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FEATURE ARTICLE

Drug-releasing implants: Current progress, challenges and perspectives

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The need for more efficient drug delivery strategies to treat resilient diseases and the rise of micro and nanotechnology have led to the development of more sophisticated drug-releasing implants with improved capabilities and performances for localised and controlled therapies. In recent years, implantable drug-releasing systems have emerged as an outstanding alternative to conventional clinical therapies. This new breed of implants has shown promising capabilities to overcome the inherent problems of conventional implants and therapies, making clinical treatments more efficient with minimal side effects. Recent clinical trials have demonstrated that this technology can improve the life of patients and increase their life expectancy. Within this context, this review is aimed at highlighting the different types and concepts of drug-releasing implants incorporating new nanomaterials and nanotechnology-based devices. Furthermore, the principles on which these drug-releasing implants are based as well as their advantages and limitations are discussed in detail. Finally, we provide a future perspective in the development of implantable clinical drug-delivery systems based on micro and nanotechnology.

1. Introduction

Current clinical therapies are based on intermittent oral or intravenous administration of drug, which provide a high level of drug in blood right after the dose is administered. However, the drug level in the bloodstream immediately decreases below the therapeutic window. This is the peak-and-valley effect, which can generate serious side effects in clinical patients as the drug concentration in the bloodstream can reach toxic levels shortly after administration and subsequently fall below the therapeutic level, making the therapy inefficient. Furthermore, given that many drugs are inactivated or eliminated by the gastrointestinal system, kidney or liver, only a small percentage of administered drug molecules (<1%) reach the targeted tissues and organs. For that reason, drugs must be administered through frequent uncomfortable injections or intravenous infusions, which are limited to hospitalised patients.[1] Therefore, more effective, efficient, localised, selective and less aggressive delivery of therapeutics with minimal side effects are urgently needed to treat clinical patients suffering from different diseases. In that regard, it is worth stressing that drug delivery is a biomedical interdisciplinary approach involving material scientists, engineers, medical scientists, biologists and clinicians. This combination of knowledge is envisaged for addressing the inherent limitations of conventional therapies by developing more efficient and rational drug delivery platforms featuring up-to-the-minute technological capabilities. Drug-releasing implants have clearly emerged as a potential alternative to traditional oral and intravenous administration of drug for a broad range of clinical treatments. Drug-releasing implants can provide sustained, remotely controlled, programmable and localised release of drugs at the site of interest in the host body, making therapies more efficient with minimal side effects for patients – capabilities of which cannot be achieved by conventional systemic administration of drug.

Pioneering drug-releasing systems were based on hormone pellets, which were implanted under the skin of livestock to improve their growth and make production more efficient.[2] Subsequently, these systems were used to administer hormones to young women suffering from premature menopause.[3] Over the past decades, implantable drug-releasing systems have become more sophisticated and implants based on silicone rubber or polymers have extensively been used for administration of steroid and thyroid hormones, anaesthetic agents, antibiotics, anticancer drugs, heparin and insulin and so on.[4-14] More recently, micro and nanofabrication techniques have enabled the development of implantable drug-releasing devices with cutting edge technical capabilities and versatility for achieving more efficient administration of drugs in a localised manner. For example, the miniaturisation of features in drug-releasing implants can enable mechanisms and capabilities to achieve a more precise control over the release rate of drugs, limiting inherent side effects related to systemic administration of drugs. However, the biggest challenges of drug-releasing systems are centred on how to regulate the releasing rate of drug to keep its concentration within the therapeutic window, how to personalise the dosage of therapeutic substances to different clinical patients and

therapies and how to target affected tissues while keeping healthy ones spared. These are critical parameters in any clinical therapy that future implantable drug-releasing implants must fulfil.

To address these challenges, micro and nanotechnology provide outstanding capabilities to fabricate materials and devices able to perform localised and remotely controlled delivery of drugs at different parts of the host body (*e.g.* transdermal, coronary system, lymphatic system, brain, bones, *etc.*).[14] Some examples of these are transdermal delivery through microneedle syringes and patches, implants featuring nanoporous covers, polymeric/hydrogel patches, microparticles/chips and so forth. In many cases, these drug-releasing systems incorporate several nanotechnological approaches, the combination of which provides more advanced drug-releasing capabilities. For instance, implants can be coated with degradable or switchable polymers loaded with different therapeutics, endowing these drug releasing implants with sustained release over extended periods of time or with remotely controlled/triggered release by external stimuli.

In this scenario, this review aims at reporting on recent advances of drug-releasing implants. The main focus of this work is to summarise the different types/concepts of drug-releasing implants incorporating new micro and nanoengineered materials, technologies and devices and their capabilities, advantages and inherent limitations. Furthermore, we provide information about their clinical applications as well as their future challenges and perspectives. Finally, this review concludes with a general overview and a prospective outlook on the future trends in this field.

2. Drug-releasing implants: Concepts and classifications

An implant is defined as an inert device that replaces a fraction of the host body for repair, support or therapy. Other concepts such as implantable microchips, capsules, micropumps, wafers and patches can be considered as temporal implants, the function of which is extended over a limited period of time due to technical or therapeutic reasons. Depending on the release performance, drug-releasing implants can be classified as passive or active. In the former type, the release of drug cannot be controlled after implantation and the drug-releasing performance is established by the material composing the implant and the drug formulation. In the latter, however, the release of therapeutics is triggered by external stimuli, making it possible to regulate the dosage of drug according to patients and therapies.[14] The benefits obtained from drug-releasing implants in clinical applications can be numerous, albeit they are susceptible to generate problems such as infections, inflammations, lack of integration within surrounding tissues and fatal incompatibility or total rejection, which imply further surgery and replacement of the implant. The most important properties to be fulfilled by any clinical implant are sterility to the biological environment, prevention from bacterial infections and integration within the organic tissues. Apart from these standards in terms of biocompatibility, drug-releasing implants must deliver therapeutics in an optimal manner under *in vivo* conditions. The performance of implantable clinical devices are periodically revised after collecting the most recent developments, successes and failures reported worldwide.[15-17]

So far, many studies have demonstrated that the synergistic combination of micro and nanotechnology with implant technology can improve and overcome inherent problems of implants such as biocompatibility, integration and sterility. The most important part of implants in terms of integration within the host body is their surface, since it acts as an interface between the biological environment and the artificial element. In that regard, micro and nanotechnology have made it possible to coat implants with different materials such as polymers or inorganic nanoporous coatings, which can be loaded with a broad range of therapeutics (*e.g.* antiinflammatory drugs, anticancer drugs, proteins, DNA/RNA, *etc.*). These molecules can be released from the implant surface *via* different mechanisms within a limited period of time, relying on the technical features of the implant and the payload of therapeutics. Among the plethora of new nanomaterials used to develop drug-releasing implants, polymer- and hydrogel-based systems and inorganic nanoporous materials produced by electrochemical anodisation/etching are especially attractive due to their cost-competitive and well-established fabrication processes as well as for their versatility in terms of geometry, drug-releasing performance and applicability. Nonetheless, other systems such as microfabricated devices (*e.g.* microchips, microneedle syringes and patches, *etc.*) must be considered too since they have demonstrated outstanding capabilities for many clinical applications (*e.g.* transdermal delivery of therapeutics). **Fig. 1** compiles a classification of these implantable drug-releasing systems as a function of base materials, concepts and medical applications.

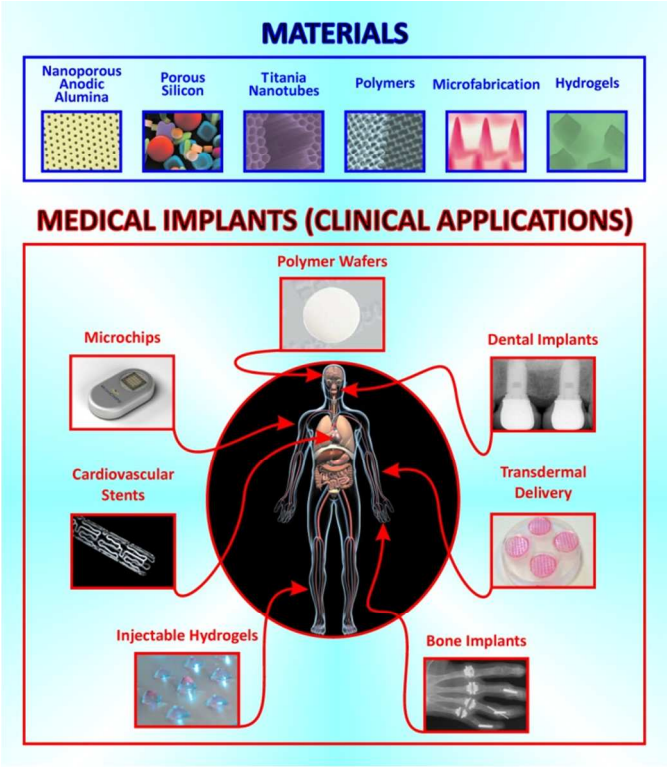

Fig. 1 Schematic diagram summarising the most common materials used to develop drug-releasing implants and the most characteristic clinical applications in which these medical devices are employed.

2.1. Polymer-based systems

The development of polymer-based drug-releasing implants started with the discovery of the first zero-order drug-releasing system in the 1960s pioneered by Folkman and Long.[4] Since

then, the progress in polymer science has made it possible to develop more sophisticated systems with outstanding capabilities for drug delivery applications.[18,19] **Table 1** summarises the most relevant polymers used to develop drug-releasing implants for clinical applications. Implantable polymeric systems can be broadly classified into biodegradable and non-biodegradable systems.

Non-degradable polymers are inert, biocompatible and offer a simple means of controlling the release of drugs by diffusion or swelling. While diffusion-controlled systems can be divided into reservoir type (*i.e.* a drug core is surrounded by a polymer coating) or matrix type (*i.e.* drug particles are dispersed in a polymer matrix), swelling-controlled systems are produced from water-soluble, cross-linked polymers. Some examples of non-degradable polymers are cellulose derivatives, silicones and acrylics.[19-21] These polymers are characterised by tissue/blood compatibility, durability, robustness of their structure and mechanical strength. Therefore, they are suitable for long-term applications such as orthopaedic and dental implants.[22] Polymeric systems based on biodegradable polymers, however, are safer alternatives for certain applications as they degrade into non-toxic monomers and by-products, which can be efficiently cleared by the host body and thus no invasive surgery is needed after the therapy is complete. To date, several drug-releasing pharmaceutical products based on biodegradable polymers have been approved by the US food and drug administration agency (FDA). These systems can release different therapeutics, including hormones, antitumour drugs and antibiotics in complex sequences of drug-releasing steps involving diffusion and erosion (either surface or bulk).[19,23,24]

Drug-releasing polymeric systems provide a unique way to administer drug, the concentration of which can be maintained within a narrow therapeutic window.[25] In addition, these implants can have a defined structural identity and shape before implantation (*i.e.* pre-formed) or can take a shape after the implantation (*i.e.* injectable implants).[18,26] Pre-formed polymeric implants have predictable and reproducible release and degradation profiles for extended periods of time as a result of their defined geometric structure. The formulation of such systems involves extrusion, compression moulding, solvent casting or melt casting of implants into the desired shape.[18,26,27] In particular, a FDA-approved polyanhyride wafer termed Gliadel® has been intensively used as intratumoural chemotherapeutic device.[28] Nonetheless, the major drawback of pre-formed implants is the invasive surgery needed to implant and remove them at the beginning and end of the therapy, respectively.[18]

In that regard, hydrogel-based systems have become a potential alternative to pre-formed implants. Hydrogels are a unique 3-dimensional network of cross-linked hydrophilic polymer structures, which imbibe large amounts of water or biological fluids. Hydrogels exhibit a swelling-controlled drug release, with environmentally sensitive, elastic, pliable, permeable and biocompatible properties.[29-33] Usually, polymers containing hydroxyl, amine, ether, carboxylate and sulfonate functional groups are suitable for forming hydrogels. Responsive polymers are envisaged for developing controlled drug-releasing hydrogels encompassing a plethora of biomedical and pharmaceutical applications to cater to effective drug-releasing performances according to the different therapies. These systems can be designed to achieve targeted and controlled release under *in vivo* conditions upon specific stimuli, which may be external (*e.g.* magnetic, ultrasonic, thermal, electric, *etc.*) or internal (*e.g.* pH-sensitive, enzyme-substrate reactions, competitive binding, metal concentration-dependent hydrolysis, *etc.*), where the release rate is controlled by self-regulation *via* feedback. It is worthwhile noting that conventional pre-formed hydrogels require complicated surgical procedures to be implanted at the diseased site in the host body and some locations are difficult to access.

