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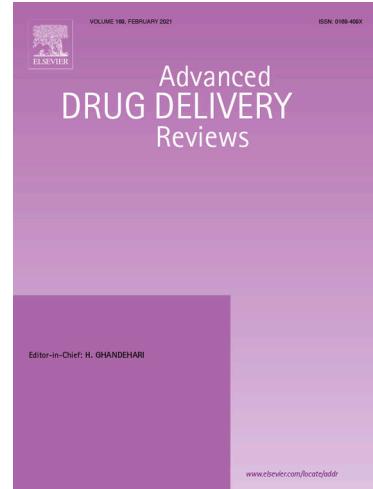
Connected Healthcare: Improving Patient Care using Digital Health Technologies

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Connected Healthcare: Improving Patient Care using Digital Health Technologies

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Abstract

Now more than ever, traditional healthcare models are being overhauled with digital technologies of Healthcare 4.0 being increasingly adopted. Worldwide, digital devices are improving every stage of the patient care pathway. For one, sensors are being used to monitor patient metrics 24/7, permitting swift diagnosis and interventions. At the treatment stage, 3D printers are currently being investigated for the concept of personalised medicine by allowing patients access to on-demand, customisable therapeutics. Robots are also being explored for treatment, by empowering precision surgery or targeted drug delivery. Within medical logistics, drones are being leveraged to deliver critical treatments to remote areas, collect samples, and even provide emergency aid. To enable seamless integration within healthcare, the Internet of Things technology is being exploited to form closed-loop systems that remotely communicate with one another. This review outlines the most promising healthcare technologies and devices, their strengths, drawbacks, and scopes for clinical adoption.

1 Introduction

Digital health is revolutionising the healthcare sector, moving away from the traditional ‘one-size-fits-all’ approach of healthcare management towards real-time personalised monitoring and therapeutic care. Digital devices have the potential to improve our ability to diagnose accurately and treat diseases and to enhance the delivery of healthcare for individual patients, as well as empowering patients to have more control over, and make better-informed decisions about, their health [1]. The concept also offers numerous opportunities to facilitate prevention, early diagnosis of life-threatening diseases, and management of chronic conditions outside of traditional health care settings.

The recent COVID-19 pandemic has highlighted the critical importance of digital technologies in healthcare [2], with many people coming to rely on the internet and digital devices for access to medical services and treatments [3]. Indeed, development of transformative digital health tools has reached peak pace, with many emerging devices promising to revolutionise aspects of patient care. Healthcare systems are gradually recognising that adoption of modern technologies could streamline the patient pathway, from identification of symptoms to treatment and long-term support. This paradigm shift has the potential to widen access to healthcare provision, reduce costs, and provide services tailored to individual needs.

Healthcare devices (which refers to medical devices that monitor patients’ vital signs) have the capability to improve real-time, accurate diagnosis and

treatment of disease. They allow medical care to percolate not just traditional clinical settings, but also homes, workplaces and travel locations. In this manner, participatory medicine lessens the burden on physical healthcare establishments, whilst providing patients with care that integrates with their daily lives. Devices can empower patients to self-advocate, gain control over their care and make better-informed decisions about their health. Digital healthcare also offers new ways to facilitate prevention and management of chronic conditions at the population level.

In the traditional model of healthcare, the general population tends to seek medical advice when new symptoms appear and they attend a general check-up with a General Practitioner (GP). This model is changing with the increasing availability of affordable consumer technology, such as wearables, which give patients direct access to information about their health by providing real-time clinical data, a relatively new trend known as Quantified Self (QS) [4]. According to a recent report, the wearable medical device market is expected to reach more than US\$90.4 billion by 2022 [5]. Currently, Apple has the majority market share (34.1%), followed by Xiaomi and Samsung [6]. Facilitated by such devices, patients are taking an enhanced interest in their own daily health, often without the support of healthcare professionals.

Within the scope of therapeutics, the use of patient-specific clinical data and Electronic Healthcare Records (EHRs) can pave the way for personalising treatments for patients. For example, 3D printing technologies have been applied for the on-demand production of dosage forms tailored to individual

patients, with tailored dosages, drug combinations, shapes, sizes, and drug release profiles, at the point-of-care such as within hospital or community pharmacies [7, 8]. The field of robotics is also being exploited to support multiple healthcare services. In particular, large robots are being used to expedite medication dispensing and perform surgical procedures, whilst smaller ones are remotely guided to accurately deliver drug substances to targeted disease sites within the body [9, 10].

Other digital tools including medical drones, can be used to improve medicine and treatment access, especially for patients who have mobility challenges or those who live in poorly accessible locations. Similarly, medical drones can be used to collect samples for delivery to local hospitals and clinics, facilitating and accelerating services that normally take time or are unattainable using road transport methods [11]. With many medical devices now having the ability to connect to and communicate with other devices or systems, remote monitoring can be performed in a continuous manner, enabling prompt interventions. Indeed, these transformative technologies are contributing towards large-scale cyber physical systems, using in-built sensors, Internet of Things (IoT), and cloud computing. These integrated systems of information and communication technologies (ICTs) allow previously isolated devices to collaborate, enabling closed-loop sensing, data collection, and on-demand outputs tailored to the needs of the individual [12].

Despite the numerous benefits of digital health technologies, a number of challenges for their adoption still remain. For example, the integration of tools

into existing healthcare structures, the need for data security and protection, as well as provision for potentially high entry costs. Moreover, the risk of making all processes autonomous should be evaluated for their effects on healthcare services (e.g., the dramatic implications in case of system failures) and social life (e.g., limited job opportunities if all man jobs are replaced by robots). To build an equitable model of digital healthcare, it is imperative that those lacking the personal funds to purchase devices are not left behind; often these patients have the potential to benefit most from the innovative technologies. The purpose of this review is to provide a timely overview of the most promising modern digital health technologies, outline where they fit into the patient pathway, and recognise the challenges they currently face. The next steps that are required to leverage emerging digital healthcare technologies from theoretical prospects to real-world assets for patients and the healthcare sector alike will also be discussed.

2 Sensors

Sensors will play a pivotal role in the future of modern medicine by facilitating remote diagnosis and patient monitoring [13, 14]. Sensors are devices used to measure and record physical, chemical, and/or biological signals [15]. Sensors which incorporate a biological component to detect signals are more precisely defined as biosensors [16, 17]. The sensor market as a whole is growing rapidly; in 2020 the global sensor market was valued at \$193.9 billion, with an expected increase to \$332.8 billion by 2025, principally driven by the COVID-19 pandemic [18].

Widespread uptake of sensors has the propensity to enhance patient care in several ways. Firstly, the portable nature of many sensors will allow for remote clinical assessment of patients. This improves accessibility to medical expertise by removing the need for individuals to visit a healthcare setting in person. Moreover, recorded clinical data may be more representative of a patient's typical physiological condition, as measurements taken within an individual's own environment have less risk of being confounded by white coat syndrome (this refers to a medical condition where patients temporarily develop high blood pressure due to stress caused by being in a clinical setting or when around a healthcare professional) [19]. In addition, increased uptake of sensors could help to reduce healthcare costs, as patients may be monitored in their own homes without needing to be admitted. Lastly, the digital nature of many sensors allows them to be combined with other advanced technologies. For example, real time sensor data can be fed through artificial intelligence (AI) algorithms to enhance the accuracy and speed of clinical interpretations [20]. Sensors may also be combined with other hardware for multiple modalities, via IoT [12]. The medical sensors field is a fast-evolving space, holding both traditional and cutting-edge devices operating at the forefront of scientific capability.

2.1 Traditional sensors

In a typical clinical setting, a clinician currently has access to a myriad of sensors, integral for monitoring the health status of patients and detecting clinical abnormalities. At present, the most prominent physical sensor deployed in hospitals is the electronic vital signs monitor, which monitors patient heart

rate, electromagnetic cardiogram (ECG), oxygen saturation (SpO_2), body temperature, and blood pressure (Figure 1). The collection of such clinical metrics is fundamental in the care of patients within all specialities, from general practice to intensive care units. Other commonplace sensors include medical imaging devices. For example, X-ray machines use high energy electromagnetic radiation to image internal structures within the body, and magnetic resonance imaging (MRI) can be used to examine internal soft tissue via radiowaves and magnetic fields. Ultrasound scanners, spirometers, audiometers, digital scales, and doppler scanners are all additional examples of commonly used physical sensors.

