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SCALE-UP OF STIRRED AND AERATED BIOENGINEERING™ BIOREACTOR BASED ON CONSTANT MASS TRANSFER COEFFICIENT

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Abstract. The scale-up studies based on the constant oxygen transfer coefficient, k_La from 16 l to 150 l of aerated and agitated bioreactor were performed. By employing the static gassing out techniques, the k_La values were calculated at different sets of impeller speeds and air flow rates performed in various viscosities and temperatures in the 16 l and 150 l Bioengineering™ stirred bioreactor. Empirical correlation was employed to correlate and investigate the dependence of k_La on specific power input and superficial air velocity. In maintaining a constant k_La upon scale-up from 16 l to 150 l, the specific power input and the superficial air velocity cannot be maintained, thus an adjustment has to be done. From the experimental results at 150 l, it was discovered that the specific power input from 0.0001 to 4.2 kW/m^3 and superficial air velocity within the range of 9×10^{-4} m/s to 7×10^{-3} m/s employed gave a comparable k_La values achieved at 16 l scale. Hence, the calculated scaling-up factor for impeller speed and air flow rate were 0.28 and 3.1, respectively. The comparable results obtained from both scales confirmed that the scale-up protocol developed works.

Keywords: Oxygen transfer, empirical relationship, stirred bioreactor, scale-up

Abstrak. Kajian penskalaan naik dilaksanakan dengan berdasarkan pekali pemindahan oksigen, k_La malar menerusi penggunaan bioreaktor teraduk berudara yang diskala naik daripada 16 l kepada 150 l. Dengan menggunakan teknik penyingkiran gas secara statik, nilai k_La dikira bagi laju pendesak dan kadar alir udara yang berbeza, pada pelbagai kelikatan dan suhu bioreaktor teraduk *Bioengineering™* 16 l dan 150 l. Sekaitan empirik digunakan untuk menyekait dan mengkaji kebergantungan k_La terhadap kuasa masukan tentu dan halaju permukaan udara. Bagi memalarkan k_La ketika pengskalaan naik daripada 16 l kepada 150 l, kuasa masukan tentu dan halaju permukaan udara tidak dapat dikekalkan. Dengan itu, penyelarasan harus dilakukan. Berdasarkan keputusan uji kaji pada 150 l, kuasa masukan tentu daripada 0.0001 kepada 4.2 kW/m^3 dan halaju permukaan udara yang berjulat 9×10^{-4} m/s hingga 7×10^{-3} m/s yang dikaji, didapati menghasilkan nilai k_La yang setanding dengan nilai yang diperoleh daripada skala 16 l. Sehubungan itu, faktor penskalaan naik yang diperoleh ialah 0.28 bagi laju pendesak dan 3.1 bagi kadar alir udara. Keputusan setanding yang diperoleh daripada kedua-dua skala tersebut mengesahkan bahawa protokol penskalaan naik mampu berfungsi dengan baik.

Kata kunci: Pemindahan oksigen, sekaitan empirik, bioreaktor teraduk, penskalaan naik

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1.0 INTRODUCTION

The oxygen transfer coefficient, k_La plays an important role towards carrying out the design, scaling up and economic of the process. Efforts have been focused in improving the design and scaling up studies to achieve adequate supply of oxygen at higher scales [1,2]. As supplying adequate oxygen is the centre of the issue in aerobic fermentation, maintaining a similar k_La has been frequently employed as the basis of scaling up exercises. There has been a significant advance in the understanding of scale-up of stirred aerated bioreactors as reported by several authors. Shukla [3] works highlight on the performance of the impeller used upon scaling up of yeast biotransformation medium on a basis of constant k_La. Wong [4] employed the correlations proposed by Wang [5] in scaling up on a basis of constant k_La and air flow rate per unit volume, Q/V. The work by Hensirisak [6] concerned more on the performance of microbubble dispersion to improve oxygen transfer upon scale-up. The work by Wernesson [7] reported the influenced of power input per unit mass on the hydrodynamics of the bioreactor. In spite of these observations, the engineering focus continued to be on maintaining the volumetric oxygen transfer constant on scale-up.

The objective of this work is to develop a simple approach that provides a reliable protocol for scaling-up exercise based on constant oxygen transfer rate in stirred aerated bioreactor. Scaling up studies performed in this work used the correlation developed by Cooper *et al.* [8]. Cooper *et al.* [8] proposed that the k_La may be empirically linked to the gassed power consumption per unit volume of broth, P_g/V_L and the superficial air velocity, v_g as described by the following equation:

$$k_La = a'\left(\frac{P_g}{V_L}\right)^b \left(v_g\right)^c \tag{1}$$

Table 1 summarises the values of constant b and c from several works. Constant b represents the level of dependence of k_La the agitation, while, constant c represents the level of dependence of k_La on sparging rate applied to the system. In this equation, the values of the constants b and c may vary considerably; depending on the bioreactor geometry and operating conditions. The k_La values achieved at 16 l scale were compared with the values at 150 l scale. Since the scaling up factor is not proportionally increasing, a trial-and-error within the predicted range was performed.