To overcome these limitations and improve patient compliance, the concept of *in situ* forming implants was introduced by Dunn *et al.* in the 1990s.[34] These systems are created by injecting a solution or suspension of the polymeric matrix and therapeutics into the target site with a hypodermic needle. The composite then solidifies into an implant, providing a stable depot in the body to release the payloads in a controlled manner.[18,35] These systems are able to adapt their shape to the surrounding tissues, making them favourable to form drug delivery vehicles, tissue engineering scaffolds, medical adhesives and dermal fillers.[36,37] The liquid polymeric matrix containing the drug solidifies in response to specific stimulus (*e.g.* water, temperature, pH, light, radiation, *etc.*). This change can be produced by phase inversion and precipitation, cross-linking or thermally induced polymerisation of the hydrogel.[38-41] The drug release mechanism in these systems can be based on diffusion, erosion, swelling-based or a combination of these.[42]

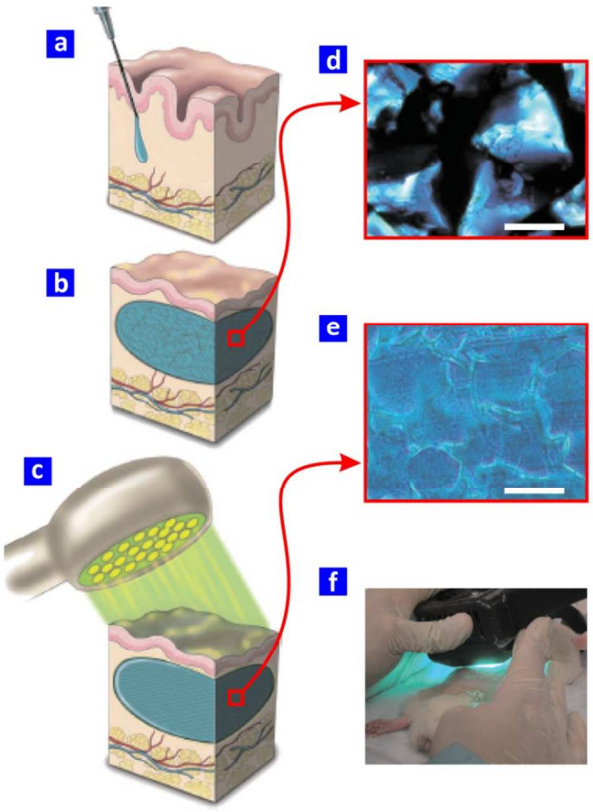

Fig. 2 Injectable polymeric implant (adapted from Ref. [52]). a) Injection of photopolymerisable polymer formulation into the dermis. b) The polymeric solution is moulded by the space in the host body to acquire the desired shape. c) Light-induced transdermal crosslinking to form the polymeric composite implant. d-e) Microscopic images of polymer structure before and after photopolymerisation (scale bars = 200 μm). f) LED exposure of the injected polymeric composite in the rat dorsum for clinical treatment.

In a recent work, Jiang *et al.* evaluated the cytotoxicity, *in vivo* degradation and drug release from thermo-

sensitive hydrogels based on poly(ethylene glycol)-grafted-chitosan. This system was subcutaneously injected into Sprague-Dawley rats. After being implanted, the hydrogel showed no cytotoxicity, maintained its integrity and performed a sustained release of cyclosporine A for three weeks.[43] So far, a number of *in situ* forming implants have been used in clinical applications (**Fig. 2**).

PLGA/polylactic acid (PLA) based implants are the most commonly used to deliver active agents for cancer therapy, hormonal therapy, immunomodulation, antiinfectious therapy, analgesia/anesthesia, neurological disorders, metabolic disorders, gene delivery and tissue reconstruction.[44] For instance, Eligard© is a clinically approved system based on an injectable PLGA formulation containing leuprolide acetate, which can be subcutaneously injected at 1 to 6-month intervals to suppress testosterone levels for inhibiting prostatic tumour growth.[45] Grayson *et al.* developed a more sophisticated system capable of releasing pulses of different drugs at different time intervals after implantation in a patient. This system is based on poly(D,L-lactic-*co*-glycolic acid), which covers reservoirs filled with radiolabelled dextran, human growth hormone or heparin. This study demonstrated that heparin can be released for more than 142 days, retaining its bioactivity.[46] Polymeric implants have also been explored for delivering sensitive proteins and genetic material. Gehrke *et al.* were able to enhance the loading capacity and activity retention of ovalbumin and α-amylase by a dextran-polyethylene glycol (PEG) hydrogel.[47] Kim *et al.* developed injectable and biodegradable poly(organophosphazene) hydrogels for long-term delivery of siRNA polyplexs for tumour targeting, the release of which lasted for up to 28 days.[48] Similarly, Tokallian *et al.* demonstrated porous and non-porous hyaluronic acid hydrogels for inducing angiogenesis in a subcutaneous murine implant model by delivering pro-angiogenic (pVEGF) and reporter (pGFPluc) plasmid nanoparticles.[49]

More recently, drug-releasing polymer-based implants have been utilised as suture material and composite scaffolds for bone and tissue regeneration.[50] Mourino *et al.* enlisted various synthetic and natural polymers for delivering antimicrobial, antibiotic and antitumour drugs as well as growth factors relevant to bone tissue engineering.[51] A new technique elucidated by Hillel *et al.*, uses a biosynthetic soft-tissue replacement composed of poly(ethylene glycol) (PEG) and hyaluronic acid (HA), which can be injected and photo-crosslinked *in situ* by transdermal light exposure. **Fig. 2** shows a schematic diagram of this system, which can replace multiple surgical procedures involved in soft-tissue reconstruction (*i.e.* adipose tissue engineering). These materials were evaluated in both rodent and human trials and demonstrated excellent biocompatibility and volume retention with minor chronic inflammation.[52]

Another type of drug-releasing implants based on polymers is contraceptive device, which can deliver hormones and fertility regulating agents as well as therapeutics for sexually transmitted diseases. These implants can be inserted subdermally or inside the uterine cavity (*i.e.* intravaginally).[24,53] Alaee *et al.* developed an implantable contraceptive device based on PLA/polyethylene glycol (PEG) to deliver levonorgestrol for 9 months.[54]

Another application of polymer-based drug-releasing implants is ocular lens, which are implanted in the eye to treat cataracts or myopia. For example, to avoid invasive subconjuctival and retro-ocular injections, Choonara *et al.* developed a novel doughnut-shaped PLGA-based intraocular implant loaded with antiretroviral drugs (*i.e.* foscarnet and ganciclovir), which is able to sustain the release of these drugs for an extended period of time.[55,56] This study was further extended by another group, which designed bioresponsive and intelligent intraocular implants for vitreoretinal disorders by delivering antiinflamatory and antibiotic drugs.[57] Recently, Wang *et al.* published a review on the *in situ* gel-forming systems used for nasal drug delivery.[58] Drug-releasing implants based on polymers present a compelling parenteral route of administration for cancer chemotherapy. Gliadel® and OncoGel® are two renowned commercially available drug-releasing implants for carmustine and paclitaxel. These systems are used to treat gliomas, esophageal and brain cancers, respectively.[59,60]

In summary, polymer-based drug-releasing implants have been intensively explored and used in a broad range of clinical applications showing outstanding capabilities in terms of versatility, flexibility, adaptability and applicability. Nevertheless, polymers have inherent limitations (*e.g.* chemical and physical stability, mechanical properties, erosion, degradability, uncontrollable drug-releasing performance, etc.) that hinder their use for certain clinical applications (*e.g.* bone implants).

Table 1 Typical polymers used to develop drug-releasing implants. P(SA-RA): poly(sebacic acid-*co*-ricinoleic acid); PMMA: Polymethacrylic methyl acid; PCPP-SA: Poly[bis(*p*-carboxyphenoxy)propane–*co*-sebacic acid]; EVAc: ethylene–vinyl acetate; PHBA: poly(hydroxy-*n*-butyric acid); PHIVA: poly(hydroxyisovaleric acid); PHICA: poly(hydroxyisocaproic acid); PFAD-SA: poly(fatty acid dimer–*co*-sebacic acid).

Polymer	Drug	Clinical Disease	References
P(SA-RA)	Paclitaxel	Antineoplastic agents	42
PLGA	Leuprolide Acetate	Cancer (prostate and breast) Uterine fibroids Endometriosis Alzheimer	45
PMMA	Mitomycin Adriamycin Cisplatin	Malignant brain tumours Osteosarcoma	61 62
PCPP-SA	Carmustine	Recurrent malignant glioma	63 66
PLA	Nimustine Chloride 5-Fluorouracil	Non-resectable or recurrent glioblastoma Hepatomas	64 65
EVAc PLA	Adriamycin Cisplatin	Mammary carcinoma Osteosarcoma	67 62
PHBA PHIVA PHICA PLA	LH-RH Agonist	Prostate tumour	63
PFAD-SA	Cisplatin	Squamous cell carcinoma	64

2.2. Nanoporous engineered drug releasing systems

Nanoporous anodic alumina (NAA), titania nanotubes (TNTs) and porous silicon (pSi) are three inorganic nanoporous materials used intensively to develop drug-releasing implants. These are produced by electrochemical anodisation and etching of bulk aluminium, titanium and silicon, respectively.[68-79] In contrast to polymer-based systems, the nanoporous structure of NAA, TNTs and pSi can be engineered by different electrochemical approaches. Therefore, their geometric features (*i.e.* pore diameter, length and shape) can be designed and

optimised for developing advanced drug-releasing implants. This is a crucial factor as the drug-releasing performance can be established by precisely engineering the nanoporous structure according to therapeutic requirements (*i.e.* drug loading, total dosage of drug, rate of release, *etc.*). Furthermore, an optimised nanoporous structure can enhance the integration of the implant within the host body, preventing it from fatal rejection during the working life. Other advantages of drug-releasing systems based on NAA, TNTs and pSi as compared to polymer-based ones are their mechanical, chemical and thermal stability, resistance to erosion and/or biodegradability, which are desired properties for many clinical applications (*e.g.* orthopaedics). In addition, these nanomaterials can be chemically functionalised with different functional molecules (*e.g.* silanes, proteins, lipids, *etc.*) through well-established protocols. This provides other interesting features such as increment of drug loading (*e.g.* by changing the surface chemistry from hydrophobic to hydrophilic or *vice versa*), extension of drug release for longer time periods (*e.g.* modification/reduction of pore mouths with biodegradable polymers), anti-biofouling properties (*i.e.* non-specific adsorption of biomolecules present in the *milieu*), enhanced biocompatibility and so forth. Moreover, the combination of NAA, TNTs and pSi with other nanomaterials such as switchable polymers and hydrogels can endow these drug-releasing implants with remotely controlled release of therapeutics for highly sophisticated clinical therapies.

2.2.1. Nanoporous anodic alumina

NAA has become one of the most popular nanomaterials as a result of its cost-competitive fabrication process, versatility and interesting chemical and physical properties (*e.g.* excellent chemical, thermal and mechanical stability, large surface area, nanoscale dimensions, organised nanoporous structure, biocompatibility, *etc.*). Pore geometry and surface chemistry in NAA can be easily modified by well-established protocols. Typically, NAA is fabricated by anodising aluminium in aqueous solutions of acid electrolytes (*e.g.* sulphuric acid, oxalic acid, phosphoric acid, *etc.*) following the two-step anodisation process.[68-71] NAA is composed of close-packed hexagonal arrays of columnar cylindrical nanopores oriented perpendicularly to the aluminium substrate (**Figs. 3a and b**). The structural features of NAA (*i.e.* pore diameter, length, shape, *etc.*) can be precisely controlled by the anodisation parameters.[80-84] Therefore, the versatility of NAA in terms of pore geometry is an advantage for developing drug-releasing implants as the diffusion of molecules from the nanopores can be tuned by geometry.

Alumina is recognised as a biocompatible material and has been intensively used to develop orthopaedic and dental implants.[85] So far, many studies have reported on the use of NAA as an active drug-releasing coating in implants (*e.g.* orthopaedic, dental, coronary, *etc.*) and immunoisolation.[86,87] Pioneering osteogenesis studies demonstrated the biocompatibility of NAA and suggested that its nanoporous structure plays an important role in bone cell adhesion and osteointegration.[87-91] The interaction between osteoblasts and NAA was reported by Popat *et al.* in a number of studies, in which several parameters were analysed. One of these studies analysed the adhesion and proliferation of osteoblast on nanoporous anodic alumina, amorphous alumina, bare aluminium and glass. Their results proved that NAA improved the adhesion of bone cells as compared to other substrates, confirming the importance of the role of nanopores in bone cell culturing and growth.[87]

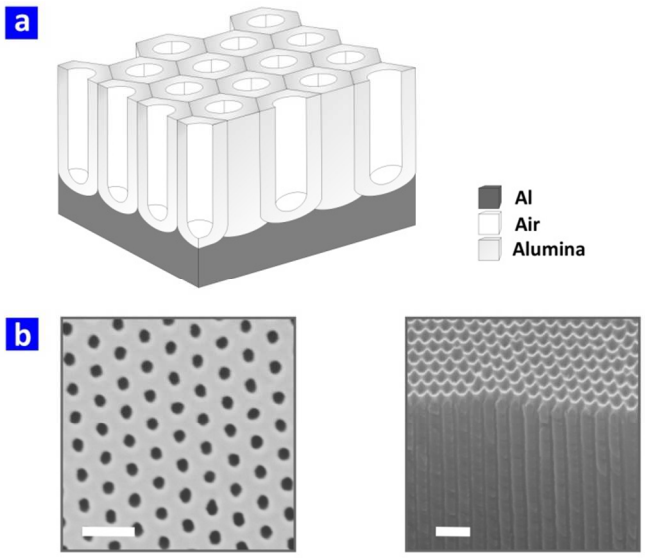

Fig. 3 Use of NAA for developing drug-releasing implants. a) Schematic illustration of the basic structure of NAA. b) Top and cross-section scanning electron microscopy (SEM) images of NAA (scale bars = 400 and 250 nm, respectively).

