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Research Paper

# Characterization and Optimization of Capryol-90, Polysorbate-80, And Peg-400 Proportion in Mefenamic Acid Self Nanoemulsifying Drug Delivery System (SNEDDS) With Simplex-Lattice-Design

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**Abstract**
Mefenamic acid as pain relief drug belongs to the biopharmaceutics classification system (BCS) class II which is practically insoluble in water causing extremely low dissolution in gastrointestinal tract. The selfnanoemulsifying drug delivery system (SNEDDS) is a new innovation pharmaceutical dosage form that has effectively known to increase solubilization of hydrophobic drug in polar solvent. In this study the capryol-90 was selected as oil phase in SNEDDS as it showed maximal solubility of mefenamic acid (20 mg/mL). Combination of polysorbate-80 and PEG-400 as a generally regarded as safe (GRAS) excipient were used as surfactant and co-surfactant in SNEDDS due to its high HLB property that can increase mefenamic acid solubility in water. The ternary phase diagram of capryol-90, polysorbate-80, and PEG-400 was constructed in advance to obtain the component concentration of spontaneous nanoemulsion region. Model simplex-lattice-design cooperated in Design-Expert® was used to define SNEDDS mefenamic acid formula. Optimized mefenamic acid SNEDDS formula consisted of 20% capryol-90, 31.62% polysorbate-80, and 48.38% PEG-400. Characterization study of Optimized mefenamic acid SNEDDS formula showed improvement of drug content (102.820 ± 4.950)%, emulsification time (421.015 ± 1.290) second, and viscosity (0.927 ± 0.017) mm2/s 30°C. One way ANOVA statistical analysis result of optimal formula SNEDDS (105.210 ± 4.425)% of drug content, commercial generic caplet (0.917 ± 0.094)%, and mefenamic acid powder capsule (10.446 ± 0,333)% gave significant value (sig*) below than 0.05. Optimal formula proved that SNEDDS can significantly increase mefenamic acid dissolution of pH 7.4 (ileum fluid). The optimal formula of mefenamic acid SNEDDS successfully formed an uniformity droplet size (PDI 0.18) with mean size 241.9 nm and the surface charge has a value of -16.5 mV respectively.

**Keywords**
Mefenamic acid, SNEDDS, Capryol-90, Polysorbate-80, PEG-400

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## 1. INTRODUCTION

Mefenamic acid as antiinflammatory non steroid (AINS) drug is used for analgesic to relief headache, toothache, dysmenorrhea, rheumatoid arthritis, osteoarthritis, muscle pain, traumatic and post operation (Mudalip et al., 2013). Mefenamic acid already known asthe most traded drug in middle-income countries and in high-income countries. This achievement shows the level of its consumption occurring in the community (McGettigan and Henry, 2013). High oral dosage of commercial mefenamic acid (500 mg) can increase the probability of side effect such as cardiovascular thrombosis, stroke, congestive heart failure, udem, ulceration, bleeding, and gastrointestinal perforation. This concern caused by the low solubility of mefenamic acid in instestinal fluid (BCS Class II), therefore it has poor bioavailability and absorption. Based on its properties, FDA (2008) recommends the use of mefenamic acid the lowest effective dose (Mudalip et al., 2013).

Nanosized particles (± 200 nm) of drug has been shown to improve the absorption of drugs so the usage dose can be reduce without decreasing the efficacy (Mardiyanto, 2013; Yoo et al., 2010). The self nano emulsifying drug delivery system (SNEDDS) is one of the nanoparticles dosage form which can increase drug solubility and maximize the absorption in gastrointestinal tract by emulsification mechanism (N.A et al., 2017; Sutradhar and Amin, 2013). The succeed level of emulsification is quite high because of the spontaneous emulsion forming of oil in water (o/w) only need weak agitation (Gursoy and Benita, 2004).

The SNEDDS composition used in this study are capryol-90 as dispersed phase, polysorbate-80 as surfactant, and PEG-

400 as co-surfactant. The hydrocarbon chain of Capryol-90 can dissolve the lipophilic drug better and make it not easily oxidized(Anton and Vandamme, 2009). The high HLB (hydrophilic lipophilic balance) of polysorbate-80 (15.0) can increase the hydrophilicity, dissolution, and diffusion of mefenamic acid in gastrointestinal tract so that the absorption process can be more effective (Chen et al., 2018; Shahba et al., 2012). PEG-400 is used for reducing the amount of polysorbate-80 usage to maintain nanoemulsion droplet size does not to be large, hence the paracellular diffusion and dissolution can increase (Sriamornsak et al., 2015).

