ISSN 2546-6462 (online), ISSN 2088-8740 (print)

DOI : 10.30644/rik.v12i2.773

# Optimization and formulation of phenopibrat transfersome using the thin layer hydration method

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Accepted: 13 July 2023; revision: 14 November 2023; published: 30 December 2023

**Abstract**

**Background:** Fenofibrate is a lipophilic drug that is used to treat hypercholesterolemia and hypertriglyceridemia in patients.. The low solubility of fenofibrate can be improved by creating a phenofibrate transfersome delivery system. The objective of this research was to determine the effect of phosphatidylcholine 90G, Tween 80, with sonication on fenofibrate transfersomes and to obtain the optimum composition of phosphatidylcholine 90G, tween 80, with sonication on critical parameters including particle size, zeta potential, absorption efficiency. For formula optimization, the factorial design method was applied. Phosphatidylcholine 90G composition, tween 80, with sonication were used as independent variables, with particle size, zeta potential, and sorption effectiveness as dependent variables.
**Method:** The optimization was carried out with critical parameters of the fenofibrate transfersomes tested including particle size, zeta potential, and adsorption efficiency. The critical parameter test data were analyzed using factorial design.
**Result:** The results showed that there was an effect of phosphatidylcholine 90G, tween 80, and sonication on fenofibrate transfersomes provide effect by including particle size, zeta potential, and sorption efficiency.
**Conclusion:** The optimum proportion of phosphatidylcholine 90G was 95%, tween 80 was 5%, and sonication was 33,39 times. The transfersome ability of fenofibrate was good in the optimum formula in the particle size test was 23,675 nm and zeta potential 52,231 mv and the entrapment efficiency was 96,915 %.

***Keyword :*** Fenofibrat, transfersome, phospatidicoline 90G, thin film layer, factorial design.

## INTRODUCTION

Fenofibrate was first introduced in 1975, and it is now available in over 85 developed countries. It is a cholesterol-lowering drug with a well-understood pharmacokinetic profile (1). Fenofibrate is a lipophilic medication that is used to treat hypercholesterolemia and hypertriglyceridemia in patients. The dissolution rate of fenofibrate can limit its absorption in the gastrointestinal system due to its poor water solubility and high lipophilicity (log P = 5,375) (2).

Fenofibrate is a third-generation fibric acid derivative with poor solubility and high permeability that belongs to BCS class II (Biopharmaceutical Classification System) (3). The technique used to increase the bioavailability of drugs is to use liposomes while liposomes introduce a new drug carrier system claimed to be transfersomes. Class II BCS drugs belong to a group of drugs that have low bioavailability. Techniques used to increase drug bioavailability include reducing particle size, formation of polymorphisms and pseudopolymerphisms, complexation, use of surfactants and use of prodrugs (4).

New technologies are being developed to improve the bioavailability of BCS class II drugs, namely transfersome, for particle or globule drug delivery systems at the nanometer scale, which have distinct physical properties when compared to larger particles, especially in improving or enhancing the delivery quality of compounds. For drugs, one of which is of great interest in terms of nanoparticles is transfersomes, in which transfersomes are perfectly superformal lipid supramolecular aggregates having at least one aqueous compartment

enclosed or surrounded by a lipid layer whose specific properties are adapted due to the presence of an upper activator in the membrane. vesicular (5).

Transfersomes contain a hydrophobic and hydrophilic architecture, and they can accommodate pharmaceuticals with a variety of solubilities. They can also alter form and pass through thin constrictions (from 5 to 10 times smaller than their own diameter) with no significant loss. This high deformability provides better penetration of intact vesicles, which are used as carriers of drugs using low and high molecular weights such as analgesics, anesthetics, corticosteroids, sex hormones, anticancer, insulin, vitamins, gap junction proteins and albumin (6).

Thin layer hydration, ethanol injection, reverse phase evaporation, and sonication are all ways that can be used to transfersomes (7). Thin-layer hydration and sonication are two methods that are frequently used to obtain smaller and homogeneous particle sizes and high adsorption efficiency values (8). According to Almahmedy (2020), thin-layer hydration uses sonication on development, optimization, and assessment of tamsulosin nanotransfersomes to improve permeation and availability (9).

