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Antibiotic-containing polymers for localized, sustained drug delivery ☆

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ABSTRACT

Many currently used antibiotics suffer from issues such as systemic toxicity, short half-life, and increased susceptibility to bacterial resistance. Although most antibiotic classes are administered systemically through oral or intravenous routes, a more efficient delivery system is needed. This review discusses the chemical conjugation of antibiotics to polymers, achieved by forming covalent bonds between antibiotics and a pre-existing polymer or by developing novel antibiotic-containing polymers. Through conjugating antibiotics to polymers, unique polymer properties can be taken advantage of. These polymeric antibiotics display controlled, sustained drug release and vary in antibiotic class type, synthetic method, polymer composition, bond lability, and antibacterial activity. The polymer synthesis, characterization, drug release, and antibacterial activities, if applicable, will be presented to offer a detailed overview of each system.

Contents

1. Introduction

1.1. Antibiotics for treating infections

Conventional methods of antibiotic delivery involve systemic administration, often via the oral or intravenous routes, to treat a myriad of bacterial infections. While many common, non-life-threatening bacterial infections can be readily treated with an antibiotic course, issues arise when bacteria are not responsive or when the infection is serious [1]. Separately, implant-related infections are also a serious health issue that complicate already difficult, complex surgical procedures; biofilm formation at the implant site can cause implant failure and

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infection, leading to secondary surgery to remove the afflicted implant. Nearly 1 million implant-associated infections occur every year, and traditional, systemic antibiotic delivery is less efficacious in many cases [2]; an estimated 1000 times the antibiotic dose can be necessary to completely eradicate the biofilm [3]. Whether a common infection or implant-related infection, the increasing prevalence of multi-drug resistant bacteria, such as methicillin resistant *Staphylococcus aureus* (MRSA), is a notable challenge in treatment and prevention [4–7]. Over-prescription of broad-spectrum antibiotics (e.g., treating a viral infection with antibiotics) only exacerbates the resistant bacteria problem [8]. Considering the rise of resistance, the development of new antimicrobial delivery systems with improved biocidal efficacy is urgently required.

1.2. Need for improved antibiotic drug delivery systems

More efficient and effective drug delivery systems improving on conventional therapies (i.e., oral, intravenous routes) are crucial for microorganism eradication related to bacterial infections. Effective antibiotic release at concentrations above the bacteria's minimum inhibitory concentration (MIC) is a necessary condition to protect against infection; to treat current infections, the antibiotic concentration must be above the minimum bactericidal concentration (MBC). Improving pharmacokinetic and pharmacodynamic profiles, overcoming short-half life issues, and using localized delivery whenever possible could lower bacterial resistance incidence [9]. Local, controlled antibiotic release leads to lower dosing, decreased toxicity, extended release, and avoidance of systemic exposure [9,10]. By localizing the drug at the specific infection sites, such as in implant-related infections, antibiotics specific for that strain can be administered at high dosage without surpassing the systemic toxicity, thereby lowering side effects and preventing resistance [2]. Additionally, avoiding systemic administration would increase patient compliance as well; oftentimes, patients who are prescribed oral antibiotics do not finish the entire course, breeding resistant bacteria. Particularly for implant-related infections, the ability for clinicians to locally administer a week-long antibiotic treatment would be a significant achievement. The advantage of a controlled, sustained release system is clear; this desired treatment is possible through polymeric delivery systems.

