Abstract

Aerated stirred tank reactors are widely used in chemical industry and bioprocess engineering in which mass transport and mixing time are among the most important parameters for the characterisation and scale-up. However, the prediction of theses parameters is still challenging due to large differences of the hydrodynamic inhomogeneities between lab scale and industrial scale. For a better understanding, a precise measurement of the two phase flow is crucial but requires an optical insight and is thus difficult to realise especially on large scales. To overcome this problem and to be able to perform both global and local measurements, a transparent stirred tank reactor on industrial scale has been erected at the Hamburg University of Technology in cooperation with Boehringer Ingelheim Pharma GmbH & Co.KG.

To identify the differences between lab scale and industrial scale, the different dispersion mechanisms and the resulting bubble size distributions within a laboratory scale reactor (3 L) and a industrial scale reactor (12 000 L) were investigated in this work. Furthermore, the influences of the bubbly flow on the mixing time and the mass transfer performance were identified. The results were compared to literature correlations. It is shown that the dispersion mechanisms are significantly different on both scales, as a result of the small power input in context of mammalian cell cultivation. In the laboratory reactor, the dispersion mainly takes place directly at the sparger, leading to a small bubble size distribution at various power inputs. On industrial scale, the gas phase is dispersed by the vortices behind the stirrer blades and thus strongly depends on the power input. Because of the limitation of the overall power input for mammalian cell cultivation, the minimum stirrer frequency at which sufficient dispersion occurs may be exceeded. This in turn can lead to a wide bubble size distribution with an inhomogeneous gaseous phase and strong buoyancy driven flow. A correlation to estimate the transition between homogeneous and heterogeneous flow regime is presented.

These flow regimes have a particularly strong influence on the mixing time. The mixing times for the homogeneous flow regime are in the same range as the values for the unaerated case. However, the mixing time at the same power input, but for the heterogeneous flow regime, can be reduced up to 80 % due to the strong buoyancy driven flow and the enhanced axial mixing. As a result, the correlations that exist for the aerated mixing time in the literature could not predict the trend sufficiently. A new model that includes heterogeneity is developed. It satisfactorily predicts aerated mixing time, especially in the transition area.

An influence of the heterogeneity on mass transport was also identified. A transition to a heterogeneous flow leads to a sudden decrease of the mass transport due to the relation between the bubble size distribution and the specific surface area. Existing correlations do not take this transition into account and therefore overestimate the mass transport in the heterogeneous flow regime. For an improved correlation, the two flow regimes have to be considered and modelled separately.

Zusammenfassung

Begaste Rührreaktoren finden in der chemischen und der pharmazeutischen Industrie immer noch große Anwendung, wobei der Stofftransport und die Mischzeit zu den wichtigsten Einflussparametern für die Charakterisierung und das Scale-Up gehören. Die Vorhersage dieser Parameter ist jedoch aufgrund der großen Unterschiede der hydrodynamischen Inhomogenitäten zwischen Labor- und Industriemaßstab nach wie vor schwierig. Für ein besseres Verständnis ist die Messung der zweiphasigen Strömung entscheidend, erfordert aber einen optischen Zugang und ist daher insbesondere im großen Maßstab schwer zu realisieren. Um dieses Problem zu lösen und sowohl globale als auch lokale Messungen durchführen zu können, wurde ein transparenter Rührkesselreaktor im industriellen Maßstab an der Technischen Universität Hamburg in Kooperation mit Boehringer Ingelheim Pharma GmbH & Co.KG errichtet.

Um die Unterschiede zwischen Labormaßstab und industriellem Maßstab zu identifizieren, wurden in dieser Arbeit die verschiedenen Dispersionsmechanismen und die daraus resultierende Blasengrößenverteilung in einem 3-L-Reaktor im Labormaßstab und einem 12-m³-Reaktor im industriellen Maßstab untersucht. Darüber hinaus wurden die Einflüsse der Blasenströmung auf die Mischzeit und die Stofftransferleistung identifiziert. Die Ergebnisse wurden mit Literaturkorrelationen verglichen. Es wird gezeigt, dass die Mechanismen der Dispergierung auf beiden Skalen signifikant unterschiedlich sind, was auf den geringen Energieeintrag bei tierischer Zellkultivierung zurückzuführen ist. Im Laborreaktor findet die Dispersion hauptsächlich am Begaser statt, was zu einer engen Blasengrößenverteilung bei verschiedenen Leistungseinträgen führt. Im industriellen Maßstab wird die Gasphase durch die Wirbel hinter den Rührerblättern dispergiert und hängt somit stark vom Leistungseintrag ab. Aufgrund der Limitierung im Leistungseintrag kann es zu einer Unterschreitung der minimalen Drehzahl kommen, bei der die Gasphase komplett dispergiert wird. Dies wiederum kann zu einer breiten Blasengrößenverteilung mit einer inhomogenen Gasphase und einer starken auftriebsgetriebenen Strömung führen. Eine Korrelation zur Abschätzung des Übergangs zwischen homogenem und heterogenem Strömungsverhalten wird in dieser Arbeit präsentiert.

