Biomedical Microdevices (2019) 21: 47
https://doi.org/10.1007/s10544-019-0389-6

Advanced implantable drug delivery technologies: transforming the clinical landscape of therapeutics for chronic diseases

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Published online: 18 May 2019

Abstract
Chronic diseases account for the majority of all deaths worldwide, and their prevalence is expected to escalate in the next 10 years. Because chronic disorders require long-term therapy, the healthcare system must address the needs of an increasing number of patients. The use of new drug administration routes, specifically implantable drug delivery devices, has the potential to reduce treatment-monitoring clinical visits and follow-ups with healthcare providers. Also, implantable drug delivery devices can be designed to maintain drug concentrations in the therapeutic window to achieve controlled, continuous release of therapeutics over extended periods, eliminating the risk of patient non-compliance to oral treatment. A higher local drug concentration can be achieved if the device is implanted in the affected tissue, reducing systemic adverse side effects and decreasing the challenges and discomfort of parenteral treatment. Although implantable drug delivery devices have existed for some time, interest in their therapeutic potential is growing, with a global market expected to reach over $12 billion USD by 2018. This review discusses implantable drug delivery technologies in an advanced stage of development or in clinical use and focuses on the state-of-the-art of reservoir-based implants including pumps, electromechanical systems, and polymers, sites of implantation and side effects, and deployment in developing countries.

Keywords MEMS · NEMS · Non-biodegradable polymers · Long-acting formulations · Implants

1 Introduction

Chronic disease can be defined as a disease that continues or reoccurs over a long period of time. Chronic diseases encompass cardiovascular diseases, diabetes, respiratory diseases, and other disorders that affect a large number of people, are costly to manage, and increase disability-adjusted life years (DALYs) (Bernell and Howard 2016). With one DALY equaling a year loss of disease-free life, DALYs are a measure of the burden of disease across the population (World Health Organization n.d.). Some chronic health disorders are manageable with appropriate treatment. However, the prevalence of chronic diseases such as cardiovascular diseases, diabetes, cancers, respiratory diseases, and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) is steadily increasing and expected to affect 157 million people in the US by 2020 (Comlossy 2013). The global burden of chronic conditions also continues to rise (Fig. 1) and is projected to account for 69% of all deaths worldwide, of which 80% will be in developing countries, by 2030 (Alwan et al. 2010; Samb et al. 2010). As the global economic impact of chronic diseases is estimated to reach $47 trillion in the next two decades, concerted efforts are focused on relieving this burden (World Economic Forum and Harvard School of Public Health 2011).

Traditional intervention via oral or intravenous administration of therapeutics has several limitations. Some drugs have poor bioavailability and require multiple doses, augmenting the risk of resistance and side effects as well as the potential for drug abuse. Additionally, poor patient adherence has direct effects on medication efficacy. Non-adherence is a major concern, 30 to 50% of adults with chronic conditions in the US do not take their medications as prescribed and this has been correlated with 125,000 deaths and 10% of hospitalizations annually. This results in an annual economic burden of $100

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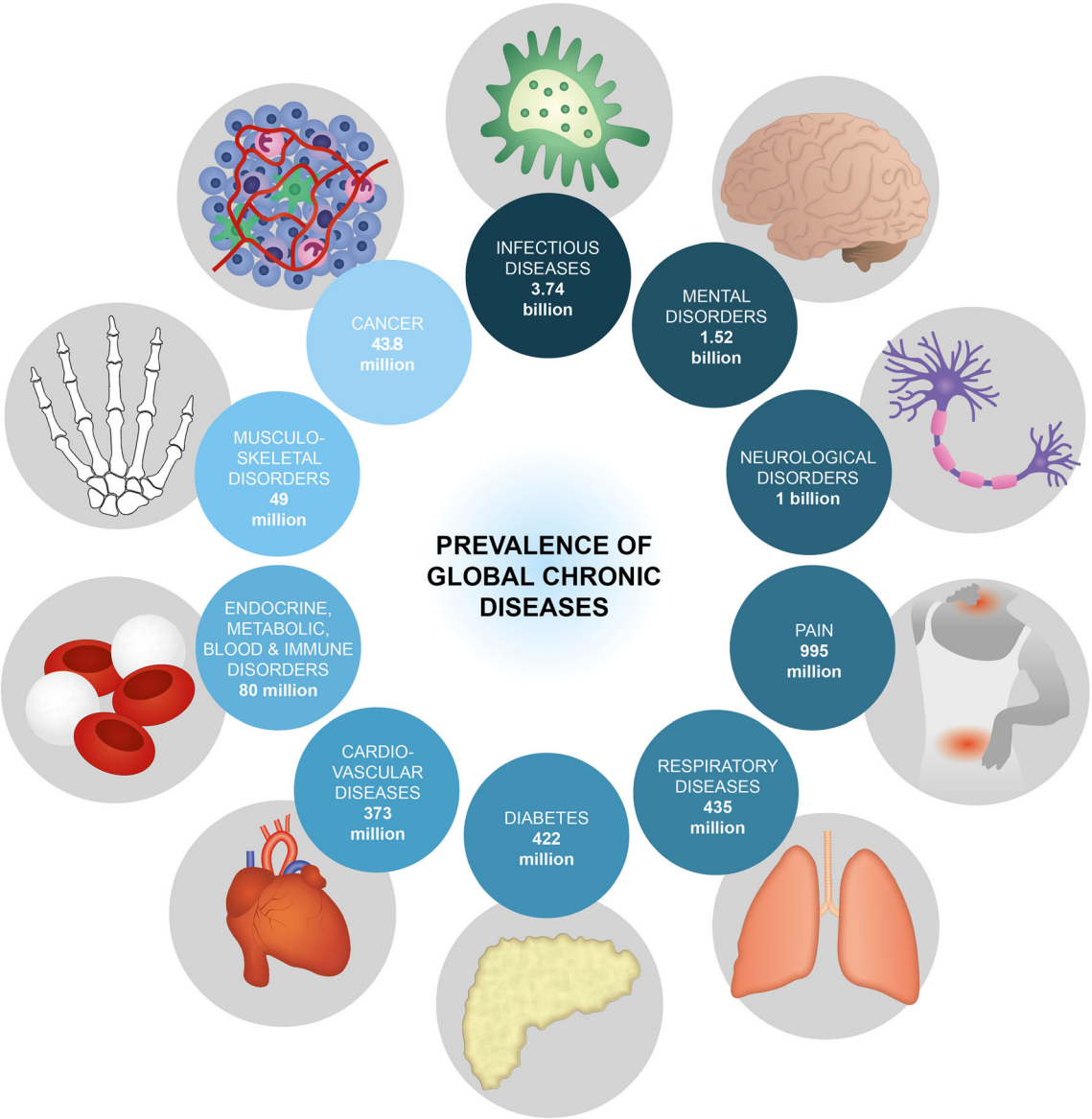

Fig. 1 Top ten global chronic diseases by prevalence (Bertolote 2005; Ferkol and Schraufnagel 2014; Goldberg and McGee 2011; Steel et al. 2014; The Global Cancer Observatory 2018; Vos et al. 2015; World Health Organization 2016)

billion USD in health care services (Cutler et al. 2018; Kini and Ho 2018; Pagès-Puigdemont et al. 2016; Oung et al. 2017). Social and technological efforts such as patient education services, health care provider interventions, reminder tools, and electronic monitoring devices have tried to tackle with medication non-adherence with no significant success (Kini and Ho 2018; Pagès-Puigdemont et al. 2016; Oung et al. 2017; World Health Organization 2003). Because of the correlation between increased non-adherence and higher illness prevalence there is an obvious need to find a solution for medication non-adherence (Atinga et al. 2018; Pagès-Puigdemont et al. 2016).

Compared with traditional systemic delivery, implantable drug delivery devices offer many advantages. Site-specific implantation can bypass the absorption and distribution phase of oral and peripheral regimens, resulting in higher drug concentrations in targeted areas (Danckwerts and Fassihi 1991). Thus, drug levels can be maintained in the therapeutic window by virtue of controlled, continuous release of therapeutics. Importantly, as this technology can be used over extended periods, it eliminates the possibility of poor patient compliance and decreases the discomfort of parenteral treatment (Park 2014). Therefore implantable drug delivery technologies provide site-specificity and deal with medication non-adherence, transforming the clinical landscape of therapeutics for chronic diseases.

Controlled drug delivery technologies have progressed over the last six decades to third-generation modulated delivery systems, with increasing interest in long-term delivery systems (Farina et al. 2017; Meng and Hoang 2012a; Park

2014; Yun et al. 2015). Accordingly, the global market for implantable drug delivery is growing—valued at $9.05 billion USD in 2013 and expected to be $12.42 billion by the end of 2018. Newer, more easily applicable machineries improve the scalability of implantable drug delivery devices. Companies and small start-ups find implantable devices profitable because they are cost-effective and lower overall treatment cost (Kumar and Pillai 2018), and there is high demand to file patents on versatile implantable drug delivery devices that can be tailored for multiple drugs (Coherent Market Insights 2017; Yang and Pierstorff 2012). Another potential benefit is the opportunity for pharmaceutical companies to exploit medications coming off patent, as patent expirations can be extended by creating new products that combine patented medications and implantable devices (Beall et al. 2016). Implantable drug delivery devices can also be advantageous for less prevalent chronic diseases such as drug abuse, pain management, and neurological disorders. Furthermore, telemedicine can allow physicians to remotely control drug release rate from the implant or maximize treatment effectiveness through the use of artificial intelligence and machine learning algorithms (Ross et al. 2017).

In this article, we highlight current technologies for long-term drug delivery in advanced stages of development or in clinical use, with a brief discussion of the use, mechanism of function, advantages, and limitations of each system. This review will demonstrate how advanced implantable drug delivery technologies can transform the clinical landscape of therapeutics for chronic illnesses. The drug delivery systems covered include reservoir-based polymer systems, pumps, and electromechanical systems, excluding polymeric fully degradable systems and long-term delivery devices that are not completely implanted, which are thoroughly revised elsewhere (Kamaly et al. 2016; Majeed and Thabit 2018). We further present a clinical perspective on sites of implantation and potential strategies to improve device development associated with patient acceptance, and device deployment in the developing world.

2 Reservoir-based polymer systems

Reservoir-based polymer systems are passive implants with a simple design consisting of a drug core surrounded by a non-degradable polymeric film (Fig. 2a). Drug release rate is controlled by polymeric coating properties, such as polymer configuration, molecular weight, and coating thickness, as well as physicochemical properties of the drug, such as solubility, particle size, and molecular weight. Historically, polymeric systems have been employed for site-specific mid−/long-term systemic drug administration after subcutaneous implantation. However, most polymeric systems suffer from an initial drug release burst, which can potentially reach toxic levels and endanger the patient. After this burst, drug core concentrations decrease, possibly to below their therapeutic window (Kumar and Pillai 2018; Yang and Pierstorff 2012).

Polymer systems require constant drug concentration within the drug core to achieve zero-order kinetic drug release. These implants often employ the polymers silicone, polyvinyl alcohol (PVA), and ethylene vinyl acetate (EVA). By contrast, biodegradable implants use naturally occurring polymers (e.g., human serum albumin, collagen, gelatin) or synthetic polymers (e.g., polylactic acid, polyglycolic acid, polylactic-co-glycolic acid copolymer) (Kumar and Pillai 2018; Yang and Pierstorff 2012).

