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Optimization and Characterization of Fenofibrate Self-Nanoemulsifying Drug Delivery System (SNEDDS) Preparations

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A B S T R A C T

Fenofibrate is a third-generation fibric acid derivative included in BCS (biopharmaceutical classification system) class II, namely high permeability, low solubility. This research aims to obtain the optimum formula for miglyol oil, cremophor RH 40 and PEG 400 according to characterization tests of emulsification time, % transmittance, drug loading, globule size, and zeta potential. This research is an experimental study by formulating fenofibrate in the form of SNEDDS, which was made in 16 formulas using the D-optimal method, which was formulated in the form of SNEDDS with the composition miglyol, cremophor RH 40 and PEG 400 and characterization tests were carried out for emulsification time, % transmittance, drug loading, size. globules, zeta potential to obtain the optimum formula, and then analyzed using the one sample T-Test. The optimization results obtained the optimum formula, namely miglyol at 4%; cremophor RH 40 is 5%, and PEG 400 at 1%. Characterization test: emulsification time was 24 seconds, Transmittance % was 98.7%, Drug loading was 181 mg, globule size was 126 nm, and zeta potential of 12.26 mV. The dissolution test of the fenofibrate capsule dissolved 57.05%, while the fenofibrate SNEDDS capsule was 64.86%. This means that the dissolution of the optimum formula for SNEDDS fenofibrate is better than pure fenofibrate.

1. Introduction

Fenofibrate is an anti-hyperlipidemia that is used as monotherapy to reduce LDL (low-density lipoprotein), cholesterol, triglycerides, and apolipoprotein B and increase HDL (high-density lipoprotein). Fenofibrate is a prodrug that is absorbed through the gastrointestinal tract and hydrolyzed by the CPY3A4 enzyme to become fenofibric acid. The problem of low solubility and bioavailability of fenofibrate can be overcome by several microemulsion/nanoemulsion methods, self-microemulsifying drug delivery system (SMEDDS), self-nanoemulsifying drug delivery system (SNEDDS) and liposomes. In One of these strategies, the development and design of SNEDDS offers potential advantages.[1-3]

The advantages of SNEDDS are that it can increase the bioavailability of drugs through oral use, transport and deliver active drug substances to target cells without affecting surrounding conditions, and improve the digestive tract. The SNEDDS formulation is a preparation consisting of oil, surfactant, and cosurfactant with a suitable composition to produce a stable isotopic mixture. SNEDDS is a drug delivery system consisting of an isotropic mixture of drug, oil, surfactant, and cosurfactant. SNEDDS is a stable system in the digestive tract. When in direct contact with the digestive tract, SNEDDS will form oil-in-water

nanoemulsions with droplet sizes smaller than 100 nm. It is believed that nano-sized droplets have the ability to accelerate the rate of dissolution and oral absorption, thereby greatly increasing bioavailability in the body and allowing time for blood to regenerate.[4-8] This study aims to explore the optimum composition of miglyol, cremophor RH 40, and PEG 400 in forming SNEDDS fenofibrate with critical parameters: emulsification time, drug loading, Transmittance percentage, globule size, zeta potential, and dissolution value (Q30) SNEDDS optimum formula fenofibrate compared to fenofibrate pure.

2. Methods

Tools and materials

The tools used in the research were analytical balance, measuring cup, measuring flask, glass beaker, micropipette, cuvette, magnetic stirrer, UV Vis spectrophotometer, particle-sized analyzer (PSA), ultrasonicator, 10 mL glass vial, USP type 1 dissolution tool (type basket) 1 chamber, centrifuge. The materials that will be used in this research are fenofibrate, miglyol, creatophor RH 40, PEG 400, methanol p.a, aquades, KH_2PO_4, and NaOH.

Making self-nanoemulsifying drug delivery system fenofibrate

Pipette each component of SNEDDS, namely miglyol, cremophor RH 40, and PEG 400, according to the formula in the D-optimal mixture design, then mixed using an ultrasonicator and stirred with a stirrer for 5 minutes with 300 rpm rotation until SNEDDS is formed. The SNEDDS formed was added with fenofibrate little by little until saturation conditions were reached, which was indicated by turbidity in the SNEDDS (mixing for 72 hours at a temperature of 25 ± 1℃). SNEDDS fenofibrate in saturated conditions was then centrifuged at 5,000 rpm for 45 minutes. Results supernatant SNEDDS Fenofibrate is stored in a microtube protected from exposure to sunlight and stored at room temperature. Results supernatant characterization tests were carried out, including emulsification time, drug loading, percent transmittance, and measurement of globule size.