2.0 MATERIAL AND METHODS

2.1 Scale-up Protocol

The scale-up protocol applied involved the application of rule of thumb, trial and error, interpolation and extrapolation on the basis of keeping the value of k_La constant

Table 1 Values of constant *b* and *c* from several works that estimated from the empirical relationship proposed by Cooper *et al.* [8].

Author	Constant *b*	Constant *c*	Type of impeller	Liquid model	Liquid volume (l)
[8]	0.95	0.67	N/A	Air-water system	66
[3]	0.68	0.58	Disc turbine and pitched blade turbine	Air-water system	5.125
[3]	0.73	0.89	Disc turbine and pitched blade turbine	Yeast fermentation broth	5.125
[9]	0.47	0.39	Flat-blade disc style turbine	*Aspergillus's* fermented broth	10
[10]	0.84	0.40	Narcissus blade	(2% w/v) CMC solution	50
[10]	0.82	0.40	Narcissus blade	(0.5% w/v) Xanthan gum solution	50
[1]	0.68	0.40	Disc turbine and pitched blade turbine	(0.7% w/v) CMC solution	5.125

as the scale increases. The protocol is shown in Figure 1. The scale-up performed by investigating the k_La values in 16 l vessel. Upon obtaining the k_La values in the 16 l scale, the limitations for the operating variables in the 150 l bioreactor were computed. In order to design the operational conditions at 150 l scale, scale-up on the basis of constant power consumption per unit liquid volume, P_g/V_L, constant superficial velocity, v_g, and constant impeller tip speed, pND_i, were performed using the scale-up equations.

The following equations are the scale-up equations to be employed in the scale-up protocol:

(1) Constant power consumption per unit liquid volume, P_g/V_L with constant superficial velocity, v_g.

$$Q_2 = Q_1\left(\frac{D_{T2}}{D_{T1}}\right)^2 \tag{2}$$

$$N_2 = \frac{\left[\left(N_1^{3.15} D_{i1}^{5.85} Q_2^{0.252} D_{T2}^2 H_2\right)\right]^{\left(\frac{1}{3.15}\right)}}{\left(Q_1^{0.252} D_{T1}^2 H_1 D_{i2}^{5.85}\right)} \tag{3}$$

(2) Constant power consumption per unit liquid volume, P_g/V_L with constant impeller tip speed, πND_i.

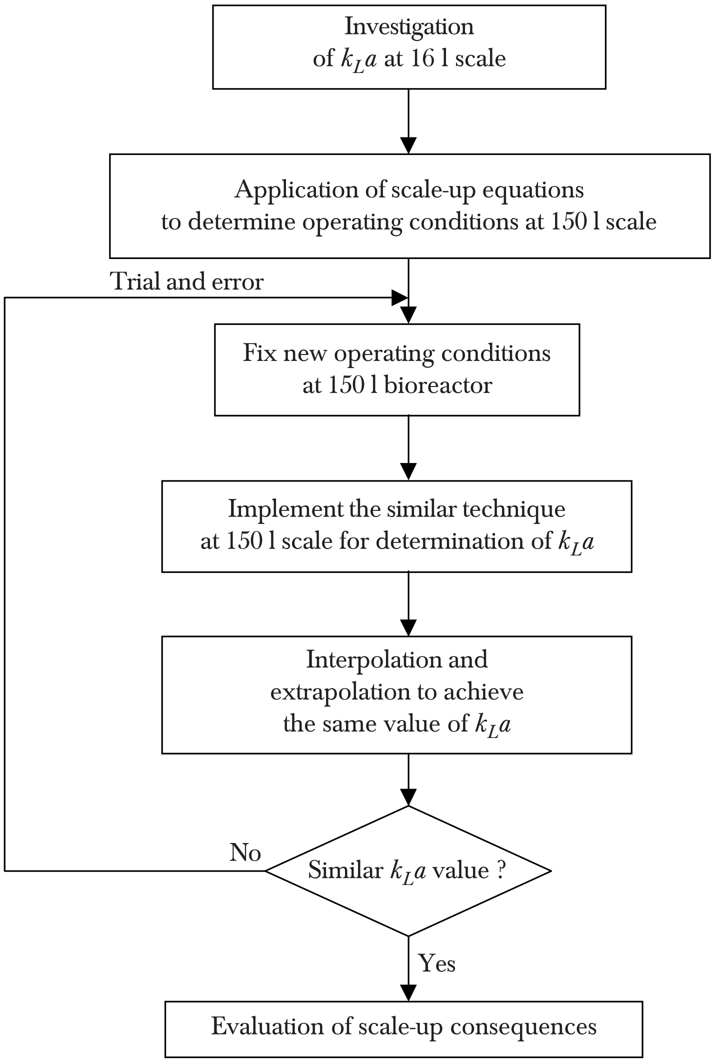

Figure 1 Scale-up protocol based on constant oxygen transfer coefficient, k_La

$$N_2 = N_1\left(\frac{D_{i1}}{D_{i2}}\right) \tag{4}$$

$$Q_2 = \frac{\left[\left(N_2^{3.15} D_{i2}^{5.85} Q_1^{0.252} D_{T1}^{2} H_1\right)\right]^{\left(\frac{1}{0.252}\right)}}{\left(N_1^{3.15} D_{T2}^{2} H_2 D_{i1}^{5.85}\right)} \tag{5}$$

