University of Wollongong
Research Online

Australian Institute for Innovative Materials - Papers

Australian Institute for Innovative Materials

1-1-2018

Advanced fabrication approaches to controlled delivery systems for epilepsy treatment

Gilles van Tienderen
University of Wollongong, Utrecht University, gsvt317@uowmail.edu.au

Marius Berthel
University of Wollongong, University Hospital Wuerzburg, mb141@uowmail.edu.au

Zhilian Yue
University of Wollongong, zyue@uow.edu.au

Mark J. Cook
University of Wollongong, University of Melbourne, mark@neurology.net.au

Xiao Liu
University of Wollongong, xiaol@uow.edu.au

See next page for additional authors

Follow this and additional works at: https://ro.uow.edu.au/aiimpapers

 Part of the Engineering Commons, and the Physical Sciences and Mathematics Commons

Research Online is the open access institutional repository for the University of Wollongong. For further information contact the UOW Library: research-pubs@uow.edu.au

Advanced fabrication approaches to controlled delivery systems for epilepsy treatment

Abstract

Epilepsy is a chronic brain disease characterized by unprovoked seizures, which can have severe consequences including loss of awareness and death. Currently, 30% of epileptic patients do not receive adequate seizure alleviation from oral routes of medication. Over the last decade, local drug delivery to the focal area of the brain where the seizure originates has emerged as a potential alternative and may be achieved through the fabrication of drug-loaded polymeric implants for controlled on-site delivery. Areas covered: This review presents an overview of the latest advanced fabrication techniques for controlled drug delivery systems for refractory epilepsy treatment. Recent advances in the different techniques are highlighted and the limitations of the respective techniques are discussed. Expert opinion: Advances in biofabrication technologies are expected to enable a new paradigm of local drug delivery systems through offering high versatility in controlling drug release profiles, personalized customization and multi-drug incorporation. Tackling some of the current issues with advanced fabrication methods, including adhering to GMP-standards and industrial scale-up, together with innovative solutions for complex designs will see to the maturation of these techniques and result in increased clinical research into implant-based epilepsy treatment. Abbreviations: GMP: Good manufacturing process; DDS(s): Drug delivery system(s); 3D: Three-dimensional; AEDs: Anti-epileptic drugs; BBB: Blood brain barrier; PLA: Polylactic acid; PLGA: Poly(lactic-co-glycolic acid); PCL: poly(ε-caprolactone); ESE: Emulsification solvent evaporation; O/W: Oil-in-water; W/O/W: Water-in-oil-in-water; DZP: Diazepam; PHT: Phenytoin; PHBV: Poly(hydroxybutyrate-hydroxyvalerate); PEG: Polyethylene glycol; SWD: Spike-and-wave discharges; CAD: Computer aided design; FDM: Fused deposition modeling; ABS: Acrylonitrile butadiene styren; eEVA: Ethylene-vinyl acetate; GelMA: Gelatin methacrylate; PVA: Poly-vinyl alcohol; PDMS: Polydimethylsiloxane; SLA: Stereolithography; SLS: Selective laser sintering.

Disciplines

Engineering | Physical Sciences and Mathematics

Publication Details

van Tienderen, G. Sebastiaan., Berthel, M., Yue, Z., Cook, M., Liu, X., Beirne, S. & Wallace, G. G. (2018). Advanced fabrication approaches to controlled delivery systems for epilepsy treatment. Expert Opinion on Drug Delivery, 15 (9), 915-925.

Authors

Gilles van Tienderen, Marius Berthel, Zhilian Yue, Mark J. Cook, Xiao Liu, Stephen T. Beirne, and Gordon G. Wallace

This journal article is available at Research Online: https://ro.uow.edu.au/aiimpapers/3269

Advanced fabrication approaches to controlled delivery systems for epilepsy treatment

ABSTRACT

Introduction: Epilepsy is a chronic brain disease characterized by unprovoked seizures, which can have severe consequences including loss of awareness and death. Currently, 30% of epileptic patients do not receive adequate seizure alleviation from oral routes of medication. Over the last decade, local drug delivery to the focal area of the brain where the seizure originates has emerged as a potential alternative and may be achieved through the fabrication of drug-loaded polymeric implants for controlled on-site delivery.

Areas covered: This review presents an overview of the latest advanced fabrication techniques for controlled drug delivery systems for refractory epilepsy treatment. Recent advances in the different techniques are highlighted and the limitations of the respective techniques are discussed.

Expert opinion: Advances in biofabrication technologies are expected to enable a new paradigm of local drug delivery systems through offering high versatility in controlling drug release profiles, personalized customization and multi-drug incorporation. Tackling some of the current issues with advanced fabrication methods, including adhering to GMP-standards and industrial scale-up, together with innovative solutions for complex designs will see to the maturation of these techniques and result in increased clinical research into implant-based epilepsy treatment.

KEYWORDS

Advanced fabrication; controlled drug delivery systems; epilepsy; implant drug delivery; three-dimensional printing

Article Highlights

- Implantable polymeric drug delivery systems (DDSs) have gained a lot of interest due to their potential ability to treat refractory epilepsy by delivering drugs to the focus area.
- A variety of drug release profiles can be tailored using electrohydrodynamic means to produce micro- and nano-scale particulate and fibrous structures, particularly through the inclusion of a core-shell configuration within the structures.
- Three-dimensional (3D) printing is particularly suitable for DDS fabrication. It enables 3D distribution of drugs and polymer matrix into complex geometries in a controlled manner, which can also be tailored to meet individual patient needs. 3D printing may offer solutions to some of the bottlenecks in epilepsy treatment that are not possible with conventional fabrication methods.
- Various 3D printing techniques are compared, through examples of implant-based drug delivery applications, to explore the advantages and limitations of each technique.
- Current challenges and future perspectives for advanced fabrication techniques in drug delivery for epilepsy treatment are discussed.

This box summarizes key points contained in the article.

1. Introduction

Epilepsy is one of the most prevalent chronic brain diseases affecting approximately 1% of the worldwide population. Even if it is regarded as a consequence of a heterogeneous group of disorders underlying brain dysfunction, epilepsies share the hallmark feature of recurrent unprovoked seizures, which can cause loss of awareness, injury, psychosocial disability and even mortality [1, 2]. Anti-epileptic drugs (AEDs) provided via an oral route still remain the mainstay of epilepsy treatment, though this method only achieves a satisfactory result with seizure control in approximately 70% of the patients. The remaining patients are unable to achieve sufficient seizure alleviation. The phenomenon of unresponsiveness to oral administration seems to be multifactorial, but there is significant evidence suggesting that the blood-brain-barrier (BBB) plays an important role [3]. The BBB segregates blood and brain interstitial fluid and protects the brain from harmful compounds circulating in the bloodstream. A key structure of the BBB is the formation of high-resistance tight junctions by brain vascular endothelial cells. These tight junctions only allow low molecular weight liposoluble molecules to cross the cerebral microvasculature barrier.

