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REVIEW ARTICLE

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Implantable drug delivery systems for the treatment of osteomyelitis

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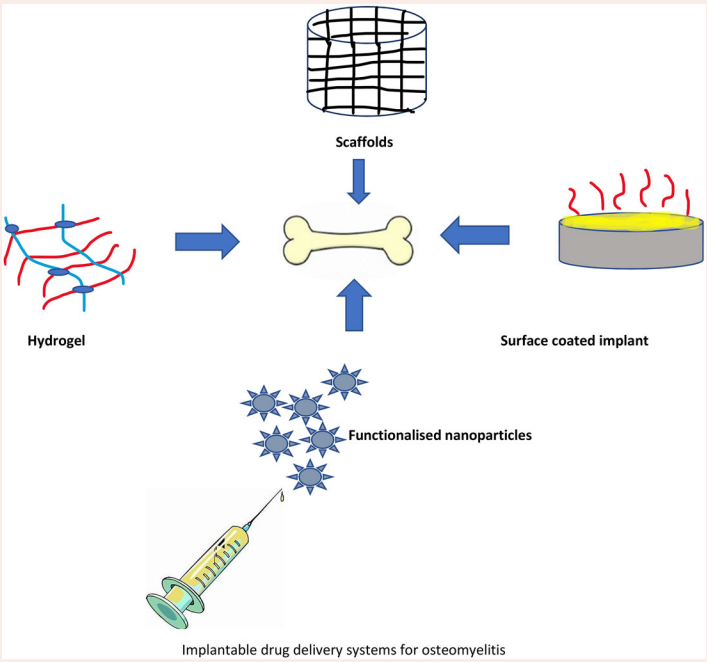
ABSTRACT

Osteomyelitis is an infection of the bone tissue and bone marrow which is becoming increasingly difficult to treat due to the infection causing pathogens associated. *Staphylococcus aureus* is one of the main bacteria that causes this infection, which has a broad spectrum of antibiotic resistance making it extremely difficult to treat. Conventional metal implants used in orthopedic applications often have the drawback of implant induced osteomyelitis as well as the requirement of a second surgery to remove the implant once it is no longer required. Recently, attention has been focused on the design and fabrication of biodegradable implants for the treatment of bone infection. The main benefit of biodegradable implants over polymethylmethacrylate (PMMA) based non-degradable systems is that they do not require a second surgery for removal and so making degradable implants safer and easier to use. The main purpose of a biodegradable implant is to provide the necessary support and conductivity to allow the bone to regenerate whilst themselves degrading at a rate that is compatible with the rate of formation of new bone. They must be highly biocompatible to ensure there is no inflammation or irritation within the surrounding tissue. During this review, the latest research into antibiotic loaded biodegradable implants will be explored. Their benefits and drawbacks will be compared with those non-degradable PMMA beads, which is the stable material used within antibiotic loaded implants. Biodegradable implants most frequently used are based on biodegradable natural and synthetic polymers. Implants can take the form of many different structures; the most commonly fabricated structure is a scaffold. Other structures that will be explored within this review are hydrogels, nanoparticles and surface coatings, all with their own benefits/drawbacks.

GRAPHICAL ABSTRACT



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Introduction

Osteomyelitis (OM) is considered a progressive infectious disease commonly affecting the bone and bone marrow [1,2] which if left untreated, can result in severe complications such as complete amputation of the infected limb. OM can result from fungi and a variety of bacteria strains [3] with the most common being *Staphylococcus aureus* (SA), a Gram-positive bacterium which on its own can provide a multitude of complications. The main one being methicillin resistant *Staphylococcus aureus* (MRSA) which can be severely difficult to treat often requiring a combination of antibiotics which subsequently increases the risk of further antibiotic resistance [4,5]. OM can be caused either by direct trauma to the bone, allowing for bacteria to reach deep into the bone *via* a fracture or break causing an infection. Or it can be a hematogenous cause, which is the spread of bacteria through the blood, most common in very young children. In hematogenous OM, SA is responsible for 80–90% of bacterial infections [4,6]. In conjunction with the route of infection, OM can also be considered acute or chronic depending on the persistence of the bacteria present [4].

Chronic OM has been a relentless problem for thousands of years, which until the introduction of antibiotics in the 1940s it was treated by simply ignoring it or attempting to surgically remove the infection [7,8]. The most common treatment for acute OM is a course of parenterally administered antibiotics [3]. The antibiotic used is dependent on the type of bacteria causing the infection and location of the infection within the bone tissue [4]. Most chronic OM infections almost always require a debridement surgery [1,3] to remove any compromised bone and reinforce with an implant, usually polymethylmethacrylate (PMMA) based, loaded with antibiotics [9,10]. However, complications associated with PMMA based polymer implants resulted in a drive to research the benefits of biodegradable polymers as a potential drug delivery system. Implantable drug delivery systems have become a staple for many medical applications across the world, in 2019 alone the market was worth roughly £60 billion [11].

In this review, the current research into the topic of biodegradable implants for orthopedic applications and drug delivery will be evaluated. Non-degradable implants for orthopedics are less expensive than biodegradable ones however, they require a secondary surgery for removal which can be traumatic for the patient and pose a further threat of infection [11,12]. Scientists began researching an implant that offered all the benefits of non-degradable implants, such as PMMA, but also degraded into biocompatible by-products once the antibiotics had been successfully released; hence, biodegradable implants. These degradable implants can be summarized into five groups, these include natural polymer based; synthetic polymer based; and composites of these polymers with metals, glass and ceramics [13]. Each material has its own benefits and drawbacks with varying applications. The main requirements of biodegradable implants are their ability to release antibiotics at a controlled rate, provide a supportive scaffold for bone regeneration to occur and degrade into by products that are nontoxic and also biocompatible as not to illicit an immune response [14].

The aim of this review is to discuss different biomaterials and their applications in osteomyelitis treatment with the benefits and drawbacks of each. The different implant structures will then be summarized along with their different fabrication and degradation mechanisms.

Osteomyelitis

Osteomyelitis (OM) is an inflammatory infection of the bone and bone marrow caused by microorganisms, typically pyogenic bacteria but could also be caused by mycobacteria and fungi [1,3]. The most common cause of infection is from SA with it causing 80–90% of cases of hematogenous OM. SA is a gram-positive bacterium with a high tendency to form biofilms [4,6,11]. OM can be caused by a hematogenous or a contiguous source. Hematogenous OM is only common in young children and is a result of the spread of bacteria *via* the blood supply to the bone, the bacteria mainly only affect the metaphysis of skeletally immature patients (>16 years) [1,15,16]. If OM is the result of a trauma (contiguous infection), then bacteria would have entered through the disrupted protective layer of skin allowing the bacteria direct access into the bone tissue [1]. Contiguous infection can also be present following a fracture or open joint surgery using a medical implant [16]. OM can be caused by either vascular or neurological insufficiencies and is found commonly in patients with diabetes. This occurs when the blood supply is poor, resulting in a loss of protective sensation, diabetic wounds and a reduction in immune defenses. It usually affects the lower extremities, often resulting in diabetic foot infection [16]. OM is considered a progressive infection, starting off as acute and developing to a more persistent chronic infection, causing inflammatory destruction, bone neoformation and necrosis [2].

Acute OM is a much simpler infection, usually evolving over a few days or weeks. Current treatment strategies only require a 4–6-week course of antibiotics for acute OM which is substantially different to chronic OM [17]. The antibiotic of choice for the treatment may be planned by harvesting a section of the infection and performing a biopsy to determine the microbial agent. Once determined, the broad-spectrum antibiotic that was originally administered can be swapped for a more tailored one. From a number of case studies on humans with chronic and acute OM, the preferred antibiotic of choice has shown to be cefoxitin [18,19]. Gentamycin is also widely approved as an effective antibiotic for OM treatment [20]. Chronic OM is a more persistent infection, developing over months to years requiring a more rigorous treatment plan. Chronic OM is often treated with surgical debridement but due to the spatial heterogeneity of the bacteria colonization within the bone it is difficult to fully eliminate it and so antibiotics are usually administered intravenously as well [17]. Debridement involves removing the compromised bone and often substituting with an implant to provide a supportive scaffold whilst the healthy bone grows back [1,3,4]. Depending on the type of antibiotic loaded implant used (biodegradable or non-degradable) will determine whether the patient will require a second surgery to remove the implant or not. Before implants were employed autografting was the original form of treatment for OM, in which bone was dissected from the patients own body to reinforce the fragile/fractured bone. The bone is usually harvested from the iliac crest as it incorporates essential characteristics for bone growth, these are osteogenicity, osteconductivity and osteoinductivity. Even though autografts are considered standard practise they are still prone to fracture, infection and severe pain for the patient, hence, the urgency for a different treatment method [13,21].

