Plagiarism Checker X - Report

Originality Assessment

7%

Overall Similarity

Date: Dec 14, 2023
Matches: 178 / 2685 words
Sources: 10

Remarks: Low similarity detected, consider making necessary changes if needed.

Verify Report:
Scan this QR Code

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

Sukarno1*, Ilham Kuncahyo2, Endang Dyah Ikasari3

1Pharmacy Study Program, ITEKES Cendekia Utama, Kudus, Indonesia

2Universitas Setia Budi, Surakarta, Indonesia

3Sekolah Tinggi Ilmu Farmasi, Yayasan Pharmasi Semarang, Semarang, Indonesia

*email: sukarnosukarno1995@gmail.com

Abstract

Fenofibrate is a third-generation fibric acid derivative included in BCS (Biopharmaceutical Classification System) class II, namely high permeability, low solubility. This study aims to obtain the optimum formula for migyol oil, Cremophor RH 40 and PEG 400 in accordance with the characterization test of emulsification time, % transmittance, drug loading, globular size, zeta potential. This research is an experimental research by formulating fenofibrate in the form of SNEDDS which is made 16 formulas using the D-Optimal method which is formulated in the form of SNEDDS with the composition of Migyol, Cremophor RH 40 and PEG 400 and characterization of emulsification time, % transmittance, drug loading, globular size, potential zeta to get the optimum formula and then analyzed using one sample T-Test. The optimization results obtained the optimum formula, namely Migyol of 4%; CremophorRH 40 is 5% and PEG 400 is 1%. Characterization test The emulsification time results are 24 seconds, % transmittance is 98.7%, drug loading is 181 mg, globular size is 126 nm and zeta potential is 12.26 mV. The dissolution test of phenofibrate capsules was dissolution of 57.05% while SNEDDS fenofibrate capsules were 64.86% This means that the dissolution of the optimum formula of SNEDDS fenofibrate is better than pure phenofibrate.

Keywords : Fenofibrate, SNEDDS, % Transmittance, Drug Loading, Globular Size

1.Introduction

Fenofibrate is an anti-hyperlipidemia used as monotherapy in reducing LDL (Low Density

Lipoprotein), cholesterol, triglycerides and apolipoprotein B and increasing HDL (High Density Lipoprotein). Phenofibrates are prodrugs that are absorbed through the gastrointestinal tract and hydrolyzed by the enzyme CPY3A4 to phenofibric 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 any of these strategies, the development and design of SNEDDS offers a potential advantage.1-3

The advantages in SNEDDS are that it can increase the bioavailability of drugs through oral use, can transport and deliver drugs of the active substance of the drug to target cells without affecting the surrounding conditions and also improves the digestive tract. SNEDDS formulations are preparations consisting of oils, surfactants and co-surfactants with suitable compositions to produce stable isotropic mixtures. SNEDDS is a drug delivery system consisting of an isotropic mixture of drugs, oils, surfactants and co-surfactants. SNEDDS is a stable system in the gastrointestinal tract. When in direct contact with the gastrointestinal 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 giving 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, globular 2 size, zeta potential and dissolution value (Q30) of the optimum formula SNEDDS fernofibrate compared to pure fenofibrate.

2.Methods

Tools and Materials

The tools 2 used in the study were analytical balance, measuring cup, beaker glass, micropipette, cuvette, magnetic stirrer, UV Vis spectrophotometer, Particel Sized Analyzer

(PSA), ultrasonicator, 10 mL glass vial, dissolution tool type 1 USP (basketball type) 1 chamber, centrifuge. The materials to be used in this study are Phenofibrate, Miglyol, Cremophor RH 40, PEG 400, Methanol p.a, Aquades, KH2PO4, NaOH.

Manufacture of Self Nanoemulsifying Drug Delivery System Phenofibrate

Pipetted each SNEDDS component, 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 a rotation of 300 rpm until SNEDDS is formed. The SNEDDS formed is added phenofibrate little by little until saturation conditions are reached which is marked by turbidity in SNEDDS (mixing for 72 hours at a temperature of 25 ± 1 °C). SNEDDS Phenofibrates under saturated conditions are then centrifuged at 5,000 rpm for 45 minutes. SNEDDS phenofibrates are stored in microtubes and protected from sun exposure and stored at room temperature. Supernatant results were characterized by emulsification time, drug loading¸percent trasmitant and globular size measurement.

