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REVIEW

3D Printing in Triggered Drug Delivery Devices: A Review

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Abstract
Triggered drug delivery devices use external stimulus to trigger the release of the drugs from the device. By controlling the exposure of the stimuli, it would allow for the control over the timing, duration and amount of drug being released from the device, improving drug efficacy. 3D printing uses on-demand deposition and crosslinking of materials to fabricate a product, increasing the customisability of the design and internal structure. By using 3D printing to fabricate triggered drug delivery devices, certain advantages such as complex geometries, gradient compositions, multi-material structures and embedded components can be conferred to the printed devices. In this review paper, triggered drug delivery devices which are fabricated using 3D printing techniques such as vat photopolymerisation and material extrusion are discussed. The advancement in certain areas of 3D printing, such as in multi-material 3D printing and hybrid additive manufacturing, which presents tremendous opportunities for fabricating future triggered drug delivery devices will also be reviewed.

Keywords 3D Printing · Drug delivery · Triggered drug delivery device

Introduction

Drug Delivery Devices (DD)

Drug delivery devices are used to delivery drugs into a patient's body or circulatory system. These devices control the amount of drugs within the patient and are used to ensure that the concentration of drug in the patient is within the therapeutic range. The therapeutic range of a drug indicates the concentration of drug within a patient's system which allows for the proper function of the drug. Above the therapeutic range, the drug becomes toxic and below this range, the drug is ineffective [1]. By keeping the drug concentration within this range, it ensures optimal treatment from the drug without causing harm to the patient.

Drug delivery devices can have various different release profiles which affect the rate which the concentration of the drugs changes within the patient [2]. However, even while traditional drug delivery devices allow for different release profiles, the time and duration of the release are fixed once they are administered [3]. Once the traditional drug delivery devices enter into the patients, the drug release would start and then subsequently stop after a predetermined amount of time. The drug release rates from these devices are also fixed once the device enters the patient. The fixed release rate, time and duration limit the control over the amount of drugs released from the device and also in turn the concentration of the drug within the patient's system [4].

Triggered Drug Delivery Devices (TDD)

Triggered drug delivery devices are a type of device which allows for the release of the drug within the device to be triggered to start and stopped as needed. The triggering of the starting and stopping of the drug release relies on the application and removal of an external stimulus to the device [5]. The external stimulus causes changes in the materials within the device, triggering the drug release. External stimuli such as the application of heat, infrared light and ultrasound are some examples of what can be used to trigger the drug release. An explanation of the different types of stimuli as well as examples of the applications will be given in subsequent chapters.

The use of triggered drug delivery devices allows for the control of the release of the drug to start and stop as needed. This allows for on-demand drug release from the device

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where the drug can be released as needed by the patient or as directed by a medical professional. By controlling the beginning and ending of the drug release, the drug release duration can be controlled [6]. This controls the amount of drug being delivered to the patient which in turn allows for the concentration of the drug within the patient to be controlled. By being able to control the concentration of drug within the patient, the optimal drug concentration can be reached [7]. Triggered delivery devices also allow for different types of drug release profiles such as pulsatile drug release to be achieved. Pulsatile release profile is useful for drugs used in treatment such as diabetes and chronic pain management [8, 9]. The triggerable release of the drug allows for the release of the drug as needed such as when the pain arises or when the glucose level increases. Figure 1 shows how the different types of drug release profiles affects the drug concentration within a patient. Note that the drug concentration profile for the triggered drug release shown in Fig. 1 is just one example of how the drug concentration can be controlled; other drug concentration profiles can also be achieved using triggered release.

Mechanism of TDD

As stated above, there are multiple different stimuli that can be used to trigger the release of drugs from the triggered drug delivery devices. Some of the different stimuli are shown in Fig. 2. The different mechanism for triggering the drug release as well examples of the applications of each of these mechanisms is given below. The focus of this review paper will be on triggered release of drugs over multiple doses similar to that shown in Fig. 1.