Son et al. (2017) developed a 3D-printed porous cylindrical device called Biocage that can be filled with a drug. The Biocage is small enough to fit inside a 22-gauge needle for direct delivery and robust enough to be implanted directly into the target issue. The Biocage has the following dimensions: 300-μm hollow inner diameter, 20-μm outer wall, 40-μm solid base, 900-μm height, and 5-μm-diameter pores (Fig. 2b). The creators demonstrated fluorescent microsphere release from the implant but did not determine the drug release rate. They also confirmed that the Biocage can be used for local drug delivery within the brain and explain how 3D printing offers structural and material versatility to the device. However, although the materials are biocompatible and biodegradable, they are not yet approved by the US Food and Drug Administration (FDA). Nevertheless, this technological platform shows much promise, as it offers drug versatility, has high drug loading efficiency, and can be implanted within the target organ.

In 2006, the FDA approved a similar reservoir-based polymer system, Implanon® (Merck, Kenilworth, NJ, USA), a 4 cm × 22 mm non-biodegradable implant, as a female hormone-based contraceptive. An EVA copolymer rod encompasses 68 mg etonogestrel, which controls the daily release of progestin for up to 3 years. However, the release rate decreases over time, from 60 to 70 μg/day in first couple of weeks to 35–45, 30–40, and 25–30 μg/day at the end of the first, second, and third year, respectively (FDA Reference IDs: 3080389, 4,100,681) (Allen et al. 2016; Huber 1998). However, another study extending its use to 5 years indicated an efficacy of 100% (Ali et al. 2016), suggesting that if the device is still effective after 5 years, patients have likely received supraoptimal doses. Therefore, this implant should be further improved to deliver at a constant rate for 3–5 years. In some cases, the Implanon® was incorrectly inserted, making its localization for removal difficult for healthcare professionals. This led to the design of Nexplanon®, a second-generation device with the addition of the radiopaque ingredient barium sulfate, which entered the US market in 2011 (FDA Reference IDs: 3080389, 4,100,681) (Allen et al. 2016; Huber 1998).

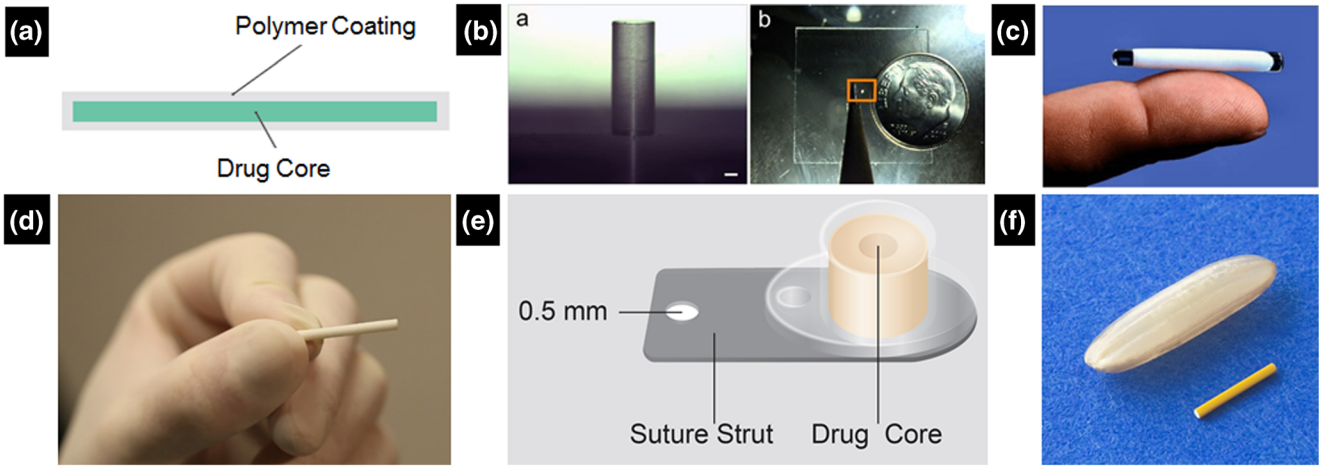

Fig. 2 FDA-approved and experimental non-biodegradable reservoir-based polymer systems. **a** Non-biodegradable polymer schematic depicting an outer polymer coating encompassing an inner drug core. **b** Drug-versatile 3D-printed Biocage device (a) Magnified light microscopy image to detect porosity with 100-μm scale bar. (b) Biocage device boxed in orange in relation to pencil tip and dime to appreciate its minute size and how it can be inserted using a 22-gauge needle. (Image 2B adapted from (Son et al. 2017) licensed under CC BY 4.0). **c** Vantas® and SUPPRELIN® LA 50 mg histrelin acetate implants for prostate cancer symptom relief and childhood central precocious puberty treatment, respectively (Image reproduced from (Rudlang and Brasso 2016). **d** Probuphine® 80 mg buprenorphine hydrochloride implant for opioid dependence treatment (Image used with permission from Titan Pharmaceuticals Inc.). **e** Retisert® implant design consists on a platform for suturing device and drug core with 0.59 mg fluocinolone acetonide enclosed in silicone elastomer cup with a PVA membrane outlet for treating chronic noninfectious uveitis. **f** Intraocular ILUVIEN® 0.19 mg fluocinolone acetonide device for diabetic macular edema treatment in relation to a grain of rice to demonstrate its size (Image is courtesy of Alimera Sciences Inc.)

The Hydron® implant (Endo Pharmaceuticals Solutions Inc., Malvern, PA, USA) consists of a hydrogel polymeric reservoir called MedLaunch™ that is spun-cast into a 3.5 cm × 3 mm tube (Stevenson et al. 2012). Two of these non-biodegradable reservoir-based polymeric system implants are already on the market: Vantas® and SUPPRELIN® LA. The drug core contains 50 mg histrelin acetate in both implants, but the drug delivery rate is modified for the treatment of two different diseases (Fig. 2c). The Vantas® implant delivers 50 μg/day for 12 months to relieve symptoms of prostate cancer, whereas the SUPPRELIN® LA implant releases 65 μg/day for 12 months to treat children with central precocious puberty (FDA Reference IDs: 4099967, 2,887,911). Currently, there are no reports of decreasing drug release rates from these implants, which could be attributed to their shorter treatment periods. The Hydron® implant technology was also adapted to deliver 84 mg octreotride, a somatostatin analog, for up to 6 months to treat acromegaly. However, the phase 3 clinical trial was terminated for business reasons (NCT01295060) (Endo Pharmaceuticals n.d.; Stevenson et al. 2012).

ProNeura™ (Titan Pharmaceuticals Inc., San Francisco, CA, USA) is a non-biodegradable rod composed of an EVA matrix and a drug formulation. The Probuphine® implant, ProNeura™ with buprenorphine, was FDA-approved in 2016 for the maintenance treatment of opioid dependence. Four 26 × 2.5 mm implants are needed to maintain therapeutic drug levels (Fig. 2d). Each device contains 80 mg buprenorphine hydrochloride, a partial opioid agonist, delivered at a controlled rate for up to 6 months (FDA Reference ID: 4215185). Probuphine® has proved more cost-effective than sublingual buprenorphine, as it minimizes fluctuations in plasma concentrations and reduces clinic and pharmacy visits by eliminating the need for daily supervision (Barnwal et al. 2017; Carter et al. 2017). Currently, preclinical studies are testing the use of ProNeura™ to deliver a dopamine agonist (ropinirole) and T3 for the treatment of Parkinson's disease and hypothyroidism, respectively (Titan Pharmaceuticals n.d.).

All above-mentioned reservoir-based polymer systems are subcutaneously implanted in the inner arm, as they require systemic therapeutic levels. However, two non-biodegradable implants are FDA-approved for intravitreal management of ophthalmology-related diseases: Retisert® (Bausch & Lomb, Rochester, NY, USA) and ILUVIEN® (Alimera Sciences Inc., Alpharetta, GA, USA). Because ocular diseases affecting the posterior chamber require constant drug exposure, both devices take advantage of the higher viscosity in the vitreous humor, which increases drug half-life. Retisert® treats chronic noninfectious uveitis and can achieve drug release for 30 months but must then be removed (FDA Reference ID: 2955048) (Borkar et al. 2017; Haghjou et al. 2011; Logan et al. 2016; Yasin et al. 2014). ILUVIEN® can maintain therapeutic levels in the vitreous humor for up to 36 months for the treatment of diabetic macular edema (DME) in vitrectomized and non-vitrectomized eyes (Carle et al. 2014; Hawrami et al. 2016; Kumar et al. 2016; Meireles et al. 2017; Pessoa et al. 2018). After 36 months, a new implant can be inserted without removing the previous implant, as no side effects have been reported from having multiple implants in the eye (FDA Reference ID: 3635981)

(Borkar et al. 2017; Hawrami et al. 2016; Logan et al. 2016; Wang et al. 2013; Yasin et al. 2014).

Retisert® consists of a drug formulation tablet enclosed in a silicone elastomer cup with an outlet consisting of a PVA membrane (Fig. 2e). The tablet contains 0.59 mg fluocinolone acetonide (FA), a corticosteroid, and the following inactive ingredients: microcrystalline cellulose, PVA, and magnesium stearate. Retisert® passively delivers FA into the vitreous humor for the treatment of chronic noninfectious uveitis affecting the posterior chamber (FDA Reference ID: 2955048) (Borkar et al. 2017; Haghjou et al. 2011; Logan et al. 2016; Yasin et al. 2014). ILUVIEN® is a 3.5 × 0.37 mm rod made of polyimide with a non-permeable cap on one end and a permeable PVA membrane on the other end. The inside of the rod is composed of a PVA matrix with 0.19 mg FA (Fig. 2f). This implant is not the first line of therapy but is only approved for DME eyes that did not respond to laser therapy and anti-VEGF therapy (Elaraoud et al. 2016a; Figueira et al. 2017; Massin et al. 2016). Real-world results indicate the efficacy of ILUVIEN®, demonstrating improved best corrected visual acuity and central foveal thickness (Alfaqawi et al. 2017; Amoaku et al. 2015; Bailey et al. 2017; Bertelmann et al. 2013; Bertelmann and Schulze 2015; Cunha-Vaz et al. 2014; Elaraoud et al. 2016b, c; El-Ghrably et al. 2017; Fusi-Rubiano et al. 2018; Gonçalves et al. 2017; Mourtzoukos 2017; Quhill and Quhill 2016; Saedon et al. 2017; Schmit-Eilenberger 2015; Syed 2017; Veritti et al. 2017; Yang et al. 2015). Another implant, Vetrisert®, was FDA-approved for the treatment of cytomegalovirus retinitis but was later discontinued. A pellet of 4.5 mg ganciclovir was enclosed between PVA and EVA and was found to relieve symptoms for up to 8 months (Yasin et al. 2014). Vetrisert® was also effective in treating cytomegalovirus retinitis in AIDS patients, extending the progression of retinitis from 15 to 226 days (Martin 1994).

In summary, reservoir-based polymer systems are the type of implant that has received the most FDA approval and has been on the market the longest. All use the same mechanism of release: drug diffusion through non-biodegradable polymer film. A comparison of their advantages and limitations is shown in Table 1.

3 Pumps

3.1 Osmotic pumps

Osmotic pumps were developed in the 1950s by Rose and Nelson for drug delivery in animals. Since then, numerous designs have found clinical use for the treatment of human diseases (Keraliya et al. 2012; Santus and Baker 1995). Implantable osmotic pumps are drug delivery devices developed for the sustained administration of therapeutics over extended periods of time ranging from months to years. Osmotic pumps are conventionally composed of a hollow cylinder containing a drug reservoir and an osmotic engine separated by a movable piston. The drug reservoir is directly connected to the outside through micro-holes, and the osmotic engine is separated from the outside by means of a semipermeable membrane.

