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Recent advances in materials for extended release antibiotic delivery system

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ABSTRACT
To maintain antimicrobial activity, frequent administration of conventional formulations of many antibiotics with short half-life is necessary. Otherwise, concentration under MIC occurs frequently in the course of anti-infective treatment, which induces antibiotic resistance. By maintaining a constant plasma drug concentration over MIC for a prolonged period, extended-release dosage forms maximize the therapeutic effect of antibiotics while minimizing antibiotic resistance. Another undoubted advantage of extended-release formulation is improved patient compliance. For better release properties, many materials have been introduced into the matrix and coating extended-release system in the past few years. Materials that have been widely used in industry are hydrophilic matrix materials such as hydroxypropylmethylcellulose. The excellent biocompatibility and extensive laboratory studies provide biodegradable polymers great potential for industrial applications. In addition, it seems like the researches on tailored materials that are obtained by chemical modification of the existing materials or combination of different carriers in physical mixtures have a long way to go. Meanwhile, with the development of polymers and inorganic porous nanocarriers, nanotechnology is applied increasingly for the extended delivery of antibiotics. This review highlights the development of materials used in extended-release formulation and nanoparticles for antibiotic delivery. We also provide an overview of the antibiotic extended-release products that have provided clinical benefit or are undergoing the clinical trial.

Keywords: antibiotic resistance, coating material, complex, extended release, matrix material, Nanoparticles.

INTRODUCTION
Since Alexander Fleming discovered penicillin in 1928, hundreds of antibacterial drugs have been introduced into clinical use and many infectious diseases have been overcome. However, with their extensive application, one of the most serious problems of current medicine antimicrobial resistance arises, which limits the therapeutic effect of conventional therapy. Many researchers are making efforts to discover new antibiotics, whereas some other studies are focused on improving the clinical outcomes of currently available antibacterial drugs by using new formulations. Extended-release delivery system is one of the investigations that is being carried out to decrease the induction of antibiotic resistance. The terms 'sustained release', 'prolonged release' and 'slow release' are synonymous with 'extended release'. As anti-infection treatments often involve a long course of therapy, sufficient antibiotic exposure is needed to ensure the eradication of the microorganism. However, many patients tend to interrupt treatment once they feel better, and thus the incomplete treatment may aggravate the development of antibiotic resistance. Besides, many antibiotics have short half-life values and need to be administered frequently, which also contributes to patient incompliance. The poor compliance often leads to treatment failure or increases the cost of health-care resources such as the requirement for additional agents and hospital admission. It is recognized that extended-release preparation is advantageous to improve patient compliance, as frequent administration can be reduced by maintaining a constant plasma drug concentration over a prolonged period of time.[1] For example, for azithromycin, a long serum half-life (~68 h) antibiotic, the conventional preparation allows for a short 3-day (500 mg day^{-1} for 3 days) or 5-day (500 mg on day 1 followed by 250 mg on days 2–5) course of therapy, whereas azithromycin sustained-release microsphere for oral suspension (Zmax) permits a single-dose administration. Clinical applications have demonstrated the undoubted advantages of improved compliance and convenience of the single-dose regimen.[1]

Furthermore, sustained-release formulations can improve the therapeutical index of antibiotics. Antimicrobial agents are commonly divided into two major categories on the basis of their pharmacodynamics: time-dependent and concentration-dependent antibiotics. The time-dependent antibiotics, such as β-lactams, macrolides (except for azalides), tetracyclines and clindamycin, exert bactericidal effect when drugs are maintained above the MIC.[2] For these agents, the time that therapeutic drug concentrations are above the MIC (T>MIC) is the primary parameter and should be kept for a minimum standard to achieve the desired clinical outcomes.[3] In addition, dosage under the threshold may promote the development of antibiotic resistance.[4] Therefore, continuous infusion has been proposed and its clinical advantage against antibiotic resistance over intermittent bolus for time-dependent antimicrobials has been confirmed.[5, 6, 7] Nevertheless, this approach has certain limitations, such as low physicochemical stability and patient inconvenience. For obtaining all the advantages of continuous infusion while avoiding the limitations, sustained-release preparation is a good substitute. For instance, amoxicillin/clavulanic acid extended-release formulation (Augmentin XR) has been demonstrated to extend amoxicillin exposure and killing time for a greater proportion of the dosing interval than that achieved by conventional formulations. Clinical trials have also indicated that the pharmacokinetic-enhanced formulation provided higher treatment success when compared with its immediate-release preparations with lower cost.[8] Another example is clarithromycin extended-release tablets (Biaxin),Compared with clarithromycin immediate release, the extended-release preparation remained T>MIC for a longer duration and achieved better clinical cure.[9]