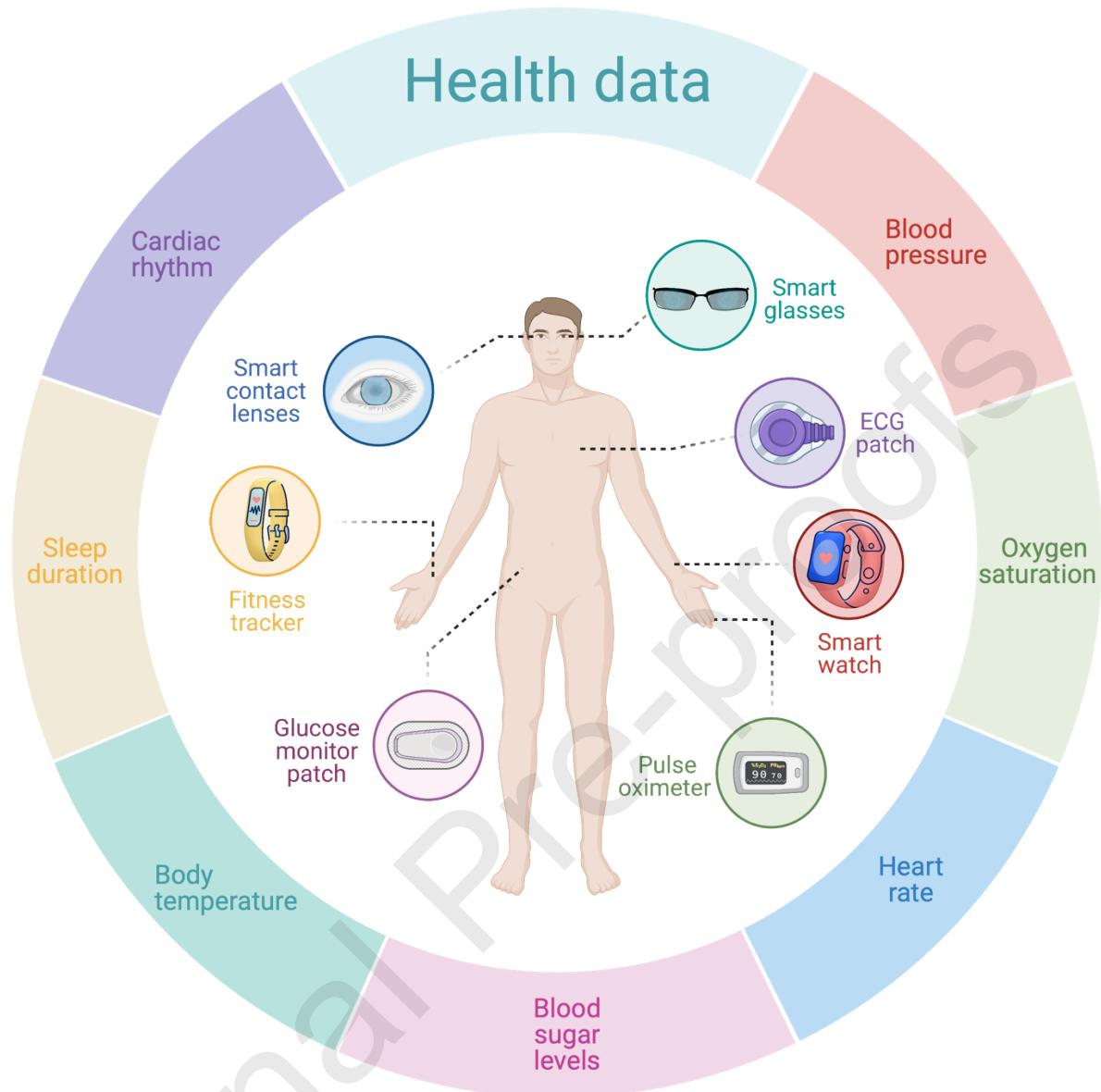


Figure 1. Graphical illustration outlining examples of different types of wearable sensors and the health data that can be obtained from them. Created with BioRender.com.

Biosensors are also hardly a novel concept. As shown in **Figure 2**, biosensors include a biorecognition element, transducer, internal electronics, and an output into their sensing infrastructure [21]. Bioreceptors are capable of detecting a myriad of analytes with high selectivity and sensitivity [22-24].

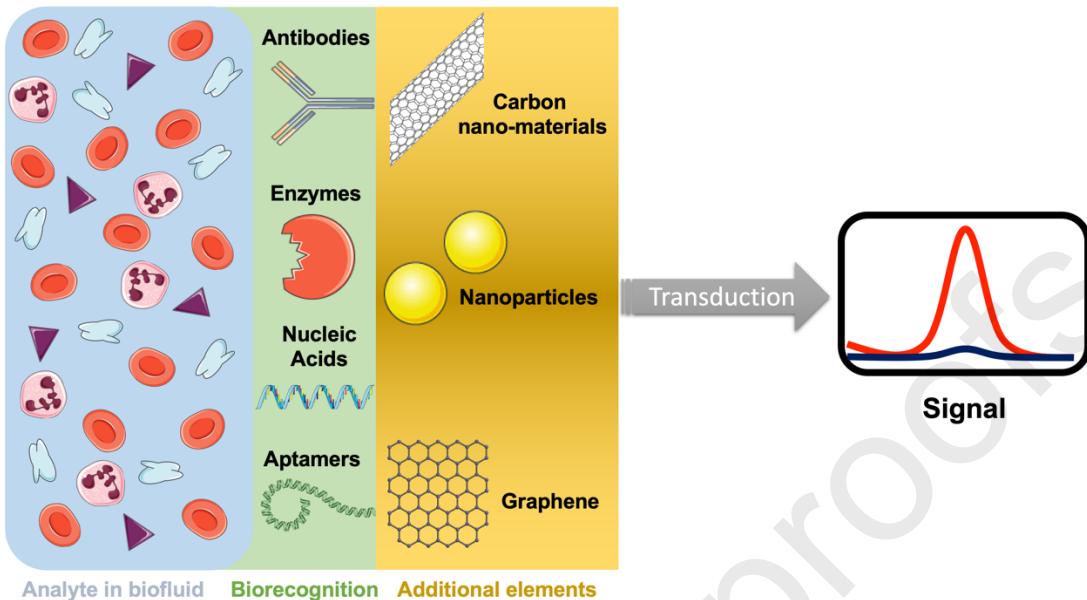


Figure 2. Diagram showing the general mechanism of biosensors. A biofluid of interest contains the target analyte as well as interferents. The target analyte is detected by the biorecognition layer, which may include additional functionalities such as nanoparticles, graphene, or carbon nanostructures. The signal from this detection can be transduced into an interpretable output, such as quantifying the analyte concentration in the biofluid.

Biosensors offer a plethora of benefits for early diagnosis and remote patient monitoring, facilitating personalised medical plans and reducing healthcare costs. Perhaps the earliest example of biosensors are blood glucose monitoring meters, which were introduced in 1962 [25]. The introduction of glucose biosensors has transformed how patients with diabetes mellitus manage their condition. Ensuring optimum glycaemic control is essential for patients self-administering insulin, for whom a slight overdose could result in hypoglycaemic shock.

2.2 Recent sensing innovation

The first ‘digital pill’ approved by the U.S. Food and Drug Administration (FDA) in 2017 was the Abilify Mycite; a small ingestion tracking system [26]. The Abilify Mycite is approved to monitor patient adherence to aripiprazole treatment, an atypical antipsychotic used in schizophrenia. The total cost of medication non-adherence is estimated at around US \$100 billion per year [27], which can be significantly reduced through patient monitoring. In the United Kingdom, ingestible cameras are now being offered as an alternative to invasive endoscopies for the diagnosis of colon cancer [28]. Known as the PillCam™, the 11 mm x 32 mm device captures images of the colonic lumen with dual cameras, which are transmitted to a sensor array and recorded for physician assessment [29]. Other ingestible sensors have been developed to monitor core body temperature [30-35] and gastrointestinal pH [36-39].

Another successful example of a sensor achieving remote physiological patient monitoring is the BPM Core, a smart arm cuff validated to monitor cardiovascular health [40]. The BPM Core is the first blood pressure monitor capable of performing ECGs and digital stethoscope measurements, with results shareable with clinicians via a bespoke smartphone app [41]. The measurements can be used for preventing hypertension and detecting atrial fibrillation and valvular heart disease [42]. In the biosensor field, point-of-care blood analysis has been advanced by the Hemo Control device (EKF Diagnostics). The Hemo Control can determine patient blood haemoglobin and haematocrit readings, with relative variations of less than 3 %, in just 25

seconds [43-45]. Improvements to traditional glucose biosensors are also being sought with wearable, non-invasive, continuous glucose monitors (Table 1). To date, these have met mixed commercial success due to reliability concerns, invasive insertion, and unpleasant skin reactions.

The COVID-19 pandemic has further highlighted the utility of remote medical sensors. Diagnosis and monitoring patients at home has been regarded as useful in reducing spread of infection, lessening burden on struggling healthcare settings, and improving patient care [46, 47]. In the United States, commercial smartphone-connected thermometers detected the spread of COVID-19 weeks ahead of national warning systems. Since then, the smart thermometer developers, Kinsa Health, have worked with the U.S. Center for Disease Control to map national infection rates and hotspots, and have launched platforms to improve safety in schools and workplaces [48].

Owing to the meteoric commercial success of smartwatches, such as the Apple Watch and FitBit, interest in developing wearable sensors to provide continuous, real-time healthcare monitoring has grown exponentially. At present, commercial smartwatches are limited to monitoring of vital signs, such as heart rate and ECG. These are measured in a variety of ways, such as using the absorption of light to measure heart rate and SpO₂, or using electrodes to measure electrical signals from the heart for performing ECGs [49, 50]. Given the gradual widespread adoption and normalisation of smartwatches in our lives, wearable biosensors will be key components of future healthcare [51-54]. This is because wearable biosensors allow for continuous monitoring of

patients' vitals without additional strain to their daily life activities. Thus, their integration within digital healthcare can be achieved seamlessly compared to other types of sensors which users may be reluctant to exploit.

Table 1. Examples of commercial non- or minimally invasive glucose monitors. Data are from those presented in the original source [55].

Product, company	Biofluid	Platform	Monitoring mechanism	Current stage
Smart contact lens, Google and Novartis	Tears	Contact lens	Electrochemistry	On hold
Freestyle Libre, Abbott	ISF	Patch (MN)	Electrochemistry	FDA approved
Dexcom G6 CGM, Dexcom	ISF	Patch (MN)	Electrochemistry	FDA approved
GlucoTrack, Integrity Applications	Blood	Finger clip	Ultrasonic, electromagnetic, thermal waves	Approved in Europe
Eversense, Senseonics	ISF	SC small stick implant	Fluorescence	FDA approved
GlucoWatch, Cygnus Inc.	ISF	Watch	Electrochemistry (reverse iontophoresis)	Retracted from market
sugarBEAT, Nemaura Medical Inc.	ISF	Patch	Electrochemistry (reverse iontophoresis)	Approved in Europe, pending FDA approval

ISF, interstitial fluid; MN, microneedle; SC, subcutaneous

2.3 Sensors of the future

Clearly, the sensor market is in demand and innovating quickly. In upcoming years, it is likely that physical sensors and biosensors with novel and advanced functionalities will break into the market. Ingestible sensors designed to diagnose and monitor gastrointestinal (GI) conditions are expected to be among those rapidly emerging. Applications of GI sensors in development include the detection of disease-specific analytes in intestinal fluid [56]; assessment of gas and fermentation activity of gut microbiota [57, 58]; detection of bleeding [59-61]; sampling of gut microbiota [62]; and early screening of cancer [63-65].

As the field of biosensors develops, increased sensitivity, specificity, and detection capabilities will also allow for the diagnosis of various infectious diseases. The early detection of COVID-19 has been crucial in many countries' response to the pandemic, with reliable testing reducing virus transmission and saving many lives [66]. The unmet clinical need for fast, reliable, and scalable COVID-19 diagnostics has led to considerable biosensing innovation. One example of this is the electrochemical detection of SARS-CoV-2 in human nasopharyngeal swab samples using a field-effect transistor-based biosensor [67]. This model is composed of a graphene-based biosensor with SARS-CoV-2-spike antibodies immobilised onto its surface (Figure 3A). Binding of SARS-CoV-2 to the antibodies induces a change in real-time current, correlating with viral load. Biosensors utilising fluorescence have also been explored for the detection of SARS-CoV-2. In particular, a CRISPR-powered fluorescence-based biosensor capable of detecting SARS-CoV-2 virus down to a limit of detection of just 2 copies per sample has been developed (Figure 3B) [68]. Herein, to allow for

a rapid analysis, a portable fluorescence reader can be used by a healthcare professional or patient at the point-of-care.