By knowing the impeller speeds, N_1 and air flow rates, Q_1 at 16 l scale, Equations (2), (3), (4) and (5) were used to determine the impeller speeds and air flow rates at

150 l scale. At different scale-up criterions, the allowable operating range at 150 l vessel was predicted. The operating variables (N_2 and Q_2) achieved in solving Equations (2), (3), (4) and (5) were used as a base line in the trial-and-error step upon scaling-up a bioreactor from 16 l to 150 l on a basis of constant k_La. In providing a similar oxygen transfer coefficient, k_La as in the 16 l bioreactor, the impeller speeds and the air flow rates was manipulated. Interpolation and extrapolation were carried out to determine the operating variables at 150 l bioreactor. The scaling-up factors upon scaling-up based on constant k_La from 16 l to 150 l bioreactor were calculated using the following equations:

$$R_1 = \frac{N_2}{N_1} \tag{6}$$

$$R_2 = \frac{Q_2}{Q_1} \tag{7}$$

2.2 Bioreactor Dimensions and Operating Conditions

The dimension of bioreactor is tabulated in Table 2. At 150 l bioreactor, different combinations of operating conditions were applied. The impeller speeds and air flow rates were determined by matching the k_La in both 16 l and 150 l scales. The range of

Table 2 Dimensions of 16 l and 150 l scale bioreactors

Dimension	16 l bioreactor	150 l bioreactor
Total volume, V_T (m^3)	0.016	0.150
Working volume, V_L (m^3)	0.01	0.1
Vessel height, H_T (m)	0.507	1.143
Liquid height, H_L (m)	0.393	0.825
Vessel diameter, D_T (m)	0.20	0.41
Surface area, a_s (m^2)	0.0005	0.1320
Impeller type	Rushton turbine	Rushton turbine
Number of impellers	2	2
Impeller diameter, D_i (mm)	70	200
Impeller thickness, T_i (mm)	3	3
Impeller width, W_i (mm)	14	40
Ratio impeller to vessel diameter	0.35	0.49
Top impeller distance from top plate, Δ_i (m)	0.26	0.47
Spacing between impeller, Δ_C (m)	0.155	0.520
Sparger diameter, D_S (m)	0.095	0.205
Sparger distance from bottom impeller (m)	0.055	0.073
Baffles	Yes	Yes

Table 3 Operating variables at 16 l and 150 l scale bioreactors

Scale	Impeller speed, N	Air flow rate, Q	Liquid model
16 l	200 - 1000	3 – 15 l/min	Water & CMC (0.25 % w/v – 1% w/v)
150 l (1st trial)	50 – 250 rpm	10 – 50 l/min	Water & CMC (0.25 % w/v – 1% w/v)
150 l (2nd trial)	60 – 300 rpm	10 – 50 l/min	Water & CMC (0.25 % w/v – 1% w/v)

operating conditions for 16 l and 150 l scale bioreactor are given in Table 3. The similar technique of static gassing out was implemented to determine the value of k_La. Experiments were carried out under the same experimental conditions namely pH, temperature and rheology properties as in the 16 l scale.

2.3 Determination of the k_La

The rate of oxygen transfer from air bubbles to liquid in a batch stirred bioreactor was given by the following relationship [11]:

$$\frac{dC_L}{dt} = k_La(C^* - C_L) \tag{8}$$

The oxygen transfer rate (OTR) was determined using the static gassing out method [15]. The change in dissolved oxygen concentration, C_L in the liquid phase was detected using a polarographic oxygen probe. At different combinations of airflow rates and stirrer speeds as described earlier, the dissolved oxygen concentration, C_L profile with respect to time was graphed. To calculate the k_La, Equation (8) was integrated with respect to the time taken for the oxygen concentration to reach the saturation level from the lowest point.

$$t = \frac{1}{k_La}\ln\left(\frac{C^* - C_L^o}{C^* - C_L}\right) \tag{9}$$

The k_La was then determined by reciprocating the slope obtained from the semi logarithmic plot of time, t versus $\frac{C^* - C_L^o}{C^* - C_L}$. The dissolved oxygen saturation concentration in the liquid or C^* that calculated from the Henry's Law was quoted from Table [12].

