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Some design considerations for polymer-free drug-eluting stents: A mathematical approach

Sean McGinty [a,*], Tuoi T.N. Vo [b], Martin Meere [c], Sean McKee [a], Christopher McCormick [d]

[a] Department of Mathematics and Statistics, University of Strathclyde, Glasgow G1 1XH, UK
[b] MACSI, Department of Mathematics and Statistics, University of Limerick, Limerick, Ireland
[c] Department of Applied Mathematics, NUI Galway, Galway, Ireland
[d] Department of Biomedical Engineering, University of Strathclyde, Glasgow G4 0NW, UK

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ABSTRACT

In this paper we provide the first model of drug elution from polymer-free arterial drug-eluting stents. The generalised model is capable of predicting drug release from a number of polymer-free systems including those that exhibit nanoporous, nanotubular and smooth surfaces. We derive analytical solutions which allow us to easily determine the important parameters that control drug release. Drug release profiles are provided, and we offer design recommendations so that the release profile may be tailored to achieve the desired outcome. The models presented here are not specific to drug-eluting stents and may also be applied to other biomedical implants that use nanoporous surfaces to release a drug.

1. Introduction

1.1. Background

Drug-eluting stents (DES) have significantly improved the treatment of coronary heart disease (CHD) and are the current gold standard in percutaneous coronary interventions (PCIs). These small drug-containing mesh-like devices are now routinely inserted into arteries which have become dangerously narrowed due to a condition known as atherosclerosis. Their role is to increase the diameter of the diseased lumen, so that adequate blood flow can be restored. Their predecessor, the so-called bare metal stents, whilst revolutionary at the time, were soon found to be inadequate due to the common occurrence of restenosis (the re-narrowing of the lumen). Subsequent stent designs included an antiproliferative drug designed to prevent smooth muscle cell proliferation and migration which is thought to contribute to restenosis: these are the drug-eluting stents [1]. The drug was typically contained within a polymer coating on the surface of the metal stent. To date there have been several generations of DES, each with design features aimed at improving clinical results. These include multi-layer polymer coatings to help control the release, thinner struts to reduce damage to the arterial tissue and more biocompatible polymer coatings and metal alloys [2]. However, several studies have raised concerns that the permanent presence of a polymer may trigger an allergic reaction and possibly a local vascular inflammatory response in some patients [3,4]. Moreover, several early studies reported evidence of delayed healing of the endothelial cell layer of the arterial wall following DES use, in comparison to bare metal stents [5,6]. These unwanted effects have been associated with the occurrence of late stent thrombosis and sudden cardiac death. With this in mind, cardiologists have recommended that anti-platelet therapy is continued for a full twelve months after stent implantation [1]. Driven by a desire to improve clinical outcomes, newer generation DES have focussed on biodegradable polymers, where the polymer carries and controls the drug release and then completely erodes, and also polymer-free coatings which do not contain any polymer at all. Whilst modelling drug release from stents which contain a non-erodible polymer (e.g. [7–11]) and a biodegradable polymer (e.g. [12–18]) has received much attention in the literature, the modelling of polymer-free DES has not. This is somewhat surprising, especially since a recent drug-eluting stent review [19] reports that "...polymer-free, controlled-release stent designs may become the substrate of choice in the longer-term, especially if they exhibit non-inferiority in terms of restenosis reduction".

To date, several polymer-free stents have been designed and some of them have reached the market. There have, however, been

* Corresponding author. Tel.: +44 141 5483286.
E-mail address: s.mcginty@strath.ac.uk (S. McGinty).

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many challenges for the stent manufacturers. For example, they have had to address how the drug release can be controlled with no polymer, how the drug can be adequately adhered to the stent surface and have had to consider carefully the stent platform material to ensure that it is biocompatible. The stent manufacturers have adopted different approaches in designing these stents, which can be roughly separated into four categories [20]: macroporous, microporous, nanoporous and smooth surface. Macroporous DES utilise precise manufacturing processes to accurately inlay the drug into holes or slits in the body of the stent. Some examples include the Janus Flex (Sorin Group), Conor Stent (Conor Medsystems), CoStar (Conor Medsystems), and Nevo (Cordis) [20,22]. Microporous polymer-free DES contain a modified surface of pits and holes whose size is of the order of microns. The drug is then coated directly on the rough surface, resulting in the micropores being filled and a nominal layer of drug on top of the surface. The purpose of the micropores is to act as a reservoir for the drug and also to aid adhesion to the stent surface. The rough surface may be created by, for example, a sandblasting technique (Yukon stent, Translumina), or by a microabrasion process (BioFreedom stent, Biosensors Inc.) [23,22]. The VESTAsync stent (MIV Therapeutics) uses a hydroxyapatite surface coating [22]. Hydroxyapatite is an organic porous material that makes up bone mineral and the matrix of teeth and is widely used as a bone substitute. Nanoporous DES are distinguishable from microporous DES by the nature and size of their pores. They exhibit a bulk porous layer (cf. a surface porous layer) and the pores are of the order of nanometres (cf. microns). This layer may be obtained electrochemically (Ceramic-coated TES, Jomed International) or through sputter coating techniques (Setagon stent, Setagon Inc). These stents have the advantage of allowing for a higher drug loading capacity. The Optima stent (CID) contains nanopores too, but the pores are arranged in a regular slotted tubular fashion [23]. Fig. 1(a) displays a nanoporous polymer-free stent whilst 1(b) displays a nanotubular polymer-free stent. Perhaps the most simple polymer-free design is where the drug is coated directly onto the unmodified (relatively) smooth surface of the metal stent. An example of this type of polymer-free DES is the Amazonia Pax (MINVASYS) [22] where a semi-crystalline paclitaxel coating is applied directly to the chromium cobalt stent (see Fig. 1(c)). With no polymer or pores to control the release, it appears that the release rate is determined solely by the solubility and diffusion coefficient of the drug in the release medium and by the thickness of the coating.