One of the typical problems of current pharmacotherapy of epilepsy is that most AEDs have a relatively short half-life and need to be taken every day, usually more than once/day, even with extended-release preparations. It has been demonstrated that prolonged AED administration can cause agonist-induced receptor desensitization and/or internalization which results in reduced pharmacological efficacy [4, 5]. Furthermore, multiple drug transporters, which decrease AED concentration in the focus [6] may play a role in refractory epilepsies. This drug resistance leads to increasing doses of often multiple agents, and the high level of AEDs in the body often leads to intolerable systemic side effects which significantly impair the patients wellbeing [7].

After failure of oral therapy with at least two AEDs, surgical resection of the dysfunctional brain can be considered in case of focal seizures. The success of the procedure highly depends on the affected brain region and varies from 25% for extra-hippocampal seizure to 70% in patient-specific seizures. However, surgical resection is inappropriate for seizure focus in deeper brain areas [8].

Over recent years a range of new strategies have been attempted to increase the penetration and persistence of AEDs in the brain parenchyma, including drug delivery systems for systemic delivery [9] , prodrugs [10], efflux pump inhibitors [11], hyperosmolar BBB opening [12] and local drug delivery to circumvent the BBB [13, 14] , as well as gene and cell therapies [15]. Amongst these methods, one promising approach is local drug delivery directly to the area of the epileptic focus, which provides a high concentration of the drug available at the desired target, while minimizing toxic effects on the surrounding neuronal network. With ongoing progress in polymer science and advanced fabrication, polymeric implantable devices that are capable of controlled and sustained release of AEDs directly to the seizure focus are regarded as potential candidates in the treatment of refractory epilepsy (Table 1).

The objective of this article is to summarize current approaches of advanced fabrication technologies for development of local drug delivery systems (DDSs) with a focus on the potential of 3D printing for future treatment of epilepsy.

2. Processable polymers for controlled drug delivery

The range of processable materials compatible with applications in drug delivery has constantly expanded over the years. Among them, polymers are one of the most intensively explored materials. Polymers can be classified as non-biodegradable and biodegradable. Drug release from a non-biodegradable polymeric matrix is mostly characterised by passive diffusion. In

contrast, drug delivery from a biodegradable polymer matrix can be mediated by both diffusion and degradation. Biodegradable polymers can be divided into synthetic or naturally-derived polymers. A typical class of synthetic biodegradable polymers that are commonly used in epilepsy treatment are aliphatic polyesters like (polylactic acid) (PLA) [16], poly (lactic-co-glycolic acid) (PLGA) [17-20] and poly(ε-caprolactone) (PCL) [21, 22]. Compared to naturally-derived polymers, such as silk fibroin [23], these synthetic materials are commercially available in a variety of composition and molecular weight. While most of the natural polymers undergo enzymatic-degradation, these synthetic biomaterials undergo polymer erosion through the cleavage of hydrolytically sensitive bonds. Early investigations of these biomaterials showed superior biocompatibility [24, 25]. Degradation of these biodegradable polymers depends on a number of parameters, including molecular weight, polydispersity, crystallinity and polymer composition [25]. In general, the degradation process of these polymers can be classified into bulk and surface erosion which has significant influence on the drug release kinetics [26]. Bulk erosion refers to a homogenous erosion of the structure when the water penetration is faster than the polymer degradation, while surface erosion addresses a heterogeneous erosion when degradation of the polymer is faster than the water penetration. Based on the different erosion mechanisms, drug release from these biomaterials can be roughly divided into (i) diffusion controlled, (ii) swelling controlled, and (iii) erosion controlled mechanisms [27]. An interesting example in the group of aliphatic polyesters is PLGA, which is a copolymer consisting of lactic acid and glycolic acid and shows degradation behaviour dependent on the monomer composition. The rate of degradation decreases with the rate of lactic acid to glycolic acid up to 6 months. As an exception to this rule, when the ratio of lactic acid and glycolic acid is 50/50, the rate of degradation is the fastest with approximately a two month degradation profile *in vivo* [28, 29].

In terms of local treatment of epilepsy, early work in the polymer-based DDSs were focused on monolithic implants such as pellets, disks or rods, using non-biodegradable polymers [30]. The drawback of these non-biodegradable brain implants is the need for additional surgeries to remove the implant once the drug is fully eluted, but this introduces risk of intracranial infections or neurological deficits. More recently researchers explored the possibility of biodegradable polymers for the treatment of refractory epilepsy to avoid the need of resective surgeries [31]. Unfortunately, these studies have failed to provide sustained long-term release of AEDs. This could be addressed by recent advancements of fabrication techniques that enable the processing of complex polymer structures through more controlled and precise deposition of polymeric materials and drugs.

3. Micro- and nanoparticle formulations

Epilepsy is a diverse disease with multiple seizure types of many epileptic syndromes. In general, there are two major classes of epilepsy: focal seizures, in which the epilepsy focus appears at a cortical site, and generalized seizures, in which the neuronal disorder is distributed in both hemispheres of the cortex. Depending on the seizure onset different therapeutic strategies need to be considered. For the treatment of focal epilepsy, where often the seizure focus is in deeper brain areas such as the hippocampus, monolithic implants are unsuitable due to low accessibility. Novel particulate formulations in the form of micro- or nanospheres, which can be injected into the brain parenchyma, represents as a promising approach for the treatment of epilepsy. A great variety of techniques have been developed for the fabrication of particle formulations. In principle these methods can be roughly divided into chemical processes (e.g. *in situ* polymerization), physico-chemical processes (e.g. sol-gel encapsulation) and physio-mechanical methods (e. g. spray drying and solvent evaporation) [32]. Amongst these methods, physio-mechanical techniques have been most intensively explored for fabrication of DDSs for epilepsy treatment. The majority of the studies have been undertaken primarily to improve

bioavailability of oral administration [33], limited studies have been focused on local delivery through intracranial injection.

Emulsification solvent evaporation (ESE) is a facile approach for encapsulation of pharmaceutical compounds (Figure 1A). For encapsulation of hydrophobic drugs, a common approach is through oil-in-water (O/W) emulsion, where a polymer matrix and target drug are dissolved in an organic phase comprising volatile solvent such as dichloromethane or chloroform, and then dispersed into an aqueous phase. Subsequent evaporation of the organic solvent results in formation of drug-loaded microspheres [32]. For encapsulation of hydrophilic drugs, one popular approach is through water-in-oil-in-water (W/O/W) double emulsion (Figure 1B). An aqueous drug-loaded phase (W1) is emulsified into a polymer containing oil phase (O1), which is then further emulsified in a second water phase (W2) to produce drug-loaded oil droplets and microspheres upon removal of the organic solvent [34].