Phospholipids and surfactants often utilized in transfersome formulations include phosphatidylcholine 90G and tween 80. Phosphodylcholine is also known as lecithin, and phosphatidic is derived from soybeans that contain 60-70 percent phospholipids. Tween 80 is used as a wetting agent, emulsifier, and solubility enhancer, among other things (10). According to research by Khan *et al*., (11) who have developed a 5-Fluorouracil transfersome formulation using tween 80 and span 80 as edge activator, concluded that tween 80 is better edge activator than span 80 which forms a formulation using a smaller particle size. small use more exquisite drug adsorption efficiency.

Phosphatidycholine 90G and tween 80 had good transfersome qualities, as evidenced by particle size, zeta potential, and sorption efficiency, all of which matched the nanovesicle criterion (12). According to Ahad *et al*., (2017), transfersomes manufactured with phosphatidycholine 90G and tween 80 could be produced as nano-sized drug carriers for transdermal distribution of eprosartan mesylate to lessen adverse effects associated with oral and other parenteral routes (13).

The thin layer hydration method is widely used in the manufacture of transfersomes because of its simplicity and practicality as well as the ability to form very small and uniform vesicles and produce high drug adsorption efficiency (14). The active ingredient is dissolved in organic solvents and combined with hydrophobic substances. The objective of the rotary evaporator in this thin layer hydration method is for the rotary evaporator to evaporate the organic solvent (chloroform: methanol) used to form a thin layer in a round flask.

Optimization was carried out, namely factorial design which was used to understand process parameters and formulations to reduce particle size, one of the studies on Sunday (2012) showed that the optimum concentrations of phospholipids, surfactants and valsartan gave the maximum transdermal flux and EE% values as a result could reduce vesicle size.

Based on this background, this study was conducted employing transfersome phenofibrate phosphatidicholine 90G, tween 80, and sonication using the thin layer hydration method in the hopes of improving fenofibrate bioavailability in the formulation.

## METHOD

### Tools and materials

The tools used in this research were Sonicator (Qsonica, Newton, U.S.A), Particle Size Analyze (PSA) and Zeta potential (Beckman Coulter Delsa Nano C, USA), magnetic stirrer (Thermo Scientific, China), centrifuge (SPLC Series, Gemmy 8 Hole, Taiwan), pH (Eutech Instruments, Ecosan hand-held series, Singapore), UV-VIS Spectrophotometer (Genesys 10s, Thermo scientific) analytical balance (Ohaus), and other research support tools.

The materials used in this research were fenofibrate, tween 80, phosphatidicin (Lipoid, Germany), methanol pro analysis (Merck), aquadest (PT. Bratachem, Indonesia), chloroform, ethanol 96% pro analysis (Merck).

## Research road

### 1. Fenofibrate Transfersome Production

**Table 1. Formula design using factorial design**

| Level | Formula | | |
|---|---|---|---|
| | Phosphatidylcholine (%) | Tween 80 (%) | Sonication (Minute) |
| Low level (-) | 75 | 5 | 15 |
| High level (+) | 95 | 25 | 35 |

| Run | Phosphatidylcholine (%) | Tween 80 (%) | Sonication (Minute) |
|---|---|---|---|
| 1 | 95 | 5 | 35 |
| 2 | 75 | 5 | 35 |
| 3 | 95 | 25 | 15 |
| 4 | 75 | 25 | 35 |
| 5 | 75 | 5 | 15 |
| 6 | 95 | 5 | 15 |
| 7 | 95 | 25 | 35 |
| 8 | 75 | 25 | 15 |

To make transfersomes, weigh all of the materials, then stir in phosphatidylcholine, tween 80, and fenofibrate dissolved in the organic phase (chloroform: methanol 1:1) for 10 minutes using a magnetic stirrer, then sonicate for the period specified in the formula. The previously obtained solution was then evaporated using a rotary evaporator at 55 C with a rotation speed of 60 rpm, and the thin film generated on the flask walls was stored overnight in a vacuum oven to guarantee total dryness, before being rehydrated using a phosphate buffer. As much as 30 ml of pH 7.4 Ultrasonic sonication at a time of 10 minutes and a 50% amplitude was used to sonicate the coarse dispersion.

