MODERN APPROACHES TO THE DESIGN AND OPTIMISATION OF REACTORS FOR PHARMACEUTICAL MANUFACTURING IN THE TRANSITION TO CONTINUOUS PROCESSES AND MICROGRAVITY RESEARCH

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Abstract

Different reactor types were examined, including batch reactors whose optimization involved studying equipment design and operating variables—traditionally under the assumption of perfect mixing. To account for non-idealities in batch reactors, a cell-model approach was proposed. In continuous processes, plug-flow (tubular) reactors are widely used, where engineers strive to achieve ideal displacement (plug-flow) conditions. Separately, biofilm reactors under simulated micro-gravity were analysed to investigate biofilm growth in spaceflight environments.

Keywords: *batch reactors, plug flow reactors, microgravity biofilm reactor*

Introductions. Pharmaceutical production remains one of the last industries that predominantly uses batch processes, which are inefficient and can cause drug shortages due to the long lead times or quality defects. Consequently, pharmaceutical companies are transitioning away from outdated batch lines, in large part motivated by the many advantages of continuous manufacturing (e.g., low cost, quality assurance, shortened lead time). As chemical reactions are fundamental to any drug production process, the selection of reactor and its design are critical to enhanced performance such as improved selectivity and yield [1].

This report aims to analyse batch, tubular, and biofilm reactors under simulated microgravity for pharmaceutical manufacturing and the study of biofilm growth in space conditions.

Materials and Methods. This work employed an analytical approach involving the review and systematization of existing scientific literature on the design, modelling, and optimization of biochemical reactors used in the pharmaceutical industry. The principles of operation, advantages, and disadvantages of batch and tubular bioreactors were examined. Modelling methods for mixing in batch reactors were analysed, particularly the cell-model approach. The design and application of a biofilm reactor under simulated microgravity were described, along with microbiological analysis methods used to assess biofilm growth.

Results and discussion. Batch reactor design has been studied from various perspectives in order to develop systematic optimization tools to improve performance. For operational variables of temperature and feed addition rate, the design of the operation leads to desired trajectories for these dynamic variables, as well as desired values of other variables that are fixed during a batch cycle.

However, the studies referred to so far were based on the assumption of perfect mixing inside reactor vessels. Unfortunately, this assumption is not valid in many situations, where non-ideal mixing often has a significant impact on reactor performance.

Traditionally, the design of batch reactors considering the impact of mixing has been dealt with by using correlations of overall parameters, including mixing time, power draw and impeller pumping capacity [2].

The compartment modelling approach proposes a simple and realistic mixing model. A compartment model divides a batch reactor vessel into a number of compartments. Each compartment connects to the other reactor compartments through streams. The assumption of perfect mixing is applied only to each compartment, instead of to the reactor as a whole. The models mainly describe macromixing patterns inside the reactor where material transport between different compartments is only by convection. However, they can also represent some degree of micromixing if diffusion is allowed between different compartments. The compartment modelling approach consumes much less computation time

For non-ideal mixing, a mixing compartment network model has been developed based on the compartment modelling approach [2]. The mixing compartment network model represents mixing patterns inside reactor vessels. Variables and parameters in the mixing compartment network model correspond to design variables of the corresponding reactor configurations and equipment. A profile-based approach has been introduced to produce optimal profiles for temperature, pressure and feed addition rate through time.

Tubular reactors are ubiquitous in the manufacture of commodity chemicals, in particular in processes wherein continuous operation is desired or required. The ideal flow condition in a tubular reactor is ‘plug flow’, and under such ideal conditions, the residence time in the reactor is the same for all elements of fluid and there is typically a uniform velocity profile across the radius of the reactor. Product mixing is also ideally limited to material the same age, i.e., mixing occurs in the radial direction only. That is, as the plug flows through the reactor, the plug components are perfectly mixed in the radial direction, with mixing in the axial direction being non-existent.

While in practice, ideal plug flow does not occur, maintaining reasonably good plug through tubular reactors provides significant benefits.

For one, plug flow provides greater separation between reacted and unreacted material than non-plug flow. This is desirable for processes where reaction rate is affected by reactant concentration. And, good plug flow permits precise control of residence time, which can be critical in processes where conversion and/or selectivity are sensitive to the same.

Many factors can impact the ability to provide plug flow conditions approximating ideal. For example, substantial mixing in the axial direction can reduce the quality of plug flow, as can wall friction and diffusion, etc. The effects of many of these can be mitigated by increasing the fluid velocity and/or reactor channel length. Achieving the right combination of residence time, efficient mixing and good plug flow can result in tubular reactors that are hundreds of meters long. Reactors of such length can then present additional difficulties in temperature control and heat transfer characteristics [3].

Biofilm research under microgravity conditions depends on one of two scenarios: collection of planktonic aggregates or conducting experiments under the microgravity of space [5].

While informative techniques, both have their limitations when studying surface-attached microbial communities. A simulated microgravity biofilm reactor (SMBR) was developed to study biofilms in microgravity, coupled with the integration of microfabricated sensors for internal system monitoring (Fig. 1). To test biofilm formation in the centre of the reactor an additional set of six coupons is temporarily integrated along the centreline of the reactor and secured to the endcaps to allow for simultaneous rotation with the reactor body. A section of aluminium pipe is threaded into the influent endcap to accommodate an electrical slip ring are connected to the aluminium pipe and the effluent endcap of the reactor to allow for fluid flow into the reactor during filling and operation. Plastic threaded barb adapters are used to connect the rotary joints to silicone tubing at both the inlet and outlet. Four threaded rods run the length of the reactor body to fasten the coupon ring, polycarbonate tubes, and endcaps together. Biofilm growth was similar on sensor and wall surfaces within the reactor. [4].

