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Formulation and Characterization of Solid Self Nano Emulsifying Drug Delivery System (S-SNEDDS) Loading Curcuma Extract

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ABSTRACT: *Curcuma* has an active component that is poorly soluble in water, resulting in limited absorption and bioavailability. Liquid Self Nano Emulsifying Drug Delivery System (SNEDDS) dosage formulations can improve its solubility and absorption due to its small particle size. Solid SNEDDS technology significantly overcomes some of problems in liquid SNEDDS preparations to improve the stability of liquid formulations. This study aims to formulate and characterize *Curcuma* S-SNEDDS preparation. SNEDDS was characterized by particle size and thermodynamic tests. The S-SNEDDS was prepared by using of porous compounds and spray drying. Characterization of the S-SNEDDS was performed using infrared spectra, X-ray diffraction, scanning electron microscopy, microbial contamination and particle flow properties. Method of making S-SNEDDS uses two ways, absorption of porous compounds and spray drying. S-SNEDDS were characterized by testing infrared spectra, X-ray diffraction, scanning electron microscopy, microbial contamination and particle flow properties. Optimal S-SNEDDS formulation with 2 formulas namely F7 and F11 mannitol carrier. FTIR testing showed no interacting compounds. SEM and X-ray diffraction testing of F7 showed that the preparation was semicrystalline. While F11 described the preparation as much more crystalline due to the high content of mannitol. The microbial contamination test detected no microorganism compounds. In addition, the particle flow properties obtained a result of 02.53 seconds with a height of 24.95 mm. It is concluded that the S-SNEDDS formula F7 of *Curcuma* has preparation criteria.

Keywords: **curcuma; liquid SNEDDS; S-SNEDDS; characterization.**

Introduction

Curcuma xanthorrhiza is widely grown in Indonesia and the world, is used as food and traditional medicine, and has clinical effects such as The main compound in *Curcuma xanthorrhiza* is *xanthorrhizol*, widely used as a bioactive ingredient. It has been widely reported that *Curcuma xanthorrhiza* has disadvantages such as quite sharp taste and odor, difficulty in dissolving in water, and low bioavailability. The characteristics possessed by *Curcuma xanthorrhiza* can be overcome with nanotechnology innovation, namely the Self Nano-Emulsifying Drug Delivery System (SNEDDS). Previously, it has been reported that the formulation study of liquid Self Nano-Emulsifying System (SNES) of *Curcuma xanthorrhiza* extract [1].

Drug development utilizing natural material has been widely done, such as the Self Nano-Emulsifying Drug Delivery System (SNEDDS) with nanometer-scale droplet size, and has been shown to increase bioavailability. Increasing the bioavailability and efficacy of drugs are formulations that use lipid carriers to produce emulsifying properties that can form clear solutions when dripped in water. SNEDDS preparations have the advantage of being better than other lipid carriers. They can be absorbed through the lymphatic pathway to avoid first-pass effects and change the droplets to be more easily absorbed by body fluids [2,3].

SNEDDS preparations produce oil-in-water nanoemulsions with droplet sizes of <100 nm. Droplet size influences drug release, absorption, and stability [4]. However, liquid SNEDDS has limitations such as leakage and incompatibility of capsule shells and unpleasant odor from oil to have sediment. Solid SNEDDS is one of the latest dosage forms capable of improving oil loading efficiency, reducing process failures, using simple formulation

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techniques, and rapidly transforming powder formulations to oral solid doses [5]. Research on the use of solid SNEDDS has been carried out on Curcumin compounds combined with lansoprazole, which can increase the effectiveness and stability of drug formulations and develop more effective products [6]. Considering the promising properties of *Curcuma xanthorrhiza* extract, it is necessary to study the development of SNEDDS into a solid form of SNEDDS that can improve the stability of nanoemulsion systems. This study aims to formulate *Curcuma xanthorrhiza* extract into a solid SNEDDS preparation that meets the characteristics of natural nanotechnology to be developed in Indonesia.