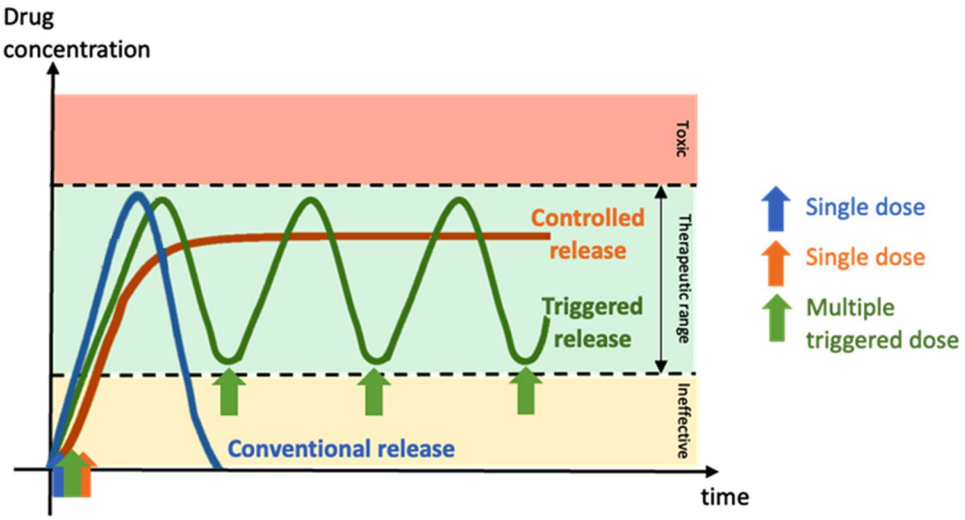

Fig. 1 The different drug concentration profile achievable from the different types of drug release

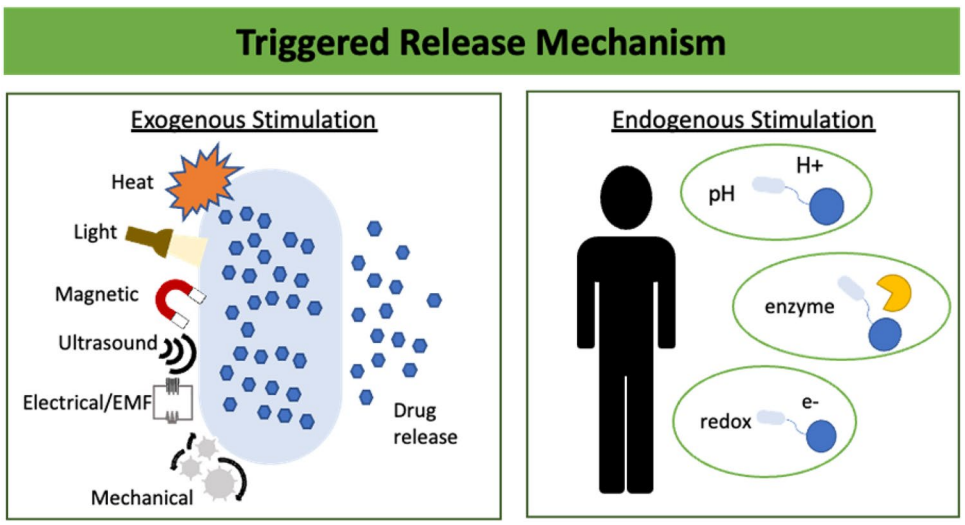

Fig. 2 Examples of different triggering mechanism used for triggered drug delivery which can come from an external source or from changes within a patient's body

Heat-Triggered TDD

The direct application of thermal energy is one of the primary methods to trigger the drug release from triggered drug delivery devices. The application of thermal energy or heat can be done through relatively simple methods such as the use of heating pads and heating coils. In one such example, heat from a heating pad was used to trigger the release of pain relief drug from a gel which can be directly applied to the skin of the patient [10]. By applying the drug-loaded gel and subsequently the heating pad to the areas which the patient suffers from pain, this allows for release of the pain medication as needed controlled by the patient. In another example, thermoresponsive hydrogel was used to trap and deliver chemotherapeutic drugs to patients [11]. When the temperature is increased, the hydrogel swells and releases the drug. The triggered drug release can be localised to the area surrounding the hydrogel. This allows for the drug to be released at specific sites within the patient's body. This helps to increase the concentration of the drug at the targeted site, increasing the efficacy of the drug while reducing the amount of drugs throughout the rest of the patient's body, reducing the side effects of the drug. Similarly, thermoresponsive phase changing material has been used to control the release of drugs stored in the pores of nanoparticles. The phase changing material acted as a gate preventing the drug from diffusion through at low temperatures and allowing for the drug diffusion and release at higher temperatures [12]. Another method for heat triggered drug release is based on the affinity of interaction between the drug and the drug-loading material. In one such example, heat was used to overcome the interaction between graphene and diclofenac that were loaded into a hydrogel. At low temperatures, the drug and graphene are bonded to each other leading to the adsorption of the drug onto the graphene. When the hydrogel and graphene were heated, there is an increase in molecular energy leading to the drug being desorbed and released [13].

