10.2. SCALE-UP AND ITS DIFFICULTIES

10.2.1. Introduction

Why would the performance of a fungal culture making an antibiotic be so different at 10,000 l than at 10 l? At first glance the reader may have difficulty understanding why performance should change with scale. The answers lie in the difficulty of maintaining homogeneity in large systems, changes in surface to volume ratios, and changes in the cultures themselves due to the increased length of culture time. To understand the problems in scale-up, we first need to describe what traditional culture vessels are and how they are operated.

10.2.2. Overview of Reactor Types

Rather than catalog the large array of suggested fermenter and bioreactor designs, we will restrict ourselves to considering some basic types:

1. Reactors with internal mechanical agitation.
2. *Bubble columns*, which rely on gas sparging for agitation.
3. *Loop reactors,* in which mixing and liquid circulation are induced by the motion of an injected gas, by a mechanical pump, or by a combination of the two.

All three reactor types (see Fig. 10.1 for schematics) invariably are concerned with three-phase reactions (gas–liquid–solid). Three-phase reactors are difficult to design, because the mass transfer of components among the three phases must be controlled. Inadequate tools for the complex fluid mechanics in such systems coupled with the complex nature of cells as reactive solids make the prediction of system performance from first principles very difficult.

The traditional fermenter is the stirred-tank reactor (Fig. 10.2), the prime example of a reactor with internal mechanical agitation. The main virtues of such systems are that they are highly flexible and can provide high k_La (volumetric mass-transfer coefficient) values for gas transfer. Stirred reactors of up to 400 m^3 are used in antibiotic production, with stirrer powers of up to 5 kW/m^3. Stirred reactors can be used commercially up to viscosities of about 2000 centipoises (2 Pa sec).

Gas under pressure is supplied to the *sparger* (usually either a ring with holes or a tube with a single orifice). The size of the gas bubbles and their dispersion throughout the tank are critical to reactor performance. Although a sparging ring will initially provide smaller bubble size and better gas distribution, spargers with a single discharge point are often preferred for media with high levels of suspended solids because they are more resistant to plugging.

Gas dispersion is mainly the function not of the sparger but of the *impeller*. The impeller must provide sufficiently rapid agitation to disperse bubbles throughout the tank, to increase their residence time within the liquid, and to shear larger bubbles into small bubbles. Too much stirring can be detrimental, owing to the shear sensitivity exhibited to varying degrees by some cells (e.g., animal cells) and the stratification of reactor contents