Methods

Materials

The materials used in this study consisted of *Curcuma xanthorrhiza* Roxb. Extract, tween 20 (Brataco, Indonesia), labral (Gattefosse, France), mannitol (Shijiazhuang, China), lactose (Hilmar Ingredient, AS), aerosil, maltodextrin, neusilin, magnesium stearate (Sigma-Aldrich, Netherlands), polyvinyl alcohol (PVA) (Sigma-Aldrich, Netherlands), sodium carboxymethyl cellulose (Na-CMC), β-cyclodextrin (Roquette, Indonesia), 70% alcohol, and distilled water.

Preparation of Liquid SNEDDS

SNEDDS preparation was carried out by mixing the ingredients, namely *Curcuma xanthorrhiza* extract, tween 20 and labrasol and then homogenized with the help of an ultrasonicator (Model 300 V/T, USA) and put into a container.

Curcuma xanthorrhiza extract, tween 20 and labral, and then homogenizing them with an ultrasonicator (Model 300 V/T, USA) and putting them into a container.

Preparation of Solid SNEDDS

Porous Compound Adsorption Method

Adsorption onto inorganic silica materials with high surface area has been commonly used to condense liquid SNEDDS into a free-flowing powder. The S-SNEDDS showed acceptable free-flowing properties reflecting the correct ratio (1:1, w/b). The free-flowing property is one of the characteristics of solid formulations to be converted into powder [6].

Spray Drying Method

The spray drying method was used to look at the results of the solubility test produced. Then spray dried using a laboratory-scale mini spray dryer (Buchi, Switzerland) under conditions of inlet temperature of 60°C, outlet temperature of 30°C, feeder flow rate of 5 mL/min, air pressure of 4 kg/cm2 and aspirator pressure of -25 mbar. Spray drying is commonly used to produce small and uniform particles [7].

Characterization of SNEDDS

Determination of %Transmittance

SNEDDS preparations were diluted 100 times using aquabidestilata and measured at a wavelength of 650 nm with a UV-Vis spectrophotometer (Shimadzu UV Specthrophotometer, UV-1800). A presentation between the range of 90 to 100% indicates a clear and transparent preparation [8].

Particle Size Determination and Zeta Potensial

Particle size and zeta potential testing was carried out by diluting the SNEDDS preparation 100 times with aquabidestilata. The test was analyzed with a particle size analyzer (Horiba SZ 100, Japan) [9].

Thermodynamic Stability Tests

Thermodynamic stability testing was carried out with three phases, namely heating-cooling, centrifugation and freeze thaw cycles. The heating-cooling test was conducted in the temperature range of 4°C to 50°C for 48 hours. Then centrifuged for 30 minutes with a rotation speed of 3500 rpm using a centrifugator (Nuve-NF 400, Turkey) to see the separation phase. Followed by freeze thaw cycles at -21°C to 25°C for 48 hours and then centrifuged again [10].

Table 1. SNEDDS liquid characteristics and thermodynamic stability.

Parameters	Particle size (nm)	index	Zeta potential
SNEDDS liquid	97.16±1.011	0.38±0.006	-35.0±0.5
Thermodynamic stability	No separation	No separation	No separation

Table 2. Testing resistance to dilution of SNEDDS liquid.

Concentration series	Particle size (nm)	index
25x	69.9 ± 0.9	0.3 ± 0.004
50x	42 ± 2.1	0.3 ± 0.006
100x	29.8 ± 0.4	0.2 ± 0.018
250x	41.2 ± 0.7	0.2 ± 0.035

Dilution Resistance Test

Resistance testing against dilution was carried out with concentrations (1:10, 1:100, 1:1000) stored for 24 hours. This test aims to analyze changes in particle size and zeta potential using a particle size analyzer (Horiba SZ 100, Japan) [11]. However, in this study, dilutions were made with concentration series of 1:25, 1:50, 1:100 and 1:250.

Characterization of Solid SNEDDS

Infrared Spectra Test

Infrared Spectra or FTIR tests were performed to evaluate possible interactions between the preparations. The chemical properties and complexation of SNEDDS solid were carried out by Fourier transform infrared spectroscopy (Thermo Nicolet Corporation, USA). The SNEDDS solid preparation was compressed for 5 min at 5 bar of KBr press, and the spectrum was scanned in the wave number range of 400-4000 cm^{-1} [6].

