



## CORRIGENDUM TO:

**EFFECTS OF MONOCARBOXYLIC ACIDS AND POTASSIUM PERSULFATE ON PREPARATION OF CHITOSAN NANOPARTICLES**

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The authors regret that in the above mentioned article bears incorrect affiliation for Yoki Yulizar and the axis labels of Figures 4-5. The correct affiliation has been mentioned above. The errors in the axis labels of FTIR spectra presented in the Figures 4-5 in the published paper should be corrected to be;

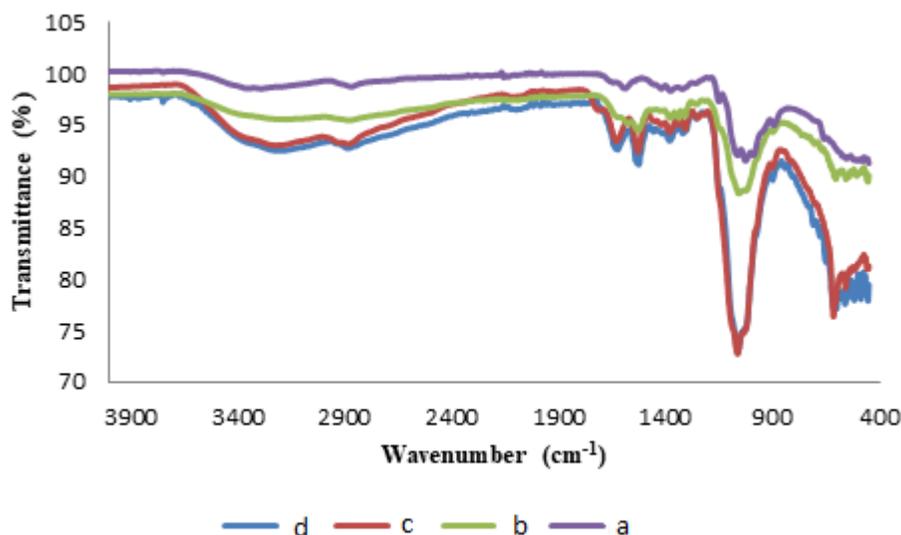


Figure 4 FTIR spectra of pristine chitosan (a), and chitosan nanoparticles formed from oven drying using (b) formic acid, (c) lactic acid, and (d) acetic acid

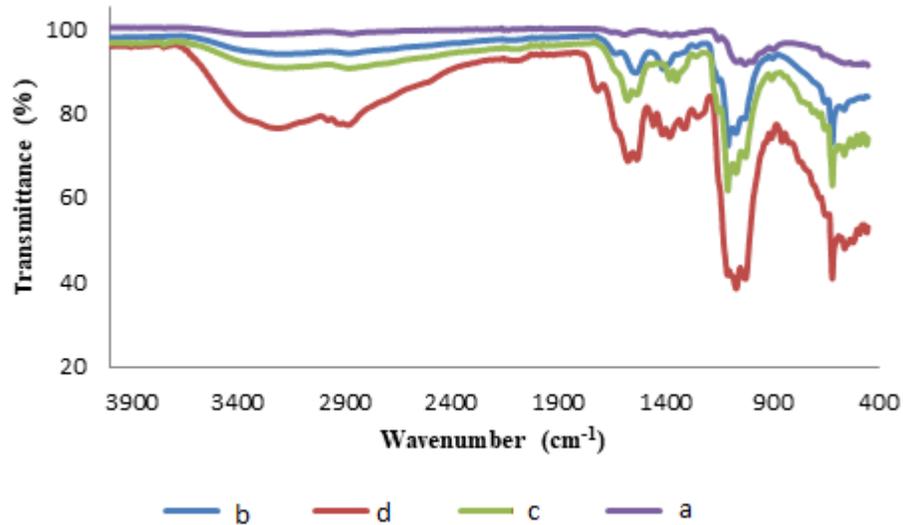


Figure 5 FTIR spectra of pristine chitosan (a), and chitosan nanoparticles prepared from spray drying using (b) acetic acid, (b) formic acid, and (c) lactic acid

## EFFECTS OF MONOCARBOXYLIC ACIDS AND POTASSIUM PERSULFATE ON PREPARATION OF CHITOSAN NANOPARTICLES

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### ABSTRACT

In this research, we studied the preparation of nanochitosan from the addition of potassium persulfate as an initiator for monomer polymerization and monocarboxylic acid—namely acetic acid, lactic acid, and formic acid—to a chitosan solution. To obtain the dried form of chitosan nanoparticles, we investigated the effects of oven and spray drying systems toward the physicochemical properties and morphology of chitosan nanoparticles. Successfully prepared chitosan nanoparticles were characterized by Fourier transform infrared spectroscopy (FTIR), Field Emission Scanning Microscopy/Energy Dispersive X-ray Analysis (FESEM-EDX), and a particle size analyzer (PSA). The structures of nanochitosan prepared in different acids were quite similar based on the FTIR spectra. By increasing the concentrations of potassium persulfate, the yields of chitosan nanoparticles also increased. The concentration of potassium persulfate had a significant influence on the production of chitosan nanoparticles. The lowest concentration of potassium persulfate (0.6 mmol) did not produce an observable formation of chitosan nanoparticles. By using formic acid and potassium persulfate in various concentrations from 1.2–3.0 mmol, chitosan nanoparticles were obtained. A particle size distribution of chitosan nanoparticles was produced from a formic acid solution having a smaller size compared to others. The acidity effect of monocarboxylic acids in the formation of chitosan nanoparticles was better compared to the addition of other acids. Furthermore, synthesized chitosan nanoparticles (50–110 nm) produced from formic acid solutions have potential applications for drug carrier purposes.

