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TECHNICAL NOTE

Conceptual Approach for Developing Sustainable, Active Antimicrobial-Delivery Nanosystems for Microbial Contamination Removal in Drinking and Industrial Water Systems

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Abstract

Effective treatments for the removal of pathogenic microorganisms in drinking water and the reduction of biofouling/biocorrosion in industrial water are beneficial to public health and industry. This article proposed a conceptual approach for the development of target specific nano-carriers with encapsulated antimicrobial agents. Three types of nanocomposites including dendrimers, liposomes, and zeolite are proposed as suitable nano-carrier candidates. Bacteriophage lytic enzymes and quorum-sensing inhibitors could be alternative antimicrobial agents. Antibody-conjugated nano-carriers are able to specifically target the microorganisms responsible for waterborne-disease and biofouling/biocorrosion. Ultimately, the proposed conceptual approach, designed to be effective against target microorganisms in low concentrations of antimicrobial agents in water, could be economical and less/non-toxic for human and the environment.

Keywords: *nano-carriers, microbial contamination, antimicrobial agents, drinking water, industrial water*

1. Introduction

Sustainable access to a sufficient supply of clean water through reliable water disinfection and adequate microbial control is essential to both public health and industry. Since waterborne pathogens including bacteria, enteric viruses, and protozoan parasites are a major cause of water-related disease outbreaks, the removal of these pathogens from water is a significant public health-related challenge (Aw and Rose, 2011). Between 1991 and 1998, waterborne infectious diseases were the cause of 429,000 cases of illness and 58 deaths in U. S. (Craun *et al.*, 2002). More recently, the Centers for Disease Control and Prevention (CDC) in U.S. reported 36 outbreaks associated with drinking water between 2007 and 2008, resulting in illness over 4,000 people and 3 deaths (Brunkard *et al.*, 2011). Conventional disinfection methods, such as chlorination, ozonation, and UV disinfection, have proven to be highly effective in bacterial and viral inactivation (Betancourt and Rose, 2004). However, concerns have been raised about the formation of harmful Disinfection By-Products (DBPs) during both chlorination and ozonation (Jee *et al.*, 2013; Richardson *et al.*, 2002). Various pathogens such as *Cryptosporidium* and *Giardia* have also shown strong resistance to these chemical disinfectants (Linden *et al.*, 2002; Shannon *et al.*, 2008; Shin *et al.*, 2001). Although DBPs are not likely to be formed by UV disinfection, it is energy-intensive and less effective against viruses.

In addition, Microbial Induced Corrosion (MIC) and biofouling can cause a significant increase in operating costs for industrial systems including oil transmitting pipelines and cooling towers (Coetser and Cloete, 2005). In the oil and gas industry, unwanted microbial growth, such as sulphate-reducing bacteria, results in the formation of hazardous chemicals (e.g., H_2S, which causes reservoir souring), flow resistance, metal corrosion, and various health hazards. Many classes of bacteria are not effectively controlled by conventional biocides, typically used in industrial water systems and oilfields.

The main disadvantage of the disinfectants and industrial biocides currently used is that they act in a non-specific manner. Consequently, undesirable reactions with natural organic matter, chemicals/additives in industrial water systems and non-target microorganisms require excessive applications of disinfectants and industrial biocides, which may negatively impact human health and the environment. In addition, since current disinfection and microbial control practices target to treat entire fluid rather than problematic areas, it can lead to excessive use of disinfectants and biocides.

This article proposed a conceptual approach for environmentally benign microbial control strategy, through the targeted delivery of green antimicrobial chemicals by nanocomposite carriers, which will minimize adverse impacts on human health and the

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environment (Hossain *et al.*, 2014). To successfully develop this proposed nano-carrier systems, three major points should be taken into consideration.

