JFSP Vol.8, No.3, November 2022, Page: 215-226, pISSN: 2549-9068, eISSN: 2579-4558

Jurnal Farmasi Sains dan Praktis

(JFSP)

http://journal.unimma.ac.id/index.php/pharmacy

NANOEMULSION CHARACTERISTICS OF ETHANOL EXTRACT FROM LEAVES OF VARIOUS PLANTS: A LITERATURE REVIEW

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https://doi.org/10.31603/pharmacy.v8i3.4786

Article info:

Submitted : 25-02-2021

Revised : 12-03-2021

Accepted : 06-08-2022

Publisher:

Universitas Muhammadiyah Magelang

ABSTRACT

Nanoemulsion is part of the development of nanotechnology with a submicron particle size of 0-100 nm, which can control over the release of active ingredients and sensory properties. Nanoemulsions of ethanolic extracts from the leaves of various plants have considerable potential in the utilization of natural ingredients. The solvent used serves as an important factor in the process. This literature review focuses on examining the ethanol extract from leaves of various plants. It aimed to review, study, and analyze the existing literature that addressed the characteristics of nanoemulsion preparations of ethanolic extracts derived from leaves of various plants, including things related to nanoemulsion components, methods for making nanoemulsions, and characteristics of nanoemulsion preparations. Using a database indexed literature review, this literature review was purported to ensure that the majority of the relevant studies were identified. The literature review of the widely used surfactants in a number of studies were Polysorbate 80 or Tween 80 surfactants. These surfactants were classified as non-ionic and non-irritating surfactants commonly used in pharmaceutical and cosmetic preparations. A number of researches used ultrasonification and microfluidation methods for making nanoemulsions, which could produce a minimum droplet diameter of nanoemulsion preparations ranging from 150 to 170 nm. The particle sizes in a number of studies ranged from 10.9 nm to 312.1 nm. The value of the polydispersity index in a number of previous studies ranged from 0.08 to 0.7, while the zeta potential value was above the number of +/- 30. Previous researches also revealed that the EE or adsorption value was above 80%, which indicated that the nanoemulsion characteristics of each study has met the requirements and can produce stable nanoemulsions.

Keywords: Nanoemulsion; Ethanol extract; Leaves; Characteristics

1. INTRODUCTION

There has been a growing use of nanotechnology in food and medicine. This technique offers many benefits including the ability to increase the bioavailability of nanoemulsion active ingredients, to assist in controlling the release of active ingredients, and to help improve sensory properties. Nanoemulsions belong to the emulsion subgroup with droplet sizes of 1-100 nm (Zhang et al., 2016). Nanoemulsions are increasingly popular in the chemical, pharmaceutical, cosmetic, and food industries due to their low standard of polydispersity, high dynamic stability, and transparency (Alvarado et al., 2015). Previous studies revealed that the submicro size of nanoemulsion can facilitate the absorption of the active substance from the small intestine wall, thereby increasing the bioavailability of the active substance. The formation of nanoemulsion preparations will also prevent the occurrence of creaming, flocculation, sedimentation and coalescence due to surface expansion resulting in increased free energy. Nanoemulsions can be formulated into several innovations, such as foams, creams, liquids, and sprays (Jusnita & Syurya, 2019). Nanoemulsion formulation also provides various advantages including increasing the bioavailability of pharmaceutical drug preparations, being non-toxic and not easily irritating, especially to the skin, and being able to increase the physical stability of the preparation.

Nanoemulsions also have a large surface area and high absorption due to their small size (Jaiswal et al., 2015).

The selected solvent for use in the extraction process is a determining factor in obtaining a good extraction and is able to produce the desired compounds containing pharmacological activity. Alcohol or a mixture of alcohol and water is an ideal solvent because it is capable of extracting most low-molecular weight compounds, such as saponins and flavonoids (Arifianti et al., 2014). One of the most common and widely used solvents in a number of laboratory studies is ethanol. Ethanol has a relatively high solubility, thereby it cannot react with other components or is inert. Ethanol has a low boiling point making it easier to separate the oil from the solvent during the distillation process (Susanti et al., 2012).