*Keywords:* Chitosan nanoparticles; Monocarboxylic acid; Oven; Potassium persulfate; Spray drying

### 1. INTRODUCTION

Chitosan is the deacylated product from chitin extracted from the shrimp shell (Kumar et al., 2000; Kumar et al., 2004). Chitosan is soluble in aqueous solutions of various acids, even though it does not have amphiphilic properties and is not able to form micelles in water. Chitosan possesses the reactive amine and hydroxyl groups that give possibilities of modification via ionic interactions (Figure 1) (Dev & Binulal, 2010). It has the potential to be used as a drug carrier because it is easily resorbed or eliminated, biocompatible, and of low toxicity (Hu & Jiang, 2002).

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Because of cationic behavior, a strong electrostatic interaction between a drug and chitosan can be observed.

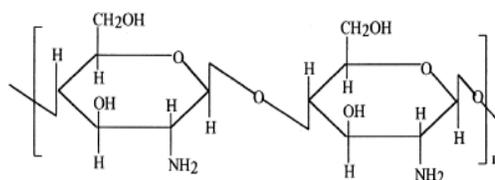


Figure 1 Structure of chitosan

Chitosan nanoparticles (nanochitosan) are natural materials with excellent physicochemical properties; further, they are environmentally friendly as well as bioactive (Agnihotri et al., 2004). For biomedical and pharmaceutical applications (e.g., drug delivery systems), the micro and nanoparticles of chitosan are preferred. Nanochitosan offers more delivery options compared to chitosan because nanoparticles can be absorbed by human organs. Material with narrow particle size distribution could result in better drug loading and more efficient drug delivery (Yang et al., 2010).

Synthesis of chitosan nanoparticles can occur in a top-down (mechanical) or bottom-up (chemical synthesis) manner. Via chemical synthesis, uniformity of chitosan nanoparticles in size and morphology can be obtained. Nanochitosan can be prepared in acidic conditions, where a homogenous chitosan solution in an acid solution would be followed by the formation of nanoparticles if it interacts with anions. Several methods have been reported to produce nanochitosan, such as coacervation, ionic gelation, emulsion cross-linking, emulsion-droplet coalescence, reverse micellar extraction, and sieving (Yang et al., 2010). Nanochitosan can be prepared with sodium sulfate as the precipitation agent (Hsu et al., 2002), glutaraldehyde as a cross-linking agent for the free amino groups of chitosan (Hsu et al., 2002), and the addition of HCl, H<sub>2</sub>O<sub>2</sub>, tripolyphosphate (TPP), and acetic acid to form chitosan with a low molecular weight (Yang et al., 2010). Much attention has been focused on the synthesis of chitosan nanoparticles; however, no chitosan nanoparticles in dried form were obtained in the previous study. These methods are complex, and dependent on the use of organic solvents, surfactants, or precipitating agents, as well as a dangerous cross-linking agent such as glutaraldehyde.

To overcome these limitations, we investigated techniques to synthesize chitosan nanoparticles simply, without an organic solvent, surfactant, and/or precipitating agent. The present work focused on the preparation of nanochitosan by adding potassium persulfate as an initiator for monomer polymerization and monocarboxylic acid (acetic acid, lactic acid, and formic acid) to a chitosan solution. This method is advantageous because it eliminates the need for a surfactant and/or organic solvent that would contaminate after the preparation of nanochitosan. The acids are weak, with different acid dissociation constants; thus, they are capable of protonation with chitosan. The monocarboxylic acids had different acid dissociation constants—acetic acid, 4.756; lactic acid, 3.86; and formic acid, 3.751. It was interesting to study the effects of pK<sub>a</sub> and the differences in acid structures on the physical and chemical properties of the nanochitosan produced. We also investigated the dried form of nanochitosan using two techniques, namely oven drying and spray drying. The heating effect on the physical and chemical properties of nanochitosan was studied in detail. Spray drying involves the formation of dried particles from hot air flow and atomization, whereas oven drying forms particles by heating at low temperatures. The synthesis of chitosan nanoparticles by lactic acid and the addition of potassium persulfate have been previously reported by Kusrini et al. (2012). In this

study, we also discussed it for comparing chitosan nanoparticles produced from acetic acid and formic acid.