Wearable diagnostic biosensors are another area experiencing growing interest. One such application is the diagnosis of cystic fibrosis. A patch electrode with an Ag/AgCl electrode for chloride ion detection, and a sodium ionophore ion-selective electrode for sodium detection, has been developed (Figure 3C) [69]. Performance was shown to be highly linear, with only small sensitivity variations between identically fabricated electrodes or those stored long-term. With the addition of a cholinergic agonist hydrogel for iontophoretic sweat stimulation, the patch could detect both ions in sweat and could clearly distinguish between individuals with and without cystic fibrosis. Elsewhere, biosensors have been explored for a diverse range of analytes and applied to numerous sites of the body [55]. For example, a laser-engraved biosensor that detects uric acid and tyrosine in sweat has been developed for the management of gout [70]. Here, the sensor comprises three key components: a graphene-based chemical sensor for detecting uric acid and tyrosine, a graphene-based physical sensor that measures temperature and respiration rate, and a microfluidic module for sampling sweat (Figure 3D). Data obtained from the biosensor correlated well with serum uric acid levels in both healthy volunteers and patients with gout.

In addition to diagnosis, sensors can also be utilised for therapeutic drug monitoring (TDM). TDM is the clinical practice of periodically measuring a drug's serum concentration to determine the appropriate subsequent dose. Such sensors could be applied externally to the patient's skin, swallowed or implanted in the patient's body, where body fluids care used for sampling. Thereafter, the sensor transmits signals to

an external transducer attached to the patient's body that wirelessly communicates with a smartphone or computer device that analyses the data. TDM is essential for ensuring safe dosing of narrow therapeutic index (NTI) drugs, i.e. drugs with minute differences between their toxic and minimal therapeutic blood concentrations. Present-day TDM involves processes that are far from ideal for routine monitoring due to their invasive, time-consuming, expensive, and specialist nature [71]. Biosensors are thus being developed to act as non-invasive platforms for real-time TDM of NTI drugs, with applications including vancomycin (Figure 3E) [72], phenoxyethylpenicillin (Figure 3F) [73], lamotrigine [74], and doxorubicin [75]. In a study focused on doxorubicin, a microfluidic device combined with an electrochemical sensor was successfully applied to the closed-loop TDM of live, conscious rabbits [75]. Biosensor drug concentration readings could directly inform drug infusion rate, achieving improved control over drug plasma concentration compared with standard infusion (Figure 3G).

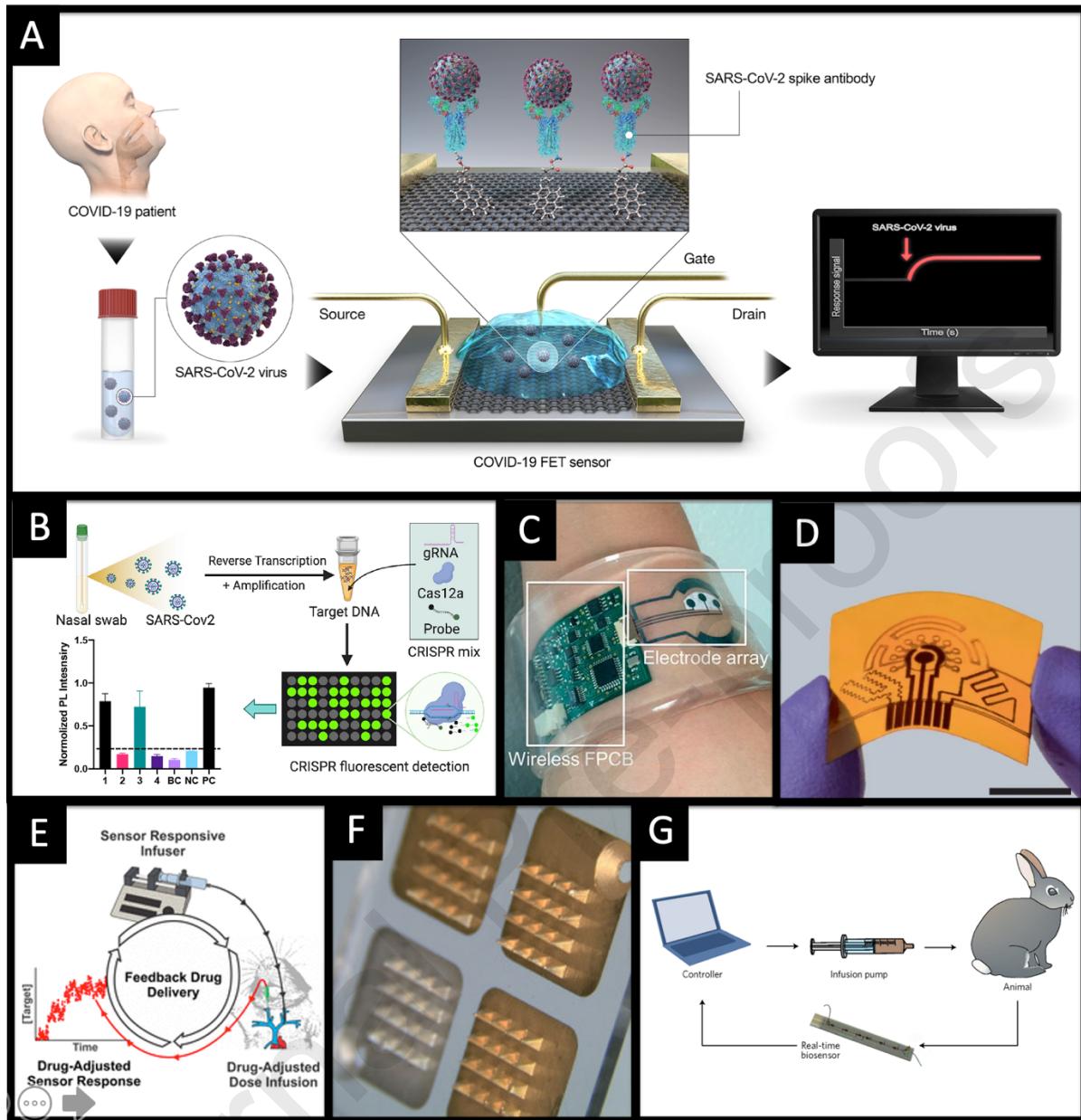


Figure 3. Examples of emerging sensors. (A) Graphical illustration of the sensing mechanism for an FET-based SARS-CoV-2 biosensor [67]. (B) Diagram of the methodology for detection for SARS-CoV-2 using a fluorescence-based CRISPR-powered diagnosis test [68]. (C) Image of an electrode and wireless analyser for sweat measurement and cystic fibrosis measurement [69]. (D) Image of a laser engraved sweat sensor for tyrosine and uric acid measurement [70]. (E) Schematic diagram demonstrating the closed loop measurement and feedback response for vancomycin monitoring [72]. (F) Image of microneedles used in phenoxymethylpenicillin detection

in interstitial fluid [73]. (G) Schematic diagram of a closed loop used for Doxorubicin monitoring in live animals [75]. Images were reprinted with permission from original sources.

2.4 Uptake of novel sensors

To fully harness the benefits of emerging sensor capabilities, it is paramount that healthcare systems prepare for newly approved devices to enter clinical practice. The FDA currently regulates medical devices through a three-tier classification system that incorporates clinical risk and associated regulatory controls [20]. The risk of new sensors will be determined by factors including whether a disease is being diagnosed, if the platform plays a role in treatment selection, and the severity of the disease to be diagnosed/monitored. To protect patient privacy, it is also important that data generated from sensors are secure. Where sensors are combined with other technologies, such as AI, there will be further translational considerations, including user trust [76]. Challenges relating to the development of novel sensors include overcoming the foreign body response (where a sensor is implanted), retaining robustness to environmental conditions and mechanical stress, reducing movement-induced noise in signals, maintaining a reliable power supply, preserving long-term stability, as well as mitigating external factors like cultural-language barriers and a lack of connectivity in remote locations [77, 78]. A more comprehensive review on the limitations of current biosensors can be found here [55].

Despite these challenges, the future of sensors in clinical practice is optimistic. Medical response to the COVID-19 pandemic has demonstrated how innovation can be rapidly incorporated into existing healthcare systems with relative ease. Whereas once

traditional healthcare structures may have been wary of adopting new technologies such as sensors, they are now embracing them. Sensors ultimately will transform the diagnosis and monitoring of disease, leading to widespread benefits for patient care.

3 3D Printing

Currently, medicines are produced in large batches, with formulations available in fixed dose strengths, shapes and sizes. However, studies have shown that medicines behave differently in patients due to inter- and intra-individual variability in pharmacokinetic responses [81]. As a result, not all medicines are effective in providing a therapeutic response, e.g., oncology and Alzheimer's medications have shown efficacy rates of no more than 25% and 30%, respectively [82]. Furthermore, the absence of flexible dosing is particularly problematic in the case of children and elderly patients due to their lower dosing requirements. By administering personalised medications, it is possible to improve patient care whilst minimising hospitalisations and healthcare costs. Thus, in recent years there has been a considerable push to move away from treating patients via a 'one-size-fits-all' approach towards personalised medicine, requiring flexible dosage forms to suit the needs of individual patients [8]. To overcome challenges associated with conventional marketed dosage forms, it is necessary to adopt novel processes that allow for such flexibility.

3D printing is an innovative technology causing a transformative change in medicines manufacture and the pharmaceutical industry [79, 80, 83]. A growing evidence base has shown that 3D printing, an additive manufacturing process, can meet the changing needs of the pharmaceutical industry by enabling bespoke design of personalised oral dosage forms using computer-aided design (CAD) software for the on-demand, layer-

by-layer production of Printlets™ (3D printed tablets) [84, 85]. Such a concept is not only applicable to patients, but could also be extended to animal models used in early pre-clinical studies [86].

Theoretically, 3D printing could be used for producing most of the medical products (including medicines, devices, implants, and even tissue engineering constructs) used in clinical practice today. In particular, 3D printing has been shown to be more cost-effective for producing small batches of individualised objects compared with mass manufacture [122]. Favourably, however, a major strength of 3D printing is that the complexity of the object does not influence the production cost [123]. To date, the pharmaceutical industry has widely researched the potential for 3D printing to create individualised medical products, including 3D printed dosage forms, patient-specific medical devices, and bioprinting in tissue engineering [124-128].

