What is k_La in bioreactors?

Bioreactors.net

Simple and practical explanation

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This article is intended for bioreactor users and manufacturers, as well as other interested parties, in order to give an intuitive idea and basic knowledge of k_La. It is an attempt to explain the essence of k_La in a simple and practical way. The aim of the article is to provide additional knowledge about the selection of bioreactors and their working regimes to achieve as best as possible fermentation results.

Introduction

In aerobic microorganism cultivation processes, it is necessary to supply nutrients and oxygen to the microorganism cells. The oxygen supply to the cells is more problematic because usually, oxygen solubility is significantly lower compared to glucose and other components of the nutrient media. Oxygen is supplied to the cells by air bubbles, which are introduced into the bioreactor through a sparger or through the headspace. These bubbles are dispersed by mixing. The latter is necessary to supply the oxygen to the cells with sufficient intensity. Insufficient oxygen supply is often the reason for not reaching the required biomass concentrations. To ensure sufficient intensity of oxygen supply, the bioreactor must be properly designed and the appropriate mixing and aeration modes must be provided. The k_La parameter is used to characterize the oxygen mass transfer.

General principle of k_La

Basically the volumetric oxygen mass transfer coefficient – k_La, is the parameter that controls the rate of how oxygen transitions from the gas phase into the liquid phase. k_La shows numerically how efficiently oxygen, which is introduced through a sparger in the vessel, is dissipated and distributed in the medium by the mixer.

The notion of k_La arises from the two-film theory, which postulates, that the mass transfer between two phases takes place through a boundary layer, between those two phases (see Fig.1.).

The rate of diffusion of a component between phases is dependent on the mass transfer coefficient, for liquids this coefficient often is written as 'k_L'. The overall rate of mass transfer between two phases apart from k_L is also dependent on the contact area between those two phases, often termed '*a*'. When we combine the two, we get our volumetric oxygen mass transfer coefficient k_La.

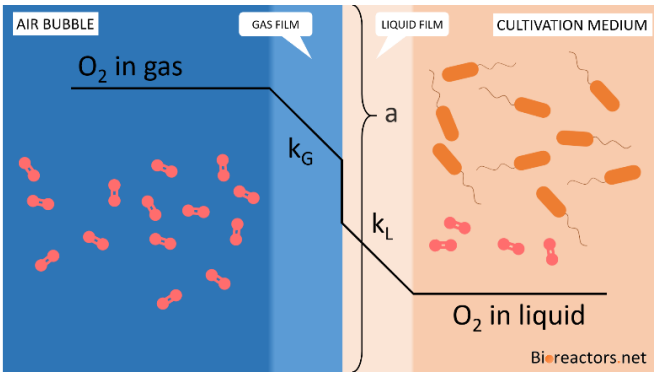

Fig.1. *Gas-liquid oxygen mass transfer according to the two-film theory*

Another important aspect of k_La can be described by using the following equation:

$$dC/dt = k_La \cdot (C^*-C_L) = OTR - OUR \qquad (1)$$

Where,

C^* – the saturated dissolved oxygen concentration;

C_L – the current concentration of dissolved oxygen in the media.

This equation shows us, that the rate of oxygen concentration change in the liquid medium is dependent on k_La and the difference between the current (C_L) and maximal possible (or sometimes termed equilibrium – C^*) oxygen concentrations. Simultaneously, the rate of the oxygen concentration change is equal to the difference between the oxygen transfer rate to the cultivation medium (OTR) and the oxygen uptake rate (OUR). If the OTR is higher than the OUR term, the medium will inevitably get saturated by oxygen until reaching the equilibrium concentration. On the second hand, if we observe a completely different situation, where the OUR term is larger than OTR, the oxygen concentration will fall below a required level, which would be unsuitable for supporting microorganism growth. Both situations are unfavourable due to the fact that most often a specific organism requires a certain concentration of oxygen to be maintained, too high oxygen concentrations

can lead to a completely different fermentation paths, too low oxygen concentrations can lead to biomass growth and/or target product secretion inhibition.