2.4 Power Consumption

The ungassed power consumption, P_o was determined from the plot power number, N_p versus Reynolds number, N_{RE} for both Newtonian and non-Newtonian fluid in a different type of flow regime [13]. The power number, N_p is:

$$\left(\frac{P_o}{\rho_L N^3 D_i^5}\right) = N_p \tag{10}$$

While the Reynolds number, N_{RE}, is given as:

$$N_{RE} = \left(\frac{N D_i^2 \rho_L}{\mu_L}\right) \tag{11}$$

The gassed power consumption, P_g, was estimated through a correlation proposed by Michel and Miller [14].

$$P_g = m\left(\frac{P_o^2 N D_i^3}{Q^{0.56}}\right)^{0.45} \tag{12}$$

Constant m depends on the impeller geometry. In this case, the value of constant m is 0.832 for Rushton turbine [9].

2.5 Oswald-de Waele Model

The behaviour of pseudoplastic fluid has been successfully investigated by published works [3,15]. Their works described the flow behaviour and determined the power-law quantities by employing the Oswald-de Waele model via Equation (10).

$$\tau = k\gamma^n \tag{13}$$

Metzner and Otto [16] suggested that the effective shear rate of the liquid may be determined using the following equation:

$$\gamma = AN \tag{14}$$

and the apparent viscosity as:

$$\mu_{app} = k[AN]^{n-1} \tag{15}$$

where A, for turbine stirrer type value was assumed as 11.5 [15]. Table 4 contains the viscometric parameters of the model fluid employed.

Table 4 Viscometric data and power-law quantities for CMC solutions

CMC concentrations	Consistency index, k (Pa.s^n) x 10^3	Flow behavior index, n
0.25%(w/v)	6.16	0.7654
0.5%(w/v)	14.6	0.8825
1%(w/v)	53.9	0.9501

3.0 RESULTS AND DISCUSSIONS

The scale-up equations were applied in order to determine the minimum and the maximum value of the operating variables (impeller speeds and air flow rates) upon scale-up on a basis of constant k_La from 16 l to 150 l bioreactor. The results for the determination of air flow rates and impeller speeds at 150 l scale on the basis of constant volumetric power input with superficial velocity and on the basis of constant volumetric power input with impeller tip speed are tabulated in Table 5.

Table 5 Base line in determining the operating variables at 150 l scale

Operating variables	Scale-up criteria		Allowable operating range at 150 l
	Constant P_g/V_L and πND	Constant P_g/V_L and v_g	
Impeller speed, N_2	65 – 326 rpm	70 – 350 rpm	50 – 600 rpm
Air flow rate, Q_2	12.6 – 63.0 l/min	30.7 – 153.0 l/min	5.0 – 100.0 l/min

The calculated operating variables achieved at 150 l scale could not be adopted directly in order to achieve a similar k_La values at 150 l bioreactor. However, the results attained were used as a base line in determining the operating variables at 150 l to achieve the similar value of k_La as in the 16 l scale. These operating variables were set as the upper level and the lower level in the trial-and-error step. In referring to the base line and the constraint of the operating variables at 150 l as shown in Table 5, it was found that the value of air flow rates were relatively out of range. Therefore, two sets of operating variables were proposed to obtain a similar k_La values as in the 16 l bioreactor. It is known that the geometry of the bioreactor is the same for both scales. However, the dimensions are different as the scale increases. Different in mixing and liquid rheology may also cause a difficulty in scaling-up a bioreactor [17]. However, through manipulation of the power input and the superficial air velocity, a comparable k_La values was successfully achieved. The objective of the trial-and-error step in the scale-up protocol was to achieve a comparable operating condition in both scales and to determine the scaling-up factor upon scaling-up from 16 l to 150 l bioreactor. At different type of liquid solution and operating variables, the scaling-up factor was

Table 6 Operating variables at 150 l scale on a basis of constant k_La

Operating variables	**Liquid system**	
	Air-water system	**Air-viscous system**
Impeller speed, N_2	59 – 395 rpm	30 – 311 rpm
Air flow rate, Q_2	9.3 – 54.0 l/min	7.0 – 50.0 l/min
Scale-up factor, R		
Scale-up impeller speed, R_1	0.318	0.245
Scale-up air flow rate, R_2	3.41	2.85

determined. The new operating variables at 150 l scale and the scaling-up factor are shown in Table 6.

The scaling-up factor was calculated to observe the influence on the operating conditions at 150 l scale if the impeller speed and the air flow rate in the 16 l was varied. Upon achieving the impeller speeds and air flow rates at 150 l scale, several hydrodynamic parameters namely the impeller Reynolds number, the volumetric power input, and the superficial air velocity in the bioreactor were computed to define the bioreactor operating conditions at larger scales. The significance and the consequences of the hydrodynamic difference upon scale-up were evaluated based on the dependence of the k_La on the operating variables. As clearly evident from the logarithmic plots in Figures 2 and 3, in maintaining a constant value of k_La upon scale-up from 16 l to 150 l at different temperatures and viscosities, similar trend of k_La proportionality to the aeration efficiency and specific power input were successfully achieved. The variability of the volumetric power consumption at 150 l scale upon scale-up was resulted from the different impeller speed employed at higher scale. The slopes in the logarithmic plots in Figure 2 are similar in both scales even though the plots are not coinciding with each other. The dependency of k_La on the power input in the non-Newtonian fluid was compared in order to observe the differences upon employing the scaling-up factor in scaling-up on a basis of constant k_La. Nevertheless, by doing so, it would create a deviation in the k_La value upon scale-up from 16 l to 150 l. Different impeller speed at higher scale would result in a different power input upon scale-up. However, the dependence of k_La on the volumetric power consumption was equivalent in both Newtonian and non-Newtonian fluids upon scale-up from 16 l to 150 l vessel.

