ORIGINAL ARTICLE

The Self-nanoemulsifying Drug Delivery System Formulation of Mefenamic Acid

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Abstract

Introduction: Mefenamic acid is one of the nonsteroidal anti-inflammatory drugs that have analgesic, antipyretic, and anti-inflammatory properties. However, in the biopharmaceutical classification system, mefenamic acid is included in Class II compounds with low oral bioavailability based on its dissolution rate or solubility in the digestive tract. One way to overcome the solubility problem of mefenamic acid is by formulating it into self-nanoemulsifying drug delivery system (SNEDDS). Previous research has shown that self-emulsifying drug delivery system of mefenamic acid produced greater drug solubility. In our research, we formulated SNEDDS of mefenamic acid to improve its solubility. SNEDDS is a mixture of isotropic oil, surfactants, cosurfactants, and drugs that form nanoemulsion oil in water when emulsified in water. The aim of this study was to formulate mefenamic acid SNEDDS using two different oil phases and compare their characteristics. **Materials and Methods:** Mefenamic acid SNEDDS formulation was carried out using the oil phase (olive oil and virgin coconut oil [VCO]), surfactant (tween 80 and tween 20), and cosurfactant (propylene glycol and polyethylene glycol [PEG] 400) with various concentrations. Optimization of the mefenamic acid SNEDDS formula was determined by observing the emulsification and clarity times, which were clarified with % transmittance. Then, further characterization of particle size, potential zeta, and stability was conducted. **Results and Discussion:** The optimization results obtained by F24 had a composition of olive oil, tween 80, and PEG 400 with a ratio of 1:8:1 and the results obtained by F53 had a composition of VCO, tween 80, and PEG 400 with a ratio of 1:5:1 meeting the requirements with emulsification time of 57 and 50 s, and transmittance values of 90% and 95%. The characterization results showed that F24 with the composition of olive oil, tween 80, and PEG 400 ratio 1:8:1 had a particle distribution of 569.4 nm, zeta potential +9.0 mV, and stability in gastric fluid media. Meanwhile, the characterization results showed that F53 having the composition of VCO, tween 80, and PEG 400 with the ratio of 1:5:1 had a particle distribution of 16.8 nm, zeta potential +2.9 mV, and stability in gastric fluid media. **Conclusion:** Based on the data, it can be concluded that the oil phase of VCO produced mefenamic acid SNEDDS formulas, which are better than the olive oil phase.

Key words: Mefenamic acid, nanoemulsion, olive oil, self-nanoemulsifying drug delivery system, virgin coconut oil

INTRODUCTION

Mefenamic acid belongs to the nonsteroidal anti-inflammatory group which inhibits prostaglandin synthesis in body tissues by inhibiting cyclooxygenase enzyme so that it has an analgesic, anti-inflammatory, and antipyretic effect.[1] In the biopharmaceutical classification system, mefenamic acid is included in Class II compounds with low oral bioavailability based on dissolution rate or solubility in the digestive tract.[2] The solubility of medicinal ingredients often becomes the main requirement for obtaining an optimal therapeutic effect. Many medicinal ingredients have small solubility in water or are expressed as practically insoluble so that the concentration of therapy is not achieved.[3] Self-nanoemulsifying drug delivery system (SNEDDS) is one of the methods for increasing the solubility of drugs.[4] Previous research has shown that self-emulsifying drug delivery system of mefenamic acid produced

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greater drug solubility.[5] Self-emulsifying formulation consisting of oil, surfactant, and cosurfactant can enhance the dissolution and absorption of mefenamic acid and improve the bioavailability of mefenamic acid.[6]

SNEDDS is a mixture of isotropic oil, surfactant, cosurfactant, and drugs that form nanoemulsion oil-in-water (o/w) when emulsified in water.[7] SNEDDS has several advantages compared to nanoemulsion preparations that are ready to use, including having higher physical or chemical stability in long-term storage, having smaller volumes of dosage forms that can be given in the form of soft or hard capsules, and improving patient compliance.[8] The solubility of drugs can be increased by changing the form of drugs into droplets.[9]

