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ORIGINAL ARTICLE

Formulation and Characterization of Dewandaru Fruit Extract in Nanocarrier System

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ABSTRACT – Dewandaru (*Eugenia uniflora* L.) is a herbaceous plant that grows in tropical and subtropical regions. The fruit extract can prevent oxidative damage and cholinergic changes. It contributes to antihyperglycemic, antihyperlipidemic, and neuroprotective due to its antioxidants and antidepressant effect. It also possesses antibacterial and anti-inflammatory activity and potentially prevents cardiovascular disease and cancer. In this study, dewandaru fruit extract was formulated in the nanocarrier system (nanoemulsion and nanoencapsulation) to preserve product stability and improve product dispersibility and bioavailability. The nanoemulsion optimum formulation condition was obtained on dewandaru fruit extract concentration 10 wt%, oil/surfactant ratio 0.25, and homogenization speed 20.000 rpm, resulting in particle size of 46.4 ± 0.4 nm and polydispersity index 0.480 ± 0.015. The optimum nanoemulsion formulation was further processed to nanoencapsulation along with milling to produce finer particles. The nanoencapsulation milled for 120 minutes produced encapsulation powder with a size of 5.8 ± 3.340 µm. Accordingly, the nanocarrier technology for dewandaru fruit extract promoted a versatile medicinal preparation both in liquid and solid form. However, the size reduction by milling might disrupt the efficiency of the encapsulation release system. Without the proper coating, as orally administrated, the compound rapidly dissolved before it reached the targeted site.

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INTRODUCTION

Dewandaru or *Eugenia uniflora* L. (Myrtaceae) is a herbaceous plant that grows in tropical and subtropical regions. It is widespread in American countries and locally known as pitagueira, the Pitanga cherry, or Brazilian cherry. Regarding its effect on human health, the fruit and leaves are used as a traditional medicine to treat diseases [1]. Several studies have been conducted on the biological activity of the extract of dewandaru fruit. The ethanolic dewandaru fruit extract can prevent oxidative damage and cholinergic changes. It contributes to antihyperglycemic, antihyperlipidemic, and neuroprotective by providing antioxidants and antidepressant effects [2]. Dewandaru fruit extract also contains a phytosterol like caffeine, vitamin E, and γ-sitosterol for lowering blood cholesterol levels [3]. Furthermore, the β-carotene in dewandaru fruit also potentially prevents cardiovascular disease and cancer [4], antibacterial and anti-inflammatory [5], [6].

Therefore, dewandaru fruit extract has the potential to be developed. However, it is necessary to prepare the formulation to increase the product's usability. The nanocarrier system is one of the strategies to preserve the product's stability, increase the release of the active substances to the targets, and improve the product's dispersibility and bioavailability.

Several methods are employed to improve dispersibility and bioavailability through nanocarrier systems. The nanocarrier system encapsulates bioactive molecules at an appropriate dosage with desired biological and physicochemical properties [7]. The formulation is carried out carefully and noted in several aspects, such as biocompatibility, biodegradability, and low-cost process [8]. Among the existing systems, nanoemulsions have been developed as encapsulation media for active compounds in food, pharmaceutical, and cosmetics products.

Nanoemulsions are colloidal dispersions of two immiscible liquids stabilized by surfactant molecules. Visually, it is clear, slightly cloudy, or milky. The dispersed nanodroplets are spherical, and the diameter usually ranges from 50–200 nm [7]. Nanoemulsions are unbalanced systems and do not form spontaneously. The preparation involves surfactants, co-surfactants, or their combination, and the formulation requires external energy input. Nanodroplets are created by converting larger droplets of the emulsion into smaller ones. This technique can be achieved by low- or high-energy homogenization methods [7]. The high-energy emulsification method is employed to break up the dispersed phase into smaller droplets in the nanometer range and produce nanoemulsions of various materials in a short time [9].

