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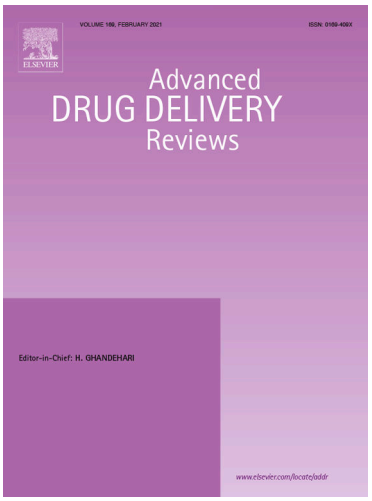

Solid implantable devices for sustained drug delivery

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Solid implantable devices for sustained drug delivery

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Abstract

Implantable drug delivery systems (IDDS) are an attractive alternative to conventional drug administration routes. Oral and injectable drug administration are the most common routes for drug delivery providing peaks of drug concentrations in blood after administration followed by concentration decay after a few hours. Therefore, constant drug administration is required to keep drug levels within the therapeutic window of the drug. Moreover, oral drug delivery presents alternative challenges due to drug degradation within the gastrointestinal tract or first pass metabolism. IDDS can be used to provide sustained drug delivery for prolonged periods of time. The use of this type of systems is especially interesting for the treatment of chronic conditions where patient adherence to conventional treatments can be challenging. These systems are normally used for systemic drug delivery. However, IDDS can be used for localised administration to maximise the amount of drug delivered within the active site while reducing systemic exposure. This review will cover current applications of IDDS focusing on the materials used to prepare this type of systems and the main therapeutic areas of application.

Keywords: Implant; sustained drug release; local drug delivery; biodegradable polymers

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1. Introduction

Conventional clinical therapies rely on intermittent administration of drugs using different routes. Oral and injectable drug administration are the most common routes for drug delivery providing peaks of drug concentrations in blood after administration followed by concentration decay after a few hours [1,2]. This effect is usually known as “peak and valley” effect. This can present some limitations as high drug levels can present toxicity issues while low drug levels are not effective in the patient [1,2]. Oral route is the ideal route of administration due to its convenience [3]. However, it present additional challenges. First, the drug should be stable within the gastrointestinal tract to avoid enzymatic degradation and to survive to the acidic environment. Additionally, drugs administered oral route suffer from first pass metabolism potentially reducing their bioavailability. Accordingly, oral administration requires repeated doses to keep drug levels within the therapeutic window of the drug. This is especially important for the treatment of long-term and chronic conditions [1,4]. Finally, it is important to note that most of new drugs do not show ideal properties for oral administration. Parameters such as drug solubility can limit oral administration of new drugs [5]. On the other hand, injectable formulations do not present many of these limitations. However, this method of administration is invasive and normally requires trained healthcare professionals to be administered [6]. Both injectable and oral routes provide systemic drug levels rather than localised effect. The treatment of certain conditions requires high drug levels at specific locations. To achieve this, high drug doses can be used. However, high doses can lead to toxicity issues [1]. Taking into consideration all these limitations it is obvious that new types of drug delivery systems with the ability to provide continuous drug administration for prolonged periods of time. Implantable drug delivery systems (IDDS) can be used for this purpose [1,4,7]. IDDS can be used to treat a broad variety of conditions including cancer and HIV among others [8]. The use of this type of systems is especially interesting for the treatment of chronic conditions.

Pharmacological treatment of chronic conditions, such as schizophrenia or HIV, requires regular drug administration. Accordingly, patient compliance is a key factor for the success of the treatment. For example, non-adherence to treatment for schizophrenic patient increase the relapse risk [9]. Moreover, relapse for this type of patient is associated with higher hospitalisation rates and higher rates of suicide [9]. All these factors have an impact not only on the health of the patient but on the cost of the treatment [10]. Therefore, IDDS can be used to address the limitations of conventional therapies for chronic conditions.

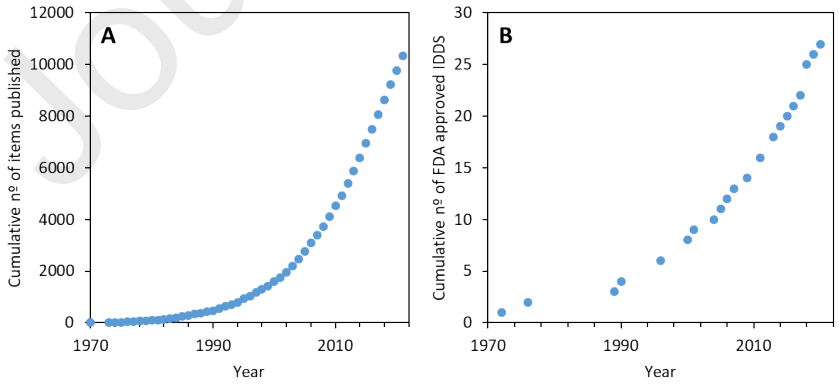

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Figure 1. Number of items published per year including the key words “drug delivery” and “implant” in Scopus® (A). Cumulative number of FDA-approved IDDS per year (data obtained from: https://www.accessdata.fda.gov/scripts/cder/daf/) (B).

IDDS have been gaining popularity over the years, however they were described for the first time during the 1930s [11]. The pioneering IDDS was a pellet loaded with a hormone. This pellet was designed to be subcutaneously implanted into livestock to improve their growth making the meat production process more efficient [11]. A few years later, in 1938, the applications of this type of devices were described for the treatment of female patients suffering from premature menopause [12]. Despite been described more than 90 years ago, there has been a growing interest in IDDS during the last 20 years (Figure 1). This interest is not only noticeable within the academic environment. Pharma companies have shown enormous interest on the development of new drug delivery systems as can be seen in Figure 1B. The global market for implantable drug delivery systems value in 2019 was estimated to be $10,091.9 million [13]. Moreover, it is predicted to grow at an annual growth rate of around 8% until 2027 reaching a value of $13,211.8 million [13].

There are a wide variety of long-acting drug delivery systems including self-assembled gels [14–17], micro- and nanoparticles [17–19] and solid preformed devices [1,4]. This review will be focused on solid IDDS covering the materials used to prepare this type of devices and their therapeutical applications.

2. Classification of IDDS

There is not a clear classification system for IDDS due to the existence of complex implants that fall within hybrid categories. However, IDDS can be classified in two groups: active implants and passive implants [4,20]. The former type of IDDS shows active energy dependant mechanisms to generate the driving force to provide drug release. On the other hand, passive implants depend on passive diffusion to provide drug release. In addition to drug delivery mechanism implants can be classified as biodegradable or non-biodegradable depending on the type of materials used to prepare them.

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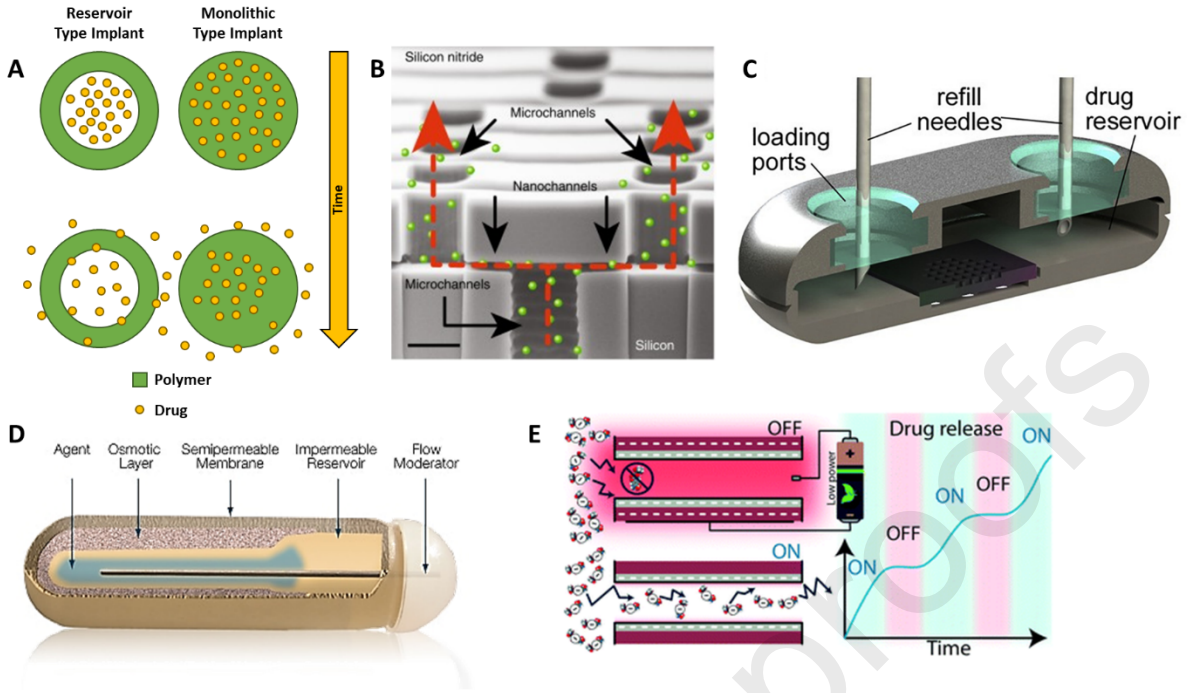

Figure 2. Schematic of reservoir-type and monolithic-type implants (A). SEM image of a rate controlling membrane made of silicon containing micro- and nano-channels (scale bar: 1 µm) (B). Diagram of a transcutaneous refillable implant (C). Diagram of ALZET® osmotic pump (D). Schematic of an electrostatically gated nanofluidic membrane (E). Reproduced with permission from DURECT Corporation, [21], [22] and [23].

Passive IDDS do not contain moving parts and depends on drug diffusion to achieve sustained drug release. This type of IDDS can be prepared using biodegradable or non-biodegradable materials. These implants are normally prepared by combining drug molecules with biocompatible polymers. They do not contain any moving parts and drug release is achieved by passive drug diffusion. Depending on the drug location within the device there are two potential types of implants: reservoir type implants and monolithic implants (Figure 2A). Monolithic-type implants contain the drug dispersed within a matrix -formed by a biocompatible compound [4,24]. In most of the cases, it is a polymeric compound. On the other hand, reservoir-type implants contain a drug loaded core surrounded by a permeable membrane that controls drug release [4,20]. Normally this type of membrane is made of non-biodegradable materials such as silicone [25]. However, there are examples of reservoir type implants prepared using biodegradable rate-controlling membranes [26–29]. In addition to conventional polymeric membranes, advanced systems have been recently developed using silicon membranes containing micro- and nano-channels to sustain drug release (Figure 2B) [21]. Interestingly, advanced refillable reservoir type IDDS have been described in the literature [22,30,31]. These systems can be refilled using a conventional needle as they have a port, or a catheter attached to them. Figure 2D shows a diagram of a transcutaneous refillable implant.

Active polymeric implants do not rely on passive diffusion of drugs from the implant matrix or trough membranes. This type of implants present a positive driving force to control drug release [24]. This type of devices are normally pump-type implants such as osmotic pumps [4,20]. A diagram of a osmotic pump can be seen in Figure 2B. Osmotic pumps are composed of a drug core surrounded by a semipermeable membrane containing a hole to allow drug release [32]. Osmotic gradients

contribute to the flow of fluid trough the membrane, forcing the drug to be release trough the orifice [32]. This type of design allows a steady drug release (zero order drug release kinetics) [4,20,32]. In addition to osmotic pumps during the last decade micro-electro-mechanical systems (MEMS) have been described as implantable devices for drug delivery [33–35]. These types of devices can be controlled externally or just respond to local changes in the environment due to the presence of sensors [33,36,37]. MEMS are reservoir type implants that rely on different mechanisms to achieve drug delivery. They can contain a single reservoir system with electro-mechanically controlled pump systems to control the release [37] or multiple smaller reservoirs [36]. Micropumps control the flux of drug formulation. In order to pump the drug formulation different mechanisms are used [37]. In some cases not even a pump is required and electric current is the driven mechanism to increase drug permeation across membranes (Figure 2D) [23,38,39]. On the other hand, micro reservoir systems contain a capping membrane that can be activated to release the cargo [36,40,41]. This type of systems are rapidly advancing and they can be prepared containing fully biodegradable electronical mechanisms to trigger drug release [42].

3. Materials used to prepare IDDS and manufacturing techniques

3.1. Natural polymers

As these polymers are found in nature, they tend to exhibit excellent biocompatibility, non-cytotoxicity, and biodegradability [4]. Despite these advantages there are still limitations, they have unpredictable properties, and in terms of production, have low batch-to-batch consistency [4]. Cellulose, chitosan, alginate, collagen, gelatin and silk protein are the main natural polymers used to produce implantable drug delivery systems.

Cellulose is a natural polysaccharide consisting of chains of β-d-glucopyranose monomers and is the most abundant organic compound on earth [43,44]. Cellulose and cellulose derivatives have been used for drug delivery applications [43].

Chitosan is obtained by the de-acetylation of chitin[4], a polysaccharide abundantly found in the cell walls of fungi. Chitosan has good biocompatibility and is easy to process, with controllable mechanics [45], suggesting a good candidate for drug delivery. Unfortunately, it is hydrophobic with low strength, so it tends to be brittle. It could, however, be mixed with other polymers to create a more ideal material [45].

Alginate is a linear polysaccharide naturally found in brown seaweed or algae. With its hydrophilicity, solubility, biocompatibility, and degradability, it makes a great polymer for drug delivery devices [45]. It has the abilities to form hydrogels and encapsulate molecules. This is one of the reasons why there is interest in alginate as a drug vehicle. It can be used to make copolymers to achieve rigidity for devices with drug carrier advantages [45–47].

Collagen is a protein molecule located in the connective tissue of animals [43]. This biomolecule presents special interest due to its biocompatibility and mechanical properties [43]. There are different types of of collagen molecules depending on their origin (skin, tendon, bone, cartilage, skin or vasculature) [48]. It is important to note that each have varying properties. Gelatin is a water-soluble protein derived from collagen, obtained by partially hydrolysing collagen [49]. Collagen and gelatin have been used extensively for tissue engineering applications [43], but also have use in implantable hydrogel drug delivery systems [50–52].

Silk protein obtained from silkworms, some arachnids and flies [53], presents high mechanical resistance due to the alignment of the protein chains parallel to its axis. It is has thus been used for the development of surgical sutures [49]. This is a highly versatile polymer used for a variety of medical applications, among these are subcutaneous implants and drug-eluting stents [54–56].

3.2. Synthetic polymers

These polymers have predictable properties and batch-to-batch consistency compared to their natural counterparts [4]. They can be either biodegradable or non-biodegradable. As mentioned earlier this review will cover solid IDDS and therefore novel materials used for long-acting injectable drug delivery systems such as depot forming formulations [57,58] or "drugamers" [59] are not described here.

3.2.1. Biodegradable synthetic polymers

3.2.1.1. Polylactic acid (PLA)

PLA is a biodegradable, aliphatic polyester [4]. This polymer is hydrophilic and degradation of the ester backbone produces lactic acid, this is a natural metabolite and can therefore be removed safely by the body.

It is important to note that PLA has two enantiomeric forms, an L-lactide (PLLA) and a D-lactide (PLDA). The two forms exhibit different properties, such as in strength and crystallinity [60]. It is a racemic mixture of PLA that is used in drug delivery devices as it has the advantages of PDLA with the control of PLLA [61]. A cautionary point to make is that, although the lactic acid product is well known to the body, a large accumulation can lead to inflammatory host responses [61]. In most cases however, PLA has a slow degradation time, 1-6 months approximately [4].

3.2.1.2. Polyglycolic acid (PGA)

This polymer exhibits many similar properties to PLA [4]. The main difference in PGA is its very rapid degradation by bulk erosion producing glycolic acid products [60]. This leads to inflammatory responses, a particular problem when the amount of polymer implanted is large [61,62].

Despite this polymer displaying excellent mechanical properties [4], it cannot be used alone for drug delivery devices for the reasons discussed above. It is, however, a great candidate for copolymeric materials.

3.2.1.3. Poly(lactic-co-glycolic acid) (PLGA)

Another aliphatic polyester, this material is a copolymer comprised of PLA and PGA[4]. The physical properties of this polymer can be altered by adjusting the composition ratio of PLA and PGA, also adjusting degradation rate [4]. The achievable precision and modification are very attractive for drug delivery [4]. Another benefit of this material is the lack of acidic degradation products [4].

Most biomedical uses of PLGA have been in the area of tissue engineering. Many drugs, however, have varying interaction profiles with the material, so allowing for more drug-based applications [60]. An example of this is the LUPRON DEPOT® [60]. The same material has also been investigated for micro

and nanoparticle drug delivery. Unfortunately, due to bulk degradation, it is difficult to achieve a zero-order release profile [60].

Some other current uses in drug delivery include anti-tumour, anti-infection, anti-thrombosis, angiogenesis, and wound healing [61]. Perhaps, also, there are opportunities for drug eluting tissue scaffolds as a new use due to excellent tissue adhesion properties.

3.2.1.4. Polycaprolactone (PCL)

The last of the aliphatic polyesters, this is possibly the most investigated polymer [4]. Comparable to the previous polymers, PCL is biocompatible and mechanically strong. One of its most notable properties, however, is its long degradation time. The degradation can range anywhere from months to years, and naturally, depends on physical and environmental properties [4]. Additionally, PCL does not create an acidic degradation environment, a huge advantage for implantable devices [63].

This polymer is hydrophobic, but it is relatively easy to increase water penetration by making copolymers with hydrophilic materials. This also allows for tuning of degradation rate[4].

PCL has a high permeability and low toxicity, making it popular in drug delivery device research. Some PCL products are already on the market, such as the contraceptive implant Capronor® [60].

Long-term drug delivery implants have become increasingly possible thanks to this polymer [63]. An exciting development is the creation of microspheres and nanoparticles using PCL/copolymers. These particles capture the advantages of PCL while adding more surface area and porosity, leading to better drug dissolution [63].

3.2.1.5. Polyester amides

The use of polyester amides as for drug delivery applications has been previously reported. In particular, the creation of microspheres has shown effective and efficient entrapment of ionic drugs as well as a slow and controlled release profile [64]. These polymers also have the ability to act as solubility enhancers if the drug in question is poorly water soluble [64]. This could be a great candidate for a copolymer with hydrophobic polymers such as PCL.

3.2.1.6. Polyphosphoesters (PPEs)

These polymers show great biocompatibility and controlled degradation [65]. PPEs are attractive materials for drug delivery due to their likeness to nucleic acids in the body [45]. In fact, they have already been successfully developed as nanocarrier for drug and gene delivery [66].

PPEs also offer the ability of altering hydrophobicity as well as polyvalence. The latter is done through the ester group pendants and backbone variations. These modifications allow for the encapsulation of specific drugs [65]. The degradation rate of PPEs may also be adjusted through the chemical structure of the backbone [65]. Wang et al. showed that faster degradation was achievable by having amino pendant groups that hydrolyse rapidly [66].

3.2.1.7. Polydioxanone (PDS)

This polymer is a polyester prepared through the polymerisation of *p*-dioxanone. With a high crystallinity and hydrophobicity, it undergoes relatively slow degradation over 9-12 months [45]. The main product of PDS degradation is glycoxylate which is either excreted or converted to glycine [45].

Applications for microsphere and nanoparticle applications are already popular, mostly as a copolymer [67]. Some examples include: copolymeric microspheres of PDS/cellulose and PDS/starch [68], copolymeric nanoparticles of PDS/chitosan and copolymeric micelles [69]. Polymers such as PEG present the ability to tailor the micelles' properties for drug release. Zhang et al. loaded these micelles with doxycycline and studied the release [70].

3.2.2. Non-biodegradable polymers

Non-biodegradable polymers have been extensively used to develop IDDS. One of the best examples of the use of this type of polymers are contraceptive implants. The advantage is that we know they are robust and strong over a prolonged period of time, and generally do not cause damage [4]. These materials are also cheaper and easier to manufacture compared to biodegradable materials [4]. The release of drugs from these materials relies on diffusion out of the matrix only, whereas biodegradables rely on degradation of the matrix itself.

The main drawback is, however, that they will not degrade inside the body, thus necessitating the process of removal. This can be off-putting to patients.

3.2.2.1. Polyurethanes (PUs)

Produced from isocyanates, these polymers are a very large family. There are a number of parameters that can be changed in these polymers, such as by changing the polyols or isocyanates used for polymerisation [4].

These polymers are great for long-term implants as they are biocompatible and resistant to hydrolysis [45]. Their physical properties such as rigidity [60] can be adjusted[4] preferentially, perhaps depending on the site of implant and usage.

3.2.2.2. Poly(ethylene-vinyl alcohol) (PEVA)

As with most copolymers, the properties of this material can be changed with differing ratios of vinyl acetate to ethylene [4]. Naturally, modifications are areas of optimisation, an appealing advantage for use of implantable devices.

Many drugs have been investigated using PEVA based implantable dosage forms: 5-fluorouricil for carcinoma [71], BCNU for brain tumours [72], and tetrodotoxin for auditory nerve blockade [73]. PEVA is a common polymer in the research of implantable drug delivery devices in the treatment of different cancers [74]. It does not stop there, PEVA has been the basis of implants previously and currently available on the market. Examples include contraceptives such as Implanon® and Nexplanon® [75], ocular implants, such as Iluvien® [76] and subcutaneous implants like Probuphine®, for the treatment of opioid addiction.

PEVA still possesses the disadvantage of non-biodegradability which can somewhat overshadow its assets. For example, ocular implants, while successful in delivery, add pressure to the inner eye and can cause retinal damage. These implants also need surgically removed.

3.2.2.3. Poly(ether ether ketone)

Poly(ether ether ketone) (PEEK) was first used as an implantable material back in 1987 [77]. It is a non-degradable-biocompatible material. It is gaining popularity for orthopaedic applications due to its high mechanical strength, wear resistance and anticorrosive nature [78]. Moreover, it presents high chemical resistance and thermal stability. These properties make it an ideal candidate for the development of IDDS. However, due to its hydrophobic nature it limits cell adhesion and protein absorption. In order to address this issue, PEEK is combined with other compounds [78].