The composition of oil in the SNEDDS formula will determine the size of the nanoemulsion formed. The choice of oil type is based on its ability to dissolve the drug. Oil is the basis of medicine in SNEDDS.[10] Many olive oils are selected as the oil phase in the SNEDDS formulation because they contain oleic acid, which has a high self-emulsifying ability and a large drug loading capacity.[11] Meanwhile, virgin coconut oil (VCO) is often chosen as the oil phase in the nanoemulsion formulation because it contains medium-chain fatty acids so that it is more easily emulsified and can produce preparations with a droplet size of <100 nm.[12]

Based on the background above, we formulated SNEDDS of mefenamic acid by comparing the oil phase (olive oil and VCO) and using variations of surfactant (tween 20 and tween 80) and cosurfactant (propylene glycol [PG] and polyethylene glycol [PEG] 400). The formula produced based on the comparison characteristics between the olive oil phase and VCO results in good stability and can increase the solubility of mefenamic acid as indicated by the distribution of particles so that it can increase the bioavailability and therapeutic effect of mefenamic acid.

MATERIALS AND METHODS

Materials and instruments

The materials used in this study were mefenamic acid purchased from Baoh Hanxin Pharmaceutical. Co., Ltd., VCO, olive oil, tween 80 (BRATACO), tween 20 (BRATACO), PEG 400 (BRATACO), PG (BRATACO), magnesium chloride (Merck), calcium chloride (Merck), potassium chloride (Merck), sodium hydrogen carbonate (Merck), sodium chloride (Merck), chloride acid (Merck), and distilled water. The instruments used in this study were digital analysis balance (Precisa XB 220A), glass cup (Pyrex), measuring cup (Pyrex), glass stirrer, pumpkin measure (Pyrex), dropper pipette, pipette volume (Pyrex), particle size analyzer (PSA) Horzer SZ-100 Nano Model, pH meter (HANNA®), vortex mixer (Bio-Rad BR 200), dissolution tester (Erweka), Ultrasonicator (Kudos®), water batch (Stuart), spectrophotometer (Perkin Elmer®), Stopwatch, and mask.

Formulation SNEDDS of mefenamic acid

The formula used in this study was based on research carried out by Wulandari.[13] The modification of the mefenamic acid SNEDDS formula was obtained as follows: The formula was made by mixing oil phases (olive oil and VCO), surfactant (tween 80 and tween 20), and cosurfactants (PEG 400 and PG) based on composition shown in Table 1, in vial bottles and homogenized with vortex for about 5 min followed by sonication for 15 min. Further mixing was done by placing the bottle on the water bath at 40°C for 10 min. The mixing results were allowed to stand for 24 h at room temperature to see the homogeneity. The formula that remains homogeneous was the formula chosen for the next formulation.

Determination of the optimum formula

Emulsion test

100 µL of the SNEDDS formula was added with distilled water to the final volume of 50 mL. Homogenization of the mixture was carried out with the help of vortex for 30 s. The emulsion formed was observed visually for each type of formula with variations in surfactant and cosurfactant.

Transmittance test

Observation of the clarity of the emulsion formed in the previous stage was carried out using ultraviolet-vis spectrophotometer by measuring absorption at a wavelength of 650 nm with distilled water as blank. If the results of the sample transmittance percentage are close to the percentage of distilled water, which is 100%, then it can be assumed that the size of nanoemulsion droplets has been nano-sized.[14]

Emulsification time test

Calculation of emulsification time was carried out on mefenamic acid nanoemulsion in three media, namely,

Table 1: Proportion of mefenamic acid, oil phase, surfactant, and cosurfactant

Mefenamic acid (mg)	Oil phase (ml)	Surfactant (ml)	Cosurfactant (ml)
150	1	1	1
150	1	2	1
150	1	3	1
150	1	4	1
150	1	5	1
150	1	6	1
150	1	7	1
150	1	8	1

distilled water, artificial gastric fluid (AGF)[15], and artificial intestinal fluid (AIF).[15] The formula for AGF and AIF is shown in Tables 2 and 3.

