Solidification of meloxicam self-nano emulsifying drug delivery system formulation incorporated into soluble and insoluble carriers using freeze drying method

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Abstract. Solidification of liquid self-nano emulsifying drug delivery system (SNEDDS) formulation is required to enhance the feasibility and flexibility for further formulation processes. This study purposed to compare the soluble and insoluble carriers namely mannitol and fumed silica, respectively on the nano-emulsion formation and physical properties. The optimized SNEDDS formulation comprising of virgin olive oil, Tween 80, and PEG 400; and meloxicam was impregnated into solid carriers e.g. mannitol and fumed silica using a freeze-drying method. The physical mixture was carried out to compare the aforementioned method. Vibrational spectroscopy, thermal analysis, and morphological characteristic, droplet size and distribution, and drug release were performed to characterize the solid SNEDDS (S-SNEDDS). The result showed that crystallization of meloxicam did not observe in the S-SNEDDS formulations, which confirmed by the vibrational spectroscopy and thermal analysis. The morphological characteristic of S-SNEDDS was similar to the native carriers. The soluble carrier did not affect the formation of the nano-emulsion compared to the insoluble carrier. In addition, the S-SNEDDS enhanced the drug release of meloxicam up to 3-4 folds increment.

1. Introduction

A poorly water-soluble drug has a big hurdle and limitation to be developed for further formulation owing to a low solubility. It has a consequence, in which a low bioavailability is achieved [1,2]. Several approaches have been introduced and purposed to enhance the bioavailability. One of them, a lipid formulation using a self-emulsification mechanism is still attractive and interesting manner to be developed to the date [3,4]. Self nano-emulsifying drug delivery system (SNEDDS) gains a wide attention owing to the simplicity in the formulation, cost efficiency, and effective for bioavailability enhancement. SNEDDS comprising of oil, surfactant, and co-surfactant as an isotropic mixture when it is introduced into the medium, the nano-droplet formation is occurred spontaneously [5]. However, the liquid lipid formulation has numerous limitations e.g. flexibility, feasibility, and stability in the packaging and further formulation [4,6].

Furthermore, the solidification of SNEDDS is addressed to solve these issues. Solid SNEDDS can be applied to the further formulation, stability enhancement, and flexibility in packaging [7,8]. Moreover, a new concept of dry nano-emulsion is achieved, when the solid SNEDDS solubilized in

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the medium [9]. However, the solidification process involves soluble and insoluble carriers, in which it differs from their characteristics [7,10]. Mannitol, a soluble material is a non-hygroscopic material and can absorb the liquid lipid at a high loading into the mesoporous of mannitol crystal structure [11]. Fumed silica, a non-soluble and generally known as a drying material had a high adsorptive capacity of liquid or viscous materials. It is usually used to solidify the liquid SNEDDS formulation using physical mixture and spray drying methods [8]. Thus, this study purposed to characterize the solid SNEDDS formulation using soluble and insoluble carriers namely mannitol and fumed silica on the nano-droplet formation and self-emulsification characteristics and drug release behavior. The vibrational, thermal, and morphological characteristics were also evaluated. Meloxicam as a poorly water-soluble drug was selected as drug model and loaded to the SNEDDS formulation.

2. Experimental

2.1. Material

Meloxicam (MLX) was obtained from Dexa Medica (Palembang, Indonesia). Olive oil was purchased from Brataco (Surakarta, Indonesia). Tween 80 and polyethylene glycol (PEG) 400 were obtained from Merck (Darmstadt, Germany), mannitol was obtained from Roquette (Lestrem, France), and fumed silica was obtained from Cabot (Tokyo, Japan).

2.2. Preparation of SNEDDS formulation

Optimized SNEDDS formulation comprising of 26% olive oil as an oil, and 61.8% Tween 80 as a surfactant. 12.2% PEG 400 as a co-surfactant was weighed separately and mixed together using ultrasonicator and stirrer subsequently for 15 min. A 0.015% MLX was incorporated into SNEDDS formulation until a homogenous and clear solution was achieved under stirring condition. SNEDDS formulation was characterized by emulsification time, transmittance, and droplet size and distribution.

2.3. Solidification of SNEDDS

Hydrophilic soluble and insoluble carriers namely mannitol and fumed silica were used to solidify the SNEDDS formulation using a freeze-drying technique. Briefly, a one part of SNEDDS was diluted 10 times and added by 5 parts of mannitol and 1 part of fumed silica separately under gently agitation until either a clear or bluish solution was achieved. Prior the drying process, the solution was stored at -20°C overnight. Thereafter, the solution was dried using a Thermo PowerDry LL1500 freeze dryer (Waltham, MA) at the temperature of -60°C, the pressure of 0.75 mBar for 24 h. The solid SNEDDS mannitol (S-SNEDDS M) and FS (S-SNEDDS FS) were collected and stored in the desiccator until further characterization was performed.

