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# IN-VITRO DRUG RELEASE ACTIVITY FROM CORE/SHELL ELECTROSPUN MATS OF sPLA-cPEG/GS and sPLA/CA-cPEG/GS

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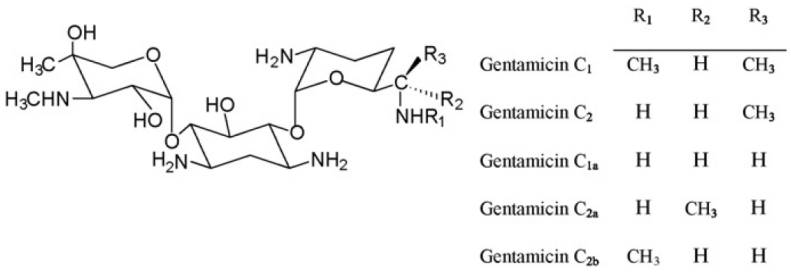
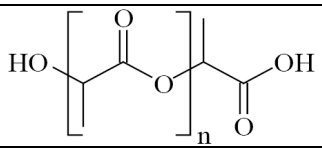
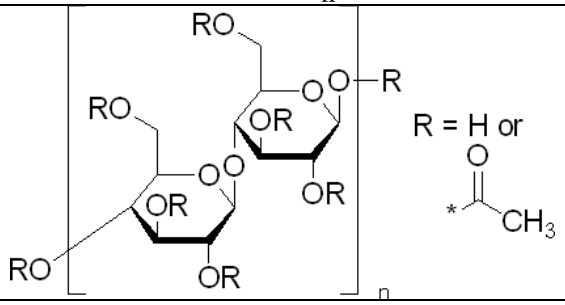
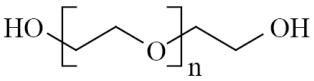
**Abstract**
In this research, the core-shell structured fiber was fabricated by coaxial electrospinning technique. A set of biodegradable polymers namely polylactic acid (PLA) and cellulose acetate (CA) were used as the shell material. Gentamicin sulfate (GS) as antimicrobial drug with polyethylene glycol (PEG) was used as the core structure. PEG formed the core section of the core–shell fibers for GS encapsulation. *In-vitro* drug release activity of the core-shell fibers was determined by total immersion method in pH 7.4 phosphate buffer solutions (PBS). It was found that core-shell fibers sPLA-cPEG/GS exhibit higher initial release compared to that of core-shell fibers sPLA/CA-cPEG/GS.

## 1. Introduction

Coaxial electrospinning is of the interest for producing continuous composite nanofibers with a core-shell structure. Based on the basic electrospinning set up, two syringes feed inter-separated and coaxial inner fluid and outer fluid to spinneret. With the high voltage applied, the electrospinning solution is drawn out from the needle and then forms a compound Taylor cone with a core-shell structure. Core-shell structured fibers can be used to enclose drug molecules by using a suitable polymer as shell to form a reservoir-type drug delivery system. The polymer shell would act as a temporary protector for the encapsulated drug and for offering controlled drug permeation [1, 2].

PLA is a natural biopolymer derived from renewable plant sources and widely used in a variety of applications [3] as drug delivery [4,5]. The chemical formula of PLA is shown in Table 1. CA (see chemical formula in Table 1) is one of the most common biopolymers on earth. CA has been fabricated as fibers and films for biomedical applications [6]. CA has been used as in the electrospun fibers in order to be developed as carriers for drugs [7]. Gentamicin sulfate is mixture of the sulfate salts of gentamicin mainly consist of $C_1$, $C_{1a}$, $C_2$, $C_{2a}$ and the minor component $C_{2b}$ [8]. GS is an aminoglycoside antibiotic. GS is insoluble in most organic liquids (including acetone and methanol) but freely soluble in water [9]. PEG is a typical hydrophilic polymer and can be dissolved in both organic solvents and aqueous solutions [10]. But PLA and CA blend solution cannot be compatible with GS. In order to further improve the insoluble drug and delivery of drugs in a core-shell structure fiber by using coaxial electrospinning. The capability of this technique for the incorporation of water-soluble drug into biodegradable polymer with the encapsulating drug molecules for drug release would be demonstrated.

