Polymeric long-acting drug delivery systems (LADDS) for treatment of chronic diseases: inserts, patches, wafers, and implants.

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Abstract

Non-oral long-acting drug delivery systems (LADDS) encompass a range of technologies for precisely delivering drug molecules into target tissues either through the systemic circulation or via localized injections for treating chronic diseases like diabetes, cancer, and brain disorders as well as for age-related eye diseases. LADDS have been shown to prolong drug release from 24 hours up to 3 years depending on characteristics of the drug and delivery system. LADDS can offer potentially safer, more effective, and patient friendly treatment options compared to more invasive modes of drug administration such as repeated injections or minor surgical intervention. Whilst there is no single technology or definition that can comprehensively embrace LADDS; for the purposes of this review, these systems include solid implants, inserts, transdermal patches, wafers and in situ forming delivery systems. This review covers common chronic illnesses, where candidate drugs have been incorporated into LADDS, examples of marketed long-acting pharmaceuticals, as well as newly emerging technologies, used in the fabrication of LADDS.

Keywords

In situ forming implants, wafer, microneedle, 3D printing, PLGA, brain disorders, diabetes, eye diseases, cancer.

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1 Introduction

Conventional immediate-release delivery systems have been critiqued for not being able to consistently provide optimum therapy for chronic disease conditions, as well as for their potential to induce adverse effects. This is mainly due to the typical rapid and pulse-release and absorption patterns of their drug cargo leading to rapidly fluctuating systemic drug concentration [1]. For locally administered drugs (e.g. ophthalmic and dermal routes of administration), this mode of release is likely to expose the tissue at administration site to high local concentrations of the drug which again could lead to erratic drug absorption as well as undesirable effects [2].

Long acting-delivery systems (LADDS) have been shown to be successful in this context. For example, both oral bioavailability and tolerability of baclofen were enhanced when formulated in sustained-release floating beads, compared to immediate release baclofen tablets [1]. With the local route , the *in vitro* irritation scores of curcumin in situ gelling inserts were significantly lowered compared to those of curcumin suspension [2].

LADDS date back to the first long-acting implanted pellets containing testosterone derivatives that were reported in the late 1930s [3]. This pharmaceutical breakthrough opened the door for other implantable devices for estradiol for prostate cancer. This was followed by the introduction of ‘depot’ systems which are one of the well-established long-acting injectable liquid dosage forms. These ‘’depots’’ can be defined as dosage forms where drugs are formulated as an aqueous suspension or as an oily/non-aqueous solutions or suspension. They offer numerous advantages, such as prolonged drug action, ease of manufacture and improved patient adherence [4]. Antipsychotic drugs and steroidal hormones have been successfully commercialized as long-acting therapeutic alternatives [4]. With the advances in the areas of biomaterials and polymer

science, innovative LADDS have been developed and entered the preclinical and clinical phases of drug development. They include injectable implants, in situ forming implants, inserts, wafers, transdermal patches, microspheres and nanoparticles (Figure 1) [5].

1.1 Implantable LADDS for systemic and topical routes of administration

Implants as drug delivery systems can be designed for either systemic or local medicinal effects. They can be injected via subcutaneous, intramuscular, or intravenous routes for systemic effects. While for localized drug effects (e.g. ocular implants and intracranial wafers), loaded drug molecules act mainly locally, with negligible absorption into the systemic blood circulation [6].

Broadly speaking, implants are considered as controlled drug release systems that consist of polymeric materials which are either biodegradable or non-biodegradable. However, most implants are designed using biodegradable polymers to overcome the need for a procedure to remove the device. Polymers used with biodegradable implants can be divided into natural polymers such as polysaccharides (e.g., cellulose derivatives, sodium alginate, dextran, chitosan and hyaluronic acid), polypeptides (e.g., collagen, elastin and albumin); and synthetic polymers (e.g., PLGA and PCL etc.). In situ forming drug delivery implants (ISFI) are polymeric solutions or suspensions/dispersions having the convenience of being in a liquid form when being administered using conventional dispensers and needles into a specific target site. Upon administration, the polymer solution undergoes a phase-change into a semisolid or solid implant. The drug molecules/particles are entrapped or encapsulated inside the formed in situ matrix. Examples of polymers that can form ISFI includes Pluronics and PLGA [7].

Factors that can trigger the phase transition of these systems include, temperature, ionic strength, pH, solvent exchange, and light. In situ gelling delivery systems allow both local and systemic drug delivery. These systems act as a platform to incorporate other drug delivery systems such as nanoparticles, liposomes, nanomicelles and microemulsions, that can modulate the rate of drug release [8, 9]. Application of in situ forming systems include delivery of drug molecules to the eye, nose, skin, vagina, brain, and tumors. Recently, Vigani et al [8] reviewed the advances in the development of in situ forming systems that have been developed in the last decade.

1.2 In situ forming LADDS

In situ gelling systems are commonly used in commercially available ophthalmic formulations for the management of anterior eye diseases (e.g., Timoptol XE® and Timolol GFS®). Current research focuses on optimizing these systems to achieve extended-release properties to increase bioavailability of the incorporated therapeutic. Application of in situ gelling inserts in the delivery of therapeutics to the anterior segment of the eye has been evaluated. Recently, Abdelkader et al [2] reported on curcumin in situ gelling polymeric insert with enhanced ocular performance. The authors demonstrated prolonged precorneal residence time of curcumin from these inserts up to 150 minutes [2]. Destruel et al [10] reported on the use of gellan gum and hydroxyethyl cellulose in enhancing the retention of cyanine dye after administration to the eye of rabbits. The residence time of this formulation in the conjunctival sac was greater than 3 hours, which can result in enhanced bioavailability of the incorporated drug [10]. Gellan gum has been used to enhance the retention of a nanoemulsion modified with a cell penetrating peptide in the conjunctiva of Sprague-Dawley rats. This formulation was reported to significantly increase corneal retention of fluorescein when compared to a control [11].

Furthermore, in situ gelling systems have been used for the delivery of therapeutics to the posterior segment of the eye. Methoxy-poly(ethylene glycol)-block-poly(lactic-co-glycolic acid) (mPEGPLGA-BOX), a thermosensitive and biodegradable triblock polymer, has been used to deliver bevacizumab to the retina of rabbits and effectively inhibit angiogenesis [12]. This formulation undergoes solution to gel transition upon administration into the vitreous and has been shown to release the incorporated protein therapeutic for up to 30 days [12].

Dai et al [13] reported on the use of an organogel system to deliver flunarizine to the brain of rabbits following administration to the conjunctival sac. Organogels are semisolid systems that comprise a liquid organic phase, locked within a three-dimensional polymeric network. They are known to increase the bioavailability of both hydrophilic and lipophilic compounds. The authors developed an organogel that undergoes sol to gel transition upon administration to the eye and provides sustained release of the incorporated lipophilic compounds. Reported pharmacokinetic parameters showed that this organogel system was superior to equivalent solution formulation as it increased the absolute bioavailability by 2-folds and the AUC by 3-folds [13].

In situ gelling systems are used to administer drugs to the nose, for the management of both local and systemic diseases. The use of the intranasal route to bypass the blood-brain-barrier and deliver drugs directly to the central nervous system (CNS) is indeed of interest. Deacetylated gellan gum has been used to enhance intranasal retention of a nano-suspension of Breviscapine, a flavonoid glycoside used mainly as an anticoagulant [14]. Gellan gum is also used in delivering Flibanserin loaded nanostructured lipid carriers via the intranasal route to the brain [15]. Other polymer combinations used in the formulation of in situ gelling systems for intranasal

administration include poloxamer 407/poloxamer 108 [16], poloxamer/chitosan, carbopol/hydroxypropyl methylcellulose/alginate [17], carboxymethyl chitosan/starch [18], deacetylated gellan gum/hydroxy propyl methylcellulose [19] and methylcellulose [20]. It is worthwhile noting that other strategies to enhance drug permeability across the nasal mucosa, such as the use of cyclodextrins [21] and nano structured carriers [14, 15] have been reported.

A key challenge of administering medications via the rectal, vaginal, and intrauterine routes is their poor retention and rapid expulsion from the site of administration, especially of aqueous formulations. Therefore, in situ gelling systems are often used to promote better retention and reduce frequency of administration of rectal, vaginal, and intrauterine formulations. Chen et al [22] reported on the use of Pluronic F127, Pluronic F68 and hydroxypropyl methylcellulose (HPMC) K4M to develop a thermosensitive in situ gelling system that increased the *in vivo* bioavailability of budesonide, which is commonly used to manage ulcerative colitis [22]. In this study, HPMC K4M was primarily incorporated in the developed formulation to provide bioadhesion whereas Pluronics were used to provide thermo-responsiveness (at 30 ^{o}C). Pharmacokinetic data showed that the gel formulation doubled the T_{max} (from 0.36 hour for solution formulation to 0.71 hour for the tested gel formulation) and significantly increased the AUC of rectal budesonide [22].

Yao et al [23] reported on the use of multiple polymers to optimize gelation behavior of an intrauterine drug delivery system. They reported on the use of Aloe Vera to reduce the gelation temperature of poloxamers where the developed AV-poloxamer hybrid hydrogel system underwent solution to gel transition at about 30℃. This platform was used to embed and deliver nanoparticles of beta estradiol (E2) to the endometrium of rats for up to 7 days via the intrauterine route [23].

External triggers such as ultrasound can also be used to modulate rate of drug release from in situ gelling systems. mPEG-PLGA-BOX diblock copolymer is such a system that was shown to alter drug release rate upon application of an ultrasound energy. The thermo-gelation of this polymer solution is dependent on polymer and drug concentrations where the release of drug from this polymeric matrix could be modulated using ultrasound. This system was reported to provide drug release for up to 7 days, demonstrating the desirable sustained release properties of this formulation [24].

In situ gelling systems were also explored as platforms to deliver anti-cancer drugs to tumors as post-surgical implants as these are highly malleable and easy to use [25]. Zhuang et al [25] developed and reported on the use of a Schiff base-based in situ forming hydrogel to deliver two anti-cancer drugs to manage breast cancer. This hydrogel supported the breast as post-tumor resection implants. The hydrogels were prepared by the combination of aldehyde hyaluronic acid and carboxymethyl chitosan. Gelation time varied from 40 to 160 seconds and was dependent on the oxidation degree of the aldehyde hyaluronic acid. The authors investigated the efficacy of this gel system in simultaneously delivering two anti-cancer drugs, doxorubicin hydrochloride and gemcitabine hydrochloride in mice. The tumor recurrence was completely prevented by the dual drug loaded gel system at day 12. The tumor recurrence of controls groups was reported as 83% and 100% for doxorubicin/gemcitabine solution and blank gel groups, respectively. This study highlighted the potential use of in situ forming gels as implants to provide sustained release of anti-cancer drugs to prevent tumor recurrence [25].

Poly (ethylene glycol)–poly(valerolactone)–poly(ethylene glycol) [PEG–PVL–PEG] block copolymers were synthesized and evaluated as thermo-gelling systems for subcutaneous delivery of two model drugs dexamethasone and 5-fluoruuracil. These new polymers were found to be biocompatible, biodegradable and were capable of

undergoing sol-to-gel phase change at physiological temperature. The investigated block copolymer gave rise to gels that maintained their integrity for seven days post subcutaneous injection [26].

Implantable drug-delivery systems fabricated using electrospinning of nano-fibers have been recently identified as an promising therapeutic approach for localized cancer treatment to prevent possible cancer relapse [27].

2 Advantages of polymeric LADDS

In addition to the previously mentioned advantages of LADDS, such as improving the efficacy and safety of many drugs by modulating their drug release and prolonging their retention at administration / target site; other advantages include:

- To minimize repeated needle potential injuries, providing local therapy to brain, joints, eyes, as it will be discussed in detail in the next section.

  To enhance patient compliance; firstly, treatment compliance of special population groups (e.g., elderly patients); those patients might encounter difficulties swallowing; and to tackle poor adherence to treatment of patients under specific clinical settings. For example, some patients do not get the expected benefit of using antipsychotic drugs. Recurrent relapses and frequent hospitalization due to exacerbations have been reported with conventional drug therapy [28].
- To enhance oral bioavailability of some drugs by bypassing absorption barriers and the hepatic first pass metabolism. For example, Nitroderm TTS 5 and 10 mg of nitroglycerine is a transdermal patch that deliver the anti-anginal drug to the systemic circulation through the skin and avoiding the extensive first pass metabolism [29].