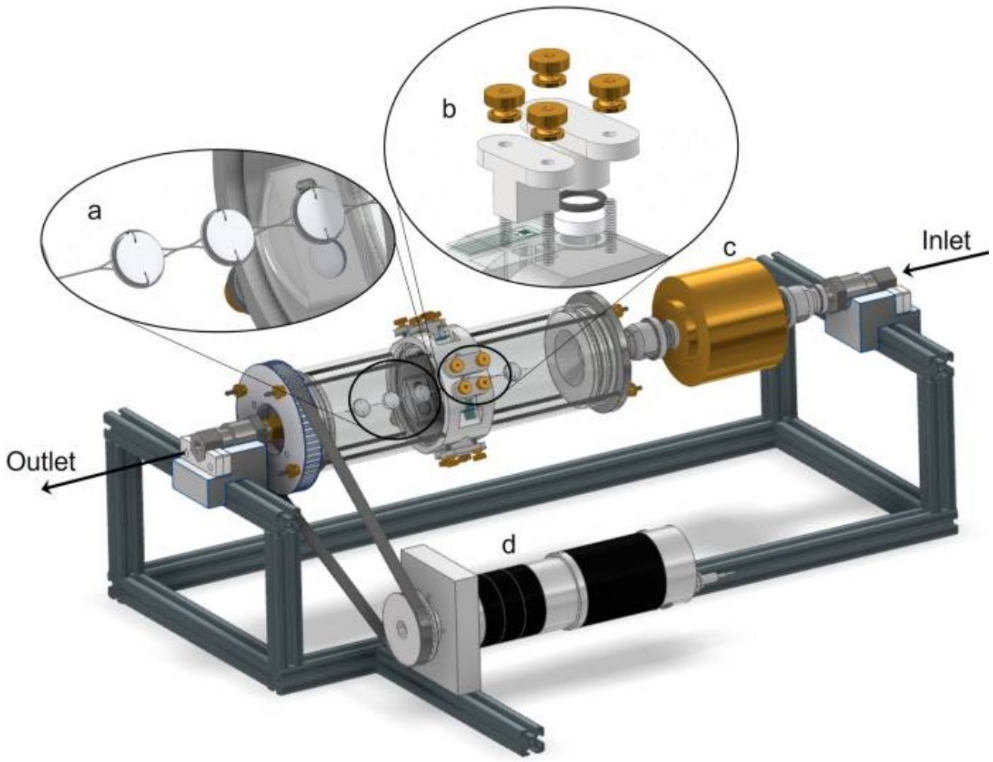

Fig. 1. CAD rendering of the Simulated Microgravity Biofilm Reactor (SMBR), with the main components indicated a) the centreline coupons, b) the sensor and biofilm coupon housing, c) the electrical slip ring, and d) the DC gearmotor. Also shown are the inlet and outlet used for filling and emptying the reactor [4].

Biofilm formation and dispersal cause corrosion, pipeline clogging, water quality issues, health concerns, and operational failures.

The reactor body consists of an 800 mL reaction chamber comprised of two 150 mm sections of polycarbonate tubing with a metallic coupon ring in the centre and

two metallic endcaps. The coupon ring features eight openings that house four microfabricated sensors and four biofilm coupons (Fig. 2). Sensors and coupons are exposed to the media through holes with a recess. The reactor endcaps achieve a watertight seal with the polycarbonate tubing.

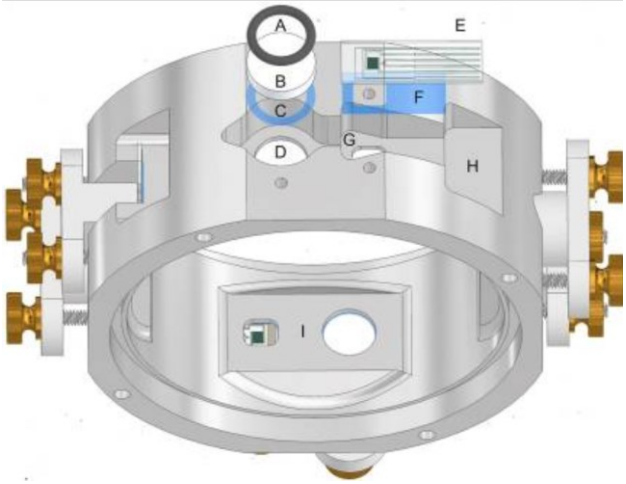

Fig. 2. CAD rendering of a machined coupon ring with integrated sensors and biofilm coupons. The coupon/sensor integration assemblies are composed of A) O-ring to accommodate different coupon thicknesses, B) biofilm coupon, C) silicone gasket for a watertight seal with the biofilm coupon, D) biofilm coupon port, E) microfabricated sensor, F) silicone gasket for a watertight seal with the sensor, G) sensor port, H) card reader slot, and I) internal view of the sensor and biofilm coupon ports [4].

Such biofilm-related issues become especially problematic where maintenance is impractical due to limited resupply capabilities. One such example is the formation of biofilms in environmental control and life support systems [5]. Spaceflight studies highlight biofilm spread on spacecraft and its risks to crew and vehicle. Biofilm control involves biocides, part replacement, and water testing [4].

Conclusions. The pharmaceutical industry aims to shift from inefficient batch to continuous production, where reactor selection and optimization boost productivity. Reactor Research and Development enhances existing methods and explores unique environments. Establishing pharma manufacturing in space presents new opportunities.

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