The mechanism of osmotic pump-driven drug release occurs after the pump is implanted. The osmotic engine, which contains high concentration of osmolytes (i.e., salts), drives an osmotic flow of interstitial fluid through the semipermeable membrane. The inward H_2O flow increases hydrostatic pressure in the osmotic reservoir, which exerts force on the piston (Fig. 3a). The piston is pushed toward the drug reservoir and causes injection of the drug solution in an equivalent amount to the volume of drug solution displaced. Ideally, this process is continuous and terminates when the piston has displaced the entire amount of drug solution and has reached the extreme end of the drug reservoir. Other osmotic pumps have a different design in which the osmotic engine surrounds the drug reservoir (Fig. 3b). In these pumps, a high salt concentration in the osmotic engine displaces the drug out through the micro-orifice at a controlled rate by compressing the drug reservoir (Cobo et al. 2015; Herrlich et al. 2012; Kumar and Pillai 2018; McConville 2011).

Viadur® (Bayer Healthcare Pharmaceuticals, Berlin, Germany) was a non-biodegradable titanium osmotic implant that utilized a DUROS® controlled release pump to administer leuprolide acetate, a gonadotropin-releasing hormone analog, for 12 months for the palliative treatment of advanced prostate cancer (FDA Reference ID: 2888026) (Rohloff et al. 2008). Despite successful clinical trials and FDA approval, Viadur® was removed from the market in 2007 due to its lack of cost-effectiveness and limited long-term market viability. In general, the fabrication and assembly procedures as well as the quality control of osmotic implants may ultimately be too expensive to justify their clinical use as an alternative to conventional drug administration approaches.

The Medici Drug Delivery System™ (Intarcia Therapeutics Inc., Boston, MA, USA) is an osmotic mini-pump tailored to hold a certain drug volume over different dosing intervals (Intarcia Therapeutics n.d.-a). ITCA 650 utilizes the Medici Drug Delivery System™ to achieve continuous delivery of exenatide, a glucagon-like peptide-1 receptor agonist, for the treatment of type 2 diabetes. The pump maintains exenatide release for 6 months and is undergoing further development for a 1-year dose (Intarcia Therapeutics n.d.-c). A challenge to delivering a 1-year dose is the necessity of maintaining a constant concentration of osmolyte in the osmotic engine over the entire duration of the treatment to achieve constant drug elution. As such, the osmolyte must be included in a supersaturated form to maintain its constant concentration despite the inward flow of H_2O. When a

Table 1 Comparison among non-biodegradable reservoir-based polymer systems

Implant	Development status	Advantages	Limitations
Biocage	Experimental	• Small size • Drug versatility • Site-specific drug release • Easy insertion procedure	• Materials not FDA-approved
Hydron® implant technology	FDA-approved	• 1-year drug release in comparison to conventional drug administration • Small size • Easy insertion and removal procedures • Alternative implantation sites	• Implant must be exchanged after 1 year • Only one drug formulation (histrelin acetate)
Implanon®/Nexplanon®	FDA-approved	• 3-year drug release in comparison to conventional drug administration • Small size • Easy insertion and removal procedures • Radiopaque • Alternative implantation sites • Soft and flexible shape	• Implant must be exchanged after 3 years • Patients likely initially receiving supraoptimal doses • Decline in drug release rate over time
Probuphine®	FDA-approved	• Small size • Easy insertion and removal procedures	• Four implants needed • Implants must be removed after 6 months • Not radiopaque
Retisert®	FDA-approved	• 30-month drug release • Site-specific drug release	• Requires invasive surgery • Implant must be exchanged • Adverse side effects • Not cost-effective
ILUVIEN®	FDA-approved	• 36-month drug release • Cost-effective • Site-specific drug release	• Non-biodegradable implant not removed from vitreous humor after treatment

substantial amount of drug has been released, release rate may decline as a result of reduced osmotic flow.

ITCA 650 has completed its phase 3 clinical trial, called FREEDOM. However, the FDA issued a Complete Response Letter regarding manufacturing aspects, and the device is currently on an FDA clinical hold (Genetic Engineering and Biotechnology News 2018). Titanium osmotic pump manufacturing can be very expensive, as these pumps require extremely tight dimensional and geometrical tolerances as well as lathe machining for minimal surface roughness in the inner implant cavity. Intarcia is currently resolving these issues, and the Medici Drug Delivery System™ will be adapted for the continuous delivery of HIV pre-exposure prophylaxis (PrEP) (Intarcia Therapeutics n.d.-b).

Osmotic pumps have been further developed to improve intravesical drug delivery using osmotic flow of H_2O from urine instead of interstitial fluid. GemRIS™ and lidocaine-releasing intravesical system (LiRIS®) (TARIS Biomedical®, Lexington, MA, USA), which utilize the TARIS® System, are elastomeric tubular osmotic intravesical implants that deliver gemcitabine and lidocaine, respectively, to treat bladder diseases. The TARIS® System is a dual-lumen silicone tube containing an osmotic engine encompassing the solid drug core in one lumen and nitinol wireform in the other (Fig. 3c). The permeability of silicone permits H_2O from the urine to diffuse through the osmotic engine into the drug core and dissolve the drug. This creates an osmotic pressure in the osmotic engine that forces drug solution out through the orifice (Fig. 3b).

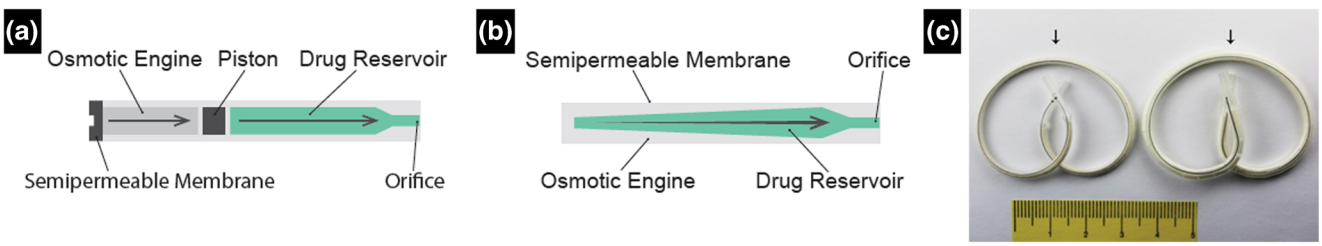

Fig. 3 Osmotic pump drug release schematics and FDA-approved osmotic pump implant. **a** Osmotic pump drug release mechanism for liquid drug formulations use a high salt concentration osmotic engine driven by osmotic flow through semipermeable membrane to move piston and displace drug through orifice. **b** Osmotic pumps with an inner solid drug reservoir encompassed by a high osmolyte concentration osmotic engine surrounded by semipermeable membrane osmotically displace solubilized drug through orifice. **c** Intravesical GemRIS™ implant loaded with solid gemcitabine for bladder cancer treatment (Image adapted from (Cima et al. 2014))

Intravesical osmotic pumps are currently undergoing clinical trials. GemRIS™ completed a phase 1b clinical trial to assess its safety and tolerability in muscle-invasive bladder cancer patients (NCT02722538) (Taris Biomedical LLC n.d.-a). GemRIS™ will also undergo a phase 1b clinical trial with Opdivo® (nivolumab) in the same patient population as well as two other clinical trials for non-muscle-invasive bladder cancer (NCT02720367) and muscle-invasive bladder cancer unfit for radical cystectomy (NCT03404791) (Taris Biomedical LLC n.d.-b; Taris Biomedical LLC n.d.-c).

An advantage of the TARIS® System is that the drug is loaded in solid form, which augments its loading efficiency. Also, the implant does not have moving components, decreasing the risk of potential failure and reducing fabrication costs. The device can achieve local sustained release of drug, minimizing side effects and frequent drug catheter injections to the bladder. These implants have received positive feedback from people who suffer from bladder diseases seeking a new drug administration strategy (Cima et al. 2014; Herrlich et al. 2012; Matheson 2014; Nickel et al. 2012; Taris Biomedical LLC n.d.-d). Nonetheless, accidental rupture of the implant can cause drug overdose from the dissolving solid drug core, and the device may be difficult to efficiently remove from the body without cystoscopy.

3.2 Peristaltic pumps

Peristaltic pumps have been used clinically for many years. In 1881, Eugene Allen was the first to patent the peristaltic pump in the US for blood transfusions (*US249285A*) (Allen 1881; INTEGRA Biosciences n.d.). Years later, cardiothoracic surgeon Dr. Michael DeBakey created the DeBakey pump that was used in the Gibbon heart-lung machine in 1953 (Winters 2015). Positive displacement is the driving force for pumping fluids contained in a tube inside the peristaltic pump. Rollers attached to the external circumference of a rotor compress the flexible tube, trapping liquid drug doses between rollers. As the rotor rotates, the rollers displace the drug in the tube and the tube returns to its natural state after passage of the drug, a process known as peristalsis (Fig. 4a). This peristalsis transports the drug toward the pump outlet and into a catheter for delivery to the target site.

This technology has been applied to create an implantable peristaltic pump capable of chronically administering therapeutics at the target site (Berg and Dallas 2013). However, the implant is relatively large to accommodate the mechanical components, battery, and drug. As such, the volumetric loading efficiency, defined as the ratio of drug reservoir volume to implant volume, is greatly limited to 22–30% (Medtronic 2011). A disadvantage of this pump is that its size restricts the implantation site, requiring a catheter to administer the drug at the target site. This technological platform is already on the market as the SynchroMed™ II pump (Medtronic, Fridley, MN, USA), an implantable FDA-approved system composed of a pump reservoir, reservoir fill port, reservoir valve, pump tubing, check valve, catheter port, and implanted catheter (Fig. 4b) (Kosturakis and Gebhardt 2012; Pope and Deer 2015). Drug is percutaneously loaded in the reservoir fill port and passes through the reservoir valve into the pump reservoir. The design of the pump reservoir involves pressurized gas stored below the reservoir. Thus, at normal body temperature, the gas expands and displaces the drug in the pump reservoir into the pump tubing. The SynchroMed™ II pump then transports the drug in a peristaltic motion through the pump tube, check valve, catheter port, and implanted catheter, where it is released at the target site (Bolash et al. 2015; Christo and Bottros 2014; Meng and Hoang 2012b; Pope and Deer 2015).

This pump is FDA-approved for the chronic delivery of treprostinil, morphine sulfate, and ziconotide. Intravenous treprostinil, epidural/intrathecal morphine sulfate, and intrathecal ziconotide are delivered for the treatment of pulmonary arterial hypertension, chronic intractable pain, and severe chronic pain management, respectively (Bourge et al. 2016; Medtronic 2017). In Sweden, the SynchroMed™ II pump is administering intracerebroventricular PDFG-BB in Parkinson's disease patients in a phase 1/2a study evaluating its safety and tolerability (NCT00866502) (Newron Sweden AB n.d.; Paul et al. 2015).