Investigations have shown that injectable particle formulations of diazepam (DZP) and phenytoin (PHT) exhibit sustained release *in-vitro* as well as efficacy *in-vivo.* DZP was encapsulated in poly(hydroxybutyrate-hydroxyvalerate) (PHBV) microspheres, and a triphasic release pattern was observed *in vitro* over a period of 30 days [35]. PHBV-microspheres showed a burst release of approximately 20% to 42% during the first day, followed by more linear controlled drug elution about 18 days. The third stage was characterised by steady state for approximately 12 days until the conclusion of the study at 30 days. The efficacy of PHT-PCL-microspheres to successfully suppress seizures was demonstrated by Jiang *et al.*[21] by injection of the microspheres into the hippocampus of a rat tetanus model of temporal lobe

epilepsy. Compared to the controls, the PHT-loaded microspheres demonstrated a one-third reduction in seizure events *in vivo* during the period of drug release.

Spray drying involves injection of a fluidic feed into a hot drying medium [36] (Figure 1C). The fast injection results in evaporation of the volatile compound and initiates a liquid-solid transition [37]. For fabrication of a DDS, depending on the solubility of the target drug and polymer matrix, a feed for spray drying can be a drug-loaded polymer solution (for a hydrophobic drug), or an emulsion (for a hydrophilic drug). In the latter case, the drug is dissolved in an aqueous phase and then emulsified in a polymer solution for spray-drying [16]. Particle formulations prepared by spray-drying were investigated *in vitro* for delivery of DZP [17], clonazepam [38] or PHT [22]. For instance, a recent work by Li et al. showed that PHT release from the spray-dried PCL microcarriers followed a multi-stage pattern [22]. PHT release followed a multi-stage pattern. For the first 4 days, PHT-release was linear, followed by a decreased release rate for the next 8 days before reaching 80% of completion after 21 days.

Recently, electrospraying, also known as electrohydrodynamic atomization, has emerged as a powerful tool for fabrication of drug-loaded microparticles [39] (Figure 1D). A liquid polymer solution is injected to a nozzle and subjected to a high electric field. When the electrostatic repulsion surpasses the surface tension of a liquid droplet, ejection of the polymer solution will occur at the surface of the droplet and subsequently break off to form microdroplets. Electrospraying shows great potential for drug delivery due to the ability to fabricate monodisperse microparticles, and composite microparticles with core-shell morphology. The latter is achieved using a coaxial nozzle, and offers a number of advantages including improved drug stability and better control of drug release kinetics and ease of loading of multiple drugs, as is compared to the monoaxial electrospraying approach. For instance, Wang *et al.* reported

a type of PLLA core-PLGA shell microparticles for dual growth factor delivery [40]. Sequential release was achieved by electrojetting simultaneously FGF-2/core phase emulsion and BMP-2/shell phase emulsion at a specific ratio though a coaxial needle. Chen *et al.* reported the preparation of core-shell structured PLGA-microcapsules loaded with anti-convulsive lacosamide by coaxial-electrospraying [41]. The release-profile of lacosamide varied significantly with the shape and morphology of the resultant core-shell DDS. Microflakes showed fast release behaviour, with over 96% of their drug payload released within 2 days. Compared to the microflakes, drug-release from the microspheres offered slower drug elution with approximately 70% of their drug payload released within 2 days and a less initial burst release. After 11 days the microspheres released over 90% of their drug payload. However, future studies are needed to improve on the efficacy of these formulations *in vitro* and *in vivo*, by optimising the core and shell structure design in terms of structural composition and respective thickness.

4. Electrospinning

Electrospinning is another electro-hydrodynamic processing method, which has been intensively employed to produce micro/nanofibrous structures for a broad range of biomedical applications [42, 43]. Similar to electrospraying, a typical electrospinning process involves injection of a polymer solution through a nozzle under a high electric field. The polymer solution at the tip of the spinneret forms a droplet. When the viscosity of the polymer solution is above a threshold, the ejected solution will not break down as microdroplets, resulting in continuous ultrathin fibres on the collector plate.

A facile approach to encapsulate pharmacological compounds into electrospun fibres is by dissolving target drug. Drug release from these devices are highly dependent on the distribution

of the drug in the electrospun fibres. Thus, the hydrophobic-hydrophilic properties of drug and polymer should be matched [44]. However, drug release from electrospun fibres prepared by dissolution of the drug into the polymer solution demonstrates a high burst release caused by the relatively high surface area to volume ratio of the fibre. To solve this issue, composite fibres with a core-shell morphology have been developed to reduce the initial burst release (Figure 2A). Zhang *et al.* demonstrated that the initial burst of fluorescein isothiocyanate (FITC)-labelled BSA from the PCL cores was significantly reduced by the polyethylene glycol (PEG) shells when compared to the structure without the PEG shells [45]. The efficacy of coaxially electrospun PLGA fibres to ameliorate seizures, where lacosamide was encapsulated only in the core, were reported by Bauquier *et al.* [23]. The PLGA fibres showed sustained elution of lacosamide over a period of 90 days *in vitro*. Subdural implantation of the lacosamide-loaded fibres above the motor cortex in a Genetic Absence Epilepsy Rat model demonstrated to significantly reduce the duration of spike-and-wave discharges (SWD) for up to 7 weeks.

Emulsion electrospinning technique refers to simultaneous spinning of two immiscible solutions to incorporate hydrophilic drugs. An aqueous solution of the drug is emulsified into an organic solution in which the fibre-forming polymer is solubilized. Due to the viscosity gradient, formed by the evaporation of the volatile solvent, aqueous droplets migrate to the centre of ejected fibres and unify [46]. Recently, Viry *et al.* reported the preparation of levetiracetam (Lev)-containing electrospun fibres. Lev-loaded fibres were prepared using a coaxial- and coaxial/emulsion-based electrospinning setup (Figure 2B and C), respectively [18]. Compared to the coaxial fibers, the *in vitro* release of Lev from the emulsion/coaxial fibres demonstrated a nearly linear, much more sustained release pattern for at least 18 days (Figure 2D).

5. 3D printing

Three-dimensional (3D) printing is a subset of additive manufacturing, which involves fabrication of a 3D object by depositing successive layers of material in a defined spatial arrangement according to a computer aided design (CAD) model. Since its original discovery by Charles Hull in 1986, 3D printing has been used as a cost-effective, rapid prototyping technique with a wide range of applications in e.g. aerospace, construction, medical and jewellery. In particular, 3D printing is highly suitable for small scale productions, including customization and personalized manufacturing while allowing for complex designs, normally difficult to fabricate with more conventional manufacturing methods. Additionally, fabrication approaches described previously rely on the use of organic solvents during processing. Residual organic solvents, such as methylene chloride which is suspected to be carcinogenic and mutagenetic, implies a health risk for patients and is strictly regulated by regulatory agencies. 3D-printing approaches offers the possibility to process in a solvent-free fabrication mode. These benefits have allowed the steady growth of 3D printing and other additive manufacturing techniques in biomedical applications, from (bone) tissue engineering to printing of anatomical models, over the last 30 years [47-49].