## 2. EXPERIMENTAL

### 2.1. Materials

Chitosan powder with a deacetylation degree of 90.77% was purchased from PT Biotech Surindo (Cirebon, West Java, Indonesia). Acetic acid ( $\text{CH}_3\text{COOH}$ ), 100% purity; formic acid ( $\text{HCOOH}$ ), 98-100% purity; and potassium persulfate ( $\text{K}_2\text{S}_2\text{O}_8$ ) were purchased from Merck (Singapore). Lactic acid ( $\text{HCH}_3\text{H}_5\text{O}_3$ ) with purity of 88.9% was purchased from Purac (Netherlands). All materials were used in the study without further purification.

### 2.2. Physical Measurements

FTIR spectra were recorded on a Perkin-Elmer system 2000 FTIR spectrophotometer in the range of  $4000\text{--}400\text{ cm}^{-1}$  by using the conventional KBr pellet method. Particle size distribution was analyzed by the Particle Size Analyzer (PSA) Zetasizer Nano series, Malvern ZEN 1600. The particle sizes of the samples were characterized by *dynamic light scattering* (DLS), and the surface morphology of the samples was analyzed by Field Emission Scanning Electron Microscopy (FESEM). These analyses were performed by putting 0.1 mg of a dry sample onto carbon tape and then into the FESEM instrument. The spray drying equipment used was the Buchi Mini Spray Dryer, and  $180^\circ\text{C}$  of hot air was disseminated with a  $3\text{ }\mu\text{m}$  nozzle atomization. The particles were collected in batch in a cyclone to form chitosan dry powder.

### 2.3. Preparation of Chitosan Nanoparticles

Chitosan powder (3% w/w) was dissolved in an aqueous solution containing various acids in concentrations of 87.5, 35.7, and 26 mmol for acetic acid, lactic acid, and formic acid, respectively. The pH of the chitosan solution was adjusted to reach 4. Then, the homogeneous solution was stirred by a hot plate magnetic stirrer; the temperature maintained throughout the reaction process was  $70^\circ\text{C}$ . Subsequently, potassium persulfate powder in various concentrations (0.6, 1.2, 1.8, 2.4, and 3.0 mmol) was added to the solutions. Each solution was vigorously stirred at a high speed for 45 min. To stop the polymerization reaction of a system, the system was suddenly put in an ice bath for 1 h. The colloidal suspension was formed and followed by the separation of the suspensions into two batches. Two colloidal systems were centrifuged at a speed of 3000 rpm for 1 h. A resulting supernatant was submitted to oven drying at  $40^\circ\text{C}$  for 3–5 h, whereas the colloidal was spray dried with a  $3\text{ }\mu\text{m}$  atomizing nozzle and hot air at  $180^\circ\text{C}$ .

## 3. RESULTS AND DISCUSSION

### 3.1. General Mechanisms of Reaction Studies

Preparation of chitosan nanoparticles using potassium persulfate (i.e.,  $\text{K}_2\text{S}_2\text{O}_8$ ) as an initiator polymerization agent and adding acrylic acid (2-propenoic acid,  $\text{CH}_2=\text{CHCOOH}$ ) has been reported (Hu & Jiang, 2002). The persulfate anion attacked and cut into the long chitosan chain, causing it to become shorter. Moura and patner also described the preparation of nanochitosan with a particle size of 60 nm using methacrylic acid (Bodnar et al., 2005).

In this research, we used potassium persulfate for degradation of the chitosan chain at a temperature of  $70^\circ\text{C}$  and as an initiator for monomer polymerization (Kusrini et al., 2012; Hsu et al., 2002; De Moura & Aouada, 2008). The formation reaction of nanochitosan occurred with a depolymerization reaction followed by an ionic cross-linking reaction. The reaction between potassium persulfate and chitosan took place in the acidic solution; after 1 h, the solution changed from a colorless solution to a yellowish solution. To stop the reaction between potassium persulfate and chitosan, the system was immediately removed to an ice bath for cooling. It should be noted that this process was important and urgent; if we had not put the

chitosan solution in the ice bath, the reaction would have been ongoing and potassium persulfate would have continued to degrade the chitosan chain. In this process, the colloidal suspension was formed after cooling (see Figure 2). The degradation of chitosan by potassium persulfate took place rapidly; it was finished after 1 h (Hsu et al., 2002), as indicated by the viscosity of the chitosan solution and the change to a colloidal system (Figure 2C).

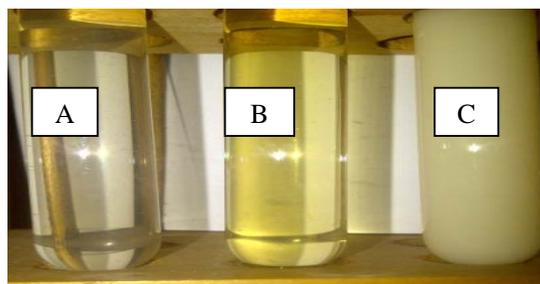


Figure 2 Preparation of chitosan nanoparticles by adding monocarboxylic acid and potassium persulfate where A = initial, B = reaction system after 45 min, and C = reaction system after cooling (colloidal is formed)