Observation of emulsification time was done visually. 500 mL of media are conditioned in a type II dissolution apparatus with a rotation speed of 100 rpm at a temperature of 37 ± 0.5°C. 1 mL of SNEDDS was inserted into the media quickly. Observations were done on time required since the delivery of SNEDDS mefenamic acid to form nanoemulsion, which was characterized by the complete emulsification of formulas in the media.[16] Calculation of emulsification time was carried out using a stopwatch.

Characterization of optimum formula

Determination of particle size distribution and zeta potential

Nanoemulsion of mefenamic acid was prepared from 100 µL SNEDDS mefenamic acid to be supplied with liquid AGF until the emulsion volume reached 50 mL and then it was homogenized with vortex for 30 s. The sample (5.0 mL) was taken from the emulsion and analyzed using PSA. Data obtained from measurements include average size, size distribution, deviation from average, and zeta potential.

Stability test

A total of 100 µL SNEDDS of mefenamic acid was added with different media, namely, aquades, AIF, and AGF up to a volume of 50 mL, respectively. The mixture was homogenized with vortex for 30 s. The media were warmed and kept at 37 ± 0.5°C as the physiological temperature of the body. Mixing results were observed every hour for 4 h to determine its stability. Stability was characterized by no formation of sedimentation. Stability observations were also carried out at room temperature as a comparison of observations.[17]

Table 2: Composition of AGF

Composition of AGF	
NaCl	1 g
HCl 37%	3.5 ml
Aquadest	Ad 500 ml
pH	1.2

AGF: Artificial gastric fluid

Table 3: Composition of AIF

Composition of AIF	
NaOH 0.2 N	95 ml
KH_2PO_4	4 g
Aquadest	Ad 500 ml
pH	7.2

AIF: Artificial intestinal fluid

RESULTS AND DISCUSSION

Formulation SNEDDS of mefenamic acid

Formulation was carried out by mixing mefenamic acid, oil phase, surfactant, and cosurfactant with predetermined concentrations [Table 1]. Observations were done based on compatibility, namely, separation or homogeneity. The results of the formulation observations are shown in Table 4.

Table 4 shows that tween 80 is better than tween 20 in the mefenamic acid SNEDDS formulation because it can produce more formulations with good compatibility with PEG 400 and PG cosurfactants. The more hydrophilic oil-surfactant mixture showed greater emulsification ability and smaller particle size.[18] The SNEDDS formulation is said to have good compatibility with oil, surfactant, and cosurfactant blends addressing homogeneous and not separate mixtures. The composition ratio of surfactants and cosurfactants shows that the composition of tween 80 is able to form a homogeneous mixture with a ratio greater than the cosurfactant used. Tween 80 has better compatibility because it has more steric effects due to the longer hydrocarbon chains, which help better emulsion stability.[19] Mefenamic acid also has a higher solubility in hydrophilic surfactant, for example, Tween 80.[6] The composition of the surfactant greatly influences the stability of the mixture; the more surfactant used, the mixture will become clearer. The increasing surfactant competition led to more formation of nanoemulsion.[20]

Determination of optimum formula

Emulsion test (clarity)

Observation of the formed nanoemulsion was done visually. The clearer nanoemulsion produced indicates the smaller the size of the droplet formed. Observation of visual clarity is a qualitative parameter of spontaneous dispersion.[21] Observation of nanoemulsion formation refers to dispersibility standard test. Observations were conducted on selected formulas, namely, F23, F24, F30, F31, F32, F53, F54, F55, F56, F62, F63, and F64, which were emulsified. Formulas with PEG 400 surfactant components tend to be clearer. Hence, the transmit test was only conducted on formulas F23, F24, F53, F54, F55, and F56.