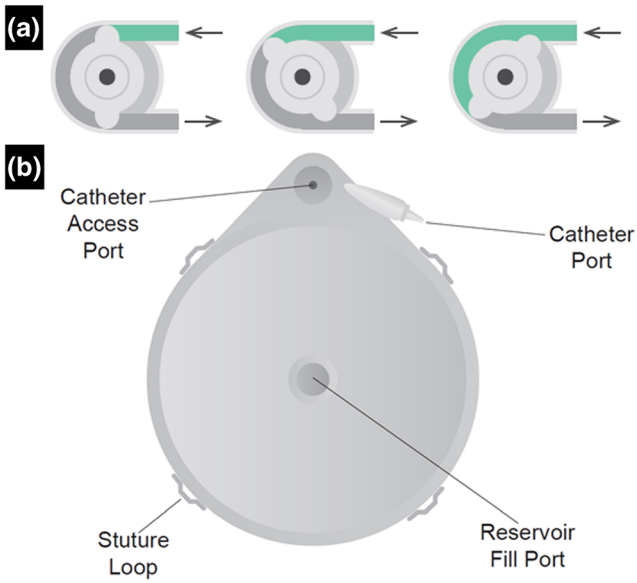

Fig. 4 Peristaltic pump drug release mechanism and design. **a** Peristaltic pump drug release mechanism: a central rotor with rollers attached to its circumference rotates, compressing the flexible tube, trapping liquid drug doses between rollers and displacing it through the catheter. **b** General outer schematic of implantable pumps: a discoidal-shaped implant with a central reservoir fill port that can be accessed percutaneously, a catheter port that connects the catheter and implant, and suture loops to securely anchor the implant in the abdominal pump pocket

Chronic drug delivery requires careful dose monitoring by a healthcare professional to maintain adequate therapeutic levels. The SynchroMed™ II pump can be programmed by telemetry to deliver a wide range of therapeutic flow rates, thus personalizing the drug dose for each patient (Li et al. 2012; Medtronic 2017). Likewise, pain tolerance differs between patients, so an advantage of this pump is that the patient can self-administer an additional dose through a personal therapy manager (PTM), a handheld accessory with a lockout system ensuring that the patient does not administer more drug than is approved by the doctor (Bhatia et al. 2014). Currently, the PTM is undergoing a phase 4 clinical trial for patient-controlled intrathecal analgesia with bupivacaine for chronic low back pain (NCT02886286) (Ilias et al. 2008; Salim M Hayek and University Hospitals Cleveland Medical Center n.d.).

Because these pumps require a battery, their lifespan is limited to 4–7 years. Also, their low volumetric loading efficiency of 22–30% requires a large pump and limits the size of the reservoir compared with the volume of the device. Consequently, patients must go to a healthcare professional to refill the pump every 3–4 months, which affects patient acceptability (Bolash et al. 2015; Christo and Bottros 2014; Meng and Hoang 2012b; Pope and Deer 2015). Another setback is reports that magnetic resonance imaging (MRI) temporarily stops the pump motor rotor. As a result, all patients must undergo assessment of pump motor function after an MRI (Kosturakis and Gebhardt 2012; Pope and Deer 2015). Peristaltic systems are also costly to manufacture (Rajgor et al. 2011).

3.3 Infusion pumps

Infusion pumps utilize a chlorofluorocarbon propellant, whose change from liquid to gas at body temperature serves as the driving force to deliver a drug. This implantable mechanical system is divided into two chambers: propellant and drug. The drug chamber is a collapsible bellow that compresses as gas expands from the propellant chamber. This forces the drug out through an exit port into the pump catheter (Fig. 5). Because body temperature is constant, the drug is delivered at a steady rate and is tunable by changing the drug concentration in the drug reservoir. An advantage of infusion pumps is that no battery is required for drug administration, avoiding the need for replacement (Rajgor et al. 2011).

The Codman® 3000 pump (Codman & Shurtleff, Inc., Raynham, MA, USA) is an infusion pump FDA-approved for intrathecal delivery of morphine sulfate for pain management and hepatic arterial infusion of chemotherapy to the tumor site. The pump achieves a constant flow rate by maintaining a pump drive pressure of approximately 0.6 bar at body temperature. There are different titanium Codman® 3000 pump drug reservoir sizes: 16, 30, or 50 ml. Thus, the Codman® 3000 pump size depends on the model and can measure 6.12–8.64 × 3.20–3.74 cm and weigh 98–173 g. As a result, a disadvantage of the pump is its low volumetric loading efficiency of 14–29%. However, the pump can be transcutaneously refilled every 4–8 weeks through a self-sealing silicone central port (Baert et al. 2008; Codman and Shurtleff 2003; Codman & Shurtleff n.d.).

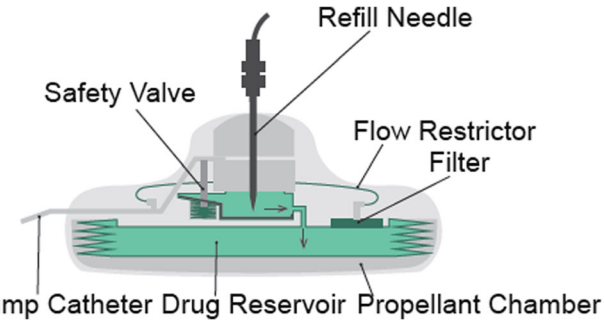

Fig. 5 Infusion pump drug release schematic. The infusion pump is divided into two chambers: a collapsible drug reservoir and a propellant chamber. At body temperature the propellant changes from liquid to gas compressing the drug reservoir thus forcing the drug out through the restrictor filter into the pump catheter. The drug reservoir is refilled with a designated needle that closes the safety valve avoiding drug release while refilling

In a study evaluating baclofen delivery for severe spasticity treatment, the Codman® 3000 pump demonstrated an accuracy higher than 90% (Ethans et al. 2005). Although this accuracy is similar to that of peristaltic pumps, the infusion pump has a lifetime warranty advantage as it omits the battery. Furthermore, a pilot study of the delivery of darunavir via the caudal vena cava by the Codman® 3000 pump for HIV PrEP confirmed a steady-state plasma drug concentration with an average of 40 ng/ml in two dogs. This study also highlights the versatility of the pump and catheter through its adaption to deliver viscous solutions (Baert et al. 2008). Although the Codman® 3000 pump is highly acceptable by patients, especially for hepatic arterial infusion for chemotherapy, its production stopped in April 2018. This halt was likely due to low profitability, with pumps costing from $7000 to $11,000 USD, and low demand, with only 300 sales per year in the US (Grady and Kaplan 2018).

Another dynamic implant that relies on a positive driving force to modulate drug dosing is the Prometra® pump (Flowonix Medical Inc., Mt. Olive, NJ, USA). This FDA-approved chronic pain management pump delivers morphine intrathecally and uses the same positive pressure gas expansion actuation design as the Codman® 3000 pump but with battery-powered valves for flow regulation (Fig. 4) (Christo and Bottros 2014; Cobo et al. 2015; Kumar and Pillai 2018; Wilkes 2014). The titanium device is relatively large to accommodate the electrical components that permit remotely controlled drug release, measuring 7.1 × 2 cm with an unfilled weight of 150 g and drug reservoir volume of 20 ml. Programmable dose changes are a big advance for implants,

as they give patients the ability to self-administer drug from an implant as they would with oral pills. The FDA-approved patient therapy controller (PTC™) offers patients flexibility to manage their pain (Deer and Pope 2015; Flowonix Medical n.d.). Also, external control of dosing is a requirement for pain management because dosing throughout the day is variable (Kumar and Pillai 2018).

In a study of 110 patients with chronic pain, Prometra® pumps had higher dosing accuracy when administering morphine sulfate compared with SynchroMed™ II pumps (Christo and Bottros 2014; Rauck et al. 2010). This could be attributed to the Prometra® pump valves delivering more precise drug doses due to their employment of simple open-and-close mechanisms. By contrast, SynchroMed™ II pumps have a fixed drug dose between rollers that cannot be finely tuned. Furthermore, the accuracy, efficacy, and safety of Prometra® pumps were demonstrated in patients for up to 12 months (Kalyvas et al. 2014; Rauck et al. 2010, 2013).

A major disadvantage of Prometra® pumps is the need to completely remove medication prior to MRI, as magnetic fields may open the valves and empty the drug reservoir, causing drug overdose (Christo and Bottros 2014; Pope and Deer 2015). To avoid this procedure and achieve an MRI-compatible implant, a flow-activated safety valve (FAV™) was incorporated in the new pump model, Prometra® II. However, the pump was recalled in 2017 due to a failure of the FAV™ during an MRI scan, resulting in a patient receiving a fatal dose (U.S. Food and Drug Administration 2018). Although Prometra® II was designed to prevent the need for pre-MRI medication removal, the recall mandates emptying the drug reservoirs in Prometra® and Prometra® II pumps before an MRI scan (Flowonix Medical 2018). However, as physicians and healthcare workers are aware of this necessity, this is not a restrictive problem with careful monitoring.

In summary, pumps with different mechanisms of action can be chosen depending on the patient's disease, drug release longevity, and site of implantation. Larger peristaltic and infusion pumps can possibly be used to treat chronic diseases due to their larger drug reservoir and refill feature, whereas smaller osmotic pumps maintain constant drug release for systemic or site-specific effects (Kumar and Pillai 2018). A comparison of advantages and limitations of peristaltic, osmotic, and infusion pumps is shown in Table 2.

4 Microfabricated systems

In the biomedical field, electromechanical systems offer distinctive solutions for drug release related to precision dosing. There is much interest in implants that incorporate this technology and are fabricated in the micro- and nanometer range (Kumar and Pillai 2018). Microscopic and nanoscopic devices with features in the microscale and nanoscale array are termed microelectromechanical systems (MEMS) and nanoelectromechanical systems (NEMS), respectively.

When these implants are scaled down, the driving forces of drug release change with respect to the decrease in area and volume; forces such as adhesion and surface tension have a greater effect on molecules, which is convenient for controlled drug delivery (Bhushan 2007). Given the incredible variety of technologies proposed, in this section we will review some representative MEMS and NEMS undergoing preclinical research or clinical development.

4.1 Mems

Fluidic MEMS show potential for drug delivery applications and can be integrated with electronic components to allow remote control over drug administration. Santini et al. (1999) developed one of the first microfluidic devices capable of pulsatile release. It consists of a microfabricated silicon wafer containing an array of drug reservoirs capped by gold membranes (Fig. 6a, b) (Maloney et al. 2005). The device allows the selective opening of single reservoirs by applying an electrical potential to the gold membranes. An electrochemical reaction causes the complete dissolution of the membrane, allowing drug release (Fig. 6c). This technology was adapted for leuprolide release by Microchips Biotech, Inc. (Bedford, MA, USA).

Micro-CHIP allows the remote control of drug delivery. This system utilizes electronic circuitry for radio-frequency communication with the remote control unit for triggering dissolution of capping reservoir membranes. This system is complex and requires a power source consisting of a battery (Fig. 6d), which occupies ~40% of the implant volume due to the significant power consumption of the device. Micro-CHIP has arrays of drug reservoirs of 300–600 nl each that can be individually opened over time, creating a pulsatile delivery profile (Farra et al. 2012; Grayson et al. 2004). To mimic constant delivery, the reservoirs should be opened at frequent time points. The rate of release from each reservoir can be controlled by modification of the dissolving capping layer (Santini et al. 2000).

Micro-CHIP devices have been developed for different experimental applications. One of the most relevant applications is the delivery of leuprolide in a canine model (Prescott et al. 2006). For this purpose, the implant contains 100 drug reservoirs providing a total reservoir volume of 30 μl, corresponding to 2.5 mg leuprolide acetate powder (Grayson et al. 2004). The device, with approximate dimensions of $4.5 \times 5.5 \times 1$ cm^3, has a volume of approximately 30 ml, meaning that its nominal loading efficiency is 0.1%. More recently, a different version of Micro-CHIP was tested in a clinical trial (Farra et al.