3.2.2.4. Poly(siloxanes)

Poly(siloxanes) are formed by a combination of silicon and oxygen atoms [79]. These types of polymer have been widely used in medical applications due to their biocompatibility, thermal stability, elastomeric characteristics and chemical inertness [79]. This polymer is hydrophobic, and therefore, it is usually loaded with hydrophobic drugs for delivery [80]. Prolonged release of drugs from PDMS is common and zero order kinetics can be achieved through the production of reservoir devices [80,81]. Silicone-based polymers are non-biodegradable materials [4], again necessitating removal. Despite this, poly(siloxanes) have been extensively used in the development of commercial implantable devices such as Norplant [82].

3.3. Metals

Most IDDS are prepared using polymeric materials. Metals, however, have been widely explored for drug delivery applications. The three main types of metals used for the development of implantable devices are: stainless steel, cobalt, and titanium. Titanium can be found as a pure metal or as alloys with aluminium or vanadium [83]. These types of compounds present a high resistance to corrosion, low density and high specific strength. Accordingly they are used for the development of joint replacement and other, spinal disc or dental implants among many other applications [83]. Titanium alloys have been used for the development of cardiovascular stents and the manufacturing of subcutaneous drug delivery systems [33,84]. Stainless steel is an alloy prepared with iron, nickel and/or chromium [85]. These types of metals present high mechanical strength and resistance to corrosion [83]. Normally, stainless steel is used for the manufacturing of spinal implants, cardiovascular stents, fracture fixation and hip stems [83]. Finally, cobalt and chromium allows present similar properties to the previously described metals and are used in orthodontics, joint replacements, stents and wires (such as pacemaker wires) [83]. Metal-based IDDS will be normally coated or they will act as a reservoir device [33,84].

3.4 Ceramics

Ceramics are inorganic non-metallic materials [86]. These materials are used extensively in dental and orthopaedic applications due to their biocompatibility [87]. Ceramics most used in these applications

include calcium phosphates, zirconia, alumina, silica, and titania. Additional beneficial properties include their easy preparation, the ability to change their size and structure, and their surface area to volume ratios [88]. Ceramic materials typically present slow biodegradability that can be potentially beneficial for long-term IDDS, such as drug-eluting scaffolds. As such, some research is focused on the benefits of this in tissue engineering.

Zirconia and alumina are known as bioinert ceramics, meaning they do not interact with biological material. Unfortunately, this can cause fibrous capsule formation around the implants [89]. These materials do, however, have advantageous antibacterial properties [90]. Bioinert ceramics are also known for their high strength and hardness [91], and therefore used mostly in load-bearing applications.

Silicon is another material that has been used for IDDS. It can have various properties for various uses depending on how it is processed. Polymerised silicon has the ability to increase serum protein cell availability by binding to them. Other silicic acids can contribute to biomolecular complexes by competing with metal ions [92]. Silicon formed into bioactive glasses as silicates have excellent osteoconductive properties and so are used in orthopaedics [91]. Porous silicon, however, has been used for therapeutic applications such as drug delivery and dietary supplements [92].

There are, on the other hand, a group of ceramics that are bioactive. These ceramics can play a part in biological processes. Calcium ceramics typically make up this group, such as calcium phosphates and hydroxyapatite [91]. Bioactivity of these materials could involve supplying ions for chemical bonding or biological processes. These materials possess excellent biocompatibility and, additionally, osteoconductivity [91]. Calcium-based ceramics are less likely to be used to bear loads, but are useful in bone/tissue engineering or regeneration. Titania is quite often used in combination or as a coating with other ceramics to increase their ceramic performance and improve wettability [93].

3.5. Manufacturing techniques

The manufacturing method is an extremely important factor to consider when developing solid implants. It is based on a variety of factors including the polymeric properties of the materials used [2]. Because each technique requires very different conditions, the implant products will have differing properties depending on the method used. These properties will include mechanical characteristics, implant-body interactions, degradation rates, and drug release profiles. While these things present challenges such as API consistency and batch uniformity [94], there are also opportunities to tailor dosing regimens.

This section will explore several manufacturing methods for solid-formed implantable devices including their relative advantages and disadvantages.

3.5.1. Hot-melt extrusion (HME)

HME is a very common method in pharmaceutical manufacturing. By controlling melting temperature and mixing, materials are homogenously dispersed and then forced through a die [95]. Advantages to using this technique to form implants include, enhancing dissolution of poorly soluble drugs to improve bioavailability, and controlling the release of the drug [96]. Additionally, the use of solvents during production is avoided with this method, thereby improving biocompatibility of the implants

[2]. HME as a process can also be easily scaled up and translated to industry without changing the product's final properties [2,96].

Unfortunately, there are some drawbacks with this technique. Due to the use of high temperatures, thermally labile drugs cannot be used, and polymer stability has to be assessed [96]. Similarly, only certain polymers can be used due to the requirement of certain physical properties [96].

3.5.2. Compression

Rather than the use of heat and/or solvents, this method applies a force to the material until it flows and takes the shape of the die it is being forced into [2,95]. Solid implants made in this way tend to have higher densities.

As stated, a main advantage to this process is the lack of solvents and heat [97], making it ideal for less stable materials and drugs [4]. The method is also basic and would be easy to scale up. However, implants made in this way tend to experience faster release rates [4]. This can be a disadvantage depending on the intended use of the implant in question. Compression has shown to cause surface irregularities with large pores and channels, contributing to the irregular release of drug [98]. To prevent this, protection would be required, such as coatings.

3.5.3. Solvent casting

In this method, the polymer and/or drug are dissolved into a suitable organic solvent and the mixture is then cast into or around a mould with the desired implant shape and size [2,4]. The solvent is allowed to evaporate leaving behind the polymer mixture set in the implant shape.

The ability to make implants in a variety of shapes and sizes with a homogenous drug/particle distribution is a main advantage of this method [99]. A drawback, however, comes with the fact that an organic solvent must be used as there can be toxicity issues. Some studies have shown that there are no significant cytotoxicity issues at the end of development [29,100,101]. Unfortunately, this may not be the case on an industrial scale where the volume of solvent would be much larger. Not to mention the environmental impact this would have [2,4].

3.5.4. Injection moulding

This method combines heat and pressure to inject a molten form of the drug/polymer mixture into a mould of the desired shape. It is then allowed to cool and set [2]. This technique holds a lot of versatility in terms of mould shape and another main advantage is it's scalability through the use of larger machines [102]. Additionally, the pressure and heat used can provide autosterilisation of the product as well as improving drug-polymer interactions, advantageous for release profiles [102].

There are, however, questions of thermal degradation of drugs with the use of such high temperatures [103]. Additionally, there has to be careful selection of polymers and drugs because the physical properties of the molecules can affect the implant properties and so this may limit the extent of use of this method [4,103].

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3.5.5. Electrospinning

Electrospinning creates ultrafine fibres through an electrostatic potential of high voltage and low current [104]. The method is known for its wide range of applications and robustness [2].

The polymers must be in the liquid form to move through the apparatus, and there are two ways of doing this: melting and solution. The first uses high temperatures and the latter uses organic solvents to liquefy the polymers [104]. As always, high temperatures can degrade some drugs if the polymer blend contains drugs thus limiting drug choices or requiring different API addition techniques. However, the use of organic solvents creates cytotoxicity and environmental problems. The decision of which method to employ also depends on the type of drug release profile desired, melting provides a longer, linear release with less initial burst compared to in-solution [105].

There are also a number of ways in which to add the drug to the fibres, giving different kinetic profiles and material properties. These methods are outlined well by Luraghi et al (2021). Each addition method again has its own benefits and costs.

Electrospinning has been applied to antibiotics [106], anticancer therapy [107], ocular treatment [108], cardiovascular disease [109], and wound healing [110].

3.5.6 3D-printing

3D-printing encompasses a number of techniques capable of providing innovative drug delivery solutions [111]. Some of these techniques include, stereolithography, selective laser sintering, fused-deposition modelling (FDM), laminated object manufacturing, ink-jet based, and bioprinting [2]. Each of these provides a variety of ways to completely fine-tune drug delivery devices to have the properties required for each type of drug release.

Prior to the printing process, the product is designed using computer-aided design software providing a lot of flexibility in the shape of the implant. The implant could be hollow, created to be filled with API [4] or the materials could be a homogenous drug blend that can be printed into the desired shape. Again, these aspects must be chosen carefully with the type of 3D printing depending on drug and polymer properties such as stability and crystallinity.

3D-printing is cost-effective, flexible, and adaptable, however there are some questions of scalability into industry as well as regulatory concerns. The FDA approval of a 3D printed drug product in 2015 [112] however gives a lot of promise in this area for future developments [2].

3.5.7. Other manufacturing techniques

Most of the implantable devices described in the literature are based on polymers. Therefore, the methods described previously are applicable to prepare such devices. On the other hand, other types of manufacturing methods are required when implants are made of metal or ceramics. In these cases, computer numerical control, sintering methods or are normally used [113,114]. On the other hand, MEMS-based implantable devices require techniques used for the manufacturing of electronic components such as photolithography [115].

4. Applications of IDDS

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IDDS have been used for different types of applications. This section will describe the main areas of applications described in the literature to date. The areas of applications are quite diverse ranging from contraception to ocular disease.

4.1. Contraception and gynaecological applications of IDDS

Subdermal contraceptive implants were one of the first commercially available IDDS [116]. In addition to subdermal implants, there are a wide variety of drug eluting implantable devices for contraceptive and gynaecological applications described in the literature. These type of devices include aforementioned subcutaneous contraceptive implants [117], intrauterine devices [118], intravaginal rings [119] and meshes for female pelvic reconstructive surgery [120].

4.1.1. Subdermal contraceptive implants

Subdermal contraceptive implants have been commercially available since 1983 when the first reversible contraceptive IDDS was introduced in the market [116]. This product commercialised under the name of Norplant consisted on 6 silicone implants loaded with a synthetic progestin hormone: levonorgestrel [116,121]. The implants were applied subcutaneously in the upper arm of the patient providing contraception for up to 7 years (30-85 μg/day) [122,123]. New systems were introduced in the market to replace and improve Norplant. Currently, levonorgestrel-based subcutaneous implants are commertialised under the brand names of Jadelle and Sino-implant [123]. Figure 3A shows a comparison of Norplant and Jadelle. On the other hand, subdermal implants containing an alternative hormone, etonogestrel, can be found in the market under the name of Nexplanon. The main difference with levonorgestrel-based implants is that these IDDS contain only a single implant improving the application procedure. These implants are reservoir type implants (40 x 2 mm) composed of a membrane made of etinyl-vinyl acetate and a core containing 68 mg of the hormone [123]. Some etonogestrel implants contain in its core 15 mg of barium sulphate to render them radiopaque [116]. In addition to levonorgestrel and etonogestrel, two other synthetic progestin hormones have been used: nestorone and nomegestrol. Nestorone implants are reservoir-type implants containing 60-80 mg of the hormone (3-4 mm length). On the other hand, nomegestrol-based implants are reservoir-type implants (39 x 2.4 mm) made of silicone containing 55 mg of the steroid. These implants provide shorter contraceptive action than levonorgestrel/etonogestrel implants. Nestorone implants can provide contraception for up to 2 years while nomegestrol provides only 1 year of contraception [123].

During the last years there has been limited developments in this area [124]. Subdermal contraceptive implants have proven to be successful, and the focus is now on developing subcutaneous injectable formulations that reduce the pain during application substantially [125]. However, a few works have been published describing new types of implantable devices for the delivery of levonorgestrel. Table 1 summarises these. The particularity of these implants is that they are prepared using biodegradable polymers. In this way they should not require extraction after depleting their drug cargo. The first type of implants were prepared using poly(glycerol sebacate) urethane, a biodegradable elastomeric poly(urethane) [126]. The resulting devices were loaded with levonorgestrel and a drug used for HIV pre-exposure prophylaxis, 4'-ethynyl-2-fluoro-2'-deoxyadenosine [127]. Interestingly this drug was hydrophilic, and the combination of both drugs allowed a faster release of the hydrophobic levonorgestrel as it acted as a porogen. This work was focused on the formulation and characterisation

of the implants and did not report any *in vivo* data. However, the resulting implants showed *in vitro* linear release kinetics over 245 days [127].

On the other hand, Zhu et al. reported the use of direct compression of PLGA microparticles loaded with levonorgestrel to obtain subdermal implants [128]. Subsequently, these implants were coated with PCL to prolong the drug release [129]. The results showed that coated implants were capable of providing in vitro drug release for up to 90 days while uncoated implants providing around 60 days [129]. Moreover, the release profile for the coated implants followed a zero-order release kinetic. Additionally, the coated implants were teste *in vivo* using a rat animal model. The results showed that the implants were capable of providing sustained levonorgestrel for at least 58 days [129].

Table 1. Recent studies describing contraception and gynaecological applications of IDDS

Type of implant	**Material**	**Target**	**Drug**	**Findings**	**Ref**
Subdermal Implant	Poly(glycerol sebacate) urethane	Contraception and HIV pre-exposure prophylaxis	Levonorgestrel 4'-ethynyl-2-fluoro-2'-deoxyadenosine	4'-ethynyl-2-fluoro-2'-deoxyadenosin as a porogen enhancing drug release. In vitro linear release for 245 days.	[127]
Subdermal Implant	PLGA loaded nanoparticles compressed into an implant and coated with PCL	Contraception	levonorgestrel	Implants were evaluated in vivo using a rat animal model. Devices provided up to 60 days of *in vivo* release.	[129]
Intrauterine Device	Zinc and copper alloy	Contraception	Zinc and copper	Zinc/copper show improved biocompatibility *in vivo* (rat model) than copper while maintaining contraceptive effect. Finally, showed a reduced initial copper release burst effect.	[130,131]
Intrauterine Device	Zinc-lithium and zinc-magnesium alloys	Contraception	Zinc	Zinc alloys displayed improved biocompatibility *in vivo* (rat model) than pure zinc.	[132]
Intrauterine Device	Micro copper, loaded into devices made of low-density poly(ethylene) and methyl vinyl silicone rubber	Contraception	Copper	Implants were tested in vivo showing satisfactory contraceptive efficacy and lower side effects than the control group with bulk copper.	[133]
Intrauterine Device	Polymerised carvacrol	Contraception	Copper	A novel method of depositing copper trough electrochemical oxidation reaction of carvacrol on	[134]

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				copper was developed. Provides sustained copper release avoiding burst release.	
Intrauterine Device	PDMS	Contraception	Levonorgestrel	PDMS-based implants were prepared using different designs, drug loadings and crosslinking ratios. These parameters have a direct influence on release kinetics. The resulting implants were tested in vitro achieving release for up to 4 years.	[135–139]
Intravaginal Ring	Silicone elastomer	Contraception and HIV prevention	Dapivirine and levonorgestrel	Devices formed using a custom-made silicone formulation to prevent drug binding to the silicone. Devices showed similar mechanical properties to commercial rings while providing in vitro sustained release of clinically relevant doses of both drugs for over 30 days.	[140–142]
Intravaginal Ring	EVA	Hormone replacement therapy and contraception	Estrogen and progestine	Reservoir-type intravaginal rings. The result provided in vitro release of estrogen over 28 days. The amounts released can be applied for local or systemic hormone replacement therapy or for contraception when combined with progestine.	[143]
Intravaginal Ring	PLA, PCL, Tween 80 and PEG	Hormone replacement therapy	Progesterone	Intravaginal rings were 3D-printed in different shapes. Formulations contained PEG and Tween 80 as excipients to enhance drug delivery.	[144]
Surgical Mesh	Poly(urethane)	Infection control	Levofloxacin	3D-printed meshes containing levofloxacin to prevent post-surgical infection. Devices provided in vitro drug delivery for up to 3 days and displayed antimicrobial properties against E. Coli and S. Aureus.	[145]
Surgical Mesh	PLA	Tissue regeneration	Estrogen	Electrospun meshes containing estrogen sustaining drug release for up to 133 days. Ex ovo	[146]

				experiments displayed tissue regeneration properties.	
Surgical Mesh	Poly(urethane)	Inflammation control and potential tissue regeneration	Estrogen	3D-printed meshes were prepared providing up to 15 days of in vitro linear estrogen release.	[147]
Surgical Mesh	Gelatine hydrogel	Inflammation control and potential tissue regeneration	Puerarin	Hydrogel-based meshes containing puerarin. In vitro tests showed release of the cargo for up to 1 month. Moreover, in vivo experiment in a rabbit model confirmed the anti-inflammatory and tissue regeneration properties of the hydrogel.	[148]

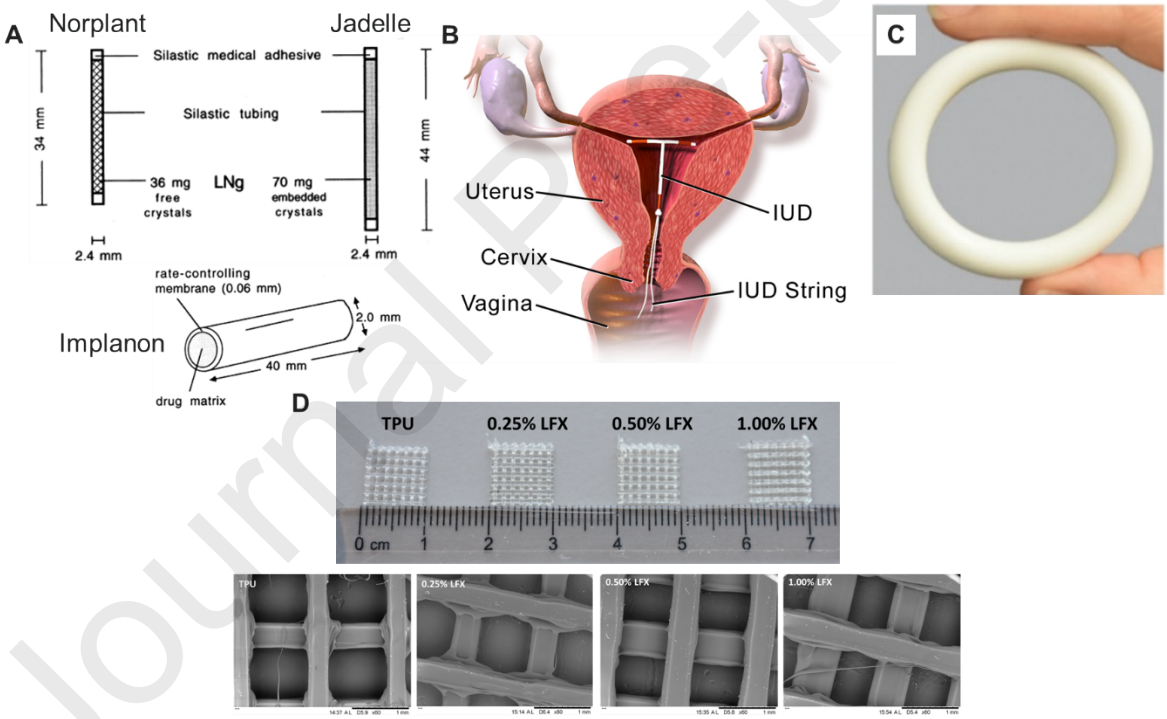

Figure 3. Diagrams showing the structure of several subdermal contraceptive implants (A), diagram showing an implanted intrauterine device (B). Image of Annovera® Intravaginal Ring (C). Pictures and SEM images of 3D printed meshes containing different levofloxacin loadings (D). Reproduced with permission from: [121,145,149,150].

4.1.2. Intrauterine devices

Intrauterine devices are an alternative to subdermal contraceptive implants. This type of IDDS are placed inside the uterus of the patient offering reversible contraception (Figure 3B) [151]. Intrauterine

devices have been commercially available since 1988 [151]. There are two types of intrauterine devices: copper-based intrauterine device and levonorgestrel-loaded intrauterine devices. The copper based devices present a T-shaped polyethylene structure (32 × 36 mm) containing copper covering part of the implant (200-375 mm^2) [152]. Copper ions are released from the device. However, the mechanism of action of copper ions allowing contraception is still unknown [153]. These devices are capable of providing contraception for up to 10 years [152]. Recently a few studies have reported alternative metal combinations or manufacturing techniques to improve the efficiency of these devices (Table 1). These novel devices use alternatives to copper such as zinc [154], combine copper with zinc [155,156] or use alternative alloys such as zinc-lithium/zinc-magnesium [154]. Moreover, the use of alternative materials, such as copper microparticles or copper loaded plant-based polymers can improve copper delivery and/or reduce side effects [133,134].

Alternatively, levonorgestrel intrauterine devices have been used. This type of devices contain between 13 and 52 mg of the synthetic progestin [151,152]. Like copper-based devices they present a T-shape made of polyethylene (32 × 32 mm) that contains a silicone capsule loaded with levonorgestrel [152]. They are capable of providing release rates of around 14 µg/day of the cargo for up to 5 years [151]. This type of implants can be used for the treatment of other conditions such as heavy menstrual bleeding, dysmenorrhea, endometrial hyperplasia or to prevent endometrial hyperplasia/cancer [152]. There are new types of intrauterine devices in development containing different hormonal compounds such as nestorone or etonogestrel among others have been described before [152]. Recently, new types of levonorgestrel loaded implants have been been reported in different studies (Table 1). These studies describe alternative materials and the effect of different parameters such as drug loading and crosslinking time [157–161]. These devices were prepared using PDMS and were capable of providing up to 4 years of levonorgestrel release [157]. It is important to note that these devices, as well as the impact of different manufacturing parameters on the performance, were tested *in vitro* [157–161]. However, the importance of these works is the information extracted, as it will help to optimise future PDMS-levonorgestrel systems.

