Drug-eluting non-vascular stents for localised drug targeting in obstructive gastrointestinal cancers

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ABSTRACT

Stents are currently the primary choice for the treatment of both vascular and non-vascular occlusions and/or stenosis. Despite the proven history of clinical safety and efficacy, the benefit of traditional vascular or non-vascular stenting is often limited by in-stent restenosis, resulting in failure of existing stent or reintervention by use of another stent. Coronary drug-eluting stents (DESs) significantly reduce restenosis of vascular stents and have revolutionised the percutaneous coronary intervention (PCI) treatment in coronary stenting patients. Following the similar concept of coronary DESs, non-vascular DESs are being investigated to reduce non-vascular restenosis caused by tumour growth, enhance stenting functions, and increase their effectiveness in the treatment of obstructive gastrointestinal (GI) cancers. This article summarises and updates the outcomes of pre-clinical and clinical studies on non-vascular DESs for localised management of malignant GI obstructions with emphasis on fabrication techniques and regulatory requirements relevant to development and marketing approval.

1. Introduction

The patient population of cancer varies greatly and their disease presentations involve multiple to complex symptoms because of various underlying pathophysiology [11]. Gastrointestinal (GI) cancer is a phrase often referred to include a group of different cancers, namely oesophageal, stomach (gastric), liver, pancreatic, gallbladder, bile duct, small intestine, appendix, colon, rectal, and anal cancers, all of which affect the human body’s digestive system. Presently, GI cancer appears as the most frequently observed form of cancer among all cancers by different body locations or systems [12,13]. An estimated 186,080 and 141,950 new GI cancer cases are expected to be diagnosed in the United States (US) during the year 2019 among males and females, respectively [14]. Many of the GI cancers can cause a partial or complete obstruction anywhere along the GI tract (GIT), but most commonly in the oesophagus, gastroduodenum, pancreas, hepatobiliary tract, and colorectum.

When a GI cancer patient develops an obstruction in the GIT, food and fluids cannot normally pass through the alimentary system, and intestinal natural bowel peristaltic movement that facilitates the passage of food and fluids towards the end part of the body causes intense acute pain. This is a serious condition and can be life-threatening to patients with advanced GI cancers [15]. Depending on the extent of the obstruction (partial or complete), GI cancer patients encounter difficulty ingesting meals and require urgent intervention to restore or improve their GI luminal patency as well as digestive functions [16]. Unfortunately, the majority of these patients are diagnosed in advanced cancer stages, when palliative care remains the only treatment option. In these medical emergencies, stent implantation is done clinically for the management of acute GI obstruction in patients with GI cancers, mainly as a palliative treatment of unresectable malignant GI strictures and as a bridge until elective GI surgery [16–21]. A successful stent placement allows the necessary time required for resuscitation, correction or improvement of significant medical comorbidities, assessing synchronous lesions (tumour staging), and relevant preparation of the GIT. The GI tumour is then operated on an elective basis; thus, patients with malignant GI obstruction can safely await for elective surgery without undergoing emergency surgery and can theoretically decrease the risk of surgery related complications and death [17,19,20].

1.1. Conventional treatment for GI cancers

Most commonly, there are four standard treatment approaches being currently employed for the therapeutic management of GI cancers: (a) surgery, (b) chemotherapy, (c) radiation therapy, and (d) targeted (or molecularly targeted) therapy [22]. Typically a
A combination of two or three of these treatment approaches is clinically applied with a view to completely eradicating the cancerous cells and minimising the chance of cancer recurrence. The selection of the treatment approach depends on the specific type, location, and stage of GI cancer at diagnosis, the patient's age, overall health status, and tolerance and response to the prescribed therapy [22–24]. The survival rates for GI cancers, as like any other cancer, vary dramatically according to the GI cancer type and stage at the time of diagnosis. For example, localised colorectal cancers (CRCs) are almost always curable (5-year survival rate is remarkably high as high as 90.0%), while localised liver & intrahepatic bile duct cancers are more difficult to treat effectively and tend to show a poor progress outlook (5-year survival rate is only 31.0%). Therefore, timely diagnosis and selection of appropriate treatment regimen are very crucial in order to achieve maximum objective clinical response and overall survival in patients with GI cancers [14,25].

For many years and still today, surgical removal of the primary tumour and/or nearby lymph nodes is the most common treatment for all early (localised) and intermediate stages of GI cancers with loco-regional lymphatic spread. Unfortunately, after surgical intervention, loco-regional recurrence rates are shown to be significantly high in some types of GI cancers (e.g., colon cancer with a recurrence rate of 11.0%) [23,26]. The molecularly targeted therapies, such as humanised monoclonal antibodies (MoAbs) and anti-angiogenic tyrosine kinase inhibitors (TKIs) are associated with the superior conception of the molecular biology and genetics and provide new strategies against the progression, invasion, and metastasis of GI cancers that are related to multidrug resistance (MDR) [27,28]. Despite these advances in the selective targeted therapies, in addition to curative surgery, the current mainstay of treatment for GI cancers remains chemotherapy, either for primary curative or palliative intent.

Chemotherapy is recommended mainly for intermediate- and late-stage GI cancers and can be used prior to surgery (neoadjuvant therapy) or after surgery (adjuvant therapy), with or without radiotherapy, instead of surgical treatment when the tumour is inoperable [22–24,26]. The use of chemotherapeutic agents has added an important milestone over the last several decades in decreasing GI cancer mortality and morbidity, and in increasing the overall quality of life among GI cancer patients worldwide [29]. However, administration of systemic chemotherapeutic agents, either single or in combination, may cause potential unacceptable side effects and/or dose-limiting toxicities to healthy tissues due to non-specific delivery and distribution of cytotoxic drugs throughout the whole body [23,29]. In contrast, radiation therapy can be very effective to treat early-stage GI cancers and is used as an alternative to surgical resection in late-stage and/or inoperable GI cancer patients, although it is technically challenging and normally associated with a reduced 5-year survival rate compared to surgery [23]. Furthermore, candidates for palliative by-pass surgery or conventional chemoradiation therapy usually need to be in good general physical health, which is the limiting factor for many GI cancer patients [30,31].

1.2. Vascular and non-vascular stents

Stents are mechanical devices that are designed as cylinder-like hollow structures and used to keep the human body passageway open. Stenting is the insertion or placement of stent devices into the lumen of hollow organs, anatomical vessels or ducts in the body for providing mural support and prevent further obstruction and/or stenosis of the stented organ. Stents have shown versatile medical applications in a wide variety of clinical emergencies since their inception by Charles Theodore Dotter in the 1960s in the US [32,33]. Based on the target organ, stents are generally classified into two broad groups: vascular stent (also known as an intravascular or endovascular stent) and non-vascular stent (Fig. 1) [34,35]. Initially, stents were utilised only for vascular purposes and their use has been gradually expanding substantially into non-vascular applications. This has been largely linked to the availability of new materials allowing novel stent designs, and more widespread and advanced stent deployment and retrieval techniques [21,33].

Vascular stents are mainly used to remove stenosis or occlusion in different vascular beds (blood vessels) like intracranial, carotid, coronary, renal, iliac, femoral, popliteal, and tibial arteries (Fig. 2) [34,36]. Today, vascular stents represent the gold standard for treatment in coronary artery disease (CAD) and provide the best therapeutic outcomes [10,34,37]. In contrast, non-vascular stents are intended primarily for clearing blockage in the non-vascular organs or body structures, such as trachea and bronchi, oesophagus, biliary tree, colon, and urinary tract (Fig. 2). [34,36]. On the basis of application areas, non-vascular stents can be divided into three major categories: pulmonary or airway bypass or tracheobronchial stents, GI stents which include oesophageal, duodenal, biliary, pancreatic and colonic stents, and urinary tract stents which include ureteral, prostate and urethral stents [33,34,36,38]. Among different non-vascular stents, GI stents currently represent the largest share of the global non-vascular stents market and are indicated for a variety of benign and malignant strictures and obstructions in various parts of the digestive tract [10,31]. While in a variety of settings, non-vascular stent placement and deployment techniques have been reported with high technical and clinical successes, it is now routinely used as the first-line therapeutic approach for GI lesions.

![Fig. 1. Stent examples. (A) Vascular stent (FACILE self-expanding peripheral vascular stent, amg International GmbH, Germany); adapted from [7] with permission, and (B) Non-vascular stents (kindly provided by Taewoong Medical, South Korea); from left to right: Niti-S™ S oesophageal stent (partially covered, bare at both ends), Niti-S™ S oesophageal stent (fully covered), Niti-S™ D pyloric/duodenal bare stent, Niti-S™ COMVI enteral colonic stent (partially covered, bare at both ends).](image-url)
The development of vascular restenosis in post-stent patients involves complex immunologic responses due to the endothelial injury caused by the stent implantation [6–21,30,31,34,39]. Therefore, a majority of GI stenting patients may need further reintervention by either using another stent or using other palliation therapies [18,31].

1.3. Drug-eluting stents (DESs)

The widespread success and benefit of vascular stenting and arterial manipulation are often limited by in-stent restenosis (ISR) problems, which appear in 10.0% to 40.0% of coronary-stented patients [40,41]. The development of vascular restenosis in post-stent patients involves mainly the formation of neointimal hyperplasia, resulting from a complex immune response due to vascular endothelial injury caused by the stent implantation [6–21,30,31,34,39]. Therefore, a majority of GI stenting patients may need further reintervention by either using another stent or using other palliative therapies [18,31].

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1.4. Market dynamics and projection of DESs

Coronary DESs currently dominate the global coronary stents market, as they are being used in millions of CAD patients all over the world. In the USA, every year an estimated 80.0% of all PCIs performed involve the use of DESs [2,9]. The FDA approved the first intracoronary stent, the Palmaz-Schatz™ stent (Johnson & Johnson Interventional Systems Co., Warren, NJ, USA), for the treatment of CAD in the USA in August 1994 [45,46]. Within a span of barely ten years, the first two coronary DESs, the Cypher™ sirolimus-eluting stent (Cordis Corporation, Miami Lakes, FL, USA) and the Taxus™ paclitaxel-eluting stent (Boston Scientific, Marlborough, MA, USA) followed with FDA approval in April 2003 and in March 2004, respectively [2,47,48]. The introduction of the first DESs marked a major breakthrough, leading the way of preclinical and clinical research resulting in FDA approval of several novel coronary DESs to treat patients with more complex CADs (e.g., multiple-vessel disease or bifurcation lesions) [34,46]. Currently, DESs dominate the global multibillion-dollar market of coronary stents, constituting around 90.0% of the total revenues [9,49].

According to “GlobalData November 2014” report, the estimated cumulative sales of coronary DESs and bare-metal coronary stents across the 10 major markets around the world were US$4.89 billion in 2013 and are expected to rise to US$6.22 billion by 2020 (Fig. 3). Furthermore, as mentioned in the same report, the global sales of coronary DESs are projected to be almost eight times more than that of bare-metal coronary stents, during the forecast period of 2011 to 2020 [9]. This considerable growing interest in the development of drug-eluting combination devices (i.e., DESs) is mainly due to the higher success rate (about 1 in 6) and shorter time (four to eight years) and lower cost (approximately US$250 million) involved in their product development and commercialization processes compared to new molecular entities (NMEs; low success rate, an average time of 14.2 years, and total cost...
per NME of US 802 million in 2000 dollars) [3,49,50]. The interest is also partly due to the reason that most active drug substances which are considered for incorporation into drug-stent combination products, have already received regulatory approval, although they may have or have not yet been registered in the setting of a DES [41,49]. Moreover, the increasing clarity of the regulatory requirements and improved support from the regulatory agencies have also contributed to address the complexities and challenges involved with DESs and make a substantial growth of the drug-stent combination products market [2,34].

On the other hand, the non-vascular stents market has reached a value of US$488.6 million in 2013 in the same 10 global markets and is projected to reach US$694.9 million by 2021 (Fig. 3). However, only a single non-vascular DES (PROPEL™ sinus implant, Intersect ENT Inc., CA, USA) has been commercially available to date [34]. While significant research is focused on overcoming the existing challenges involved with coronary DESs, not many studies have been conducted to improve and develop DESs for non-vascular applications [34,36].

