REVIEW PAPER

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Emerging Technologies Transforming Therapy

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ABSTRACT

The advancement of healthcare therapies is under constant development due to changing demographics and evolving disease-states. To ensure continuous furtherance of the healthcare system capacity to treat such ailments, emerging technologies (ETs) are coming to the forefront of medicine. It's the hope that ETs are capable of covering a broad scope of therapeutic treatment areas, enabling novel pharmaceutical pathways to be established. Highlighted in this mini review are examples of focus ET areas, including additive manufacturing (AM), microfluidics (MFs), microelectromechanical systems (MEMS) and machine learning (ML), that have shown promising qualities and should be targeted further to improve patient outcomes.

Introduction

ETs have developed greatly over the last decade, opening new manufacturing channels within pharmaceutical industry. Although many of their potentials are far from being actualised, their development is likely to affect the future of therapeutic treatment methods. Included in this mini review are some of the most promising technologies that are being used for novel healthcare applications, with the aim of sustaining an efficacious level of medical management for future treatments. A brief mention of related advantages and disadvantages is discussed also for each ET.

Additive Manufacturing and 4D Printing

AM, known commonly as 3D printing (3DP), allows for the in-house production of highly-customised drug delivery systems and medical devices, marshalling towards an era of feasible personalised-healthcare. The development of new printing technologies has allowed for a huge range of materials to be manipulated with this technology, ranging from metals to living tissues [1]. Developing areas of AM could bring about huge advancements for healthcare, for example bioprinting and 4D printing using "smart" polymers, which could

negate the requirement for allograft/xenograft tissue donation whilst simultaneously reducing the likelihood of immune rejection [2]; **Figure 1**.

Research into the AM of personalised drug-eluting scaffolds and Microneedles (MNs), used for sustained drug delivery and wound repair, has seen a rise in interest, allowing for the treatment of complex diseases such as various cancers (e.g., breast), diabetes and HIV [3, 4]. The production of specialist medical devices, including personalised pieces, is possible using AM, which has been used for purposes including surgery, prosthetics and pre-operative planning [5]. Custom printing inks are routinely used for pharmaceutical AM, for example the use of drug-incorporated filaments for fused deposition modelling (FDM) printing [6].

The availability of 3DP has increased greatly, to the point that it's not uncommon for households to own a printer. Whilst this may differ from pharmaceutical printing, it's important to consider the impact that will be experienced for the technology as a whole due to the increase of technology users, as it could help fast track innovation being developed in the area. A skilled operator will have the capacity to optimise the print design, with a view about the chosen material's strengths and weaknesses.

4D Printing (4DP) is a further extension of AM, which incorporates smart materials capable of possessing a level of responsiveness to external and internal stimuli. The material responses often include shape and property changes, including chemical, structural and size alteration [7]. This adaptiveness of the materials can lead to more efficient medical treatment, for example allowing concise control of active pharmaceutical ingredient (API) release [8], occupying void space [9] or controlling the swelling potential of a hydrogel [10]. Polymers are a common choice of material used in 4DP due to their printable nature, modifiable structure and biocompatibility. Smart polymers often used for 4DP include carboxymethyl cellulose sodium (CMC) [11], polylactic acid (PLA) and polycaprolactone (PCL) [12]. Elastomers, a subsection of polymers and shortened from the name "elastic polymer", are also often used for shape responsive 4DP. 4DP allows for the adaptability of the medical device post-administration, which is a key advantage over 3DP. For 3DP the printed device won't alter its mechanism of action as a response to its environment due to a lack of smart material sensitivity.

Advantages of AM include the ability to produce individualised treatment options on-site, using a wide range of compatible materials. Current disadvantages include the risk of print failures and the fact that AM can be a time-consuming process for large or complex prints.