Another study demonstrated that osteoblasts produce an active fibrous matrix containing calcium and phosphorus, which extends to the nanopores of NAA.[88] Moreover, the same group demonstrated further improvement in bone cell adhesion and proliferation after chemical modification of the NAA surface with vitronectin and a cellular adhesive peptide (*i.e.* arginine-glycine-aspartic acid-cystine, RGDC). These results revealed the potential of NAA as a biocompatible and active platform for bone growth and orthopaedic applications.[89] Another study by Karlsson *et al.* reported on the interactions between primary human osteoblast cells (HOB) and NAA. Successful cell adhesion was observed with cells displaying a flattened morphology and filipodia attached to the pores of NAA. Although a trace amount of aluminium ions was observed to leach into the surrounding medium, no adverse effects on cell activity was detected.[89]

Furthermore, the interaction between NAA and whole blood and platelet rich plasma was demonstrated by exposing blood cells to NAA substrates. This led to a series of linked events such as protein adsorption, platelet and leukocyte activation/adhesion and complement/coagulant activation. Plasma proteins were observed to cover the NAA surface almost instantly upon contact with blood. The hypothesis that protein adsorption is dependent on the pore diameter of NAA substrate was also demonstrated. While NAA samples featuring pores of 200 nm in diameter induced higher platelet and microparticles adsorption and lower complement activation, NAA samples featuring nanopores of 20 nm in diameter caused higher complement activation and negligible platelet and microparticles adsorption.[92] Similarly, neutrophile and phagocyte adsorption/adhesion were found to be dependent on the pore diameter of NAA.[93,94]

In vitro immunoisolation studies carried out in NAA capsules suggest that NAA is non-toxic and does not generate significant complement activation. Although *in vitro* studies showed no toxic effects of NAA capsules, transient inflammatory response was observed for unmodified and PEG-functionalised NAA capsules after implantation into the peritoneal cavity of rats. However, reduction in granulation

along with the existence of blood vessels in the tissue surrounding the capsules suggested that the inflammation was mainly due to the implantation procedure itself.[86]

The use of NAA as a drug delivery platform has been explored in several realms as therapeutic devices for bone and dental implants, active drug-releasing layer on coronary stents and immunoisolation (*i.e.* vector/carrier for transplanted cells). For example, Orosz *et al.* demonstrated the suitability of NAA loaded with catalase, vitamin C and endostatin as sustained, quasi-linear drug-releasing platform for ophthalmic applications.[95] Gong *et al.* reported on the controlled release of model drugs through tubular NAA membranes.[96] These NAA membranes were filled with model drugs and converted into biofiltration capsules by sealing the ends of the tube. In this way, the diffusion of drug was correlated with the pore diameter of NAA. A similar strategy was later used to investigate the performance of NAA for immunoisolation towards the treatment of diabetes. In that study, NAA capsules were characterised for their ability to transport glucose, insulin and antibodies (IgG). The obtained results showed that while glucose and insulin were transported through the NAA membranes, the diffusion of IgG through the nanopores was hindered significantly.[96]

In terms of drug-releasing capabilities, our group has demonstrated that the release of drugs from NAA implants not only can be controlled by manipulating its pore geometry but also by other approaches (*e.g.* changing its surface chemistry, coating its surface with polymers, encapsulating drug molecules into a micellar carrier and so on).[97-99] Our results showed that drug molecules are eluted more rapidly from nanopores with bigger diameters, which is in good agreement with previous studies. Furthermore, we demonstrated that the initial burst release of indomethacin can be drastically reduced from 50% to around 25% by functionalising the NAA surface with amine- or penta-fluoro-terminated silanes.[97,98] Another successful strategy to control and extend the release of drug from NAA implants is to coat its top surface with polymers by plasma deposition. In our study, NAA substrates were coated with polyallylamine (Paa) after loading the nanopores of NAA with a model drug (*i.e.* vancomycin).[99] Different thicknesses of polymer were used for studying the release of vancomycin from NAA substrates with modified pore mouths. Drug release from uncoated NAA samples only lasted for 45 min while the release from NAA coated with Paa was extended up to approximately 200 and 500 h for coating times of 50 and 120 s, respectively. This study demonstrated that this method can extend the release of small molecules up to 2-3 weeks and the release of larger molecules can be sustained for almost one month.[99]

Another approach to develop drug-releasing implants based on NAA was reported by Jeon *et al.*, who developed a sophisticated system by combining NAA chips with electrically responsive polymers.[100] In this study, the pore mouths of NAA were modified with polypyrrole doped with dodecylbenzenesulfonate anion (PPy/DBS) by electropolymerisation on the upper surface of NAA platforms. Taking advantage of the large volume change of that polymeric blend, they achieved pore mouth actuation (*i.e.* from small to big pore diameter) by an external electrical stimulus (**Fig. 4**). With this strategy, they implemented a pulsatile drug-releasing implant, which was assessed by analysing the release of a model protein (*i.e.* FITC-labelled bovine serum albumin–BSA).

More recently, Kumeria *et al.* studied the release of indomethacin from NAA implants in real-time and dynamic flow conditions by means of reflectometric interference spectroscopy. These experiments were carried out in a microfluidic device that enables the simulation of the conditions in the host body (*e.g.* flow rate, temperature, pH, *etc.*).[101] The release of indomethacin was measured at different buffer flow rates, varying from 0 to 50 μL min^{-1}. The obtained results showed that the faster the flow rate the higher the drug release rate is.

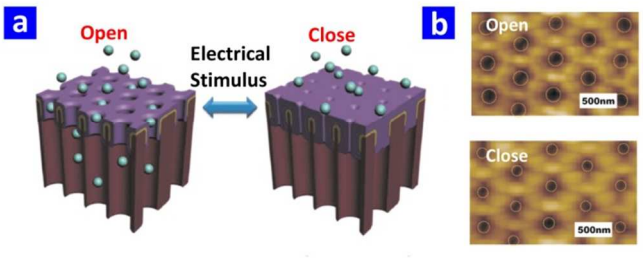

Fig. 4 Electrically responsive drug-releasing NAA chip (adapted from Ref. [100]). a) Schematic diagram showing the mechanism of an electrically responsive drug-releasing chip based on NAA and PPy-DBS (reversible cycle). b) Atomic force microscopy (AFM) images of these NAA chips before and after the application of voltage (pore mouth reduction).

These studies have demonstrated that, as a result of its versatile pore geometry, biocompatibility, physical and chemical stability, NAA is an excellent platform to develop drug-releasing implants for a broad range of clinical applications. Nevertheless, similar to other materials, NAA presents certain limitations that can restrict its use for some applications. For instance, NAA implants are not envisaged for developing brain implants given the *in vivo* leaching of aluminium ions, which are linked to Alzheimer's disease. Furthermore, the mechanical properties of aluminium (*i.e.* ductility, malleability) are not suitable to develop orthopaedic implants. In these cases, other inorganic nanoporous materials such as titania nanotubes could provide comparably better performances.

2.2.2. Titania nanotubes

Likewise in NAA, self-organised arrays of TNTs can be produced by anodising metallic titanium (Ti) in different acid electrolytes. This process was pioneered by Zwilling *et al.*, who used an electrolyte composed of a mixture of chromic and hydrofluoric acids.[102] However, in contrast to NAA, TNTs feature a nanotubular structure, which is produced by the dissolution of the cell boundaries during the anodisation process (**Figs. 5a and b**). Different electrochemical approaches have made it possible to engineer the nanoporous structure of TNTs.[103] In that regard, it is worth acknowledging the contribution made by Schmuki and co-workers.[103-107]

Orthopaedic and dental implants based on metallic titanium have been intensively used in clinical applications as a result of their biocompatibility, outstanding mechanical properties and *in vivo* chemical stability. The incorporation of TNTs layers grown on Ti-based implants *via* anodisation has enabled the development of drug-releasing implants for treating bone-related diseases (*e.g.* cancer) and preventing implants from post-implantation infections.[108-110] Feschet-Chassot and co-workers evaluated the biocompatibility of TNTs through a series of *in vitro* toxicity studies for the first time using a protozoaic cell model (*i.e. Ciliated Protozoan T. pyriformis*).[111] Later studies demonstrated that TNTs coatings improve the osseointegration of Ti-based implants by promoting the

adhesion and proliferation of osteoblast cells on the implant surface.[112-114] Another biomedical capability of TNTs is that their nanoporous structure can be loaded with different payloads of therapeutics. In that regard, TNTs have shown to be a suitable platform to develop drug-releasing implants for post-surgical treatments of acute and chronic infections in necrotic or avascular bone tissues.[115] Currently, TNTs-based implants are recognised as one of the most promising nanomaterials to address the inherent drawbacks of conventional systemic drug administration due to their capability to localise the release of drugs over affected bones sites in a controllable manner.[116,117]

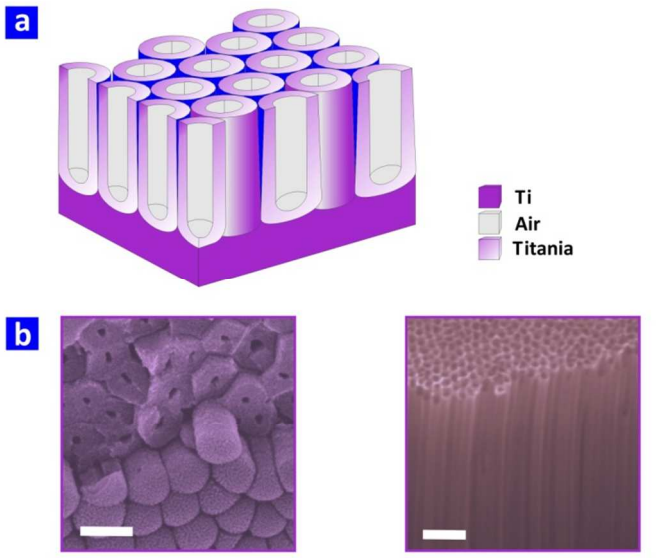

Fig. 5 Use of TNTs for developing drug-releasing implants. a) Schematic illustration of the basic structure of TNTs. b) Top and cross-section scanning electron microscopy (SEM) images of TNTs (scale bars = 100 and 500 nm, respectively) (adapted from Ref. [118]).

The drug loading and release properties and capabilities of TNTs layers have been extensively explored in the past years by several groups (**Table 2**). These studies have been focused on improving aspects such as total dosage of drug, release kinetics, implementation of different payloads and enhancing the integration and antibacterial properties of TNTs-Ti implants.[116,117] This has become a vital factor for controlling the release of drug molecules, since the diffusion of drug molecules from the implant surface is pore size dependent (*i.e.* hindered or restricted diffusion).[98] Furthermore, it is worthwhile mentioning that surface charges of TNTs can be rendered hydrophobic or hydrophilic to accommodate a variety of drug molecules. Through these physicochemical modifications, release kinetics of drug molecules can be controlled to tailor to different therapeutic requirements to treat patients suffering from a broad range of diseases. Different approaches proposed by our group have made it possible to achieve various drug-releasing patterns from Ti implants featuring drug-loaded TNTs coatings. Some examples are extended *in vitro* drug release with the aid of polymeric micelles as drug nano-carriers,[116,117] extended drug release with biopolymer coatings using poly(lactic-*co*-glycolic) acid (PLGA) and chitosan on TNTs,[118] multi-drug release,[119] delayed drug release using drug-loaded micelles and blank micelles[120] and targeted drug release by means of gold nanoparticles stimulated by radiofrequency (RF) field[121] and magnetic nanoparticles under the influence of a magnetic field[122] (**Fig. 6**).

Table 2 Summary of the most representative studies carried out to develop drug-releasing implants based on TNTs for different clinical applications.

Implant	Drugs/cell culture	Application	References
Titanium implant with TNTs coating	None	Artifical joint replacement prostheses	108
TNTs on Ti chips	d-α-tocopheryl polyethylene glycol 1000 (TPGS) Pluronic F127 PEO_{260}–PPO_{400}–PEO_{260} 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy (polyethylene glycol)-5000 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy (polyethylene glycol)-2000]	Design of porous therapeutic implants for an extended elution time of poorly water soluble drugs using polymer micelles as drug nanocarriers	116
TNTs on Ti chips	Indomethacin BMPs Human osteoblastic cells adhesion and proliferation	Orthopaedic applications and bone therapies (*e.g.* infections, local delivery of anabolic agents for bone repair, antiresorptive agents, bone cancer, osteomyelitis, etc.).	118
Sequential-step prepared biocompatible TNTs films	Dexamethasone	Design of anticoagulants, analgesics and antibiotics drug-releasing TNTs implants to prevent inflammatory reactions	131
TNTs on chips	Penicillin/streptomycin Dexamethasone	Prolonged drug delivery in orthopaedic implants to prevent infection, inflammation and to promote osseointegration	115
TNTs on Ti and Ti6Al4V alloy	Bone cells	Long-term bone implant	112
TNTs on Ti chips featuring various topologies	Marrow stromal cells (MSCs)	Antibacterial adhesion for controlled, guided, and rapid wound healing, prevent acute or chronic inflammation/infection or fibrosis	113
Annealed TNTs on Ti chips	-	Biomimetic carbonated hydroxyapatite (CHA)	132
Titania bioceramic implants	Anti-epileptic drug	Treatment for epileptic seizures	133

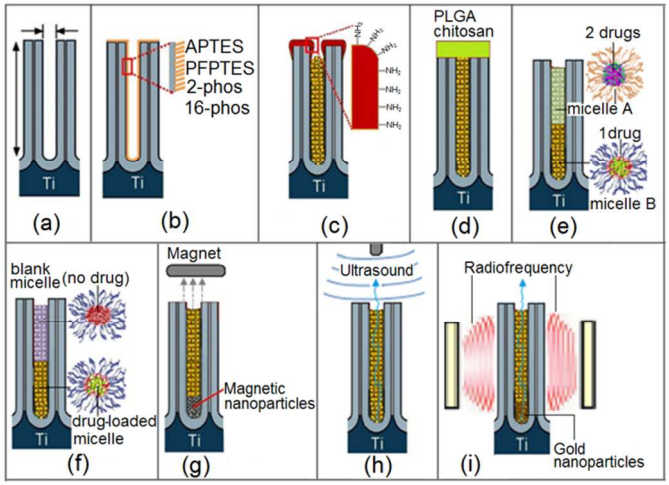

Fig. 6 Schematic diagram showing different strategies developed by our group for controlling drug release from drug-releasing implants based on TNTs (adapted from Ref. [98]).