The direct application of heat to trigger release of drugs is one of the basic triggering methods, thus researches have gone into the use of different materials which can convert different stimuli sources to heat. Different materials such as graphene and nanoparticles have been used to convert different sources into heat. By adding these materials, it allows for a wider range of different sources to be used to trigger the drug release from the devices.

Light-Triggered TDD

The use of light as a method to trigger drug release offers more flexibility as different types of light sources can be used. UV, infrared and visible light have all been used to trigger drug release from triggered drug delivery devices. Using light as a triggering mechanism also offers other advantages such as remote triggering, skin and tissue penetration and minimal negative effects on to the patient [14]. For the use of UV light as a triggering method, in one such example, a photo-sensitive polymer was loaded with drugs. Upon exposure to UV light, the polymer changes from a hydrophobic state to a hydrophilic state [15]. This triggers the release of the drug stored within the polymer. When the light source is removed, the hydrophobicity of the polymer is reversed and the drug release is stopped. In another example, a self-assembling hydrogel was used to encapsulate insulin [16]. When exposed to UV light, the hydrogel degrades and disassembles. This allows for the drug which is trapped within the hydrogel to be released.

Infrared light (IR) is another type of light source which has been used to trigger drug release. Reduced graphene oxide has been used to both convert IR to heat in a photothermal heating effect and to also be loaded with drugs [17]. The reduced graphene oxide was deposited onto Kapton films for use as transdermal skin patches. When exposed to IR, the reduced graphene oxide absorbs the IR and converts it to heat. The affinity of the reduced graphene oxide and the loaded drug changes with the increasing heat and the drug is released. The photothermal effect of reduced graphene oxide has also been used with thermoresponsive material for triggering drug release [18]. In another example, photothermal carbon was added to a thermoresponsive drug-loaded hydrogel [19]. When IR is shown on the hydrogel, the heat generated from the photothermal carbon triggers the thermoresponsive hydrogel to shrink releasing the loaded drug. Other materials such as gold nano-rods have also been used to convert IR light radiation to heat [20]. The increase in heat allows for increased drug diffusion and increased drug release rate. The heat generated dissipates when the IR light is removed, reducing the diffusion coefficient and the release rate. This allows for the switching between the start and stop of the drug release as well as pulsatile release of the drug by toggling the IR supplied. Similarly, other IR photothermal material such as black phosphorus and carbon nanotubes can also be used in a similar way [21–23].

Visible light has also been used as a triggering source for triggered drug delivery device. In one such example, hybrid thermoresponsive hydrogel beads containing magnetite nanoparticles were loaded with drugs [24]. Upon exposure to visible light, heat generated by the magnetite nanoparticles causes the hydrogel beads to shrink, releasing the drug stored within. These thermoresponsive beads were loaded into a hydrogel-based transdermal patch. The patch was covered and the drug loaded into the hydrogel beads can be released by removing the covering and exposing the patch to visible light. The release rate of the drug from this patch can also be controlled by adjusting the intensity of the light supplied.

Other Triggering Methods

Many other triggering methods also involve the use of additional materials which react to different sources of stimulus. One such example of other triggering sources are devices which are magnetically triggered. In one such example, a drug reservoir was covered with a magnetic membrane. When a magnetic field is applied, the membrane deforms which causes the drug from the reservoir to be released through an aperture in the membrane [25]. In other examples, magnets were used to move a magnetic plunger upwards, drawing drugs into a barrel. When the magnets were removed, the plunger moves back down and pushes the drug out through an outlet port to be released [26, 27]. In another example, magnetic iron oxide was used to control the drug release from a reservoir through a porous membrane. When a magnetic field was applied above the membrane, the particles are attracted upwards and block the pores in the membrane preventing drug release. When the magnetic field is applied to the bottom of the device instead, the magnetic particles are attracted downwards, the pores become unblocked and the drug in the reservoir is released [28]. These magnetically triggered devices could also contain materials which can convert magnetic fields into heat. In one such example, superparamagnetic nanoparticles were used to convert oscillating magnetic fields into heat [29]. These nanoparticles were loaded into a membrane. The membrane contains thermoresponsive hydrogel nanogel beads; these nanogel forms channels within the membrane which allows for the drug to travel through and be released. In the "off" state of the device, the hydrogel nanogels are swollen, blocking the channels within the membrane from the drug flow. When drug release is needed, a magnetic field is applied to the device. The nanoparticles absorb the magnetic field and convert it to heat. Upon heating the hydrogel nanogels shrink and open the channels in the membrane allowing for drug to flow. Alternatively, these heat-generating magnetic nanoparticles have also been used to increase the temperature of drug-loaded polymers, increasing the mobility of the polymer chains and the free volume. This allows for the increased diffusion rate of the drug from the polymer [30].

