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Polymeric nanoparticle constructs as devices for antibacterial therapy

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Diseases related to bacterial infections represent a relevant challenge for public health. Despite the success obtained with the conventional antibiotic therapies, indeed, new drawbacks have been identified. In addition to poor drugs solubility and stability, adverse side effects, and many other factors which together lead to a low patient compliance, the antibiotic resistance and the lack in the development of new antimicrobial agents are the main problems. On the basis of these considerations, the research interest is focused on the exploration of new strategies able to circumvent these drawbacks improving the efficacy of current antibiotics. In this context, nanosized systems, which allow to enhance both the pharmacokinetic profiles and the mechanism of action of drugs, play a key role.

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Introduction

Nowadays, infectious diseases still represent a significant challenge in health care, being one of the major causes of mortality in the world [1]. Currently available antibacterial drugs are characterized by several limitations including poor solubility and stability, low bioavailability, difficulty in reaching the site of action, high frequency of administration, severe side effects and toxicity, which result in a very low patient compliance. In addition, the extensive and inappropriate use of antibiotics contributes to the evolution of bacteria that become able to survive and adapt and do not respond to standard treatments (bacterial resistance) [2,3]. Several mechanisms are involved in the onset of resistance including DNA modifications, changes in membrane permeability, efflux pumps and enzymes responsible for drug elimination and degradation [4]. The most common resistant bacteria are *Mycobacterium tuberculosis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Streptococcus pneumoniae* [5].

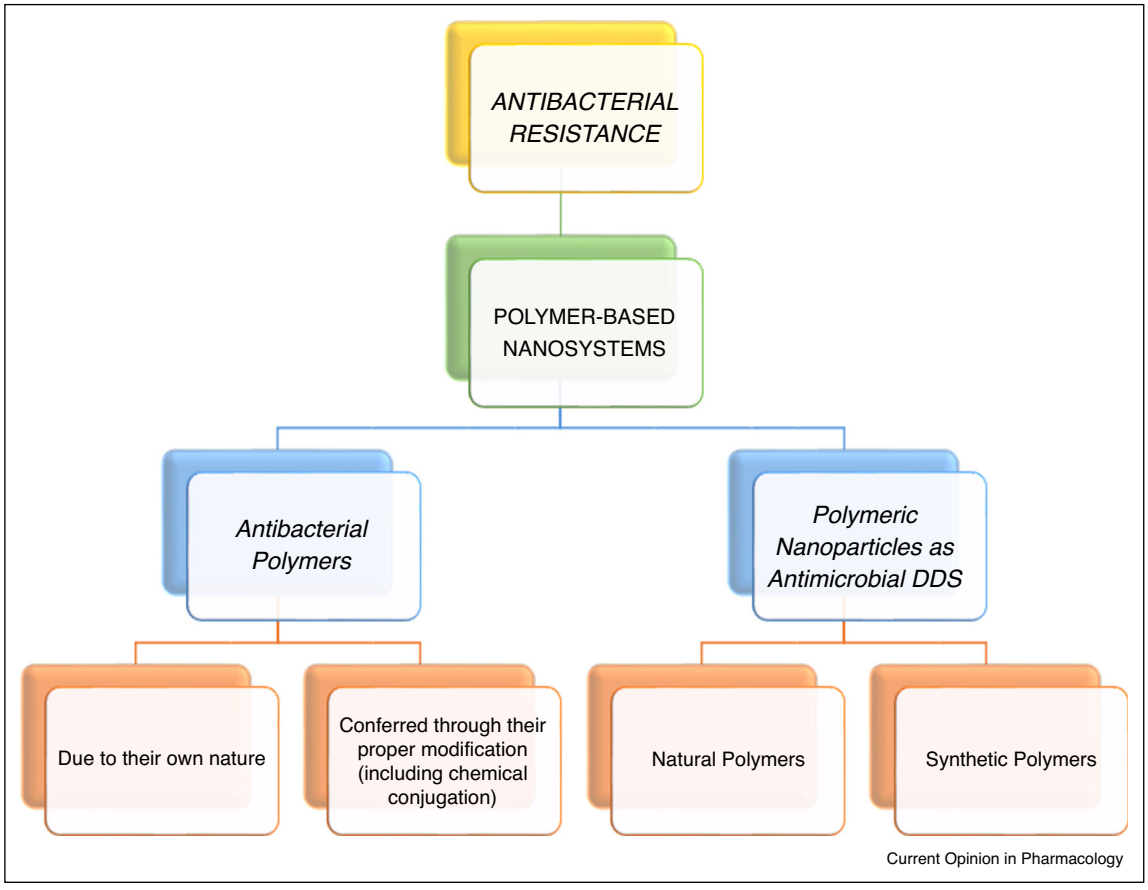
The bacterial resistance, combined with the lack in the development of new drugs, results in the failure of the antibiotic therapy and exerts a relevant societal and economic impact. The introduction of novel antibacterial agents, indeed, represents a hard and long process due to the effort to synthesize new effective and safe molecules, the high research costs and the time required for the regulatory approval. On the basis of these considerations, the research interest is focused on the exploration of new strategies able to circumvent these drawbacks increasing the efficacy of current and available antibiotics. In this context, nanotechnology plays a key role in improving the efficacy of existing drugs by the use of nanoengineered drug delivery systems, which allow to enhance both the pharmacokinetic profiles and the mechanism of action due to their unique properties as function of their composition, size, shape and surface (charge and functional groups). This kind of nanosized systems, indeed, are characterized by small size, high surface/volume ratio, the ability to interact with biological systems, such as microorganism and host cells, and to be structurally modified [6]. These features allow to overcome the problems associated to the conventional antibacterial therapies through improved drug solubility and stability, enhanced cellular internalization, sustained and controlled release, targeted delivery and prolonged systemic circulation compared to corresponding free drugs with a reduction of the side effects [7,8].