Table 1.Formula Design with 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 Phenofibrate percentages are made with a ratio of: Miglyol = 20-40%, Cremophor RH 40 = 50-70% and PEG 400 = 10-30%.

Characterization of Self Nanoemulsifying Drug Delivery System Phenofibrate

Emulsification time. 10 Emulsification time is the time it takes SNEDDS to form an emulsion spontaneously when diluted into water media (1 part SNEDDS added to 100 parts aquadest) at a temperature of 37 ± 20 C and stirrer with a magnetic stirrer of 100 rpm.

% transmittance. % transmittance (1 part SNEDDS added to 100 parts aquadest) at 37 ± 20 C and steered with a 100 rpm magnetic stirrer. The absorbance 2 of each formulation was measured with a UV-Vis spectrophotometer at 650 nm using aquadest as a blank.

Drug loading. The drug loading determination test was performed using a UVVis spectrophotometer. First, Memipipette 1 mL sample of SNEDDS formulation of phenofibrate into a 10 mL measuring flask, then filled with 10 mL methanol until line mark and shaken gently until clear solution. Second, Reading with absorption of absorbance solution on UV-Vis spectrophotometer according to the maximum length of phenofibrate 297.8. Third, phenofibrate drug levels are calculated using a linear regression equation with a calibration standard curve The determination of drug loading is used to calculate fenofibrate drug levels in the composition of SNEDDS, if the results obtained are higher then the sample can be used properly when entering the body.

Globular size. Determination of globular size is diluted into water media (1 part SNEDDS added to 100 parts aquadest) at a temperature of 37 ± 20 C and stirrer with a magnetic stirrer of 100 rpm (Wijiyanto et al., 2016). Particle size is measured by dynamic light scattering (DLS) method with Horiba SZ-100 particle size analyzer (PSA). 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. The measurement is repeated three times for each formula.

Zeta Potential. Determination of Zeta potential diluted into water medium (1 part SNEDDS

added to 100 parts aquadest) at a temperature of 37 ± 20 C and steered with a magnetic stirrer of 100 rpm. Zeta Potential was measured by Electrophoretic Light Scattering (ELS) technique using the Horiba SZ-100 particle size analyzer (PSA). 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. The measurement is repeated three times for each formula.

SNEDDS Phenofibrate Optimization

The determination of the optimum formula of SNEDDS phenofibrate was determined using D-Optimal from Softwere Design Expert. The data needed for optimal determination are data on several factors such as miglyol, Cremophor RH40 and PEG 400 from the test results of 16 formulas. Optimization is useful in determining the composition of SNEDDS Phenofibrates which are able to produce stable nanoemulsions and there is no separation between phases after mixing. Goal critical parameters of SNEDDS such as Less emulsification time

Optimum Formula of SNEDDS Phenofibrate

This research after obtaining several formulas that have been tested for the characterization of each formula then the results are included in the application of the Expert Design D-Optimal mixture method for optimization so that the optimum formula SNEDDS Phenofibrate is obtained then tested emulsification time, % transmittance, Globule Size, Drug loading, Zeta Potential and Dissolution.

SNEDDS Dissolution Test

Dissolution Test is carried out with the aim of determining the release of drugs. SNEDDS Phenofibrate testing is carried out by inserting the preparation into the shell of a gelatin capsule. Pure phenofibrate powder is included in capsule cankang (dose 300 mg) and SNEDDS preparation of fenofibrate (1.65mL). The shell was tested using a 1 USP dissolution taster (type basket) set to a rotation speed of 100 rpm. The temperature of the

medium is maintained at 37±0.50C. The flask was dissolution with a phosphate dapar medium pH 6.8 as much as 900 ml. Sampling using a 5 mL syringe at minutes 5,10,15,30,45 and 60 minutes. Each sampling solution is 2 replaced with the same media so that the volume in the chamber is fixed. The sample solution was measured for absorbance using a blank solution of pH 6.8 phosphate with a UV-Vis spectrophotometer at a maximum λ of 294 nm. The absorption measurement is repeated three times for each test time and then the Q30 parameter is calculated.

3.Results and Discussion

Optimum Formula of SNEDDS Phenofibrate

Optimum Formula Prediction using Design Expert 12 application on D-Optimal Program. Where it consists of 3 components, namely the oil phase of migyol, surfactant Cremophor RH 40 and cosurfactant PEG 400. A comparison of the optimum prediction formula and the optimum formula characterization test can be seen in table 2.