Similar study by Montes, et al (2017) only examined the general aspect of the physicochemical properties and stability of nanoemulsions. Sarmah, et al (2019) focused on the characteristics and identification of the use of nonionic surfactants, whereas Pavoni, et al (2020) had also conducted a research related to the formulation, preparation and stability of nanoemulsions using essential oils. Nonetheless, there was no research to address nanoemulsion preparations, especially nanoemulsions using ethanol extract on leaves and there were only few studies to evaluate the characteristics of nanoemulsions. Therefore, this study aims to review, study, and analyze the existing literature to address the properties of nanoemulsion preparations from ethanol extracts derived from leaves of various plants in terms of their nanoemulsion materials, manufacturing processes, and properties of nanoemulsion preparations. This study provides information on the characteristics of nanoemulsion preparations of ethanol extracts from various plants and will facilitate further researchers in making nanoemulsions of ethanol extracts from various plants.

2. METHOD

2.1. Research Design

Using literature review or narrative review, this study searched for published scientific literature indexed in various databases. Article searches were conducted through various databases to ensure the identification of the majority of relevant studies.

2.2. Inclusion Criteria

The inclusion criteria in this study were articles published from 2015-2020, articles written in English, articles available in full text, original articles, nanoemulsion articles of ethanol extract from leaves.

2.3. Exclusion Criteria

The exclusion criteria in the study were irrelevant articles, non-full-text articles, duplicated articles and review of articles.

2.4. Data Collection

2.4.1. Data source

Data were derived from articles and reports that were searched based on the research results and publication in national and international online journals. Articles were searched via Google Scholar and Science Direct.

2.4.2. Article Search Strategy

The first step is to search for articles on Google Scholar and Science Direct by entering the keywords "Formulation AND Nanoemulsion AND Extract Ethanol AND Leaves AND Characteristics", which obtained 79 articles. The collected articles were then screened to eliminate those that did not meet the inclusion criteria. The screening resulted in 8 articles from Google Scholar and 3 articles from Sciencedirect as shown in **Figure 1**.