Another way to trigger drug release is the use of ultrasound. In order to enhance the effects of ultrasound, one research used a lipophilic sonosensitiser, chlorin e6 [31]. Chlorin e6 can absorb ultrasound and generate reactive oxygen species. This leads to the sonodynamic effect and the release of the stored drug. Ultrasound has also been used to increase the mesh size and volume ratio in silk fibroin hydrogel. This was used to trigger the release of the drug that was loaded into the hydrogel [32]. High-intensity focused ultrasound has been used to induce mild heating deep within tissues. This increase in temperature was then used to trigger the release of drugs loaded into temperature-sensitive liposomes. These effects have been used for targeted and triggered drug delivery to tumours [33].

Enzymes and pH change have also been used to trigger the release of drugs. In one such example, specifically designed hydrogel nanogel beads were loaded with drugs used for cancer treatment [34]. In the neutral pH, where the drug was loaded into the nanogels, there is a strong ionic attraction between the hydrogel and drug. When the pH value is lowered, the ionic attraction decreases and the drug is released from the hydrogel. In another example, a gelatin-based hydrogel was fabricated with pH triggered drug release behaviour [35]. The hydrogel has low drug release values at neutral pH and higher drug release at low pH. These pH triggered drug release behaviour can be used for triggered drug release at tumour sites which have lower pH than the surrounding area [36]. Another condition that occurs within tumours is low oxygen levels also known as hypoxia. This allows for the use of hypoxia-sensitive molecules for triggered drug release. In one such example, hypoxia-sensitive molecules were bonded to a doxorubicin-loaded polymer allowing for the release of the drug in the low oxygen conditions within a tumour [37]. Enzymes that are found in specific areas within the body have also been used to trigger drug release. In one such example, nanoparticles were synthesised that reacted to enzymes found specifically in the colon [38]. The nanoparticles were able to have minimal drug release in simulated gastric and intestinal fluids, where the enzyme was not present. While in the colonic medium, which contained the enzyme, the nanoparticles had a significantly higher drug release percentage.

Microfabrication of TDD

Traditional Fabrication Methods

Traditional or conventional fabrication of triggered drug delivery devices includes casting, chemical vapour deposition and drop casting [17, 20, 24, 39]. These methods can be used for the making of thin films, patches and moulds with different designs. This allows for the fabrication of devices such as transdermal patches, membrane-controlled drug reservoir devices, implantable and injectable devices. However, the use of traditional fabrication methods has certain drawbacks. Mainly, the use of traditional fabrication methods does not allow for the fabrication of certain shapes, designs and internal structures. When using traditional fabrication methods, it can be difficult to fabricate certain shapes and designs. Certain designs and internal structure are also impossible to fabricate. This limits the designs of the device that can be fabricated through traditional methods. The limited internal structure that can be fabricated also limits the drug storage and drug delivery capabilities of certain

drug delivery device [40]. The use of 3D printing in the fabrication of triggered drug delivery device allows for the shape, design and the internal structure to be customised. 3D printing involves the use of layer-by-layer deposition and crosslinking to fabricate the object [41]. This allows for the design of the drug delivery device to be highly customisable and hold certain advantages when compared to devices fabricated through traditional methods. In the next few sections, the use of different 3D printing methods in the fabrication of triggered drug delivery devices and the advantages they have will be discussed.

Extrusion-Based 3DP

Extrusion-based 3D printing involves the use of material deposited through a nozzle to form the final object. The nozzle or the platform on which the material is deposited into moves in a combination of all three dimensions. This allows for controlled deposition of the material onto the platform to fabricate the object. The shape, dimensions and internal structure of the object can be highly customised due to layer-by-layer fabrication allowing for fabrication of unique objects and devices [42]. In one such example, extrusion-based 3D printing was used to fabricate the drug reservoir and capsule of a magnetically triggered drug release device [43]. The capsule contained a magnetic PDMS sponge, which was loaded with drugs, and an aperture at one end for drug release. By controlling the direction and strength of the magnetic field applied to the device, the drug release could be controlled to start and stop. The use of 3D printing in fabricating the drug reservoir and capsule also allows for the shape, dimensions and volume to be changed for individual patients.