Pharmaceutical applications of 3D printing are still in the relative early stages, and only recently has there been attention directed towards the fabrication of DDSs with 3D printing. This culminated in the approval of Spritam® (levetiracetam), the first 3D printed orodispersible tablet with FDA approval, in 2016. Although the approval shows the potential of 3D printing for tablet-based DDSs for epilepsy, part of the focus has shifted towards the fabrication of implant-based systems [31, 50]. A schematic depiction of the different 3D printing techniques used in pharmaceutical manufacturing can be found in Figure 3. The next sections will describe in more detail the different printing techniques used for drug delivery implant fabrication and highlight some potentially useful articles that, although not using antiepileptic agents as the model drugs, could translate well to the treatment of epilepsy.

5.1 Fused Deposition Modelling (FDM)

FDM is a technique in which thermoplastic polymers are extruded as filaments through a nozzle-based system. The polymer is mechanically pushed past a heating block, of which the temperature can be tuned depending on the melting temperature of the desired polymer, and as a result the polymer gets liquefied. Upon deposition onto the build plate the polymer cools down and solidifies, allowing for a relatively precise spatial arrangement in the deposition. Some of the more commonly used polymers with FDM are acrylonitrile butadiene styrene (ABS), PLA, PCL and ethylene-vinyl acetate (EVA) [51]. However, ABS is rarely used in pharmaceutical 3D printing due to its low biodegradability and high toxicity [52]. FDM has widely been used for the fabrication of tablet-based DDSs, but more limited research has been conducted on implants with drug delivery capabilities.

An implant for contraceptives has been manufactured by Genina *et al.* [53] using EVA copolymers. They investigated a range of different concentrations of vinyl alcohol and were able to successfully fabricate custom T-shaped intrauterine systems and subcutaneous rods with drug delivery capabilities. However, rigorous optimisation is required for each new drug-loaded and drug-free feedstock for FDM, as a main limitation of this technique is that the drugs usually have to go through the whole material fabrication process, often requiring high temperatures or toxic chemicals. A recent study by Visscher *et al.* [54] evaded this issue through combining FDM printing with salt-leaching and as a result were able to introduce microporosity into the drug-loaded scaffold. By further coating this scaffold with gelatin methacrylate (GelMA) a sustained release of cefazolin over multiple days was attained.

Previous studies have been limited by the use of only a single type of polymer. For future developments of 3D printed implants, it is important to assess and compare different polymers and drug loads. Kempin *et al.* [55] used quinine as a model drug with 4 different polymers. The amount of drug released was highly dependent on both the polymer used and the drug load. Further research could establish correlations between a wide range of desired drug release profiles and the appropriate polymer and drug load to use.

These applications show that FDM is a reliable, low-cost and efficient alternative technique for producing customizable shaped implants, and that long-term release profiles are possible. However, the degradability of specific drugs at the high temperatures used should be taken into careful consideration and problems might occur when switching to different polymers and/or drugs. Particularly, exploration of a combination of FDM and other techniques to prevent drugs from degradation by the fabrication process could provide opportunities for novel drug/polymer combinations.

5.2 Extrusion-based printing

Extrusion-based printing employs a pneumatic-, mechanical- or solenoid-based system to deposit materials from a nozzle in a layer-by-layer fashion onto a build plate to create a 3D construct. Mostly viscous and semi-liquid materials are used in this method, with the viscosity and viscoelastic properties of the materials being vital for their printability. A pioneering approach has been reported utilizing a custom liquid extrusion-based printer for the fabrication of a DDS with relative long-term release profile [56]. Two types of liquid ink materials, dexamethasone-loaded polyvinyl alcohol (PVA) solution and poly(lactic-co-glycolic acid) (PLGA), were employed to print a construct with dexamethasone-PVA located in the core (Figure 4A and B). By changing the thickness of the construct through addition of extra layers of PVA and PLGA in a sandwich-like structure a sustained drug release of up to 4 months was

achieved. Although PCL and PLGA are popular materials to use with this technique, a study by Holländer *et al.* [57] showed the versatility of extrusion-based printing by using polydimethylsiloxane (PDMS), which previously had not been used for the fabrication of DDSs. They were able to fabricate 3D-printed drug-loaded PDMS constructs with drug-release profiles of prednisolone for at least 28 days.

By employing a coaxial set-up using air-powered and mechanically-powered extrusion of alginate and $CaCl_2$, respectively, Do *et al.* [58] fabricated a DDS with a core-shell structure. The construct was shown to be non-cytotoxic and different fluorescent dyes were used to mimic drug release profiles. To note, although the alginate-PLGA tubes show high mechanical strength, incorporation of drugs decreases the overall mechanical properties and thus would need minor adjustments to improve the strength to a suitable level for implant-based applications. On the other hand, Song *et al.* [59] were able to achieve proper mechanical properties by combing a drug-loaded PLGA hydrogel with a PCL-based polymeric framework for extra stability. This carrier allowed for sustained local delivery of cyclosporin A and a resulting reduction in a xenogeneic cell-based immune response. Extrusion-based printing of hydrogels has potential to be applied for local AED delivery because hydrogel-based DDSs have been shown to provide site-specific, sustained delivery to brain tissue [60, 61]. Furthermore, polymer hydrogel systems are mechanically compliable with the soft CNS tissue [62].

5.3 Stereolithography (SLA)

SLA is based on a photopolymerization process, where typically a UV laser is used to produce a specific pattern according to the accompanying CAD design and via layer-by-layer curing of ink materials (monomers or polymer precursors). Traditionally, SLA is not suitable for drug manufacturing because of the scarcity of biocompatible/biodegradable photopolymerizable raw

materials used in pharmaceutical manufacturing and the toxic effects of some uncured material and free radical formation [63, 64]. More recently, research employing SLA for DDS applications produced systems including a topical patch [65], transdermal micro-needles [66] and tablet forms [67]. However, to the best of our knowledge no implant-based application has been explored for this technique. Potential advantages of this technique would be the superior resolution and accuracy compared to other conventional fabrication techniques [67, 68]. Additionally, the UV photo polymerization has shown little effect on drug degradation, allowing the encapsulation of thermally labile drugs due to the minimization of localized heating [69].

5.4 Binder jetting

Binder jetting, in some cases referred to as 3DP, is a printing technique in which a liquid is deposited onto a powder bed. The layer of powder is spread out onto the build plate via a roller after which the liquid binding material is jetted onto the powder bed. This binds the powder together and results in an object being produced by the agglomeration of multiple layers stacked on top of each other forming dense powder compacts. It is similar to conventional powder tablet manufacture in material composition, but the binder jetting technique can create highly porous structures for rapid disintegration and quick drug release. The previously mentioned drug Spritam®, is produced in this manner. One of the first implant applications of this technique was by Lin *et al.* [70] who fabricated sub dermally implantable DDSs with a drug release of five weeks in one of their designs. Various other groups have used binder jetting to produce implants with antibiotics loaded in, either singular [71, 72] or with multiple drugs [73, 74]. Overall, the implants produced have a relative moderate duration of drug release, continuously releasing for over 6 weeks [74]. More recently, Wu *et al.* [75] produced a cylindrical shaped drug releasing implant incorporating levofloxacin and tobramycin in a specific sequence (Figure 4C and D). Although drug loading was relatively low in this study due to the dispersion

of the drug in the solution, a sustained release was achieved for at least 50 days. In all, an advantage of using binder jetting for potential AED delivery applications is that implants can have highly defined micro- and macro-porosities to allow for complex multi-drug release profiles. Still, it is important to establish different material and drug combinations on a case-by-case basis, as the efficacy can be affected by the manufacturing process significantly.