As Table 5 indicates, PG is less able to help tween 80 in reducing the surface tension of mefenamic acid in the base of olive oil and VCO. From the type of cosurfactant, PEG 400 has a higher hydrophilic-lipophilic balance (HLB) than PG. A higher HLB value means a higher level of hydrophilicity so that the emulsification time is faster.[22] Previous research showed that mefenamic acid has a higher solubility in PEG 400 (29.79 ± 3.07 mg/ml) than in PG (0.82 ± 0.21 mg/ml).[6]

Transmittance test

Values greater than or equal to 90% reflect small droplet sizes so that they can be selected as suitable candidates for the best

Table 4: Formulations of mefenamic acid SNEDDS

Formula	Mefenamic acid (mg)	Oil phase (ml)		Surfactan (ml)		Cosurfactan (ml)		Appearance
		Olive oil	VCO	Tween 20	Tween 80	PEG 400	PG	
F1	150	1	-	1	-	1	-	Coalescence
F2	150	1	-	2	-	1	-	Coalescence
F3	150	1	-	3	-	1	-	Coalescence
F4	150	1	-	4	-	1	-	Coalescence
F5	150	1	-	5	-	1	-	Coalescence
F6	150	1	-	6	-	1	-	Coalescence
F7	150	1	-	7	-	1	-	Coalescence
F8	150	1	-	8	-	1	-	Coalescence
F9	150	1	-	1	-	-	1	Coalescence
F10	150	1	-	2	-	-	1	Coalescence
F11	150	1	-	3	-	-	1	Coalescence
F12	150	1	-	4	-	-	1	Coalescence
F13	150	1	-	5	-	-	1	Coalescence
F14	150	1	-	6	-	-	1	Coalescence
F15	150	1	-	7	-	-	1	Coalescence
F16	150	1	-	8	-	-	1	Coalescence
F17	150	1	-	-	1	1	-	Coalescence
F18	150	1	-	-	2	1	-	Coalescence
F19	150	1	-	-	3	1	-	Coalescence
F20	150	1	-	-	4	1	-	Coalescence
F21	150	1	-	-	5	1	-	Coalescence
F22	150	1	-	-	6	1	-	Coalescence
F23	150	1	-	-	7	1	-	Homogeneous
F24	150	1	-	-	8	1	-	Homogeneous
F25	150	1	-	-	1	-	1	Coalescence
F26	150	1	-	-	2	-	1	Coalescence
F27	150	1	-	-	3	-	1	Coalescence
F28	150	1	-	-	4	-	1	Coalescence
F29	150	1	-	-	5	-	1	Coalescence
F30	150	1	-	-	6	-	1	Homogeneous
F31	150	1	-	-	7	-	1	Homogeneous
F32	150	1	-	-	8	-	1	Homogeneous
F33	150	-	1	1	-	1	-	Coalescence
F34	150	-	1	2	-	1	-	Coalescence
F35	150	-	1	3	-	1	-	Coalescence
F36	150	-	1	4	-	1	-	Coalescence
F37	150	-	1	5	-	1	-	Coalescence
F38	150	-	1	6	-	1	-	Coalescence
F39	150	-	1	7	-	1	-	Coalescence
F40	150	-	1	8	-	1	-	Coalescence
F41	150	-	1	1	-	-	1	Coalescence
F42	150	-	1	2	-	-	1	Coalescence
F43	150	-	1	3	-	-	1	Coalescence

(Contd...)

Table 4: *(Continued)*

Formula	Mefenamic acid (mg)	Oil phase (ml)		Surfactan (ml)		Cosurfactan (ml)		Appearance
		Olive oil	VCO	Tween 20	Tween 80	PEG 400	PG	
F44	150	-	1	4	-	-	1	Coalescence
F45	150	-	1	5	-	-	1	Coalescence
F46	150	-	1	6	-	-	1	Coalescence
F47	150	-	1	7	-	-	1	Coalescence
F48	150	-	1	8	-	-	1	Coalescence
F49	150	-	1	-	1	1	-	Coalescence
F50	150	-	1	-	2	1	-	Coalescence
F51	150	-	1	-	3	1	-	Coalescence
F52	150	-	1	-	4	1	-	Coalescence
F53	150	-	1	-	5	1	-	Homogeneous
F54	150	-	1	-	6	1	-	Homogeneous
F55	150	-	1	-	7	1	-	Homogeneous
F56	150	-	1	-	8	1	-	Homogeneous
F57	150	-	1	-	1	-	1	Coalescence
F58	150	-	1	-	2	-	1	Coalescence
F59	150	-	1	-	3	-	1	Coalescence
F60	150	-	1	-	4	-	1	Coalescence
F61	150	-	1	-	5	-	1	Coalescence
F62	150	-	1	-	6	-	1	Homogeneous
F63	150	-	1	-	7	-	1	Homogeneous
F64	150	-	1	-	8	-	1	Homogeneous

