Major Advances in Magnetic Mixing Technology Permit its Broad Industrial Use

Abstract

Magnetic mixing technology stands out with its many advantages compared to mechanically sealed agitators. In particular, the lower risk of contamination and the resulting cost reduction are powerful arguments for the application of magnetic agitators. The development of magnetic mixing technology has progressed in giant strides in recent years, making its use possible for a wide range of stirring processes. Scaling up mixing processes to industrial level is a major challenge because of the conflicting demands on the mixing time, shear forces and hygienic design. Equipping bioreactors of 15,000 L and more with magnetic mixers was altogether inconceivable only a few years ago. This was the case even though the demand from the biotech industry has always been huge for large volume vessels to handle cell cultures without quality losses from inadequate mixing. A bottom-mounted magnetic agitator was developed and tested to meet these requirements for use in XXL fermenters. The results confirmed that the prototype is suitable for vessel sizes up to 30,000 L.

Introduction

Ideal mixing conditions for the equalization of concentration and temperature differences and short mixing times are prerequisite for the optimal homogenization process. In order to draw up a specification for the mixing process, it is essential to accurately understand and define the hydrodynamic flow regimes and the specific power inputs of the mixing rotors and their geometry.

Magnetic agitators are agitator types that are particularly suitable for aseptic processes, in which the motive force is transmitted via magnetic fields without a physical contact between the motor and the impeller. This has the advantage that there is no connection between the sterile interior of the reactor vessel and the unsterile space outside, which reduces the risk of contamination associated with the mechanical seal of shaft-driven agitators.

In the biopharma industry, magnetic agitators are frequently used for preparation systems of up to 20 m^3 working volume and for bioreactors up to 10,000 liters with a low specific power input, < 100 W/m^3. A few years ago, magnetic agitators were mainly used in cases with only moderate demands on mixing time and mass transport. Their technical development has now progressed so far, however, that they are currently being chosen for increasingly complex applications.

ZETA developed the first magnetic agitator with a drive torque of 700 Nm for a bioreactor with a volume of 15 m^3. This design of this bottom-mounted magnetic agitator for bioreactors (BMRF) is small and compact. The goal of the homogenization process in a bioreactor is to maximize the biological productivity. Regarding mass transfer, the need is to achieve an efficient phase transfer of gases into the liquid phase (oxygenation) and vice versa (CO_2 stripping). All these processes are highly complex and interdependent.

One of the main key performance indicators of magnetic agitators is the maximum power input, which rises with increasing rotational speed and viscosity of the liquids. When the admissible torque value, which is transferred from the magnets to the agitator shaft, is exceeded, the magnetic field is disrupted and the impeller starts to slip. In cooperation with Boehringer Ingelheim and the Institute of Multiphase Flows of Hamburg-Harburg University of Technology, a test series was carried out to quantify this performance limit for the newly developed agitator BMRF 40000.

Testing the performance limit

Methods

The agitator was tested in a test vessel with a total volume of 15 m^3 with a series of different impeller geometries (Figure 1) to determine their power transfer to the stirred liquid and their mixing characteristics. The vessel wall was made of acrylic glass, in order to allow the use of optical measurement methods in the whole interior space of the vessel. The mixed liquid was water (density ρ = 999.44 kg/m^3, viscosity η = 1.22 mPas) at T = 12.5 °C.

