Microfluidic Marvels: Oral Cavity-on-a-Chip Transforming Dental Science

Namrata Dagli [1], Mainul Haque [2,3], Santosh Kumar [4]

Please Click on Photo



ABSTRACT

Keywords
Oral Cavity-on-a-Chip, Organ-on-a-Chip, Tooth-on-a-Chip, Mucosa-on-a-Chip, Gingiva-on-a-Chip, Microfluidic chip, Personalized medicine, Personalized dentistry

In recent years, microfluidics has witnessed unprecedented advancements, paving the way for transformative breakthroughs in various scientific disciplines. Among these innovations, the development of organ-on-a-chip technology stands out as a remarkable stride toward imitating the complexity and functionality of human organs in a controlled, miniature environment [1]. One such pioneering endeavor is the creation of the "Oral Cavity-on-a-Chip," a cutting-edge platform that holds immense promise for revolutionizing dental research, drug development, personalized medicine, and personalized dentistry [2].

The oral cavity is a complex and dynamic environment, pivotal in various physiological processes such as digestion, immune response, and communication. Traditional in vitro models often fail to replicate the intricate interactions within the oral cavity. Oral Cavity-on-a-Chip is a sophisticated microfluidic system designed to mimic the physiological conditions of the oral environment with unmatched accuracy. This innovative technology can potentially recreate the critical components of the oral cavity, including the mucosal surfaces, salivary glands, and even the microbiome, on a miniature chip. By incorporating living cells, such as epithelial cells, fibroblasts, and bacteria, researchers can now observe and manipulate cellular behaviors in a controlled setting, providing insights into the intricate dynamics of oral health and disease [1,2]. The editorial delves into the basic design of these microfluidic models, their practical applications in various scientific domains, the distinct types tailored for specific research inquiries, and the anticipated directions for ongoing and future investigations.

1. Karnavati Scientific Research Center, Karnavati School of Dentistry, Karnavati University, Gandhinagar, India.
2. Unit of Pharmacology, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia (National Defence University of Malaysia), Kuala Lumpur, Malaysia.
3. Department of Research, Karnavati Scientific Research Center (KSRC) Karnavati School of Dentistry, Karnavati University, Gandhinagar, Gujarat-382422, India.
4. Department of Periodontology, Karnavati School of Dentistry, Karnavati University, Gandhinagar, Gujarat, India- 382422.

Correspondence
Mainul Haque. Unit of Pharmacology, Faculty of Medicine and Defence Health, Universiti Pertahanan Nasional Malaysia (National Defence University of Malaysia), Kem Perdana Sungai Besi, 57000 Kuala Lumpur, Malaysia. **Email**: runurono@gmail.com, mainul@upnm.edu.my. Cell Phone: +60109265543

Bangladesh Journal of Medical Science Vol. 23 No. 03 July'24

DOI: https://doi.org/10.3329/bjms.v23i3.75011

BASIC STRUCTURE

The oral cavity-on-a-chip model is a specialized version of the broader organ-on-a-chip technology designed to replicate the unique features and challenges of the oral environment. The oral cavity is a highly dynamic and complex environment with distinct features such as the presence of teeth, salivary glands, mucosal surfaces, and a diverse microbiome. Designing an oral cavity-on-a-chip involves mimicking these specific structures and interactions, making it more intricate than other organ-on-a-chip models.

Creating an essential structure for an oral cavity-on-a-chip model involves designing a microfluidic chip that replicates essential components and creating a microenvironment that mimics the complexities of the oral cavity. Microfluidic chips can be made from various materials, including glass, silicon, and polymers. Standard fabrication techniques for microfluidic chips include soft lithography, photolithography, and injection molding. These methods enable the creation of intricate microstructures and channels on the chip. The microfluidic chip should replicate the critical components of the oral cavity, including cell culture compartments representing diverse oral tissues, such as epithelial cells, fibroblasts, and salivary gland cells, embedded within an extracellular matrix. The extracellular matrix may incorporate hydrogels or other materials to provide structural support and a substrate for cell attachment and growth. Incorporating a perfusion system simulates blood flow, enabling the delivery of nutrients, oxygen, and drugs [2,3].

Additional features like simulated saliva production, microbiome components, and realistic pH and temperature control enhance the physiological relevance of the model and facilitate the study of drug absorption and metabolism in the unique microenvironment. Mimic saliva production and flow by incorporating components representing salivary glands involve microchannels to simulate saliva ducts and compartments with appropriate cells for saliva production. A microbiome component can be integrated to simulate the diverse microbial communities present in the oral cavity. This may involve introducing bacteria strains relevant to oral health and disease [4,5]. For the research on dental applications, structures representing teeth, including enamel, dentin, pulp, cementum, and periodontal ligaments, can be incorporated. This allows for studying dental diseases and drug interactions within a tooth microenvironment. Implementing mechanisms for controlling pH and temperature to replicate the dynamic conditions within the oral cavity accurately makes it possible to study the effects of varying environmental conditions on drug interactions and cellular responses [2].