Table 1 Chemical formula of gentamicin, PLA, CA and PEG

| Name | Chemical formula |
|---|---|
| Gentamicin |   |
| Polylactic acid |  |
| Cellulose acetate |   |
| Polyethylene glycol |  |

## 2. Experimental sections

### 2.1 Materials

Poly(lactic acid) (PLA; commercial grade 4042D; Mw ~ 390,000 Da) used in this research was obtained from NatureWorks LLC. Cellulose acetate (CA; white powder; Mw = 30,000 Da; acetyl content = 39.7 wt%; degree of acetyl substitution ≈ 2.4) was purchased from Sigma–Aldrich (Switzerland). Polyethylene glycol (PEG; Mw ~ 1,500 Da) was supplied from Scharlau Chemie S.A. Gentamicin sulfate (GS) was purchased from T.P. Drug Laboratories (1969) Co., Ltd. The solvents used in this work were dichloromethane (DCM) and N,N-dimethylformamide (DMF) from Labscan (Asia) (Thailand).

### 2.2 Solution preparation

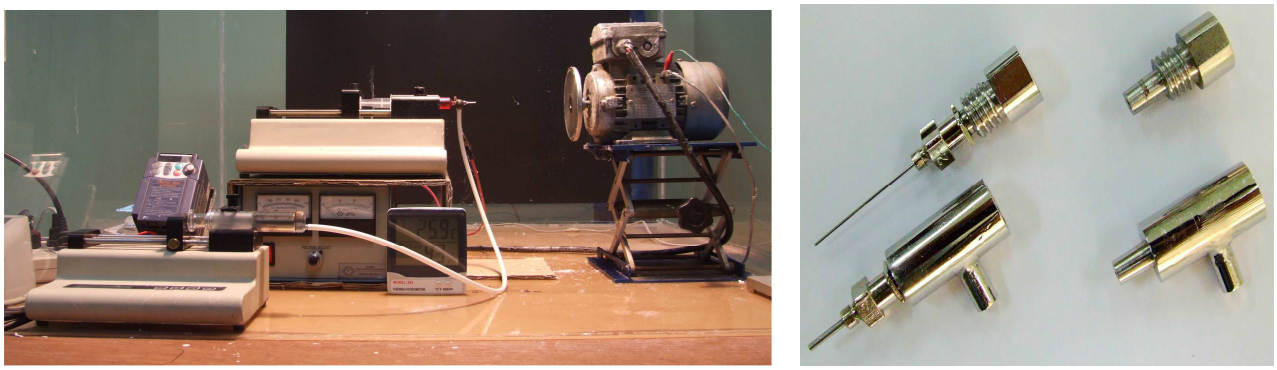
In PLA solutions 10 wt.% was dissolved in 70:30 wt.% DCM: DMF mixtures, it was found that the optimum ratio used for electrospun fibers [11,12]. Addition of CA into PLA solutions were to prepare by dissolving CA in the amount of 1 and 3 % based on the weight of total polymer. PLA and PLA/CA solutions were used as the shell fluid. A GS-loaded PEG was prepared by dissolving PEG 10 g in GS solution 3 ml used as the core fluid. Each solution and its content can be tabulated and its nomenclature as shown in Table 2. Solution viscosity was carried out for all the solutions by use of a viscometer (Brookfield Model LV Co., USA).

Table 2 Composition of coaxial electrospinning solutions

| Sample | Shell | | Core | | |
|---|---|---|---|---|---|
| | PLA [wt.%] | CA [wt.%] | PEG [g] | Water [ml] | GS [ml] |
| sPLA-cPEG | 100 | 0 | 10 | 3 | 0 |
| sPLA-cPEG/GS | 100 | 0 | 10 | 0 | 3 |
| sPLA/CA1-cPEG | 99 | 1 | 10 | 3 | 0 |
| sPLA/CA1-cPEG/GS | 99 | 1 | 10 | 0 | 3 |
| sPLA/CA3-cPEG | 97 | 3 | 10 | 3 | 0 |
| sPLA/CA3-cPEG/GS | 97 | 3 | 10 | 0 | 3 |

### 2.3 Electrospinning and Coaxial electrospinning process

Typical coaxial electrospinning, both the shell and core solutions were fixed at 1 ml/h and 0.01 ml/h respectively by syringe pumps (KD Scientific Inc., USA). The special metallic needle was connected to a high DC power supply (Gramma High Voltage Research, Inc.) with a voltage at 17 kV, and a piece of aluminum foil (placed 20 cm away from the tip of the needle) was grounded and used as the collector. Coaxial electrospinning setup is shown in Figure 1. All electrospinning processes were carried out under ambient conditions.



a b

Figure 1 Electrospinning setup: (a) experimental setup; (b) coaxial nozzle.