4.1.3. Intravaginal rings for contraceptive and gynaecological applications

In addition to subdermal and intrauterine IDDS the use of intravaginal rings has been described before [119,162]. Figure 3C shows an intravaginal ring. This type of devices are torus-shaped devices loaded with different compounds designed to be introduced inside the vaginal cavity. Thus, the device can provide prolonged local drug release [119,162]. These devices can provide sustained drug release during periods of time ranging between 1 month to 1 year [119]. This type of devices were first described in the 1970 for the delivery of medroxyprogesterone acetate, a contraceptive drug [119]. However, it was during the 1980s when the first clinical trial was conducted in the USA [163]. Intravaginal rings are used for the delivery of a wide variety of hormones for a wide variety of purposes such as contraception, the treatment of urogenital atrophy, hormone supplementation, estrogen replacement therapy and HIV prophylaxis or [150,164,165]. This type of application will be discussed in a later section. Different polymers can be used to prepare this type of devices such as EVA, PU or silicone elastomer [119]. Additionally, the drug can be dispersed within the polymeric matrix or encapsulated inside the ring forming a reservoir type implant [119]. For contraceptive applications, these IDDS are normally loaded with a different drug combinations: etonogestrel/ethinylestradiol, nesterone/ethinylextradiol or etonogestrel/etinyl estradiol [119,150]. For estrogen replacement therapy or hormone supplementation 17β-estradiol or progesterone are loaded into intravaginal rings [150]. Currently, new types of intravaginal rings are being developed (Table 1). One of the trends in this area of research is to develop devices capable of providing contraception and HIV-prophylaxis

(Table 1) [140–142]. These devices are made of silicone and contain dapivirine and levonorgestrel within the polymer matrix [140–142]. In addition to silicone, EVA-based reservoir intravaginal rings have been developed for the delivery of estradiol and progestine for hormone replacement therapy and contraception (Table 1) [143]. The use of EVA presents certain advantages over silicone as it does not require curing [143]. The curing process of silicones can present issues as drugs can react with the silicone backbone [142]. Finally, the use of novel manufacturing techniques, such as 3D-printing, have been described to prepare intravaginal rings [144]. These systems were loaded with progesterone for hormone replacement therapy (Table 1) [144]. The main difference of this type of device is that they are formulated using biodegradable polymers, PCL and PLA, rather than EVA or silicones [144]. The use of 3D-printing allows the preparation intravaginal rings on demand, adapting the device to patient's needs [144].

4.1.4. Meshes for pelvic floor reconstructive surgery

A large percentage of women worldwide suffer from pelvic floor disorder such as stress urinary incontinence or pelvic organ prolapse [120]. It is difficult to establish the true prevalence of these conditions. However, it is estimated that a one in nine women are affected by pelvic organ prolapse while one in tree is affected by stress urinary incontinence [166]. These conditions are not life-threatening but they reduce significantly the quality of life women suffering them [167]. One of the proposed treatment for this conditions is the implantation of surgical meshes to support the pelvic organs [168]. Surgical meshes are conventionally made of polymers such as poly(propylene) [120,169]. However, the report of serious complications related with the implantation of meshes made of this material has encourage the development of safer surgical meshes [170]. A wide variety of surgical meshes have been described in the literature for the treatment or pelvic organ prolapse. Only drug eluting meshes will be covered in this article. Table 1 shows recent developments in this area of research.

There are two main types of drugs loaded into surgical meshes: antibiotic/antimicrobial compounds to prevent infections [169] and anti-inflammatory compounds [120]. The active compound can be coated into the device or incorporated within the mesh matrix. Dominguez-Robles et al. developed thermoplastic polyurethane-based surgical meshes for pelvic floor repair loaded with levofloxacin using 3D printing (Figure 3D; Table 1) [145]. The resulting devices showed elastic properties as opposed to more rigid poly(propylene) meshes. Moreover, they were capable of providing *in vitro* sustained release of levofloxacin for up to 3 days. Due to this, these devices showed antimicrobial properties against *E. coli* and *S. aureus*. These bacterial strains are responsible of the majority of nosocomial infections [145]. Alternatively, Mangir et al. described an electrospinning method to prepare PLA-based meshes loaded with oestradiol (Table 1) [146]. This compound has demonstrated to have anti-inflammatory properties as well as stimulate tissue regeneration [146]. The resulting meshes were capable of in vitro releasing the drug for up to 133 days. These meshes were tested using an *ex ovo* chick showing the potential of these meshes to stimulate tissue regeneration trough angiogenesis and extracellular matrix production [146]. Similarly, Farmer et al. developed 3D printed meshes based on thermoplastic poly(urethane) loaded with oestradiol (Table 1) [147]. These meshes showed zero order drug releases for periods of up to 15 days [147]. However, the effect of cargo on tissue regeneration was not evaluated using biological models. The development of anti-inflammatory meshes for pelvic floor repair can be achieved using alternative materials such as hydrogels. Qin et al. developed hydrogels based on gelatine loaded with puerarin (an anti-inflammatory natural compound) to regulate inflammation post-surgery (Table 1) [148]. The resulting hydrogels showed *in*

vitro puerarin releases of up to 1 month. Moreover, these implants were tested in a rabbit animal model reducing inflammation and improving tissue regeneration [148].

4.2. Cancer treatment applications of IDDS

Cancer treatment is a complex and challenging undertaking. Depending on the stage and location, surgical resection is the first-line therapy but cannot be applied in all cases. Moreover, microscopic cancer lesions may persist after mass removal and require coupling with additional treatment, such as chemotherapy. Still, this approach often presents severe side effects due to unspecific drug delivery and difficulty achieving the appropriate dosage to the tumour site. IDDS specifically designed for *in situ* cancer therapy represent an efficient way to reach the therapeutic dose while minimising the systemic toxicity of the anticancer drug by reducing its concentration in blood circulation; indeed, they provide precise spatial control of the drug release preventing damage to healthy cells and increasing the overall survival rate. To investigate their potential application, this section will review the solid IDDS proposed in cancer therapy, reporting the type of implant, the target, and the drug employed, focusing on the preclinical evaluations and the *in vivo* studies, if available. Figure 4A provides a general overview of the IDDS used in local cancer chemotherapy here reviewed. Moreover, Table 2 summarises recent applications of IDDS for cancer treatment.

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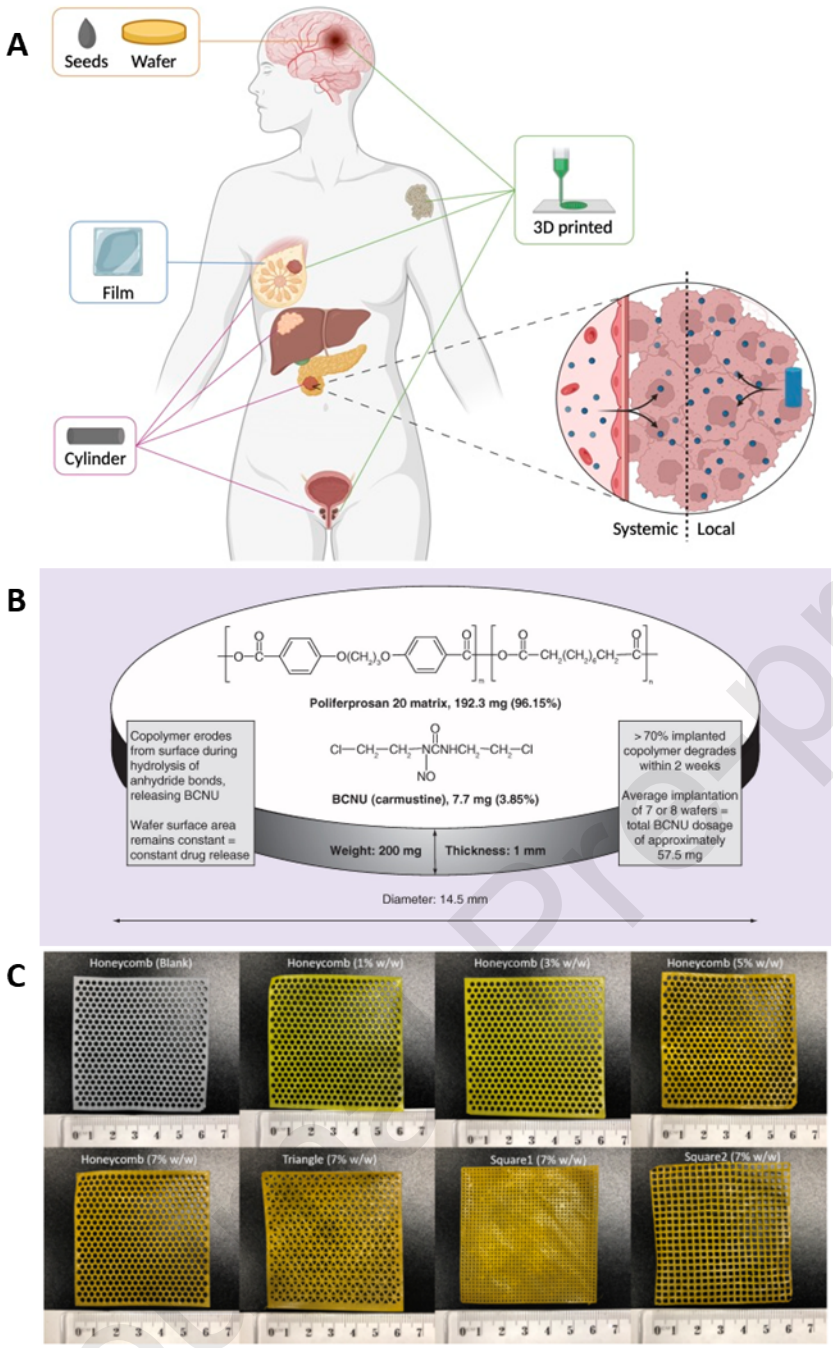

Figure 4. Schematic representation of the application of IDDS in local cancer therapy (A). Schematic representation of Gliadel wafer (B). SEM image of cylindrical PLGA implants loaded with oseltamivir phosphate (C). Images showing 3D-printed scaffolds loaded with curcumin (D). Reproduced with permission from [171,172].

Table 2. Recent studies describing IDDS for cancer treatment.

Type of Implant	Material	Target	Drug	Findings	Ref
Multilayered polymer coated-drug	PLGA	Glioblastoma	Carmustine Temozolomide	80% of drug release in 30 days (*in vitro*). Increased survival rate.	[173]

Polymer porous scaffold	POC	Glioblastoma	All-trans retinoic acid	Total degradation in 5 months (*in vitro*). 3.2% of drug release over 90 days (*in vitro*). Longer-term cytostatic effect compared to a single dose of free drug (*in vitro*).	[174]
Cylinder containing nanoparticles	PLGA and Chitosan	Breast Cancer	Doxorubicin	60% of drug release in 120 hours (*in vitro*); tumour growth reduction and total degradation in 20 days *(in vivo*)	[175]
Cylinidrical and spherical devices	PLLA	Osteosarcoma	Doxorubicin ifosfamide methotrexate	Shape affects implant characteristics (*in vitro*). Implant biosafe; drug plasma peak reached in 2 weeks, sustained release for 12 weeks at high concentration (*in vivo*).	[176]
Porous scaffolds	PLGA	Breast cancer	NVP-BEZ235 5-fluorouracil	Total drug release in 30 days with a burst during the first week (*in vitro*). Reduction of the drug dosage needed to maintain the same efficacy (in vivo)	[177]
Porous scaffolds	PCL	Breast cancer	doxorubicin	Biphasic monotonic drug release up to 28 days (in vitro). Dose-dependent activity, reduction of the drug dosage needed, reduction of cytotoxicity and metastatisation (*in vivo*)	[178]
Nanoporous spherical scaffolds	TPU with PVA	Prostate cancer	doxorubicin	60-75% of drug release over 7 days, reduced metabolic activity and proliferation of cancer cells (*in vitro*).	[179]
Flexible scaffolds	PCL	Glioblastoma	Curcumin	Drug loading and geometry affect the spatiotemporal characteristics; drug release adjustable up to 77 hours (*in vitro*).	[172]
Gelatin-based scaffold	Gelatin PDA-hybridised nanosized zeolitic imidazolate framework Hydroxyapatite	Anticancer therapy and bone regeneration	Cisplatin BMP-2 (growth factor)	Tissue ingrowth and inhibition of tumour recurrence (*in vivo*).	[180]

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Bullet-shaped reservoir	PLA Tetradecyl alchol lecithin	Malignant solid tumours	Cytoxan	Implant coating and reservoir-nature affect the drug release profile (in vitro).	[181]
Membrane	Glycerol PLA PCL	Breast Cancer	Doxorubicin Apatinib	The structure and materials of the membrane affect drug release profile (*in vitro*). Dual drug release provided a synergistic therapeutic effect (*in vivo*).	[182]
Drug-eluting seeds	PLGA	Glioblastoma	Irinotecan	Sustained drug release for up to 7 days (*in vitro*) Prolonged survival rate without increasing toxicity (*in vivo*).	[183]
Nanofluidic eluting seeds	Stainless steel and silicon	Breast Cancer	Antibodies (CD40 and PDL1)	Increased local and systemic immune response, tumour reduction (*in vivo*).	[184]
Nanofluidic eluting seeds	Stainless steel and silicon	Pancreatic Cancer	Antibodies (CD40)	Sustained low-dose intratumoral delivery of CD40 antibodies modules tumour immune microenvironment *in vivo* (murine model) while reducing tumour sizes.	[185]
Engineered mesh	PLGA PVA	Glioblastoma	Docetaxel Diclofenac	Flexible pattern. Drugs continuously released in the tumour bed. Increased median survival (*in vivo*).	[186]
Tubular reservoir	Silk fibroin	Breast Cancer	Letrozole	Zero-order drug release kinetic respecting the daily dosage needed (*in vitro*)	[54]

Wafers are the most studied IDDS to treat cerebral cancer, starting with the well-known Gliadel® wafer (Figure 4B). Gliadel® is a solid biodegradable copolymeric wafer made of carmustine (BCNU)-loaded Polifeprosan 20 microspheres. It was first approved in 1996 by FDA (Reference ID: 4358718) as an adjuvant to treat newly diagnosed high-grade glioma and recurrent glioblastoma (GBM) via intracranial implantation [171]. Clinical studies proved the efficacy of Gliadel® to treat both primary and recurrent gliomas with no marked increase in adverse effects [187–189]. Nevertheless, the limitations of this system have been documented such as rapid drug concentration decline and the onset of inflammatory or neurodegenerative responses to the IDDS [173,174,179]. To decrease the drug release rate, Shapira-Furman *et al.* [173] employed a polyester polymer poly(lactic acid-glycolic acid) (PLGA) with anti-hydrolysis features to prepare a wafer loaded with a combination of temozolomide (TMZ) and BCNU to treat GBM. The *in vitro* studies revealed a relatively slow release of the TMZ during the initial five days, increasing over the following 30 days to release almost 80% of the drug. The release of BCNU was not investigated in TMZ-BCNU wafers due to degradation issues. Animal studies advantageously performed on 9 L gliosarcoma-implanted rats proved that the TMZ-BCNU dual loading in wafer highly in treating GBM since the median survival rate increased to 28 days,

compared to the 15 days of the BCNU wafer-treated group. Jones *et al.* [174] developed a wafer loaded with all-trans retinoic acid (ATRA) using poly(1,8-octanediol-co-citric acid) (POC) as a polymer, obtaining a soft-flexible device able to conform to the shape of the tumour site, also to improve the drug amount delivered directly to the tissue. Moreover, POC allowed slower wafer degradation, as 50% of the wafer degraded within three months, reaching the entire degradation in five months.

The use of chemotherapeutics-loaded polymer cylindrical-shaped implants has been extensively documented in cancer therapy [190–192]. The applications of these types of implants continue and recent developments have been described. Kefayat et al. produced biodegradable PLGA cylindrical implants containing doxorubicin-loaded chitosan (CS-DOX) nanoparticles (ca. 100 nm and ca. 20 mV of zeta potential) to treat breast cancer in a mouse model [175]. These particles were combined with blank PLGA microspheres and compressed to prepare cylindrical implants (5 mm diameter, 2 mm lenght). *In vivo* studies on 4T1 breast tumour-bearing mice showed the efficient reduction of the tumour growth following the implantation of the PLGA/CS-DOX implant, which proved to be even more significant than the injection of the same amount of DOX in multiple doses. After 20 days from implantation, PLGA/CS-DOX implant was completely degraded without any residues. Alternatively, Jonas et al. developed cylindrical devices (820 µm diameter, 3 mm length) study the in vivo tumour response to the simultaneous administration of microdoses of different anticancer agents (doxorubicin, sunitinib, lapatinib, cetuximab, dasatinib and gemcitabine) [193]. This study presented a really interesting approach as these micro-devices were implanted inside the tumour using biopsy needles. Microdevices were made of medical-grade Delrin acetal resin, and circular reservoirs (150 to 350 µm) were shaped on the outer surface of the device. Anticancer drugs were separately packed in solid form into the device reservoirs, and once implanted into a mouse model, they were released into spatially distinct regions of the tumour. The authors concluded that the local drug activity readout obtained from releasing drugs into confined tumour regions at clinically relevant doses might be used as a prognostic marker of drug sensitivity of tumours, furthermore, offering new insights into intratumor pharmacodynamics.

In recent years advanced manufacturing techniques such as 3D-printing have been used to prepare IDDS for cancer treatment [176]. Wang *et al.* designed 3D-printed poly L-lactic acid (PLLA) implants as an individualised local osteosarcoma therapy, testing the co-loading of doxorubicin, ifosfamide, methotrexate and cisplatin [176]. The authors proposed two different shapes, spherical and cylindrical, to discover that the drug loading of the spherical implant was much greater than the cylindrical one highlighting the importance of this parameter in the encapsulation efficiency of 3D-printed devices. The biodegradability, *in vitro* cytotoxicity and blood compatibility, *in vivo* toxicity and sensitisation tests have proved loaded implants' biocompatibility and pharmaceutical properties. Furthermore, the *in vivo* drug release kinetics from the spherical implant demonstrated that all the drugs reached the plasma peak value after two weeks. The sustained release could last twelve weeks, showing a higher drug concentration in the target tissue than the whole blood. Finally, the research showed that local chemotherapy by the 3D-printed device was more effective than traditional chemotherapy. Similarly, Yang *et al.* developed a drug delivery implant for breast cancer therapy to suppress tumour growth and reduce pulmonary metastasis by combining 5-fluorouracil (5-FU) and NVP-BEZ235 [177]. The authors used the electro-hydrodynamic jet (E- jet) 3D-printing technique to construct loaded PLGA scaffolds with 50, 100 and 150 µm aperture size. The drug release occurred first through a burst during the first week, followed by a slow-release and a final fast stage, releasing the total drug within 30 days; this profile has been attributed to the complex degradation process of PLGA. The aperture size affected the release rate, accelerating with a larger size. The *in vivo* studies deduced that, compared to the repeated systemic injections of chemotherapeutics, the system significantly reduced the drug dosages needed while maintaining effectiveness and the therapeutic

drug levels at the tumour site for an extended time. 3D-printed scaffolds are widely reported in the literature to assist cancer therapy. The well-known and model chemotherapeutic drug doxorubicin (DOX) was included as well in scaffolds for breast and prostate cancer application [172,178]. In the first case, Dang *et al.* produced a poly(ϵ-caprolactone) device with macroscale pores of 300–500 μm and intrastrut microscale pores of 5–35 μm in size to obtain a drug loading efficacy of 90%. Compared to a single intravenous injection of 40 μg DOX, implantation of scaffolds containing 2-8 μg of DOX after tumour removal show reduced cytotoxicity and cancer recurrence correlated with a lower metastasis progression in 28 days of treatment. In the case of prostate cancer investigation, Ahangar *et al*. developed and *in vitro* tested nanoporous discoid scaffold intended to deliver DOX to the bone metastases that could also potentially serve as a bone substitute. Jiang et al. recently reported a 3D-printed scaffold for the simultaneous release of chemotherapeutic drugs and growth factors for anticancer therapy and bone regeneration to contrast the tumour-induced bone loss [180]. In this study, the IDDS was realised by assembling polydopamine (PDA)- hybridised nanosized zeolitic imidazolate framework-8 (pZIF-8 nanoMOFs) and PDA-decorated-hydroxyapatite nanoparticles (pHA NPs) on the surfaces of the 3D-printed gelatin-based scaffolds through PDA-assisted layer-by-layer (LbL) assembly strategy. Cisplatin was used as a chemotherapeutic agent and BMP-2 as a growth factor, separately loaded into the pZIF-8 nanoMOFs. The goal was to release cisplatin early and provide a sustained release of BMP-2 over time. Thus, following the fabrication of the gelatin scaffold via the fuse deposition modelling technique, the scaffold was first coated with BMP-2-loaded nanocomposite and subsequently with cisplatin-loaded nanocomposite, the last one resulting on the top of the BMP-2 layer. The newly developed IDDS presented rectangular pores with the optimal size for cell penetration and tissue ingrowth (width of about 500 μm). The IDDS also responded to the tumour microenvironment to release cisplatin, effectively inhibiting the tumour recurrence; furthermore, the system protected the encapsulated vulnerable growth factors from direct exposure to body fluid, allowing a sustained release and an accelerated bone regeneration. A further example of 3D-printed IDDS is reported by Yang et al., who developed a bullet-shaped implant loading cytoxan (CTX) to treat malignant solid tumours [181]. The IDDS was represented by a 3D-printed PLA hollow supporting structure of bullet shape, including a CTX-loaded tetradecyl alcohol or lecithin matrix, and finally coated with PLA. The implants presented a porous surface, an outer diameter of about 3 mm and a height of about 10 mm. The drug release from the IDDS could be effectively controlled by PLA coating. The pore sizes and tetradecyl alcohol or lecithin as matrices affected the drug release to some extent. The drug release from the implants was best fitted with the first-order equation. Nonetheless, even non-conventional anticancer drugs, such as curcumin, were loaded in 3D-printed scaffolds. Li *et al.* proposed the use of flexible and biodegradable scaffolds loaded with curcumin for intracranial therapy of GBM to overcome the limits of Gliadel® previously mentioned [172] (Figure 4C). The scaffold was printed by extruding polycaprolactone filaments and was evaluated *in vitro* to establish biodegradation and anticancer activity. The authors investigated the influence of various parameters, such as geometric models, the pore shapes, and thicknesses of the final implant. The properties can be modified by 3D printing to perfectly match the implant with the size and shape of the tumour cavity.

Among IDDS, fibre membranes are often employed for localised delivery of drugs due to high specific surface area, adjustable porosity, and excellent drug loading ability [182]. Li *et al.* developed an IDDS trilayer-structured fibre device made of glycerol, poly(l-lactic acid), and poly(ε-caprolactone) for the time-programmed release of DOX and apatinib in breast cancer therapy. The authors reported an enhanced therapeutic efficacy based on the dual drug release, regulated by the thickness and the degradation of the fibre-matrix [182]. PLGA nanofibrous membranes were proposed to treat GBM using a multidrug approach based on BCNU, irinotecan and cisplatin [194]. Similarly, the *in vivo* study

related the drug release to the degradation of the PLGA matrix, reporting a drug concentration significantly higher in brain compared to blood. Moreover, the survival rate of the treated group was notably higher than the control one, and the tumour growth rate slower.

