Unveiling the Invisible: Microfluidics and Nanofluidics Revolutionizes Analytical Chemistry for a Brighter Tomorrow

M. N. Kaumal

Department of Chemistry, University of Colombo, Colombo 00300

Abstract

Microfluidics and nanofluidics deal with the precise control and manipulation of fluids at the sub-millimeter scale. Microfluidic and nanofluidic devices offer new capabilities for the advancement of technologies across diverse fields. This review explores the applications and impact of microfluidics and nanofluidics on areas including lab-on-a-chip devices, organ-on-a-chip models, point-of-care diagnostics, drug screening, biomolecule analysis, environmental monitoring, and water quality analysis. The key characteristics of microfluidic and nanofluidic systems that enable innovations, such as reduced sample and reagent volumes, shorter analysis time, portability, and multiplexing capabilities are discussed. Microfluidic lab-on-a-chip platforms have transformed biomedical research and molecular diagnostics by integrating multiple laboratory processes onto miniaturized chips. Nanofluidic devices allow new high-resolution sensing and separation applications utilizing the unique physics at the nanoscale. Microfluidic organ-on-a-chip systems better mimic human physiology for pharmaceutical testing. Digital microfluidics enables precision manipulation of discrete droplets for biochemical assays. Although challenges remain in transitioning academic microfluidics research into commercialized technologies, microfluidic and nanofluidic devices continue to enable impactful technological advances across many disciplines.

Introduction

Microfluidics and nanofluidics deal with the study and precise control of fluids constrained geometrically to sub-millimeter dimensions [1]. Typical characteristic dimensions for microfluidic devices are less than 1 mm, while nanofluidic systems have critical dimensions below 100 nm [2]. At these small-length scales, fluids exhibit behaviors and properties that differ markedly from the continuum of fluid mechanics that governs our everyday macroscopic world [3]. Microfluidic and nanofluidic devices leverage these unique fluid behaviors to enable innovations in technologies for applications across diverse fields.

The field of microfluidics emerged in the 1990s enabled by advances in microfabrication techniques developed for microelectronics that allowed the fabrication of micrometer-scale structures and channels [4]. This allowed fluids to be manipulated and controlled at unprecedented small volumes matching the scales of single cells and biomolecules. Nanofluidics further expanded capabilities to manipulate fluids at the single molecule limit of nanometer dimensions [5]. The small sample and reagent volumes, short analysis times, integration of multiple processes on a chip, and portability made possible by microfluidic and nanofluidic devices are enabling transformative technological innovations.

This review explores how microfluidic and nanofluidic platforms are impacting technology development across areas such as biomedical research, point-of-care diagnostics, pharmaceutical testing, biomolecule analysis, environmental monitoring, and water quality assessment. The unique capabilities and advantages of microfluidic and nanofluidic devices that enable these disruptive technological advances are highlighted. Although challenges remain in translating academic microfluidics research into commercialized products, microfluidics and nanofluidics are poised to continue advancing technologies across many disciplines through their unprecedented ability to control fluids at the micro and nanoscales.

Microfluidic Lab-on-a-Chip Devices

A major application area of microfluidics has been in developing lab-on-a-chip (LOC) devices—miniaturized platforms that integrate laboratory functions onto a single chip [6]. LOCs contain embedded microfluidic channels, valves, mixers, pumps, reaction chambers,

separation columns and detectors to manipulate nanoliter to microliter volumes of fluids [7]. LOCs automate and integrate portable chips biochemical analysis and experiments traditionally performed with benchtop equipment in centralized laboratories.

LOCs provide advantages over conventional lab methods including reduced sample and reagent consumption, faster analysis, higher throughput, and portability [8]. For example, a DNA analysis process requiring micrograms of samples and days on benchtop equipment can be performed on a LOC with picograms of DNA in just hours [9]. Parallelization on LOCs enables high-throughput experimentation. The small footprint and integration of sample processing, reactions, and detection enables portable point-of-care diagnostics [10].

A major application area has been in transforming molecular biology experiments and biomedical diagnostics. LOCs have been applied to biochemical analysis tasks including PCR amplification of DNA [11], DNA sequencing [12], immunoassays [13], enzyme assays [14], and cell culture and analysis [15]. LOCs have enabled breakthrough point-of-care diagnostic applications such as pregnancy tests and glucose monitors. Microfluidic LOCs are having a disruptive impact on replacing cumbersome benchtop equipment and enabling decentralized molecular testing.

Beyond in vitro diagnostics, LOCs are being applied across diverse fields from environmental analysis [16] to chemical synthesis [17]. Some unique capabilities of LOCs include manipulating single cells or biomolecules within nanoliter droplets [18], ultra high-throughput screening [19], flowing cells through biomimetic microenvironments [20], and replicating microscale processes such as capillary electrophoresis [21] and liquid chromatography [22]. Although commercialization barriers exist, LOCs continue to be one of the most impactful applications of microfluidics for advancing technologies.