Software Design Expert® Version 10 (DX®10) is used for minimazing the trial of SNEDDS optimized formula study which has the best droplet size and dissolution. Simplex lattice design (SLD) is chosen as the appropriate optimization model for 3 component formulation. SLD model is very appropriate for this study because it can calculate the response value of experiment total to the effect of differences in the amount of material on each formula (Armstrong, 2006). This study is expected to determine the optimized formula of SNEDDS mefenamic acid that can improve the absorption of mefenamic acid.

## 2. EXPERIMENTAL SECTION

### 2.1 Materials

The materials which used in this study were mefenamic acid (Dexa Medica), capryol (TM 90 type NF) (Gattefosse), polysorbate-80 (Gattefosse), PEG-400 (Gattefosse), ethanol p.a (Merck®), NaOH p.a. (Merck®), $KH_2PO_4$ (Pfizer®), methanol p.a. (Merck®), anhydrous $CH_3COOH$ (APS), anhydrous $CH_3COONa$ (Merck®), and aquabidest (IPHA Laboratories).

### 2.2 Methods

### 2.3 Determination Mefenamic Acid Solubility in Capryol-90

The solubility test was performed by dissolving mefenamic acid (2.4; 2.6; 3.4; 10; dan 20 mg) in 0.5 mL capryol-90 in a vial. The mixture was then stirred with a magnetic strirrer in 150 rpm for 15 minutes and then sonicated (bath-sonicator Covaris S220) for 45 minutes. Formation of the precipitate at each mixture was observed to determine the maximum solubility of mefenamic acid in capryol-90 (Sriamornsak et al., 2015).

### 2.4 Ternary Phase Diagram Construction

Capryol-90 (0-100% v/v), PEG-400 (0-100% v/v), and polysorbate-80 (0-100% v/v) as continues oil phase, surfactan, and co-surfactan were combined into 21 ternary phase. Mixture of capryol-90, PEG-400, and polysorbate-80 were stirred (IKA-47) with magnetic stirrer 300 rpm at room temperature for 15 minutes (Taha et al., 2004).

### 2.5 Self-emulsification and Precipitation Ternary Phase Diagram Study

Self-emulsification of 21 ternary phase was studied by slowly dropping of 80 $\mu$L ternary phase solution into 50 mL aquadest in Beaker glass (1:625) while stirring on magnetic stirrer 100 rpm. Self-emulsification ability of 21 ternary phases were assessed after all components were dispersed homogeneously through the color, clarity, and the presence of globules in emulsion. Precipitation parameter, such as clarity, separation phase, and the presence of precipitation or globule were observed after 24 hours self-emulsification study with light observation (Craig, 1995).

### 2.6 Ratio Component SNEDDS Mefenamic Acid

Composition ratio of capryol-90, polysorbate-80, and PEG-400 was determined using simplex lattice design method software DX®10. The sum of three components was 1 with low value 0 while high value was 1 (Table 1). It was replicated 3 times so the selected model was quadratic. There were 3 responses result that was entered in DX®10 to determine optimized formula; drug content, emulsification timefor 13 formulas.

**Table 1.** Proportion of capryol-90; polysorbate-80; PEG-400

| Level | Proportion (%) | | |
|---|---|---|---|
| | Capryol-90 | Polysorbate-80 | PEG-400 |
| Low | 20 | 20 | 40 |
| High | 40 | 40 | 60 |

### 2.7 SNEDDS Mefenamic Acid Preparation

Mefenamic Acid SNEDDS (Table 2) was prepared by dissolving mefenamic acid in capryol-90 on magnetic stirrer 150 rpm, then it was sonicated for 45 minutes at room temperature. PEG-400 was added and the mixture was resonicated for 45 minutes. At the last, polysorbate-80 was added and the mixture using bath sonicator for 10 minutes to obtain the yellowish solution.

### 2.8 SNEDDS Characterization

#### 2.8.1 Drug Content

Mefenafic acid SNEDDS of 10 $\mu$L was diluted in 5 mL metanol p.a then the absorbance was measured by spectrophotometer (Fischer Scientific evolution-201/220)UV-Vis in $\lambda$max 285 nm (Yadav et al., 2014). The process was replicated in three times.

#### 2.8.2 Emulsification Time and Precipitation

Emulsification time was observed at room temperature. SNEDDS of 20 $\mu$L was diluted in 12.5 mL aquadest with magnetic stirrer 150 rpm until SNEDDS (clear solution or milky without globul of oil) was formed. Precipitation using centrifuge (Lab-DS 1001SD)parameter; such as clarity and phase stability after 24 hours, was observed under the light (24 hours start from the last stirred) (Craig, 1995; Pouton, 1997).