2. Regulatory landscape for DESs

2.1. Regulatory basis

It is well accepted that all medical devices and drug substances pose some degree of clinical risk, as every year approximately six to eight medical devices and one to two drug substances are withdrawn from the US commercial market due to safety related issues [5]. Like any other products, the regulatory requirements for DESs form the basis of ensuring common therapeutic goals of clinical quality, safety, and efficacy (performance). While drug substances are incorporated as an integral part in a DES and function to enhance the device performance, drugs and stent devices differ in their primary intended purposes and also their primary modes of action. The addition of ancillary drug substances into a bare stent exhibits properties that are usually uncharacteristic for either drugs or stents alone, depending on the information known about the drug substances and stent platform [41]. Although it has been established that the total amount of drug substances contained in a DES is significantly lower than used clinically in systemic therapies, evaluation of the safety and clinical risk-benefit profiles of drugs in the context of DESs are complex because the influence of drugs and stent cannot be differentiated easily in case of overlapping adverse events [2,41]. It is undoubtedly true from a technical standpoint that expertise in medical device understanding is qualitatively different from that of drug substances [41]. As a consequence, development and selection of appropriate test methods to assess very small amounts of drugs incorporated into DESs require innovation from experts with an adequate understanding in both areas [2]. Therefore, with the high technical and clinical success, DESs present numerous challenges to manufacturers as well as regulatory authorities in evaluating their clinical safety and performance and cannot solely rely on conventional procedures used to assess the stent and drugs alone [2,41].

Performing regulatory assessments and determining whether a DES is appropriate for marketing approval is always difficult and needs a rigorous balance between its safety and efficacy profiles. Nevertheless, the clinical safety aspects should always be weighted over the harm that might be caused by withholding the benefits of DESs from patients. Being a pioneer in the field of stenting, all currently available regulatory guidelines for developing DESs are based on coronary DESs and there is no established regulatory framework-recommended only for non-vascular DESs. There are also marked differences in the regulatory systems across regulatory authorities in different countries with well-organised health-care systems, such as the FDA (USA), Therapeutic Products Directorate (Canada), European Medicines Agency and European Commission (European Union (EU)), and Therapeutic Goods Administration (Australia). These differences usually have a great impact on the total time and cost investment required to gain marketing approval of DESs from different regulatory bodies in different countries [51]. However, this section briefly reviews the regulatory issues related to the development and assessment processes of DESs following the US FDA guidance and recommendations on the content of DESs.

2.2. US FDA perspective

The FDA regulates a wide variety of drugs and medical devices that are available in the US market. The development and regulatory assessment of DESs involves regular interactions between the device manufacturer (or sponsor) and the FDA counterparts (Fig. 4). The specific details of the preclinical and clinical study requirements and designs needed to support the marketing application of a DES are supposed to be discussed during the product development stage, in fact [2,6]. The FDA approval and post-approval surveillance requirements for DESs can be different for different target organs [6,34]. Currently regulation of all drugs and medical devices is under the scope and jurisdiction of the US Federal Government and managed through three major centres within the FDA: Center for Drug Evaluation and Research (CDER) for regulating drugs and biopharmaceuticals; Center for Devices and Radiological Health (CDRH) for regulating medical devices; and Center for Biologies Evaluation and Research (CBER) for regulating biological products [1,5]. Some products like DESs do not fit completely into either of the categories of drug or medical device, but instead, they fall under the FDA’s classification of combination products. The FDA’s Office of Combination Products (OCP) is responsible to classify each new combination product (as either a drug or a medical device or a biological) based on a determination of each product’s PMOA. Once the PMOA of a new combination product has been determined, it is then assigned to one the most relevant FDA’s centres (CDER, CDRH or CBER) as a primary regulatory centre by the OCP for conducting premarket review and approval processes [5]. Hence, the primary responsibility

![Fig. 4. FDA approval process of drug-stent combination products in the United States [1-6]. IDE, Investigational device exemption; IRB, Institutional review board; PMA, Premarket approval.](image-url)
for premarket review and regulation of DES devices resides with the FDA/CDRH, in substantial coordination with the FDA/CDER [6]. To date, there are numerous FDA-approved vascular DESs available worldwide, while in the non-vascular category there is only one DES that has been approved by the FDA since August 2011, PROPEL™ sinus implant (Intersect ENT Inc., CA, USA) (Table 1) [34,52,53]. Although regulatory requirements are likely to be more stringent in case of non-vascular DESs, reviewing the FDA regulation on coronary DESs and the PROPEL™ sinus DES can give a fair idea about the current regulatory obligations that are pertinent to the development and approval of non-vascular DESs for the commercial market.

2.2.1. Drug and drug-eluting coating

The application of drug substance(s) and polymer coating or carrier material(s) to a bare stent platform may adversely affect the biocompatibility and performance characteristics (e.g., corrosion fatigue properties, surface coating composition, integrity and durability, etc.) of the complex DES system [41]. The physical, chemical and mechanical attributes of the drug and the drug-loaded polymer coating or carrier system are critical for finished DES placement, biocompatibility, and stability. Therefore, development and regulatory assessment of new or generational DES requires a thorough biocompatibility testing and characterisation of all of the relevant product-specific components (e.g., drug substance, polymer coating/carrier material, and stent platform) [6]. For DESs that come into the direct human body (tissue) contact and indirect contact with circulating blood (such as non-vascular DESs), the biocompatibility evaluation typically includes cytotoxicity and haemolysis testing without requiring complement activation or thrombogenicity test, as generally required for direct blood-contacting vascular DESs [54]. Both the drug substance and the finished DES are supposed to have undergone evaluation in regards to their chemistry, manufacturing and controls (CMC) aspects, which include physicochemical identification and characterisation, content and dose uniformity, in vitro drug release testing, impurities/degradation products/residual solvents determination, sterility/packaging integrity testing, and particle counts and bacterial endotoxin detection [6,34]. In the context of CMC evaluation, the physicochemical tests required to be performed involve morphology, composition, thickness and uniformity, and erodability of the polymer coating/carrier system [6]. If the DES contains biodegradable polymer coating/carrier system, additional tests need to be carried out to characterise both the in vitro and in vivo degradation profiles, the trend/pattern of particulate matter generation, and the effects of sterilisation process on integrity and stability of the biodegradable polymer(s) [6,34]. The stability of the drug substance itself and polymer coating/carrier system is also very crucial and requires to be ensured/maintained throughout the shelf-life of the DES product. In general, stability tests involving the assessment of DESs include appearance, total drug content assay and dose uniformity, total and individual impurities, in vitro drug release, particulate matter, endotoxin, and sterility [6,34,55].

2.2.2. Application and approval process

The medical device evaluation process by the FDA has become more intricate since the last decade of the 20th century, requiring more detailed information about the possible risks and benefits associated with new devices [5]. Essentially, there are two pathways required to be followed for obtaining FDA approval (clearance) of new medical devices before marketing in the US: the 510(k) premarket notification submission and the premarket approval (PMA) application. The selection of submission type between these two FDA premarket review processes is determined by the CDRH based on the classification of each medical device.

2.2.2.1. Product classification aspects. According to the Federal Medical Device Amendment of the Food, Drug, and Cosmetic Act (FDCA) of 1976, the FDA classifies all medical devices (that include existing
devices introduced in the US market after 28 May 1976 and also future devices) into three categories, considering the extent of risk they pose to respective patients and/or users [1,5]. Medical devices which already existed in the US market before 28 May 1976 are classified as grandfather devices and do not require any retrospective FDA review to demonstrate their safety and/or efficacy for commercial marketing [5]. These previously cleared grandfather devices are called predicate devices that serve as a standard of comparison for FDA premarket review of all new devices brought to the US market after 28 May 1976. Overall, the FDA has different standards of regulatory control to different classes of medical devices and generally the FDA requirements for premarket scrutiny increase with the increase of the risk of devices to patients and/or users [1,5].

However, class I medical device is the simplest device with the lowest level of risk and subject to the least FDA premarket oversight and regulation (general controls), e.g., band-aids, oxygen masks, tongue depressors, etc. [1,5,34]. Most class I medical devices are exempt from submitting the formal 510(k) premarket notification application, and some of them are also exempted from complying with the requirements of Quality System Regulations (QSRs) [1]. Class II medical devices pose a greater risk than class I medical devices and require both general and special FDA controls. Most class II medical devices are approved for sale in the US using the traditional 501(k) premarket notification submission, a process requiring demonstration of substantial equivalency of safety and efficacy of a new device with a pre-existing (previously cleared) predicate device [1,5]. True clinical trial testings to illustrate safety and efficacy are not required for a vast majority of medical devices that undergo the 510(k) notification submission, and therefore devices evaluated through the 510(k) premarket notification process are described to be FDA-cleared, but not FDA-approved [5]. Examples of class II devices include home pregnancy test kits, surgical lasers, ultrasound imaging systems, etc. On the other hand, class III medical devices are generally considered as significant risk-bearing products intended to support or sustain human life by preventing health impairment and are subject to the highest level of FDA controls to meet strictest clinical testing standards. These are usually technologically novel devices and examples of class III medical devices include DESs, heart valves, pacemakers, etc. [1,5]. Most class III medical devices must typically require a PMA application submission and approval for commercial marketing in the US. A device that has been PMA-approved is not a substantially equivalent predicate device to any of the class II devices and cannot be used for supporting a 510(k) premarket notification submission [1]. All new devices that do not demonstrate substantial equivalence to any already marketed predicate device automatically fall into the class III category [5]. However, a device manufacturer or sponsor can submit a formal request for designation (RFD) to the FDA (OCP) to reclassify the device from class III to either class I or class II, when the CDRH assigned classification remains unclear or in dispute [1,5].

2.2.2.2. PMA application. The PMA is a much more rigorous medical device evaluation process than the 510(k) premarket notification and its approval requirements are almost similar to that of a New Drug Application (NDA) relevant to new drugs and biological products. The submission of a PMA application always needs clinical testing that typically involves a much small number of subject patients [1]. Medical devices evaluated through a PMA review process are claimed to be FDA-approved [5]. The fairly complex PMA review process can be subdivided into four major steps, three of which must take place before the FDA approval: (1) pre-investigational device exemption/preclinical testing (step I), (2) investigational device exemption (IDE)/clinical testing (step II), (3) preclinical and clinical study data review-PMA application (step III), and (4) post-marketing surveillance (step IV) [1,51]. In the first step of a PMA review process, device preclinical evaluations (i.e. benchside and animal testing) and clinical study plans are discussed with the FDA (CDRH). When the extent and duration of preclinical tests and proposed clinical study becomes rationalised and settled by the device manufacturer or sponsor to the point of FDA (CDRH) acceptance, a complete IDE application is officially registered that contains device rationale, benchside and animal test results, clinical data generated outside the US (OUS), instructions for intended use of the device, and the proposed clinical test protocol. The FDA (CDRH) approval on IDE application tells about the positive results from preclinical testing of the device as well as its appropriateness for the intended clinical use and thereby permits clinical studies to be performed in support of a PMA application. After getting an IDE approval from the FDA (CDRH), the second step of the PMA process starts with recruiting clinical sites and at the same time ethical review of the proposed clinical test protocol is done by the institutional review board (IRB) for each different clinical site. As part of the PMA requirements to generate and maintain high-quality data, it is incumbent for the manufacturer or sponsor to conduct device clinical trial(s) under Good Clinical Practice (GCP) compliance. In addition, when Medicare-receiving patients are involved, approval of Centers for Medicare and Medicaid Services (CMS) is also processed before starting a clinical trial. In the next step, if clinical study shows positive outcomes, the manufacturer or sponsor prepares and submits a formal PMA application containing preclinical and OUS clinical data (same as submitted previously in support of the IDE application) accompanied with a completely analysed clinical study data to FDA (CDRH). After submission, the PMA application is assessed by an FDA (CDRH) advisory committee to make a determination on approval or rejection and specify specifics on the proposed device indications, as well as any post-approval studies (PASs) that might be needed. In the final step, after receiving approval on a PMA application, FDA surveillance inspections are carried out regularly at the device manufacturer's premise(s) to ensure compliance of the manufacturing activities with current Good Manufacturing Practice (cGMP) requirements [1,6,34,51].

