needed. It is mentioned that multiple spargers may be used in some cases. However, the document is silent on specific geometric arragements of those. The different spargers 47 or 301 as described are according to figure 1 located at the same height at the bottom of the reactor, yet without a specific teaching related to the physico-chemical impact thereof.

The possible position, design and size of a sparger in relation to a stirrer is evaluated and discussed in Sardeing et al.: “Gas-liquid mass transfer”, Chemical Engineering Research and Design, Elsevier, Amsterdam, NL, Vol. 82, No. 9, 2004, pp. 1161-1168; Birch et al.: “The Influence of Sparger Design and Location on Gas Dispersion in Stirred Vessels”, Chemical Engineering Research and Design, Elsevier, Amsterdam, NL, Vol. 75, No. 5, 1997, pp. 487-496 and Rewatkar V. B. et al.: “Role of sparger design on gas dispersion in mechanically agitated gas-liquid contactors”, Canadian Journal of Chemical Engineering, 1993, Vol. 71, No. 2, pp. 278-291. In order to evaluate the effects only single spargers are used. The presence of two spargers in a reactor at the same time and the distance between them is not relevant and not mentioned.

It is therefore an object of the present invention to overcome the deficiencies of prior art and to provide a modified bioreactor or fermenter which allows to manage the carbon dioxide concentration independently from the oxygen concentration within an aerated stirred bioreactor or fermenter on industrial scale.

Furthermore, it is a further object to provide a method to control cell culturing or fermentation processes by an independent management of carbon dioxide concentration and oxygen concentration within an aerated stirred bioreactor or fermenter on industrial scale.

SUMMARY

Surprisingly, it was found that the disadvantages known from prior art may be overcome, particularly an independent management of O_2- and CO_2-concentration in industrial scale aerated stirred bioreactors or fermenters may be achieved when a

second gas supply (or optionally more gas supplies) is (are) arranged in a predefined distance from the first gas supply within the bioreactor.

Therefore, in order to overcome the above mentioned disadvantages, a modified and thereby improved bioreactor or fermenter for the culturing of cells or microorganisms in suspension in a liquid medium in industrial scale is provided. A bioreactor or fermenter 100 for the culturing of cells or microorganisms in suspension in a liquid medium in industrial scale according to the present disclosure comprises

a vessel 102 containing the culture in a liquid medium having a determined filling height;

a stirrer 120 provided in the vessel to stir the liquid medium;

a first sparger 150 arranged in the bottom portion 105 of the vessel 102 provided to supply gas bubbles 10, 10.1, 10.2, 10.3 continuously to the liquid medium, the gas being selected from air and/or oxygen gas; and

a second sparger 160 arranged in the vessel 102 and provided above the first sparger 150 to supply additional air bubbles and/or additional oxygen gas bubbles 20, 20.1, 20.2, 20.3 continuously to the liquid medium,

whereby

the second sparger 160 is located at a position in the bioreactor or fermenter 100 above the first sparger 150 in a distance ɳ whereby ɳ is selected to be in the range from at least about 0.4 m above the first sparger 150 to at most about 0.5 m below the filling height of the bioreactor or fermenter 100 or

about 0.4 m above the first sparger to about 2/3 of the filling height of the bioreactor or fermenter 100 or

about 0.4 m above the first sparger to about 1/2 of the filling height of the bioreactor or fermenter 100 or

about 0.4 m above the first sparger to about 3.0 m above the first sparger or about 0.4 m to about 2.5 m or about 0.4 m to about 2.0 m or about 0.4 m to about 1.5 m or about 0.4 to about 1.0 m or about 0.45 to about 0.90 m or about 0.5 to about 0.80 m or about 0.55 to about 0.70 m or at about 0.6 m.

Therefore, in order to enhance the mass transfer performance for CO_2, whereby at the same time the mass transfer performance for O_2 is not adversely affected, according to the disclosure an additional second gas sparger is provided within the

bioreactor or fermenter at a higher position than the first sparger in a distance η, to achieve a much shorter residence time of the additional gas supplied compared to the gas provided from the submerse or first sparger. Due to the short residence time of the gas injected by the second sparger, a smaller amount of oxygen is transferred to the liquid phase whereas an increased amount of CO_2 can be stripped.

According to an example the second sparger may be a side-sparger, i.e. a sparger which provides the additional gas bubbles nearby the sidewall.

In one aspect, the present disclosure provides a process to control and adjust the content of dissolved CO_2 and the content of dissolved O_2 in a liquid medium in a bioreactor or fermenter for the culturing of cells or microorganisms in suspension in industrial scale comprising a vessel containing the culture in a liquid medium;
stirring the liquid medium;
continuously supplying gas bubbles from a first sparger arranged in the bottom portion of the vessel to the liquid medium, the gas being selected from air and/or oxygen gas;
continuously supplying gas bubbles from a second sparger arranged in the vessel to the liquid medium, the gas being selected from air and/or oxygen gas, whereby the second sparger being arranged above the first sparger and the second sparger is a side-sparger;
selecting and adjusting a modified gas flow rate $q_{mod}(O_2)$ and selecting and adjusting a modified gas flow rate $q_{mod}(CO_2)$ which are both suitable for the culturing process, based on the gas flow rate q_{sub} of the submerse or first sparger and the gas flow rate q_{side} of the side or second sparger, whereby the following equations apply:

$$q_{mod}(O_2) = q_{sub} + C_{O2} \times q_{side} \quad [1a]$$

and

$$q_{mod}(CO_2) = q_{sub} + C_{CO2} \times q_{side} \quad [1b]$$

wherein

q_{sub} represents the gas flow rate of the submerse or first sparger;

q_{side} represents the gas flow rate of the side or second sparger;

C_{O2} represents an influence factor C of the volumetric oxygen mass transfer, whereby $C_{O2} = 0.15$; and

C_{CO2} represents an influence factor C of the volumetric carbon dioxide mass transfer, whereby $C_{CO2} = 0.6$.