Non-degradable Implants

A biomaterial can be considered a synthetic or natural substance that has been engineered to safely interact with the human body to provide a therapeutic or diagnostic effect [13]. More recent treatment methods for OM have involved using implants loaded with antibiotics to allow local delivery of the drugs rather than parenteral delivery, which often leads to a reduction in systemic

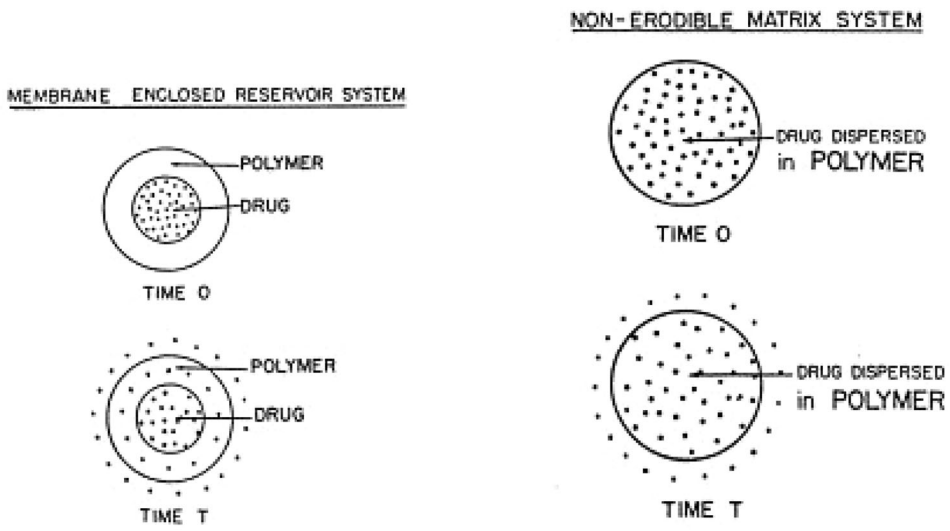

Figure 1. simple diagram representing the dispersion of drug molecules within a reservoir system and a matrix system after time *T* [14,22].

side effects [9]. These biomaterial implants can be considered biodegradable or non-biodegradable, but both have the same requirements. Implants should be able to release antibiotics at a controlled rate, be biocompatible to ensure an immune response doesn't occur and be nontoxic. However, with consideration to non-degradable implants they must be tolerated by the body long term and not issue any adverse inflammatory effects [12]. The mechanical properties of an implant are just as important as the chemical properties. They need to perform as an ideal fixation device in which they can reduce the stress shielding. When considering scaffolds, the mechanical properties of the implant must match the mechanical properties of the tissue that is being regenerated. The mechanical properties of a scaffold include the compressive strength, the tensile strength, the load baring capacity and the stiffness. If the mechanical properties do not match up, then an improper bone formation will result or an implant failure [13].

Non-degradable implants can be grouped into two common categories: matrix systems and reservoir systems, these are summarized in Figure 1. A polymeric matrix system (also referred to as a monolithic system) is described as a homogeneous dispersion of polymer with drug molecules mixed within, such as within the pores of the matrix. The drug molecules can slowly diffuse through the matrix and into the surrounding fluid allowing for a sustained release from the implant. Alternatively, a reservoir system consists of solid core of drug surrounded by a permeable, non-degrading polymer shell. The thickness and level of permeability of the polymer membrane will determine the rate of drug release into the body. A reservoir system is ideal as it is able to reach zero order drug release kinetics allowing for constant therapeutic levels, however it is unfavorable over a matrix system for a number of reasons. There is a significant risk of membrane rupture, leading to an effect called dose dumping which would result in a massive peak of drug blood plasma concentration, and serious toxic side effects for the patient [14,22,23]. The drug release mechanism of an implantable delivery system can be considered either passive or active. Active release utilizes a mechanical system such as magnetic, laser or electrical to stimulate and release drug. These can also be considered as 'smart implants'. Whilst passive release is predetermined by the implant's materials such as the fabrication of the implant, this mechanism of drug release can then not be changed once implanted [23].

Polymethylmethacrylate (PMMA)

The most commonly explored and used non-degradable implant is PMMA based, which has been used to treat chronic OM for the past 20 years and general orthopedic applications since the 1930s [20,24]. PMMA can exist as either antibiotic loaded bone cement or antibiotic loaded beads, both with different applications. Bone cement is used as a prophylactic and is applied to arthroplasties whilst PMMA beads tend to be used for musculoskeletal infections. PMMA beads are more favorable due to their large surface area, as they allow a quicker antibiotic release. However, PMMA beads are often made non-commercially by surgeons which results in an uneven bead size, resulting in an uneven release rate of the antibiotic [25]. If made commercially then all PMMA beads would have a consistent diameter of 7 mm [20,25,26]. It has been found that antibiotics elute out of the PMMA beads in a bimodal trend; an initial burst release of drug followed by a further slower release typically over a period of 4–6 weeks but more usually up to a month [20,25,27,28]. Many researchers found that the highest concentration of antibiotic release is within the first 48 h, with 5% of the total antibiotic being released within the first 24 h [20,25,28]. Some larger PMMA beads with a smaller surface area to volume ratio (in comparison to smaller bead) also have significant antibiotic levels up to four years post implantation [28,29]. However, these levels of antibiotics are still relatively low and resistant bacteria may appear on the carrier surface [20].

Only certain antibiotics can be used with PMMA beads and PMMA cement because they do not release all antibiotics at the same rate. Aminoglycosides such as gentamycin are very stable at high temperatures and are most commonly used in beads whilst vancomycin is more commonly associated with PMMA cement [20,28]. The antimicrobial agents loaded into the implants have to meet certain criteria: they must be unable to enter systemic circulation; unable to induce any adverse side effects; must be released locally at a concentration often ten times more than that of the minimum inhibitory concentration (MIC); be active against most pathogens commonly associated with chronic OM; be stable at body temperature and; be water soluble as to allow diffusion out of the carrier [20]. A study carried out in 2013 to determine the effect of storage temperature and storage time on the release of vancomycin from PMMA beads showed that the storage conditions displayed no significant effects on the release rate of the drug from the beads [30]. However, this is not always the case as

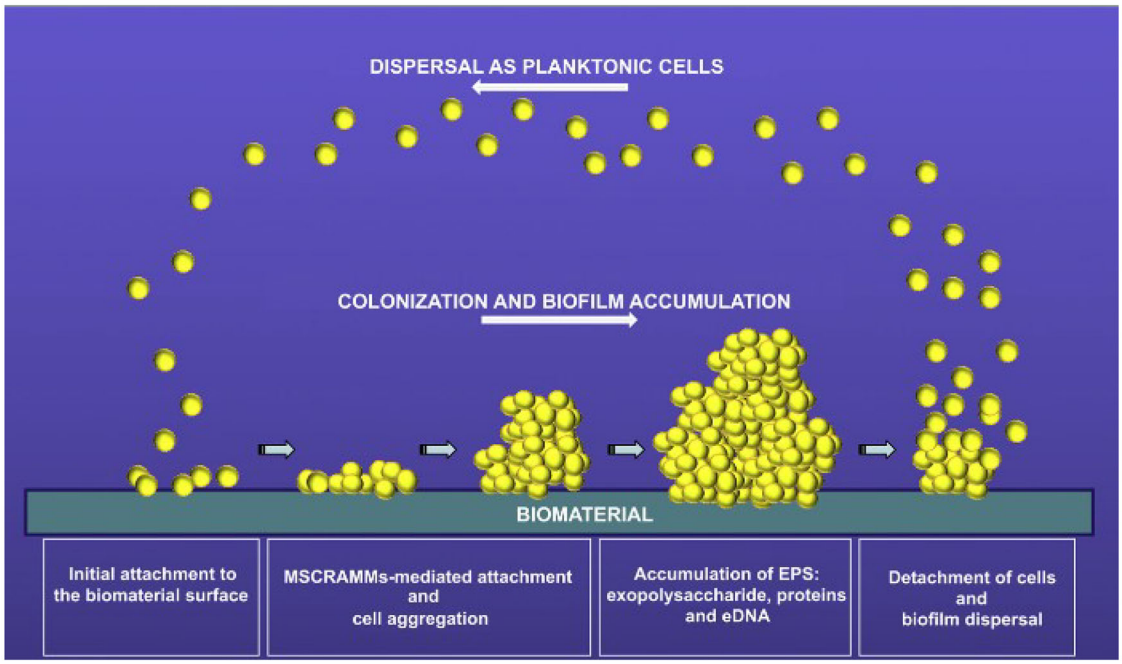

Figure 2. The process of biofilm formation is summarized. This shows the initial attachment of singular bacteria cells up, followed by the cell aggregation to form a matured biofilm. The dispersion of cells to produce planktonic cells allows for a new biofilm to form elsewhere [34]. [Biomaterials journal support sharing research].

some drugs are incompatible with PMMA. Some antibiotics are heat labile and cannot withstand the exothermic polymerization process therefore, gentamicin, tobramycin, vancomycin, and cephalosporins are only used in conjunction with PMMA carriers. However, rifampicin, a well-known antibiotic, cannot be used with PMMA due to its ability to scavenge free radicals and obstruct the polymerization process [17].

Drawbacks of PMMA bone cement

The use of medical implants as drug delivery systems has propelled antibiotic efficacy in the medical field but many drawbacks associated with PMMA specifically have made scientists explore other materials for their use as medical implants. The most obvious implication of PMMA is that it's non-biodegrading and so a secondary surgery is required to remove the implant after it no longer provides any therapeutic benefits-andthis can be very distressing and painful for the patient [9,14]. It has been observed that the elastic modulus (1700–3700 MPa) and compressive strength (85–114 MPa) of PMMA cement can be problematic [14]. PMMA bone cement is much stronger than that of cancellous bone (0.1–15 MPa) and cortical bone (10–900 MPa) in the human body which results in a high risk of fracture in the adjacent bone [24]. A recent study observed a compressive fracture in the adjacent bone to the PMMA cement implant in 36 patients a year after a vertebroplasty procedure [24,31,32]. A potential solution to this was explored by a study in 2019 to determine whether the addition of gelatin as a porogen to PMMA bone cement would reduce the elastic modulus of PMMA enough relatively to that of cancellous bone [24]. Increasing porosity will also improve drug elution levels as PMMA is known for poor drug release efficacy (approximately 25%) [9,24]. During the dough period the drug can dissolve and disperse from the implant, but during curing the PMMA quickly hardens on the outer surface trapping any remaining antibiotic within [24]. Increasing porosity to increase drug elution levels can also be done by adding dextran or polyethylene glycol to the beads [25]. The process of polymerization of PMMA to form beads incorporating the antibiotic is a heat generating exothermic process. The heat generated can have a detrimental effect on any thermally sensitive drugs. Most antibiotics are heat sensitive so this limits the number of drugs that can be used with PMMA beads [9,33].