### 2.4 Morphology analysis of fiber mats

The morphological appearance was observed by use of CAMSCAN mx200 scanning electron microscope (SEM). The specimens for SEM observation were prepared by cutting an aluminum flat sheet covered with the electrospun fibers and the cut sections were carefully affixed to copper stubs. Each specimen was gold-coated using a sputtering device before SEM observations. The structure of core-shell electrospun fibers was observed using a JEM-1230 transmission electron microscope (TEM).

### 2.5 In vitro drug release

The release of GS from the core-shell electrospun fibers was determined by colorimetric procedure [13] for gentamicin quantification. Triplicate samples of 35 mg of core-shell electrospun GS-loaded fibers e.g., core-shell electrospun of sPLA-cPEG/GS, core-shell electrospun of sPLA/CA1-cPEG/GS and core-shell electrospun of sPLA/CA3-cPEG/GS were prepared. Each core-shell PEG/PLA fibrous sample was immersed in 10 ml phosphate buffer saline (PBS) in tubes. The tubes are placed in water bath at 37 $^{o}$C. The buffer solution was collected at 0.5, 1.0, 1.5, 2.0, 3.5, 4.5, 5.5, 9.5, 13.5, 17.5, 24, 36, 48, 60 and 72 hour [14] and replaced with an equal amount of fresh PBS each time. Aliquots (5 ml) of this buffer solution were mixed with the ninhydrin reagent 1.5 ml and pH 7.4 phosphate buffer 3.5 ml and heated in a water bath at 95°C for 30 min. After the UV–visible absorption at 400 nm, the results were presented in terms of cumulative release (%) as a function of release time [1]:

$$\text{Cumulative amount of release (\%)} = \frac{M_t}{M_\infty} \times 100\% \quad (1)$$

where $M_t$ was the amount of GS released at time (t) whereas the amount of GS added to electrospinning solution was regarded as $M_\infty$ in this study.

## 3. Results and Discussion

### 3.1 Effect of CA and GS content on morphology of Core/Shell electrospun sPLA-cPEG fibers

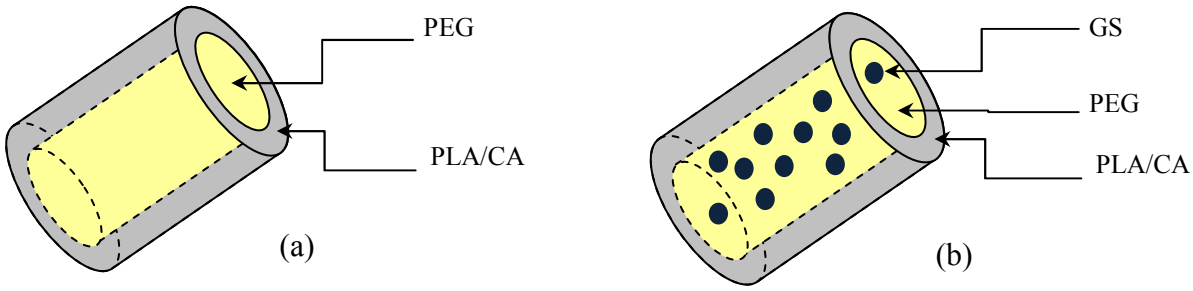
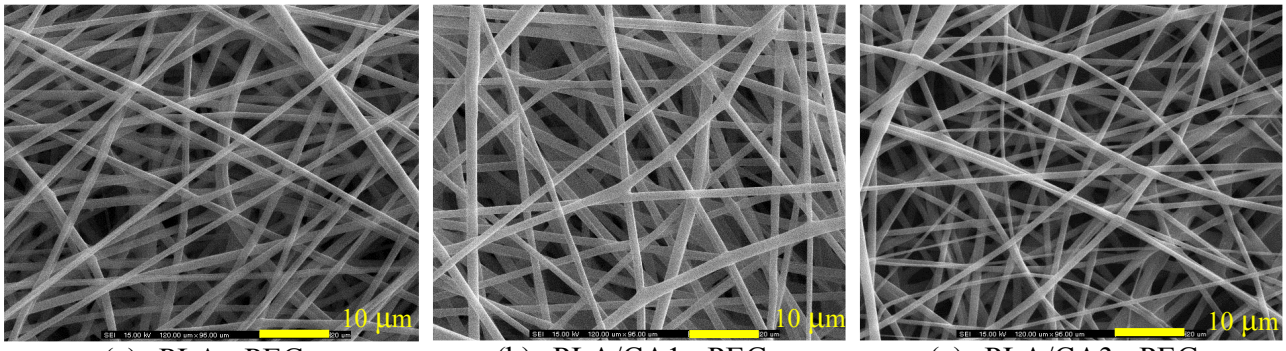