- To promote targeting and minimize the multi-organ toxicities of extremely poorly soluble, yet highly potent chemotherapeutic drugs. For example, paclitaxel is a practically insoluble (< 1µg/ml) anticancer drug; surfactants such as Cremophor® and Tween 80® were used to solubilize paclitaxel; however, the conventional injection solution of paclitaxel has been associated with strong and side effects. Paclitaxel-loaded into polymeric micelles and nanoparticles have been successfully used to enhance paclitaxel targeting and reduce possible site reactions (local irritation) post-injection [30].
- To reduce unwanted systemic toxicity by offering a local action at the target area. For example, Gliadel® wafer contains 7.7 mg of the anticancer drug carmustine; this completely biodegradable wafer is designed to be placed intracranially in the resection cavity. Gliadel® wafer circumvents the blood brain barrier, reduces systemic toxicities and provides direct, prolonged, and high dose of the alkylating drug to residual cancer cells [31].

3 Potential candidate drugs for long-acting injections/inserts/implants/patches/wafers

Pain killers used to alleviate moderate to severe pain such as the opioid drug fentanyl have been successfully commercialized as long-acting and non-invasive transdermal patches. Durogesic® 1.25, 2.5, 5, 7.5 and 10 mg of fentanyl per patch provides controlled release of the analgesic drug at a rate of 12, 25, 50, 75 and 100 µg/hour, respectively (Table 1). A drug reservoir is basically composed of the drug fentanyl and hydroxyethyl cellulose with an ethylene-vinyl acetate copolymer membrane.

Biopharmaceuticals (biologicals or biologics), include proteins, peptides, nucleic acids, vaccines, gene therapy, living cells, blood products or tissues that have

therapeutic applications. One class of biologics that is of particular importance to suppress pathological neovascularization and is of clinical value in cancer, and retinal diseases is the anti-vascular endothelial growth factor (anti-VEGF) [28]. LADDDS are likely to improve efficacy and safety of such biopharmaceuticals [32]. The anti-VEGF medicines are ideal candidates for long-acting implantable drug delivery. The VEGF is known to be upregulated in pathological neovascularization of the retina and macula. Bevacizumab (Avastin®), Ranibizumab (Lucentis®), and Aflibercept (Regeneron®) have been approved and used in clinical practice in many parts of the world. Conbercept, Brolucizumab, Abicipar Pegol and Faricimab are still under clinical investigation [33, 34]. These biopharmaceuticals are available in the market as a solution for injection into the vitreous of the eye on regular basis. Patients would require between 9-12 injections during the first year of diagnosis of diabetic retinopathy, wet age-related macular degeneration and macular edema [35]. Unlike steroid implants, these Anti-VEGF injections are only available as immediate release formulation, hence the desperate need for long-acting ocular formulations.

Other drugs that can be considered for formulation as LADDS include antipsychotics, anticancer drugs, contraceptive and anti-inflammatory steroids. LADDS can promote improved local drug delivery to specific organs (brain , joint, anterior and posterior segments of the eye) [28, 36, 37]. As discussed earlier, intracranial placement of Gliadel® wafer is a well-established adjunct therapy to surgery for glioblastoma patients; it offers an increased survival rate and reduced number of deaths compared with placebo [38]. The steroid implants (Ozurdex® and Retisert®) can offer long-acting local treatment of retinal diseases for up to 6 and 30 months respectively without the well-known systemic side effects of steroids [35, 36]. Patients benefit from these

implants by minimizing the number of visits to the clinic to receive their monthly intravitreal injection of conventional corticosteroid injectable suspensions.

4 Chronic diseases that may benefit from long-acting drug delivery using patches/inserts/wafers/implants

4.1 Cancer

Cancer remains a major human life menace due to its reported hallmarks (Figure 2), [39]. In recent decades, remarkable improvements have been made for earlier cancer diagnosis combined with more efficient therapeutics to increase the life span of cancer patients, even for those suffering from advanced cases where there is usually a low chance of patient survival (Figure 2) .

Although current standard cancer treatment approaches including chemotherapy, radiotherapy and more recently immunotherapy have enabled many patients to live for years after being diagnosed, finding that elusive ‘‘magic bullet’’ to specifically target cancerous cells have long been the goal [40]. Nevertheless, there are several hurdles against delivery of chemotherapeutic agents to the tumor sites. These drawbacks include limited bioavailability, serious side effects due from non-target drug distribution, development of multiple drug resistance and the need for high doses and repeated drug administration for relatively longer periods of time [41].

The potency and specificity of anti-cancer agents has been improved in the past decades. The systemic side effects of chemotherapy necessitate the direct delivery of therapeutic molecules to the tumor site. Furthermore, the need for administration of large quantities of anti-cancer drugs has significantly limited the impact of allowable maximum dose of drug molecules in the chemotherapy [42].

Antitumor potency of chemotherapeutic agents can be augmented by improving the method of drugs administration; implementing methods which provide drug release in a targeted, controlled, sustained and long-acting manner at the tumor site. Thereby, engineering efficient and safer drug delivery systems has been a topic of interest [43].

The increase in the number of surviving patients with cancer alongside the advancements in current diagnosis and treatment approaches has changed the perception of cancer from an inevitably fatal into a more manageable disease similar to other chronic diseases [44, 45].

Paclitaxel is an anticancer drug that is commonly used for treatment of ovarian, prostate, breast and bladder cancers. It is available as a solution (Taxol® 6 mg/ml paclitaxel) for intravenous injection or infusion. Paclitaxel is an irritant drug where it may cause inflammation, pain and swelling of veins at the site of the injection. OncoGel® developed for extended local delivery of paclitaxel. OncoGel® was shown to be well tolerated where it remained at the local injection site for up to 1.5 months [46]. OncoGel is a hydrogel that is based on a thermosensitive polymer. This hydrogel is comprised of PLGA and PEG copolymer arranged as PLGA-PEG-PGLA that undergoes thermal gelation (sol-gel transition) at physiological temperature of the body 37ºC [46, 47].

A pH-sensitive polymeric micellar system for the concomitant delivery of paclitaxel and rapamycin with different dosing regimens were prepared and evaluated [48]. Both drugs were covalently linked to a poly (ethylene glycol)-block-poly (β-benzyl l-aspartate) via a pH-sensitive linker. The developed polymeric micelles released both drugs preferentially at pH 5.5 (endosomal/lysosomal pH). The developed hybrid polymeric micelles have been shown to exert synergistic antiangiogenic and apoptotic

effects, that would provide a targeted therapy to tumor cells or the tumor microenvironment for the potential treatment of ovarian cancer [49].

4.2 Diabetes mellitus

Diabetes is a chronic endocrine and metabolic disorder that affects approximately half a billion people worldwide. This figure is projected to increase to 700 million by 2045 [50]. Diabetes can be classified into three categories: type 1 diabetes mellitus, type 2 diabetes mellitus and gestational diabetes with type 2 diabetes mellitus being the most prevalent form. Uncontrolled diabetes can lead to various complications such as retinopathy, nephropathy and neuropathy. Cornerstone of preventing these complications is the tight control of blood glucose levels with lifestyle modifications and anti-diabetic medications such as insulin, insulin analogues and non-insulin oral hypoglycemic drugs such as metformin and gliclazide. Many formulations of insulin and other antidiabetic medications have been developed to enhance patient adherence to medication to optimize therapeutic outcomes [51].

Currently available insulin formulations include insulin analogues with modification of insulin structure to provide variable pharmacokinetics of insulin, such as long acting insulin glargine and short acting insulin aspart [51]. Research now focusses on novel modes of administering insulin to avoid the invasive nature of current insulin injections and enhance patient adherence. These include microneedle patches [52] and ingestible self-orienting millimeter scale applicators [53]. Of growing interest are glucose-responsive systems that release insulin in response to elevated plasma glucose concentrations. Such systems abolish the need for frequent glucose monitoring and dose adjustment by patients. Yu et al [14] developed a glucose-responsive microneedle (GR-MN) patch with the use of phenylboronic acid as the glucose sensitizing element. This patch was evaluated *in vivo* using an Streptozotocin (STZ)-induced diabetic mouse

model and an Streptozotocin-induced diabetic model. The authors demonstrated that this GR-MN patch is superior to non-responsive crosslinked microneedle patch of insulin, as it inhibits the increase in plasma glucose levels after an oral glucose load (glucose tolerance test). This GR-MN patch was shown to regulate plasma glucose levels for over 20 hours and the patches were able to maintain the bioactivity of incorporated insulin for over 8 weeks at room temperature[14]. Similarly, Zhang et al [27] demonstrated the regulation of plasma glucose levels with a GR-MN patch for up to 48 hours using a gold nanocarrier system to enhance drug loading percentage [54]. These studies demonstrate the translational nature of glucose responsive microneedle patches that could transform the management of diabetes .

Besides, implants and patches play a key role in managing complications of diabetes. Diabetic macular edema is the most common form of diabetic retinopathy that leads to irreversible vision loss. The progression of this condition is reduced by therapeutics such as Anti-VEGF agents and steroids. Iluvien® (fluocinolone acetonide) is a non-biodegradable intravitreal implant used to manage diabetic macular edema and releases the incorporated steroid over a period of up to 3 years.

Neuropathy, peripheral vascular disease, and other metabolic abnormalities of diabetes lead to impaired wound healing. Therefore, management of diabetic wounds remain challenging and require multidisciplinary approaches. Current treatments for diabetic wounds include wound patches, oxygen therapy, gene therapy and stem cell therapy [55]. Recent research focuses on the development of wound patches that can deliver growth factors to enhance wound healing. Augustine et al [56] evaluated the *in vitro* and *in vivo* efficacy of a poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV), gelatin-methacryloyl (GelMA) polymeric patch in delivering epidermal growth factor (EGF). The authors utilized electrospinning technology to create a mesh of PHBV and

the hybrid patch was developed on the wound by crosslinking GelMA with UV radiation. Higher rate of wound healing was reported for patches that incorporated EGF in comparison to patches without the growth factor [56]. These findings indicate the use of patch technology to provide sustained release of therapeutics for the management of diabetic wounds. However, further investigations are needed to elucidate the clinical significance of such therapies .

4.3 Brain diseases

The most common diseases affecting the brain include Alzheimer's, dementia, brain cancer, epilepsy, depression, psychosis or mental disorders and Parkinson's diseases. Brain diseases are essentially chronic disorders that usually require long-term/life-long management and treatment [57]. Lack of clear understanding of specific pharmacological sites to target and extend, drug delivery to the brain is not a trivial task due to the formidable nature of the blood brain barrier (BBB). Only small drug molecules with a relatively high lipophilicity and a molecular weight of less than 400 Da can freely cross the BBB. Epilepsy is a common central nervous system (CNS) disease affecting more than 60 million people worldwide; almost 30% of cases are not adequately treated; albeit various antiepileptic pharmaceuticals being available [58].

The complex criteria for effective drug delivery to the brain from the systemic circulation has been reported to hamper 95% of drugs under investigation of being successfully developed to a viable medicine [59]. This necessitates the search for new technologies such as CNS drug implants to bypass the BBB and effectively target the brain. The idea of implanting drug-loaded polymeric systems intracranially for treating brain diseases is an appealing proposition, although not devoid of controversy [60]. A successful example is the Gliadel® wafer (7.7 mg carmustine implant) which was approved by the FDA in 1996. This drug delivery system can be surgically implanted

during brain surgeries to provide localized delivery of carmustine to the brain. Gliadel® wafer has a diameter of 14.5 mm and thickness of 1 mm. It is based on polifeprosan 20, a biodegradable copolymer used to control the release of carmustine. The carmustine implant provides controlled release of the anti-tumor carmustine indicated as an adjuvant to surgery and radiation therapy for recurrent glioblastoma multiforme [61]. A dose of up to 8 wafers (a total of 61.6 mg carmustine) can be implanted per treated area after surgical removal of the tumor.

Another concept for brain implantable systems includes programmed implantable pumps. Such a system is composed of an implantable pump powered with batteries, an implantable catheter, reservoir fill accessories, and a remote controlled release system for the delivery of sodium valproate [58] and opioids analgesics (e.g. morphine) to the cerebrospinal fluid [62]. These implantable devices are programmable and can benefit patients with chronic illnesses; therefore, both the dose and delivery rates can be adjusted as response to disease conditions. For example, implanted pump provides insulin delivery through subcutaneous route as response to glucose levels. This pump has been able to eliminate repeated daily insulin injections for type 1 diabetes for 24 hours [63].