Table 2 Comparison among peristaltic, osmotic, and infusion pumps

Implant	Development Status	Advantages	Limitations
SynchroMed™ II pump	• FDA-approved • Clinical trials: NCT00866502, NCT02886286	• Transcutaneous refilling • Telemetry dosing • PTM patient self-administration • Site-specific drug release with catheter	• Large size • Needs battery • Movable mechanical components • Low volumetric loading efficiency • Requires invasive surgery • Pump and catheter malfunctions • Requires specific drug formulation • Drug instability requires refill every 3–4 months
Medici Drug Delivery System™	• FDA clinical hold	• Small size and optimal shape • Drug versatility	• Holds less than 1 year dose • Implant must be exchanged after 6 months • Movable mechanical components
TARIS® System	• Clinical trials: NCT02722538, NCT02720367, NCT03404791	• Small size and optimal shape • Site-specific (intravesical) • Drug released for weeks to months for optimal treatment	• Difficult insertion and removal procedures
Codman® 3000 pump	• FDA-approved • Discontinued	• Transcutaneous refilling • Overfill safety features • Drug reservoir versatility • Nominal flow rate versatility • No battery • Site-specific drug release with catheter	• Large size • Requires invasive surgery • Requires refill every 4–8 weeks to expand bellow • Low volumetric loading efficiency • Requires specific drug formulation
Prometra® and Prometra® II pumps	• FDA-approved • Recalled by Flowonix Medical Inc.	• Dosing accuracy • PTC™ patient self-administration • Programmable drug doses • Transcutaneous refilling • Site-specific drug release with catheter	• Large size • Needs battery • Movable mechanical components • Low volumetric loading efficiency • Requires invasive surgery • Pump and catheter malfunctions • Requires specific drug formulation • Drug instability requires refill every 3 months • Drug reservoir must be emptied prior to MRI scan

2012). This implant delivers teriparatide, synthetic human parathyroid hormone fragments [hPTH(1–34)], which is the only treatment approved for anabolic osteoporosis and requires daily injection (Watson 2012). The device, with approximate dimensions of $5.4 \times 3.1 \times 1.1$ cm^3, contains 20 reservoirs containing 40 μg teriparatide each, providing a total reservoir volume of 12 μl. This Micro-CHIP has a volume of approximately 15 ml and a nominal loading efficiency of 0.08%. However, Farra et al. (2012) report that the drug loading procedure does not allow complete yield of all drug reservoirs, which reduces the effective loading efficiency to below 0.08%.

These implants have the benefit of being made of components that can be microfabricated with conventional semiconductor technologies. The shell can be machined or injection-molded for the low-cost parallel fabrication of a large number of parts. Nonetheless, the assembly, loading, and sterilization of the device is expensive. Additionally, the extremely low loading efficiency significantly limits its applicability for long-term sustained delivery of therapeutics. However, the Micro-CHIP will be tested with a variety of chronic drug therapies since Teva Pharmaceuticals partnered with Microchips Biotech Inc. in 2015 (Microchips Biotech 2015).

Humayun et al. developed prototypes of one of the first ocular MEMS pumps for the treatment of DME and noninfectious uveitis. The Posterior MicroPump Delivery System (PMP) is implanted on the sclera beneath the conjunctiva and delivers micro- and nanodoses intravitreally. The PMP can be wirelessly programmed with The Eye™. The device is $13 \times 16 \times 5$ mm in size and is custom-contoured for a reduced front height to fit on the outer surface of the eye. The PMP has a drug reservoir with a refill port, battery, electronics, electrolysis chamber, and cannula (Fig. 7a). When the device is turned on, an electrical potential electrolyzes H_2O into H_2 and O_2, which returns to H_2O when turned off. The gases generate pressure on the drug reservoir and force the drug into the cannula at a desired dose (Fig. 7b) (Cobo et al. 2015; Gutiérrez-Hernández et al. 2014; Humayun et al. 2014; Yasin et al. 2014). Use of the PMP for delivering ranibizumab, an angiogenic inhibitor, for 90 days was demonstrated to be safe. However, four of the eleven patients received a lower than target dose (Humayun et al. 2014). PMP safety was

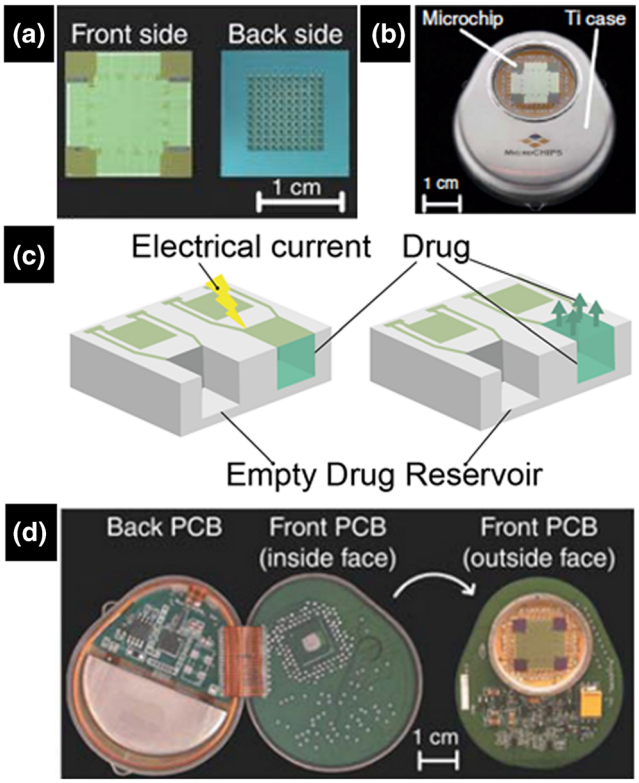

Fig. 6 30-ml Micro-CHIP device used for leuprolide release in dogs. **a** Silicon wafer with 100 30 μl drug reservoirs capped by gold membranes. **b** Assembled 30-ml Micro CHIP device. **c** Micro-CHIP drug release schematic: an electrical potential to the gold membrane permits selective opening of specific reservoir for drug release. **d** Internal circuitry of the implant. (Image 6A, 6B, 6D adapted from (Prescott et al. 2006))

previously assessed in a 1-year canine study (Gutiérrez-Hernández et al. 2014). Humayun et al. patented the technology and created the company Replenish Inc. (Pasadena, CA, USA), which produces Replenish MicroPumps.

4.2 NEMS

4.2.1 NEMS for constant delivery

At the nanoscale, the properties of fluids under confinement can be beneficially leveraged. Nanochannels constitute highly precise and accurate delivery vehicles for the delivery of therapeutics in a controllable manner. When the size of the channels shrinks to the size of the diffusing analytes, wall-to-molecule interactions play a dominant role in molecular release, causing constrained and saturated diffusion (Ziemys et al. 2011; Ziemys et al. 2010). Therefore, nanochannels can passively control the release of molecules through concentration-driven transport as long as the drug reservoir is supersaturated (Bruno et al. 2018). Taking advantage of these nanoscale effects, constant, sustained release of drugs can be achieved by judiciously tailoring the size and surface chemistry of nanochannels. This nanochannel approach was developed by various groups, with pioneering studies of silicon nanochannels conducted by Ferrari et al. and Desai et al. in the 1990s (Chu et al. 1997; Desai et al. 1999; Ferrari et al. 1995; Grattoni et al. 2009; Chu et al. 1999).

Nanochannel membranes can easily be mounted on a drug reservoir to achieve constant rate, zero-order kinetic drug release from the reservoir. These implants are still in the preclinical phase but have a high market acceptability due to low manufacturing costs. The titanium oxide nanotube membrane, NanoPortal Membrane (Nano Precision Medical, Emeryville, CA, USA), is attached to a small, rice grain-sized cylindrical implant (Fig. 8a). This implant was designed to be subcutaneously implanted through an in-office procedure. Currently, this technology is in preclinical development to release glucagon-like peptide-1 agonists for 3 months to up to 1 year (Nano Precision Medical n.d.-a; Nano Precision Medical n.d.-b; Nano Precision Medical n.d.-c). A larger cylindrical titanium device measuring 4 cm × 4 mm has two membranes with NANOPOR™ (Delpor Inc., San Francisco, CA, USA) technology fixed at each end (Fig. 8b) (Delpor n.d.-a; Delpor n.d.-f). DLP-202 and DLP-414 can release hGH for 3 months and exenatide for 3–6 months, respectively (Delpor n.d.-d; Delpor n.d.-e). To maintain constant release, drugs must be soluble to form supersaturated solutions within the drug reservoir to saturate the nanochannels. Insoluble drugs cannot saturate nanochannels and thus do not have zero-order kinetics. Prozor™ (Delpor Inc., San Francisco, CA, USA) technology enables release of insoluble drugs by maintaining an acidic pH in the drug reservoir (Delpor n.d.-g). DLP-114 and DLP-119 are a 6–12-month formulation of risperidone and 3-month

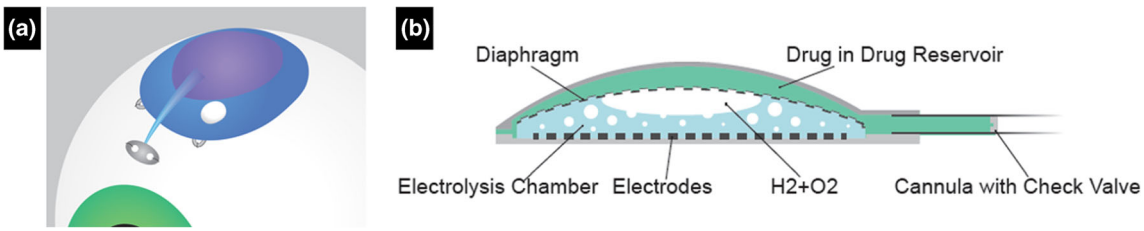

Fig. 7 Replenish MicroPump schematic and drug release mechanism. **a** Replenish MicroPump implanted on the sclera beneath the conjunctiva. **b** Replenish MicroPump drug release mechanism: electrodes in the electrolysis chamber generate an electric potential electrolyzing H_2O into H_2 and O_2 when the device is turned on. This creates pressure on the diaphragm that shifts drug in drug reservoir and displaces it through the cannula

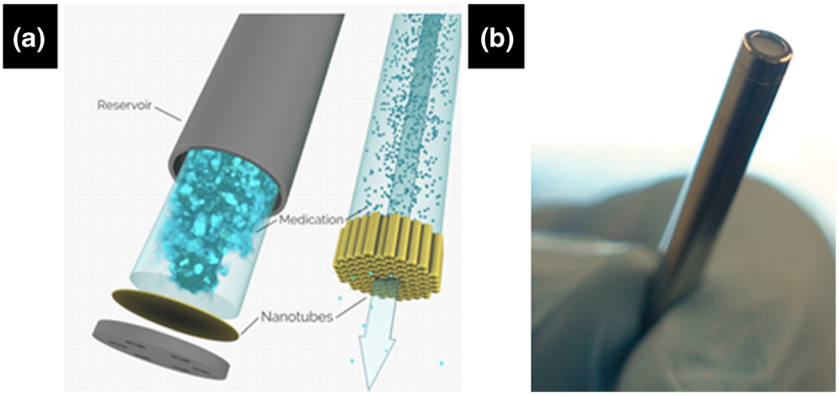

Fig. 8 NEMS translational research devices. **a** Schematic of nanoportal membrane from Nano Precision Medical showing how the nanotubes are the rate-limiting step for drug release from the reservoir (Image used with permission from Nano Precision Medical). **b** Drug-versatile Delpor Inc. implant with two membranes with NANOPOR™ technology fixed at each end (Image used with permission from Delpor Inc.)

formulation of olanzapine, respectively. Both are antipsychotic drugs, with risperidone used to treat schizophrenia and olanzapine used to treat bipolar disorder (Delpor n.d.-b; Delpor n.d.-c).

