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Electrosprayed Polyvinylpyrrolidone (PVP) Submicron Particles Loaded by Green Tea Extracts

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Abstract. Electrospraying technique has been successfully used to synthesize composite submicron particles of polyvinylpyrrolidone (PVP) and green tea extract (GTE). The precursor solutions were PVP in ethanol (15 wt%) and GTE in ethanol (10 wt%), which were then mixed at varying ratio. The mixed solution then underwent electrospraying process at an applied voltage of 15 kV, a distance of collector to the nozzle at 15 cm, and a flow rate of 3 μ L/min. The composite submicron particles of PVP-GTE showed smooth and fine spherical morphology without fibers or beaded fibers. To a certain degree, the increase of GTE content in the PVP-GTE mixed solution decreased the average diameter of PVP-GTE composite particles. Moreover, the analysis of the FTIR spectra confirmed the existing molecular interaction between PVP and GTE in the composite submicron particles as shown by the shift of PVP wavenumber towards GTE, which has typically smaller wavenumber.

Keyword. Electrospraying, FTIR, green tea extract (GTE), and polyvinylpyrrolidone (PVP).

1. Introduction

Green tea has a typical taste and flavor [1] that has many benefits such as high antioxidant activity [2, 3], ability to inhibit the proliferation of cancer cells [4], and many others. However, there are some problems existing in the application of green tea that must be solved as well. The phenolic compound of green tea, i.e., catechin, has low bioavailability in the body, low solubility in water, and large molecular weight [5]. These problems have to be unraveled partly by reducing the size down to nanoscale. The solid polymeric nanoparticles, at a size range of (10 – 1000) nm, have been studied thoroughly to be used as carriers of various molecules of drugs in many types of research related to drug delivery system [6]. By encapsulating the green tea extract (GTE) into the nanoparticles, it is then expected the problem regarding the low availability can be solved. Previously, there were already efforts made to reduce the insolubility of the compound by mixing it with a polymer, as the carrier [7] or reduced the size down to nanoscale as previously mentioned. From the literature, there are reports on the reduction of the size of green tea leaves by grinding [8] and green tea extract composites nanostructures [9].



In more than two decades, electrohydrodynamic atomization (EHDA) has been used widely to produce fibers, specifically named as electrospinning, as well as particles (electrospray) [10, 11] and has been applied for drug delivery systems. For creating micro-particles to nano-particles, electrospraying is preferred that the conventional techniques (such as nanoprecipitation, emulsion-diffusion, double-emulsification, and layer by layer) due to its simplicity, low-price, low use of a solvent, while the particles can be produced in only a single step [11]. Electrospraying technique can be potentially used to encapsulate bioactive molecules such as drugs, DNA, and many functional active ingredients in nanostructures [12] particularly in the shape of spherical particles. However, the production of drug delivery media for natural plant extract, used for many therapeutic purposes, is still very rare.

In this research, the polymer used as the carrier was polyvinylpyrrolidone (PVP) that has been standardized by the Food and Drug Administration (FDA) and widely applicable for various plant extracts such as *Garcinia mangostana* extracts [13, 14] and *Anredera cordifolia* leaves extract [15], in which all were in nanofibers form. Previously, GTE has been successfully encapsulated in nanocomposites as a combination of agglomerated beads (less spherical particles) and nanofibers [9]. Thus, this paper reports on the synthesis of composite solid particles of GTE-loaded PVP produced by electrospraying and presents the formation of purely composite spherical particles that have not been reported yet. The morphology and the size were analyzed by scanning electron microscopy (SEM) images. The existing functional groups and the intermolecular interactions of the composite particles were detected using a Fourier Transform Infra-Red (FTIR) spectrometer.

2. Materials and methods

2.1. Materials

Polyvinylpyrrolidone (PVP) with a molecular weight of 40000 g·mol⁻¹ was purchased from Sigma-Aldrich. The leaves of green tea were obtained from a local market in Bandung, Indonesia. The technical grade ethanol with purity 96 % and deionized water were obtained from Bratachem, Indonesia.