Alzheimer's and Parkinson's diseases are common age-related neurodegenerative diseases leading to progressive loss of cognitive and motor functions, respectively [64]. Dementia (memory loss) is the main problem with Alzheimer's disease; however it can be a common feature of Parkinson's disease [65, 66]. The total number of people with dementia worldwide is expected to rise to 115.4 million in 2050 [67]. Dementia affects 1 in 20 persons after the age of 80 [67]. In 2010, an estimate of the total global social costs of dementia was US$ 604 billion. It is estimated that most European countries spend around 1 % of their gross domestic product (GDP) on dementia, rendering

dementia a public health priority [66, 67]. Alzheimer's and Parkinson's diseases progress very slowly over a life-long period. For those patients, premature discontinuation of treatment leading to poor adherence to treatment is common.

Memantine is a blocker to N-methyl-d-aspartate (NMDA) receptors that is a commonly used for treatment of moderate to severe symptoms of dementia. The extended-release form of memantine (Namenda® XR) gained US and EU market approvals in the past decade. Namenda® XR 7 mg tablet taken once daily and gradually increased up to 28 mg has demonstrated statistically significant benefits in improving cognition and clinical status [68]. Memantine transdermal patch to be applied once every seven days has been developed by Corium International and is currently in Phase I clinical trials in Australia.

Rivastigmine is a cholinesterase inhibitor used for the treatment of mild to moderate Alzheimer's and Parkinson's diseases. Transdermal patches commercially known as Exelon® are available in three strengths 4.6, 9.5 and 13.3 mg/24 hours (5 cm^2). Rivastigmine patches help bypass first-pass metabolism by cholinesterase in the gut; therefore, transdermal patches show prolonged and non-erratic bioavailability. For example, a rivastigmine patch (4.6 mg/24 hours) can be equivalent to a 6 mg/day capsule [69].

Furthermore, the long-acting depot injection of the antipsychotic drug risperidone has been shown to be superior over conventional oral risperidone administration in terms of enhanced patients adherence/compliance, side effects profiles and social life ratings [70]. The long acting depot injection has been shown to be an effective LADD for treatment of schizophrenia [71].

4.4 Eye diseases

The eye is the second most complex organ after the brain; the eye endows the human with the one of the most important senses which is sight. The human eye is dramatically affected by age. It undergoes inevitable age-related changes leading to diseases/conditions that eventually impair the human sight [72]. For simplicity, the eye can be divided anatomically into two segments: anterior part (including the ocular surface) and posterior segment. Amongst, the main chronic and age-related diseases affecting the ocular surface and anterior segment are keratopathy [73], age-related cataract [74] , anterior uveitis and glaucoma [36]. Age-related diseases affecting the posterior segment of the eye include retinopathy and age-related macular degeneration (AMD) [75]. According The World health Organization (WHO), there is an estimate of at least 2.2 billion people with disease-related sight impairment with almost half of those (1 billion people) in need of an intervention (most notably cataract surgery) and/or treatment to prevent an avoidable blindness [76]. The majority of those people are elderly (> 50 years) [77]. Amidst diseases that causes avoidable blindness, there are five on the WHO priority list including cataract, corneal opacity, glaucoma, AMD and diabetic retinopathy and account for 47%, 20%, 12% and 10% of sight impairment and blindness worldwide, respectively [76, 77]. With the exception of cataract and corneal opacity, there are pharmacological agents and drugs that can treat the other diseases. Cataract and corneal opacity so far are treated surgically by replacing the cataractous lens with an intraocular lens and keratoplasty (corneal transplantation), respectively.

LADDS could provide modalities with improved efficacy and better patient adherence [78]. For example, topical long-acting inserts, contact lenses, punctal plugs (intracanalicular inserts) and ocular films have been suggested for potential treatment of glaucoma, post-operative ocular inflammation and keratopathy in order to provide

long acting delivery systems with better efficacy and less frequent administration, compared to conventional eye drops [79].

Ocular inserts for prolonged intra-ocular delivery of ocular hypotensive drugs were marketed in the early 1970s [80, 81].

Ocusert® (Pilo-20 and Pilo-40) are non-biodegradable ocular inserts loaded with pilocarpine that provided constant pilocarpine release onto the surface of the eye for 7 days. However, Ocusert® is no longer commercially available.

Lacrisert® is a biodegradable ocular insert comprising HPMC as a lubricant for treatment of dry eye. It is administered as a single daily dose [82]. Lacrisert lends itself as preservative free alternative for repeated administration of artificial tears eye drops and is used for treatment of chronic moderate to severe forms of dry eye diseases.

Limitations of ocular insert (both non-erodible and erodible inserts) are confounded by the fact that a solid device/object is physically inserted into the a highly sensitive area of the conjunctival sac resulting in eye discomfort, interfering with blinking, incurring a foreign body sensation, and leading to inadvertent expulsion of the insert during sleep [81, 83]. These drawbacks have been minimized or resolved by adopting two different strategies:

changing the design and insertion site of the insert from the conjunctival sac to a wider ring-shaped insert to be placed on the ocular surface. Bimatoprost insert (BIM ring) was made as a silicone-O-ring-like insert of 24 to 29 mm diameter loaded with 13 mg of bimatoprost mixed into a silicone matrix over an inner polypropylene ring. This ocular ring can provide up to 6 months of IOP reduction. Further, a double-blind randomized multicenter Phase II clinical trial has been conducted to compare the long-term tolerability and safety of BIM ring versus

Timolol (0.5%) eye drops administered twice daily for 13 months. Results are encouraging where the majority (90%) of patients reported that bimatoprost ring was comfortable [84].

modified solid ocular inserts have been made using polymeric films with more favorable dimension, sufficient malleability to adjust to the curvature of the eye globe along with mucoadhesion characteristic that allows better adherence to the conjunctival surface. These ocular films are solid before insertion and quickly transform into gel on the surface of the eye [83, 85].

Dextenza® is an unconventional insert/plug containing 0.4 mg dexamethasone that intended for intracanalicular insertion (Figure 3). This corticosteroid insert was developed by Ocular Therapeutix, Inc; and has a 3 mm cylindrical shape. Dextenza® is indicated for treatment of post-surgical inflammation and pain after cataract surgeries. It has been proposed as a more practical alternative for the repeated administration of steroid eye drops needed post cataract surgery [86]. Dextenza® punctual plugs offers slow release of dexamethasone for a month; it can be visualized when illuminated by a blue light source [87]. At the end of treatment period Dextenza® undergoes biodegradability and drains through the nasolacrimal duct. Dextenza® is composed of a polyethylene glycol-based hydrogel conjugated with fluorescein. Saline irrigation or manual expression can be performed to remove the insert and terminate the therapy if necessary.

Contact lenses loaded with ocular hypotensive drugs have been investigated extensively [82, 88, 89]. Contact lenses composed of the hydrophilic polymer poly-2-hydroxy ethyl methacrylate (p HEMAP) were prepared and soaked in drug solution for 1 to 24 hours.

The antibiotics ciprofloxacin, gentamycin, ofloxacin and tobramycin were loaded into soft contact lenses by presoaking [88]. Serious safety concerns are associated with therapeutic contact lenses that include corneal opacity, corneal neovascularization and corneal ulcers [82].

Furthermore, contact lenses have been nano-coated with timolol maleate using an electrohydrodynamic (EHD) engineering process[90]. The coated lenses exhibited a sustained drug release effect with no sign of corneal irritation. This novel method can enhance drug ocular residence time, reduce drug nasolacrimal drainage, and therefore improve its ocular bioavailability. Mehta et al., used permeation enhancers with electrospun coating materials of contact lenses, this has improved timolol maleate's permeation across excised bovine eyes[91, 92].

Implantable drug delivery systems injected through the *pars plana* into the eye have been investigated for long-acting treatment of various diseases of the posterior segment of the eye such as non-infectious uveitis, macular edema and age-related macular degeneration [36]. These systems may offer a better patient adherence by reducing the numbers of intravitreal injections which are usually needed on monthly basis, especially during the first year of diagnosis.

Ozurdex® is biodegradable dexamethasone (0.7 mg) implant for treatment of macular edema [93]. Ozurdex® is made of poly(lactic-co-glycolic) acid (PLGA) adopting the Novadur® solid dosage form technology. Ozurdex® is a rod-shaped implant and comes preloaded into a single use applicator; to be injected under aseptic conditions; and provides extended release of dexamethasone for over 6 months. The insert is completely biodegradable [94]. Retisert® is non-biodegradable fluocinolone acetonide (0.59 mg) implant surrounded by a polyvinyl acetate/silicone thin layer fixed

onto a structural base [95]. Retisert® has been reported to reduce recurrence rates of non-infectious uveitis with acceptable tolerability and reduced side effects [96].

Another non-bioerodible corticosteroid delivery systems is commercially known as Iluvien® implant which contains fluocinolone acetonide (0.19 mg) for the treatment of diabetic macular edema. Iluvien® implant is manufactured with a dimension of 3.5 mm in length and 0.37 mm in diameter containing non-bioerodible polyimide tube, polyvinyl alcohol (PVA) and silicone adhesive. Iluvien® releases its steroid cargo from one permeable (PVA membrane) end with the other end being sealed with an impermeable silicone cap. The external wall is made of non-bioredobile polyimide tube that releases the drug from one orifice and it comes in a prefilled syringe and the injectable applicator is a 25-gauge needle and it is injected in clinic or day surgery. Unlike Retisert®, Iluvien® requires no surgical incision for intravitreal administration and it provides an initial drug release of 0.25 μg/day for up to 36 months of treatment per a single dose of Iluvien® [97]. It is used for treatment of diabetic macular edema. It is obvious that both Ozurdex® and Iluvien® implants have the convenience of being administered through syringe needles and they are relatively less invasive and do not cause excessive injuries to ocular tissues compared to that incurred through administration of the non-biodegradable Retisert® implant. Drug content, product name, polymers used, therapeutic indications and duration of action of Ozurdex®, Retisert® and Iluvien® are summarized in Table 1. Figure 3 reveals a cross section of the human eye with the inserting / injection positions of Ozurdex®, Dextenza, Retisert® and Iluvien®

4.5 Contraception and hormonal replacement therapy

According to WHO estimates, there are around 2 billion women worldwide at fertile age (15-49 years) require one of contraceptive methods. There is a variety of

contraceptive methods including contraceptive pills, intra-uterine devices (IUDs), implants, vaginal rings, patches and injectables. The IUDs and implant are among the most effective reversible contraceptive methods available. Contraceptive methods are categorized by their effectiveness as follows: very effective (< 1 pregnancies per 100 women), effective (1 to 9 pregnancies per 100 women), moderately effective (10 to 19 pregnancies per 100 women), less effective (≥ 20 pregnancies per 100 women) [98].

Progstasert® is a contraceptive intrauterine implantable device that was developed by ALZA Corporation in the late 1970s. This implantable device can control birth by dual functions; it benefits from the T-shaped device (mechanical contraceptive) and small ‘’mini’’ doses of progesterone that continuously release into the uterus and endometrium for up to 1 year [99]. This system was fabricated using poly ethyl vinyl acetate.

Norplant® is a contraceptive implant of levonorgestrel that is administered subcutaneously and can provide birth control for up to 6 months [100]. This implant is composed of 6 silicone rubber tubes (crosslinked polydimethylsiloxane) [28].

Hormone replacement therapy (HRT) as the name suggests it replaces sex hormones at lower levels. For example, HRT is a treatment for relieving symptoms of the menopause such as hot flushes, night sweats, mood swings and vaginal dryness.

Testopel® is an implant to help restore testosterone levels in elderly men and children with delayed puberty due to hypogonadism. Testopel® provides sustained release of testosterone for up to 3-4 months, compared to the monthly oil injection (depot) formulation of testosterone. Testopel® 75mg testosterone implant is a cylindrically-shaped pellet 3.2 mm diameter x 9 mm length that is implanted subcutaneously [101].

Levonorgestrel implant has been fabricated from poly (epsilon-caprolactone) and Pluronic F68. The implant provided extended release rate of the contraceptive drug for 2 years in rats without observed toxicity [102].

Menostar® 1 mg estradiol transdermal patch is designed and fabricated with a surface area of 3.25 cm^2 to provide a low daily dose of estradiol (14 µg/day) for 7 days to alleviate the majority of menopausal symptoms caused by the decline of estrogen production, or lack of production in patients undergone ovariectomy [103].

5 Preparation of inserts/implants/wafers/patches: research and development scale techniques

5.1 Solvent-casting

Solvent casting is a simple and scalable method for preparation of polymeric films, inserts and wafers. The method is outlined in Figure 4; the polymeric solutions can be casted and processed under various conditions (ambient, heat or after freeze drying) depending on the nature and chemical stability of the drug. The diameter, therapeutic dose and subsequently the size of dosage form can be tailored to suit different clinical applications.