**Table 2.** Formula SNEDDS Mefenamic Acid

| Formula | Mef Ac (mg) | Capryol (mL) | Polysornat80 (mL) | PEG-400 (mL) |
|---|---|---|---|---|
| Run 1 | 40 | 20,00 | 40,00 | 40,00 |
| Run 2 | 40 | 30,00 | 30,00 | 40,00 |
| Run 3 | 40 | 40,00 | 20,00 | 40,00 |
| Run 4 | 40 | 23,33 | 33,33 | 43,33 |
| Run 5 | 40 | 20,00 | 40,00 | 40,00 |
| Run 6 | 40 | 20,00 | 30,00 | 50,00 |
| Run 7 | 40 | 30,00 | 20,00 | 50,00 |
| Run 8 | 40 | 23,33 | 23,33 | 53,33 |
| Run 9 | 40 | 20,00 | 20,00 | 60,00 |
| Run 10 | 40 | 20,00 | 20,00 | 60,00 |
| Run 11 | 40 | 40,00 | 20,00 | 40,00 |
| Run 12 | 40 | 26,67 | 26,67 | 26,67 |
| Run 13 | 40 | 33,33 | 23,33 | 43,33 |

#### 2.8.3 Formula Optimization

SNEDDS component of 13 formulas was optimized using SLD method in DX®10was based on the result of 3 responses with specific criteria arrangement. Combination of SNEDDS component that had the highest desirability in solution was chosen as optimized formula.

#### 2.8.4 Study Response SNEDDS Mefenamic Acid

Response test point was re-studied to 3 batches of the SNEDDS optimized formula (Table 2) along with in vitro dissolution study, diameter measurement, PDI, and zeta potential of SNEDDS globules. Drug content measurement of the final physical stability sample was evaluated furthermore.

#### 2.8.5 In Vitro Dissolution

Dissolution study using dissolution equipment (Pharmatest ptsw-D62) of SNEDDS, capsule, and generic caplet of mefenamic acid were studied in triplo. Transparent hard-capsule of number 0 (0.82 mL) was filled with 0.6 mL SNEDDS of optimized formula while capsule number 0 (1,2 mL ≈ 600 mg) was filled with 500 mg pure mefenamic acid. Capsule contain SNEDDS, pure mefenamic acid, and generic caplet were put into 500 mL buffered SIF pH 7.4 at 37 ± 3°C with rotation speed 100 rpm for 60 minutes. Aliquot (5 mL) was taken in minutes of 0; 5;10; 15; 20; 25; 30; 35; 40; 50 and 60. Caplet and Capsule pure drug aliquot was filtered using Whatmann filter 0.22 $\mu$m. Aliquot absorbance was measured with spectrophotometer UV-Vis in $\lambda$max 285 nm (Sriamornsak et al., 2015).

#### 2.8.6 Diameter, PDI, and Zeta Potensial SNEDDS Globules

SNEDDS mefenamic acid 500 $\mu$L was dropped into 5 mL aquabidest (emulsion 1:10) on a magnnetic stirrer 150 rpm, then stirred for 1 hour. Emulsion of 5 mL was poured into microcuvette of particles size analyzer (Horiba-SZ100) to measure the size, PDI, and zeta potential SNEDDS droplet (Mardiyanto, 2013).

### 2.9 Statistic Analysis

#### 2.9.1 Optimized Formula

Differences bipolysorbate result study of drug content, and emulsification time of SNEDDS optimized formula and DX®10 prediction was analyzed using one sample t-test method in Minitab 17 Statistical® software. Analysis result was indicated to be significantly different if p-value< 0.05.

#### 2.9.2 In Vitro Dissolution Study

% Release and DE60 differences bipolysorbate SNEDDS capsule, pure drug capsule, and generic caplet was analyzed using one-way ANOVA method in software SPSS®20. Comparison post hoc result of each group can be seen from Tukey dan LSD report. Analysis result wasindicated to be significantly different if sig value <0.05.

## 3. RESULTS AND DISCUSSION

### 3.1 Determination of Mefenamic Acid Solubility in Capryol-90

The maximum solubility of mefenamic acid in oil phase (capryol-90), surfactant (polysorbate-80), and co-surfactant (PEG-400) were used as the basis for determination the amount of mefenamic acid that can be added in the SNEDDS formula. The Phase plays important role to maintain active drugs and remain in dissolved state in emulsion, therefore It was important to know the solubility of mefenamic acid in capryol-90 (Sriamornsak et al., 2015). Based on the former study result, capryol-90 was the best oil phase to dissolve mefenamic acid (20 mg/mL) compared with clove oil (9.95 mg/mL) (based on study conducted by Sriamornsak et al. (2015). It was caused by the natural surfactant properties of capryol-90 medium chain that can dissolve more hydrophobic substances (Constantinides, 1995; Karim et al., 1994).