2.2. Preparation of green tea extract (GTE) and precursor solution

The leaves of green tea were extracted using maceration method. The dried and grinded leaves were immersed in ethanol solution for two days with frequent stirring to dissolve the leaves. The liquid taken from the extracted leaves was then filtered and evaporated to achieve powdered extract of green tea. The extraction process was conducted at the Laboratory of Natural Product, Bioscience, and Biotechnology Research Centre, ITB. PVP was dissolved into an ethanol solvent diluted in deionized water (at ratio 7:3 w/w) with the concentration of PVP solution of 15 wt%. On the other hand, the GTE has dissolved in ethanol the concentration of 10 wt%. The PVP solution was then mixed with the GTE solution at several ratios by asymmetric composition. Each PVP and GTE solution was stirred for about one hour, and subsequently, the mixed PVP-GTE solutions were stirred using a magnetic stirrer for 2 h at the room temperature. The homogeneous solution of the PVP-GTE solution was then inserted into a syringe to undergo electrospraying process to produce PVP-GTE composite particles.

2.3. Solution properties

The characteristics of the precursor solution, including the viscosity, conductivity, and surface tension, were then measured. All solutions, which are the PVP, GTE, and PVP-GTE solutions, were measured using Fenske-Ostwald viscometer (Fisher), du Noüy tensiometer (Fisher), and conductometer (Mettler-Toledo), for their viscosities, surface tensions, and conductivities, respectively.

2.4. Electrospraying process, morphology, and size

The PVP solution and PVP-GTE solutions were placed in a 1-mL syringe (Terumo), and a high voltage (15 kV) was applied so that the electrospraying process took place. A plate collector was used

as the ground electrode with an aluminum foil coated on the surface. The collector was put at 15 cm from the needle whose diameter was 27 gauge. The humidity was kept at (60 to 70) % while the temperature was at the room temperature. The flow rate of the electrospraying process was three $\mu\text{L}/\text{min}$ which was pushed by the syringe pump connected to a PC and controlled by software. During electrospraying process, a high-speed digital camera (Panasonic, M2050) was operated to detect the formation of spraying modes. The morphology of the particles was observed using a scanning electron microscope (SEM) (Hitachi, SU3500). The SEM was operated at an excitation voltage of 5 kV with a magnification of 4000 times. The geometric mean diameter of the particles was measured with Image-MIF v3.0 software taken at 300 measurement points, and each graph was fitted by Origin 9.0 software to find the particle size distribution.

2.5. Fourier transform infra-red spectroscopy

Fourier Transform Infra-Red (FTIR) spectroscopy was used to identify the existing functional groups and the intermolecular interactions between the PVP and the GTE as PVP-GTE composite particle. The FTIR spectrometer (Bruker, Alpha 1-176-396) was performed with the wavenumber in the range of (500 to 4000) cm^{-1} .

3. Results and Discussion

3.1. Solution mixture and characteristics

The PVP and GTE solutions were mixed by asymmetric combination ratios. The precursor solution colors of PVP and GTE was white transparent and dark brown, respectively. The color of PVP-GTE solution varied according to the amount of addition of GTE from light to dark brown following the color of GTE. The homogeneous solutions of PVP-GTE were at ratios of 9:1, 8:2, 7:3, 6:4, while other compositions were not chosen since there was residue on the bottom part indicating that the solutions were not homogeneous. The selected solutions were then measured for their solution properties and then underwent electrospraying process for producing composite particles of PVP-GTE. Table 1 shows the measurement results on the viscosity, conductivity and surface tension of the solutions subjected to the electrospray.

Table 1. The viscosity, conductivity, and surface tension of various solutions at room temperature

PVP-GTE Solution Ratio (w/w)	Concentrations (wt%)	Viscosity (centiPoise)	Conductivity ($\mu\text{S}/\text{cm}$)	Surface Tension (dyne/cm)
10:0	15.0	12.189	0.63	35.3
9:1	14.5	12.835	0.84	35.2
8:2	14.0	11.265	1.12	34.2
7:3	13.5	9.092	1.90	33.4
6:4	13.0	7.368	2.36	32.1
0:10	10.0	1.112	4.56	29.8

The selection of polymer concentration PVP 15 wt% ($\text{Mw } 40 \text{ kg}\cdot\text{M}^{-1}$) was an approximation by referring to the previous report [10] that correlates to particle formation. Meanwhile, the GTE concentration of 10 wt% was selected by the solubility of the GTE solution. As similar principle processing between electrospinning and electrospraying, the different morphology resulting from the electrospraying/electrospinning was found to depend strongly on the solution parameters [10].

3.2. Spraying modes, morphology, and size

The spraying mode, SEM images, and the diameter distribution of PVP particles and the PVP-GTE composite particles are shown in Figure 1. During the electrospraying process, the spraying mode of PVP (inset Figure 1.a) solution was classified as silver bullet mode that was very promising for the production of the particles and was already used in previous reports [16, 17]. The spray modes

transformed as the GTE ratio was changed in the PVP-GTE solutions. When the ratio of GTE increased, the spray mode was unstable, and the multi-jet mode was constructed (inset Figure 1.b to Figure 1.e) since the addition of GTE affected to the characteristics of the solution. This finding proves that the solution characteristic is one of the critical parameters for determining the spraying mode in electrospray process. According to the solution characteristics, the viscosity and the surface tension of the solution decreased along with the addition of GTE. On the contrary, the conductivity of the solution was increased following the amount of GTE ratio.