Concentration-dependent antibiotics include aminoglycosides, quinolones, azalides (azithromycin), ketolides and vancomycin. Different from the time-dependent antibiotics, these agents achieve increased bacteria killing with increased levels of drugs. In addition, these agents have an associated concentration-dependent postantibiotics effect. The peak concentration (C_{max}) and area under the concentration curve determine the clinical outcomes of these antibiotics. It is demonstrated that higher C_{max}/MIC and area under the concentration curve/MIC correlate with a significantly higher survival rate in preclinical models of infection and help prevent the development of resistance.[10] Sustained-release formulations can provide controllable drug release to maximize the C_{max} and minimize the toxicity. For example, ciprofloxacin extended-release formulation (Cipro XR or Cipro XL), which permits convenient once-daily treatment, provides a more favorable C_{max} value and less interpatient variability than the immediate-release twice-daily formulation.[11]

Many sustained-release antibiotic preparations have come into the market and have shown superiority over conventional formulations, as is summarized . Obviously, matrix-type extended-release technology occupies the major market share of sustained-release antibiotic products. Besides, a sustained-release formulation of amikacin (Arikace, liposomal amikacin for inhalation) will enter clinical trial phase III in August 2011.[12] With the development of nanotechnology, researches on nanoparticle-based antibiotic delivery system may become a trend.

Therefore, sustained-release preparation has a primary important role in the antibiotic delivery field. In the past few years, great progress in extended-release formulations for antimicrobial drugs has been achieved. One of the driving factors for the advances is the development of slow-releasing materials. This review provides an overview of the novel formulation materials that are introduced into antimicrobial modified release delivery system and the existing materials are also summarized here.

Although the development of sustained-release preparations is closely related to the update of equipment and processes, the development and application of new materials have a key role. Introducing more appropriate materials into drug-delivery systems can promote the clinical outcomes of drugs, further bringing in economic and social effects. According to the mechanism underlying the prolonged action, the materials can be divided into two major categories: matrix materials and coating materials. In addition, the complex formations are also imported as carriers for the retarded release of antibiotics.

Matrix materials

Matrix system is the simplest and the most cost-effective method to fabricate an extended-release dosage form and it is easy to produce on an industrial scale in conventional equipment. In the matrix system, the drug is combined and made into granules with excipients that alter the release rate of the drug. According to the

materials used, the matrix systems have different mechanisms toward the controlled action. The most commonly used matrix materials are swellable hydrophilic materials. Once they are exposed to an aqueous medium, a successive progress of hydration of the polymer, gel formation on the surface of the polymer and subsequent continuous release of drug is followed. Another group of matrix materials is biodegradable materials. By embedding the drug in the slowly eroding matrix materials that erode in body fluids, the progressive release of the drug is realized. For the matrix materials that retain their shape during their passage through the alimentary tract, the drug is slowly released from the matrix by diffusion. In addition, a mucoadhesive drug-delivery system can prolong the residence time of drugs at the site of absorption or application, and thus extend the absorption time.

Hydrophilic matrix materials

Hydrophilic matrix system has enjoyed widespread attention and application in sustained-release delivery system owing to its excellent uniformity and ease of manufacture. The matrix can be obtained either by direct compression of the blend or from a wet granulation containing the active ingredient and hydrophilic carriers. Among all the hydrophilic materials, cellulosic polymers are probably used most frequently, such as hydroxypropylmethylcellulose, methylcellulose, hydroxypropylcellulose, hydroxyethylcellulose and sodium carboxymethylcellulose. Other non-cellulosic hydrophilic materials include gum/polysaccharides (for example, sodium alginate, xanthan gum, carrageenan, locust bean gum, chitosan, guar gum, pectin and crosslinked high amylase starch), polyethylene oxide, homopolymers and copolymer of acrylic acid. These materials are commonly used for the fabrication of matrices either alone or in conjugation.