Designing the oral cavity-on-a-chip to be compatible with other organ-on-a-chip models creates multi-organ systems. This can provide a more comprehensive understanding of systemic interactions [6]. Compatibility with advanced imaging techniques can allow real-time observation of cellular behaviors, drug interactions, and dynamic changes in biophysical and biochemical parameters within the oral cavity-on-a-chip [7]. The flexibility of this basic structure allows adaptation to specific research goals, fostering collaboration among experts in microfluidics, cell biology, and engineering for successful model development.

APPLICATIONS

The Oral Cavity-on-a-Chip holds immense potential for advancing dental and medical research, offering a platform to study pathological processes involved in oral diseases, the pharmacokinetics of various drugs in an oral microenvironment, and the impact of multiple treatments (Figure 1). It allows investigation of the mechanisms underlying conditions such as periodontal disease, dental caries, and oral cancers in a more physiologically relevant context [4,8]. This technology accelerates the pace of discovery, facilitating the development of targeted therapies and preventive strategies for oral health issues.

The pharmaceutical industry faces constant challenges in developing effective and safe human-use drugs. The Oral Cavity-on-a-Chip provides a valuable tool for testing the efficacy and safety of oral medications in a realistic environment. This platform enables researchers to assess drug absorption, metabolism, and potential side effects more accurately, reducing the reliance on animal models and expediting drug development. Oral cavity-on-a-chip models enable the exploration of drug interactions with the oral mucosa, saliva, and the microbiome, fostering the development of targeted therapies for dental applications, microbiome-related conditions, and oral cancers [4,5,8]. Additionally, the technology offers a platform to evaluate localized drug delivery systems within the oral cavity, contributing to the refinement of drug development processes