The logarithmic plots in Figure 3 show the dependence of k_La on the superficial air velocity. It was found that the superficial air velocity in the 16 l vessel was higher compared to the 150 l ones. However, the slopes of the trend achieved are the same in both scales of operation. In practicing the scale-up protocol, a maximum aeration of 1.5 vvm was applied at 16 l bioreactor and only 0.5 vvm of aeration was employed at 150 l scale. By implying the scaling-up factor for the air flow rate, similar k_La values as in 16 l scale was successfully achieved in the 150 l bioreactor. The increase of air flow rates necessitates in compensating with increase of bioreactor volume. A greater volume

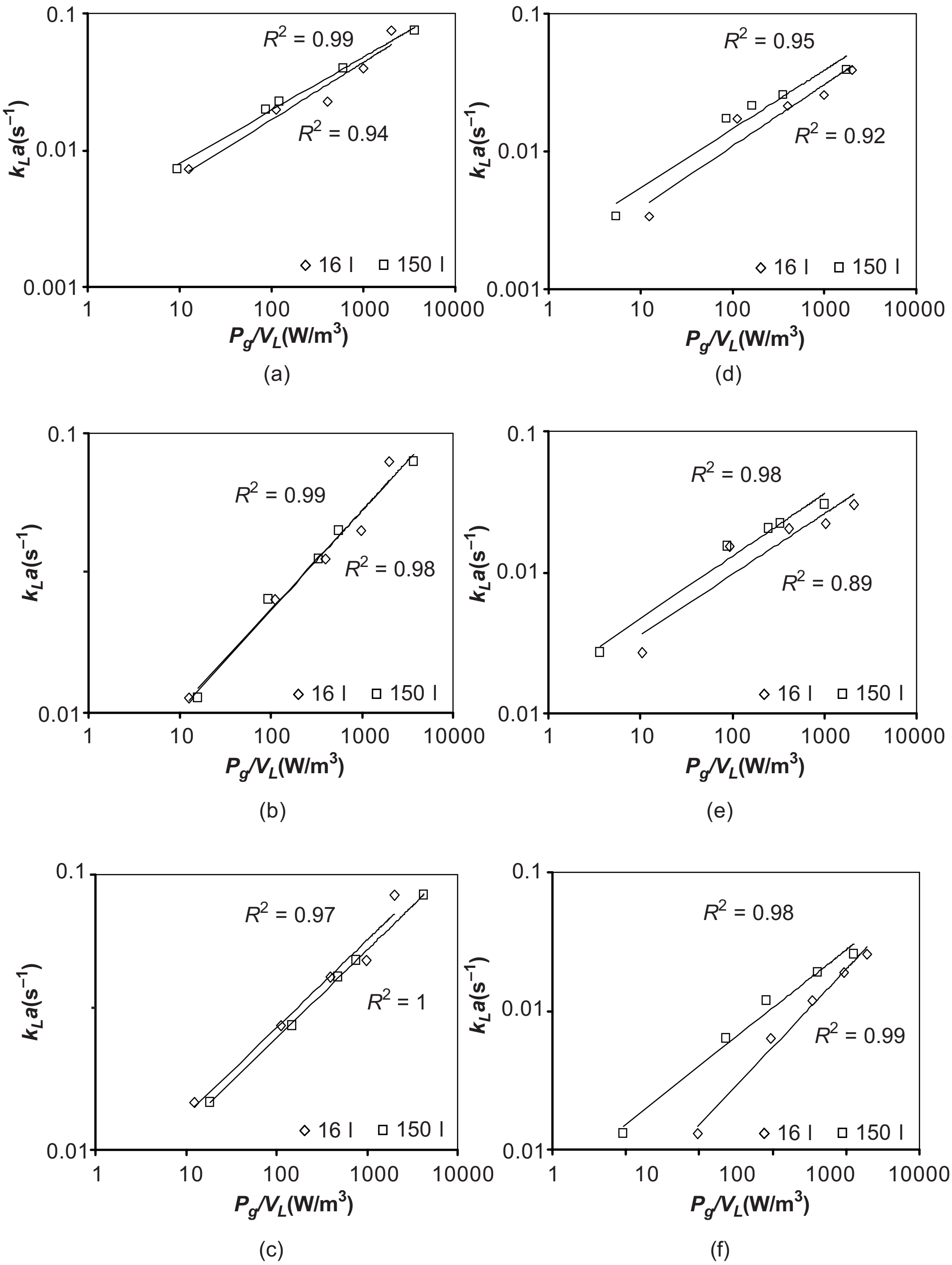

Figure 2 Dependence of k_La on the volumetric power consumption at (a) Distilled water T = 30°C, (b) Distilled water T = 40°C, (c) Distilled water T = 50°C, and Carboxy methyl cellulose at (d) 0.25%(w/v), (e) 0.5%(w/v) and (f) 1.0%(w/v)