The reaction mechanism for formation of chitosan nanoparticles included two reactions: depolymerization and cross-linking with a sulfate anion reaction. A persulfate anion dissociated into two sulfate radical ions. In this scenario, a radical was attracted by the amino group of chitosan because of electrostatic force. Additionally, a degradation reaction occurred. It was expected that the radical ions would be transferred to C4 of the chitosan structure, and a radical ion would bind to a hydrogen ion from the C4, causing it to lose an ion. Hence, the C-O-C bond between chitosan monomers would be severed and two oligomers would form—one with a radical at the end and another with a C=O bond at the end. In this study, the degradation reaction produced the bisulfate anion. Oligomers were not stable; as such stability would not be characteristic until the termination stage. At the termination stage, oligomers with radicals at the end and or radical sulfate ions could attack double bonds at the end of oligomers with C=O. Ultimately, stable chitosan chains with single C-O bonds would be formed.

We assumed that the chitosan nanoparticles formed after the termination stage would contain lower molecular weights than those formed before this stage because of the severance. In this research, we observed that the effects of potassium persulfate and monocarboxylic acids (acetic, lactic and formic acids) in the chitosan solution would degrade and shorten the chitosan chain with a distribution of nanosized particles. To stop the reaction and deactivation of persulfate anions, the system temperature of 70°C was suddenly decreased to 5°C. The amino groups from chitosan cross-linked with other amino groups of chitosan via sulfate anions, forming the sulfate bridge (Al-Remawi, 2012; Harish Prashanth & Tharanathan, 2006). In this research, the proposed mechanisms to produce chitosan were adopted from the previous study by Hsu et al. (2002), as shown in Figures 3A and 3B. Chitosan nanoparticles were composed of a dense network structure of interpenetrating polymer chains cross-linked to each other by sulfate anions. Confirmation on the structure identification was studied in detail using FTIR.

The yields of chitosan nanoparticles obtained from oven and spray drying are listed in Table 1. Various concentrations of potassium persulfate were added to the chitosan solution to influence the yields of chitosan nanoparticles. When potassium persulfate levels were increased, the yields of chitosan nanoparticles also increased. It was noted, however, that yields of chitosan nanoparticles (30%) were obtained only with the addition of potassium persulfate in the initial amount of 1.2 mmol using a formic acid solution. The lowest concentration of potassium persulfate (0.6 mmol) did not yield an observable formation of chitosan nanoparticles, probably

because this amount was not enough to initiate monomer polymerization of chitosan. Thus, degradation did not occur.

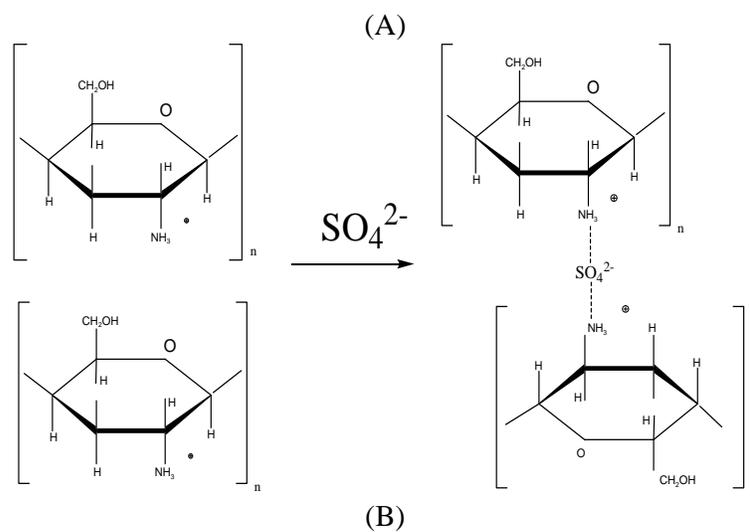
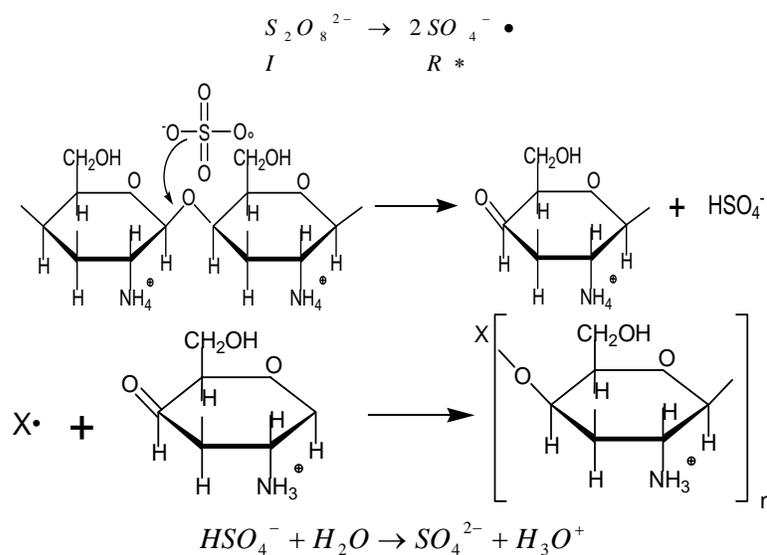


Figure 3 Proposed depolymerization reaction mechanism (A), Cross-linking with the sulfate anion reaction mechanism (B), where I = initiator,  $R^* = SO_4^{\cdot -}$  radical ions

Yields of chitosan nanoparticles obtained from spray drying were only observed for additions of potassium persulfate with a concentration level of at least 1.8 mmol. For all of the acids, no significant differences in yields of chitosan nanoparticles were produced. It was noted that the yield of chitosan produced from formic acid was the highest (79%).