The previous study regarding the dewandaru extract had been conducted from the leaves part. The extract was formulated into oil in water emulsion with micro-scale size [10]. Further, the dewandaru leaf extract was encapsulated using gelatin and chitosan [11]. This study used dewandaru fruit extract and formulated in nanoscale emulsion below 200 nm. The encapsulation used a combination of maltodextrin and gum arabic. This paper aimed to make a novel

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nanocarrier of dewandaru fruit extract in the form of nanoemulsion and nanoencapsulation. Dewandaru nanoemulsion (DNe) was made by adding olive oil, tween 80, and buffer pH 7. Several parameters, such as oil and tween 80 ratios, homogenizing speed level, and active agent concentration, were employed. The nanoencapsulation was made using maltodextrin and gum arabic as the matrix. Further, the nanoencapsulation was milled to reduce the particle size with different milling times. To determine the optimum condition, the parameters such as physical appearance, particle size, polydispersity index, and surface morphology, were observed.

EXPERIMENTAL METHOD

Materials and Instruments

The materials used in this study were ethanolic extract of dewandaru fruit from Research Center for Pharmaceutical Ingredients and Traditional Medicine, National Research and Innovation Agency (BRIN, Indonesia), tween 80 for synthesis, potassium phosphate monobasic (KH_2PO_4), sodium hydroxide (NaOH) from Merck (Germany), olive oil food grade from local market (Indonesia), maltodextrin technical grade, gum arabic technical grade from Bratachem (Indonesia).

The equipment used in this study was a homogenizer digital ultra turrax IKA T25 (Germany) for the nanoemulsion formation process, a mini spray dryer Buchi B-290 (Switzerland) for encapsulation powder formation, shaker mill manufactured by the Research Center for Physics, BRIN (Indonesia) for reducing the size of encapsulation powder. Particle size analyzer Horiba Nanopartica SZ-100 (Japan) for droplet size analysis, scanning electron microscopy (SEM) Jeol JSM-IT200 (Japan) for morphology characterization,

Method and Procedure

Formulation of Dewandaru Nanoemulsion (DNe)

The ethanolic dewandaru fruit extract was obtained using the method of Dewi et al. (2022) [12]. The formulation of dewandaru nanoemulsion (DNe) was carried out based on the composition shown in Table 1. The amount of 1–5 gr of dewandaru extract was added into a mixture of olive oil and tween 80 in different mass ratios of oil:tween 80 (1:4; 2:4; 3:4) in 50 gr work volume while stirring and heated at 70°C until the mixture homogeneous. Simultaneously, the phosphate buffer was prepared by mixing 39.1 ml NaOH solution 0.2 M with 50 ml KH_2PO_4; the pH was adjusted to pH 7.0, then tare with distilled water in a 200 ml measuring flask. Then, a pH 7.0 phosphate buffer was added dropwise to the oil phase and stirred for one hour at 70°C with a magnetic stirrer. Finally, the pre-emulsion from the previous process was homogenized using Ultra Turrax by varying the speed in the range of 10.000–20.000 rpm for 30 minutes. The DNe formed was characterized by the parameters of particle size, polydispersity index, and physical stability. The optimum condition was determined from the formulation with the smallest particle size.

Table 1. The formulation of dewandaru nanoemulsion (DNe)

Sample	Dewandaru Fruit Extract (gr)	Olive Oil (gr)	Tween 80 (gr)	Buffer pH 7 (gr)	Ultra Turrax Speed (rpm)
A1	1	1	4	45	10.000
A2	1	2	4	44	10.000
A3	1	3	4	43	10.000
B1	1	1	4	45	15.000
B2	1	2	4	44	15.000
B3	1	3	4	43	15.000
C1	1	1	4	45	20.000
C2	1	2	4	44	20.000
C3	1	3	4	43	20.000
C12	2	1	4	45	20.000
C13	3	1	4	45	20.000
C14	4	1	4	45	20.000
C15	5	1	4	45	20.000

Formulation of Dewandaru Nanoemulsion (DNe) Encapsulation

An encapsulation matrix was used with the combination of maltodextrin and gum arabic based on Meliana et al. (2017) [13]. The filler material (216 gr maltodextrin and 24 gr gum arabic) was mixed into 700 gr aquadest. The mixture was stirred until homogeneous and continued with a homogenizer at 15.000 rpm for 15 minutes. Next, 300 gr of DNe was added to the filler solution and mixed using a homogenizer for 30 minutes at 15.000 rpm. Finally, the mixture was dried using a spray dryer with a condition inlet temperature 140°C, outlet temperature 77°C, aspiration rate 80%, and pump 35%. The powder obtained was mashed using a shaker mill for 30, 60, 90, and 120 minutes.