Figure 2 Model of core-shell electrospun fibers: (a) without; (b) with GS

PLA/CA is prepared to act as the shell for providing the wrap of drug molecule such as GS. Meanwhile either PEG or PEG/GS would be added as the core. Models of core-shell electrospun fibers are illustrated in Figure 2. Figure 3 shows SEM micrographs of core-shell sPLA-cPEG electrospun fibers with varying content of CA. The uniformity of electrospun fibers was observed to be decreased with the percentage of CA increment. Moreover, the CA addition would increase the viscosity of PLA solution as shown in Figure 4. And undoubtedly, the rise of viscosity would have impact onto the pendant drop formed at the needle tip as shown in Figure 5. This could contribute to the fact that shell-formed fluid jetted out of the coaxial orientation and splitted into a number of sub-jets during the electrospinning process. As a result, this would form monolayer structure instead of core-shell electrospun fibers [15]. Therefore, the core-shell electrospun fiber sizes were not in the uniform distribution.




(a) sPLA-cPEG (b) sPLA/CA1-cPEG (c) sPLA/CA3-cPEG

Figures 3 SEM micrographs of core-shell PEG/PLA fibers at different CA loading (a) 0% (b) 1% and (c) 3% by weight at magnification of 2,000

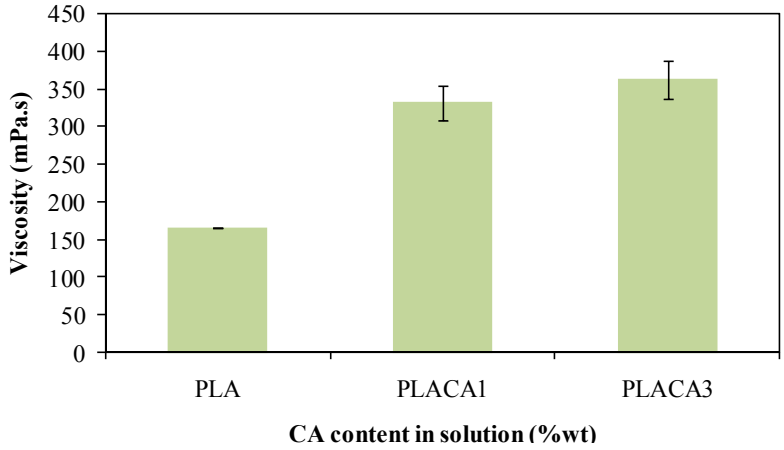