### 3.2 Selection of SNEDDS Mefenamic Acid Component

Selection of oil phase, surfactant, and co-surfactant become critical point to increase the active drug solubility and drug loading in self emulsifying dosage form. Selected components were preferable having maximum solubility.Miscibility towards all components that contained in the dosage form was to produce a stable formula. Capryol-90 was chosen as oil phase because it had solubility ± 2 times than clove oil. Amphiphilic nature of hydroxy group capryol-90 had natural surfactant characteristic. This benefit can reduce the amount of surfactant used so it also can minimize the toxicity risk as result of high concentration use of surfactant (Jaiswal et al., 2014).

Besides that, clove oil can irritate the mucus membrane, so capryol-90 finally was chosen (Sriamornsak et al., 2015). Another benefit of using capryol-90 as oil phase is its biodegradable properties and ability to form nanoemulsion. Polysorbate-80 is chosen as surfactant because it has high HLB (15.0) so it can dissolve mefenamic acid efficiently. Polysorbate-80 is safe for human consumption because its non-ionic characteristic has low toxicity. Besides that, hidrophilic characteristic of polysorbate-80 is very appropriate with watery condition of gastric and intestine that had much hydrophilic fluid (Sriamornsak et al., 2015). Although polysorbate-80 (31.94 mg/mL) has lower solubility than polysorbate-20 (36.96 mg/mL) (Sriamornsak et al., 2015) but polysorbate-80 is more selected than polysorbate-20 according to the result study of lornoxicam SNEDDS shows that the need of Smix (surfactant and cosurfactant) toform capryol-90 into emulsion is reduced by the use of polysorbate-80 as surfactant than polysorbate-20. This result showed that the ability of polysorbate-80 to form capryol-90 into emulsion state was greater than polysorbate-20.

Combination of polysorbate-80-capryol-90, polysorbate-80-transcutol and polysorbate-80-PEG-400 is categorized as GRAS (generally regarded as safe) (FDA LL WL 1349) (Jaiswal et al., 2014). The reason to choose PEG-400 (29.79 mg/mL) than Transcutol® HP (38.76 mg/mL) (Sriamornsak et al., 2015) was based on SNEDDS hydrochlortiazid study by Yadav et al. (2014) that showed the necessary amount of surfactant to expand the nanoemulsion region in Smix of PEG-400 and polysorbate-80 was less than using Smix transcutol and polysorbate-80. Using polysor-bate 80 in high concentration can make the size of globul bigger, therefore PEG-400 was chosen as co-surfactant SNEDDS. Based on this data, capryol-90, polysorbate-80, and PEG-400 were chosen as component SNEDDS mefenamic acid to be studied furthermore.

### 3.3 Determination Nanoemulsion and Ternary Phase Diagram of mefenamic acid SNEDDS

Proportion of capryol-90, polysorbate-80, and PEG-400 that able to form spontaneous nanoemulsion was determined by preparationof 21 combination of ternary phase diagram. Ability of forming nanoemulsion spontaneously was assessed after aquadest was added drop by drop into ternary phase solution. This assessment was designed like that because emulsion will only be formed if one of the emulsion phases had dispersed into small droplet form.

Nanoemulsion of ternary phase has just formed spontaneously (blue and green circle) in Figure 1 if minimal proportion of polysorbate-80 is 20%. The increase proportion of polysorbate-80 and PEG-400 can make the emulsion more clear or transparent because of the adsorption surfactant and co-surfactant on oil and water surface reduce the tension surface energy and cohesion force in emulsion system so emulsion became more stable (Sriamornsak et al., 2015). SNEDDS solution become clear because nanoemulsion globul was < 100 nm, meanwhile the turbid SNEDDS was formed because the globule size is > 10 $\mu$m (Porter et al., 2007).

The increase of capryol-90 proportion caused oil globules can not be dispersed but coalesced on the surface. This was happened because HLB polysorbate-80 and PEG-400 didn't comply with the HLB requirement. As the result, polar and non polar group of polysorbate-80 and PEG-400 as capryol-90 and aquadest as illustrated in Figure 3, the joint was not available enough. This affects the stability of dispersion system and then the unstable emulsion was formed (Azeem et al., 2009).

Component proportion that form nanoemulsion region in 13 SNEDDS formulas determination (Table 2) was rearranged in order to comply the total component of optimized SLD model into 100% so the software showed the combination proportion of nanoemulsion component which then will be studied.