Diese Strömungsregime haben einen besonders starken Einfluss auf die Mischzeit. Die Mischzeiten für das homogene Strömungsregime liegen im gleichen Bereich wie die Werte für den unbegasten Fall. Die Mischzeiten bei gleichem Leistungseintrag, aber im heterogenen Strömungsregime, können aufgrund der starken auftriebsgetriebenen Strömung und der verbesserten axialen Vermischung um bis zu 80 % reduziert werden. Infolgedessen konnten die vorhandenen Korrelationen die Mischzeiten im begasten Zustand nicht korrekt vorhersagen. Unter Berücksichtigung der Heterogenität konnte im Rahmen dieser Arbeit eine neue Korrelation entwickelt werden, die die Mischzeiten auch im Übergangsbereich zuverlässig wiedergibt.

Ein Einfluss der Heterogenität auf den Massentransport wurde ebenfalls identifiziert. Ein Übergang zu einer heterogenen Strömung führt zu einer plötzlichen Abnahme des Stofftransports aufgrund des Zusammenhanges zwischen der Blasengrößenverteilung und der spezifischen Oberfläche. Bestehende Korrelationen berücksichtigen diesen Übergang nicht und überschätzen daher den Stofftransport im heterogenen Strömungsbereich. Für eine verbesserte Korrelation müssen die beiden Strömungsregime separat betrachtet und modelliert werden.

1. Introduction

The pharmaceutical industry is a continuously growing market in which new products are developed and launched every year. Due to the easy handling, the production of these pharmaceuticals is usually carried out in aerated stirred tank reactors with a volume of several cubic meters. However, before the products are launched on the market, the manufacturing processes must undergo strict quality assurance, which often takes place in small reactors with a size of two to five litres. The qualification includes proving that the fermentations on the laboratory scale behave in exactly the same way as on industrial scale. This is often done by adapting the laboratory scale to the large scale, which is a time-consuming and costly undertaking.

The lack of reliable models is primarily based on the fact that investigations on important parameters such as mass transport and mixing time are mainly carried out in small laboratory scales. Only at these scales is it possible to obtain in addition to integral measurements also local information such as bubble size distributions or local flow structures. It has been shown that for the reliable prediction of mass transport as well as for the mixing time, these local data are of great importance. In industrial reactors, these measurements are often not feasible, because of a lack of time and optical access. However, some mechanisms, such as the bubble size distribution or the formation of local flow structures are fundamentally different on various scales. Additionally, many existing correlations have been established for microbial cultivation, working at significantly higher energy inputs and aeration rates compared to mammalian cell cultivation. Both parameters have a significant influence on the process and therefore a transfer of the existing correlations is only possible to a limited extent.

In order to design industrial reactors as well as to adapt laboratory scales for qualification more effectively, it is important to obtain a better understanding on both global and local interrelations for the small and the large scale reactors. To overcome this problem of optical access, a transparent pilot plant on an industrial scale with a volume of V_{Reac} = 12 000 L was set up together with Boehringer Ingelheim Pharma GmbH & Co.KG. The aim of this work is to determine the influence of the local flow structure on mass transfer and mixing time and to identify main differences between laboratory scale and industrial scale. With the help of the transparent reactor, it is now possible to determine a reliable mixing time and to compare the results with existing correlations. The influence of the aeration can also be included in the modelling. In addition, it is possible to determine the bubble size distribution and to identify the influence on the mass transport in order to understand basic mechanisms and to develop more reliable models for mass transport.

2. State of the art

Aerated stirred tank reactors are among the earliest types of reactors, but because of their simple handling and flexibility they are still frequently used. These reactors are particularly common in the pharmaceutical industry, where reliable and safe processes are essential. For a high performance of the cell culture, the reactors need to fulfil different tasks. A good mixing is necessary to provide a homogeneous environment for the cells and to prevent local differences in concentrations of nutrients, pH values or temperatures. Additionally, the mass transfer is of great importance to maintain the oxygen supply in aerobic processes. In this chapter the general background of aerated stirred tank reactors will be given.

For a better understanding of the complex two phase flow, first the characteristics of the unaerated agitation will be presented in chapter 2.1. After that the state of the art of hydrodynamics of two phase flows will be provided.

2.1 Mechanically stirred vessels

In the following a general background on the flow characteristics in agitated tanks for the unaerated case is given. It has been shown that a varity of basic concepts are valid for both the unaerated and the aerated cases.