In result, one of the most widely used means of controlling the dissolved oxygen concentration is regulation of the mixing intensity during fermentations (dissolved oxygen concentration also can be controlled by airflow, oxygen enrichment, overpressure, substrate feeding).

k_La evaluation possibilities

k_La evaluation is important for the selection of a bioreactor for a particular cultivation process. The latter is critical for pilot and industrial scale applications because in laboratory scale bioreactors usually it is easier to achieve necessary oxygen transfer rates. Often, based on the cultivation results in a laboratory scale system, pilot and/or industrial scale bioreactors are selected. It is more convenient to start k_La evaluations by using theoretical calculation equations. Although, following factors can limit the applicability of theoretical k_La calculations:

1. The chemical composition of the applied medium differs in principle;
2. The applicability of a particular k_La empirical equations depends on the limits of the parameters at which it was developed.

While the applicability of experimental k_La determination methods is narrowed in the following cases:

1. The existing k_La formulas are not applicable to the selected bioreactors design;
2. The necessity to evaluate k_La in real fermentation processes.

Theoretical k_La evaluation

One of the most revered methods of correlating k_La with different bioreactor working modes is the empirical correlation proposed by Van't Riet in 1979 [1]. He proposed to correlate the volumetric oxygen mass transfer coefficient in a stirred-tank bioreactor with the specific power input and superficial gas velocity.

$$k_La = C \cdot (P_g/V)^{\alpha} \cdot v_g^{\beta} \qquad (2)$$

Where,

P_g – aerated power input, W/m^3;

V – working volume, m^3;

v_g – superficial gas velocity, m/s;

$$v_g = Q \cdot S^{-1} \qquad (3)$$

Where,

Q – air flow rate, m^3/s;

S – cross-section area in diameter plane, $S = \pi \cdot D^2 \cdot 0.25$, where D – diameter of the vessel.

C, α, β – empirical constants, which incorporate the geometry of the vessel (mixer rotors, baffles, other parts), and in according to Van't Riet the mentioned coefficients are estimated as: C=0.026, α=0.4 and β=0.5 [1].

This formula was developed based on data for pure water, the volume of applied reactors reaches 2600 litres and specific power inputs can be in the ranges 500 – 10 000 W/m^3.

Although the correlation proposed by Van't Riet was quite adequate in predicting k_La over a broad range of specific power input values, people soon began to realize, that another term should be added to this equation. The remaining term was viscosity μ, so the modern modification of the original Van't Riets equation looks like this [2]:

$$k_La = C \cdot (P_g/V)^{\alpha} \cdot v_g^{\beta} \cdot \mu^{\delta} \qquad (4)$$

Where,

μ – dynamic viscosity, Pa·s;

To determine P_g, firstly it is necessary to calculate the power input by the mixer P in ungassed conditions (without introducing gasses into the media):

$$P = K_N \cdot N \cdot \rho \cdot n^3 \cdot d^5 \qquad (5)$$

Where,

K_N – power number (Newton`s number) of the mixer;

ρ – density of liquid media, kg/m^3;

d – diameter of mixers rotor, m;

N – coefficient, depends on the number and mutual location of mixer rotors.

There is limited data and correlations, which can be used for precise calculation of N. In principle, if the distance between mixers L is more than $2d$, then N can be assumed equal to the number of rotors installed on the mixer, because in this case the interaction between rotors is negligible [3].

$$L > 2 \cdot d \qquad (6)$$

Where,

L – distance between mixers, m;

If this distance is less, then N will decrease depending on the interaction between mixer rotors.

There are different equations, which describe the relation of P_g/P. To select the most appropriate one for the particular case, it is necessary to study the parameters of the applied system and the defined ranges, for which a particular empirical correlation is applicable. The following equation was derived based on the experimental data from 0.4 –7 m diameter vessels equipped with ≤ 3 stage standard Rushton turbines [4]:

$$P_g = P/\sqrt{(1+A\cdot v_g/\sqrt{(g\cdot d)}} \qquad (7)$$

Where,

The constant A depends on the number of mixers:

1 mixer: A = 750;

2 mixers: A = 490;

3 mixers: A = 375.

