Emerging Technologies in the Delivery of Proteins and Peptides

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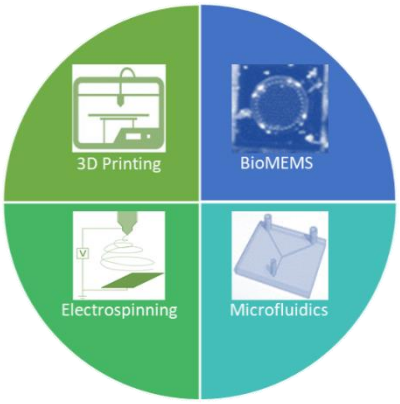

Advances in drug design have led to the development of new drug molecules peptides, and proteins. However, the limited ability to deliver selectively these molecules at well-defined dosing regimens remains a significant challenge. Therefore, new materials and manufacturing techniques are emerging, with the ability to meet the challenges associated with the formulation and delivery of biopharmaceuticals and pharmaceuticals.

Emerging technologies (e.g., 3D Printing and Bioprinting, electrospinning, and Microfluidics), are aiming to prepare systems that can be used for personalized medicine, be able to be adapted to patient's needs and teach to old drugs new tricks[1,2]. For example, proteins and peptides can be encapsulated into particles formulated by microfluidics or be delivered using lab-on-a-chip approach or in combination with microelectromechanical systems (MEMS and Biological MEMS). Biologic molecules can be encapsulated in nanofibers by electrospinning for drug delivery and other biomedical applications (e.g., wound dressing and tissue engineering). Peptide formulations can be combined with additive manufacturing (AM) techniques for an effective delivery of biologics or to be used for the manufacturing of microneedles for the delivery of vaccines.

Additive Manufacturing (3D Printing & Bioprinting)

AM is a promising set of technologies for the production of drug delivery systems and medical implants. 3D printing (3DP) has been widely explored for the manufacturing of dosage forms and drug delivery systems, such as drug-eluting implants and for wound healing applications. The main advantage of AM is the flexibility in the preparation of systems with variety of shapes and sizes, and the use of Food and Drug Administration (FDA) approved polymers (synthetic and natural). The main AM technologies that have the potential to be used for the delivery of proteins or peptides are Stereolithography (SLA), Digital Light Processing (DLP), inkjet-based 3DP, pressure-assisted microsyringe (PAM) printing, and Bioprinting[3]. A

great progress has been made in the development of long-acting biologics for local or targeted therapeutics. For example, Microneedles can be prepared by SLA for the delivery of proteins and peptides through the skin, avoiding issues off the gastrointestinal tract. 3DP can also be used for the manufacturing of patient-matched devices specific to their anatomy using data obtained by Nuclear magnetic resonance (NMR) imaging or Computer tomography (CT), for example, implants for cancer treatment that loaded with biologically active molecules. Moreover, antioxidant and anti-infective agents can incorporated within 3DP-personalized systems. In addition, bioprinting has the potential to build objects using bioinks that can contain cells or other biologic molecules that have incorporated into natural polymers. Our facility hosts a large number of 3D printers (>15) that are covering every available printer in the market (e.g., Bioprinters, DLP, FDM, Food, Pellet, SLA, SLS, and UV LCD).

Electrohydrodynamic Processes (Electrospinning & Electrospraying)

Electrospinning & Electrospraying are techniques that utilizes electric forces to create Nano- and microfibers or microparticles. The process, involves applying electric charges across a metallic needle that contains a polymeric solution[4]. The type of drugs being studied range from antibiotics to steroids. Medical implants have also manufactured using Electrohydrodynamic (EHD) processes, since can be implanted at the required tissue site, provide sustained released, provide low toxicity and reduce the chance of unwanted reactions with irrelevant organs or tissue. EHD processes have be used for the delivery of peptides and proteins using a variety of dosage forms such as oral films, vaginal meshes, and for wound dressing applications. EHD process have also be used for the encapsulation of antibodies, enzymes, growth factors, hormones, nucleic acids, Stem cells, and vaccine antigens. Our facility hosts three solution electrospinners that can also be used as electrospraying for polymeric particle fabrication, and one melt electrospinner, including co-axial electrospinning for the manufacturing of advance systems with multiple drugs.

Microfluidics & Nanofluidics

Microfluidics (MFs) is a fluid technique that allows handling of fluids on a small scale using channels, chambers, fluid paths and other features. It uses small volumes of liquids and allows the control of fluid transport and the mixing of molecules for the manufacturing of delivery systems such as Poly Lactic-co-Glycolic Acid (PLGA) or Liposomes loaded with biologic molecules[5]. MFs and Nanofluidics (NFs) market

includes drug delivery and in-vitro diagnostics, among many other applications. MFs have also all the potential to be used in the fight against a pandemic for the manufacturing of vaccines or rapid diagnosis, as have the ability to deliver cells or biologics and can greatly improve the efficacy of biologics as can encapsulate and protect them from harsh environments, thus increasing their stability. Over 90 vaccines are under development for COVID-19 across the world, and without the use of lipid nanoparticles that can easily prepared by microfluidics techniques, there would be no possible to deliver mRNA, therefore, having a successful vaccine for COVID-19. MF Lab-on-a-chip approach can be used for the detection of viruses and also to test new drugs without the use of animals. Moreover, the technique is energetically economical, convenient, cheaper and faster than traditional formulation methods, and molecules that have not encapsulated into the particles can reuse, providing a sustainable and continues manufacturing. Our microfluidic facility hosts five microfluidic devices, including temperature controllers and high-speed microscope for the evaluation of the particles and flows in the microfluidic chips, including the manufacturing of customized chips by 3DP.

Microelectromechanical Systems (MEMS & BioMEMS)

Microelectromechanical systems (MEMS & BioMEMS) allows the development of innovative devices for variety of applications, including drug delivery. The use of MEMS and BioMEMS as point-of-care (PoC) diagnostic devices and drug / protein delivery devices, in combination with 3D Printed (e.g., microneedles) or MF systems have create new opportunities for the delivery of biologics and non-invasive continuous diagnosis and monitoring of a disease[1]. MEMS drug delivery devices can be manufactured with various Nano- and Microstructures such as reservoirs, pumps, valves, and needles, as implantable, reservoir-based or transdermal-based devices.

Conclusions

Advances in biotechnology have produced an increasing number of biopharmaceuticals. However, the successful delivery of these molecules is a major challenge. Therefore, researchers are developing a number of new delivery technologies and materials in order to enable the delivery of biologics. By using emerging technologies, researchers can produce easier and faster systems that are safer and have better properties than existed ones. Moreover, personalized delivery systems (e.g., nanomedicines) or medical implants are also achievable. These novel methods of protein and peptide drug delivery systems showing

a promising future for therapeutics, and future innovations using emerging technologies may hold the key for the development of biologics with optimal clinical properties.

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Dimitrios Lamprou (Ph.D. MBA) is a well-known expert in Emerging Technologies for Drug Delivery and Medical Implants. He is the author of over 100 peer-reviewed publications and of over 250 conference abstracts, and has over 100 Oral Invited Talks in institutions and conferences across the world. You can reach him at www.EmergingTechnologiesLab.com