Colloid and Interface Science Communications 24 (2018) 24–34

Contents lists available at ScienceDirect

Colloid and Interface Science Communications

journal homepage: www.elsevier.com/locate/colcom

A Review on Recent Achievements and Current Challenges in Antibacterial Electrospun *N*-halamines

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ARTICLE INFO

Keywords:
N-halamine
Electrospinning
Synthesis
Characterization
Antibacterial

ABSTRACT

Protection against bacterial infections is a significant research field in modern society. It is generally recognized that use of antimicrobial agents is an effective approach to prevent bacterial infections. Recognized as effective antibacterial agents, *N*-halamines have received considerable attention due to their wide-spectrum effectiveness to eliminate harmful pathogen-associated diseases. Electrospinning technique has conferred a whole new perspective to antimicrobial *N*-halamines in the context of multifarious applications. This review presents recent achievements and current challenges in antibacterial electrospun *N*-halamines, concentrating on their synthesis, characterization, and antibacterial action. Our aim is not only to offer a systematic and comprehensive survey of the significant advances in antibacterial electrospun *N*-halamines but also to provide suggestions for their potential future development.

1. Introduction

Since microbial contamination is becoming particularly serious in past several decades, control of microbial contamination has been regarded as a hot spot in today's research [1]. In fact, using antimicrobial compounds is an effective way to prevent and control microbial contamination [2–5]. Up to date, many chemicals have been successful in eliminating pathogenic microbe, such as metals [6], metal oxides [7], chitosan [8], salt of hypochlorite [9], quaternary ammonium/phosphonium salts [10], peptides [11], guanidine [12], *N*-halamines [13], zwitterions [14], etc. On the basis of the research of antibacterial efficacy, *N*-halamines have been reported to possess comparable activities against bacteria to other praised antibacterial agents (as typically shown in Table 1). Of a variety of antimicrobial chemicals, *N*-halamines have become the focus of attention due to their unique chemical structure and excellent physical/chemical properties [15–25]. *N*-Halamines that contain one or more N—X (X represents Cl, Br, or I) covalent bond(s) are synthesized facilely via a simple halogenation of their precursor compounds containing amine, amide and/or imide groups [26–36]. Thanks to its oxidative property, the halogen in N—X bond can offer high sterilization activity [37–40]. Compared with the traditional halogen disinfectants, N—X covalent bond in *N*-halamines can make the active halogen stable [41–45]. More importantly, once halogen released from N—X bond, it can be rechargeable by a re-halogenation reaction, which makes *N*-halamines recyclable in antibacterial fields [46–50].

In contrast to bulk counterparts, nano-antibacterial materials possess smaller size and higher surface area, as a result showing enhanced antibacterial activity, which makes them have been favored by many researchers [51–55]. Accordingly, many techniques, such as template synthesis, solvothermal method, and electrospinning technique, have been explored to produce antibacterial nanostructures, with electrospinning technique being the most popular [56]. After the term electrospinning was coined in mid 1990s, electrospinning technology has gained a great achievement because it is unique both in terms of ease of operation and cost-effectiveness [56]. By the assistance of electrospinning technique, numerous antibacterial materials have been successfully electrospun [57–71]. In certain recent, researchers have concentrated on fabricating *N*-halamine-based nanofibers using electrospinning technique, which can not only simplify the synthesis but also make *N*-halamines endow high antibacterial activity [72]. After electrospinning carried out on *N*-halamines, solvent evaporation is fast and solidification time is short, which can prevent the aggregation of *N*-halamine molecules and make antibacterial agent evenly distribute into fibers.

In this review, we brought out recent achievements and current challenges in the exploration and exploitation of antibacterial electrospun *N*-halamines, focusing primarily on their synthesis, characterization, and antibacterial properties. The main part of this review was divided into three sections: (i) synthesis of *N*-halamine-containing nanofibers using electrospinning, (ii) characterization of *N*-halamine-containing nanofibers, and (iii) antibacterial property of *N*-halamine-containing nanofibers. In each section, progresses were introduced with

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https://doi.org/10.1016/j.colcom.2018.03.004
Received 15 December 2017; Received in revised form 15 March 2018; Accepted 21 March 2018

Table 1
A brief comparison for different antimicrobial compounds.

Types	Typical examples	MIC (*bacteria species*) (μg/mL)	References
Metal	Am-PGMA/Ag	20 (*E. coli*)/20 (*S. aureus*)	6c
Metal oxide	ZnO NPs	25 (*E. coli*)/6.25 (*S. aureus*)	7b
Chitosan	Sulfonated chitosan	130 (*E. coli*)/2000 (*S. aureus*)	8
quaternary ammonium/ phosphonium salt	Poly(QPM-r-AM-r-ATC)	3.1-60 (*E. coli*)/ 1.3-20 (*S. aureus*)	10b
N-halamine	PSA-N-Cl MNPs	0.2 (*E. coli*)/0.2 (*S. aureus*)	13b

examples from the recent research, and then the corresponding challenges were pointed out as well. In the end, a short summary and perspective of *N*-halamine-containing nanofibers was given, which would be fruitful to thoroughly understand and develop *N*-halamine-based antimicrobial nanofibers in terms of both broad and in-depth research.

2. Synthesis of *N*-halamine-containing Electrospun Nanofibers

Liang's reported that the loadings of oxidative halogen onto *N*-halamine(s) and the contact area of *N*-halamine(s) with the bacteria are two important factors that determine the antimicrobial efficiency of *N*-halamine-based materials [73]. Accordingly, the researchers have committed to the design and synthesis of antimicrobial materials with not only high oxidative halogen loadings but also large specific surface area, and researchers' focuses were taken on *N*-halamine electrospun nanofibers due to the convenience of electrospinning in controlling both *N*-halamine loadings and materials' size [74–82]. Until now, *N*-halamine-containing electrospun nanofibers can be divided into two sub-categories, i.e., low-molecular *N*-halamine-containing electrospun nanofibers and polymeric *N*-halamine-containing electrospun nanofibers. Table 2 summarizes the some typical studies where *N*-halamine-containing nanofibers have been produced via electrospinning method.