Characterization

The stability test was done at room temperature. DNe was placed into a 10 ml sample vial, and its physical stability was observed after seven days. Any visible destabilization was recorded by picture.

The particle size and polydispersity index (PI) were measured using a dynamic light scattering particle size analyzer (Horiba SZ-100). Laser source DPPS 532 nm, with automatic settings. The morphology was analyzed using scanning electron Microscopy (SEM) Jeol JSM-IT200 (Japan), temperature 20°C, Vacc 5.0 kV, probe current 40 with magnification 1000×.

RESULT AND DISCUSSION

Visual Appearance, Particle Size, and Polydispersity Index (PI) of Dewandaru Nanoemulsion (DNe)

Table 2 shows that the visual appearance of each formulation does not change significantly from day 0 to 7 [14]. It confirms that DNe is physically stable. Visually, the dewandaru nanoemulsion is clear and translucent. This translucent appearance is due to the diameter particle of less than 100 nm, where the particles are smaller than the optical wavelength of the visible light spectrum [15]. Thus, the scattering of visible light is very weak. In Table 2, the differences in samples 1, 2, and 3 are in the ratio of the addition of olive oil. The increase in oil phase concentration causes an increase in droplet size [16]. It corresponds with the nanoemulsion appearance; as the oil phase concentration oil increased, the droplet size also increased and changed the visual of the nanoemulsion. As the droplet size is above 100 nm, the emulsion visual changes due to multiple scattering become hazy, and further, when the particle is bigger, it appears white [17].

The nanoemulsion has a particle size in the range of 20–200 nm, which is considered safe and can be absorbed into the stratum corneum (epidermis) for drug delivery through the skin [18]. This corresponds to the results of the study shown in Table 2, where DNe had a minimum particle size of 48.5 nm and a maximum of 128.2 nm. The safety of nanoemulsion corresponds with its composition, structure, and administration route. The nanoemulsion composition for cosmetics, food, and pharmaceuticals usually uses safe ingredients required for the respective level. The size of the nanoemulsion determines the rate of penetration. The smaller droplet can penetrate through the mucus layer pores, leading to faster absorption. The previous study on various test subjects reported the nanoemulsion with a range of 20–250 nm was non-toxic [19].

Simultaneously with the particle size measurement, the polydispersity index (PI) value is also obtained. The polydispersity index indicates the uniformity of particle size on samples, which ranges from 0 to 1. The low polydispersity index value shows the uniformity of the globule size of the sample. In contrast, a PI value close to 1 indicates the presence of various droplet sizes in the sample, which suggests that the sample is not monodisperse [20]. The results of the study show PI from 0.492 to 0.508. A value less than 1 indicates that DNe is monodisperse and has a homogeneous size distribution.

The nanoemulsion in this study possesses optical clarity and good physical stability against aggregation and gravitational separation. The particle sizes of all samples are below 200 nm with a narrow distribution. The system with this characteristic is potentially unchanged for a long time, up to six months [21].

Table 2. The visual appearance, particle size, and PI of dewandaru nanoemulsion (DNe)

Sample	Particle Size (nm)	Polydispersity Index (PI)	Day-0	Day-7
A1	112.8 ± 0.6	0.480 ± 0.011		
A2	107.8 ± 0.5	0.402 ± 0.013		
A3	128.2 ± 1.5	0.432 ± 0.017		
B1	67.4 ± 0.3	0.598 ± 0.003		
B2	82.5 ± 0.2	0.569 ± 0.030		