Beyond wafers, other implants were proposed to treat GBM. Di Mascolo *et al.,* [186] engineered a biodegradable implant composed of a micrometre-sized PLGA mesh laid upon a poly(vinyl alcohol) layer loaded with docetaxel-polymeric nanoparticles and diclofenac. Docetaxel nanoparticles act as an anticancer agent, whereas diclofenac was used to sensitise glioblastoma cells to the chemotherapy. The implant was flexible enough to conform to the resected tumour cavity. *In vivo* animal study pointed out that a single implant application is more effective than a single intracranial administration of the two drugs-loaded nanoparticles; specifically, over 250 days after tumour resection, a single treatment with the micro-mesh promoted an 80% and 100% survival rate in U-87 MG and hCSC tumours, respectively. Recently, nanofluidic drug eluting seeds (NDES) were proposed for sustained intratumoral delivery of combinational antibodies CD40 and PDL1 to treat a murine model of advanced triple-negative breast cancer [184]. A 3.5mm-long stainless-steel reservoir was loaded with the lyophilised antibodies. The nanofluidic silicon membrane controlling the drug release was mounted on one end of the reservoir. In vivo studies showed that the current IDDS increased local and systemic immune responses. In combination with radiotherapy, significant tumour burden reduction and liver inflammation mitigation was achieved compared with systemic treatment. A similar approach was followed by Liu et al. using NDES loaded with CD40 for pancreatic cancer treatment [185]. In vitro experiments showed that the implants released cargo (ca 100 µg of CD40 in total / ca. 8 µg/day) for up to 15 days *in vitro*. Moreover, in vivo experiments in a murine model suggest that intratumoral implantation of these devices were capable of reducing the tumor burden of the animals via the modulation of tumour immune microenvironment. Alternatively, Seib *et al.* focused on the design of implantable film to apply directly to breast tumours [195]. The group decided to employ silk as a material to create DOX-loaded films, based on the documented broad toleration of silk protein *in vivo* with minimal inflammation or immune response when implanted into tissues. The manipulation of silk crystallinity provided control over drug release, ranging from immediate to prolonged over four weeks. This approach minimised systemic and local adverse effects, but maximised therapeutic efficiency compared to the equivalent DOX dose administered intravenously. Silk fibroin was also used by Wolfe et al., [54] to construct a tubular reservoir-type implant for sustained drug delivery. The authors carried out a study mainly focused on the characterisation of the implant, further loaded with two model drugs, one of which represented by the anticancer agent letrozole prescribed in treating hormonally responsive breast cancer in postmenopausal women. The *in-vitro* release profile was characterised by a zero-order kinetic with a direct match to the daily oral dosage administered in the current therapeutic scheme, concluding a potential clinical application.

4.3 IDDS for HIV treatment/prophylaxis

Immune deficiency syndrome (AIDS), caused by human immunodeficiency virus (HIV), has been well-known as one of the global epidemic health problems [196–198]. The use of the combination antiretroviral therapy (cART) has considerably suppressed the replication of the viruses, stopped the transmission of HIV, and decreased the death case and morbidity of HIV infections [199]. However, for several years, many cases have been reported where treatment failure has still been experienced by many patients following the treatment of cART [200–202]. IDDS are an ideal candidate for HIV treatment and pre-exposure prophylaxis (PrEP). Table 3 summarises recent studies describing the use of IDDS for HIV treatment and PrEP.

4.3.1. Subdermal implants for HIV treatment/prophylaxis

In the effort to develop IDDS to prevent HIV transmission using PrEP containing ARV drugs, Pons-Faudoa and co-workers developed a nanofluidic IDDS containing cabotegravir (CAB) administered subcutaneously to achieve sustained delivery for 3 months. In combination with 2-hydroxypropyl-β-cyclodextrin (βCAB), the pharmacokinetic profiles of CAB were considerably improved in Sprague-Dawley rats compared to CAB. Importantly, the plasma concentration of CAB, following the administration of this device, was more than 2 times of the protein-adjusted concentration required to suppress the replication of the virus by 90% (2 × PA-IC90). Furthermore, CAB was also found in the several tissues connected to HIV-1 transmission. Pharmacokinetic model analysis was successfully constructed and the apparent elimination half-life was calculated to be 47 days [203].

Table 3. Recent studies describing the use of IDDS for HIV treatment and PrEP.

Type of implant	**Material**	**Target**	**Drug**	**Findings**	**Ref.**
Subcutaneous nanofluidic implant	Polyether ether ketone (PEEK), 6AI4V titanium and 2-hydroxypropyl-β cyclodextrin	HIV pre-exposure prophylaxis	Cabotegravir (CAB)	implant formulation could sustain the release of CAB in Sprague-Dawley rats over 91 days and the plasma concentrations of CAB were two-fold of PA-IC_{90} with half-life of 47 days.	[203]
Subcutaneous implant	hydrophilic poly(ether-urethane)	HIV prevention	Cabotegravir (CAB)	In vivo release of CAB in rhesus macaques was found to be more than 350 µg/day in 90 days with approximate plasma concentration of 373 ng/ml.	[204]
Implantable microneedle patches	PLGA	HIV treatment and prevention	Tenofovir alafenamide	In 24-h ex vivo study, the microneedles could deposit 1208.04 ± 417.9 µg of TAF in the skin. Compared to intramuscular injection, the implantable could improve the mean residence time of TAF in rats.	[205]
Polymeric solid implants	PLGA	HIV treatment and prevention	Dolutegravir (DTG) and rilpivirine (RPV))	In in vivo studies in Balb/c mice, the implants were found to be safe and well tolerated. After one dose injection, the formulation could control the release of both drugs for 6	[206]

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				months with concentrations above four times of PA-IC90.	
Subcutaneous biodegradable implants	Poly(ε-caprolactone) (PCL)	HIV pre-exposure prophylaxis	Tenofovir alafenamide	Implant could control the release of drug over 8 months and the purity of the drug was maintained under simulated physiological conditions.	[207]
Long-acting biodegradable implants	Poly(ε-caprolactone) (PCL)	HIV pre-exposure prophylaxis	Tenofovir alafenamide and etonogestrel	Long-acting implant could sustain release of both drugs for 1 year. Interestingly, the stability of drugs was also maintained. In in vivo study, the release of Teno. Ala., and Eto., were controlled over 6 months and 1 year, respectively.	[201]
Reservoir-style implant	Poly(ε-caprolactone) (PCL)	HIV pre-exposure prophylaxis	Tenofovir alafenamide	Different thickness of implants, 45 and 200 µm, the release profiles of the drug were found to be around 0.91 and 0.15 mg/day respectively over 180 days	[28]
Vaginal ring implant	Silicone elastomers based on polydimethylsiloxane	HIV pre-exposure prophylaxis	Dapivirine and levonorgestrel	Vaginal rings were found to possess adequate mechanical properties and comparable with commercial product with the similar purpose.	[141]
Vaginal rings with exposed cores	Silicone elastomer rings, comprising cores loaded with HPMC and either lysozyme	HIV pre-exposure prophylaxis	5P12-RANTES	The implants were investigated for pharmacokinetics in sheep, showing that the concentration of 5P12-RANTES in the range of 10 -10,000 ng/g for 28 days in vaginal fluid and tissue. These values were reported to be around 50-50,000 fold of previous IC50 value.	[208]
Intravaginal ring	Silicone elastomer rings	HIV pre-exposure prophylaxis	Tenofovir disoproxil fumarate	Administration of the vaginal ring did not alter normal microbiota of the vaginal. Importantly, the level of the inflammatory cytokines after the administration of the	[209]

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vaginal ring were significantly higher after 14 and 20 days.

Using a similar drug, Karunakaran et al designed a subcutaneous reservoir IDDS containing CAB which could sustain the release for several months. CAB was incorporated into tubular pellets, and which were further incorporated into heat-sealed tubes prepared from hydrophilic poly(ether-urethane) (Figure 5A). This IDDS possessed wall thickness of 200 µm, outer diameter of 3.6 mm and lumen length of 47 mm. In this study, each membrane contained four cabotegravir pellets, resulting in 274 ± 3 mg of total drug loading. Furthermore, 348 ± 107 µg/day of CAB was successfully released in an *in vivo* study in rhesus macaques. Specifically, in *in vivo* study, five implants' formulations produced a mean plasma concentration of CAB of 373 ng/ml in rhesus macaques. Essentially, it was found that the animal model could tolerate the administration of the IDDS without showing any pathology issues or microscopic signs of histopathology. After 14 days following the removal of the IDDS, the plasma concentration of CAB was found to be below detectable levels [204].

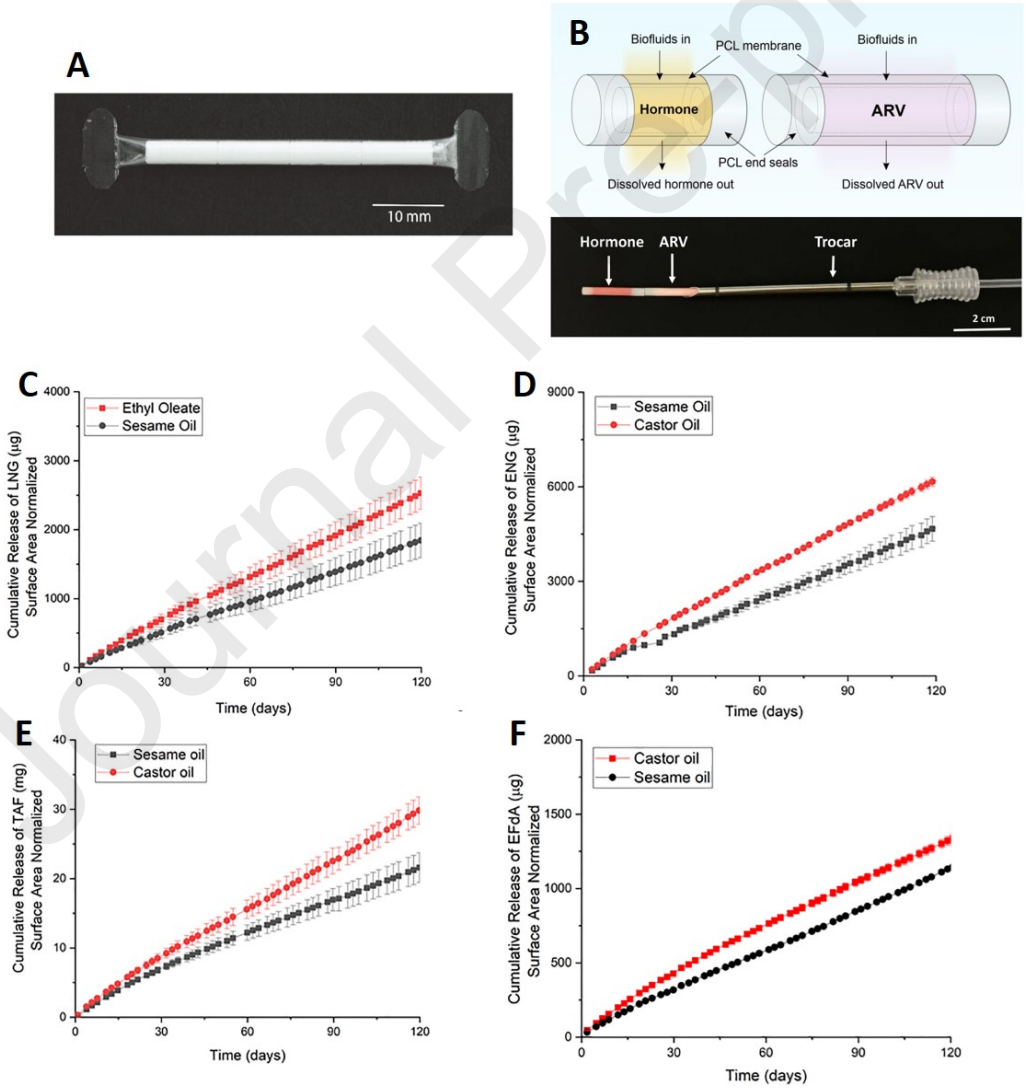

Figure 5. Implant formulation containing CAB (A). Reprinted with permission from [204]. A schematic illustration (Top) and digital camera image (bottom) of subcutaneous IDDS containing LNG and ENG

(Top) (B). *In vitro* cumulative release behavior of LNG (C), ENG (D), TAF (E) and EFdA (F) using two different excipients. Reproduced with permission from [201]

Delivered subcutaneously, Johnson et al developed a subcutaneous IDDS containing tenofovir alafenamide (TAF). Poly(ε-caprolactone) (PCL) was used for the reservoir-style IDDS which was prepared using extruder devices. The reservoir was then filled with a formulation of TAF and castor oil. Several characterizations influencing the release profile of TAS were performed, namely the thickness of the PCL cylinder walls (in the range of 45 - 200 µm), the superficial area of the IDDS, and the characteristics of the PCL following the formulation. The results suggested that the in vitro release behavior of TAF had a linear connection with the surface area of the IDDS. This showed that the mechanism of release of TAF from PCL matrix was membrane-controlled release. Furthermore, the rate of TAF release from PCL matrix was observed to be contrariwise with the thickness of implant wall. The rates of release of TAF were around 0.91 mg/day for 45 µm and 0.15 mg/day for 200 µm. Importantly, approximately 0.28 ± 0.06 mg/day of TAF was sustainedly released from the implant for 6 months, showing the potential application in the HIV treatment/PrEP [28]. In a different study, Schlesinger developed a thin-film polymeric system as implant administered subcutaneously using PCL. It was found that the shape and the size of the implants were tunable. Essentially, this approach could provide a release profile of 1.2 mg TAF/day and 2.2 mg TAF/day for 90 days and 60 days, respectively [210]. In another study, a different type of implant, nanochannel delivery implant containing TAF was developed by Chua et al. Evaluated in rhesus macaques, the release of TAF was sustained over 83 days with the plasma concentrations were clinically relevant with the required concentration of TAF in HIV transmission prevention [22].

Combined with contraceptive drugs, levonorgestrel (LNG) or etonogestrel (ENG), Li et al also developed a subcutaneous IDDS containing TAF (Figure 5B). The similar matrix, PCL, was also used in this study. Interestingly, the authors showed the ability of the IDDS to sustain the in vitro release of three drugs for 13-17 months. Importantly, the stability of drugs was maintained in the reservoirs of the implant. Following the optimization process, the implant formulation was investigated in *in vivo* delivery study with a rodent model, showing that the implant formulation was able to sustain the release of TAF and ENG for 6 months and 12 months, respectively (Figure 5C-F) [201].

Recently, Maturavongsadit and co-workers designed an ultra-long-acting biodegradable polymeric solid implant (PSI) containing dolutegravir (DTG) and rilpivirine (RPV), in a PLGA based-single implant with at adaptable human doses (65% wt.). The incorporation of DTG and RPV into PSI did not change physicochemical properties of either drugs. Importantly, following a single subcutaneous application, this approach was able to sustain the *in vivo* delivery of both drugs for 6 months with concentrations of above 4× PA-IC90. Furthermore, the device was found to be well tolerated and can be detached effectively to stop the treatment if mandatory [206].

4.3.2. Intravaginal rings for HIV treatment/prophylaxis

Another type of IDDS, intravaginal rings (IVR) [141,211–214] have been widely used in the treatment of HIV or PrEP in female patients. Ugaonkar et al. developed novel core–matrix IVR containing four drugs, namely MIV-150, targeting HIV-1; zinc acetate (ZA), targeting HIV-1 and HSV-2; carrageenan (CG), targeting HPV and HSV-2; and levonorgestrel (LNG) as a contraceptive agent (Figure 6A and 6B). The matrix of IVR was prepared from ethylene vinyl acetate (EVA-28) using hot melt extrusion. The *in vitro* study showed that the release of all compounds was controlled for 94 days (Figure 6D).

Importantly, the *in vivo* delivery study in macaques revealed the controlled-release behavior of four drugs during a 28-day period, with the drug concentrations found able to suppress the viral replication and unintended pregnancy [215]. In another study, a novel Pod-IVR containing tenofovir disoproxil fumarate (TDF) and maraviroc (MVC), an inhibitor of the receptor CCR5, has been successfully developed by Moss et al. This approach could improve the adherence and the effectiveness in comparison with vaginal gels and oral preparations. Furthermore, *the in vivo* pharmacokinetic study in the ovine model showed that the administration of IVR could sustain the release of TDF and MVC for 28 days. Essentially, the concentration of both drugs was considerably kept at steady state concentrations in cervicovaginal fluids. During the experiment, there were no adverse effects found [216].

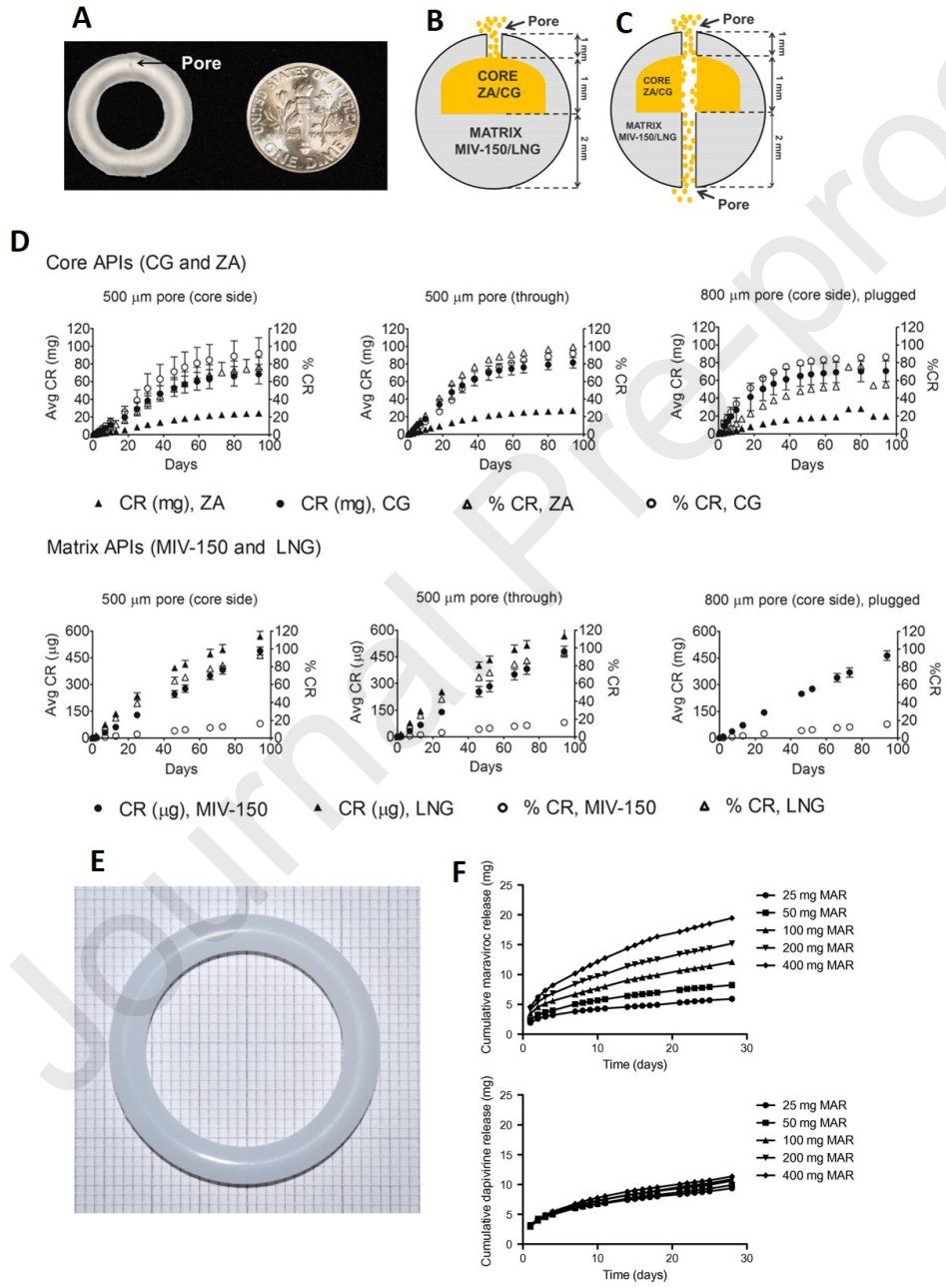

Figure 6. Digital photograph of IVR containing drug combinations (20 mm × 4 mm) (scale: US dime = 17.91 mm) (A). Cross segments representing compartments of core and of the similar IVR formulation with a core side pore (B) and a drilled through pore (C). *In vitro* release behaviour of all

compounds from IVR formulations (D). Reprinted with permission from [215] Digital photograph of IVR containing containing 25 mg dapivirine and 100 mg maraviroc (E). *In vitro* release behaviour of maraviroc (Top) and dapivirine (Bottom) from IVR formulations (D). Reproduced with permission from [217].

Fetherston et al developed silicone elastomer matrix-type IVR containing dapivirine and maraviroc. In this study, IVR contained 25 mg dapivirine and different amounts of maraviroc (50–400 mg) (Figure 6C). Following the characterization process, IVR loaded with 25 mg of dapivirine and 100 mg of maraviroc was selected as the best IVR candidate. The formulation was able to control the release of both drugs for 28 days and possessed excellent stability performances for a one-year stability evaluation [217]. A novel IVR containing protein microbicide candidate 5P12-RANTES was developed by McBride et al. The extensive studies showed the drug release was controlled over one-month period and the formulations possessed excellent mechanical and stability properties (Figure 6D). *In vivo* pharmacokinetic study in sheep revealed the sustained release behavior of 5P12-RANTES for 28-day period of study. Importantly, it was found that the concentration of 5P12-RANTES in vaginal fluid and vaginal tissue was observed be in the range of 10 and 10,000 ng/g. These concentrations were at least 50 and up to 50,000 times of IC50 values to inhibit the replication of the viruses [208].

The Bill & Melinda Gates Foundation has started making investment in the development of long-acting ARV drugs to prevent HIV in both men and women [218]. Specifically, the application of vaginal ring containing ARV drugs in clinical study has also been examined. A study performed by Baeten et al. using vaginal ring containing 25 mg of dapivirine showed that this approach could decrease the occurance of HIV-1 by 30% in comparison with placebo administration. Interestingly, 92.2% of women preferred to use the vaginal ring. Importantly, amongst 1456 women participating in this study, there were no severe adverse effects found following the administration of the vaginal ring [219].