X-Ray Diffraction Test

X-ray Diffraction (XRD) (Bruket Corporation, Germany) tests were evaluated using a diffractometer with a range of 2θ: 3-30° and a moving speed of 0.5 degrees/minute. The tube anode was cu (copper) with Ka (Anode wavelength) of 0.154 nm and monochromatized with graphite crystal. The tube voltage was set at 40 kV, and the tube current at 40 mA. Measurements were performed in stepwise scan mode with a calculation time of 1 second per step and a step size of 0.02° [12].

Particle Morphology

The *Curcuma xanthorrhiza* SNEDDS Solid preparation was SEM (JEOL series 6510 LA, Japan) analyzed and coated with a gold layer using a scanning electron microscope. Observations were made to evaluate the morphological characteristics of the formulation, surface structure, and signs of poor solidification attributes. SEM observations and evaluations were made to understand the *Curcuma xanthorrhiza* SNEDDS solid morphology and detect signs of poor solidification or morphological changes that may affect the formulation's performance [12].

A B

Figure 1. Thermodynamic test, (A) Freeze Thaw cycle, (B) Heating cooling.

Table 3. Solid SNEDDS formulation design using spray drying method.

Formulation	Solid carrier materials	SNEDDS : solid carrier	Solubility	Hygroscopicity
F1		1:5	Dissolve	Hygroscopic
F2	Maltodextrin	1:25	Dissolve	Hygroscopic
F3		1:50	Dissolve	Hygroscopic
F4		1:5	Dissolve	Slightly hygroscopic
F5	Lactose	1:2	Dissolve	Slightly hygroscopic
F6		1:1.5	Dissolve	Slightly hygroscopic
F7		1:1.5	Dissolve	Non hygroscopic
F8		1:2	Dissolve	Non hygroscopic
F9	Mannitol	1:2.5	Dissolve	Non hygroscopic
F10		1:4	Dissolve	Non hygroscopic
F11		1:5	Dissolve	Non hygroscopic

Particle Flow Properties

The powder's flowability was evaluated using two characterizations: the Hall flowmeter test and the powder Granule rheometer. SNEDDS solid preparation was used up to 8 g. The Hall Flowmeter test measured the powder flow rate, while the Granule Rheometer characterized the effect of internal friction between particles and powder force [13].

Microbial Contamination

Ten grams of SNEDDS solid was weighed aseptically and placed in 90 mL of sterile gram peptone solution containing 0.1% peptone and 0.8% sodium chloride with pH adjusted to 7.2. The sample was homogenized in a Stomacher for 30 seconds at normal speed. Dilute the sample 5 times (10^{-1} to 10^{-6}). Each dilution was made by adding 1 mL of the previous dilution into 9 mL of sterile saline peptone water. Appropriate media were added for enumeration and isolation using the pour cup method. Total plate counts were calculated using agar plate count media and incubated at 30°C for 72 hours. Coliform bacteria were enumerated on Tryptone Soya Agar medium and incubated at 37°C for 24 hours. E.coli bacteria were counted on Trypsin Soya agar medium and incubated at 44°C for 24 hours. Yeast and mold were counted on Dichloran Rose Bengal Chloramphenicol medium and incubated at 25°C for 3-5 days [14].

Result and Discussion

Lipid-based delivery systems have been shown to effectively enhance the absorption of poorly water-soluble drugs. SNEDDS preparations consist of a mixture of surfactants, oils and co-surfactants that form an aqueous (o/w) emulsion. The resulting nanoscale droplet size provides a large interfacial area [15]. Droplet size <100 nm will form a more stable nanoemulsion. Polydispersion index testing on the scale of <1 indicates perfect mixing [16]. The particle size and polydispersion index testing data of SNEDDS formula are shown in Table 1.

Administration of lipid-based drugs affects lymphatic absorption. Small droplet size can enhance intestinal absorption. Resistance to dilution to evaluate how well a material, solution or mixture remains effective despite being diluted with various concentration series [17]. Observations of resistance to dilution are shown in Table 2. Evaluation with particle size and polydispersion index and the results met the acceptance criteria.

Thermodynamic testing was carried out with the aim of seeing the stability in different temperatures for 7 days. The SNEDDS formula was stored at room temperature (25-30°C) and refrigerator (2-8°C) to see the microscope changes in the form of phase separation caused. Observations are shown in figure 1 and table 1. No significant microscopic changes occurred [18].

