Development of Amoxicillin-Loaded Modified Polycaprolactone Microparticles in Medical Application

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***Abstract*—Amoxicillin is realized as significant drug due to their essential inhibition of bacterial infections. However, the effective time of amoxicillin in clinical position is less than 8 hours. Therefore, this research was to prolong the drug delivery system. Chitosan was modified by PCL (PCL/CS) microparticles were fabricated by oil in water emulsion (o/w emulsion) techniques for the protection and controlled the release of amoxicillin. The ratio of PCL: chitosan at different ratios were investigated for their influences on the zeta potential, size, morphology, swelling ratio and the release rate of amoxicillin from PCL/CS microparticles. The encapsulation efficiency was 74% to 83% and the maximum cumulative released amounts of amoxicillin from the PCL/CS at ratio 1:5 was about 6.5±0.03 mg for 7 days. Furthermore, the antimicrobial of amoxicillin was demonstrated by antimicrobial activity assays, which are effective in treating *Escherichia coli (E. coli)* and *Staphylococcus aureus (S. aureus)*. The PCL/CS was enough for the bacterial inhibition growth of *E. coli* and *S. aureus*. The PCL/CS could be appropriate to supply a model the drug delivery system for the medical application.**

***Index Terms*—polycaprolactone, chitosan, amoxicillin, microemulsion, antibacterial**

I. Introduction

Amoxicillin is semi-synthetic of penicillin used for the treatment of gastric acid and antibacterial in the oral cavity [1]. It is executed to a patient at a dose of 250-500 mg every 8 hrs. after administration in the body. Amoxicillin is most effective during bacterial growth, both gram-positive (*E. coli*) and gram-negative (*S. aureus and S. epidermidis*) [2]. Amoxicillin is very well absorbed from the gastrointestinal tract. Amoxicillin is progressive absorbed from the gastrointestinal tract [3]. However, the half life of drug is 8 hrs. The clearance of amoxicillin is relatively quick in the body. As a consequence of the drug delivery system to prolong controlled drug release using the development of microparticles. Microparticles can be controlled drug release to safely achievement for desired therapeutic effects. Thus, the development of microparticles can be protected and controlled by the release of the drug for a limited time [4]. The microparticles were prepared from biopolymers such as proteins, polysaccharides, and synthetic polymers [5]. Biopolymers are biodegradable, biocompatible, non-toxic, low cost and easy to chemically modify. The microparticles were prepared using the emulsion technique for sustained drug delivery systems based on the encapsulation of drug and proteinaceous compounds [6], [7].

PCL is commonly used in biomedical applications due to its unique biocompatible, biodegradable structure and non-toxicity. It was approved by the FDA for medical applications and drug delivery systems [8]. It can be influenced by hydrolysis of the ester group and the degradation structure can eventually be metabolized or eliminated by the body. However, there are disadvantages including strong hydrophobicity [9]. Therefore, the efficiency of the drug maintains in PCL is lower than the hydrophilic group. The problem has been PCL modified with chitosan.

Chitosan is non-toxic, biodegradable and biocompatible [10]. Therefore, chitosan applied of biomedical field such as antibacterial agents, prolong for the release of protein and drugs [11]. Also, the combination of amoxicillin and chitosan can be reacted due to chitosan demonstrates antibacterial activity. [12]. Although emulsion techniques are effective in drug stores, there are limitations might be a rapid release and the inability to control the release is maintained [13]. This work prepares PCL/CS microparticles by oil in water emulsion (o/w emulsion) techniques for inhibiting of antibacterial, leading to controlled release of amoxicillin for 7 days.

Manuscript received November 13, 2020; revised February 27, 2021.

doi: 10.18178/ijpmbs.10.2.88-93

II. Method

A. Preparation of the Amoxicillin Loading-PCL/CS Microparticles

1) Materials

Polycaprolactone: PCL (Mw ≈ 70,000-90,000 g/mol and chitosan were purchased from Sigma-Aldrich (Singapore). Poly(vinyl alcohol) : PVA (MW ~31,000 Da) were purchased from Sigma-Aldrich (USA).Acetone (A.R. grade) and dichloromethane (A.R. grade) were purchased from Lab-Scan (Asia) (Thailand).Amoxicillin (Trimox 500 mg) was purchased Chumohon Pharmaceutical (Thailand).Di-Potassium hydrogen orthophosphate (Mw 174.18 g/mol) and potassium dihydrogen orthophosphate (Mw 136.09 g/mol) was purchased from Univar (Australia). All chemical agents were of analytical grade.