4.4. IDDS for ocular drug delivery

IDDS for the eye are being investigated with greater frequency in current research due to their capacity to reduce the number of separate treatments patients require. This is particularly pertinent in chronic diseases, including glaucoma, age-related macular degeneration and diabetic retinopathy. For example, glaucoma needs eye drops to be used several times a day, making compliance difficult for patients. In contrast, AMD and DR commonly require intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents every 4-6 weeks. Whilst individual intravitreal injections pose a low risk when given repeatedly, as is the case in chronic disease treatment, the risk of significant complications, including endophthalmitis and retinal detach, increases [220]. Sustained release systems capable of providing similar efficacy to the treatments currently used for treating chronic diseases in both the anterior and posterior segments could be game-changers.

Initially attempts were made to provide continuous release using periocular devices that were placed under the eyelid. This includes the Ocusert® ocular implant, the first FDA-approved ocular implant in 1974 to reach the market, which was designed to treat glaucoma. On the other hand, Lacrisert®, a hydroxypropyl cellulose rod used to treat dry eyes, is placed in the conjunctival sac in the same way. Unlike the Ocusert®, this device was launched in the early 1980s and is still in use today. In 47 years since the invention of Ocusert® implants, only eight implants for anterior and posterior segments of the eye have been successfully launched into the market.

Recently, in October 2021, the FDA approved Dextenza® and Susvimo™. Dextenza is an intracanalicular insert that is placed in the canaliculus after being put through the lower lacrimal punctum, which is a natural opening in the eyelid [221]. Dextenza® is intended to administer a gradually decreasing dosage of the steroid dexamethasone to the surface of the eye for a period of up to 30 days. After therapy, Dextenza resorbs and leaves the nasolacrimal system on its own, therefore it is not necessary to remove it [222]. Susvimo™, a port delivery system (PDS) containing ranibizumab [223]. (Figure 7A-B). The port delivery system is a non-degradable implant designed for continuous delivery of ranibizumab into the vitreous. The innovative feature of this device is that can be refilled trough a septum when the drug cargo is depleted [31,224]. The implant contains a rate controlling metallic membrane capable of sustaining the release of the drug for up to 6 months depending on the initial drug loading [31]. It is important to note than the majority (63.5%) of the patients tested with the lower drug cargo (10 mg/mL) did not require a refill after 6 months [31].

More recently the Susvimo device had to be recalled by Roche due to a potential leakage problem. This was due to a manufacturing issue with the seal that is designed to stop the payload leaking out after it's injected into the system, with Roche communicating that there was a concern about the possibility that the seal could fail with repeated dosing. Patients who already have the implant inserted were advised to keep getting refills, but no new patients will be able to have an implant inserted until the issues are resolved. Roche estimate this could take approximately one year [225].

Retisert®, Iluvien®, and Yutiq™ (containing fluocinolone acetonide); Vitrasert® (ganciclovir) are non-degradable implants with zero-order release kinetics, that are inserted or delivered into the vitreous humour. Once the drug has exhausted, these implants need surgical removal – making it a more invasive therapy than its biodegradable competitors. VItrasert®, developed by Bausch and Lomb, was approved in 1996 for the treatment of cytomegalovirus retinitis linked to AIDs. Each implant was loaded with 4.5 mg of ganciclovir with a release duration of 5-8 months [226]. Retisert®, developed by Bausch and Lomb, was designed to treat non-infective uveitis. It contains 0.59 mg of drug and is designed to deliver its payload for approximately 30 months. This implant, in a similar way to Vitrasert®, is inserted surgically and sutured to the scleral wall [227]. Illuvien®, developed by Alimera, contains 0.19 mg of fluocinolone acetonide and is indicated for the treatment of diabetic macular oedema. This implant, composed of PVA, is designed to sustain release over a 36 month period. One major difference to Retisert® is that Illuvien® does not require surgical insertion and is instead inserted by direct intravitreal injection using a 25 gauge needle [228]. Yutiq®, developed by Eyepoint, is the most recent implant to be developed for the sustained delivery of fluocinolone acetonide. This implant, which contains 0.18 mg of the steroid drug, is indicated for the treatment of non-infective uveitis. This implant, like Illuvien®, is delivered directly into the vitreous humour, and does not require surgical insertion. Yutiq® is designed to sustain release for 36 months [229].

A biodegradable implant for posterior segment administration, Ozurdex®, launched by Allergan's NOVADUR® technology is intended for the continuous delivery of dexamethasone to treat macular oedema and intraocular inflammation [230]. The NOVADUR® approach makes use of a PLGA polymer matrix, which gradually degrades into lactic acid and glycolic acid over time, allowing for continuous drug release for up to six months [231]. Another biodegradable ocular implant is Durysta®, which received FDA approval in March 2020. This is an intracameral implant designed to deliver bimatoprost to treat patients with open-angle glaucoma or ocular hypertension. Durysta® is composed of PLGA, making it the first approved biodegradable intracameral implant, and has a 4-6 month release duration. This implant is delivered using an applicator with a pre-loaded 28 gauge needle [232].

IDDS described in the previous paragraphs are commercially available or in clinical trials. However, researchers are currently developing a wide variety of IDDS for ocular drug delivery. Table 4 summarises recent developments of IDDS for ocular drug delivery.

Cocarta et al. developed a bilayer hydrogel-based implant, comprising of an inner pHEMA core surrounded by an outer protective barrier of hydrophobic pEOEMA for the treatment of retinoblastoma following administration to the sclera. The implant core was loaded with vincristine and topotecan, which demonstrated significant cytotoxicity towards retinoblastoma cells in vitro. Moreover, sustained release of both therapeutic agents was achieved through the hydrogel implant, with 2 and 6 days for topotecan and vincristine respectively [233]. Through later testing in an in vivo rabbit model, topotecan release was further extended (14 days) and reached therapeutic levels (10 ng/ml) in the vitreous 8 hours post administration [234].

The treatment of retinal degenerative diseases has also been a major focus regarding the development of implantable drug delivery systems. Zhou et al. recently demonstrated the ability of macroporous PDMS implants loaded with 2 mg bevacizumab to lower VEGF levels at the retina in approximately 3 months, in addition to promoting corneal re-epithelialisation [235]. Furthermore, the sustained release of unoprostone to the retina through a PEGDM/TEGDM-based implant was demonstrated in vivo by Nagai et al., with rabbits showing retinal thickness preservation and a reduction in long-term retinal function decline [236].

Table 4. Recent studies describing IDDS for ocular drug delivery

Type of Implant	Material	Target	Drug	Findings	Ref.
Bilayer hydrogel implant	pHEMA and pEOEMA	Retinoblastoma	Topotecan	14-day release of TOP *in vivo* using a rabbit model. TOP reaches therapeutic levels (10 ng/ml) in the vitreous 8 hours post administration. Long-term biocompatibility against Rb Y79 cell line.	[234]
3D printed porous capsule	PEGDM and TEGDM	Degenerative retinal diseases	Human retinal epithelial cells	3D printed photocurable capsule loaded with ARPE-19 cells. Provided 16-day *in vitro* release of BDNF to the retina. Limited large molecule diffusion for cell protection, whilst enabling small molecule diffusion for cell survival.	[237]
Biodegradable	PDMS	Corneal and retinal neovascularisation	Bevacizumab	Administration of BEV-loaded (2 mg) macroporous implant in neovascularisation rabbit models Rapid and complete corneal re-epithelialisation (5 days) Lowered VEGF levels at the retina in approx. 3 months.	[235]
Sheet-shaped implant	PEGDM and TEGDM	Retinal diseases	Fluoroscein	Multi-layered sheets of photopolymerised polymers. Guard layer: unidirectional release.	[238]

				Morphology enabled compaction on administration and unfolding in the eye. 4-week release of fluroscein to the retina in a rabbit animal model.	
Bilayer hydrogel implant	pHEMA and pEOEMA	Retinoblastoma	Vincristine and topotecan	Cytotoxicity towards retinoblastoma cells. 2-day release of TOP and 6-day release of VIN from HEMA reservoir *in vitro.* VIN was stable but topotecan stability influenced by drug concentration and temperature.	[238]
Sheet-shaped implants	Gelatin and chitosan PEGDM	Choroidal neovascularisation	FITC conjugated albumin	Sheets loaded with collagen microparticles. Degradation of gelatin/chitosan sheets by week 24 in rat sclera, with detection of FITC in the retina by week 6. Microparticle-loaded PEGDM did not degrade, with FITC detected in the retina by week 18.	[239]
Implant	PEGDM and TEGDM	Retinitis pigmentosa	Unoprostone	Initial daily release of 10.2 ±1.0 µg following transscleral administration. Rabbits showed retinal thickness preservation by OCT at week 24. Slowed long term retinal function decline (> 32 weeks).	[236]

Various implant morphologies have also been investigated, with Sato et al. creating polymer-based sheet-like implants which were capable of being compacted for administration through a needle before unfolding in the eye. The multi-layered implants were provided sustained delivery of fluorescein to the retina which was detectable four weeks post administration in an in vivo rabbit model [238]. Sheet-like implants fabricated from gelatin/chitosan and PEGDM were also developed by Nagai et al. Degradation of the gelatin/chitosan sheet implants occurred within 24 weeks in the in vivo rat model, with the detection of FITC in the retina occurring by week 6. PEGDM implants were loaded with collagen microparticles, delivering FITC to the retina by week 18, however did not degrade within the timeframe studied [239]. Innovative approaches such as 3D printed implants have also demonstrated the ability to deliver sustained release of BDNF through human retinal pigment epithelial cells in vitro for approximately two weeks [237].

There has also been research into the use of IDDS for periocular delivery. Periocular delivery refers to the area that immediately surrounds the eye, which potentially offers a good compromise between achieving therapeutic concentrations in the posterior segment without the invasiveness of a direct intravitreal injection [240]. The use of periocular routes exploit the permeability of the sclera for retinal delivery and are particularly useful for the administration of sustained release systems, including IDDS [241]. Indeed, there is an example of a bioerodible dexamethasone implant that was developed for the treatment of uveitis and postoperative cataract inflammation that could sustain release for 6 weeks with near zero-order kinetics. Histological assessments from the study showed no

signs of inflammation after use of the implant [242]. Okabe et al were able to develop a biodegradable intrascleral implant composed of PLA that was able to deliver therapeutic levels of betamethasone phosphate for up to 8 weeks. The implant was placed in a scleral pocket that was formed surgically [243,244]. Furthermore, Kawashima et al. designed an implant to sustain protein release, for transscleral delivery. The system was fabricated with TEGDM, which is impermeable to macromolecules, and a controlled-release membrane [245]. Initially this implant was tested in rabbits and achieved zero-order release of fluorescent dyes. Work by Onami et al. utilised a sustained release vasohibin-1 device and tested in a rat model with laser-induced choroidal neovascularisation, with results showing a significant reduction in lesion size after 2 weeks, when compared to direct intravitreal injection of vasohibin-1 [246]. A modified version of the implant was tested for long-term pharmacokinetics and safety of uroprostone in monkeys, with results showing no changes in retinal function, intraocular pressure, or retinal histology after 12 months [247].

Despite the promise that this route offers there has not been any products of this type released commercially to date. This could be partially due to the use of much smaller needles for intravitreal injections (30 gauge and smaller) in more recent times, which significantly reduce the invasiveness of such procedures, in combination with the long durations of release that are now possible from delivered IDDS that will reduce injection frequency. Furthermore, whilst periocular delivery does result in high drug concentrations in the posterior segment compared to topical and systemic delivery, it cannot match direct intravitreal injections in this regard.

4.5. IDDS for schizophrenia treatment

Schizophrenia is a chronic mental disorder which severely distorts perception and the way of thinking [248–250]. The most commonly used treatments consist of oral administration of tablets once daily, which often leads to pill fatigue and finally discontinuation of the medication [10,251]. Poor adherence to treatment can result in higher relapse rates, increased hospitalisation, low quality of life and increased levels of residual symptoms [252]. Moreover, non-adherence to treatments has been demonstrated to have a detrimental economic impact on hospitalisation expenses and medication costs [253–256]. Long-acting injectable formulations have been developed for this purpose including solid IDDS [257,258]. Currently, two IDDS for the treatment of schizophrenia are in development stages. DLP-160 is a 6-12 month risperidone subcutaneous implant, developed by Delpor (Delpor Inc., San Francisco, CA, USA) is in phase II trials [259]. This implant uses the Prozor™ technology [260,261] which involves a small tubular reservoir containing risperidone, through which release is controlled by membranes located at both ends of the cylinder (Figure 7C). The drug is loaded together with excipients that alter the pH to maintain an acidic environment. The acid improves risperidone solubility, resulting in its steady diffusion out of the reservoir and potentially the maintenance of therapeutic plasma levels in the body for up to one year [33].

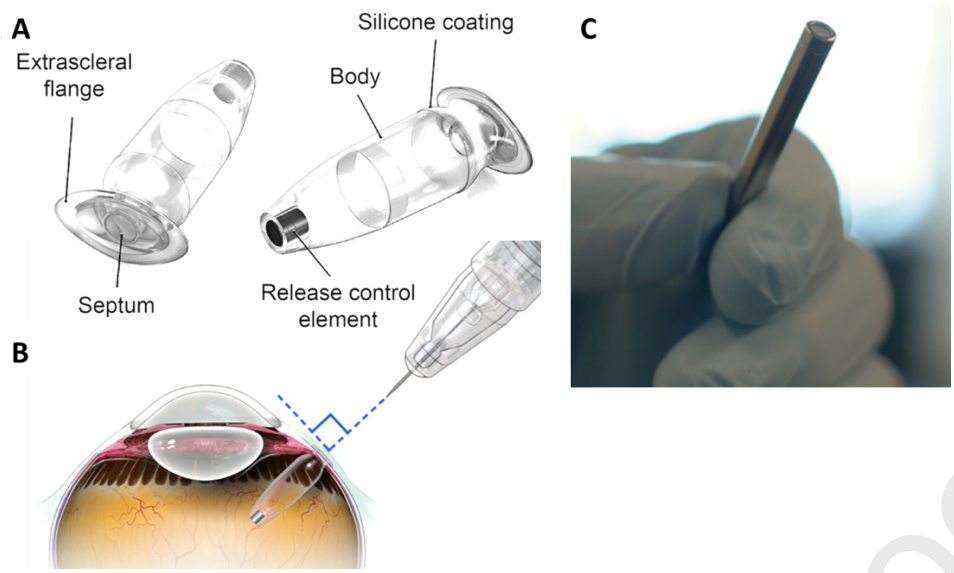

Figure 7. Diagram showing the main components of the Susvimo™ implant (A) and the refilling procedure (B). Image of Delpor titanium implant (C). Reproduced with permission from [31] and Delpor Inc.

To date, there are no solid implants in the market that can replace oral therapy for schizophrenia. Therefore, the development of new implantable formulation for the management of schizophrenia is actively sought out. In this section, recent reports on the field are critically reviewed. Table 5 shows a summary of recently developed IDDS for schizophrenia treatment. Most of the implants described in the literature aiming to treat schizophrenia described the use of biodegradable polymers such as PLA, PCL or PLGA (Table 5) [262–264]. These implants contain mainly one of the following drugs, olanzapine, paliperidone palmitate or risperidone (Table 5). Olanzapine has been combined with PCL using hot melt extrusion and 3D printing techniques to prepare subcutaneous implantable devices. The implants included matrix type implants [101,263] and reservoir type implants using a biodegradable PCL-based rate controlling membrane [29]. The resulting devices were capable of providing in vitro sustained delivery for more than 150 days [29,101,263]. However, no in vivo performance was reported for these implants. In addition to olanzapine, risperidone has been extensively used IDDS for schizophrenia treatment (Table 5). Risperidone has been used in subcutaneous formulations [264,265]. These formulations were evaluated in vivo using animal models and even in clinical trials [264,265]. Braeburn Pharmaceuticals Inc tested TPU-based subcutaneous implants containin risperidone in adult patient's suffering from schizophrenia [265]. This study showed that patients receiving implants showed comparable risperidone levels than the control group that received oral risperidone [265]. In addition to subcutaneous implants, novel intranasal IDDS for the delivery of this drug have been reported (Table 5) [99,266]. These implants were made of biodegradable polymers (PCL and PLGA) and they showed that they were capable of providing sustained risperidone release in a rat animal model [266]. Finally, paliperidone palmitate IDDS were prepared using PCL and PLA via-3D-printing extrusion techniques [267,268]. The resulting systems could provide in vitro drug release for times ranging between 90 and 180 days. No in vivo evaluation for these implants was reported (Table 5).

Table 5. Recent studies describing IDDS for the treatment of schizophrenia.

Type of implant	Material	Target	Drug	Findings	Ref
Subcutaneous implant	TPU	Schizophrenia	Risperidone	Drug release for 6 months at a constant rate after implantation to human volunteers. Mean concentrations of RIS were 81.3% of the min. oral concentration and 27.5% of the max. oral concentration. Moreover, the concentration of RIS released from the implant was comparable to the min. oral concentration.	[265]
Subcutaneous implant	PCL	Schizophrenia	Paliperidone palmitate	Implants made by pressure-extrusion based 3D-printing. Independent of the blend, the release from the rings were higher than the disks. After 3 months, devices with PCL 5% released 63 ± 3% (disks) and 79 ± 3% w/w (rings) of drug.	[268]
Subcutaneous implant	PLA and magnesium stearate	Schizophrenia	Risperidone	Implant consists of microspheres of PLA combined with magnesium stearate (0.5%) directly compressed to form a 3mm diameter implant. Implants were coated with a PLA membrane. Zero-order in vitro release kinetics and capability of providing sustained drug release in vivo for 164 days.	[264]
Subcutaneous implant	PCL	Schizophrenia	Olanzapine	Implants produced by hot-melt extrusion. Implants were loaded with 6.78 ± 0.56 mg of the drug each. In vitro release study was performed for 4 days and showed controlled release of OLZ that followed Higuchi's model.	[263]
Subcutaneous implant	PCL and PEO	Schizophrenia	Olanzapine	Implants made by 3D-printing technology with a cylindrical shape and wrapped in a PCL film. The core consists of OLZ and PEO. The release was assessed for 190 days delivering ca. 77% and ca. 64% for implants containing 50% and 80% (w/w) of drug, respectively.	[29]
Subcutaneous implant	PCL and PEG	Schizophrenia	Olanzapine	Implants made by 3D-printing technology with a cylindrical shape using concentrated high concentrated polymer/drug solutions. The resulting implants	[101]

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				contained up to 80% (w/w) drug loading. Implants containing a combination of PCL and PEG rather than only PEG showed sustained *in vitro* drug release over 200 days.	
Subcutaneous implant	PLA	Schizophrenia	Paliperidone palmitate	To create the implants two different methods were used, hot-melt extrusion and fused deposition modelling 3D-printing. The in vitro release study was developed for 3 months obtained a total of drug release of 15.0 ± 0.8 % for the implants loaded with 20% of paliperidone palmitate, and 5.6 ± 0.6 % for the implants loaded with 100% drug.	[267]
Intranasal implant	PCL, PLGA	Schizophrenia	Risperidone	The resulting implants were developed by a casting method with a range between 25 (PCL-based) and 50 % (PLGA-based) of drug. The devices showed a sustained drug release profile for 90 days.	[99]
Intranasal implant	PLGA	Schizophrenia	Risperidone		[266]

4.6. Drug-eluting cardiovascular IDDS

Cardiovascular disease (CVD) is a general term used for conditions affecting the heart or blood vessels, which are the leading cause of death in the world and represent a main contributor to reduced quality of life [269–271]. The purpose of drug delivery in cardiovascular IDDS can be targeted at preventing the blocking of the target blood vessels after treatment or the synthetic vascular grafts used for the restoration of blood flow in damaged vessels [162,272]. The process of this complication (restenosis) is usually due to platelet deposition and thrombus formation, and neointimal hyperplasia [273]. Several therapeutic agents, including antiproliferative drugs such as Paclitaxel (PTX), sunitinib, sirolimus and other limus-family related drugs (everolimus, biolimus A9, zotarolimus, tacrolimus, and pimecrolimus); antithrombotic agents such as heparin, cilostazol (CIL), dipyridamole (DIP), acetylsalicylic acid (ASA) or nitric oxide (NO); and antibiotics such as sisomicin, rapamycin, vancomycin or rifampicin (RIF), among other molecules, have been loaded into cardiovascular IDDS to combat either thrombus formation or neointimal hyperplasia [109,162,271,272,274–279]. The use of drug-delivery systems in cardiovascular applications drastically decreased the rate of restenosis. For instance, Scheller et al. showed that only 5% of the patients treated with a PTX-coated balloon presented restenosis in comparison with 43% of patients in the control group [280]. Moreover, the use of drug-eluting stents has significantly decreased the restenosis rate to 3−20% [281]. Therefore, these drug-delivery systems are a valuable alternative to combat these risks.

IDDS for the treatment of CVD include drug-eluting small diameter vascular grafts (SDVGs) and stents [282] (Figure 8), since drug-eluting balloons are removed after providing the therapeutic benefit [283]. Thus, the latter devices will not be included in this section. These IDDS are usually made from a polymeric matrix. Such matrices not only allow to increase the upper limit of the drug amount loaded/deposited onto these devices, but also can protect drugs against enzymatic degradation or regulates the release rate, among other benefits [162,284]. Moreover, these polymeric matrices can be manufactured from non-degradable or permanent polymeric materials including ethylene vinyl acetate (EVA), poly (ethylene-co-vinyl acetate) (PEVA), poly (n-butyl methacrylate) (PBMA), poly(styrene–b-isobutylene–b-styrene) (SIBS) and thermoplastic polyurethane (TPU); or biodegradable polymeric materials such as polylactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA) and polycaprolactone (PCL), among others [162,272,285]. However, it has been reported that non-degradable polymeric materials could potentially lead to side effects such as thrombosis, chronic inflammation and neointimal hyperplasia, after remaining in the body for extended periods of time [284,286].

