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Mixing characteristics of shaken microtiter plates: Important criteria for high throughput systems in downstream processing

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Process development in high throughput screening systems has been established for several production steps in up and downstream to reduce material and cost on the way to market. Microplates with typical well numbers of 6 to 1586 are state of the art for high throughput screening. For many unit operations it is still a challenge to transfer processes from µ-scale to laboratory and industrial scale. Differences of applied mixing techniques come into play. While microtiter plates are preferentially processed on orbital shakers, on laboratory and industrial scale solutions are stirred. Many reactions depend on efficiency of mixing by which the energy dissipation is controlled. Therefore mixing is one of the most crucial parameters in scale up. So far no technique to determine power input or energy dissipation on μ-scale has been available. A measure for the effective power input is temperature change; the underlying concept used for micro-calorimetry. Mixing leads to an increase of a system's entropy which is related to the specific heat capacity, the mass of the liquid and the time. The effective power input is direct proportional to temperature difference in the system. The maximal energy dissipation ε_m in an agitated system of defined geometry is a measure for the shear/particle stress. Therefore determination of ε_m is an essential step for characterisation of an agitated system. Three model particle systems are described for as indirect methods for the maximal energy dissipation; the clay/polymer flocculation, the enzyme resin, and the silicone oil/water droplet method. Their destruction kinetics is a measure for particles stress and the shear forces these are exposed to and consequently a measure for energy dissipation in a system of arbitrary geometry. In the present study an experimental setup enabling the determination of the temperature change related to the power input by mixing in microtiter plates and laboratory scale stirred tank reactors is established. The clay/polymer system has also been adapted for both scales. The applicability of temperature change and model particle systems to measure the effective power input and energy dissipation in microtiter plates is shown and compared to a laboratory scale reactor. Temperature curves and destruction kinetics have been determined for several mixing conditions in both agitated systems. The characteristic dimensionless process numbers for agitated systems *Ph, Re,* and *Fr* are correlated to the determined values. The effective power input of the system determined by these orthogonal methods enables the correction of the calculation of Ne for the agitated μ-scale systems, which has so far been carried out based on empirical data only available for stirred reactors. The established methods allow the engineering based scale up of mixed systems from μ-scale to pilot scale.

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Commercializing fermentation technology or "overcoming the dead zone"

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Many new developments in fermentation technology are coming out of Universities and small start-up companies. They all face similar challenges in taking their technology to market. There is a substantial gap between the development of a technology and steps required to get it to market, a so called "dead zone". We have been fortunate in proceeding through this region with two fermentation based technologies. Our progress in both a pharmaceutical application and a biofuel application will be used to illustrate some of the steps necessary to bring a product to production.

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