Implants are highly susceptible to bacterial infections post-implantation, which can lead to serious clinical complications and total failure of the implant, especially in orthopaedics applications. To address these problems, the application of TNTs layers on Ti implants has been extensively explored for localised release of antibacterial and antiinflammatory drugs, the release of which in simulated body fluid (SBF) was prolonged and sustained.[115] Popat *et al.* reported a total of 70% decrease in the population of bacteria colonies with the use of drug-releasing TNTs coatings, as compared to bare titanium implant or TNTs without antibiotic drugs upon 4 h of bacteria incubation.[123] Osteoblast differentiation and bone matrix

production was observed after 3 weeks of osteoblast cell incubation on Ti implants featuring TNTs coatings with and without antibiotics. The former exhibited better osteoblast cell adhesion and growth. Controlled antibiotic drug release from TNTs coatings, as well as the capability of TNTs for preventing bacterial adhesion and also to preserve osseointegrative properties of bones adjacent to the nanostructured surface were successfully proved in this study. It has been reported that TNTs are capable of loading and releasing antibiotic drugs (e.g. indomethacin and gentamicin)[124] as well as other types of bioactive molecules such as Cu,[125] Ag,[126] Au,[127] and calcium-phosphate (Ca–P) particles.[128] For instance, Ca-P-loaded TNTs coatings were fabricated by anodising an implant based on Ti–6Al–7Nb alloy. The resulting drug-releasing coating enhanced the osteoblastic differentiation in dental implants.[129]

In conclusion, one of the most important properties of drug-releasing coatings based on NAA and TNTs is that they do not degrade under *in vivo* conditions and are mechanically robust, chemically stable/inert, biocompatible and can provide controllable drug release.[130] However, these properties are not suitable for some applications, in which biodegradability is a definite requirement (*e.g.* drug-releasing implants for treating eye-related diseases). Other inorganic nanoporous materials such as porous silicon can be used to develop biodegradable drug-releasing implants with improved capabilities for these clinical applications.

2.2.3. Porous silicon

Porous silicon was discovered by the Uhlirs in the mid 1950s when they were looking for a method to electropolish silicon in a hydrofluoric acid electrolyte.[134] However, the potential use of pSi in biomedical applications was neglected until 1995, when Canham proved its biocompatibility.[135] This work was the origin of a flood of studies about pSi focused on bioapplications. Porous silicon is produced by electrochemical etching of silicon wafers in hydrofluoric acid electrolytes. Typically, pSi presents spongy-like pore morphology, with random pore distribution (**Figs. 7a and b**). However, highly ordered pSi structures can be produced through microfabrication techniques. Porous silicon structures can load and release drugs over affected tissues/organs and enable the monitoring of this process simultaneously as a result of its optical/electrical properties.[136,137] In contrast to NAA and TNTs, pSi degrades into the natural form of Si (*i.e.* silicic acid – $Si(OH)_4$), which can be efficiently excreted by the host body through urination. Nevertheless, the biodegradability and bioactivity of pSi are highly dependent on its porosity.[138] Initial tests provided evidence that pSi is capable of promoting *in vivo* calcification and its tissue compatibility is comparable to that of pure titanium.[139] Cell studies on pSi chips were carried out in order to confirm its ability to promote cell growth and adhesion. For instance, Sapelkin *et al.* studied the adhesion and growth of rat hippocampal neurons and Chinese hamster ovary cells on pSi substrates in a simulated body environment.[140] Similarly, Low *et al.* studied the adhesion of mammalian cells (*i.e.* human lens cells and rat pheochromocytoma cells) to pSi with a chemically modified surface.[141] They also observed poor cell adhesion on oxidised pSi surface (*i.e.* hydrophilic), which is in good accordance with previous studies reported by Sailor and co-workers.[142]

In the last few years, pSi in the form of micro and nanoparticles has gained huge attention as a result of its outstanding capabilities for drug delivery and imaging applications.[143-146] Micro and nanoparticles based on pSi are highly biocompatible and non-toxic for most human cell lines.[147-150] In addition to cell studies, pSi micro and nanoparticles have been assessed through a significant number of *in vivo* studies with animal models. These studies evidence that pSi micro and nanoparticles are non-toxic, can be easily cleared by kidneys and are capable of accumulating inside tumours for simultaneous bioimaging and drug delivery applications.[148,151]

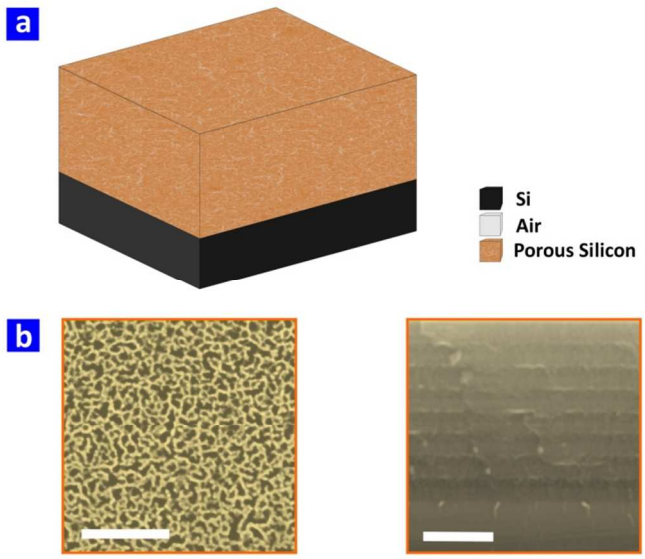

Fig. 7 Use of pSi for developing drug-releasing implants. a) Schematic illustration of the basic structure of pSi. b) Top and cross-section scanning electron microscopy (SEM) images of pSi (scale bars = 200 and 2.5 μm, respectively).

In this review we will focus our attention on those studies using pSi for localised and sustained drug delivery applications. Li *et al.* reported on the loading and release of three platinum-based antitumour drugs (*i.e.* cis-platin, $Pt(en)Cl_2$, and carbo-platin) using calcium phosphate-doped pSi substrates as drug-releasing platforms.[152] Furthermore, pSi highly doped with radioactive phosphorus (^{32}P) has been utilised in cancer chemotherapy.[153] In that study, human hepatocellular carcinoma cells (HepG2) and human pancreatic carcinoma cells were implanted in male nude mice. On day 15 after implantation of tumour cells (*i.e.* when the tumours were about 1 cm in diameter), ^{32}P-doped pSi was implanted at the tumour centre. The obtained data suggested that such intratumour local radiation therapy could potentially offer patients with a more efficient therapy against hepatocellular carcinoma and pancreatic tumours, which could extend the life expectancy of clinical patients suffering from these resilient cancers. Similarly, intratumoural localised *in vivo* delivery of cholambucil, an anticancer drug, from pSi platforms resulted in 10% animal mortality. In contrast, the direct injection of the same dose of drug over the tumour site in mice resulted in 90% animal mortality, demonstrating that the delivery from pSi is much more efficient than the direct injection of drug at the tumour sites.[154] A hierarchical pSi structure featuring macropores (~2 μm in diameter) covered with a layer of nanopores (~200 nm in thickness) by adjusting the fabrication parameters was produced by Vaccari *et al.* This bilayered porous structure was loaded with doxorubicin and a sustained release was observed, reaching a stable plateau after 5 h.

Cytotoxicity analysis with two human colon adenocarcinoma cell lines (LoVo and HT29) showed a time-dependent antiproliferative effect, which was in accordance with the doxorubicin release curve.[155] Batra *et al.* showed controlled/reversible fluorescent release from calcinated pSi coated with poly-caprolactone (PCL).[156] Wu *et al.* reported that pSi with oxidised or hydrosilanised surface can be employed for sustained release of such anthracyclic drugs such as daunorubicin and doxorubicin, which are susceptible to redox degradation under reducing environment inside the pores of pSi.[157] Park *et al.* used an innovative strategy to obtain sustained release of platinum-based anticancer drugs. Porous silicon particles were first loaded with anticancer drugs followed by capping the pores with platinum metal using electroless deposition. The release of anticancer drugs was studied in different buffers (*i.e.* phosphate buffer solution–PBS, isotonic PBS, and fetal bovine serum–FBS) and this was related to the dissolution rate of pSi particles. The highest release rate was observed for particles in FBS with approximately 40% of total drug eluted in the course of 15 h.[158]

Porous silicon is an optically active material (i.e. photonic crystal), the optical properties of which can be manipulated by engineering its nanoporous structure. Anglin *et al.* demonstrated that drug loading and release from pSi can be monitored in real-time by measuring the changes in its optical thickness. Using this strategy, these authors studied the loading and release of dexamethasone from pSi photonic crystals.[136,137] Notice that the most extended clinical application of pSi in drug release is in cancer therapy. However, other diseases such as eye-related diseases require controllable, monitorable, minimally invasive and long-acting local delivery of therapeutics. In that regard, pSi-based photonic crystals were demonstrated to be suitable nanostructures for treating intraocular diseases affecting the retina and choroid (**Fig. 8**).

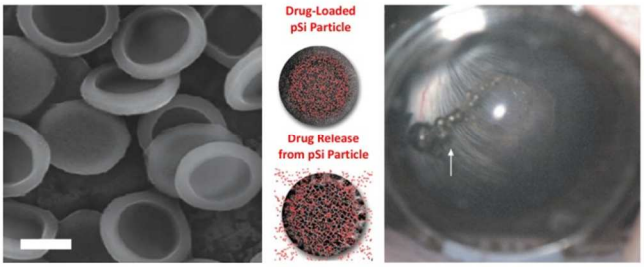

Fig. 8 SEM image of porous silicon microparticles produced by lithography combined with electrochemical etching (scale bar = 1 μm), schematic diagram showing how these particles load and release drug (adapted from Ref. [165]) and surgical microscope image obtained immediately after intravitreal injection of fresh pSi microparticles in the vitreous cavity (arrow) of a New Zealand Red rabbit (adapted from Ref. [159]).

Initial intraocular biocompatibility has already been established by injecting pSi particles into rabbit vitreous.[159-163] From the clinical point of view, pSi particles provide an excellent way to monitor the release of drug *in situ* as they can be visualised from inside the ocular cavity by simple optical measurements. Additionally, pSi structures are very useful as supports for delivering cells over the ocular surface and improving existing therapeutic strategies in patients with epithelial stem cell dysfunctions and ocular surface diseases.[164] Besides these applications, a recent study has demonstrated that pSi can be used for localised delivery of nucleotides in cancer treatment.[146,165] Disc shaped pSi particles with diameter of 1 μm were prepared by combining lithography and electrochemical etching. Poly-ethyleneimine (PEI) was attached to discoidal pSi particles to protect their fast degradation in buffer solution. These PEI coated pSi particles were subsequently loaded with siRNA. The gene knockdown assay against ataxia telangiectasia mutated cancer gene (ATM) showed exceptional efficiency with no apparent *in vivo* toxicity. Recently, Neta *et al.* developed a pneumatic capillary gun system with the ability to launch drug-loaded pSi particles and implant them locally into a tumour.[166] They demonstrated that this pressurised gas-driven system is capable of delivering drug-loaded pSi particles at the tumour site, deeply underneath the skin with high spatial resolution. They also compared the cell viability of mitoxantrone dihydrochloride-loaded–MTX and unloaded pSi particles launched into the tumour using their biolistic delivery system. It is expected that a unique combination of pSi carriers and that payload delivery device could provide a profound and solid base for developing more efficient drug-releasing systems to combat a broad range of diseases through a rational and localised delivery of therapeutics over inflicted areas.

These studies have demonstrated that pSi is one of the most promising and applied inorganic nanoporous materials in drug delivery applications. Its biocompatibility, biodegradability, pore versatility and optical/electronic properties make pSi an excellent candidate for developing highly sophisticated drug-releasing systems. Nevertheless, some of these properties could prevent pSi from being used in other clinical applications, where mechanical and chemical stability are needed.

2.3. Implantable hybrid composites based on carbon

In the past few years, carbon-based nanomaterials, especially carbon nanotubes (CNTs) and graphene oxide (GO), have gained enormous interest for biomedical applications due to their unique set of intrinsic physical and chemical properties.[167] Numerous studies have reported on the use of CNTs and GO for drug delivery, biosensing and tissue engineering applications.[168-170] In this section, however, we will focus our attention on the most recent and relevant combinations of CNTs and GO with polymer-based materials such as hydrogels, nanofibres and polymer films for drug-releasing applications. The resulting hybrid composites present improved mechanical, electrical, thermal and drug-releasing performances, which are technical features of great importance for therapies based on localised administration of drug from implants (**Table 3**).

2.3.1. CNTs as enhancers in drug-releasing implants

Although hydrogels exhibit excellent biocompatibility and biodegradability and can be used as an implantable drug-releasing systems, the unfavourable and uncontrollable burst release (*i.e.* initial high release of drug) is still an inherent problem of this nanomaterial for therapeutic applications.[171] Several recent works have shown that CNTs can resolve the problem by serving as excellent enhancers in polymer-based drug-releasing implants. Arindam *et al.* found that multiwall carbon nanotubes (MWCNTs) can reduce the initial burst release of drug in carboxymethyl guar gum (CMG) hydrogels.[172] The hybrid hydrogel showed steady and non-burst release when the concentration of MWCNTs was ranged from 1 to 3 *wt%*. Li *et al.* reported on a similar result in hybrid collagen-CNTs hydrogels.[173] This study found that the network formed by CNTs absorbs drug molecules through the use of

non-covalent bond and prevents fast diffusion of water into the hydrogel structure.

