PAPER • OPEN ACCESS

The Influence of Chitosan Concentration on Polyelectrolytes Complexes (PECs) of Chitosan – Poly-2-Acrylamido-2-Methylprophane Sulfonic Acid (PAMPS) as Potential Drug Carrier in Pulmonary Delivery Application

View the article online for updates and enhancements.

IOP | ebooks™

Bringing you innovative digital publishing with leading voices to create your essential collection of books in STEM research.

Start exploring the collection - download the first chapter of every title for free.

The Influence of Chitosan Concentration on Polyelectrolytes Complexes (PECs) of Chitosan – Poly-2-Acrylamido-2-Methylprophane Sulfonic Acid (PAMPS) as Potential Drug Carrier in Pulmonary Delivery Application

Arie Wibowo[1,2,*], Mumtaziah[1], Systi Adi Rachmawati[1], Fitriyatul Qulub[1], Lia Amelia Trisna Wulan Asri[1], Akfiny Hasdi Aimon[3], Rochim Suratman[1]

[1]Department of Materials Engineering, Faculty of Mechanical and Aerospace Engineering, Institut Teknologi Bandung

[2] Research Center for Nanoscience and Nanotechnology, Institut Teknologi Bandung

[3]Department of Physics, Faculty of Mathematics and Natural Sciences, Institut Teknologi Bandung

*Corresponding author: ariewibowo@material.itb.ac.id

Abstract. Pulmonary drug delivery system is one of potential way to effectively treat lung-based disease, such as tuberculosis, because this route offers a possibility to reduce systemic toxicity and achieving higher drug concentration at the main site of infection. One of potential drug carrier for this purpose is chitosan based polyelectrolytes complexes (PECs) because micron-sized particles with good biocompatibility, non-toxic and antibacterial properties, that was inherited from chitosan, could be achieved. In this research, PECs were prepared by simple mixing method between chitosan solution and poly-2-acrylamido-2-methylprophane sulfonic acid (PAMPS) solution. The influence of chitosan concentration on obtained PECs were studied by varying chitosan concentration from 0.1 to 2.0% w/v. Based on dynamic light scattering (DLS) and zetasizer results, increasing chitosan concentration lead to increase the particle size from 1.1 µm to 10.7 µm and their net surface charge of particles were changed from -4,2 mV to 32.8 mV. Considering that particle size of pulmonary drug carrier should be around 1-3 µm and preferable possesses positive net surface charge, PECs prepared from chitosan solution 0.5% w/v might be potentially useful as drug carrier for pulmonary drug delivery system.

Keywords: chitosan, PAMPS, polyelectrolytes complexes, pulmonary drug delivery system

1. Introduction

Tubercolosis (TB) is an infectious disease that was caused by mycobacterium tuberculosis bacteria and classified as one of the top 10 causes of death worldwide. Currently, the most common method to treat TB are using anti-TB drugs via oral and injectable intramuscular treatment [1]. However, both of them still have a problem with drug's efficacy since the drug still subjected to first-pass metabolism [1,2]. Therefore, an alternative strategy to deliver anti-TB drugs with better drug efficacy is needed.

Nowadays, pulmonary drug delivery systems (PDDS) have been widely investigated as attractive strategy for the treatment of pulmonary-related diseases because it could directly deliver anti-TB drugs to the lungs. Thus, it is expected that side effects of systemic administration could be reduced and therapeutic efficacy could be enhanced [1-6]. For effective delivery of drugs using this strategy, drug carrier with aerodynamic diameter between 1 and 3 μm are required for successful deposition in deep-lung [3]. One of attractive materials as drug carrier is polyelectrolytes complexes (PECs) because of its simplicity, low toxicity, high drug loading efficiency, and desired structural stability [7-9]. Previously, we have been successfully prepared PECs from chitosan as positively charged polymers and Poly-2-Acrylamido-2-Methylprophane Sulfonic Acid (PAMPS) as negatively charged polymers by simply mixing of their water-based solution [9]. Chitosan are appealing natural polymers for biomedical applications due to their non-toxic, good biocompatibility, biodegradability, and antimicrobial activity [10-12]. Besides their application as biomaterials, chitosan can also be used as chelating agent for heavy metal recovery [11,12], solid state batteries [12,13], etc. In this experiment, chitosan-PAMPS based PECs were prepared by simple mixing and various chitosan concentration (0.1; 0.5; 1.5 and 2.0% (w/v)) were used to know the influence of chitosan concentration to particles size of obtained PECs.