This method has been utilized for generation of ophthalmic films and inserts for oxidizable drugs such as naltrexone and curcumin in an attempt to enhance chemical stability and enhance ocular residence time [2, 85]. Hydroxy propyl methyl cellulose and hydroxy ethyl cellulose-based inserts containing Eudragit L 100-based nanoparticles loaded with azithromycin were prepared using the solvent casting method in an acrylic mold at 60^oC [104].

Etoposide silk wafers were prepared by the solvent casting technique. Aliquots (100 µl) of silk solutions containing 1mg/ml etoposide were placed in each well of 96-well

plate, dried overnight and lyophilized. The lyophilizate foams were compressed into wafers. These etoposide wafers were suggested for treatment of neuroblastoma.[105]. The results demonstrated that 50% of the cells were killed using etoposide (1 μg/ml) and the wafer showed marked cytotoxicity for up to three weeks when compared to untreated cells.

5.2 Microneedles

MNs (MNs) are devices that can be produced in an array, usually with an area of less than 1 cm^2, and comprised of hundreds of micro size needles with varying lengths, fabricated from diverse materials and by various methods to deliver (mainly via the transdermal route) therapeutics including biopharmaceuticals. Upon application, these devices create micro size pores at the application site that enable the drug to easily pass through a biological membrane. In particular, MNs can overcome many of the limitations related to the transdermal drug delivery including needle phobia, needle injuries, the requirement of trained staff to deliver injections and most importantly the permeability barrier where MNs can bypass the stratum corneum. In addition, MNs can be used to deliver macromolecules and biologics which can be translated to promising future and market expansion for the pharma industry.

MNs can be divided into different types such as solid, drug-coated, dissolving, and hollow MNs [106]. The type of material used in MNs depend on the clinical application and the design. Commonly used materials include silicone, stainless steel, glass and polymers such as hyaluronic acid, hydroxypropyl methylcellulose, carboxymethyl cellulose and poly(lactic-co-glycolic) acid [107].

Currently, various microfabrication techniques have been explored to optimize the manufacturing of these devices. The method of choice depends on number of factors

such as the clinical application, drug of interest, material used and target site. The simplest technique used is the solvent casting method. However, this method lacks the accuracy and reproducibility required for commercial manufacturing. Other commonly used techniques include laser ablation, photolithography and 3D printing [107-110]

Following manufacturing, MNs are characterized to determine physical appearance, strength and performance. Scanning electron microscopy (SEM) is often used to determine the MN geometry. This technique enables the researcher to determine the needle dimension, surface morphology and MN distribution. It is important to produce MNs of uniform geometry and sharpness to achieve a good clinical response with these devices [111]. It has been reported the obelisk geometry is important for efficient insertion of solid MNs whereas pyramidal geometry is preferred for hollow MNs. Fluorescent tagged molecules are often used to determine the incorporation of drugs in these devices. Fluorescent microscopy or confocal microscopy can be used to determine the distribution of the fluorescent tagged molecules. Such information is required to determine the reproducibility of fabrication methods [112]. The axial compression test or the needle failure test are commonly used to determine the strength of microneedles. This is an important parameter to assess, as it indicates the ability of the MNs to penetrate the biological membrane and deliver the therapeutic agent of choice [113]. Following a compression test, the geometry of the MNs is examined to determine the deformations [112].

Performance studies specific to MNs include insertion studies on excised animal tissue (depending on clinical application), permeation studies using Franz diffusion cells and *in vivo* studies to determine the safety and efficacy of the MN device. The

reviews by Lutton et al (2015) and Sabri et al (2020) provide an overview of these techniques used to characterize the MN devices[112, 114] .

Hollow MNs as devices was first explored for different applications including the delivery of drugs into cells, local regions of tissue, and across the skin [115]. The interest has continued and MNs have shown promising results for a wide range of applications such as cancer drugs [112, 116], vaccine delivery [117], diagnosis [118-120] dentistry related applications [121]; long acting release and drug delivery [122] and for non-transdermal drug delivery [123, 124]..

Park et al., was the first to investigate the use of MNs for controlled-release drug delivery [125]. In this study, both calcein and bovine serum albumin were incorporated within biodegradable PLGA microneedle or within carboxymethylcellulose (CMC) or poly-L-lactide microparticles, which were then encapsulated within the needle matrix. Sustained release of sulforhodamine from CMC microneedle patches inserted into human cadaver skin with an initial lag time of a few hours, followed by steady release for several days was reported [126]. Similar approach was adopted in fabricating MNs for the transcutaneous delivery of a subunit vaccine formulation in a controlled-release manner [127]. The new approach provided similar initial immunogenicity compared with traditional vaccine immunization when the vaccine was encapsulated into composite dissolving MNs which was applied on a mice model for 5 minutes resulting in rapid delivery of PLGA microparticles to form cutaneous depots that can promote sustained release over few months [127]. Many strategies including altering drug binding affinity, polymer type and polymer hydration were applied to manipulate drug release in MNs. Chen et al., studied the effect of molecular weight of polymers used to fabricate MNs in controlling the rate of drug delivery both in *in vitro* and *in vivo* using

a mice model [128]. The use of genipin as a crosslinking agent has been shown to be effective in controlling the release of insulin from biodegradable MNs [129] .

The use of biodegradable and swellable polymers for promoting prolonged drug release from MNs has been reported. In particular, the review by Chen et al., [122] summarized the use of such polymers for the fabrication of long-acting MNs with different drug release times ranging from 48 hours to 16 weeks. Chen et al (2020) compared the release time of drugs incorporated in different fabricated MNs with different biodegradable and swellable polymers (Figure 5). An Influenza vaccine MN loaded with the biodegradable polymer chitosan (CS) achieved the slowest release rate where the MN induced immune-enhancing effect was obvious 4 week after the vaccination and lasted for at least 16 weeks.

Using biodegradable polymers in the manufacture of MNs have some limitations in terms of stability and mechanical strength. Bioceramic MNs provided controlled release of clonidine HCl. Those MNs penetrated the stratum corneum when studied using a vertical diffusion cell and an ex vivo porcine skin [130]. Optical coherence tomography was used to monitor dissolution of the MNs and drug release in real time, *in vivo* and in situ [131]. Yang et al., used Eudragit RL100 as a coating material for swellable MNs [132]. Their work demonstrated a dose-dependent plasma concentration; the controlled release of 2.1 mg dose of the drug granisetron base was observed in plasma for 144 hours [132] .

For the treatment of retinal diseases, repeated eye injections are usually required and therefore, the use of MNs as a less invasive system for ocular drug delivery remains of interest. Mahadevan et al., built on the use of MNs for the intraocular delivery of sulforhodamine and micro/nanoparticles into human cadaver sclera [133]. They reported on embedding hollow glass MNs within a soft and flexible poly (dimethyl

siloxane) (PDMS) substrate, for drug targeting to the intraocular tissues using a more friendly approach when compared with conventional hypodermic needles [133]. The release of a selected dye from the novel device was tested using bovine vitreous (ex vivo), where the dye was visually evident in the vitreous after 8 hours of insertion [133]. One of the challenges related to securing eye patches is their poor adhesion on the ocular surface. A new design of hydrogel MNs which were developed with interlocking features after swelling to achieve self-adhesion have been reported [134] .

Despite the large interest in the application of MNs, most of their current commercial uses are for cosmetic and skin care purposes. This can be explained by the many challenges and disadvantages related to this technology including the possible irritation and microbial contamination with its delivery [135], the challenges related to delivering large hydrophilic molecules through the skin and the biodegradability of the polymers used in MNs[136]. The challenges also include the lack of uniformity and Quality requirements by the regulatory bodies[137]

In the last decade different types of MNs devices have emerged and are currently under advanced stages of clinical trials [138]. Commercially available MN devices include Bullfrog® Micro-Infusion Device® (Mercator MedSystems, Inc.), Micronjet600® (Nanopass technologies), Microstructure transdermal system® (Kindeva Drug Delivery), SCS Microinjector® (Clearside Biomedical), SkinJect® (SkinJect Inc.) and Zosano patch® (Zosano Pharma Corporation). Table 2 provides an update on the clinical trials of MN devices.

5.3 Three-dimensional (3D) Printing

Three-dimensional printing (3DP) technology has emerged as a promising technology to improve patient medication adherence and provide an option for medicine personalisation[139].

3DP technology, is a computer-aided design (CAD), layer by layer material deposition process, which in the recent years, has been explored and implemented in different fields of biomedical research as well as developing novel drug delivery systems and tissue/organs engineering for regenerative medicine or in vitro disease modelling applications [141 ,140]. In general, the 3D CAD design of the object is transformed to a file format readable stereolithography (SLA) machine to print the materials in a solid or porous geometry construction [142].

For the first time, 3D printing method of materials fabrication was originated from a stereo-lithography process in the late 1980s and gradually utilized in versatile industrial prototyping such as aerospace, motor vehicles, industrial machines, consumer products, electronics, military, medical, dental, applications etc [143].

More recently, the applications of 3D printing have expanded to the pharmaceutical industry where it is used to manufacture novel drug delivery systems in pharmaceutical products as well as drug loaded, implants [144].

Pharmaceutical and medical applications of 3D printing have rendered this technology of specific interest for personalized dosage forms, prosthesis and implantable medical devices [145]. Precise control over the material's spatial dispersion in different shape, have enabled fabrication of versatile types of pharmaceutical dosage forms with different drug molecule combinations to deliver drugs to the targeted site with controllable release profile based on the patient's need [146].

To optimize the characteristics of 3D printed pharmaceutical products, various 3D printing techniques have been reported; they include Material Extrusion, Material Jetting, Binder Deposition, Binder Jetting, Selective Laser Sintering, and Stereolithography[147] . Figure 6 outlines the 3D printing technologies that are of pharmaceutical relevance and will be discussed below.

5.3.1 Binder Deposition

Material deposition on a powder bed which is known as (Binder Deposition) has been implemented as the primary approach of pharmaceutical products 3D printing. An injecting printer, sprays small droplets of drug formulations at precise speed, motion, and size onto a powder bed. The inkjet contains a binder or drug/binder mixture and the powder bed may contain the active ingredient (API) with additional excipients. Alternatively, APIs can be jetted onto powder bed as solutions or nanoparticulate suspensions. In this method of object fabrication, unbound powder serves as the supportive material for the 3D printed object to maintain free-standing or porous structures [141, 148].

In a study reported Yu et al., a novel drug delivery device for providing linear release profiles was fabricated by powder bed deposition strategy as sustained release implants. [149].

Chang et.al, have reported on indomethacin 3D printed tablet like dosage form, fabricated via binder-jet 3D printing. They investigated the effectiveness of different pharmaceutical-grade feedstock materials on creating tablet-like dosage forms. The physical properties of fabricated tablets from different pharmaceutical-grade powder and liquid binder precursors were investigated optimized [150].

5.3.2 Material Jetting

To print jetting materials the presence of powder bed is not always necessary; molten polymers, waxes, and UV-curable material (resins, solution and suspensions) can be printed free from supportive solidifying structures [151]. Printing with high resolution has been reported as the major advantage of a non-powder-bed 3D printing approach compared to binder deposition and other approaches. In this approach, the diameter of inkjet expelled droplets is smaller than 100 μm. The reduced droplet size is a consequence of surface wetting, solvent evaporation, or shrinkage of material during jetting / printing process. These practical properties, has enabled researchers to print microparticles for drug delivery applications [152].

Lee et al. reported on a piezoelectric inkjet printing system that was used for arbitrary, well-defined, and controlled-shape 3D printing of drug loaded microparticles for drug delivery applications. For this purpose, different geometries of paclitaxel (PTX)- loaded PLGA microparticles, including spheres, grids, honeycombs, and rings, were printed via piezoelectric inkjet printing to study the effect of geometry on the drug release [153].

5.3.3 Extrusion Printing

Amongst the various 3D printing approaches, the extrusion-based 3D fabrication methods, have been widely adopted by the industry. The high versatility of this method has captured the growing attention of pharmaceutical product manufacturers [154]. Fused deposition modeling™ (FDM®), the most prominent extrusion technique, is the trademarked of fused filament fabrication, where solid filaments of polymeric materials are printed by a robotically- actuated heated nozzle assembly [155].

Stewart et al., have employed hot- melt extrusion 3D printing for manufacturing hollow, polycaprolactone (PCL) coated, PLA-PVA based biodegradable, subcutaneous implant

for prolonged delivery of drugs. The mechanical properties and in-vitro drug release profile form manufactured implants validated the promising potential of extrusion-based 3D printing technique for localized treatment of chronic diseases by prolonged delivery of chemotherapy agents, antibiotics or localized anaesthetics drugs [156].