3.1 3D printing of medicines

3D printing allows the production of flexible dosage forms, i.e., those with a personalised dosage, geometry, drug combinations and drug release kinetics [79]. This poses significant benefits for those patient groups with specific dosing needs (such as within paediatrics and geriatrics) or for certain medicines that require frequent dose adjustments based on activity and blood levels (e.g., NTI drugs [129, 130]). Although the American Society for Testing and Materials (ASTM) classifies seven main categories of 3D printing technologies [87], five main technologies have been researched within pharmaceuticals (e.g., binder jet printing [88, 89, 131, 132]; fused deposition modelling, FDM [92, 93, 133-135]; semi-solid extrusion, SSE [96, 97, 136-139]; selective laser sintering (SLS) [99-104]; and vat photopolymerization [109, 115,

140-143]). More recently, there has been a considerable interest in a sixth technology, termed direct powder extrusion (DPE) or melt extrusion deposition (MEDTM), which reduces risks of thermal drug degradation by simplifying the extrusion procedure into a single-step process [105-107, 144]. The mode of action, benefits and drawbacks of each 3D printing technology for pharmaceuticals has been summarised elsewhere and will not be discussed in detail in this review [7, 116, 117].

One of the main benefits of 3D printing is the ability to personalise dosages based on the needs of each patient. As an example, FabRx recently integrated a personalised medicine 3D printer into a hospital pharmacy setting to treat children (3 – 16 years) with a severe metabolic disorder (maple syrup urine disease; MSUD) (Figure 4A) [145]. Patients who suffer from this disease require constant monitoring and adjustments of dietary amino acids (e.g., isoleucine) depending upon their plasma levels. Herein, the use of 3D printing enabled the production of chewable and palatable Printlets containing isoleucine in a variety of dosages, colours, and flavours, which were evaluated for patient acceptability and therapy control. The researchers found that the 3D printed formulations enabled a tighter control over target blood concentrations in comparison to the standard therapy (capsules), and that the flavours and colours of the 3D printed dosage forms were well accepted amongst all patients. This study demonstrated the true benefits of such technology in the personalised medicines arena.

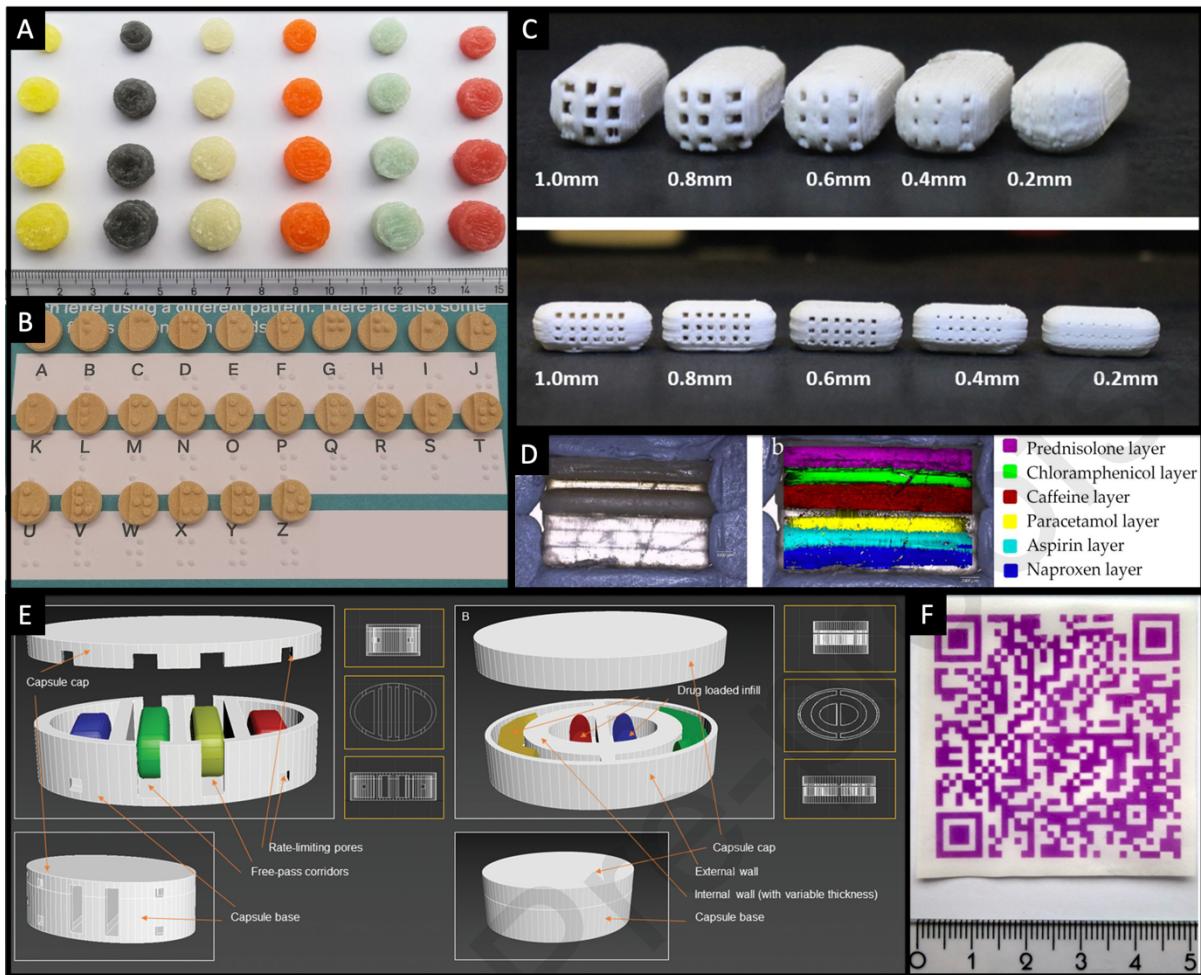


Figure 4. (A) 3D printed chewable tablets (Printlets) fabricated using SSE 3D printing in different flavours, colours, and doses. From left to right: Lemon-yellow, coconut-black, banana-light green, orange-orange, raspberry-light blue, strawberry-red. From top to bottom: 50 mg, 100 mg, 150 mg and 200 mg. Scale shown in cm [145]. (B) Images of SLS Printlets for patients with visual impairment containing Braille tactile patterns on their surface [146]. (C) Images of channelled FDM 3D printed tablets with decreasing channel size, having (top) 9 long channels and (bottom) 18 short channels [147]. (D) Image of a six-layer SLA polyprintlet, taken using (from to right) optical light microscopy and Raman mapping [148]. (E) 3D design of capsule base and cap of (left) PLA capsules of parallel compartments with free-pass corridors and rate-limiting pores and (right) PVA capsules of concentric compartments design and varying internal wall

thicknesses [149]. (F) Image of printed QR code containing 2.5 mg haloperidol [150].

Images were reprinted with permission from original sources.

Several research groups have explored the use of 3D printing to produce dosage forms with complex geometries that are unattainable using tabletting processes. Using SLS (Figure 4B) and FDM, researchers were able to produce orodispersible Printlets that were designed to have Braille and Moon patterns on the surface, providing an innovative and practical medicine strategy for patients with visual impairment [146, 151]. Such a concept could revolutionise medicine taking for patients with visual impairment, e.g., by reducing medication errors and supporting increased independence. A single-site, two-part survey was completed children aged 4-11 years in 2020 to determine their preference and opinions based on visual inspection of Printlets produced using four different 3D printing technologies, namely digital light processing (DLP; a subtype of vat photopolymerization technology), SLS, FDM and SSE [152]. Interestingly, the DLP Printlets were the most visually appealing to the children (61.7%) followed by the SLS Printlets (21.2%), and with both the FDM (5.4%) and SSE (11.7%) Printlets receiving the lowest scores. Other researchers have also explored the impact of different internal and external structures on drug release, showing the potential for immediate through to controlled release systems to be easily fabricated (Figure 4C) [147, 148, 153-155]. The benefits of 3D printing could also have a wide-reaching impact on global health, tackling the challenges arising from opioid abuse [107, 156] and substandard and falsified medicines [157, 158].

3D printing holds substantial potential for patients prescribed complex medication regimes, such as in the case of polypharmacy (the administration of several concurrent

medicines), which can lead to confusion and errors to medication management [159]. Researchers have used SLA, SLS and FDM to print or load multiple drugs into the same dosage form to create 3D printed polypills (also known as polyprintlets) [160, 161]. As an example, six different drugs were printed in two multi-layered configurations, reducing the number of tablets from six a day to just one (Figure 4D) [163]. In another study, polyprintlets for the treatment of cardiovascular diseases were produced using FDM combined with hot-filling syringes (Figure 4E) [148]. Using SLS, miniprintlets (e.g., 1 or 2 mm pellets) were created having two different drugs with distinct release profiles [164]. To permit real-time quality control during printing, spectroscopic methods can be used to confirm the dosage of the drugs within the formulations [165]. Such a concept revolutionises the capability for on-demand quality control and dispensing of 3D printed dosage forms at the point-of-care [166]. In another approach, 3D printed formulations were prepared with QR codes and data matrices on their surface, enabling the tracing-and tracking of dosage forms seamlessly (Figure 4F) [150, 157, 167].

3.2 Patient-specific prosthetics, implants, and medical devices

The main product application for the invention of 3D printing was initially prosthetics. Designing and printing personalised implants and prostheses have become the gold-standard method and solution for many patients who require specific constructs. Prostheses can be rapidly custom-made using 3D printing both in geometry and material with images from medical scanning (such as radiographs, magnetic resonance imaging; MRI and computer tomography; CT) used to input specifications for production of these devices including cardiovascular and dental prostheses alongside part- or full-limb replacements [169, 170]. One example is that of Osteoid™

3D printed lattice-structured medical casts customised to the wearer [171]. By designing bespoke casts based on the patient's arm 3D scan, accurate and secure fitting to the patient's arm is ensured. Moreover, the use of 3D printing allows the creation of casts with low infill, resulting in very light structures, providing more comfort to the wearer. The Osteoid technique also employs ultrasound waves to encourage more rapid bone healing by up to 38% versus standard plaster casts. The cast's ultrasound system (known as LIPUS) pulsates for 20 min per day around the fracture site and has additionally been shown to improve healing of non-union fractures by up to 80% versus conservative methods.

3D printing has also been utilised for the production of personalised drug-eluting implants and medical devices [172-175]. For example, researchers have combined the use of scanners with 3D printing in order to create drug-eluting anti-acne masks, anatomically tailored wound dressings, mouthguards, and bespoke anti-biofilm multi drug-loaded hearing aids [128, 176-178]. In other studies, 3D printing has been utilised to create personalised 3D-printed intravesical [179, 180], intrauterine [181, 182], intragastric [79, 183] and subcutaneous devices [184, 185].