Precipitation was observed to investigate the risk of precipitation of capryol-90 after dispersed in water (Mohsin et al., 2009). Precipitation of capryol-90 affects the reduction of the absorbed mefenamic acid amount. 21 ternary phase stability show that at least there is 80% ternary phase component in dissolve state during 24 hours (Shahba et al., 2012).

### 3.4 Visual Observation of SNEDDS Mefenamic Acid

Formulas SNEDDS of 13 and optimized formula produced slightly viscous yellow transparent solution without precipitation with slightly coconut odor (Figure 2). The yellow color of SNEDDS became intense with increasing the amount of polysorbate-80 because polysorbate-80 had concentrated yellow color (Rowe et al., 2009).

### 3.5 Drug Content Measurement

Drug content was measured to know the mefenamic acid concentration in SNEDDS. This data was used to determine the usage dose (Tzafriri et al., 2012). Methanol was chosen as SNEDDS solvent in drug content measurement because methanol was known as universal solvent that had ability to extract whole mefenamic acid that covered inside globul (Cole, 2003).

Results of SNEDDS drug content had good precision because their RSD (Table 3) > 7.3 % so % drug content 13 formulas can be continued at DX®10 analysis (AOAC Intenational, 2012). Result of % drug content SNEDDS mefenamic acid (Table 3) showed that run 13 (93.04 %) has the highest % drug

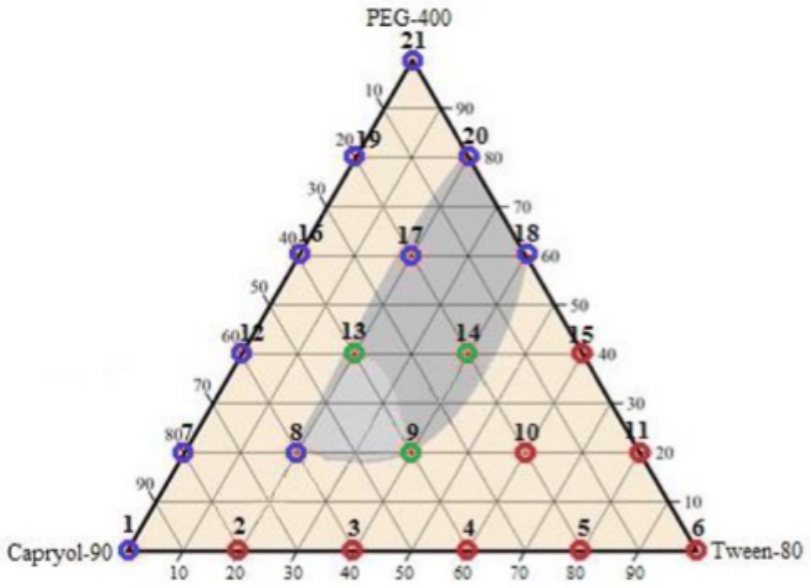


**Figure 1.** Diagram of ternary phase capryol90, polysornate80 and PEG400


**Figure 2.** The image of SNEDDS mefenamic acid

content while run 12 (79.80 %) was the lowest and did not meet the requirement because exceeded the minimum ICH limit (2005) (80 - 120%). This causes the therapeutic did not to be achieved thepain relief effect (Abraham et al., 2013). The SNEDDS component was thought to play role in influencing the drug content, therefore the analysis of the effect of SNEDDS components on drug content using DX®10 was discussed further.

Special quartic was chosen by DX as analytical model because p-value lack of fit of this model was most unsignificant (0.3120 > 0.10). The combination of A2BC, AB, ABC2 had significant effect on % drug content because the factor had p-value < 0.05. The influence of A2BC > AB >ABC2 because the relationship bipolysorbate p-value and the factor effect was opposite, so lower p-value make the greater factor effect. DX®10 Analysis formed 3 equations which express the influence of each component to % drug content (Stat-ease, 2016).

$$Y = 88{,}09\ A + 83{,}98\ B + 86{,}5\ C - 26\ AB + 3{,}34\ AC + 18{,}38\ BC + 879{,}82\ A2\ BC - 194{,}16\ AB2\ C - 511{,}45\ ABC2$$

Description:

Y = % drug content
A = capryol-90 proportion
B = polysorbate-80 proportion
C = PEG-400 proportion

Florentia (2013) reported that positive coefficient A2BC value give synergic effect, while the negative AB dan ABC2 value showed antagonist effect to the response. More double combination of capryol-90 (A2BC) can increase % drug content because hydrophobic property of capryol-90 causes mefenamic acid easier to dissolve. AB and ABC2 factors decrease % drug content because the non-polar carbon chain of polysorbate-80 and PEG-400 caused capryol-90 to break their bond with mefenamic acid, hence the solubility of mefenamic acid is decreased.