The customisability and unique designs that is conferred by 3D printing also allows for different methods of triggering drug release. In one example, the use of 3D printing in fabricating an oral drug capsule allows for the control of the shape and dimension of the capsule to break under different physiological pressures [44]. This allows for the capsule to break in specific parts of the digestive system, delivering the drug at specific areas of the stomach increasing drug absorption rate. Extrusion-based 3D printing also allows for the fabrication of unique geometries such as long hollow fibres filled with drug-loaded materials within the fibres. This is also known as a core–shell design, fabricated using coaxial 3D printing. Combined with 3D printing, the fibres can be printed and used as porous drug-loaded scaffolds in tissue engineering. In one such example, polydopamine was mixed into the shell material of the fibres [45]. Polydopamine is a polymer which can absorb IR light and convert it to heat. When polydopamine is mixed with the shell material of the fibres, it allows for the shell of the printed fibres to heat up when exposed to IR light. The core material of the fibres was a drug-loaded hydrogel which can reversibly turn from a gel into a solution when heated. This core material when printed together with the shell material, forms a core–shell scaffold which has IR triggered drug release. When exposed to IR light, the shell of the fibres generates heat and increases in temperature. The temperature can then be allowed to decrease by removing the IR light allowing for cyclic heating of the shell as shown in Fig. 3b. The increase in temperature causes the drug-loaded hydrogel core to melt. The hydrogel would then flow out and cause the drug to be released as shown in Fig. 3d. When the IR is removed, the shell cools down and the hydrogel core solidifies back to a gel and stops the drug release. This allows for triggered, on-demand drug release as shown in Fig. 3c through exposure to IR light as needed. Through controlling the duration and position of the IR exposure, the drug release from the scaffold can be controlled [46].

In another example of triggered drug release from core–shell fibres, iron oxide nanoparticles were mixed into the shell material. The addition of the iron oxide nanoparticles caused the shell structure to be affected by magnetic fields [47]. The core material consisted of a low concentration hydrogel loaded with drugs. When subjected to a magnetic field, the hollow tubes of the shell will deform and flatten as shown in Fig. 4c & f. When printed together to form the core–shell scaffold structure, the soft hydrogel core would be surrounded by the shape changing magnetic shell. When subjected to a magnetic field, the shell would flatten squeezing the soft drug-loaded hydrogel core out causing the drug to be released as shown in Fig. 4i. This would allow for triggered and on-demand drug release from the device by subjecting it to a magnetic field. Through the use of 3D printing, the materials can be printed into a scaffold structure such as the one shown in Fig. 4b. This structure would help to promote the cell growth and wound healing when implanted along with the drug which has been loaded into the device.

Vat-Based 3DP

In vat-based 3D printing, light or lasers are used to crosslink photocurable materials within a vat into the desired design. In most cases, the printing is done on the surface of a moving platform. After each layer is printed and cured, the platform would shift vertically allowing for more material to flow in replacing the material which was cured. This will be repeated until the final product is completed [48]. In one such example, vat-based printing was used to fabricate a soft robot that can be controlled through magnetic fields [49]. The ends of the soft robot consisted of material mixed with magnetic nanoparticles. This allowed for the soft robot to move and turn by applying magnetic fields to the robot. A drug reservoir was designed and fabricated to be