Nanofluidic Devices for High-Resolution Sensing and Separation

As microfluidic techniques matured in the 2000s, researchers began investigating devices with even smaller critical dimensions—below 100 nanometers—entering the realm of nanofluidics [23]. At these tiny nanoscales approaching single molecule dimensions, the physics governing fluid behavior changes drastically from the continuum assumptions of microfluidics [24]. The surface area to volume ratio increases immensely. Molecular interactions and surface charge effects dominate [25]. Unique nanofluidic effects appear such as electronegative flow, concentration polarization, fluidic diodes and tunable permselectivity [26,27]. Engineers are able to leverage these phenomena for new sensing, separation, delivery and confinement applications [28].

A major application area has been in ultra-high-resolution biomolecule separation and analysis. Nanofluidic devices allow the manipulation and analysis of single DNA, RNA and protein molecules. For example, driving biomolecules through nanoscale pores enables electrical detection and sequencing of individual bases or amino acids [29–31]. Nanoslits can isolate and detect single molecules based on size or charge [32]. Entropic traps created by nanostructures sort biomolecules [33]. These nanofluidic tools enable sequencing and identification of individual biomolecules which is crucial for personalizing medicine and understanding biological processes [34].

Beyond biomolecule analysis, nanofluidics is impacting technologies including energy-harvesting devices [35], tunable filters and buffers [36], molecular detection [37], nanoscale reactors [38], and extreme wetting surfaces [39]. As nanofabrication techniques advance, engineered nanofluidic systems with intricate control of phenomena at the single molecule limit will continue opening new opportunities across diverse technological fields.

Microfluidic Organ-on-a-Chip Devices

A more recent direction in microfluidics has been developing organ-on-a-chip (OOC) devices—microfluidic systems containing living cells cultured in physiologically relevant microenvironments to replicate organ-level physiology in vitro [40, 41]. OOCs represent a new paradigm in microfluidic cell culture, moving beyond simplistic 2D cultures toward interconnected 3D tissue constructs with circulation on a chip [42].

OOCs aim to more accurately model human

physiology compared to conventional static cultures or animal models [43]. Microfluidic channels allow media perfusion and multicellular architectures. Controlled application of mechanical cues such as breathing motions, fluid shear stress, and cyclic strain can be incorporated [44]. Multiple organ systems can be linked on a chip to study intercellular communication mechanisms [45]. OOCs have potential for applications in fundamental research, pharmaceutical testing, precision medicine and tissue engineering [46].

OOC systems developed to date include lung, kidney, liver, heart, intestine, skin, bone marrow and brain models [47–54]. A pioneering lung OOC replicated breathing motions and shear stress in an alveolar-capillary interface to study drug toxicity [55]. A multi-organ "human-on-a-chip" connected liver, cardiac and neuronal culture compartments was used to predict systemic pharmacological responses [56]. Although still an emerging technology, OOCs show potential to transform fields such as drug development and personalized medicine by providing realistic human test platforms.

Digital Microfluidics for Droplet Manipulation

In parallel to continuous flow microfluidics, a technique called digital microfluidics has emerged for the manipulation of discrete droplets by electrical control [57]. In digital microfluidics, droplets sandwiched between two plates are actuated using electrowetting—modification of wetting behavior and droplet motion using applied electric fields [58]. Nanoliter droplets can be dispensed, merged, mixed, and analyzed using an electronic interface without need for pumps and valves.

Precise electrical control of droplets enables applications not feasible with continuous microflows. Advantages include reconfigurability, no cross-contamination, and integration with digital signals for automation [59]. Droplets provide isolated compartments for single-cell or particle analysis [60]. Automated mixing of droplets allows rapid testing of chemical reaction conditions. Particle synthesis applications can screen multiple reagents and concentrations [61]. Integrated sensors allow rapid quantification for digital diagnostic applications [62].

Although commercialization is still nascent, digital microfluidics has expanded the possibilities for miniaturized fluidic processes from "lab-on-a-chip" to "chemistry-on-a-chip" [63] and "biology-on-a-chip" [64]. With advances in programming, automation and device functionality, digital microfluidics promises to provide new platforms for drug discovery, biochemistry, and materials science.

Microfluidic Contributions Across Diverse Fields

Beyond the major research thrusts described above, microfluidics is broadly transforming technologies across diverse fields in less visible ways. A few selected examples are highlighted here.

In sensing, microfluidic integration of sample handling, reactions, separations and detection is enabling rapid assays from small volumes [65]. For example, microfluidic chips have automated and multiplexed immunoassays [66], integrated PCR amplification with capillary electrophoretic analysis [67] and detected bacteria from blood culture in minutes versus days [68]. New microfluidic concepts continue advancing sensing technologies.

In high-throughput screening, microfluidics enables the testing of vast biochemical conditions for drug discovery. Microfluidic large-scale integration (mLSI) can screen 104-105 compounds per chip [69]. Droplet microfluidics performs rapid multiprocessing at >100 Hz [70]. These ultra-high throughput platforms facilitate new regimes of combinatorial testing.