The nanochannel Delivery System (nDS) has nanochannels as small as 2.5 nm with tight tolerances on size, geometry, and surface properties. It was further developed by Grattoni et al. and is currently in clinical translation (Grattoni et al. 2009, 2011a c). The nDS membrane, a 5 × 20 × 12.3 mm or 43 × 28.5 × 8.7 mm silicon chip, represents the core of the nDS implantable technology (Fig. 9a). The membrane exploits the previously mentioned nanoscale phenomena to passively control the constant release of drugs, biological molecules, and nanoparticles without requiring movable components or actuation (Fig. 9b) (Fine et al. 2010; Grattoni et al. 2011a). The implant contains the nDS membrane, a mechanically robust shell, and loading ports with sealing components. This simple architecture allows for high effective loading efficiency, which, depending on the size and shape of the implant, may range from 60 to 90% (Fig. 9c). This technology is suitable for the use of drugs in liquid, suspension, solid, and powder forms in water, organic solvent, or lipid-based formulations. This offers flexibility in terms of its employment for a broad spectrum of therapeutic applications, enabling the delivery of drugs in their most stable formulation for long-term treatment. Transcutaneous refilling allows the treatment of chronic pathologies over several years without need for explantation and replacement.

The nDS technology was validated *in vitro* and *in vivo* in rodents, dogs, pigs, and non-human primates with a constant, sustained release of drug molecules and nanoparticles over a broad range of molecular sizes at release rates relevant for medical applications (Di Trani et al. 2019; Ferrati et al. 2013 2015; Filgueira et al. 2016; Fine et al. 2010; Grattoni et al. 2011c; Sih et al. 2013). The nDS can sustain release of HIV PrEP antiretroviral drugs, tenofovir alafenamide fumarate, and emtricitabine for 83 days in non-human primates and allow transcutaneous drug refilling (Chua et al. 2018b). Grattoni et al. developed a cylindrical intratumoral device approximately 3.5 mm long with a silicone cap at one end and a smaller nDS on the other end (Fig. 9d). This device, termed the nanofluidic-based drug eluting seed (NDES), has a reservoir capacity of 3.3–5 μl and is percutaneously delivered intratumorally via minimally invasive insertion with a trocar. The authors demonstrated that the intratumoral sustained release of CD40 and OX40 from the NDES increases immune cell infiltration. Thus, the nDS nanochannel platform has the potential to expand available clinical options for intratumoral immunotherapy delivery (Chua et al. 2018a; Di Trani et al. 2017; Hood et al. 2016).

4.2.2 NEMS for tunable delivery

Some diseases require a variable rather than a constant drug delivery dose. The passively controlled nDS membrane can be accompanied by electrodes to adjust the delivery rate of drugs, allowing for programmable dose modulation, remote titration, and responses to sensor feedback (Fine et al. 2011; Grattoni et al. 2011b). After applying a 1 .5V direct current electrical field across the membrane, ionic species redistribute across the nanochannels, causing ionic concentration polarization that can be modified to tune drug release rate (Bruno et al. 2015, 2016; Di Trani et al. 2017; Grattoni et al. 2011a). The dynamically controlled nDS membrane can be mounted on a drug reservoir remotely controlled via Bluetooth Low Energy communication (Fig. 9e). This technology has been validated *in vitro,* demonstrating changes in methotrexate release when transmembrane potential is applied. A disadvantage of this device is that its volumetric loading efficiency is low (22%) due to the volume of the circuitry chamber. However, this implant is an adaptable research tool for drug development and pharmacological studies (Di Trani et al. 2017).

To summarize, MEMS and NEMS take advantage of micro- and nanoscale transport properties for drug delivery. Nanofluidics enables zero-order drug release kinetics for months with no potentially dangerous initial burst release. Although most are not yet FDA-approved, there is great potential to make small implants that can treat a wide variety of diseases. Table 3 shows a comparison of advantages and limitations of MEMS and NEMS.

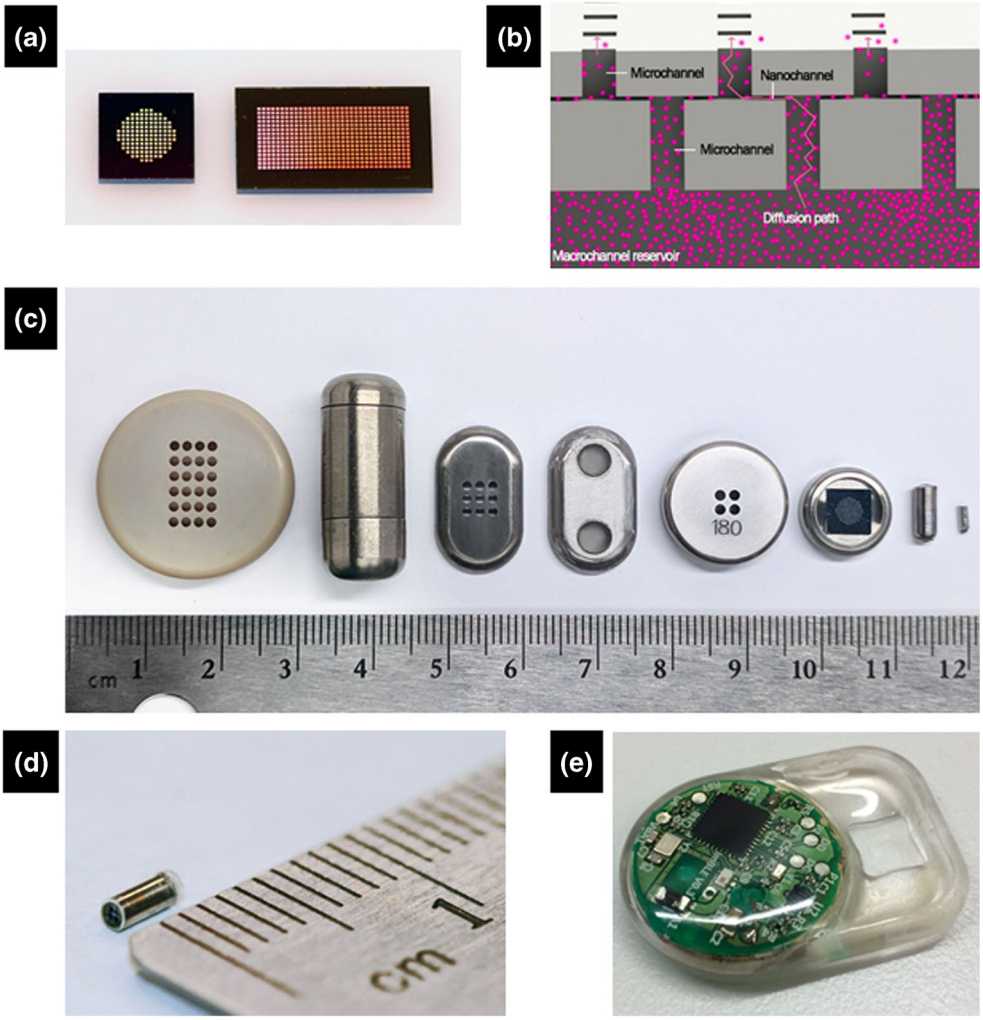

Fig. 9 nDS. **a** Differently sized mechanically robust silicon microfabricated nDS membranes, which house a defined number of densely packed slit-nanochannels to achieve constant and sustained delivery of therapeutics over extended periods of time. **b** Drug release diffusion path through nDS membrane: first from drug reservoir to perpendicular microchannels, then rate-limiting horizontal nanochannels, and then out through perpendicular microchannels. **c** The membrane is conveniently mounted on a drug delivery reservoir with a size and shape that can be optimized for the therapeutic application, drug, duration of treatment, and site of implantation. **d** Image of NDES with nDS membrane next to ruler to illustrate its small size. **e** Dynamically controlled nDS membrane mounted on polyether ether ketone, sized 24 × 34 × 4.5 mm^3, with an 800-μl drug reservoir chamber and a circuitry chamber with the electronics and battery

5 Sites of implantation

Although implants offer refined and efficacious means for controlled drug delivery, they all require placement by a healthcare professional. Surgical procedures vary based on the site of implantation and are associated with potential challenges and adverse effects. Although side effects are usually mild, they can be significant in some cases. Here, we describe various insertion procedures and provide an overview of their most common challenges to provide insight that can aid in the development of the next generation of drug delivery implants. Figure 10 illustrates the different sites of implantation for implants.

5.1 Intraocular placement

In addition to drug loading efficiency, the implantation procedure of a device is also of great importance when designing an implant. The end goal is the use of a minimally invasive in-office procedure by a trained healthcare professional that does not require post-operative care. Both ILUVIEN® and Retisert® posterior chamber implantations are performed in a doctor's office, as they require aseptic conditions and anesthesia. ILUVIEN® is minimally invasive, whereas Retisert® is invasive due to its shape. The small cylindrical shape of ILUVIEN® fits inside a needle and permits intravitreal injection (Fig. 11a). A benefit is that there is no need for stitches as the sclera can self-heal from the needle wound, reducing complications (Borkar et al. 2017; Logan et al. 2016). By contrast, Retisert® requires sclerotomy along with blood vessel cauterization to insert the irregularly shaped device and sutures to anchor it within the posterior chamber (Fig. 11b). The sclerotomy incision also requires subconjunctival antibiotics and a steroid injection (Bausch & Lomb n.d.; Yasin et al. 2014). The incision must be re-opened for removal, but the implant can be replaced using the same anchoring suture in the sclera. However, some ophthalmologists prefer to insert a new Retisert® at another incision site, leaving the old implant in place. If the patient requires a third implant, ophthalmologists will replace the first implant (Nicholson et al. 2012). Retisert® limitations could be addressed by changing the implant shape to a cylinder to allow a non-invasive procedure. The

Table 3 Comparison between MEMS and NEMS

Implant	Development status	Advantages	Limitations
Microchip	Human trial	• Reservoir-specific trigger • Drug versatility • Remote control of drug administration	• Large size • Extremely small drug reservoir • Very low loading efficiency • Complex technology • Requires battery • Difficult insertion and removal procedures • High fabrication and assembly costs • Pulsatile drug release • Rigid implant
Replenish MicroPump	Human trial	• Refillability • Drug versatility • The Eye™ programmable doses • Human safety evaluated	• Requires battery • Difficult insertion procedure • High manufacturing cost • Rigid implant
nDS	Translational research	• Zero-order kinetics • High loading efficiency • Drug and reservoir versatility • Scalability • Transcutaneous refilling • Remote tunable release • Systemic or site-specific drug release	• High rates of drug delivery (mg/day) require large membrane surface area • Difficult insertion and removal procedures • Rigid implant
NanoPortal Membrane	Translational research	• Drug versatility • Zero-order kinetics • Small size and optimal shape • High loading efficiency	• Drug release for 3 months to 1 year • Implant must be exchanged • Rigid implant
NANOPOR™ technology	Translational research	• Zero-order kinetics • Prozor™ technology for insoluble drugs • Small size and optimal shape • High Loading efficiency • Low manufacturing cost	• Implant must be exchanged Rigid implant

irregularly shaped Retisert® device contains 0.59 mg FA compared with 0.19 mg in the smaller, cylinder-shaped ILUVIEN®. Accordingly, multiple smaller cylinder implants could be injected into the vitreous humor to maintain the therapeutic dose for DME treatment.