3. Localised drug delivery

It has been proposed that a potential reason for the failure of investigational drugs in late-stage clinical studies or existing drugs in routine clinical practices is that the agents given orally or intravenously do not reach therapeutic concentrations at the sites of disease or injury or infection [23,24,40,56,57]. In dealing with such therapeutic issues that are often refractory to available traditional methods of drugs administration, site-specific, localised drug delivery has been commonly regarded as a useful strategy to achieve improved therapeutic advantages by increasing the therapeutic dose of the drugs at the intended (target) site of action for required periods of time. Furthermore, localised drug delivery causes a reduction in the systemic amount (dose) of drug needed to produce the same desired therapeutic response, thus minimising or reducing the risk of potential treatment-associated side effects and/or adverse events [40,57,58]. However, for cancer treatment, despite advances in the knowledge and understanding of cancer biology and drug delivery, most current chemotherapeutic drugs, single or combination, frequently suffer from low efficacy in producing the expected clinical outcomes. This is usually due to the development of MDR and suboptimal drug availability within or adjacent to the tumour tissues [24,28,56,59].

Given that systemic chemotherapy treatments are not directly targeted to the tumour cells, they often require administration of high or increasing systemic doses of anticancer drugs to achieve and maintain therapeutic concentrations locally in the immediate tumour micro-environments. In addition, in systemic chemotherapy strategies significant amounts of cytotoxic anticancer drugs (mostly having narrow therapeutic windows) are frequently seen to accumulate in non-cancerous healthy tissues, leading to potential unacceptable side effects as well as dose-limiting toxicities. Therefore, conventional chemotherapeutic strategies still pose significant limitations with regard to
mortality/morbidity, systemic toxicity, loco-regional tumour recurrence rates, and other treatment outcome measures for most cancers [23,24,56,60]. In contrast, localised application of chemotherapeutic drugs directly to the sites of malignancy has been advocated in literature as a means of maximising drug efficacy locally while minimising or reducing the risk of systemic and non-target organ toxicity using lower drug doses.

Compared to conventional systemic chemotherapy, locally controlled and/or prolonged delivery of cytotoxic anticancer drugs is more likely to ensure adequate drug diffusion, distribution, and uptake into the surrounding cancer cells over multiple cycles of tumour cell division that leads to better control on the tumour cells replication and subsequent spread. Although there is a clinical bias that localised chemotherapy has low utility for systemic malignancies, there are critical intervention points in every stage of cancer progression where local delivery of anticancer drugs, either for primary curative or palliative reason, could enhance or supplement or even replace the existing treatment options [23,60].

To date, there have been extensive research efforts to develop local drug delivery systems (LDDSs) by utilising a wide variety of delivery vehicles as presented in the literature [23,40,42,43,57,60]. Among these efforts, stent-based drug release (i.e. DESs) has received growing interest from both medical device and drug manufacturers as a promising platform for localised controlled delivery of therapeutic drugs. Although the clinical introduction of (bare) stents in 1977 was a major breakthrough in the treatment of CAD and currently their use has expanded significantly with high clinical success rates, the widespread benefit of PCI has always been limited by restenosis since their first use. In fact, the acute beneficial effect of traditional vascular stenting did not improve remarkably the incidence of restenosis [9,41,43,57]. As mentioned previously (Section 1.3) the neointimal restenotic process involves a series of immune events through thrombus production, inflammation and signal transduction, followed by intimal accumulation of smooth muscle cells (SMCs) and extracellular matrix (ECM) at the site of arterial injury. This accumulation of vascular SMCs and ECM proteins occurs locally in the arterial wall and usually remains limited within the area of vascular interventions, and has important implications in the development of restenosis [6,41,57].

In order to suppress and/or prevent the vascular restenosis following PCI, a large number of techniques involving conventional pharmaceutical drugs and novel gene therapies have been developed and applied, but most of them have generally shown disappointing clinical outcomes. Furthermore, insufficient concentrations of the drugs at the stenotic lesion sites following systemic administrations are believed to be the main reasons for poor treatment successes that have been reported from many of these efforts [40,42,43]. However, drug-eluting stenting technologies have already shown outstanding potential in overcoming or minimising the long-standing clinical problem of vascular restenosis, among the various techniques that have been developed so far. Since restenosis is principally a localised event and develops as a localised lesion, coronary DESs create the potential for maximising local elution of drug from the stent and bioavailability within local tissue, as well as limiting systemic drug absorption [2,6,34,41,43]. Ultimately, due to the great success of novel drug-stent combinations in treating ISR, many types of coronary DESs have been developed and are being used in current clinical practices [34,42,43].

However, due to the absence of anti-tumour functions, most conventional non-vascular stents frequently suffer from ISR or re-occlusion, similar to coronary stenting, caused by malignant tumour cell growth. This major drawback of conventional non-vascular stenting frequently results in shortening the life expectancy of the non-vascular stent devices and the effective duration of the treatment, and further re-intervention using another stent or other palliation therapies are often required [30,39,61–65]. Therefore, following the similar concept of coronary DESs, localised delivery of anticancer drugs via non-vascular stents has been investigated over the last decade for the treatment of GI cancers and related stenosis and/or obstructions. The development of these non-vascular DESs is guided by the aim to improve drawbacks associated with the present use of GI stenting by using anticancer drugs in combination with different types of GI stents (e.g., oesophageal, biliary, or colorectal stents). These specialised functional stents are primarily intended to deliver and distribute anticancer drugs locally at the sites of malignant GI tumours in a controlled-dosing regimen over sustained time periods. Using localised and controlled anticancer drug delivery, drug-eluting GI stents have great potential to efficiently suppress the growth of malignant GI tumours around the stents, and so achieve optimal stenting function and prolonged patency of the non-vascular stent platforms. Thus, local drug-eluting GI stents could significantly decrease the need for GI stent reinterventions and improve the overall quality of life and survival of malignant GI obstruction patients [30,61,62,64–66].

Whereas restenosis in coronary stents is considered to be a local vascular presentation of the normal biological response to vascular arterial injury, restenosis in non-vascular stents is mostly due to the development of tumours that are associated with malignant cascades of genetically complex multicellular and molecular events [30,39,57,62–65]. Furthermore, the local biology of different human body organs is uniquely different from each other, and likewise, the local cardiovascular biology differs widely from that in each part of the GIT. Although there are some similarities between all organ systems in the local tissue responses after stent insertion, the type of the reactive tissue varies with the specific region/location of the body where the stent is implanted. This regional (organ) specificity is composed of the local fluid (e.g., blood, mucus, acid, bile, or food), which normally flows continuously through the specific body region/cavity. The different physicochemical characteristics (e.g., composition, pH, temperature, viscosity, flow rate, etc.) of the organ-specific fluids can markedly affect the DES coating integrity, delivery of effective drug doses, and kinetics and duration of local drug release from the DES devices. Therefore, when developing non-vascular DES combination products, careful considerations should be given to the local environmental characteristics of each intended (target) stent implant site [34,36,43]. Conversely, poor local drug delivery from DESs can cause large amounts of drug doses available at the stenting site that may increase the risk of local toxicity while sub-therapeutic or sub-inhibitory drug doses cannot produce the desired pharmacological effect [43,67].

4. Drug-eluting GI stents

Due to a variety of malignant GI luminal strictures and obstructions, the most common sites in the GIT for non-vascular stent placement are the oesophagus, stomach (gastric) outlet, duodenum, biliary tract system, pancreas, and the colorectum (Fig. 5). There are inherent differences in the size and shape of these different anatomical parts of the GIT, and each one has a remarkably different internal environment with unique local biology. In turn, the morphological and clinical features of malignant tumours or obstructions that appear in these tubular GI organs vary widely and can profoundly affect the clinical performance of DES products [34,36]. For a DES to be optimal for each situation, selection of the stent platform requires considerations on the anatomical location, morphology, and clinical characteristics of the obstruction as well as the surrounding structure of the GI organ that need to be stented, in line with the stent platform-related design variables [36,68–70].

4.1. Anatomical and clinical considerations

4.1.1. Oesophageal malignancy and related obstructions

The adult human oesophagus is a hollow muscular tube ranging from 18 to 25 cm in length that connects the pharynx to the stomach, and topographically has three distinct regions; cervical, thoracic, and abdominal [71,72]. The oesophagus functions as a dynamic tube or
passageway to push food bolus down from the oropharynx and into the stomach in which physiological transit, digestion and absorption of food occurs [71,73]. Normally, oesophageal peristalsis propels food or other materials from the cervical oesophagus to the abdominal part through active contractions. Structurally like the other parts of the GIT, the oesophagus wall consists of four layers: (a) innermost mucosa, (b) submucosa, (c) muscularis propria, and (d) adventitia [71]. The wall of the oesophagus is internally lined with mucous membranes containing glands that secrete mucus to provide lubrication and help the passage of food [71,73]. There are two high-pressure functional zones present at the upper and lower ends of the oesophagus for preventing backflow of gastric contents from the stomach or small intestine: the upper oesophageal sphincter (UOS) and the lower oesophageal sphincter (LOS). In the endoscopic view, the normal oesophageal lumen shows as a smooth, light pink tube-like appearance with readily visible fine submucosal blood vessels [71].

Malignancies of the oesophagus are often diagnosed in advanced disease stages, with dysphagia or difficulty swallowing due to intraluminal obstruction (> 50.0%) appearing as the predominant symptom in the majority of the oesophageal cancer patients, followed by weight loss and malnutrition. The choice of stent platform for oesophageal DES needs to consider several aspects depending on the location and size of the stricture or tumour present in the oesophagus, as well as the patient’s projected prognosis [74,75]. The stent platform should be long enough to bridge the entire length of the oesophageal stricture and extend 2 to 4 cm beyond each end of the tumour or stricture to prevent the chance of subsequent tumour overgrowth at both ends of the stent. The luminal diameter of the stricture or tumour should also be considered to allow for easy passage of the pre-loaded DES introducer through the access tract of the oesophagus [33,75,76]. Mid-oesophageal strictures are considered optimal for stenting, while traditionally, tumoural obstructions located close to the UOS (proximal oesophagus) and the oesophagogastric junction (distal oesophagus) pose significant challenges for the placement of stents [75,77]. When the DES is intended for placement across the oesophagogastric junction, the effect of gastro-oesophageal acid reflux needs to be taken into consideration for obtaining optimal patency of the stent platform of oesophageal DES [75,78,79]. Usually, the stent platforms tend to fit well in strictures or tumours that allow a relatively straight alignment after insertion. The tortuosity or irregularity of malignant oesophageal strictures can pose difficulty for oesophageal drug-eluting stenting and needs particular attention [75].

4.1.2. Stomach, duodenal and hepato-pancreato-biliary malignancy and related obstructions

In the human body, the stomach is a J-shaped hollow enlargement of the GIT, located primarily in the upper left quadrant, just underneath the diaphragm, and is connected proximally to the oesophagus and distally to the duodenum (first part of the small intestine) [80,81]. Based on shape and functions, the stomach is divided into four main anatomical portions: (a) the cardia (proximal part), (b) the body (central part), (c) the antrum (distal part of the stomach body), and (d) the pylorus (distal part) [80]. The inner wall of the stomach is full of longitudinal gastric folds or rugae that allow the stomach to stretch and expand in order to easily accommodate large ingested food, as well as help to grip and move food further down to the small intestine during digestion. The stomach ends at the funnel-shaped pylorus of the stomach, which contains the pyloric sphincter that controls the flow of gastric contents out of the stomach and into the small intestine through the duodenum [81]. The duodenum begins immediately after the pyloric sphincter and wraps around the top of the pancreas. It can be classically divided into four parts: (a) the superior (first part), (b) the descending (second part), (c) the horizontal (third part), and (d) the ascending (fourth part) [80,81]. The duodenum is intimately connected with the hepato-pancreato-biliary (HPB) system organs, involving the liver, pancreas, gallbladder, and bile ducts; thus, a malignancy of any adjacent structures can cause malignant obstruction anywhere in the stomach, duodenum, or HPB organs due to intrinsic or extrinsic tumour invasion or compression [80].