Figure 4 Effect of CA content on viscosity of PLA/CA blend solution

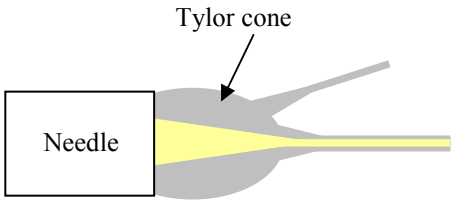
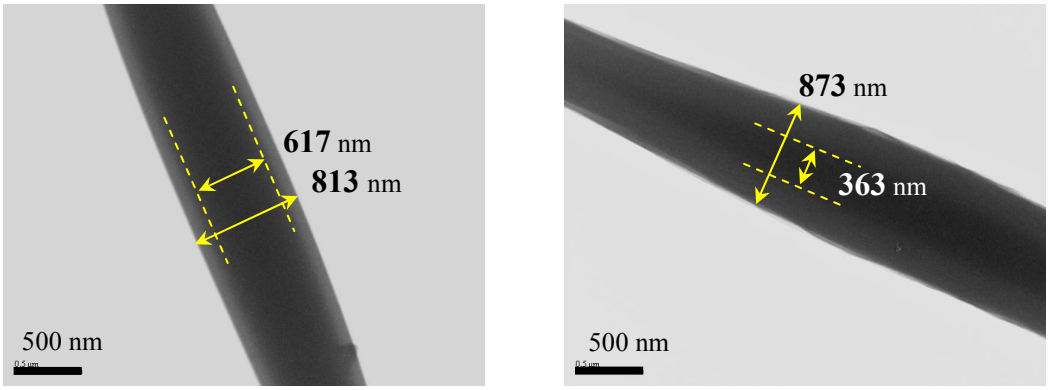



Figure 5 Model of monolayer structure instead of core-shell electrospun fibers

As mentioned earlier, once the viscosity was increased with the increment of CA loading, it would have the influence on the variation of the shell thickness as demonstrated in Figure 6. TEM micrographs suggested that the thickness of the shell of electrospun sPLA-cPEG fibers as in Figure 6 (a) were obviously thinner than the shell of electrospun sPLA/CA1-cPEG fibers as shown in Figure 6 (b). Nonetheless, the overall diameter of electrospun fibers compared between core-shell sPLA-cPEG and sPLACA1-cPEG are somewhat equivalent in size. By looking at the core-shell electrospun fibers more specifically, the diameter of the core of electrospun sPLA-cPEG is approximately twice as large compared to the core of electrospun sPLACA1-cPEG.

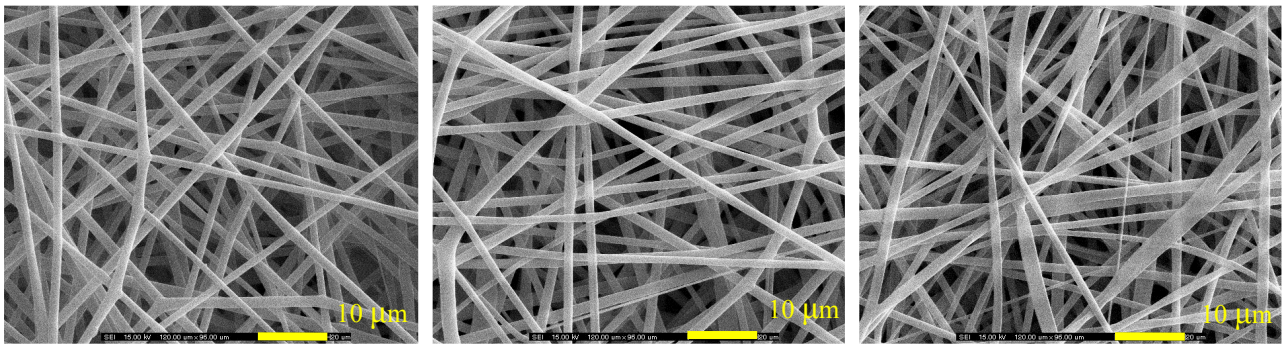
When more CA loading was added into polymer solution, it would lead to a relatively higher viscosity and as a result making for the shell formation to possess variable in thickness. A higher viscosity at the skin would make the inner contents in its core more difficult to be dilated.