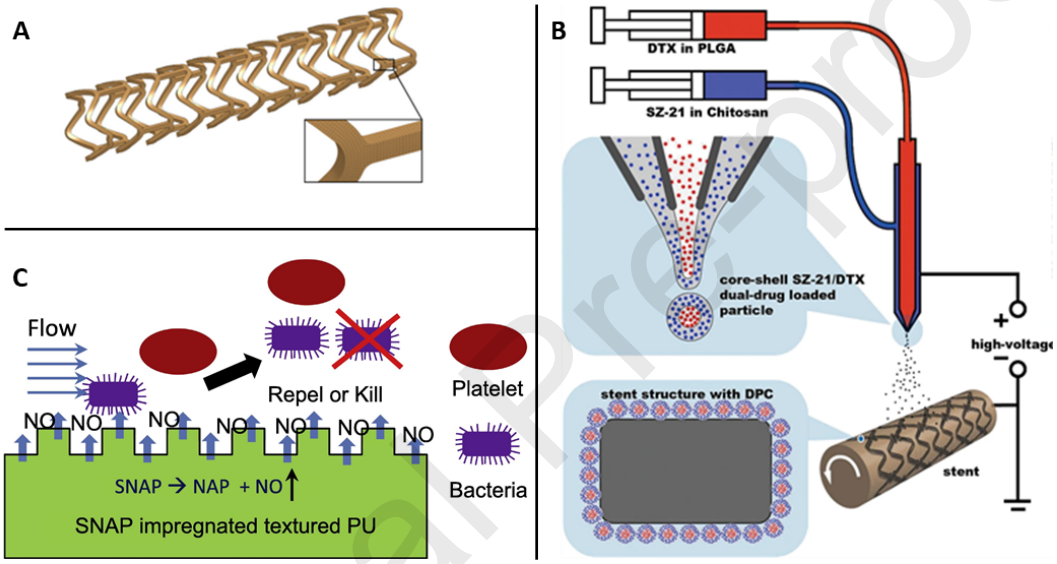

Figure 8. PLGA-based model for the manufacture of biodegradable-based stents (A). Coaxial electrospray process used for the development of a drug-eluting coating for cardiovascular IDDS consisting of a core coating of the anti-proliferative drug docetaxel (DTX) and a shell coating of the platelet glycoprotein IIb/IIIa receptor monoclonal antibody SZ-21 (B). Scheme showing the strategy of SNAP impregnated polyurethane-based membrane to mimic the inner surface of blood vessels and thus inhibits platelet and bacterial adhesion (C). Reproduced with permission from the cited references [287–289].

4.6.1. Drug loaded cardiovascular stents

Cypher®, marketed by Cordis (a Johnson & Johnson Company) in 2003, was the first commercially available drug-eluting implant [272,290]. This device was made from a non-degradable polymer coating layer including PEVA and PBMA which were used as a platform for the release of PTX or sirolimus [162,284]. Moreover, for this device, a top coating layer made from the same polymers but containing no drug was employed to avoid any burst release. Another example of these first-generation drug-eluting stents (made from non-degradable polymers) is Taxus™. This PTX-eluting coronary stent system was made from an elastomeric triblock copolymer (SIBS). This implantable

device was marketed by Boston Scientific (MA, USA) and was approved by the US FDA between 2003 and 2004 [290]. Although these drug-eluting non-degradable polymeric stents seemed to be very promising, the use of them led to a delayed healing and late thrombosis as potential risks [286,289,291]. In order to avoid the risk of thrombosis, NO has been investigated [289,291]. For instance, some researchers showed the potential of the NO donor S-nitoroso-N-acetylpenicillamine (SNAP)-loaded polyurethane disks (5% and 10% SNAP) released NO at a valuable rate for 9 and 19 days, respectively (Figure 10C) [289].

For the second-generation of drug-eluting stents more attention was paid to the type of polymeric materials used in their manufacture. These stents are made from biodegradable polymers such as PLA, PLGA, PCL or poly(D,L-lactic acid) (PDLLA), among others, thus avoiding the abovementioned side effects caused by the non-degradable polymeric materials [162,272,292]. One of these second generation drug-eluting stents commercially available is Biomatrix®, which used a poly(L-lactic acid) (PLLA) platform for the delivery of biolimus [293,294]. The use of this biodegradable platform showed lower prevalence of adverse cardiac events (15.7%) in comparison with a first generation sirolimus-eluting stent (19%) (LEADERS clinical trial) [162,294]. Moreover, Abbott Vascular (IL, USA) manufactured a bioresorbable everolimus-eluting stent (Absorb™), which consisted of a 150-µm-thick bioresorbable PLLA stent with a 7-µm-thick bioresorbable PDLLA coating [162,295]. Absorb™ was the first drug-eluting fully-erodible stent implanted in a human, which also presented a clear reduction in the rate of adverse cardiac events after 12 months (from 14% to 3.3%) when compared to non-drug loaded PLLA-based stents [295,296]. DREAMS from Biotronik AG (Berlin, Germany) comprise a couple drug eluting absorbable metal stents [162,297]. The manufacturer used magnesium-based alloy as the main scaffold for both DREAMS 1G and 2G [162,297]. However, the first generation of these stents was coated with PTX-loaded polylactic-co-glycolic acid (PLGA) layer of 1 µm, while the second generation was coated with PLLA incorporated with sirolimus [297]. Moreover, the clinical trial performed using DREAMS 2G did not report any episode of stent thrombosis after 12 months [297]. Finally, Endeavor (Medtronic CardioVascular Inc., Santa Rosa, CA) is an example of a zotarolimus-eluting stent. This device consisted of a cobalt–chromium alloy as base with a zotarolimus-containing phosphorylcholine (PC) coating [298]. In contrast to other polymeric coatings, PC is able to avoid hypersensitivity and inflammatory reactions, since this coating mimics the cell membrane of red blood cells in the plasma. However, most of the drug (95% of the loaded zotarolimus) is released within first 15 days [299]. In addition, multiple researchers are still studying the use of novel biodegradable polymeric coatings with the aim of sustaining the release of the therapeutic agents, which is a potential approach to solve the problem of late stent thrombosis due to delayed vascular healing and re-endothelialization in patients following first-generation drug-eluting stents implantation. The latest and most relevant studies addressing this issue are shown in Table 6. Despite their unquestionable advantages, biodegradable polymers have shown weaker mechanical properties compared with the alloys used in the non-degradable drug-eluting stents [272]. Therefore, more research is needed to enhance the mechanical properties of the biodegradable-based drug eluting stents.

Table 6. Latest findings in the development of second-generation of drug-eluting stents and drug-eluting vascular grafts

Type of implant	Material	Target	Drug	Findings	Ref
Stent	Coating of poly(L-lactide-cocaprolactone)	Cardiovascular diseases	Atorvastatin and fenofibrate	Sustained release of Ator. and Feno. for more than 60 days. Combination of both drugs	[300]

	(PLCL) on a stainless steel stent.			provided antithrombotic and anti-inflammatory effects and significantly retarded smooth muscle cell proliferation, showing its effectiveness to overcome restenosis.	
Stent	Coating of chitosan (inner surface) and PLGA (outer surface) on a stainless steel stent.	Cardiovascular diseases	Monoclonal platelet glycoprotein IIIa receptor antibody SZ-21 and docetaxel	A sustained release of both bioactive compounds. This novel combination provided antithrombotic effect at earlier period and inhibition of vascular smooth muscle cells proliferation at later period.	[301]
Stent	Coating of PLA on a cobalt chromium alloy stent.	Cardiovascular diseases	Sirolimus, abciximab and alphalipoic acid (ALA)	The combination of these three drugs had synergistic effects showing a superior neointimal and vascular inflammation suppressive effect in comparison to those containing no drugs or only sirolimus.	[302]
Stent	Sirolimus loaded PLGA nanoparticles, phosphatidylglycerol-bivalirudin complex and bare metal stent.	Cardiovascular diseases	Sirolimus and bivalirudin nanoparticles	Superior antiproliferative activity of sirolimus loaded PLGA nanoparticles over native sirolimus in smooth muscle cells.	[303]
Stent	Zein, alginate and stainless steel stent.	Cardiovascular diseases	Rutin	The addition of alginate succeeded in sustaining rutin release profile over 21 days. Moreover, this plant-based coating showed excellent vascular cell biocompatibility.	[304]
Stent	Coating of a blend of PLGA and PLLA on a cobalt chromium alloy stent.	Cardiovascular diseases	Sirolimus	Developed stents in this study were able to prevent stent-induced tissue hyperplasia in the porcine Eustachian tube model.	[305]
Stent	Coating of PDLLA on magnesium–neodymium-zinc-zirconium alloy stent.	Cardiovascular diseases	Sirolimus	The coating performed on this patented alloy prevented smooth muscle cells adhesion and sustain the drug release rate *in vitro*.	[306]

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Stent	Polymeric scaffolds of PLLA/PDLA using a polydopamine (PDA) intermediate layer.	Cardiovascular diseases	Everolimus	The PDA intermediate layer was able to sustain drug release. Therefore, it can be used as a potential approach to prevent complications of the current drug-eluting stents, such as the late-stent thrombosis.	[307]
Stent	Coating of heparin-loaded alginate and atorvastatin calcium-loaded polyurethane on nickel-titanium (Ni-Ti; also known as nitinol) stents.	Cardiovascular diseases	Heparin and atorvastatin calcium	The coating approach provided a sustained release of both drugs. In addition, this approach was biocompatible, hemocompatible, and enhanced human umbilical vein endothelial cells attachment.	[308]
Stent	Coating of tacrolimus (polymer free) on the outer surface and N-doped titanium dioxide (N-TiO_2) coating on the inner surface of the cobalt chromium alloy stent.	Cardiovascular diseases	Tacrolimus	The abluminal coating of tacrolimus provided anti-inflammatory effects and reduced in-stent restenosis. In addition, the coating on the inner surface (N-TiO_2) was useful for increasing re-endothelialisation and preventing thrombosis.	[309]
Stent	The model stent was a silver coated copper wire, which was then coated with poly(n-butyl methacrylate) (PBMA).	Cardiovascular diseases	Leoligin	The authors proposed an inexpensive drug eluting stent model using natural compounds, which have the potential to inhibit intimal hyperplasia and the regrowth of endothelial cells	[310]
Stent	A polymer blend of PLA and EVA	Cardiovascular diseases	Aspirin	The polymers blend coating proposed in this work showed superior mechanical properties and controlled release of aspirin.	[311]
Stent	Coating of Poly 3-Hydroxybutyrate 4-Hydroxybutyrate (P34HB) on a stainless steel stent.	Cardiovascular diseases	Sirolimus	The polymer coating of this work showed the ability of sustaining release rate.	[312]

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Stent	Coating of a PLGA/PEVA on a nickel-titanium alloy stent.	Cardiovascular diseases	Paclitaxel	The coating composite approach of this work was able to sustain the PXL release for at least 30 days, showing a zero-order release profile after initial burst release.	[313]
Stent	Coating of a PC-based copolymer on a PLLA-based biodegradable stent.	Cardiovascular diseases	Sirolimus	This novel biodegradable coating approach showed a sustained sirolimus release profile as well as the potential to inhibit neointimal hyperplasia in a porcine artery injury model *in vivo*.	[314]
Stent	Coating of a citric acid solution on on nickel-titanium alloy stent	Cardiovascular diseases	Citric acid	The use of citric acid was able to promote endothelial adhesion, migration, and proliferation *in vitro* on the stent surfaces. However, to support these claims about citric acid for vascular healing, *in vivo* studies should be performed.	[315]
Vascular graft	PCL and decellularized rat aorta (DRA)	Cardiovascular diseases	Sirolimus	Hybrid tissue-engineered vascular graft showed a sustained sirolimus release, thus preventing intimal hyperplasia. Moreover, these grafts had superior mechanical properties compared to DRA, showing a great clinical translational potential.	[316]
Vascular graft	PCL and Pluronic 123	Cardiovascular diseases	Cilostazol	The addition of Pluronic 123 improved tensile properties of electrospun fibres and increased the cilostazol release rate, however, significantly reduced the cell viability when compared to more hydrophobic PCL formulation.	[317]
Vascular graft	PCL, Polyethyleneimine (PEI) and epigallocatechin gallate (EGCG)	Cardiovascular diseases	Dexamethasone and heparin	A coating of PEI and Hep. in combination with EGCG and Dex. was used to functionalize the electrospun PCL vascular	[318]

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				grafts. This coating provided a sustained release. In addition, this system prolonged anticoagulant and anti-inflammatory properties as well as the anti-fibrinogen denaturation ability of the vascular grafts.	
Vascular graft	TPU	Cardiovascular diseases	Dipyridamole and rifampicin	Vascular grafts developed in this study were able to sustain the release of RIF, thus preventing vascular graft infections. Moreover, dual extrusion FDM 3D printing technology enabled to manufacture grafts containing the two different drugs. These grafts were cytocompatible and hemocompatible.	[285]
Vascular graft	PCL	Cardiovascular diseases	Dipyridamole	This 3D printed drug SDVGs were able to provide a sustained and linear drug release for at least 30 days, as well as a significant antithrombotic effect. These grafts were cytocompatible and hemocompatible.	[271]
Vascular graft	TPU	Cardiovascular diseases	Dipyridamole	Drug-eluting SDVGs showed a sustained DIP release for at least 30 days and comparable mechanical properties than natural blood vessels. Moreover, the outcomes of this work suggested that the drug load and also the surface properties were decisive for platelet adhesion.	[319]

4.6.2. Drug loaded vascular grafts

Surgical bypass grafting is another valuable strategy for the treatment of some specifics CVD. IDDS have been successfully used to replace large blood vessels, however, some risks of thrombus formation and neointimal hyperplasia can occur when replacing when used to replace SDVGs (> 6 mm

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internal diameter). Therefore, the combination of vascular grafts with some therapeutic agents such as heparin, CIL, DIP, acetylsalicylic acid or NO is a simple way to prevent these complications.

Different techniques including electrospinning, mould-casting and 3D printing [269,320] can be used for the manufacture of drug-eluting SDVGs. The use of electrospinning has been extensively reported in the literature. Moreover, PCL is one the most common biodegradable polymers used for this purpose. For instance, electrospun PCL-based fibers or nanofibers have been loaded with rapamycin [316], CIL [317], heparin and dexamethasone (Figure 9D-E)[318], ASA [276] or even fibrin [321]. Overall, these works showed a potential anticoagulant ability and/or the capacity to inhibit intimal hyperplasia. Additionally, other biodegradable polymers such as poly(D,L-lactic acid-co-glycolic acid) (PDLLGA), poly(L-lactic acid-co-ε-caprolactone) (P(LLA-CL)) or biodegradable elastic polyurethane (BPU) were successfully used to prepare electrospun tubular scaffolds as a vascular drug-delivery grafts loaded with vancomycin [322], heparin and VEGF [323] and DIP (Figure 9A-C) [109], respectively. The former device achieved a local and sustainable delivery of antimicrobial compound, thus, it could be used for preventing infections when grafts are implanted, while the last two studies showed excellent anticoagulant properties, hemocompatibility and the potential to promote rapid endothelialisation.

More recently, some authors have proven that 3D printing technology can be successfully used for the manufacture of drug-eluting SDVGs. For this purpose, a combination of two types of PCL (50 kDa and 550 Da) and DIP was achieved without using any solvent by using a centrifugal laboratory mixer prior to the loading the mixture into a semi-solid extrusion 3D-printer [271]. Moreover, the same procedure was used to combine PCL and ASA [274]. Figure 9F-J shows representative images of the resulting 3D-printed vascular grafts containing DIP and ASA. Both studies suggested that the amount of antithrombotic agents in the material surface was more important than the amount of released drug to avoid the platelet adhesion to the surfaces of the 3D printed SDVGs. Additionally, the authors of one of the aforementioned studies [274] showed the possibility of loading more than one therapeutic agent (ASA and RIF), and thus multiple complications could be avoided. In this regard, a different study also explored the use of dual extrusion FDM printer to prepare non-biodegradable TPU-based drug-eluting SDVGs containing DIP and RIF [285]. Moreover, FDM technology was used by Dominguez-Robles et al. to obtain antiplatelet SDVGs [319]. In this case TPU was combined with DIP (up to 20% w/w) using hot melt extrusion. Subsequently, FDM was used to print SDVGs. Interestingly, SDVGs containing lower DIP content (5%) showed better antiplatelet activity than grafts containing higher drug loading (10 and 20%) [319]. This was mainly due to surface properties of the resulting grafts [319]. Moreover, FDM is a better option than semi-solid extrusion for the development of medical devices due to its higher resolution. The latest and most relevant studies designing and developing drug-eluting vascular grafts by using electrospinning and 3D printing techniques are shown in Table 6 The advent and the continuous development of 3D-printing technologies during the last years could make possible a different approach towards the manufacture of drug-eluting SDVGs personalised to each individual. Such a concept provides benefits for patients and physicians. In this way SDVG can be produced on demand adapting the geometry of the device to the anatomy of the patient [271,274,285,324].

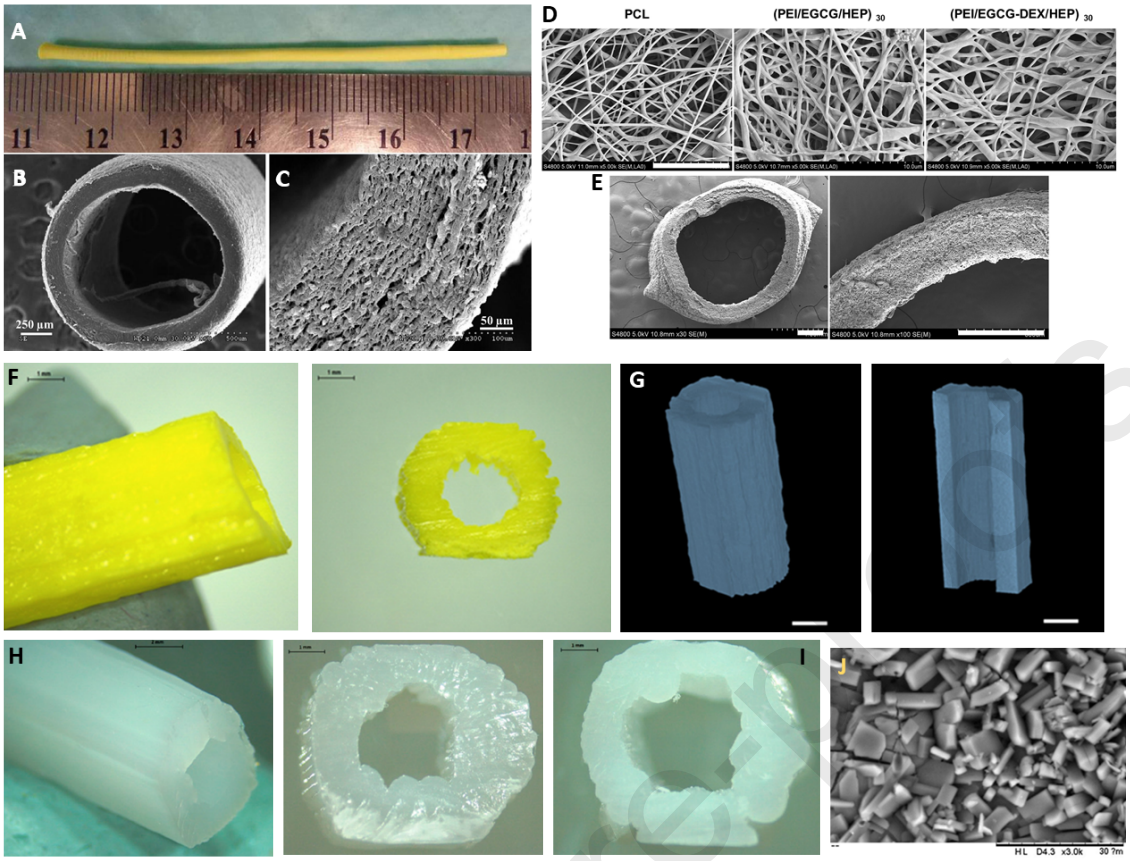

Figure 9. A macroscopic view of the electrospun DIP-eluting SDVG (A) and its electronic cross-section images (B and C). Scanning electron microscope (SEM) images of the electrospun PCL-based SDVGs before and after modification (D) and their cross-sections (E). Scale bars were 10 and 500 µm, respectively. PCL-based 3D-printed SDVGs containing 20% DIP (F), and images of the performed X-ray microcomputed tomography in this study, indicating a homogeneous structure was obtained. (G). PCL-based 3D printed SDVGs with no drug (H) and containing 10% ASA (I), and a SEM image of the surface of the last SDVGs containing 10% ASA (J). Reproduced with permission from the cited references [109,271,274,318].

4.7. Implantable devices for cell encapsulation

Therapeutic transplanted cells are in shortage, and they need lifelong immunosuppression to prevent their rejection from the body, limiting the widespread application of islet or cell transplantation [325]. The main objective of encapsulated devices is to provide a protected environment that increases cells' survival rate, providing an immunoisolation barrier to avoid rejection and maintain their sustenance and functions [326]. The most critical factors of materials for cell encapsulation are stability, biocompatibility, flexibility, permeability and maintaining the survival of encapsulated cells [327]. Advanced preparation methodologies for these devices include water and oil systems, microfluidic systems, conformal coating, 3D printing and bioprinting [328–330]. Cell encapsulation devices come in various designs, such as tubular hollow fibers, tubular ultra-filtrate chambers and planar devices [331,332]. These systems acts as diffusion chamber enveloping a large transplant mass within a single well-defined 3D-device, allowing for device retrievability in case of adverse reaction or failure [326]. These devices allow for greater control over membrane parameters, such as pore size and porosity, but have limited mass transportation of nutrients, oxygen, and waste products, leading to necrosis in

the middle of the capsule [333]. Some researchers have described a combined approach using microencapsulation devices loaded with microcapsules containing cells [332]. Nanoencapsulation system offers advanced control of uniform capsule thickness and pore size to enhance permeation selectivity and increase oxygen delivery [334].

Currently, basic, and clinical research focuses on encapsulation materials, transplantation sites and methods to improve immune modulation and neovascularization. One of these studies is the encapsulation of Mesenchymal Stem Cells (MSCs) for bone tissue engineering [335]. Recent progress and clinical trials in the world of cell encapsulation that have been conducted or are ongoing to cure many diseases, mainly focused on diabetes [336]. Stem cells are used in these systems to tackle diabetes and many other diseases such as hyperlipidemia, osteoporosis, heart disease, brain tumors, and hemophilia [337,338].

