

# Characterization on the reduction of burst release via biodegradable polymers from chlorhexidine-release on coated Foley urinary catheter by chlorhexidine-loaded micelles

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**Abstract :** In this work, chlorhexidine-loaded block copolymer was fabricated into micelles (CHX-micelles) and was then coated on foley urinary catheter by dip technique. The number cycles of coating were alternated the bilayers between (CHX-micelles) and poly(acrylic acid) which presented the suitable cycles of coating at 90 bilayers. This cycle of coating presented enough CHX quantity on coated catheter but their still showed burst CHX-release in early stage at first day. Hence, poly (lactic acid), PLA and poly ( $\epsilon$ -caprolactone), PCL were also used to coat on top of 90 bilayers of catheter surface to reduce the burst release. The CHX quantity was then investigated on coated catheter and were studied the CHX-release. Results showed that the coated catheters at 90 bilayers and then coated the PLA and PCL presented the reduction of burst CHX-release from 80% to 42% for PLA coating and 38% for PCL. Moreover, coating PCL nanospheres (PCL-NS) on coated of 90 bilayers (CHX-micelles/PAA) can assist to reduce the burst release of CHX and prolonged the CHX-release up to two weeks. Thus, this strategy can be reduced the burst CHX-release on coated urinary catheter at early stage and can be prolonged the CHX-release.

**Keywords:** chlorhexidine micelles, burst release, urinary catheter, biodegradable polymers

## 1. Introduction

Nowadays, medical devices which are orthopedic implantation (bone plates, dental implants, schanz pin, artificial hips)[1, 2] and urinary catheter have been reported in term of risk to infections, especially urinary catheter[3]. Urinary catheter has been used in patients who received the surgery and bladder dysfunction. These diseases need to catheterize the urinary catheter in long term and lead to colonize of biofilm on catheter substrate. Long-term catheterization is an indwelling urinary catheter that are prone to urinary tract infection (UTI). Currently, many researches have been reported the technique to prevent the UTI in term of coating with antibacterial agent, drug, and silver which promoted the potential of antibacterial on catheter surface. This strategy needs to reduce the bacteria adherent and formation on the catheter surface. Nanotechnology as an encapsulation the drug into nanocarrier is the one technique that purpose to control and prolong the drug release to the target site. Nanocarrier as nanoparticles in form of micelles, nanospheres, and noisome has been used to contain the drug for sustained-release application. Thus, the drug encapsulated in nanocarrier provides the burst release at early phase due to unencapsulated-drug on nanocarrier surface. Hence, this work aims to reduce the burst release via coating PLA, PCL on coated urinary catheter by chlorhexidine-loaded micelles (CHX-micelles).

## 2. Materials and methods

### 2.1 Material and polymers

Chlorhexidine(CHX)was medical gradeand purchased from Evonik Nutrition & Care GmbH, Germany. The two ways Foley urinary catheters with 14 Fr. 30 ml were produced from Well Lead Medical Co., Ltd. and were purchased through the F.C.P. Company Limited Bangkok, Thailand.The biodegradable polymer to produce micelles was poly(ethylene glycol)-block-poly( $\epsilon$ -caprolactone) (PEG and PCL, Mw = 5 and 5 kDa). It was synthesized by NanoPolyPEG, Co., Ltd. as previously reported [4]. Polymers including poly(acrylic acid) (PAA), poly( $\epsilon$ -caprolactone) (PCL) (Mn 70- 90kDa), and poly (lactic acid)



(PLA)(MW = 75 kDa) were purchased from Aldrich (St. Louis, MO). Tetrahydrofuran (THF), Dimethyl sulfoxide (DMSO), and chloroform were purchased from RCI Lab scan Bangkok, Thailand.

### 2.2 Preparation CHX-loaded micelles, PLA & PCL solution and PCL nanospheres (PCL-NS)

Preparation of CHX-loaded micelles and PCL nanospheres (unencapsulated CHX) were reported as previous work by solvent evaporation method [5, 6]. For PLA and PCL were also dissolved with DMSO with concentration 2 mg/mL.

### 2.3 Preparation of coating urinary catheter

Layer by layer (LbL) dip coating and spray coating were the techniques as reported previous study [5, 6]. The suitable cycles of LbL dip coating at 90 bilayers between coating CHX-micelles alternating PAA. Coated urinary catheters at 90 bilayers were then coated via the PLA solution, PCL solution, and PCL nanospheres solution.

### 2.4 CHX-release study

Coated urinary catheters in each condition were cut and immersed in artificial urine at pH 6.6. All catheter samples were picked-up at selected time interval to measure the CHX-release by UV-vis spectrophotometer at wavelength 270 nm. The interferent between CHX, PAA, PLA, and PCL were also investigated.