5.3.4 Semisolid extrusion technique

Unlike extrusion printing where a heated nozzle prints the fed filament, semisolid extrusion expands the printing capacity of an extrusion-based printing systems to a wider range of temperature and material [157]. A wide range of material ranging from small molecules all the way to living cells are printed using pneumatic/mechanical extrusion forces instead of a heated nozzle [158]. This feature has allowed the evolution of a new era of printing known as ‘’bioprinting’’ which has been particularly promising for tissue engineering and regenerative medicine [159].

Liu et al., implemented semisolid 3D printing method to manufacture PEGylated liposomal doxorubicin loaded hydrogel patches for local cancer treatment strategies. UV cured fish gelatin methacryloyl (F-GelMA) derived from cold fish gelatin, was used as the main component of the printer ink. Carboxymethyl cellulose sodium (CMC), was added to the ink, in order to improve the viscosity of (F-GelMA). PEGylated liposomal doxorubicin (DOX) was incorporated into the hydrogel ink and three types of 3D-designed patches (cylinder, torus, gridlines) were printed. In vitro release behaviour of these three different patches, was controlled by implant architecture, intensity and the exposure time of UV-LED. These implants could be used for treating cancer or in the site of tumour after surgical removal [160].

Sjöholm et al., have compared the function of three different semi-solid extrusion (SSE) technique for extemporaneous veterinary applications of Prednisolone containing orodispersible films. In vitro dissolution studies for all of the fabricated dosage forms followed non-Fickian diffusion mechanism. The results of this studies indicated the potential of SSE technique of 3D objects manufacturing of LADDS specifically for veterinary purposes [161].

5.3.5 Stereolithography (Photopolymerization) (SLA)

Stereolithography (SLA), also known as photopolymerization, is another 3D printing approach which is gaining increasing attention specifically in the field of biomedical engineering. Here, the prototype is created through exposing a responsive liquid resin to ultraviolet light or another high-energy light source for inducing polymerization reactions [162]. Although, photopolymerization has been considered the fastest and highest resolution 3D printing method, toxicity issues associated with photopolymerizable raw materials and uncured residual resin during printing have limited its acceptability and applicability for manufacturing of drug delivery systems. In recent years, the applications of photopolymerizable 3D printed drug loaded hydrogels have been reported [163]. There are numerous studies that have used non-toxic photo-initiators for fabricating 3D-printed drug-loaded hydrogels. Due to the effective crosslinking effect of riboflavin on dextran-methacrylate hydrogels, riboflavin (vitamin B2) was used as a non-toxic photo-initiator for fabricating controlled ibuprofen release stereolithography approach 3D-printed Poly(Ethylene Glycol) DiAcrylate (PEGDA) hydrogel [164] .

5.3.6 Selective Laser Sintering (SLS)

Similar to binding jetting where objects are printed from a powder bed, in selective laser sintering (SLS), a high-power laser beam is used, instead of a binder, to fuse the

powder particles. High fabrication speed is amongst the main advantages of SLS technology. SLS methods have been of interest for fabricating a wide array of dosage forms, with different geometries and release profiles ranging from orally-disintegrating, sustained releasing tablets to immediate release formulations.

Awad et al., reported on the potential of SLS 3D-printing to manufacture multiple-unit dosage forms with enhanced therapeutic benefits to the patients due to dosing flexibility compared to single unit dosage forms. Accordingly, paracetamol and ibuprofen loaded 3D printed ethyl cellulose/ Kollicoat based multicompartment matrix, termed *miniprintlets*, were fabricated using this approach to achieve both immediate and prolonged drug release patterns [165]. Kulinowski et al., reported of high dose-controlled release *printlets* of paracetamol using this technology [166].

5.3.7 Pressure-Assisted Microsyringe (PAM)

Low-temperature operating conditions have rendered Pressure-Assisted Microsyringe [167]FDM in the form of printing used, however, PAM allows a drug-loaded polymeric complex to be printed in low temperatures [168].

Welsh and her coworkers, employed thermoplastic, high pressure, droplet 3D deposition modelling (DDM) technique by a Free-former printer for developing LADD vaginal rings for long term releasing of Dapivirine (DPV). It was found that the bioavailability for poorly water-soluble DPV was increased by increasing the exposed surface area of the polyurethane ring through tailoring the in-fill density part of the ring, the DDM process [167].

5.3.8 Digital Light Processing (DLP)

Digital Light Processing (DLP) is similar to SLA 3D printing with one modification, where, instead of using a focused UV laser beam, a UV light from a

projector is used to cure each layer of the 3D printed object . Kadry et al. fabricated modified released oral tablets through this technology. Thus, a digital micromirror device was used to reflect and focus ultraviolet light on the surfaces of poly (ethylene glycol) diacrylate (PEGDA) and poly (ethylene glycol) dimethacrylate (PEGDMA) as photoreactive polymers for encapsulation of theophylline as a model drug. Release studies from this 3D printed drug eluting implants demonstrated that by altering the number of perforations in the tablets structure, the period of drug release can be modified[169] .

5.3.9 Embedded 3D Printing

Embedded 3D printing is a new and advanced form of 3D additive manufacturing in which a viscoelastic ink is extruded into a solidifying reservoir by means of a deposition nozzle at a predefined direction Rycerz et al. reported on fabricating a chewable oral dosage forms loaded with two drugs. Paracetamol and ibuprofen were used as the two model drugs; they were suspended in a locust gum solution and gelatin-based medium. This proof-of-concept study, offered an innovative approach for manufacturing personalized oral dosage forms with two APIs [170] .

3D printed drug-containing implants are promising for applications such as individualized drug delivery. Nevertheless, more research is needed to assess the performance of 3D-printed drug delivery implants before clinical trials testing commences[171].

5.3.10 Applications of 3D printing technology in development of LADDS:

In recent years, researchers have devised novel strategies to improve and enhance properties of drugs by encapsulating them in modified/ nanosized carriers to exclusively release these drug molecules to the site of action in a controlled manner [172]. To reach this goal, 3DP LADDS have been developed to deliver drug molecules for a long period

of time to the sites of action [173]. 3DP LADDS are promising for long term and local delivery of drugs with improved pharmacokinetics properties. In the following sections, the applications of conventional and 3DP LADDS in the treatment of selected chronic diseases will be discussed [174]. Table 3 summarises the technology and drugs used, polymers, clinical indications and duration of action of 3D printed LADDs

Human Immunodeficiency Virus (HIV) applications:

Acquired immunodeficiency syndrome (AIDS), is a viral based chronic disease caused by human immunodeficiency virus (HIV). Because of the unknown window of HIV virus activation period, substantial efforts have been made for providing strategies to allow the infected and at risk uninfected individuals to have a normal and longer life style [175]. Implementation of HIV controlling therapeutic approaches such as pre-exposure Prophylaxis and Anti-retroviral Therapy via long-acting drug releasing implants have been proposed as promising methods for this purpose. Tenofovir, tenofovir disoproxil fumarate and Cabotegravir are among the exclusive drugs used in combination with implants for controlling/prevention of HIV [176, 177].

Long term sustained drug release polymeric implants have received interest for manufacturing drug releasing implants for continues monitoring and treatment of the HIV disease [178, 179]. As sexual intercourse has been proposed as one of the leading ways of HIV transmission, intravaginal rings have been designed and fabricated for localized, topical delivery of therapeutic molecules to vaginal tissue [180]. Meanwhile, Numerous studies have reported on the potential of 3DP techniques in developing drug-loaded LADDS for localized drug delivery applications [178].

Ugaonkar et al., reported on a novel, multipurpose, core–matrix, intravaginal ring fabricated via FDM 3D printing for reducing the risk of HIV-1, HSV-2, HPV infection

and preventing unintended pregnancy. For this purpose, MIV-150 (for targeting HIV-1), zinc acetate (ZA; for targeting HIV-1 and HSV-2), carrageenan (CG) as anti-HPV and HSV-2), and levonorgestrel (LNG; for decreasing the risk of unintended pregnancy) were loaded in the core-matrix structure of the 3D printed vaginal ring. In vitro and in vivo studies for the drug release behavior of the multifunctional manufactured vaginal ring prototype demonstrated a continuous in vitro release of encapsulated APIs for 94 days and up to 28 days in macaques environment, which shown a proof-of-concept for a multipurpose virginal LADDs [181].

Antibacterial and antifungal applications:

Vaginitis or vaginal infections by pathogens yeasts (bacteria, and fungi) is the most prevalent type of gynecological infections [182]. In conventional treatment approaches, various drug formulations including (creams, gels, tablets) containing antibacterial and antifungal drug are applied to the infected site for multiple days [183, 184]. Tiboni et al., reported on flexible, biocompatible 3D printed Clotrimazole loaded thermoplastic polyurethanes based vaginal rings for the treatment of recurrent vaginal candidiasis. FDM method was implemented for fabricating thermoplastic materials in to desired 3D structure [185, 186].

Contraceptive applications:

Contraceptive implants are flexible polymeric drug releasing devices that have been employed for long term release of drugs for controlling pregnancy and other diseases related to the female reproductive system [187].

All the marketed contraceptive implants are produced with fixed and inflexible shapes; 3D printing technology has solved this limitation by providing a unique opportunity to manufacture patient specific implants [188].

Vaginal rings, suppositories, IUDs, subcutaneous inserts, and microneedle-based skin patches are among the LADDS which can be fabricated via 3DP technology for contraceptive applications [189].

Vaginal rings are types of flexible, polymeric based drug delivery devices which are locally employed for controlled releases HRT of menopause and hypogonadism [190]. Numerous studies have reported on 3DP technology for long-acting drug releasing vaginal rings [182]. Fu et al., developed a personalised 3D printed vaginal rings for increasing bioavailability of progesterone. FDM was implemented to print the prepared filaments into "O", "Y" or "M"- shaped rings. The 3D fabricated vaginal rings showed a long-term in vitro release of progesterone for more than 7 days with diffusion-controlled release behavior [191].

Tappa and his co-worker, proposed biodegradable polymers utilization in manufacturing contraceptive implants. For this purpose, Estrone, Estradiol and Estriol and Progesterone were coated with e PCL biodegradable pellets and printed in the shape of surgical meshes, subdermal rods, intrauterine devices and pessaries by using a FDM based 3D printer. The 3D printed implants demonstrated prolonged hormonal release over 7 days. These PCL implants could act as a form of personalised medicine [192].

Customization of contraceptives have been made possible through 3DP of customised long-acting implants for veterinary applications [161]. Long et al., engineered a projectile composed of polylactic acid (PLA) containing different doses of progesterone through combining FDM 3D printing and hot melt extrusion (HME).

In vitro release profile revealed the potential of the fabricated prototype to release the encapsulated drug over a five-month period [193].

Localized Cancer Therapy

Delivering chemotherapeutic drugs using systemic oral or intravenous routes is the main approach of cancer treatment [194]. However, disadvantages such as systemic side effect due to the need for high dosage of chemotherapeutic drugs is a limitation of the current conventional cancer chemotherapy approach [195]. 3DP technology allows the manufacturing patient specific, customisable medical implants/prosthesis. Numerous studies have demonstrated the potential of 3DP technology in fabrication LADDs for local delivery of chemotherapeutic drugs [196].

3DP drug-eluted implanted prosthesis was developed by Hao et al., to prevent tumor recurrence and metastasis after breast conserving surgery. FDM 3DP technique was used to fabricate polydimethysiloxane (PDMS) containing PLGA loaded paclitaxel (PTX) and doxorubicin (DOX) microspheres. The in vitro drug release and in vivo cytotoxicity effect of the fabricated prosthesis on a mouse model with local recurrence and metastasis of breast cancer model demonstrated that, this 3DP LADDS can provide a sustained local drug release profile for a period more than 3 weeks and potently suppressed cancer recurrence with reduced side effects [197].

Yang et al., have used Electrohydrodynamic jet (E-jet) 3DP technique in developing LADD implants to inhibit growth and metastasis of orthotopic breast cancer by long term delivery of 5-fluorouracil and NVP-BEZ235 from PLGA implant. Results indicated an effective long term (> 4 weeks) anti-tumour performance for the developed LADDS for combinational therapy of tumours [196].

Li et al., reported on a flexible, biodegradable drug-loaded 3DP scaffolds as localised LADDS for intracranial therapy of Glioblastoma Multiforme. FDM was employed for fabricating various geometry of curcumin-loaded PCL filaments. results suggest the therapeutic potential of drug loaded implants for controlling the recurrence of malignant cancers [198].