Biofilms

PMMA implants are particularly susceptible to microbial colonization leading to an infection [34]. When this happens a biofilm forms which is defined as communities of bacteria that are encased within an extracellular polymeric substance that is directly produced by the bacteria involved [15]. The formation of a biofilm can be essentially considered a four step process: Firstly, the bacteria cells (often SA) attach onto the surface of the implant; this allows the cells to aggregate and accumulate into multiple cell layers; propagation of the multiple cell layers results in a mature biofilm and; finally, the detachment of bacteria cells from the biofilm turns them into planktonic cells which are able to spread and initiate new biofilm formation at a different site within the body [34]. Figure 2 summarizes the formation of biofilms.

When the cells are in the planktonic state, they are susceptible to systemic antibiotics, but when formed into a sessile growth phase then the bacteria within the biofilm have reduced susceptibility to antibiotics [7]. The antibiotic tolerance of the bacteria leads to an increase in the MIC by 100-fold in most cases [15,35,36]. This tolerance is brought about by a number of factors. Antibiotics have poor penetration into the biofilm matrix. an induced stress response from low antibiotic levels, deep within the biofilm there is a low metabolic state which for antibiotics that rely on metabolic activity are rendered ineffective, and finally the presence of bacterial persistent cells that are in a dormant state [15,36]. A combination of all these factors results in an antibiotic resistant biofilm of bacteria on the site of an implant. As well as being resistant to antibiotics, a biofilm can allow a

Table 1. Biomaterials used for treating bone infection.

Material	Degradation property	References
Polymethylmethacrylate (PMMA)	Non-degradable-Synthetic polymer	Nandi et al. [20,25], Wentao et al. [27], Roeder et al. [28], Chen et al, [30].
Collagen	Biodegradable-Natural polymer	Mulchandani et al. [13], Langer, [22], Ipsen et al. [39], TRAFNY et al. [40]
Fibrin	Biodegradable-Natural polymer	Inzana et al. [17], Mader et al. [41]
Chitosan		Ahsan et al. [42], Aimin et al. [43], Wei et al. [44], Tao et al. [45], Ho et al. [46]
Alginates	Biodegradable- Natural polymer	Gonen-Wadmany et al. [47]
Polyesters	Biodegradable-Synthetic polymers	
PLGA, PLA, PCL		
PLA		-Prajapati et al. [48], Rancan et al. [49].
PLGA		-Makadia et al. [50], Ye et al. [51]
PCL		-Ray, [52]
Polyurethanes	Biodegradable-Synthetic polymers	Cherng et al. [53], Kamaci, [46], Polo Fonseca et al. [54], Li et al. [55], Mandru et al. [56], Chen et al. [57],
Polyanhydrides	Biodegradable-Synthetic polymers	Pandey et al. [58], Brin et al. [59], Samavedi et al. [60],
Metal alloys	Biodegradable	Chen et al. [61], Staiger et al. [62], Purnama et al. [63], Li et al. [64], Zhai et al. [65], Vojtěch et al. [66], Tang et al. [67], Schinhammer et al. [68], Peuster et al. [69], Prakasam et al. [70]
Bioglass and Bioceramics	Biodegradable	Lee et al. [71], Khurana et al. [72], Fernandes et al. [73], Zambanini et al. [74], Zhang et al. [75], Lindfors et al. [76],
Composites	Biodegradable	Radwan et al. [77], Miyai et al. [78], Kuang et al. [79], Bai et al. [80].

significant defence for the bacteria cells against host immune responses, these include phagocytosis by immune cells [15,36]. The only known antibiotic with an effect against staphylococcal biofilm is rifampicin [15,37] whereas ciprofloxacin is effective against gram-negative bacteria biofilms [15,38]. The complications associated with biofilms are the reason why OM is very difficult to treat. Despite the many drawbacks of PMMA impregnated cement and beads, they still remain the most viable option for the treatment of OM as concluded in a study performed in 2017 [27].

Biodegradable implants

Biodegradable implants offer all the benefits of non-biodegradable implants, but they eventually degrade *in situ* and are replaced with newly generated bone [13,21]. Table 1 summarizes the biomaterials used for implants formulations for bone infection. As well as being both chemically and mechanically stable, the biomaterial must have osteoconduction which allows the biomaterial to facilitate the growth of new bone tissue. It must also have osteoinduction which is the process of inducing osteogenesis and; it must also have osteointegration which allows the integration of the biomaterial into the surrounding bone tissue. Chemically, the biomaterial must be inert but should also be able to induce vascularization [81]. The pore size of the implant is also essential for the function of the implant. A pore size of 200–350 μm is expected to allow efficient transport of nutrients and oxygen [21]. The most widely used resorbable biomaterial before polymers which extensively explored was calcium sulfate. Antibiotic laden calcium sulfate that had many applications in the treatment of chronic OM [17], were tobramycin loaded calcium sulfate [82] and gentamycin loaded calcium sulfate. Both formulations have successful results with gentamycin loaded calcium sulfate having a higher blood plasma concentration of the drug after 72 h in comparison to gentamycin loaded PMMA beads [83].

There are many additional materials that can take the form of biodegradable implants, the most commonly explored are resorbable polymers; both synthetic and natural. Polymers offer advantages over other biodegradable materials which make them more favorable. Polymers reduce the stress shielding within implants by gradually unloading the pressure onto the healing bone as the polymer degrades, which is a major drawback with metal implants as they tend to have greater stiffness compared to that of natural bone [13]. In this section the use of different biodegradable biomaterials and their composites as drug delivering medical implants will be explored.

Natural polymers

Synthetic polymers are often preferred over natural polymers as they can be tailor made to suit the specific requirement, they also have less batch to batch variation when compared to natural polymers [84]. However, natural polymers also have their advantages in that they are made up of naturally abundant materials such as collagen, chitosan, cellulose, alginates, albumin, fibrin, etc. This allows for a much better biocompatibility and ensures any by-products of degradation will not have any toxic effects on the body. They also ensure that there is no inflammation response from the body as they won't be recognized as foreign.

Collagen. Collagen is one of the most abundant proteins found in the human body and is a material found in connective tissue. There are 28 known types of collagen in the human body with type 1 being the most common [13,84]. Collagen has a number of attributes that make it ideal for use as a biomaterial. Collagen doesn't illicit an inflammatory response, it has a high-water affinity, it's nontoxic and has low antigenicity [13]. Collagen sheets with gentamycin incorporated within have been used as a treatment for chronic OM for over 20 years [22,39]. They are highly porous allowing nutrients and oxygen easy access through the structure however, the overly porous structure has poor compression strength so can't be used in any load baring applications [13]. Hence, pure collagen is not ideal as an orthopedic implant as there will be limited support to allow bone regeneration. There are ways to manufacture collagen scaffolds to make them more favorable as an implant. Many researchers have enhanced the mechanical strength of collagen by reinforcing with other materials such as apatite. It was noticed that the biological performance of collagen was not negatively affected by this incorporation but that the osteogenicity and osteoconductivity were increased allowing for easier bone regeneration [85–87]. By providing

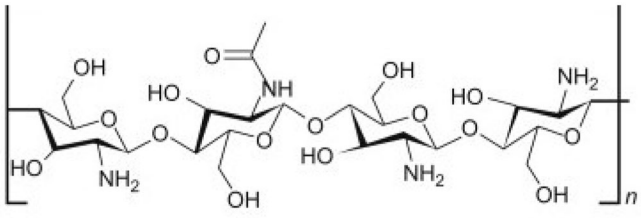

Figure 3. Chemical structure showing the repeat unit of chitosan [91].

physical and chemical queues, the principle of a scaffold is to direct the growth and differentiation of cells to form new functional tissue. Once completed, the scaffold will then degrade into by products that don't generate any adverse side effects [84]. Collagen has excellent biocompatibility and biodegradability, but this often leads to rapid degradation when *in vivo* which can lead to other complications such as dose dumping or implant failure. Researchers in a 2013 study produced a composite scaffold of collagen using electrospinning techniques which incorporated alginate, chitosan and hydroxyapatite into the collagen scaffold [13,88]. Electrospinning is a form of nanotechnology that manufactures materials in the nano size range [89]. They found that the disintegration of collagen was reduced by 35% over a 10-day period making this scaffold much more useful [13,88]. Another study reported that when polymyxin B antibiotic was encapsulated within liposomes and combined with the collagen sponge, the release rate (in comparison to free antibiotic) was substantially slower [20,40]. Another application of collagen is as a coating for titanium implants. Using collagen as a surface modification allows titanium implants to perform as an orthopedic implant without eliciting an immune response, collagen is a natural material and so won't cause inflammation [90].

Fibrin. Fibrin is a biopolymer which is involved in blood clotting and has many advantages over other natural polymers [17]. It is naturally found in damaged tissue so it is unlikely it would illicit an immune response. Fibrin also has the ability to cross link to the surrounding tissue which ensures the delivery of antibiotics to the correct site. Drug delivery usually occurs either by the dissolution of a fibrin membrane or the direct diffusion of drug out of a fibrin matrix. A study performed in 2002 to test the efficacy of a fibrin sealant implant loaded with tobramycin in comparison with tobramycin loaded PMMA beads using female white rabbits that were surgically infected with MRSA OM. The results of the study showed that antibiotic loaded fibrin sealant implants work just as well as antibiotic loaded PMMA beads but with additional advantage of being biodegradable and therefore didn't require a second surgery to remove the implant as in case of PMMA implants [41].