Because of the closely related organ systems, tumoural strictures or obstructions appearing in the stomach, duodenum, and HPB system organs share somewhat similar clinical features. Despite the clinical similarities, selection of stents intended for these organ systems requires consideration of the anatomical location and morphology of the obstructing tumour, similarly to oesophageal DESs [68-70,82-85]. If a DES is intended for stricture in the stomach body, it may not be allowed to have a good expansion after placement and so may tend to migrate easily, and this difficulty needs to be considered beforehand [86]. For tumours present at or near the ampulla of Vater (located in the duodenal wall), a DES may not be anchored easily and can increase the chance of migration; thus, for periamppullary cancers DESs without a proximal flange may be more appropriate [83]. In addition, the tortuous stricture and curved anatomy of the distal portions of duodenum may require DESs that are more flexible [68,87]. Importantly, the stent length should be long enough to cover obstructions around the duodenal flexures or bends and that also needs to be considered for intended drug-eluting duodenal stents [68].

4.1.3. Colorectal malignancy and related obstructions

Colorectal malignancy commonly refers to cancers of the colon and rectum, both of which belong to the large intestinal part of the human digestive system and function important roles in eliminating food waste (stool) produced after digestion. Both colon and rectum are closely surrounded by organs, including the liver, spleen, pancreas, urinary bladder, and reproductive organs [88]. The colon is an inverted U-shaped organ measuring 1.5 to 1.8 m in length and ~7.6 cm in width, and is divided into four major segments: (a) the ascending (right) colon, (b) the transverse (middle) colon, (c) the descending (left) colon, and (d) the sigmoid colon [89,90]. The ascending colon is the beginning of the colon, running upward to a bend in the right colon called the hepatic flexure, where it turns as the transverse or middle colon, which then continues and ends with a sharp bend known as the splenic flexure [88]. At the splenic flexure, the transverse colon is connected with the descending colon, which travels down the left side of the colon and curves inwards to become the S-shaped sigmoid colon just before the rectum [88,89]. Both right and left sides of the colon are supported in the abdomen by long peritoneal folds of tissue called mesentery [88,91]. The normal colonic wall has a similar histological structure as the other GI organs: mucosa, submucosa, muscularis propria, and the

![Diagram: Common gastrointestinal sites of non-vascular stent placement that might be considered for drug-eluting GI stent applications. Adapted from reference [8].](image)
serosa (visceral peritoneum) [91]. After the sigmoid colon, the rectum is the last anatomical part of the large intestine that controls the flow of faecal material by thick bands of muscle (sphincters) in the anorectal canal and aids in moving faecal material further downward and to the anus [89,91].

This irregular anatomy of the human colorectum complicates the selection of stents, and colorectal DESs will require careful consideration of the location and anatomy of the obstruction and/or stenosis [16,70,84]. Patients having left-sided colonic obstruction always experience more complications than patients with a right-sided obstruction due to the relatively large amount of retained faecal material in the left colon and are identified as more suitable for colorectal drug-eluting stenting therapy [21,84]. To treat these patients, larger-diameter stents are generally recommended to prevent solid faecal impaction, as opposed to smaller diameter stents that are better suited to patients with right-sided malignant colorectal obstructions [84]. Careful consideration of the stent length is required to allow good anchorage with the colorectal wall. Insufficient stent lengths in relation to the obstruction may lead to DES migration [70,92]. If the DES is intended for use in a very angled position within the colorectum, where it might tend to straighten the curved anatomy inside and get stretched, the risk of migration and perforation of the stent may be increased [70]. For DESs, the colorectal obstruction or tumour might shrink due to treatment and that may also contribute to the migration of the stent [21,70]. If the drug-eluting colorectal stent is intended to place close (within 5 cm) to the anal verge, it may be associated with severe anal pain and incontinence, which can be contraindicated for stented patients [16,70].

4.2. Stent platform

DESs usually contain three essential components, a stent platform, a polymer coating/carrier system, and the drug substance [6,93]. Currently, the clinical manifestations of malignant GI obstruction are so common worldwide that the use of traditional GI stents is to a certain extent the commonest therapeutic option for the palliation and/or treatment in nonsurgical patients with obstructive GI cancers [10]. With the availability and application of new materials of construction and more widespread deployment techniques, considerable advances have been observed over the past two decades in the composition and design of non-vascular stent platforms and their use for a variety of malignant obstructions within the GIT, besides the improvement in clinical expertise [21,70,94]. Thus, depending on the intended organ to be stented, a vast number of GI stent platforms with varying shapes and sizes are now available commercially for clinical use, from various manufacturers, as published extensively in the literature [10,21,34,70,77,79].

Non-vascular stent platforms can be classified as either metal or polymeric stents on the basis of construction material (Fig. 6). Furthermore, depending on the basis of the expansion technique, metal stents can be subdivided into two types, self-expanding metal stents (SEMSs) and balloon expandable metal stents [33,34,36,94]. SEMSs can self-expand substantially to a predetermined dimension (length and diameter), without the need for mechanical assistance [33,34,36,95]. Based on the presence of a stent covering film or membrane, SEMS can further be divided into three subtypes, uncovered (bare), fully covered, and partially covered SEMSs (Fig. 7). Uncovered SEMSs consist of a metal mesh that is fully bare (not covered with any membrane throughout its length). Fully covered SEMSs consist of a metal mesh that is fully covered with a film or membrane throughout its length (without any exposed bare metal stent), and partially covered SEMSs contain a film or membrane covering that has a small portion of exposed bare metal mesh at either proximal or distal or both ends of the stent [21,70,75,77,94].

Balloon expandable metal stents, on the other hand, are inserted compressed onto a dilatation balloon which, by inflation, stretches the stent platform to attain its desired expanded size and shape at the target site after deployment [33,34,36,95]. The polymeric stents can also be subdivided into two broad types, biodegradable (or bioerodable) and biostable (or non-biodegradable) stents [34,42]. Like metallic stents, biodegradable polymeric stents are also available in self-expandable versions, such as PROPEL™ sinus stent (Intersect ENT Inc., CA, USA) and SX-ELLA oesophageal BD stent (ELLA-CS, s.r.o.; Hradec Kralove, Czech Republic) [34,76]. Additionally, besides biodegradable polymeric stents, there are also metal based biodegradable stents that have been developed more recently [93,96]. In a few instances, some other devices are also utilised for stenting purposes, such as the Relieva Stratus™ MicroFlow Spacer (Acclarent, Inc., Menlo Park, USA), which is a reservoir-based ethmoid stent and has been indicated for use in the treatment of inflammatory disease of the ethmoid sinus [97].

4.3. Stent materials

For insertion, drug-eluting GI stents are supposed to be delivered in a compressed form at the intended target sites within the GIT using a suitable delivery catheter system, similarly to normal vascular coronary or non-vascular GI stenting. To fulfil the desired short-term or long-term stenting functions at the intended GI site, DESs are required to be expanded in diameter up to two to four fold their initial compressed diameter upon release from the delivery catheter system [31,79,93,95,98]. Even inside the obstructed tubular body structures,
released DESs require sufficient radial strength at their full nominal expansion to withstand external pressures as well as bending and twisting (or torsional) forces [93]. Thus, DESs must be able to withstand mechanically stressful events related to their delivery and deployment. The construction material of the stent is a major determinant factor of the expected mechanical behaviour of DESs [42,93]. In addition to the mechanical properties of the core material of the stent body, the properties of the stent covering (for fully/partially covered stent platforms) or polymer coating/carrier materials also need to be considered in selecting appropriate materials and making educated stent choices for DES applications [42].

In general, materials intended for use in the development of DESs are required to have (a) adequate elasticity to allow the expansion needed for the implanted DES in a tortuous structure of the GIT, (b) sufficient tensile strength and ductility to resist the deformation of the DES upon expansion, (c) optimal relationship between their stress-strain responses, (d) deep strain-hardening (or work-hardening) rate for optimal enhancement of their stiffness during DES expansion, and (e) optimal yield stress to facilitate firm crimping of the DES onto the delivery system catheter and balancing its maximum shape recoverability against minimum compression (i.e. optimal hysteretic behaviour), as well as DES expansion at manageable pressures. These desirable mechanical properties of materials are always supposed to be matched with the requirements for achieving optimum in vivo clinical performance of the DES, including surface characteristics, biocompatibility, flexibility, shape memory, corrosion resistance, slipperiness, conformability to assist complete circumferential DES-GI lumen contact, radiopacity, magnetic resonance imaging (MRI) compatibility, and long-term stability [42,93,95,96,99]. To select the polymer coating/carrier material, its ability to control the drug release and to bond to the stent surfaces without delamination upon DES expansion and deployment must be considered in line with their mechanical and clinical attributes [6]. Unfortunately, all these different properties may not be found in a single material and are somewhat unique to each individual material (either metal or plastic), selection of which needs to be based on the intended location of stenting as well as the intended duration of DES therapy [34]. For example, super-elastic properties are necessary or advantageous for DESs intended to be placed in tortuous strictures of the GIT. Besides, the shape memory characteristic of materials is very important for compacting DES inside the delivery system catheter with their smallest possible diameter [42]. However, each material has its pros and cons, and so the selection of appropriate material for stent construction or DES coating is not a straightforward task and always needs to satisfy and balance between this multitude of requirements [93,96].

Whereas historically stents were hard polyvinyl plastic tubes, contemporary stents are usually composed of different varieties of metal alloys such as elgiloy (cobalt-chromium-nickel alloy) and nitinol (nickel-titanium alloy), stainless steel (SS, typically grade 316L), and tantalum [31,34,70,75,95]. The 316L SS [major chemical composition: iron 63 wt%, chromium (16–18) wt%, nickel (10–14) wt%, and molybdenum (2–3) wt%] is a low carbon (maximum 0.03 wt% carbon) and high molybdenum SS grade that is particularly suitable for use in the manufacture of implants. With regard to its greatly decreased risk of intergranular corrosion, 316L SS is easily deformable when fully annealed and quite readily available; however, it is a non-MRI compatible material having poor fluoroscopic visibility and high susceptibility to crevice corrosion in comparison to other implant alloy materials [21,34,95,96,100]. Furthermore, biocompatibility is an important concern with 316L SS-based implants as the elution of metal ions, such as nickel, chromium, or molybdenum from SS stents may increase local immune and inflammatory reactions resulting in the development of ISR [34,96].

Elgiloy alloy [major chemical composition: cobalt (39–41) wt%, chromium (19–21) wt%, nickel (14–16) wt%, molybdenum (6–8) wt%, silicone 1.2 wt%, and manganese (1–2) wt%] is extremely corrosion resistant, non-magnetic, and capable of producing high radial forces [79,100,101]. However, the elastic deformation of either elgiloy or 316L SS can reach up to approximately 1% strain, which is significantly different elastic deformation to that exhibited by living human tissues [42]. In contrast, nitinol is an intermetallic alloy compound (major chemical composition: nickel 55 wt% and titanium 45 wt%) that shows high radial resistive force (RRF) and possesses super-elastic (can recover up to 10.0% of elastic deformations) and shape-memory properties. These characteristic features have made nitinol the most widely used material for the construction of commercial stents as compared to 316L SS or other metal alloys [21,34,42,70,95,100,101]. However, the limitation of using nitinol is its ferromagnetic nature, which makes nitinol a poorly visible fluoroscopic material compared with elgiloy alloy. To overcome this limitation, nitinol-based stents are generally used in combination with radiopaque markers (ROMs) made from other materials e.g., gold, silver [21,34]. Tantalum is a MRI compatible material that has excellent corrosion resistance due to the highly stable surface tantalum oxide layer and offers fluoroscopic visibility and good biocompatibility. Although its fluoroscopic visibility and biocompatibility properties are superior to those of the 316L SS, tantalum has poor...
mechanical properties, which in turn makes it prone to fracture [34,96,101].