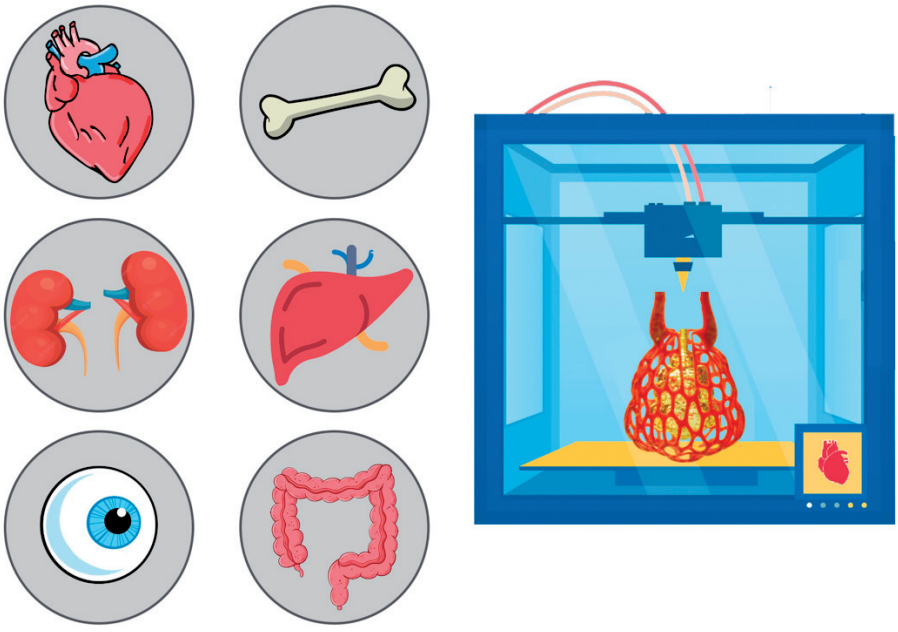

Figure 1. Graphic depicting the potential for the additive manufacturing of tissues and organs via bioprinting.

Microfluidics & Lab-on-a-chip

MFs has seen a great resurgence in popularity, owed largely to its capacity for high-quality formulation. MFs has quickly adopted processes that allow for the self-assembly of materials into nano/microparticles, allowing for the concise control of particle characteristics [13]. As evident during the COVID-19 pandemic [14, 15], the use of nanoparticles (NPs) for therapy is an effective and sought-after approach. MFs can act as a platform for chemical synthesis (**Figure 2**), enabling reactions to occur in a time efficient manner with high atom economy [16], following closely with the guidance of the 12 principles of green chemistry [5, 17].

The customisability of the MF system lies at the forefront of the attractiveness of the technology, whether it's required for individual sample preparation, or for high-throughput functionality. MF chip designs can vary widely, permitting various applications, other than formulation, for example, the micro-scaling of laboratory production, often referred to as lab-on-a-chip (LoC). The propensity of MFs for analysis and monitoring too has become an area of interest. A few therapy areas that have evolved thanks to this include point-of-care (PoC) analysis in combination also with biological microelectromechanical systems (BioMEMS [18]), disease-state progression monitoring [19] and closely mimicking *in vivo* conditions (Organ-on-a-chip) [20], as seen in **figure 2**. A common barrier to MFs has often been deemed to be its industrial scalability, however, solutions to this are currently being investigated, aiming towards increasing flow outputs whilst maintaining process quality [21].

Advantages of this technology include high levels of control of experimental conditions, coupled with high degrees of accuracy and low volumes of reagent needed. MFs and LoC are highly customisable technologies that allow for a wide range of experimental procedures. Disadvantages of the technologies include barriers to scalability, potential high costs and issues with device-reagent compatibility.

Microelectromechanical Systems

Closely coupled with LOC, MEMS devices are expanding treatment areas via coupling electrical components with a mechanical response. Integration of MEMs within various technologies e.g., MFs, has given rise to highly responsive systems capable of providing accurate therapeutic care. A poignant example of effective coupling of MEMS with other ETs comes with the use of

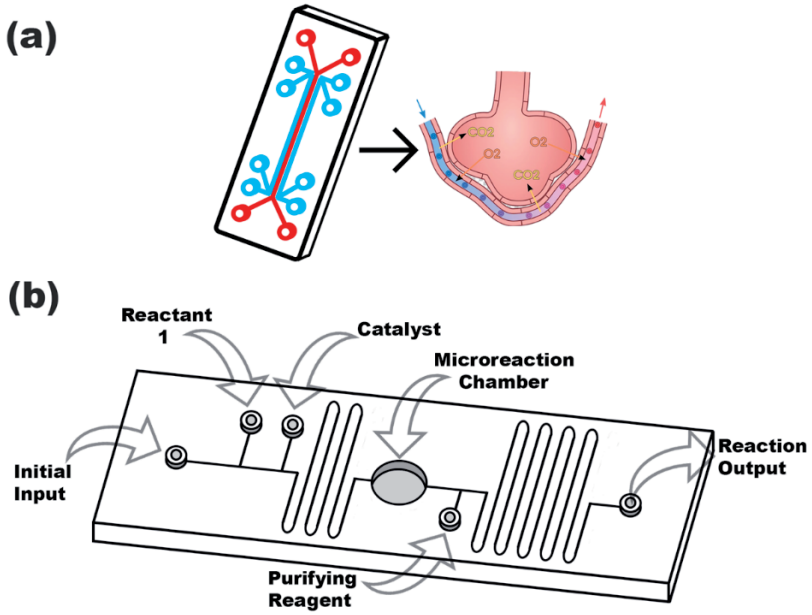

Figure 2. (a) Organ-on-a-chip technology, allowing *in vitro* mimicking of lung function oxygen transfer between vasculature and alveoli; (b) Example of the propensity of microfluidics for lab on a chip technology.

