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Review

Metallic implant drug/device combinations for controlled drug release in orthopaedic applications

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ABSTRACT

The study of metallic drug/device combinations for controlled drug release in orthopaedic applications has gained significant momentum in the past decade, particularly for the prevention and reduction of implant associated infection. Such combinations are commonly based upon a permanent metallic implant (such as stainless steel or titanium) and are then coated with a drug-eluting polymer or ceramic system. Drug elution is also possible from the implant itself by utilising metallic foams, porous architectures and bioresorbable metals. This review will explore the current research into metallic implant drug/device combinations via a critical review of the relevant literature.

Contents

1. Introduction

Metal-based drug eluting systems have received little attention in the literature in comparison to polymer-based systems; however they do offer some unique advantages over polymer-based systems in local drug delivery. This review is focused on current drug delivery systems

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Table 1
Important constituents and physical characteristics of extracellular fluid [14].

Constituent	Normal value	Normal range	Approximate short-term nonlethal limit
Oxygen (mm Hg)	40	35–45	10–100
Carbon dioxide (mm Hg)	40	35–45	5–80
Sodium ion (mmol/L)	142	138–146	115–175
Potassium ion (mmol/L)	4.2	3.8–5.0	1.5–9.0
Calcium ion (mmol/L)	1.2	1.0–1.4	0.5–2.0
Chloride ion (mmol/L)	108	103–112	70–130
Bicarbonate ion (mmol/L)	28	24–32	8–45
Glucose (mg/dl)	85	75–95	20–1500
Body temperature (°C)	37	37	18.3–43.3
Acid-base (pH)	7.4	7.3–7.4	6.9–8.0

that involve a combination of metallic implants and local drug delivery, primarily for orthopaedic applications. A combination product is defined by the US Food and Drug Administration (FDA) as a product comprised of two or more regulated components i.e.: drug/device, biologic/device, drug/biologic or drug/device/biologic that are physically, chemically or otherwise combined and produced as a single entity [1]. The FDA has categorised combination products into 9 types, including: prefilled drug or biologic delivery device/system, device coated/impregnated/otherwise combined with drug or biologic, drug/biologic combination or other type of combination product. Examples of approved combination devices include transdermal patches for the treatment of early Parkinson's disease and ADHD in children, antibiotic bone cement and collagen with lidocaine for aesthetic use.

There are two standout applications for drug/device combination products containing metallic devices: cardiovascular stents that elute drugs to prevent restenosis and implants that deliver drugs to prevent infection associated with orthopaedic and dental implants. Other applications of drug delivery associated with metallic implants involve alternative delivery of drugs, for example the delivery of chemotherapeutics to the brain from titania nanotube arrays on the surface of titanium implants [2], delivery of eye drops from polymer coating on titanium wires to the eye [3] and folic acid protected silver nanoparticles for cancer therapy [4]. Drug delivery using metals is most commonly in the form of embedding drugs into coatings applied to the metallic implant that is either polymeric or ceramic in nature. Other methods involve incorporation of the drug itself to the implant surface via covalent bonding [5–7], self-assembled monolayers (SAMs) [8], as well as embedding silver nanoparticles into the surface of titanium [9,10]. Metals themselves can be used for delivering pharmaceutics via porous magnesium foam or utilisation of the antimicrobial nature of some metals including silver. However to the best of our knowledge there has been no current research into the possibility of resorbable metallic implants that can provide a route to drug delivery through the degradation of the metal itself. This concept provides advantages as the implant can provide mechanical support, deliver controlled (local) drug delivery, serve the functional implant role, degrade and be resorbed *in vivo*. An added benefit of resorbable implants is that more than one mode of drug release may be employed. For example the resorbable implant can contain antibiotics to stem infection long term, while a degradable coating can provide short-term delivery of anti-inflammatory drugs. Thus, there are an array of options and opportunities for the use of metallic based systems for drug delivery, and this review provides a current state of the art in this field.

1.1. Implant biomaterials

Materials implanted into the body are exposed to a relatively harsh and dynamic environment that can also be corrosive to metals. Beyond crystallography: the study of disorder, nanocrystallinity and crystallographically challenged materials with pair distribution functions [11].

Table 2
Comparison of commonly used biomaterials (data from [17–19]).

Material	Composition	Applications	Advantages	Disadvantages
Titanium	Pure F67 Ti6Al4V F136, F1472 Ti6Al7Nb F1295 Ti15Mo F2066 Ti12Mo6Zr2Fe F1813 Ti15Mo5Zr3Al	Joint replacement, dental implants, fracture fixation, spinal fusion implants, spinal disc replacements	Corrosion resistance, high specific strength, low density, microarchitecture, osteointegration	Poor shear strength, notch sensitivity
Stainless steel	316 L Rex 734™ 22-13-5™ BioDur® 108	Fracture fixation, stents, hip stems, spinal implants, cables	Mechanical strength, non-magnetic, corrosion resistance, fatigue strength	Corrodes in high stress, low oxygen conditions (fixation devices)
Cobalt–chromium alloys	F75 (Cast CoCrMo) F562 (Wrought CoNiCrMo)	Joint replacements, stents, pacemaker conductor wires, spinal disc replacements, dental bridgework	Mechanical strength, durability, corrosion resistance, fatigue strength, wear resistance	High modulus, high density
PMMA	Poly methylmethacrylate $-(C_5O_2H_8)-$	Cements in orthopaedics and dentistry	Adhesive strength, interface fracture, fast setting	Nondegradable, sets exothermally, causes stress shielding
UHMWPE	Ultra high molecular weight polyethylene $-(C_2H_4)-$	Joint replacements, orthopaedic bearings	Fracture, fatigue and impact strength, low friction, creep and wear resistance, durability	Nondegradable
PLGA	Copolymer of poly(lactide) (PLA) and poly(glycolide) (PGA)	Biodegradable sutures, bone fixatives, dentistry, artificial blood vessels, drug delivery	Biodegradable, predictable degradation rates,	Low compressive strength
Hydroxyapatite Tricalcium phosphate	$Ca_5(PO4)_3OH$ $Ca_3(PO_4)_2$	Osteointegration, drug delivery, bone implants Osteointegration, artificial bone, solid and porous coatings	Excellent biocompatibility, high modulus, zero creep Resorbable, component of bone	Brittle, insoluble, very slow *in vivo* degradation Brittle, rapid unpredictable degradation *in vivo*, low mechanical strength
Zirconium	Zr, ZrO_2	Dental restoration, joint replacement	Wear resistance	Difficult to manufacture