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Iodine-loaded metal organic framework as growth-triggered antimicrobial agent

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ABSTRACT

Zeolitic imidazolate framework-8 (ZIF-8) is one of easily available metal organic frameworks because of its facile preparation via mixing aqueous solutions of zinc nitrate and 2-methylimidazole. It turned into a very effective pH-responsive bactericide after loading with iodine. Approximately, 0.9 g of iodine could be readily loaded into one gram of ZIF-8 from iodine dissolved n-heptane solution. Both Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus epidermidis* and *Staphylococcus aureus* could be very effectively killed by iodine loaded ZIF-8 (ZIF-8@I) at pH 6.0 within 3 min. In contrast, at pH above 7.0, no appreciable antimicrobial activity could be detected. The bacteria killing effect is resulted from the iodine released from ZIF-8@I disintegrated at acidic pH. ZIF-8@I coated surface also showed its acidic pH-triggered antimicrobial activity against deposited bacterial cells. The antimicrobial activity of ZIF-8@I against actively grown bacterial lawns on a pH neutral agar plate was also observed. The result demonstrates that iodine was released from the disintegrated ZIF-8@I to kill bacteria in response to the bacterial growth-induced pH lowering.

1. Introduction

Iodine, a highly effective and well-known disinfectant, not only has broad-spectrum antimicrobial activity against bacteria, molds, and certain viruses but also relatively inexpensive and easy to use [1–3]. Its bactericidal activity is mainly resulted from a non-specific mode of action causing irreversible damage to the bacterial cell with no tendency to form resistance [4]. However, the direct application of iodine for disinfection was unsatisfactory due to its inherent low solubility in water. By dissolving the iodine in alcohol made alcoholic iodine solution become a popular antiseptic agent for a quite long time. Started from 1950's, Povidone iodine (PVP-Iodine), a stable chemical complex of polyvinylpyrrolidone (PVP) and iodine, was developed to be a benign antiseptic agent. PVP is a popular biocompatible polymer with very good iodophor property (having the ability to bind iodine). Thus, PVP-Iodine carries all the iodine in a complexed form so that the free iodine concentration in the solution is always very low that solve the unpleasant side effects associated with alcoholic iodine solution including painfulness, irritation and skin staining [4,5]. Based on its good iodophor and biocompatible properties, PVP has been physically or chemically modified on various material surfaces [5–8] for complexing with iodine and very effective antimicrobial activity delivered from these surfaces was observed. The antimicrobial action of iodine-PVP complex is dependent on the freely mobile iodine released from the complex. However, the release is continuous and cannot be controlled. Therefore, the development of novel controlled release of iodine is a very challenge task for achieving cost-effective disinfection.

Metal Organic Frameworks (MOF) materials are a class of porous hybrid materials with defined cage structure, their assembly and functionalization recently have captivated much attention because of their intriguing structures and potential applications in gas separation, chemical sensors, catalysts, optical devices and many others [9–11]. Different MOF preparations have been demonstrated to be very effective for the dispose of radioactive iodine gas due to their strong iodine adsorption capacity [9,12–18]. Novel 3D MOF has also shown its ability in controlled uptake and release of iodine in alcohol solution [19]. Zeolitic imidazolate framework-8 (ZIF-8) is one of easily available MOF and can confine iodine in its cage with binding energy approximately 3-fold higher over charge-transfer complexes on other organic adsorbents [9]. Particularly, ZIF-8 has also been favorably employed for proteins encapsulation [20] and as drug delivery vehicles [21,22] due to its high biocompatibility. To the best of our knowledge, the application of iodine loaded MOF as an antimicrobial agent has never been investigated before.

Bacterial adhesion and antibiotic resistance biofilm development on medical devices are becoming a critical issue in clinic medical treatments [23]. Recently, several smart antibiotic delivery systems have been developed using pH-responsive layer-by-layer (LBL) film to supply antibiotics on demand [24–26]. This antibiotic supply-on-demand

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coating has been demonstrated to be very effective for preventing the bacteria from forming biofilm because once bacterial cells colonize the surface the local pH will be lowered by the acidic metabolites of bacteria to disrupt the pH sensitive coating and the antibiotic will be released to kill bacteria in the vicinity. The antibiotic supplied in the response to the presence of bacteria will also possibly reduce the chance for bacteria to develop antibiotic resistance.

In this work, we take the advantage of high iodine loading capacity of ZIF-8 and its pH-responsive property to develop as bacteria-triggered antimicrobial nanoparticles. ZIF-8 was first prepared to demonstrate its pH susceptibility and iodine uptake capacity. The bactericidal activity of iodine loaded ZIF-8 (ZIF-8@I) against acids producing pathogenic bacteria *Escherichia coli*, *Staphylococcus aureus* and *Staphylococcus epidermidis* were evaluated. The antibacterial efficacy of ZIF-8@I coated surface in response to different pH was also studied. The bacteria-triggered antimicrobial effect of ZIF-8@I was demonstrated by inhibition zone test using agar plates with actively grown bacterial lawn.