Table 1 Yield of dried chitosan nanoparticles from oven and spray drying

Type of acid/potassium persulfate concentration (mmol)	Yield of chitosan nanoparticles (%)				
	0.6	1.2	1.8	2.4	3.0
	Oven drying				
Acetic acid	NO	NO	8	11	28
Lactic acid	NO	NO	21	35	57
Formic acid	NO	30	37	41	69
	Spray drying				
Acetic acid	NC	NC	75	NC	NC
Lactic acid	NC	NC	78	NC	NC
Formic acid	NC	NC	79	NC	NC

Note: NO = Not Observed; NC = Not conducted

### 3.2. Structure Studies

FTIR spectra of the pristine chitosan and nanochitosan as prepared in acetic acid, lactic acid, and formic acid solutions, respectively, by using oven and spray drying are shown in Figures 4 and 5. In pristine chitosan, the absorption peaks at 1654 and 1596  $\text{cm}^{-1}$  were assigned to the amide I and amide II bands, which shifted to lower frequencies of 1629 and 1525  $\text{cm}^{-1}$ , respectively, for chitosan nanoparticles.

The broad absorption peak appearing at 3400  $\text{cm}^{-1}$  also confirmed the presence of hydroxyl (OH) groups in pristine chitosan and nanochitosan. Based on the FTIR spectra, no differences in the absorption peaks of nanochitosan prepared from different acids were observed. This observation confirmed that the structures of nanochitosan produced with various monocarboxylic acids are similar. We observed no intra- or intermolecular hydrogen bonding among monocarboxylic acids. These structures are not similar for nanochitosan prepared with dicarboxylic and tricarboxylic acids (Bodnar et al., 2005). Based on the FTIR spectra, no new polymers were formed, as reported by De Moura and Aouada (2008). This finding indicates that chitosan was not polymerized with acids. The monocarboxylic acids only acted similarly in reactions where they functioned as proton donors to chitosan.

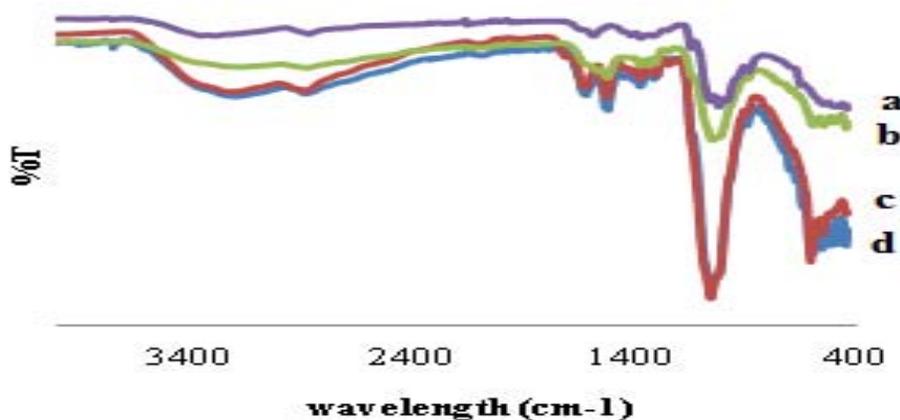


Figure 4 FTIR spectra of chitosan nanoparticles formed from oven drying: a) pristine chitosan; b) in formic acid; c) in lactic acid; and d) in acetic acid

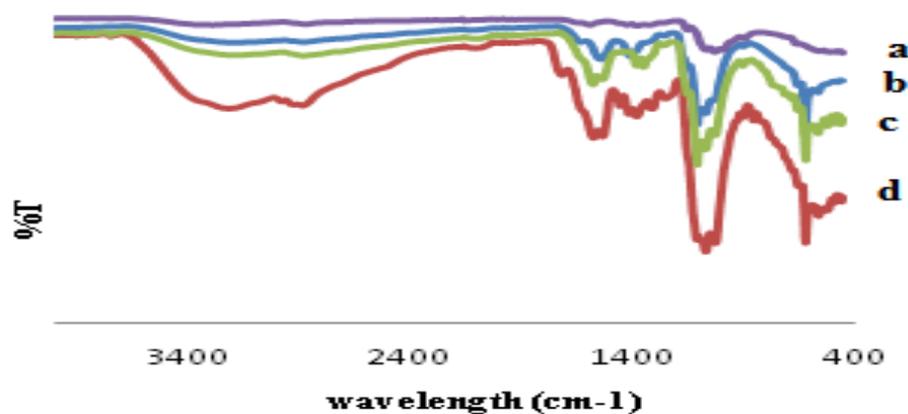


Figure 5 FTIR spectra of chitosan nanoparticles formed from spray drying: a) pristine chitosan; b) in acetic acid; c) in formic acid; and d) in lactic acid

