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SEGMENTED FLOW TECHNIQUE IN LIFE SCIENCES – APPLICATIONS OF THE TECHNOLOGICAL PLATFORM „PIPE BASED BIOREACTORS“

Keywords: segmented flow, screening, cell cultivation.

1. INTRODUCTION

There is a lasting trend to miniaturize bioreactor systems in order to take advantage of properties like the possibility to run those systems in parallel for screening purposes or to save cell cultivation reagents. This trend of miniaturisation has yielded into a couple of different basic systems characterized by the integration of those physical, biophysical and microtechnical effects that are not or only slightly important for conventional bioreactor systems. Currently there are two different attempts for microbioreactors including new analytics, (i) microtiter plates as a parallel system [1] or (ii) sequential systems like specially developed and manufactured small bioreactors [2]. The segmented flow based technique “pipe based bioreactors” (*pbb*) represents one of these attempts. This platform including representative applications will be described here.

2. “PBB” - PRINCIPLE AND APPLICATIONS

2.1 Principle

Based on the long lasting knowledge on developing bioreactors in the Institut für Bioprozess- und Analysenmesstechnik in Heilbad Heiligenstadt there was developed a segmented flow based bioreaction system together with our partner institutes HKI and IPHT in Jena as well as the Technical University in Ilmenau [3], [4]. The bioreactors, called “compartments”, are situated in tubes having diameters of typically 100 µm to 1000 µm. The generation of compartments can be realized by different technical principles, usually microchips having T-junctions are used [5]. On those microchips the compartments, having water like properties concerning permitivity and viscosity, are hydrodynamically injected into a liquid stream having properties of oil. Leaving the microchip the compartments are guided e.g. into a PTFE-tube or a storage chip. Usually there are about 550 compartments in a PTFE-tube having a length of 3 m. If there are biological cells inside the compartments, the tube has to be incubated at defined temperature to establish optimal growth conditions for the cells.

2.2 Applications

Isolation of rare microorganisms

The isolation and characterization of new microorganisms is of particular interest for the exploitation of the natural gene pool of microorganisms. It is assumed, that the majority of microbial species is uncultured up to now - and therefore not known - because of insufficient methods of microorganisms separation and cultivation. The reason for this is the predominance of the majority of microorganisms with the weak ones, e.g. in soil probes. To overcome this problem, a segmented-flow-system was developed to generate compartments from water-solved soil containing unknown microorganisms. Statistically, compartments were generated having one microorganism inside at most. Thus, weak microorganisms were not influenced by others, so that they could grow and proliferate. In the MINIKULT project it could be shown that rarely isolated microorganisms can be separated and cultivated. After cultivation they can be proliferated in larger scale for further investigations.

Drug screening of mammalian cells

The research project SERIZELL focused on the development of microfluidics based assays for the screening of cells under the influence of drugs. To reduce the amount of reagents, cells were incubated in nL-scaled compartments. Different drug concentrations were added to the compartments. After incubation the viability of the cells was detected optically by means of a fluorescence sensitive high speed camera. As the result it could be shown, that it is possible to detect fluorescent dyes as well as fluorescent cells in compartments applying in a high

throughput procedure. The figure depicts a compartment containing mammalian cells.

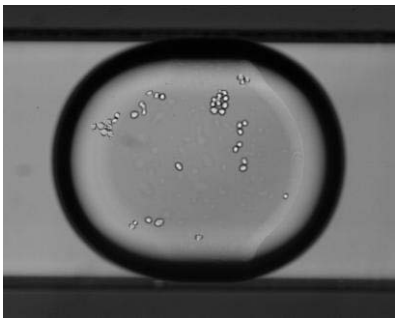

Fig.: Mammalian cells inside a compartment (channel diameter: 500 µm).

Food pathogen detection

Conventional methods for food pathogen detection base on culturing methods and cause time-consuming procedures because a pre-enrichment step is essential. One approach to avoid the pre-enrichment steps is to separate the target organism directly from the sample using specifically binding magnetic beads, known as "biomagnetic separation technique". The combination of this technique with the microfluidic system "pipe based bioreactors" opens the possibility to increase the sensitivity of the analytics, to reduce the volume of reagents and thus the waste volume [6]. The detection time will decrease from a couple of days to 8 hours. This new approach was developed together with the Technical University of Dresden in the frame of the research project "LÖBISENA".

3. CONCLUSION

The above described applications prove, that microbiological techniques can easily be transferred into small volumes of aqueous compartments. Microbiological methods as well as investigations of mammalian cells could be adapted onto the segmented-flow technique. Further applications especially in the fields of biomedicine and individual medicine are expected.

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