Chitosan. Chitosan is a type of polysaccharide (Figure 3) that is produced by the deacetylation of chitin, which is found in abundance most commonly in the exoskeleton of crustacean creatures [17,21]. There are many advantages of chitosan over other biomaterials, one of them being the structural similarities of chitosan compared to glycosaminoglycans (GAGs) [21]. They can form polyelectrolyte complexes due to the cationic nature of chitosan and the anionic nature of GAGs; these complexes can help in modulating and potentially excel bone regeneration [42]. Chitosan offers flexible physico-chemical properties meaning it can be molded into many structures such as sponges, porous scaffolds and fibers membranes [13,42]. The use of a gentamycin loaded chitosan beads were tested as a possible treatment method for chronic OM; the study was performed *in vitro* followed by *in vivo* on rabbits. They concluded that chitosan implants have good release kinetics of gentamycin and so can act as a good adjuvant method for the treatment of OM [43]. Chitosan already naturally has antimicrobial activity against a wide range of bacteria due to its polycationic nature, which is potentially a result of the molecules ability to react with the negatively charged surfaces of pathogens such as teichoic acids [17]. Chitosan is soluble at acidic pH's but insoluble at neutral and more basic pH's, the instability at low pH can be improved by adding chemical crosslinks with formaldehydes. Adding crosslinks can also enhance the mechanical stability of chitosan improving their use as an implant or scaffold [13,17,44]. One of the most favored characteristics of chitosan is its biocompatibility; it has the ability to promote cell adhesion, proliferation and differentiation [45]. Scientists found that cell adhesion properties of chitosan could be further improved with the electrospun nanofibrous product of chitosan rather than pure chitosan films. Using mouse models, they were able to identify improved adherence between mouse osteoblasts and the nanofibers due to an increased surface area; and so improved osteoinductive effects when compared to pure chitosan membranes [45,92].

Alginates. Alginates are obtained from brown seaweeds and are of the most abundant type of biopolymers [13,21]. They are water soluble due to their polar nature and they are also polyanionic so can form crosslinks with divalent cations to form hydrogels [13]. Hydrogels are composed of polymers in a crosslinked 3 D network that contain a high water and biological fluid uptake capacity. Structurally, they resemble a cell of the body or soft tissue and have many applications as well as drug delivery [46]. Hydrogels are highly desirable as drug delivery systems due to their drug release kinetics. However, its use as a material for bone and tissue engineering is limited due the poor mechanical properties of alginate; it has poor cell adhesion and is rapidly degraded. Therefore, alginate is often mixed with other polymers to help promote better mechanical strength whilst maintaining good biocompatibility and good biodegradability. Alginate possesses chelating ligands which is an ideal characteristic when forming scaffolds for bone regeneration. Freeze drying is the most conventional method for producing scaffolds, but 3D printing has now been utilized more as it allows for more precise control over the pore sizes [13]. There is a greater drive behind producing alginate composites for implants rather than just pure alginate because of its poor mechanical strength [13]. Alginate that has undergone PEGylation has been reportedly used as a hydrogel drug delivery system with good success. This modification enhanced the implants cell adhesion and enhanced the polymers mechanical strength [47].

Synthetic polymers

Natural polymers offer a level of biocompatibility that is hard for synthetic polymers to achieve on the other hand, synthetic polymers have their own advantages that make them more suited as biodegradable implants. Some of the many drawbacks of natural polymers include batch-to-batch variations and lack of control over degradation. Synthetic polymers allow consistent quality through-out stock, allow for a slower degradation and more controlled release kinetics of the drug [17]. Synthetic polymers are highly sort after for use by surgeons due to their high penetrability in soft tissue and bone infections and their extensive compatibility with a wide range of antibiotics, including polymyxin-B, ampicillin and gentamycin [25].

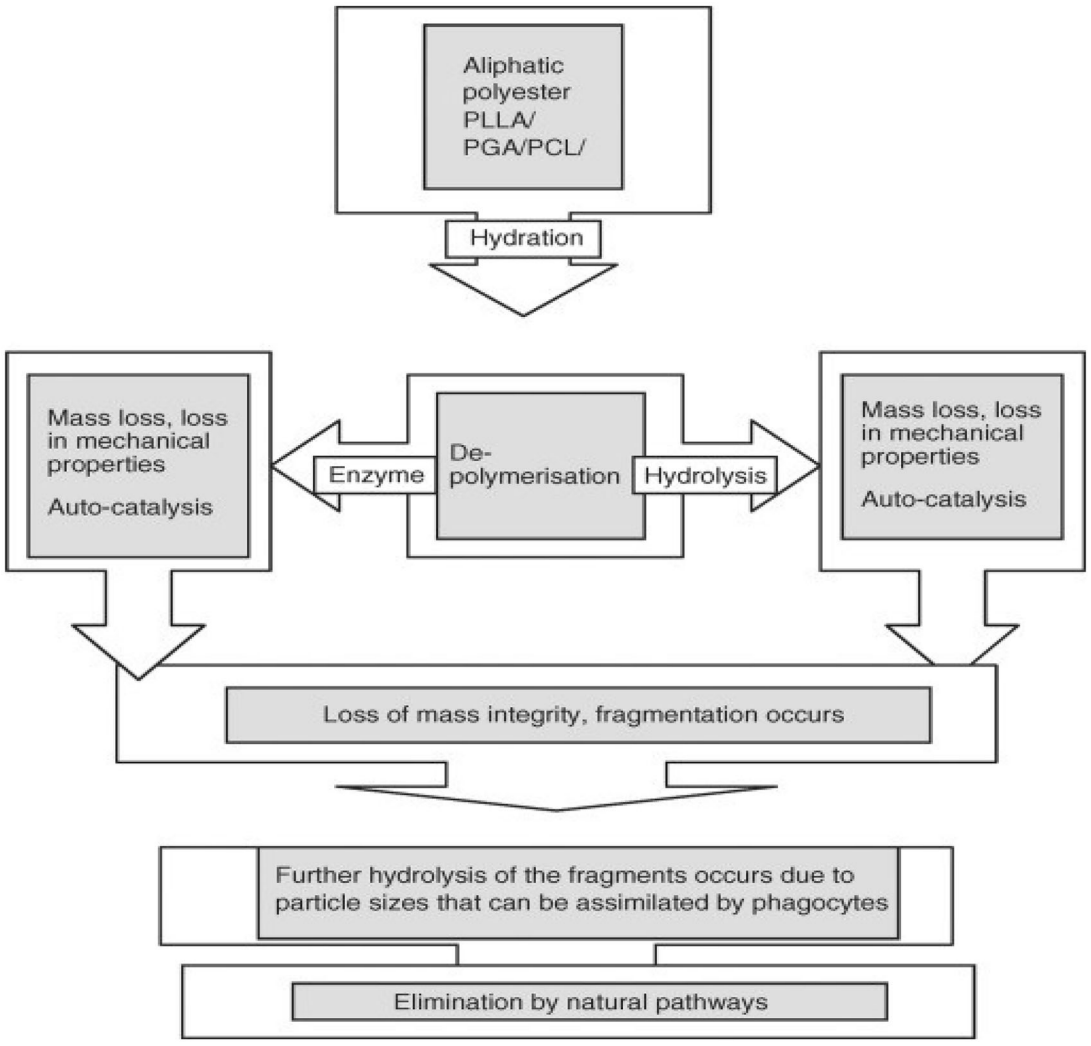

Figure 4. Shows a simplified overview of the degradation sequence for polyesters [84].

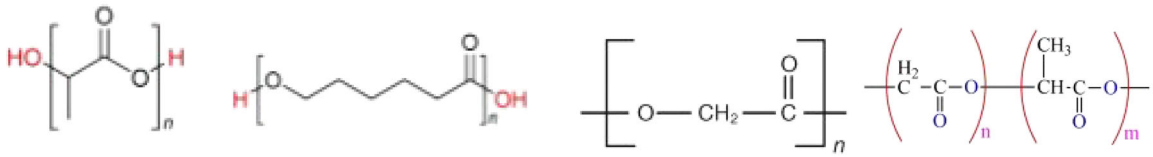

Figure 5. Structure of (From left to right) PLA, PCL, PGA and PLGA [13,48,84].

Polyesters. Polyesters are the most commonly used synthetic polymer. This group includes poly(lactic acid)(PLA), poly(ε-caprolactone)(PCL) and poly(glycolic acid)(PGA). This is because of their easy degradation mechanism *via* hydrolysis of ester linkages within the backbone of the polymer [13]. This occurs when the aliphatic polymers come into contact with tissue fluids or moisture. In the initial stages of degradation, chain scission occurs at the ester linkages yielding lower molecular weight molecules. However, the rate of degradation is determined by how easily accessible the ester bond is and the hydrophilicity of the polymer. These polymers tend to be semi-crystalline meaning they contain areas of crystalline polymer molecules held together by amorphous regions of polymer. The amorphous regions degrade quickly resulting in a material with reduced mechanical strength and so this leads to fragmentation of the polymer implant. Further hydrolysis of the polymer fragments occurs to produce natural degradation products that can be easily eliminated from the body. In reference to PLA, PLA is degraded to lactic acid which is then converted to pyruvic acid and finally eliminated from the body as carbon dioxide and water. Figure 4 summarizes this sequence. By varying parameters of the polymers, the rate of degradation can be altered. Parameters include crystallinity, molecular weight, composite formation and fabrication techniques [84].