Table 1. Formula design using the D-optimal method.

Formula	Miglyol	Cremophor RH 40	PEG 400
1	33,3	53,3	13,3
2	40	70	10
3	40	50	10
4	30	50	20
5	28,3	58,3	13,3
6	40	50	10
7	28,3	53,3	18,3
8	30	60	10
9	23,3	53,3	23,3
10	20	60	20
11	20	60	20
12	20	70	10
13	20	50	30
14	20	50	30
15	30	60	10
16	23,3	63,3	13,3

SNEDDS fenofibrate is made in percentages with the ratio: miglyol = 20-40%, cremophor RH 40 = 50-70% and PEG 400 = 10-30%.

Characterization of self-nanoemulsifying drug delivery system fenofibrate

Emulsification time. Emulsification time is the time required for SNEDDS to form an emulsion spontaneously when diluted in water media (1 part SNEDDS added to 100 parts distilled water) at a temperature of 37 ± 2^{0}C and stirrer with a magnetic stirrer at 100 rpm.

% Transmittance. % Transmittance (1 part SNEDDS added to 100 parts distilled water) at a temperature of 37 ± 2^{0}C and stirrer with magnetic stirrer 100 rpm. The absorbance of each formulation was measured by UV-vis spectrophotometer at 650 nm using distilled water as a blank.

Drug loading. Determination test drug loading was carried out using a UV-vis spectrophotometer. First, pipette 1 mL of the SNEDDS fenofibrate formulation sample into a 10 mL measuring flask, then fill with 10 mL of methanol to the line mark and shake gently until the solution is clear. Second, read the absorbance solution using a UV-Vis spectrophotometer according to the maximum length of fenofibrate 297.8. Third, drug levels of fenofibrate are calculated using a linear regression equation with a calibration standard curve drug loading used to calculate drug levels of fenofibrate in the composition of SNEDDS; if the results obtained are higher, then the sample can be used properly if it enters the body.

Globules size. Determination of globule size by diluting into water media (1 part SNEDDS added to 100 parts distilled water) at a temperature of 37 ± 2^{0}C and stirrer with a magnetic stirrer at 100 rpm (Wijiyanto et al., 2016). Particle size was measured by the method of dynamic light scattering (DLS) with the p tool particle size analyzer (PSA) Horiba SZ-100. A total of 3 mL of nanoemulsion was filled in the cuvette and inserted into a particle size analyzer (PSA) to measure the droplet size. Measurements were repeated three times for each formula.

Zeta Potential. Determination of zeta potential diluted into water media (1 part SNEDDS added to 100 parts distilled water) at a temperature of 37 ± 2^{0}C and stirred with a magnetic stirrer at 100 rpm. Zeta potential was measured using the electrophoretic light scattering (ELS) technique using a tool particle size analyzer (PSA) Horiba SZ-100. A total of 3 mL of nanoemulsion was filled in the cuvette and inserted into a particle size analyzer (PSA) to measure the droplet size. Measurements were repeated three times for each formula.

Optimization of fenofibrate SNEDDS

The determination of optimum formula of SNEDDS fenofibrate was determined using D-optimal from Softwere design expert. The data needed to determine the optimum is data on several factors such as miglyol, cremophor RH 40, and PEG 400 from the test results of 16 formulas. Optimization is useful in determining the composition of SNEDDS Fenofibrate, which is capable of producing stable nanoemulsions with no separation between phases after mixing. SNEDDS critical parameter goals such as less emulsification time

Optimum formula of SNEDDS fenofibrate

In this research, after obtaining several formulas, characterization tests for each formula were carried out, then the results were entered into the D-optimal mixture method expert design application for optimization to obtain the optimum formula for SNEDDS Fenofibrate, then tests were carried out for emulsification time, % transmittance, globule size, drug loading, zeta potential, and dissolution.