The example of k_La calculation

The task is to evaluate k_La in a bioreactor with the following design and operation parameters: Working volume – 2000 litres; bioreactor diameter (D) – 1 m; mixer rotor diameter (d) – 350 mm; number of rotors – 2; distance between rotors – 720 mm; the applied rotors are standard Rushton turbines with a power number (K_N) – 7. The bioreactors maximal operation parameters: mixer rotation speed n = 300 rpm; airflow rate Q = 1200 L/min.

Firstly, it is necessary to convert all values into SI:

$N = 300/60 = 5$ rps

$Q = 1200\text{x}10^{-3}/60 = 0.02$ m^3/s

$V = 2000$ L $= 2$ m^3

$D = 350$ mm $= 0.35$ m

Distance between both mixer rotors is $2d$, and according to equation (6):

$N = 2$

The ungassed power input P can be calculated by using equation (5):

$P = 7 \cdot 2 \cdot 10^3 \cdot 5^3 \cdot 0.35^5 = 7 \cdot 2 \cdot 10^3 \cdot 125 \cdot 5.25 \cdot 10^{-3} = 9187.5$ W

The cross-sectional area S of the bioreactor is:

$S = 3.14 \cdot 1^2/4 = 0.785$ m^2

The superficial gas velocity is:

$v_g = Q / S = 0.02 / 0.785 = 0.025$ m/s

Now according to equation (7) the maximum gassed power input can be calculated:

$P_g = P/\sqrt{(1+A\cdot v_g/\sqrt{(g\cdot d)}} =$

$= 9187.5/\sqrt{(1+490\cdot 0.025/\sqrt{(9.8\cdot 0.35)}} =$

$= 3328.8$ W

To determine k_La, the obtained values are used in equation (2):

$$k_La = C\cdot (P_g/V)^{\alpha}\cdot v_s^{\beta} =$$

$$= 0.026\cdot (3328/2)^{0.4}\cdot 0.025^{0.5} =$$

$$= 0.024\cdot 19.43\cdot 0.158 =$$

$$= 0.074\ \text{s}^{-1}$$

Experimental k_La determination methods

The following are the most popular experimental k_La determination methods:

- The sulphite oxidation method;
- The static gassing out method;
- The dynamic gassing out method;
- Oxygen balance method.

The ***sulphite oxidation*** was the first applied method for k_La determination [5]. It is based on the determination of oxygen transfer rates in aerated vessels by the oxidation of a sodium sulphite solution:

$$Na_2SO_3 + 0.5O_2 = Na_2SO_4$$

The rate of reaction is such that as oxygen enters the solution it is immediately consumed in the oxidation reaction of sulphite, so that the the sulphite oxidation rate is equivalent to OTR. The dissolved oxygen concentration, for all practical purposes will be zero and k_La may then be calculated from the following equation:

$$\text{OTR} = k_La\cdot C^* \qquad (8)$$

During the experiment, chemical measurements of the sulphite solution are carried out during solution agitation at different mixer rotation speeds and air flow rates in fixed time intervals. This is usually done by titrating the solution with thiosulphate. In this way, a graphical relationship is obtained between the amount of thiosulfate and time. The

graph has a trend with a linear characteristic, where the slope of the line is equal to OTR.

The method is rather simple, but it is time consuming and relatively inaccurate. This method is almost no longer used today.

One of the most widely used experimental methods for k_La evaluation is ***the static gassing-out method*** [6]. When using this method, the medium inside the vessel first is stripped from oxygen. This can be done by introducing a second soluble gas (nitrogen is most commonly used). After the oxygen level in the medium stabilizes at zero, or somewhat close to zero value, the supply of nitrogen is switched off. Next, air is introduced into the medium at a constant flow rate, and then the increase in dissolved oxygen concentration is monitored, which can be described by the following equation:

$$dC_L/dt = k_L a \cdot (C^* - C_L) \qquad (9)$$

Integration of equation (9) yields:

$$\ln (C^* - C_L) = - k_L a \cdot t \qquad (10)$$

Thus, a plot of $\ln (C^* - C_L)$ against time will yield a straight line of slope - $k_L a$, as shown in Fig. 2.