The ongoing exploration under *in vitro* and *in vivo* studies mostly treating type 1 diabetes, spinal cord injury (SCI), cartilage regeneration and cancer as summarized in Table 7. The refillable neovascularized implantable cell homing and encapsulation (NICHE) cell reservoir produced by nanoporous membranes, promotes vascularization and independently delivery of two different drugs locally [339]. This NICHE device has been licensed by NanoGland LLC and is undergoing first levels of the FDA regulatory aspects while keeps being studied more in-depth. A recent study about implantable NICHE device has showed localized immunosuppression, thus preventing islet transplant rejection for type 1 diabetes treatment (Figure 10A) [340]. Another study applying the same encapsulation platform, showed a local immunosuppressant delivery of neovascularized allogeneic cell transplantation (Figure 10B) [341]. Also, for type 1 diabetes treatment, the Nanofiber Integrated Cell Encapsulation (NICE) device, enables safe and long-term delivery of insulin-producing cells [342]. Additionally, a semipermeable encapsulation system containing gas-permeable, liquid-impermeable alginate hydrogel/silicone membrane leads to nutrients and O_2 transport and insulin delivery, blocking the infiltration of immune effector cells for several months without intervention [343]. Figure 10C shows another example of hydrogel-based device for islet transplantation [344]. Many more studies in the literature about insulin producing cell encapsulation systems, which can also incorporate growth factors, can be seen in the Table 7. 3D printed scaffolds from collagen, silk fibroin or chitosan, carrying cells and growth factors have been proposed as a potential therapeutic method for clinical treatment of SCI, accelerating neural regeneration [345,346]. Studies have also demonstrated the potential of enhanced cartilage repair tissue engineering devices, promoting chondrogenic differentiation of stem cells [347,348]. The Electrospun Microtube Array Membranes (MTAMs) encapsulated systems have shown the potential for cancer treatment, providing a continuous secretion of antibodies which suppress the cancer cells [349].

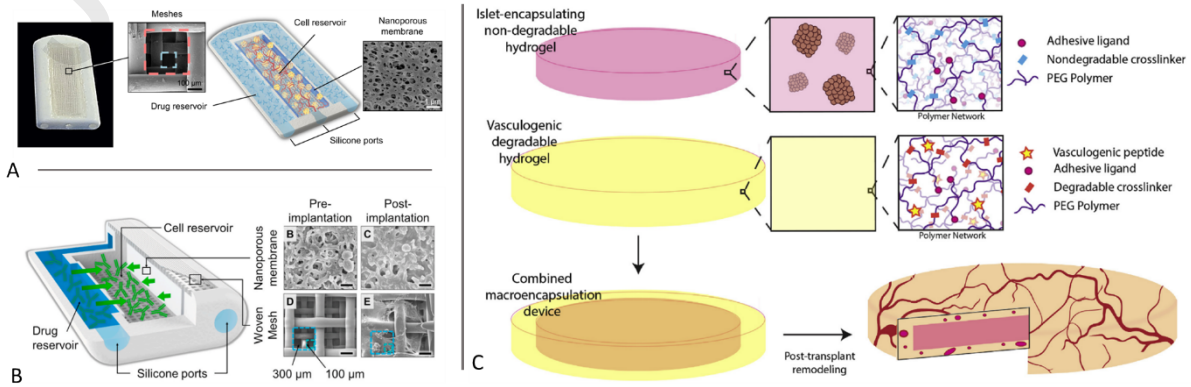

Figure 10. A) Optical and scanning electron microscopy (SEM) image of the two-layer mesh and nanoporous membrane NICHE. B) Cell and drug reservoir sites of NICHE and SEM image of nanoporous membrane. C) Design of synthetic hydrogel macroencapsulation device. Reproduced with permission from the cited references [340,341,344].

Despite these significant advances, extensive efforts have recently focused on investigating the ideal cell encapsulation approach, selecting the suitable material and site of transplantation, and investigating the cell behaviour after encapsulation [350]. Given the donor shortage, stem cells have the potential to be a replenishable source. Further work is necessary, however, to find an effective strategy and develop better methods for generating stem cells with all the necessary characteristics in a sufficient number, showing higher production yield, and without the risk of teratogenicity [351]. The current drawbacks of immune system activation, hypoxia, fibrotic overgrowth and poor clinical response still create obstacles [352]. Future success is promised with the continuous incorporation of material design, nanotechnology and immunomodulation.

Table 7. Recent studies describing cell encapsulation in IDDS

Type of implant	**Material**	**Target**	**Findings**	**Ref**
3D printed Neovascularized Implantable Cell Homing and Encapsulation	Polyamide, resin, polyethersulfone (PES), nylon, silicone and hydrogrel	Type 1 diabetes	Allogeneic islets transplanted from pre-vascularized NICHE led to functional engraftment, revascularization, reverting diabetes in rats for over 5 months.	[340]
3D printed Neovascularized Implantable Cell Homing and Encapsulation	Polyamide, nylon, silicone, hydrogel	Type 1 diabetes	NICHE, preloaded with mesenchymal stem cells (MSCs), subcutaneously implanted, integrated *in situ* pre-vascularization and local immunosuppression.	[341]
Nanofibrous tube encapsulation of insulin-producing islets and stem cell-derived beta (SC-β) cells	Alginate hydrogel	Type 1 diabetes	Long-term cell engraftment, corrects diabetes in mice in vivo for up to 399 days.	[353]
Semipermeable encapsulation system containing a gas-permeable, liquid-impermeable silicone membrane	Alginate hydrogel/ silicone membrane	Type 1 diabetes	Transports nutrients, O2 and the delivery of insulin but blocks the infiltration of immune effector cells for several months without intervention.	[343]

Speedy Oxygenation Network for Islet Constructs insulin releasing scaffold	Alginate hydrogel	Type 1 diabetes	Improves cell survival under hypoxic conditions in immunocompetent diabetic mice for over 6 months.	[354]
Macroencapsulation device for insulin-secreting β cells	Acrylic sheet - poly(methyl methacrylate)	Type 1 diabetes	Enhances the survival and insulin secreting function of the cells in vivo, improves glucose tolerance, and reduces fibrosis.	[355]
Islet-encapsulation device to secrete glucose, insulin, and IgG	Alginate hydrogel	Type 1 diabetes	Improves glycemic control without immunosuppressants.	[356]
Nanofiber Integrated Cell Encapsulation device for the safe delivery of insulin-producing cells	Thermoplastic silicone polycarbonate urethane and alginate hydrogel	Type 1 diabetes	Enables long term delivery of insulin producing cells including human stem cell derived β (SC-β) cells.	[342]
Encapsulation device augmented with controlled release of amino acids (alanine and glutamine)	PCL nanoporous and nonporous films	Type 1 diabetes	Improves the survival of encapsulated stem cell-derived insulin-producing cells in the poorly vascularized subcutaneous space for several weeks	[357]
3D bioprinted construct insulin-secreting β cells	Alginate/ PCL	Type 1 diabetes	Enables proliferation and insulin release normally, proposing a better alternative to portal vein islet transplantation.	[358]
3D printed scaffolds carrying human umbilical mesenchymal stem cells (HUCMSCs)	Collagen/silk fibroin	Spinal cord injury	Has the potential to become a novel and safer treatment for SCI repair.	[345]
3D printed scaffold integrated with the brain-derived neurotrophic factor (3D-CC-BDNF) and Human umbilical cord mesenchymal stem cells (HUCMSCs)	Collagen/chitosan	Spinal cord injury	Accelerates neural regeneration after SCI, thus could be a potential therapeutic method for clinical treatment of SCI.	[346]

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3D bioprinted nerve scaffold composed of rat Schwann cells	Gelatin/alginate hydrogel	Neurodegenerative diseases	Improves cell adhesion and related factor expression.	[359]
3D-printed scaffold loaded with Mesenchymal stem cells	PCL/methacrylated alginate	Cartilage repair	Demonstrates a potential for enhanced cartilage tissue engineering.	[347]
3D bioprinted construct with bone marrow mesenchymal stem cells	Silk fibroin/ decellularized extracellular matrix	Cartilage repair	Releases TGF-β3, promoting chondrogenic differentiation of BMSCs and provides a good cartilage repair environment.	[348]
Electrospun Microtube Array Membranes (MTAMs) encapsulated with Hybridoma cells	Polysulfone/ PEG	Cancer Treatment	Provides a continuous secretion of antibodies which suppressed the cancer cell line A549, MDA-MB-468 throughout the entire 21 days of in vitro experiment.	[349]
Porous microneedle patch that accommodates CAR T cells and allows in situ penetration-mediated seeding of CAR T cells	Ethacryloyl chloride modified 4-arm-PLGA/andtriethylene glycol diacetate/CaCO3 microparticles	Cancer Treatment	Augments T cell infiltration within the solid tumor, preventing local tumor recurrence and potential metastatic dissemination.	[360]

4.8. MNs-assisted delivery of IDDS

Microneedles (MNs) are minimally invasive devices that bypass the skin's *stratum corneum(SC)* barrier with a painless and bloodless insertion [361,362]. MNs, which range in height from 10 to 900 μm and are manufactured using microfabrication in a variety of geometries and materials, have been extensively investigated for enhanced transdermal drug and vaccine delivery [363]. As MN array is inserted into the skin, it creates pathways for drug molecules to diffuse through the *SC* and through the other layers of the skin for localized or systemic drug delivery [364]. Therefore, when compared to conventional oral and injectable administration, this approach offers a number of benefits, including prevention of gastrointestinal degradation, avoidance of first-pass hepatic metabolism, improved bioavailability, painless application, reduced infection danger and the ease of self-administered by the patient [365].

Recently, MNs have received great attention as they are the minimally-invasive devices that can bypass the skin's *SC* barrier for the delivery long-acting drug delivery systems. Because of the tunable features of biodegradable polymers, controlled drug delivery can be achieved by using polymeric MN [366].

There are several types of implantable MNs, and the mechanism of delivery described in the literature as seen in Figure 11A and 11D, including nano/microparticles loaded dissolving MN, fast separable solid implantable MN, hydrogel-forming MN [367,368].

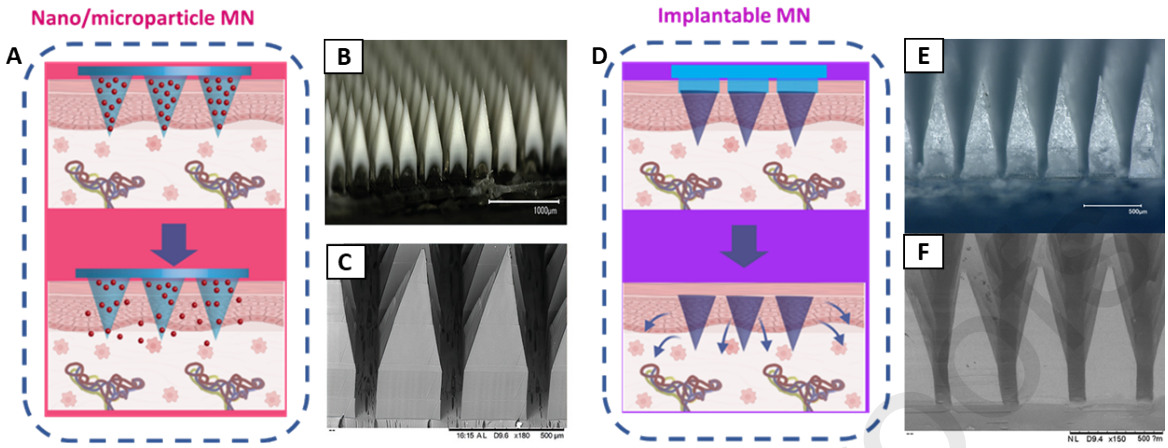

Figure 11. Schematic of nano/microparticle-based MNs for sustained drug delivery (A) and optical microscopy and scanning electron microscopy images of MN arrays loaded with a cabotegravir nanosuspension (B). Schematic of MN arrays loaded with micro-implants for IDDS minimally invasive administration (C) and optical microscopy and scanning electron microscopy images of MN arrays containing PLGA tips loaded with tenofovir alafenamide (D). Reproduced with permission from: [205,369].

4.8.1. Implantable nano/microparticles combined with MNs

Polymeric micro/nanoparticles (MPs/NPs) are promising carriers have been extensively studied for a wide variety of drug delivery applications [370]. To maximize the benefits of both particulate and MN delivery systems, some combinatorial techniques have been developed over the last two decades. These systems can be loaded into MN arrays to obtain minimally invasive IDDS capable of depositing IDDS based on MPs/NPs (Figure 11A). Table 8 summarises recent developments in this area of research.

Tekko et al. reported the application of drug nanosuspension-loaded bilayer-dissolving MN for the sustained delivery of cabotegravir for HIV PrEP [369] (Figure 11B-C). After single MN application *in vivo* in the rats, they demonstrated that MNs were able to provide drug levels in plasma above therapeutic levels over 28 days study period. Similarly, McCrudden et al. developed MN patches loaded with a long-acting rilpivirine formulation for intradermal and intravaginal administration of a rilpivirine nanosuspension [371,372]. In both cases the drug was detected in plasma even 56 days after the administration of the MN array. Similarly, Moffat et al. developed a combined approach to administer both rilpivirine and cabotegravir achieving in vivo drug release for periods longer than 4 weeks (Table 8) [373]. Alternative compounds such as Vitamin D3 or etravine have been formulated into nanosuspensions for MN-mediated long-acting drug [374,375]. Additionally, hydrogel-forming MNs (HFMNs) itself could help to deliver the drug intradermally to generate the long-acting micro-depots. Naser et al. recently showed the long acting intradermal drug depot generation once solid dispersion of Atorvastatin delivered through HFMN [376]. Evidently MN assisted intradermal drug delivery holds potential as a non-invasive long-acting system to improve the patient compliance and adherence. Therefore, this method offer high versatility as it allows loading of proprietary

nanosuspensions/nanocrystals used for conventional injection into MN minimally invasive systems [369,371].

Table 8. Recent studies describing MNs-assisted delivery of IDDS

Type of implant	Material	Target	Drug	Findings	Ref
HFMNs with a solid drug dispersion loaded in a separate patch	Gantrez-based HFMN containing a PEG-based drug reservoir	Hyperlipidemia	Atorvastatin	A single skin application of the system for 24 h in a rat animal model resulted in a sustained release the drug for over 2 weeks.	[376]
MN loaded with long-acting suspension	Drug nanosuspension loaded in PVA/PVP MNs	HIV	Etravirine	The resulting MN arrays were capable of providing between 30-40 days of drug release in vivo after skin administration in a rat animal model.	[374]
MN loaded with long-acting suspension	Drug nanosuspension loaded in PVA/PVP MNs	HIV	Rilpivirine and cabotegravir	MN assisted micro-depot formation allowing sustained delivery of RIL and CAB for up to 63 and 28 days respectively after skin administration (rat model).	[373]
MN loaded with long-acting suspension	Drug nanosuspension loaded in PVA/PVP MNs	HIV	Cabotegravir	MN assisted micro-depot formation allowing sustained drug delivery for up to 1 month in vivo (rat model).	[369,377]
MN loaded with long-acting suspension	Drug nanosuspension loaded in different formulations containing PVP, PVA, PEG and Gantrez	HIV	Rilpivirine	MN assisted delivery of nanosuspensions for prolonged vaginal drug delivery for up to 56 days in vivo (rat model).	[372]
MN loaded with long-acting suspension	Drug nanosuspension loaded in PVA MNs	HIV	Rilpivirine	MN assisted delivery of nanosuspensions for prolonged drug delivery after skin application for up to 56 days in vivo (rat model).	[371]

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MN-based mini-implants	Silk protein MN tips and poly(acrylic acid) baseplate	Growth hormone deficiency	Growth hormone	Rapidly detachable silk protein mini-implants were administered into the skin of rats to provide sustained hormone release for more than 7 days with a single administration.	[378]
MN-based mini-implants	PLGA core/shell micro tips loaded into a PVA baseplate	Contraception	Levonorgestrel	Core-shell micro tip MN arrays were prepared. The shell was prepared using PLGA and a more sustained drug release than core only micro tips over 6 months in vitro.	[379]
MN loaded with long-acting suspension	PLGA loaded with drug MN tips and PVA/PVP baseplate	Alopecia and prostatic hyperplasia	Finasteride	Micro-tip PLGA MN arrays were prepared and compared with drug loaded dissolving MNs in vitro. The PLGA system was capable of providing slower drug release than conventional dissolving MN arrays over 14 days.	[361]
MN-based mini-implants	PLGA MN tips combined with a Gantrez-based HFMN array	Cutaneous fungal infections	Amphotericin	The manufacturing of tapidly detachable PLGA mini-implants loaded into HFMNs was optimised. The resulting devices were tested in vitro for the delivery of amphotericin.	[380]
MN-based mini-implants	PLGA/PLA MN tips and PVP baseplate	Contraception	Levonorgestrel	Rapidly separating/biodegradable MN, made of PLA and PLGA for continuous drug release up to 3 months in vivo (rat model).	[381–383]

4.8.2. Implantable microtips based MNs

Implantable biodegradable tips-based MNs are mostly fabricated by a variety of biodegradable polymers, including PLA, chitosan, PGA, PCL, or PLGA [384,385]. Once slow-dissolving MN tips are implanted intradermally, after a short duration of MN application into the skin, the biodegradation of the polymer allows the drug to release intradermal space (Figure 13D) [366]. Table 8 summarises recent developments in this area or research.

PLGA, PLA and silk protein have been previously used to prepare the tips of this type of MN arrays due to their high biocompatibility, strong mechanical capabilities, and safe profiles. They have been used for the delivery of different compounds such as levonorgestrel, finasteride or growth hormone (Table 8). The cargo inside implanted PLGA MN tips can be released in a sustained way to provide a long-

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acting effect. According to reports, the release time ranges from days to periods of up to three months. Drug loading, length of the polymeric chain, and the presence of porogens (ie. trehalose) could all have an influence on the release rate of drugs from implanted PLGA tips [386]. The kinetics of drug release from PLGA MN tips may be easily adjusted, according to Aung Than et al, by mixing PLGA polymers with different molecular weights and copolymer ratios [387].

One of the first studies describing this type of system providing in vivo drug release studies was performed by Li et al [381]. This work describes fast detachable PLGA tips loaded with levonorgestrel achieving up to 30 days of drug release in vivo. This type of system further explored optimizing different parameters in the MN array formulation [382,383]. One of the latest developments for PLGA tip MN arrays was the development of core-shell micro-tips to achieve a more sustained drug release than with conventional PLGA tips [379]. This system was tested in vitro for levonorgestrel delivery achieving 6 months of sustained drug release. Recently, some two-layer and three-layer MN designs were tried in order to reduce application times while accelerating the implantation of PLGA/PLA tips [205,388] (Figure 13E-F). Peng et al. introduced a novel microneedle patch that combined implantable PLGA tips with hydrogel-forming microneedle bases (HFMB) using a dissolvable material. The combination of the pre-formed HFMB improved not only the insertion ability but also the *ex vivo* drug delivery efficiency up to 80% of the loaded drug and faster implantation process within a minute when compared to the traditional dissolving baseplate PLGA tipped MN design. Therefore, these novel implantable MN patches could have potential use in long-acting drug delivery [380,384].

4.9 Implantable devices for vaccine delivery

Implantable devices are considered a suitable platform for vaccine delivery due to several advantages. Based on the materials and formulations, the implants can sustain the release of the vaccine at the target site, especially the skin which is a rich source of immune cells (*e.g.,* Langerhans's cell and dermal dendritic cells) and muscles, resulting in robust immune responses [389]. More importantly, the implant can be used as a single-shot vaccine that has the release kinetics similar to the natural infection by providing both prime and booster immunization in a suitable timeframe, minimizing the need for multiple doses required when traditional vaccine administration approaches are performed [390]. Importantly, the materials must not generate undesired immunogenicity that can interfere with the vaccine's effect on immune responses and cause adverse effects. Table 9 summarises recent IDDS designed for vaccine delivery.

There were attempts to produce implants from the components found in the human body [391,392]. Even et al. produced lipid implants for tumour therapy from the mixture of cholesterol, soybean lecithin, trimyristin, trehalose, a tyrosinase-related protein-2 (TRP2) peptide, and Quil-A using a twin-screw extruder [393]. The *in vivo* study in a melanoma mouse model showed that the lipid implants loaded with 56 µg TRP2 peptide antigen and 100 µg Quil-A adjuvant could significantly suppress tumor growth when compared to the control (without the vaccine components). Although the outcomes were satisfied, the release kinetics and stability of the vaccine were dependent on lipid aging and components in the formulations. Therefore, many studies opted to explore using either natural or synthetic polymers to fabricate implantable devices. Amssoms et al. fabricated a core-shell implant to mimic the concept of a single-administration vaccine that could provide a prime immunization and followed by a boost immunization [394]. The core of the implant contained ovalbumin antigen and the shell was made of PLGA, which functioned as a release controller. The *in vitro* release revealed that increasing the ratio between lactic acid and glycolic acid for the PLGA shell resulted in a longer lag time, causing a delayed release of ovalbumin. Corresponding to the delayed release of antigen, the

core-shell implant induced a delayed ovalbumin-specific IgG1 antibody response in mice and higher IgG1 antibody titers than conventional subcutaneous vaccination with ovalbumin dissolved in PBS. Najibi et al. also highlighted the need for a single-administration vaccine as reflected in their study on the development of porous PLGA scaffolds for vaccine delivery [390]. The study reported that mice that were implanted with the PLGA scaffold encapsulating gonadotropin-releasing hormone (GnRH)-ovalbumin conjugate as an antigen and cytosine-guanosine oligodeoxynucleotide (CpG) as an adjuvant had a prolonged germinal center formation, T follicular helper cell response, and robust anti-GnRH IgG1 response. Moreover, the PLGA vaccine scaffold elicited robust anti-HER2 IgG1 titers against HER2 peptide, and anti-RS218 IgG titers against pathogenic *Escherichia coli* strain RS218. Another study focusing on a single-administration vaccine was conducted by Shao et al. The implant was prepared by encapsulating L2 peptide antigens from human papillomavirus 16 strain-bacteriophage Qβ virus-like particle conjugate (HPV-Qβ) into a PLGA implant using a benchtop melt-extrusion [395]. The single-dose HPV-Qβ/PLGA implant could sustain the release of HPV-Qβ and generated IgG titers equivalent to conventional soluble injections in mice and showed a neutralizing effect against the HPV pseudovirus. This study showed the feasibility of using a single-dose vaccine implant to prevent cervical cancer caused by HPV. Ortega-Rivera et al. developed a single-dose multi-target vaccination platform from PLGA and bacteriophage Qβ-based virus-like particles [396]. The implant contained a trivalent vaccine candidate targeting proprotein convertase subtilisin/kexin-9 (PCSK9), apolipoprotein B (ApoB), and cholesteryl ester transfer protein (CETP). The plasma levels of PCSK9 and ApoB proteins were decreased, and the activity of CETP was inhibited.