Generally speaking, matrix materials with fast polymer hydration ability are preferable in hydrophilic matrix formulations. Otherwise, premature diffusion and disintegration may occur, especially for water-soluble drugs, because of fast penetration of water. The initial burst effect for highly water-soluble drugs is often incontrollable and potentially unsafe in drug-delivery applications. The burst can be suppressed by insoluble coating or by modifying the excipients into suitable viscosity and chemistry. For instance, poly(2-hydroxyethyl methacrylate) (pHEMA), an extensively used hydrogel, showed an initial 'burst release' when used in controlled-release systems. To counter this intrinsic burst release and achieve a sustained release, the pHEMA surface was modified with octadecyl isocyanate to form a dense, hydrophobic brush coating. This surface modification created a rate-limiting barrier for molecular transport into and out of the polymer matrix, modulating hydration and controlling drug delivery, and hence the near zero-order release of norfloxacin from the matrix was obtained.[18]

The most common adverse event of antibiotics (for example, macrolides) is gastrointestinal (GI) stimulus that appears to be dose related; therefore, bypassing the absorption site in the upper GI tract is necessary especially in sustained-release preparations with larger dosage. It is known that variations of pH occur at GI tract, and hence application the pH-responsive carriers may be a solution. Non-ionic hydrophilic polymers such as cellulose ether exhibit pH-independent drug-release profiles, whereas there are pH-responsive hydrogels composed of polymeric backbones with ionic pendant groups. The commonly studied pH-responsive polymers include synthetic polymers such as poly(acrylamide), poly(acrylic acid), poly(methacrylic acid), poly(diethylaminoethyl methacrylate) and poly(dimethylaminoethyl methacrylate), and natural polymers such as albumin and gelatin.[19] For instance, owing to the nature of sol-to-gel transition upon changes in pH, alginates polymers and carbopol were used to deliver ciprofloxacin, and then the antimicrobial efficiency test proved that the formulation prolonged the antimicrobial effect of ciprofloxacin.[20] However, all these environment-sensitive hydrogels have a significant weakness; that is, their response time is too slow. Hence, it is necessary to develop fast-acting hydrogels with enough mechanical strength.

Biodegradable materials

In this system, the release of drugs from the matrix mainly depends on the degradation of the matrix materials and diffusion of drugs from the polymers. Biodegradable materials used in sustained-release formulations can serve as matrix materials, microsphere and implants carriers. Biodegradable polymers include two categories: natural (for example, hemaleucin, gelatin) and synthetic polymers (for example, polyesters, polyorthoesters, polyalkyl α-cyanoacrylate, polyamino acid). These materials

can be hydrolyzed or degraded by enzymes in the physiological environment, and eventually absorbed or metabolized to water. Their biocompatibility and non-allergenic immunogenicity make them good application prospects in drug-delivery systems, many biodegradable materials have been used to deliver antibiotics and have exhibited good activities.

Naturally derived materials have the advantage of similarity to extracellular matrix, excellent biocompatibility and easy surface modification. Nevertheless, their application is limited by inadequate mechanical properties and processability.[21] For this reason, natural materials are often surface modified or used with other materials. One of the most commonly used material is chitosan, a copolymer of *N*-acetylglucosamine and glucosamine derived from chitin, which has been included in European Pharmacopoeia and US Pharmacopeia. Owing to its biocompatibility, mucoadhesion and permeation-enhancing properties, chitosan has extensive applications in the medical field. More than a drug carrier for antibiotics delivery, chitosan has been demonstrated to possess a wide spectrum of antimicrobial activity and high killing rate against Gram-positive and Gram-negative bacteria, but lower toxicity toward mammalian cells. They may be incorporated into fibers, membranes or hydrogels, and used for contact disinfectants in many biomedical applications, including wound dressing, orthopedic tissue engineering, drug-delivery carrier and hemodialysis.[22] Chitosan has its distinct superiority for antibiotic delivery, yet its application is restricted because of the solubility in weak acid solutions. Chitosan microspheres were optimized for higher acid resistance by the virtue of being crosslinked with pentasodium tripolyphosphate through two different microencapsulation procedures. The crosslinked microspheres were not only more stable in simulated gastric fluid, but also slower in the release of ampicillin.[23]