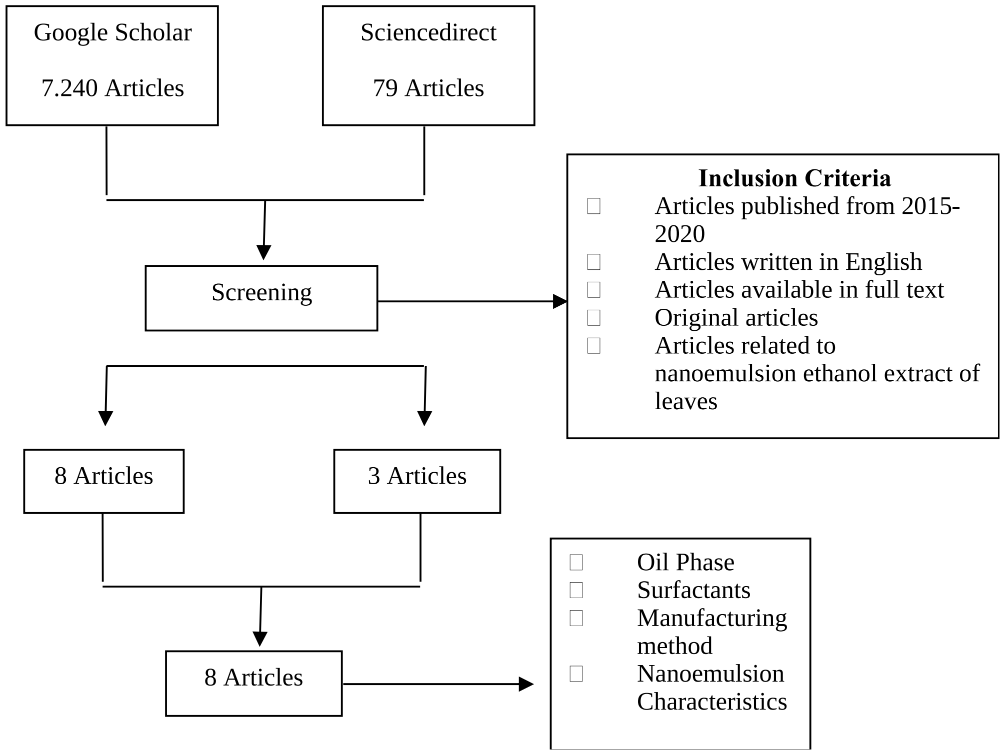

Figure 1. Data Collection

2.4.3. Article Extraction

Articles that met the inclusion criteria were collected and summarized in a table that describes their titles, oil phase, surfactant, manufacturing process and nanoemulsion properties, to be discussed and concluded. This article review was integrated into a table using the narrative review by grouping data taken from similar articles to answer the research objectives. Summaries of research papers were inserted in a table in alphabetical order, year of publication of the journal, and in a specific format by including title, oil phase, surfactant, method of preparation, and characteristics of the nanoemulsion. In subsequence, the summaries of the articles were analyzed in terms of their contents and research objectives to identify the similarities and differences between the articles.

3. RESULTS AND DISCUSSION

Nanoemulsion is one of the currently emerging technologies, especially in the food and pharmaceutical industry as a new delivery system for drugs and lipophilic materials such as flavours, colors, fatty acids and so on (Gadhave, 2014). Since nanoemulsions cannot be formed spontaneously, the role of mechanisms in nanoemulsion formulation is pivotal. Nanoemulsions consist of oil droplets in the nano-range size, between 10 to 100 nm, which are dispersed in an aqueous continuous phase, with each oil droplet surrounded by surfactant molecules.

The main components of nanoemulsion are oil, emulsifying agent, and water phase. The oil can be of any type such as castor oil, corn oil, coconut oil, evening primrose oil, flaxseed oil, mineral oil, olive oil, peanut oil, etc. A mixture of oil and water can produce a crude temporary emulsion which, if left unchecked, will separate in two distinct phases due to the incorporation of the dispersed droplets. Emulgens or emulsifying agents can provide stability to the system (Jaiswal et al., 2015).

This research examined formulation of w/o type nanoemulsion (water in oil) from leaf ethanol extract in various plants based on literature review. It began with article search and found 11 articles, which were relevant to the topic under study. These articles were analyzed in terms of their nanoemulsion components, nanoemulsion manufacturing methods, and nanoemulsion characteristics. The literature review of these articles is presented in **Table 1**.

Table 1. Literature Review of the Collected Scientific Articles

Titles	Oil Phase	Surfactant	Manufacturing Method	Nanoemulsion Characteristics	Author
Preparation of catechin extracts and nanoemulsions from green tea leaf waste and their inhibition effect on prostate cancer cell PC-3	lecithin	Tween 80	sonification	zeta potential particle size encapsulation efficiency	(Tsai & Chen, 2016)
Formulation and Characterization of Nanoemulsion of Tread leave Ethanol Extract (Catharanthus roseus (L.) G. Don) as Antihyperglycemic	Sesame oil	Tween 80	Stirring using a hot plate magnetic stirrer at a temperature of 700 C for 6 hours followed by 1 hour using sonification	Particle size	(Mariadi et al., 2019)
Optimization of Mangifera indica L. Kernel Extract-Loaded Nanoemulsions via Response Surface Methodology, Characterization, Stability, and Skin Permeation for Anti-Acne Cosmeceutical Application	Safflower oil	PEG 400	PIT	Particle size, zeta potential, and polydispersity	(Poomanee et al., 2020)
Evaluation of in vitro and in vivo safety of the by-product of Agave sisalana as a new cosmetic raw material: Development and clinical evaluation of a nanoemulsion to improve skin moisturizing	Caprylic/ Capri Triglyceride	Tween 80	Ultra sonification	Particle size zeta-potential	(Barreto et al., 2017)
Formulation of Nanoemulsion from Moringa oleifera Extract	Moringa leaf extract	Tween 80	homogenization	Droplet size	(Jusnita & Nasution, 2019)
Nina Application of nanotechnology in Eichhornia crassipes extracts	VCO	Tween 80 and Span 80	homogenization	Droplet size	(Limthin & Phromyothin, 2017)

