Development of Hybrid Gelatine/Alginate/PVA Hydrogels for Extended Delivery of Antibiotics

A. Mujono, J. Evelyn, and E.A. Prasetyanto
Dept. of Pharmacy, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia.
Jl. Pluit Raya no 2, Jakarta 14440 Indonesia

E-mail: prasetyanto@atmajaya.ac.id

Abstract. Low compliance during consumption of antibiotics will result higher risk to antibiotic resistance. By modifying the release rate of the antibiotic, the patient will be able to consume antibiotics in less frequency while maintaining a stable drug concentration in the plasma, thus lowering the risk of antibiotic resistance. In this work, we report the use of hybrid hydrogels based on the Gelatine/Alginate/PVA as drug release controller of Cefixime, one of the most used antibiotics in Indonesia. The presence of Gelatine, PVA and Cefixime in the hydrogel system was analysed by FTIR spectroscopy. The release of Cefixime from the system is monitored under simulated gastric fluid. The results show that the release rate of the cefixime can be controlled by varying formulation of the hydrogels system. The presence of PVA in the formulation increase the release rate of the Cefixime.

1. Introduction
Typhoid fever is an infectious disease caused by Salmonella enterica serovar Typhi. Typhoid fever is common in populations that have poor sanitation and have difficulty accessing clean water. The management of typhoid fever is by administering antibiotics. One of the antibiotics that can be used is the class III cephalosporin class of antibiotics. Cephalosporins are one of the antibiotics belonging to the β-lactam group. Like other β-lactam antibiotics, cephalosporins have β-lactam rings and work by inhibiting the synthesis of bacterial cell wall peptidoglycan [1]. Cephalosporins consist of several classes, namely the first to third generation, antipseudomonal cephalosporins, and anti-MRSA cephalosporins (Methicillin-resistant Staphylococcus aureus). Each cephalosporin group has different antimicrobial activity. The first class cephalosporins have good activity against gram-positive bacteria and good activity against gram-negative bacteria. The second class cephalosporins have better activity in gram negative bacteria but not as good as the third generation cephalosporins. Third generation cephalosporin activity against gram-negative cocci is less active but has very good antistreptococcal activity. In addition, third generation cephalosporins also have better activity against Enterobacteriaceae compared to previous generation cephalosporins. Antipseudomonal cephalosporins have better activity against gram negative bacteria compared with third generation cephalosporins especially against Pseudomonas aeruginosa. The last class, namely anti-MRSA cephalosporin is an antibiotic that is able to fight the MRSA bacteria by sticking to the modified PBP (Penicillin Binding Protein) surface. Cefixime has t1/2 plasma for 3-4 hours and is excreted in urine and eliminated in bile. The standard dose for adults is 400 mg/d for 5-7 days and is extended for cases of S. pyogenes infection. Standard doses for children under 6 months and older and weighing less than 45 kg are
given based on body weight (8 mg/kg/d). Cefixime is given orally to fight urinary tract infections caused by *E. coli* and *P. mirabilis*, otitis media caused by *H. influenzae* and *S. pyogenes*, and pharyngitis caused by *S. pyogenes*. Cefixime has a high effectiveness for curing typhoid fever [2, 3].

There are 2 main classifications of the Drug Delivery System, namely immediate release and modified release [4, 5]. Modified releases can be divided into extended release, delayed release, targeted release, and orally disintegrating tablets (ODT) [6, 7]. Antibiotics are generally produced in the form of immediate release drug (IR). IR is a drug whose speed or absorption is not manipulated. IR is formulated to release the drug directly after consumption. Slow release drug is a variation of extended release drug. Extended release drugs can control the release of drugs in a certain time, speed, duration, and location. The use of slow release drugs will help reduce the minimum frequency of drugs, which in turn will reduce the number of non-compliance with taking antibiotics [8, 9].

In this work, we would like to encapsulate third generation cephalosporins such as cefixime, which are usually used to treat gastrointestinal infection in a nano-hybrid hydrogel system for oral drug delivery [10]. The system will consist of PVA/Alginate, in which the drug will be loaded, that will be encapsulated in a micrometres size gel particle to allow the protection of the drug and avoid its early release. The gel microparticles is a biocompatible soft material permeable to small molecules and through which the drug can be easily released. The regulator of slow release in slow release drugs can be made with various materials. In this study, gelatine was used as a regulator of slow release. Gelatine is a natural polymer. Natural polymers have the advantage of being biocompatible, biodegradable and do not cause systemic toxicity when administered. In addition, gelatine is also easily available at inexpensive prices.