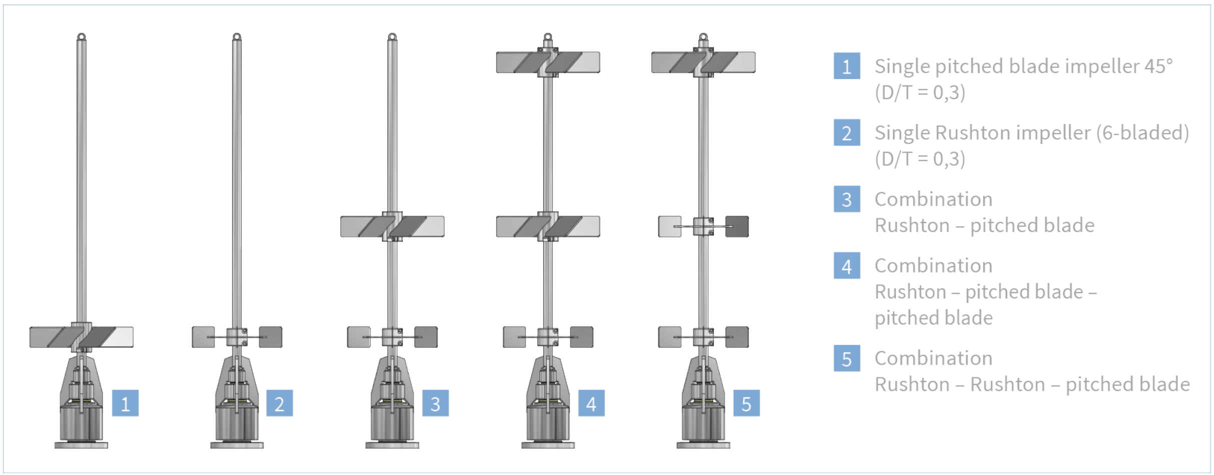

Figure 1: Tested combinations of impeller stages

The agitator is driven by a magnetic field; the impeller assembly rides on a bearing shell with ceramic surfaces. In principle, the higher the density of the fluid and the rotational speed, the higher the power input, whereby also the gassing rate has an influence on this process. In order to measure the actual power input of each impeller combination, it is necessary to know the loss of power generated by the bearing and the mixing head. To do this, the agitator was submersed in water with the water level lying slightly above the agitator shaft. Then the power input of the agitator was measured at different rotational speeds. A measuring flange between the drive and the bearing serves to measure the transferred torque and the actual rotation speed. The torques of the individual impeller combinations were measured and recorded while increasing the rotation speed stepwise. The corresponding power input was determined based on the recorded values. Figure 2 shows results for a pitched blade impeller, illustrating the increases in torque; broadly similar patterns were observed with the other impeller types. After a brief transitional phase, the measured torque changes with the rotational frequency in a plausible way.

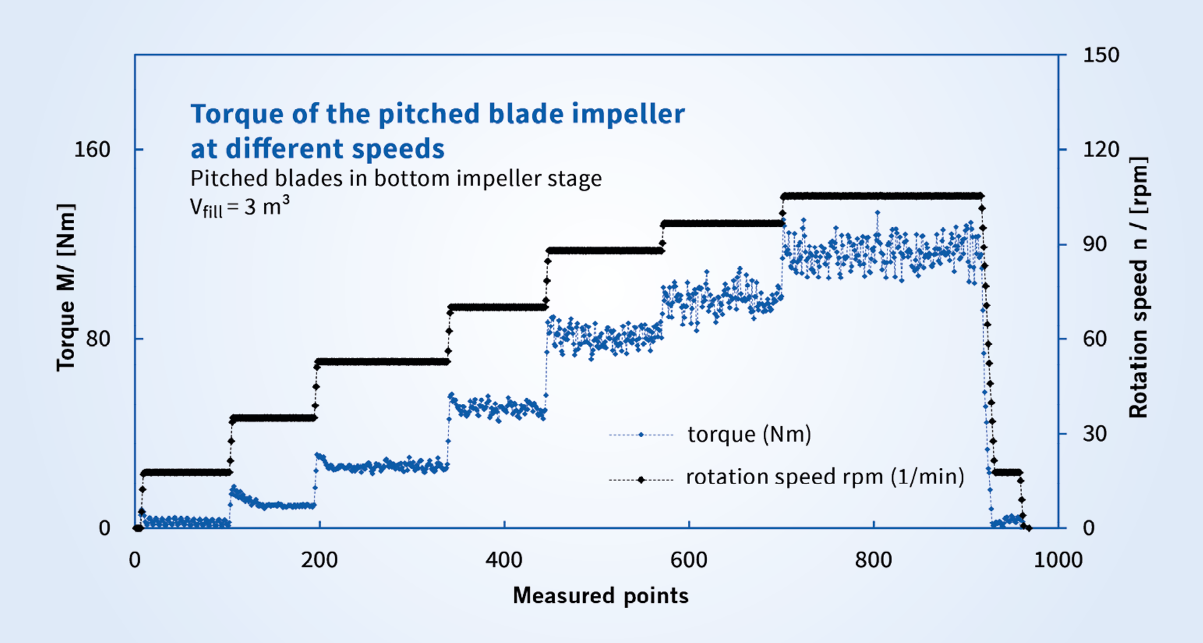

Figure 2: Example of dynamic torque measurement

The performance of an impeller is described by the dimensionless Newton number (Ne value). To determine the Newton number, the mean torque M at steady state is calculated and Equation 1 is used:

$$Ne = \frac{P}{\rho\, d^5 n^3} = \frac{2\pi n M}{\rho\, d^5 n^3}$$

Equation 1: Determination of Newton number

In the course of the test series, comparisons were made between the characteristics of the 6-bladed Rushton impeller and the pitched blade impeller and also multiple stages combinations. According to conventional calculation methods for multi-stage impellers, the total power input of the impeller is equal to the sum of the power inputs of the stages. However, this can only be assumed if the individual stages of the impeller are far enough apart to have no hydrodynamic influence on one another. The test series was designed to characterize the interactions between the impeller stages.

