor, which is designed for multiple use or single use, in particular a single use bioreactor (SUB).

3. The foam destruction device according to any of the preceding claims 1 or 2,
characterized in that
the attachment point of the first end of the tube to the fluid line is located on the central axis of the reactor in the liquid-free upper part of the reactor.

4. The foam destruction device according to any of the preceding claims 1 to 3,
characterized in that
at least 2 tubes are provided in the reactor and are attached with their respective first end to a respective rigid fluid line.

5. The foam destruction device according to any of the preceding claims 1 to 4,
characterized in that
the reactor further comprises a stirrer having a stirrer rod, a head portion and side walls, whereby
- a stirrer is driven from below, a single tube is provided, in particular installed centrally, offset from the centre or installed in a sidewall of the reactor; or

- a stirrer is driven from below, at least two tubes are installed in the head portion but not the side walls of the reactor, in particular the at least two tubes are spaced apart from each other in the head portion and the lengths L_T of the at least two tubes are selected in such a manner that the tubes do not contact each other during their chaotic movement and do not contact the side walls; or
- a stirrer is driven from below, at least 2 tubes are installed in the side walls, in particular opposite one another in the reactor whereby the lengths L_T of the at least two tubes are selected in such a manner that the tubes do not contact each other during their chaotic movement; or
- a stirrer is driven from above, at least 2 tubes are installed in the side walls, in particular opposite one another in the reactor whereby the lengths L_T of the at least two tubes are selected in such a manner that the tubes do not contact each other during their chaotic movement and do not contact the stirrer rod; or
- a stirrer is driven from above, at least 2 tubes are installed in the head portion but not the side walls of the reactor, in particular the at least two tubes are spaced apart from each other in the head portion and the lengths L_T of the at least two tubes are selected in such a manner that the tubes do not contact each other during their chaotic movement, do not contact the stirrer rod and the side walls.

6. The foam destruction device according to any of the preceding claims 1 to 5,
characterized in that
at least one, two, three or more of the following features are present in the foam destruction device:
- the reactor is designed for laboratory scale or industrial scale;
- the compressed fluid is selected from a gas of the group consisting of air, oxygen, or an inert gas, in particular nitrogen, or noble gas;
- the compressed fluid is selected from a liquid of the group consisting of water, organic solvent(s), the liquid medium used in the reactor or mixtures thereof;
- the material of the tube is selected from the group consisting of silicone, polyvinyl chloride (PVC), rubber, in particular natural rubber, synthetic rubber, in particular vulcanised rubber (rubber), acrylonitrile butadiene rubber (NBR), acrylonitrile butadiene rubber (NBR) with ethylene propylene diene rubber (EPDM), chlorobutadiene rubber (CR neoprene), Teflon, polyether ether ketone (PEEK), polyethylene (PE) and/or polyamide;
- for each tube in the reactor a rigid fluid line is provided;
- the length L_T of the tube being chosen such that the second end of the tube does not come into contact with the liquid medium in the reactor but can come into contact with the foam formed on the liquid medium;
- if the second end of the tube does not come into contact with the liquid medium in the reactor, the selected length L_T of the tube determines the minimum distance ΔL between the second end of the tube and the liquid level in the reactor and thus the maximum foam height $H_{F(max)}$ in the foam-generating method;
- when 2 tubes are provided, the two attachment points of the two tubes to the two rigid fluid lines are provided at the same height and at a distance from each other which is equal to or greater than the sum of the lengths of the two tubes, in particular corresponding to the diameter of the reactor;

- if more than 2 tubes are provided, they are distributed in the liquid-free upper part of the reactor in such a way that they do not contact each other when the chaotic movement pattern is executed.