3.3 Future Perspectives of 3D Printing in Pharma

In 2015, the first 3D printed drug product, Spritam ®, was approved by the FDA for the treatment of epilepsy [186]. In February 2021, Triastek received FDA clearance for their 3D printed drug product, T19, for the treatment of rheumatoid arthritis [187] and perhaps more drug products will be approved in the near future. The integration of 3D printing into clinical pharmacy practice could facilitate a digital health revolution, changing the way medicines are designed and prescribed for patients.

Whilst still in its infancy, it can be envisioned that 3D printing could be seamlessly integrated into other digital health technologies, such as AI and machine learning [188-193], and point-of-care diagnostics [149], enabling a closed loop system from diagnosis [194], prescribing [195] and personalised medicine production [196-201]. Challenges are still required to be overcome, ranging from regulatory and technical hurdles to ensure drug product and medical device safety and efficacy. Nowadays, several companies are working to overcome this by developing pharmaceutical 3D printers (binder jet, extrusion-based and inkjet printing) that can be fully validated to Good Manufacturing Practice (GMP) to enable pharmaceutical manufacture. As an example, in 2020, FabRx revealed the world's first pharmaceutical 3D printer, the M3DIMAKER™, made specifically for personalised medicines [202]. More recently, Merck has announced that it will be using 3D printing to speed up and simplify clinical trials [203]. Other researchers are looking at integrating process analytical technologies (PAT) into 3D printing systems in order to ensure real-time drug product quality [165, 204, 205]. This research will contribute towards overcoming the major barrier to entry of 3D printing into pharmaceuticals, enabling the concept of personalised and bespoke medicines to become a reality.

4 Robotics

Increasingly, robots are being applied to automate and/or provide high level precision for the operation of a myriad of medical tasks. Key examples include minimally invasive surgery [10]; hospital disinfection [206]; communication with isolating or infectious patients [207]; lifting patients [208]; and phlebotomy [209]. In addition, the pharmaceutical sector is embracing robotics for streamlining their manual services

and as drug delivery tools. More and more, ingestible microrobots are being explored for drug delivery and diagnosis, whilst drones are being exploited to improve the accessibility of medications in rural regions. The following section will focus on the application of robotics in modernising pharmaceutical logistics, and as ingestible drug delivery or diagnostic agents.

4.1 Robots for pharmaceutical logistics

The use of robots has been rapidly increasing in different aspects of the pharmaceutical industry. Pharmaceutical robots can span from large pharmacy robots all way to small drug delivery robots. Within hospitals, large pharmacy robots can be centralised or decentralised. Centralised robots are mainly used for medication stocking, storing and picking [210]. Their use has been shown to lower dispensing errors and optimise space [211]. Whilst these robots aid pharmacy workflow, they do not actually provide many benefits to patients [212]. Decentralised pharmacy robots have also been applied to pharmaceutical services (e.g., managing stocks, tracking and dispensing medications) [212]. By tailoring the robots to the requirements of each ward or department, improved patient services can be provided in a timely and remote manner, even in the physical absence of pharmacists. This enhanced the efficiency of services while reducing time and costs associated with staff traveling.

High-tech centralised hubs that supply and dispense medications to hospitals, clinics, and homes have also been previously described [213]. Similarly, an automated ‘hub-and-spoke’ concept could be utilised in pharmacies [214]. The system involves a prescription being sent electronically from a spoke pharmacy to a hub; the medications are then assembled and collected from the hub and are sent to the spoke, where they

are dispensed to patients. By implementing these novel automation technologies, productivity could be improved by providing perpetual services while decreasing chances for errors. Moreover, due to the extensive scanning system, individual tablets can be traced all the way down to the patient that took them. The downside to this system is its complexity and high operating costs. In the case where an error relating to electric supply or internet access occurs, the whole hub will be down causing disruption to services. Furthermore, as the medicines are delivered through robots, this would mean that individual pharmacist-patient consultations are unavailable, which for some patients is necessary.

Electronic cabinets could also be utilised for supply management and control, enabling the tracing of medications' locations and thus facilitating the removal of recalled or expired medicines [215]. These automated cabinets have shown to be particularly useful in the management of controlled drugs, restricting access to authorised personnel only. Despite their benefits, risks with such cabinets involves the inability to access them in case of power cuts or system failure.

4.2 Miniaturised robots for oral drug delivery

With the recent advancements in smart materials and manufacturing technologies, the field of robotics has seen remarkable progress within the pharmaceutical arena. As an example, 4D printing, whereby 3D printed products become dynamic and undergo predetermined changes when subjected to a stimulus, is an enabling technology that has seen particular interest [216]. Miniature robots have been investigated as programmable tools to perform site-specific actions *in vivo*. Such programming can be achieved via various mechanisms, including mechanical or physical control, chemical

reactions and/or biological responses. An example of such are origami robots which can be folded inside capsules, facilitating their ingestion (Figure 5A) [217]. Once in the stomach, the capsule shell dissolves, releasing the robots, which are then remotely directed to the desired location to perform their intended action (e.g., wound closure, drug delivery, or elimination of exogenous particles or substances), after which they biodegrade. Similarly, a multi-material soft robot has been fabricated using 3D printing for the on-demand drug delivery to tumours [124]. The robot can be controlled externally using a magnet, allowing precise, site-specific drug release to the tumour microenvironment.

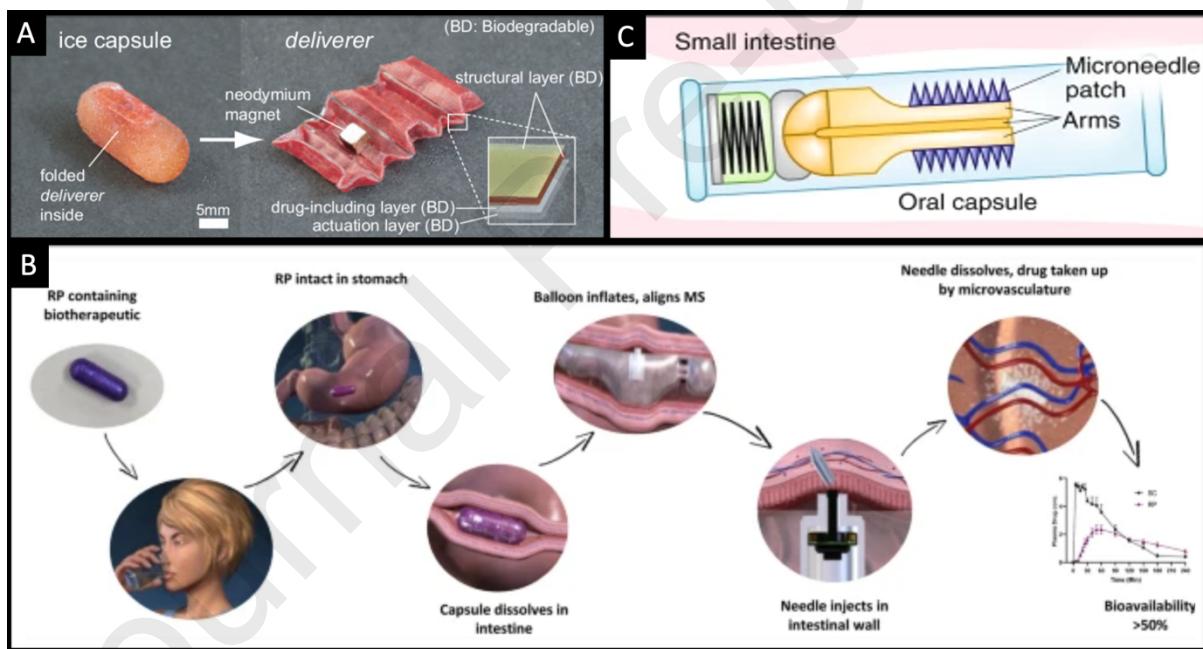


Figure 5. (A) Image of an iced, origami robotic capsule, in its (left) folded and (right) unfolded forms, used for drug delivery [217]. (B) Graphical illustration of the mechanism of action of the RaniPill™ [218]. (C) Graphical illustration of an unfolding microneedle patch for drug delivery [219]. Images were reprinted with permission from original sources.

By combining the latest advancements in the fields of robotics and 3D printing, it is possible to design drug depots that can be guided into the tumour site. As an example, helical microrobots comprising Fe_3O_4 magnetic nanoparticles and 5-fluorouracil (5-FU) were fabricated using two-photon polymerization 3D printing (a subtype of vat photopolymerization) [168]. Using rotating magnetic fields, the microrobotic device can be wirelessly navigated. Once in the tumour site, the release of 5-FU from the 3D microrobot is acoustically controlled via a focused ultrasonic beam, wherein a significant reduction in cancer cell viability was observed.

The RaniPill™ is an example of a miniature robot shown to be capable of delivering biological therapeutics (e.g., peptides and proteins) in a minimally invasive manner (Figure 5B). Biologics are challenging to administer orally, due to their sensitivity to degradation in the GI tract, and instead are typically administered via parenteral injections. The RaniPill™ presents a novel way of delivering biologics by using microneedles that auto-inject the active biologic (e.g., insulin, octreotide, teriparatide, and immunoglobulin G) into the jejunum wall [220-222]. A clinical study using this robotic pill has shown that its success rate at delivering oral biologics ranged between 25% to 80%, wherein the presence or absence of food did not affect its action [218].

A similar capsule has been developed by Massachusetts Institute of Technology, where radially arranged microneedles capable of piercing the GI wall enable delivery of large biological molecules with enhanced bioavailability. With the same premise, an unfolding microneedle patch has been produced (Figure 5C) [219]. Spread between three flexible arms, 96 microneedles are completely soluble with the ability to act as individual drug depots. The ingestible capsule houses the folded patch, and upon its

entry into the intestine dissolves, releasing the patch. As the patch unfolds, the microneedles pierce into the intestinal epithelium, releasing drug directly into systemic circulation as they slowly dissolve. A self-orienting robotic system has also been introduced for drug delivery [223]. The system consists of a biodegradable needle with an insulin tip, which is connected to a compressed spring coated with sugar. Once in the body, the sugar coating dissolves, releasing the spring and forcing the needle into the mucosal wall. Herein, this system enables the oral delivery of insulin or other drug agents (e.g., proteins and peptides) by directly releasing them into the bloodstream. Such technologies could revolutionise how biological therapeutics are administered; lessening the discomfort caused by injections and reducing the need for regular patient visits to healthcare professionals, and overall, improving compliance to treatment.