In chitosan nanoparticles prepared in a lactic acid solution, two new absorption bands at 1737 and 1634  $\text{cm}^{-1}$  could be assigned as the carboxyl group from lactic acid. In FTIR spectra of chitosan nanoparticles, the absorption peaks at 1111–1124 and 630–619  $\text{cm}^{-1}$  were confirmed by the presence of asymmetric and symmetric sulfate anions, respectively. Furthermore, the presence of absorption peaks at 1125–1075  $\text{cm}^{-1}$  were confirmed by the C-O-C group. The absorption peaks at 1561–1543  $\text{cm}^{-1}$  and 1410–1390  $\text{cm}^{-1}$  were assigned to asymmetric and symmetric stretching vibrations of carboxyl groups. These peaks indicated that the carboxylate groups of monocarboxylic acids were deprotonated and dissociated into carboxyl ( $\text{COO}^-$ ) and hydrogen ( $\text{H}^+$ ) ions; thus, the amine group protonated to become  $\text{NH}_3^+$ . The absorption peak at 1590  $\text{cm}^{-1}$  assigned to the N-H group in the pristine chitosan shifted to a higher wavenumber at 1635  $\text{cm}^{-1}$ , indicating that the cross-linking reaction between sulfate anions and  $\text{NH}_3^+$  took place.

Because the systems must have a pH level of 4, the amounts of acids added to the chitosan solution are different—acetic acid, 87.5 mmol; lactic acid, 35.7 mmol; and formic acid, 26 mmol. Acid dissociation constants ( $K_a$ ) of acetic acid (i.e.,  $\text{CH}_3\text{COOH}$ ), lactic acid (i.e.,  $\text{HCH}_2\text{H}_5\text{O}_3$ ), and formic acid (i.e.,  $\text{HCOOH}$ ) were  $1.77 \times 10^{-4}$ ,  $1.38 \times 10^{-4}$ , and  $1.76 \times 10^{-5}$ , respectively. Of these, formic acid had the highest  $K_a$  value. Thus, only a small amount of formic acid added to the chitosan solution is required to reach a pH value of 4. Strong acids completely dissociate in aqueous solution when  $K_a > 1$  and  $\text{p}K_a < 1$ .

We suggested that the formation of chitosan nanoparticles from the use of potassium persulfate was also influenced by the amount of acids added. Lower concentration of acids added to the chitosan solution were favorable for obtaining chitosan nanoparticles. This outcome occurred because at high concentrations of acid, the persulfate ion sustained low ionic dissociation (weakened by the dissociation of acids that obstructed the degradation profile of persulfate anions). The formation of chitosan nanoparticles was not induced solely by the acid solution but rather by the concentrations of acids in the solutions. The stronger acidity of monocarboxylic acids was more favorable for producing chitosan nanoparticles compared to the addition of other acids.

### 3.3. Morphology and Composition Studies

The morphology and composition of chitosan produced from acid solutions and followed by oven or spray drying were analyzed by FESEM-EDX. The morphology of pristine chitosan is different from chitosan modified by potassium persulfate and an acid solution (see Figures 6 and 7).