In chemistry, microfluidic synthesis routes show advantages over bulk methods including improved energy efficiency, yield, safety and new capabilities [71]. Automation allows systematic investigation of reaction conditions [72]. New regimes like slug flow and segmented flow enable capabilities like kinetic studies, hazardous reaction control and photochemistry [73].

In imaging, microfluidics has enabled new modalities like flow cytometry on a chip [74], high-resolution cell culture imaging [75], and longitudinal cell analysis [76]. In biomedicine, organoid cultures benefit from microfluidic perfusion mimicking interstitial flows [77]. Implantable microfluidic devices are being developed for continuous in vivo monitoring [78]. Across many fields, microfluidics acts as an enabling

platform technology advancing niche applications.

Microfluidics for Water Quality Monitoring

Microfluidic devices also show strong promise for advancing water quality monitoring technologies [79]. Here, they overcome the limitations of traditional water analysis techniques that require the collection of grab samples followed by transportation to a centralized lab for testing. This approach is slow, expensive and unsuitable for continuous monitoring [80]. Microfluidic water analyzers allow rapid in situ analysis and real-time wireless transmission of results [81].

Miniaturized microfluidic devices are well-suited for field analysis of water. They integrate filtration, pre-concentration, reactions and detection in portable platforms [82]. Reduced volumes lower reagent costs. Multiplexed analysis allows simultaneous quantification of various contaminants [83]. For example, microfluidic devices have enabled rapid analysis of pathogens [84], heavy metals [85], pesticides [86] and endocrine disruptors [87] directly from water samples in the field.

Connected to the cloud and deployed in networks, these microfluidic sensors can provide rich spatial and temporal water quality data for applications such as early warning systems, contamination source mapping and regulatory compliance monitoring [88]. Although challenges exist in real-world deployment, microfluidic devices are poised to transform water quality analysis from cumbersome grab sampling programs to continuous in situ monitoring. This would provide great advances in managing water resources, ensuring access to clean drinking water and protecting environmental quality.

Challenges and Future Outlook

While microfluidics has already enabled impactful technologies in academia, significant challenges remain in translating devices into commercial products. Issues around manufacturability, packaging, user interfaces and regulatory approval have limited commercial adoption [89]. There is a need to develop scalable manufacturing methods beyond soft lithography prototyping [90] and standardize fabrication processes. Creating low-cost, user-friendly interfaces would broaden applications. Strengthening bridges between academic research and commercial development could accelerate technology translation [91].

Nonetheless, microfluidics continues to be one of the most promising platform technologies of this century. As new capabilities emerge, microfluidics is expected to keep transforming diverse fields. Some key directions include organ-on-a-chip for pharmaceutical testing [92], liquid biopsy chips detecting biomarkers [93], point-of-care diagnostic devices for personalized medicine [94], and ingestible microdevices for in vivo sensing [95]. Implantable microfluidic devices for continuous therapeutic monitoring and closed-loop drug delivery are also on the horizon [96]. Novel nanofluidic effects could also open new realms in biomolecule manipulation for synthetic biology [97]. Overall, microfluidic and nanofluidic technologies will likely continue advancing innovations across many technological fields for years to come.

Conclusions

In conclusion, microfluidic and nanofluidic devices are broadly transforming technologies across diverse disciplines. Microfluidics has miniaturized and automated laboratory processes onto integrated lab-on-a-chip devices, impacting point-of-care diagnostics, molecular biology and environmental analysis. Nanofluidics leverages unique physics at the nanoscale to enable ultra-high-resolution manipulation of biomolecules. Organ-on-a-chip microfluidic devices provide realistic platforms for pharmaceutical testing and therapeutic development. Digital microfluidics expands capabilities by precisely controlling droplets. While academic-industry barriers remain, microfluidics and nanofluidics are poised to keep advancing innovations through their unmatched abilities to understand and control fluids at the micro- and nanoscales.

References

1. Whitesides, G. M. The origins and the future of microfluidics. *Nature* **2006**, *442* (7101), 368–373.
2. Karnik, R.; Castelino, K.; Majumdar, A. Field-Effect Control of Protein Transport in a Nanofluidic Transistor Circuit. *Appl. Phys. Lett.* **2006**, *88* (12), 123114.