Different from natural materials, synthetic polymers show good mechanical properties and mass production potential with high reproducibility. Synthetic biodegradable polymers have been used in various administration routes. In addition, some multifunctional materials can not only prolong the drug release, but also have an additional role in treatment. An instance was polyurethane, whose capacity of promoting new bone formation had been proved *in vivo*. Hafeman *et al.*[24] verified the potential of polyurethane as injectable biodegradable polyurethane scaffold for long-term drug delivery. In spite of the prolonged action, the total release of antibiotics was greater than current clinical treatment poly(methyl methacrylate) (PMMA) beads.[24] In another research, the porous polyurethane scaffold and the reduction of water solubility of vancomycin were combined to acquire a slower release. The decreased water solubility weakened the burst release and this was achieved by precipitating the hydrophilic vancomycin hydrochloride at pH 8 for the free base form, which is more hydrophobic and less soluble.[25]

Biodegradable materials are ideal for the local treatment of infection because a second surgical intervention to remove the carrier is avoided. For the treatment of severe wound infection, lasting release of antibiotics lessens the frequent replacements that cause inconvenience and financial burden. Nevertheless, the most frequently investigated biodegradable materials such as poly(lactic acid) or poly(glycolic acid) produce acidic degradation products that may accumulate and become concentrated, leading to toxicity.[26] A biocompatibility polymer poly(trimethylene carbonate) (PTMC) with no influence on the pH was explored. The surface erosion of PTMC occurred only in the presence of lipase and thus provided constant release of the antibiotics.[27] Materials degraded by enzymes hold promise for antibiotic-modified release. Dave *et al.*[28] have reported biocatalytic-based antimicrobial coatings. In the research, the sustained release of gentamicin sulfate was controlled by the degradation of the polycaprolactone (PCL), whereas the latter was controlled by the enzyme concentration.[28]

One of the important utilization for synthetic polymers is biodegradable microsphere. Microsphere technology is an established technique that is successful in offering long-lasting effects of agents. Depending on the physicochemical properties of encapsulated drugs and polymeric excipients, microspheres can be programmed for content release by diffusion or erosion, or a combination of both. Materials that have come into wide use and those that generated the most profit for microspheres seem to be the aliphatic poly(esters) such as poly(lactide) (PLA), poly(glycolide) (PGA) and especially the copolymer of lactide and glycolide poly(lactide-co-glycolide) (PLGA).[29] An important feature of this class of polymers is that it is widely

approved by the FDA (Food and Drug Administration). Polymeric microspheres are attractive because of their biocompatibility, biodegradability and capability of encapsulating various drugs via both oral and injection route. However, it is difficult to manufacture microspheres in large quantities and maintain drug stability as well.

By the combination of two or more materials, the extended-release delivery system can offer the advantage of facilitated adjustment of desired drug-release patterns, mechanical properties and drug release mechanisms.[30] However, the system based on polymer blend is more complex than that of single polymer; for example, the polymer mixture can be incompatible, and aqueous polymer dispersions might flocculate during long-term storage. For this reason, more attention has to be paid when using this type of formulation. Composite microspheres combined with bioactive wollastonite with biodegradable poly(hydroxybutyrate-polyhydroxyvalerate) (PHBV) showed much lower release rate of gentamicin than the pure PBHV microspheres, which was credited to the formation of apatite layer on their surface.[31] an additional study showed that when the wollastonite was used *in vivo*, an apatite layer was formed by which the new bone tissue bonded to the implant.[32] Thence, the chemical fixation of biomaterials to bone tissue and ultimately *in vivo* success of the bone grafting materials was facilitated. Besides, incorporation of microspheres into scaffolds can abolish the initial burst by a combination of pore diffusion and polymer erosion.[33,34]