### 2.5 Antibacterial activity

Uncoated and coated catheter were examined the bacteria inhibition by zone inhibition and bacteria fixation techniques.

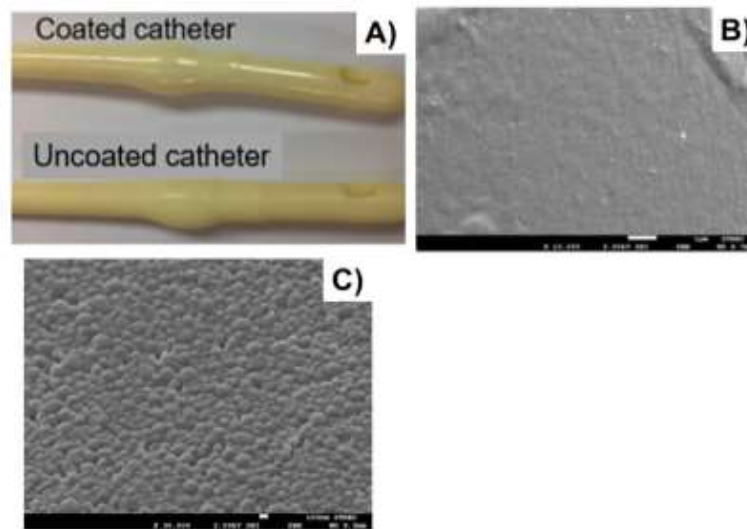
## 3. Results and discussion

### 3.1 Characterization of coated urinary catheter

**3.1.1 Amount of CHX on coated urinary catheter and morphology of coated urinary catheter** Previous work, CHX-micelles and PAA were used to coat on urinary catheters by alternating into layer-by-layer (LbL) nanocoating as shown in Figure 1A and 1B, but the CHX-release from this system provided within one week [5]. LbL nanocoating is the alternating layer coating by CHX-micelles and PAA which called bilayers. The number of coating into bilayers was varied and reported as previous work [1, 5]. Results of CHX-release presented the high level of burst release at 80% in first day. Hence, this work aimed to reduce the burst release of condition A by coating the PLA and PCL on top of catheter surface at condition A. Both of biodegradable polymers were dip-coated and varied the cycles of coating (1 and 3 cycles) and then measured the CHX quantity. Results showed the reduction of CHX content on coated catheters as shown in Table 1. While condition F (PCL nanospheres, PCL-NS) was also used to coat by spraying on the surface of condition A and provided the preventing of CHX losing during coating with unchanged the amount of CHX on coated catheter. In addition, PCL-NS (unencapsulated CHX) were measured the size as  $159.5 \pm 18.7$  nm and freeze-dried for investigation under FE-SEM as shown in Figure 1C. These results showed narrow size distribution of nanospheres as reported by Srisang, S. and Nasongkla, N. [6]. Although, the reduction of CHX content on coated urinary catheter found in condition B, C, D, and E but these conditions could help to decrease the burst release. Result of CHX reduction was due to the elution during polymer coating into polymer solution (PLA and PCL solution). Therefore, condition A, C, E, and F were selected to further study the CHX-release profile.

**Table 1.** CHX quantity of coated catheter in each condition

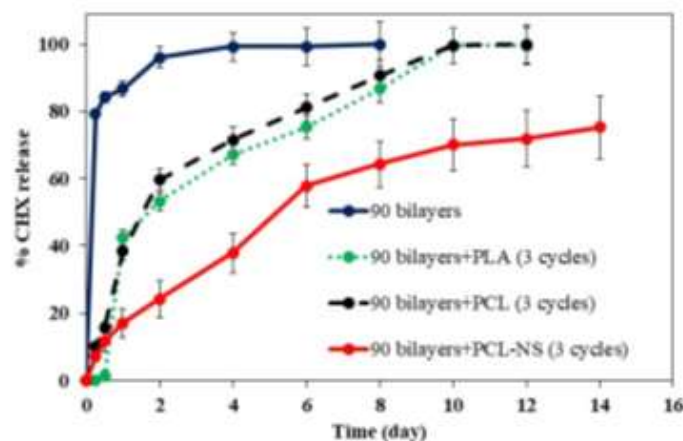
|   | Coating conditions                                | CHX content<br>( $\mu\text{g}/\text{cm}^2$ ) |
|---|---|--|
| A | 90 bilayers (CHX-micelles/PAA)                    | $32.3 \pm 1.4$                               |
| B | 90 bilayers (CHX-micelles/PAA), PCL (1 cycle)     | $28.9 \pm 2.0$                               |
| C | 90 bilayers (CHX-micelles/PAA), PCL (3 cycles)    | $24.2 \pm 2.2$                               |
| D | 90 bilayers (CHX-micelles/PAA), PLA (1 cycle)     | $27.5 \pm 1.8$                               |
| E | 90 bilayers (CHX-micelles/PAA), PLA (3 cycles)    | $23.7 \pm 2.4$                               |
| F | 90 bilayers (CHX-micelles/PAA), PCL-NS (3 cycles) | $31.9 \pm 0.5$                               |