### 2. Fenofibrate Transfersome Characterization

**Particle Size Analyzer Test.** The size of the phenofibrate transfersome can be measured using a particle size analyzer (PSA). Particle size analysis of fenofibrate was carried out with Zetasizer Nano ZS90. A total of one drop of transfersome dispersion is placed on the sample and then the intensity of the scattered light is adjusted to obtain the particle size (15).

**Zeta Potential Test.** The size of the phenofibrate transfersome can be measured using a zeta potential device, where the zeta potential measurement is carried out using the Zetasizer Nano ZS9. A total of one drop of transfersome dispersion is placed on the sample and then the intensity of the scattered light is adjusted to obtain the particle size (15).

**Entrapment Efficiency**. The adsorption efficiency was expressed as the percentage of adsorption of the added drug. The adsorption efficiency was determined by transfersome (10 ml) transferred to a test tube and centrifuged for 1 hour at 6000 rpm and 4 C using an ultracentrifuge. After being centrifuged, the supernatant files were collected and then the samples were analyzed by spectrophotometry (14).
The adsorption efficiency is calculated using the following equation:
The adsorption efficiency (%) :

$$\% \text{ EP} = \frac{TD - FD}{TD} \times 100\%$$

Note:
TD= Total compounds in formula
FD= The number of compounds in the supernatant (not adsorbed)

### 3. Formula Optimization and Determination of Optimum Transfersome Fenofibrate

Formula Determination of the optimum formula for phenofibrate transfersome was determined using the Factorial Design method from Design Expert software. The data needed to determine the optimum formula is data from the test results on critical parameters which include particle size, zeta potential and sorption efficiency of the 8 formulas. Goal critical parameters of fenofibrate transfersome such as maximum adsorption efficiency, particle size below 1000 nm, zeta potential ±30 mV.

**Tabel 2. Layout out design (action) design expert**

| Run | Phosphatidyl choline | Tween 80 | Sonication | Particle Size | Zeta potential | entrapment efficiency |
|---|---|---|---|---|---|---|
| 1 | 95 | 5 | 35 | 14,4 | 41,9 | 91,6 |
| 2 | 75 | 5 | 35 | 13,6 | 13,2 | 86,1 |
| 3 | 95 | 25 | 15 | 59,2 | 45,0 | 83,1 |
| 4 | 75 | 25 | 35 | 13,8 | 14,3 | 80,3 |
| 5 | 75 | 5 | 15 | 51,2 | 42,1 | 84,2 |
| 6 | 95 | 5 | 15 | 50,4 | 59,2 | 85,7 |
| 7 | 95 | 25 | 35 | 36,2 | 18,3 | 89,1 |
| 8 | 75 | 25 | 15 | 42,1 | 55,2 | 80,3 |

## Data Analysis

The transfersom data were processed using Design Expert software and statistically using SPSS 21. The analysis of the selected formula was carried out by comparing the data calculated by the Design Expert with the test results of the selected formula using the t-test (T-test) and the Kolmogorov-Smirnov test with a 95% confidence level.

## RESULTS AND DISCUSSION

### Optimization Based on *Factorial Design*

1. Results of particle size analysis with software *design expert* 12

   Knowing the effect of each factor, the equation obtained is as follows:

   Y= +119,8406 – 0,4625 (A) – 4,6225 (B) – 2,7125 (C) + 0,0493 (AB) + 0,0086 (AC) + 0,0278 (BC) .....(1)

   Where y is the particle size, A is 90G phosphatidycholine, B is tween 80, and C is sonication.

   Based on the regression coefficients, it shows that 90G phosphatidycholine, tween 80 and sonication have negative values, which means they have an effect on particle size, while the interaction with 90G phosphatidicin addition with sonication and tween 80 with sonication is positive, meaning it increases particle size.