Titles	Oil Phase	Surfactant	Manufacturing Method	Nanoemulsion Characteristics	Author
Optimization of Iranian golpar (Heracleum persicum) extract encapsulation using sage (Salvia macrosiphon) seed gum: chitosan as a wall material and its effect on the shelf life of soybean oil during storage	medium chain triglycerides	Tween 80 Vetec	high-pressure (HP) homogenization	Particle size, zeta potential, polydispersity, Encapsulation efficiency	(Di Maio et al., 2019)
Protective effect of the functional yogurt based on Malva parviflora leaves extract nanoemulsion on acetic acid-induced ulcerative colitis in rats	M. parviflora leaves extract	Tween 60	spontaneous emulsification method	Particle size	(El-Naggar et al., 2020)
Antioxidant Effect of Nanoemulsions Containing Extract of Achyrocline satureioides (Lam) D.C.—Asteraceae	Extract	lecithin	spontaneous emulsification	Particle size Zeta potential	(Zorzi et al., 2016)
Formulation and Stability Testing of Nanoemulsion Lotion Containing Centella asiatica Extract	Olive oil	Tween 80	High Pressure Homogenizer	Particle size Zeta potential	(Hanifah & Jufri, 2018)

3.1. Nanoemulsion Component

The nanoemulsion system must contain components that can increase the stability of the preparation. The components include surfactants and oils. Selection of materials such as oils and surfactants can affect the stability of nanoemulsion preparations (Ahsan et al., 2016). A review of several articles regarding nanoemulsion preparations stated that the most widely used surfactants were Polysorbate 80 or Tween 80. This result was in accordance with researches conducted by (Atun et al., 2020; Barreto et al., 2017; Di Maio et al., 2019; Hanifah & Jufri, 2018; Jusnita & Nasution, 2019; Limthin & Phromyothin, 2017; Mariadi et al., 2019; Tsai & Chen, 2016), which used a surfactant type Polysorbate 80 or Tween 80 in the formulation of nanoemulsion preparations, while (Poomanee et al., 2020; Zorzi et al., 2016) used Tween 60 and lecithin. Swardini (2019) mentioned the use of lecithin as a surfactant because lecithin is a non-toxic and non-irritant surfactant. Surfactants serve as an emulsifying agent with the aim of increasing the stability between the immiscible water and oil phases. In her research, Suzetti (2017) used Tween 20, Tween 60, and Tween 80, which are non-ionic non-irritating surfactants commonly used in pharmaceutical and cosmetic preparations.

Jaiswal et al., (2015) described that an emulsifier in addition to serving as emulsifying properties must be non-toxic and contain taste, odor and chemical stability that must be compatible with the product. Some desirable properties of an emulsifier are: (1) being able to reduce the surface tension to below 10 din/cm, (2) being rapidly adsorbed around the dispersed phase globules to form a complete and coherent film to prevent coalescence, (3) assisting in establishing adequate zeta potential and viscosity in the system so as to provide optimal stability, and (4) being effective in sufficiently low concentrations. Emulgens form monomolecular, multimolecular, or particulate films around the dispersed droplets.

The nanoemulsion formulation is able to reduce the size of the emulsion, which can produce a small droplet size. In addition, the nanoemulsion has a transparent or clear form, high bioavailability, and stability. Sundararajan et al (2018) mentioned that nanoemulsions are characterized by low thermodynamic stability with droplet sizes ranging from 20 to 200 nm. Similarly, Sundararajan et al. (2018) also mentioned that nanoemulsion preparation is highly dependent on surfactant concentration and is indirectly related to external exposure of droplet size and oil/water interfacial tension.

These articles used oil phase of vegetable origin, and thus the formation of nanoemulsions did not affect the difference in stability of the nanoemulsions. A research conducted Yuliani et al (2016) mentioned that nanoemulsion preparations with variations in vegetable oil did not show significant differences in globule size, pH, and viscosity. The oil phase in the presence of surfactants and cosurfactants can form droplets in the dispersion medium. The selection of the oil phase greatly affects the stability of the resulting nanoemulsion, and thus oils that have short to medium chains are more stable than long chains (Khor et al., 2014).