CNTs are conductive and can endow hydrogel composites with electro-responsive properties, which enable the remote 'on demand' control of drug release.[172-178] Recently, Servant *et al.* reported on the first *in vivo* pulsatile drug release from poly(methacrylic acid) (PMAA)–CNTs hybrid hydrogels.[177] These hybrid hydrogels were synthesised by *in situ* radical polymerisation of methacrylic acid (MAA) in an aqueous dispersion of MWCNTs. Drug release from the resulting electro-responsive hydrogels can be activated by voltage. In this study, voltage pulses of 10 V were applied during short time intervals within which the hybrid hydrogel exhibited excellent ability to release drug dosages in an ON/OFF fashion. This implantable nanomaterial was tested both *in vitro* and *in vivo* in CD-1 mice, showing good biocompatibility as indicated by histological analysis. No significant inflammation or necrosis was found although dermal tissue in contact with the electrode showed signs of inflammation.

Table 3 Summary of the different hybrid implantable materials produced by combining CNTs and GO with polymers and hydrogels.

Hybrid Material	Features	References
CNTs-based hydrogel	Electric-responsive system Reduced burst release	172,173,174,177,178,179
CNTs-based nanofibre	Electric-responsive system Efficient drug release	175,176
GO-based hydrogel	Temperature-responsive pH-responsive	181,182,183,184,185
GO-based film	Sequential biomolecular release	186

Another study combined MWCNTs with PPy films to produce a hybrid system where MWCNTs served as nanoreservoirs for achieving higher drug loading capacity and controllable drug release capability.[179] Oxidised MWCNTs with open ends were first loaded with dexamethasone, an antiinflammatory drug, and then sealed with PPy by electropolymerisation (**Fig. 9a**). In this way, given that the positively charged polymer back-bone can be electrochemically reduced to neutral state during negative bias, the drug release of negatively charged drug molecules from the film to the *milieu* can be activated by electrical bias. Since CNTs are highly conductive, the MWCNTs-PPy composite film can effectively respond to electric stimulations (**Fig. 9b**). Moreover, it was found that CNTs featuring bigger inner diameters and smaller outer diameters have better distribution and drug loading capacity in PPy films. As mentioned before, traditional transdermal drug delivery systems suffer from the extremely slow drug release rate from the matrix and the low permeability of the human skin.[176] To solve this problem, Im *et al.* combined MWCNTs and polyethylene oxide (PEO)/pentaerythritol triacrylate (PETA) to synthesise electric-responsive nanofibres for controlled drug release.[175] These hybrid nanofibres were produced by electrospinning with the addition of MWCNTs in the polymer solution. The resulting nanofibres contained well-aligned MWCNTs at the centre and have enhanced electric conductivity. Drug release experiments showed that nanofibres without MWCNTs released 45% of the loaded drug after 600 min when a voltage of 15 V was applied. In contrast, the hybrid nanofibres incorporating MWCNTs released 90% of the loaded drug under the same experimental conditions. The drug release mechanism of this system relies on the increment in the water solubility of PEO upon the application of voltage. This creates sufficient space inside the nanofibres that enhances the release of drug molecules from the nanofibres to the *milieu*. Since MWCNTs increased the conductivity inside the polymer network, PEO dissolved more efficiently with the application of voltage, resulting in a more efficient drug-releasing performance.

2.3.2. Graphene oxide in drug-releasing implants

Graphene and graphene oxide (GO) have been extensively explored for biomedical applications due to their unique set of chemical and physical properties (*e.g.* large surface area, oxygen-containing functionalities, good conductivity, excellent biocompatibility, imaging and hypothermia capabilities, *etc.*).[169,180] In addition, GO solutions can perform a sol-gel transition when charged molecules (*e.g.* polymer molecules, drug molecules, *etc.*) are added.[181-186] These charged molecules act as cross-linkers between adjacent GO sheets. The resulting GO-based hydrogel is formed from the assembly of individual GO sheets constructed in an interconnected 3-dimensional porous network, which is sustained by non-covalent bonds (*i.e.* hydrogen bonding, π-π stacking and electrostatic interactions). Compared to traditional polymer hydrogels, GO-based hydrogels exhibit advanced stimuli-responsive properties and reduce the characteristic burst release of traditional hydrogels. Bai *et al.* reported on the production of a GO/poly(vinyl alcohol) (GO/PVA) hybrid hydrogel by adding PVA into a GO solution (**Fig. 9c**).[181] A very small amount of GO (5 mg mL^{-1}) and PVA (0.5–2.5 mg mL^{-1}) were combined to form a GO-PVA composite. The hybrid hydrogel is sensitive to pH, performing a reversible transition from solution (pH>7) to gel (pH<7). The analysis of its *in vitro* drug release performance showed that 84% of vitamin B_{12}, which was used as a model drug, was released into the PBS solution after 48 h. Nevertheless, only 51% of the drug was released in acidic medium (pH = 1.7) under the same experimental conditions (**Fig. 9d**). This was associated with the tightly packed GO sheets under acidic conditions, which hindered the diffusion of drug molecules from the hydrogel to the medium.

Similarly, Wang *et al.* synthesised konjac glucomannan/sodium alginate hydrogel by using GO as a drug loading enhancer. The hybrid hydrogel possesses enhanced drug loading capacity and can perform *in vitro* pH-responsive release of 5-fluorouracil.[186] The release of drug was sustained for 3 h and no burst release was observed at pH 6.8. The synthesis of implantable GO-based hydrogels is not limited to the use of polymers as cross-linkers. Small molecules, such as vitamins and drug molecules can also trigger the sol-gel transition of GO solutions. Furthermore, Sui *et al.* reported a green synthesis route of reduced graphene oxide (RGO) hydrogel by simultaneously using vitamin C (VC) as a reducing agent and model drug.[182] It was found that the mass ratio of VC to GO played a significant role in the synthesis of RGO hydrogels. The optimal mass ratio of VC to GO was in the range of 1:2–832:1. The resulting RGO-based hydrogel presents hierarchical macro and mesoporous structures on the stacked solid walls, which increase the specific surface area of the resulting system (500 m^2 g^{-1}). After VC reduction, the excess of VC can be released in a sustained fashion for 25 h in ultra-pure water. Although RGO/MWCNTs and RGO/platinum hybrid hydrogels can be prepared, the conductivity and mechanical strength of the resulting hybrid hydrogels are not as good as RGO, probably due to the occupation of cross-linking sites of GO sheets by MWCNTs and platinum. Tao *et al.*[185] and Ma *et al.*[183] reported on the concept of *in situ* gelation of GO-drug molecules hydrogels. In the former work, metformin hydrochloride (MFH) was chosen as a drug model and cross-linker. A small amount of MFH (*i.e.* weight ratio 1:10 to GO in the solution) can trigger the gelation of GO at neutral pH

efficiently. In the latter study, doxorubicin (Dox) was employed as a model drug and cross-linker to fabricate a hybrid GO-Dox hydrogel. This demonstrated a sustained release that lasted for 14 days without the undesirable burst release phase.

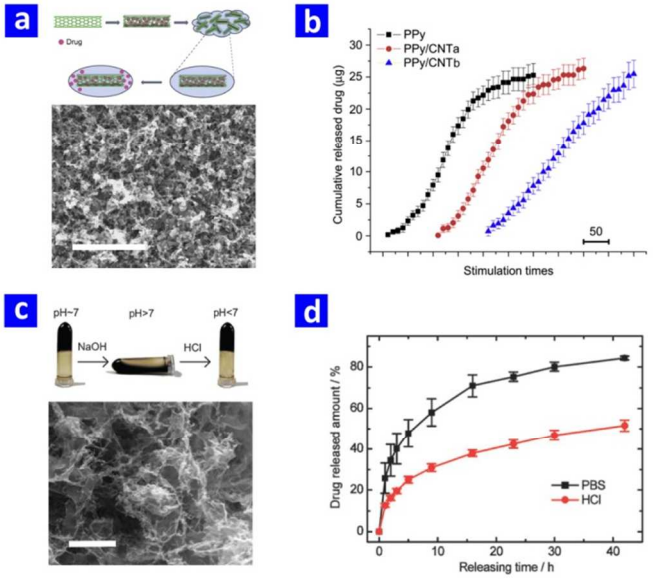

Fig. 9 Implantable drug-releasing hybrid polymers/hydrogels incorporating carbon nanotubes and graphene oxide. a) Schematic diagram showing the fabrication process of CNTs-PPy hybrid polymeric composites and SEM image of the resulting composite (scale bar = 5 μm) (adapted from Ref. [179]). b) Dexamethasone-releasing performance under stimulation for different CNTs-PPy composite formulations (adapted from Ref. [179]). c) Schematic diagram showing the pH-switchable transition of GO/PVA composites and SEM image of the resulting hybrid material (scale bar = 5 μm) (adapted from Ref. [181]). d) Vitamin B-releasing performance under different *milieu* conditions (*i.e.* PBS and hydrochloric acid) (adapted from Ref. [181]).

An *in vivo* study using an injectable GO hydrogel system was reported by Sahu *et al.* Briefly, three types of pluronic, namely F68, F127 and P105, were used as model drugs and cross-linkers to synthesise temperature-responsive GO hydrogels. In this system, the composite is a solution at room temperature but becomes a gel at body temperature. This transition of state can also be triggered by near infrared radiation. *In vivo* temperature-induced gelation of the hydrogel was successfully achieved after subcutaneous injection into mice models. No signs of acute inflammation, tissue necrosis, haemorrhaging or hyperaemia were found after 8 weeks of implantation, proving the biocompatibility of this novel hybrid hydrogel. Finally, a GO-based layer by layer (LBL) approach has been used to release ovalbumin for up to 90 days.[181] Taking advantage of the low permeability of GO, GO layers were intercalated between poly(β-aminoester)/ovalbumin(Poly1/ova) layers by LBL deposition. This system makes it possible to sustain the diffusion of proteins from the hybrid hydrogel. Negatively charged GO (GO-COO^-) and positively charged GO (GO-NH_3^+) were prepared and then used to cap Poly1/ova layers. GO layers formed a smooth and stable coating on the Poly1/ova surface. *In vitro* release studies showed a sustained release pattern without initial burst release. Moreover, they found that the protein release was significantly influenced by the thickness (*i.e.* number of layers) of the GO-based hydrogel. By labelling the protein layers sequentially with different fluorescent dyes, this study proved that GO layers are able to release multiple biomolecules in a differential fashion from the same multilayered architecture. The resulting hybrid composite showed excellent biocompatibility to haematopoietic stem cells and did not affect the cell population in the first 4 days, despite showing mild toxicity after 10 days.

These studies have verified the promising potential of hybrid carbon-based nanocomposites for developing implantable drug-releasing systems with outstanding performances. Although some of these technical features, such as stimuli responsiveness, can be used to develop advanced drug-releasing implants (*e.g.* systems with 'on demand' capabilities), carbon-based nanocomposites are still far from being considered as highly sophisticated systems. In contrast, the use of microfabrication techniques to develop drug-releasing systems has made it possible to produce a variety of highly sophisticated implantable drug-releasing systems.

2.4. Microfabricated devices

Microelectronics industry has used microfabrication technology for many decades. This well-established technology, which has been more recently combined with nanoengineering technologies, has demonstrated outstanding versatility and capabilities in order to produce a broad range of micro and nanostructures with precisely controlled geometry and physical and chemical properties at the micro and nanoscale. In the last decade, many works have demonstrated the potential applicability of micro and nanofabrication technologies to develop innovative drug-releasing systems for biomedical applications. These new biotechnological devices can overcome inherent problems of current drug-releasing technologies. Furthermore, given the industrial capability of micro and nanofabrication technologies, these devices can be produced at industrial scale with high throughputs and low manufacturing costs. Some examples of these devices are microneedle syringes, patches, micropumps and implantable drug-releasing microchips. These have been tested in many clinical trials and applications and have demonstrated potential to revolutionise current medical practices and therapies (*e.g.* vaccination).

2.4.1. Microneedle syringes combined with drug-releasing patches

Human skin is a natural barrier that hinders the transdermal diffusion of drugs. The *stratum corneum* is the outermost layer of the epidermis, formed basically by stacked layers of dead cells. The objective of this natural barrier is to protect the underlying tissues from infections, dehydration, mechanical stress and chemicals. This layer can be up to 20 micrometres thick. Therefore, therapies based on transdermal delivery of drugs must overcome this natural barrier in order to perform an efficient delivery of drug over targeted tissues.

Microneedle patches and microsyringes fabricated by microtechnology have been developed as new medical devices to release drugs through the *stratum corneum* with controlled dosage and without causing pain to patients, since the nerve terminals are located a few hundred of micrometres below that layer. Microneedle technology was initially developed in the 1980s. Since then, different microfabrication approaches have made it possible to produce microneedles based on different materials (*e.g.* silicon, polymers, metals, *etc.*) featuring solid or hollow structures with exquisitely defined dimensions.[187-189] In the former type, the microneedle surface is coated with drug, which is then delivered to the site of interest from the microneedle surface. The latter one, however, enables transdermal and intradermal delivery of drugs from external

reservoirs to the site of interest by bypassing the *stratum corneum*. This makes it possible to deliver drug over an extended period of time in a controlled/regulated fashion. As for their structure, microneedles can be produced in a broad range of geometries and shapes (*e.g.* blunt cylinders, tapered cylinders, volcano-like, saw-like, citadel-like, *etc.*), which can range from hundreds to thousands of micrometres.[190-197] Traditionally, microneedle syringes have been produced by deep reactive ion etching using silicon as a base material. Nonetheless, they can be based on other materials such as metals or biodegradable polymers loaded with drugs.[187] The delivery of macromolecules (*e.g.* DNA, antibodies, enzymes, *etc.*) through the skin can be a challenge for this technology as these molecules can aggregate on the microneedle walls. However, the combination of sonophoresis and microneedle syringes for transdermal delivery of macromolecules has shown excellent results to address this limitation.[182] Arrays of microneedles can be integrated into drug-loaded transdermal patches, which can be applied over larger surface areas (**Figs. 10a and b**).