Bioadhesive materials

The objective of using mucoadhesive or bioadhesive controlled drug delivery system is to prolong their residence at a specific site of delivery, thus facilitating the drug absorption process. For mucoadhesive agent, first-pass metabolism in the liver and presystemic elimination in the GI tract is avoided as the mucosa is well supplied with both vascular and lymphatic drainage. The commonly used bioadhesive polymers include polyacrylic acid, cellulosic, polysaccharide and natural polymers such as acacia gum and alginic acid. Besides, high-molecular-weight polymers such as polyvinylpyrrolidone and poly(ethylene glycol) (PEG) also have the feature of bioadhesion. Carbomer, one of the most commonly used materials of bioadhesion, can adhere strongly to mucosal membranes without causing irritation. Carbomer and hydroxypropylmethylcellulose were used to swell and form a gel adhering to the mucosa, and a prolonged action for antibiotics into the oral cavity was obtained.[37, 38]

As a carrier, mucoadhesive improves drug delivery by various routes of administration, for example, oral, buccal, nasal, ocular, vaginal and rectal, either for systemic or for local effects. For the delivery of antibiotics, oral cavity and stomach are the most attractive mucoadhesive sites because dental diseases are regarded as one of the most common diseases afflicting mankind throughout the world, and *Helicobacter pylori* infection is believed to be the main pathogenic factor in the development of peptic ulcer disease. For the treatment of periodontitis or peptic ulcer disease, system administration of antibiotics often causes a rapid decline of the plasma antibiotic concentration to subtherapeutic levels, thus developing microbial resistance.[39] Hence, the delivery system that localizes the antibiotics at the site of infection to achieve sustained bactericidal concentrations is desirable.

On the gastric mucoadhesive dosage form, the heavy and bulky mucoadhesive tablet is apt to detach from the mucosa when traveling through the GI tract, which can be avoided by microspheres. Besides prolonging the residence time, mucoadhesive microspheres have additional advantages such as efficient absorption and enhanced bioavailability of the drugs, owing to a high surface-to-volume ratio and a much more intimate contact with the mucus layer.[40] In addition, the stability of antibiotic in the low pH should be taken into account for gastric mucoadhesive formulation since some antibiotics such as benzylpenicillin, macrolides and tetracyclines are unstable in acid. Chitosan microspheres for gastric mucoadhesive administration have been prepared and demonstrated to increase bioavailability of clarithromycin and tetracycline.[41, 42] As gastric mucoadhesive carrier, chitosan is reported to have some advantages; that is, gel-forming ability at low pH, antacid and antiulcer activities that prevent or weaken drug irritation in stomach, the ability to swell and expand in the acid medium and enhancement toward the penetration of molecules across mucosal surface.[42]

Coating materials

In the coating system, a drug-loaded core is coated with coating material solutions,

dispersions or even organic solvents. This system is considered as a reservoir system and the extended release of the drug is realized by diffusion. Therefore, the permeability of the membrane materials is directly related to the body fluid penetration and the release rate of drugs can be regulated by the variation in the thickness of the coatings. To optimize the drug release, pore formers that are less hydrophobic and allow opening channels in the membrane are often incorporated. Besides the film coating, novel polyelectrolyte multilayers have been developed as coatings for implantable devices.

Film coating materials

The film coatings broaden the application of tablets as they are prone to being prepared into gastric, enteric, slow-release or targeting formulations. Many coating materials are polymers with high molecular weight and capable of retarding the release of a wide range of drugs, such as cellulose acetate, ethylcellulose, polyacrylic resin and polyethylene. For instance, ethylcellulose, the most commonly used sustained-release coating material, is insoluble in water and thus it can serve as a hydrophobic coating agent to modify the drug release. In recent years, aqueous polymer dispersions such as Aquacoat and Surelease have been extensively used for extended-release coating because of their high solid content, low coating viscosity, easy operation and coating uniformity. Other known polymers are those belonging to the Eudragit group that represent poly(meth)acrylates dispersion: Eudragit RL and RS polymers with alkaline are insoluble but permeable in digestive fluids and Eudragit NE polymers with neutral groups enable controlled time release of the active ingredient by pH-independent swelling.