Solid carriers have been widely used as drug delivery media. Solid carriers are used in formulations to increase the solubility and dissolution rate of active substances that generally have low solubility in water. The critical role of solid carriers in drug delivery systems is that they can improve properties related to the safety, effectiveness, and delivery of drugs during storage or use [19]. All formulations were evaluated based on physicochemical testing, which included solubility and hygroscopicity tests. The formulations are presented in Tables 4 and 5 using spray drying and absorption of porous compounds,

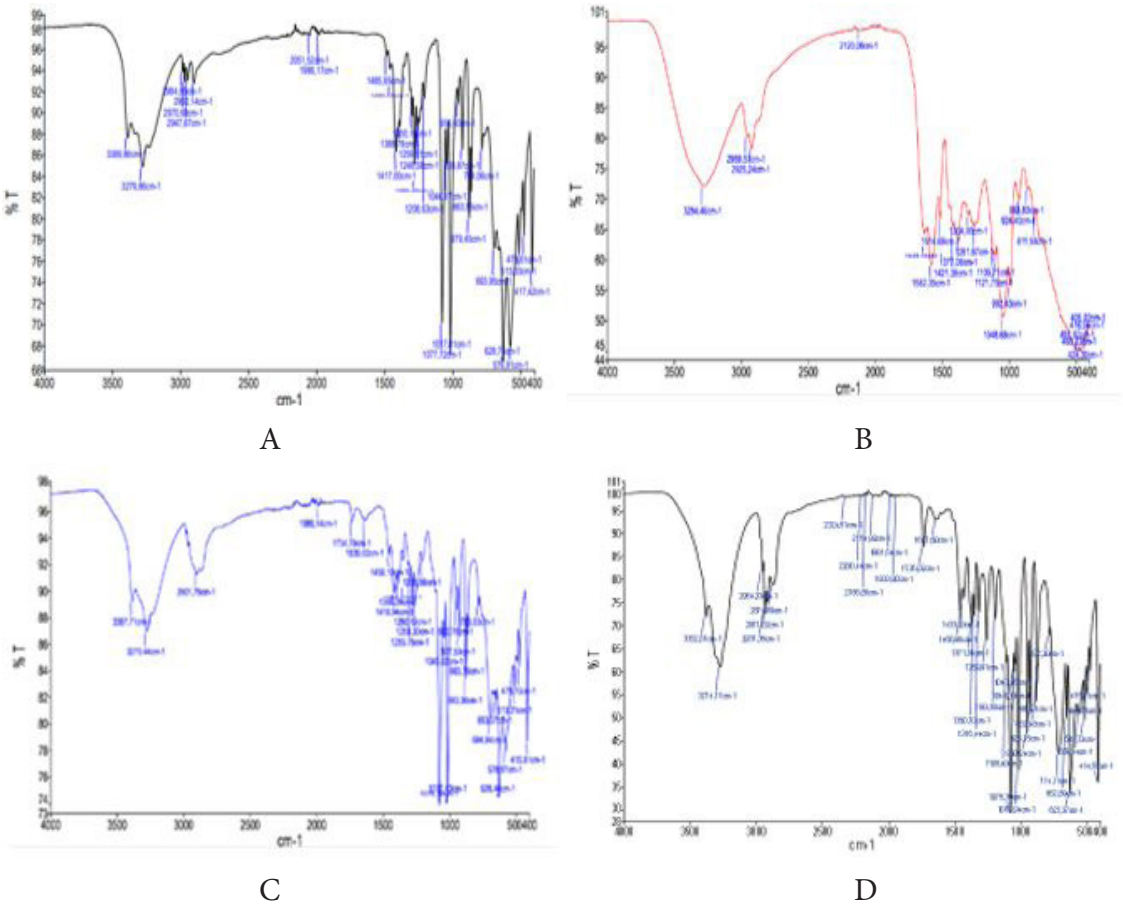

Figure 2. FTIR testing of *Curcuma xanthorrhiza* extract solid SNEDDS, (A) Mannitol, (B) *Curcuma xanthorrhiza* extract, (C) S-SNEDDS *Curcuma xanthorrhiza* (1:5), (D) S-SNEDDS *Curcuma xanthorrhiza* (1:1.5).

respectively.