So far, this drug-releasing technology using microneedles has been tested in several clinical trials, showing an outstanding potential for diverse medical applications.[14] Systems combining microneedle syringes and drug-releasing patches can be used for broad clinical applications such as localised delivery of anaesthesia, nicotine, influenza vaccine, insulin and eye therapeutics.[190-192,195,199-202] Currently, some commercial products based on microneedle syringes and patches are in phases 2 and 3 of clinical trials. As a result of its cost-competitive and scalable fabrication process, it is expected that this technology will deliver enormous benefits for medical treatments in undeveloped countries and poor areas, where underprivileged people in need are without access to conventional medication.

2.4.2. Implantable micropumps

Implantable micropumps are drug-releasing devices based on different actuation principles (*i.e.* manual, electrolysis, piezoelectric, resistive heating, magnetic and mechanical actuation). Among them, micropumps based on osmotic engines have demonstrated the most promising capabilities for real clinical applications. These devices are composed of different elements, including a diffusion moderator, a drug container, a piston, an osmotic engine and a semi-permeable membrane. In osmotic micropumps, the piston is moved forward by mechanical expansion of the osmotic engine when water diffuses through the membrane. This process is activated by an osmotic gradient between the engine itself and the moisture in the surrounding interstitial fluid. Then, the composition of therapeutics loaded in the drug reservoir is progressively released over the site of implantation at a particular rate, which is established by the characteristics of the micropump. In that regard, the release rate can be partially regulated by the diffusion moderator and the osmotic engine, enabling the generation of different drug-releasing profiles.

So far, many commercial drug-releasing systems based on micropumps have been released and used for different clinical applications such as cancer treatments, hepatitis, chronic pain alleviation, diabetes, glaucoma, age-related macular degeneration, diabetic retinopathy and tissue regeneration (**Figs. 10c and d**).[203-215] The working life of micropumps can range from several weeks to several years. They offer a broad range of drug-releasing rates, which can be constant or adjustable, can be achieved (*e.g.* from 40 ng day^{-1} up to 12 μg day^{-1}). This makes it possible to generate different profiles for different clinical patients and treatments. Usually, micropumps are based on biocompatible materials such as titanium or titanium alloys. Therefore, they must be removed by further surgery at the end of the clinical treatment as these materials are not biodegradable. However, these devices can also be based on bioerodible/biodegradable materials such as polymers. In this way, no additional surgery is required at the end of the treatment.[209]

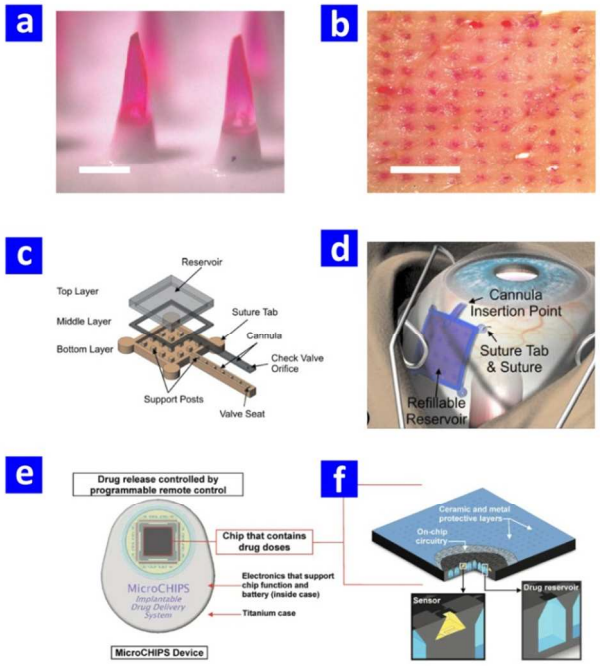

Fig. 10 Implantable drug-releasing systems produced by micro and nanofabrication techniques. a) Polymer microneedles encapsulating lyophilised vaccine for delivery (adapted from Ref. [201]) (scale bar = 250 μm). b) Porcine cadaver skin after insertion, removal of microneedles and vaccine release (adapted from Ref. [201]) (scale bar = 1 mm). c) Schematic illustration of a microfabricated device used in the treatment of eye-related diseases (adapted from Ref. [210]). d) Schematic diagram showing the implantation of this microdevice underneath the conjunctiva (adapted from Ref. [210]). e) A prototype implantable microchip-based device for controlled release: the microchip is mounted in a biocompatible case containing electronics, power source, and antenna for wireless communication (adapted from Ref. [188]). f) Close-up view of the microchip shown in (e) combining arrays of biosensor for the detection of biomarker levels (adapted from Ref. [188]).

2.4.3. Microchips

Another type of implantable drug-releasing microdevices are microchips, which basically consist of a microfabricated platform that features different sealed arrays of multireservoirs containing one or more drugs (**Figs. 10e and f**). In these devices, the release of therapeutics can be remotely activated by different actuation principles (*e.g.* electrothermal, laser-based, electrochemical, *etc.*).[203-215] The versatility of microchips is very broad as compared to other microdevices, since different drug-releasing profiles of a variety of drug payloads can be generated. Therefore, more efficient clinical treatments can be implemented by a synergistic strategy based on the administration of different drugs/formulations at controlled periods of time in diverse fashions (*e.g.* parallel, sequential, intermittent, *etc.*). However, the release rate is established by

the dissolution and subsequent diffusion of drug molecules from the reservoirs to the *milieu*.

To date, different drug-releasing concepts based on microchips have been developed. The pioneering system consisted of a silicon chip containing drug reservoirs produced by microfabrication, which were sealed by a gold membrane.[188, 216-220] After applying an electric potential between the anode and cathode in the microchip, the gold membrane becomes soluble in saline medium and thus the release of drug from the reservoirs is activated. This system, however, presents some disadvantages for *in vivo* applications given the complex composition of the medium.[221,222] These inherent drawbacks can be overcome by changing the activation principle from electrochemical to electrothermal.[223,224] In that case, the metallic layer sealing the reservoirs is dissolved by electrical resistive heating after an electrical current is applied between electrodes.

More advanced features such as remotely controlled activation have been recently incorporated into these systems by including microprocessors and wireless antennas. This kind of implantable drug-releasing systems has been employed for the administration of therapeutics used in hormone-based clinical treatments (*e.g.* cancer, osteoporosis, *etc.*).[225,226] However, more sophisticated configurations can be implemented in microchips in order to treat diseases in complex organs such as eyes (*e.g.* retinal disease, age-related macular degeneration, diabetic retinopathy, *etc.*). In that respect, rod-like microchips containing hermetically sealed reservoirs have been developed in order to treat some ocular diseases. First, these microchips are implanted into the periphery of the vitreous by intravitreal injection. After implantation, the release of drug from the different reservoirs is activated by focusing a laser beam on the covers sealing the reservoirs. Then, drug molecules are released into the vitreous and diffused to the retina from the open reservoirs. The remaining reservoirs are kept close for further dosage in future sessions. This clinical treatment is more comfortable for clinical patients as they do not need to suffer periodic invasive injections.

In conclusion, many commercially available drug-releasing devices produced by micro and nanotechnology have been developed. This is a research area with rapid development and it is expected that many of these devices will be commercially available soon. Nevertheless, before any implantable drug-releasing microdevice can become a feasible technology in medicine, it must fulfil stringent regulations/requirements such as total biocompatibility of the different elements composing the device, ability to meet the need for a broad range of patients and clinical treatments, economical competitiveness of the whole fabrication process and well-established *in vivo* stability/performance.

3. Clinical application of drug-releasing implants

As previous sections have shown, even though drug-releasing implants incorporating technology based on new micro and nanomaterials are still at their developing stage, they have demonstrated outstanding capabilities in terms of applicability and versatility for a broad range of clinical applications. Some examples of these are bone implants, cardiovascular stents, brain treatments, dentistry and eye-related diseases. In many cases, the use of implantable drug-releasing devices can make the therapy more efficient, extending the life expectancy and improving the patient's life with less invasive treatments.

3.1. Orthopaedics and bones

Bone-related diseases are a major health problem worldwide with highly deleterious effects on both the life quality of patients and health expenditure. Typically, these diseases are treated by conventional therapies based on systemic administration of drugs, which present the aforementioned inherent limitations and associated side effects. Particularly, local administration of drugs from implants offers many potential advantages for treating bone-related diseases (*e.g.* selective targeting of affected tissues leaving healthy ones spared, avoiding serious side effects associated with drug toxicity, providing locally optimal concentration of often expensive and highly toxic drugs, optimising bioavailability without rapid breakdown and clearance, *etc.*).

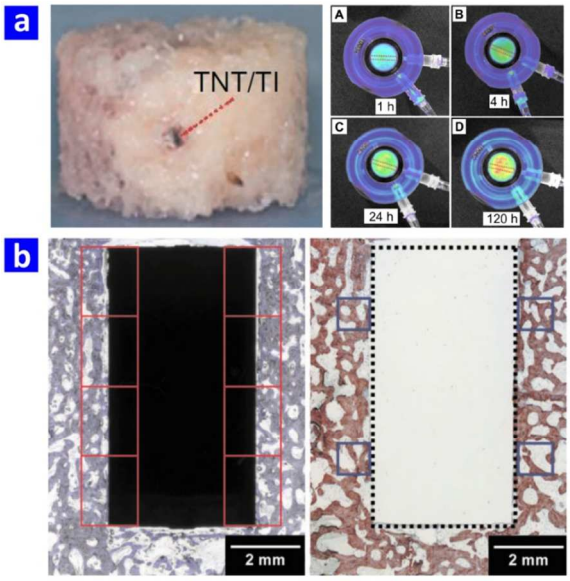

Fig. 11 Clinical examples of implantable drug-releasing systems. a) Drug-releasing implant based on a Ti wire featuring titania nanotube (TNTs) arrays on the surface, embedded in the centre of the bone and bioluminescence images of an *ex vivo* bone model. b) *In vivo* study of TNTs-Ti implants in the frontal skull of domestic pigs showing regions of interests for the histological and immunohistological evaluations of the bone-implant contact (adapted from [235]).

The pioneering concept of drug-releasing implants for treating bone-related diseases was initiated by Buchholz *et al.* in the 1970s.[227] This study was the origin of a flood of works on the development of biocompatible drug-releasing materials to treat bone-related diseases. Since then, numerous materials (*i.e.* biodegradable, inert, natural, synthetic, *etc.*) have been explored and their capabilities and performances assessed through a series of *in vitro*, *ex vivo* and *in vivo* studies.[228-233] Some examples of materials used to develop drug-releasing implants for treating bone-related diseases are collagen, chitosan, calcium phosphate cements, fibrin, silk, hydroxyapatite, ceramics, hyaluronan, and polymers (*e.g.* PMMA, poly(lactic-*co*-glycolic acid), *etc.*). Typically, these materials are moulded into different forms (*e.g.* granules, matrices, coatings, foams, hydrogels, membranes, sponges, fibres, *etc.*) and loaded with therapeutic agents to treat specific bone-related diseases.[228-233]

However, these materials present inherent limitations such as poor mechanical stability and heterogeneous porosity distribution. Given that the release of drug molecules from these implantable devices is established by their porosity, a

heterogeneously distributed porosity leads to non-reproducible and inefficient bone therapies.[234] In this context, TNTs layers grown on the surface of Ti implants *via* electrochemical anodisation have become a promising alternative to traditional drug-loaded polymeric or ceramic coatings. An *ex vivo* study reported by our group showed that implantable TNTs-Ti wires can be used and inserted directly into the bone to provide extended release of drugs (**Figs. 11a and b**). The Zetos™ bone bioreactor was used for *ex vivo* study of drug distribution in bone to demonstrate the application of TNTs coatings as viable drug-releasing implants.[234] On the other hand, Schmuki and co-workers have analysed the *in vivo* performance of TNTs-Ti implants in pigs. They evaluated the effects of these implants on the periimplant bone formation, bone-implant contact and immunohistochemistry. This study demonstrated that TNTs coatings enhance osteoblast functions and resist shearing forces evoked by implant insertion.[235]

The implant surface is the key factor in terms of integration within the host body, given that it acts as an interface between artificial element and biological environment. In that regard, it has been demonstrated that the surface roughness and surface chemistry of bare orthopaedic implants are crucial factors with a direct impact on osteoblasts and chondrocytes growth.[114] For instance, a study conducted by Kunze *et al.* reported that electrochemically fabricated and annealed TNTs coatings with anatase phase are good precursors for the formation of calcium hydroxyapatite ceramic (CHA).[132] They explored the initial and later phases of apatite formation from simulated body fluid on TNTs as compared to compact titania, which is of a different surface morphology. More nuclei were formed on TNTs surfaces than on flat compact titania at the early phases of apatite growth. The nanotubular morphology on TNTs with an anatase type structure can form apatite layers with a thickness of >6 nm in less than 2 days. This demonstrated that TNTs are more favourable as an implant material for osseointegration than titania featuring flat compact surfaces. Furthermore, TNTs can load and release osteogenic agents gradually at the implantation site in bones.[236]

TNTs-Ti implants were studied for the delivery of bone morphogenetic protein-2 (BMP-2). These showed that the implant can also promote the proliferation, migration and differentiation of mesenchymal stem cells (MSCs) at the same time.[237] Specifically, the adhesion, spreading and differentiation of MSCs were shown to be affected by the diameters of TNTs.[238,239] These authors concluded that TNTs with larger diameters are more effective for protein adsorption.[240] Therefore, the physical dimension of TNTs in Ti implants is a governing factor for the modulation of biological functions in bone cells and tissue engineering and the key parameter in terms of drug-releasing performance. Ti implants featuring drug-loaded TNTs coatings can be considered as a safe drug-releasing implant with promising potential for localised delivery of therapeutics to treat a broad range of bone-related diseases, including infections, inflammations and cancers.[234]

3.2. Coronary stents

Coronary stents are tubes implanted in the coronary arteries that supply the heart to avoid their occlusion in the treatment of coronary heart disease. These medical devices are traditionally based on metals and are implanted by percutaneous coronary intervention (**Figs. 12a and b**). The objective of cardiovascular stents is to improve the survivability of patients suffering from a coronary artery disease. However, traditional coronary stents present some inherent clinical complications such as restenosis, which still remains as a crucial challenge in cardiology.[241] So far, several technological approaches have been used to overcome these drawbacks. Examples of these are coronary stents coated with drug-loaded polymeric covers. These have demonstrated to overcome neointima proliferation after implantation by releasing antiinflammatory, immunosuppressive and cytostatic drugs (*e.g.* tacrolimus, sirolimus, paclitaxel, *etc.*). Nevertheless, the inflammatory reaction produced by these polymers has seriously limited the clinical applicability of these alternative coronary stents.