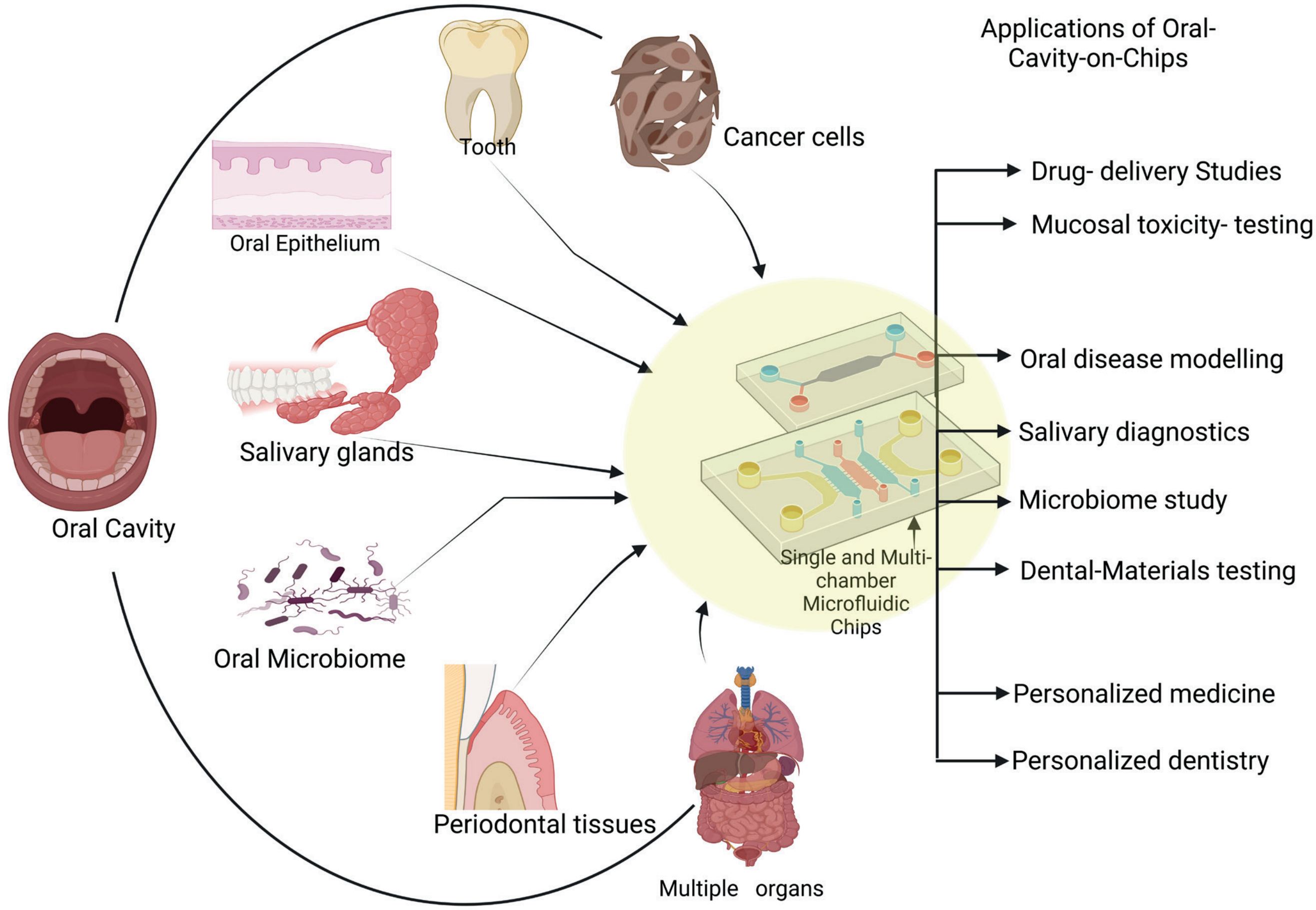

Figure 1: Applications of Oral Cavity-on-Chip Technology in Biomedical Research.

Notes: This figure has been drawn with the premium version of BioRender (https://biorender.com/ accessed on 9th March 2024) with the license number ZD26JY9RC1.

Image Credit: Namrata Dagli

and potentially expediting the translation of novel therapeutics into clinical applications.

In addition, this innovative approach provides a controlled and physiologically relevant platform for studying the interactions between dental materials and the complex environment of the oral cavity. The technology allows researchers to assess dental materials' biocompatibility, degradation, and performance in a more realistic setting. The researchers can investigate how dental materials interact with saliva components and the diverse microbial communities in the oral cavity, providing insights into potential effects on material degradation and oral health. Researchers can use oral cavity-on-a-chip models to assess dental materials' wear resistance and durability more accurately. Oral cavity-on-a-chip technology facilitates the study of dental material interactions with oral tissues, including their impact on tissue regeneration. This is particularly relevant for materials used in procedures such as dental implants, where the integration with surrounding tissues is critical for long-term success. The technology offers a more efficient and accelerated testing environment for dental materials [5].

Furthermore, the personalized nature of the Oral Cavity-on-a-Chip allows researchers to customize the chip with patient-specific cells, paving the way for personalized medicine and personalized dentistry approaches. This opens new avenues for tailoring treatments based on an individual's unique oral environment, ensuring more targeted and effective therapies.

TYPES OF ORAL CAVITY ON CHIP MODELS

The development of oral cavity-on-a-chip technology has led to various models, each tailored to address specific research questions. These models utilize cells derived from individual patients to create personalized oral cavity-on-a-chip models to enable the study of patient-specific responses to drugs, pathogens, and therapeutic interventions. Here are several types of oral cavity-on-a-chip models that have been developed or proposed:

Salivary Gland-on-a-Chip

It focuses on replicating the microenvironment of salivary glands by mimicking the physiological processes of saliva production, composition, and secretion. It enables the study of salivary gland function, dysfunction, and responses to stimuli. In addition, it serves as a valuable tool for exploring the radiosensitivity of glands and screening potential radioprotective drugs that are both less toxic and more efficient than currently employed options [9,10].

Gingiva-on-a-Chip

It incorporates epithelial and connective tissue components to replicate the gingival microenvironment. It aims to study the interactions between oral bacteria, immune cells, and gingival tissues. Targets the gingival tissues to investigate periodontal diseases and tissue regeneration [4,11].

Oral Mucosa-on-a-Chip

It replicates the mucosal linings of the oral cavity to study interactions with drugs, pathogens, therapeutic agents, and dental materials. It offers insights into mucosal immunity, barrier function, and responses to inflammation [5,12].

Microbiome-on-a-Chip

It focuses on the microbial communities within the oral cavity. It allows for the co-culture of different bacterial strains to study microbiome dynamics and responses to environmental changes. It aids in understanding the role of the oral microbiome in health and disease [4, 13].

Tooth-on-a-Chip

It aims to mimic the structure and function of a tooth 14 and includes components such as enamel, dentin, pulp, cementum, and periodontal ligament cells. It enables the study of dental diseases, drug interactions, tissue regeneration, and cytotoxicity [3].