2) Fabrication of PCL Microparticles

PCL microparticles were fabricated using an o/w emulsion technique, containing 100 mg PCL powder was first dissolved in 3:1 mL of organic solvent (dichloromethane: acetone) [7]. Next, A solution of amoxicillin 100 mg/mL in deionized water was added 10 mL of an aqueous solution. The mixture was then polyvinyl alcohol (PVA) 0.5%w/v was added into 30 mL of emulsified under constant agitation by homogenizer (IKA RW 20 digital mechanical stirrer) at 8,000 rpm for 40 °C at 30 min [14] to obtain an o/w emulsion. Next, the emulsion was magnetically stirred for 5 hrs. at 45°C to evaporate organic solvent. Finally, the microparticles were obtained by centrifugation, washed three times with deionized distilled water and freezed dry (Lyoph – Pride series freeze dryer, IlShin).

3) Fabrication of Chitosan was modified by PCL (PCL/CS) microparticles

Chitosan was modified by PCL (PCL/CS microparticles) were fabricated using an o/w emulsion technique, containing 100 mg PCL powder was first dissolved in 3:1 mL of organic solvent (dichloromethane: acetone). PCL microparticles were mixed by varying the chitosan concentrations of 100, 300 and 500 mg in acetic acid 1%w/v into 10 mL of an aqueous solution. The ratio of PCL/CS was 1:1, 1:3 and 1:5. Next, A solution of amoxicillin 100 mg/mL in deionized water. The mixture was then Polyvinyl Alcohol (PVA) 0.5%w/v was added into 30 mL of emulsified under constant agitation by homogenizer (IKA RW 20 digital mechanical stirrer) at 8,000 rpm for 40 °C at 30 min to obtain an o/w emulsion. Next, the emulsion was magnetically stirred for 5 hrs. at 45°C to evaporate organic solvent. Finally, the microparticles were obtained by centrifugation, washed three times with deionized distilled water and freezed dry (Lyoph – Pride series freeze dryer, IlShin).

B. Size and Surface Morphology Analysis

The morphology of PCL and PCL/CS 1:1, 1:3 and 1:5 microparticles was examined using a JEOL JSM 6400 Scanning Electron Microscope (SEM). The average diameter was analyzed with SemAfore 5.21 software.

C. Zeta Potential Measurement

The zeta potential of the microparticles was determined by dynamic light scattering technique (DLS, Malvern. Zetasizer Nano ZSP, UK). The microparticles were dispersed in distilled water. The zeta potential value is the average of three consecutive measurements.

D. Swelling Behavior

The swelling behavior of the control PCL and PCL/CS 1:1, 1:3 and 1:5 microparticles was examined by immersion in 10 mL of 10 mM Phosphate Buffered Saline (PBS) at 37 °C. After 24 hrs. the swollen microparticles were examined by Dynamic Light Scattering technique (DLS, Malvern. Zetasizer Nano ZSP, UK). The Swelling ratio was calculated using the following equation Equation (1) [15]:

$$\text{Swelling ratio} = \left[\frac{D_{swell}}{D_{dry}}\right] \times 100 \quad (1)$$

where D_{dry} is the average diameter of dry microparticles; D_{swell} is the average diameter of microparticles swollen in buffer solutions after 24 hrs.

E. Encapsulation Efficiency

Amoxicillin loaded PCL and PCL/CS 1:1, 1:3 and 1:5 microparticles were prepared by magnetically stirred at room temperature. The percentages of the encapsulation efficiency was determined for each batch of PCL and PCL/CS 1:1, 1:3 and 1:5 microparticles. The amount of amoxicillin encapsulated in PCL/CS microparticles was measured by UV-Visible spectrophotometer at a wavelength of 273 nm. The percentages of the encapsulation efficiency was calculated using the following equation Equation (2) [13]:

$$\% \text{ Encapsulation Efficiency} = \left[\frac{W_1}{W_0}\right] \times 100 \quad (2)$$

where W_1 is the total milligram amoxicillin encapsulated at PCL/CS microparticles; W_0 is the initial milligram amoxicillin loaded.