2. Conceptual Approach for Developing Sustainable, Active Antimicrobial-Delivery Nanosystems

2.1 Development of Nano-carriers Containing Antimicrobial Agents with Controlled Release

The direct delivery of antimicrobial agents into targeted cells is significantly related to the development of efficient and safe carriers to transport contents. Nanoparticles, such as gold nanoshells, fullerenes, dendrimers, liposomes, zeolite nanoparticles and quantum dots have been extensively researched for drug delivery applications in the past decade, because of their unique physicochemical properties, such as controllable size, large surface area to mass ratio, high interactions with microorganisms, and structural/functional versatility (Huh and Kwon, 2011). Dendrimers can be a suitable carrier candidate for disinfectants delivery purpose, due to the empty internal cavities in the core for loading a wide range of molecules, and enormous surface area that generate great reactivity and multitude of functional groups on the surfaces. Poly-Amidoamine (PAMAM) dendrimers, in specific, have widely studied and are commercially available for research purpose (Sajja *et al.*, 2009). PAMAM dendrimers consist of an alkyl-diamine core molecule and tertiary amine branches, and the exterior primary amine groups can be easily modified for further functionalization. Modified PAMAM dendrimers with high solubility can be used for water application (Cheng *et al.*, 2007).

Liposomes, which are spherical closed vesicles with concentric lipid bilayers, can be a suitable carrier for delivery of an antimicrobial agent, because of their large carrying capacity, the ability to encapsulate a wide variety of polar, nonpolar, and amphipathic agents and protect contents by rigid encapsulation from degradation, and easy surface modification (Wright and Huang, 1989). However, molecule release from the liposome is difficult due to the relatively rigid membrane. Molecules such as toxins, immune, proteins, synthetic compounds (e.g. poly-l-lysine, protamine, Triton X-100) have pore-forming activity, which can be incorporated into lipid membrane and form a central pore. A recent study reported that bacterial toxin was used to trigger antibiotic release from liposomes (Pornpattananangkul *et al.*, 2011). However, this approach is only feasible for bacteria that secrete toxins.

Zeolites, a family of crystalline porous molecular sieves, are also ideal candidates for nano-carriers of antimicrobials. Zeolites are chemically inert, and are not subject to microbial attack. Zeolites can be synthesized with a wide range of pore sizes to serve as hosts for molecules of various sizes. However, because of the open-pore framework structure of zeolites, enhancing encapsulation without the leaching of antimicrobial agents until the molecules arrive at target sites is a key challenge.

Synthesis of nanocomposites as nano-carriers with antimicrobials may be more time-consuming and expensive than conventional methods for disinfection and biofilm control. Thus, it is important to make the surplus of the non-deteriorated nano-carriers containing reusable agents for the sustainable water disinfection and microbial control. The use of magnetic nanoparticles with the application of an external magnetic field can be a promising method for effective separation and recovery of nano-carriers. Iron oxide (Fe_3O_4) magnetic Nanoparticles (NPs) demonstrated the easy separation of metal ion laden magnetic NPs by applying an external magnetic field (Ngomsik *et al.*, 2005). For example, liposome-iron oxide (Fe_3O_4) NPs (Shinkai *et al*., 1999) or PAMAM dendrimer-iron oxide nanocomposites (Shi *et al.*, 2007; Zhang *et al.*, 2009) can be used as nano-carrier with magnetic NPs.

In addition to the suitability of nano-carriers with antimicrobial agents, controlled release of antimicrobials is critical to achieving maximum efficacy in pathogen inactivation and biofilm control. Boas and Heegaard (2004) demonstrated the release of entrapped contents inside PAMAM dendrimers triggered by lowering the pH. A protease-cleavable peptide could be used for the controlled release of antimicrobials in nano-carriers. Proteases are enzymes that catalyze the hydrolytic cleavage of specific peptide bonds (Barrett *et al.*, 2004). The cleavage specificity of proteases against peptides has been used for *biological*, diagnostic and therapeutic *purposes*. A protease-cleavable peptide as a closure molecule can block the nanopore entrances to keep the antimicrobial chemical from being released until cleaved by protease (Fig. 1). For example, Sutherland *et al.* (2006) developed peptide-linked antibody conjugates cleavable by intracellular proteases for anti-cancer therapeutics. At the same time, many different bacteria also secrete extracellular proteases for protein hydrolysis in cell-free environments to utilize hydrolytic products (Gupta *et al.*, 2002). When relatively high concentrations of bacterial proteases are present near the exterior of target bacteria (upon binding to a target bacterium, through the antibody-antigen interaction on the surface of target cell) this peptide "door keepers" will be cleaved, triggering the release of the encapsulated antimicrobial agents. Previous studies have also reported that an amino group or a carboxylate group was used to block or close the opening of nanopores in zeolites (Huber and Calzaferri, 2004; Li *et al.*, 2006).