Protein and polypeptide-based drugs always need special attention on account of their rapid degradability and toxicity at high concentrations. Therefore, more tailored materials should be used. Collagen, which has good biocompatibility with an exceptional ligand encapsulating property, has been exploited as a film material for protein and polypeptide. Pexiganan, a 22-amino-acid peptide-based antimicrobial agent, was coated with different concentrations of collagen. The results revealed that 2.5% w/w of collagen film showed a maximum sustainable activity over 72 h with effective antimicrobial concentrations.[43] By the utilization of collagen membrane, sustained release of peptide-based antimicrobial in infected wounds was probable. Sripriya *et al.*[44] prepared a collagen bilayer dressing containing ciprofloxacin. The investigation *in vitro* and *in vivo* suggested a sustained release of ciprofloxacin from the collagen bilayer dressing, and they were capable of serving as a dressing for an on-site delivery system.[44]

In addition to the system administration in tablets in dosage form, film coatings are also utilized in local administration. The ocular bioavailability of the conventional forms is low because of rapid, extensive precorneal loss and the eye physiological barriers. Consequently, frequent administration or highly concentrated solutions are required, which result in poor patient compliance. With the aid of contact lenses, sustained-release delivery system for ophthalmic administration has been developed to combine prolonged ophthalmic action with the ease of application. Many attempts of the delivery device have failed to achieve constant drug release, including conventional soft contact lenses, 'biomimetic' and molecularly imprinted hydrogel contact lenses.[45, 46, 47] Ciolino *et al.*[48] succeeded in delivering drugs to the eye with zero-order kinetics. The device they designed was a dual polymer system, with one polymer film PLGA containing the test compounds and the other polymer pHEMA used as a component of the contact lenses. The release pattern was a brief and minimal initial burst followed by a controlled release of ciprofloxacin with zero-order release kinetics under infinite sink conditions for over 4 weeks. And the rate of drug release can be regulated by changing either the ratio of drug to PLGA or the molecular mass of the PLGA used.[48]

Catheters and other indwelling devices such as surgical implant placed inside the human body are prone to bacterial infection, thereby causing serious risk to patients. To circumvent and mitigate local infection for a long period, the surfaces of the graft or device are usually coated with antibiotic-containing composites. The silica sol–gel composites are novel controlled-release materials that are resorbable and biocompatible.[49] Thin sol–gel films coating vancomycin on a Ti-alloy substrate were synthesized for the prevention and treatment of bone infections. The vancomycin-containing sol–gel film decreased profoundly the number of *Staphylococcus aureus* when evaluated in a rat osteomyelitis model. A close correlation between vancomycin release and sol–gel film degradation rates indicated that film degradation is the main mechanism underlying the control of release.[50, 51]

Polyelectrolyte multilayer materials

Although many antimicrobial orthopedic implant coatings are developed, drug dosage or release rate cannot be easily tuned in most cases. Apart from the bacteria introduced during the surgical process, most often the implant-associated infections are ascribed to the attachment of bacteria in bloodstream. Thus, developing the antibiotics delivery system that discourages bacterial adhesion is imperative. Polyelectrolyte multilayers are proposed to overcome this disadvantage. With the development of layer-by-layer (LbL) deposition technique, polyelectrolyte multilayers were prepared. LbL deposition is a nanoscale polymer thin film formed by alternating deposition of polyelectrolytes or other multiply charged species on surface materials of any size and geometry. Polyelectrolyte multilayers using the LbL technology platform have demonstrated controlled erosion and tunable drug release in physiological buffers. In addition, by changing the number of deposited layers, encapsulated dosage can be readily and precisely tuned. The LbL films are degraded via a hydrolytic mechanism that enables continuous elution of drugs without the need of enzymic or cellular interaction, and the degradation products were non-toxic. The top-down erosion principle of the film has a primary role against bacterial attachment.[52]

Polyelectrolyte multilayers incorporating gentamicin were fabricated using the LbL deposition process as a device coating to address an existing bone infection in a direct-implant exchange operation. The films eluted ~70% gentamicin *in vitro*during the first 3 days and subsequently continued to release drug for more than 4 additional weeks. In the *in vivo S. aureus* bone infection model, the bactericidal ability of polyelectrolyte multilayers overwhelmingly surpassed uncoated devices.[53] Moreover, the multilayers are capable of incorporating and releasing different therapeutic agents with different release rates. Dual functional polyelectrolyte multilayers with a bolus delivery of gentamicin to eradicate infection and a retarded release of diclofenac to minimize foreign body response at implant site were prepared.[54] The versatility and tunable release for drugs of these polyelectrolyte multilayers make them attractive as coatings for implantable devices.