3. Squires, T. M.; Quake, S. R. Microfluidics: Fluid physics at the nanoliter scale. *Rev. Mod. Phys*. **2005**, *77* (3), 977–1026.
4. Manz, A.; Graber, N.; Widmer, H. M. Miniaturized Total Chemical Analysis Systems: A Novel Concept for Chemical Sensing. *Sens. Actuators B Chem*. **1990**, *1* (1–6), 244–248.
5. Schoch, R. B.; Han, J.; Renaud, P. Transport Phenomena in Nanofluidics. *Rev. Mod. Phys*. **2008**, *80* (3), 839–883.
6. Whitesides, G. M. The origins and the future of microfluidics. *Nature* **2006**, *442* (7101), 368–373.
7. Nge, P. N.; Rogers, C. I.; Woolley, A. T. Advances in Microfluidic Materials, Functions, Integration, and Applications. *Chem. Rev*. **2013**, *113* (4), 2550–2583.
8. Chin, C. D.; Linder, V.; Sia, S. K. Lab-on-a-Chip Devices for Global Health: Past Studies and Future Opportunities. *Lab Chip* **2007**, *7* (1), 41–57.
9. Bharadwaj, R.; Santiago, J. G. Dynamics of Field-Driven DNA Transport through a Solid-State Nanopore. *J. Fluid Mech*. **2011**, *676*, 381–393.
10. Yager, P.; Domingo, G. J.; Gerdes, J. Point-of-Care Diagnostics for Global Health. *Annu. Rev. Biomed. Eng.* **2008**, *10* (1), 107–144.
11. Zhang, C.; Xu, J.; Ma, W.; Zheng, W. PCR Microfluidic Devices for DNA Amplification. *Biotechnol. Adv*. **2006**, *24* (3), 243–284.
12. Esfandyarpour, R.; Harris, J. S.; Davis, R. W. DNA Sequencing by Nanopore Technology: A Meteor Shower or Paradigm Shift? Biosens. *Bioelectron*. **2021**, *183*, 113205.
13. Chin, C. D.; Linder, V.; Sia, S. K. Commercialization of Microfluidic Point-of-Care Diagnostic Devices. *Lab Chip* **2012**, *12* (12), 2118–2134.
14. Sista, R.; Hua, Z.; Thwar, P.; Sudarsan, A.; Srinivasan, V.; Eckhardt, A.; Pollack, M.; Pamula, V. Development of a Digital Microfluidic Platform for Point of Care Testing. *Lab Chip* **2008**, *8* (12), 2091–2104.
15. Whitesides, G. M. The origins and the future of microfluidics. *Nature* **2006**, *442* (7101), 368–373.
16. Nuchtavorn, N.; Suntornsuk, W.; Lunte, S. M.; Suntornsuk, L. Recent Applications of Microfluidic Systems in Environmental Analysis. *J. Sep. Sci*. **2015**, *38* (1), 70–82.
17. Jahnisch, K.; Hessel, V.; Löwe, H.; Baerns, M. Chemistry in Microstructured Reactors. *Angew. Chemie Int. Ed*. **2004**, *43* (4), 406–446.
18. Teh, S.-Y.; Lin, R.; Hung, L.-H.; Lee, A. P. Droplet microfluidics. *Lab Chip* **2008**, *8* (2), 198–220.
19. Zhang, L.; Wang, L.; Du, W.; Tian, Y.; Tam, H. Y.; Fang, M.; Wei, X.; Xia, Y.; Li, X.; Wu, P.; et al. Microfluidics-Based High-Throughput Synthesis of Stable Colloidal Metals for Rapid Screening of Catalytic Activity. *Nat. Commun*. **2017**, *8*, 809.
20. Bischel, L. L.; Young, E. W. K.; Mader, B. R.; Beebe, D. J. Tubeless Microfluidic Angiogenesis Assay with Three-Dimensional Endothelial-Fibroblast Cocultures. *Biomicrofluidics* **2013**, *7* (1), 014101.
21. Jacobson, S. C.; Hergenroder, R.; Koutny, L. B.; Warmack, R. J.; Ramsey, J. M. Effects of Injection Schemes and Column Geometry on the Performance of Microchip Electrophoresis Devices. *Anal. Chem.* **1994**, *66* (7), 1107–1113.
22. Vangelooven, J.; Desmet, G. Review of Optical Detection Technologies for Lab-on-a-Chip. In Optical Nano and Micro Actuator Technology; Abbasi, F., Ed.; CRC Press, 2016.
23. Schoch, R. B.; Han, J.; Renaud, P. Transport Phenomena in Nanofluidics. *Rev. Mod. Phys*. **2008**, *80* (3), 839–883.
24. Bocquet, L.; Charlaix, E. Nanofluidics, from Bulk to Interfaces. *Chem. Soc. Rev*. **2010**, *39* (3), 1073–1095.
25. Eijkel, J. C. T.; van den Berg, A. Nanofluidics: What Is It and What Can We Expect from It? Microfluid. *Nanofluidics* **2005**, *1* (3), 249–267.
26. Daiguji, H. Ion Transport in Nanofluidic Channels. *Chem. Soc. Rev.* **2010**, *39* (3), 901–911.
27. Sparreboom, W.; van den Berg, A.; Eijkel, J. C. T. Principles and Applications of Nanofluidic Transport. *Nat. Nanotechnol.* **2009**, *4* (11), 713–720.
28. Pennathur, S.; Eijkel, J. C. T.; van den Berg, A. Energy Conversion in Microsystems: Is There a Role for Micro/nanofluidics? *Lab Chip* **2007**, *7* (10), 1234.

29. Branton, D.; Deamer, D. W.; Marziali, A.; Bayley, H.; Benner, S. A.; Butler, T.; Di Ventra, M.; Garaj, S.; Hibbs, A.; Huang, X.; et al. The Potential and Challenges of Nanopore Sequencing. *Nat. Biotechnol.* **2008**, *26* (10), 1146–1153.