2.1.1 Equipment for stirred tank reactors

The task of mixing is a wide field ranging from laminar mixing of high viscous liquids to turbulent flows in low viscous media and cannot be achieved with a single stirrer type. Thus, the number of different impeller types is high. Typically they are classified according to the viscosity of the used medium and the main induced flow direction [Zlo03], [Dor13]. In Figure 2-1 the main used stirrer types are listed. On the left side the impellers for media with very low viscosity are presented. Due to the low viscosity of the medium, these agitators are mainly used for turbulent mixing with high stirrer frequencies. The diameters of those impellers are around 1/3 to 1/2 of the reactor diameter. The anchor and the helical ribbon impeller on the right side are usually used in highly viscous media and thus are used for laminar mixing. To provide a good mixing despite the laminar flow, those impellers are often larger than the agitators used for low viscosity liquids. [Zlo03], [Tat91]

In most fermentation processes, for instance with algae, the fermentation broth is a critical factor in the design, as the viscosity increases by several orders of magnitude during the process and often

develops a non- Newtonian behaviour. The fermentation broth in mammalian cell cultivation on the other hand, often changes mainly in the surface tension. The density and the viscosity remain in the same range as water. Thus, in those processes often the radial pumping Rushton stirrer and the axial pumping pitched blade or segment stirrer are used [Nie98], [Dor13].

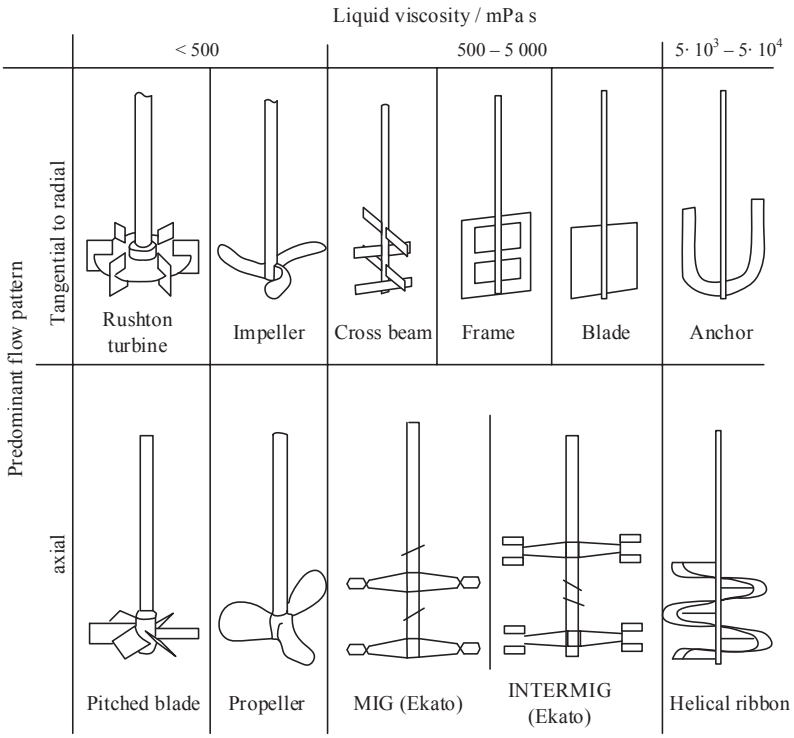

Figure 2-1: Classification of stirrers according to the flow pattern and range of viscosity [Jud76]

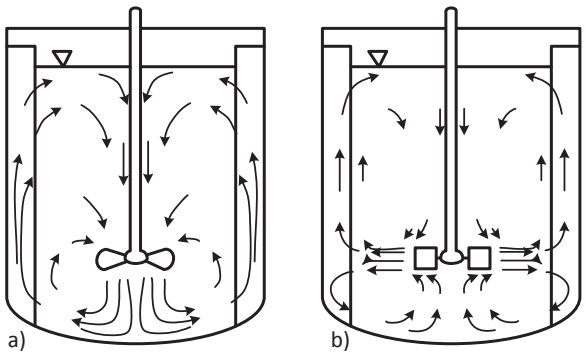

Figure 2-2: Flow pattern on a baffled tank – a) axial flow impeller b) radial flow turbine [Zlo03]

In Figure 2-2 the main induced flow structure of the axial a) and the radial b) pumping impellers can be seen [Zlo03], [Tat91], [Dor13]. Radial pumping impellers such as the Rushton turbine are inducing a high-speed radial flow at the impeller region. At the wall the flow is redirected which leads to an axial flow. The high-speed flow at the discharge of the impeller leads to good dispersion characteristics and makes the Rushton impeller the preferred one when a gaseous phase needs to be dispersed. A disadvantage of this flow behaviour is the tendency to form two compartments, one above and one below the impeller. Within one compartment good mixing can be assumed, but the exchange flow between these compartments is limited. This can lead to a highly increased overall mixing time and is undesirable for industrial processes. [McF96], [Nie98], [Tat91], [Zlo03], [Dor13]

The axial pumping impeller is discharging the material mainly axially but can also lead to a radial flow for a low bottom clearance and large *H/D* ratio [KW93]. The main tasks of the axial impeller are blending and the dispersion of solids. In fermentation processes they can be found as the second stirrer, mounted above a Rushton turbine, and are used to increase the axial mixing. Furthermore, a downward pumping impeller can also be used to extend holding times of gas bubbles in the system to increase the mass transfer rate [Tat91], [Zlo03], [Dor13].