2.4. Characterization of solid SNEDDS

The S-SNEDDS was characterized by a vibrational spectroscopy using an attenuated total reflectance-Fourier transform infrared (ATR-FTIR) spectrophotometry Thermo Nicolet iS50 (Waltham, MA), differential thermal-thermogravimetric analysis (DT-TGA) Shimadzu DT-TGA 60 (Tokyo, Japan), Morphology using a JEOL JSM-6510LA scanning electron microscopy (SEM) (Tokyo, Japan) equipped with a JEOL JEC-3000PC auto fine coater (Tokyo, Japan), and the drug release using an Erweka DT-820 dissolution tester (Heusenntam, Germany).

2.5. Drug release characterization

An equivalent to 15 mg of MLX for each solid SNEDDS was weighed accurately and filled in a gelatin capsule. The drug release characterization was carried out using an Erweka DT-820 dissolution tester (Heusenntam, Germany) equipped with a type II model USP. A 900 mL of phosphate buffer 0.05M pH 6.8 was used as the medium at 37±0.5°C. The sample was withdrawn at predetermined sampling time and analyzed spectrophotometrically using a validated analytical method.
2.6. Data analysis
The obtained data was compared statistically with confidence level of either 95% (p=0.05) or 99% (p=0.01).

3. Results and Discussion
MLX has been successfully incorporated into the SNEDDS formulation. Furthermore, the solidification process was carried out by using a water-soluble carrier, mannitol, and water-insoluble carrier fumed silica. The ET and %T of SNEDDS and S-SNEDDS formulation is presented in figure 1a. The liquid SNEDDS formulation was the lowest ET among solid formulations (p<0.05) owing to spontaneous emulsification without releasing from the carrier. SNEDDS produced nano-droplet formation when it introduced into water [3]. However, the emulsification process of S-SNEDDS M subsequently occurred after the solubilization of the water-soluble carrier [7]. Therefore, the emulsification time of S-SNEDDS M was lower than that of S-SNEDDS FS formulation and higher than that of SNEDDS. The ET of S-SNEDDS FS proved the highest value owing to the interaction and retardant action of the hydrophilic group in silica. Naturally, FS is not soluble but it has a hydrophilic characteristic [12]. However, it has a unique interaction by means of chemical interaction between Si-OH groups and hydrophilic groups in the SNEDDS formulation [8,12]. Hence, it produced the longest ET. The shorter ET, the more appropriate formulation was. The ET contributes to the critical quality attributes of the formation of nano-emulsion during dilution [13,14].

![Figure 1](image1.png)  
**Figure 1.** Emulsification time (ET) and transmittance (%T) (a) and drug release profile (b) of meloxicam and solid SNEDDS meloxicam

![Figure 2](image2.png)  
**Figure 2.** Droplet size distribution of SNEDDS, solid SNEDDS using mannitol (S-SNEDDS M) and fumed silica (S-SNEDDS FS)

The transmittance (%T) depicts the particle size owing to its color. Generally, clear to bluish nano-emulsion when it diluted with the medium had a nano-size range of droplet size. Thus, the higher the
%T, the more acceptable formulation was [15]. The %T of SNEDDS and S-SNEDDS M formulations was not a significant difference (p>0.01). Although, the %T of S-SNEDDS FS was reduced significantly because fumed silica did not soluble in the medium thus produced the turbid solution and reduced the %T. The drug released of MLX and S-SNEDDS formulations is presented in figure 1b. Both of S-SNEDDS formulations increased the drug release about 3.0-4.0 folds compared to the MLX drug release profile. This result proved that significant increasing of drug released had a great probability to enhance the bioavailability [8,10]. The drug release of S-SNEDDS M was higher than that of S-SNEDDS FS. It was affected by the interaction between a hydrophilic component in the SNEDDS formation and non-soluble FS, thus it reduced the drug release rate. Chemical interaction between the droplet (hydroxyl in fatty acid side chain) and the non-soluble fumed silica, a hydrogen bonding has significantly reduced the drug released. The S-SNEDDS M proved that the drug release occurred subsequently by the solubilization of carrier and the lipid formulation was emulsified. The drug released figured out the release in term of “formation of nano-droplet size from S-SNEDDS” [10].