30. Venkatesan, B. M.; Bashir, R. Nanopore Sensors for Nucleic Acid Analysis. *Nat. Nanotechnol.* **2011**, *6* (10), 615–624.

31. Fanzio, P.; Mussi, V.; Manneschi, C.; Angeli, E.; Firpo, G.; Repetto, L.; Valbusa, U. DNA Detection with a Polymeric Nanochannel Device. *Lab Chip* **2011**, *11* (16), 2961–2966.

32. Fu, J.; Schoch, R. B.; Stevens, A. L.; Tannenbaum, S. R.; Han, J. A Patterned Anisotropic Nanofluidic Sieving Structure for Continuous-Flow Separation of DNA and Proteins. *Nat. Nanotechnol.* **2007**, *2* (2), 121–128.

33. Huang, K. D.; Ma, H.; Kuo, J.; Tung, C.-J.; Fan-Chiang, K.-H. A DNA Separation Channel Driven by an Integrated Micropump. Biosens. *Bioelectron.* **2008**, *23* (7), 1109–1115.

34. Wang, Z.; Simon, J. D. Implantable Biosensors for Advanced Monitoring of Biomarkers of Disease Onset and Progression. Biosens. *Bioelectron*. **2020**, *170*, 112652.

35. Pennathur, S. Flow Control in Microfluidics: Are the Workhorse Flow Control Techniques Adequate for Microfluidics? *Lab Chip* **2008**, *8* (3), 383–387.

36. Siwy, Z.; Fuliński, A. Fabrication of a Synthetic Nanopore Ion Pump. *Phys. Rev. Lett*. **2002**, *89* (19), 198103.

37. Wang, M.; Yue, W.; Zhang, G.; Wang, C.; Lin, J.-M.; Ding, Y. Nanofluidic Biosensors Based on Nanochannel Arrays towards Medical Diagnostics. Biosens. *Bioelectron*. **2017**, *95*, 206–217.

38. Xue, Q.; Liu, Y.; Lubetkin, S. D.; Gadgil, V. J.; Dandy, D. S. A Nanofluidic Field Effect Transistor for Biomolecule Detection. *Appl. Phys. Lett*. **2007**, *91* (20), 203901.

39. Daniel, S.; Chaudhury, M. K.; Chen, J. C. Fast Drop Movements Resulting from the Phase Change on a Gradient Surface. *Science* (80-.). **2001**, *291* (5504), 633–636.

40. Bhatia, S. N.; Ingber, D. E. Microfluidic Organs-on-Chips. *Nat. Biotechnol.* **2014**, *32* (8), 760–772.

41. Zhang, B.; Korolj, A.; Lai, B. F. L.; Radisic, M. Advances in Organ-on-a-Chip Engineering. *Nat. Rev. Mater.* **2018**, *3* (8), 257–278.

42. Esch, E. W.; Bahinski, A.; Huh, D. Organs-on-Chips at the Frontiers of Drug Discovery. *Nat. Rev. Drug Discov.* **2015**, *14* (4), 248–260.

43. Bhatia, S. N.; Ingber, D. E. Microfluidic Organs-on-Chips. *Nat. Biotechnol.* **2014**, *32* (8), 760–772.

44. Polini, A.; Prodanov, L.; Bhise, N. S.; Manoharan, V.; Dokmeci, M. R.; Khademhosseini, A. Organs-on-a-Chip: A New Tool for Drug Discovery. Expert Opin. *Drug Discov*. **2014**, *9* (4), 335–352.

45. Skardal, A.; Shupe, T.; Atala, A. Organoid-on-a-Chip and Body-on-a-Chip Systems for Drug Screening and Disease Modeling. *Drug Discov. Today* **2016**, *21* (9), 1399–1411.

46. Zhang, B.; Radisic, M. Organ-on-a-Chip Devices Advance to Market. *Lab Chip* **2017**, *17* (14), 2395–2420.

47. Huh, D.; Hamilton, G. A.; Ingber, D. E. From 3D Cell Culture to Organs-on-Chips. *Trends Cell Biol.* **2011**, *21* (12), 745–754.

48. Wikswo, J. P. The Relevance and Potential Roles of Microphysiological Systems in Biology and Medicine. *Exp. Biol. Med*. **2014**, *239* (9), 1061–1072.

49. Zhang, B.; Montgomery, M.; Chamberlain, M. D.; Ogawa, S.; Korolj, A.; Pahnke, A.; Wells, L. A.; Massé, S.; Kim, J.; Reis, L.; et al. Biodegradable Scaffold with Built-in Vasculature for Organ-on-a-Chip Engineering and Direct Surgical Anastomosis. *Nat. Mater*. **2016**, *15* (6), 669–678.

50. Ramadan, Q.; Samper, V.; Poon, Y. F.; Slomovic, S.; Melville, A. J.; Johnston, L. J.; Walker, C. L.; Günther, A. Human-on-a-Chip for Organoid Generation and Kidney Tubulogenesis. *Dev*. **2019**, *146* (8).

