Colloids and Surfaces B: Biointerfaces 170 (2018) 648–655

Contents lists available at ScienceDirect

Colloids and Surfaces B: Biointerfaces

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

Encapsulation of green tea polyphenol by pH responsive, antibacterial, alginate microgels used for minimally invasive treatment of bone infection

Zhenhua Chen*,[1], Xinyan Lv[1], Mengen Zhao, Peng Zhang, Xiuli Ren*, Xifan Mei*

Jinzhou Medical University, Jinzhou, 121001, People's Republic of China

ARTICLE INFO

Keywords:
Osteomyelitis
Oxidative stress
Tea polyphenol
Microgel
Delivery vehicle

ABSTRACT

The treatment of bone infection requires drug carriers take large number of cargo, be antibacterial, promote proliferation and differentiation of osteoblasts. Herein, we proposed a strategy of preparing pH responsive, antibacterial, multistage structured microspheres encapsulated with green tea polyphenol used for minimally invasive treatment of bone infection. Tea polyphenol (TP) were encapsulated by porous silica nanospheres (SiO_2 NSs). Then, sodium alginate (SA) microgel spheres (MSs) were prepared to encapsulate a lot of TP loaded SiO_2 NSs. The outer layer of obtained TP@SiO_2@SA microgel spheres were further wrapped by pH sensitive $CaCO_3$. Mineral out-layer of the composite microspheres is used to neutralize the acidic environment caused by bacterial infection. At the same time, encapsulated TP is released pH sensitively to resist oxidative stress. Our results exhibited excellent drug delivery properties including drug loading efficiency (DLE) of 92.96% and drug loading content (DLC) of 19.62%. Besides, results demonstrated that TP@SiO_2@SA@$CaCO_3$ MSs can effectively kill *Staphylococcus aureus* and promote proliferation and differentiation of osteoblasts under stimulation of H_2O_2 at pH = 5.5.

1. Introduction

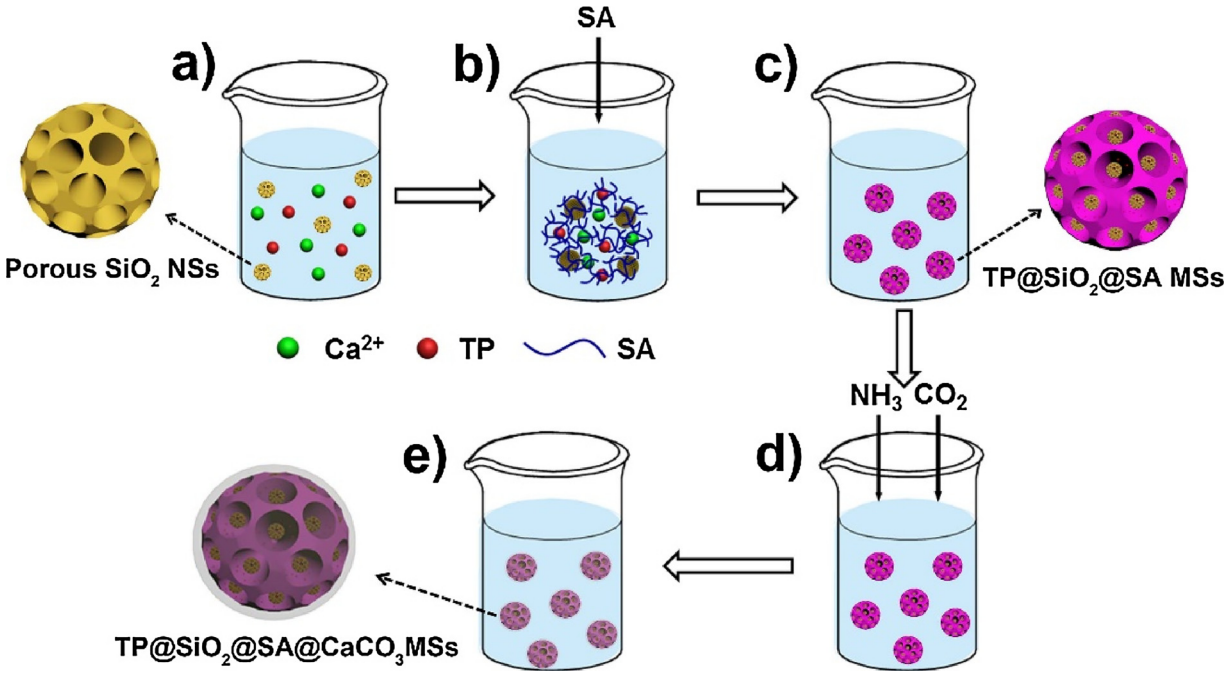
Ideal drug carriers for treatment of bone infection should take large number of cargo, antibacterial, promote proliferation and differentiation of osteoblasts. Osteomyelitis is defined as an inflammatory process localized in the bone and a notoriously difficult disease to treat, primarily caused by *Staphylococcus aureus* (*s. aureus*) [1]. It becomes a major problem worldwide and can be devastating due to the potential for limb-threatening sequelae and mortality [2–4]. The current approaches to treat osteomyelitis are mainly antimicrobial in clinically and requiring frequent and heavy doses of systemically administered antibiotics [5,6]. These approaches are effective to bactericidal profile, but the local acidic environment of osteomyelitis, brought on by the bacterial infection, has not been improved. Oxidative stress, known to damage all cellular bio-macromolecules (lipids, sugars, proteins, and polynucleotides) plays an important role in regulating osteoblast apoptosis during osteomyelitis development. It not only inhibits osteoblast differentiation and affects bone formation [7,8], but also causes inflammation [9–11]. Therefore, it's necessary to exploit new and effective drug carriers which take large number of cargo, antibacterial, promote proliferation and differentiation of osteoblasts resisting oxidative stress.