B3	100.7 ± 0.2	0.578 ± 0.015		
C1	48.5 ± 0.4	0.512 ± 0.009		
C2	57.6 ± 0.3	0.431 ± 0.018		
C3	86.6 ± 0.2	0.468 ± 0.021		

The Effect of Oil/Surfactant Ratio on Dewandaru Nanoemulsion (DNe) Particle Size

Particle size and polydispersity are essential parameters for nanoemulsion stability [22]. Figure 1 shows that the variation of the oil/surfactant (O/S) ratio in the formulation affected the particle size. The O/S ratio with a value of 0.25 exhibits the smallest particle size among all variations and shows an increasing trend on the O/S ratio of 0.75. The particle size change is observed in formula A from 112.8 nm to 128.2 nm, formula B from 67.4 nm to 100.7 nm, and formula C from 48.5 nm to 86.6 nm. The addition of oil increases the particle size and, hence, does not affect the polydispersity, as shown in Table 2. The proper amount of oil content can increase the nanoemulsion stability and maintain small particle size. The oil phase contributes to the nanoemulsion's stability by reducing the dispersed phase's solubility and decreasing Ostwald ripening [23]. However, excessive oil concentration increases the particle size. This is because the excess oil can not be entirely encapsulated by the surfactant micelles in the aqueous phase and increases coalescence [24]. As the oil concentration increased, the energy density per amount of oil also decreased, thus constricting the energy for droplet size reduction [25]. This result was in accordance with the study by Ren et al. (2018), where the smaller particle was maintained in lower olive oil concentrations (1–5%), but the particle size increased in higher oil concentrations (10–20%) [23]. However, in sample A, the trend is different from the sample B and C. Theoretically, when the O/S ratio increased, the particle size also increased. The inconsistency trend in sample A might be affected by the sample preparation during particle size analysis. The particle size analysis and the dilution of the sample play an important role. If the sample was too concentrated, the sample would be affected by multiple scattering or viscosity effect. This will cause the measured particle size artificially low [26].

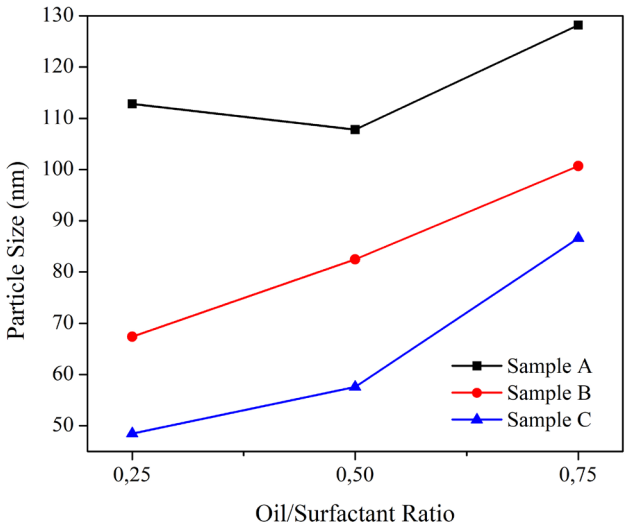


Figure 1. The effect of O/S ratio on dewandaru nanoemulsion (DNe) particle size

In this study, the amount of surfactant was fixed while the amount of oil increased. According to Chang & McClements (2014), the amount of surfactants influenced the particle size [27]. A high surfactant concentration causes a decrease in the particle size. This phenomenon is related to the physicochemical mechanism. A higher surfactant concentration stabilizes more oil-water interfacial tension; thus, smaller droplet size is obtained [28]. From this study, it is known that the lower oil content with the O/S ratio of 0.25 produced the smallest particle size. It was also noted that the speed of homogenization was taken into account, as discussed in the next section.

The Effect of Homogenization Speed on Dewandaru Nanoemulsion (DNe) Particle Size

Figure 2 shows that the increase in homogenization speed causes a decrease in particle size. In the high-speed homogenization method, the mixing head of the rotor-stator device rotates at high speed. It creates a mixture of radial, longitudinal, and rotational velocity gradients in the liquid. It destroys the oil-water boundary, makes the liquid mix, and breaks the larger droplets into smaller ones [29]. The process with a speed of 10,000 rpm produces larger particle size in O/S ratio of 0.25, which is 112.8 nm; O/S ratio of 0.5, which is 107.8 nm; and O/S Ratio of 0.75, which is 128.2 nm. The particle size trend decreases as the homogenization speed increases to 20,000 rpm, with particle size range for O/S ratios 0.25, 0.5, and 0.75 are 48.5 nm, 57.6 nm, and 86.6, respectively.