F. In Vitro Drug Release

Amoxicillin loaded PCL and PCL/CS 1:1, 1:3 and 1:5 microparticles were immersed into phosphate buffer solution pH 7.4 and left into the incubator at 37 °C. Sampling 3 mL of solution was taken out every 10 minutes until 7 days. In each time of sampling, 3 mL phosphate buffer were added into the solution. The release of amoxicillin from PCL and PCL/CS 1:1, 1:3 and 1:5 microparticles in phosphate buffer was determined by UV-VIS spectrophotometer (SPECORD® 210 PLUS) at a wavelength of 273 nm.

G. In Vitro Antibacterial Activity Assay

The strains of bacteria used in this research were *Escherichia coli (ATCC 25922)* and *Staphylococcus aureus (ATCC 25923).* The antibacterial activity was assessed by the agar well diffusion method (Muller-Hinton agar, Diag-Med, Poland). Molten nutrient agar (15 mL) was inoculated with 0.1 mL of test bacteria. Twenty μL of

the sample solution was filled in the well and incubated at 37°C for 24 hrs. The diameters[mm] of inhibition zone was then measured and compared with a disc containing 100 mg/mL of amoxicillin (control) [16].

III. Results and Discussion

A. Morphology of Microparticles

Scanning electron micrographs of PCL and PCL/CS 1:1, 1:3 and 1:5 microparticles are showed the formation of spherical shape and a smooth surface but different sizes (Fig. 1 and Fig. 2). The average diameters of PCL microparticles are 1.093±0.37 µm. PCL was modified with the addition of chitosan in the o/w emulsion process had calculated mean diameters of PCL/CS 1:1, 1:3 and 1:5 are 1.464±0.58, 1.8230±0.49 and 2.249±0.75 µm, respectively. The average diameters of PCL/CS microparticles increased when the amount of chitosan increased in Fig. 2 [17] because the average diameters increase is due to the chitosan amount led to an increase of the viscosity, chain entanglement and opposite charge interaction between PCL and chitosan.

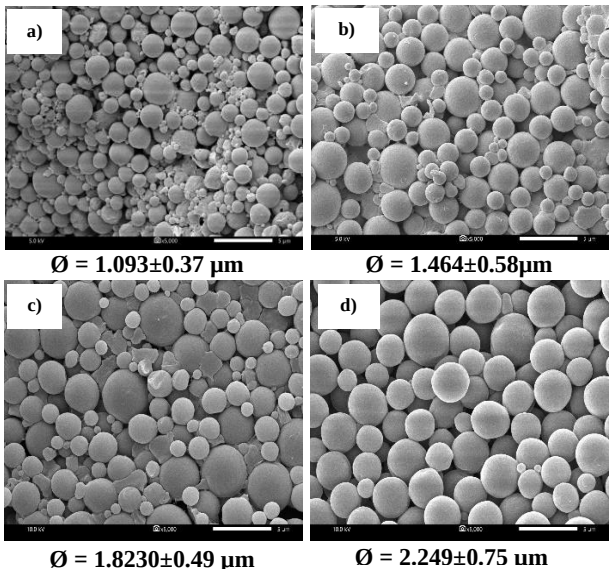

Figure 1. Scanning electron microscope (SEM) of PCL (a), PCL/CS 1:1 (b) PCL/CS 1:3 (c) and PCL/CS 1:5 (d) microparticles (magnification 5,000x).

B. Zeta Potential of Microparticles

Zeta potential measurements of PCL and PCL/CS 1:1, 1:3 and 1:5 microparticles are presented in Fig.3a. The zeta potential of -22.96±0.43 mV of PCL microparticles is mainly derived from the negatively charged groups (carbonyl groups) on the backbone. The o/w emulsion process of PCL/CS 1:1, 1:3 and 1:5 resulted in zeta potential values of +15.23±0.09, +33.50±2.2 and +39.60±0.95 mV respectively, due to the positively charged amino groups of CS.