The power input of the following impeller combinations was tested:

- Single-stage – pitched blade (combination 1)
- Single-stage – Rushton (combination 2)
- Rushton – pitched blade (combination 3)
- Rushton – pitched blade – pitched blade (combination 4)
- Rushton – Rushton – pitched blade (combination 5)

These impeller configurations were tested for the two process conditions, gassed and ungassed. A gassing rate of 120 L/min was set, corresponding to a bioreactor gassing of approximately 0.008 vvm (volume per volume and minute).

When changing the rotation direction, pitched blade impellers produce a flow parallel to the central axis. The rotation of a pitched blade impeller in counterclockwise direction creates a flow parallel to the central axis going upwards (up-pumping). If the rotation direction changes, a downward flow is created (down-pumping). For the impeller combination Rushton – pitched blade (combination 3), the power inputs for both directions of rotation were compared.

Furthermore, the stability of the impeller shaft was monitored by means of optical measurements of the upper section of the shaft with a camera. The degree of shaft oscillation was determined at various speeds and then evaluated by means of digital image analysis. In the course of this, the lateral oscillation of the impeller was quantified.

Results

The bearing torque increases with increasing rotation speed, but at 4-13 Nm it is negligible compared to the torque of the different combinations of impeller stages in the liquid (Figure 3).