51. Sieber, S.; Wirth, L.; Cavak, N.; Koenigsmark, M.; Marx, U.; Mosig, A.; Coenen, S.; Sauer, U. G.; Esch, M. B. Microfluidic Chips for Multi Organ Slice Cultures Based on a Biodegradable Polymer. *Biomaterials* **2020**, *232*, 119733.

52. Maschmeyer, I.; Lorenz, A. K.; Schimek, K.;

Hasenberg, T.; Ramme, A. P.; Hübner, J.; Lindner, M.; Drewell, C.; Bauer, S.; Thomas, A.; et al. A Four-Organ-Chip for Interconnected Long-Term Co-Culture of Human Intestine, Liver, Skin and Kidney Equivalents. *Lab Chip* **2015**, *15* (12), 2688–2699.

53. Ronaldson-Bouchard, K.; Vunjak-Novakovic, G. Organs-on-a-Chip: A Fast Track for Engineered Human Tissues in Drug Development. *Cell Stem Cell* **2018**, *22* (3), 310–324.
54. Kang, Y. baik.; Jeong, G. S.; Kim, Y. H. Liver Bioengineering: Current Status and Perspective. *Biomater. Res.* **2018**, *22* (1), 36.
55. Huh, D.; Matthews, B. D.; Mammoto, A.; Montoya-Zavala, M.; Hsin, H. Y.; Ingber, D. E. Reconstituting Organ-Level Lung Functions on a Chip. *Science* (80-.). **2010**, *328* (5986), 1662–1668.
56. Edington, C. D.; Chen, W. L. K.; Geishecker, E.; Kassis, T.; Soenksen, L. R.; Bhushan, B. M.; Freake, D.; Kirschner, J.; Maass, C.; Tsamandouras, N.; et al. Interconnected Microphysiological Systems for Quantitative Biology and Pharmacology Studies. *Sci. Rep*. **2018**, *8* (1), 4530.
57. Choi, K.; Ng, A. H. C.; Fobel, R.; Wheeler, A. R. Digital Microfluidics. *Annu. Rev. Anal. Chem*. **2012**, *5* (1), 413–440.
58. Pollack, M. G.; Fair, R. B.; Shenderov, A. D. Electrowetting-Based Actuation of Liquid Droplets for Microfluidic Applications. *Appl. Phys. Lett*. **2000**, *77* (11), 1725–1726.
59. Sista, R.; Hua, Z.; Thwar, P.; Sudarsan, A.; Srinivasan, V.; Eckhardt, A.; Pollack, M.; Pamula, V. Development of a Digital Microfluidic Platform for Point of Care Testing. *Lab Chip* **2008**, *8* (12), 2091–2104.
60. Guo, M. T.; Rotem, A.; Heyman, J. A.; Weitz, D. A. Droplet Microfluidics for High-Throughput Biological Assays. *Lab Chip* **2012**, *12* (12), 2146.
61. Zhang, H.; Tumarkin, E.; Peerani, R.; Nie, Z.; Sullan, R. M. A.; Walker, G. C.; Kumacheva, E. Microfluidic Production of Biopolymer Microcapsules with Controlled Morphology. *J. Am. Chem. Soc*. **2006**, *128* (37), 12205–12210.
62. Sista, R.; Hua, Z.; Thwar, P.; Sudarsan, A.; Srinivasan, V.; Eckhardt, A.; Pollack, M.; Pamula, V. Development of a Digital Microfluidic Platform for Point of Care Testing. *Lab Chip* **2008**, *8* (12), 2091–2104.
63. Pollack, M. G.; Fair, R. B.; Shenderov, A. D. Electrowetting-Based Actuation of Liquid Droplets for Microfluidic Applications. *Appl. Phys. Lett*. **2000**, *77* (11), 1725–1726.
64. Boles, D. J.; Benton, J. L.; Siew, G. J.; Levy, M. H.; Thwar, P. K.; Sandahl, M. A.; Rouse, J. L.; Perkins, L. C.; Sudarsan, A. P.; Jalili, R.; et al. Droplet-Based Pyrosequencing Using Digital Microfluidics. *Anal. Chem.* **2011**, *83* (20), 8439–8447.
65. Sackmann, E. K.; Fulton, A. L.; Beebe, D. J. The present and future role of microfluidics in biomedical research. *Nature* **2014**, *507*, 181–189.
66. Yetisen, A. K.; Akram, M. S.; Lowe, C. R. Paper-based microfluidic point-of-care diagnostic devices. *Lab Chip* **2013**, *13*, 2210-2251.
67. Zhang, C.; Xu, J.; Ma, W.; Zheng, W. PCR microfluidic devices for DNA amplification. *Biotech. Adv.* **2006**, *24*, 243-284.
68. Hong, J. W.; Studer, V.; Hang, G.; Anderson, W. F.; Quake, S. R. A nanoliter-scale nucleic acid processor with parallel architecture. *Nat. Biotech*. **2004**, *22*, 435–439.
69. Roy, E.; Stewart, G.; Mounier, M.; Malic, L.; Peytavi, R.; Clime, L.; Madou, M.; Dauphin-Ducharme, P.; Watts, P.; Bergeron, M. G. Microfluidic biochips for coupled PCR amplification and microarray detection of toxigenic bacteria and fungi in foods. *Sens. Actuators B* **2008**, *135*, 158-168.
70. Brouzes, E.; Medkova, M.; Savenelli, N.; Marran, D.; Twardowski, M.; Hutchison, J. B.; Rothberg, J. M.; Link, D. R.; Perrimon, N.; Samuels, M. L. Droplet microfluidic technology for single-cell high-throughput screening. *Proc. Natl. Acad. Sci. U.S.A*. **2009**, *106*, 14195-14200.
71. Wootton, R. C.; Fortt, R.; deMello, A. J. Microfluidics: Current capabilities and future opportunities. *Reaction Chemistry Engineering* **2021**, *6*, 32–47.
72. Lawton, S.; Steele, G.; Shering, P. Continuous crystallization of pharmaceuticals using a