3.2. Preparation Method for Nanoemulsion

The making of nanoemulsions consists of several methods, including high energy emulsification and low energy emulsification. High energy emulsification comprises several methods, such as ultrasonic, microfluidation, high pressure homogenization and high energy stirring, while low pressure emulsification consists of point emulsification inverse, temperature inversion, and spontaneous emulsification. There are two techniques in the manufacture of nanoemulsions, namely spontaneous and non-spontaneous techniques. Spontaneous technique is carried out when the active substance, oil, surfactant, and cosurfactant are mixed automatically in a simple way using a magnetic stirrer. This technique produces a clear nanoemulsion, while the non-spontaneous technique is carried out when the spontaneous technique cannot produce a clear nanoemulsion by providing high energy from the outside to reduce the size of the particle dimensions of the substance as a way to produce a clear nanoemulsion (Suzetti, 2017).

Researches conducted by (Barreto et al., 2017; Di Maio et al., 2019; El-Naggar et al., 2020; Hanifah & Jufri, 2018; Limthin & Phromyothin, 2017; Mariadi et al., 2019; Tsai & Chen, 2016; Zorzi et al., 2016) used a high-pressure emulsification method. Modarres-Gheisari et al (2018) mentioned that the ultrasonification and microfluidation methods were able to produce nanoemulsion preparations with a minimum droplet diameter of 150 to 170 nm. This study explained that nanoemulsions with the microfluidation method produced better stability, but nanoemulsions with the ultrasonication method were superior because they were able to produce larger amounts of production and were also energy efficient. The ultrasonication method is an alternative method of non-thermal extraction that is more efficient, faster and allows a reduction in the use of solvents, resulting in pure extracts and higher yields compared to conventional extractions (Manasika & Widjanarko, 2015).

Previous researches conducted by (Jusnita & Syurya, 2019; Mazzarino et al., 2018) applied the homogenization method, where the high pressure homogenization method was considered very effective for providing several advantages, including low polydispersity and the better dispersion of formulations with high lipid concentrations. The dimensions of the resulting droplets depend on several aspects, including the type of homogenizer equipment used, the temperature of manufacture, the amount of energy and time, the oil concentration, the type of emulsifier or surfactant selected, and the physicochemical properties of the substance (viscosity and interfacial tension) (Hu et al., 2015) (Lee & McClements, 2010). The rotating speed used can produce nanoemulsions with an average particle size of less than 100nm. The longer the rotation and the higher the speed of the homogenizer, the smaller the nanoemulsion grain size, which is due to an increase in intermolecular contact. In other words, an increase in the force will further reduce the grain size produced (Jusnita & Nasution, 2019).

The manufacture of nanoemulsions with the low energy method is found in several articles including: (Atun et al., 2020; Poomanee et al., 2020; Zorzi et al., 2016) applying the low energy method in the process of making nanoemulsions. A research conducted by (Sundararajan et al., 2018) explained that the low energy method presented a small nanoemulsion droplet size of 200 nm on storage for 30 days with low polydispersity. Poomanee et al (2020) used the PIT method or phase inversion temperature, which was the most widely used method in the industry to produce nanoemulsions (Gadhave, 2014). The PIT method relies on changes in the solubility of non-ionic surfactants, resulting from changes in temperature. At low temperatures, the non-ionic surfactant head groups are highly hydrated, which favors the formation of O/W type nanoemulsions. As the temperature increases, these head groups become progressively dehydrated favoring the formation of the W/O nano nanoemulsion (Montes de Oca-Ávalos et al., 2017). The low and high energy methods can be improved by dissolving the oil phase in the solvent and adding an evaporation step. This combination of methods is very successful for protein stabilized emulsions (Montes de Oca-Ávalos et al., 2017).

3.3. Nanoemulsion Characteristics

A good and stable nanoemulsion can be seen from the test results of nanoemulsion preparations, along with the tests carried out to determine the characteristics of the nanoemulsion including particle size, polydispersity index or PDI, zeta potential and EE or adsorption. A good and stable nanoemulsion preparation has a particle size of < 100 nm (Koroleva & Yurtov, 2012). Kamea (2019) revealed that the polydispersity index or PDI of 0.08-0.7 was the upper range in which the distribution algorithm operated best, while the potential zeta value was above (+/-) 30 mV (Yuliasari et al., 2014) and the higher the EE or adsorption value, the more stable the nanoemulsion.