Table 4 shows that the spray drying method of mannitol and lactose formulation produces a clear solution when mixed with aquabidestilata, then stored for one month to see hygroscopicity. Lactose preparations became hygroscopic, while mannitol was not hygroscopic. Formulations F7 and F11 were then subjected to further evaluation. Formulation F7 showed that SNEDDS *Curcuma xanthorrhiza* (1 g) and mannitol (1.5 g) produced better solubility than other formulations using the spray drying method.

Fourier transform infrared (FTIR) testing is based on the rotation of atoms. Molecules with dipole moments will be detected to see different substances, atomic numbers, and atomic positions by generating absorption spectra [20]. FTIR analysis is based on the resulting spectrum. The spectrum is divided into three regions, namely the far IR spectrum (<400 cm-1), the middle IR spectrum (400-4000 cm-1), and the near IR spectrum (4000-13000 cm-1). In the S-SNEDDS F7 test, the resulting peak of 3273 cm-1 identifies the O-H stretch, 2935 cm-1 indicates the presence of C-H compounds in the aliphatic chain most likely derived from the oil phase resulting from the SNEDDS formulation, 1737 cm-1 indicates the stretching of C=O derived from fatty acids or esters, 1074 cm-1 produces C=N stretching and 625 cm-1 indicates C-O bonds in organic compounds. While S-SNEDDS F11 showed O-H strain at 3387.71 cm-1 peak, C-H of alkane at 2901.79 cm-1 strain and aromatic compounds from 628.4 cm-1 spectrum [21]. See figure 2 for FTIR observations. The resulting peak spectrum of the mannitol carrier is 3400 cm-1 O-H strain. The bands at 2956 cm-1 and 2903 cm-1 produce C-H, -CH and CH2 strains. The peaks of 1421 cm-1, 1289 cm-1 and 630 cm-1 bands show the -CH2, O-H stretches in CH2OH [22]. In this study, the spectrum of mannitol produced was 3389 cm-1 O-H stretching. 2984 cm-1 and 2902 cm-1 spectral bands showed C-H stretching. *Curcuma xanthorrhiza* produced a spectrum of 3400 cm-1 with O-H absorption, 2800 to 3000 cm-1 showing symmetrical (-CH3) and asymmetrical methyl (-CH2) stretching. The spectrum of 1740 to 1680 cm-1 stretches C=O and 1510 shows the aromatic framework [23].

Table 4. Solid SNEDDS formulation design using porous compound adsorption method.

Formulation	Solid carrier materials	SNEDDS : solid carrier	Solubility	Hygroscopicity
F1	Aerosil	1:1	Insoluble	Non hygroscopic
F2		1:0.5	Insoluble	Non hygroscopic
F3		1:0.25	Insoluble	Non hygroscopic
F4		1:0.75	Insoluble	Non hygroscopic
F5	Neusilin	1:1	Insoluble	Slightly hygroscopic
F6		1:2	Insoluble	Slightly hygroscopic
F7	Lactose	1:1	Slightly dissolved	Slightly hygroscopic
F8		1:2	Slightly dissolved	Slightly hygroscopic
F9		1:4	Dissolve	Slightly hygroscopic
F10		1:5	Dissolve	Slightly hygroscopic
F11	Mannitol	1:1	Dissolve	Slightly hygroscopic
F12		1:1.5	Dissolve	Slightly hygroscopic
F13		1:2	Dissolve	Slightly hygroscopic
F14		1:2.5	Dissolve	Slightly hygroscopic
F15		1:3	Dissolve	Slightly hygroscopic
F16		1:3.5	Dissolve	Slightly hygroscopic
F17		1:4	Dissolve	Slightly hygroscopic
F18		1:4.5	Dissolve	Non hygroscopic
F19		1:5	Dissolve	Non hygroscopic