5.5 Selective laser sintering (SLS)

SLS uses a powder bed as the base material, similar to the previously mentioned binder jetting technique. However, instead of using a liquid material, in SLS a laser binds the powder particles together. The laser is used to make a specific pattern on the powder bed, after which new powder is rolled on top of the previous layer and a new pattern is created. An interesting advantage for this technique compared to some of the other advanced fabrication techniques is that it does not require a solvent, which could potentially be harmful or degrade drugs encapsulated inside. On the other hand, the use of a laser results in tough printing conditions, mainly due to the high temperatures and high-energy laser required. This can lead to the degradation of drugs contained in the powder bed [76]. Originally, the only DDSs produced with this technique loaded the drug after the printing process [77, 78]. Recently Fina *et al.* [79] showed a proof-of-concept for using SLS to produce a tablet form DDS with two different polymers by utilising excipients to protect the loaded drug from degradation.

Table 2 shows the advantages and disadvantages associated with the different 3D printing techniques previously discussed. As may be evident, each technique is vastly different and choosing the appropriate technique for each application is critical. Clearly some techniques, e.g. FDM and extrusion-based printing, have been explored more in the context of implant-based DDS fabrication and could thus be more suited for future implant-based epilepsy treatment research. Particularly the latter seems to be well-suited for AED release applications,

considering the potential of hydrogels for drug delivery in brain tissue and the validation of extrusion-based printing for implantable DDS, although in a different application, in both an *in vitro* and follow-up *in vivo* mouse model study [80, 81].

6. Expert opinion

The versatility of the advanced fabrication techniques described in this review show the exciting new possibilities for development of DDSs that can contain multiple drugs with variable release profiles within the same system. This exceptionally high degree of flexibility and control are optimally suited for pharmaceutical manufacturing because of the need for customized, complex and innovative DDSs. The different methods of fabrication are expected to support new developments of implants for personalizing drug therapy to address intricate dosing regimens and patient specific needs. It is clear that there is not a one-method-fits-all solution to drug products, but rather that each problem requires a solution encompassing different techniques and material compositions. With constant research into novel advanced fabrication methods it will be possible to engineer the desired technique and material from a certain objective for the amount of drugs released, the release profile and degradation of the material used. With the end goal in mind, an important focus of future research should be to translate the advantages of these described techniques into tangible benefits for the patient.

However, there are a range of issues that will need to be addressed before industry acceptance of these techniques including quality control, GMP-compliance, throughput scale-up, among other legal, regulatory and administrative issues. Another important focal point is the need to identify novel compatible materials alongside exploration of new technologies.

The wide range of techniques discussed herein have been used to produce implant-based DDSs for a wide variety of medical applications but have scarcely been applied towards epilepsy

treatment. This is partly due to the ongoing exploration of the full spectrum of capabilities of these techniques. Furthermore, a primary focus of some novel techniques is proving the efficacy of different materials using model drugs as a proof-of-concept, rather than exploring the versatility of the implant for different applications. As research into implantable DDS intensifies, and with the recognition of their potential and the amount of research increasing into fabricating DDS for epilepsy treatment with more conventional methods, it is expected that the research into advanced fabrication methods for anti-epileptic implantable devices will increase concurrently.

It is evident that in the future, establishing new collaborations, both within academia as well as with industry partners and clinicians, will be vital for full integration into the industrial pharmaceutical manufacturing market. The further maturation of these techniques will result in an accelerated process from bench to bedside. A vital first step has already been taken with the approval of Spritam® and we expect more to follow in the coming years. Innovative solutions are needed to solve some of the inherent limitations of the various advanced fabrication techniques, in particular 3D printing, and combining different techniques for synergistic effects may be the approach of choice to overcome limitations of singular fabrication methods.

Acknowledgements

The authors wish to acknowledge funding from the Australian Research Council (ARC) Centre of Excellence Scheme (CE140100012), the use of facilities at the University of Wollongong Electron Microscopy Centre, support of the Australian National Fabrication Facility (ANFF) – Materials Node. Professor Gordon Wallace acknowledges the support of the ARC through an ARC Laureate Fellowship (FL110100196). Funding from the Australian Government through the International Education and Training program in relation to project BIOFABrication for

Future Manufacturing and the EU ICI ECP international joint program biofabrication mobility grant are gratefully acknowledged.

References

1. Goldberg, E.M. and D.A. Coulter, *Mechanisms of epileptogenesis: a convergence on neural circuit dysfunction.* Nature Reviews Neuroscience, 2013. **14**(5): p. 337.
2. Shorvon, S.D., *Drug treatment of epilepsy in the century of the ILAE: the second 50 years, 1959–2009.* Epilepsia, 2009. **50**(s3): p. 93-130.
3. Oby, E. and D. Janigro, *The blood–brain barrier and epilepsy.* Epilepsia, 2006. **47**(11): p. 1761-1774.
4. Blair, R.E., et al., *Prolonged exposure to WIN55, 212-2 causes downregulation of the CB1 receptor and the development of tolerance to its anticonvulsant effects in the hippocampal neuronal culture model of acquired epilepsy.* Neuropharmacology, 2009. **57**(3): p. 208-218.
5. González, S., M. Cebeira, and J. Fernández-Ruiz, *Cannabinoid tolerance and dependence: a review of studies in laboratory animals.* Pharmacology Biochemistry and Behavior, 2005. **81**(2): p. 300-318.
6. Bennewitz, M.F. and W.M. Saltzman, *Nanotechnology for delivery of drugs to the brain for epilepsy.* Neurotherapeutics, 2009. **6**(2): p. 323-336. ** Summarizes approaches in nanotechnology to traverse the blood-brain barrier to increase AED penetration into the brain.
7. Löscher, W., *Mechanisms of drug resistance.* Epileptic disorders, 2005. **7**(1): p. 3-9.
8. Kwan, P. and M.R. Sperling, *Refractory seizures: try additional antiepileptic drugs (after two have failed) or go directly to early surgery evaluation?* Epilepsia, 2009. **50**: p. 57-62.
9. Dong, W., P. Maincent, and R. Bodmeier, *In vitro and in vivo evaluation of carbamazepine-loaded enteric microparticles.* International journal of pharmaceutics, 2007. **331**(1): p. 84-92.
10. Cundy, K.C., et al., *XP13512 [(±)-1-([(α-isobutanoyloxyethoxy) carbonyl] aminomethyl)-1-cyclohexane acetic acid], a novel gabapentin prodrug: II. Improved oral bioavailability, dose proportionality, and colonic absorption compared with gabapentin in rats and monkeys.* Journal of Pharmacology and Experimental Therapeutics, 2004. **311**(1): p. 324-333.
11. Summers, M.A., J.L. Moore, and J.W. McAuley, *Use of verapamil as a potential P-glycoprotein inhibitor in a patient with refractory epilepsy.* Annals of Pharmacotherapy, 2004. **38**(10): p. 1631-1634.
12. Van Vliet, E., et al., *Blood–brain barrier leakage may lead to progression of temporal lobe epilepsy.* Brain, 2006. **130**(2): p. 521-534.
13. Tamargo, R.J., et al., *The intracerebral administration of phenytoin using controlled-release polymers reduces experimental seizures in rats.* Epilepsy research, 2002. **48**(3): p. 145-155.
14. Kokaia, M., et al., *Seizure suppression in kindling epilepsy by intracerebral implants of GABA- but not by noradrenaline-releasing polymer matrices.* Experimental brain research, 1994. **79**(2): p. 385-394.
15. Fisher, R.S. and J. Ho, *Potential new methods for antiepileptic drug delivery.* CNS drugs, 2002. **16**(9): p. 579-593.
16. Zhang, J., et al., *Spray-dried oil-in-water emulsion to improve the intestinal absorption and oral bioavailability of ZLR-8, a nitric oxide-releasing derivative of diclofenac.* Journal of Pharmacy and Pharmacology, 2011. **63**(12): p. 1531-1538.
17. Giunchedi, P., et al., *In vitro degradation study of polyester microspheres by a new HPLC method for monomer release determination.* Journal of controlled release, 1998. **56**(1-3): p. 53-62.