Choosen formula. VCO: Virgin coconut oil, PEG: Polyethylene glycol, PG: Propylene glycol, SNEDDS: Self-nanoemulsifying drug delivery system

Table 5: Clarity test

Formula	Mefenamic acid (mg)	Oil phase (ml)		Tween 80	Cosurfactan (ml)		Appearance
		Olive oil	VCO		PEG 400	PG	
F23	150	1	-	7	1	-	Clear
F24	150	1	-	8	1	-	Clear
F30	150	1	-	6	-	1	Cloudy
F31	150	1	-	7	-	1	Cloudy
F32	150	1	-	8	-	1	Cloudy
F53	150	-	1	5	1	-	Clear
F54	150	-	1	6	1	-	Clear
F55	150	-	1	7	1	-	Clear
F56	150	-	1	8	1	-	Clear
F62	150	-	1	6	-	1	Cloudy
F63	150	-	1	7	-	1	Cloudy
F64	150	-	1	8	-	1	Cloudy

Choosen formula. VCO: Virgin coconut oil, PEG: Polyethylene glycol, PG: Propylene glycol

formula.[23] The transmitan test results in Table 6 showed that SNEDDS mefenamic acid in AGF media produces transmittance values ranging from 71 to 95%. The results of the transmittance test showed that only F24 and F53 have transmittance values equal to or more than 90%, indicating that F24 and F53 have small droplets produced. This shows that PEG 400 as cosurfactant can help tween 80 in reducing the surface tension of mefenamic acid in the oil phase better than PG.

Emulsification time test

Table 6 shows the emulsification time of the SNEDDS formula. Emulsification time test was conducted to obtain time needed by SNEDDS to form nanoemulsions spontaneously in gastrointestinal fluid with the aid of agitation. Good SNEDDS have an emulsification time of <1 min.[23] The resulting emulsification time results in F54 and 55 <1 min. However, F54 and F55 have percentage below 90%, whereas the results of testing the emulsification and transmittance times of F24 and F53 address the emulsification time of <1 min and the percentage transmittance of ≥90%. The results showed that combination surfactant and cosurfactant of tween 80-PEG 400 form nanoemulsions rapidly than other formulas. It also demonstrated that combined use of tween 80-PEG 400 had excellent emulsification for mefenamic acid both in olive oil and VCO. Based on these data, F24 and F53 are the formulas that will be carried out for further characterization.

Characterization of optimum formula

Determination of particle size and distribution

Characterization of the distribution and size of nanoemulsion particles produced by mefenamic acid SNEDDS was carried out on AGF media or AGF. Measurement of particle size and distribution was carried out using the PSA (Horiba SZ-100 ModelNano). Measurements were made on the optimum formula (F24 and F53), and the measurement results are shown in Table 7 and Figures 1 and 2.

Table 7 and Figures 1 and 2 show that F24 has a particle distribution of 569.4 nm with a polydispersity index (PI) of 0.365. Meanwhile, F53 has a particle distribution of 16.8 nm with a PI of 0.245. Based on the theory, the distribution and particle size produced for nanoemulsion are <100 nm.[12]

Table 6: Percentage of transmittance dan emulsification time

Formula	Percentage of transmittance	Emulsification time (s)
F23	76	62
F24	90	57
F53	95	50
F54	71	39
F55	77	71
F56	84	45

Choosen formula

Table 7: Distribution and PI of nanoemulsion

Formula	Droplet size	PI of particle	Zeta potential
F24	569.4 nm	0.365	+9.0 mV
F53	16.8 nm	0.245	+2.9 mV

PI: Polydispersity index

Therefore, F53 shows a good SNEDDS formula because it has a particle size of <100 nm. Based on the oil phase, VCO contains medium-chain fatty acids so that it is more easily emulsified and can produce preparations with a droplet size of <100 nm.[24] In addition, VCO is also safe for oral consumption and has a good dissolving capacity.[25] Meanwhile, the olive oil fatty acid chain is longer than VCO.

