HASIL CEK_Development of black cumin seed oil (Nigella sativa L.) SNEDDS into solid-SNEDDS and its characterization

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Submission date: 25-Nov-2021 08:30AM (UTC+0700)
Submission ID: 1712324890
File name: 60010299_Dwi_Utami.pdf (361.26K)
Word count: 4597
Character count: 24836

Pharmaciana
Vol.11, No.2, July 2021, Page. 203-212
ISSN: 2088 4559; e-ISSN: 2477 0256
DOI: 10.12928/pharmaciana.v11i2.18230

Development of black cumin seed oil (*Nigella sativa L.)* SNEDDS into solid-SNEDDS and its characterization

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Submitted: 18-10-2020 ***Reviewed: 20-01-2021*** ***Accepted: 22-07-2021***

ABSTRACT

Black cumin seed oil (MBJH) (*Nigella sativa L.*) is a well-known herb with pharmacology activities such as anticancer and anti-thrombocytopenia. The limitation of MBJH has poor absorption when using oral dosage form. The liquid SNEDDS (Self-nanoemulsifying drug delivery system) of MBJH as an alternative formulation. However, the disadvantage of liquid-SNEDDS of MJBH was the interaction between the active ingredients with soft gelatin capsules. Hence, this study proposed to develop solid-SNEDDS as a new formulation of MBJH. Solid-SNEDDS of MBJH was prepared from liquid-SEDDS of MBJH by adsorption to solid carrier method, consisting of aerosil and crospovidone as the adsorbent. The characterization of S-SNEDDS was determined by emulsification time and percent transmittance. Micromeritics properties of S-SNEDDS such as the angle of repose, bulk and tap density parameter, compressibility index, and Hausner ratio were measured before and after stored in stress condition (40˚C ± 2˚C and relative humidity of 75% ± 5% for 14 days). The result showed S-SNEDDS of MBJH with aerosil absorbent had better S-SNEDDS performance in both characteristics and micromeritics properties under stress conditions than crospovidone absorbent. In conclusion, the s-SNEDDS of black cumin oil by solid aerosil carrier method is promising for future research development of S-SNEDDS dosage form.

Keywords: black cumin seed oil, SNEDDS, S-SNEDDS, characterization, micromeritics properties

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INTRODUCTION

Black cumin seed oil (BCSO) or *Minyak Biji Jinten Hitam* (MBJH), is known as herbs with antihypertensive, antidiabetic, anticancer, analgesic, immunomodulatory, antimicrobial, anti-inflammatory, and antioxidant properties (Santoso and Suryanto, 2017; Wahyuningsih and Putranti, 2015; Ahmad et al., 2013). Thymoquinone, which is the largest active component in MBJH, responds to Black cumin seed oil (Anlar and Bacanli., 2020). Unfortunately, Thymoquinone has had the stability problem in aqueous solutions and revealed the rapid degradation in several media such as water, acid, and phosphate buffer (Salamani et al., 2014). As the major component in Black cumin seed, MBJH also has the solubility and stability problem in water and liquid media that impact uncertain bioavailability (Alwadei et al., 2019). One of the strategies to improve the active compound's solubility and stability problem is a lipid and surfactants-based formulation, particularly self-emulsifying (Obitte et al., 2014).

Self-nano emulsifying drug delivery systems (SNEDDS) is a self-emulsifying formulation system with several advantages: improving drug dissolution, reducing dissolution time, and facilitating the dissolved phase (Umeyor, 2016). SNEDDS is an isotropic mixture of oil, surfactant, cosurfactant, and drug in the form of a fine oil-in-water nano emulsion when put in the water phase with light stirring. SNEDDS spreads easily in the gastrointestinal tract, and gastric and intestinal motility provides the necessary agitation for spontaneous emulsification (Patel et al., 2010). Conventional SNEDDS is usually made in the form of a liquid introduced in soft gelatin capsules. It has several disadvantages, such as high production costs, incompatibility with capsule shells, low stability,and irreversible drug deposition. (Nasr et al., 2016; Yi et al., 2008).

Recently, S-SNEDDS has become an alternative formulation technology in increasing the bioavailability of oral drugs with low solubility. The S-SNEDDS system combines the SNEDDS liquid form's advantages in the solid dosage form, overcoming the liquid formula's limitations. S-SNEDDS also has advantages, for example, low production costs and high patient acceptability (Nasr et al., 2016).