4.3 Ingestible robots for treatment of disease

Aside from drug delivery, robotic capsules can also be leveraged for the treatment of certain health conditions. For instance, a miniature robot has been developed for the treatment of GI haemorrhage [224]. The capsule utilises an inflatable “balloon” that inflates with carbon dioxide gas generated by the reaction between acetic acid and sodium bicarbonate. Here, the balloon’s inflation volume is directly controllable through modulation of the reagent concentrations. Inflation of the balloon at the site of bleeding can reduce blood loss by compression. A similar concept has been introduced for the treatment of obesity [225]. In another approach, a robotic pill has been suggested for the treatment of *Helicobacter pylori* infection in the stomach [226]. *H. pylori* infection is relatively common, affecting around 40% of people worldwide, and is a major cause of gastric cancer [227]. For this reason, it is recommended that *H. pylori* is completely eradicated when detected, typically requiring concurrent

administration of two antibiotics. The robotic pill offers an alternative to prescription of oral antibiotics, by eradicating the pathogenic bacteria with light. This photodynamic concept involves the emission of light using low current light sources (e.g., LEDs connected to a battery) at specific wavelengths (624 nm – red light or 405 nm – blue light), to which the bacteria are sensitive. Both red and blue lights have achieved a high bactericidal efficacy of ~96%.

Whilst having shown promising results, a major concern surrounding ingestible robots is their size. If a robot is too large it poses a risk of intestinal obstruction, potentially leading to grave adverse effects and necessitating surgical intervention. In other cases, some robots may instigate pressure on the wall of the gut, which could cause pain, physical damage, or even intestinal perforation [228]. Clearly, to be safe, ingestible robots should be sized with their entire target population in mind and should account for inter-individual differences in GI physiology [229]. A solution could include combining 3D printing with 3D scanning, to produce bespoke robots sized appropriately to meet the needs of their intended patient.

4.4 Assistive Robots

In recent years, assistant technologies have been increasingly used to support rehabilitation patients. These are commonly referred to as *personal care robots* or *carebots* and refer to autonomous robots that provide services and physical assistance to patients with physical impairment [230]. In this context, several types of physical assistive robots have been introduced, including prosthetic limbs, exo- and endo-skeletons (Figure 6). Whilst prosthetic devices replace ambulated body limbs, exo- and endo-skeletons are attached to the patient's limb to substitute for or improve

its functionality. Such robots have shown favourable results in stroke patients or those who require gait rehabilitation and reach-to-grasp motion support [231, 232]. These robots have shown to be more efficient for training purposes by providing quantitative feedback to patients and resulting in superior rehabilitation outcomes [233].

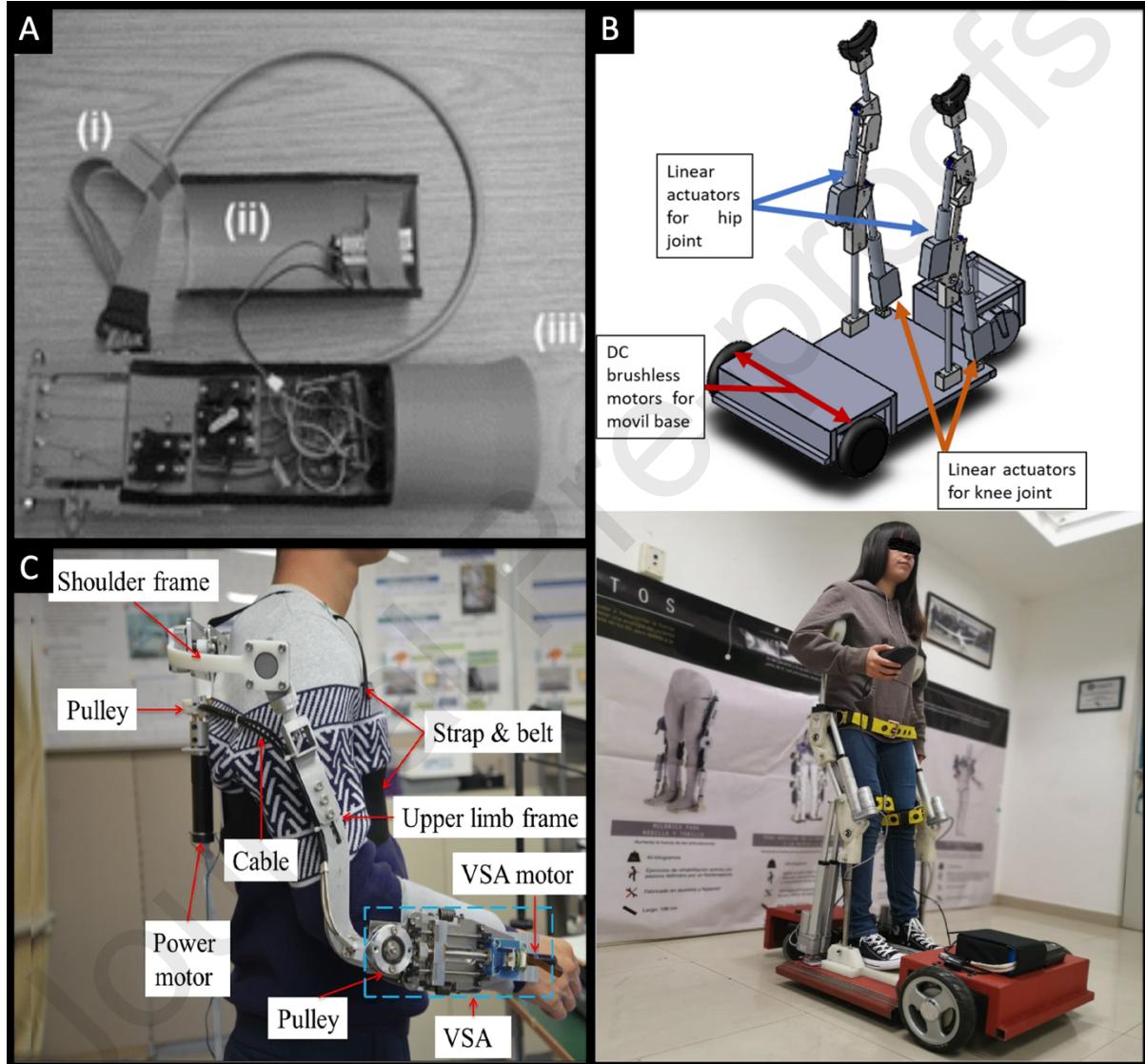


Figure 6. Examples of assistive robots. (A) Image of a 3D printed robotic prosthetic for transradial amputees [234]. (B) 3D design and image of a mobile lower limb exoskeleton [236]. (C) Image of a powered variable-stiffness exoskeleton device (PVSED) for upper limbs, outlining its individual components [235]. Images were reprinted with permission from original sources.

Examples of assistive robots include devices such as ExoLite™ [237], HAL [238] and HiBSO [239, 240]. As these are wearable devices, several features need to be taken into consideration and optimised with respect to individual patients. As an example, due to their standardised shapes and dimensions, these devices have limited restrictions in terms of patient weight and height that they can support. A solution to this would be to create bespoke robots that are specific to each patient using advanced technologies such as 3D scanning and 3D printing [234]. However, when designing such robots, it is essential to make sure that the weight of the robot does not exceed the maximum weight a patient could carry, preventing any discomfort or hindrance to their movement. Other considerations, include the autonomy, functionality, speed and battery-life. Like other robots, a risk relating to system failure exists, requiring routine checks and maintenance [241].

4.5 Drones

Drones are aerial robots that are revolutionising the pharmaceutical industry by enabling the streamlined delivery of essential medical supplies within rural communities and remote areas worldwide. Favourably, drones offer a unique way to deliver a product with a short transit time compared with road transportation which may be limited or congested or during a disease outbreak. During a global pandemic such as COVID-19, delivering samples faster to centralised facilities for testing has proven crucial, as it enables clinicians to make treatment decisions more quickly and improve patient outcomes.

4.5.1 Delivery of Medicines and Medical Supplies

In 2019, the United Parcel Service (UPS), AmerisourceBergen and CVS Pharmacy signed a deal to use drones to deliver medicines, supplies and records to hospitals and distribute prescriptions and retail items to consumer homes in the United States. During the COVID-19 pandemic in 2020, CVS and UPS were able to use drones to deliver prescription medications to more than 135,000 residents in a Florida retirement community in an effort to maintain social distancing measures [242]. Merck, Sharpe and Dohme in collaboration with telecom giant AT&T, have been involved in testing the potential of drones to transport temperature-controlled drugs and vaccines [243]. This involved medical supply delivery to remote mountain villages in Puerto Rico that were severely impacted and cut off by Hurricane Maria. The same team recently piloted the first over-sea drone delivery to the Bahamas. Even though the unmanned air vehicle (UAV) was beyond the operator's line of sight, live continuous temperature tracking was possible using cloud-based real-time data analysis, enabling the maintenance of a steady cold-chain system at -70 °C [244]. Merck has also carried out successful test runs in Lugano, Switzerland and further testing is planned to be undertaken in remote parts of Africa and Latin America. Another major pharmaceutical company, Novo Nordisk, with its partners Vodafone Ireland, trialled the use of drones to deliver medications for diabetes and to collect blood samples from a remote island off the west coast of Ireland [245]. Such practices using drone delivery have also been investigated elsewhere for insulin delivery to diabetic patients, ensuring that they have constant access to the critical treatment (Figure 7) [246, 247].

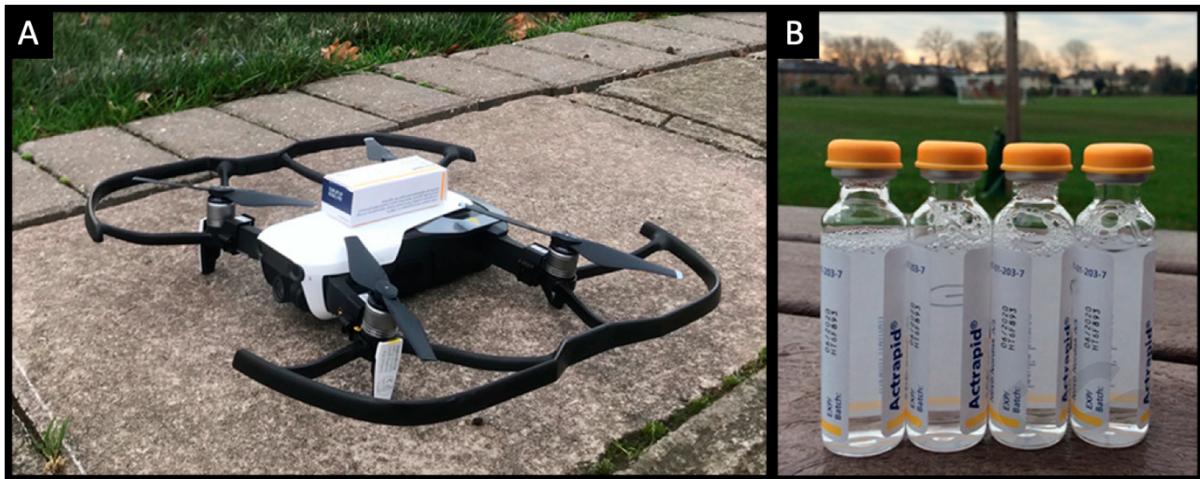


Figure 7. (A) Image of Insulin (Brand: Actrapid) in its original packaging attached onto the Mavic Air drone and (B) visual appearances of the vials after flight (9 ± 2 minutes, $n = 3$ control on the left). Reprinted with permission from [246].