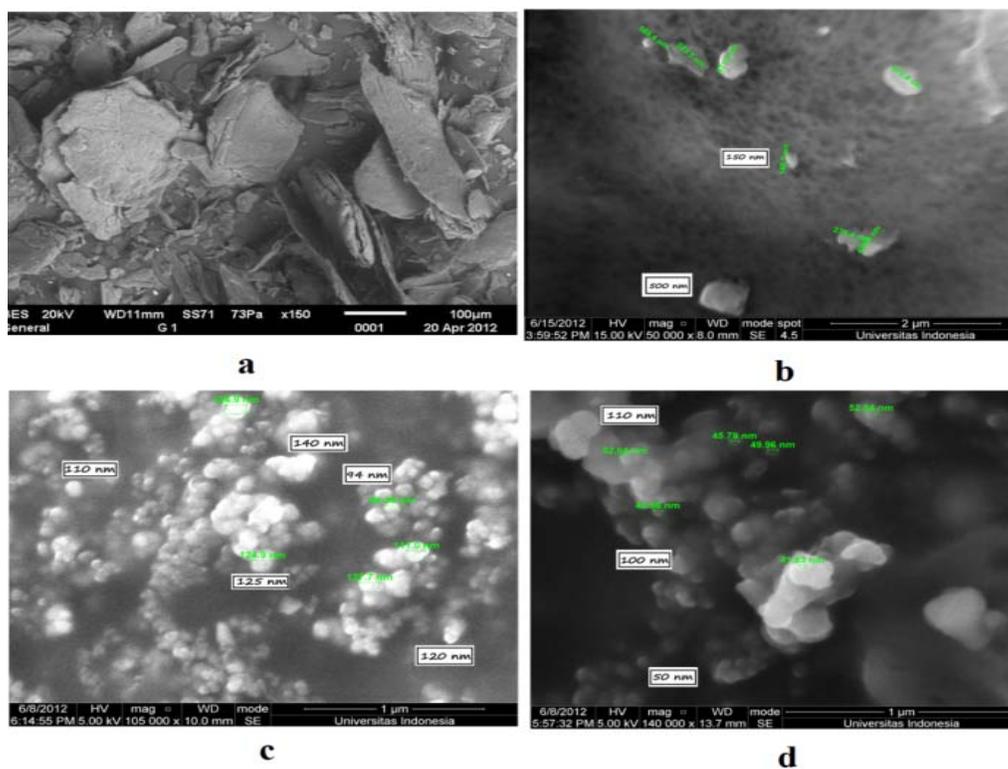


Figure 6 FESEM imaging of dried chitosan nanoparticles formed from oven drying: a) pristine chitosan; b) in acetic acid; c) in lactic acid; and d) in formic acid

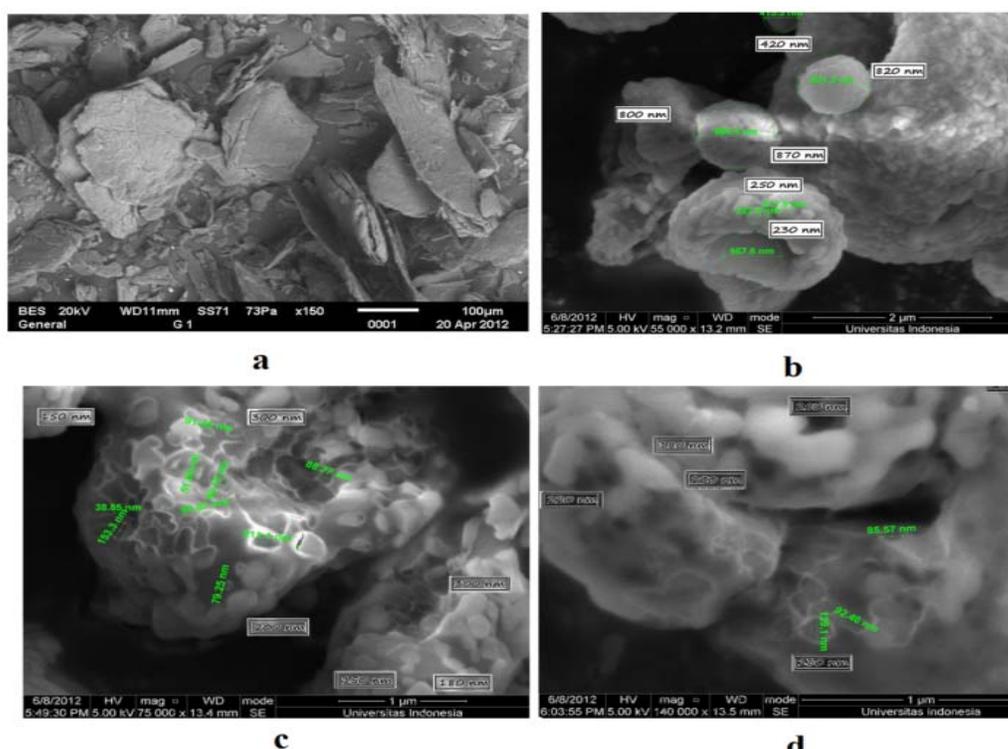


Figure 7 FESEM imaging of dried chitosan nanoparticles using spray drying: a) pristine chitosan; b) in acetic acid; c) in lactic acid; and d) in formic acid

From conventional oven drying, the particle sizes of dried chitosan nanoparticles as prepared in acetic acid, lactic acid, and formic acid were 150, 94, and 230 nm, respectively (see Figure 6). From spray drying, the dried chitosan nanoparticle sizes were 230, 150, and 130 nm as obtained in the same respective order of acid solutions (i.e., acetic, lactic, and formic). See Figure 7. Chitosan had sheet-like imaging for size in micrometers. Nanoparticles had round shapes like imaging size varied below 1  $\mu\text{m}$ . The nanoparticles of chitosan were obtained in the ranges of 150–500 nm, 94–140 nm, and 50–110 nm in acetic acid, lactic acid, and formic acid, respectively. It can be seen that the formic acid solution produced chitosan nanoparticles with smaller particle sizes than those found in lactic acid (Kusrini et al., 2012) and acetic acid.

From spray drying, dried chitosan nanoparticles were obtained in the ranges of 230–870 nm, 150–300 nm, and 130–250 nm in acetic acid, lactic acid, and formic acid solutions, respectively. The sizes of chitosan nanoparticles produced from spray drying were larger than those resulting from oven drying because of the atomization of liquid into particles through a 3  $\mu\text{m}$  nozzle during spray drying. The size of the nozzle proved to be significant relative to the size of the chitosan nanoparticles produced. Additionally, the shape of the particles produced from spray drying differed from those produced during oven drying. Spray drying formed shrunken particles with round shapes; shrinkage was attributed to rapid evaporation of the solvent and the formation of an external crust during the first stages of drying. After the external crust was formed, the solvent present in the inner parts of the droplet evaporated, leading to partial shrinkage of the chitosan.