To overcome these limitations, Wieneke *et al.* performed an *in vivo* study using coronary stents featuring a coating of inorganic nanopores. These were produced by electrochemical anodisation of aluminium coatings covering the stainless steel stents.[242] The resulting nanopores based on NAA were infiltrated with two solutions of tacrolimus at different concentrations. Subsequently, these drug-loaded stents were implanted in the common carotid artery of rabbits. Drug release was monitored by measuring the tacrolimus level in blood periodically. It was observed that the maximum concentration of drug in the bloodstream of rabbits was reached 1 h after implantation. This decreased gradually over the course of the next 48 h and the drug concentration in blood never exceeded the therapeutic window during the experiment and the detection limit was reached after 48 h. This experiment demonstrated the potential use of drug-loaded NAA coatings in cardiovascular stents for real clinical applications.

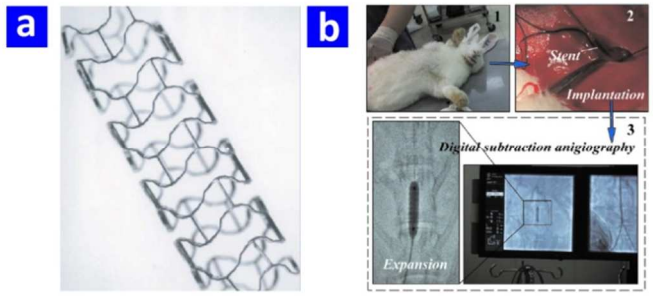

Fig. 12 Clinical examples of implantable drug-releasing systems. a) Bioabsorbable magnesium stent developed by BIOTRONIK (adapted from Ref. [264]). b) Digital and actual images showing the surgical procedure for drug-releasing stent implantation and performance monitoring in a rabbit model (adapted from Ref. [245]).

However, more recent *in vivo* studies with porcine models demonstrated that the shedding of particle debris from the nanoporous anodic alumina coating produced a significant increase of neointimal hyperplasia as compared with bare stainless steel stents.[243] Particle debris of NAA released from coated stents was found in the media. Histological analysis revealed neointima produced by NAA particles, which was associated with an augmented vascular inflammation through histomorphometric analysis. So far, different materials have been used to overcome inherent drawbacks of drug-releasing coatings based on polymers and nanoporous inorganic materials. Some examples are microporous hydroxyapatite and composites based on magnetic mesoporous silica nanoparticles and carbon nanotubes.[244,245]

Another outstanding alternative to conventional stents are absorbable drug-releasing stents.[246] Notice that stents are temporary implants, which may only be needed to prevent immediate recoil and negative vessel remodelling during the healing period of a vascular injury related to the implantation of the stent itself.[246,247] In that respect, absorbable drug-releasing

stents may allow the restoration of vasomotion and long-term remodelling of the stented vessels.[248,249] Furthermore, these implants can be made suitable for infant patients with congenital cardiovascular diseases, the vessels of which are still in a developing phase and thus no additional surgery is required to replace the stent as the patients grow older. So far, absorbable stents have been developed from polymers and metals. These feature a broad range of mechanical properties and degradation times. Many types of polymers have been used to develop absorbable drug-releasing stents. The most representative examples are self-expanding and shape-memory biocompatible polymers (*e.g.* poly-*DL*-lactide (PDLLA), poly-*L*-lactide (PLLA), poly-lactide-*co*-glycolide (PLGA), *etc.*).[250-252] These stents have shown promising results both *in vitro* and *in vivo* tests with animal models (*e.g.* pigs).[253,254] A variant of absorbable drug-releasing stents based on polymers are the so-called balloon-expandable fibre-based stents, which can be composed of different polymers and blends of polymers (*e.g.* PLLA, polydioxanone (PDO), poly-glycolide-*co*-ε-caprolactone (PGCL), *etc.*).[254-257] Abbott Vascular developed the absorbable balloon-expandable stent BVS®, which is based on PDLLA and is currently studied in 30 clinical patients. This absorbable drug-releasing stent can keep a sustained release of everolimus over 120 days. After 3 years of clinical trial, it was reported that the BVS® stent has been safe for 29 patients, with absence of cardiac death, re-intervention or stent thrombosis. Among these 30 patients, only one suffered from myocardial infarction.[258,259] Furthermore, there was no detectable difference in echogenicity of stent structures from surrounding tissues, revealing that the BVS® stent is absorbed progressively by the host body.[260]

Another type of absorbable stents based on corrodible metals (*e.g.* iron, magnesium, *etc.*) has been developed recently. Some of them have been tested in animal models through preclinical trials (*i.e.* New Zealand white rabbits and young pigs).[261,262] The obtained results revealed that these stents are highly biocompatible and do not produce toxicity issues related to the corrosion of the stent. As for real clinical applications, Biotronik tested its absorbable stent AMS® based on magnesium in 63 clinical patients.[263] This trial revealed that the AMS® stent is absorbed within 4 months after its implantation. Nevertheless, 45% of the patients were operated 1 year after the implantation.[264,265] Although no test has been carried out in that regard, the AMS® stent could be implemented with drug-releasing capabilities by coating its structure with drug-loaded coatings (*e.g.* polymers, inorganic porous materials, *etc.*). The most important drawback to be addressed by absorbable drug-releasing technology is to establish the period of time that the stented segments of arteries will require for mechanical scaffolding provided by the stent. Nevertheless, this process is not yet fully understood.[266] Therefore, in spite of their potential applicability, absorbable drug-releasing implants present some potential drawbacks.

Finally, it is worth stating that any of the aforementioned drug-releasing stents must address technical challenges such as high deliverability, adequate mechanical scaffolding, minimal vessel trauma, minimal inflammation, antirestenotic properties, efficient endothelialisation, no need for long-term antiplatelet therapy and a good support of positive vessel remodelling before they become a feasible technology for commercialisation and real clinical applications.[245,267,268]

3.3. Dentistry

In comparison with other medical fields, current treatment for diseases and trauma of dental, oral and craniofacial (DOC) structures using localised drug-releasing systems is not well-developed. Local dental drug delivery systems can either be preventive, restorative or regenerative. Preventive systems prolong the release of active agents and offer great advantages in preventing and treating dental caries, periodontitis and gingivitis. Restorative/regenerative systems involve matrices and scaffolds to deliver active agents, cells and signalling molecules responsible for tissue regeneration.[269,270] Dental carries are caused by bacterial fermentation of the dietary carbohydrates which lead to partial or complete destruction of tooth tissues.[271] Flouride is a highly researched functional ingredient that not only prevents caries but also enhances the remineralisation of enamel lesions.[272-274] In that regard, some fluoride-releasing devices can provide controlled release of fluoride ions into the saliva, without increasing the fluoride levels in urine or serum and prevent teeth form caries.[275,276]

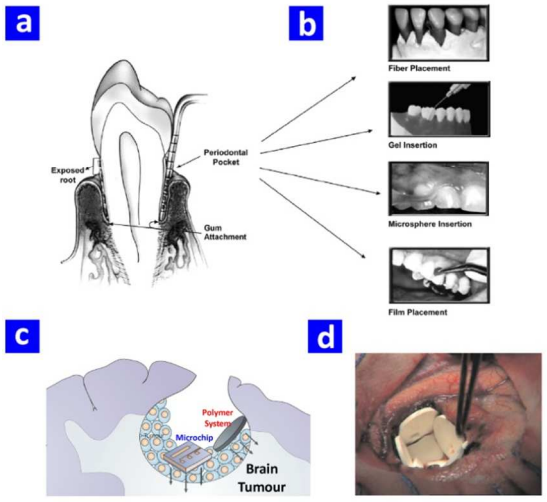

Fig. 13 Clinical examples of implantable drug-releasing systems. a) Illustration of a tooth structure (adapted from Ref. [279]). b) Intrapocket drug-releasing devices for periodontitis treatment (adapted from Ref. [279]). c) Schematic diagram describing the use of polymer/microchip drug-releasing implants to treat brain tumours by overcoming the blood-brain barrier (adapted from Ref. [306]). d) Implantation of Gliadel® wafers after resection of a malignant glioma, up to eight carmustine-loaded polymer wafers are placed within the tumour cavity. As the wafers dissolve, they release carmustine locally and provide localised delivery of chemotherapeutic agents to the tumour cavity. (adapted from Ref. [306]).

To date, these devices have been developed in copolymer membranes, glass, hydroxyapatite-eudragit-RS 100 (diffusion-controlled fluoride system) and hydroxyapatite-eudragit-ethylcellulose matrix (slow fluoride-releasing tablets).[275] Periodontitis is a bacterial infection of the subgingiva, which is characterised by the formation of periodontal pocket by migration of junctional epithelial tissue at the base of gingival sulcus down to the root of the tooth. This disease causes the destruction of bone and soft-tissue.[277,278] These intracanal and periodontal infections can be treated by the local application of antibiotics, antiinflammatory and antibacterial agents such as tertracycline, chlorhexidine, minocycline and metronidazole in the root canal or in periodontal pockets.[270,272] Goodson developed the pioneering periodontal drug-releasing system in

1979. Ever since, intra-pocket controlled drug-releasing systems have been explored for periodontal treatments. In a recent review, Kaplish *et al.* described these systems which are commercially available.[278] For instance, polymeric hollow fibres based on polycaprolactone, polyurethane, cellulose acetate propionate or ethyl vinyl acetate can act as drug reservoirs and release drugs to the periodontal pocket in a sustained fashion (**Figs. 13a and b**).[279] Some examples of commercially available products are Periochip® (chlorhexidene/gluconate-loaded biodegradable device) and Periochop® (chlorhexidene/tetracycline-loaded film) based on hydrolysed gelatine.[280] Other systems such as Arestin®, which is composed of minocycline-loaded bioadhesive, bioresorbable polylactide or glycolide microspheres, can be directly injected into the pocket and release drug slowly throughout 21 days.[281] Atridox® (doxycycline-loaded biodegradable mix in syringe) and Dentamycin® (minocycline-loaded biodegradable mix in syringe) are similar injectable systems available in the market.