C. PCL and PCL/CS 1:1, 1:3 and 1:5 Microparticles Swelling Studies

The swelling ratios of the PCL and PCL/CS 1:1, 1:3 and 1:5 microparticles at pH 7.4 before and after swelling in phosphate buffer were studied at 37ºC for 24 hrs. The diameters of dry and wet PCL and PCL/CS 1:1, 1:3 and 1:5 microparticles were determined and reported in Fig.3b. The diameter of PCL, PCL/CS 1:1, 1:3 and 1:5 microparticles before and after swelling were 112.16±1.2, 232.99±0.46, 243.24±0.17 and 271.82±0.81µm, respectively. The swelling ratios increased with increasing the amount of CS due to the hydrophilicity [12].

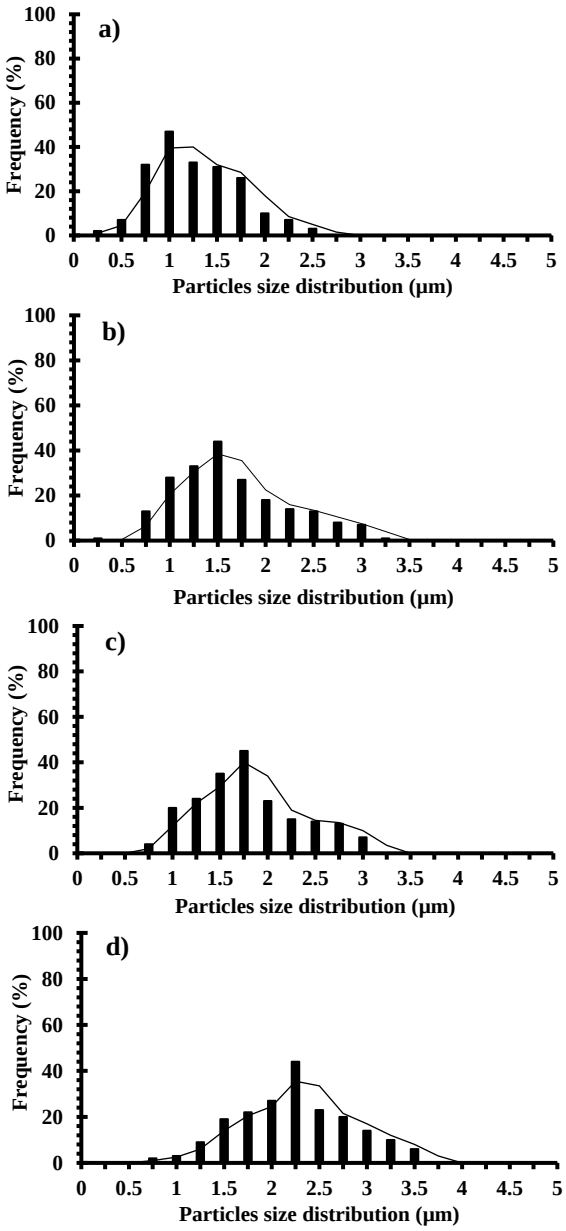

Figure 2. Size distribution of PCL (a), PCL/CS 1:1 (b) PCL/CS 1:3 (c) and PCL/CS 1:5 (d) microparticles (magnification 5000x, n = 200).