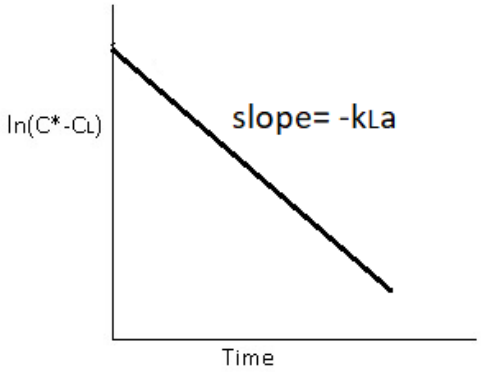

Fig.2. *Graph of ln(C*-C_L) vs. experiment time (for determining of k_La)*

The static gassing-out method is quite easy to perform although multiple aspects have to be taken into account in order to obtain precise k_La data: the response delay of the probe, which is used for oxygen measurements, and temperature/pressure control during the experiment.

Considering the case of the ***dynamic gassing-out method*** it is quite similar to the static method, although, it has a couple of advantages [7]. Using the dynamic method, it is possible to determine the volumetric oxygen mass transfer coefficient during fermentation processes. This is done by ceasing the aeration (point A in Fig.3) until the oxygen concentration reaches a critical point (point B in Fig.3). After that, the aeration is restored (point B in Fig.3) and DO level vs. time data is gathered.

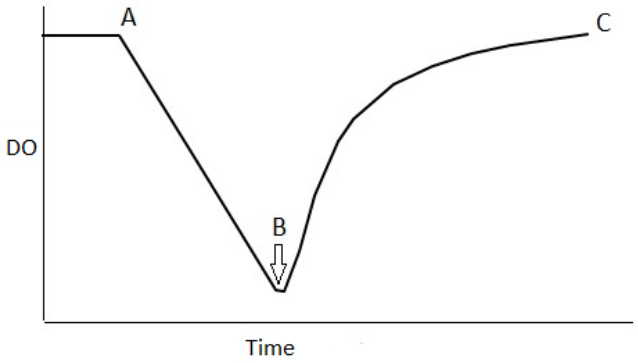

Fig.3. *Dynamic gassing out experiment time dependent process data*

The transition of oxygen from the gas to the liquid phase is described by the following equation [2]:

$$\ln((C^* - C)/(C^* - C_o)) = - k_L a \cdot t \qquad (11)$$

Where,

C_o – dissolved oxygen concentration before restarting the aeration (see point B in Fig.3);

C – dissolved oxygen concentration at time t (within the line segment BC).

By performing DO measurements and using the obtained data in equation (7), the following graph (Fig.4) is created:

$$f(t) = \ln((C^* - C)/(C^* - C_o)) \qquad (12)$$

Where the slope of this graph is - $k_L a$.

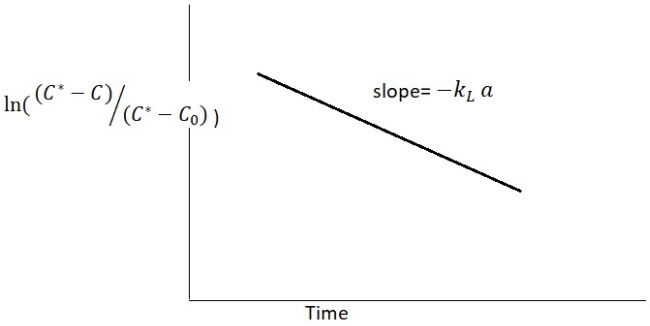

Fig.4 *Graphical function to determine k_La according to equation* (11)