1.3. Controlled release of bioactives from polymers

The chemical conjugation of drug molecules to polymers offers numerous advantages for simple, small molecule delivery; the unique polymer properties allow for sustained and controlled release of bioactives [11,12]. Additionally, the bioactive release rate can change based on the bonds that link the drug to the polymer (e.g., ester, amide, and urethane) [11–13], formulation (e.g., powder, hydrogel, coating, microsphere) [14–16], and polymer chemical composition (e.g., non-bioactive backbone or "linker" molecule) [17,18]. Through simple chemical modifications, the bioactive release rate can potentially be fine-tuned from days to many months, depending on the desired application and need. By covalently linking the drug, higher drug loading is achieved compared to physical incorporation [19]. Two methods of realizing this goal will be discussed, and each method has its advantages. Section 2 focuses on drug conjugation to already-made polymers, whereas Section 3 describes synthesizing a monomer that contains the antibiotic and subsequently polymerizing it. This review focuses on the chemical conjugation of known antibiotic molecules with polymers; physical incorporation (e.g., admixtures, encapsulation) will not be discussed. Additionally, we will not discuss all small, novel molecules that display antibacterial activity or polymers with inherent bioactivity (e.g., cationic, antimicrobial peptides) but instead known antibiotics. Antibiotic classes, including beta-lactams, fluoroquinolones, aminoglycosides, and sulfonamides, will be detailed herein (Scheme 1). These antibiotics are coupled to a wide range of polymers through hydrolytically labile (e.g., esters), enzymatically labile (e.g., amides), and non-labile bonds. The systems presented in this review have the potential to improve antibiotic delivery and reduce incidence of bacterial resistance.

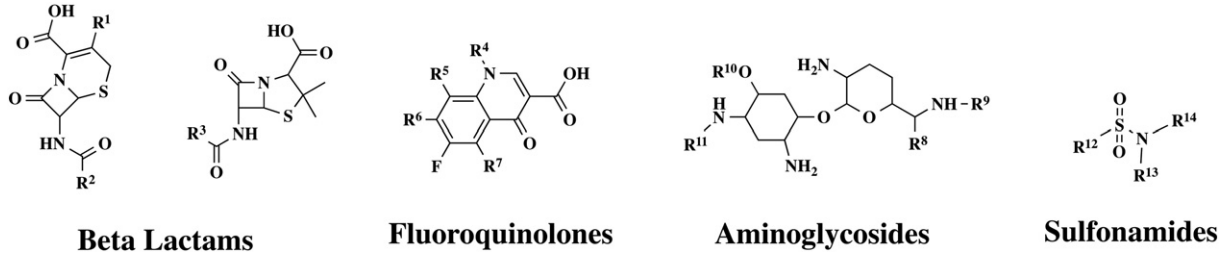
2. Chemical conjugation of antibiotics to polymers

The chemical conjugation of antibiotics to an existing polymer is described in this section (Scheme 2). As shown in Scheme 2, a covalent bond is formed between an existing polymer and drug molecule. Although this approach often leads to lower drug loading, it is possible to add several different drugs and/or targeting moieties to the polymer backbone. Examples of these types of systems are demonstrated below and have been organized based on antibiotic class.

2.1. Beta lactams

Penicillin, one of the oldest beta-lactam antibiotics discovered, has been a target drug for many researchers [20]. Penicillin V has been used as a ligand and conjugated using hydrolytically degradable ester linkages via carbodiimide coupling to prepare a water-soluble poly(ether-urethane) derived from poly(ethylene glycol) (PEG) and L-lysine [21]. Initially, PEG of varying molecular weights was coupled to both amino groups of lysine through urethane linkages, resulting in a block copolymer containing a free carboxylic acid allowing for further functionalization. Through dicyclohexylcarbodiimide (DCC) coupling, ethanolamine or ethylene diamine was attached to the copolymer via ester or amide bonds, leaving a free hydroxyl or amine, respectively. Penicillin was attached to the ethanolamine derivative via DCC coupling to form a hydrolysable ester bond (Fig. 1a). Drug release in phosphate buffered saline (PBS) at 25 °C was monitored spectrophotometrically; over 95% of the drug was released in the first 24 h. To elucidate the antibacterial efficacy of the polymer-released drug, five different strains of microorganisms were tested, including *Klebsiella pneumoniae*, *Escherichia coli*, *S. aureus*, *Streptococcuspyogenes group A*, and *Enterococcus faecalis*. Inhibited bacterial growth was observed for the latter three strains for both free drug and the polymer-bound drug, thus demonstrating potential as a drug delivery system superior to the status quo.

Highly branched macromolecules, or dendrimers, have also been investigated as beta-lactam delivery system due to their unique structures. The carboxylic acid moiety of penicillin V was modified with amino- or hydroxyl-terminated PEG through carbodiimide coupling



Scheme 1. General structures of antibiotic classes discussed in this review.