**(a) sPLA-cPEG** **(b) sPLA/CA1-cPEG**

Figure 6 TEM micrographs of core-shell electrospun (a) sPLA/cPEG and (b) sPLA/CA1-cPEG fibers at magnification of 30,000

Figure 7 shows SEM micrographs of sPLA-cPEG fibers with GS encapsulation by varying the percentage of CA. The morphology of core-shell electrospun fibers with GS encapsulation was found to be in a similar pattern to the ones without GS as depicted in Figure 3. In other words, when the CA contents were increased, the electrospun fibers were observed to be splitted out from the core uniformity. Similarly, the morphology of GS added electropun sPLA/CA-cPEG/GS fibers were observed to be in similar fibrous pattern in comparion with the electrospun sPLA/CA-cPEG fibrous without GS.




sPLA-cPEG/GS sPLA/CA1-cPEG/GS sPLA/CA3-cPEG/GS

Figure 7 SEM micrographs of core-shell PEG/PLA fibers with GS encapsulation at different CA loading (a) 0% (b) 1% and (c) 3% by weight at magnification of 2,000.

### 3.2 Effect of CA on In-vitro gentamicin sulfate release of core/shell electrospun PEG/PLA mats

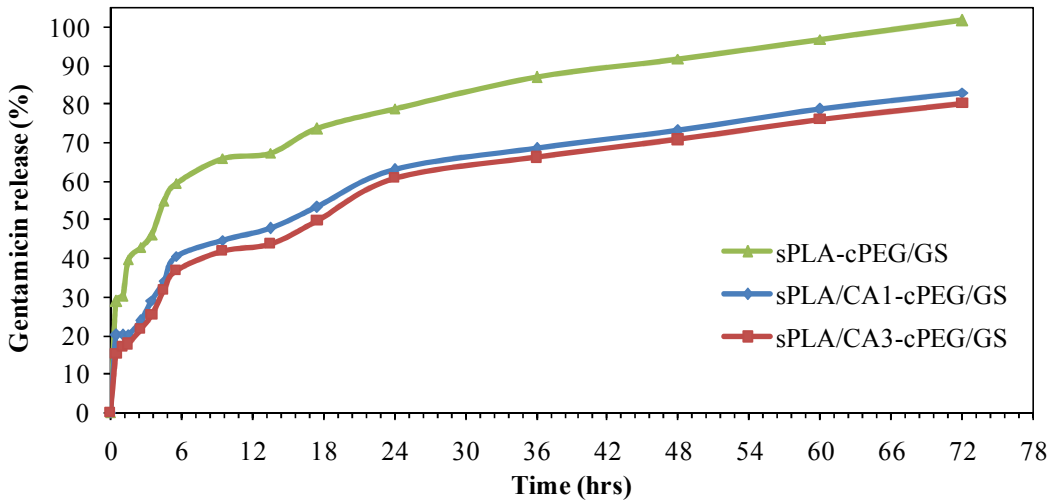



Figure 8 In-vitro drug releases from core-shell electrospun sPLA/CA-cPEG/GS fiber mats at different CA content of 0%, 1% and 3% by weight.

The drug release profiles of the core-shell sPLA/CA-cPEG fiber mats containing GS are shown in Figure 8. At the first 2 hours as its initial stage, the GS burst release from the medicated core-shell sPLA-cPEG, sPLA/CA1-cPEG and sPLA/CA3-cPEG fiber mats are approximately at 30, 20.2, and 17.6 wt.% respectively. The initial release rate of core-shell sPLA-cPEG/GS fibers is substantially higher than the one from the core-shell sPLA/CA1-cPEG/GS and sPLA/CA3-cPEG/GS fibers. TEM micrographs in Figure 6 illustrated that the shell thickness of core-shell sPLA-cPEG fibers were thinner than the shell of core-shell sPLA/CA1-cPEG electrospun fibers. Therefore, the drugs would be permeating through the thinner shell of PLA much faster than the one of PLA/CA. Basis models in Figure 9 were employed to show the diffusion through a thinner shell wall easier than the thicker shell. It would also diffuse from higher to lower concentration as it

transport from core to the shell material either by passing through the pores or the polymer chains. Due to the fact that can be seen from the drug release rate of core-shell sPLA-cPEG/GS fiber mats compared to the one from the core-shell sPLA/CA1-cPEG and sPLA/CA3-cPEG fiber mats, our study can be said to capable of controlling the drug release rate.