The oxygen balance method is considered more precise than the two previously mentioned k_La determination approaches because the response delay of the DO measurement probe can be neglected [8]. The principle behind the oxygen balance method is the application of gas analysers, to determine the oxygen concentration in the gas phase, thus obtaining information on the amount of oxygen that is being supplied to the fermentation medium, up-taken by the microorganisms and ejected into the exhaust line. At steady state, when the concentration of oxygen in the medium is maintained constant, the oxygen transfer rate OTR is equal to the oxygen uptake rate OUR, thus by constructing an oxygen mass balance for this particular state, we can determine the k_La coefficient:

$$OTR = OUR \quad (13)$$

$$OTR = Q_{O2\text{-}IN} - Q_{O2\text{-}OUT} \quad (14)$$

Where,

$Q_{O2\ IN}$ and $Q_{O2\ OUT}$ are inlet and outlet oxygen volumetric flow rates.

$$OUR = Q_{O2\text{-}V} \cdot V \quad (15)$$

Where,

$Q_{O2\text{-}V}$ – volumetric oxygen uptake rate,

V – volume of fermentation or model media.

At steady state, the rate at which oxygen transfers from the gas phase to the liquid phase is equal to the rate of consumption of the oxygen by microorganisms:

$$k_La \cdot (C^* - C_L) = OUR/V \quad (16)$$

Combining (9) - (12), the equation for determining k_La is obtained:

$$k_La = (Q_{O2V\text{-}IN} - Q_{O2\text{-}OUT})/(V \cdot (C^* - C_L)) \quad (17)$$

Although the method gives quite precise estimates of the volumetric oxygen mass transfer coefficient, it is significantly more expensive to perform, taking into account that gas analysers are required.

The influence of the bioreactor`s design on k_La

The equation (2) shows the influence specific power input and aeration (superficial gas velocity) on k_La. Although, the mentioned equation does not encompass the effect of mixer rotor design on the mass transfer rate.

Mixer rotor design

The mixers rotors have to ensure both bulk mixing and dispersion of gas bubbles in the medium. For example, if two axial mixers (for example, pitched-blade impellers) are installed in the bioreactor, then bulk mixing in the whole volume will be ensured, but dispersion of gas bubbles most likely will not be optimal. If gas flow rates are high, but dispersing is not effective, then, for example, such unfavourable effect as impeller flooding can appear which drastically decreases the OTR. To intensify gas bubble dispersion, one possible solution could be the installation of a primary rotor (in the bottom part of the vessel) with good gas dispersing properties (e.g. SCABA, Rushton etc.).

Sparger design

The sparger design determines the bubble size and their distribution in bioreactors volume. Theoretically, if the bubble size is smaller, then k_La must be higher, due to the increasing of a (contact area between the gas and liquid phases). However, smaller bubbles also pose a negative effect on oxygen mass transfer. Considering that small enough bubbles begin to express rigid body properties. The bubbles behave like a rigid sphere with less internal recirculation, so that oxygen gas molecules within the bubble do not reach the surface. If the bubble diameter is less, the bubble rise velocity will also be less. In result smaller bubbles contain a smaller quantity of oxygen, which would be transferred quickly. According to the literature data the optimal size of the bubble is about 2-3 mm [9], and this must be taken into considerations when selecting the appropriate gas sparger.

The correlation of k_La and cell growth rates during cultivation

By determining k_La theoretically or experimentally in model media, an obviously assumption is that higher k_La will ensure higher biomass growth rates. Although, in real applications different phenomena can manifest, which can negatively affect the process performance depending on applied mixing and aeration regimes. In such cases, theoretically 'better' bioreactor designs will not always guarantee higher biomass growth rates at a higher predetermined k_La values.

The following phenomena can potentially drive the deviations of the predicted vs. real biomass growth rate in respect to k_La:

1. *Rheological properties of the fermentation media*

If the viscosity of the cultivation media and the related parameters (for example, pseudo plasticity) increases during the process, the distribution of the introduced mixing

energy in the reactor volume changes. For example, in the case of relatively small viscosities, most effective mixing will be achieved using standard Rushton turbines. However, at higher viscosities, other mixer rotor designs will be more suitable. The latter can be explained by the fact that Rushton turbines generate pronounced locally intense flux zones and the agitation energy value falls lower faster near the reactor walls at higher viscosities. As a result, the decrease of OTR using standard Rushton turbines can be more pronounced in this case.