2.2 Selection of Suitable Antimicrobial Agents for Nano-carriers

The stable and effective antimicrobial agents, such as silver particles, quaternary ammonium chlorides and triclosan (Balogh *et al.*, 2001; Chen *et al.*, 2003; Gardiner *et al.*, 2008), are needed to be selected for suitable entrapment inside nano-carriers with consideration of their inactivation efficiency against pathogenic viruses and bacteria. However, increasing resistance to these available antimicrobial agents has become a major challenge for disinfection and microbial control. For examples, Several silver-resistant bacteria, including *Acinetobacter baumannii*, *Enterobacter cloacae*, *Pseudomonas aeruginosa*, and *Salmonella typhimurium*

have been reported (Deshpande and Chopade, 1994; Hendry and Stewart, 1979; McHugh *et al.*, 1975; Modak and Fox, 1981). Chlorine and ozone appear to be ineffective in the inactivation of various pathogenic viruses, bacteria, and protozoa (Linden *et al.*, 2002; Shannon *et al.*, 2008; Shin *et al.*, 2001). Various triclosan-resistant microorganims also have been observed in aquatic environments (Yazdankhah *et al.*, 2006). Thus, new alternative approaches to the inactivation of microorganisms are required.

Bacteriophage lytic enzymes are produced by bacteriophage in the lytic cycle and digest the bacterial cell wall to release progeny phage. Thus, these lytic enzymes can potentially function as antimicrobial agents (Borysowski *et al.*, 2006). PlyV12 enzyme, which displays a broad spectrum of antimicrobial activity, can be a candidate of alternative antimicrobials. In addition, quorum-sensing, a microbial cell–cell signaling system, controls bacterial virulence and biofilm formation (Bjarnsholt and Givskov, 2007). Thus, inhibition of quorum-sensing could serve as another alternative method for the treatment of biocorrosion, biofouling, infection, and disease caused by biofilm-forming bacteria. (5Z)-4-bromo-5-(bromomethylene)-3-*butyl*-2(5H)-furanone, *N*-(propylsulfanylacetyl)-L-homoserine lactone, *N*-*butyryl*-L-homoserine lactone, and 4-nitropyridine-*N*-oxide are representative quorum-sensing inhibitors (Pan and Ren, 2009).

2.3 Development of Target Specific Nano-carriers with Encapsulated Antimicrobial Agents

The recognition of specific biomolecules on targeted microbes can be achieved by employing the recognition elements such as antibodies, nucleic acid aptamers, carbohydrates, and antimicrobial peptides, which have an specific affinity to the surface of targeted microorganisms (Vikesland and Wigginton, 2010). In particular, antibody-base methods for bacterial detection are most widely used, because highly selective antibodies are readily available for a variety of waterborne-microorganisms. With advance of nano-technology, antibody-nanomaterial conjugation methods have been well established. For example, antibody-conjugated polymeric nanoparticle, quantum dot and carbon nanotubes have been used for specific recognition of pathogens such as *E. coli* O157:H7, *Cryptosporidium*, and *Salmonella* (Elkin *et al.*, 2005; Lee *et al.*, 2004; Yang and Li, 2006). An antibody-dendrimer conjugate was synthesized and applied for the targeted delivery in prostate cancer Therapeutics by (Patri *et al.*, 2004). Li *et al.* (2011) reported the antibody-zeolite nanoparticle conjugation by modifying its surface with carboxylic acid groups. Peptide linker is one of the ideal candidates in facilitating conjugation between antibodies and nanomaterials, without interfering with antibody activity (Teicher and Chari, 2011).