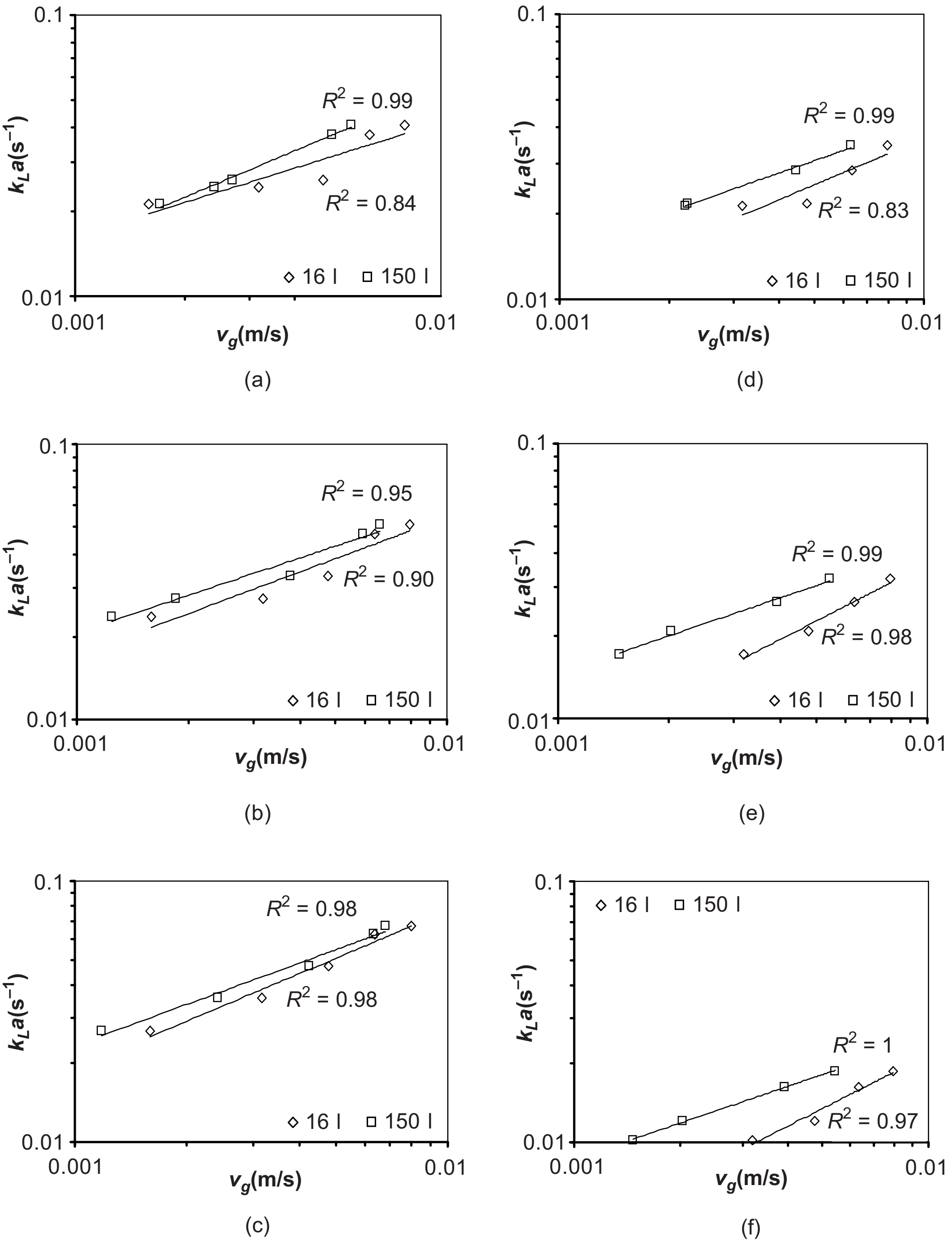

Figure 3 Dependence of k_L a on the superficial velocity at (a) Distilled water T = 30°C, (b) Distilled water T = 40°C, (c) Distilled water T = 50°C, and Carboxy methyl cellulose at (d) 0.25%(w/v), (e) 0.5%(w/v) and (f) 1.0%(w/v)