Even though implantable devices offer the obvious and needed advantages of site-specific therapeutic delivery, there are some limitations and challenges directly related to the physical presence of an object in the eye. Patients must be monitored for the most common complications, intraocular pressure elevation and endophthalmitis, after implantation, because a foreign device is introduced into a pressure-regulated chamber (FDA Reference IDs: 2955048; 3635981) (Alfaqawi et al. 2017; Bausch & Lomb n.d.; Borkar et al. 2017; Logan et al. 2016; Parrish et al. 2016; Wright and Hall 2016; Yasin et al. 2014). Although ILUVIEN® has the convenience of a sutureless procedure, there are reports of implant migration into the anterior chamber, blocking the visual axis, and dislodgement into the infusion cannula during vitrectomy (Andreatta et al. 2017; El-Ghrably et al. 2015; Moisseiev and Morse 2016; Papastavrou et al. 2017). Reported Retisert® adverse effects are mostly sclerotomy-related: hypotony, temporary decrease in visual acuity, cataract formation, choroidal detachment, retinal detachment, vitreous hemorrhage, wound dehiscence, implant dislocation, and scleral melt (FDA Reference ID: 2955048) (Almeida et al. 2015; Chang et al. 2015; Freitas-Neto et al. 2015; Petrou et al. 2014; Yasin et al. 2014). For these reasons, the doctor performs indirect ophthalmoscopy to verify correct placement of the implant, adequate central retinal artery perfusion, and absence of complications (FDA Reference IDs: 2955048; 3635981) (Bausch & Lomb n.d.; Yasin et al. 2014). Nonetheless, as previously mentioned, the benefits of both of these implants outweigh the few complication reports.

An approach to avoiding placement of foreign devices in the vitreous humor is to anchor an implant episclerally and deliver drugs into the posterior chamber through a cannula, like the Replenish MicroPump. The PMP reservoir and intraocular cannula are sutured episclerally between the superior and lateral rectus muscles to impede movement (Fig. 11c). A sclerotomy is required, but the incision is small as only the cannula must be inserted into the posterior chamber, followed by suturing of the conjunctiva (Humayun et al. 2014). An advantage of the PMP is its ease of access and the possibility of refilling the drug reservoir, eliminating future device removal or replacement (Yasin et al. 2014). A major limitation of the PMP is that it has not undergone clinical trials, so although it has a refill feature, its safety and efficacy have yet to be established.

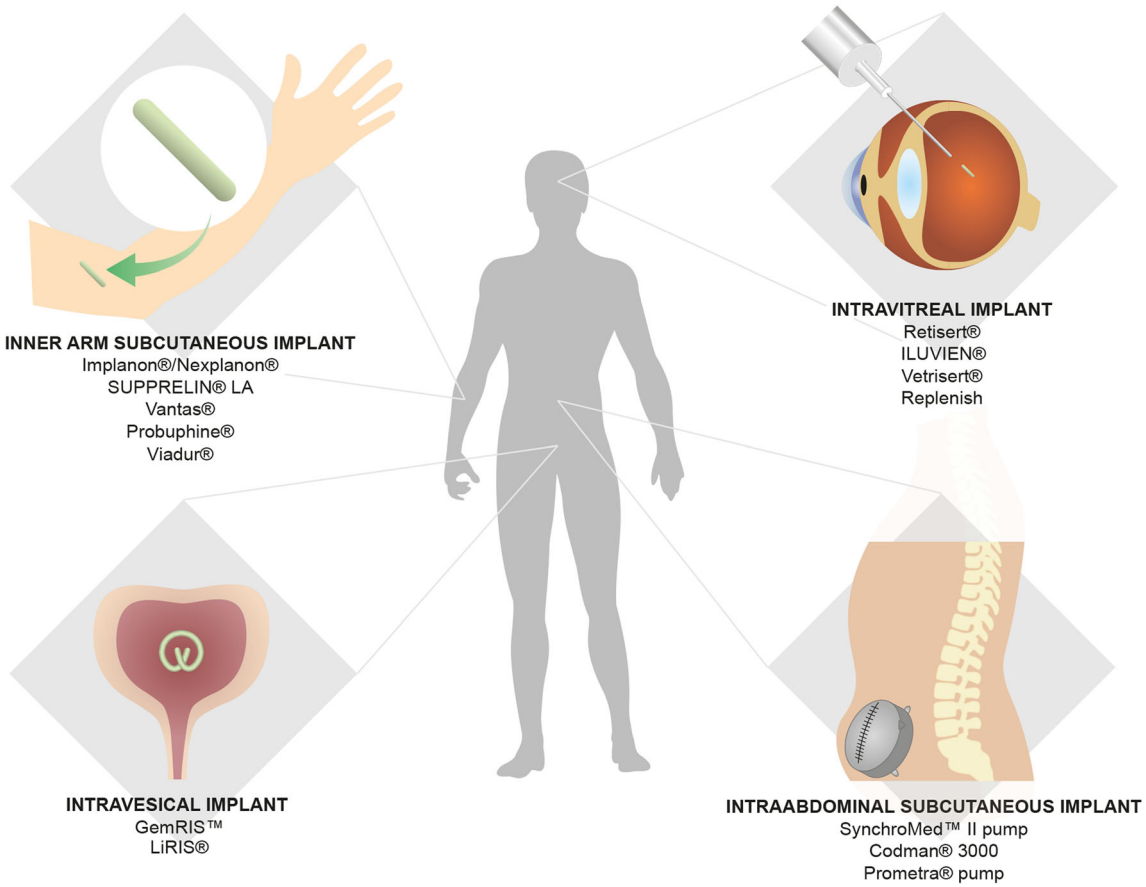

Fig. 10 Sites of implantation for FDA-approved implants and devices in clinical trials

5.2 Upper inner arm subcutaneous placement

The subcutaneous tissue is advantageous for drug delivery because the gastrointestinal tract is bypassed, thus improving drug bioavailability for systemic administration (Kumar and Pillai 2018). Also, the implantation site should be discrete but readily accessible for a quick in-office procedure and not uncomfortable to the patient. Thus, the most widely used implantation site in the clinic is the upper inner arm, for which implants are cylindrical and have a personalized applicator device that facilitates their insertion. Implant placement is an in-office procedure performed by a trained healthcare provider that takes approximately 10 min. Implanon®, Nexplanon®, SUPPRELIN® LA, and Vantas® are inserted in the inner side of the non-dominant upper arm approximately 8–10 cm above the medial epicondyle of the humerus after injection of local anesthesia (Fig. 11d) (FDA Reference IDs: 2887911; 3080389; 4099967; 4100681).Probuphine® implants are inserted at the same site but require a minor incision followed by insertion of four implants. These are positioned in a close fan-shaped distribution 4–6 mm apart with the fan opening toward the shoulder (Fig. 11e) (FDA Reference ID: 4215185) (Itzoe and Guarnieri 2017; Smith et al. 2017). Interestingly, different subcutaneous implantation sites have been adapted to meet the patient's needs. Nexplanon® was inserted in the scapular region in patients at risk of self-removal of the implant (Pragout et al. 2018). In elderly patients, Vantas® is subcutaneously inserted in the abdominal region due to patient-limited arm mobility (Woolen et al. 2014).

When inserting implants into the upper arm, it is important to avoid the sulcus between the biceps and triceps muscles and the neurovascular bundle that lies deeper in the subcutaneous tissue to avoid complications such as peripheral nerve injury and paresthesia (Laumonerie et al. 2018). Equally important, the presence of the device must always be verified immediately after insertion to circumvent implant migration. There are reports of difficulty removing Implanon®/Nexplanon® devices associated with peripheral nerve injury and implant migration (Barlow-Evans et al. 2017; Chevreau et al. 2018; Chung et al. 2017; Diego et al. 2017; Guiahi et al. 2014; Laumonerie et al. 2018; Odom et al. 2017). Regardless, the benefits are indisputable given the high efficacy rate and that most common adverse effects reported for these implants include erythema, hematoma, application site pain, and edema are quick to resolve (FDA Reference IDs: 2887911; 3080389; 4099967; 4100681; 4215185) (Davis et al. 2014; Donnelly et al. 2015; Eugster 2015; Fisher et al. 2014; Itzoe and

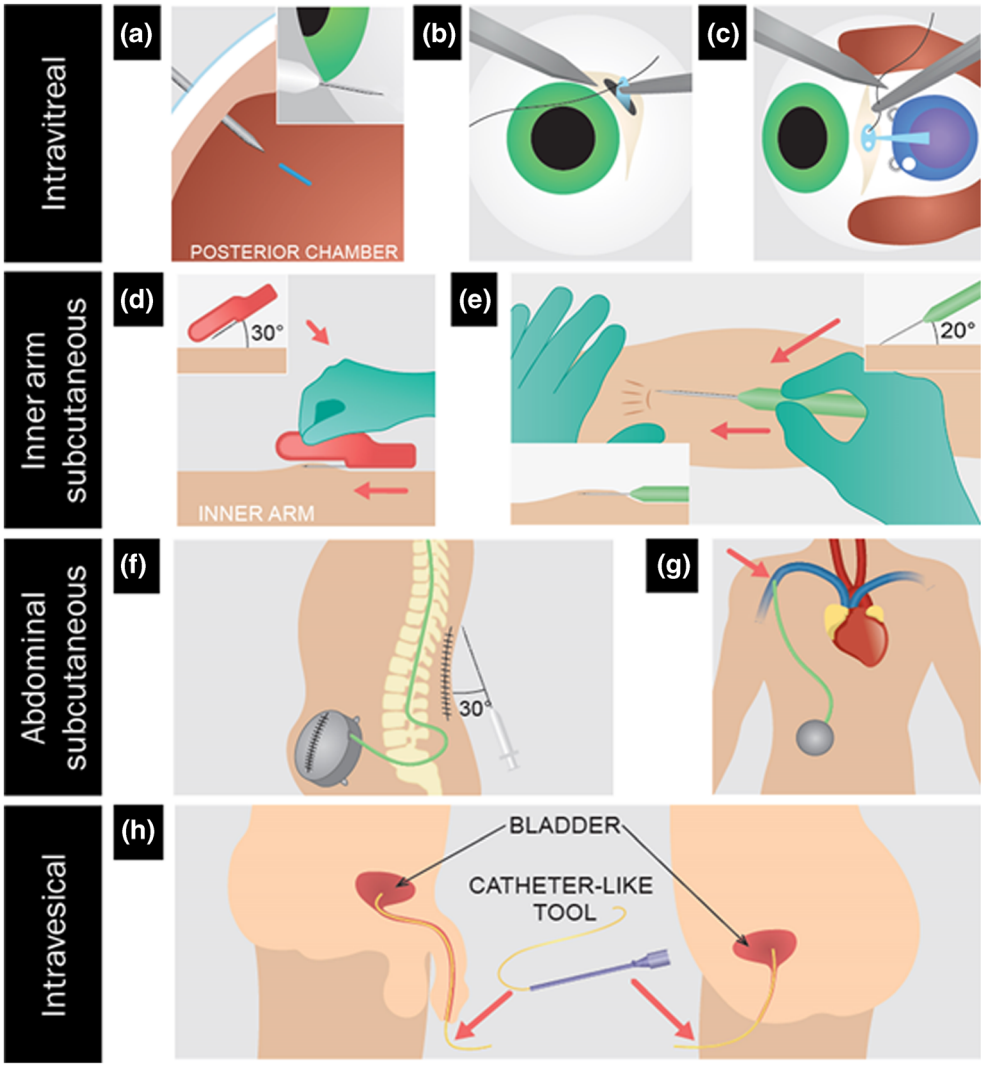

Fig. 11 Implantation procedures. **a** ILUVIEN® intravitreal insertion. **b** Retisert® sutured in posterior chamber. **c** Replenish MicroPump episcleral placement. **d** Implanon®, Nexplanon®, SUPPRELIN® LA, and Vantas® insertion in the inner arm with personalized applicator. **e** Four Probuphine® implants positioned in fan-shaped distribution in the inner arm. **f** SynchroMed™ II, Codman® 3000, and Prometra® pump surgery for abdominal subcutaneous placement of the pump and intrathecal catheter. **g** SynchroMed™ II pump surgery for abdominal subcutaneous placement of the pump and intravenous catheter. **h** GemRIS™ and LiRIS intravesical insertion with a catheter-like tool

Guarnieri 2017; Pedroso et al. 2015; Serati et al. 2015; Shumer et al. 2016; Silverman et al. 2015; Simon et al. 2016; Smith et al. 2017).