Green tea polyphenols (TP) is a group of polyphenol compounds extracted from green tea, known by its excellent anti-oxidative and antibacterial activities [12]. It is reported that TP have been found to be active through radical scavenging by electron transfer and hydrogenatom transfer as antioxidants [13,14], which can scavenge free radicals and inhibit oxidative damage of cell. However, green tea polyphenols are easy to be oxidized, they need assist by carriers to delivery of their activity site-specifically.

Recently, numerous drug delivery vehicles with the capability to deliver multiple drugs and control release rate have been designed, such as foams [15], films [16], hydrogels [17,18], microparticles [19], and nanoparticles [20]. In recent decades, hydrogels have attracted much attention for their applications as drug carrier for enhancing drug solubility, sustained release time, reducing side effects [21–23]. Therefore, the strategy of preparing hydrogels to encapsulate drugs is extremely urgent because it permits loading large quantities of drugs. Sodium alginate (SA) is a biopolymer, and it can be gelated in presence of positive ions such as calcium ion [24]. The sodium alginate hydrogel has been extensively used in the encapsulation because of its distinctive features such as biodegradable, biocompatible, and non-toxic biopolymer [25]. Herein, in this paper, we proposed a strategy of preparing pH responsive, antibacterial, multistage structured microspheres

* Corresponding authors.
E-mail addresses: zhchen561@yahoo.com (Z. Chen), rxlrenxiuli@163.com (X. Ren), meixifan1971@163.com (X. Mei).
[1] These authors contributed equally.

https://doi.org/10.1016/j.colsurfb.2018.06.065
Received 13 April 2018; Received in revised form 15 June 2018; Accepted 30 June 2018
Available online 02 July 2018



Scheme 1. The preparation process of the TP@SiO_2@SA@$CaCO_3$ MSs.

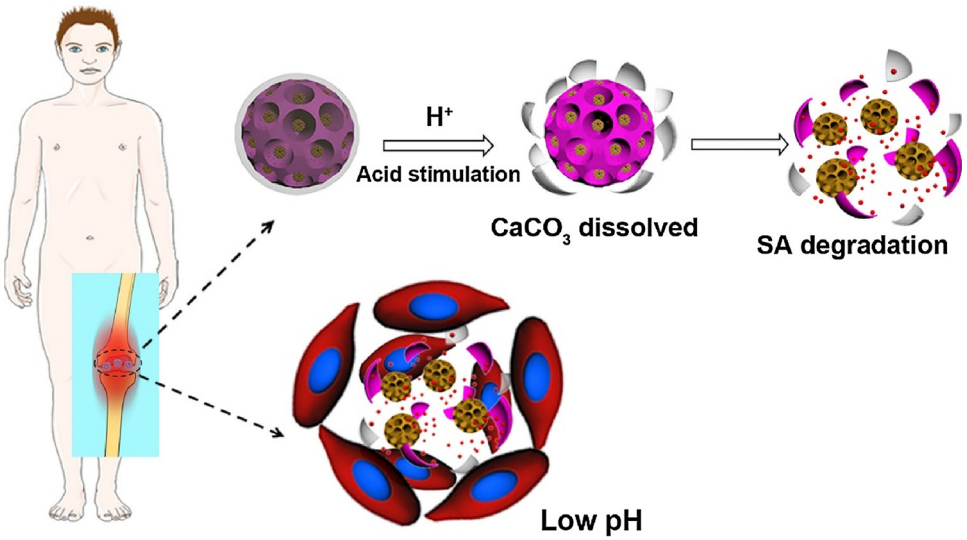
encapsulated with green tea polyphenol used for minimally invasive treatment of bone infection. Minimally invasive treatment (surgery) can limit the size of incisions needed and so lessen wound healing time, associated pain and risk of further infection. Open surgery, in which incisions made can sometimes leave large wounds that are painful and take a long time to heal. However, minimally invasive surgery is much less invasive in that it involves much smaller incisions than the corresponding open surgery procedure. This minimally invasive surgery became the most common and important method of repairing abdominal aortic aneurysms [26].

AS illustrated in Scheme 1, TP were encapsulated by porous SiO_2 NSs. Then, SA microgel spheres were prepared to encapsulate a lot of SiO_2 NSs loaded with TP. Such strategy of encapsulation of numerous silica nanospheres by gel beads can package abundant tea polyphenols and protect their antioxidant activity. The outer layer of obtained TP@SiO_2@SA microgel spheres were further wrapped by pH sensitive $CaCO_3$ [27]. As shown in Scheme 2, mineral out-layer of the composite microspheres is used to neutralize the acidic environment caused by bacterial infection [28]. At the same time, encapsulated TP is released pH sensitively to resist oxidative stress.

2. Experimental

2.1. Materials

Ammonia solution (28%) and Ethanol were purchased from Tianli Chemical Reagent Co., Ltd, China. Tetraethyl orthosilicate (TEOS, A. R.) was purchased from Tianjin Guangfu Fine Chemical Research Institute, China. Sodium hydroxide (G. R.) was purchased from Beijing Chemical Reagent Factory. Sodium alginate and ammonium carbonate were purchased from Tianjin Guangfu Fine Chemical Research Institute. Calcium chloride anhydrous (analytical reagent) was purchased from Tianjin Damao Chemical Reagent Factory. Tea polyphenols (≥98wt%) was purchased from Wuxi Sunset Lvbao Technology Co., Ltd. Deionized



Scheme 2. The release process of TP in the TP@SiO_2@SA@$CaCO_3$ MSs on the treatment of osteomyelitis.