The SEM images and the histogram of diameter distributions are presented with a magnification of 4000 times and log-normal fit, respectively. The SEM image of PVP electrospray (Figure 1.a) shows the agglomeration or coalesced particles near the droplet source, and therefore the diameter of the particles is difficult to measure while the distribution of diameter is difficult to calculate. Supposedly, it appears due to the low molecular weight [16] and hygroscopic characteristic of the PVP [18]. The images of particles made from the precursor solution with a ratio of PVP-GTE of 9:1 (Figure 1.b) shows less coalesced particles compared to that in Figure 1.a. The existing GTE was then able to reduce the coalescent of the particles although there were still coalesced since the hygroscopic polymer PVP was still largely dominant over GTE. Otherwise, the composite particles made from precursor solutions of PVP-GTE at ratio of 8:2, 7:3, 6:4 (Figure 1.c, Figure 1.d, and Figure 1.e, respectively) shows composite particles with smooth spherical shape and perfectly free of fibers or beaded-fibers with wide range size from micro to the nanometer.

The measurement of the diameter from the SEM images of the electrosprayed PVP-GTE composite particles made from precursor solution at ratios of 9:1, 8:2, 7:3 and 6:4 was distributed within the range of (312 to 1932) nm, (298 to 2127) nm, (298 to 2234) nm, and (195 to 2190) nm, respectively. The geometric mean diameters of PVP-GTE at a ratio of 9:1, 8:2, 7:3 and 6:4 were 895 nm, 858 nm, 775 nm, and 684 nm, respectively. These results show that the average diameter of the particle reduced as the GTE content increased. The reason is that the concentration of PVP decreased as the amount of GTE increased, therefore, reducing the diameter [14, 19]. The geometric standard deviation of PVP-GTE composite particles with a ratio of 9:1, 8:2, 7:3 were 1.37, while for 6:4 was 1.41, respectively. From the value of geometric standard deviation, the particles can thus be categorized as non-uniform (it is categorized as uniform if the standard deviation geometry was ≤ 1.22 ; otherwise it is non-uniform [20]). This result was related to the spraying modes of PVP-GTE solutions that were in multi-jet modes, which were strongly influenced the production of the inconsistent size of particles [18].

3.3. Theoretical models

We also compare the empirical results of the particles diameter to the theoretically predicted size. The scaling law models of the electrosprayed particle diameter to the solution flow rate and conductivity is given as [16, 17]:

$$D_{drop} = G(\kappa) \left(\kappa \varepsilon_0 \frac{Q}{K} \right)^{\frac{1}{3}} \quad (1)$$

$$D_{comp} = G(\kappa) \left(\phi \kappa \varepsilon_0 \frac{Q}{K} \right)^{\frac{1}{3}} \quad (2)$$

where D_{drop} is the diameter of the droplet and D_{comp} is the diameter of the electrosprayed composite particles, κ is the dielectric constant, Q is the flow rate, ϕ is the volume fraction of the combined polymer and bioactive substances, and ε_0 is permeability. K is the electrical conductivity, and $G(\kappa)$ is the dimensionless function given by:

$$G(\kappa) = -10.9\kappa^{-\frac{6}{5}} + 4.08\kappa^{-\frac{1}{3}} \quad (3)$$

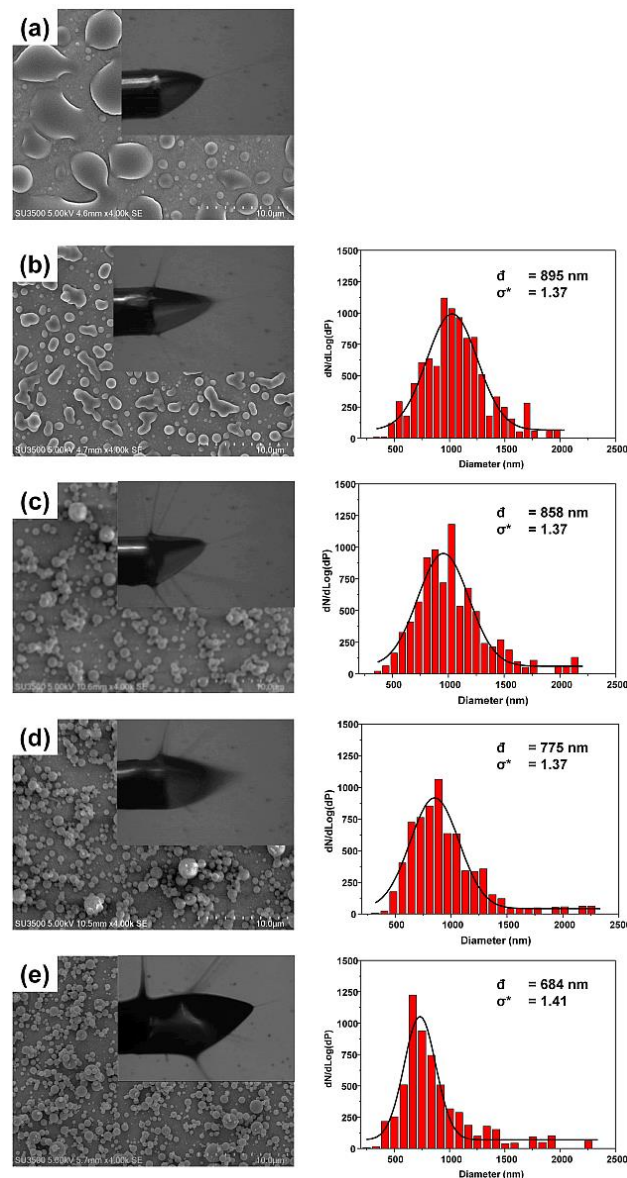


Figure 1. The spraying modes (inset), SEM images, and the histogram of the distribution of diameters of the electrospay (a) PVP and PVP-GTE with different ratios (b) 9:1, (c) 8:2, (d) 7:3, and (e) 6:4.

As seen in Figure 2, the dashed lines show the approximate size of the droplets as predicted from Equation 1 and Equation 2. The square, the circles, and the triangles are the data obtained from polymer-pigment-nanoparticles composites [17], pure polymer [16], as well as the present experiment by plotting the log of diameter against the log of Q/K , respectively.

Based on Figure 2, it was found that the experimental data, approximately, match to the theoretical model. For this research, the experimental data fitted to the theoretical model for Q/K approximately from 10^4 to 10^5 , which is about ten times of magnitude. Therefore, the average diameter of the electrospayed particles can be estimated by the prediction equations, and the diameter can thus be controlled by adjusting the flow rate and the properties of the precursor solution.

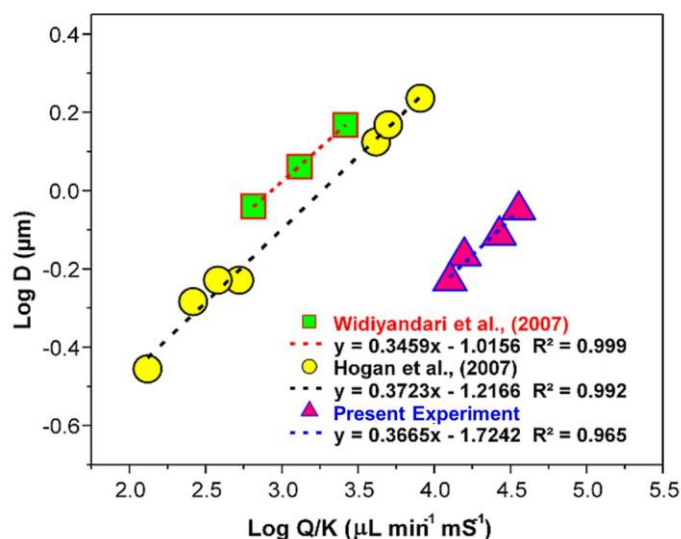


Figure 2. The log of droplet diameter from both the empirical data and theoretical calculation as a function of the solutions flowrate to electrical conductivity (Q/K)