In the case of polymers, there are mainly three applications for which a broad range of polymeric materials has been investigated or utilised so far, as a component of the stent platform itself or the DES coating. Although a number of different polymers have been tested or used as vehicles for the controlled delivery of therapeutic drugs from stents, only a few of them have been tested or used for constructing the entire stent and/or for covering (fully/partially) the SEMSs to serve a range of therapeutic support [42,93,96,100]. Degradable or resorbable polymers that have been commonly researched or used for the purpose of making entirely biodegradable stents or biodegradable DES coatings are poly(lactic acid) (PLLA), poly(glycolic acid) (PGA), poly(e-caprolactone) (PCL), poly(D,L-lactic-co-glycolic acid) (PLGA), polydioxanone (PDO), and poly(D,L-lactic acid) (PDLLA) [34,42,93,96,99,100]. Both the semi-crystalline PGA and PLLA polymers have high degradation times (PGA: approximately 6–12 months, PLLA: approximately 24 months) and are suitable for DESs that are aimed to provide long-term drug release, so as to be considered as life-supporting or life-sustaining [34,99]. With the same degree of crystallinity as PGA or PLLA, PCL exhibits lower tensile mechanical strength and elastic modulus (for minimal recoil) due to its lower glass transition temperature than both PGA and PLLA [99]. While PDO is also a semi-crystalline biodegradable polymer with a lower glass transition temperature, similar to that of PCL, both PDO and PCL are preferred for moderate to short-term DES applications [70,99].

Although biodegradation is desirable for DESs containing fully bioabsorbable polymer stents or coating/carrier, there is no consensus regarding the optimal duration required to complete mechanical integrity and degradation of the bioabsorbable polymer stent platform or coating/carrier [6,93]. However, unlike coronary vascular stents, the use of biodegradable polymers for non-vascular DES purposes is still questionable, since biodegradation of the stent or DES component (e.g., stent covering polymer film, drug-releasing polymer coatings) could result in stricture recurrence, stent migration, or early stent obstruction due to malignant tumour ingrowth [42].

On the other hand, non-degradable polymeric materials that have been frequently used for making biodurable stents, stent coverings or DES coatings are silicone, polyurethane (PU), polytetrafluoroethylene (PTFE), and polyethylene terephthalate (PET) [34,42,93,96,100,102]. Among these, silicone and polysiloxanes are stable at high temperature, possess excellent biocompatibility, and exhibit good mechanical properties and low-temperature elastomeric properties. However, because covering stent platforms with silicone usually needs harsh organic solvents and curing (or vulcanisation) at high temperatures, incorporation of drugs into silicone-covered stent platforms is difficult [42]. Silicone is therefore mostly used as a drug-carrying polymer for PTFE membrane-covered stent platforms instead. In contrast to silicone, PU has been extensively used in the stenting field, both as a polymer carrier for localised delivery of drugs as well as a covering material for SEMSs. PUs are rubbery in nature with good shape-memory and have been shown to be effective with a wide range of drugs using PU-based coating formulations, due to its solubility in different organic solvents [33,42]. In stent covering applications, the medical grade aliphatic polycarbonate-based PU (Chronoflex AL, AdvanSource Biomaterials, Wilmington, USA) has been widely used in short-term and long-term drug-delivering implants or medical devices [42,103]. Nevertheless, the use of PU in stent covering is not fully convincing because of its predisposition to early biodegradation [100,104]. Expanded PTFE (e-PTFE) in turn, is a fluorinated, nonreactive microporous membrane having pore sizes from 0.02 to 40 μm. It is well-known for its excellent haemocompatibility and has been employed in a wide range of medical applications involving stents or stent coverings [16,42]. However, e-PTFE is less biodurable and was more prone to biofilm formation in comparison to both PU and silicone in a bile phantom flow study [105].

4.4. Drug component

4.4.1. General considerations

The drug component selection for the DESs essentially requires an appropriate understanding of the systemic pharmacology, toxicology, and safety of the drug substance and its major active metabolites (if any). For any DES, the safety and effectiveness is assessed mainly by the amount of prior information available about its drug component. Therefore, the initial determination of whether the DES incorporating previously approved (studied) drugs, about which much information is already available, or investigational new (unstudied) drugs, about which little or no information is available, is crucial in the design and development of the DES. If the DES is intended to incorporate previously approved or studied drugs, the pre-existing information available from the nonclinical systemic use may be considered to adequately support the preliminary safety of the drug component. In the case of using unstudied drug that does not have appropriate safety information available or has never been approved for human use, systemic non-clinical pharmacology, toxicology, and safety testing are usually required to be performed to fully understand the potential drug-related effects and toxicities.

For drug-eluting GI stents, the drug exposure is supposed to occur primarily at the GI wall surrounding the DES and the exposure is always expected to be much lower in other parts of the body. Consequently, the GI luminal drug concentration at the specific DES implantation site may be significantly higher than that available systemically after its oral or intravenous administration. Therefore, whether previously approved or newly developed drugs are chosen, the selection of the total drug dose (amount of drug/DES) and drug dose density (amount of drug/mm² of DES) is critical with respect to potential loco-regional and systemic drug effects and toxicities following DES placement. However, to minimize potential drug-related local, regional, and systemic adverse effects/toxicities, the lowest effective drug dose is required to be considered for delivery at the intended site of DES deployment [6,41].

4.4.2. Release characteristics and performance evaluation

The rate, extent, and duration of drug release from the DES are likely to correlate directly with the loco-regional biological responses and toxicity at the stented part of the GIT. Drug release from DESs is generally expected to show biphasic kinetics; an initial first-order (or relatively rapid) release for short-term (e.g., over several hours), followed by a zero-order (or extended) release over a long period of time. The cumulative release of the drug is generally greater than 80.0% of the total loaded drug over the intended duration of the DES placement or before reaching the plateau of drug release [6]. Usually, the design, type, and composition of the polymer carrier impregnated on the stent platform dictate the release kinetics of the drugs over an extended period following the DES implantation in situ. Therefore, the mechanism of drug release from the DES polymer coating is particularly important and needs to be considered. Potential drug release mechanisms include: (i) release of the drug through diffusion from the polymer carrier-rate-limiting polymer coating, (ii) swelling of the coating, (iii) bioerosion of the polymer coating, (iv) hydrolytic/enzymatic degradation of the polymer, (v) micro/nanopore-based reservoirs, and (vi) from different coating layers. However, it is desirable that the drug substance remains associated with the polymer carrier in such a way as to ensure a uniform distribution of the drug on the DES surface and retention of the drug during DES deployment, and loco-regional delivery [48,106]. Furthermore, the duration of in vitro drug release is expected to cover a sufficient time period with appropriate number of time points to mimic and/or support the intended duration of in vivo drug release. The in vitro drug release characteristics can provide relevant information on the time course of the drug release as well as the amount of drug still remaining to be released from the DES. Therefore, in vitro drug release testing is more likely to be considered in evaluating the in vitro and in vivo performance of the intended DES [6].
4.4.3. In vitro-in vivo correlation (IVIVC)

To establish a predictive relationship between the in vitro drug release kinetics from DESs and its in vivo GI tissue uptake, it is useful to develop a mathematical IVIVC model. There are several important factors that need to be considered in developing the IVIVC model, including the in vitro DES deployment factors, the mechanism of drug release, the DES formulation and fabrication process factors that influence the release profile of the drug, and the in vitro drug release testing method and conditions (e.g., composition and pH of release media, hydrodynamics). While constructing the IVIVC model, the amount (most often percentage) of the drug to be released from the DES in vitro is to be plotted against the amount of the drug to be released in vivo at the same time points to identify whether a linear point-to-point relationship (i.e. level A correlation) exists.

For DESs, in vivo drug release data can be obtained either by measuring the systemic (blood and/or tissue) concentration of the drug or by determining the amount of the drug remaining to be eluted from the explanted (recovered) DES. The in vivo release profile of the drug to be generated from both of these methods can be utilised in developing the IVIVC model. However, due to the possibility of quantitation of low systemic concentration of the drug, it is likely to be more feasible to use the in vivo drug release profile of the explanted DES. In developing the IVIVC model, the in vitro drug release profile of the DES is supposed to be considered for modifications (if required) by altering the in vitro release test conditions, whereas the in vivo drug release data needs to be kept fixed in order to obtain a consistent relationship between the two data sets. Thus, a predictive IVIVC is likely to establish the relevant performance of the expected final DES [6,107].

4.4.4. Drug candidates

Many therapeutic agents with anti-proliferative or anti-inflammatory properties have been incorporated in various coronary stents to investigate their potential to inhibit vascular restenosis. Based on the fact that in-stent neointimal growth shows some parallels to hyperplastic tumour growth, antiproliferative agents (e.g., sirolimus, paclitaxel, gemcitabine) that generally work by stopping the cell cycle progression through inhibiting DNA synthesis were selected among different classes of therapeutic agents for developing the coronary DESs. Following remarkable clinical success of precedent coronary DESs in combination with anti-proliferative agents, various other agents, including antimitotics (e.g., methotrexate), migration inhibitors and ECM modulators (e.g., batimastat), and enhanced healing and re-endothelialisation factors (e.g., vascular endothelial growth factors (VEGFs)) have been incorporated with coronary stents and are being tested for their localised release and anti-restenotic effects [42,47,57,67]. In contrast, there are not many drugs that have been incorporated with non-vascular stents to study the possibility of inhibiting the benign or malignant restenosis associated with non-vascular stenting. A number of anticancer drugs have been approved and are widely used, either alone or in combinations, in conventional oral and intravenous systemic chemotherapy for GI cancers treatment. The process of selecting the most appropriate anticancer drug or drug combination and the optimal way to combine them is not clearly known, and still remains a great challenge for oncologists, although many anticancer drugs have been in clinical use for GI cancers treatment for many years [27,108]. However, the anticancer drugs that have been delivered locally via non-vascular DESs for the treatment of obstructive GI cancers are 5-fluorouracil (5-FU), paclitaxel (PTX), gemcitabine (GEM), sorafenib, and vorinostat (or suberoylanilide hydroxamic acid) [30,39,61,62,64–66,109-111].

4.5. Drug-stent fabrication method

In most DESs the drug is loaded into and released from a polymer coating or carrier of adequate capacity to encapsulate the selected drug dose and to create the designed platform for controlled drug delivery and release at the intended DES implant site and for the required duration of time [6]. Many techniques of polymer coating stents with therapeutic drugs have been developed for the fabrication of DESs, but most are based on four basic stent coating techniques: dip coating, electrospraying, spray coating, and hot-melt coating, as described below [6,30,39,61,62,64–66,109,111–114]. The drug release from the drug-polymer mixture-coated stent is tailored by modifying both the polymer coating formulation and the coating pattern (e.g., coating design, composition, or type) [47,67]. The control of DES film or coating thickness is a very important aspect of whatever stent coating technique is utilised, since larger stent profile of the DES increases the risk of DES deployment failure [93,114]. However, depending upon the inherent complexity of stent platforms and their uncharacterised properties as medical devices, each of these stent coating techniques has their own capabilities and limitations that need to be considered carefully in selecting the specific coating technique for fabricating the intended DES [6,41,113].

4.5.1. Dip coating

Among the available stent coating techniques, the dip coating involves simple processing steps and results in high-quality coatings with low costs, and thus is the most commonly used technique for the fabrication of DESs. In dip coating technique, typically a homogenous liquid coating (or dipping) medium is prepared by adding drug and carrier polymer in a suitable solvent (or a mixture of different solvents). The stent is immersed in the drug-containing polymer coating medium and slowly withdrawn vertically from the liquid coating medium at a controlled speed as shown in Fig. 8. After that, the drug-polymer mixture-incorporated stent is left exposed in the air or an oven to dry for a certain time period for obtaining the final DES coating. The process of drug-polymer film deposition on the stent surface is repeated for multiple cycles to add subsequent layers of coat on top of the already coated drug release layer, depending on the stent coating and drug release profile desired. Various factors, such as polymer concentration, the viscosity of the coating medium, dwell time, number of cycles, stent withdrawal speed, and solvent composition influence the dip coating process parameters as well as the quality and thickness of the stent coat. However, stents coated with dipping technique may show various surface irregularities or defects in the DES coating, including bridging, webbing, or pooling between adjacent stent struts, and lack of thickness uniformity, particularly with a coating thickness of < 0.5 mm [113–116].