3. Conclusions

This article aims to offer a conceptual idea for developing a target-specific nano-carrier entrapped with antimicrobial agents for active sustainable antimicrobial delivery systems employing nanotechnology. Dendrimers, liposomes, and zeolite could be used as nano-carriers with antimicrobials. As proposed here, bacteriophage lytic enzymes and quorum-sensing inhibitors are suitable candidates as alternative antimicrobial agents. The specificity of nano-carriers could be achieved by developing antibody-conjugated nano-carriers targeting specific microorganisms responsible for waterborne-disease and biofouling/biocorrosion. For example, antibody-PAMAM dendrimers entrapped with alternative antimicrobials including bacteriophage lytic enzymes and quorum-sensing inhibitors for waster disinfection and microbial control can be developed (Fig. 1). Specific antibody for targeting microbes can be immobilized on PAMAM dendrimers. The development of pore-forming compound-conjugated antibody-liposomes, encapsulated with antimicrobial agents and magnetic NPs could be also one form of antimicrobial delivery systems (Fig. 2). In addition, zeolite materials can be chosen and synthesized/modified to provide the desirable pore size and structure to maximize the loading capacity for the antimicrobial chemicals, while providing desirable release rates once the pores are opened. Antimicrobial agents can be initially encapsulated into zeolites, before adding peptides onto the zeolite surfaces (Fig. 3).

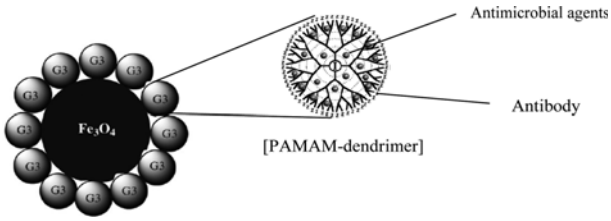

Fig. 1. Schematic Representation of Iron Oxide (Fe_3O_4) NPs-Conjugated Antibody-PAMAM Dendrimers Entrapped with Disinfectants (Cited with Modification from Balogh *et al.* (2001) and Shi *et al.* (2007))

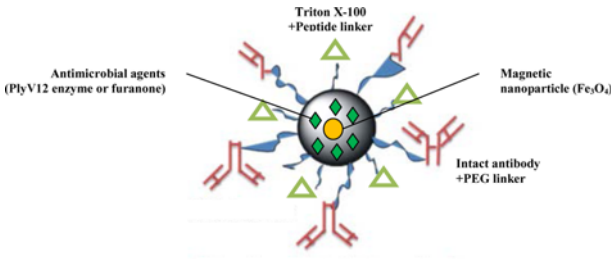

Fig. 2. Schematic Representation of Pore-forming Compound-conjugated Antibody-liposomes Encapsulated with Antimicrobials and Magnetic Nanoparticles

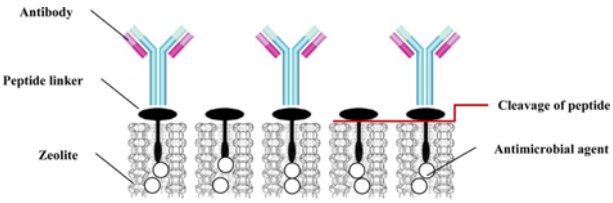

Fig. 3. Schematic Representation of Peptide-gated Antibody-zeolite Conjugates Encapsulated with Antimicrobial Agents (Cited with Modifications from Huber and Calzaferri (2004))

Then the peptide-gated zeolite surfaces can be conjugated with monoclonal antibodies specific to the surface of targeted microorganisms. Ultimately, these proposed approaches would enhance the delivery of antimicrobials to target microorganisms and reduce the toxicity of free antimicrobials to non-target microorganisms.

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