Orthopedic implant and prosthesis, have been widely used as an alternative for treatment of bone related disorders as well as knee replacement, and critical bone size defect as a result of cancer [199]. Wang et al., reported on biodegradable, controlled drug releasing implants as a personalized LADDS for local chemotherapy of osteosarcoma. Findings of this study revealed that this system can increase therapeutic efficiency of anticancer drugs by providing the required dosage of the anticancer drugs and release them in a prolonged manner for a period of 12 weeks at the tumour site [200].

Applications of 3DP LADDS in Cardiovascular Diseases (CVDs):

Bare metal stents (BMSs) and angioplasty balloons were implemented as one of the strategies for the treatment of atherosclerosis. Although BMSs showed a remarkable impact on the treatment of atherosclerosis, stent thrombosis and restenosis can obstruct the blood vessel and resulted in vessel closure recurrence [201, 202]. To overcome these limitations, various approaches including polymer-coated drug-eluting stents made of new metallic alloys such as cobalt-chromium and platinum-chromium alloys with higher radiopacity were developed. However, late-stent thrombosis and inflammatory reaction against the polymeric coating is a major drawback which needs to be addressed [203].

3DP biodegradable DDS with different drug release profile for various pathological conditions have been developed [173, 204, 205]. Park et al., reported on a sirolimus spray-coated 3D-printed PCL based stent fabricated using pressure assisted HME technique for the prevention of coronary thrombosis. Results demonstrated a sustained drug release profile for a period of 32 days [206].

Lee et al., reported on the developing of a personalised heparin-coated biodegradable poly lactide acid (PLA) based stent to prevent thrombosis. [207].

Applications of 3DP LADDS in wound healing

3DP personalised implants were investigated as a patient specific wound dressings to control prospective wound infection and enhance healing process [208, 209].

Hassan et al., have explored the utility of 3DP technology in manufacturing patient specific antibacterial wound dressings. HME technique was employed to incorporate antibacterial metal ions (such as zinc, copper and silver) into PCL filament and construct the 3D models of a wound in the area of nose and ear. Controlled release of antibacterial ions for period of 7 days at the wound site in addition to the enhancement of the wound healing process, demonstrated the potential of this concept for developing customized shape and size wound dressings [208].

Si et al., developed a 3D-bioprinted, double-crosslinked, hyaluronic-acid hydrogel wound dressing for controlled release of Nafcillin. This wound dressing was capable of releasing the encapsulated drug cargo up to 11 days [210].

Alizadehgiashi et al., have engineered a multifunctional, multicomponent 3D printed substrate for fabricating a customized wound dressing. Various therapeutic agents including small molecules, metal nanoparticles, and proteins were selectively integrated within the hydrogel base. The results of in vitro and in vivo studies demonstrated an

improvement in granulation tissue formation and differential levels of vascular density [211].

Other applications of 3DP LADDS in treatment of chronic diseases:

Inflammatory bowel diseases are considered as groups of chronic inflammatory disorders of the gastrointestinal tract (GIT) impacting millions of patients around the world [212].

Notwithstanding, wide range of oral based DDS were developed to deliver required drugs to the site of inflammation in GIT specifically in intestine, but, due to the harsh environment of GIT where only a fraction of drug molecules can reach to the targeted site, the therapeutic efficiency of oral administered drugs was drastically subsided. According to this substantial limitation of oral delivery route of drugs for diseases related to the GIT system, researchers have focused their research and studies to developed novel local DDS to enhance pharmaceutical properties of administered drugs [213].

Rectal delivery of drugs, has been proposed as an effective promising approach of local delivery of drug molecules to enhance therapeutic efficacy and maximizing drug bioavailability at the intended site of action. Suppositories are class of dosage forms that used by insertion into the body orifice (rectum) and release the containing drugs by dissolving or melting inside it [214, 215].

Recently, thanks to the tremendous advantages of 3DP technology, researchers have taken one step further in manufacturing personalized pharmaceutical products. In industry, design and fabricating complex molds by 3DP technology is turned to a common technique for manufacturing objects in high numbers. With the advent of 3DP technology in pharmaceutical science, researchers have implemented the potential of

3D printing mold fabrication techniques, for developing shell molds with constant geometry but patients specific drug formulation [141, 216].

Ulcerative colitis known as one the most common disease of GIT resulted of harsh inflammation in the large part of intestine (colon and rectum) [217]. Rectal delivery of immunosuppressive therapies using suppositories have been introduced as a promising strategy to maximize the pharmaceutical properties of drug formulation at the targeted site of action [218]. In a study reported by Viano et al., a 3DP drug loaded rectal suppository was developed for treatment of Ulcerative colitis. To do so, two lipid pharmaceutical excipients (Gelucire 44/14 or Gelucire 48/16) and coconut oil were 3DP printed for encapsulation of tacrolimus suppositories in three different sizes by using a pharmaceutical semi-solid extrusion (SSE) technique. Developed suppository systems showed controlled drug release profile within 120 min after administration [219].

In another similar approach, Persaud et al., have prepared personalized 3D printed controlled drug release rectal suppository for pre-referral treatment of severe malaria, in children under 6 years of age. For this purpose, FDM 3DP technique were used to prepare three types of polyvinyl alcohol (PVA) loaded artesunate suppositories. To prolong the drug release profile, artesunate were PEGylated in three different formulations: (i) polyethylene glycol (PEG)-based suppositories carrying free artesunate (non-modified artesunate), (ii) PEG-based suppositories carrying artesunate-loaded micelles and (iii) 3D-printed suppositories carrying a PEG/artesunate mixture. In vitro drug release profile demonstrated that among all the formulated suppositories, formulation (iii) showed slowest release profile in comparison to the others [220].

Tagami et al., have employed FDM 3DP technique for developing unique water-soluble polymer (polyvinyl alcohol) suppository shell molds for preparing tailored drug suppository formulations with desired drug release profile. To control over the drug

release profile in the suppository, three holes with different diameters were designed in the structure of the mold. Pulsed release drug release behavior was observed for the Matryoshka-type Progesterone loaded suppository formulations for intravaginal drug delivery applications. This study proved the concept of 3DP technology in developing unique and complex DDS for tailormade medicine applications [221].

5.4 Other technologies

Other drug delivery technologies that have been utilized to fabricate LADDS include lipid/surfactant vesicles (liposomes, niosomes and cubosomes), microemulsion and microparticles. PLGA microspheres have been amongst the most successful LADDS. Microspheres can be in the range of 1 to 1000 µm. These microspheres are administered as injectable suspensions in aqueous vehicles. The microspheres may have different structures such as a polymeric matrix where the drug molecules are homogeneously dispersed in (microparticle), or a membrane-like wall surrounding core-containing drug (microcapsule) [222].

The terms microspheres and microcapsules are often used interchangeably. There are numerous drugs and biologics that have been researched for development as pharmaceutical microspheres such as proteins (e.g., albumin, gelatin, and collagen). Excipients are mainly in the form of hydrophilic polymers such as (dextran and chitosan as well as PLGA [223].

Amongst the common techniques used for manufacturing of microspheres such as coacervation, spray drying which promote processes like solvent evaporation, ionic gelation and cross-linking to create the polymeric microspheres. These techniques were

extensively reported before [224]. Products based PLGA microspheres include Lupron Depot®, Trelstar® depot, Nutropin® depot, and Risperdal Consta® (Table 1).

Liposomes (phospholipid vesicles) are one of the most investigated lipid-based nanostructured vesicles for chemotherapeutic/anticancer drugs; liposomes have demonstrated ability to target cancer cells, prolong circulation time and reduce systemic drug toxicity [225]. Surface decorated phospholipid with polyethylene glycol (PEG) polymers forming PEGylated liposomes are sterically stabilized and can escape phagocytosis, prolong circulation time and reduce rapid elimination [226]. More recent surface modified version of liposomes using hyaluronic acid, peptide, transferrin have been studied [226].

Beclomethasone cubosomes-based gels have the capacity to prolong precorneal residence time (> 300 minutes), enhance ocular bioavailability (7.8 times as normalized for $AUC_{0\text{-}10h}$), compared to the control suspension formulation. This is translated into delivery of therapeutic quantities of the steroid topically to the posterior segment of the eye to successfully treat experimentally induced uveitis in rabbits [227]. The prepared cubosomes comprised monoolein (glyceryl monooleate) and were prepared using a top-down method [227].

EyeCRO™ has reported on a microemulsion-based drug ocular penetration system called (MiDROPS™) that has the capacity to solubilize high concentration of lipophilic drugs and deliver therapeutics to both anterior and posterior segments of the eye [228]. Cyclosporine A- based MiDROPS have been shown to be superior over a conventional formulation in reducing dry eye as well as providing reduced frequency of administration (once daily application) [228].

6 Future perspectives and concluding remarks

LADDS can hold a promise for treatment of numerous chronic diseases by providing more effective and safer options than conventional (immediate-release) of drug administration. Both efficacy and safety can be enhanced by formulating APIs (small drug molecules or biologics) using long-acting drug delivery systems (LADDS). LADDS possess benefits that have been recognized and ratified by regulatory authorities, clinicians, and patients. They can provide both prolonged systemic and localized effects for those patients that would usually require life-long treatment of debilitating chronic conditions such as eye diseases, diabetes, cancer and brain disorders [222].

Simple and scalable LADDS fabrication techniques like the solvent casting method and other innovative delivery systems such as microneedles fabrication, and technologies like electrospinning and 3-D printing can yield personalized implantable devices [229]. PLGA microspheres have gained regulatory approval by the US Food Drug Administration (FDA) and European Medicines Agency (EMA) as part of the dossier of many long-acting injectable products. Cost-effectiveness and safety of the polymers used to manufacture LADDS have been an issue mainly for regulatory bodies. Some LADDS require complex manufacturing methods where organic solvents might be used which poses safety concerns. Nevertheless, LADDS have proven to be a success in improving treatment outcomes for patients suffering from chronic eye diseases, diabetes, cancer, and brain diseases; either through improving bioavailability, reducing unwanted side effects, achieving drug targeting or promoting better patient treatment adherence [230, 231]. Several issues are yet to be resolved such as the cost and availability of biomaterials used to fabricate LADDS, the nature of complex systems of some LADDS, reliance of drug on external stimuli (light, laser and

application of Magnetism) of the carrier for obtaining consistent drug release that make the regulatory approval of some LADDS. The spiraling cost of biomaterials and poor understanding and limited availability of excipients that suit the newly emerging technologies such as 3-D printing and microneedle systems. Most of innovative ideas of long-acting anticancer drug delivery systems have been tested in animal models; extending such success in animal models to clinical phases faces many ethical and technical criticism by regulatory bodies.

7 References

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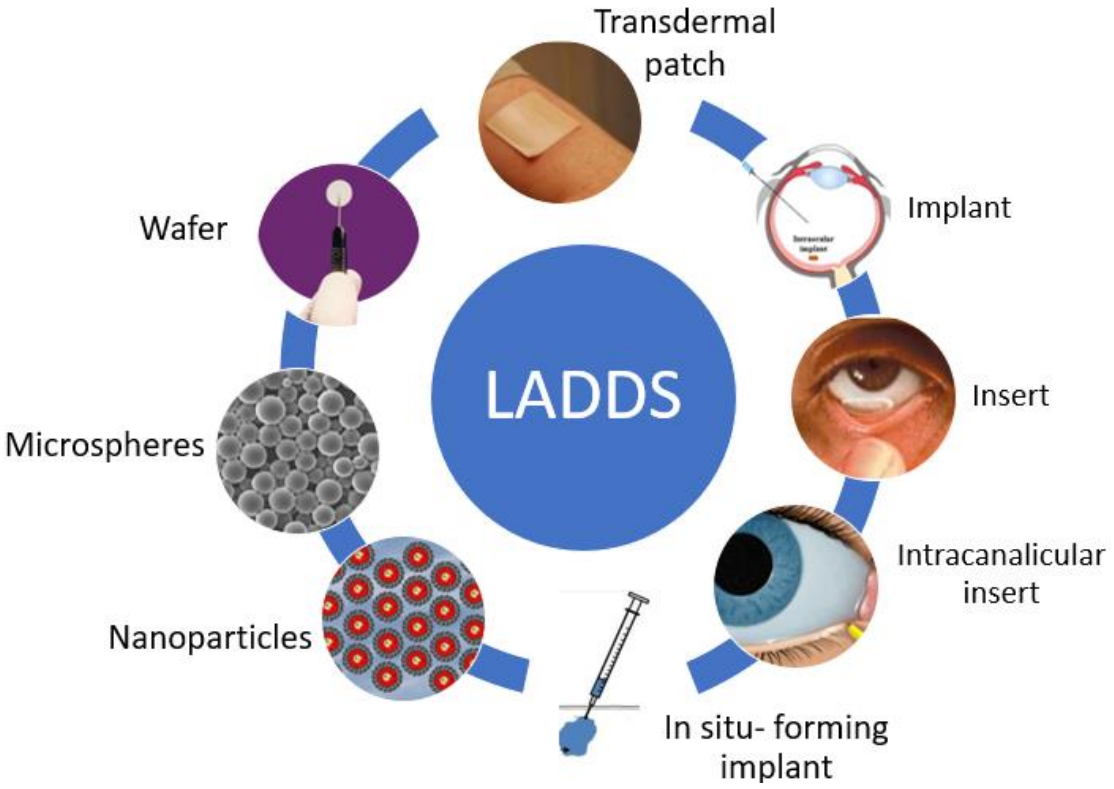