4.5.2. Spray coating

The spray coating technique, which involves the spraying of liquid coating medium through spray nozzles, is another most widely employed technique for coating stents with drugs and polymer carriers [113]. In this coating technique, two spray coating mediums are prepared by dissolving or suspending the carrier polymer and the drug separately in a similar solvent or a mixture of different solvents (Fig. 9). The polymer- and drug-containing coating mediums are applied either simultaneously or sequentially on the stent surface by spraying, to form a uniform composite coating layer of the polymer and the drug. In spray coating, the DES coating or film thickness is controlled primarily by measuring the stent coating weight and therefore spraying process is continued until the desired thickness of the stent coat is achieved [117–119]. In general, the spray coating technique allows for greater variability in the DES coating designs and provides better optimization and control of the drug release characteristics [113]. However, there are shortcomings associated with the spray coating technique, including, webbing or pooling between the adjacent stent struts and a significant amount of drug-polymer spray material loss during the coating process. In addition, spray nozzle clogging is a frequent problem to the spray-based stent coating techniques and that can adversely affect the quality of the DES coating [117,119]. However, based on the principle of the spraying technique, several innovative spray coating
systems, such as ultrasonic atomisation, airbrush coating, and electro-hydrodynamic spraying (electrospraying) have been developed to ensure more precise and continuous coating applications on the surface of stent platforms [113].

4.5.3. Electrospinning

The electrospinning (or electrostatic spinning) technique for the fabrication of DESs involves coating the stent platforms with the drug-polymer-loaded electrospun (e-spun) ultrafine nanofibres through the application of electric fields. In the typical single-needle electrospinning (Fig. 10), a uniform electrospin coating solution is prepared by dissolving the drug and the polymer carrier in a suitable organic solvent (or a mixture of different solvents). The drug-polymer mixed electrospinning solution is loaded into a syringe (glass or plastic), attached through a tube to a metal blunt tip needle (the spinneret) at the end. With the use of a suitable pump, the drug-polymer solution is fed (or forced) continuously through the hollow needle at a constant and controlled rate. One electrode from a high voltage power source is connected to the syringe needle holding the drug-polymer mixed electrospinning solution and the other electrode is connected to an electrically grounded rotating collector (e.g., a drum-roll or a mandrel). The stent rotated by a motor is mounted horizontally into the rotating collector platform. When a high voltage direct current is supplied to the metallic needle, the surface of the drug-polymer solution droplet held together by its own surface tension forces becomes electrostatically charged at the tip of the needle. In turn, the charged drug-polymer solution droplet acquires a conical shape, termed the Taylor cone, due to the interaction of electrostatic forces. Once the supplied voltage exceeds a certain critical voltage, the mutually repulsive electrostatic forces between the surface charges overcome the surface tension of the drug-polymer mixed solution droplet and force the subsequent ejection of the charged drug-polymer solution jet from the needle tip (i.e. the Taylor cone). Then, the charged drug-polymer solution jet is accelerated towards the horizontally rotating stent that is mounted on the rotating collector (i.e. the counter electrode). The drug-polymer solution jet elongates and becomes thinner since it travels further in the air under the repulsive electrostatic forces, undergoes rapid solidification due to the evaporation of solvent, and consequently deposits directly onto the surface of the rotating stent as dry and thin nanofibres [120–128]. The e-spun drug-polymer-loaded nanofibre-coated stent is placed in a vacuum oven to allow for evaporation of the remaining solvent if required [66,127]. Furthermore, in the same way, it is possible to deposit multiple drug-loaded e-spun thin nanofibre layers onto the stent [121].

Fig. 8. Fundamental steps involved (sequentially) in dip coating of stent.
4.5.4. Hot-melt coating

The hot-melt coating technique is a modification of the conventional film coating technique and involves the application of a thin layer of drug-incorporated polymer coating material over the stent platform as a melt, rather than as a solution or dispersion. The hot-melt direct blending coating technique uses molten thermoplastic polymers as the coating materials that solidify to form the coating layer and achieve the desired mechanical strength on cooling [131–134]. In brief, two separate polymeric layers are prepared; a drug-loaded layer and a drug-free protective layer. The drug-loaded polymeric layer is prepared by direct blending of the drug particles and the melted polymer under heating/stirring at a certain temperature/rpm. Afterwards, the drug-polymer blends are compressed into films (with the desired thickness) by processing through a rolling mill (i.e. the heat source). The drug-free...
A protective polymeric layer is prepared in the same way under similar conditions without using drug. To prepare the drug-release coating, one drug-loaded polymer layer and one drug-free protective polymer layer are agglutinated under certain temperature and pressure. Finally, the agglutinated drug-release coating mass is coated around the outer surface of the stent at a certain temperature and pressure, with the protective polymer layer facing towards the stent lumen \[61,62,64\]. The resultant thickness of the DES coating or film is directly related to the mechanical properties of the thermoplastic polymer used, and generally, a low or moderate viscosity of the drug-polymer melt is required to produce a uniform thin coating layer \[131,135\]. As the hot-melt coating technique is devoid of solvent use, the process is much faster, economical, and environment-friendly. However, common polymer coating materials are not suitable for use in this technique and there is a need to find alternative coating materials \[132\].

4.6. Placement technique

While placement of the varieties of marketed non-vascular stents is performed safely and successfully with the varieties of available stent delivery techniques, the delivery and placement of the drug-eluting GI stent within a stenosed lumen of the GIT is more likely to be done in a similar way like traditional GI stenting \[93\]. Typically, before stenting, optimum visualization and characterisation of the malignant stricture or obstruction must be done by either using endoscopic cameras mounted on scopes with flexible or rigid operative working channels (e.g., oesophagogoscope, duodenoscope, colonoscope), or radiologically using imaging techniques (e.g., X-ray, angiography, computed tomography scan, MRI). This initial evaluation helps to determine precisely the location, the underlying aetiology, the length (proximal and distal extent), and the degree of severity of the obstruction, along with the other concurrent medical comorbidities, and thus the feasibility and safety of direct stenting \[34,70,84,92\].

The stent placement technique is usually performed under conscious (light or moderate) sedation or after induction of local or general anaesthesia, as appropriate, by specialised interventional endoscopists or by interventional radiologists (specialist imaging doctors) \[19,33,34,75,87,98\]. Guidewires (GWs) with an appropriate length are used to establish access to the target non-vascular stricture sites and to facilitate safe and smooth delivery and placement of the stents during interventional stenting procedures (Fig. 11) \[34,93,136\]. The majority of stent placement techniques are performed using mainly two types of stent delivery systems (SDSs): through-the-scope (TTS) which requires passing through the operative channel of the scope, and over-the-wire (OTW) which does not need any such requirement \[70,87,98\]. However, after identification and characterisation of the tumoural stricture, a GW is inserted and passed through the obstruction, followed by a SDS preloaded with the compressed stent is introduced along the GW through the operating channel of the SDS. Thereafter, the tip of the SDS is placed appropriately within or close to the obstruction and the pre-compressed stent is pushed out of the SDS and across the stricture \[42,79\]. Then, in consideration of the stricture length previously delineated, the stent is positioned and subsequently deployed under endoscopic or fluoroscopic guidance alone or a combination of both endoscopic and fluoroscopic guidance by means of releasing of the constraining mechanism \[16,19,70,75,79\].

Additionally, in cases when a severe malignant stricture prevents the passage of the SDS, dilation of the stricture is often required before the stent placement, depending on the anatomical location and/or character of the malignant stricture and the type of stent being used \[31,34,75,76,79\]. Following delivery and deployment, the stent opens and expands to its intended size over a course of hours to days against both the stricture and the surrounding tissue by radial forces, thereby anchoring the stent in place and helping to reopen the obstruction in non-vascular tubular body structures. Besides, after completion of stent placement, proper stent positioning and degree of expansion are confirmed endoscopically as well as fluoroscopically \[34,42,75,76,79,92,98,137\]. However, depending on the different location of stent insertion, post-stent placement complications may involve bleeding, pain, discomfort, bacterial biofilm formation, and benign tissue overgrowth, in addition to other site-specific localised symptoms \[19–21,33,34,70,75,98\].
4.7. Study outcomes

Although non-vascular stenting has been implemented in every human body passageway, including tear ducts to rectum, the large majority of the research and clinical data that are available on DESs are from their use in the obstructive CADs. However, until today a number of preclinical studies and a few clinical studies have been conducted to evaluate the safety and/or effectiveness of the use of non-vascular DESs in the management of GI cancers and related obstructions and/or stenosis [21,34,36,104]. Table 2 shows the list of drug-eluting GI stents that have been developed and investigated so far in preclinical studies, along with their drug loading, accompanying, polymer/carrier systems, fabrication methods, and drug-release profiles. The results of published clinical studies using GI DESs are summarised in Table 3.

4.7.1. Oesophageal DESs

4.7.1.1. Preclinical testing. In one study, PTX-eluting metallic stents (PEMSs) were prepared with the loading of 10.0% of PTX and was compared with drug-free SEMS as a control group. The stents were inserted in male New Zealand white rabbit oesophagus (n = 48) and examined for 1, 2, 4, and 6 weeks consecutively. The endoscopic observation showed no migration or procedural complication occurred in the rabbits. The rabbits were sacrificed and microscopic and histological examination revealed similar tissue reaction in both groups for 1, 2, and 4 weeks while inflammatory cell infiltration was significantly more severe in the control SEMS group compared to the PEMS group. However, inflammatory cell infiltration increased in the control SEMS group at 1 and 2 weeks and in the PEMS group at 4 and 6 weeks. The results presented that the PEMS may provide a safe and effective treatment for malignant oesophageal obstructions but further investigations on the effect of PTX on cancerous cells (tumour models) might be needed in the future [144]. Shaik et al. developed a docetaxel (DTX)-loaded drug-eluting film for the treatment of oesophageal cancer. The films were made of PU as a polymer into which the drug (DTX) was embedded. The developed films showed a sustained release of DTX for one month. They used a xenograft model for in vivo studies. Although their formulation showed marginal activity against oesophageal cancer cell lines, skin toxicities were observed in the nude mice. It was suggested that a sufficient dose and suitable animal model can be considered in the future in vivo studies [37,145].

In a study conducted by Jieying Liu and her team, a 50.0% of 5-FU or PTX-loaded oesophageal stent combined with ethylene-vinyl acetate (EVA) polymer was evaluated in the porcine oesophagus. The drug (5-FU or PTX) loaded EVA layer was combined with a drug-free backing layer of EVA and rolled around an expandable stent and implanted in the oesophagus of pigs. The results from 120 days follow up displayed that the drug concentrations remained in the oesophagus at the highest level compared to the lung, kidney, heart, spleen, liver, and blood. It confirmed the unidirectional and sustained release of the drugs in the oesophagus. In addition, no significant systemic toxicities were observed [64,138].

In another study, SEMSs were fabricated by electrospay of PTX and PU solution (in tetrahydrofuran). In vitro drug release profile indicated that 50.0% of the PTX was released in the early phase followed by a sustained drug release for 6 weeks. Rabbits were chosen as the animal model in this study and using a stent introducer, the stents were inserted in rabbit’s oesophageal lumen. Non-drug-loaded stents were compared with PTX-SEMS. After 45 days, the rabbits were sacrificed and the stents were separated from the surrounding tissues. It was hard to remove the non-drug-loaded stents from oesophageal tissues while PTX-loaded stents were removed easily and no damage was observed after removing the stents. The in vivo drug (PTX) release was similar to in vitro release profile. The results from macro-pathologic examination showed no perforation or stent destruction in oesophageal tissues. Histopathologic examination displayed no perforation in any of the samples, although the inflammatory cell infiltration was higher in PTX-SEMS group. The same as the previous study, PTX-SEMS showed safe and effective palliative action for control of oesophageal obstruction [140]. Self-expanding nitinol stents coated with 5-FU as a model drug and EVA as polymer was developed by Guo and group. The in vivo efficacy of 5-FU-containing self-expandable nitinol stents was evaluated on New Zealand rabbits by implantation into their oesophagus. It was observed that higher the drug content, higher was the 5-FU concentration. In addition, drug concentration in oesophageal tissue was found to be significantly higher compared to that in liver and serum. The results also revealed that the amount of drug was higher in the mucosal tissue than in the muscle layer of the oesophagus suggesting that mucosal accumulation was higher which may be beneficial in the treatment of epithelial carcinoma [62].