In addition to exploiting PLGA polymer, there have been several attempts to use other biodegradable synthetic polymers to form an implant for a vaccine. Schaut et al. created a cyto-exclusive implant as a single-dose vaccination platform that permitted the release of antigen and adjuvant loaded in the polyanhydride rod enclosed in the polyethylene implant body through a porous poly(vinylidene fluoride) membrane cap [397]. The study reported that the implant could stimulate antigen-specific cellular and humoral responses for up to 41 weeks post-implantation. Another study conducted by Song et al. prepared a 3D porous polypeptide hydrogel from PEGylated poly(l-valine) copolymer [398]. The implant was loaded with tumor cell lysates (antigen) and poly(I:C) (immunopotentiator) for dendritic cell modulation. *In vivo* study demonstrated that the implant induced strong cytotoxic T cell responses, suppressing the growth of melanoma cancer. Nishiguchi and Taguchi demonstrated that a biodegradable implant fabricated from sulfonated nanocellulose-gelatin was able to activate immune cells like macrophages and dendritic cells *in vivo* and allowed cell infiltration to occur while delivering ovalbumin antigen locally [399].

In general, biodegradable polymers are preferable to avoid surgical-associated implant removal at the end of treatment. However, non-biodegradable polymers can be considered as alternatives if the advantages outweigh the disadvantages (*e.g.*, release kinetics and desirable immune responses are achieved). Poloxamer or pluronic F127, which consists of polyethylene glycol and poly(propylene oxide) blocks, is one of the most commonly used thermoresponsive polymers for implant fabrication although it is not a biodegradable polymer. Regarding vaccine implant formulations, poloxamer can be used alone or as a copolymer to constitute the injectable implant. For instance, Bansal et al. prepared rabies plasmid DNA-PLGA-chitosan nanoparticles and later dispersed them in a poloxamer 407 hydrogel, which turned into a solid gel at 37 °C [400]. Adams et al. developed a cationic pentablock copolymer based on pluronic F127 and methacrylated poly(diethyl amino)ethyl methacrylate outer blocks, and reported that the cationic pentablock copolymer could be used to form an antigen depot for sustained release without major adverse effect on antigen stability, and elicited adjuvanticity effect in mice [401].

Chen et al. presented the utilization of implantable porous scaffolds as an mRNA vaccine delivery platform [402]. Porous poly (2-hydroxyethyl methacrylate) (pHEMA) scaffold containing single-stranded mRNA-Stemfect™ lipoplexes showed superior efficiency in the prolonged local release of mRNA, mRNA uptake by cells, and GFP transgene expression at the implantation site *in vivo* when compared to the naked RNA-loaded porous scaffold and systemic bolus injection. This is highly likely that nanoparticles protected the mRNA from enzymatic degradation and facilitated transfection. While the implant maintained the concentration of gene payload at the implantation site and enhanced cellular internalization.

Interestingly, Viswanath et al. developed a refillable 3D-printed implant for antigen-specific antitumour immunomodulation called NanoLymph [403]. The device consists of two reservoirs for immunostimulants (granulocyte-macrophage colony-stimulating factor (GMCSF) and a Toll-Like Receptor 7/8 agonist, Resiquimod (R848)) and ovalbumin antigen (Figure 12). The study showed that the implant could sustain the release of both immunostimulants and ovalbumin, leading to enhanced local dendritic cell recruitment and activation. Moreover, antigen-specific T lymphocytes were generated within 14 days post-implantation. According to the seminal work, the development of implantable devices for vaccine delivery is an active and dynamic research area. However, many aspects in the field are underexplored. It is arduous to find a universal platform that can provide a complete compatibility with every type of vaccine as each vaccine type is unique and has its distinct stability and release kinetic profiles.

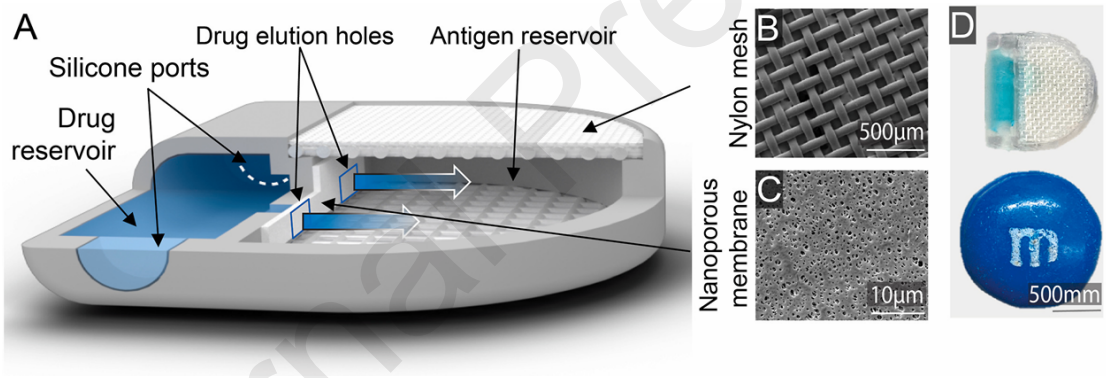

Figure 12. Diagram showing NanoLymph structure (A). SEM images of the nylon mesh (B) and nanoporous membrane (C) used to limit the diffusion from the reservoirs. Image showing the size of the implant next to a commercial M&M (D). Scale bar: 500 mm. Reproduced with permission from: [403].

Table 9. Recent studies describing IDDS for vaccine administration.

Type of implant	Material	Target	Vaccine	Findings	Ref
Lipid implant	A mixture of cholesterol, soybean lecithin, trimyristin, and trehalose	Melanoma	TRP2 peptide (antigen) and Quil-A (adjuvant)	Delayed tumour growth (3 days).	[393]

Polymeric implant	PLGA	-	Ovalbumin	Delayed ovalbumin-specific IgG1 antibody response. Higher IgG1 antibody titers.	[394]
Polymeric implant	PLGA	Breast cancer and infectious disease	GnRH-ovalbumin conjugate (antigen) and CpG (adjuvant)	Prolonged germinal center formation and T follicular helper cell response. Robust anti-GnRH IgG1 response. Strong anti-HER2 IgG1 titers against HER2 peptide. Anti-RS218 IgG titer against E. coli strain RS218.	[390]
Polymeric implant	PLGA	Cervical cancer	L2 peptide epitopes from HPV16	Equivalent IgG titers to conventional soluble injections. Neutralizing effect against the HPV pseudovirus.	[395]
Polymeric implant	PLGA	Hypercholesteremia and cardiovascular diseases	Proprotein convertase subtilisin/kexin-9 (PCSK9), apolipoprotein B (ApoB), and cholesteryl ester transfer protein (CETP)	Reduced PCSK9 and ApoB plasma levels. Inhibition of CETP. Decrease in total plasma cholesterol.	[396]
Polymeric implant	Polyanhydride rod, polyethylene implant body, and poly(vinylidene fluoride) membrane	-	Gonadotropin-releasing hormone multiple antigenic peptide (antigen) and monophosphoryl lipid A (adjuvant)	Antigen-specific cellular and humoral responses for up to 41 weeks post-implantation.	[397]
Polymeric implant	Polypeptide hydrogel made of PEGylated poly(l-valine) copolymer	Melanoma	Tumor cell lysates (antigen) and poly(I:C) (immunopotentiator)	Strong cytotoxic T cell responses. Suppression of tumor growth.	[398]
Polymeric implant	Sulfonated nanocellulose and gelatin	-	Ovalbumin	Increased interferon-γ-producing cells. Filtration of macrophages and dendritic cells.	[399]

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Polymeric implant	Poloxamer	Rabies	Rabies plasmid DNA vaccine	Stimulated cellular and humoral immune responses.	[400]
Polymeric implant	Pluronic F127 and methacrylated poly(diethyl amino)ethyl methacrylate outer blocks	-	Ovalbumin	Exhibited adjuvanticity effect.	[401]
Polymeric implant	pHEMA	Cancer	Single-stranded mRNA-Stemfect™ SF lipoplexes	Prolonged local release of mRNA. Enhanced mRNA uptake by cells. Superior GFP transgene expression	[402]
Polymeric implant	Resin and nylon	Cancer	Ovalbumin (antigen), GMCSF, and R848 (immunostimulants)	Enhanced local dendritic cell recruitment and activation. Production of antigen-specific T lymphocytes within 14 days.	[403]

4.10. Other applications of IDDS

In addition to the main areas described in the previous sections, IDDS have been used in the treatment of other conditions such as the treatment of certain endocrine conditions or addiction. Regarding the treatment of endocrine conditions, implantable drug delivery systems have been described for the treatment of central precocious puberty, testosterone replacement therapy or hypothyroidism.

Central precocious puberty can be treated using IDDS. This conditions is chracterised by premature activation of the hypothalamic-pituitary-gonadal axis that is normally inactive during childhood [404]. If this condition is not treated results in advance will impact bone development resulting in a reduction of full adult-heigh [404]. Gonadotropin releasing hormones can be administered to suppress pubertal development [404]. IDDS can be used to ensure continuous drug release of this type of compounds. Suprelin LA™ is a subcutaneous implant capable of providing release of histrelin to treat central precocious puberty [404]. This implant provide 1 year of treatment with a single implant containing 50 mg of histrelin. This implant is a hydrogel based reservoir-type implant. The core contains the drug while the implant is made of a methacrylate-based hydrogel [405,406].

Testosterone replacement therapy is used to treat hypogonadism. With age, testosterone levels in men can decline [407]. Therefore, an external supply of this compound can be administered to address this issue [407]. The administration of testosterone is normally carried out using injections or topical application of gels. Due to the need of continuous drug administration patient compliance tend to be low, especially in the case of injections [407]. An alternative to these dosage forms is the use of testosterone implantable pellets (Figure 13A-C). These pellets contained testosterone, stearic acid and poly(vinyl pyrrolidone) and provide release rates ranging between 3 and 6 months [408]. This product was approved by the FDA in 1972 but it was not marketed until 2008 (Testopel®) [407].

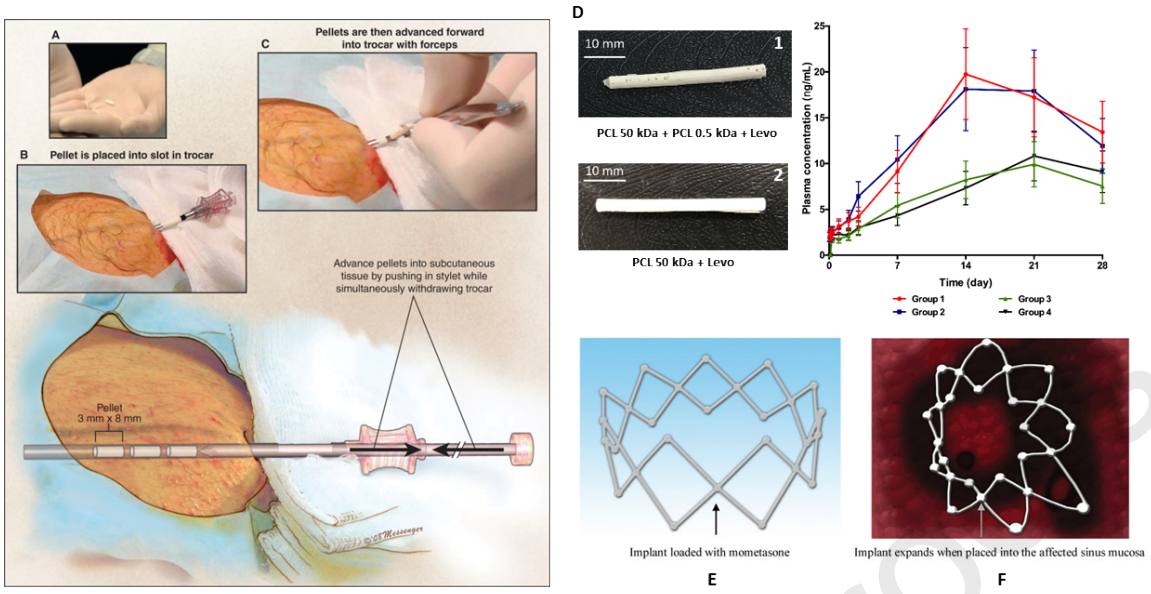

Figure 13. Implantation procedure of Testopel (A-C). PCL-based implants loaded with levothyroxine and levothyroxine rat plasma concentration after subcutaneous implantation of Implants 1 (Group 1 male Wistar rats; Group 2 female Wistar rats) and Implant 2 (Group 3 male Wistar rats; Group 4 female Wistar rats) (D). Propel™ sinus implant (E and F). Reproduced with permission from: [409–411]

Hypothyroidism is characterized by decreased levels of thyroid hormones within the body resulting in symptoms such as weight gain, chronic fatigue or cold intolerance [412]. Treatment using levothyroxine sodium is available. However, patient compliance and variability in drug absorption depending on food intake can limit the success of this treatment. In order to find alternative ways to delivery Stewart et al. described a PCL-based implantable system loaded with levothyroxine [410,413] (Figure 13D). The system provided *in vitro* sustained release for at least 100 days. On the other hand, this type of implants showed promising results in vivo in a rat animal model. Drug plasma levels were detected for at least 28 days (Figure 13D). In addition to this work, Titan Pharmaceuticals is evaluating the use of implantable devices for the delivery of triiodothyroxine for hypothyroidism treatment [414,415].

Opioid addiction to illegal and prescription drugs is a growing issue. There are available therapies to address this issue such as the administration of opioid agonists (such as buprenorphine, oxycodone or methadone), opioid antagonist (such as naltrexone or naloxone) or a combination of both [416]. Pharmacological treatment combined with psychological counseling has proven to be a successful way to address this growing problem [416]. IDDS can be used to administer these drugs in a sustained way avoiding continuous oral or injectable administration. Naltrexone implants have tested successfully to reducing relapse rates in 83% 1 year post implantation [417]. This implant contains 1.1g of naltrexone formulated using microspheres made of a PLA-derivative compressed into a solid tablet and coated with a PLA membrane [417]. Based on the same approach described for risperidone delivery, Delpor is in phase I trials of the development of DLP-160 [418]. DLP-160 is a 12-month naltrexone subcutaneous implant that also uses the Prozor™ technology to treat Opioid Use Disorder [419]. The aim of this work is to study pharmacokinetics and local tolerability to complete preclinical proof of concept trials. In addition to naltrexone, buprenorphine implants have been described. This type of implant was approved by the FDA in 2016 [416]. It is manufactured by Titan Pharmaceuticals and commercialized under the brand name of Probuphine™ [33,416]. These implants are made of EVA

and contained 80 mg of buprenorphine hydrochloride [33,408]. They can provide sustained drug release for up to 6 months [33]. These devices provide more consistent drug plasma levels than conventional approaches [33]. In 2020 Titan Pharmaceuticals announced that the sales of Probuphine implant will be discontinued due to commercialization difficulties [420].

In addition to systemic drug delivery, there are other FDA approved implants that can be used for local drug delivery. Propel™ (Figure 13E-F) and Sinuva™ are biodegradable implants based on PLGA used for the treatment of nasal polyps [408,411]. They are loaded with mometasone furoate and they can provide sustained release of this compound for up to 3 months to prevent nasal polyp recurrence [408,411]. Interestingly, they are biodegradable implants, so they do not need to be removed after depleting their drug cargo.

5. Clinical translation of IDDS

There are multiple aspects that need to be considered for the clinical translation of IDDS such as foreign body response, scale up manufacturing and sterility. These aspects will be all considered by regulatory bodies, such as FDA or EMA among many others, before an IDDS can be commercialised and used clinically.

Once an IDDS has been designed, optimised, and tested in vitro one of the potential problems that can be experienced during *in vivo* experiments is foreign body response. The application of implanted device generally triggers a host response, which may lead to foreign body reaction. This condition occurs when the implant is recognised as a foreign material by the body and elicits the innate immune system cells to develop an inflammatory and fibrotic process [421,422]. The process starts when the implant adsorbs plasma protein on its surface. This is followed by the coverage of the implant by a layer of proteins (e.g. fibrinogen, fibronectin, and vitronectin) leading to the formation of a fibrous capsule surrounding the implant that prevents it from functioning as intended [422,423]. The failure rate of implantable devices varies depending on their surface characteristics, design, and features, and is estimated to be 10% for some types of implantable devices [424]. This failure can be life-threatening for patients who receive these treatments. The surface properties of IDDS such as porosity roughness or charge play a key role on the onset of foreign body reaction [425–428]. Moreover, the size and shape of the implant plays a critical role on foreign body response [429]. Therefore, these factors need to be considered when selecting the materials, manufacturing technique, size, and shape of IDDS as they will influence foreign body response.

Another critical factor is scale up manufacturing of IDDS. Many of the IDDS described in this manuscript were prepared using manufacturing methods that cannot be easily translated to an industrial setup such as 3D-printing or electrospinning [430,431]. Moreover, some of the works described here used complex approaches to produce the implants involving many steps that will not be easy to transfer to an industrial setup for large scale manufacturing. It is important to mention that even if the manufacturing methods can be translated large scale manufacturing can change the properties of the final devices leading to performance issues.

Sterility is another crucial aspect that needs to be considered when translating IDDS to clinic. IDDS are required to be sterile [432,433]. Established methods for the sterilisation of implantable devices includes dry heat, steam, ethylene oxide, hydrogen peroxide, ozone or radiation [433]. Not all materials are suitable for dry heat or steam as moisture or high temperature can damage the IDDS or the drug cargo. Additionally, devices with electronic components can be damaged too. Ethylene oxide and gamma/electron beam sterilisation are extensively used for the sterilisation of medical devices as

they do not require high temperatures [433]. However, they have some limitations too. Ethylene oxide can leave toxic residues post sterilisation [433]. On the other hand, gamma or electron beam radiation can lead to changes in the material properties such as chemical composition, crystallinity, molecular weight, or density [433]. The effects of radiation will be heavily dependent on the dose and the type of materials present in the IDDS.

6. Conclusions

Since the approval of the first IDDS during the 1970s this field of research has experienced a large evolution. The application of this type of systems has evolved significantly over the last 30 years expanding from contraceptive implants to other areas of research such as ophthalmology or cancer treatment. These applications have been described in this review article. The future present exciting opportunities to improve IDDS. Conventional monolithic/reservoir implants are advancing by incorporating more advances features such as nano-engineered rate controlling membranes, stimulated drug release capabilities or the ability to be refilled externally.

The development of new materials can expand the applications and improve treatments. Development of biodegradable materials with prolonged degradation times can be used to expand treatment duration. Additionally, new materials can be used to improve IDDS manufacturing methods. For example, the development of IDDS that can be prepared at low temperatures will improve the applicability of this technology to deliver thermolabile compounds such as antibodies, peptides, or vaccines. Another promising aspect in the evolution of IDDS manufacturing technologies is the use of additive manufacturing technologies. This type of technology has evolved significantly in the last ten years and currently they can be used to prepare customised medical devices or pharmaceutical products adapted to patient's needs. However, before this can be widely applied to patient, more work is required. The future looks promising as regulatory bodies such as the US FDA or the UK Medicines and Healthcare products Regulatory Agency (MHRA) are engaging with researchers to address regulatory concerns associated with this type of technology.

Even though all the advantages and therapeutic options described in this article, IDDS still present certain drawbacks. The first limitation is that this type of systems normally requires invasive implantation procedures. In some cases, the implantation is minimally invasive but in other cases such as stent/cardiovascular graft implantation it requires surgical procedures. This is a limitation as the implantation could generate discomfort and pain even when anaesthetic drugs are used to minimise them. This can influence patient willingness to use IDDS specially in patients suffering from needle fear. This has been observed for the administration of long-acting injectable formulations and accordingly will be applied to implant administration too. Moreover, some of the implantation procedures will generate sharp wastes requiring expensive disposal procedures and potentially leading to needle-stick injuries. Finally, IDDS must be administered by healthcare professionals. This increases the cost of the therapy. Moreover, this is a problematic issue whenever the access to trained healthcare professionals is limited. To overcome these issues, there are novel alternatives such as the use of MNs or micro-implants to administered IDDS in a painless and minimally invasive way. Moreover, these novel technologies will allow patients to self-administer this type of IDDS.

It is important to mention that despite all these limitations associated with IDDS applications the advantages provided by IDDS overcome the limitations of the application process. For example, in many cases such as ocular implants, a single implantation will replace multiple invasive procedures like intra-ocular injections. Additionally, the use of IDDS can provide higher patient compliance

preventing serious complications derived from the lack of compliance associated with the oral route. This will result not only in higher quality of life for patients but a reduced cost for the healthcare services.

In the future IDDS can be key to treat chronic conditions. This is especially important considering that due to the increase in life expectancy and changes I societal behaviour are contributing to the increase on chronic conditions and long-term health problems. Areas of special interest are cardiovascular disease and cancer that are the main causes of death globally. However, the treatment of conditions such as Parkinson's disease or Alzheimer's disease can be significantly improved by using IDDS.

The development of IDDS is growing as has been discussed trough this article. However, development of implantable devices presents especial challenges. To start implantable drug delivery systems, need to be sterile. Therefore, or they are prepared under aseptic conditions increasing manufacturing costs or they need to be terminally sterilised. The latter is more cost effective but terminal sterilisation methods require the use of gamma radiation or ethylene oxide and can potentially affect the properties of the IDDS. Moreover, due to their nature this type of drug delivery systems is designed to provide drug delivery over prolonged periods of time ranging from a few days up to years. In that case, development and trials are longer and cost significantly more than the treatment of other types of drug delivery systems. To accelerate the development of new IDDS researchers have access to novel technologies such as machine learning. This technology can be used to predict performance of new devices reducing development times and costs.

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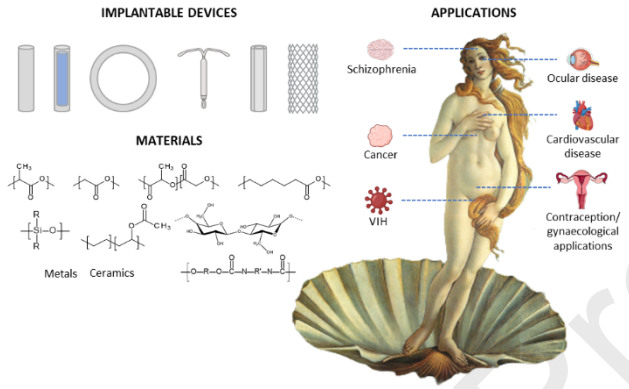

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