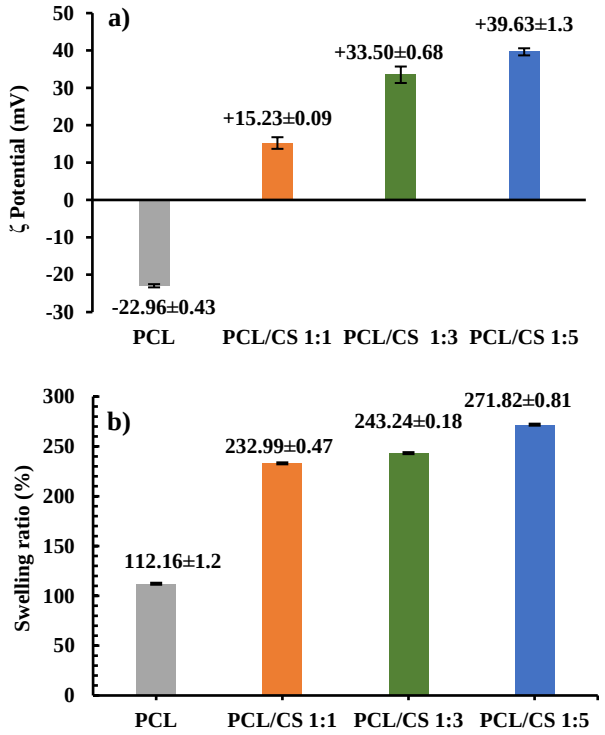

Figure 3. Zeta potential at conducted in deionized water 25°C (a) and swelling behavior at 24 hrs. (b) of PCL, PCL/CS 1:1, 1:3, and 1:5 microparticles by dynamic light scattering (n=3).

D. Encapsulation Efficiency

The percentages of the encapsulation efficiency were determined amoxicillin in the microparticles as observed in Fig. 4.

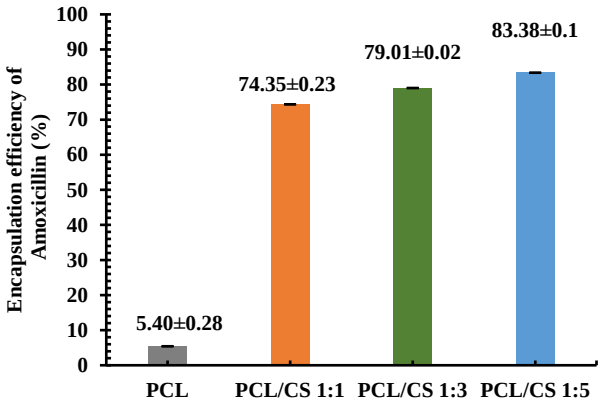

Figure 4. Encapsulation efficiency for PCL/CS 1:1, 1:3 and 1:5 microparticles loaded amoxicillin (drug) 100 mg/mL (Data 57 present as mean ± S.D. and n=9).

The result was shown that the encapsulation efficiency of amoxicillin in PCL/CS 1:1, 1:3 and 1:5 microparticles was 74.35±0.23, 79.01±0.02 and 83.38±0.11%. This revealed that amoxicillin concentration increased when chitosan increased due to polyion complexation [18].

Polyion complexes can be reacted electrostatic interactions between positively charged (the amino group of chitosan = +53.93±5.00 mV) and negatively charged (the carbonyl group of amoxicillin = -20.03±2.2 mV) species. So, that would promote electrostatic interaction between positive and negative charged molecules to maintain the release of drug from microparticles. While, the encapsulation efficiency of amoxicillin in PCL was 5.40±0.28% due to the PCL and amoxicillin were negatively charged. Therefore, PCL microparticles showed a lower encapsulation efficiency of the drug.

E. Amoxicillin Released from PCL, PCL/CS 1:1, 1:3 and 1:5 Microparticles

The microparticles were immersed in 0.05 M phosphate buffer pH 7.4 and incubated in a shaking water bath at 37 °C with shaking at 70 rpm continues 7 days. The release profiles are paid as the percentages of the cumulative of amoxicillin released as presented in Fig. 5. The release rate of amoxicillin in microparticles was found that PCL microparticles provided a higher release rate more than PCL/CS microparticles because of PCL was lower of encapsulation efficiency, amoxicillin was released quickly within 12 hrs. PCL was modified surface with chitosan control the release within 7 days.

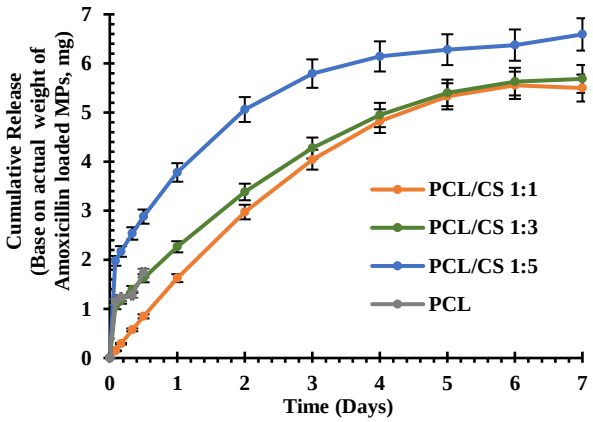

Figure 5. Release profile for PCL, PCL/CS 1:1, 1:3 and 1:5 microparticles loaded amoxicillin (drug) 100 mg/mL and incubated in test with 3.0 mL at pH 7.4 and 37 °C for 7 day. (Data are present as mean ± S.D. and n=9).