2. *The morphological changes of microorganisms by mixing*

Some types of microorganism cells are sensitive to intense mixing. This regards, for example, to mammalian and plant cells, mycelial microorganisms and algae cultures. Too intense mixing can induce changes to the cell morphology, resulting in a decrease in growth rate. Although, the mentioned growth rate decrease is attributed to a decrease in OUR. In such cases, mixers and their operating modes must be selected which do not yet induce critical shear stresses to the cells. For shear sensitive cultures, standard Rushton turbines are usually not the best choice. In such cases, the use of shear sensitive mixers, such as pitched-blade impellers, propellers or similar are recommended.

3. *Foaming*

The high degree of aeration and agitation required in fermentations frequently gives rise to the undesirable phenomenon of foam formation. The presence of foam may also have an adverse effect on OTR. From the other side, all antifoams are surfactants and are expected to have some effect on OTR. Antifoams tend to decrease OTR, it also causes a collapse of bubbles in foam but they may favour the coalescence of bubbles with the liquid phase, resulting in larger bubbles with reduced surface area to volume ratios and hence a reduced OTR [10].

Oxygen uptake rate

During biomass growth, the microorganism oxygen demand increases. This demand is characterized by the volumetric oxygen uptake rate OUR. This is described by the term:

$$OUR = Q_{O2} \cdot X \qquad (18)$$

Where

Q_{O2} – specific oxygen uptake rate (mmoles O_2/g biomass, h^{-1});

X – biomass concentration, g/L.

Q_{O2} depends on the microorganism strain and applied substrate. In the following table the specific oxygen uptake rates Q_{O2} for different microorganisms and substrates are summarized [11]:

Type of microbial culture	Carbon source	Q_{O2}, (mmol/g·h)
Aspergillus niger	Glucose	1.6
Beneckea natriegens	n-Propanol	12
Penicillium chrysogenum	Lactose	1.2
Saccharomyces cerevisiae	Ethanol	10
Streptomyces aureofaciens	Corn starch	7.0
Streptomyces coelicolor	Glucose	7.4
Streptomyces griseus	Meat extract	4.1
Xanthomonas campestris	Glucose	4.5

The task of the bioreactor is to ensure the supply of oxygen to the cells until no other growth limiting factors come into play. This characterizes the volumetric oxygen transfer rate OTR:

$$OTR = k_L a \cdot (C^* - C_L) \qquad (19)$$

Where the designations are according to equation (1).

This means that until OTR > OUR, the growth of microorganisms will continue. If the OTR value is higher, then higher biomass yields will be possible to achieve. By analyzing equation (19), it can be seen that OTR will be proportional to k_La and ($C^* - C_L$). By applying equation (19) it is necessary to take into account the cell specific oxygen consumption Q_{O2} dependence on C_L. When C_L is less than C_{crit}, Q_{O2} decreases (Fig. 5).

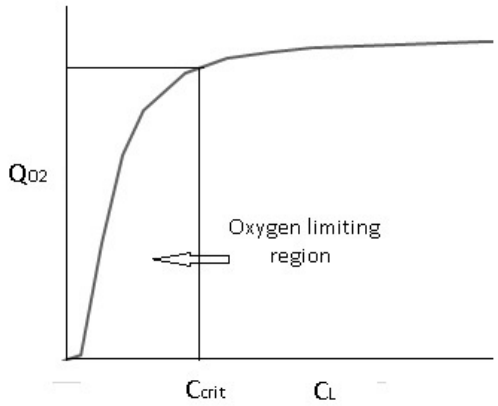

Fig.5. *Relation between the specific oxygen consumption Q_{O2} and dissolved oxygen concentration C_L.*

C_{crit} can differ depending on microorganism strain and process conditions. Often C_{crit} is about 10-20% from the

equilibrium oxygen concentration C^*. C^* typically varies in range 6 – 9 mg/l.