### 3.6 Emulsification Time and Precipitation Observation

Self-emulsification ability become the main point in SNEDDS evaluation because bioavailability and oral absorption efficiency of practically insoluble drug can be increased by self-emulsification process that generate fine dispersion and micellar to avoid drug precipitation and recrystallization (Pouton, 1997). The Formula indicated to have good self-nanoemulsification ability if emulsion components (capryol-90, polysorbate-80, and PEG-400) can completely disperse in short time when mixed with aqueous phase with a little help from low agitationof peristaltic activity (Porter et al., 2007; Parmar et al., 2011).

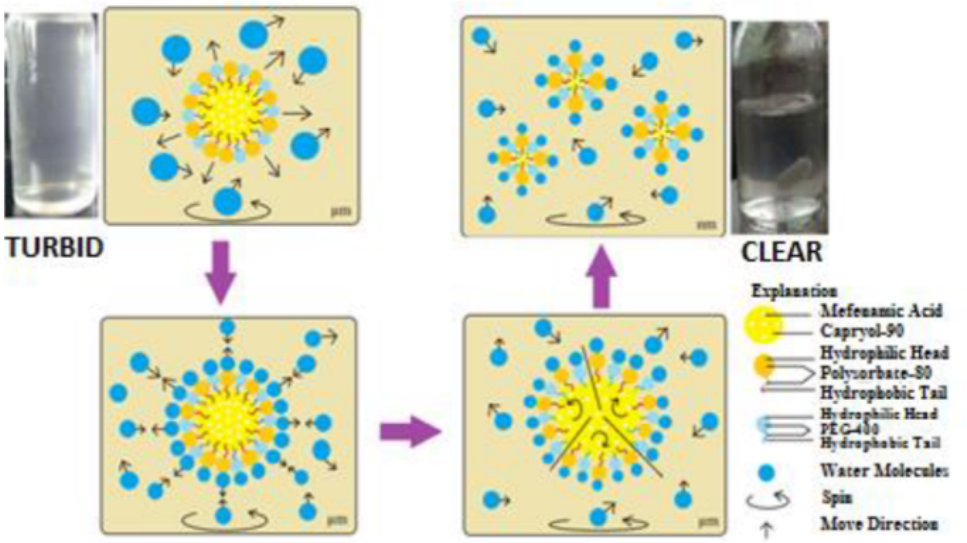


**Figure 3.** The formation of SNEDDS mefenamic acid globul during self-nanoemulsification

### 3.7 Observation of Physical Stability

Physical stability was carried out to determine the maximum storage duration which can lead to the separation of emulsion (creaming or cracking) phases. The test results show if SNEDDS mefenamic acid had good stability because for 3 cycles heating cooling does not show phase separation, viscosity change and SNEDDS color. This proves the statement of (Hintzen et al., 2014) and (Weerapol et al., 2014) if the SNEDDS dosage form has good physicochemical stability. This was because the mefenamic acid dissolving well in the SNEDDS component has improved the stability of the preparation (Parmar et al., 2011).

Capryol-90 which has maximum solubility to mefenamic acid and the use of polysorbate-80 30-60% (w/w) can dissolve more mefenamic acid so can minimize the mefenamic acid precipitation. PEG-400 as co-surfactant according to Jaiswal et al. (2014) can dissolve hydrophilic surfaces and drugs in the oil phase so can help maintain SNEDDS stability.

### 3.8 Response of the SNEDDS Mefenamic Acid Optimum Formula

Run 6 of formulas were selected as representatives of 13 formulas because they have SNEDDS component proportions that resemble the proportion of the optimum formula. The drug content response of the optimum formula was different enough while the viscosity, emulsification time, pH SNEDDS (5.5) depends on capryol-90, polysorbate-80, and PEG400 compositions so that the difference in measurement results of the optimum formula and formula was not much different. The physical stability of optimum formula SNEDDS was physically stable because it did not show separating emulsion phase or the deposition of mefenamic acid during the 3 heating cooling cycles test. However, the result of stability test determination showed that there was degradation of mefenamic acid from 8.2 ppm to 7.0 ppm. Mefenamic acid degradation is estimated to occur due to increasing temperature extremely in the heating cooling process. (Martin and Bustamante, 1993) describes if the rate of degradation reaction can increase 2-3 times every 10°C temperature increase due to increased kinetic energy of the molecule resulting in the decomposition of the molecular complex of mefenamic acid.

### 3.9 Statistical Analysis of Drug Content, and Emulsification Time of Optimum Formula SNEDDS

Precision of 3 responses test method has suitable precision because RSD (4,819%) <7.3%. The test results of the difference of one sample t-test with $\alpha$ 0.05 indicate if the drug content, emulsification time, and viscosity of predicted value DX®10 differed significantly (p-value <0.05 on the experimental results (Table 4). This difference was expected to occur because the DX®10 program did not relevant to the effects of variations in test conditions (such as environmental conditions, testing tools, human error) in predicting response (Stat-ease, 2016).