4.5.2 Delivery of Lab Specimens to Hospitals

Due to the ability to quickly transport goods ‘as the crow flies’, much work has been invested in delivering patient samples to hospitals and clinics within urban locations, as well as hard-to-reach areas. Drones enable a more flexible and more eco-friendly means of transporting such samples, as well as a rapid delivery due to less dependence on the traffic situation. One such area with large deployment of drones is within Switzerland, including cities such as Lugano, Bern, and Zürich. Swiss Post, together with the drone manufacturer Matternet and partners from the healthcare sector, are leading the initiative and are using drones to transport laboratory samples [248, 249]. Taking activities in Zürich as an example, between June 2018 – Spring 2019, Swiss Post transported laboratory samples high above the basin of Lake Zürich and linked the ZLZ Emergency Laboratory at Hirslanden Klinik Im Park with the Central laboratory in Zollikon [250]. The drone was able to scale the distance in 7 minutes, a service which was 5 times faster than that can be delivered by car.

Another major example includes Zipline, which designs, builds and operates fixed-wing and battery-powered drone aircraft to deliver critical supplies and lab samples in Rwanda and Ghana [251]. Zipline's drones are mostly used to deliver payloads of whole blood; however, platelets, frozen plasma, cryoprecipitate, and medical supplies have also been loaded onto aircraft. The fixed-wing drones enable the delivery of medical supplies to anywhere within 80 km in under 45 minutes, wherein they can fly at a speed of up to 128 km/h and have a range of 160 km round trip while carrying up to 1.75 kg at an altitude of 400–500 metres [249, 252, 253]. Once the drone has reached its destination, it releases its payload via parachute for a person on the ground to collect and then re-navigates to the distribution centre for collection and re-loading by staff [254]. These drones are being used in Ghana to deliver vaccines, blood and medicines. As of May 2019, more than 65% of blood deliveries in Rwanda outside of Kigali use Zipline drones [255]. To date, Zipline's drones have been used to deliver ~150 essential medicinal products to an estimated 2,500 health facilities and 15 million citizens in rural Ghana. More recently, Zipline drones have been used in Ghana to transport COVID-19 samples [256].

In 2019, two major pharmaceutical companies (Pfizer and Novartis) announced agreements with Zipline to improve distribution of medicinal products within hard-to-reach areas [257]. Novartis, in partnership with the Sickle Cell Foundation and Zipline, commissioned the service to make sickle cell treatments more readily available in Ghana, Uganda, and Tanzania [258]. In addition, a successful trial was conducted whereby Zipline airlifted three packets of hydroxyurea capsules to a paediatric sickle cell patient at the Asamankese Government Hospital. Pfizer, in collaboration with Gavi

Alliance, the Bill & Melinda Gates Foundation, and the UPS Foundation, is working to support Ghana in establishing a medical drone delivery system to improve medicines access in rural locations [258]. Zipline technologies have also been readily utilised during the COVID-19 pandemic for the delivery of medical supplies and personal protective equipment to hospitals in North Carolina [259].

4.5.3 Emergency Response Drones

As well as enabling collection and delivery of blood samples, drones are also being designed to be first-responders and provide medical supplies or even personnel to emergency situations [260, 261]. TU Delft have recently developed the world's first Ambulance Drone, equipped with onboard automated external defibrillator (AED) and cardiopulmonary resuscitation (CPR) aids, that is being designed as a first-responder to patients in cardiac arrest [262]. Whilst still in development, the UAV is being designed to quickly find and navigate to the patient's location via the caller's mobile phone signal and makes its way there using GPS. The system is also designed to provide a livestream video and audio connection, enabling the drone to provide direct feedback to the emergency services as well as instructing and communicating with civilians on site around how best to treat the patient.

A company called Ehang has developed a two-seat passenger-grade drone that is able to carry medical supplies, organs and even personnel to emergency scenes [263], and has recently demonstrated its progress in enabling Urban Air Mobility applications. In recent exercises, the drone was trialled to aid in the prevention and control of the COVID-19 epidemic organised by the local authorities of Hezhou city in Guangxi province. Ehang 216 drones successfully transported medical supplies from Hezhou

Square to the Hezhou People's Hospital (4 km distance apart) by accurately landing on a 25-story rooftop of the hospital [264].

Before drones can be fully implemented into healthcare systems, current challenges such as management of airspace, and assurance of sufficient device battery life, need to be addressed. Additionally, the limited capacity, low autonomy and weight and temperature restrictions associated with drones curtail the amount and type of cargo which they can carry [249, 265, 266]. Other concerns include the strict flight regulations in urban environments, weather restrictions, airway traffic and data security.

5 Internet of Things

IoT refers to a set of physical, electronic devices that communicate with one another by remotely exchanging data over the internet. It is a platform that aims to automate processes by interconnecting multiple devices (e.g. sensors, robots and computers), removing need for human involvement (Figure 8) [267]. IoT seeks to converge a myriad of physical and virtual digital technologies to enact the decisions but in an automated manner. It is ultimately driven by the need to reduce costs, expedite processes, mitigate human errors, and minimise the need for expertise. Furthermore, when connected to computers and tablets with specialised software and applications, IoT offers the opportunity for real-time clinical analysis, detecting nuanced changes that would otherwise may have been overlooked by human users.

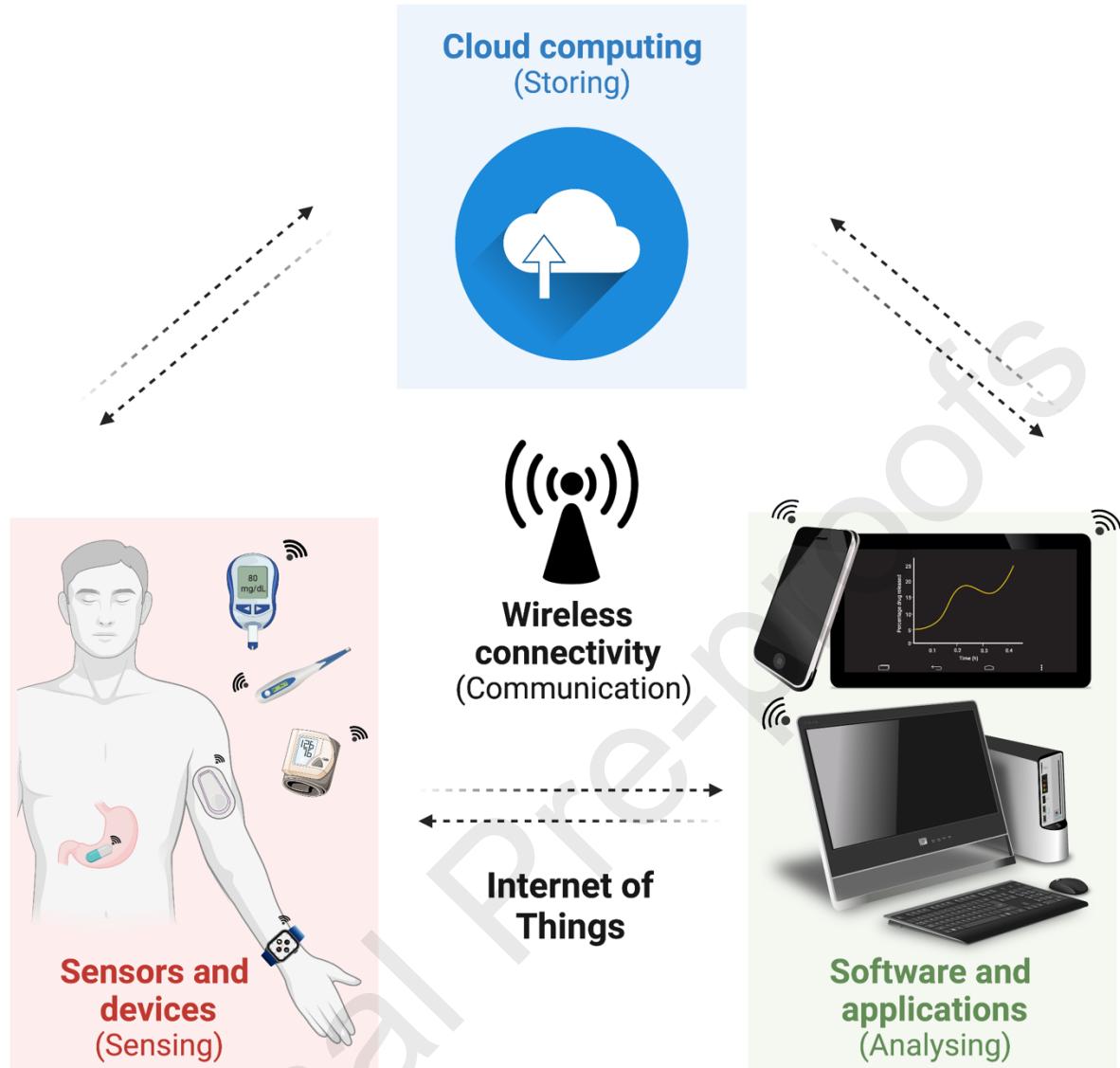


Figure 8. Graphical illustration of the internet of things platform. Created with BioRender.com.

The implementation of IoT depends on key enabling technologies, of which some have been discussed in the above sections, such as sensors and robots. The stages involved in IoT can be broadly categorised as (a) sensing, (b) storing, and (c) analysing data (Figure 8). The first stage is highly dependent on sensors, which provides inputs into the system in the form of data and transmit it for storage [268]. These can either

be biosensors for monitoring clinical treatments, or sensors applied in manufacturing and supply chains. The latter are sensors used to provide information regarding instrumentation performance and monitoring supply content, with the aim of preventing unnecessary and costly downtime. Sensors can be readily incorporated with communication components for transmitting the data, such as Bluetooth, WiFi and 5G. The data are then received and can be analysed by software stored on smartphones, tablets, or computer devices. As both sensory (e.g., smartwatches) and analytical devices are widely in-use in daily-life activities, the integration of the IoT framework within healthcare can be realised more easily than other digital technologies.