By knowing k_La, C^* and C_{crit}, the maximum achieved biomass concentration (or in this case called critical biomass concentration X_{crit}) can be determined. In opposite, if we know what biomass concentration X_{max} must be achieved in the certain cultivation process, then the necessary k_La of the bioreactor can be evaluated by maximal operating values of mixer rotation speed n and gas flow rate Q (of course, if another limiting factor does not comes into play).

Taking into account the above mentioned information, it can be concluded that the maximal biomass concentration will be achieved, if OTR = OUR and $C_L = C_{crit}$.

$$k_La \cdot (C^* - C_{crit}) = Q_{O2} \cdot X_{crit} \qquad (20)$$

and from equation (20) follows:

$$X_{crit} = k_La \cdot (C^* - C_{crit}) / Q_{O2} \qquad (21)$$

The biomass concentration calculated by equation (21) is, of course, a theoretical maximum and it will be achieved only if all other cultivation conditions are maintained optimal.

The calculation example using equations of OUR

A strain of *Streptomyces coelicolor* is cultivated in a 2000 liter bioreactor according to the example mentioned above using glucose as the substrate. Equilibrium oxygen concentrations C^* is 8 mg/L. C_{crit} is 20 % from C^*.

What maximal biomass concentration can be achieved is this case?

Let's assume that $X_{max} = X_{crit}$. Firstly, all parameters are to be defined in SI units:

$k_La = 0.074\ s^{-1}$

$C^* = 8$ mg/L; (mg/L = 10 [kg/10^6mg] / 1 [m^3/10^3 L] = $10^3/10^6 = 10^{-3}$ kg/m^3); = $8 \cdot 10^{-3}$ kg/m^3

$C_{crit} = 0.2 \cdot 8 = 1.6 \cdot 10^{-3}$ kg/m^3

Q_{O2} according to the table seen above for *S. coelicolor* is 7.4 mmol/g·h.

1 mol O_2 = 32 g O_2; 1mmol O_2 = $32 \cdot 10^{-3}$ g O_2 ; 1mmol O_2 = $32 \cdot 10^{-6}$ O_2 kg

1 g=10^{-3} kg; 1h=$3.6 \cdot 10^3$ s;

Q_{O2} = 7.4 mmol/g·h = $(7.4 \cdot 32 \cdot 10^{-6}) / (10^{-3} \cdot 3.6 \cdot 10^3) = 65.8 \times 10^{-6}$ kg/kg·s

$X_{crit} = (0.074 \cdot (8-1.6) \cdot 10^{-3}) / (65.8 \cdot 10^{-6}) = 7.2$ kg/m^3 = 7.2 g/L

This means that the maximal biomass concentration of 7.2 g/L can be achieved during *Streptomyces coelicolor* cultivations in the defined bioreactor.

Resume-conclusions

From the information presented above, the following conclusion can be drawn regarding k_La as a bioreactor efficiency parameter:

1. The theoretical calculation equations of k_La with satisfactory accuracy are applicable to popular mixer rotor types (Rushton turbine, pitched-blades, etc.) and for bioreactor volumes of up to 3000 liters.

2. Experimental methods are labor-intensive, but if the mixing system consists of different or not widely applied mixers rotors, then it is recommended to determine k_La experimentally for scale-up purposes.

3. By using experimental methods it is possible to determine k_La during running cultivation processes (dynamic gassing-out and oxygen balance methods).

4. The determined k_La usually correlates sufficiently with the growth of biomass during the cultivation process, as long as it is not significantly affected by cultivation-related phenomena (rheology, morphology, foaming).

5. Oxygen uptake rate differs for different cultivation processes depending on the microorganism type and applied carbon source. This means that when selecting the scale-up bioreactor and it`s parameters for a particular process, it is desirable to know Q_{O2} of the applied microorganism strain. The latter will dictate what k_La bioreactor should be chose to provide sufficient OTR for obtaining targeted biomass/product yields.

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