SNEDDS dissolution test

Dissolution tests are carried out with the aim of determining drug release. Testing for SNEDDS Fenofibrate is carried out by inserting the preparation into a gelatin capsule shell. Pure fenofibrate powder is included in the capsule shell (dose 300 mg) and SNEDDS fenofibrate preparation (1.65 mL). Shell tested using dissolution tester 1 USP (basketball type) with a rotation speed of 100 rpm. The medium temperature was maintained at 37 ± 0.5^{0}C. Dissolution flask with 900 ml of pH 6.8 phosphate buffer medium. Take the sample solution using a

syringe in a 5 mL pipette at 5, 10, 15, 30, 45 and 60 minutes. Each time the sample solution is taken, it is replaced with the same medium so that the volume in the chamber remains constant. The absorbance of the sample solution was measured using a blank phosphate buffer solution with a pH 6.8 UV-vis spectrophotometer at a maximum λ of 294 nm. Absorption measurements were repeated three times for each test time, and then the Q30 parameter was calculated.

3. Results and Discussion

The optimum formula of SNEDDS fenofibrate

Optimum formula prediction uses the Design Expert 12 application in the D-optimal program, which consists of 3 components, namely migyol oil phase, cremophor RH 40 surfactant, and PEG 400 cosurfactant. A comparison of the optimum prediction formula and optimum formula characterization test can be seen in Table 2.

Table 2. Prediction of the optimum formula using D-optimal.

SNEDDS components	Optimum formula		Characterization of SNEDDS			
		Emulsification time	% Transmittance	Drug loading	Globules size	Zeta potential
Miglyol	4 %	24.74 seconds	85,13 %	194,90	125,73 nm	-7,06 mV
Cremophor RH 40	5 %					
PEG 400	1 %					

The desirability value is an optimization objective function value that shows the program's ability to fulfill desires based on specified criteria. The range of desirability values is between 0 and 1.0. The desirability value that is closer to 1.0 indicates that it is more perfect. The aim of optimization is not to obtain a desirability value of 1.0 but to find the best condition that meets all objective functions. Desirability states that the value corresponds to what is desired. Achieving the maximum value for desirability indicates that the goal selection for the five characterizations is correct.[9-12] The results in Table 2 show that the optimal prediction formula for the SNEDDS component is miglyol at 4%; The results for cremophor RH 40 are 5%, and PEG 400 are 1% which will produce characterization test values for emulsification time of 24.74 seconds, % Transmittance 85.13%, Drug loading 194.90 mg, globule size 125.73 nm and zeta potential -7.06 mV.

Verification of optimum formula of SNEDDS fenofibrate

The optimal formulation chosen is a formulation containing SNEDDS components fenofibrate with 4% migyol, 5% cremophor RH 40, and 1% PEG 400. Characterization results of fenofibrate SNEDDS tested based on the optimal formula are shown in Table 3.

Table 3. Results of SNEDDS fenofibrate characterization tests according to the optimum formula.

Characterization of SNEDDS	D-optimal prediction	Experiment results
Emulsification time	24.74 seconds	24±1**
% transmittance	85,13 %	98,73333±0,251661*
Drug loading	194,90 mg	181±76,66*
Globules size	125,73 nm	126±6,82*
Zeta potential	-7,06 mV	-12,26±0,65*

*: no significant difference (p>0.05), ** there is a significant difference.

Table 4. Average percent dissolution of powder capsules and SNEDDS fenofibrate.

Time	% dissolution of fenofibrate powder capsules	% dissolution of SNEDDS capsules
5	15,96±2,57	24,12 ± 1,32
10	26,29±2,19	32,00 ± 1,99
15	32,39 ±1,84	39,67 ± 1,65
30	39,30±2,03	47,84 ± 3,36
45	48,18 ±1,00	`59,49 ± 0,37
60	57,08 ±1,41	64,86 ± 2,99

The results of the % dissolution of fenofibrate powder capsules can be seen in Appendix 19. The results of the SNEDDS fenofibrate dissolution test are described by the straight-line equation between time vs. % dissolution of the drug dissolved in phosphate buffer pH 6.8. Depiction of the drug release profile at 30 minutes can also be called the Q30 value. On the SNEDDS fenofibrate dissolution graph with the active substance, fenofibrate has almost the same pattern, namely an increase in dissolution from 5-60 minutes. The dissolution percentage of fenofibrate capsules was better than that of SNEDDS capsules. The fenofibrate capsule dissolved 39.30%, while the SNEDDS capsule dissolved 47.84%.[13-15]

4. Conclusion

Characterization test: emulsification time was 24 seconds, transmittance % was 98.7%, drug loading of 181 mg, globule size of 126 nm, and zeta potential of -12.06 mV. The optimization results obtained the optimum formula, namely miglyol at 4%, cremophor RH 40 at 5%, and PEG 400 at 1%. Dissolution test on value (Q30) of capsules fenofibrate 39.30% while SNEDDS capsules fenofibrate 47.84 %. This means that the dissolution of the optimum formula for SNEDDS fenofibrate is better than pure fenofibrate.