Complex materials

When chemically or physically combined with certain other chemical agents, some drug molecules form complexes that may be slowly soluble in body fluids. This slow dissolution rate provides the extended release of the drug. Cyclodextrins (CDs) are unique molecules with cage structure providing a wide range of applications in the pharmaceutical field owing to their complex forming capability, which allows them to include hydrophobic molecules in their hydrophobic cavity and to mask the physicochemical properties of the guest molecule.[55] For water-soluble drugs, hydrophobic CDs such as alkylated and acylated derivatives are useful as slow-release carriers. The use of such complexes always results in a biphasic release, immediate release because of the molecules unbound and subsequent delayed action as the drug molecules are progressively released by a complex dissociation mechanism. This is desirable for antibiotic delivery especially for graft infection.[56]In addition, it is reported that CDs have the ability to increase the antimicrobial activity of cefdinir[57] and interact with ciprofloxacin.[58]

Vascular prostheses are widely used to replace or bypass damaged arteries. However, there is a high mortality rate for vascular prosthesis infections.[59]Hence, vascular prostheses are always coated with antibiotics. Compared with only antibiotic-loaded vascular prostheses, antibiotic-β-CD inclusion complexes exhibited a prolonged antimicrobial effect and more antibiotics could be loaded. Furthermore, the microbiological test showed better antimicrobial activity for complex-coated vascular prostheses, and also showed that a wide range of antibiotics can be included into CDs, which makes them potential for the treatment of multigerm vascular prostheses infections.[56, 60, 61] Not only are CDs used alone as a carrier, but they are also incorporated into other carriers, such as bioactive glasses[62] and polymers,[63] to obtain an extended release.

On the basis of the fact that chemical bonds have lower energy like the van der Waals forces, ionic bonds and coordinate or chelate bonds, it should be possible to develop sustained-release system conceptually. Various small molecular bioactive agents have been bound via degradable covalent linkages to many different polymeric systems to control the release of the agents.[64] For example, cellulose xanthate–metal–tetracycline complex was prepared to arrest the release of agents. Compared with a mixture of cellulose, metal and tetracycline, the tetracycline release from the cellulose-metal-tetracycline complexes was greatly sustained,

which have been manifested by the antibacterial activity lasted for 7–22 days.[65] In addition, formation of complex can modify the hydrophobicity of the drug, which also has an influence on the drug release. Gentamicin was assembled into a hydrophobic complex by hydrophobic ion pairing with the anionic surfactant bis(2-ethylhexyl) sulfosuccinate sodium salt (AOT). Compared with the gentamicin-loaded nanoparticles, the gentamicin–AOT complex moderated the initial high burst release. The reduction was attributed to the enhanced hydrophobicity, which may allow an increased retention of the drug on the nanoparticle surface. Besides, the low solubility of the gentamicin–AOT complex in aqueous environments could result in a slow diffusion of the drug through the polymeric matrix, and therefore, in a more sustained-release kinetic of the drug.[66]

Polymers
Many biocompatible and biodegradable polymers and their derivates have been used as antibiotic nanocarriers to retain longer antimicrobial effect. Among them, amphiphilic polymers have received increasing attention because they can form self-assemblies composed of hydrophilic regions of the molecules in contact with surrounding solvent and the hydrophobic tail in the center. The hydrophobic cores can serve as reservoirs to trap hydrophobic drugs and gene for extended action. In addition, reducing toxic side effects and improving therapeutic effects also make amphiphiles attractive.[70] Amphiphilic polymers include PLA, PGA, PLGA, PCL and poly(cyanoacrylate) (PCA). As the amphiphile should be biodegradable and non-toxic, much attention has been paid to natural biomaterials, of which chitosans were studied frequently. Various hydrophobic modifications have been made for chitosans to enable them to form nanosized self-aggregates, and some of them show promise as carriers for hydrophobic drugs.[70, 71, 72] Longer hydrophobic chains and bigger hydrophobic groups benefit the stabilization of the micelle structure and the protection for drug compounds from the environment. Oleoyl-chitosan self-assembled nanoparticles loaded with doxorubicin were reported obviously superior to doxorubicin solution, and the blank nanoparticles showed no cytotoxicity to mouse embryo fibroblasts. Meanwhile, the nanoparticles exhibited a sustained release after a burst release at phosphate-buffered saline (pH 7.4).[73]