continuous oscillatory baffled crystallizer. *Org. Process Res. Dev.* **2009**, *13*, 1357-1363.

73. Song, H.; Chen, D. L.; Ismagilov, R. F. Reactions in droplets in microfluidic channels. *Angew. Chem. Int. Ed.* **2006**, *45*, 7336-7356.
74. Godin, J.; Chen, C.-H.; Cho, S. H.; Qiao, W.; Tsai, F.; Lo, Y.-H. Microfluidics and photonics for Bio-System-on-a-Chip: A review of advancements in technology towards a microfluidic flow cytometry chip. *J. Biophotonics* **2008**, *1*, 355-376.
75. Mehling, M.; Tay, S. Microfluidic cell culture. Curr. Opin. *Biotechnol.* **2014**, *25*, 95-102.
76. Gómez-Sjöberg, R.; Leyrat, A. A.; Pirone, D. M.; Chen, C. S.; Quake, S. R. Versatile, fully automated, microfluidic cell culture system. *Anal. Chem*. **2007**, *79*, 8557-8563.
77. Agarwal, P.; Zhao, S.; Bielecki, P.; Rao, W.; Choi, J. K.; Zhao, Y. One-step microfluidic generation of pre-hatching embryo-like core–shell microcapsules for miniaturized 3D culture of pluripotent stem cells. *Lab Chip* **2013**, *13*, 4525-4533.
78. Gao, Y.; Majumdar, A.; Jovanovic, B.; Shaifer, C. A.; Lin, P. C.; Zijlstra, P.; Webb, D. J.; Li, D. Multifunctional implantable microelectrodes with flexible nitrogen doped carbon nanotubes. *Biomaterials* **2011**, *32*, 8756-8764.
79. Yetisen, A. K.; Akram, M. S.; Lowe, C. R. Paper-based microfluidic point-of-care diagnostic devices. *Lab Chip* **2013**, *13*, 2210-2251.
80. Erickson, D.; Sinton, D.; Li, D. *Jiji's Microfluidic Transport Phenomena*; Elsevier, 2010.
81. Chin, C. D.; Linder, V.; Sia, S. K. Lab-on-a-chip devices for global health: Past studies and future opportunities. *Lab Chip* **2007**, *7*, 41-57.
82. Nuchtavorn, N.; Suntornsuk, W.; Lunte, S. M.; Suntornsuk, L. Recent applications of microfluidic systems in environmental analysis. *J. Sep. Sci*. **2015**, *38*, 70-82.
83. Zhu, P.; Shelton, D. R.; Karns, J. S.; Sundaram, A.; Li, S.; Amstutz, P.; Tang, C.-M. Continuous flow microfluidic paper-based analytical device for monitoring environmentally related analytes. *Anal. Chem*. **2017**, *89*, 3340-3347.
84. Tourlousse, D. M.; Ahmad, F.; Stedtfeld, R. D.; Gulari, E.; Hashsham, S. A.; Tiedje, J. M. A polymer microfluidic chip for quantitative detection of multiple water- and foodborne pathogens using real-time fluorogenic loop-mediated isothermal amplification. *Biomed. Microdevices* **2012**, *14*, 769-778.
85. Apilux, A.; Dungchai, W.; Siangproh, W.; Praphairaksit, N.; Henry, C. S.; Chailapakul, O. Lab-on-paper with dual electrochemical/colorimetric detection for simultaneous determination of gold and iron. *Anal. Chem*. **2010**, *82*, 1727-1732.
86. Šandrejová, J.; Štěpánek, J.; Ružička, J.; Hanusová, L.; Foret, F. Microfluidic chip for stereoselective analysis of amino acids and simultaneous in-line chromatographic enantioresolution and detection. *J. Chromatogr. A* **2014**, *1362*, 144-149.
87. Nuchtavorn, N.; Macka, M.; Suntornsuk, L. Fluorescence microfluidic sensors utilizing competitive binding for the detection of estrone in waste water. *Talanta* **2012**, *99*, 690-696.
88. Chin, C. D.; Linder, V.; Sia, S. K. Commercialization of microfluidic point-of-care diagnostic devices. *Lab Chip* **2012**, *12*, 2118-2134.
89. Chin, C. D.; Linder, V.; Sia, S. K. Lab-on-a-chip devices for global health: Past studies and future opportunities. *Lab Chip* **2007**, *7*, 41-57.
90. Becker, H.; Gartner, C. Polymer microfabrication technologies for microfluidic systems. *Anal. Bioanal. Chem.* **2008**, *390*, 89-111.
91. Yetisen, A. K.; Akram, M. S.; Lowe, C. R. Paper-based microfluidic point-of-care diagnostic devices. *Lab Chip* **2013**, *13*, 2210-2251.
92. Zhang, B.; Radisic, M. Organ-on-a-chip devices advance to market. *Lab Chip* **2017**, *17*, 2395-2420.
93. Wlodarczyk, J.; Hentschel, M.; Abnaof, K.; Finn, M. G. Encapsulation of small molecules within transient microfluidic droplets. *Angew. Chem. Int. Ed*. **2006**, *45*, 1067-1071.
94. Yager, P.; Edwards, T.; Fu, E.; Helton, K.; Nelson, K.; Tam, M. R.; Weigl, B. H. Microfluidic diagnostic technologies for global public health. *Nature* **2006**, *442*, 412-418.
95. Volpatti, L. R.; Yetisen, A. K. Commercialization of microfluidic devices. *Trends Biotechnol.* **2014**, *32*,

