Abstract

Drug development is a long and expensive process during which more than 90% of drug candidates fail due to unforeseen adverse effects or lack of efficacy. One of the underlying reasons for such a high rate of failure is that methods used to evaluate and study drug candidates in the preclinical phase, such as static cell cultures and animal models, are not representing human physiology and pathological conditions well enough. These conventional, widely used *in vitro* and *in vivo* models established decades ago and used for studying complex biological processes in the human body, led to one of the main bottlenecks in drug development - the inability to mimic human-specific responses and organs *ex vivo*. Consequently, models capable of bridging the gap between the conventional static cell cultures and preclinical *in vivo* testing are required. *In vitro* microfluidic cell-based systems have emerged as tools designed to better mimic and understand the mechanism of action of drugs, human physiology and pathology.

There are different approaches for culturing cells in microfluidics, such as lab-on-a-disc (LOD) system, which requires a simple spindle motor and exploits the centrifugal forces for liquid movement and lab-on-a-chip (LOC) system, where external pumps, tubing and connectors are used for fluidics. The aim of this PhD project was to develop *in vitro* microfluidic cell-based systems and evaluate their usability with drug delivery systems and model drugs. In the frame of this project, a cell culture and microscope on disc (CMoD) platform, based on a LOD approach, and a gut-on-a-chip (GoC) platform, based on a LOC approach, were developed. Both platforms were fabricated from a common thermoplastic using rapid prototyping techniques.

The CMoD is easy-to-use, compact and portable system, containing a spindle motor, cell culture unit and integrated microscope, which can be placed in a conventional incubator. To the best of our knowledge, long-term mammalian cell culture has not been reported in the centrifugal microfluidics setting. The developed centrifugal platform allowed culturing cells for up to 6 days under continuous perfusion conditions. In addition, a cytotoxicity assay was performed where the time dependent effect of an anticancer drug was evaluated. Cell attachment, growth and division in real-time was monitored with the integrated microscope. The CMoD can be used to investigate the dynamic cell processes during the perfusion culture in real time becoming an indispensable tool in the pharmaceutical research.

The GoC was designed to facilitate long-term Caco-2 cell culture for drug transport studies. Under continuous flow, Caco-2 cells in the GoC differentiated into the columnar-shaped cells, formed tight junctions and villi-like undulations, and expressed mucoprotein-2 in the apical surface of the cells. The chosen materials and fabrication techniques for the GoC allowed to create a system that is easy to fabricate, assemble and use in drug transport studies. In addition, the possibility to easily change the design of the chip increased the flexibility of the optimization process of the GoC system. For the first time, the GoC system was used to assess drug transport from a drug delivery system instead of transport of a free drug. The self-nanoemulsifying drug delivery system was evaluated in a complex biorelevant medium, while cell culture medium or buffer solutions were used in previously reported GoC systems. This level of complexity regarding the drug transport study in a GoC system has not been reached before and could result in an improved predictability of the behaviour of a drug or drug delivery system.