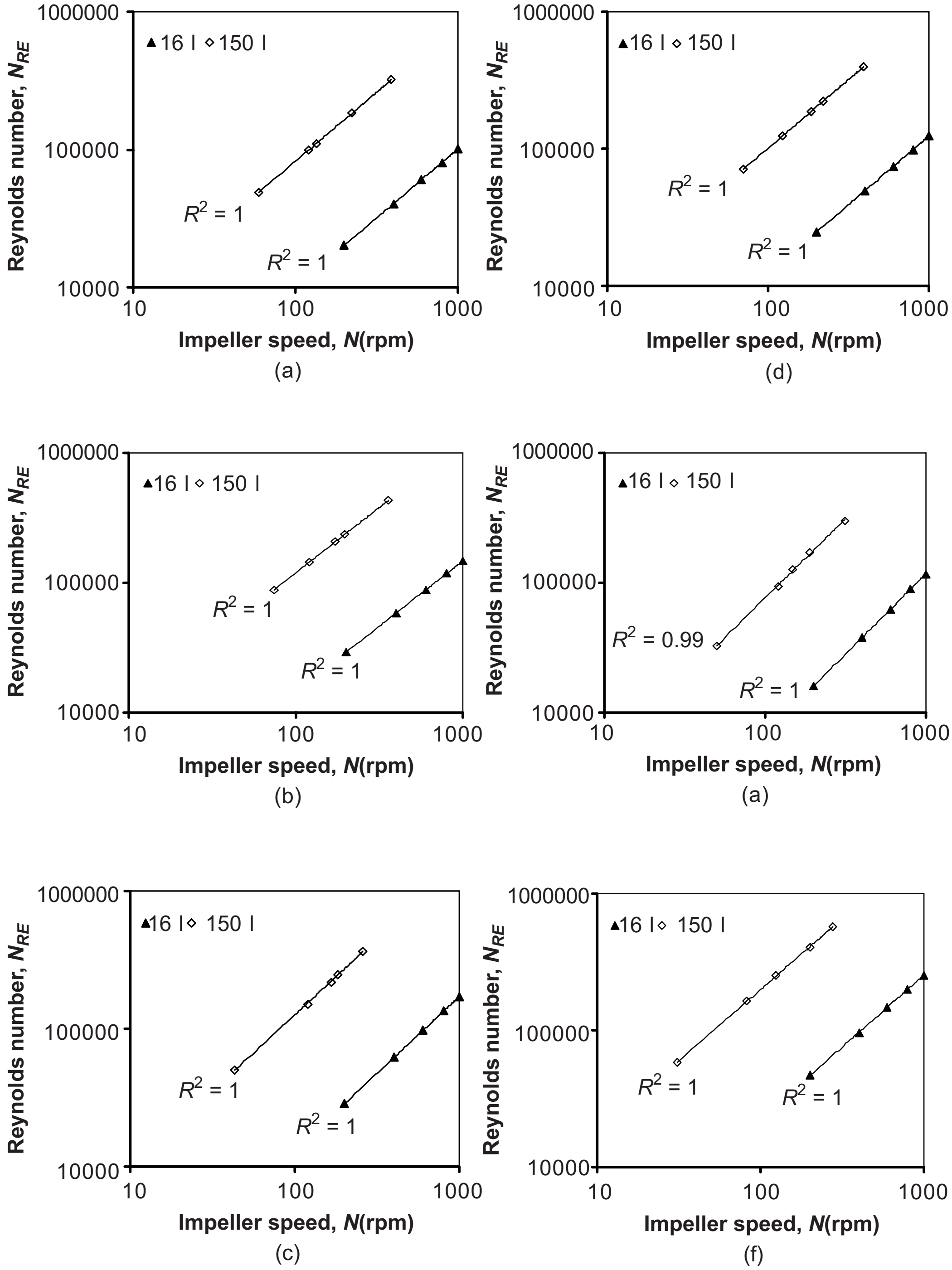

Figure 4 Dependence of Reynolds number on impeller speed at (a) Distilled water T = 30°C, (b) Distilled water T = 40°C, (c) Distilled water T = 50°C, and Carboxy methyl cellulose at (d) 0.25%(w/v), (e) 0.5%(w/v) and (f) 1.0%(w/v)

at 150 l and changes in surface to volume ratio upon scale-up, require a higher air flow rates to be employed. Interestingly, by manipulating the operating variables, a similar turbulence was successfully achieved in promoting a similar oxygen transfer rate in both scales. The turbulence in both scales was compared at different impeller speeds as shown in Figure 4. The trend in Figure 4 shows that the Reynolds number at 150 l scale was found to be 2.5 times higher in the air-water system and nearly twice more in the air-viscous system compared to the Reynolds number achieved at 16 l scale. This was due to the high residence time of bubbles, greater volume and higher vessel in 150 l scales [18].