Nanoemulsions have the characteristics of a very small droplet size so that it looks transparent when seen with the naked eye. The larger the droplet size, the more it becomes non transparent (Herbianto, 2018). From the literature review, it was clear that 5 articles produced nanoemulsions with particle sizes of < 100 nm. A research conducted by Jusnita & Nasution (2019) was able to produce an average nanoemulsion particle size of less than 100 nm. Meanwhile, Mariadi et al Mariadi et al (2019) produced a smaller and more homogeneous globule size with the percentage of nanoemulsion size distribution being 97.2% below <500. **Table 2** show the nanoemulsion characteristics.

PDI testing aims to determine the size of the molecular mass distribution system in a particular sample. If the resulting value is close to zero, the distribution is getting better (Hidayati, 2020). The PI that lies in the range of 0.01-0.7 indicates that the particle size is distributed as monodispersion (Suzetti, 2017). In this line, Dewandari et al (2019) stated that an IP value that is smaller than 0.3 or close to 0 is an indication of the test sample having a narrow distribution system and showing a uniform nanoparticle formula, while the polydispersity index which produces a higher number greater than 0.5 indicates that the sample has a wider particle size distribution system. On this basis, it is conclusive that the lower the measured value of particle uniformity, the higher its heterogeneity. The PDI test in the study of Poomanee et al (2020) resulted in 0.16 ± 0.02. PDI decreased due to increased cocoon of glyceryl HLB and PEG. As the surfactant concentration increases, the PDI then decreases. In the research of Atun et al (2020), the PDI test resulted in a polydispersity index value between 0.1 to 0.4. The low polydispersity index value highlighted that the formulated dispersion system is more stable for a long period of time. On the polydispersity index test that had been carried out with the aim of indicating the uniformity of droplet size in nanoemulsions, Listyorini et al (2018) mentioned that the lower the polydispersity index, the more homogenous the droplet size in the nanoemulsion.

Table 2. Nanoemulsion Characteristics

Author	Nanoemulsion Characteristics
(Tsai & Chen, 2016)	Zeta potential: a highly stable nanoemulsion can be achieved when the zeta potential is 0.30 mv or, -30 mv due to the high electrostatic repulsion between the particles. The zeta potential of the nanoemulsion is -66.3 ± 1.1 mv, implying much higher stability Particle Size: 11.4 nm, 10.9 nm and 11.2 nm EE: The adsorption of cathecin nanoemulsion after day 0 and day 120 of storage was 88.1% and 86.2%, respectively.
(Mariadi et al., 2019)	Particle size: using the Particle Size Analyzer (Fritsch Analysettee 22 NanoTec). sesame oil) gave smaller and more homogeneous globule size and the percentage of nanoemulsion size distribution was 97.2% under <500 nm
(Poomanee et al., 2020)	Particle size: sesame oil nanoemulsion has a size of 20 nm Zeta potential: 20.47 mV Polydispersity: PDI of 0.16 ± 0.02. PDI decreased due to increased cocoon of glyceryl HLB and PEG. As the surfactant concentration increases, the PDI then decreases.
(Barreto et al., 2017)	Droplet size: droplet size was tested using a Dynamic Light Scattering (DLS) (Malvern, United Kingdom) at 25 °C. Nanoemulsion showed droplet size with an average of 83 nm-155 nm Zeta potential: The zeta potential of the nanoemulsions was measured by light scattering phase analysis, (Malvern, United Kingdom) at 25 °C.
(Jusnita & Nasution, 2019)	Droplet size: Moringa leaf extract nanoemulsion at a concentration of 20% produced a grain size of 7.9 nm and at a concentration of 30% obtained a particle size of 26.2 nm
(Atun et al., 2020)	Particle size: quercetin nanoemulsion has a particle size of 10.2 to 36.5 nm Zeta potential: -1.8 to 11.9 mV (p 0.05) Polydispersity: the polydispersity index value is between 0.1 to 0.4. A low polydispersity index value indicates that the dispersion system formed is more stable for a long period of time
(Limthin & Phromyothin, 2017)	Particle size: particle size at 60 minutes with a stirring speed of 2000 rpm produces nanoemulsions with a size of 302.1 nm, while at a speed of 4000 rpm at 60 minutes produces nanoemulsions with a size of 312.7 nm
(Di Maio et al., 2019)	Particle size: 5% concentration (181.7 ± 1.85b), 10% concentration (175.6 ± 1.11c), 15% concentration (166.7 ± 0.41d) Zeta potential: 5% concentration (- 35.30 ± 1.48b), 10% concentration (- 40.03 ± 2.06c), 15% concentration (- 38.60 ± 0.26c). Polydispersity: polydispersity index (0.138–0.156) PDI value lower than 0.2 indicates that the particles in the nanoemulsion are monodisperse EE: 85.6%
(El-Naggar et al., 2020)	Particle size: nanoemulsion of M. parvifora leaf extract is 67 nm
(Zorzi et al., 2016)	Particle size: 172.5 – 300 nm
(Hanifah & Jufri, 2018)	Particle size: The average particle size of nanoemulsion was 19.88 ± 2.3 nm and nanoemulsion in lotion was 198.4 ± 11.52 nm