Multi-Organ Systems

These systems integrate the oral cavity-on-a-chip with other organ-on-a-chip models to comprehensively represent systemic interactions. They allow for studying how oral health influences other organs and vice versa [6,15].

Disease-Specific Models

These models focus on replicating specific oral diseases, such as oral cancers [8]. They allow researchers to investigate disease mechanisms, test potential therapies, and study the impact of genetic factors.

These diverse oral cavity-on-a-chip models provide researchers with versatile tools to explore various aspects of oral health and disease. As the technology evolves, ongoing innovations will likely lead to more sophisticated and tailored models, expanding the applications and impact of oral cavity-on-a-chip technology in biomedical research and healthcare.

CHALLENGES AND FUTURE DIRECTIONS

While the Oral Cavity-on-a-Chip marks a groundbreaking advancement, addressing challenges in its complexity, scalability, and reproducibility is crucial for widespread adoption, necessitating collaboration between researchers and engineers. The future of oral cavity-on-a-chip technology holds promising avenues, including integrating multi-organ systems to enhance the understanding of systemic interactions [6,15]. Advanced imaging and sensing techniques are expected to improve the real-time monitoring of cellular responses. Researchers are likely to explore the complexity and dynamics of the oral microbiome, studying microbial interactions under diverse conditions. Additionally, a focus on incorporating immune components into these models will enable studying immune responses within the oral environment [16]. Anticipated developments include disease-specific models, high-throughput screening, and integration of bioprinting technologies for a more comprehensive understanding of oral health and disease. Standardization and commercialization efforts may further drive the adoption of oral cavity-on-a-chip technology in pharmaceutical and biotechnology industries, advancing personalized therapeutic interventions in oral medicine. Creating effective organ-on-a-chip (OOC) devices poses challenges in mimicking native extracellular matrix (ECM) microenvironments, necessitating the development of materials and precise methods that accurately replicate the diverse and dynamic nature of the natural ECM, further compounded by the need for innovative hybrid materials and fabrication methods at the intersection of biological and engineering domains [17].

In summary, the advent of the Oral Cavity-on-a-Chip marks a pivotal moment in the intersection of microfluidics, biology, and medicine. This innovative technology propels dental research forward and holds the potential to reshape drug development and usher in a new era of personalized oral healthcare. As scientists continue to refine and expand the capabilities of this miniature marvel, we can anticipate a future where the Oral Cavity-on-a-Chip plays a central role in advancing our understanding of oral health and improving patient outcomes.

CONSENT FOR PUBLICATION

The author reviewed and approved the final version and has agreed to be accountable for all aspects of the work, including any accuracy or integrity issues.

DISCLOSURE

The author declares that they do not have any financial involvement or affiliations with any organization, association, or entity directly or indirectly related to the subject matter or materials presented in this editorial. This includes honoraria, expert testimony, employment, ownership of stocks or options, patents, or grants received or pending royalties.

DATA AVAILABILITY

Information is taken from freely available sources for this editorial.

AUTHORSHIP CONTRIBUTION

All authors contributed significantly to the work, whether in the conception, design, utilization, collection, analysis, and interpretation of data or all these areas. They also participated in the paper's drafting, revision, or critical review, gave their final approval for the version that would be published, decided on the journal to which the article would be submitted, and made the responsible decision to be held accountable for all aspects of the work.