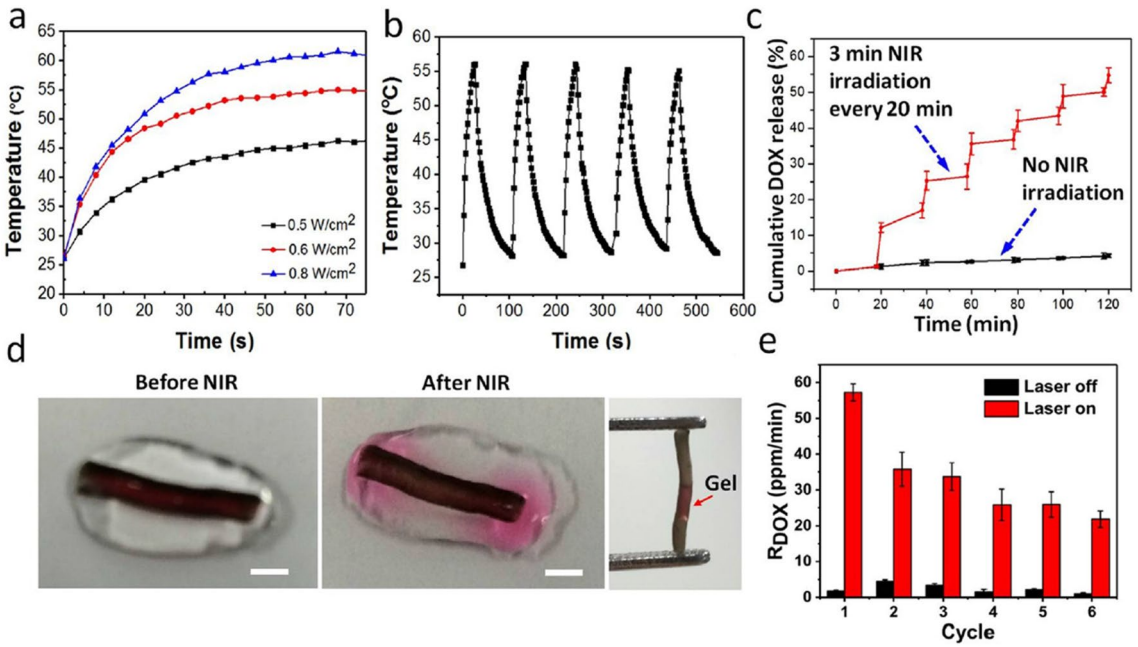

Fig. 3 **a** The temperature of the core–shell fibre when exposed to lasers of different power. **b** Cyclic heating test of the core–shell fibre. **c** DOX release from the core–shell fibres with and without IR irradiation. **d** Photos of the core–shell fibre before and after IR irradiation with red dye added to the core. **e** Release rate of DOX with and without IR irradiation. [45]

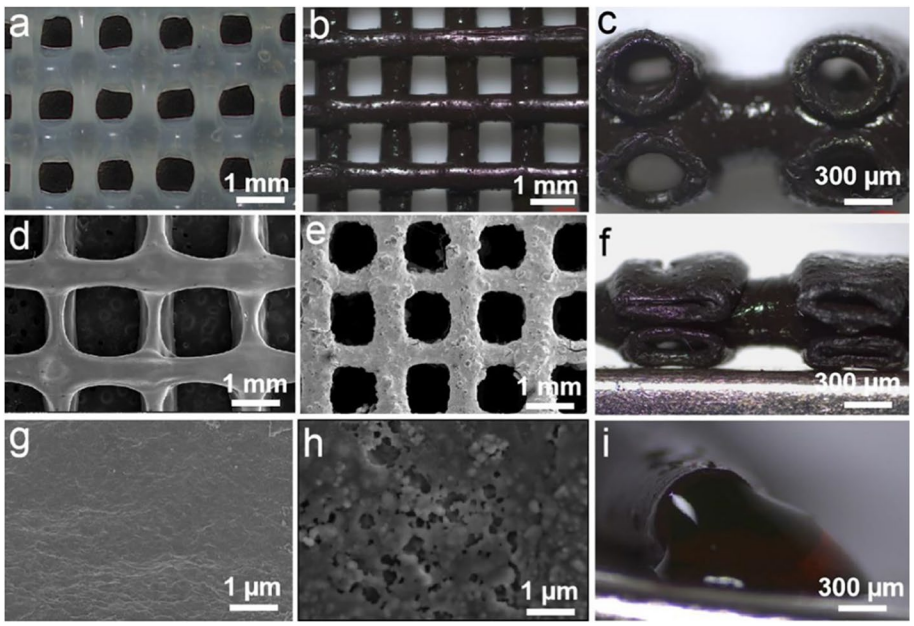

Fig. 4 **a**, **d**, **g** Microscopic and SEM images of 3D printed hollow alginate scaffold. **b**, **e**, **h** Microscopic and SEM images of alginate scaffold with iron oxide nanoparticles. **c**, **f**, **i** The alginate and iron oxide nanoparticles scaffold before and after being subjected to a magnetic field and the release of the core gel within. [47]

incorporated into one end of the robot. This drug reservoir can be controlled to release the drugs stored within through applying a magnetic field. The drug release rate and duration and be controlled by controlling the strength and duration of the applied magnetic field. The controllability of the soft robot allows for the robot to be moved to specific position within the patient's body such as the stomach and have on-demand controlled drug release.

In other similar examples, vat-based 3D printing was used to fabricate microswimmer drug delivery devices. Superparamagnetic iron oxide nanoparticles were incorporated into the printing material prior to printing [50]. Vat-based 3D printing allowed for the fabrication of unique

designs and the micrometre dimension of the microswimmers. These microswimmers can be controlled and steered to move in different directions through the application of magnetic fields. When the microswimmers have been steered to the desired location, the drug loaded onto the microswimmers can be triggered for release through light exposure. On demand drug release from the microswimmers can be controlled by the intensity and exposure duration of the light. Other triggering methods can also be used to trigger the drug release from the drug-loaded microswimmers. The microswimmers can also be designed to have pH and enzyme triggered drug release [51, 52]. By changing the fabrication material of the microswimmers, the microswimmers can have a pH responsive shape change. When exposed to higher pH, the microswimmers will absorb water and swell, this allows for the drugs that are loaded into the microswimmers to diffuse out and be released. This swelling process is reversible, when the pH of the medium surrounding the microswimmers is lowered, stopping the drug release. Similarly, enzymes can also be used to trigger the drug release from microswimmers. When exposed to certain enzymes, the microswimmers will rapidly swell and degrade. This swelling and degradation can be used to release the drug that has been loaded into the microswimmers.