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

SNEDDS components

Formula Optimu m

SNEDDS characterization

Emulsification time

% Transmittance

Drug Loadimg

Ukura n

Globules

Zeta Potential

Migyol

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 the value of the optimization objective function that indicates the program's ability to fulfill the wishes based on set criteria. The range of desirability values is between 0 to 1.0. A desirability value that is closer to 1.0 indicates more perfect. The goal of optimization is not to obtain a desirability value of 1.0, but to find the best conditions that bring together all the functions of the goal. Desirability states the amount of value that is in accordance with the desired, achieving the maximum value in desirability indicates that the selection of goals in the five characterizations is correct.9-12 The results in Table 2 show

that the optimal prediction formula for SNEDDS components is Migyol by 4%; Results for Cremophor RH 40 of 5% and PEG 400 of 1% which will result in a characterization test value of 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.

SNEDDS Phenofibrate Optimum Formula Verification

The optimal formulation chosen is one containing SNEDDS components fenofibrate with 4% Migyo, 5% Cremophor RH 40 and 1% PEG 400. The results of SNEDDS fenofibrate characterization tested based on the optimal formula 4 are shown in table 3.

Table 3. SNEDDS phenofibrate characterization test results according to the Optimum formula

SNEDDS characterization

D-optimal prediction

Experimental Results

Emulsification time

24.74 seconds

24±1**

% Transmittance

85,13 %

98.73333±0.251661*

Drug Loading

194.90 mg

181±76.66*

Globular 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

Dissolution Test

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

Time

% dissolution capsules of phenofibrate powder

% dissolution capsule SNEEDS

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 result of % dissolution of phenofibrate powder capsules can be seen in appendix 19. The dissolution test results of SNEDDS fenofibrate are described by a straight-line equation between time vs. % dissolution drug dissolved with phospate pH 6.8. The depiction of the drug release profile at minute 30 can also be called the Q30 value. On the SNEDDS dissolution chart, fenofibrate with the active substance fenofibrate has almost the same pattern, namely there is an increase in dissolution from minutes to 5-60 minutes. The percent dissolution of phenofibrate capsules is better than SNEDDS capsules. In fenofibrate capsules dissolved 39.30% while SNEDDS capsules dissolution 47.84%.13-15

4.Conclusion

Characterization test The emulsification time results are 24 seconds, % transmittance is 98.7%, Drug loading is 181 mg, globular size is 126 nm and zeta potential is -12.06 mV. The optimization results obtained the optimum formula, namely Migyol of 4%; CremophorRH 40 at 5% and PEG 400 at 1%. Dissolution Test on Value (Q30) of fenofibrate capsules 39.30% while SNEDDS fenofibrate capsules 47.84%. This means that the optimum formula dissolution of SNEDDS phenofibrate is better than pure phenofibrate.

5.References

1. Sulkhan, A., Artanti, A., Ermawati, D., &; Prihapsara, F. (2019). Optimization 2 of Self-Nanoemulsifying Drug Delivery System (SNEDDS) of Annona muricata L. leaves chloroform extract using VCO (Virgin Coconut Oil) as an oil phase Optimization of Self-Nanoemulsifying Drug Delivery System (SNEDDS) of Annona muricata.

2. Syukri, Y., Kholidah, Z., &; Lutfi, C. (2019). Formulation and Stability Study of Self-Emulsifying Propolis using Musk Oil, Cremophor RH 40 and PEG 400 as Carriers. Journal of Pharmaceutical and Climatic Sciences, 6(3), 265–273.

3. Thakur, A., Walia, M, K., &; Kumar, S, I. (2013). Nanoemulsion in Enhancement of Bioavailability of Poorly Soluble Drug. A Review , Pharmacophore, 1(4), 15–19.

4. Makadia, H, A., Bhatt, A, Y., Parmar, R, B., Paun, J, S., &; Tank, H, M. (2013). Self Nanoemulsifying Drug Delivery System. Future Aspects,Asian Journal of Pharmaceutical and Clinical, 1(3), 21–24.

5. Michaelsen, M. H., Siqueira Jørgensen, S. D., Abdi, I. M., Wasan, K. M., Rades, T., &; Müllertz, A. (2019). Fenofibrate oral absorption from SNEDDS and super-SNEDDS is not significantly affected by lipase inhibition in rats. European Journal of Pharmaceutics and Biopharmaceutics, 142(July), 258– 264.