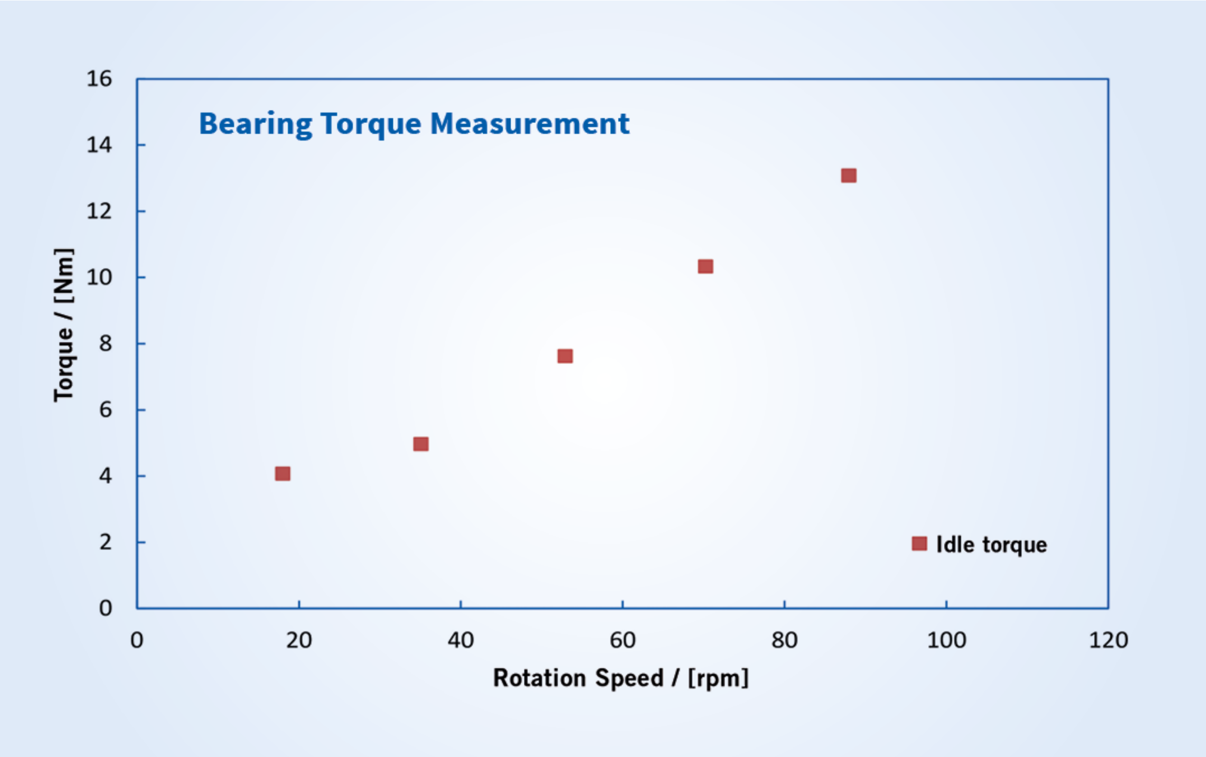

Figure 3: Torque of the bearing at different speeds

The characteristics of the individual impeller stages – Rushton and pitched blade – were found to be as expected. The pitched blade impeller (combination 1) showed Ne = 1.8 and the Rushton impeller Ne = 3.7 (Figure 4).

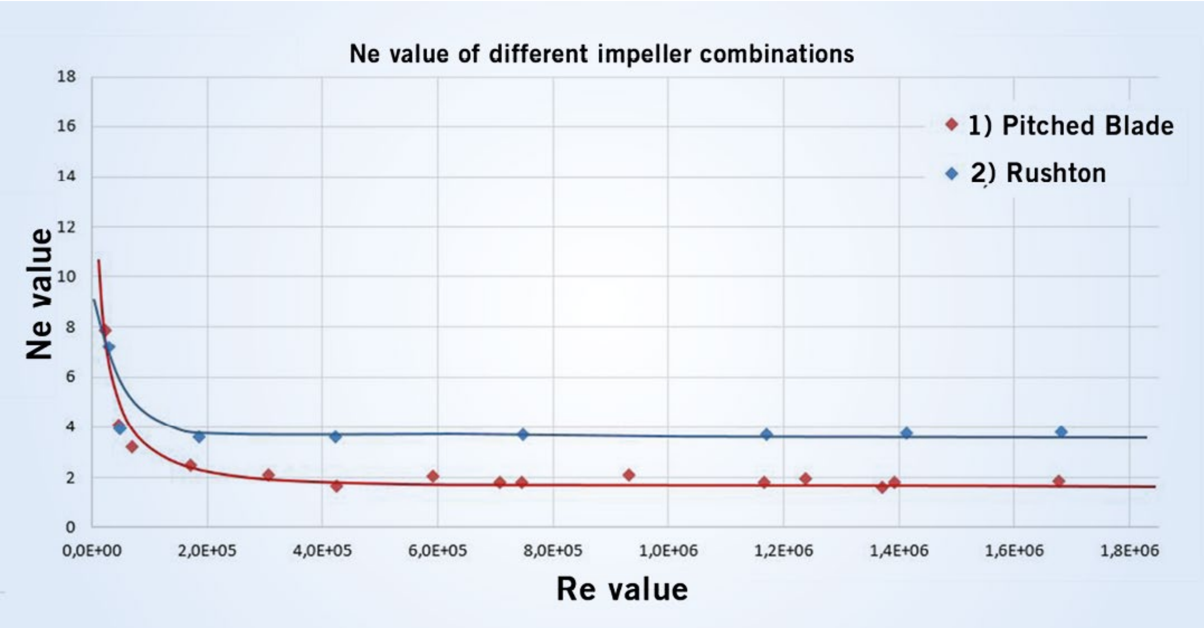

Figure 4: Comparison of the Ne values of single impeller stages: pitched blade (combination 1) and Rushton (combination 2)

If Rushton and pitched blade impeller stages are combined, they influence each other. This is reflected in the total power consumption of the agitator (Figure 5).