PLA is a derived from natural sources such as corn starch and sugar cane and is considered a bioactive thermoplastic. Its structure is shown in Figure 5. PLA is a chiral molecule and so can exist as a D- or L-isomer. The L isomer has the better biological characteristics and very high glass transition temperature and therefore can be processed into fibers, blocks and films for use as medical implants [84,93]. Surface modifications of PLA can be exploited for use in tissues and bone engineering applications [13]. These modifications can enhance the polymers mechanical strength since the mechanical strength of pure PLA is poor and insufficient to support bone regeneration [13,21]. PLA degrades to produce lactic

acid which when found in high concentrations in the surrounding tissues can cause irritation and inflammation. For this reason, PLA is routinely used in conjunction with other synthetic polymers [13]. However, the use of PLA nano-/microparticles has been investigated for applications in topical treatments and systemic carriers of medication with great success [48,49].

PGA is an aliphatic polymer with a very crystalline morphology. Because of this it has a very high melting point of 185–225 °C and a glass transition temperature of 35–40 °C [13,94]. Its structure is shown in Figure 5. In comparison to PLA, PGA is less hydrophobic and so is less protected from hydrolysis and therefore has a much quicker bulk degradation [13,48]. A quicker degradation results in a reduced mechanical strength. PGA is a versatile, easy to process polymer that can be formed into 3D scaffolds for bone tissue engineering [13]. However, as with PLA, PGA is degraded to form glycolic acid which at high concentrations lowers the pH of the surrounding tissue causing inflammation [13,84]. A reduction in the pH can also result in an increase in hydrolytic erosion and cause an autocatalytic degradation of the polymer. This in turn will increase the release rate of the drug [17]. PLA and PGA are often combined to form a co-polymer of poly(lactic-co-glycolic acid) (PLGA) which is a much more widely used biodegradable, non-immunogenic drug delivery system [48]. Its structure is shown in Figure 4. PLGA also has the added benefit of being stimuli responsive and so allowing for a controlled rate of drug release [48]. PLGA vesicles has many applications in the delivery of anti-cancer drugs directly to the site of action and for protein delivery [48,50,51].

PCL is an aliphatic polyester with a melting point of approximately 60 °C and a glass transition temperature of −60 °C [17,48]. Its structure is shown in Figure 5, from which it can be seen that PCL has a higher hydrophobic content than the other polymer structures. Due to the increase in hydrophobic content, the susceptibility to bacterial degradation is increased. However, the advantages of PCL over PLA and PGA are that the by-products of degradation do not cause any adverse effects hence no inflammation of surrounding tissue and they degrade much slower and so PCL implants can maintain their structure for up to 2 years [17]. PCL can often be mixed with starch to produce a better biodegradable material for targeted drug delivery but at a much lower price [52].

Polyurethanes. Polyurethanes (PUs) are considered flexible polymers that are biologically stable and biocompatible that carry a urethane bond (-NH-COO-) in their main chains [48,53]. The biodegradability of PUs can be enhanced by swapping non-hydrolyzable groups for hydrolyzable linkages within their backbone [48]. The building blocks of PUs can be altered to allow for a variety of characteristics such as having a positive charge and to be thermo-responsive, meaning their structure may change to release drugs to their surroundings when exposed to certain temperatures. Isocyanates and polyols make up the building blocks of polyurethanes, using aliphatic diisocyanates produces a PU that is resistant to UV radiation but then using an aromatic diisocyanate can produce a PU that is susceptible to photodegradation [53]. Applications of PU in hydrogels, scaffold and electrospun fibers have been extensively researched in the biomedical industry for use as drug delivery systems. They are considered a good candidate because of their good mechanical strength [46], which comes from the alteration between soft segments composed of polyesters or polyethers, and hard segments composed of urethane linkages. Varying the composition of soft segments to hard segments can influence the degradation rate of the polymers. A study which

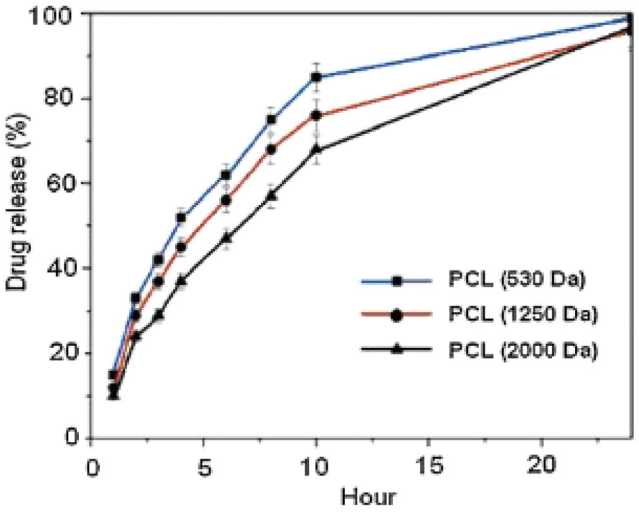

Figure 6. Showing the relationship between the release rate of sulfamethoxazale drug and the molecular weight of the soft segment within the polymer [53,95]. [Int J Pharm supports sharing research].

involved the synthesis of PUs with different molecular weights of PCL within the soft segments concluded that this variation has an influence on the rate of degradation. The study also showed that the compositions with the lowest molecular weight of PCL degraded rapidly within minutes whilst the systems with a high molecular weight of PCL took up to 96 h to degrade [53,95]. This evidence can be summarized in Figure 6. Urethane linkages take part in hydrogen bonding and so providing additional mechanical strength whilst the soft segments allow elasticity [54]. Polyurethanes scaffolds containing vancomycin have been researched for their efficacy in the treatment of bone infections in polycomparison to PMMA beads loaded with vancomycin. The study revealed that their performance was comparable with the added benefit that PUs didn't require a second surgery to remove and that they allowed bone regeneration and vascularization to occur *in situ* with implant degradation [55]. Pure PU hydrogels have many applications in the biomedical industry however they are often mixed with other biomaterials to enhance their effectiveness. PU based hydrogels have been mixed with chitosan for the controlled drug delivery of 5-fluoro uracil [46] as well as freeze-thawing with poly(vinyl alcohol) for the release of neomycin sulfate [56]. The release of drugs from a PU based system can occur in a number of ways. They can be in the form of a membrane releasing system as shown in a study performed in 2011 which explored the use of thermally responsive PU membrane systems [53,57]; they can be in the form of nano/micro particulate systems, these include micelles, pellets, nanocapsules; or they can be in the form of matrix system such as scaffolds and gels as discussed earlier [53].

Polyanhydrides. Polyanhydrides are different to other synthetic polymers in the way they erode *via* surface erosion rather than bulk erosion. They are hydrophobic in nature, consisting of two carbonyl groups bound by an ether linkage. Due to surface erosion, water doesn't usually enter the polymer matrix until degradation starts so the drug is often protected from the aqueous environment [17,48]. These polymers degrade at the anhydride bond into diacid monomers which are nontoxic to the body and so easily metabolized [58], however at high concentrations they have been known to cause inflammation of the surrounding tissue when the polymers are sebacic acid-based [17]. The surface

erosion allows a constant rate of drug release over a long period of time essentially allowing for a zero order of release [17]. The rate of degradation can be enhanced by altering the pH, polyanhydrides degrade slowly at low acidic pH solutions and faster at high basic pH solutions [48]. Poly(sebacic-co-ricinoleic-ester-anhydride) loaded with gentamycin was used in a study on rats to determine its effectiveness in treating OM caused by a SA strain of bacteria. The infection was not completely eradicated from their test group, but the study concluded that polyanhydride delivery systems could be a good alternative to PMMA loaded gentamycin beads [59]. By adjusting the polymer composition of polyanhydrides then the physical properties can also be altered. By adding polymers of PEG to the composition, the hydrophilicity can be increased as well as synthesizing copolymers of polyanhydrides-co-imides to enhance the polyanhydrides mechanical strength. The compressive strengths of these copolymers are in the range of 50-60MPa which is comparable to that of cancellous bone [60].

Metal alloys

Metal alloys as biodegradable implants is a new avenue that has not been massively explored within the pharmaceutical industry as of yet. The main focus of employing biodegradable metal alloys is to replace the non-degradable metal counterparts within an implant such as the screws, plates, stents and bone fixations. They must degrade at a rate steady enough to allow proper bone formation but also provide enough mechanical strength to support the bone formation but not too much as to induce stress shielding. Copper alloys are not as widely researched for their use as biodegradable implants however, their benefit over other metal alloys for already being naturally antibacterial and so minimize the risk of infection and formation of biofilms [96]. Other metals more widely researched include magnesium-based, zinc-based and iron-based, which are all essential nutrients found naturally in the body. However, the recommended daily intake for zinc and iron is roughly 8-18mg day^{-1} which for a pure zinc or pure iron implant would result in high toxic levels of both [61]. Hence why alloys are usually employed as implants rather than their pure form.

Out of all metal alloys tested for their suitability as biodegradable implants, Mg-based implants have shown the most potential with the most research associated. The physical properties of magnesium alloys are comparable with that of natural bone with an elastic modulus of approximately 41–45 GPa [61,62] whilst natural bone has a value of 3–20 GPa. When comparing their values to that of zinc (~90GPa) and iron (~211.4 GPa) [61,63], magnesium is considerably more similar and so would not result in complications from stress shielding. Zinc and iron have a much higher elastic modulus and so stress shielding would be induced resulting the potential for a further fracture. Magnesium is considered very biocompatible and naturally required at high doses by the body (300–400 mg day^{-1}) [63] so high amounts found in the body after degradation will not result in any negative side effects. However, magnesium has limited uses due to a very high degradation rate. The mechanical integrity of magnesium is lost when exposed to environments in the pH range of 7.4–7.6 i.e. physiological conditions [61]. Magnesium and magnesium alloys have been researched amongst scientist for their treatment in osteomyelitis, with several *in vitro* and *in vivo* studies confirming their antimicrobial activity. Mg-based implants have been found to promote new bone formation and accelerate osteogenesis [64,65]. Magnesium alloys incorporating Cu^{2+} ions have been investigated for their treatment in osteomyelitis as copper is known to enhance antimicrobial activity and slow the corrosion rate of magnesium. It was found that incorporating 0.25 wt% of copper enhanced the magnesium-based implant performance during an *in vivo* test and limited the extent of biofilm formation on the implant [64].

