Study of the mixing time evolution during the scale-up of an animal cells culture in a stirred tank bioreactor

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The biotechnology aspect of the research

Animal cells are used in industrial biotechnology to product proteinic compounds. Especially, the company GlaxoSmithKline Biologicals develops an industrial scale culture of animal cells in a stirred tank, in which cells are adsorbed on microcarriers. Microcarriers are non-porous beads made of reticulated dextran, their mean size equals 250 µm and they are suspended in the culture medium.

In that kind of semi-batch process, the injections of nutrients or alkali create concentration gradients which could be penalizing for the cells development. In laboratory scale, these concentration gradients are rapidly eliminated by the turbulence induced by the impeller motion. But these concentration gradients could stay a longer time when the size of the bioreactor increases. Therefore, the mixing time, which characterizes the time needed to reach concentration homogeneity, can become an important criterion in the scale-up strategy.

So, the aim of this study is to measure the mixing time by conductometry in three bioreactors with increasing size in order to fit a correlation on these experimental data. Later on, this correlation will be useful for the scale-up strategy.

Apparatus and methods

Three bioreactors were used and their volume equals respectively 20 L, 80L and 600 L. Their common geometry is illustrated in figure 1. Their height, H, to diameter, D, ratio equals to 1. They are equipped with a hemispheric bottom and two baffles (1/12 D in width) equally spaced and installed at the periphery of the tank. Two kinds of impellers are placed at one third of the tank height:

- Impeller TTP (Mixel) with the impeller diameter to tank diameter ratio equals to 0.4 or 0.5.
- Impeller Elephant Ear (Applikon) with the impeller diameter to tank diameter ratio equals to 0.5

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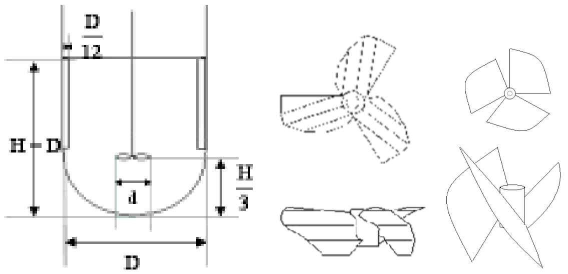

Figure 1: from left to right: tank geometry, impeller TTP geometry, impeller EE geometry

To determine the mixing time, a NaCl solution is injected at the top surface of the liquid. The conductivity evolution of the liquid is measured by a conductivity probe also placed at the surface of the liquid. The mixing time θ is determined by choosing a 95% homogeneity criterion. The choice of the rotating speed of the impeller is based, firstly, on those used during a culture and, secondly, on the upholding of the range of the Reynolds number.

Results

The correlation of Greenville et al. is used as a starting point because that correlation shows the separate effect of the rotating speed (N), the impeller type (indirectly by the power number N_p) and impeller diameter to tank diameter ratio (D/T).

$$\theta_{95\%} = A\left(\frac{1}{N}\right)\left(\frac{1}{N_p}\right)^{\frac{1}{3}}\left(\frac{T}{D}\right)^2$$

The parameter A is determined by the least square roots method and its value is around 3 for all impellers.

The figure 2 shows the comparison of the mixing time obtained experimentally for the propeller TTP (D/T=0.5, N_p=0.4) and the values predicted by the correlation (A=3.1)

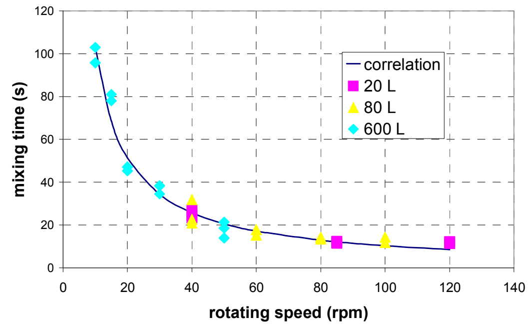

Figure 2: Experimental and predicted mixing time created by the propeller TTP (D/T=0.5)

The agreement between experimental values and those predicted can be considered good for all impellers in view of the fluctuations of the experimental mixing time in the same experimental conditions. This correlation will therefore be used with some confidence in the scale-up process.

Acknowledgment

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References

Greenville,R.K, Ruszkowski,S. and Garred, E. (1995), 15th NAMF Mixing conference, Banff, Canada.