The present review aims to describe polymer-based nanosystems characterized by antibacterial activity, due to their own nature or conferred through their proper modification, or able to act as nanocarriers for antibacterial agents (Figure 1).

Antibacterial polymers and antibiotic-polymer conjugates

Antibacterial polymers can be divided into two main classes: polymeric materials characterized by antimicrobial properties by themselves and polymers that present antibacterial activity due to proper modification including conjugation with antibiotic drugs.

Figure 1



Classification of polymer-based nanosystems for antibacterial applications according to the present review.

Among the natural polymers, chitosan has received considerable attention due to its mucoadhesive and antimicrobial properties, biocompatibility and the ease with which it can be chemically modified [9–12]. The antibacterial activity of this polysaccharide is ascribable to the ability of binding the negatively charged bacterial cell walls, with a consequent alteration of the cell envelope structures and permeability, and to inhibit DNA replication [13,14]. However, chitosan application in pharmaceutical and biomedical fields is limited by its poor water solubility. In the aim to improve chitosan solubility and antibacterial properties, Wang *et al.* synthesized sulfopropyl chitosan (SP-CS) characterized by various degrees of substitution (DSs) [15]. The reaction was carried out under mild and eco-friendly conditions and the synthesized SP-CS showed a significantly improved water solubility. The antibacterial activities of the SP-CSs with various DSs were investigated by performing *in vitro* tests on *E. coli* and *S. aureus* as Gram-negative and Gram-positive representative bacteria, respectively. The obtained results confirmed the enhanced antimicrobial properties of SP-CS, with diameters of the inhibition zones ranging from 10.2 to 12.3 mm, which increased with increasing the DS.

Several studies report on the biological properties of another naturally derived polysaccharide, acemannan, including antimicrobial and anti-inflammatory activities [16]. Salah *et al.* suggested a new extraction method based on deacetylation to obtain water-soluble acemannan derivatives preserving their antibacterial properties [17]. *In vitro* antibacterial assessment, indeed, highlighted that the less deacetylated polymer showed the highest efficiency against gram-positive and gram-negative bacteria reaching an inhibition greater than 98%.

The conjugation of existing antibiotic drugs to polymeric materials represents an effective strategy to overcome the drawbacks associated to the traditional antibacterial therapies. Two different approaches can be used for the preparation of antibiotic–polymer conjugates: the chemical conjugation and the polymerization of antibiotics [18]. In the first one, the covalent bond is established between a pre-formed polymer and a drug molecule; the second