18. Viry, L., et al., *Emulsion-coaxial electrospinning: designing novel architectures for sustained release of highly soluble low molecular weight drugs.* Journal of Materials Chemistry, 2012. **22**(22): p. 11347-11353.
19. Bauquier, S.H., et al., *Antiepileptic effects of lacosamide loaded polymers implanted subdurally in GAERS.* International Journal of Polymer Science, 2016. **2016**.
20. Chen, Y., et al., *Development of drug-loaded polymer microcapsules for treatment of epilepsy.* Biomaterials science, 2017. **5**(10): p. 2159-2168.
21. Jiang, J.L., et al., *Injectable phenytoin loaded polymeric microspheres for the control of temporal lobe epilepsy in rats.* Restorative neurology and neuroscience, 2015. **33**(6): p. 823-834.
22. Li, Z., et al., *Formulation of spray-dried phenytoin loaded poly (ε-caprolactone) microcarrier intended for brain delivery to treat epilepsy.* Journal of pharmaceutical sciences, 2007. **96**(5): p. 1018-1030.
23. Szybala, C., et al., *Antiepileptic effects of silk-polymer based adenosine release in kindled rats.* Experimental neurology, 2009. **219**(1): p. 126-135.
24. Frazza, E. and E. Schmitt, *A new absorbable suture.* Journal of Biomedical Materials Research Part A, 1971. **5**(2): p. 43-58.
25. Nair, L.S. and C.T. Laurencin, *Biodegradable polymers as biomaterials.* Progress in polymer science, 2007. **32**(8-9): p. 762-798.
26. von Burkersroda, F., L. Schedl, and A. Göpferich, *Why degradable polymers undergo surface erosion or bulk erosion.* Biomaterials, 2002. **23**(21): p. 4221-4231.
27. Winzenburg, G., et al., *Biodegradable polymers and their potential use in parenteral veterinary drug delivery systems.* Advanced drug delivery reviews, 2004. **56**(10): p. 1453-1466.
28. Miller, R.A., J.M. Brady, and D.E. Cutright, *Degradation rates of oral resorbable implants (polylactates and polyglycolates): rate modification with changes in PLA/PGA copolymer ratios.* Journal of Biomedical Materials Research Part A, 1977. **11**(5): p. 711-719.
29. Middleton, J.C. and A. Tipton, *Synthetic biodegradable polymers as medical devices.* Medical Plastic and Biomaterials, 1998. **5**: p. 30-39.
30. Halliday, A. and M. Cook, *Polymer-based drug delivery devices for neurological disorders.* CNS & Neurological Disorders-Drug Targets (Formerly Current Drug Targets-CNS & Neurological Disorders), 2009. **8**(3): p. 205-221.
31. Halliday, A.J., et al., *Novel methods of antiepileptic drug delivery - Polymer-based implants.* Advanced Drug Delivery Reviews, 2012. **64**: p. 953-964. **Gives an extensive overview on polymeric drug delivery systems for the treatment of epilepsy.
32. Jyothi, N.V.N., et al., *Microencapsulation techniques, factors influencing encapsulation efficiency.* Journal of microencapsulation, 2010. **27**(3): p. 187-197.
33. Fresta, M., et al., *Preparation and characterization of polyethyl-2-cyanoacrylate nanocapsules containing antiepileptic drugs.* Biomaterials, 1996. **17**(8): p. 751-758.
34. Iqbal, M., et al., *Double emulsion solvent evaporation techniques used for drug encapsulation.* International journal of pharmaceutics, 2015. **496**(2): p. 173-190.
35. Chen, J. and S. Davis, *The release of diazepam from poly (hydroxybutyrate-hydroxyvalerate) microspheres.* Journal of microencapsulation, 2002. **19**(2): p. 191-201.
36. I Ré, M., *Microencapsulation by spray drying.* Drying technology, 1998. **16**(6): p. 1195-1236.
37. Chan, H.-K. and P.C.L. Kwok, *Production methods for nanodrug particles using the bottom-up approach.* Advanced drug delivery reviews, 2011. **63**(6): p. 406-416.
38. Benelli, P., et al., *Clonazepam microencapsulation in poly-D, L-lactide-coglycolide microspheres.* Journal of microencapsulation, 1998. **15**(4): p. 431-443.
39. Davoodi, P., et al., *Coaxial electrohydrodynamic atomization: microparticles for drug delivery applications.* Journal of Controlled Release, 2015. **205**: p. 70-82.
40. Wang, S., et al., *Core–shell microspheres delivering FGF-2 and BMP-2 in different release patterns for bone regeneration.* Journal of Materials Chemistry B, 2015. **3**(9): p. 1907-1920.