5.3 Abdominal subcutaneous placement

The size of peristaltic and infusion pumps necessitates catheters for site-specific drug delivery and restricts them to a subcutaneous abdominal implantation site. SynchroMed™ II, Codman® 3000, and Prometra® pumps require surgery under general anesthesia, resulting in a significantly higher costs, as this procedure take 1–3 h in an operating room due to the requirement for fluoroscopy for intrathecal catheter placement and verification (Flowonix Medical Inc. 2017; Medtronic 2017). At this implantation site, 27% of reported complications of intrathecal delivery are related to surgical procedures (Stetkarova et al. 2010). A surgeon implants a filled pump subcutaneously in the abdomen in a pump pocket no more than 2.5 cm from the surface of the skin and connects the intracatheter (Fig. 11f). The pump pocket and the spinal incision site are irrigated, sutured, and covered in dressing to avoid infection (Flowonix Medical Inc. 2017; Medtronic 2017). For intravenous treprostinil administration, a catheter is inserted into the superior vena cava via a subclavian, cephalic, jugular, or axillary puncture, anchored to the venotomy site, and connected to the abdominal pump pocket (Fig. 11g) (Bourge et al. 2016).

A benefit of these pumps is transcutaneous drug refill, allowing longer treatment durations. However, potential severe complications from erroneous subcutaneous injection of drug during device refilling have been reported (Maino et al. 2014; Perruchoud et al. 2012; Ruan et al. 2010). With this in mind, ultrasound-guided pump refill is a feasible and simple technique that reduces the probability of refill-related complications (Gofeld and McQueen 2011; Saulino and Gofeld 2014). Common minor adverse effects reported for SynchroMed™ II, Codman® 3000, and Prometra® pumps are implant site pain, edema, and hematoma (Codman & Shurtleff; Ethans et al. 2005; Pope and Deer 2017; Rauck et al. 2013). As previously mentioned, these pumps have

movable components that control drug delivery, increasing the risk of device malfunctions. There are reports of cases in which the pump had to be explanted due to pump failures (Kalyvas et al. 2014; Riordan and Murphy 2015; Sgouros et al. 2010). These discoidal pumps are limited by their size and therefore necessitate catheters to deliver the drug to the site of interest. Given that most complications are attributable to catheter malfunctions, implants should be redesigned to omit the need for catheters (Ethans et al. 2005; Kalyvas et al. 2014; Miracle et al. 2011; Stetkarova et al. 2010). Even though abdominal subcutaneous placement of pumps clearly has limitations and challenges, the devices have had a positive impact on improving patient health and living conditions, outweighing the complications and reported adverse effects.

5.4 Intravesical placement

Other implants that have a drug release rate dependent on the targeted organ are GemRIS and LiRIS. Both of these site-specific devices are placed in the bladder as an in-office procedure that does not require an operating room. Insertion of the implant was a priority in their design, as it changes shape after it is implanted in the bladder. At first, it is shaped as a long tube positioned in a catheter-like tool that enables easy insertion into the bladder (Fig. 11h). After delivery, the implant wire restructures the implant into a pretzel-like shape that impedes expulsion of the device through the urethra. After the treatment period, the implant is removed via cystoscopy (Matheson 2014; Nickel et al. 2012). Possible complications are yet to be reported, as these implants are currently in clinical trials.

5.5 Next generation of implantable drug delivery systems

The complexity and limitations of surgical procedures for implantation and explantation have significant effects on patient acceptability of the technology. As such, future device designs should employ minimally invasive approaches, smaller implant volumes, and fewer insertion-explantation procedures to fully leverage their potential. Cylindrical devices, such as the polymeric implants Implanon®/Nexplanon®, SUPPRELIN® LA, Vantas, and ILUVIEN® and the osmotic pumps GemRIS, LiRIS, and Viadur®, have minimally invasive insertion procedures. Yet, their major disadvantage is the need for implant replacement if the patient wishes to continue the medication. For this reason, implants intended to be inserted subcutaneously in the inner arm need to incorporate a drug refill feature, like pumps. As previously mentioned, the discoidal subcutaneous abdominal pumps SynchroMed™ II, Codman® 3000, and Prometra® II have this feature, but the pump size is a key limitation, as it requires surgery for implantation-explantation. If implants are to become a mainstream drug administration route, implants should be carefully designed with a small volume for minimally invasive implantation and chronically sustained drug delivery eluding insertion-explantation with drug refillability.

Even if new implants are designed with these considerations, patient counseling will be crucial to increase acceptability. Implantation procedures lower patient acceptance because all procedures guarantee pain and discomfort, even if only from the local anesthetic. Therefore, patients will require counseling to show the potential cumulative benefits of prolonged compliance-free therapy, with optimized drug delivery far outweighing potential risks and immediate discomfort (Danckwerts and Fassihi 1991; Kumar and Pillai 2018; Rajgor et al. 2011). Also, data demonstrating the value of using implants over conventional treatment could drive insurance companies to cover the costs. Insurance companies may be more willing to pay for less expensive conventional therapy than to reimburse an outpatient procedure to insert the implant as well as cover the costs associated with the implant (i.e. refilling, removal, etc.).

6 Deployment in the developing world

The burden of chronic diseases in developing countries is rapidly increasing and has unfavorable social, economic, and health consequences (Alwan et al. 2010). Often, these countries have unreliable healthcare services that incite poor health practices, medication non-adherence and subsequently increase mortality rates. An important cause of non-adherence in developing countries is the high cost of therapeutics and paucity of health resources, which results in waste and underutilization of already limited resources. Also, healthcare center visits are linked to patient compliance since these trips are time-consuming and expensive. To ensure that all countries receive quality healthcare, national and international agencies must invest in developing countries (Atinga et al. 2018; Fullman et al. 2017; Pagès-Puigdemont et al. 2016; World Health Organization 2003). A proposal to resolve medication non-adherence due to lack of health resources and healthcare centers are long-term drug delivery devices. The Bill and Melinda Gates Foundation, among others, strive to resolve this issue by supporting different companies for the development of long-term sustained release implants that can be administered in developing countries.

Pregnancy is not a chronic disease but does require sustained prenatal care to ensure that both the baby and mother are healthy. Sustainable Development Goals call for a reduction in maternal deaths to fewer than 70 per 100,000 by 2030 (Kassebaum et al. 2016). Moreover,

Millennium Development Goals call for universal access to reproductive healthcare, specifically contraceptives. Providing free contraception implants to girls and women in developing countries could benefit 120 million women and help prevent approximately 30 million unintended pregnancies, which in turn would reduce infant and maternal mortality by 280,000 and 30,000 deaths, respectively (Bill & Melinda Gates Foundation n.d.).

The Bill and Melinda Gates Foundation invested in Microchips Biotech to develop a microchip that releases levonorgestrel, a progestin, for 16 years and can be stopped at any time with a wireless controller (Lee 2014). Jadelle® (Bayer, Leverkusen, Germany) is a polymer-based levonorgestrel-releasing implant similar to Implanon®. Jadelle® was prequalified by the World Health Organization in 2009, and the Jadelle Access Program was launched by the Bill and Melinda Gates Foundation and Bayer in 2013. The goal of this program is to deliver 27 million implants in 6 years. Bayer will supply the Jadelle® implants, and the Foundation will cover default risk. Although Jadelle® is approved in the US, it was not sold as of 2015 (Bayer AG Pharmaceuticals n.d.).

The Bill and Melinda Gates Foundation has also taken interest in the prevention of HIV and supported the research of Intarcia Therapeutics, Inc. to develop a pump that can store enough drug doses for 6–12 months, enabling people in developing countries to have HIV protection (Intarcia Therapeutics Inc n.d.-b). Although the Bill and Melinda Gates Foundation has taken a big step toward investing in drug delivery implants in developing countries, more efforts are needed.

The feasibility of deploying implants in developing countries largely depends on cost, simplicity in device implantation, and patient acceptance. The cost of devices can certainly represent a barrier for their deployment. In principle, the implant cost should be close to the cost of the drug itself. Complex electromechanical systems and pumps may be too expensive to achieve ample utilization. Due to the limited health care resources, deployment in developing countries may be exclusively limited to implants which require minimally invasive procedures such as subcutaneous placement in the inner arm. In this case, the surgical technique and expertise needed is nominal and can be easily taught ad hoc. As previously discussed, larger systems for either subcutaneous or deeper implantation would not be as attainable because of the invasive surgery required and the needs for follow-ups and longer recovery periods. Refillable implants could be very relevant in the context of preventive therapies for infectious diseases or for chronic treatments. Transcutaneous refilling can extend the life span of an implant while avoiding repeated surgical removal and replacement procedures. However, as it has been shown for SynchroMed™ pump-like systems, refilling requires specilized training to avoid failures that could be catastrophic with drug leakage in the surrounding tissues. Patient acceptability is key for the success of implantable systems. In cases such as the treatment and prevention of HIV, the use of implants is faced with the issue of 'stigma' associated with the disease. In these circumstances, the implantation site is determinant as patients may be concerned about the visibility of the device underneath the skin. Other factors, such as religion and spiritual beliefs also play an important role: studies revealed one of the reasons for medication non-adherence is that patients usually prefer spiritual or divine healing causations beyond medical treatment, as a result of low trust in new medication technologies, their efficacy and fear of side effects (Atinga et al. 2018; Pagès-Puigdemont et al. 2016).

On a different note, implants have the potential of addressing one key problem in deliverying medical treatments. Implants can minimize the frequency with which patients have to visit the health care centers, avoiding multiple lengthy travels and thus improving adherence to treatment. Ideally, tunable implants where clinicians can remotely adjust medication regimes and monitor patients through telemedicine could be advantageous. However, these systems may in turn be more expensive and therefore not implementable.

7 Conclusions

The treatment of chronic diseases will shift from oral dosing to implantable drug delivery devices as they obviate patient non-adherence and potentially limit side effects. Different passive and dynamic drug delivery technologies have received FDA approval, are in clinical trials, or are in an advanced stage of development. Consideration of current implantation procedures can further improve implant designs and thereby increase patient acceptability. Long-term delivery devices for chronic illness treatment with minimally invasive approaches for implantation should be employed for use in developing countries and to reduce DALYs. In conclusion, advanced implantable drug delivery devices hold promise as more effective treatment tools, transforming the clinical landscape of therapeutics given the growing incidence of chronic diseases.

Acknowledgements We thank Virginia Facciotto (virginia.facciotto @gmail.com) for the design of graphics and figures. Funding support from The Nancy Owens Breast Cancer Foundation, Center for the Advancement of Science in Space (CASIS) GA-2013-118, CASIS GA-2014-145, NIH NIAID R01 AI120749-01A1, NIH NIGMS R01 GM 127558.

Compliance with ethical standards J.S and A.G. disclose a financial interest in NanoMedical systems, Inc. F.P.P. and A.B. disclose no competing financial interest.

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