Additionally to the impeller, further installations such as baffles can manipulate the flow structure in the vessel. In a vessel without baffles and with a central stirrer, the liquid starts to rotate as a solid body as illustrated in Figure 2-3. In this flow regime, the liquid moves like a solid and only poor mixing takes place. For higher stirrer frequencies, the absence of baffles can lead to the formation of a surface vortex that can even reach the impeller with the result of air entrainment. This can lead to high shear forces and is thus undesirable for mammalian cell cultivation. [Tat91], [Zlo03], [Nie98]

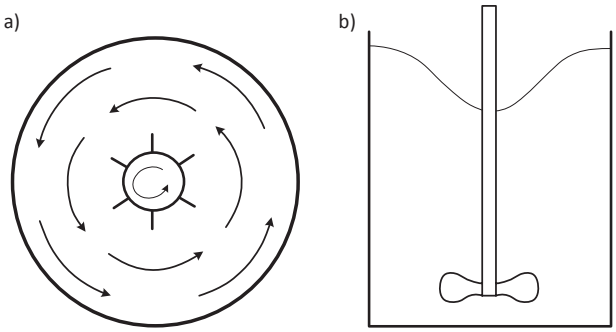

Figure 2-3: Flow field in an unbaffled agitated tank - a) solid body rotation - b) central surface vortex [Tat91]

To prevent a solid body rotation and air entrainment, typically wall baffles are installed that disturb the liquid flow and lead to a redirection of the flow. To reach a “complete baffling” of a cylindrical reactor, four baffles are needed that are installed vertically at the reactor wall. [Tat91], [Dor13]

2.1.2 Basic fluid dynamic parameters

The turbulent flow in stirred tank reactors has a high complexity including many different time dependent flow structures that have to be described. These flow structures include the flows at the agitator with the high-speed discharge flow, at the blade wake regions and at the vortex. Additionally, there are the flow at the wall with the corner flows and the flows around the baffles as well as the bulk flows that includes large circulation zones and toroidal vortices. Due to this complexity, the equations of motion cannot be solved. To be able to describe the liquid flow and mixing in a stirred tank reactor the important, mechanisms need to be found that are often described with the help of dimensionless numbers. [Tat91]

The studies within those reactors occur on different scales- (1) the large - or gross scale studies and (2) the local or detailed studies [Tat91]. The gross scale studies include the overall flow pattern and the gross integral flow measurement (e.g. power input [Zlo67a], [Zlo73], [Arm99] or pumping capacity [Cha16]). It is a rather crude technique that assumes that the flow is reproducible in an average way and that temporal and spatial sequences are repeating. The results of these studies are very simple but also very useful for the basic understanding. The more detailed studies often rely on time depending measurements. It is assumed that the flow is very complex and random so that statistical descriptions are necessary. These measurements include the average velocity profiles and turbulent intensities and are often recorded in lab scale reactors (e.g. [Cut66], [CC88], [KW91], [SC95], [OOK08]).

Due to the size of the reactor this study mainly focuses on the gross scale studies, but for a better understanding of the overall flow, structure a short review about the local phenomena will also be given in this chapter. At first, the global flow structures for different impeller types are presented with the help of important dimensionless numbers for the description of the process. After that, the local flow structures close to the impeller blade and within the bulk of the reactor are described.

Power consumption and global flow pattern

To reduce the complexity, dimensionless numbers are used to describe the flow pattern within the agitated tank. The Reynolds number in stirred tank reactors is defined as

$$Re = \frac{n \cdot d^2}{\nu_L} \tag{2.1}$$

with the stirrer frequency n, the impeller diameter d and the kinematic viscosity of the liquid ν_L. In stirred tanks, the flow is considered to be laminar for Reynolds numbers $Re < 10$ and turbulent for $Re > 2 \cdot 10^4$ [Nie98]. Animal cell cultivations never operate in the laminar region because the viscosity of the liquid is, during the whole process time, in the same range as water, which leads to Reynolds numbers larger than $Re = 10^4$, even for small stirrer frequencies. [Tat91], [Zlo03], [Dor13]