#### **3.4. Particle Size Distribution Studies**

The particle size distribution of the prepared chitosan nanoparticles based on oven drying was in the range of 780–940 nm, 350–400 nm, and 100–10 nm in acetic acid, lactic acid, and formic acid, respectively. On the other hand, the particle size distribution of chitosan produced from spray drying exhibited a larger range compared with oven drying, namely 1350–1610 nm, 420–490 nm, and 300–330 nm in acetic acid, lactic acid, and formic acid, respectively. The particle size distribution of chitosan nanoparticles is shown in Figures 8 and 9.

Use of the PSA caused particle sizes of chitosan to be larger compared to FESEM-EDX characterization because the PSA characterization was carried out in aqueous media. Chitosan nanoparticles were dispersed in a aqueous solution with a pH level of 7 and then measured by PSA. The pH value of the medium affects the particle size because of aggregation and swelling of chitosan. The aggregation of the particles occurred at pH levels above 7. The positive charge group of chitosan  $\text{NH}_3^+$  bonded with the  $\text{OH}^-$  group from the aqueous solution, then formed  $\text{NH}_2$ . Particles that lost their charge aggregated with other particles to form an agglomeration. This behavior was possible because there was no electrostatic repulsive force between them. Hence, this phenomenon explained the larger particle size distribution from PSA measurements.

Chitosan nanoparticles produced from formic acid solutions resulted in a more narrow distribution compared to those produced from lactic acid and acetic acid solutions. The narrow distribution indicates that the chitosan nanoparticles produced would be suitable as drug carriers for delivery. Drug carriers characterized by homogeneous and small particle sizes and similar morphology are more efficient for drug loading and delivery (Yang et al., 2010; Kusrini et al., 2014).

Chitosan nanoparticles produced from formic acid solutions are smaller with narrow particle size distributions for both oven and spray drying compared to chitosan nanoparticles produced from acetic acid and lactic acid solutions (Kusrini et al., 2012).

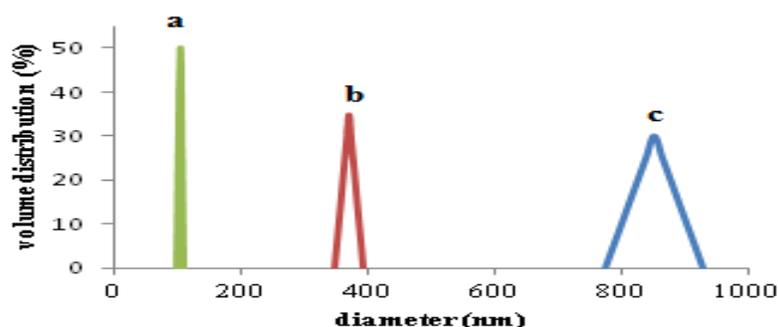


Figure 8 PSA measurements of chitosan nanoparticles produced by oven drying: a) in formic acid; b) in lactic acid; and c) in acetic acid

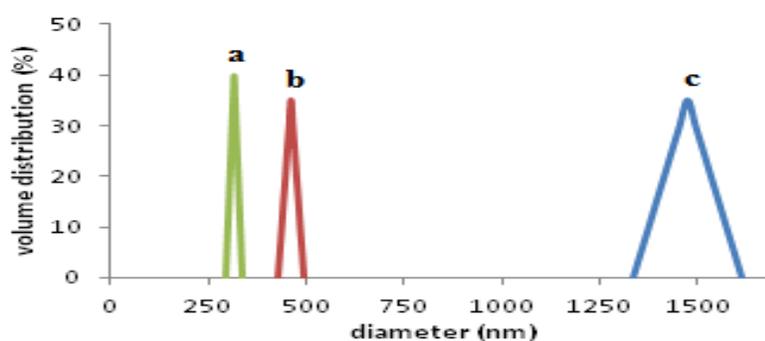


Figure 9 PSA measurements of chitosan nanoparticles from spray drying: a) in formic acid; b) in lactic acid; and c) in acetic acid.

#### 4. CONCLUSION

In the present study, we investigated the effects of monocarboxylic acids (formic acid, lactic acid, and acetic acid) and potassium persulfate on the morphology, structure, and particle size distribution of chitosan nanoparticles. The nanochitosan prepared in the different acids had similar structures based on the FTIR spectra. The concentration of potassium persulfate had a significant influence on the production of chitosan nanoparticles. The lowest concentration of potassium persulfate capable of producing chitosan nanoparticles was about 1.2 mmol; yields of nanoparticles increased with increased concentrations of potassium persulfate. We also studied the effects of heating in a conventional oven and spray drying to form dried chitosan nanoparticles. Particle size distribution of chitosan nanoparticles produced from the formic acid solution was the smallest (50–110 nm); it was obtained from oven drying. Therefore, the morphology and size of chitosan nanoparticles (50–110 nm) produced from formic acid solutions have the potential to be used as drug carriers.

#### 5. ACKNOWLEDGEMENT

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