Several methods have been used to convert liquid SNEDDS to S-SNEDDS, such as adsorption to the solid carrier, spray drying, freeze-drying, and melt granulation. The simplest method for S-SNEDDS preparation is adsorption to a solid carrier. This method has several advantages: an easy way for preparation, inexpensive, easy to optimize, and industrially scalable. This method can also be used on materials that unresistant to heating (Kuruvila et al., 2017). In this study, aerosil (AE) and crospovidone (CR) were used as solid carriers in the S-SNEDSS formulation. Aerosil was used as a solid carrier in the S-SNEDDS formulation of lutein to produce a nanoemulsion with a droplet size of 90 nm. It has a fine article morphology without crystalline form. This indicates the complete adsorption of S-SNEDDS lutein into the aerosil pore. Crospovidone has a very porous structure that can adsorb drugs and does not form a gel when it comes into contact with water to speed up the disintegration time. Reddy and Srayavanthi (2017) were using crospovidone in the S-SNEDDS formulation of atorvastatin, and the result showed a droplet size of 36.22 nm.

Regarding to the development of MBJH in S-SNEDSS formulation, we performed the study of S-SNEDDS preparation by using aerosil and crospovidone as the absorbent and determined its characterization from emulsification time and percent transmittance. This study evaluated the micromeritics properties of S-SNEDSS before and after stored in stress conditions as part of a S-SNEDSS dosage form of black cumin seed oil development.

MATERIAL AND METHOD

Material

The black cumin oil (MBJH) was ordered from CV. Lansida Herbal Yogyakarta). Other materials such as tween 80 and glyserol were purchased from Brataco. Aerosil 200 and crospovidone were ordered from Merck. The equipments that have been used in this study were the analytical balance (Ohaus PA21), vortex (Thermolyne Type 16700 Mixer), micro pipet (Socorex Acura 825),

hotplate stirrer (Thermo Scientificcimarec Hot Plate Stirrer SP131325), *ultrasonic*, and UV-visible spectrophotometry (Shimadzu).

Method

Preparation and characterization of SNEDDS

The SNEDDS was prepared by Iswari's (2016) method. The stoppered glass vials containing MBJH (13 %), tween 80 (52%), and glycerol (35%), shake on a vortex mixer for 5 min to ensure complete mixing followed by sonification for 1 hour.

Emulsification time

Self-emulsifying properties of SNEDDS formulation were determined by visual assessment. The emulsification time was determined by dispersing 0.1 mL of SNEDDS MBJH in 5 mL of aquadest, followed by mixing in a vortex mixer (2000 rpm) for 30 sec at room temperature to attain homogenization. The time required for the forming of homogenous emulsion of SNEDDS was recorded (Wahyuningsih and Putranti, 2015).

Transmittance

The percent transmittance of the emulsion formulations was determined by measuring the absorbances by spectrophotometry (Shimadzu UV-visible spectrophotometer) within 650 nm and aquadest as blank.

Preparation and characterization of S-SNEDDS

The solid self-emulsifying powder was prepared based on Chavda et al. (2013) with some modifications. An amount of 4 mL of liquid SNEDDS of MBJH was added and mixed vigorously with crospovidone or aerosil in the mortar until it became free-flowing. aerosil or crospovidone as absorbent was added gradually to achieve free-flowing powder.

Time emulsification

The emulsification time of S-SNEDDS was determined by solving 1 part of *solid* SNEDDS (equal to 72 mg) in 500 mL of aquadest with gentle agitation by using a magnetic stirrer within 500 rpm at room temperature. The time required for the complete disappearance of S-SNEDDS was recorded (Chavda et al., 2013).

Transmittance

Percent transmittance of prepared emulsion of S-SNEDDS as stated in preparation of emulsion in time emulsification measurement, was determined spectrophotometrically by Shimadzu UV-visible spectrophotometer at 650 nm and using aquadest as blank (Shanmugam et al., 2011).