2. Experimental

2.1. Materials

Zinc nitrate hexahydrate ($Zn(NO_3)_2 \cdot 6H_2O$) and 2-methylimidazole were purchased from Sigma–Aldrich. Iodine (99.8% ACS) was obtained from Acros Organic. Bacteria *Staphylococcus aureus* (ATCC6538P) and *Escherichia coli* (BL21) were obtained from TTRI (New Taipei City, Taiwan) and Novagen (Madison, WI, USA), respectively for the antimicrobial activity test. All other chemicals were reagent grade.

2.2. Preparation and characterization of iodine loaded ZIF-8

2.2.1. Synthesis of ZIF-8 nanoparticles

ZIF-8 was synthesized according to the rapid room temperature method as described elsewhere [11,27]. Briefly, aqueous solutions of 2-methylimidazole (1.25 M, 10 mL) and zinc nitrate hexahydrate (250 mM, 1 mL) were mixed together and immediately sonicated in an ultrasonic bath for 15 min to give the opaque mixture. For the synthesis of ZIF-8 with PVP (ZIF-PVP), the 2-methylimidazole (1.25 M, 10 mL) solution containing 15 mg/mL of PVP was prepared. The very tiny particles in opaque mixture were grown at room temperature for 12 h without stirring. The product was collected by centrifugation at 6000 rpm for 10 min, then washed 3 times with ethanol and dried under vacuum overnight at 100 °C.

Fig. 1. Photo images of ZIF-8 powder and iodine solution. (a) and (d) ZIF-8 before iodine adsorption; (b) iodine dissolved in n-heptane, (c) iodine solution after ZIF-8 adsorption; (e) ZIF-8 powder after iodine adsorption.

2.2.2. Loading iodine into crystalline ZIF-8 (ZIF-8@I)

ZIF-8 and PVP coated ZIF-8 (ZIF-PVP) of 2 mg was dispersed in 1 mL iodine solutions with a concentration of 1–4 mg/mL prepared in n-heptane at room temperature for 24 h. At the end of iodine adsorption, the ZIF-8@I was collected by centrifugation and washed repeatedly with water and n-heptane to remove the free iodine. After dried under vacuum at room temperature, the samples were ready for characterization and antimicrobial test. The amount of iodine loaded into ZIF-8@I (g/g particles) was calculated according to standard calibration curve of iodine in solution of 1 M KI prepared in 1 × PBS of pH 6 measured by spectrophotometer at 350 nm. Briefly, 5 mg of each sample was well-dispersed in 5 mL releasing solution of 1 M KI in 1 × PBS of pH 6 by shaking at 120 rpm at room temperature to completely dissolve ZIF-8@I. The amount of iodine released in the supernatant was quantified by spectrophotometer was considered as the total amount of iodine loaded into

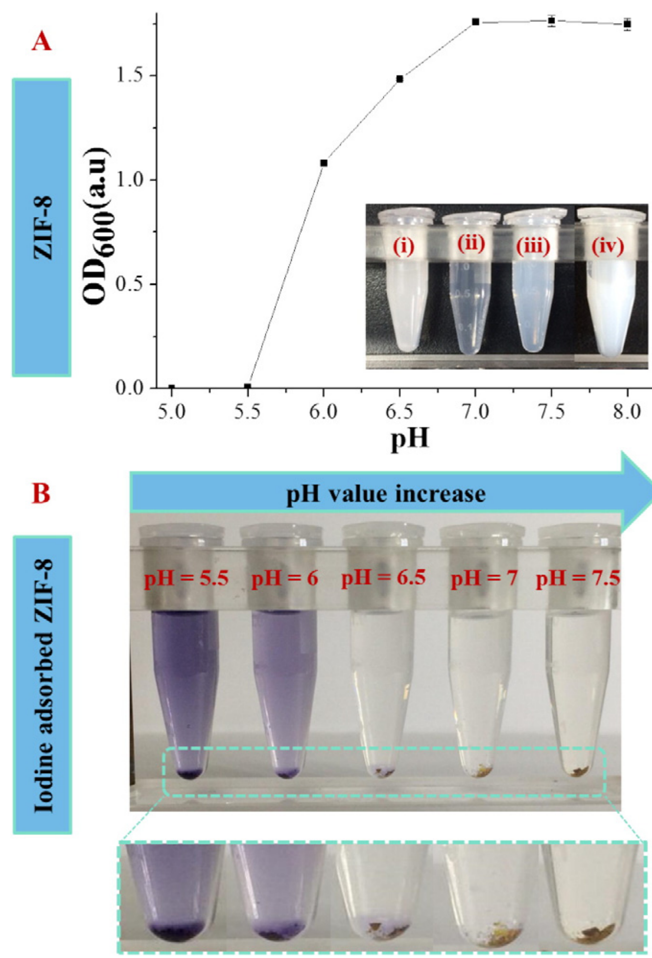

Fig. 2. pH effect on disintegrating ZIF-8 and iodine loaded ZIF-8@I. (A) Turbidity of 1 mg/mL ZIF-8 suspension in response to pH. Inset image (i) ZIF-8 suspended in water of neutral pH, (ii) dissolved in acidic pH, (iii) 1 min after pH adjusted back to neutral, and (iv) after 30 min. (B) pH effect on iodine release from ZIF-8@I. Starch was used as indicator in the solutions of different pH.