### 3.10 In Vitro Dissolution

Dissolution tests were performed to determine the process of release of mefenamic acid from SNEDDS dosage form, generic caplets, and pure mefenamic acid capsules. Dissolution becomes the most important characteristic in testing the mefenamic acid SNEDDS response because the faster the dissolution is, the more likely it is to minimize the elimination caused by the first pass effect. This may increase the amount of absorbed mefenamic acid so that the analgesic effects of mefenamic acid can be felt only by the low dose of mefenamic acid. The rapid increase in the release of cumulative mefenamic acid of SNEDDS in minute-5 (Figure 4) occurred due to the rapid formation of spontaneous nanoemulsion which increased the solubility of mefenamic acid in water.

**Table 3.** Response test result of 13 formulas SNEDDS mefenamic acid

| Formula | Average Drug Content (%) ± SD | RSD | Average Emulsification Time (second) ±SD | RSD |
|---|---|---|---|---|
| Run 1 | 85.01 ± 0.87 | 3.137 | 165.58 ± 0,72 | 0.434 |
| Run 2 | 79.80 ± 0.59 | 1.018 | 900 ± 0 | 0 |
| Run 3 | 86.84 ± 2.72 | 3.364 | 900 ± 0 | 0 |
| Run 4 | 82.29 ± 2.48 | 4.944 | 900 ± 0 | 0 |
| Run 5 | 83.08 ± 0.06 | 0.742 | 166.52 ± 1,35 | 0.81 |
| Run 6 | 90.10 ± 0.70 | 5.509 | 457.51 ± 3,64 | 0.795 |
| Run 7 | 88.39 ± 2.91 | 2.964 | 900 ± 0 | 0 |
| Run 8 | 83.06 ± 3.45 | 4.154 | 900± 0 | 0 |
| Run 9 | 87.49 ± 2.94 | 0.076 | 720.35 ± 2,40 | 0.333 |
| Run 10 | 85.65 ± 4.72 | 3.296 | 732.75 ± 0,25 | 0.034 |
| Run 11 | 89.46 ± 4.42 | 3.01 | 900 ± 0 | 0 |
| Run 12 | 89.04 ± 1.04 | 1.169 | 900 ± 0 | 0 |
| Run 13 | 93.04 ± 2.76 | 0.773 | 900 ± 0 | 0 |

Explanation: Run 5, 10 and 11 is replicate formula of Run 1, 9, and 3

**Table 4.** The results of the statistical analysis of predictive value of DX®10 of formula SNEDDS

| Evaluation | DX®10 Prediction | Experiment (N=3) ± SD | p-value |
|---|---|---|---|
| Drug content (%) | 89,512 | 102,820 ± 4,950 | 0,043 |
| Emulsification Time (second) | 428,933 | 421,015 ± 1,290 | 0,009 |
| Viscosity (mm2/s 30°C) | 0,868 | 0,927 ± 0,017 | 0,026 |

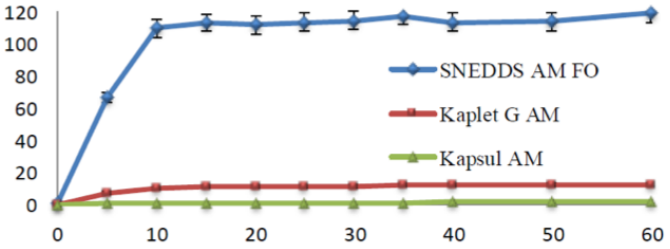


**Figure 4.** The dissolution profile of SNEDDS mefenamic acid

The result of ANOVA% release of mefenamic acid and DE60 from SNEDDS, caplet, and pure capsule showed significant dissolution (sig. <0.05). Post hoc LSD and Tukey in the minute-10 (when% release 100%) and the minute-60 (final stage of dissolution) showed if%release bipolysorbate dosage form also different significantly (sig. <0.05). The DE60 SNEDDS value was greater than pure capsules and commercial generic caplets because the % release SNEDDS has been able to reach 109% at the minute-10. The ANOVA results and the dissolution graph (Figure 4) show that SNEDDS able to improve the mefenamic acid dissolution significantly. Kinetics of mefenamic acid release from SNEDDS, caplet, or pure capsule follows order 0 so that the rate of release of mefenamic acid was not affected by concentration but by the solubility of mefenamic acid to dissolution media (Martin and Bustamante, 1993). This was because the difficulty in dissolving mefenamic acid in the SIF medium (0.01 mg/mL) became strength the stagnant diffusion layer to eliminate the sink conditions during the test. The KH value of the Higuchi kinetics model ≥ 1 illustrates the release of mefenamic acid from SNEDDS, generic capsules and caplets also undergoing diffusion processes (Gursoy and Benita, 2004). The mefenamic acid nanoemulsion formation increases solubility in the SIF so that SNEDDS could narrow the distance of the stagnant diffusion layer thus accelerating the dissolution of mefenamic acid.