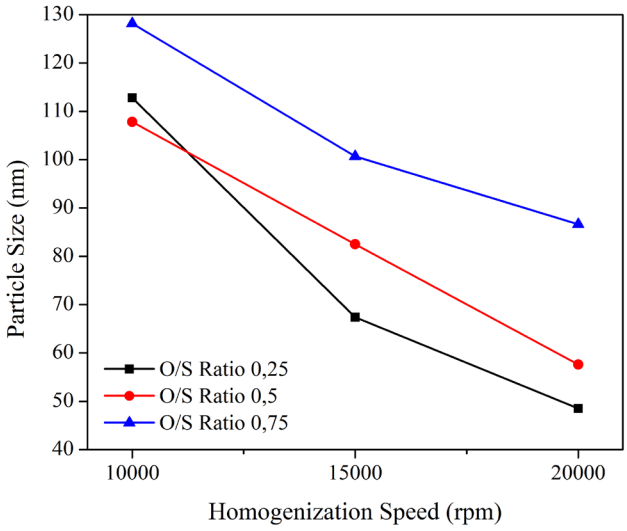


Figure 2. The effect of homogenization speed on dewandaru nanoemulsion (DNe) particle size

Nanoemulsion with a high-shear homogenization method significantly affects decreasing particle size and polydispersity index [30]. The more homogenization time and mixer speed used, the smaller the droplets formed. The increase in energy supplied to the system causes a decrease in the viscosity and resistance of the emulsion to deformation, which causes more disturbance of emulsion droplets [31]. The high force and cavitation effects lead to more active agents being adsorbed on the surface of the oil phase droplets, preventing aggregation and increasing the nanoemulsion's stability [32]. However, similar to the O/S ratio variation, homogenization speed does not significantly affect the polydispersity index (PI), as seen in Table 2, which was around the value of 0.4–0.5. The value of PI that is bigger than 0.7 has a broad particle distribution [33], and the PI value resulting from this study is considered to have a monodisperse distribution. It is agreeable that homogenization speed at 20.000 rpm produced the smallest particle size below 100 nm.

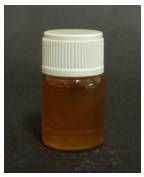
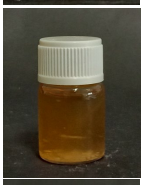
The Effect of Extract Concentration on Dewandaru Nanoemulsion (DNe) Particle Size

The previous study showed that the optimum condition which produced the smallest particle size was on O/S ratio of 0.25 and a homogenization speed of 20.000 rpm. Further, the loading of dewandaru extract was optimized as follows in the composition seen in Table 1. Table 3 presents the visual appearance, particle size, and PI data of the optimized dewandaru extract loading. Increasing the extract concentration was done to observe the maximum concentration that can be added while maintaining the nanoemulsion stability. It is seen in Table 3 that DNe is visually clear and stable without any separation for seven days of observation at room temperature. Yet, the increase in concentration caused a darker color. The particle sizes range from 48.5–46.4 nm with polydispersity index value less than 0.7, indicating a monodispersed particle size distribution.

Figure 3 shows that the increase in extract content produces smaller droplet size. This is caused by the highly surface active compound contained in dewandaru extract that could act as a natural emulsifier [34]. The dewandaru fruit extract was known to have flavonoids, tannins, and saponins content [12]. A similar result is also reported in a study by Ralla et al. (2017) [34] and Patel et al. (2017) [35], where the active agent contained saponins content and protein that

acted as a natural emulsifier that supported the performance of the synthetic emulsifier to decrease the particle size. The surface tension decreases by the increasing extract concentration, indicating the adsorption of the surface-active saponins to the oil-water interface. This was also attributed to the surface-active compound that can counteract the Laplace pressure produced in the emulsion droplets and, accordingly, improve droplet disruption during homogenization [36].