2. Materials and Methods

Chitosan (with degree of deacetylation (DD) 77% [9]) was purchased from CV. Biochitosan Indonesia. Before used, molecular weight of chitosan and PAMPS were roughly determined by dilution viscometry method using Mark-Houwink-Sakurada equation (Eq. 1) [14,15].

$$[\eta] = K\, M_v^{\alpha} \tag{1}$$

where K and α are Mark-Houwink constants that depend on the polymers − solvent interaction. This characterization step is essential for assigning the possible range of PECs charge ratio.

Then, PECs were prepared by simple mixing of water-based solution chitosan and PAMPS following procedures that has been describe previously [9]. To detect the present of colloid and qualitative predict particle size of colloid in solution of obtained samples, Tyndall effect were observed by exposing laser pointer light to colloidal solution samples. Then, 20 mL of colloidal solution of obtained samples were characterized by Dynamic Light Scattering (DLS) to measure their particle size and Zetasizer to measure their surface charge using Delsa^{TM} Nano Series. The particle size measurement was carried out with accumulation time 30 s at scattering angle 165°. The zeta potential measurement was conducted at 24.9 °C with scattering angle 34.1° and average electric field 7.45 V/cm.

3. Results and Discussion

3.1. Molecular weight measurement analysis

The molecular weight (M_v) of chitosan and PAMPS were calculated using Eq. (2.1) by considering K and α values of chitosan and PAMPS in their solvents. The value of K and α for chitosan in acetic acid 1% are $4.74x10^5$ dL/g and 0.72 respectively [14]. While the value of K and α for PAMPS in sodium chloride 0.1 N are $1.67x10^5$ dL/g and 0.88 respectively [15]. The calculated M_v of chitosan and PAMPS can be seen in Table 1.

Table 1. Molecular weight from dilution viscometry method

Polymers	M_v [g/mol]	R^2
Chitosan	231,736	0.88
PAMPS	568,238	1.00

The composition of these two polymers could be predicted in order to fabricate the PECs with positive net charge. Regarding to Table 1, the molecular weight of PAMPS is roughly 2.5 times higher than molecular weight of chitosan. Since DD of chitosan that was used in this experiment is about 77%, it could roughly predicted that neutral PECs from PAMPS and chitosan could be formed if the amount of chitosan is about 3.2 times than PAMPS. Considering this prediction, chitosan concentration were varied from 0.1% w/v (ratio of chitosan/PAMPS = 1; PAMPS-rich composition) to 2.0% w/v (ratio of chitosan/PAMPS = 20; chitosan-rich composition) to obtain some insight about characteristic of obtained PECs as a function of chitosan concentration.

3.2. Visual observation of colloidal solution samples

Visual observation of Tyndall effect of samples solution after exposing with laser pointer light can be seen in Fig.1. Generally, bigger the particle size induced light is being more dispersed. According to visual observation, it was predicted that as chitosan concentration increased, the bigger the particle size.
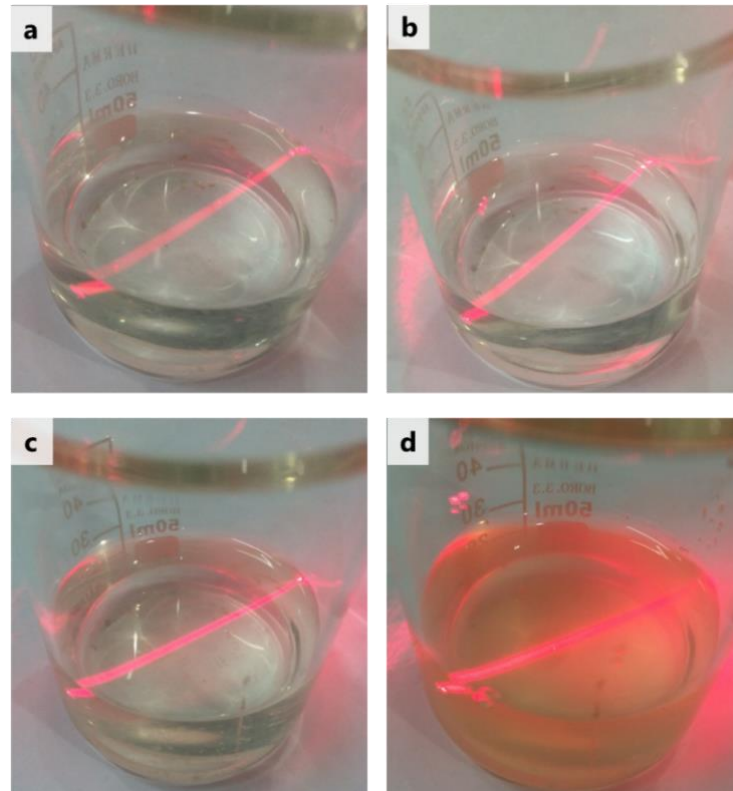
Figure 1. Visual observation of Tyndall effect of samples solution with various chitosan concentration: a) 0.1% w/v, b) 0.5% w/v, c) 1.5% w/v, d) 2.0% w/v, after exposing with laser pointer light