Based on the results presented in the previous logarithmic plots, equal liquid motion was attained and the corresponding velocities are approximately the same in both scales. Hence, equal mixing capacity was also achieved for both Newtonian and non-Newtonian fluids upon scale-up from 16 l to 150 l bioreactor. It was discovered that the operating temperature and the liquid viscosities are independent of scale. Similar temperature was employed at 150 l scale and it did not show a significant effect on k_La upon scale-up (Figures 2 and 3). A variation of k_La dependency on the operating parameters in the non-Newtonian fluid showed that it is difficult to maintain a similar hydrodynamics in the non-Newtonian fluid compared to the Newtonian fluid. The impeller speeds, air flow rates, volumetric power consumption and the superficial air velocity were known to be the manipulated variables and scale-dependent in employing the scale-up factor upon scale-up from 16 l to 150 l bioreactor on a basis of constant k_La.

3.1 The Dependence of K_La on the Operational Parameters at 150 l Scale

It was previously illustrated in the logarithmic plots that the trend of k_La dependency on the operating variables was almost identical in both scales. However, to examine how close the slope of the logarithmic plots was, the constant *b* and *c* in both scales were compared. The parameter estimates (constant *b* and *c*) presented in Table 7

Table 7 The values of constant *b* and *c* upon scale-up from 16 l to 150 l at different operating temperatures for air-water and air-viscous system

Liquid system	Temperature (°C)	Constant *b* 16 l	Constant *b* 150 l	Constant *c* 16 l	Constant *c* 150 l
Water-air	30	0.4196	0.388	0.4063	0.5493
	40	0.3561	0.3541	0.5009	0.4491
	50	0.3179	0.3207	0.6046	0.5257
0.25%(w/v) CMC - air	30	0.4485	0.4282	0.278	0.4458
0.5%(w/v) CMC - air	30	0.4305	0.4421	0.4849	0.4611
1%(w/v) CMC - air	30	0.5626	0.4177	0.6264	0.5449

show a similarity upon scale-up from 16 l to 150 l. However, it was seen a minor variation in the dependence of k_La on superficial air velocity in the air-viscous system. As presented in Table 7, at 150 l scale, the range of the constant b is within $0.32 < b < 0.39$ in the air-water system and $0.41 < b < 0.44$ in the air-viscous system. The degree of k_La dependence on superficial air velocity is within the range of $0.44 < c < 0.54$ for both distilled water and the CMC solutions. The empirical correlation at 150 l is tested for specific power input and superficial air velocity within the range of $0.0001 < P_g/V_L < 4.2$ kW/m^3 and $9 \times 10^{-4} < v_g < 7 \times 10^{-3}$ m/s, respectively. Based on the experience in predicting the k_La values, an average deviation of 10% and maximum deviation of 20% standard error were expected. The experiment data fitted well with the empirical correlation proposed by Cooper [8] with a high correlation coefficient, R_2.

4.0 CONCLUSIONS

A simple protocol for scaling-up exercise based on constant k_La in stirred aerated bioreactor was developed. The dependence of k_La on the specific power input and superficial air velocity at 16 l and 150 l bioreactor operated at different liquid viscosities and temperatures were compared. This was achieved by evaluating the effect of increasing broth viscosity on the oxygen transfer rate. Scale-up of the bioreactor from 16 l to 150 l scale must meet the oxygen transfer requirements while maintaining a low variation in power input and a controlled flow pattern. Technically, to obtain a similar value of k_La in both scales, the differential in the constant b and c was kept as low as possible. Similar trend of k_La dependence on the volumetric gassed power consumption and superficial air velocity showed that the effects of agitation speed and aeration rate on the oxygen transfer rate in both scales were identical. From this study, it could be concluded that the dependence of k_La on volumetric gassed power consumption was more evident in 16 l than in 150 l scale. Hence, the impeller speed gave significant effect on the k_La at 16 l scale compared to 150 l scale. The manipulation of specific power input and superficial air velocity may be a useful approach in maintaining a constant k_La value upon scale-up from 16 l to 150 l bioreactor.

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NOTATION

a', b, c	constants in Cooper's *et al*. (1944) equation
a	specific interfacial area (m^{-1})

A	parameter in Meztner-Otto's equation
C^*	dissolved oxygen saturation concentration in liquid (mg/l)
$C^o{}_L$	initial dissolved oxygen concentration (mg/l)
C_L	dissolved oxygen concentration (mg/l)
D_i	impeller diameter (m)
D_t	tank/vessel diameter (m)
k_La	volumetric mass transfer coefficient (s^{-1} or hr^{-1})
k	consistency index in power-law model (Pa.s^n)
m	constant in Michel & Miller's equation
n	flow behaviour index in power-law model (-)
N	impeller speed (rpm)
N_p	power number (-)
N_{RE}	Reynold number (-)
P_o	ungassed power consumption (W)
P_g	gassed power consumption (W)
Q	air flow rate (m^3/s)
t	time (s)
V_L	liquid volume (m^3)
v_g	superficial gas velocity (m/s)
γ	shear rate (s^{-1})
μ_L	liquid viscosity (kg/m.s)
μ_{app}	apparent viscosity in Oswald-de Waele model (Pa.s)
τ	shear stress (N/m^2)
ρ_L	liquid density (kg/m^3)
1	16 l scale
2	150 l scale

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