7. The foam destruction device according to any of the preceding claims 1 to 6,
characterized in that
a force ratio of the momentum force F_I to the weight force F_G is chosen so that the following formula (3) applies:

$$F_I / F_G < 10 \qquad (3)$$

or $F_I / F_G < 5$ or $F_I / F_G < 4$ or $F_I / F_G < 3$ or $F_I / F_G < 2$, especially $F_I / F_G < 1$,

wherein the following formula (1) applies to the momentum force:

$$F_I = \rho * u^2 * A \qquad (1),$$

wherein

F_I	momentum force in [N]
ρ (rho)	density of the tube material in [kg m^{-3}]
u	gas exit velocity in [m s^{-1}]
A	cross section of the tube in [m^2]

and the following formula (2) applies to the weight force:

$$F_G = \rho * \pi/4*(d_2^2 - d_1^2) * g \qquad (2)$$

wherein

F_G	weight force in [N]
ρ (rho)	density of the tube material in [kg m^{-3}]
π	circle number or Archimedes' constant (pi)
d_2	outer diameter (OD) of the tube in [m]
d_1	inner diameter (ID) of the tube in [m]
g	acceleration due to gravity in [m s^{-2}].

8. A process for destroying foam and/or controlling the foam height H_F in a reactor in which a foam-generating method is to be carried out, comprising the steps of:
- providing a reactor in which a method is to be carried out in which foaming occurs comprising a liquid medium having a liquid level;
- providing a flexible tube having a first end, a second end, a selected length L_T and a selected inner and outer diameter;
- providing a rigid fluid line that is placed above the liquid level of the liquid medium in the reactor;
- providing a fluid connection that is connected to the rigid fluid line;
- attaching a first end of the tube to the fluid line connected to the fluid connection, the second end of the tube not being fixed and remaining free to move;

- allowing the tube to hang loosely downwards from the point of attachment with the fluid line into the reactor, the length L_T of the tube being chosen such that the second end of the tube comes into contact with the liquid level of the liquid medium in the reactor or does not come into contact with the liquid level of the liquid medium;
- as soon as foam forms in the foam-generating method, adjusting the fluid flow through the tube so that the second end of the tube performs a chaotic pattern of movement in the reactor; and
- destroying the formed foam and/or controlling the foam height H_F of the formed foam by contact of the tube with the foam and by the compressed fluid exiting from the tube.

9. The process according to claim 8,
characterized in that
the reactor is selected from a bioreactor or chemical reactor, which is designed for multiple use or single use, in particular a single use bioreactor (SUB).

10. The process according to any of the preceding claims 8 or 9,
characterized in that
the attachment point of the first end of the tube to the fluid line is arranged on the central axis of the reactor in the liquid-free upper part of the reactor.

11. The process according to any of the preceding claims 8 to 10,
characterized in that
at least 2 tubes are provided in the reactor and are attached with their respective first end to a respective rigid fluid line.

12. The process according to any of the preceding claims 8 to 11,
characterized in that
the reactor further comprises a stirrer having a stirrer rod, a head portion and side walls, whereby
- a stirrer driven from below is used, a single tube is provided, in particular installed centrally, offset from the centre or installed in a sidewall of the reactor; or
- a stirrer driven from below is used, at least two tubes are installed in the head portion but not the side walls of the reactor, in particular the at least two tubes are spaced apart from each other in the head portion and the lengths L_T of the at least two tubes are selected in such a manner that the tubes do not contact each other during their chaotic movement and do not contact the side walls; or
- a stirrer driven from below is used, at least 2 tubes are installed in the side walls, in particular opposite one another in the reactor whereby the lengths L_T of the at least two tubes are selected in such a manner that the tubes do not contact each other during their chaotic movement; or
- a stirrer driven from above is used, at least 2 tubes are installed in the side walls, in particular opposite one another in the reactor whereby the lengths L_T of the at least two tubes are selected in such a manner that the tubes do not contact each other during their chaotic movement and do not contact the stirrer rod; or

- a stirrer driven from above is used, at least 2 tubes are installed in the head portion but not the side walls of the reactor, in particular the at least two tubes are spaced apart from each other in the head portion and the lengths L_T of the at least two tubes are selected in such a manner that the tubes do not contact each other during their chaotic movement, do not contact the stirrer rod and the side walls.