5.1 Smart home and community

IoT has been extensively tested in monitoring patients in the comfort of their own home [269]. The driving factor is that patients can maintain their lifestyle and independence. Equally, it reduces the need to burden healthcare institutes through having patients occupy resources in, for example, hospitals. A comprehensive recommendation system that recommends food and drugs to patients according to their biometric and lifestyle has been proposed [270].

Monitoring of glucose levels has proven to be challenging for diabetic patients, particularly during sleeping hours. Recent developments have seen a closed-feedback loop, whereby the glucose is monitored, and insulin is released according to the fluctuations of glucose levels. The readings are recorded and stored for the patient or clinician to observe [271]. Currently, there are no predictive analytics involved, but the

technology is still in its primary years and has the potential to incorporate predictive analysis.

For at-home care, the use of IoT for a ‘smart pillbox’ to facilitate prescription has been suggested [272]. The prototype demonstrated that the pillbox could house and track the use of nine different medications. Such functionalities include determining the amount of remaining medication, and when to take the pill, which is reinforced with an alarm incorporated into a smart device. The motivation for IoT-based smart boxes is to sustain the independence of the elderly, which is expected to become an economic burden as the aging population increases. The use of an IoT-based smart reminder, that also tracks medicine usage, and provides alerts for carers to track their progress, has also been advised. However, the limitations for adopting this technology includes lack of portability and lack of cellular connection [273]. IoT could also be implemented for smart medicine transportation. An example includes a system that was called EPharmacyNet [274]. The application was developed for developing countries where pharmacies are sparse. Here, the Cloud is used to monitor patient and transport vehicle GPS coordinates, and offer the best route to avoid congestion and roads with poor infrastructure.

A smart box with anti-fraud functions has also been implemented to protect against counterfeits. Drug counterfeits is of topical concern that poses a serious threat to society, particularly if the side effects are severe. An IoT-based system was proposed to authenticate medicine dosage via mobile devices, which in turn relays the information to an authentication server [275]. The authentication server then verifies

the authenticity of the drug and relays the information back to the patient to inform them accordingly.

5.2 Smart manufacturing

Manufacturing approaches used by pharmaceutical companies have been criticised for their lack of efficiency, particularly the supply chain and machine maintenance, which are crucial in ensuring that costs are maintained at viable levels and obviating the need for unnecessary downtime [276]. IoT-based systems have been adopted by the manufacturing industry, with Samsung, Philips and Airbus for improved energy management, logistics and product quality, respectively [277, 278].

5.3 The future of smart healthcare

Evidently, the implementation of IoT in the pharmaceutical industry is yet to be realised, despite all the enabling technologies being present. Since IoT is intrinsically linked to these enabling technologies, advances in IoT will depend on their respective advances. To date, IoT systems have been used discretely on Smart Home, Smart Manufacturing and Smart Disease Progression, and it is likely that all will soon be merged for a holistic approach towards patient healthcare. Furthermore, interest shown by non-medical companies, such as Apple and Google, will facilitate IoT progression in medicine. Such companies have existing wearable technologies that can be leveraged by medical practitioners, knowing that consumers are already comfortable with these brands.

A proposed IoT pathway would include using biosensors and wearable technologies to send real-time patient data to the physician through wireless communication (Figure

9) [85, 158]. The physician can review the disease state of the patient and generate a digital prescription, which is then sent to a manufacturing facility. Upon receiving the prescription, the facility designs and fabricates a suitable dosage form using 3D printing, wherein process analytical technologies (PAT) can be used for in-process quality control measures. Once ready for dispensing, the personalised prescription is sent to the patient. Herein, this process can be facilitated or sped up by using drones for delivery services, enabling swift interventions in case of emergencies or natural disasters.

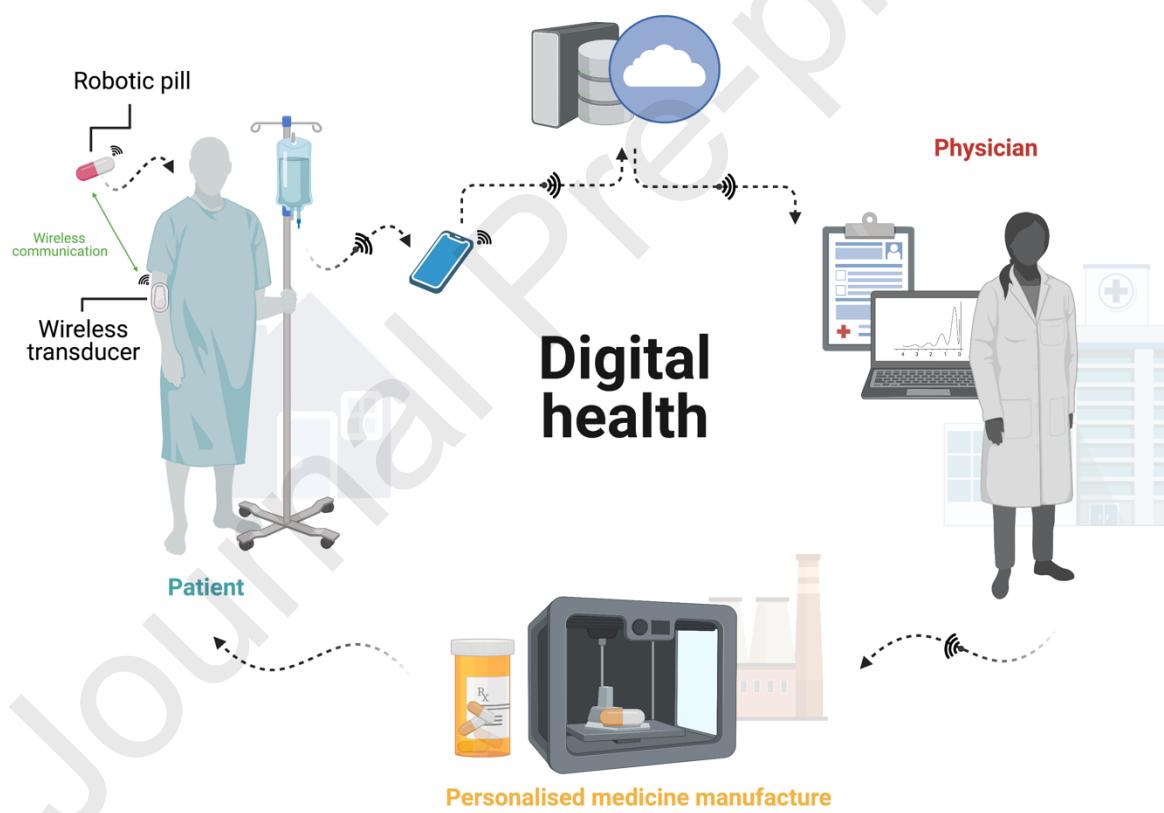


Figure 9. Graphical illustration showing how the internet of things can be used to empower the adoption of digital healthcare. Created with BioRender.com.

6 Regulatory Specifications and Challenges

At present, the lack of thorough regulatory and legal framework remains the principal barrier restricting the free uptake and use of digital technologies within healthcare. One of the main concerns for the regulatory systems is to ensure that patients can use digital technologies with confidence, whilst their identities and data are safeguarded. In this regard, it has been proposed to create a “Meaningful Regulation”, which is a regulatory framework that regulates the use of digital technologies within healthcare [279]. Such regulation should not only cover hardware and medical devices but also extend to cover the program interface, i.e., software and applications used as part of the IoT framework.

It is of paramount importance to ensure that those providing digital services abide by good practices that protect patient privacy and data security. As such, service providers are required to prioritise ethical considerations over commercial interests. The General Data Protection Regulation (GDPR) is currently in place for such purpose. It is particularly concerned with the confidentiality and processing of personal data, ensuring that patient data are collected and used in a lawful and fair manner, and preventing potential misuse [280].

With regards to dosage forms and medical devices, it is necessary to ensure that the quality of the products complies with regulatory standards (e.g., dose uniformity and end-product consistency) [281]. Although a guidance on the “technical considerations for medical devices manufactured using additive manufacturing” exists [282], currently, there is not one dedicated for 3D printed drug-laden products. It is also equally important to confirm that the way products are produced is also in accordance with current good manufacturing practices (GMP), especially when implementing a

manufacturing technology that was originally developed for other applications, such as in the case of 3D printing [283, 284]. Furthermore, the concept of personalising dosages or medical devices for specific patients will require the use of multiple, decentralised manufacturing sites, which is not typical in current “standard models” of pharmaceutical production and does not provide all the necessary control measures for medicinal products. In this regard, the Medicines & Healthcare products Regulatory Agency (MHRA) has recently issued a proposal for a new regulatory framework specific for “Point of Care manufacture”, wherein they describe the establishment of a Control Site that oversees and regulates the activities of individual point-of-care sites [285].

Nonetheless, as digital technology is a dynamic field that is constantly changing and growing, it is challenging for regulatory bodies to keep up, resulting in a delay in the release of legislations concerning such technologies. Furthermore, given that digital systems undergo regular revision and modifications, regulatory approval should be reassessed in case of hardware upgrades or software updates [286]. More importantly, in this emerging field, it is imperative for regulatory agencies to find the correct balance between issuing regulations that protect patients and healthcare practitioners but still do not detract manufacturers and service providers from making use of these technologies to improve patient care.

7 Conclusions

Digital transformation has instigated a paradigm shift within healthcare, changing the way treatment is managed and provided. The use of sensor devices has empowered clinicians, enabling them to monitor and diagnose disease conditions more efficiently

and accurately. 3D printing has been increasingly investigated as a modern way for manufacturing medicines to meet patients' individual needs. In the case of robots, their applications span across several healthcare applications, ranging from manufacturing and dispensing, all the way to drug delivery, diagnostics, and rehabilitation. In addition, the accessibility, availability, and affordability of medical care to patients can be improved by the proper integration of the IoT platform. Despite these advantages, regulatory and reliability concerns are yet to be addressed, hindering the use and implementation of such technologies at present. In particular, the rapid advancement in this field requires constant updates, making challenging for regulatory systems to adapt. The integration of these digitised tools is not foreseen to replace healthcare professionals, but to rather complement the existing healthcare systems by supporting medical interventions. As such, the true potential of digital healthcare can only be realised when the optimal balance between the use of digital technologies and human involvement has been determined.

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