The PI value obtained at the optimum formula (F53) was 0.245. The PI shows a uniform size of particles. The smaller the PI, the more uniform the droplet size distribution is.[26] The larger PI value illustrates the wide range of droplet size distributions.[27] Different droplet sizes will result in different characters from each droplet that can affect the absorption process. The PI value of F53 <0.3 suggests good uniformity of the droplet size. Droplet size distribution is one of important characteristics of *in vivo* absorption and stability of the nanoemulsion.[22]

Zeta potential

Zeta potential is a parameter of electrical charge between colloidal particles. Potential characterization of zeta nanoemulsion droplets was carried out to determine the stability of SNEDDS preparations. The nanoemulsion droplets produced from this study have zeta potential values, as presented in Table 7 and Figures 3 and 4.

Based on these results [Table 7 and Figures 3 and 4], F24 and F53 have zeta potential values that do not exceed +30 mV and are not <−30 mV. The low zeta potential results in the

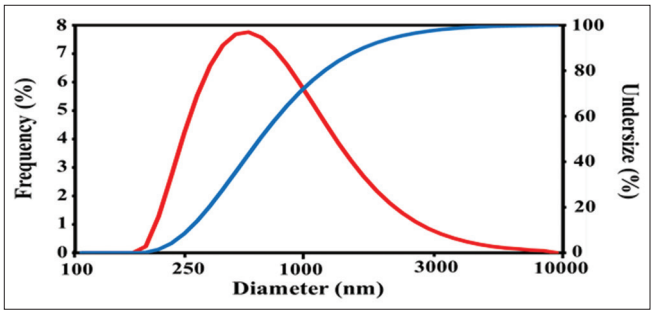

Figure 1: Droplet size distribution of F24

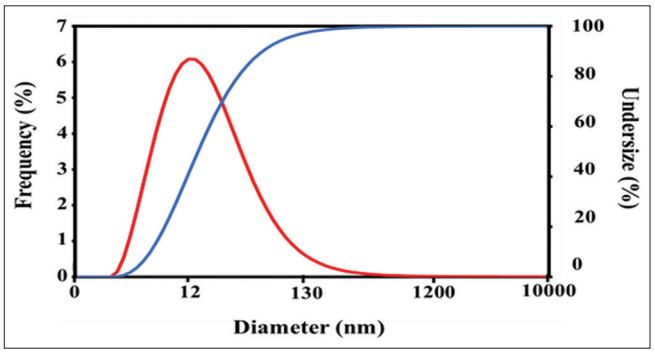

Figure 2: Droplet size distribution of F53

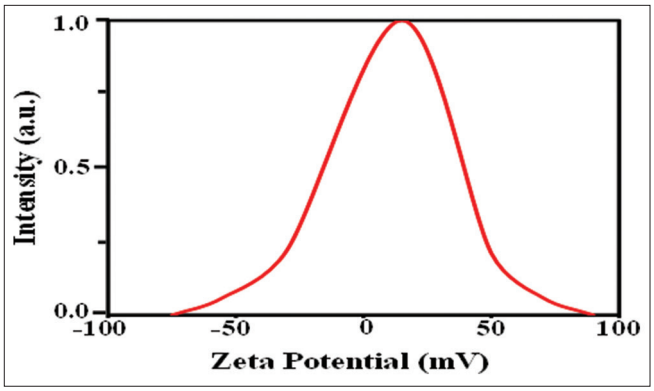

Figure 3: Zeta potential of F24

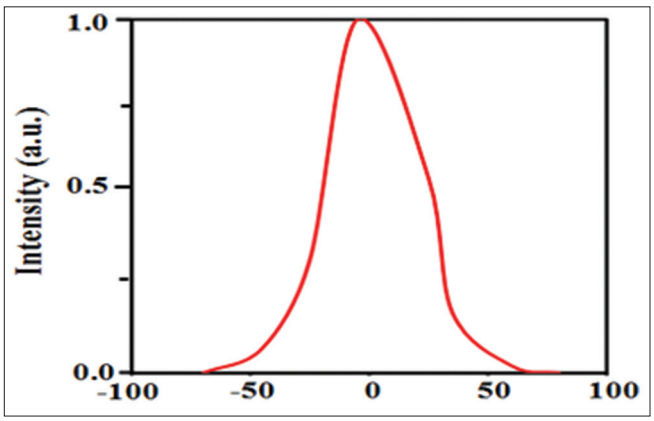

Figure 4: Zeta potential of F53

pulling attraction of the charge between the dispersion particles exceeding the resistive force so that the likelihood of flocculation is greater. Zeta potential values can be influenced by various factors, such as type of surfactant, ionic strength, morphology and particle size, pH of solution, and hydration.[28] The surfactant used is tween 80. Tween 80 is one of the nonionic surfactants. Tween 80 has no charge in the hydrophobic group. Hence, the oil phase droplet surface covered by surfactants tends to be uncharged.[29]

Stability test