Zeta potential is one of the important parameters regarding permeation properties of drug delivery systems through physiological barriers such as mucus and cell membranes (Zaichik et al., 2020). In the research of Tsai & Chen (2016), highly stable nanoemulsions could be achieved when the zeta potential was 0.30 mv or, -30 mv due to the high electrostatic repulsion between particles. A study conducted by Atun et al (2020) stated that nanoemulsions with zeta potential values above 30 mV or below -30 mV were able to show a more stable colloidal system. Therefore, large particle loads could prevent particle aggregation based on Zeta electrostatic repulsion strength potential of the nanoemulsion of -66.3 ± 1.1 mv, implying much higher stability. Meanwhile, a research by Poomanee et al. (2020) obtained a zeta potential of -20.47 mV. Suzetti (2017) in her research stated that the test results obtained a potential zeta charge value of -30.12 mV. Thus, at a storage time of 1 month the potential zeta value changed to 0.1 mV, in which the value close to 0 would have the potential to form aggregates, so that the value become uncharged.

Testing the absorption of active substances in preparations is essential, especially in drug delivery systems, but it is also an important factor for industries that use active substances at relatively expensive costs (Wang et al., 2018). Encapsulation methods have been developed with the aim of protecting bioactive components, such as polyphenols, micronutrients, enzymes, and antioxidants obtained from adverse environments and accompanied by controlling release at the intended target (Dewandari et al., 2019). The study of Tsai & Chen (2016) stated that the adsorption of cathecin nanoemulsions after day 0 and day 120 of storage was 88.1% and 86.2% respectively. The greater the adsorption efficiency, the better the nanoemulsion system (Rahmaniyah, 2018). The literature review of several articles found that the EE results or adsorption were in accordance with the provisions so as to produce good and stable nanoemulsions.

4. CONCLUSION

From the literature review of 80 articles, it can be ascertained that the most widely used surfactant in the pharmaceutical industry is Polysorbate 80 or tween in the type of non-ionic surfactant. This type of surfactant is also non-irritating and is commonly used in the manufacture of pharmaceutical and cosmetic preparations, and thus the use of nonionic surfactants is more certain. The most frequently applied method of making nanoemulsions in the manufacture of nanoemulsions is homogenization, which is able to produce the smallest size up to 7.9 nm. The examination on particle size on these articles revealed that the particle sizes ranged from 7.9 nm – 312.1 nm. The polydispersity index produced a range of 0.08, while the measurement of the zeta potential resulted in a value above +/-30. The EE in some articles indicated a value above 80%, which ensures that the nanoemulsion characteristics of each article meet the requirements and produce a stable nanoemulsion. On this basis, it is recommended to do further research and further reviews on the good type of formulation in terms of physicochemical and pharmacokinetic aspects.

5. ACKNOWLEDGEMENT

Grateful acknowledgement is made to the University of Muhammadiyah Magelang for supporting the implementation of this research.

6. CONFLICT OF INTEREST

The author declares that there are no competing conflicts of interest.

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