Vat-based 3D printing has also been used to fabricate other triggered drug delivery devices. In one example, an implantable bone scaffold with triggerable drug release for bone regeneration was fabricated through vat-based 3D printing [53]. The 3D printed bone scaffold contains nanoparticles which were loaded with drugs which aids in bone regrowth. The nanoparticles can be triggered to release the loaded drug when there is a change in pH in the surrounding area. This change in pH naturally occurs during bone regeneration allowing for the drug to be released as needed. 3D printing would allow for the bone scaffold to be printed with the necessary microstructure to mimic natural bones and also for the design of the scaffold to better suit the patient. The ability for 3D printing to fabricate unique shape and designs has also been used for fabrication of triggered oral drug delivery doses. In one such example, vat-based 3D printing was used to fabricate oral drug dosage with unique designs that cannot be fabricated through conventional fabrication methods [54]. The material used in the fabrication of the oral drug dosage exhibits pH-dependent swelling. When printed into the unique shapes, the different shapes have different amount of swelling, also known as the swelling index, when exposed to higher pH. The swelling index of the material affects the rate in which the drug loaded within is released. By controlling the design of the drug dosage, the swelling index can also be controlled. This in turn affects the rate and duration of the drug release from the oral drug dosage. 3D printing allows for design of the oral drug dosage to be fully customised, this allowed for the swelling and thus drug release to be customised as well.

Advantages of Using 3DP in the Fabrication of TDD

The use of 3D printing for the fabrication of triggered drug delivery devices confers several advantages over traditional methods. 3D printing fabricates the object through a layer-by-layer method. This allows for the device that is being fabricated to be embedded with different components. The layer-by-layer fabrication allows for the fabrication process to be paused, the necessary components embedded and then for the fabrication process to continue. This can be used to embed components that can be used as triggering mechanism for the triggered drug delivery device. For example, components such as heaters can be embedded directly into a device during the fabrication process [55]. The heater can then be for triggering of drug release from heat triggered delivery devices. Sensors can also be directly embedded into devices which allows for monitoring of the patient's conditions. Sensors such as temperature sensors can be embedded into a device allowing for real time monitoring of a patient's temperature [56]. This allows for the devices, which are equipped with sensors, to monitor and transmit the data to the healthcare professional or user to provide better care to the patient [57].

3D printing also allows for the fabrication of certain designs and internal structure which might be difficult or even impossible for traditional fabrication method to achieve. This allows for the designing and fabrication of unique shapes and geometries which can aid in the release of drugs [58]. The internal structure can also be customised and changed to modify the drug release from the devices [59]. This allows for 3D printing to achieve unique drug release profiles which cannot be normally achieved with traditional fabrication. The unique designs conferred from 3D printing also allows for the fabrication of devices with specific functions such as long-term retention in the stomach and microfluidic mixing channels [60, 61]. This allows for an increase in the areas of application the 3D printed device can be applied to by customising the device's design. Through the use of 3D printing, the internal structure could also be tailored for individuals by changing the drug release profile to suit different patients. This allows for better control of the drug concentration within each patient by adjusting the drug release rate [62]. This would help ensure that the drug concentration stays within the therapeutic range.

Furthermore, there are new developments in the area of 3D printing such as multi-material 3D printing and hybrid 3D printing that could be explored for use in the fabrication of triggered drug delivery device [63, 64]. Multi-material 3D printing and hybrid 3D printing allows for the deposition of different materials and the use of different 3D printing

methods when fabricating an object, respectively. These methods allow for a greater flexibility when it comes to the fabrication of drug delivery devices by increasing the types of materials which can be used and also the designs which can be achieved. Hybrid 3D printing also allows for the advantages conferred by the different 3D printing methods used to be added to a single device [65]. For example, through the use of multi-material and hybrid 3D printing, a drug delivery device with customisable drug depots has been fabricated [66]. Vat-based 3D printing was used to fabricate the matrix which contained the drug depots. The vat-based printing process can be paused and subsequently, by using droplet-based 3D printing, the desired drug can be deposited within different areas of the matrix. Drug depots with different drugs can be locally incorporated into different parts of the device. This allows for customised release of multiple drugs by controlling the size, position, amount and loaded drug of the different drug depots. Examples of some of the printed samples are shown in Fig. 5. Samples such as those with different amounts of drug depots shown in Fig. 5a, b & c and also two individual drug depots loaded with different compounds shown in Fig. 5d can be fabricated using this method. By applying such methods to triggered drug delivery devices, it would allow for greater customisability of the device being fabricated. Through the combination of multiple different materials within the device, it could also allow for the use of different triggering mechanism for the individual triggered release of multiple drugs stored on the device.