Figure 1 Graphical representation of various long-acting drug delivery systems (LADDS)

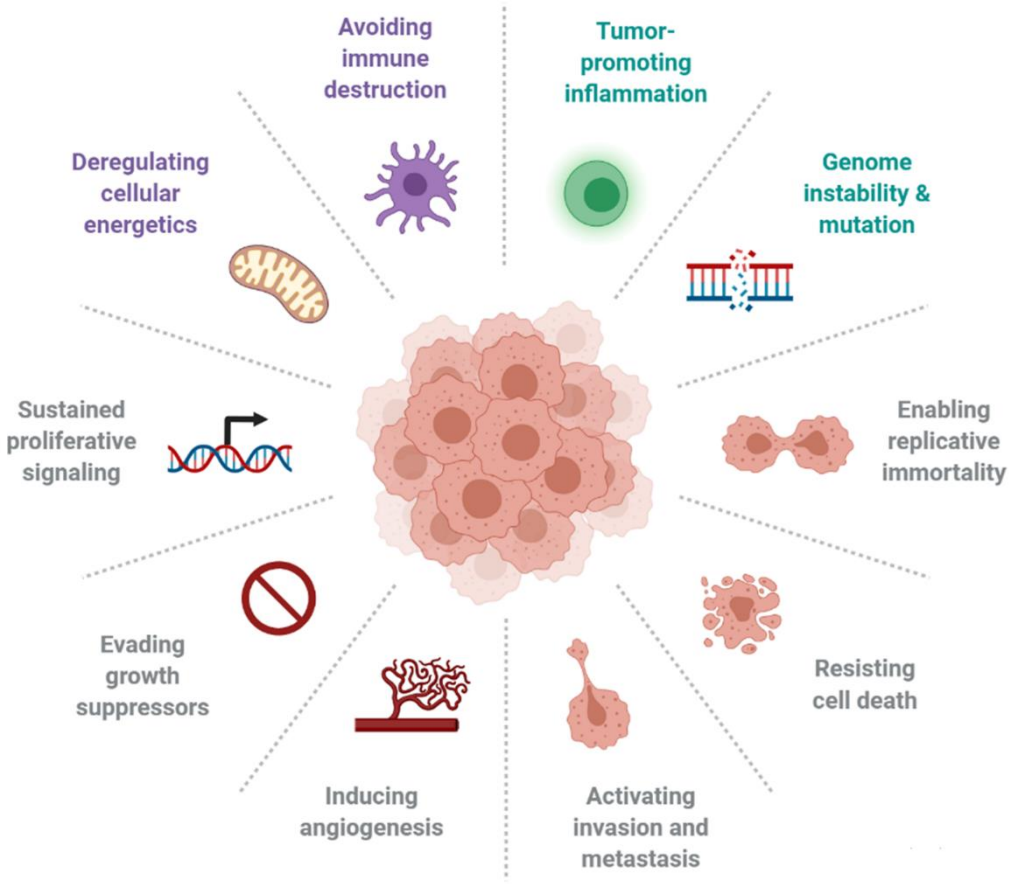

Figure 2 Schematic representation of cancer hallmarks. Created with BioRender.com

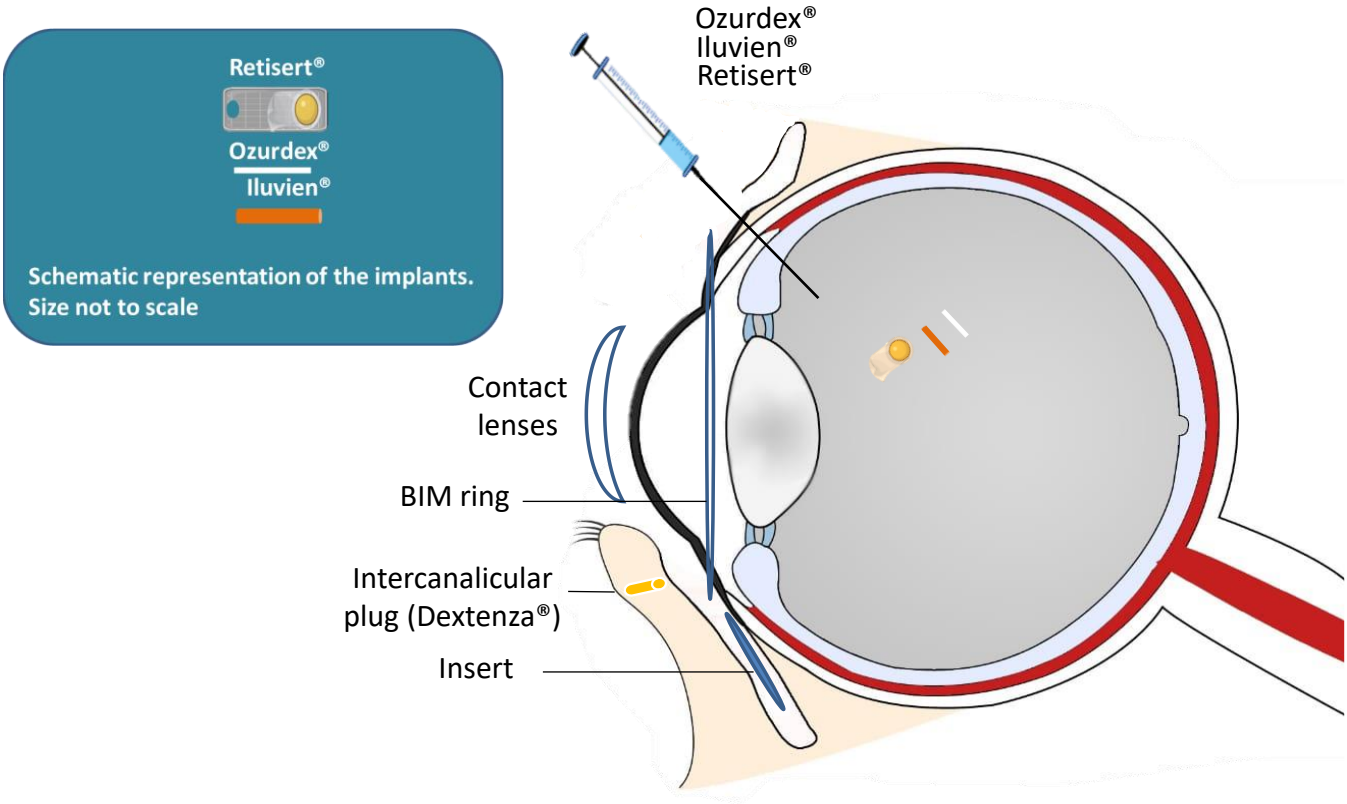

Figure 3 Cross section of the human eye showing the inserting / injection positions of commercially available long-acting drug delivery systems (LADDS).

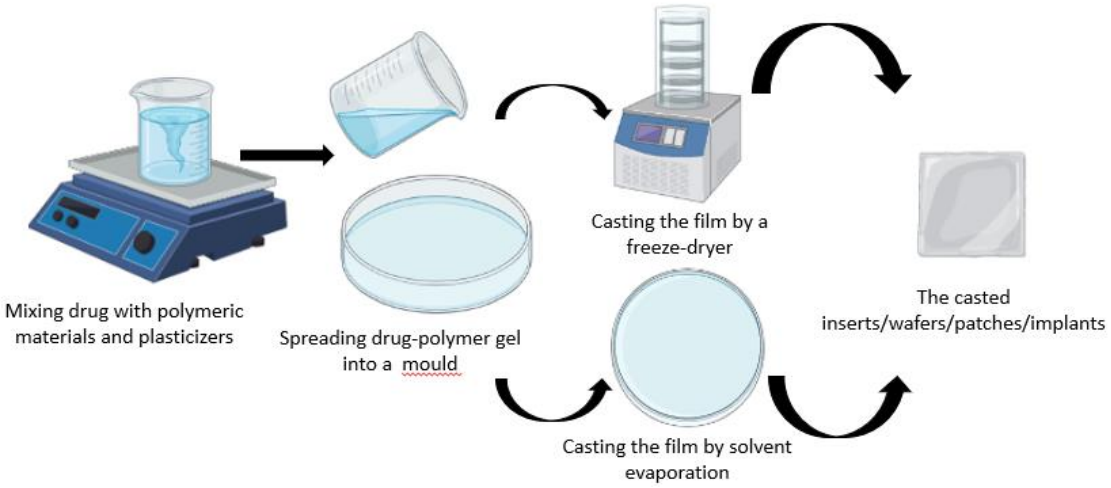

Figure 4 Schematic diagram outlining the steps of the solvent-casting method for preparation of films, inserts and wafers, adopted from [85].

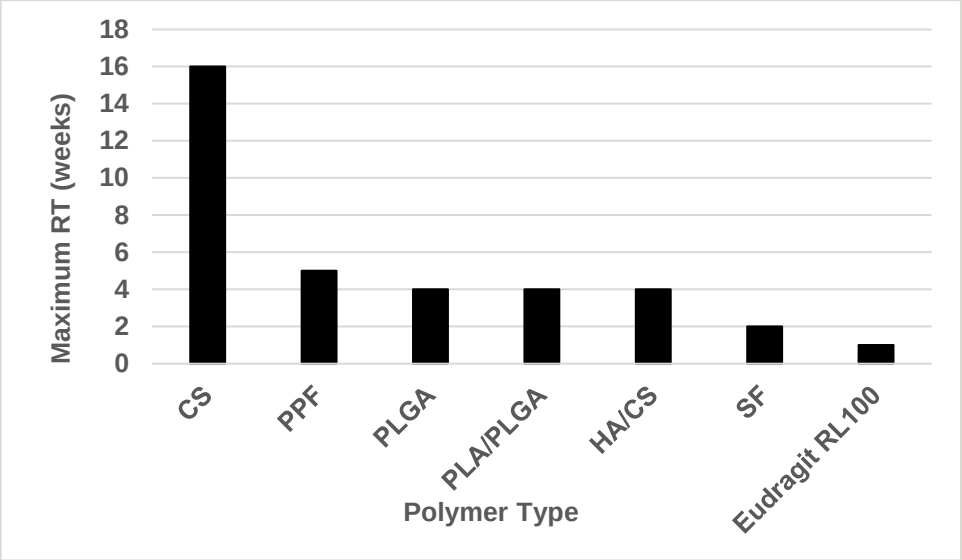

Figure 5 Maximum Release Time (RT) for different drugs achieved by fabricated MNs with different polymers. This data was extracted from [122].