6. Mohsin, K., Alamri, R., Ahmad, A., Raish, M., Alanazi, F. K., &; Hussain, M. D. (2016). 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, 11, 2829–2838.

7. Parmar, N., Singla, N., Amin, S., &; Kohli, K. (2011). 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, 86(2), 327–338.

8. Patel, A. R., &; Vavia, P. R. (2007). Preparation and in vivo evaluation of SMEDDS (self-microemulsifying drug delivery system) containing fenofibrate. AAPS Journal, 9(3), 344–352.

9. Wahyuningsih, I., Sugiyanto, Yuswanto, A., &; Martien, R. (2015). Solubility Test for Oil, Surfactant and Cosurfactant Phase Selection in Furosemide Self-Nano Emulsifying rug Delivery System (SNEDDS) Preparation. Proceedings of the National Seminar on Herbal Opportunities as an Alternative Medicine, 99–104.

10. Wijiyanto, B., Damayanti, P., Sitorus, M. A., Dyah, R., Dea, A. C., & Syukri, Y. (2016). Formulation of Tempuyung Herbal Nano Preparation (Sonchus arvensis L.) in the Form of Self Nano-Emulsifying Drug Delivery System (SNEDDS). 3(1), 50–53.

11. Yuliani, S. H., Hartini, M., Stephanie, Pudyastuti, B., &; Istyastono, E. P. (2016). Comparison of Physical Stability of Pomegranate Seed Oil Nanoemulsion Preparations with Long-Chain Triglyceride Oil Phase and Medium Chain Triglyceride. Traditional

Medicine Journal, 21(August), 3–7.

12. Zhao, Y., Wang, C., Chow, A. H. L., Ren, K., Gong, T., Zhang, Z., & Zheng, Y. (2010). Self-nanoemulsifying drug delivery system (SNEDDS) for oral delivery of Zedoary essential oil: Formulation and bioavailability studies. International Journal of Pharmaceutics, 383(1–2), 170–177.

13. Zhongcheng, Zhu, Z. P., Xu, Z. Y., Fang, C., &; Hu, S. Q. (2015). Formulation design and in vitro evaluation of berberine-loaded self-nanoemulsifying drug delivery system. Tropical Journal of Pharmaceutical Research, 14(5), 747– 752.

14. Zhu, T., Ansquer, J. C., Kelly, M. T., Sleep, D. J., &; Pradhan, R. S. (2010). Comparison of the gastrointestinal absorption and bioavailability of fenofibrate and fenofibric acid in humans. Journal of Clinical Pharmacology, 50(8), 914–921.

15. Ziessman, H. A., Bonta, D. V., Goetze, S., & Ravich, W. J. (2007). Experience with a Simplified, Standardized 4-Hour Gastric-Emptying Protocol. Journal of Nuclear Medicine, 48(4), 568–572.

Sources

1	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4280499/ INTERNET 2%
2	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6572212/ INTERNET 1%
3	https://www.researchgate.net/publication/304000443_Development_of_self-nanoemulsifying_drug_delivery_systems_for_the_enhancement_of_solubility_and_oral_bioavailability_of_fenofibrate_A_poorly_water-soluble_drug INTERNET 1%
4	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7827561/ INTERNET 1%
5	https://www.researchgate.net/publication/334175488_Fenofibrate_oral_absorption_from_SNEDDS_and_super-SNEDDS_is_not_significantly_affected_by_lipase_inhibition_in_rats INTERNET 1%
6	https://www.researchgate.net/publication/282314942_Formulation_Design_and_In_vitro_Evaluation_of_Berberine-_Loaded_Self-Nanoemulsifying_Drug_Delivery_System INTERNET 1%
7	https://www.semanticscholar.org/paper/Comparison-of-the-Gastrointestinal-Absorption-and-Zhu-Ansquer/2fb9ea5f8e97d2cddbb927fab769b8929f63f049 INTERNET 1%
8	https://jnm.snmjournals.org/content/48/4/568 INTERNET <1%
9	https://www.semanticscholar.org/paper/Formulasi-Sediaan-Nano-Herbal-Tempuyung-(Sonchus-Wijiyanto-Damayanti/23500ef1184095b149f161311270d5948d62569c INTERNET <1%
10	https://www.sciencedirect.com/science/article/pii/S0927776513005420 INTERNET <1%

EXCLUDE CUSTOM MATCHES	ON
EXCLUDE QUOTES	ON
EXCLUDE BIBLIOGRAPHY	ON