Scanning Electron Microscope testing is shown in Figure 3. The S-SNEDDS preparation showed irregular, district, and uniformly shaped particles. However, large particles were evidenced due to the solidified aggregation of the SNEDDS formulation. Previous research has been conducted on curcumin and thymoquinone compounds developed into Self Nanoemulsifying Drug Delivery Systems (SNEDDS), then formulated into solid preparations with styloid and muslin carriers. The results showed that the muslin carrier formed finer and more stable granules in amorphous form than syloid [24]. The mannitol carrier affects crystallization in the formulation process. The crystalline form is affected by temperature during the heating process. Mannitol is stable under humidity due to its non-hygroscopic nature [25,26]. See Figure 3. for Scanning Electron Microscope observation. S-SNEDDS F11 is more crystalline than F7 due to the high content of mannitol. *Curcuma* preparations produce crystalline morphology, distributed particle size, rod-shaped, elongated and equal in diameter [27].

X-ray diffraction testing of S-SNEDDS *Curcuma xanthorrhiza* is presented in Figure 4. The resulting peaks indicate the preparation has a crystalline phase. Peaks at certain 2θ angles, such as at 17.21° (highest intensity), 18.637°, 20.337°, 24.382°, and 26.479°, indicate the presence of an ordered crystal structure. One component that most likely contributes to this crystallinity is mannitol, known to have crystalline solid properties. However, not all parts of the formula show the same regularity, which means there is also an amorphous phase in the sample. This amorphous phase may not be visible as a diffraction peak but rather as a more diffuse and poorly defined

Table 5. Testing the flow properties of Curcuma xanthorrhiza extract SNEDDS solid particles.

No.	Solids carrier	Flow time (Sec)	Height (mm)	Solid method
1	Lactose	01.99	13.98	Spray Drying
2	Neusilin	03.12	29.77	Spray Drying
3	Mannitol	02.53	24.95	Spray Drying
4	Aerosil	0.26	9.21	Porous Compound Adsorption