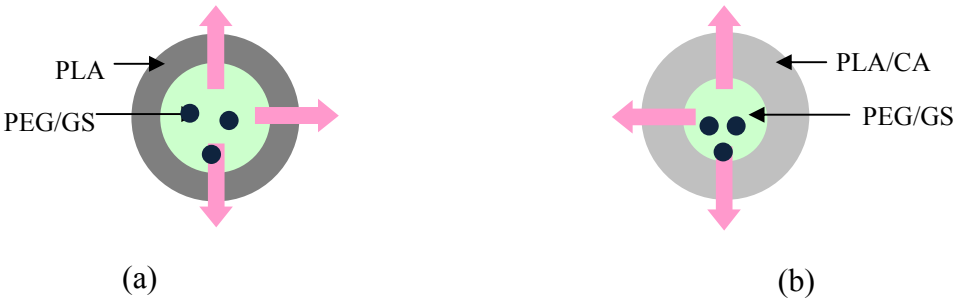



Figure 9 Model of drug releases from core-shell electrospun fibers: (a) sPLA-cPEG/GS and (b) sPLA/CA-cPEG/GS

## 4. Conclusions

PLA/CA are prepared to work as the shell for the provision of the wrapping and delivering medium of the drug molecule e.g. GS. While PEG/GS would be added as the core by using coaxial electrospinning technique, the combination of shell and core materials were fabricated to produce a so called core-shell structured fibers. The addition of CA into PLA solution would increase the viscosity and hence made the thickness of the shell of core-shell electrospun fibers is substantially noticed. The thinner shell of core-shell fibers sPLA-cPEG/GS would lead to a higher release rate of GS when compared to the core-shell fibers sPLA/CA-cPEG/GS.

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## References

[1] D.Z. Yang, Y.H. Long and J. Nie: Front. Mater. Sci. Vol. 2 (2008), p. 261–265.

[2] H. Jiang, Y. Hu, Y Li, P. Zhao, K. Zhu and W. Chen: J. Control. Release Vol. 108 (2005), p. 237–243.

[3] B. Gupta, N. Revagade and J. Hilborn: Prog. Polym. Sci. Vol. 32 (2007), p. 455–482.

[4] Y.Y. Huang, T.W. Chung and T.W. Tzeng: Int. J. Pharm. Vol. 156 (1997), p. 9-15.

[5] V. Lassalle and M.L. Ferreira: Macromol. Biosci. Vol. 7 (2007), p. 767–783.

[6] P. Taepaiboon, U. Rungsardthong, and P. Supaphol: Eur. J. Pharm. Biopharm. Vol. 67 (2007), p. 387-397.

[7] O. Suwantong, U. Ruktanonchai and P. Supaphol: Polymer Vol. 49 (2008), p. 4239–4247.

[8] H. Curiel, W. Vanderaerden, H. Velez, J. Hoogmartens and A.V. Schepdael: J.Pharm.Biomed. Anal. Vol. 44 (2007), p. 49–56.

[9] H.I. Chang, Y. Perrie and A.G.A. Coombes: J. Control. Release Vol. 110 (2006), p. 414 – 421.

[10] H. Peng, S. Zhou, T. Guo, Y. Li, X. Li, J. Wang and J. Weng: Colloids and Surfaces B: Biointerfaces Vol. 66 (2008), p. 206–212.

[11] F. Yang, R. Murugan, S. Wang and S. Ramakrishna: Biomaterials Vol.26 (2005), p. 2603–2610

[12] S. Saewong, T. Tangsupa-anan and T. Siamsakul: Bachelor thesis of engineering, Department of Material Science and Engineering, Faculty of Engineering and Industrial Technology, Silpakorn university (2009).

[13] P. Frutos, S. Torrado, M.E. Perez-Lorenzo and G. Frutos: J. Pharm. Biomed. Anal. Vol. 21 (2000), p. 1149–1159.

[14] K. Vichitchote, P. Threepopnatkul, S. Saewong, T. Tangsupa-anan and S. Suttiruengwong: Proceeding of 14$^{TH}$ European Conference on Composite Materials, Budapest, Hungary, June 1-10, 2001.

[15] C.L. He, Z.M. Huang, X.J. Han, L. Liu, H.S. Zhang and L. Chen: J. Macromol. Sci.- Phys. Vol. 45 (2006), p. 515 – 524.