A nanoemulsion is said to be stable if it does not experience sedimentation during storage at a certain temperature. The stability of nanoemulsion was carried out at 37°C and room temperature for 4 h. The results of stability testing are shown in Figures 5 and 6. The optimum formula can be said to be stable because precipitation did not occur. Mefenamic acid nanoemulsions can be stable because of the influence of several factors, including particle size and steric stability factor. Droplets that are very small in diameter will move more actively than large droplets. This is due to the dominance of brown motion, which is able to defeat the gravitational force so that it does not result in coalescence. The nanoemulsion system is stabilized by the steric effect because tween 80 is non-ionic surfactant that can improve emulsion stability by forming a surface film with high elasticity to maintain the distance between particles.[30]

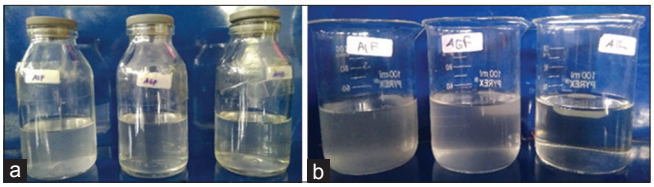

Figure 5: (a) Result of physical stability of F24 self-nanoemulsifying drug delivery system (SNEDDS) at 37 ± 0.5°C (b) result of physical stability of F24 SNEDDS at room temperature

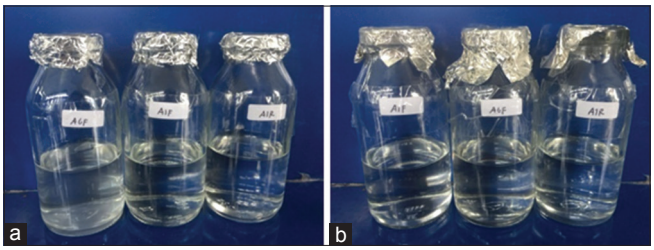

Figure 6: (a) Result of physical stability of F53 self-nanoemulsifying drug delivery system (SNEDDS) at 37 ± 0.5°C (b) result of physical stability of F53 SNEDDS at room temperature

CONCLUSION

Based on the research carried out, the following conclusions can be drawn:

a. The optimum results were obtained by F24 having the composition of olive oil, tween 80, and PEG 400 with a ratio of 1:8:1 and F53 having the composition of VCO, tween 80, and PEG 400 with a ratio of 1:5:1 which meet the requirements with an emulsification time of 57 and 50 s and a transfer rate of 90% and 95%
b. Characterization was done in terms of particle size, potential zeta, and stability. The characterization results show that F24 having the composition of olive oil, tween 80, and PEG 400 with a ratio of 1:8:1 has a particle distribution of 569.4 nm, zeta potential +9.0 mV, and stability in gastric fluid media. Meanwhile, the characterization results show that F53 having the composition of VCO, tween 80, and PEG 400 with a ratio of 1:5:1 has a particle distribution of 16.8 nm, zeta potential +2.9 mV, and stability in gastric fluid media. Based on these data, the oil phase of VCO produces mefenamic acid SNEDDS formulas, which are better than the olive oil phase.

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