Micromiretic properties of S-SNEDDS

Angle of repose

The angle of repose was determined by the funnel method. The accurately weighed 5 g S-SNEDDS powder was allowed to flow freely through the funnel's 4 cm onto the surface. The diameter of the powder cone was measured, and the angle of repose (θ) calculated using the following equation (1) (Reddy et al., 2015):

$$Tan\ \theta = \frac{h}{r} \quad (1)$$

where h = height of the heap, r = radius of the heap

Bulk and tapped density

A quantity of 2 g of solid SNEDDS powder was accurately weighed, introduced into 10 ml measuring cylinder, and observed the initial volume (Vo). The cylinder was tapped 500 times until no further change in volume (V). The Bulk Density (BD) and Tapped Density (TD) were calculated using the following equation (Kuruvila et al., 2017):

$$BD = \frac{Weight\ of\ Powder}{Vo} \quad (2)$$

$$TD = \frac{Weight\ of\ Powder}{V} \quad (3)$$

Compressibility index

Carr's compressibility index determined the compressibility of the S-SNEDDS in the following equation (Nasr et al., 2016):

$$Carr's\ compressibility\ index\ (\%) = \frac{TD - BD}{TD} x\ 100\% \quad (4)$$

Hausner ratio

The Hausner ratio is the ratio of tapped density to the bulk density that presents powder particles' flow character. The Hausner ratio was calculated as follow: (Reddy et al., 2015):

$$Hausner\ ratio = \frac{TD}{BD} \quad (5)$$

Stress testing

The S-SNEDDS powder was stored in the climatic chamber (Binder GmbH, Tuttlingen, Germany) at a temperature of 40˚C ± 2˚C and relative humidity of 75% ± 5% for 14 days. The characterization and micromeritics properties of S-SNEED were measured at the end of stress observations (ICH, 2003).

Droplet size

To evaluate S-SNEDDS aerosol and crospovidone as a solid carrier by measured droplet size and polydispersity index (PDI). Droplet size and PDI was measured by particle size analyzer (PSA). Testing was conducted in the FMIPA UII laboratory, Yogyakarta.

RESULT AND DISCUSSION

Preparation and characterization of SNEDDS

The Black cumin (MJBH) SNEDDS was prepared from a mixture of 13% MBJH, 52% tween 80, and 35% glycerol (Iswari, 2016). The characterization of SNEDSS was determined by emulsification time and transmittance. Several requirements for the nanoemulsion product by SNEDDS were clear, had an O/W nanoemulsion type, the percent transmittance value was up to to 100%, and the formation time of the nanoemulsion was less than one minute (Chavda et al., 2013; Kuruvila et al., 2017).

Table 1. The emulsification time and transmittance of SNEDDS MBJH

Parameter	R1	R2	R3	$\bar{x}$ ± SD
Emulsification time (sec)	27	30	29	28.67 ± 1,53
Clarity	Clear	Clear	Clear	Clear
Transmittance (%)	96.59	96.73	95.80	96.37 ± 0.50

As shown in Table 1, the emulsification time was less than 1 min and met the SNEDDS requirement (Kuruvila et al., 2017). The short emulsification time is mediated by surfactants and cosurfactants, which can immediately form the interface layer of oil and water. The mechanism of

action of cosurfactants is to create empty spaces between the surfactants; therefore, they can be formed rapid nanoemulsions due to their high fluidity. Cosurfactants with longer hydrophobic alkyl chains will more easily speed up the emulsification time (Wahyuningsih and Putranti, 2015). The results obtained by the transmittance parameter on the SNEDDS sample were 96.37 ± 0.50%. This test's results have met the requirements for the transmittance value on SNEDDS, close to a value of 100% (Chavda et al., 2013). Based on the assessment of emulsification time and percent transmittance, it was qualified for the conversion of the liquid SNEDDS of MJBH to solid SNEDDS by using an adsorbent.

Preparation and characterization of Solid-SNEDDS

The preparation of S-SNEDDS MBJH was carried out using the adsorption to solid carrier technique with aerosil and crospovidone as the adsorbents, which can absorb large amounts of self-emulsification formulations and the qualified flow properties powder (Gupta et al., 2013). This method was the simplest one, resulting in a uniformity of powder size, and adsorbed up to 70% w / w with the appropriate carrier (Katteboina et al., 2019). One ml liquid SNEDDS required 300 mg of aerosil as an adsorbent to create the free-flowing form of S-SNEDDS, while crospovidone as an adsorbent required 625 mg. This result revealed that aerosil as an adsorbent more efficient compares with crospovidone.

The characterization of S-SNEDDS MBJH were performed by emulsification time and transmittance and also micromiretic properties. The summarized of its characterization was shown in Table 2.