41. Chen, Y., et al., *A simple and versatile method for microencapsulation of anti-epileptic drugs for focal therapy of epilepsy.* Journal of Materials Chemistry B, 2015. **3**(36): p. 7255-7261.
42. Hu, X., et al., *Electrospinning of polymeric nanofibers for drug delivery applications.* Journal of Controlled Release, 2014. **185**: p. 12-21.
43. Arinstein, A. and E. Zussman, *Electrospun polymer nanofibers: mechanical and thermodynamic perspectives.* Journal of Polymer Science Part B: Polymer Physics, 2011. **49**(10): p. 691-707.
44. Zamani, M., M.P. Prabhakaran, and S. Ramakrishna, *Advances in drug delivery via electrospun and electrosprayed nanomaterials.* International journal of nanomedicine, 2013. **8**: p. 2997.
45. Zhang, Y., et al., *Coaxial electrospinning of (fluorescein isothiocyanate-conjugated bovine serum albumin)-encapsulated poly (ε-caprolactone) nanofibers for sustained release.* Biomacromolecules, 2006. **7**(4): p. 1049-1057.
46. Xu, X., et al., *Ultrafine medicated fibers electrospun from W/O emulsions.* Journal of Controlled Release, 2005. **108**(1): p. 33-42.
47. Chia, H.N. and B.M. Wu, *Recent advances in 3D printing of biomaterials.* Journal of Biological Engineering, 2015. **9**: p. 4.
48. Gross, B.C., et al., *Evaluation of 3D Printing and Its Potential Impact on Biotechnology and the Chemical Sciences.* Analytical Chemistry, 2014. **86**: p. 3240-3253.
49. Mota, C., et al., *Additive manufacturing techniques for the production of tissue engineering constructs.* Journal of tissue engineering and regenerative medicine, 2015. **9**(3): p. 174-190.
50. Moulton, S.E. and G.G. Wallace, *3-dimensional (3D) fabricated polymer based drug delivery systems.* Journal of Controlled Release, 2014. **193**: p. 27-34.
51. Mohamed, O.A., S.H. Masood, and J.L. Bhowmik, *Optimization of fused deposition modeling process parameters: a review of current research and future prospects.* Advances in Manufacturing, 2015. **3**: p. 42-53.
52. Long, J., et al., *Application of Fused Deposition Modelling (FDM) Method of 3D Printing in Drug Delivery.* Current Pharmaceutical Design, 2016. **23**: p. 433-439.
53. Genina, N., et al., *Ethylene vinyl acetate (EVA) as a new drug carrier for 3D printed medical drug delivery devices.* European Journal of Pharmaceutical Sciences, 2016. **90**: p. 53-63.
54. Visscher, L.E., et al., *Novel 3D printed Polycaprolactone scaffolds with dual macro-microporosity for applications in local delivery of antibiotics.* Materials Science and Engineering: C, 2018.
55. Kempin, W., et al., *Assessment of different polymers and drug loads for fused deposition modeling of drug loaded implants.* European Journal of Pharmaceutics and Biopharmaceutics, 2017. **115**: p. 84-93.
56. Rattanakit, P., et al., *Extrusion printed polymer structures: A facile and versatile approach to tailored drug delivery platforms.* International Journal of Pharmaceutics, 2012. **422**: p. 254-263.
57. Holländer, J., et al., *3D printed UV light cured polydimethylsiloxane devices for drug delivery.* International Journal of Pharmaceutics, 2017.
58. Do, A.-V., et al., *Controlled and Sequential Delivery of Fluorophores from 3D Printed Alginate-PLGA Tubes.* Annals of Biomedical Engineering, 2017. **45**: p. 297-305.
59. Song, T.-H., et al., *3D-Printed Drug/Cell Carrier Enabling Effective Release of Cyclosporin A for Xenogeneic Cell-Based Therapy.* Cell Transplantation, 2015. **24**: p. 2513-2525.
60. Wang, Y., et al., *Hydrogel delivery of erythropoietin to the brain for endogenous stem cell stimulation after stroke injury.* Biomaterials, 2012. **33**: p. 2681-2692.
61. Vashist, A., et al., *Recent advances in hydrogel based drug delivery systems for the human body.* J. Mater. Chem. B, 2014. **2**: p. 147-166.
62. Aurand, E.R., K.J. Lampe, and K.B. Bjugstad, *Defining and designing polymers and hydrogels for neural tissue engineering.* Neuroscience Research, 2012. **72**: p. 199-213.
63. Norman, J., et al., *A new chapter in pharmaceutical manufacturing: 3D-printed drug products.* Advanced Drug Delivery Reviews, 2017. **108**: p. 39-50.

64. Goole, J. and K. Amighi, *3D printing in pharmaceutics: A new tool for designing customized drug delivery systems.* International Journal of Pharmaceutics, 2016. **499**: p. 376-394.
65. Goyanes, A., et al., *3D scanning and 3D printing as innovative technologies for fabricating personalized topical drug delivery systems.* Journal of Controlled Release, 2016. **234**: p. 41-48.
66. Ali, Z., et al., *Fabrication of Polymer Micro Needles for Transdermal Drug Delivery System Using DLP Based Projection Stereo-lithography.* Procedia CIRP, 2016. **42**: p. 87-90.
67. Wang, J., et al., *Stereolithographic (SLA) 3D printing of oral modified-release dosage forms.* International Journal of Pharmaceutics, 2016. **503**: p. 207-212.
68. Melchels, F.P.W., J. Feijen, and D.W. Grijpma, *A review on stereolithography and its applications in biomedical engineering.* Biomaterials, 2010. **31**: p. 6121-6130.
69. Vehse, M., et al., *Drug Delivery From Poly(ethylene glycol) Diacrylate Scaffolds Produced by DLC Based Micro-Stereolithography.* Macromolecular Symposia, 2014. **346**: p. 43-47.
70. Lin, S., et al., *In vitro and in vivo evaluations of biodegradable implants for hormone replacement therapy: Effect of system design and PK-PD relationship.* AAPS PharmSciTech, 2001. **2**: p. 55-65.
71. Huang, W., et al., *Levofloxacin implants with predefined microstructure fabricated by three-dimensional printing technique.* International Journal of Pharmaceutics, 2007. **339**: p. 33-38.
72. Gbureck, U., et al., *Low temperature direct 3D printed bioceramics and biocomposites as drug release matrices.* Journal of Controlled Release, 2007. **122**: p. 173-180.
73. Wu, W., et al., *A programmed release multi-drug implant fabricated by three-dimensional printing technology for bone tuberculosis therapy.* Biomedical Materials, 2009. **4**: p. 065005.
74. Wu, W., et al., *The controlled-releasing drug implant based on the three dimensional printing technology: Fabrication and properties of drug releasing in vivo.* Journal of Wuhan University of Technology-Mater. Sci. Ed., 2009. **24**: p. 977-981.
75. Wu, W., et al., *A therapeutic delivery system for chronic osteomyelitis via a multi-drug implant based on three-dimensional printing technology.* Journal of Biomaterials Applications, 2016. **31**: p. 250-260. *A Very interesting study combining multiple drugs within one implant and achieving a relatively long-term release profile, particularly in the context of 3D printing.
76. Mazzoli, A., *Selective laser sintering in biomedical engineering.* Medical & Biological Engineering & Computing, 2013. **51**: p. 245-256.
77. Leong, K.F., et al., *Building Porous Biopolymeric Microstructures for Controlled Drug Delivery Devices Using Selective Laser Sintering.* The International Journal of Advanced Manufacturing Technology, 2006. **31**: p. 483-489.
78. Cheah, C.M., et al., *Characterization of microfeatures in selective laser sintered drug delivery devices.* Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine, 2002. **216**: p. 369-383.
79. Fina, F., et al., *Selective laser sintering (SLS) 3D printing of medicines.* International Journal of Pharmaceutics, 2017. **529**: p. 285-293.
80. Yi, H.-G., et al., *A 3D-printed local drug delivery patch for pancreatic cancer growth suppression.* Journal of Controlled Release, 2016. **238**: p. 231-241.
81. Shim, I.K., et al., *Locally-applied 5-fluorouracil-loaded slow-release patch prevents pancreatic cancer growth in an orthotopic mouse model.* Oncotarget, 2017. **8**: p. 40140-40151. *An interesting study that successfully validated an 3D-printed implantable DDS within an in vivo model.

