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Development of a Biosensor Platform Measuring the Electrical Resistance in a Tailor-Made System for Biological Barriers to Assess the Barrier Integrity

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Summary:
Monitoring the electrical resistance across biological barriers can serve as an indicator of barrier integrity. Our biosensor system offers an alternative for electrical resistance measurements in a tailor-made system for biological barriers. Measurements of agarose gels at different concentrations (0.5%, 2% w/v) and volumes (150, 300 µl) should demonstrate the ability to distinguish between different conductive barriers. Resistance differences of intact and perforated barriers should highlight the sensor´s potential to assess the barrier integrity and its application in pharmaceutical research.

Keywords: biosensor, electrical resistance, biological barrier, pharmaceutical research, transepithelial electrical resistance

Introduction

Biological barriers, such as the intestinal epithelium, play a crucial role in pharmaceutical research. Studying these barriers often involves monitoring their integrity using the transepithelial electrical resistance (TEER), an accepted technique that quantifies electrical resistance across the cellular layer [1,2]. A high electrical resistance indicates an intact barrier, while weakened cell junctions display a reduced resistance value. Commercially available devices have the drawback of limited flexibility concerning electrode placement [1,3]. Common "chopstick" electrodes, with fixed design and spacing, restrict customization options.
Our work presents a biosensor platform integrated in a 3D printed made tailor-made system for biological barriers, designed to measure electrical resistance. The continuous monitoring of the electrical resistance is essential to ensure a stable and intact barrier and prevent disturbances of the barrier during experiments. The sensor system offers an adaptable alternative for electrical resistance measurements across barriers, with flexibility in electrode positioning, electrode geometry, and the applied potential, current, and frequency. This adaptability makes it suitable for assessing barrier integrity in dynamic environments, such as during transport studies.

Methods

The 3D printed polylactic acid (PLA) based module, consisting of a cover component and a base component, is linked to a peristaltic pump (BMT Fluid Control Solutions GmbH, Germany). The cell culture insert (Corning, USA) includes a porous polyethylene terephthalate (PET) membrane with a pore size of 0.4 µm. Before starting the measurements, the modules are filled with Hanks' balanced salt solution (HBSS buffer, gibco, Thermo Fisher Scientific, USA). The sensor set-up features two stainless steel wires as electrodes, one in the upper compartment and one in the lower compartment (Fig. 1) The circuit consists of a voltage divider circuit linked to an Arduino microcontroller (Fig. 2). The space between the electrodes contains the buffer and the barrier, which includes the PET membrane and the barrier model. Agarose gel is prepared at varying concentrations (0.5%, 2% w/v) in HBSS buffer, boiled at 200 °C, and pipetted onto the membrane in volumes of 150 µl or 300 µl, to simulate a barrier model. To assess the sensor’s ability to distinguish between intact and disrupted barriers, the respec-

tive gel is perforated with a 1000 µl pipette tip and remeasured.

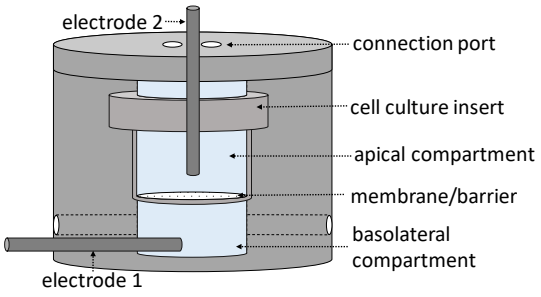

Fig. 1 Customized electrode set-up integrated into a specially designed module that can accommodate a cell culture insert with a barrier

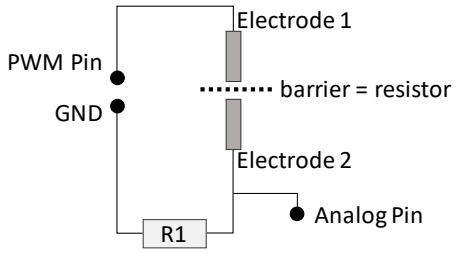

Fig. 2 The measurement principle involves a voltage divider with R1 as a resistor, two electrodes and a barrier that acts as a resistor.

Results

Initial data indicate the sensor´s potential to distinguish between an insert containing only buffer (without membrane), an insert with a PET membrane, and inserts filled with 150 µl 2% w/v or a 300 µl 2% w/v agarose gel. A 150 Ω resistor was chosen as R1.

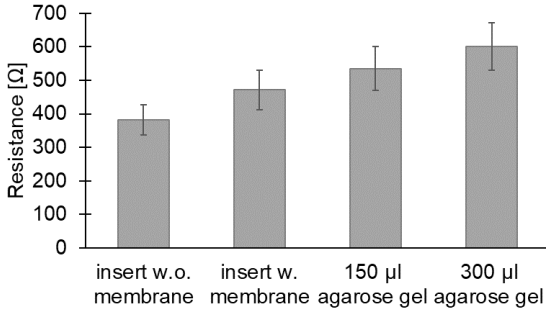

Fig. 3 Comparison of measured resistance across different barriers (n=5), including inserts without a membrane (w.o.), with a membrane (w.), and with 150 µl or 300 µl of 2% w/v agarose gel.

Preliminary resistance measurements (2000 Ω resistor chosen as R1) of the perforated gel resulted in a decrease in resistance for the disrupted agarose barriers of 105 Ω for the 150 µl 0.5% w/v gel and 131 Ω for the 150 µl 2% w/v gel (Fig. 4), showing the potential to differentiate between the intact barrier and a perforated gel barrier.

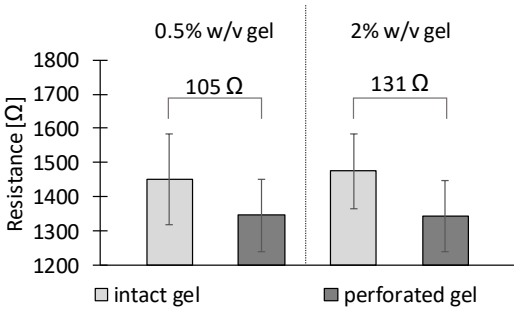

Fig. 4 Resistance measurements of agarose gels with 150 µl 0.5% w/v and 150 µl 2% w/v , comparing intact versus perforated gels (n=5).

Conclusion

In conclusion, a sensor platform was developed to perform electrical resistance measurements of biological samples. Measurements using different conductive substrates, such as varying concentrations and volumes of agarose gel, indicate the platform's potential to distinguish between substrates with different electrical conductivity properties and between intact and perforated gel barriers. This advantage shows great potential for pharmaceutical research, as monitoring the barrier integrity is crucial for assessing the impact of environmental factors on the cell or tissue models during experiments. This is especially important in *in-vitro* models designed to simulate physiologically relevant environments, intending to reduce the need for animal studies. Future steps will focus on integrating cell monolayers to further validate the sensor's functionality in a biologically relevant model. Additionally, the platform could offer the potential to assess pharmaceutical-induced toxicity, as reduced electrical resistance indicates cell barrier disruption, which might correlate to cytotoxicity.

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