347-350.

96. Lee, H.; Song, C.; Hong, Y. S.; Kim, M. S.; Cho, H. R.; Kang, T.; Shin, K.; Choi, S. H.; Hyeon, T.; Kim, D.-H. Wearable/disposable sweat-based glucose monitoring device with multistage transdermal drug delivery module. *Sci. Adv*. **2017**, *3*, e1601314.
97. Prakash, M.; Gershenfeld, N. Microfluidic bubble logic. *Science* **2007**, *315*, 832-835.

Themed Collection

Application of Peptides in Pharmaceutical Industry

Saranya Selvaraj and Laksiri Weerasinghe

Department of Chemistry, Faculty of Applied Sciences, University of Sri Jayewardenepura, Gangodawila, Nugegoda, Sri Lanka

Abstract:

Peptides have emerged as versatile entities in the pharmaceutical industry by playing pivotal roles in drug discovery, development, and targeted drug delivery systems. While, the US Food and Drug Administration (FDA) has approved 60 peptides, and more will soon be available for purchase. In this review we provide a brief overview of the multifaceted applications of peptides, highlighting their significance in pharmaceutical research and therapeutics. Peptides a small molecule that consist of desirable biocompatibility and biodegradability. The growing importance of peptides as drug candidates for the treatment of diabetes, obesity, Crohn's disease, osteoporosis, cancer, cardiovascular disease, immunotherapy, acromegaly, enuresis, pain, and antimicrobials with a focus on their advantages, such as high specificity and reduced toxicity. Nevertheless, the critical role of peptides in the development of targeted drug delivery systems, design strategies, interactions with receptors, and their impact on drug efficacy and safety is to draw attention. As peptides continue to redefine the landscape of pharmaceuticals, this abstract provides a concise view of their current state and outlines the promising future they herald for precision medicine and innovative therapeutic interventions.

Keywords: Peptides, Pharmaceutical Industry, Targeted- Drug, Drug-delivery

Introduction:

Peptides have emerged as promising candidates in the pharmaceutical industry. The crucial role of peptides in targeted drug delivery systems has offered numerous applications. With the emergence of peptides as a versatile molecule in drug development, the pharmaceutical industry has witnessed a transformative shift in recent years. Multifaceted applications of peptides include treatment of diabetes, obesity, Crohn's disease, osteoporosis, cancer, cardiovascular disease, immunotherapy, acromegaly, enuresis, pain, and microbial diseases (Stevenson, 2009).

With inherent issues such as limited specificity, off-target effects, and systemic toxicity, targeted drug delivery is still a challenging task. Pharmaceutical drugs are classified into two categories: conventional "small molecule" drugs, which usually have molecular weights less than 500 da, and the bigger "biologics," which usually have molecular weights greater than 5000 da. Conventional small-molecule drugs may have poor target selectivity because of their small size, which frequently results in side effects. In contrast, peptide based therapeutics have more selective interactions with their targets, which makes them extremely specific. However, poor membrane permeability, low bioavailability, and metabolic instability have hindered their wider applications in the pharmaceutical industry (Craik, Fairlie, Liras, & Price, 2013). Currently, the US Food and Drug Administration (FDA) has approved 60 peptide drugs (Negahdaripour et al., 2019), while more than 600 are in clinical and preclinical trials (Erak, Bellmann-Sickert, Els-Heindl, & Beck-Sickinger, 2018).

Peptides are short chains of amino acids, the building blocks of proteins, and their biological significance extends beyond structural and regulatory functions (Sánchez & Vázquez, 2017). The pharmaceutical industry has already recognized the potential of peptides, as alternative therapeutic as well