In order to investigate the nano-droplet formation, the particle size distribution after solidification was carried out. It is presented in figure 2. The SNEDDS produced monodisperse system and had the particle size of 137.7 nm and PDI of 0.279. This result suggested that the optimal formulation for nano-emulsion delivery was achieved. This system had a narrow distribution of particle under nano-droplet size [5,16]. Solidification altered the formation of nano-droplet size after dilution. In S-SNEDDS M, a new peak was observed around the droplet range of 3-11 nm owing to the micellar

![Figure 3. FTIR Characterization of meloxicam (a), mannitol (b), fumed silica (c), solid SNEDDS mannitol (d) and solid SNEDDS fumed silica (e)](image)

![Figure 4. Thermogram of DSC and TGA of Meloxicam and Solid SNEDDS mannitol (S-SNEDDS M) and fumed silica (S-SNEDDS FS)](image)
formation. The solidification not only affected the emulsification process, but also it had interaction between the lipid formulation and solid carrier, thus it altered the phase behavior of nano-droplet formation. The nano-droplet formation was observed at peak of 50-400 nm. The nano-emulsion peak of S-SNEDDS M had a lower droplet size than SNEDDS, but it had a wider droplet size distribution. The obtained data of PDI was 0.461 owing to the formation of the micellar formation thus it increased the PDI. On contrary, the poly disperses system was observed in the S-SNEDDS FS after dilution. It was affected by the micellar formation at the range particle from 8-20 nm, nano-emulsion formation at the range of 30-80 nm and non-soluble fumed silica at the range of particle of 200-500 nm. The blatant alteration was observed owing to a high intensity of a peak was observed in the micellar region. This interaction between SNEDDS formulation and hydrophilic side of FS altered the phase behavior and induced formation of the micelle. The intensity of micelle was higher than that of the nano-emulsion owing to the separation of the isotropic mixture. In particular, the surfactant and co-surfactant induced the formation of the micellar solution. The micelle has different transport mechanism compared to the nano-emulsion passed through p-gp efflux and tick junction opening [5,14].

In order to characterize the S-SNEDDS formulation, vibrational spectroscopy, thermal behavior, and morphological characteristics were evaluated. The vibrational spectra of MLX and S-SNEDDS formulation are presented in figure 3. MLX (figure 3a) had specific peaks at 3305 cm⁻¹ according to the N-H stretching vibration and 1627 and 1162 cm⁻¹ according to the C=N and S=O stretching vibrations, respectively. A similar report of MLX spectra has been reported by a previous research [17]. There was no significant and specific peak shifting between fumed silica and S-SNEDDS FS owing to a low fraction of MLX in the S-SNEDDS FS. As similar results as to the S-SNEDDS M, there was no significant peak shifting between the mannitol and S-SNEDDS M. Hence, it indicated there was no interaction between the solidified material and SNEDDS formulation.

![S-SNEDDS M 1000x mag.](image1.png) ![S-SNEDDS FS 1000x mag.](image2.png)

**Figure 5.** SEM photograph of solid SNEDDS mannitol and fumed silica using freeze drying method

The thermal analyses are presented in figure 4. A board endothermic peak was observed on the MLX thermogram around 40-100°C according to the loss of water adsorption (4.98%) in the solid MLX. Moreover, the sharp endothermic peak at 270.6°C according to the melting point of MLX followed by decomposition which was confirmed by loss of its weight about 65.4% from 260 to 300°C. The S-SNEDDS M had a weak and board endothermic peak owing to the evaporation of water adsorption. The sharp endothermic peak was observed at 179.8°C owing to the mannitol melting point. There was no peak observed around of MLX melting point, thus it was indicated there was no crystallization of MLX in the S-SNEDDS M. The slowly decreasing the gravimetric line from 260 to 300°C indicated that there was a decomposition of MLX followed by the mannitol decomposition. The thermogram of S-SNEDDS FS showed a broad endothermic peak was observed around 50-150°C owing to the water absorption and adsorption evaporation. In addition, the similar pattern of decreasing the heat flow around 255-300°C and confirmed by a slow decreasing of gravimetric line confirmed the amorphous form in the surface of the fumed silica. Owing to the adsorption phenomena of MLX in the surface the fumed silica, there was a possibility of formation of the amorphous state of
MLX during drying. According to the morphological characteristics on the surface of S-SNEDDS formulation (figure 5), there was no crystallization in the surface of the S-SNEDDS formulation. The S-SNEDDS M had an irregular characteristic and the agglomerate had a spherical characteristic and rough at the surface without a cracking after the freeze-drying process. The absorption phenomena of the soluble carrier promoted a different characteristic in the surface of insoluble carrier, especially under the freeze-drying treatment. The agglomerate of fumed silica was observed owing to the presence of SNEDDS formulation. The SNEDDS as a liquid form increased the cohesiveness of fumed silica particle thus the agglomerate was formed.

4. Conclusion
The solidification using mannitol and fumed silica as soluble and insoluble carriers, respectively promoted different characteristics by which it was affected by a different mechanism of solidification. The soluble carrier had a positive effect on the drug release and formation of the nano-emulsion. On contrary, the insoluble carrier had an advantage on the powder appearance. Although, it disturbed the nano-droplet and self-emulsification formations. For further development, the soluble carrier could be developed to enhance the flowability and loading capacity on solidifying the SNEDDS formulation.

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