13. The process according to any of the preceding claims 8 to 12,
characterized in that
at least one, two, three or more of the following features are selected for the method:
- the reactor is designed for laboratory scale or industrial scale;
- the compressed fluid is selected from a gas of the group consisting of air, oxygen, or an inert gas, in particular nitrogen or inert gas;
- the compressed fluid is selected from a liquid of the group consisting of water, organic solvent(s), the liquid medium used in the reactor or mixtures thereof;
- the length L_T of the tube being chosen such that the second end of the tube does not come into contact with the liquid medium in the reactor but can come into contact with the foam formed on the liquid medium;
- if the second end of the tube does not come into contact with the liquid medium in the reactor, the length L_T of the tube is selected to determine the minimum distance ΔL between the second end of the tube and the liquid level in the reactor and thus the maximum foam height $H_{F(max)}$ in the foam-generating method;
- the material of the tube is selected from the group consisting of silicone, polyvinyl chloride (PVC), rubber, in particular natural rubber, synthetic rubber, in particular vulcanised rubber (rubber), acrylonitrile butadiene rubber (NBR), acrylonitrile butadiene rubber (NBR) with ethylene propylene diene rubber (EPDM), chlorobutadiene rubber (CR neoprene), Teflon, polyether ether ketone (PEEK), polyethylene (PE) and/or polyamide;
- a rigid fluid line is provided for each tube in the reactor;
- when two tubes are provided, the two attachment points of the two tubes to the two rigid fluid lines are provided at the same height and at a distance from each other chosen to be equal to or greater than the sum of the lengths of the two tubes, in particular corresponding to the diameter of the reactor;
- if more than 2 tubes are provided, they are distributed in the liquid-free part of the reactor in such a way that they do not contact each other when the chaotic movement pattern is executed.

14. The process according to any of the preceding claims 8 to 13,
characterized in that
a force ratio momentum force F_I to weight force F_G is chosen so that the following formula (3) applies:

$$F_I / F_G < 10 \qquad (3)$$

or $F_I / F_G < 5$ or $F_I / F_G < 4$ or $F_I / F_G < 3$ or $F_I / F_G < 2$, especially $F_I / F_G < 1$,

wherein the following formula (1) applies to the momentum force:

$$F_I = \rho * u^2 * A \qquad (1),$$

whereby

F_I	momentum force in [N]
ρ (rho)	density of the tube in [kg m^{-3}]
u	gas exit velocity in [m s^{-1}]
A	cross section of the tube in [m^2]

and the following formula (2) applies to the weight force:

$$F_G = \rho * \pi/4*(d_2^2 - d_1^2) * g \qquad (2)$$

whereby

F_G	weight force in [N]
ρ (rho)	density of the tube material in [kg m^{-3}]
π	circle number or Archimedes' constant (pi)
d_2	outer diameter (OD) of the tube in [m]
d_1	inner diameter (ID) of the tube in [m]
g	acceleration due to gravity in [m s^{-2}].

15. A method for culturing prokaryotic or eukaryotic cells in liquid cell culture in a bioreactor, wherein foam is generated during the method, wherein a foam destroying device according to any one of claims 1 to 7 is used in the bioreactor performing a process for destroying foam and/or controlling the foam height H_F in the reactor according to any one of claims 8 to 14.

16. A method for producing a recombinant protein, the method comprising the steps of:

step a) culturing prokaryotic or eukaryotic cells expressing a recombinant protein in cell culture in a bioreactor, wherein foam is generated during culturing of the cells;

step b) harvesting the recombinant protein;

step c) purifying the recombinant protein;

wherein in step (a) a foam destroying device according to any one of claims 1 to 7 is used in the bioreactor performing a process for destroying foam and/or controlling foam height H_F in the reactor according to any one of claims 8 to 14.