In another study conducted by a group of Korean researchers in 2009, canines (n = 14) were selected to evaluate the tissue reaction and hyperplasia of PTX-SEMS in the healthy oesophagus. An endoscopic examination was performed for a period of 8 weeks. They observed hyperplasia in the control group (non-drug-loaded stents) for > 4 weeks. In contrast, very little tissue reactions were observed with PTX-SEMS. This group also suggested that these novel designed DESs may provide an alternative treatment to manage oesophageal obstructions in the future [146].

4.7.1.2. Clinical testing. The first prospective blinded randomised human trial with non-vascular DESs was conducted among 21 patients with inoperable adenomatous cancer of the oesophagus. In this human trial, a total 11 patients out of 21 received oesophageal stenting with tantalum Strecker stents (Boston Scientific, USA), polymer-coated with 3.0% PTX, and the remaining 10 patients were stented with the similar Strecker stents without any coating and drug (bare Strecker stents). Although this human study failed to support the effectiveness of non-vascular DESs in preventing ingrowth of tumour tissue, but has provided evidence of no notable complications linked with the placement of these devices and fronted the possibilities of further research [36,65].

An iodine-eluting oesophageal stent was developed by a group of researchers and a clinical study was performed in advanced oesophageal cancer patients. In this study, a total of 71 patients with malignant oesophageal cancer were divided into two different groups; group A received conventional stents (without drug) and group B received iodine-eluting stents. After 8 days of observation, there were no significant differences in dysphagia grades between the two groups. However, after two months, the dysphagia grade improved significantly in the patients with iodine-eluting stent (group B). The endoscopic examinations revealed that the iodine-eluting stent has an inhibitory effect on the tumour growth and significantly improves the survival rate of the patients. The statistically significant results indicate that iodine-eluting oesophageal stents are relatively safe and can be effective on malignant oesophageal carcinoma [147]. In a similar attempt; a multicenter, randomised phase 3 trial was performed in 148 patients with unrecteatable oesophageal cancer from 16 different hospitals in China. Iodine seed loaded stents (irradiation group) were compared with conventional stents (control group). Chest pain was the major complication in both groups and median overall survival time with irradiation group was 177 days while it reduced to 147 days in the control group [148].

4.7.2. Gastroduodenal, pancreatic, and hepatobiliary DESs

4.7.2.1. Preclinical testing. A nanofibre-coated stent was prepared with vorinostat (suberoylanilide hydroxamic acid; Zolinza™) and PLGA using the electrospinning technique. Antitumour activity was evaluated in a animal tumour xenograft model. HuCC-T1 cholangiocarcinoma (CCA) cells suspension (in phosphate-buffered saline) were injected subcutaneously into the backs of male nude mice, the mice were divided into four groups; a) control group, b) vorinostat injection group, c) drug-free nanofibre group, and d) vorinostat-incorporated...
Table 2
Preclinically developed drug-eluting GI stents with their drug components, drug loading, polymer/carrier systems, fabrication methods, and drug release profiles.

<table>
<thead>
<tr>
<th>Stenting organ</th>
<th>Drug</th>
<th>Drug loading</th>
<th>Polymer/Carrier system</th>
<th>Drug-Stent fabrication method</th>
<th>Drug release profile</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice bile duct cancer</td>
<td>Vorinostat</td>
<td>9.0% w/w</td>
<td>Silicone-PLGA</td>
<td>Electrosprinning</td>
<td>Initial burst release (approximately 60.0% at day 1) in RPMI 1640 cell culture media and almost all released over 4 days; release rate was very slow in 10 mM PBS (pH 7.4) and approximately 45.0% released over 10 days</td>
<td>Kwak et al. [66]</td>
</tr>
<tr>
<td>Porcine oesophagus</td>
<td>Paclitaxel</td>
<td>12.049 µg/cm²</td>
<td>EVA</td>
<td>Hot-melt coating (direct blending)</td>
<td>11.0 and 21.0% release over 13 and 95 days, respectively; 58.0 and 92.0% release over 13 and 95 days, respectively Initial rapid release for approximately 2 weeks, followed by a slow and sustained release up to 95 days</td>
<td>Liu et al. [64]; Wang et al. [138]</td>
</tr>
<tr>
<td>Mice bile duct cancer</td>
<td>Paclitaxel</td>
<td>0.27 mg/cm³</td>
<td>PTFE-PU</td>
<td>Electrosprinning</td>
<td>Initial burst release (approximately 20.0%) for 2 days and then approximately 2.5 µg/cm³ release per day for 58 days</td>
<td>Jeong et al. [109]</td>
</tr>
<tr>
<td>Bile duct cancer</td>
<td>Paclitaxel</td>
<td>0.461 to 0.467 mg/cm³</td>
<td>PU</td>
<td>Dip coating</td>
<td>34.0 to 43.0% release over 19 days</td>
<td>Seo et al. [111]</td>
</tr>
<tr>
<td>Malignant/Benign stenosis/occlusion</td>
<td>Paclitaxel</td>
<td>5.0% w/w</td>
<td>Silicone-PU</td>
<td>Dip coating and electrosprinning</td>
<td>6.48 ± 0.50 µg/cm³ release per day for 10 days and 1.28 ± 0.01 µg/cm³ release per day for the next 20 days</td>
<td>Kim et al. [139]</td>
</tr>
<tr>
<td>Mice colorectal cancer</td>
<td>Paclitaxel</td>
<td>1.0 to 20.0% w/v</td>
<td>PU</td>
<td>Electrospray</td>
<td>Burst release (approximately 50.0%) in first 10 h and most released over a period of 50 h</td>
<td>Zhao et al. [140]</td>
</tr>
<tr>
<td>Rabbit oesophagus</td>
<td>Paclitaxel</td>
<td>3.2, 6.4 and 12.8% w/w</td>
<td>PDO-PLLA</td>
<td>Electrosprining</td>
<td>Fast bursting release in 24 h and highest 20 mg/L release over a period of 400 h</td>
<td>Li et al. [30]; Kim et al. [110]</td>
</tr>
<tr>
<td>Mice bile duct cancer</td>
<td>5-FU</td>
<td>45.28 to 236.11 mg/cm³</td>
<td>PCL</td>
<td>Electrosprining</td>
<td>Approximately 50.0% release over 30 days</td>
<td>Yü et al. [141]</td>
</tr>
<tr>
<td>Malignant/Benign stenosis/occlusion</td>
<td>Paclitaxel</td>
<td>5.0% w/w</td>
<td>PLGA-PEVA</td>
<td>Ultrasonic spray coating</td>
<td>Initial burst release (approximately 30.0%) in 2 days and then almost zero-order release up to 30 days</td>
<td>Lee et al. [39]</td>
</tr>
<tr>
<td>Malignant/Benign stenosis/occlusion</td>
<td>Gemcitabine</td>
<td>2.33 ± 0.05 mg/membrane</td>
<td>PTFE-PU</td>
<td>Dip coating</td>
<td>Initial burst release of up to 35.0% and 70.0% release over 35 days; 23.3 µg release per day after initial burst release</td>
<td>Chung et al., 2012 [142]</td>
</tr>
<tr>
<td>Porcine bile duct</td>
<td>Gemcitabine</td>
<td>10.0, 15.0 and 20.0% w/v</td>
<td>Silicone-PU</td>
<td>Dip coating</td>
<td>64.8 (149 µg), 68.2 (223 µg) and 74.3% (318 µg) release, respectively, over 2 weeks; 67.8 (156 µg), 71.9 (235 µg) and 78.7% (337 µg) release, respectively, over 4 weeks</td>
<td>Moon et al. [65]</td>
</tr>
<tr>
<td>Malignant/Benign stenosis/occlusion</td>
<td>Gemcitabine</td>
<td>186.1, 212.7 and 216.5 µg/cm³</td>
<td>PTFE-PA</td>
<td>Dip coating</td>
<td>Initial burst release (15.0 to 50.0%, 32.7 to 93.0 µg/cm³) in 6 h and 85.0 to 95.0% release over 30 days</td>
<td>Lee et al., 2009 [143]</td>
</tr>
<tr>
<td>Rabbit oesophagus</td>
<td>5-FU</td>
<td>20.0, 40.0 and 60.0% w/w</td>
<td>EVA</td>
<td>Hot-melt coating (direct blending)</td>
<td>Burst release for initial 2 days, followed by steady release until day 10; only slightly released from day 10 to day 55; 673 ± 1.1 mg/cm³ release from drug-loaded and drug-free protective layers, respectively, over 30 days</td>
<td>Guo et al., 2010 [62]</td>
</tr>
<tr>
<td>Canine bile duct</td>
<td>Paclitaxel</td>
<td>20.0% w/v</td>
<td>PU</td>
<td>Dip coating</td>
<td>Not known</td>
<td>Lee et al., 2009 [143]</td>
</tr>
<tr>
<td>Dog oesophagus</td>
<td>Paclitaxel</td>
<td>20.0 to 60.0% w/w</td>
<td>EVA</td>
<td>Hot-melt coating (direct blending)</td>
<td>Initial faster release (at day 1) followed by a decrease in release; 10.0 to 34.0% release in 10 days and 41.0 to 60.0% release over 275 days</td>
<td>Guo et al., 2007 [61]</td>
</tr>
<tr>
<td>Porcine bile duct</td>
<td>Paclitaxel</td>
<td>10.0 and 20.0% w/v</td>
<td>PU</td>
<td>Dip coating</td>
<td>1290 and 1067 µL/mL release, respectively, over 1 week; 1822 and 1864 µL/mL release, respectively, over 6 weeks</td>
<td>Lee et al., 2005 [112]</td>
</tr>
</tbody>
</table>

PLGA, Poly(lactic-co-glycolic acid); PBS, Phosphate-buffered saline; 5-FU, 5-Fluorouracil; EVA, Ethylene-vinyl acetate; PTFE, Polytetrafluoroethylene; PU, Polyurethane; PDO, Polydioxanone; PLLA, Poly(L-lactic acid); PCL, Poly(ɛ-caprolactone); PEVA, (Poly(ethylene-co-vinyl acetate); PA, Pullulan acetate.
Table 3
Summary of clinical studies of different types of drug-eluting GI stents.