3.4. Fourier transform infra-red (FTIR) spectra

The FTIR spectroscopy was performed to investigate the compatibility between GTE as the active ingredient and PVP as the polymeric matrix. The FTIR characterization of PVP, GTE, and PVP-GTE composite particle for identifying the functional groups and their peaks are shown in Figure 3. The specific peaks of PVP at 3406 cm^{-1} and 2954 cm^{-1} indicates the O-H stretching vibration and C-H asymmetric stretching vibration [21], respectively. The peak at 1652 cm^{-1} is carbonyl groups (C=O stretch vibration) [21], the peak at 1290 is CH wagging [9, 18], and the peak at 1074 is the C-N vibration [21]. The peak at 570 cm^{-1} indicates N-C=O bending [9, 18]. The specific peaks of GTE at 3193 cm^{-1} indicates the stretching vibrations of O-H groups in water, alcohol, and phenols as well as N-H stretching in amines [22]. These indicate the presence of polyphenol in GTE. The GTE peaks at 2927 cm^{-1} indicate the C-H stretch in alkanes [22]. The specific band at 1692 cm^{-1} to 1602 cm^{-1} indicates the C=C stretch in the aromatic ring and C=O stretch in polyphenols [9, 22]. The Peak at 1342 cm^{-1} is C-N stretch of amide-I in protein [22] and the peak of GTE at 1036 cm^{-1} indicates C-O stretching in amino acid [9, 22]. The functional groups of both PVP and GTE as shown by the FTIR spectra in this experiment are already similar to the previous reports. The composite particles of PVP-GTE, for all ratios, also show the peak characteristics as contributed by PVP and GTE contribution. The existing intermolecular interactions of these composite particles are confirmed by the shifting of the band wavenumber between PVP and GTE.

The PVP-GTE composite particles at ratios of 9:1, 8:2, 7:3, and 6:4 have the O-H stretching peaks at 3402 cm^{-1} , 3396 cm^{-1} , 3376 cm^{-1} , and 3372 cm^{-1} , respectively. These peaks are lower than that of PVP at 3406 cm^{-1} and higher than that of GTE at 3193 cm^{-1} . It implies that the O-H stretching peak of PVP-GTE composite particle shifted to a lower wavenumber along with the increase of GTE content. Therefore, these shifted peaks indicate that the PVP-GTE particle composites with the ratios of 9:1, 8:2, 7:3, and 6:4 do have molecular interactions between carbonyl groups of PVP and hydrogen bonds of GTE [18]. The shifted peaks of PVP-GTE composite particles with the ratios of 9:1, 8:2, 7:3, and 6:4 were 1074 cm^{-1} , 1050 cm^{-1} , 1047 cm^{-1} , and 1045 cm^{-1} , respectively, which are lower than that of PVP (1072 cm^{-1}) and higher than that of GTE peak (1036 cm^{-1}). These peaks indicate that the particles do have molecular interaction between the C-N vibration of PVP and the C-O stretching in an amino acid of GTE in PVP-GTE composite particles. These results are similar to our previous work that construct the nanostructures of PVP-GTE [9]. Overall, FTIR spectra in this experiment also confirmed that the GTE was successfully loaded into PVP as the composite submicron particles.

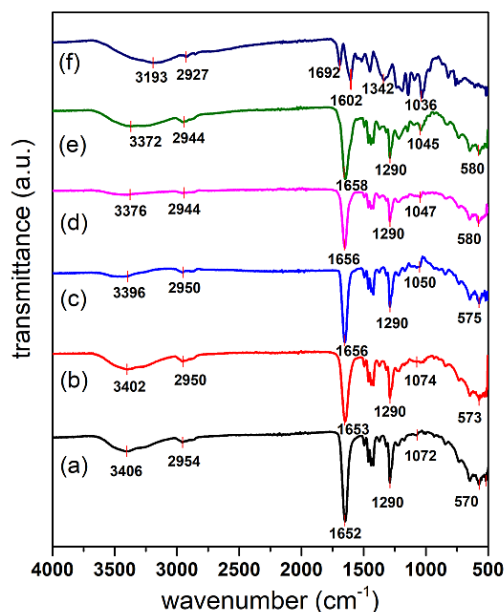


Figure 3. FTIR spectra of (a) PVP, composite particle of PVP-GTE with the ratios of (b) 9:1, (c) 8:2, (d) 7:3, (e) 6:4, and (f) GTE.

4. Conclusions

The electrospray polyvinylpyrrolidone (PVP) submicron particles loaded by green tea extract (GTE) as the bioactive substance has successfully been done. The spray mode of PVP was classified as a single jet silver bullet mode. It was then changed to unstable multi-jet by the introduction of GTE with different contents. As a result, it also affected the size and distribution of PVP-GTE composite particles. The SEM images showed that PVP-GTE composite particles have a purely smooth and spherical shape. The average diameter of PVP-GTE composite particles decreased along with the increase of the GTE content. Moreover, the average diameter of the particles was also approximately similar to the theoretical model developed from the previous reports. The FTIR spectra of PVP-GTE composite particles have confirmed the existing intermolecular interaction between PVP and GTE.

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