Zn-based alloys are often employed with a small percentage of magnesium (~3%) as this creates a more desirable implant corrosion rate. Zinc is a key component in the function of various biological functions such as protein synthesis, wound healing and supports immune functions. Implants prepared with up to 50% zinc can be tolerated by the body during degradation for a few days, anything more can result in severe side effects. However, the preparation of zinc alloys is more favorable over magnesium ones and zinc is more chemically inert than magnesium in the body [66]. Most industrial applications of zinc-based medical implants use copper and aluminum as the main alloying elements since pure zinc has poor ductility and strength [67].

Fe-based are less developed and less frequently used as implants for medical uses although, previous animal studies have found they do not induce immunogenic side effects [68,69]. However, long term animal studies found that the corrosion products of iron can accumulate in the body for up to 9 months collecting in the arterial wall and causing severe damage [61]. Pure iron applications are unfavored and considered non-degradable due to their extremely low degradation rate, so iron alloys are more favored [68].

Bioglass and bioceramics

Bioresorbable ceramic based on calcium phosphate and bioglasses based on silica have many applications in orthopedic implants. The most common bioceramics employed are calcium phosphate, hydroxyapatite (HAp), dicalcium phosphate and tricalcium phosphate [96]. Tricalcium phosphate has a very similar chemical composition to that of natural bone and so displays excellent biocompatibility [70]. Bioceramics in general have a lower mechanical strength in comparison to their nonresorbable counterpart but this can be counteracted by reducing the percentage of pores found within the structure. Drugs can be incorporated within the implant for local antibiotic release, this usually occurs *via* one of two methods. Drug can be incorporated within the pores of the structure or they can be temporarily attached to the surface of the implant. As mentioned before, increasing the extent of pores within the structure will allow a higher percentage of drug loading but will decrease the mechanical strength of the implant and therefore, a compromise must be met. Drug delivery *via* surface interactions allows for a more compact implant with enhanced mechanical strength. It also results in a slower rate of degradation and reduced systemic clearance [96]. Bioceramics are composed of an inorganic phase which assists toward the synthesis of proteins and cell adhesion (osteoconduction) which when coupled with its resorbable nature, make it an ideal candidate for orthopedic implants [70]. When a calcium phosphate implant is secured in the body it begins to degrade through a dissolution/re-precipitation process producing crystals of Ca^{2+} and PO_4^{3-}. These are major constituents of enamel and bone which only further enhances the osseointegration [71]. Bioceramics commonly associated with the treatment of osteomyelitis is β-tricalcium phosphate (β-TCP) which has been observed to safely release gentamycin at a controlled rate [72,97]. When modified with a PEG-based plasma polymer coating, the extent of drug release was seen to be more controlled but still maintaining the good biological activity associated with pure β-TCP [72].

Table 2. Biomaterials approved or in clinical trials for formation of implants for bone repair.

Company	Material	Form	Stage
FORTITUDE (Amaranth Medical, USA)	UHMW-PLLA	Stent	Clinical trial
IDEAL I (Xenogenics., USA)	PAE salicylic acid	Stent	Clinical trial
Firesorb (MicroPort Medical, China)	PLLA	Stent	Clinical trial
Allgens, China	synthetic HA and Col I	Strip, granule, and buck	Approved 2015
Sorrento™	b-TCP and Col I	Strip, sponge	Approve 2019
SurGenTec, USA	HA,a-TCP, b-TCP and BG	Nano-putty	Approved 2020
Molecular Matrix, CA	Porous hyper cross-linked polymeric carbohydrate	Granules, sheets, cubes, wedges, and cylinders	Approved 2017

Glass biomaterials are produced by either sol-gel methods or by melt-quench method more traditionally [73]. Glasses produced by sol-gel can be manufactured with a variety of pore arrangements, such as nanopores, macropores and mesopores [74]. The main glass biomaterials explored is '45S5 bioglass' which has excellent bioactivity and bone bonding. Bone bonding occurs when 45S5 degrades to form a HAp layer on the implants surface which mimics the composition of natural bone allowing it to bond with the surrounding living tissue. The degradation mechanism takes place *via* the following steps with the dissolution of ions from the implants occurring first; followed by the precipitation reaction of dissolved Ca^{2+} ions and $(PO_4)^3$ from the surrounding media to form an amorphous calcium phosphate layer. The amorphous layer continues to grow, supported by the increased dissolution of ions. Finally, OH and CO_3^{2-} ions are incorporated from the surrounding media which allows the amorphous layer to crystallize into a HAp layer [73]. Due to their release of ions to the surrounding tissue fluid which consequently changes the local pH, glass biomaterials naturally display antimicrobial activity without any added antibiotics therefore, making them a good candidate for OM treatment [73,75,76]. Ion doped glass has displayed better results for the treatment of OM, by incorporating ions such as silver, copper and zinc oxides then the antimicrobial activity is increased without disrupting the dissolution of the glass [74].

Composites

All biomaterials explored within this section are potential candidates as effective local drug delivery vehicles or already are in regular clinical use. However, each material has their own drawbacks whether that be poor mechanical strength, insufficient drug release kinetics, or the lack of ability to support tissue regeneration [17]. One potential solution that is widely researched and applied is the combination of synthetic or natural polymers with bioceramics or bioglass materials [98]. Bioceramics are often very brittle but offer excellent compression strength, which when combined with polymers can be beneficial to increase their mechanical performance whilst also improving the flexibility and drug release kinetics. Natural polymer such as collagen or chitosan are often mixed with bioceramics or used as a coating to increase the biocompatibility of the implant through increased cellular interactions without compromising the mechanical strength [17]. This was recently explored by scientists who developed different compositions of chitosan-calcium phosphate composite implants to test their effectiveness in treating post-operative OM. The scaffolds were loaded with moxifloxacin hydrochloride (MOX) which was found to be very effective in treating induced OM in the animal models where the bacteria growth was significantly reduced [77].

Research has also been applied to the composition of synthetic polymer PCL combined with a porous β-tricalcium phosphate scaffold loaded with antibiotic gatifloxacin (GFLX). The use of a biodegradable synthetic polymer provided sustained release of the antibiotic whilst the bioceramic scaffold allowed for bone tissue regeneration. The antibacterial activity of the antibiotic was retained for approximately 4 weeks whilst bone tissue regeneration and vascularization occurred after 50 weeks on the PCL/TCP interface. The study concluded that the composite of materials worked better as a scaffold over the individual material applications [78].

Often multiple types of biomaterials are combined with each material contributing some sort of benefit. This idea was used by scientists to produce a composite scaffold consisting of HAp, polyurethanes (PUs) and mesoporous silica nanoparticles (MSNs) loaded with Levofloxacin. HAp offered excellent biocompatibility and mechanical strength due to its physical and chemical similarities to natural bone. PU provided good biodegradability and enhanced osteoinductive properties. Whilst MSNs are used widely in nanomedicine to encapsulate the drug and enhance the local drug release kinetics. Levofloxacin encapsulated within MSNs that were then incorporated within a porous PU/HAp composite scaffold provided an excellent alternative to the treatment of chronic OM. The composite displayed good mechanical strength, ideal drug release kinetics and improved bone tissue regeneration [79].

Other composites containing biomaterials of the same type can still be employed and offer enhanced benefits. This usually occurs with synthetic polymer which was the case with a composite composed of PCL and PEG loaded with roxithromycin (ROX). The addition of PEG within the scaffold was proved to enhance the hydrophilicity and the composite overall had better drug release kinetics. This combination also displayed effective antibacterial activity against microorganisms of *E.coli* and *SA* and displayed effective support to enhance bone tissue regeneration [80].

Types of implants for bone repair

Throughout this review we have focused on the different materials an implant may be composed of and the different ways they can be fabricated to produce varying drug release kinetics. Table 2 shows examples of biomaterials approved or in clinical trials for formation of implants for bone repair. In this section we will explore the different types of implants used in orthopedic applications, whether that be hydrogels, rods, plates, scaffolds or nanoparticles. The type of implant used will depend on the type of bone application [13].

Smart implants

Many of the implants mentioned above work on the 'burst release' basis which can be beneficial when the infected area requires a fast, high concentration of drug. This mechanism of drug release is not ideal when the infected area would benefit more from a gradual, constant supply of drugs over a longer period of time. To achieve this release rate, the drug carriers incorporated within the implants structure can be tailored to react to environmental or physical stimuli such as change in pH; temperature; magnetic field; light or; enzymes [99]. Implants composed of

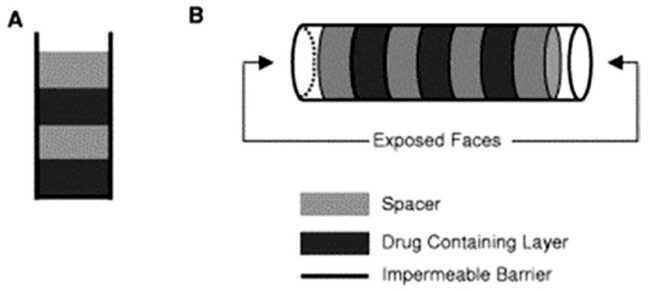

Figure 7. simplified diagram of a pulsatile drug delivery system [101]. [The publisher Elsevier and the journal support responsible sharing of research].