MNs for non-invasive prolonged transdermal API delivery and real-time monitoring have seen healthcare therapy in this area transform.

The combination of MN technology with BioMEMS ushers the possibility of real-time detection followed by subsequent automated pharmaceutical intervention. A simple feedback loop for insulin detection coupled with a syringe pump via a MN-MEMS array can allow for accurate detection and delivery of insulin (**Figure 3**), improving the quality of life of a diabetic patient [22].

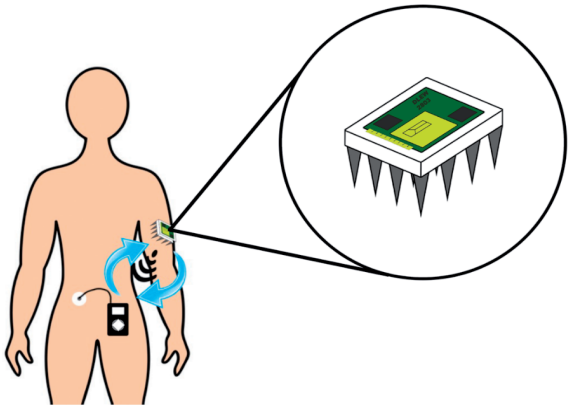

Figure 3. Graphical representation for a wirelessly communicating MN-MEMS device exchanging feedback with an insulin pump device.

MEMS devices have advantages such as portability, high sensitivity and high customisability, however, suffer from drawbacks mostly linked to economic reasons due to the high costs of research and device fabrication.

Machine Learning

Existing as a subsection of artificial intelligence (AI), ML has become an integral part of design of experiment (DoE) approaches, as well as experimental innovation [23]. ML has been used extensively for data analysis within the pharmaceutical sector [24], providing in-depth examination of big data within a reduced amount of time (**Figure 4**).

The applications of ML for pharmaceutical development include bettering experimental design, such as complimenting computer-aided design (CAD) processes, in-line analytical monitoring applications [25] and predictive modelling [24]. ML can also be viewed as improving the

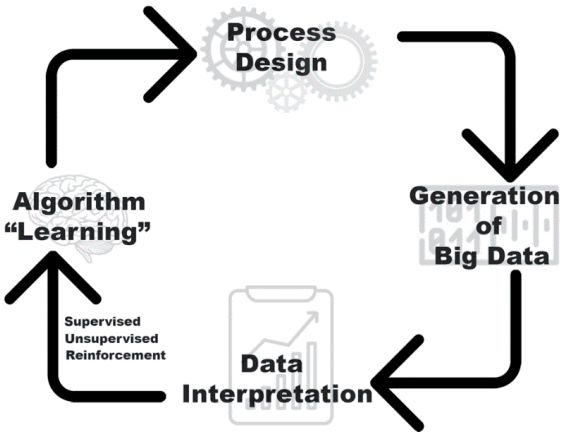

Figure 4. A typical design pathway for the active enrolment of ML within an exploratory system.

sustainability of many approaches, by helping decrease the environmental and economic burden of a technology due to pre-process analysis [17]. The recent influx of AI services on a commercial level, e.g., ChatGPT (OpenAI), is likely to open access and understanding to a wider population base, allowing for the next generation of scientists to have a greater understanding of the potential held by ML for pharmaceutical applications.

ML can process large datasets in a relatively short duration of time, however its major pitfall is the requirement for the initial production of large datasets for input, as well as the stipulation for high core-processing levels.

Conclusions

The mentioned ETs show great promise over a wide range of therapy areas. It is yet to be mentioned in this review how frequently the technologies are inter-compatible, leading to a fortification in functionality; for example, the use of AM to print highly-customised MF devices. An attribute common to all the technologies in this mini review is the high degree of customisability, which again is bridging the gap towards the final goal of a more individualised level of healthcare. The issues relating to ETs lies in their novelty, meaning that their true potential is far from being actualised, including optimisation of process parameters and key applications. For example, a highlighted goal for future healthcare is the capacity to provide individualised patient care on a wide-scale. To address this goal, factors

such as print speed for AM, or cost reduction for MEMS technology must be addressed. Scalability is also an issue associated with current healthcare technologies and especially some ETs, such as MFs. Future directions to enhance the scalability of these technologies is an issue that must be investigated, to allow technologies to truly benefit the area of healthcare. It's clear that ETs are beginning to have an impact felt by the wide scale medical field, however, further work is still needed to be performed.

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Conflict of interest statement
The authors declare no conflict of interest.

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