2. Materials and Methods

All materials used in this experiment were analytical grade without further purification. UV-Vis and FTIR measurement were done on Shimadzu UV-1800 UV Vis Spectrophotometer and Shimadzu IRTracer-100 Spectrophotometer, respectively. Pepsin-less Simulated gastric fluid was prepared by dissolving 2.0 g of sodium chloride and 7.0 ml of hydrochloric acid in 1000mL of deionized water with final pH of 1.2. Alginate hydrogel beads and hybrid alginate/gelatine/PVA hydrogel beads were synthesized by pipette dropping pre-mix composition alginate/gelatine/PVA/Cefixime (200 mg of Alginate, and 100mg of Cefixime) in total of 17,5 mL solution into solution of calcium chloride (3% w/v concentration).

3. Results and Discussion

The millimetre size Gelatine/Alginate/PVA hydrogels beads were obtained by drop casting a mixture alginate/gelatine/PVA/Cefixime into solution of calcium chloride. After stirring for 25 minutes in the calcium chloride solution, a semi hard hydrogels beads with opaque colour were formed. The longer the beads stay in the calcium chloride solution harder beads will be obtained due to higher degree of crosslinking. After drying of the beads in the desiccator, the beads were able to swell again with quite high swelling ratio (up to 300% in volume).
Figure 1 shows the FTIR spectra of the alginate, hybrid alginate/gelatine loaded with cefixime and hybrid alginate/gelatin/PVA loaded with cefixime (all in dried bead condition). The dried samples were measured by attenuated total reflection (ATR) technique with the range of from 4000 to 480 cm\(^{-1}\). From the spectra shown in Figure 1, it is clearly showed the presence of Cefixime and Gelatine in the hybrid hydrogels system. The presence of cefixime was recognized by CH stretching band at around 2800 cm\(^{-1}\). While the incorporation of gelatine gave additional bands at 1750 cm\(^{-1}\) and 1500 cm\(^{-1}\).

The measurement was done in triplicate with different samples and the spectra were consistent meaning the hybrid system are relatively homogeneous. Further addition of PVA did not alter the spectra of the samples.

The release profile of cefixime from the hybrid hydrogels we examined under condition mimicking human gastric. For this purpose, the hydrogels containing cefixime were stirred in the pepsin-less simulated gastric fluid. From the UV-Vis spectroscopy analysis, cefixime has absorption maximum at 285 nm. Figure 2 shows UV-Vis spectra of simulated gastric solution after in contact with cefixime contained hybrid hydrogels for certain minutes.

The samples were obtained by vigorously mixing Hybrid Gelatine/Alginate and Hybrid Gelatine/Alginate/PVA Hydrogels containing 40 mg (Figure 2a and c) and 80 mg (Figure 2b and d) in 100mL of pepsin-less simulated gastric fluid. Samples were taken every 30 minutes for 5 hours and immediately analysed by UV-Vis spectroscopy. The concentration of cefixime in the simulated gastric fluid increased by increasing of contact with hydrogel beads. In comparison with hybrid system without PVA, the Hybrid Gelatine/Alginate/PVA Hydrogels release cefixime faster. The release of cefixime is not yet done at 5 hours of contact time.
4. Conclusions
We successfully incorporated cefixime into the Hybrid Gelatine/Alginate/PVA Hydrogels and the results show that the release rate of the cefixime can be controlled by varying formulation of the hydrogels system. The presence of PVA in the formulation increase the release rate of the Cefixime.

5. Acknowledgement
The authors would like to thank to Indonesian Ministry of Research, Technology and Higher Education for financial support.

6. Reference
[1] Brunton L L, Knollmann B C and Hilal-Dandan R 2018 Goodman & Gilman's : The Pharmacological Basis of Therapeutics
[2] Joshi R D, Khadka S, Joshi D M, Shrestha B, Dangol G, Acharya K P, Shrestha S and Dongol Y 2018 Antimicrobial Sensitivity Trend in Blood Culture Positive Enteric Fever J Nepal Health Res Coun 16 228-32
[3] Nawaz A, Aslam A and Haq G 2018 Potent Antibiotic to Treat Typhoid Fever in Patients of Pediatric Age-group Asian Journal of Research in Medical and Pharmaceutical Sciences 3 1-5
[4] Kogan S, Zeng Q, Ash N and Greenes R A 2001 Problems and challenges in patient information retrieval: a descriptive study Proc AMIA Symp 329-33
[5] Turnidge J J 1998 The pharmacodynamics of β-lactams 27 10-22
[6] Venkatesh G M, Stevens P J and Lai J-W 2012 Development of orally disintegrating tablets comprising controlled-release multiparticulate beads Drug Dev. Ind. Pharm. 38 1428-40
[7] Bruschi M L 2015 Strategies to Modify the Drug Release from Pharmaceutical Systems: Elsevier Science)
[8] Fair R J and Tor Y 2014 Antibiotics and bacterial resistance in the 21st century Perspect Medicin Chem 6 25-64
[9] Gao P, Nie X, Zou M, Shi Y and Cheng G J 2011 Recent advances in materials for extended-release antibiotic delivery system 64 625
[10] Kaurthe J 2013 Increasing antimicrobial resistance and narrowing therapeutics in typhoidal salmonellae J Clin Diagn Res 7 576-9