PLGA polymers can be tailored to produce these smart implants [100]. Osteomyelitis produces a microenvironment which can be used as exploitable stimuli for the release of drugs. An acidic local pH is produced whilst enzymes such as phospholipase and hyaluronidase are also present. Hyaluronidase is excreted by SA which is the main OM causing pathogen. Therefore, nanocarriers are often composed of hyaluronic acid which can break down when in the presence of hyaluronidase enzymes [99]. pH sensitive nanocarriers often incorporate carboxylic acids or amines within their backbone, these groups become either protonated or deprotonated during a change in the local pH subsequently releasing the drug molecules. An OM infection causes a reduction in pH and so pH sensitive drug carriers can be used for this application [99].

Smart implants can be stimuli responsive as just discussed or they can be pre-programmed to have a specific drug release profile determined by the design and fabrication of the implant. The most desired release rate profile is that of zero order; a continuous steady release of drug within the therapeutic window. A pulse release delivery system can be achieved by fabricating the implant with alternating active and inactive layers. A pulsatile drug delivery system is composed of a multi-layered polymer matrix and spacer layers (Figure 7). The polymer matrix contains the drug which is only released upon degradation of the polymer matrix. The length of time between release of drug can be altered by changing the thickness of the blank spacer layer. The multilayer implant is usually encased within an impermeable membrane with one face exposed to the external environment to allow for degradation of the alternating layers [101].

Scaffolds

Scaffolds are porous structures, with the extent and diameter of pores playing an important role in their function. There are various principal requirements of a scaffold that have been briefly mentioned before. The first and most important is that the scaffold is biocompatible with the body which allows cells to adhere, migrate and proliferate without inducing an inflammatory response. The scaffold should provide adequate mechanical support for the regenerating bone but also degrade at an ideal rate. The scaffold should also possess a good level of osteoconductivity which is the ability of bone cells to adhere to, proliferate and form an extracellular matrix on the scaffolds surface and pores. This allows for a bond to be formed between the surrounding bone tissue and the scaffold. The last basic requirement of a scaffold is that it should be producible on a large scale and environmentally sustainable [102].

All of these properties are determined by the type of biomaterial used and the fabrication process. Recently 3D printing of scaffolds has had success in pre-clinical and clinical studies in which the microstructure (porous network) can be tailor made for specific applications within the body [102]. A side from 3D printing, scaffolds can be produced using more conventional techniques such as melt molding, phase separation, gas foaming, solvent casting particulate leaching and freeze drying. Each fabrication method has its own benefits and can produce a scaffold with different characteristics compared to those produced by an alternative method such as freeze-drying, which produces flexible 3D structures but with a longer processing time and having smaller than ideal pore sizes. Whilst thermally induced phase separation fabrication method produces complicated scaffold structures that are highly porous for cellular transportation but with a morphology that is unpredictable [13]. Electrospun fibrous scaffolds are ideal as they mimic the extracellular matrix (ECM) however, electrospinning typically only produces 2D structures with small pores. 3D printing counteracts this but lacks the textured fibrous surface that mimics the ECM. Therefore, a study performed by Chen et al. attempted to combine both techniques to produce a 3D fibrous scaffold. They have done this by processing electrospun fibers made of gelatin/PLGA into ink suitable for 3D printing. The outcome was successful in which a fibrous scaffold was produced with easily tunable shapes and pores sizes [103].

A total porosity of 90% of the scaffold is ideal to promote osteogenesis but to also maintain an adequate mechanical strength. Osteogenesis is a bone repair process which involves different signaling molecules at different stages of the process [104]. The average pore diameter should be within the range of 100–300μm to promote vascularization and provide a clear path for nutrient delivery [102,105]. However, a pore size that is too big can allow multiple cells into the scaffold and so obstruct proliferation and differentiation [13]. The need to promote vascularization within a bone regenerating scaffold is significant; vascularization helps to avoid oxygen deprivation, promotes a significant decrease in cell necrosis and so consequently helps in bone formation [106]. The configuration and shape of pores can also influence the mechanics of the scaffold. A study by [107] using two different implants investigated this theory; one implant had a high porosity percentage and monomodal pore size distribution whilst the other had a low porosity percentage with elongated pore structures. The study reported that scaffold resorption and bone neoformation was significantly lower in the animal model containing the scaffold with non-uniform pore distribution [107]. The microporous structure not only determines the extent of vascularization within the scaffold, but it also determines the release behavior of drug molecules either from the matrix or by desorption from the surface of the scaffold [108].

The cell surface of a scaffold is also extremely important as this is what determines what proteins and nutrients are to be absorbed from the surrounding tissue fluid. Therefore, it is ideal for scaffold surfaces to include certain topographic and chemical features to directly target the adhering proteins for certain biological responses to occur. Surface roughness also influences attachment of proteins and nutrients. A surface that is too smooth will not be able to secure a temporary fibrin matrix upon its surface which will disrupt directional cell migration. However, a rough surface will act as a nucleation site for calcium phosphate molecules from the body fluid which will promote osteogenic differentiation. Angiogenic growth factors can also be added to the scaffold surface modifications. These are currently employed to improve new blood vessel formulation and thus, improve vascularization. Angiogenic growth factors include platelet derived growth factors, fibroblast growth factors, epidermal growth factors, etc [109].

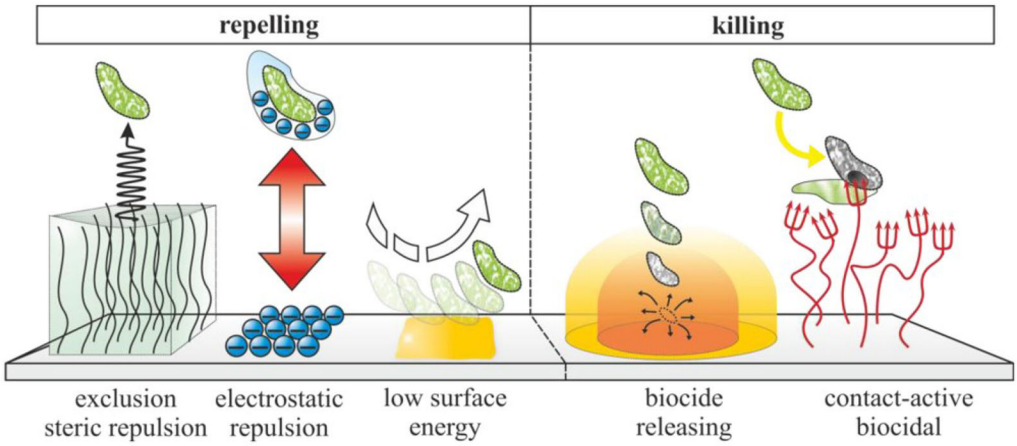

Figure 8. antimicrobial action of polymer surface. Mode of action can either be repelling or killing approaching planktonic cells [113].

Hydrogels

Hydrogels are 3D hydrophilic porous networks that have recently shown promising applications in supporting bone regeneration and drug delivery. Their structure is flexible, made up of interlinked polymer chains creating an ideal microenvironment for cell adhesion and proliferation [110]. Hydrogels have the ability to mimic the natural extracellular matrix (ECM) of the bone so as improving their biocompatibility and mechanical strength. Drugs and other essential proteins can be incorporated within the porous structure and released as the hydrogel degrades or *via* the ingress of water. By increasing or decreasing the extent of crosslinked polymer then the rate of degradation can also be tailored [111]. The only major drawback to the use of hydrogels as drug delivery vehicles/bone regenerative scaffolds is their painful and long administration process. Pre-formed hydrogels require long invasive and painful surgery to implant them whilst also being very expensive. Therefore, there has been a recent push to produce injectable hydrogels that require noninvasive applications to reduce the pain and increase patient compliance [110,111]. A gelatin based hydrogel, Arcgel was tested against clinical standard autograft and a collagen biomaterial in the treatment of bone defects in a study by Lohmann et al. [112]. They found that arc gel acted as a highly osteoinductive material over other materials used, with only the hydrogel material producing a complete bone regeneration [112].

There is always potential for improvement in regard to hydrogels through improving their osteoconductivity, biocompatibility, osteoinductivity and osteogenesis capabilities. The three most explored hydrogel structures are hydrogel microbeads, nanogels and hydrogel fibers. Microbeads can be formulated through many techniques including emulsification and have many benefits over conventional hydrogels. They have an increased surface area which facilitates and enhances the mass transfer of stem cells to bone defect sites. Hydrogel nanoparticles (nanogels) are chemically or physically cross-linked polymers that can swell in water. They are ideal for drug delivery due to their tunable size, uniformity and their ease in design and formulation. Hydrogel fibers are a fibrous structure fabricated through a two-step process of spinning and crosslinking. They can be injected directly into the defect site and remain at the defect site for an extended period over hydrogels and microbeads. They have a large surface area to volume ratio making them a potential candidate for bone tissue engineering. However, hydrogel fibers have some major drawbacks in comparison to other structures, they have poor mechanical strength so unable to bear load and a high swelling ratio [111].

Bone cement

Bone cements were some of the simplest to use drug delivery implants during the 1970s and 1980s. Typically made of PMMA, they can be directly mixed with the antimicrobial agent in powder form, which upon contact with bone can polymerize to form a rigid bond between the implant and the bone. More recently, calcium phosphate bone cements become more common, which upon implantation can polymerize into hydroxy apatite. Bone cements are typically composed of materials that don't degrade and so a second removal surgery is required. Bone cements also have the drawbacks of tending to fragment, promote wear debris and cause inflammation at the site of the implant. In addition, bone cement tends to have below optimal surface area to volume ratios for drug elution [11].