Table 3. The visual appearance, particle size, and polydispersity index (PI) of dewandaru nanoemulsion (DNe) with concentration variation

Sample	Particle Size (nm)	Polydispersity Index (PI)	Day-0	Day-7
C1	48.5 ± 0.4	0.512 ± 0.009		
C12	49.2 ± 0.6	0.511 ± 0.008		
C13	49.1 ± 0.3	0.499 ± 0.006		
C14	48.6 ± 0.8	0.502 ± 0.007		
C15	46.4 ± 0.4	0.480 ± 0.015		

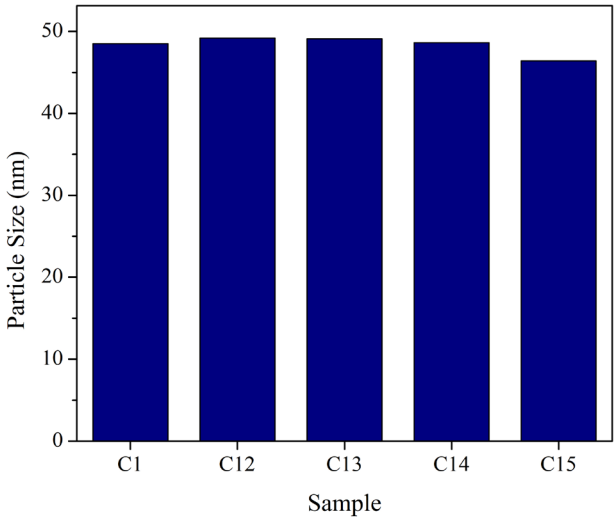


Figure 3. The effect of dewandaru fruit extract concentration on nanoemulsion droplet size

The Effect of Milling Time on Encapsulated Dewandaru Nanoemulsion (DNe) Particle Size

Formula C15 produces the stable nanoemulsion with the smallest particle size; thus, this formulation is used for further encapsulation. The encapsulation was carried out using maltodextrin and gum arabic as matrix and processed using a spray dryer. Figure 4 shows the morphology profile of encapsulated DNe before and after the milling process. Morphological observations of the encapsulated samples result in irregular particle shapes and wrinkles along with several cracks. The presence of hollows or flattens on the surface is a characteristic feature of microspheres produced by atomization using gum arabic as an encapsulating agent [37]. Mazuco et al. (2018) formulated microcapsules with mixed maltodextrin and gum arabic coating with a slightly wrinkled and irregular surface compared with maltodextrin only [37].

Figure 4 (a) shows encapsulation without milling treatment. The shape of the particles is almost spherical. However, there are indentations or shrinkages in the particles. The formation of indentations on the particles' surface, which occurred due to the spray dry method, is commonly associated with the shrinkage of the particles due to the drastic loss of moisture followed by cooling [38], [39]. The shrinkage of the capsule core might be caused by the high temperature of the spray dryer or the thin wall layer of the microcapsule. Higher inlet temperatures drive a higher drying rate that can cause some cores to diffuse and evaporate, resulting in shriveled capsules [40].