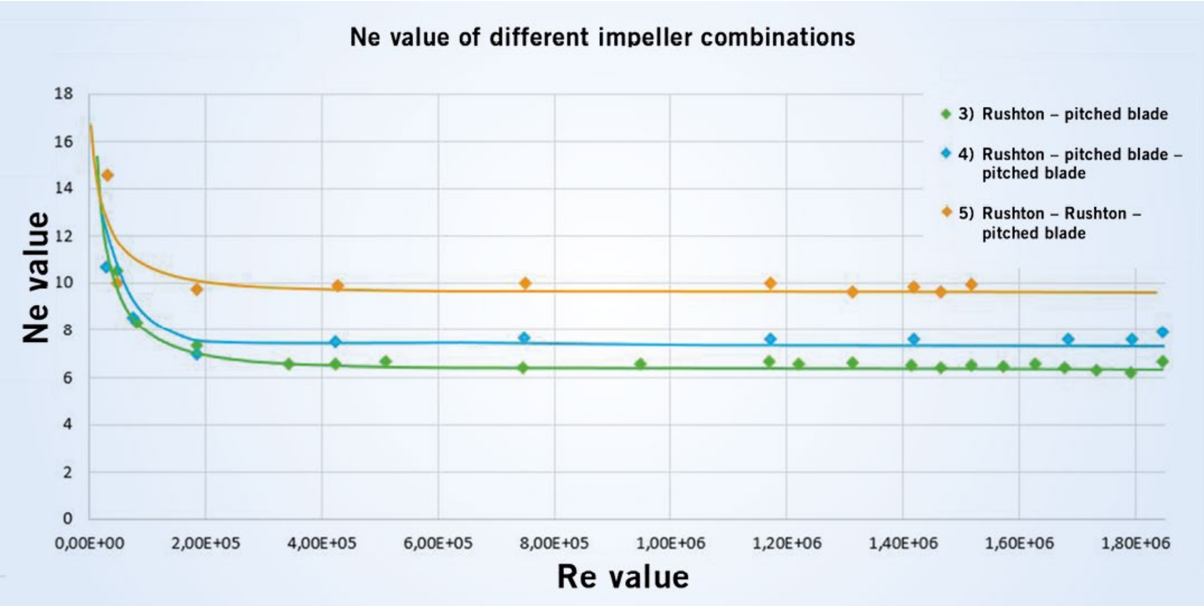

Figure 5: Comparison of impeller combinations

With the combination Rushton – pitched blade (combination 3) a higher power input was observed in the up-pumping mode than in the down-pumping mode, as was expected. The difference in power input between the two modes was about 20 %. In the rotation direction, which corresponds to up-pumping, the upper pitched blade impeller stage evidently has a smaller effect on the lower Rushton stage than in the opposite rotation direction, given the spacing between the two stages used in this case.

The low gassing rate of approximately 0.008 vvm had, as expected, a very small effect on the power consumption of the agitator. Table 1 summarizes the power inputs for the different impeller combinations without gassing.

COMBINATIONS	NEWTON NUMBER **no gassing**	NEWTON NUMBER **with gassing 0.008 vvm**
1) Single pitched blade	1,8	Gassing with low volume flow rates did not have a relevant influence on the Newton number.
2) Single Rushton	3,7	
3) Rushton – pitched blade	6,9	
4) Rushton – pitched blade – pitched blade	7,6	
5) Rushton – Rushton – pitched blade	9,8	

Table 1: Results of power measurements

The rotation speed was increased to find the threshold at which the magnetic coupling breaks down for the three-stage magnetic agitator. The target in the research design was a sustainable, steady speed of 80 rpm. This was achieved both with combination 4 (Rushton – pitched blade – pitched blade) and with combination 5 (Rushton – Rushton – pitched blade). Even at an applied torque of M = 500 Nm no slipping of the magnetic coupling was observed.

With combination 4 (Rushton – pitched blade – pitched blade) a speed of n = 88 rpm was achieved with a torque of M = 340 Nm. With combination 5 (Rushton – Rushton – pitched blade) the torque at this speed was M = 450 Nm. With this combination, even a speed of n = 110 rpm was reached, with a mean torque of M = 555 Nm and peaks of up to 600 Nm.

The agitator model tested did not exhibit critical oscillations that could threaten the stability of the impeller in operation. The tests showed that the operationally relevant speeds of n ≤ 80 rpm did not cause any oscillation of the impeller. With the single Rushton stage (combination 2), the oscillation of the impeller shaft had an amplitude of only 0.5 mm. Even at a speed of up to 105 rpm this amplitude did not increase (Table 2, Figure 6).