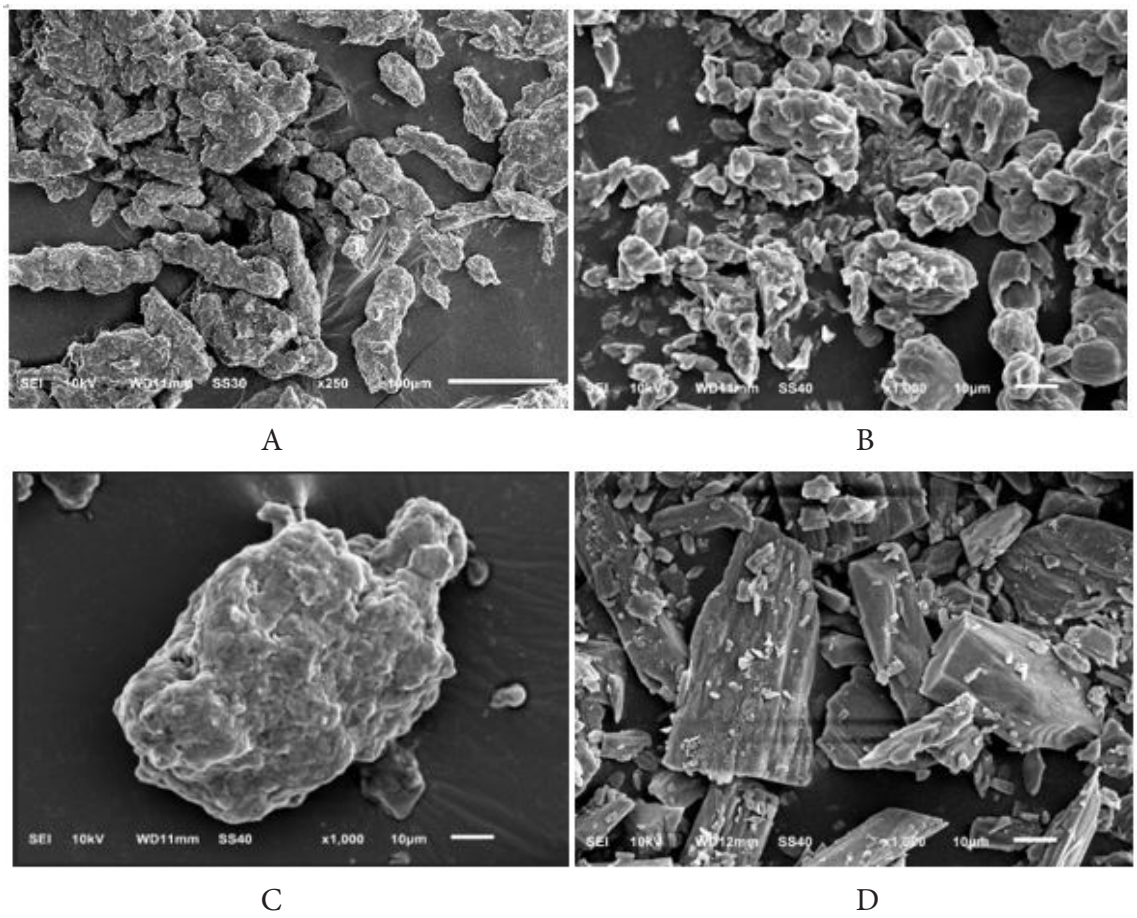

Figure 3. Scanning Electron Microscope testing of *Curcuma xanthorrhiza* extract solid SNEDDS, (A) S-SNEDDS *Curcuma xanthorrhiza* (1:1.5), (B) S-SNEDDS *Curcuma xanthorrhiza* (1:5), (C) *Curcuma xanthorrhiza* extract, (D) Mannitol.

diffraction pattern. This suggests that the S-SNEDDS F7 formula has semicrystalline properties with a combination of crystalline and amorphous phases [25]. Mannitol is described as having crystallinity with a low intensity but well-defined peak (9.7° 2θ characteristic peak). Mannitol will crystallize in samples with a high ratio [28]. The analysis of curcumin is explained by the specific diffraction peaks of 7 to 27°. This forms the crystal structure. The change may result from the carrier forming a crystalline to amorphous preparation [29].

Particle flow properties test aims to determine the ability of particles or powders to flow, which is helpful in the manufacturing process. Mannitol is widely used because it has been shown to affect granules. The large and dense granules of the principal preparation have cohesive properties that cause poor flow [30]. Particle flow properties testing is shown in Table 3. The evaluation results are good due to the large particle size. The smaller the particle size, the powder will not flow well, while the larger the particle size, the powder will flow well.

Microbial contamination testing was conducted to detect the presence of microorganisms. Total Plate Count (TPC) observations of S-SNEDDS F11 and F7 bacteria were 4.4 x 10^1 and <10 CFU/g. The maximum microbial contamination Total Plate Count (TPC) limit is 1 x 10^4 CFU/g [31]. The acceptability of Mold Yeast Count is

Table 6. Microbial contamination testing of Curcuma xanthorrhiza S-SNEDDS preparations.

Sample	Test parameters	
	Total Plate Count (CFU/g)	Mold Yeast Count (CFU/g)
S-SNEDDS (1:5)	4,4 x 10^1	≤ 10
S-SNEDDS (1:1.5)	≤ 10	≤ 10