This result was shown that the swelling of PCL/CS at ratio 1:5 demonstrated the highest of 83.38±0.11% because the chitosan has a hydrophilic group, so the phosphate buffer diffuses into the particles can be easy. PCL/CS 1:5 microparticles were profiled *in vitro* release provided biphasic modulation. The first day was characterized by a relatively rapid initial release and followed by the second day of a slower release [19]. PCL/CS 1:5 microparticles had the maximum amount of amoxicillin released 6.56±0.03 mg, it can release of amoxicillin more than PCL/CS 1:1 and PCL/CS 1:3 was released at 5.76±0.93 and 6.26±0.05 mg, respectively for 7 days.

F. In Vitro Antibacterial Activity Assay of Microparticles

The *in vitro* antibacterial activity of the PCL, Chitosan, PCL loaded amoxicillin and PCL/CS 1:5 microparticles loaded amoxicillin using *E.coli* and *S. aureus* as a model bacterium in a liquid medium. Fig. 6 showed the result of antibacterial activity assay. From the experiment provided

that, PCL loaded amoxicillin, and PCL/CS 1:5 microparticles loaded amoxicillin in a liquid medium. Amoxicillin was able to inhibit both of bacterial growth (*E. coli and S. aureus*) at each studied concentration, while the bacterial inhibition of PCL and PCL/CS microparticles increased with the amount of amoxicillin released. This is likely due to the increased encapsulation efficiency of PCL/CS 1:5, which can be released amoxicillin in antibacterial [20].

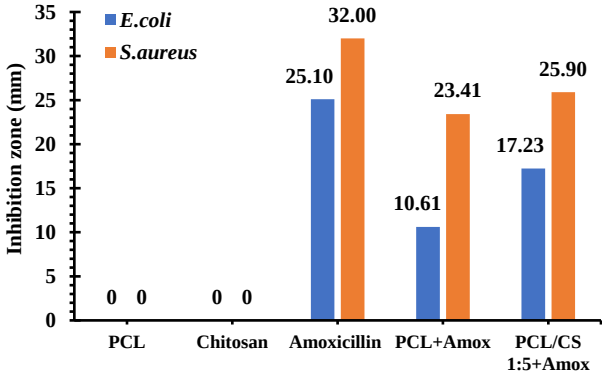

Figure 6. Growth inhibition of *Escherichia coli (E. coli) and Staphylococcus aureus (S. aureus)* after treatment with PCL, Chitosan, amoxicillin (100 mg/mL), PCL loaded amoxicillin and PCL/CS 1:5 microparticles loaded amoxicillin for 24 hrs. at 37 °C in liquid medium.

IV. Conclusion

The PCL microparticles modified surface with chitosan were prepared by oil in water emulsion (o/w emulsion) techniques. The PCL/CS at ratio 1:5 containing amoxicillin presented the %EE of 83.38±0.11%. The maximum release profile was 6.56±0.03 mg within 7 days. Moreover, The bacterial inhibition growth of *E.coli* and *S. aureus* can be antibacterial of 17.23 mm and 25.90 mm, respectively. This could be appropriate to provide the model drug delivery system for the medical application.

Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

C. Metheeparakornchai performed the experiment, modified microparticles, analyzed the data; and co-wrote the paper; N. Kreua-ongarjnukool and S. T. Niyomthai conceived the study and were in charge of overall direction and planning, processed the experimental data, co-wrote the paper, visualization, reviewing and editing; P. Pavasant and C. L. Nakalekha had conceptualization, reviewing and editing for *in vivo* antibacterial activity assay; all authors commented on the paper and had approved the final version submitted for publication.

Acknowledgment

The authors would like to express sincere thanks to Science and Technology Research Institute for financial support from Science and Technology (grants No. KMUTNB-62-DRIVE-036). Special thanks to Graduate College and Industrial Chemistry Department, Faculty of Applied Science, King Mongkut's University of Technology North Bangkok for their supporting.

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