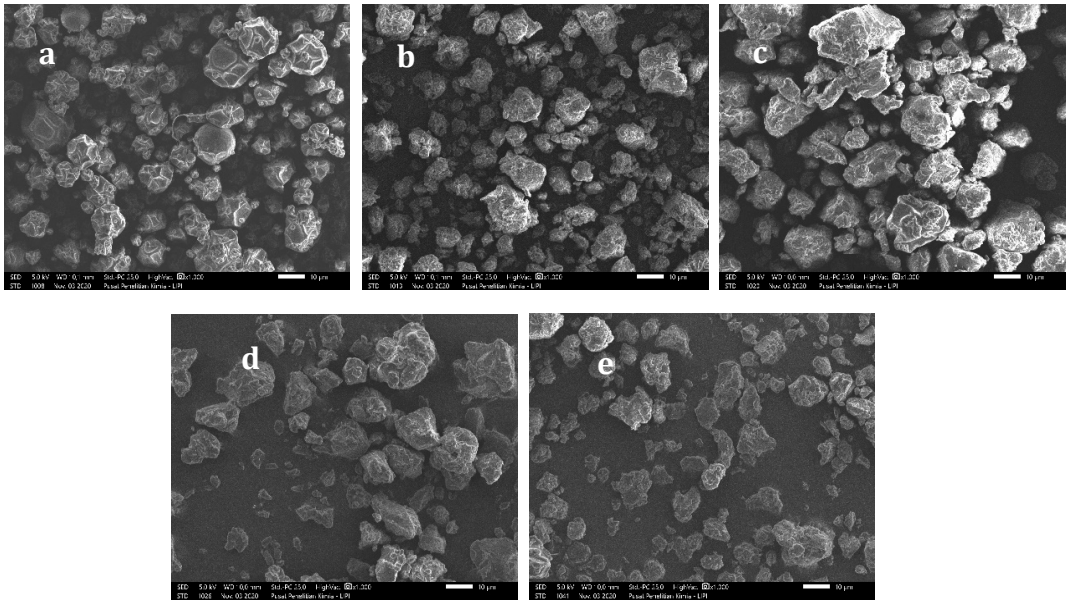


Figure 4. Surface morphology of encapsulated DNe with variations in milling time: (a) 0 minutes; (b) 30 minutes; (c) 60 minutes; (d) 90 minutes; and (e) 120 minutes

Table 4. Particle size of DNe encapsulation

Milling Time (minutes)	Particle Size (μm)			
	Mean	Standard Deviation	Min.	Max.
0	9.890	5.365	2.074	19.250
30	7.449	5.262	1.946	19.557
60	8.942	8.123	2.495	35.956
90	6.812	4.248	1.935	16.018
120	5.853	3.340	1.450	12.938

Figure 4 (b) to (e) shows the milled sample morphology in time variations with a structure like flakes of varying size, observed in all images. It is also seen that the particles after milling had uneven shapes and not uniform particle distribution. This is likely due to the grinding of the particles after the milling process [41]. During the milling process, the samples underwent repeated processes by ball collision; the sample was trapped between the balls, resulting in sample deformation and disintegration [42]. The milling time also affected the final size of the sample, as seen in Table 4. It was seen that longer milling time produces smaller particle sizes. The initial sample particle size is 9.890 ± 5.365 μm, and the smallest particle size is produced in a milling time of 120 minutes with a particle size of 5.854 ± 3.340 μm. The particle size of the encapsulated product was changed during the spray drying compared with the emulsion form; this is caused by the speed of the atomizer and the size of the nozzle during the drying process [43].

However, the milling process results in an uneven shape and not uniform size. There is also a presence of dents and cracks in the particles. The encapsulation structure prefers a uniform and smooth surface, a slightly rounded shape with few cracks and collapses on the walls [44]. The cracked particle might not encapsulate and protect the active agent

properly; thus, it might disrupt the controlled release of the encapsulation. Smoother and smaller particles are associated with the ratio between maltodextrin and gum arabic to build an effective and efficient encapsulation system [45]. The aim of the encapsulation is to establish a protective barrier to improve stability, activity, targeted delivery, and controlled release. Nevertheless, due to milling, the initial spherical form was destroyed, causing the bioactive compound to be unprotected. Without the proper coating, as orally administrated, the compound rapidly dissolves before it reaches the targeted site [46].

CONCLUSION

The nanoemulsion of dewandaru fruit extract is successfully formulated with an optimum concentration of dewandaru extract 10 wt% with an oil/surfactant ratio of 0.25 and homogenization speed of 20.000 rpm, which produced a particle size of 46.4 ± 0.4 nm. The nanoemulsion was encapsulated by the mixture of maltodextrin and gum arabic processed by a spray dryer that produced encapsulated powder with particle size 9.890 ± 5.365 µm, and further with 120 minutes milling process produced the powder with particle size 5.854 ± 3.340 µm. The nanoemulsion particle size changes after the spray dryer process due to atomization speed and nozzle size. However, the size reduction by milling might disrupt the efficiency of the encapsulation release system. It is recommended to adjust the ratio of maltodextrin and gum arabic to produce smaller particles.

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