Surface coatings

Surface coatings of antimicrobial polymers have become popular for the treatment of OM due to their ability to release antimicrobial agents directly into the site of infection by being on the surface but still maintaining adequate biocompatibility. They can limit the potential for biofilm formation by preventing bacteria adhesion onto the surface of the biomaterial either by directly incorporating antibiotics into the surface coatings or by producing a polymer surface that is naturally antimicrobial. Coating can also limit bacteria adhesion indirectly by promoting tissue integration on the surface of the implant which will limit the available surface area for bacterial adhesion [11]. Polymers surfaces that are naturally antimicrobial reduce the risk of biofilm formation by either killing or repelling approaching planktonic cells as can be seen in Figure 8. Electrostatic repulsion can occur by surface coatings composed of negatively charged polymers such as PLA. Killing of bacteria cells using surface coating can be achieved by a number of ways, among them by releasing of biocides. A biocide is a polymer that consists of multiple repeating bioactive monomer units which, upon degradation, are released to the surrounding environment [113]. Surface coatings can also have a much more controlled degradation rate which promotes a higher efficacy [11] as well as relatively easy fabrication techniques. In one of the studies, layer-by-layer deposition of biocidal polymers was performed on a stainless-steel orthopedic implant. The researchers modified the implant with a chitosan based polymeric surface coating which improved the implants biocompatibility whilst also provided antimicrobial activity against gram negative E.coli bacteria [114]. However, the effectiveness of chitosan surface coatings in the treatment of gram-positive SA bacteria still required further research.

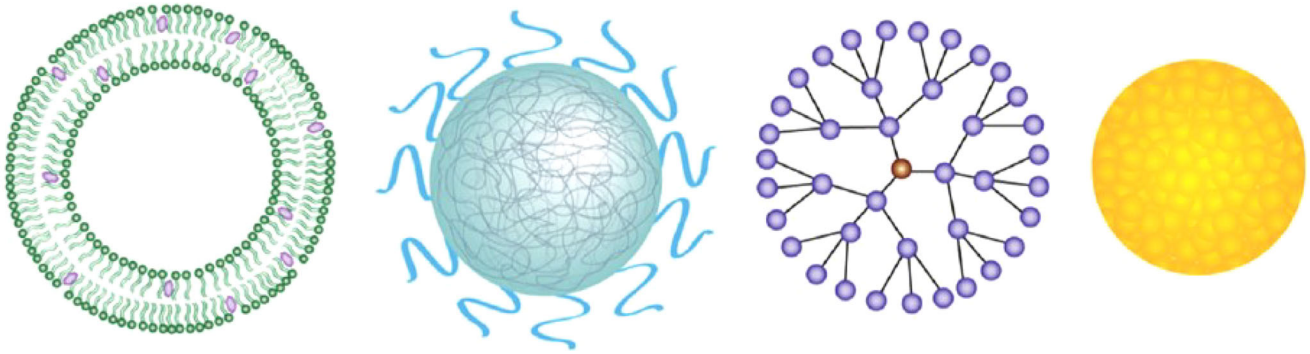

Figure 9. schematic illustration of the different forms of nanoparticles, from left to right; liposome, polymeric nanoparticle, dendrimer and inorganic nanoparticle [117]. [Permission has been obtained see attached].

Nanoparticles

The use of antibiotics encapsulated within nanoparticles (NPs) has proven to be very successful in the treatment against antibiotic resistant bacteria. NPs allow for a high concentration of drug to be directly delivered and held at the site of infection. They reduce the potential for the drugs to be cleared from the body and so the chance for an effective dose is increased. Nanoparticle drug delivery systems offer enhanced drug solubility, modulate the drug release kinetics, prevent clearance by the immune system, are able to deliver multiple drugs to target at once and can provide targeted drug delivery to the site of infection [115]. NPs are more desirable over other structures due to their small controllable size, large surface area to mass ratio, possess a structure that can be easily functionalized and high reactivity [116]. NPs can come in the form of liposomes, polymeric nanoparticles, dendrimers and other inorganic nanoparticles such as metal nanoparticles; these can be seen in Figure 9.

Regarding the treatment of osteomyelitis, uncoated liposomes as well as PEGylated liposomes tend to accumulate in tissue that has been infected with SA bacteria. This allows for a direct and long-term delivery of antibiotics from the NPs. As mentioned with certain metal alloys implants, pathogenic bacteria have a negatively charge surface and so nanoparticles are often functionalized to have a cationic surface capable of electrostatically targeting the bacteria [117]. As well as antibiotics, NPs have been shown to deliver regenerative materials to bone and cartilage, along with genes and growth factors [118].

A study performed by Ferreira-Ermita et al. used magnetite NPs (Fe_3O_4) loaded with ciprofloxacin to determine the effectiveness in treating OM. The NPs were coated with a HAp layer to improve their biocompatibility. They concluded that their use for the treatment of bacterial infection OM was successful and found that the NPs acted as a supportive implant whilst also promoting bone regeneration [119]. Another study using HAp nanocarriers introduced silica into the carriers using surface wrapping. They found the addition of silica to the NPs controlled and sustained vancomycin release whilst also counteracting the side effects induced by having a high concentration of drug at the site of infection. They concluded that the vancomycin loaded nanocarriers eradicated the OM infection whilst also promoting bone healing [120].

Prospectives and challenges

Local delivery of antibiotics using biodegradable implants is an attractive approach for the treatment of OM infections. Local implants have many advantages over conventional treatment methods and can be easily modified to treat various conditions and illnesses. With the recent advanced and sophisticated technologies, it becomes possible to design systems that fit the purpose using different types of biomaterials as well as providing various options of antimicrobial therapeutics. Despite the exciting opportunities that this field offers, there are still many challenges that need addressing. Firstly, attention should be given to the effect of the implant and its degradation end products on the host response. A logical approach will be to understand the degradation mechanism and profile of the biomaterial and impact of this on the safety and effectiveness of the formulation to the host. Another important challenge is the bacterial colonization which results in formation of antibiotic resistant biofilm on the site of an implant. This problem can lead to implant removal and increased morbidity [121]. Apart from antibiotics, bacteriophages and nanotechnology have been proposed to eradicate bacteria [122]. Bacteriophages are viruses that are capable of infecting and killing bacteria and can be an effective biotechnological strategy. Phages bind to specific receptors on the surface of bacterial cells and transfer their own genomes (DNA or RNA materials) to bacteria. By doing so, they can either make the bacteria produce viral proteins and viral genomes, with subsequent assembling of viral particles, lysing of bacterial cells and releasing many new phages. Or they insert their DNA into the host bacterial cell as a free plasmid or integrated into the chromosome. At the last stage, the phage genome will be released from the host chromosome, become encapsulated and then the phage particles will be released from the host bacterium, killing it. The phage therapy can be used to treat many bacterial infectious diseases including *S. aureus* in humans and overcome the problem of antibiotic resistance in pathogenic bacteria. They can replicate at the site of infection and specifically to their host without causing secondary infection [123]. Recent studies (2016) showed that patients with diabetic foot ulcer infected with MRSA and failed to respond to antibiotic alone were save from amputation after being treated with phages [124]. Moreover, *in vitro* and *in vivo* studies revealed that combining phage with antibiotics can synergistically enhance the anti-infective property of phage by increasing the number of viruses produced and decreasing the density of bacteria and thus preventing antibiotic resistance and biofilm formation [125].

On the other hand, there is evidence that nanotechnology can promote bone regeneration. Nanoparticles have offered great opportunities for bone tissue engineering owing to their unique physicochemical properties and functionality. They can also be synthesized for intracellular delivery of antibacterial agents using biodegradable polymers. Ikono et al. reported that chitosan hybridized with titanium dioxide nanoparticles improves its bone regeneration capability [126]. Liu et al. designed inside-outside Ag

nanoparticles-loaded polylactic acid electrospun fiber [127]. The resultant system has good biological activity, osteoinductivity and long-lasting antibacterial property which makes it potentially a feasible bone repair material for inhibiting bone infections. Calcium phosphate nanoparticles have been incorporated into gelatin-based hydrogel to promote bone tissue regeneration [128]. The authors found the nanoparticles promoted preosteoblasts cell viability and bone differentiation ability.

The above-mentioned findings suggest that there are many interesting future research directions which could create new avenues for the antimicrobial biomaterials for bone infection. For instance, research could be directed toward designing bio-implants coated with phage for the delivery of antibiotics for irradicating bacteria and preventing biofilm formation as research has demonstrated that antibiotics are more effective if they are combined with phages. The approach is worth considering for clinical translation but the safety of bacteriophages for human use should be addressed. Another interesting approach is the use of nanoparticles for targeted delivery of antimicrobial agents to bone infection as this could improve the antibacterial efficacy of the antibiotics and also promote bone tissue regeneration of the affected area.

Conclusion

To conclude, antibiotic loaded biomaterials are a promising future for the treatment of OM infections. They have many advantages over conventional treatment methods and can be easily modified to treat various applications. They have proven to be just as good or in some cases superior to non-biodegradable PMMA beads with the added advantage of not requiring a second surgery removal. Biodegradable polymers are considered the most advantageous biomaterial, composite materials of both natural and synthetic polymers provide both the excellent biocompatibility and mechanical strength required. Various types of implants for bone infection have been designed and discussed in this review. Scaffold implants are the most explored fabricated implant. Their porous structure provides an ideal framework for the incorporation of drugs for the treatment of osteomyelitis whilst also allowing the flow of nutrients essential for bone tissue regeneration. Biodegradable polymeric surface coatings offer the advantage of enhanced biocompatibility and biofilm prevention whilst also providing excellent mechanical strength from the steel implant which pure polymer implants would not provide. More recently, research into silica incorporated nanoparticles has been explored due to their benefits in modulating the drug release rate as well their size and flexibility to be molded into any desired shape. Many alternative treatment methods for OM have been explored but most new techniques are yet to reach clinical trials.

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