Whilst the application of nanoporous drug-eluting coatings to stents is relatively recent, the use of nanoporous surfaces in drug delivery is not new. It is worth briefly mentioning here a few of the other (that is, not stent-based) drug delivery systems that have

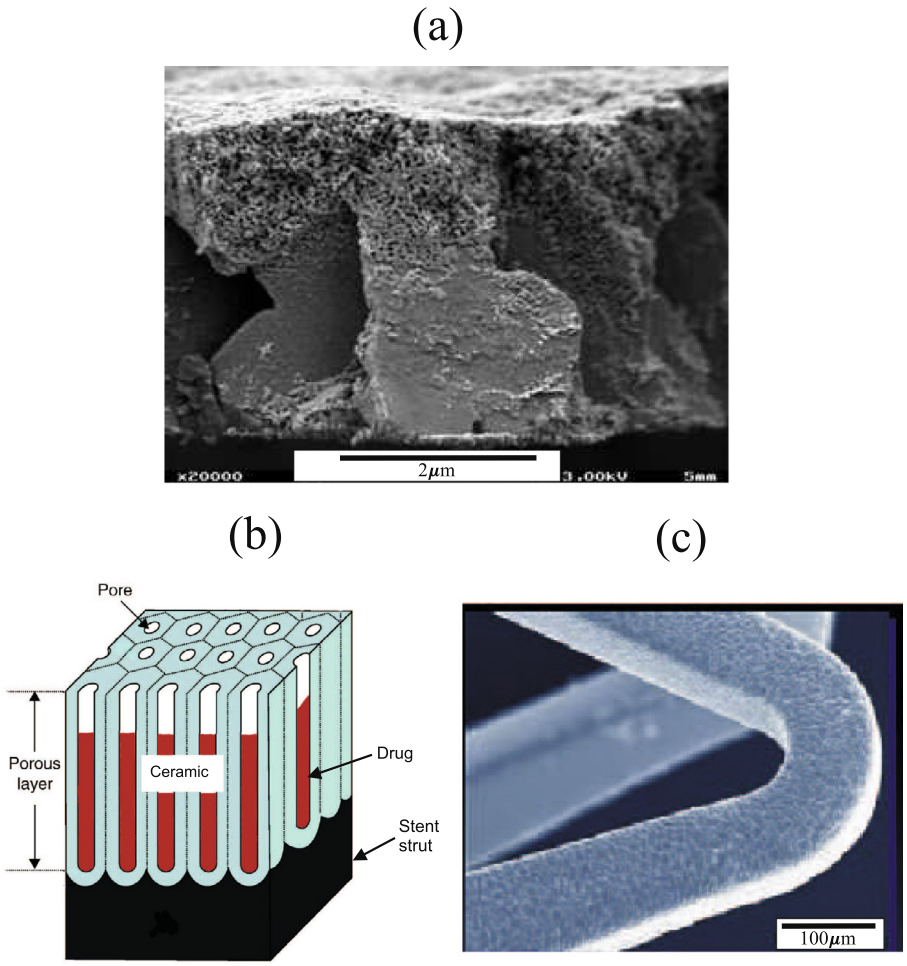

Fig. 1. Some of the polymer-free drug-eluting stent systems modelled in the current study. (a) A scanning electron microscope image of the Setagon stent [20]. A nanoporous drug-infused layer covering a steel strut acts as a reservoir for the prolonged release of drug. The pore diameters here are of the order of 10 nm. (b) A schematic representation of part of a ceramic-coated tacrolimus-eluting stent. The pore diameters here are again of the order of 10 nm. Nanotubular systems of this kind have also been investigated in the context of orthopaedic and dental drug releasing implants. (c) An image of the drug-coated surface of an Amazonia Pax stent [21]. In this polymer-free system, a layer of semi-crystalline paclitaxel of thickness ≈5 μm covers the stent strut surface.