As the anomalies of temperature are common and important signs of various diseases, especially for bacterial infection, temperature-responsive polymers have become increasingly attractive as carriers for the controlled drug-delivery systems. In addition, the controlled release of drugs can also be achieved by the exertion of the local thermal field *in vitro*. The thermo-sensitive polymers can protect drugs or bioactive molecules away from denaturing aggregation and undesired chemical reactions under the low temperature condition. When temperature exceeds the gelling temperature, the loaded drugs or bioactive molecules can be released in a controlled manner. For antibiotic delivery, temperature-response technology can be applied into local infections such as osteomyelitis. A biodegradable thermo-sensitive implant composed of poly(ethylene glycol) monomethyl ether (mPEG) and PLGA copolymer (mPEG–PLGA) as a sol–gel drug-delivery system for treating bone infection was prepared. The release of teicoplanin from the formulation showed near-linear profile and lasted up to 4 weeks. *In vivo* study confirmed that the sustained release of teicoplanin from mPEG–PLGA hydrogel could efficiently treat the osteomyelitis in rabbits without the disadvantages of PMMA cement beads.[74]

Nanoparticle with positive charge is an effective strategy to prolong mucosa residence time and continuously release the drugs. As epithelial cells in the various tissues, including GI tract, carry negative charges on their surface, the positively charged particles can strongly interact with epithelia.[75] Accordingly, it is anticipated that positively charged delivery systems can lead to extended residence time. The longer absorption time will ultimately result in better bioavailability of the drugs. Positively charged Eudragit RS100 and RL100 polymer nanoparticles have been reported to extend the release of antibiotics.[76, 77] In addition, PLGA nanoparticles prepared by lyophilized nanoprecipitation technique were confirmed to be capable of improving precorneal residence time and ocular penetration so as to extend the release of antibiotics with a longer shelf life than conventional marketed formulations[78, 79]

Many other polymeric nanoparticles have also been studied for various applications. A micron-scale porous particle filled with self-assembled rifampicin nanoparticles was served as aerosol formulations. It received extended-release

profile *in vitro* and guinea pigs.[80] Polymeric micelles self-assembled from cholesterol-conjugated PEG successfully delivered ciprofloxacin across the blood-brain barrier (BBB) after being anchored with transcriptional activator TAT peptide.[81] Plasma half-life of three antitubercular drugs encapsulated with in wheatgerm agglutinin-coated PLGA nanoparticles are significantly longer than uncoated PLGA nanoparticles upon oral/inhalation routes in mice because of lectins that can be recognized by glycosylated structures in the gut and the lung mucosa.[82]

DISCUSSION AND OUTLOOK

Over the past several years, many progresses in extended-release field have been achieved and new antibiotic sustained-release formulations have constantly come into the market. Most of the preparations are hydrophilic matrix delivery systems because of their ease of manufacture and excellent uniformity. Furthermore, the applications of new materials have optimized these delivery systems. Among them, biodegradable materials that include naturally derived materials (for example, chitosan and collagen) and synthetic polymers (for example, polyurethane, PHBV and pHEMA) have shown potential for clinical availability owing to their low toxicity, biodegradability and multifunction for antibiotic delivery. In addition, materials that are obtained by chemically modifying the existing materials or combining different carriers in physical mixtures are more tailored for the slow release of antibiotics, yet their complexity and long-term stability should be taken into consideration.

In spite of the progress achieved in conventional delivery, increasing attention has been paid to the nanoparticles whose main advantage lies in their ultrasmall size and long circulation characteristics. However, until now, only few nanoparticle-based antimicrobial agents have been approved for clinical use. The limitation of their application is mainly caused by the high cost and unsatisfactory drug loading. These shortcomings may be overcome by the development of polymers (for example, amphiphilic polymers) and inorganic porous materials. As Arikace has thrown light on the nanoparticle-based extended-release antibiotic delivery, we anticipate that more antibiotic nanoparticle products will come to sight in the future.

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