Nanocomposite mesoporous silica-alginate hydrogels for extended delivery of antibiotics

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Abstract. Bacterial infection is one of major health problems in Indonesia. Improper use of antibiotics can further trigger antibiotics resistant bacteria which then worsen the situation. One of key challenges to avoid problem is to provide antibiotics delivery system that can release antibiotics in certain time window. In this work, we develop drug delivery system with tuneable release rate of antibiotics. The system will consist of porous silica nanoparticles of size of about 150 to 200 nm, that will be encapsulated in large micrometres size gel particles to allow the protection of the drug and avoid its early release. To understand the release behaviour, the system is tested under simulate gastric fluid.

1. Introduction

The use of antibiotics in a sub-MIC (Minimal Inhibitory Concentration) condition can cause a microbial resistance to antibiotics. This phenomenon can be found in the use of fluoroquinolone which can cause S. aureus bacteria to be able to transfer antibiotic resistant genes [1]. Treatment with conventional medicine needs to be taken many times to ensure that the plasma concentrations of antibiotics are sufficient, and the desired results can be achieved. Consumption of conventional antibiotics will increase the likelihood of a person having sub-MIC antibiotic concentrations that can trigger the mechanism of antibiotic resistance due to peak and valley effect [2].

One strategy to avoid sub-MIC (Minimal Inhibitory Concentration) condition in the blood plasm is to formulate antibiotics into extended release tablets [3, 4]. Other advantage of this extended release of antibiotics is to allow patients to consume antibiotics once a day [5]. This is important since patients tend to drop antibiotics medication once they feel better [6]. There are several extended releases of antibiotics in the market. The Biaxin® ER is a clarithromycin antibiotic that has extended release characteristics used to treat chronic bronchitis, pneumonia, and acute maxillary sinusitis. Another example of an extended release antibiotic that has been marketed is the Ceclor® CD tablet, a Cefaclor antibiotic. It is reported that both formulations were able to maintain antibiotics concentration higher than its MIC for longer period [7].

To control the release rate of the antibiotics, several materials have been used. Cellulosic polymers (such as hydroxypropylmethylcellulose, methylcellulose, hydroxypropylcellulose, hydroxyethylcellulose and sodium carboxymethylcellulose) are probably used most frequently to create swellable hydrophilic matrix [6]. In the case of Biaxin® ER and Ceclor® CD, they used substituted hydroxy cellulose (either as hydroxypropylmethyl cellulose or hydroxypropyl cellulose) and methacrylic acid copolymer [7]. In this work, we explore the use of nanocomposite mesoporous alginate as materials to control the release of the antibiotic from the matrices.
2. Experimental
All materials used in this experiment were analytical grade without further purification. FTIR and UV-Vis measurement were done on Shimadzu IRTracer-100 and Shimadzu UV-1800 UV Vis Spectrophotometer, respectively. Mesoporous silica was synthesized according to the reported literature [8]. Nanocomposite Mesoporous Silica-Alginate hydrogel beads were synthesized by dropping pre-mix composition Alginate/Mesoporous silica/Cefixime (200 mg of Alginate, 100 mg of Mesoporous Silica, and 100 mg of Cefixime) in total of 17.5 mL solution into solution of calcium chloride (3% w/v concentration). Simulated Gastric Fluid (without Pepsin) was prepared by mixing solution of 0.2% sodium chloride and hydrochloric acid in 1000 mL of deionized water with final pH of 1.2.

3. Results and Discussion
To produce the nanocomposite mesoporous silica-alginate, firstly we synthesized mesoporous silica nanoparticles. The mesoporous silica nanoparticles were synthesized using modified Stober technique under basic condition and CTABr was used as structured directing agent. The surfactant used during synthesis was then removed by calcination techniques. The morphology and the pore orientation of the particles were characterized by SEM (Figure 1a) and TEM (Figure 1b). From the both analysis techniques we can see that the homogeneous particles are spherical shaped and with a diameter of around 100 nm. The pores are clearly seen under TEM. The pores are arranged parallel with each other without any inter-connection in between. This means that all pores are accessible.

![Figure 1. (a) SEM, (b) TEM image, (c and d) nitrogen adsorption isothermal curve and pore distribution of the MCM-41 type mesoporous silica particles.](image)

From the nitrogen adsorption measurement, we can see that the adsorption and desorption gave us typical IV isothermal curve (Figure 1c-d). The capacity condensation of the nitrogen gas molecules in small mesopores during the adsorption process is overlapped with the region of the multiple-layer
adsorption. It is suggested that we have small mesopores in MCM-41 type mesoporous silica. In the condensation process, no adsorption hysteresis was observed suggest that the pore diameter is constant without variation. By DFT model the pore distribution was calculated. The pores are mono-dispersed and the diameter of the pore is 2.95 nm. Since the diameter of the particles is only 100 nm, the aggregation of particles has formed large spaces (>50nm) in between the particles at high relative pressure in the right part of the isothermal curve. Traditionally BJH method has been applied for measuring the mesopore structure [9]. By BJH and DFT method, the obtained pore diameter is 2.1 nm and 2.95 nm respectively, the error of almost 30% is comparable with the earlier report [10].

The nanocomposite mesoporous silica alginate was synthesized by dropping pre-mix composition Alginate/Mesoporous silica/Cefixime (200 mg of Alginate, 100 mg of Mesoporous Silica, and 100 mg of Cefixime) in total of 17.5 mL solution into solution of calcium chloride (3% w/v concentration). The release behavior of antibiotics from the micrometer sized beads containing cefixime antibiotic were examined by mixing certain number of beads with pepsin-less simulated gastric fluid.

Figure 2 shows the release profile of cefixime under different condition. The green line depicted the release behaviour of release from pristine alginate beads having 40 mg of cefixime, green line depicted the release behaviour of release from pristine alginate beads having 20 mg of cefixime, and the red line depicted release behaviour from nanocomposite mesoporous silica-alginate having 40 mg of cefixime. Form the pictures we can see that nanocomposite beads gave lowest initial release, meaning that the mesoporous silica particles were able to keep cefixime from early release. A constant release can be observed and after 5 hours the nanocomposite did not reach the plateau. Prolonged experiment is needed to understand the release in long period of time.

4. Conclusion
The incorporation of mesoporous silica into nanocomposite mesoporous silica-alginate able to control the release of antibiotics in better way.
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