Table 2. The self emulsification and micromeritic properties of S-SNEDDS MBJH aerosil and crospovidone day-0 and day-14

Parameter	S-SNEDDS Aerosil		S-SNEDDS Crospovidone	
	Day-0	Day-14	Day-0	Day-14
Emulsification time (sec)	8.0 ± 1.00	7.67 ± 1.53	19.33 ± 2.52	18.33 ± 1.53
Transmittance (%)	96.05 ± 0.2	96.31 ± 0.51	92.70 ± 0.35	92.75 ± 0.54
Angle of repose (^{0})	30.96 ± 0.31	29.89 ± 0,93	43.15 ± 0.55	42.61 ± 1.17
Bulk Density (g/mL)	0.44 ± 0.12	0.34 ± 0.01	0.23 ± 0.01	0.28 ± 0.04
Tapped Density (g/mL)	0.52 ± 0.15	0.40 ± 0.01	0.33 ± 0.01	0.39 ± 0.05
Carr index (%)	16.39 ± 0.84	15.90 ± 1.03	31.93 ± 0.24	28.68 ± 0.38
Hausner ratio	1.20 ± 0.01	1.19 ± 0.01	1.48 ± 0.01	1.40 ± 0.01

The MBJH S-SNEDDS characterization included emulsification time and transmittance. This test was carried out on the 0th and 14th day, and the 0th-day test was carried out after the S-SNEDDS was completed. Regarding stress testing, the test was carried out after the 14th day the sample inserted into the temperature of the climatic chamber by 40˚C ± 2˚C and humidity relative 75% ± 5%. The emulsification time and transmittance of the MBJH S-SNEDDS with aerosil and crospovidone dryers are presented in Table 2.

Based on the result of emulsification time and transmittance of S-SNEDDS with aerosil and crospovidone in Table 2, the aerosil adsorbent's characterization was better than the crospovidone adsorbent. The emulsification time of S-SNEDDS by using aerosil absorbent was only 8 ± 1.00 sec compared to S-SNEDDS by using crospovidone absorbent that was 19.33 ± 2.52 sec. The aerosil absorbent has a high specific surface area than the crospovidone absorbent, therefore the less time required to form a stable emulsion. The high specific surface area of absorbent will enriched at the oil/water interfaces formation and stabilize the oil droplets (Alkotzer et al, 2019)

The emulsification time of S-SNEDDS with aerosil and crospovidone adsorbent on the 0th day was 8 seconds and 19.33 seconds, and the 14th day was 7.67 seconds and 18.33 seconds. The percent transmittance of S-SNEDDS aerosil and crospovidone adsorbent on day 0 was 96.05% and 92.70%, and on day 14 were 96.31% and 92.75%. After the 14th day of storage in the climatic chamber. Two-way ANOVA as a statistical test was used to compare the characteristic of S-SNEDDS. There were no

significant changes (p>0,05) in the characteristics of both S-SNEDDS by using aerosil and crospovidone adsorbent in stress conditions. This result indicated the stability of both S-SNEDDS in stress conditions and the potential to be developed as the S-SNEDDS dosage form. Moreover, the micromeritrics properties evaluation of new solid material is important, particularly in solid-state development. Therefore, we continued the research in micromeritics properties of S-SNEDDS involved angle of repose, bulk density and tapped density, and Hausner ratio.

Micromiretic properties of s-SNEDDS

The micromeritics properties of S-SNEDDS powders were carried out on day 0 and day 14, covered by the angle of repose, bulk density and tapped density, and Hausner ratio evaluations. Table 2 presented the angle of repose parameter test results in the S-SNEDDS sample with aerosil and crospovidone as the adsorbent on the 0th day were 30.96 30 and 43.15 and on the 14th day were 29.89, and 42.61^0. The angle of repose test results from the S-SNEDDS aerosil adsorbent on the 0th day met the acceptance requirements by 20-40° (Kuruvila et al., 2017). S-SNEDDS with crospovidone as the adsorbent does not meet the criteria because it had a value > 40°. This angle of repose test shows the flow properties of the S-SNEDDS powder produced. The S-SNEDDS, an erosive adsorbent, has good flow properties, while the S-SNEDDS crospovidone adsorbent has poor flow properties. On day 14, the aerosil adsorbent S-SNEDDS powder did not change significantly compared to the 0th day, while the crospovidone adsorbent S-SNEDDS powder showed a change in value that was smaller than on day 0.

The S-SNEDDS crospovidone powder's consistency tends to be wetter than the aerosil S-SNEDDS. The ability to bind to moisture is lower than the aerosil. When stored in a higher temperature (climatic chamber), the powder is drier and has slightly better flow properties than before. In S-SNEDDS powder, the aerosil adsorbent has good flow properties because of its properties, which have the advantages of high moisture-binding ability and the ability to overcome particles' stickiness one another, thereby reducing friction between particles and being able to maintain good flowability.