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 general description 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:

Figure 1 shows a schematic illustration of the processes and reactions with regard to the distribution of O_2 and CO_2 which take place in a gas bubble in a bioreactor or fermenter;

Figure 2 shows the volumetric mass transfer coefficient for carbon dioxide k_La_{CO2} in dependency of the volumetric stirrer power input P/V for different superficial gas velocities w^0_g on laboratory scale;

Figure 3 shows the volumetric mass transfer coefficient for carbon dioxide k_La_{CO2} in dependency of the volumetric stirrer power input P/V for different superficial gas velocities w^0_g on industrial scale;

Claims

1. A process to control and adjust the content of dissolved CO_2 and the content of dissolved O_2 in a liquid medium in a bioreactor or fermenter for the culturing of cells or microorganisms in suspension in industrial scale comprising a vessel containing the culture in a liquid medium;

stirring the liquid medium;

continuously supplying gas bubbles from a first sparger arranged in the bottom portion of the vessel to the liquid medium, the gas being selected from air and/or oxygen gas;

continuously supplying gas bubbles from a second sparger arranged in the vessel to the liquid medium, the gas being selected from air and/or oxygen gas, whereby the second sparger being arranged above the first sparger and the second sparger is a side-sparger;

selecting and adjusting a modified gas flow rate $q_{mod}(O_2)$ and selecting and adjusting a modified gas flow rate $q_{mod}(CO_2)$ which are both suitable for the culturing process, based on the gas flow rate q_{sub} of the submerse or first sparger and the gas flow rate q_{side} of the side or second sparger, whereby the following equations apply:

$$q_{mod}(O_2) = q_{sub} + C_{O2} \times q_{side} \quad [1a]$$

and

$$q_{mod}(CO_2) = q_{sub} + C_{CO2} \times q_{side} \quad [1b]$$

wherein

q_{sub} represents the gas flow rate of the submerse or first sparger;

q_{side} represents the gas flow rate of the side or second sparger;

C_{O2} represents an influence factor C of the volumetric oxygen mass transfer, whereby $C_{O2} = 0.15$; and

C_{CO2} represents an influence factor C of the volumetric carbon dioxide mass transfer, whereby $C_{CO2} = 0.6$.

2. The process according to claim 1,

characterized in that

q_{sub} is adjusted to be greater than q_{side}.

3. The process according to any of the preceding claims 1 or 2,
characterized in that
the position of second sparger in the bioreactor or fermenter is selected to be above the first sparger in a distance ɳ whereby ɳ is selected to be in the range from at least 0.4 m above the first sparger to at most 0.5 m below the filling height of the bioreactor or fermenter or
0.4 m above the first sparger to 2/3 of the filling height of the bioreactor or fermenter or
0.4 m above the first sparger to 1/2 of the filling height of the bioreactor or fermenter or
0.4 m to 3.0 m above the first sparger or 0.4 m to 2.5 m above the first sparger or 0.4 m to 2.0 m above the first sparger or 0.4 m to 1.5 m above the first sparger or
0.4 to 1.0 m above the first sparger or 0.45 to 0.90 m above the first sparger or 0.5 to 0.80 m above the first sparger or 0.55 to 0.70 m above the first sparger or at 0.6 m above the first sparger.

4. The process according to any of the preceding claims 1 to 3,
characterized in that
a third sparger and optional (a) further sparger(s) are provided in the bioreactor or fermenter above the first sparger and second sparger, the distance between two consecutive spargers, one arranged above the other, is selected to be ɳ.

5. The process according to any of the preceding claims 1 to 4,
characterized in that
the stirrer has a strirrer radius r_s which is located around a central axis A through the bioreactor or fermenter,
whereby the first sparger is arranged at a distance from the central axis A of the bioreactor or fermenter such that the gas bubbles provided enter the liquid medium at a distance which is equal to or less than the stirrer radius r_s;
and/or
whereby the second sparger is arranged at a distance from the central axis A such that the bubbles provided enter the liquid phase at a distance which is larger than the stirrer radius r_s.

6. The process according to any of the preceding claims 1 to 5, characterized in that
(an) additional stirrer(s) is(are) provided in addition to the first stirrer, the additional stirrer(s) being located above and/or below the second sparger.

7. The process according to any of the preceding claims 1 to 6, characterized in that
the first sparger is a central sparger or a side sparger and the second sparger and the optional third sparger and optional further spargers are side-spargers.

8. The process according to any of the preceding claims 1 to 7, characterized in that
the first sparger, the second sparger and the optional further spargers are static spargers selected from spargers with a pipe-geometry, for example tube type spargers such as open-tube spargers, sintering plates, perforated slabs, ring spargers, spider type spargers, disc type spargers, sheet type spargers, cup type spargers, and bushing type spargers.