Nanotechnology applied to dentistry has provided innovative approaches to treat dental-related diseases. For example, nanoparticles-based dental drug-releasing systems have been shown to penetrate inaccessible regions in the mouth. Biocompatible nanoparticles comprising 2-hydroxyethyl methacrylate (HEMA) and polyethyleneglycol dimethacrylate (PEGDMA) have been incorporated in a hydrogel matrix for dental applications.[282] A formulation containing triclosan-loaded polymeric nanoparticles was shown effective in penetrating the junctional epithelium in an *in vivo* study in dogs.[283]

A major part of dentistry is restorative implant/inserts, which serve as abutments for replacing the missing tooth and providing support to dental crowns and bridges. This technique known as guided tissue regeneration (GTR), helps to replace and enhance the formation of new bone cells and gingiva, which is destroyed in periodontitis.[284,285] The most common method to improve GTR is to coat the existing implants by polymeric or inorganic matrices embedded with relevant therapeutics. Calcium phosphates, hydroxyapaptite and ß-tricalcium phosphate are the most widely researched and clinically applied dental restorative materials, although other nanomaterials such as carbon nanotubes, bioactive glass, titania, silica and collagen have also been explored for this application.[286]

Titanium and its alloys are widely used as dental implants, but new strategies to load drug onto implant surfaces have recently been explored to enhance osseointegration and reduce healing time.[287,288] A coating of bioactive/drug-eluting biomaterial can improve the implant fixation and tissue integration.[289] A thin bisphosphonate-releasing fibrinogen coating on a titanium tooth implant has been demonstrated to improve the implant fixation.[290] A dip-coated poly(*L*-lactide) implant incorporating tetracycline, ibuprofen and the combination of both drugs has shown a sustained release over a period of 6 months, enhancing the integration of tissue.[291] Norowski *et al.* applied chitosan coatings to titanium implants to locally deliver antimicrobials for up to 7 days.[292] To further improve the implant properties and ossteointegration, Shim *et al.* developed titanium discs with anodised surface for controlled release of fibroblast growth factor-2 loaded poly-(lactide-*co*-glycolide) nanoparticles. The releasing performance was extended over 2 weeks, enhancing the regeneration of bone tissues.[293] Furthermore, Battarai *et al.* examined the feasibility of chitosan-gold nanoparticles conjugated with plasmid DNA/c-myb (Ch-GNPs/c-myb)-coated Ti implants and revealed an increase of newly formed bone volume and bone mineral density in the mandibles of Sprague Dawley rats.[294]

Studies involving successful gene delivery from TNTs-modified dental implants have demonstrated that molecules such as c-myb transcription factor can promote tissue regeneration to speed up the healing.[295] It has been demonstrated that the restoration and regeneration of damaged periodontium can be complicated as a result of the complexity in the composite tissue structure, which involves alveolar bone, periodontal ligament (PDL) and tooth cement. Furthermore, the healing of carious lesions infecting tooth pulp involves the repair of multiple cells such as neurons, odontoblasts, vascular cells and fibroblasts.[296,297] As for this, the regenerative potential of progenitor/stem cells along with various growth factors, signalling cues and proteins form the basis of ultimate regeneration of tooth as an organ.[298-301] Controlled release of these bioactive factors can locally regulate related processes such as cell chemotaxis, attachment, proliferation, differentiation and morphogenesis.[269] Tissue engineering coupled with controlled release of bioactive factors involves administering signalling molecules that belong to the transforming growth factor-ß (TGF-ß), fibroblast growth factor (FGF), Hedgehog and Wnt families, which is another aspect of the application of drug-releasing implants in dentistry.[302] Within the reparative process, stem cell fates may be influenced by the incorporation of multifaceted release technologies that offer physiological levels of growth factors, mimicking the natural wound healing cascade in a specific spatiotemporal mode. A wide range of biomaterials such as polymeric hydrogels, porous scaffolds, nanofibres and microparticles have been explored in DOC regeneration. For instance, some matrices used in PDGF delivery are self-assembled nanofibres, chitosan-poly(*L*-lactide), PLLA composite matrices, porous chondroitin-4-sulfate-chitosan sponge, ethylene vinyl acetate copolymer (EVAc)-coated stainless steel Kirschner wire (K-wire) and PLGA microspheres.[269]

In short, these studies demonstrate that nanotechnology can provide outstanding alternatives to develop more efficient and rational clinical treatments for dental diseases, with very promising results for real clinical applications.

3.4. Brain tumours

Advances in surgical techniques and radiation therapy delivery have made it possible to treat brain tumours in a more efficient manner. However, given the complexity of brain, more efficient approaches must be developed in order to treat the broad range of brain-related diseases. Among these, malignant glioma is the most widespread type of brain tumour in adults, which still reports a very poor median survival. Therefore, alternative therapies are urgently needed to treat this disease in a more efficient and effective manner. Traditionally, this disease is treated by a combination of surgical resection, radiation therapy and systemic chemotherapy. While recent progresses in surgery and radiation have enhanced the treatment of brain tumours, systemic chemotherapy still has inherent drawbacks such as toxicity, short half-life of therapeutics in the body and limitations in traversing the blood-brain barrier (BBB). These factors significantly limit the clinical effectiveness of therapeutics used in systemic treatments.

A localised chemotherapy is desirable to treat malignant glioma as this disease is often locally recurrent. In that regard, Gliadel® wafers, which are polymer-based drug-releasing implants, have demonstrated outstanding capabilities to carry

out localised delivery of chemotherapeutics over malignant glioma (**Figs. 13c and d**). To date, Gliadel® implants have been used to treat more than a hundred thousand patients across USA and Europe. Typically, Gliadel® wafers are implanted on the surface of the resected tumour beds. These wafers contain an anticancer drug, carmustine, which can be constantly released from them in the course of 2 to 3 weeks after implantation. Clinical trials have demonstrated that these drug-releasing wafers can enhance current clinical therapies for treating malignant glioma.[59,133,303] Nevertheless, these drug-releasing implants present some inherent limitations as well (*e.g.* invasive surgery is required for their insertion, burst and uncontrollable drug release, large amount of degraded polymer is released at the implantation site, *etc.*).

To address these limitations, other drug-releasing implants based on nanotechnological approaches can provide alternative ways to release neurological therapeutics to the brain. For example, López *et al.* developed an implant based on nanostructured titania combined with bioceramic. The implant was fabricated in the form of titania xerogels loaded with an antiepileptic model drug (*i.e.* valporic acid). This system was aimed at overcoming the conventional systemic administration pathway hindered by the BBB. This device was implanted in the temporal lobe of rats to achieve localised and sustained drug release to treat epileptic seizures. *In vivo* biocompatibility of that titania xerogel was proved by groups of ten rats: one control group without implantation (rats that demonstrated seizures), one group with only titania without drugs and lastly, another group with the nanostructured titania/bioceramic xerogel loaded with drugs. Upon a year of implantation, the outcome showed that the implant was neither dispersed nor degraded. There was no observable neuronal damage in the rats and microglial cells were able to access the nanostructured implant. Rats showed perfectly normal behaviour with the implant intact for 15 months. This confirmed the biocompatibility of that device with the brain tissue, which proves the viability of its safe implantation in the brain and its effectiveness for treating epilepsy.[133]

Recently, our group reported on a new alternative to conventional localised treatment of brain-related diseases.[304] This drug-releasing implant was produced by anodising thin titanium wires to obtain TNTs layers on their surface for drug-releasing applications. Drug loading and release characteristics of this system were assessed by two model drugs, which are commonly used in brain therapy (*i.e.* dopamine, a neurotransmitter agent; and doxorubicin, an anticancer drug). The obtained *in vitro* results showed that titanium wires featuring TNTs coatings can load a considerable amount of drugs (up to 1000 μg) and provide a sustained release of them (from 1 to several weeks) and thus feasibility for their use as drug-releasing implants for localised treatment of brain-related diseases.

More recently, Rahman *et al.* developed a polymer-based drug-releasing system for intracavity treatments to target microdeposits of cancer cells in brain parenchyma beyond the resected cavity.[305] This system consists of PLGA/PEG microparticle matrices moulded by an *ex vivo* brain pseudoresection cavity. *In vitro* toxicity of this system was assessed by tumour and endothelial cells. Furthermore, they studied the *in vitro* drug-releasing performance for trichostatin A, etoposide and methotrexate. No toxicity was observed after tumour or endothelial cells were grown on control matrices through *in vitro* experiments. Trichostatin A, etoposide and methotrexate were released from these matrices in the course of 3-4 weeks. Moreover, etoposide released over 3 days was assessed by *in vivo* experiments, revealing that the released agent retained its cytotoxic capabilities. This system was demonstrated to be non-toxic, suggesting good biocompatibility for *in vivo* applications.

4. Conclusions and future perspectives

This review has summarised the recent advances in the field of drug-releasing implants based on micro and nanotechnology approaches. The different micro and nanomaterials and nanoengineering technologies used to develop these implants, their advantages, inherent drawbacks and clinical applications have been presented in detail. The combination of micro and nanomaterials with implants has endowed these clinical devices with up-to-the-minute capabilities such as controlled and localised drug-releasing performance, enhanced biocompatibility and improved integration into the host body. These have propelled the applicability of drug-releasing implants towards more sophisticated clinical applications (*e.g.* cancer treatments, replacement of bones, cardiac diseases, ocular diseases, mental and hormonal disorders, brain tumours, *etc.*), where innovative approaches are urgently needed to overcome inherent drawbacks of traditional therapies.

So far, a broad range of preclinical trials with model animals and clinical patients have been carried out. The obtained results are very promising and, in many cases, drug-releasing implants provide better capabilities and performances than conventional therapies, offering alternative ways to deliver therapeutics effectively over different parts of the host body and reducing the side effects associated with excessive dosages of highly toxic drugs. Nevertheless, in spite of the successes described in the studies mentioned throughout this review, more exhaustive fundamental research must be carried out in order to make drug-releasing implants feasible for real clinical applications. To this end, many technical and commercial challenges should be addressed by drug-releasing implant technology. For instance, one of the main objectives of any localised drug delivery therapy is to deliver drugs selectively to specific types of tissue, ensuring that healthy ones remain spared.

Another challenge to be addressed by implantable drug-releasing technology is the 'on demand' drug delivery capability, which requires drug-releasing implants to have automated decision-making ability and fully developed autonomy to deliver suitable dosages of drug over affected areas of the host body at opportune time, according to the corresponding therapy and clinical criteria. New concepts of 'intelligent' drug-releasing implants have been developed. These are composed of drug reservoirs equipped with switchable gates, which are controlled by actuators connected with sensors that monitor levels of indicators or biomarkers in the host body. In that way, sensors can activate or deactivate the release of drug from these reservoirs when necessary (*e.g.* when the levels of drug are above or below the therapeutic window), enabling the implementation of fully autonomous and personalised clinical therapies for a broad range of treatments and patients. Basic prototypes of 'on demand' systems have been mentioned throughout this review and some of them have been clinically tested for the treatment of diabetes by measuring the changing levels of glucose *in situ*. Nevertheless, as emphasised previously, more in-depth fundamental research is required before this technology becomes feasible for real clinical applications. These studies, essentially, are an important step towards developing highly sophisticated and

versatile drug-releasing implants. Finally, it is worth stressing that the synergistic combination of these devices and localised drug-releasing systems with other traditional treatments such as surgery, radiation and systemic chemotherapy could provide more robust and efficient clinical therapies for treating the most challenging and resilient diseases such as cancer with minimal drawbacks.

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Polymer	Drug	Clinical Disease	References
P(SA-RA)	Paclitaxel	Antineoplastic agents	42
PLGA	Leuprolide Acetate	Cancer (prostate and breast) Uterine fibroids Endometriosis Alzheimer	45
PMMA	Mitomycin Adriamycin Cisplatin	Malignant brain tumours Osteosarcoma	61 62
PCPP-SA	Carmustine	Recurrent malignant glioma	63 66
PLA	Nimustine Chloride 5-Fluorouracil	Non-resectable or recurrent glioblastoma Hepatomas	64 65
EVAc PLA	Adriamycin Cisplatin	Mammary carcinoma Osteosarcoma	67 62
PHBA PHIVA PHICA PLA	LH-RH Agonist	Prostate tumour	63
PFAD-SA	Cisplatin	Squamous cell carcinoma	64

Implant	Drugs/cell culture	Application	References
Titanium implant with TNTs coating	None	Artifical joint replacement prostheses	108
TNTs on Ti chips	d-α-tocopheryl polyethylene glycol 1000 (TPGS) Pluronic F127 PEO_{260}–PPO_{400}–PEO_{260} 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy (polyethylene glycol)-5000 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy (polyethylene glycol)-2000]	Design of porous therapeutic implants for an extended elution time of poorly water soluble drugs using polymer micelles as drug nanocarriers	116
TNTs on Ti chips	Indomethacin BMPs Human osteoblastic cells adhesion and proliferation	Orthopaedic applications and bone therapies (*e.g.* infections, local delivery of anabolic agents for bone repair, antiresorptive agents, bone cancer, osteomyelitis, etc.).	118
Sequential-step prepared biocompatible TNTs films	Dexamethasone	Design of anticoagulants, analgesics and antibiotics drug-releasing TNTs implants to prevent inflammatory reactions	131
TNTs on chips	Penicillin/streptomycin Dexamethasone	Prolonged drug delivery in orthopaedic implants to prevent infection, inflammation and to promote osseointegration	115
TNTs on Ti and Ti6Al4V alloy	Bone cells	Long-term bone implant	112
TNTs on Ti chips featuring various topologies	Marrow stromal cells (MSCs)	Antibacterial adhesion for controlled, guided, and rapid wound healing, prevent acute or chronic inflammation/infection or fibrosis	113
Annealed TNTs on Ti chips	-	Biomimetic carbonated hydroxyapatite (CHA)	132
Titania bioceramic implants	Anti-epileptic drug	Treatment for epileptic seizures	133

Hybrid Material	Features	References
CNTs-based hydrogel	Electric-responsive system Reduced burst release	172,173,174,177,178,179
CNTs-based nanofibre	Electric-responsive system Efficient drug release	175,176
GO-based hydrogel	Temperature-responsive pH-responsive	181,182,183,184,185
GO-based film	Sequential biomolecular release	186

Drug-releasing implants: Current progress, challenges and perspectives

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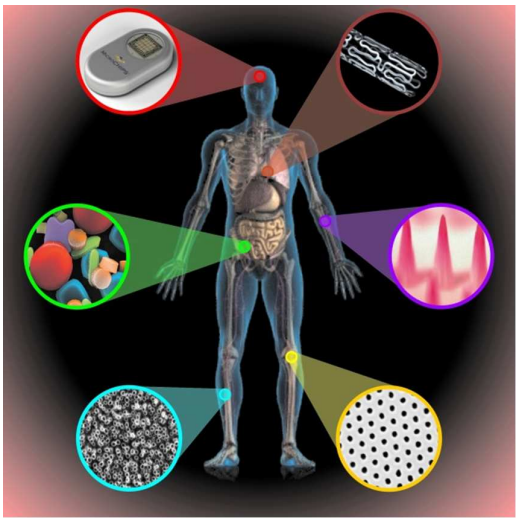

This review presents the different types and concepts of drug-releasing implants using new nanomaterials and nanotechnology-based devices