IMPELLER COMBINATION	SPEED [rpm]	AMPLITUDE [mm]
Rushton, combination 2	35 88 105	± 0,5 ± 0,4 ± 0,5
Rushton – pitched blade, combination 3	105	± 1,3
Rushton – pitched blade – pitched blade, combination 4	35 88 105	± 1,0 ± 0,6 ± 3,0

Table 2: Overview on impeller oscillation

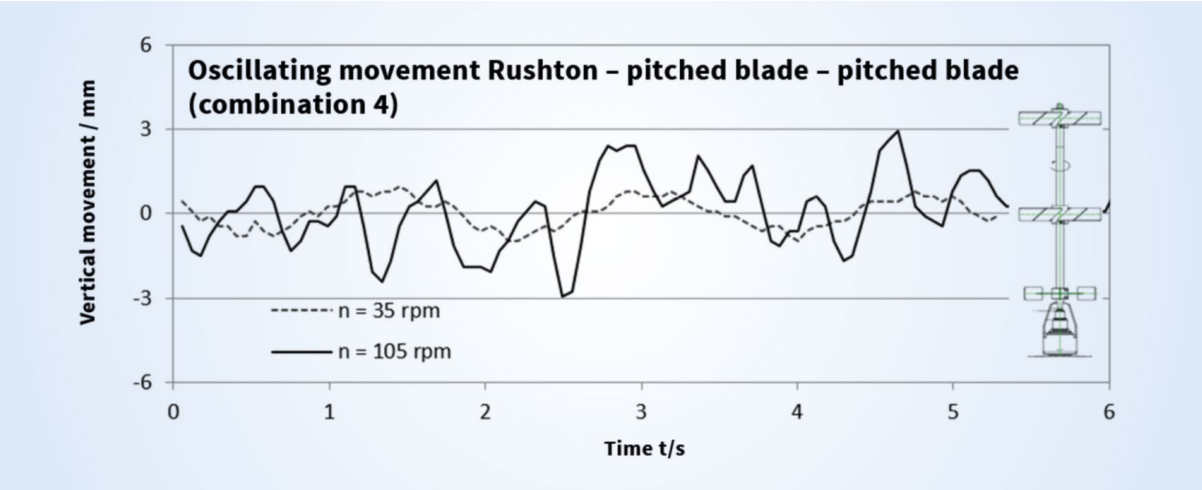

Figure 6: Oscillation of Rushton –pitched blade – pitched blade (combination 4)

A larger effect on the oscillation of the impeller was caused by changing the number of impeller stages. With two stages, the amplitude of oscillation increased to approximately 1.3 mm at 105 rpm. With three impeller stages, the amplitude increased further, to a maximum of 3 mm, which can still be seen as uncritical.

Conclusion

The test series demonstrated the performance and the market readiness of the ZETA BMRF, bottom-mounted magnetic agitator, for large bioreactors with a working volume of 15 m^3.

The BMRF has a negligible loss of power in the impeller bearing.

The expected torque transmission across the magnetic coupling was not only confirmed experimentally, but was exceeded by more than 50 %.

Even with a very compact design, the new agitator displays stable running characteristics across the whole range of speeds used, with three-stage impellers. The design of the agitator enables it to be installed and deinstalled rapidly in any new and existing bioreactors without requiring changes in the geometry or functionality of existing agitator flanges or sparger systems.

The testing method developed is applicable for magnetic agitators of all sizes to determine the operating characteristics and power input of the impeller, and thus to enable rational planning of any mixing process. The valid testing method can be applied to existing as well as new stirred reactors.

The characterization of individual impeller stages and the whole impeller is the methodological basis for a calculation of the mixing time, the mass transfer values (liquid, solid and gaseous), as well as for scaling of impellers and mixing processes.

Broad range of applications for magnetically coupled agitators

The bottom-mounted magnetic agitator system for fermenters and bioreactors on an industrial scale has proved to be successful. However, the benefits of optimized agitator technology are not limited to bioreactors. With the new BMRT XXL, the powerful magnetic coupling of this system was used to transfer the standard impeller technology to other applications, like preparation and buffer systems as well as aseptic mixing in food processing for volumes up to 70,000 L or more, depending on the mixing application.

Magnetic agitators have undergone a substantial development over the past few years. The stirring process can even be conducted in a high volume or under complex conditions. With a powerful magnetic coupling of 700 Nm, an agitator type was developed that can be used in cell culture volumes of up to 30,000 L. The BMRF agitator possesses a magnetic drive with excellent power transmission and a long, vibration-resistant agitator shaft. It was tested in a unique, see-through 15,000 L acrylic glass fermenter. The process equipment could be precisely characterized thanks to the transparent vessel. The extensive tests confirmed the suitability of the equipment for industrial applications. The quantum leaps in its development enable more and more companies to benefit from the advantages of magnetic mixing technology, whether applied in new plants or for the retrofitting of existing vessels.

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