3.3. Particle size and zeta potential analysis

Particles size and zeta potential results of obtained samples can be observed in Fig. 2a. and 2b respectively.
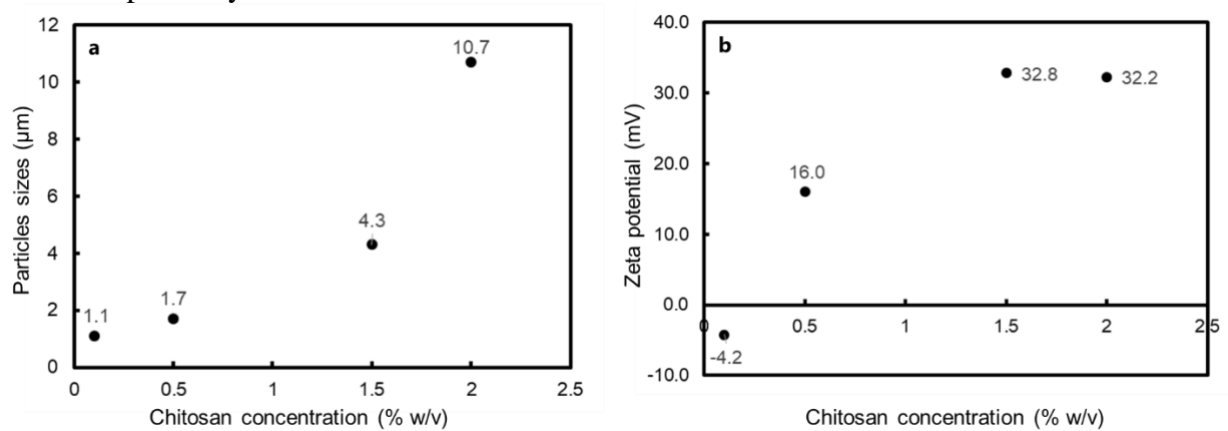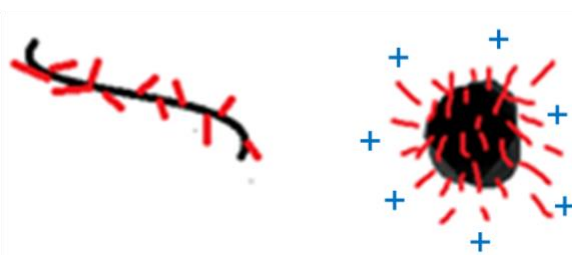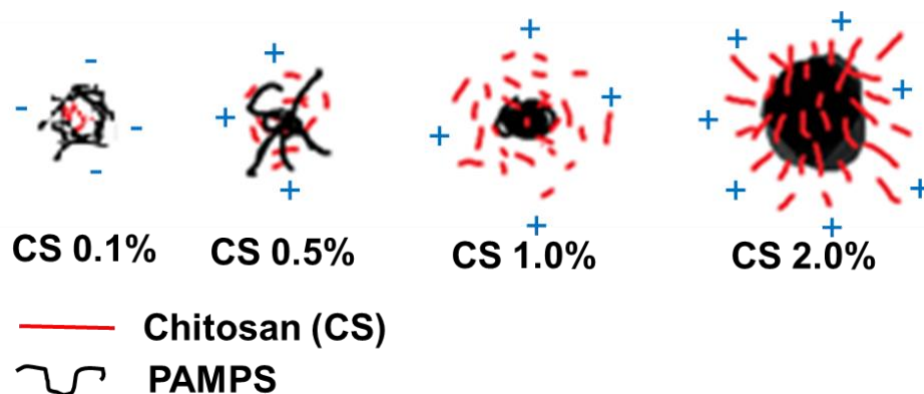

Figure 2. a) Particles size and b) zeta potential results of colloid in samples solution as a function of chitosan concentration

As can be seen in Fig 2.a, only samples with chitosan concentration 0.1 and 0.5% w/v (with particle size 1.1 and 1.7 μm respectively) are potential as drug carrier for PDDS application because their particles size are within the range of good carrier for PDDS (1-3 μm) [3]. While samples with chitosan concentration 1.5 and 2.0% w/v might not suitable as drug carrier for PDDS application because their particles size are higher than 3 μm. Zeta potential data (Fig. 2.b) showed that net surface charge of samples with chitosan concentration 0.1 and 0.5% w/v are -4.2 and 16.0 mV respectively. Considering that positively charge biomaterials possesses better antimicrobial effect than negatively charge biomaterials [10], it is expected that sample with chitosan concentration 0.5% w/v are better candidate than 0.1% w/v.