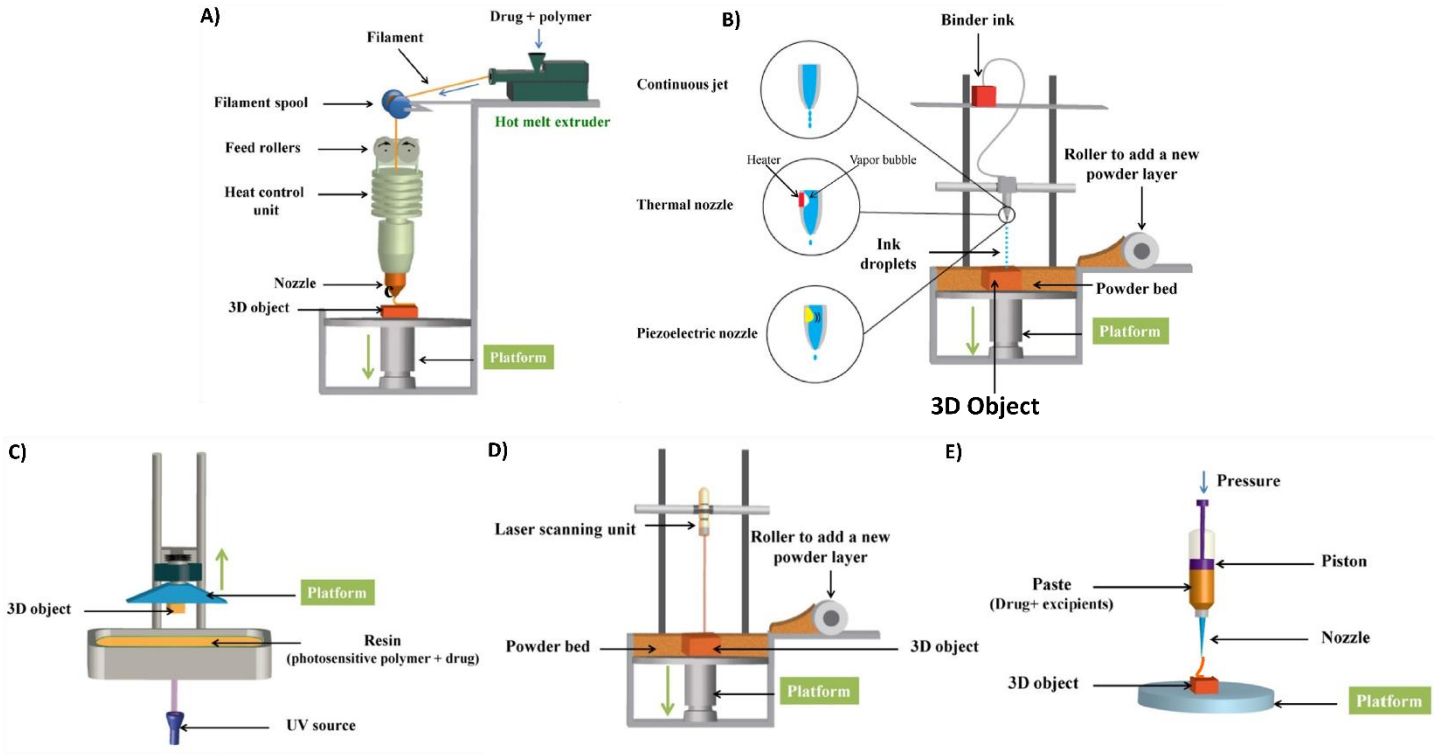

Figure 6 Schematic representation of various 3Dprinting technologies. A) Fused Deposition Modeling (FDM), B) inkjet-based printers, C) Stereolithography (SLA), D) Selective Laser Sintering (SLS) and E) Pressure Assisted Microsyringe (PAM) [232].

Table 1 Drug, product name, polymers, therapeutic indications and duration of commercially available long-acting drug delivery systems (LADDS)

LADDS	Drug	Product name	Polymers	Indications	Duration of action	References
Implant	Dexamethasone 0.7 mg	Ozurdex® implant	poly (D, L-lactic-co-glycolic) acid (PLGA)-based on Novadur® solid polymer DDS	Macular edema Non-infectious uveitis	6 months	[36]
	Fluocinolone acetonide 0.59 mg	Retisert® implant	polyvinyl acetate/silicone	Non-infectious uveitis	30 months	[36]
	Fluocinolone acetonide 0.19 mg	Iluvien® implant	polyimide tube and polyvinyl alcohol	Diabetic macular edema	36 months	[36]
	Progestogen	Progstasert® implant	polyethylene co-vinyl acetate (PolyEVA)	Contraceptive	1 year	[28]
	Levonorgestrel	Norplant® implant	6 silicone rubber tubes, crosslinked polydimethylsiloxane	Contraceptive	6 months	[28]
Insert	Pilocarpine 20 and 40 mg	Ocusert®	PolyEVA	Glaucoma	7 days	[233]
	HPMC 5 mg	Lacrisert®	Hydroxypropyl methyl cellulose (HPMC)	Moderate-to- severe dry eye	1 day	[233]
	Bimatoprost 13 mg	BIM ring	Silicone matrix over an inner polypropylene ring.	Glaucoma	6 months	[84]
	Dexamethasone 0.4 mg	Dextenza®	polyethylene glycol-based hydrogel conjugated with fluorescein	Inflammation and pain after eye surgeries	30 days	[36]
Transdermal patch	Estradiol 1 mg	Menostar® patch	polyethylene film and acrylate adhesive matrix and	Menopause	7 days	[28]
	Fentanyl 1.25, 2.5, 5, 7.5 and 10 mg	Durogesic® patch	hydroxyethyl cellulose; and rate controlling membrane of ethylene-vinyl acetate copolymer	Severe chronic pain	72 hours	[5]
	Nitroglycerin 5 and 10 mg	Nitroderm® patch	Reservoir-based hydroxyethyl cellulose; and rate controlling membrane of ethylene-vinyl acetate copolymer	Prevent or reduce the frequency of angina attacks	24 hours	[5]

	Rivastigmine 4.6, 9.5 and 13.3 mg	Exelon® patch	a 4-layer laminate containing the backing layer, drug matrix, adhesive matrix and overlapping release liner	treatment of mild to moderate Alzheimer's and Parkinson's diseases	24 hours	[57]
Wafer	Carmustine 7.7 mg	Gliadel® intracranial wafer	Polifeprosan 20	treatment to surgery for recurrent glioblastoma multiforme	8 wafers implanted into the site after surgery	[28]
ISFI	Bupivacaine 660 mg/ 5 ml	Posidur™	Sucrose acetate isobutyrate/benzyl alcohol ISF system	Treatment of post-operative pain killer	48-72 hours	[234]
	Paclitaxel 6.3 mg/ml	OncoGel™	PLGA and PEG (A-B-A or B-A-B)	Esophageal Cancer (locally injected into tumor)	6 weeks	[234]
Microspheres	Leuprolide 3.75 mg	Leupron intramuscular (IM) Depot®	PLGA	Treatment of prostate cancer	1 month	[224]
	Triptorelin 22.5 mg	Trelstar IM Depot®	PLGA	Treatment of prostate cancer	6 months	[224]
	Somatropin (rhGH) 13.5 mg	Neutropin subcutaneous Depot®	PLGA	Growth hormone deficiency	1 month	[223]
	Risperidone 12.5 – 50 mg	Risperdal Consta IM Depot®	PLGA	Bipolar mania and Schizophrenia	2 weeks	[223]

Table 2 – Overview of recently completed and on-going clinical trials with microneedle devices.

Microneedle device	**Company**	**Therapeutic field**	**Study phase**	**Reference**
Bullfrog® Micro-Infusion Device	Mercator MedSystems, Inc.	Chronic limb ischemia. Adventitial delivery of temsirolimus (Torisel) after revascularization of lesions below the knee in symptomatic patients with critical limb ischemia.	Phase 2	[235]
		Chronic limb ischemia. Adventitial delivery of dexamethasone after balloon angioplasty of lesions below the knee in symptomatic patients with critical limb ischemia	Phase 2	[236]
		Peripheral arterial disease. To determine ability for adventitial dexamethasone to safely delay restenosis in patients	Phase 4	[237]
Micron	Micron Biomedical	Vaccination. Microneedle patch of measles and rubella vaccine.	Phase 1/2	[238]
Micronjet600®	Nanopass technologies	Allergy immunotherapy – intradermal administration of a vaccine	Phase 1	[239]
		Cancer immunotherapy – intradermal administration of a novel immunotherapy agent (ID-LV305)	Phase 1	[240]
		Delivery of varicella zoster vaccine	Phase 2	[241]
		Intradermal vaccination with Sci-B-Vac™ for occult Hepatitis B	Phase 2/3	[242]
		For type 1 diabetes immunotherapy With a Proinsulin Derived Peptide. To determine the safety of C19-A3 Gold Nanoparticle peptide administered intradermally every 28 days for 8 weeks.	Phase 1A	[243]

		Intradermal influenza vaccine delivery.	Phase 1	[244]
		Autoimmune disease. Intradermal delivery of adalimumab	Phase 1/2	[245]
Microstructured transdermal system® (MTS)	Kindeva drug delivery	Postmenopausal osteoporosis. To determine safety and pharmacokinetics of Abaloparatide delivered using solid microneedles (sMTS)	Phase 1	[246]
Pilocarpine microneedle patch	N/A	Cystic fibrosis	N/A	[247]
SCS Microinjector®	Clearside Biomedical	Neovascular age-related macular degeneration. To determine safety and tolerability of axitinib (a tyrosine kinase inhibitor) injectable suspension administered via suprachoroidal route.	Phase 1/2	[248]
		Uveitis. Suprachoroidal administration of triamcinolone	Phase 3	[249] [250]
SkinJect®	SkinJect Inc.	Basal cell carcinoma. To determine safety and efficacy of dissolvable doxorubicin microneedle array patch	Phase 1/2	[251]
Zosano patch®-	Zosano Pharma Corporation	Cluster headaches. Zolmitriptan microneedle patch	Phase 2/3	[252]
Other	N/A	Cutaneous T cell lymphoma. Dissolvable microneedle array patch containing doxorubicin.	Phase 1	[253]

Table 3 – Examples of 3D printed LADDS, technology and drugs used, polymers, clinical indications and duration of action

3D printed LADDS	Technology	Drug	Polymers	Indications	Duration of action	Reference
Vaginal Rings	Fused Deposition Modeling (FDM)	Progesterone + Polyethylene glycol (PEG) 4000	poly(lactic acid) (PLA)/polycaprolactone (PCL) (8:2) and Tween 80	Contraception (menopause and hypogonadism)	> 7 Days	[191]
	Fused Deposition Modeling (FDM)	Estrogen + Progesterone	polycaprolactone (PCL)	Contraception (obstetric and Gynecologic)	> 7 Days	[192]
	Fused Deposition Modeling (FDM)	Progesterone	poly(lactic acid) (PLA)	Contraceptive in veterinary	> 5 Month	[201]
	Pressure-Assisted Microsyringe (PAM)	Dapivirine	Thermoplastic polyurethane	HIV prevention	> 7 Days	[167]
	Fused Deposition Modeling (FDM)	MZC combination microbicide	Carrageenan (CG) (95:5, lambda: kappa)	HIV-1, HSV-2, HPV prevention	>94 Days	[181]
	Fused Deposition Modeling (FDM)	Clotrimazole	thermoplastic polyurethanes	vaginal infections	> 5 Days	[186]
Suppository	Fused Deposition Modeling (FDM)	Progesterone	Polyvinylalcohol (PVA)	Contraception	NA	[221]
	Fused Deposition Modeling (FDM)	Artesunate	Polyvinylalcohol (PVA)	Malaria	> 1 h	[220]
	semi-solid extrusion (SSE)	Tacrolimus	Gelucire 44/14 or Gelucire 48/16)	Bowel Disease	> 2 h	[219]
Hydrogel Patch	Semisolid extrusion technique	Silver Nanoparticle + Carbon Nanotubes +	UV- crosslinked chitosan- methacrylate	Wound Healing	> 7 Days	[211]

		VEGF				
	3D bioprinter	Nafcillin	hyaluronic-acid, methacrylic anhydride (HA-MA) and 3,30 - dithiobis(propionyl hydrazide) (DTP) (HA-SH)	Wound Healing	> 11 Days	[210]
	Hot Melt Extrusion (HME)	Antiacne	antibacterial metal ions (such as zinc, copper and silver) + polycaprolactone (PCL)	Wound Healing	> 7 Days	[208]
Biodegradable Cardiovascular Stent	Hot Melt Extrusion (HME)	Sirolimus	polycaprolactone (PCL)	Cardiovascular Diseases (CVD)	>32 Days	[206]
	3D bioprinting	Heparin	poly(lactic acid) (PLA)	Cardiovascular Diseases (CVD)	NA	[207]
Cancer	Semisolid extrusion technique	PEGylated liposomal doxorubicin	UV cured fish gelatin methacryloyl (F-GelMA)	Cancer	NA	[160]
	Fused Deposition Modeling (FDM)	poly lactic-co-glycolic acid (PLGA) loaded paclitaxel (PTX) and doxorubicin (DOX) microsphere	polydimethysiloxane (PDMS)	Cancer	> 3 Weeks	[254]

	Electrohydrodynamic jet (E-jet)	5-fluorouracil and NVP-BEZ235	poly-lactic-co-glycolic acid (PLGA	Cancer	> 4 weeks	[196]
	Fused Deposition Modeling (FDM)	Curcumin	polycaprolactone (PCL)	Cancer	>77 h	[198]
	Fused Deposition Modeling (FDM)	(cisplatin), ifosfamide, methotrexate, and doxorubicin	poly L-lactic acid (PLLA)	Cancer	> 12 Weeks	[200]