2.1. Low-molecular N-halamine-containing Electrospun Nanofibers

With one or more N—X bonds in their chemical structures, low-molecular *N*-halamines could be synthesized easily via a halogenation of N—H bond-containing low-molecular precursors, such as hydantoin, imidazolidinone, and 4-piperidinol. By the aid of a simple combination of halogenation and electrospinning, low-molecular *N*-halamine-containing electrospun nanofibers could be obtained, using N—H bond-containing low-molecular compound as a starting material [74–77]. Interestingly, when the synthetic order was investigated, the synthesis of low-molecular *N*-halamine-containing electrospun nanofibers could be divided into pre-halogenation and post-halogenation method.

Table 2
Classification, synthetic method, and some typical examples for *N*-halamine-containing electrospun nanofibers.

Classification	Synthetic method	Some typical examples	Ref
Low-molecular *N*-halamine-containing electrospun nanofibers	Pre-halogenation method	PMMA-DCDMH	74
		PMMA-DBDMH	74
		Nylon 6-CDMH	75
		Nylon 6-CDDMH	75
		Nylon 6-CTMIO	75
		CA-Cl-BTMP	76
		PMMA-DCDMH/ DBDMH	74
	Post-halogenation method	PAN-chlorinated I	77
		PAN-TTDD-Cl	78
Polymeric *N*-halamine-containing electrospun nanofibers	Physical approach	CA-chlorinated PBA	79
		CA-chlorinated *β*-CD-MAH-VBDMH	80
	Chemical approach	Chlorinated poly (ADMH-*co*-MMA)	81
		N-Halamine chitin	82

2.1.1. Pre-halogenation Method

Pre-halogenation method for obtaining low-molecular *N*-halamine-containing electrospun nanofibers is in term of a halogenation-electrospinning approach. The low-molecular *N*-halamines employed in the pre-halogenation method primarily are cyclic *N*-halamines with a five-membered or six-membered ring [74–76].

As the most familiar in five-membered cyclic *N*-halamines, the hydantoin-bearing *N*-halamines, such as 1,3-dichloro-5,5-dimethylhydantoin (DCDMH) and 1,3-dibromo-5,5-dimethylhydantoin (DBDMH), are marked as the most ideal candidates owing to their easiness to synthesis and high efficiency in killing bacteria. In a typical pre-halogenation method, it was noted that 5,5-dimethylhydantoin (DMH) undergoes firstly a simple halogenation process to obtain an *N*-halamine, followed by an electrospinning treatment to attain the low-molecular *N*-halamine-containing electrospun nanofibers. For example, our group [74] carried out pre-halogenation method, in which two *N*-halamines (DCDMH and DBDMH) and poly(methyl methacrylate) (PMMA) were utilized as *N*-halamine models and support matrix, respectively, to yield DCDMH- and DBDMH-containing PMMA nanofibers (see Fig. 1). In contrast, Tan and Obendorf [75] used nylon 6 instead of PMMA when implementing pre-halogenation method to synthesize low-molecular *N*-halamine-containing electrospun nanofibers.

In accordance with Sun's work [76], six-membered cyclic *N*-halamines are also one of the intermediates in pre-halogenation synthesis of low-molecular *N*-halamine-containing electrospun nanofibers. Using pre-halogenation method, Sun's group developed cellulose acetate (CA) nanofibers bearing a *N*-halamine agent of bis(N-chloro-2,2,6,6-tetramethyl-4-piperidinyl)sebacate (Cl-BTMP). They declaimed that the uniform dispersion of the Cl-BTMP into CA fibers endowed superior antimicrobial efficacy toward bacteria, as well as good biocompatible characteristics.

Unlike the common mode of involving one *N*-halamine component in electrospun polymer nanofibers mentioned above, two kinds of *N*-halamines in some case could also be introduced in one single fiber entity using pre-halogenation method. For instance, Bai et al. [74] reported on low-molecular *N*-halamine-containing electrospun PMMA nanofibers containing both DCDMH and DBDMH molecules. It was definitely demonstrated in their report that two *N*-halamines can co-exist harmoniously in PMMA matrix without provoking each other, rendering good antibacterial activity against bacteria.

2.1.2. Post-halogenation Method

It has been reported that the post-halogenation method is also successful to form low-molecular *N*-halamine-containing electrospun nanofibers [77,78]. In contrast to the pre-halogenation method above, the post-halogenation method is defined as an electrospinning-halogenation approach, in which a *N*-halamine precursor is spun firstly to attain precursor nanofibers, with a subsequent halogenation treatment. We summarize the relevant techniques as follows.

Hydantoin constitutes the main moiety of low-molecular *N*-halamine-containing nanofibers in the post-halogenation method. A typical example is the work of Worley's group [77], in which by running a three-step synthesis on hydantoin-based compound, low-molecular *N*-halamine-containing electrospun nanofibers were fabricated by the assistance of post-halogenation method. In addition, 7,7,9,9-tetramethyl-1,3,8-tri-spiro [4,5]-decane-2,4-dione-containing *N*-halamine (TTDD-X) is also identified as a ideal candidate to yield low-molecular N-halamine-containing electrospun nanofibers because TTDD-X features three kinds of N—X bonds (i.e., amine, amide, and imide N—X