5. References

1. Sulkhan A, Artanti A, Ermawati D, Prihapsara F. Optimization of self-nanoemulsifying drug delivery system (SNEDDS) of *Annona muricata* L . leaves chloroform extract using VCO (virgin coconut oil) as an oil phase. IOP Conf Ser: Mater Sci Eng. 2019.
2. Syukri Y, Kholidah Z, Lutfi C. Formulation and stability study of self-emulsifying propolis using Kasturi oil, cremophor RH 40, and PEG 400 as carriers. Journal of Pharmaceutical and Clinical Science. 2019; 6(3): 265–73.
3. Thakur A, Walia MK, Kumar Sl. Nanoemulsion in enhancement of bioavailability of poorly soluble drug. a review, Pharmacophore. 2013; 1(4): 15–19.
4. Makadia HA, Bhatt AY, Parmar RB, Paun JS, Tank HM. Self nanoemulsifying drug delivery system. future aspects, Asian Journal of Pharmaceutical and Clinical. 2013; 1(3): 21–24.
5. Michaelsen MH, Jørgensen SDS, Abdi IM, Wasan KM, Rades T, Müllertz A. Fenofibrate oral absorption from SNEDDS and super-SNEDDS is not significantly affected by lipase inhibition in rats. European Journal of Pharmaceutics and Biopharmaceutics. 2019; 142: 258–264.
6. Mohsin K, Alamri R, Ahmad A, Raish M, Alanazi FK, Hussain MD. Development of self-nanoemulsifying drug delivery systems for the enhancement of solubility and oral bioavailability of fenofibrate, a poorly water-soluble drug. International Journal of Nanomedicine. 2016; 11: 2829–38.
7. Parmar N, Singla N, Amin S, Kohli K. Colloids and surfaces B : biointerfaces study of cosurfactant effect on nanoemulsifying area and development of lercanidipine loaded

(SNEDDS) self nanoemulsifying drug delivery system. Colloids and Surfaces B: Biointerfaces. 2011; 86(2): 327–38.

8. Patel AR, Vavia PR. Preparation and in vivo evaluation of SMEDDS (self-microemulsifying drug delivery system) containing fenofibrate. AAPS Journal. 2007; 9(3): 344–52.
9. Wahyuningsih I, Sugiyanto, Yuswanto A, Martien R. Solubility test for oil, surfactant and cosurfactant phase selection in furosemide self-nano emulsifying rug delivery system (SNEDDS) preparation. Prosiding Seminar Nasional Peluang Herbal Sebagai Alternatif Medicine. 2015; 99–104.
10. Wijiyanto B, Damayanti P, Sitorus MA, Dyah R, Dea AC, Syukri Y. Formulation of Tempuyung herbal nano preparation (*Sonchus arvensis* L.) in the form of self nano-emulsifying drug delivery system (SNEDDS). Journal of Pharmaceutical and Clinical Science. 2016; 3(1): 50–53.
11. Yuliani SH, Hartini M, Stephanie, Pudyastuti B, Istyastono EP. Comparison of physical stability of pomegranate seed oil nanoemulsion preparations with long-chain triglyceride oil phase and medium-chain triglyceride. Traditional Medicine Journal. 2016; 21: 3–7.
12. Zhao Y, Wang C, Chow AHL, Ren K, Gong T, Zhang Z, Zheng Y. Self-nanoemulsifying drug delivery system (SNEDDS) for oral delivery of Zedoary essential oil: Formulation and bioavailability studies. International Journal of Pharmaceutics. 2010; 383(1–2): 170–7.
13. Ke Z, Zhu Z, Xu Z, Fang C, Hu S. Formulation design and in vitro evaluation of berberine-loaded self-nanoemulsifying drug delivery system. Tropical Journal of Pharmaceutical Research. 2015; 14(5): 747– 52.
14. Zhu T, Ansquer JC, Kelly MT, Sleep DJ, Pradhan RS. Comparison of the gastrointestinal absorption and bioavailability of fenofibrate and fenofibric acid in humans. Journal of Clinical Pharmacology. 2010; 50(8): 914–21.
15. Ziessman HA, Bonta DV, Goetze S, Ravich WJ. Experience with a simplified, standardized 4-hour gastric-emptying protocol. Journal of Nuclear Medicine. 2007; 48(4): 568–72.