Future Perspectives and Conclusion

Currently, 3D printing has been used in the fabrication of triggered drug delivery devices in order to provide improvement to the design and drug release of the devices. This includes allowing for different unique methods to trigger the drug release, unique designs of the devices and also improved drug loading and release capabilities. However, further improvements through the use of 3D printing can be added. For instance, while some of the devices can be triggered through natural changes within the body such as a change in pH, most of the devices requires external inputs in order to trigger the drug release. This could be one direction for future trends of 3D printed triggered drug delivery devices. For example, for devices which are triggered through heating, the heating element which is used to trigger the drug release can be fabricated together with the device through 3D printing. 3D printed heating coils have been incorporated into triggered drug delivery devices but currently only singular components of the triggered drug delivery devices has been fabricated using 3D printing [67]. By using 3D printing to fabricate more components of the drug delivery device, the customisability conferred by 3D printing can be applied to more parts of the device. This also improves the customisability of the overall device. 3D printing can also be used to print certain electronics to be added to the drug delivery devices. 3D printed electronics such as biological sensors which can measure glucose, temperature and sweat can be printed [68–70]. The desired design can also be directly printed into or onto the device [71]. By using 3D printing to fabricate electronics, the size, design and location of the printed electronics can be customised [72]. This would allow for the addition of sensors to the devices to monitor patient's condition and also for triggering and controlling of the devices [73, 74].

In addition, there have been developments in 3D printing such as multi-material and hybrid 3D printing. Hybrid 3D printing would allow for the use of different 3D printing techniques in the fabrication of a product. This would allow for different advantages and printable materials of the different 3D printing methods to be incorporated into one device. This allows for the combination of different materials with vastly different material properties such as having a soft,

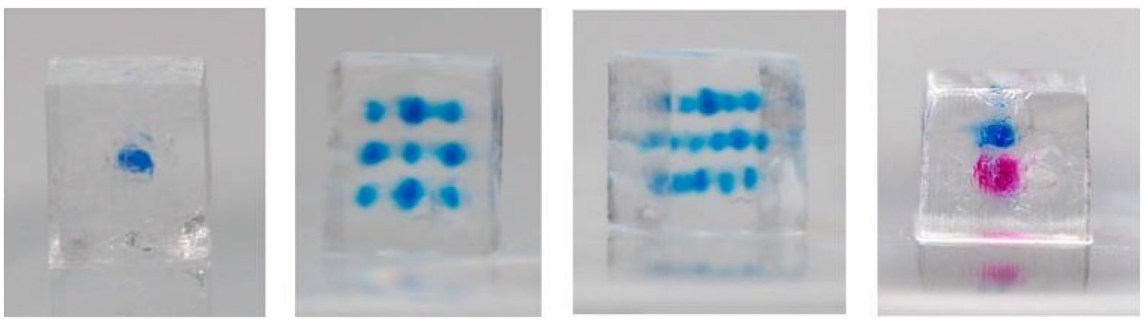

Fig. 5 A poly(ethylene glycol) diacrylate (PEGD) matrix with different configurations of locally incorporated drug depots. Different coloured ink solution was used as drug substitutes. **a** With one single drug depot. **b**, **c** With thirteen individual drug depots. **d** With two individual drug depots loaded with different compounds [66]

elastic blister being printed onto a hard, rigid 3D printed body for microfluidic applications [75]. Hybrid printing of different designs and materials into a single device would allow for the fabrication of triggered drug delivery devices with multiple different triggers for multi-drug release. This would greatly increase the customisability of the drug release from such devices.

In conclusion, using 3D printing to fabricate triggered drug delivery devices has multiple advantages over using traditional fabrication methods. This includes improvement to the customisability of the device design, drug storing and drug release capabilities. Currently, 3D printing has mainly been used fabricate singular or individual triggering components of the triggered drug delivery device. However, with further developments in areas of 3D printing such as multi-material, hybrid 3D printing as well as 3D printed electronics; 3D printing could be used to fabricate additional components of the device allowing for more customisability. This would increase the areas of application of the devices and allow for additional functions to be added to the devices.

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Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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