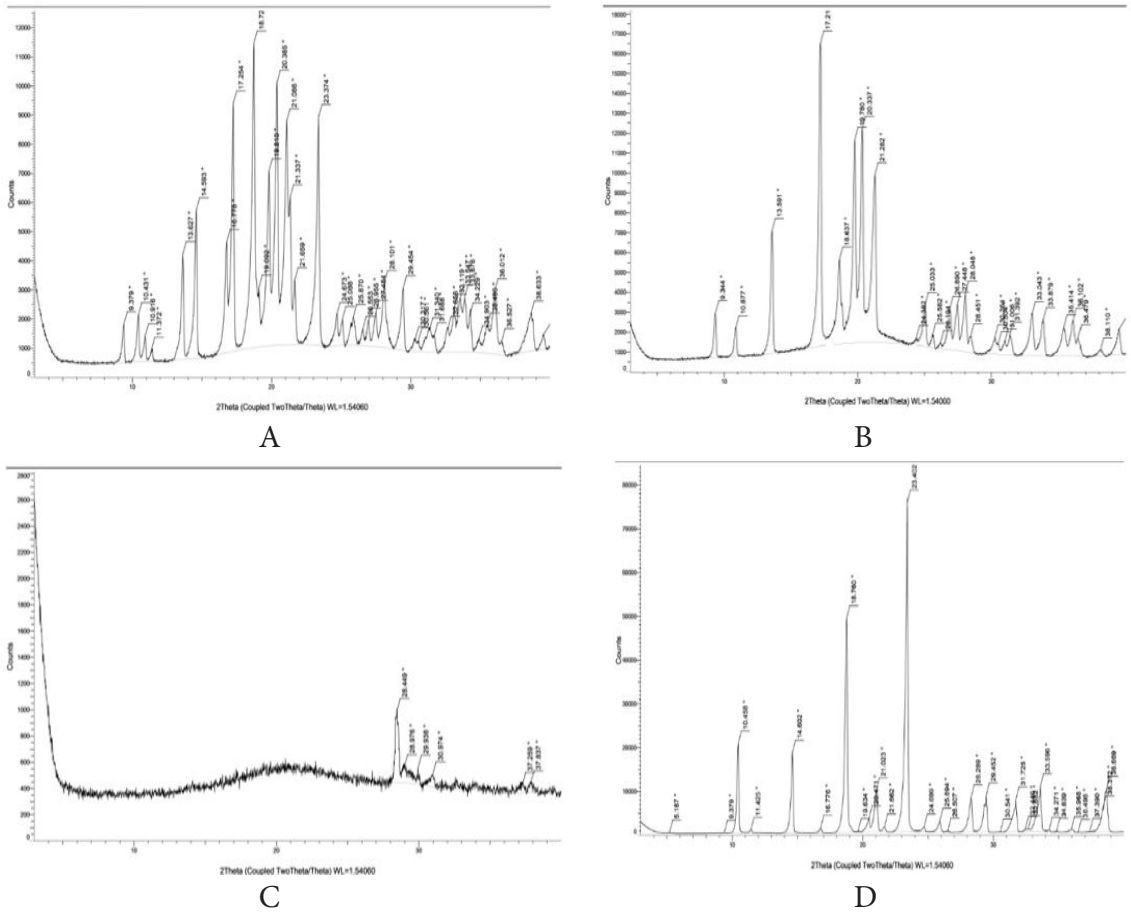

Figure 4. X-Ray Diffraction testing of solid SNEDDS of *Curcuma xanthorrhiza* extract, (A) S-SNEDDS *Curcuma xanthorrhiza* extract (1:5), (B) S-SNEDDS *Curcuma xanthorrhiza* extract (1:1.5), (C) *Curcuma xanthorrhiza* extract, (D) Mannitol.

$<10^3$ CFU/g and Total Plate Count is $<10^5$ CFU/g [32]. Observations of *Curcuma xanthorrhiza* S-SNEDDS F11 and F7 presented in Table 6, meet 2 acceptance requirements of Total Plate Count and Mold Yeast Count. This shows that the S-SNEDDS preparation has a good level of hygiene.

Conclusion

SNEDDS preparation of *Curcuma xanthorrhiza* extract has a particle size below <100 nm and has no phase separation in the thermodynamic test. Then solubility testing on SNEDDS solid carrier was continued. S-SNEDDS preparation of *Curcuma xanthorrhiza* extract with mannitol carrier can increase solubility. Fourier transform infrared test S-SNEDDS F7 formed -OH, C-H, C=O, C=N, C-O and aromatic compounds while S-SNEDDS F11 produced -OH, C-H, C-H and aromatic compounds. Scanning Electron Microscope testing of S-SNEDDS F11 and F7 showed a crystalline material structure due to the influence of the mannitol carrier while X-ray diffraction of S-SNEDDS F11 and F7 explained the S-SNEDDS preparation had semicrystalline properties with a combination of crystalline and amorphous phases. The microbial contamination test showed that S-SNEDDS preparations F11 and F7 did not contain microorganisms. The results of the selected formulations confirm that the S-SNEDDS formulation of *Curcuma xanthorrhiza* F7 has semicrystalline properties. Whereas S-SNEDDS F11 showed a much more crystalline preparation due to the large amount of mannitol carrier. The flow properties test of mannitol-containing S-SNEDDS F7 obtained a result of 02.53 seconds with a height of 24.95 mm.

Conflict of Interest

The authors have no conflicts of interest regarding this investigation.

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