Meanwhile, in the bulk density and tap density evaluations, the S-SNEDDS sample with aerosil and crospovidone adsorbent on day 0 was 0.44 g/mL and 0.23 g/mL day 14 were 0.34 g/mL and 0.28. g/mL. The results of tapped density in the S-SNEDDS aerosil and crospovidone adsorbent samples on day 0 were 0.52 g/mL and 0.33 g/mL and on day 14 were 0.40 g/mL and 0.39 g/mL. The compressibility index results on the S-SNEDDS sample with aerosil and crospovidone adsorbent on day 0 were 16.39% and 31.93%, and on day 14 were 15.90% and 28.68%. The compressibility index results of the S-SNEDDS aerosil adsorbent on the 0th day met the acceptance requirements, namely <25% (Kuruvila et al., 2017). The S-SNEDDS crospovidone adsorbent was disstatisfy the requirements because it had a value of> 25%. The compressibility index test shows that the S-SNEDDS aerosil adsorbent powder has good flow properties, while the S-SNEDDS crospovidone powder has poor flow properties. The S-SNEDDS aerosil adsorbent is easier to produce the free-flowing powder than S-SNEDDS crospovidone adsorbent, which is more difficult to produce free-flowing and tends to be cohesive and difficult to flow. On day 14, there were no significant changes in the bulk and tap density of aerosil absorbent S-SNEDDS powder, but there was a decrease in the crospovidone adsorbent. Therefore, in micromeritics evaluation, the aerosil absorbent S-SNEDDS of MBJH had better quality than crospovidone absorbent S-SNEDDS.

The compressibility index and Hausner ratio of S-SNEDDS aerosil and crospovidone were presented in Table 2. As showed in Table 2, the Hausner ratio of aerosil and crospovidone adsorbent S-SNEDDS on the 0 days were 1.20 and 1.48, and the 14th day were 1.19 and 1.40. Based on the result, the Hausner ratio of the S-SNEDDS aerosil adsorbent on days 0 and 14 met the acceptance requirements by <1.25 (Kuruvila et al., 2017), while the S-SNEDDS with crospovidone as the adsorbent does not meet the criteria (> 1.25). The result of the Hausner ratio value >1.25 showed S-SNEDDS have better powder flow properties while the Hausner ratio value <1,25 showed poor

powder flow properties. These powder flow properties will have an impact when S-SNEDDS is formulated into a tablet or capsule.

Table 3. Droplet size and PDI of S-SNEDDS MBJH aerosil and crospovidone

Parameter	AE	CR
Droplet size (nm)	193.8	243.7
PDI	0.122	0.291

The droplet size and PDI of S-SNEDDS aerosil and crospovidone were presented in Table 3. The particle size of *solid*-SNEDDS with aerosol as an adsorbent is 193.8 nm, and droplet size with crospovidone as an adsorbent is 243.7 nm. The smaller droplet size will expand the surface contact area of the droplet with gastric fluid. Therefore drug releases way faster than the bigger droplet size (Heshmati et al., 2013), the smaller particle size will then make it easier for the drug to reach the target cells.

The polydispersity index (PDI) is the standard deviation value from the average particle size, which indicates the uniformity of the nanoemulsion size. The polydispersity index in S-SNEDDS with aerosol as an adsorbent is 0.122. In comparison, polydispersity index pada S-SNEDDS crospovidone as an adsorbent is 0.291. PDI value less than one showed uniformity of the nanoemulsion size was created. S-SNEDD with aerosil as an adsorbent in this study showed a better droplet size and polydispersity index.

Finally, the micromeritics properties evaluation of S-SNEDDS MBJH aerosil and crospovidone as the absorbent, as summarized in Table 2. It showed micromeritics properties of aerosil adsorbent were better than crospovidone as the adsorbent. The S-SNEDD of MBJH by using aerosil as the absorbent also revealed the robustness of powder in stress condition (40˚ C ± 2˚ C with humidity relative 75% ± 5%). These study results depicted the new promising solid SNEDDS of black cumin oil and potentially in further solid-state material development.

CONCLUSION

The black cumin oil was successfully developed as S-SNEDDS formulation using aerosil and crospovidone adsorbents as solid absorbents. The black cumin oil S-SNEDDS using aerosil adsorbent had better characteristics, flow properties, and stability at temperature changes than S-SNEDDS with crospovidone adsorbent.

ACKNOWLEDGMENT

This research was supported by the Ministry of Research, Technology, and Higher Education through the master thesis grant scheme in 2020.

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