REFERENCES

1. Kumar S, Dagli N, Haque M. Miniature Biodevices with Mighty Impact: the Current Applications and Future Challenges of Organ-on-Chip Technology. *Bangladesh Journal of Medical Science*. 2023; **22**(4):725–728. doi:10.3329/bjms.v22i4.68667
2. Huang C, Sanaei F, Verdurmen WPR, Yang F, Ji W, Walboomers XF. The Application of Organs-on-a-Chip in Dental, Oral, and Craniofacial Research. *J Dent Res*. 2023;**102**(4):364-375. doi: 10.1177/00220345221145555.
3. Hu S, Muniraj G, Mishra A, Hong K, Lum JL, Hong CHL, Rosa V, Sriram G. Characterization of silver diamine fluoride cytotoxicity using microfluidic tooth-on-a-chip and gingival equivalents. *Dent Mater*. 2022;**38**(8):1385-1394. doi: 10.1016/j.dental.2022.06.025.
4. Ardila CM, Jiménez-Arbeláez GA, Vivares-Builes AM. Potential Clinical Application of Organs-on-a-Chip in Periodontal Diseases: A Systematic Review of In Vitro Studies. *Dent J (Basel)*. 2023;**11**(7):158. doi: 10.3390/dj11070158.
5. Rahimi C, Rahimi B, Padova D, Rooholghodos SA, Bienek DR, Luo X, Kaufman G, Raub CB. Oral mucosa-on-a-chip to assess layer-specific responses to bacteria and dental materials. Biomicrofluidics. 2018;12(5):054106. doi: 10.1063/1.5048938.
6. Koning JJ, Rodrigues Neves CT, Schimek K, Thon M, Spiekstra SW, Waaijman T, de Gruijl TD, Gibbs S. A Multi-Organ-on-Chip Approach to Investigate How Oral Exposure to Metals Can Cause Systemic Toxicity Leading to Langerhans Cell Activation in Skin. *Front Toxicol*. 2022;**3**:824825. doi: 10.3389/ftox.2021.824825.
7. Zhang YS, Aleman J, Shin SR, Kilic T, Kim D, Mousavi Shaegh SA, Massa S, Riahi R, Chae S, Hu N, Avci H, Zhang W, Silvestri A, Sanati Nezhad A, Manbohi A, De Ferrari F, Polini A, Calzone G, Shaikh N, Alerasool P, Budina E, Kang J, Bhise N, Ribas J, Pourmand A, Skardal A, Shupe T, Bishop CE, Dokmeci MR, Atala A, Khademhosseini A. Multisensor-integrated organs-on-chips platform for automated and continual in situ monitoring of organoid behaviors. *Proc Natl Acad Sci USA*. 2017;**114**(12):E2293-E2302. doi: 10.1073/pnas.1612906114.
8. Pandya D, Nagarajappa AK, Reddy S, Bhasin M. Lab-on-a-chip-oral cancer diagnosis at your doorstep. *J Int Oral Health*. 2015;**7**(11):122. https://www.ispcd.org/userfiles/rishabh/V7I11/V7I11A27.pdf
9. DeLouise L, Piraino L, Chen CY, Mereness J, Dunman P, Benoit D, Ovitt C. Identifying novel radioprotective drugs via salivary gland tissue chip screening. *Res Sq [Preprint]*. 2023:rs.3.rs-3246405. doi: 10.21203/rs.3.rs-3246405/v1.
10. Song Y, Uchida H, Sharipol A, Piraino L, Mereness JA, Ingalls MH, Rebhahn J, Newlands SD, DeLouise LA, Ovitt CE, Benoit DSW. Author Correction: Development of a functional salivary gland tissue chip with potential for high-content drug screening. *Commun Biol*. 2022;**5**(1):315. doi: 10.1038/s42003-022-03274-3.
11. Muniraj G, Tan RHS, Dai Y, Wu R, Alberti M, Sriram G. Microphysiological Modeling of Gingival Tissues and Host-Material Interactions Using Gingiva-on-Chip. *Adv Healthc Mater*. 2023;**12**(32):e2301472. doi: 10.1002/adhm.202301472.
12. Ly KL, Rooholghodos SA, Rahimi C, Rahimi B, Bienek DR, Kaufman G, Raub CB, Luo X. An Oral-mucosa-on-a-chip sensitively evaluates cell responses to dental monomers. Biomed Microdevices. 2021;23(1):7. doi: 10.1007/s10544-021-00543-6.
13. Makkar H, Zhou Y, Tan KS, Lim CT, Sriram G. Modeling Crevicular Fluid Flow and Host-Oral Microbiome Interactions in a Gingival Crevice-on-Chip. *Adv Healthc Mater*. 2023;**12**(6):e2202376. doi: 10.1002/adhm.202202376.
14. França CM, Tahayeri A, Rodrigues NS, Ferdosian S, Puppin Rontani RM, Sereda G, Ferracane JL, Bertassoni LE. The tooth on-a-chip: a microphysiologic model system mimicking the biologic interface of the tooth with biomaterials. *Lab Chip*. 2020;**20**(2):405-413. doi: 10.1039/c9lc00915a.
15. Kumar S, Dagli N, Haque M. Human-on-Chip Technology: Current State and Future Challenges. *Bangladesh Journal of Medical Science*. 2024:23(1);7–11. doi:10.3329/bjms.v23i1.70657
16. Ramadan Q, Hazaymeh R, Zourob M. Immunity-on-a-Chip: Integration of Immune Components into the Scheme of Organ-on-a-Chip Systems. *Adv Biol (Weinh)*. 2023;**7**(12):e2200312. doi: 10.1002/adbi.202200312.
17. Ding C, Chen X, Kang Q, Yan X. Biomedical Application of Functional Materials in Organ-on-a-Chip. *Front Bioeng Biotechnol*. 2020;**8**:823. doi: 10.3389/fbioe.2020.00823.