<table>
<thead>
<tr>
<th>Study type</th>
<th>GI cancer type</th>
<th>DES description</th>
<th>Study subjects</th>
<th>Outcomes and remarks</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective, blinded and randomised</td>
<td>Oesophageal adenocarcinoma ( unresectable)</td>
<td>Self-expanding tantalum Strecker oesophageal stent coated with 33.0% PTX-incorporated EVA</td>
<td>21 11</td>
<td>Uncoated self-expanding tantalum Strecker oesophageal stent (10)</td>
<td>Manifold et al. [149]</td>
</tr>
<tr>
<td>Prospective, single-arm, and multicentre pilot</td>
<td>Malignant biliary obstruction ( unresectable)</td>
<td>SEPS dip-coated with 10.0% (w/v) PTX-incorporated PU</td>
<td>21 21</td>
<td>Not applicable</td>
<td>Suk et al. [150]</td>
</tr>
<tr>
<td>Prospective, non-blinded, randomised, and single-centre pilot</td>
<td>Malignant biliary obstruction ( unresectable)</td>
<td>Silicone-covered (inner layer) SEPS dip-coated with 20.0% (w/v) PTX-incorporated PU (outer layer)</td>
<td>52 (49)⁎ 26 (24)⁎</td>
<td>Silicone-covered (inner layer) SEPS dip-coated with PU (out layer) [26 (25) ]</td>
<td>Song et al. [151]</td>
</tr>
<tr>
<td>Prospective, two-arm, and multicentre comparative</td>
<td>Malignant biliary obstruction ( unresectable)</td>
<td>SEPS dip-coated (single layer) with 10.0% (w/v) PTX-incorporated PU</td>
<td>106 (100)⁎ 60 (58)⁎</td>
<td>SEPS dip-coated (single layer) with PU [46 (42) ]</td>
<td>Jang et al. [152]</td>
</tr>
<tr>
<td>Prospective, randomised, and single-centre comparative</td>
<td>Malignant oesophageal stricture</td>
<td>Oesophageal nitinol stent covered with iodine-incorporated PU membrane</td>
<td>71 (67)⁎ 31</td>
<td>Conventional covered metal stent (36)</td>
<td>Dai et al. [147]</td>
</tr>
<tr>
<td>Prospective, single-blind, randomised, and multicentre phase 3</td>
<td>Malignant oesophageal stricture ( unresectable)</td>
<td>Oesophageal stent coated with iodine radioactive seeds</td>
<td>148 73</td>
<td>Conventional covered self-expanding nitinol stent (75)</td>
<td>Zhu et al. [148]</td>
</tr>
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DES, Drug-eluting stent; n, Respective total number of study subjects; PTX, Paclitaxel; EVA, Ethylene-vinyl acetate; SEPS, Self-expanding metal stent; PU, Polyurethane.

⁎ Value in parentheses indicates the number of subjects included in the final analysis.

No significant differences were observed between DESs and uncoated control stents.
No control group was included. Demonstrates technical feasibility, safety, and effectiveness of DESs.
Proves the safety of DESs with acceptable complication rates. No significant differences were observed in the stent patency duration or overall patient survival time between DESs and control stents.
Demonstrates the safety of DESs. In terms of stent patency and patient survival duration, no significant differences were seen between DESs and control stents.
Demonstrates safety, feasibility, and effectiveness of DESs. In case of severe complication rates, no significant differences were observed between DESs and conventional metal stents.
Compared with control group, DES demonstrates efficacy in relieving dysphagia and prolonging patient survival time.
nanofibre group. Vorinostat-incorporated nanofibre and drug-free nanofibre were implanted under the tumour. The size of the tumours was evaluated at 2-5-day intervals for a 22-day period. The in vivo antitumour activity results showed a noticeable reduction in the volume of the tumours in the vorinostat nanofibre group, indicating the continuous release of vorinostat that suppressed the growth of tumour cells in the xenograft model. The mechanism suggested for this action was the inhibition of histone deacetylase (HDAC) protein and induction of Ac-histone. Furthermore, the tumour growth inhibition rate with vorinostat nanofibres was higher in HuCC-T1 bearing mice than vorinostat injections which confirms the higher efficacy of the vorinostat nanofibre formulation [66].

Jeong and his group successfully demonstrated the antitumour efficacy of sodium caprate incorporated PU membrane-covered PTX-eluting non-vascular stents (PUSC-PTX) against bile duct carcinoma. The stents were implanted at tumour sites in male BALB/c nude mice. One day after implantation, a 50.0% reduction in tumour volume was observed in PUSC-PTX implanted mice as compared to PU-PTX-implanted mice. This indicates that sodium caprate incorporated in the implant acted as a penetration enhancer thereby improving the local delivery of the drug by altering the mucus substance [109].

In another attempt, Chung et al. incorporated GEM (four different concentrations; 0%, 10.0%, 15.0%, and 20.0% w/v) with self-expanding metallic biliary stents and evaluated in a porcine model. After 4 weeks of evaluation, they found that GEM caused severe inflammation in the bile duct with 15.0% and 20.0% GEM-loaded stents compared to mild inflammation with 10.0% GEM-loaded stents. No inflammation with drug-free stent and also no perforations or transmural necrosis were observed in the animals. They concluded that 10.0% GEM-loaded stents may be appropriate for clinical trials, but evaluation of the effect of GEM on the tumour tissue and persistent human clinical study may be needed [142].

Lee et al. evaluated the safety of PTX-eluting stents in a canine biliary model by analysing tissue reactions via histological examination. The results revealed no migration of stents in the canines. The DESs were placed in six animals and control stents were placed in five animals and followed up for 6 weeks. Histologic analysis showed mucosal hyperplasia in three out of six dogs in the PTX-eluting metallic stent group, whereas there was no such evidence in the control stent group. Significant histologic changes in the biliary mucosa were observed in the dogs treated with PTX-eluting stents compared with the control stent group which suggests the importance of incorporating optimum dose sufficient to show antitumour effect without damaging the surrounding normal tissues [143]. PTX-loaded metallic stents with PU were developed for the plausible treatment for malignant biliary obstruction. These stents were evaluated for their safety and their effects on biliary epithelium in domesticated pigs. The stents covered with 10.0 and 20.0% w/v of PTX showed slight epithelial denudation with mucosal inflammation. However, no significant complications were observed during the study [112].

4.7.3. Colorectal DESs

4.7.3.1. Preclinical testing. PTX-eluting nanofibre membrane (PTX-NFM)-covered stents for palliative chemotherapy of GI cancers were evaluated in a preclinical study. A double-layered DES was designed with silicone dip coating (backing layer) and electrospinning of a mixture of PTX and PU (top layer). CT-26 murine CRC cells were injected subcutaneously on the flank side of female BALB/c mice. The mice were divided into four groups of 6 mice: a) non-treated, b) PTX-injection treated, c) Blank (drug-free) NFM implanted, and d) PTX-NFM implanted. The results from in vivo study showed that the e-spin nanofibre-covered DESs significantly inhibited the growth of CT-26 colon cancer [139]. In another study, Li et al. demonstrated the effectiveness of 5-FU-loaded weft-knitted PDO monofilament stents for using in the treatment of CRC. In their study, after determining the “safe” concentration in vivo and appropriate loading dosage of 5-FU through pilot works, the biodegradable PDO tubular stents were electrospun and coated with three PLLA nano-fibrous membranes containing 3.2%, 6.4% and 12.8% of 5-FU (added to PLLA by weight), respectively, on the stents surface by utilising a modified (experimental) electrospinning equipment. As a control, they fabricated a similar PDO stent with pure PLLA membrane (free of 5-FU) only and following the same experimental conditions. They investigated the surface morphologies, internal chemical structures, and in vivo drug release properties of the three 5-FU-loaded PLLA coating membranes.
The characterisation data of these 5-FU-incorporated membranes exhibited that 5-FU had been well integrated into the PLLA fibrous coating membranes after using the electrospinning technology. The in vitro release of 5-FU was shown as significantly enhanced with the increase of the 5-FU loading. Their research study also estimated the in vitro and in vivo cytotoxicities of the released 5-FU using HCT-116 (human CRC cells) and female tumour-bearing athymic 6 to 8 weeks old BALB/c nude mice. Together, the cell cycle and apoptosis analysis were reported that the higher loading percentage of 5-FU had provided superior antitumour and anti-ISR effects in comparison to the pure 5-FU solution at half maximal inhibitory concentration (IC50), due to releasing stable drugs over a sustained period of time from the 5-FU-loaded fibrous membranes [30].

GEM-eluting stents developed using PU films were found to inhibit cancer growth when tested in CT-26 colon carcinoma-bearing mice. The films were developed using PTFE-PU loaded with GEM. Poloxamer 407 was used as the rate controlling membrane. On assessing the in vivo efficacy in mice, it was observed that the GEM-loaded films showed a reduction in tumour volume. No major adverse effects were observed in the animals treated with the films [39]. Moon et al. fabricated GEM-eluting SEMS as a localised controlled drug delivery platform for the therapeutic treatment of GI cancers and associated stenosis. These drug-eluting GI stents showed a more sustained release of GEM over 30 days, with biological stability as well as apoptotic capability. The in vivo antitumour efficacy of these DESs was evaluated and confirmed using murine colorectal carcinoma cell line (CT-26) study, and thus offer potential applications in malignant GI obstructions [65].

4.7.3.2. Clinical testing. No clinical studies were found on colorectal DESs.

4.8. Current challenges

4.8.1. Selection of appropriate drug dose

The use of appropriate loading dose of the drug, both total dose and dose density, is very important to ensure the clinical safety, performance and effectiveness of the DES systems. Currently, a number of anticancer drugs, including both systemic and non-systemic categories, have been approved and are clinically used, either alone or in combination, for the treatment of GI cancers and related stenosis and/or obstructions. These anticancer drugs already have clinically established dosage and treatment regimens. However, although it has been established that the total amount of drug to be incorporated in the DESs is almost always significantly lower than that required for systemic or oral applications, there is no authentic clinical/nonclinical evidence regarding the appropriate doses of anticancer drugs for non-vascular DES applications [6,41].

4.8.2. Animal models and preclinical safety/effectiveness evaluation

In light of the current available literature, there are several animal models that have been developed for preclinical safety and/or effectiveness evaluation of the DESs. Unfortunately, there are no animal species still known which can serve as a suitable in vivo local model of spontaneous malignant tumour ingrowth equivalent to human GI cancers. The in vivo large animal (e.g., pig) testing so far carried out in the field of DES is either lack of a sufficient number of experimental animals, or limited to the safety evaluation, instead of sustained efficacy. The commonly used arbitrary small animal models such as mice, rats, and rabbits, to simulate the magnitude of medical benefits of DESs in humans are not fully reliable, and a poor correlation exists between human and animal study results [2,6,36,41,104].

5. Conclusions

This review presents an integrated overview on using non-vascular DESs for localised management of obstructive GI cancers with regard to biological factors of the target implant sites influencing the selection of DES components (e.g., stent platform, polymer coating material), fabrication and stenting procedure, safety and effectiveness, market potential, and FDA requirements for their development and marketing approval. Although currently there is only little preliminary clinical understanding about the safety and/or effectiveness of DESs in the GIT, the preclinical research conducted to date indicates that there are considerable prospects for development of non-vascular DESs for localised controlled drug-release applications. Furthermore, substantial clinical experiences from the use of coronary DESs in patients with CADs since 2003 have also provided knowledge and understanding of the common issues associated with the DES systems. Instead of simply applying systemic non-specific chemotherapy, the need to deliver cytotoxic anticancer drugs at the precise site of malignancy has already gained the greatest importance. In this respect, DESs that can provide controlled release of anticancer drugs could be a potential non-systematic (localised) chemotherapy treatment for GI cancers and related obstructions and/or stenosis, since many DESs have demonstrated their usefulness in treating local diseases. There are a number of FDA-approved anticancer drugs and drug combinations available which have been routinely used in conventional chemotherapy treatment for GI cancers but not yet been studied in the setting of a DES. The ongoing cancer DES development research offers to investigate various possibilities ranging from the use of new anticancer agents ( singly or in combination) to local gene therapy that are already in clinical use but have not yet been explored in combination with stents for the treatment of obstructive GI cancers.

However, as acknowledged by the FDA, DESs are complex products to develop and present numerous challenges from both manufacturing and regulatory aspects. Currently, there are no established regulatory guidelines for non-vascular DESs or cancer DESs, and the existing research on non-vascular DESs is essentially based on the regulatory guidance specific to coronary vascular DESs. It is true that many further issues still need to be resolved before taking the preclinical experimental model studies of non-vascular DESs into reliable clinical applications. Nevertheless, increasing willingness of regulatory authorities to interact closely with the DES manufacturers has played an important role in addressing many critical issues related to the preclinical laboratory and animal testing or human clinical trial of coronary DESs. It is highly likely that the adoption of GI DESs, in place of simple GI stents, may become a clinical reality for the treatment of obstructive GI cancers in the near future. It is therefore crucial to performing critical laboratory studies that can synergize the current pace of non-vascular DES research and advance both the entire fields of stenting and cancer to a great extent.

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