The super-case-II transport (n> 1) model was influential if the release of mefenamic acid was done by reducing the polymer chains in the SNEDDS (capryol-90, polysorbate-80 and PEG-400) preparations and caplets (Costa and Lobo, 2001; Lawrence and Rees, 2012). Dissolved mefenamic acid in either a non-polar solvent (capryol-90) after passing through a stagnant diffusion layer could immediately reduced the bond to the capryol-90 polymer followed by the breaking of the polysorbate-80 and PEG-400 polymers to form the SIF emulsion so that there became a reduction of the polymer chain, polysorbate-80, and PEG-400 from micro to nano-size.

The value of pure mefenamic acid capsule (0.1798) illus-

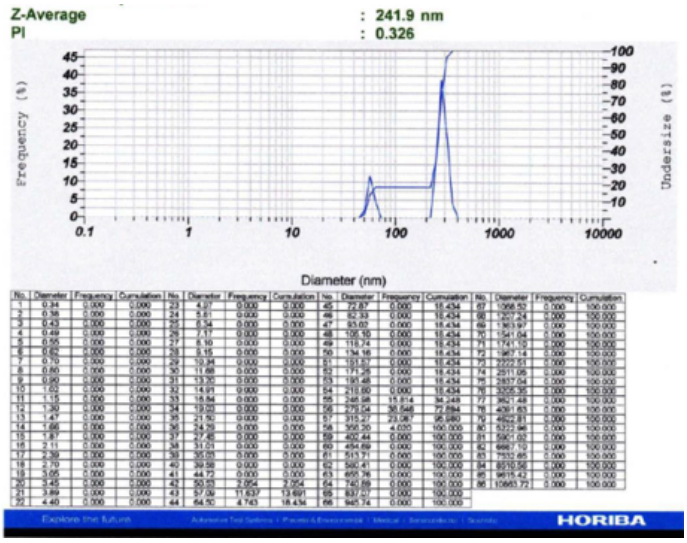


**Figure 5.** Physical properties of SNEDDS mefenamic acid

trates if the release of mefenamic acid only follow Fick diffusion process (Costa and Lobo, 2001). This was because the pure capsule preparations were not added to the polymer so that the release only relied on the transfer of mefenamic acid through the homogeneous membrane which was strongly influenced by the sink conditions (Martin and Bustamante, 1993).

### 3.11 Diameter Analysis, PDI, and Potential Zeta of SNEDDS Droplet

Measurement of diameter of droplets on PSA aims to determine the size of nanoemulsion droplets when in the digestive tract fluid. Average diameter of the established SNEDDS droplets was 241.9 nm with good size uniformity (PDI (18%) <20%) (Figure 5).

SNEDDS zeta potential in -16.5 mV indicates if nanoemulsion dispersion tends to have slow coagulated and flocculated (Martin et al., 1995). This was because a potential zeta value of ± 25 mV has been able to form a stable nanoparticle through the mechanism of forming a protective layer around the droplet from the pull of bonding together the dispersing medium to avoid the unification of SNEDDS droplet. The negative droplet surface SNEDDS droplets was due to the negative electron oxygen (O) atom in the mefenamic acid group, polysorbate-80, PEG-400 created an electron cloud on the emulsion molecule.

## 4. CONCLUSIONS

The proportion of capryol-90, polysorbate-80, and PEG-400-forming nanoemulsion regions of SNEDDS mefenamic acid were 20-40%, 20-40%, and 40-60%, respectively. The proportion of capryol-90, polysorbate-80, and PEG-400 in optimal formula of SNEDDS mefenamic acid was (20; 31.62; 48.38)%. An optimal formula SNEDDS showed the drug contentof (105.210 ± 4.425)%, the commercial generic caplet (0.917 ± 0.094)%, and mefenamic acid powder capsule (10.446 ± 0.333)%. An optimal formula revealed that the SNEDDS could significantly increase mefenamic acid dissolution of pH 7.4 (ileum fluid). The physical properties of mefenamic acid SNEDDS successfully formed an uniformity droplet size (PDI 0.18) with mean size 241.9 nm and the surface charge had a value of -16.5 mV respectively.

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