Abbreviations

GMP = Good manufacturing process

DDS(s) = Drug delivery system(s)

3D = Three-dimensional

AEDs = Anti-epileptic drugs

BBB = Blood brain barrier

PLA = Polylactic acid

PLGA = Poly(lactic-co-glycolic acid)

PCL = poly(ε-caprolactone)

ESE = Emulsification solvent evaporation

O/W = Oil-in-water

W/O/W = Water-in-oil-in-water

DZP = Diazepam

PHT = Phenytoin

PHBV = Poly(hydroxybutyrate-hydroxyvalerate)

PEG = Polyethylene glycol

SWD = Spike-and-wave discharges

CAD = Computer aided design

FDM = Fused deposition modelling

ABS = Acrylonitrile butadiene styrene

EVA = Ethylene-vinyl acetate

GelMA = Gelatin methacrylate

PVA = Poly-vinyl alcohol

PDMS = Polydimethylsiloxane

SLA = Stereolithography

SLS = Selective laser sintering

Table 1. Examples of polymer-based implants for epilepsy treatment.

Polymer	Fabrication process	Morphology	Drug	Reference
Non-biodegradable				
Poly (ethylene-vinyl acetate (EVA)	Casting	Pellets	Phenytoin	[13]
	Casting	Tubes	Gamma-aminobutyric acid	[14]
Biodegradable				
Silk fibroin	Casting	Disk	Adenosine	[23]
Poly lactic acid (PLA)	Emulsion, Spray drying	Microspheres	Diazepam	[17]
Poly (lactic-*co*-glycolic) acid (PLGA)	Emulsion, Spray drying	Microspheres	Diazepam	[17]
	Electrospinning	Microfibres	Levetiracetam	[18]
	Electrospinning	Microfibres	Lacosamide	[19]
	Electrospraying	Microspheres	Lacosamide	[20]
Poly (ε-caprolactone) (PCL)	Emulsion	Microspheres	Phenytoin	[21]
	Spray drying	Microspheres	Phenytoin	[22]

Table 2: Advantages and disadvantages of the printing techniques employed for implantable DDS fabrication

Printing technique	Advantages	Disadvantages
FDM	• Simple and low-cost • Versatility in scale (industrial and laboratory) • Good mechanical properties	• High temperature usually required for printing • Complex geometries requiring extra waste (support structures)
SLA	• Relative high resolution • Suitable for thermally sensitive drugs	• Limited compatible materials available • Difficulties with multi-drug loading within one DDS
Extrusion-based	• Moderate cost • Easy incorporation of multiple materials/drugs • Moderate resolution	• Low mechanical properties when using hydrogel-based materials for printing • Materials require certain viscosity to be printable
Binder jetting	• Relative fast printing at room temperature • High versatility through adjusting bulk material and/or binding solution	• Low resolution • Binding solution may result in bleeding (migration of liquid) resulting in heterogeneous DDSs • Post-printing process is required to remove residual solvents and excess powders accumulated during printing
SLS	• No solvent required • One-step process with high resolution	• High-power lasers and high temperatures may be required for printing, resulting in degradation of drug • Slow printing speed

Abbreviations: FDM – Fused Deposition Modelling, SLA – Stereolithography, DDS – Drug Delivery System, SLS – Selective Laser Sintering

Figure 1. Fabrication techniques of drug-loaded microspheres. (A) Single emulsion method for hydrophobic drugs, (B) Double emulsion method for hydrophilic drugs, (C) Spray drying and (D) Coaxial electrospraying.

Figure 2. Fabrication of levetiracetam (Lev)-releasing microfibres consisting of 75:25 PLGA core and 85:15 PLGA shell. (A) Illustration of a typical coaxial electrospinning process. (B) Coaxial-setup, with the core composed of 75:25 PLGA/Lev solution in dichloromethane, and the shell composed of 85:15 PLGA in dichloromethane/dimethylformamide (70/30). (C) Emulsion-coaxial-setup with the core composed of 75:25 PLGA/Lev emulsion in dichloromethane, and the shell composed of 85:15 PLGA in dichloromethane/dimethylformamide (70/30). (D-I) SEM micrographs of the Lev-releasing microfibres: top view (D and E) and cross-section (F, G, H and I). (D and F) present the coaxial electrospun PLGA microfibers. (E, G, H and I) present the emulsion/coaxial electrospun PLGA microfibers. For emulsion-coaxial electrospinning, the dispersed-to-continuous phase volume ratio in the emulsion core is used to control the cavity size and diffusive length of the released system. A big volume ratio (1/5) (H) of the dispersed-to-continuous phase results in the formation of large cavities (line arrow) and short diffusive lengths (dash arrow). In contrast, a much lower ratio (1/55) (I) results in smaller cavities (line arrow) and larger diffusive membranes (dash arrow). Scale bars are 1 μm. (J) In vitro release of Lev from the coaxial (□) and emulsion/coaxial (◊) PLGA electrospun fibres. Drug amount (M_t) released relative to drug loading (M_{total}). Adapted with permission from Viry *et al.* [18]

Figure 3. Schematic representation of commonly used 3D printing techniques employed for drug delivery. (A) Fused-Deposition Modelling, (B) Extrusion-based printing, (C) Stereolithography, (D) Binder Jetting and (E) Selective Laser Sintering. Adjusted with permission from Mota *et al.* [49]

Figure 4. Implantable drug delivery systems with complex geometries. (A) Schematic depiction of the side view of dexamethasone-loaded PVA within PLGA in a 1 layer and 2 layer set-up. (B) Drug release profiles of dexamethasone from different layer scaffolds. Adapted with permission from [56]. (C) Three-dimensional perspective and longitudinal section of an implant with multiple drugs included (layer 1 and 3 contained rifampicin (RFP) and layer 2 and 4 contained isoniazid (ISH)). (D) *In vitro* release profiles of INH and RFP. Adapted with permission to be obtained from [73].