**Figure 1.** A) Image of urinary catheters, B) SEM image of coated urinary catheter's surface (condition A), and C) SEM image of PCL- nanospheres (unencapsulated CHX).

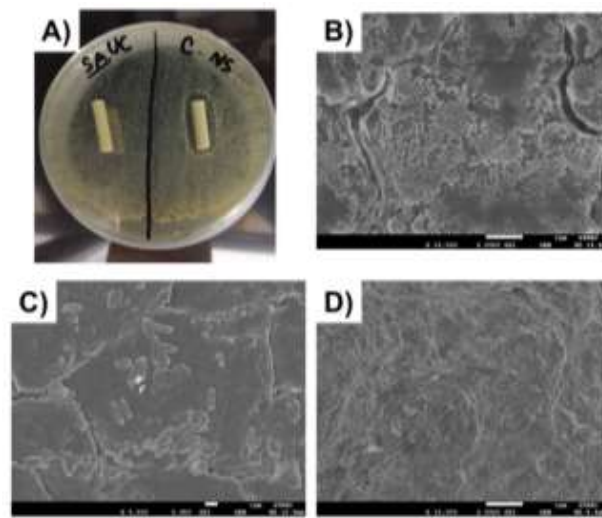
### 3.1.2 Release of CHX from coated urinary catheter

The period of drug/antibacterial release divided into two parts: burst release and sustained release. The first stage is burst release which presents in the initial time points and need to show the burst release of drug to the target site. This character at first stage starts by the drug that located on the surface [7]. The second stage is controlled & prolonged release that present the drug release from the inside of nanocarrier (encapsulated drug). In this work, coated urinary catheter in each condition was cut and immersed into artificial urine at time interval. CHX-release of condition A provided the high burst release at 80 % at first day, while coating the PLA and PCL on top of coated catheter at condition A showed the reduction of burst CHX-release from 80% to 42% for PLA coating and 38% for PCL as shown in Figure 2. Although, CHX content on coated catheter decreased during PLA and PCL coating but it assisted to prevent the burst release due to the polymer coating on top of catheter surface at condition A and helped to prolong the CHX release up to day 12. Moreover, coating PCL-NS on top of catheter surface at condition A also provided the reduction of burst release and prolonged release up to day 14. It was due to the spray coating by PCL-NS on the surface of condition A that prevented the disappearance of CHX and increasing the carrier as layer thickness on coated catheter's surface. Hence, the reduction of burst release via PCL nanospheres coating on the catheter surface of condition A can assist to decrease the burst CHX-release and help to prolong CHX-release.



**Figure 2.** Release profile of chlorhexidine in each condition (condition A, C, E, F).  
3.2 Antibacterial activity

Catheter samples were investigated the zone inhibition of *S.aureus* as shown in Figure 3A. Result showed that uncoated catheter showed no zone inhibition while coated catheter at condition F presented zone inhibition. For the bacteria adhesion with two microorganisms (*S.aureus* and *E.coli*) at first day (burst release stage), uncoated catheter presented the high bacteria adhesion with located on catheter surface as shown in Figure 3B&3C. Results of bacteria adhesion on coated catheter showed no bacteria on catheter surface. It was because on coated catheter was enough CHX content and burst release at first day. In addition, CHX-release on coated catheter provided the high level of CHX-release above the minimum inhibitory concentration (MIC) [6, 8]. It showed the potential to prevent the bacteria colonization on catheter surface.



**Figure 3.**Antibacterial activity of A) *S. aureus* zone inhibition of condition F, B) *S. aureus* fixation of uncoated urinary catheter at Day 1, C) *E. coli* fixation of uncoated urinary catheter at Day 1, and D) coated catheter at Day 1.

#### 4. Conclusion

Coated urinary catheter by PLA, PCL, and PCL nanospheres on top of coated urinary catheter (90 bilayers) can be reduced the burst CHX-release and provided the prolonged of CHX- release up to two weeks. Moreover, coated catheter by biodegradable prevented the bacteria formation on their surface more than uncoated urinary catheter.

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