Characteristic of PECs from their oppositely charged polymers are following the nature of their forming polymers. PAMPS are naturally flexible and able to be folded [16], while chitosan are naturally rigid and cannot be folded easily [17]. As can be seen in Fig. 2a and 2b, PECs with negative charge in their surface (chitosan concentration 0.1% w/v) are smaller than PECs with positive charge (chitosan concentration 0.5-2.0% w/v). At chitosan concentration 0.1% w/v, the dominant polymers in their composition are PAMPS (which is indicated by their negative charge in their surface). As the consequences, most of polymers in this composition are flexible and could be folded to form small particles of PECs. At chitosan concentration 0.5-2.0% w/v, chitosan are more abundant than PAMPS in the PECs (which is indicated by their positive charge in their surface). Thus, particles size of PECs increased as chitosan concentration increased because most of polymers in this composition are rigid and difficult to be folded. The possible PECs formation and their characteristic regarding to their charge ratio is illustrated in Fig. 3 below.

Figure 3. PECs formation model based on PAMPS and chitosan

4. Conclusions

Formation and characteristic of chitosan-PAMPS based PECs has been studied by varying chitosan concentration from 0.1 – 2.0% w/v. PECs that prepared from 0.5% w/v of chitosan concentration might be the most promising for pulmonary drug delivery system because their particle size (1.1 um) are within the range of good carrier for PDDS (1-3 μm). Also, obtained PECs possesses positive charge in their surface (16.0 mV) might possesses better antimicrobial effect against bacteria that are useful for tuberculosis treatment.

5. Acknowledgements

6.   References

1. Pham, D. D.; *International Journal of Pharmaceutics,* **2015**, *478,* 517
2. Wan, F.; Moller, E. H.; Yang, M.; Jorgensen, L.; *Drug Discovery Today: Technologies,* **2012**, *9 (2)*, e141
3. Yang, W.; Peter, J. I.; William III, R. O.; *International Journal of Pharmaceutics,* **2008**, *356,* 239
4. Sung, J. C.; Pulliam, B. L.; Edwards, D. A.; *Trends in Biotechnology,* **2007**, *25(12),* 563
5. Bailey, M. M.; Berkland, C. J.; *Medicinal research Reviews,* **2009**, *29*, 196
6. Mansour, H. M.; Rhee, Y.-S.; Wu, X.; *International Journal of Nanomedicine,* **2009,** *4*, 299
7. Luo, Y.; *International Journal of Biological Macromolecules* **2014**, *64*, 353– 367
8. Zhang, L., Wang, J., Ni, C., Zhang, Y., Shi, G., *Materials Science and Engineering C,* **2016**, *58*, 724 – 729
9. Wibowo, A.; Indrawan, R. F.; Triadhi, U.; Aimon, A. H.; Iskandar, F.; Ardy, H.; *Materials Research Express*, **2018**, *5*, 024005 (DOI: 10.1088/2053-1591/aaac86)
10. Rabea, E. I.; Badawy, M. E.-T.; Stevens, C. V.; Smagghe, G.; Steurbaut, W.; *Biomacromolecules*, **2003**, *4(6)*, 1457 – 1465
11. Zargar, V.; Asghari, M.; Dashti, A.; *ChemBioEng Reviews*, **2015**, *2(3)*, 204-226
12. Kumar, M. N. V. R.; *Reactive and Functional Polymers*, **2000**, *46(1)*, 1-27
13. Asri, L. A. T. W.; Nuruddin, A.; Hidayatullah, S.; Simatupang, M.; Wibowo, A.; Septawendar, R.; Purwasasmita, B. S.; *Journal of Australian Ceramics Society*. **2017**, (DOI 10.1007/s41779-017-0103-1)
14. Kasaai, M. R.; Arul, J.; Charlet, G.; *Journal of Polymer Science Part B: Polymer Physics*, **2000**, *38*, 4325-4332
15. Tan, J. S.; Fisher, L. W.; Markus, P.; ACS National Meeting in Philadelphia, division of organic coating and plastic Preprints, **1992**, *35(1)*, 348
16. Setoyama, H., Murakami, Y., Inoue, K., Iwata, H., Kitamura, H., Shimada, T., Kaji, H., Ikada, Y., Imamura, M., *Transplantation Proceedings*, **1999**, *31*, 2818-2822.
17. Terbojevich, M.; Cosani, A, Conio, G.; Marsano, E.; Bianchi, E.; *Carbohydrate Research*, **1991**, *209*, 251-260