   In Figure 1(A) it can be seen that there is an intersection of the lines showing the interaction between 90G and tween 80 phosphatidicin factors, meaning that the combined use of 90G and tween 80 phosphatidicin will increase the particle size response. In Figure 1(B) the results of the *contour plot* examination, the yellow color indicates the higher the phosphatidicin and tween concentrations, the lower the particle size, the lower the tween 80 concentration, the higher the particle size, which is marked in green. this is indicated by the color gradient on the *contour plot*.

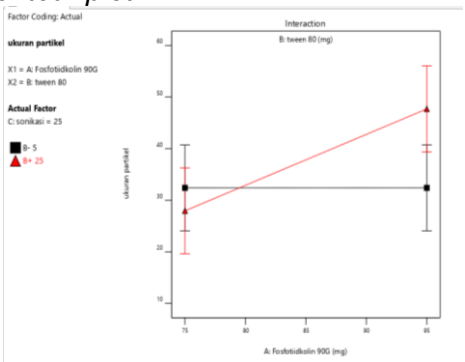
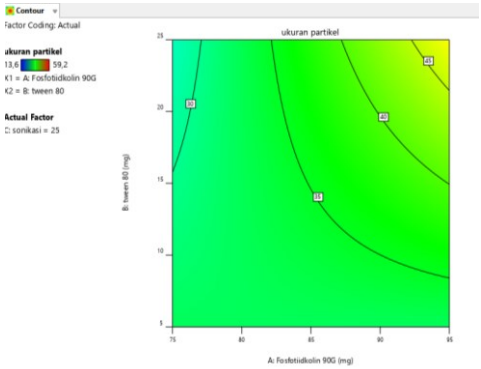



**Figure 1. (A) Transfersome particle size interaction diagram of fenofibrate**




**(B) Countor plot particle size value**

2. Result of zeta potential analysis with software *design expert* 12

   Knowing the effect of each factor, the equation obtained is as follows:

   Y= +9,9490 + 0,6611 (A) + 5,8910 (B) – 3,7691(C) – 0,0649(AB) + 0,0323(AC)- 0,0266 (BC) .....(2)

   Where y is the zeta potential, A is 90G phosphatidycholine, B is tween 80, and C is sonication. Based on the regression coefficient, it shows that 90G phosphatidycholine, tween 80 has a positive value, which means it has an effect on the zeta potential, while the interaction of 90G phosphatidicin addition with sonication and tween 80 with sonication is positive, meaning it increases the zeta potential.

In Figure 2(A) it can be seen that the interaction lines intersect on the graph, which means that the combined use of phosphatidicin 90G and tween 80 will increase the potential zeta response. Figure 2(B) the results of the yellow color control plot show that the higher the 90G and tween 80 phosphatidicin concentrations, the lower the zeta potential, and vice versa, the lower the 90G and tween 80 phosphatidicin concentrations, the higher the zeta potential, indicated by the light blue color.

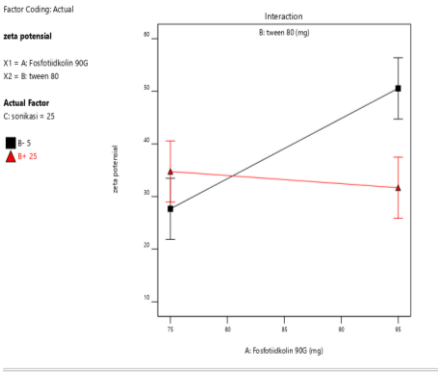
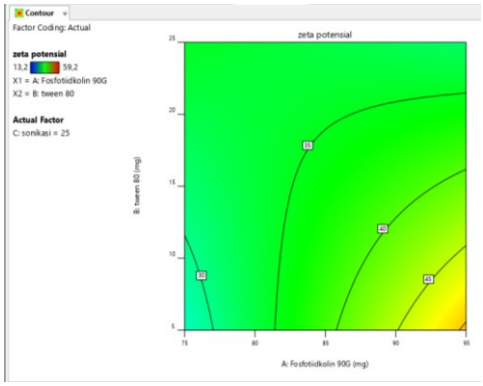



**Figure 2. (A) Transfersome zeta potential interaction diagram of fenofibrate**




**(B) *Contour plot* of potential zeta value**

3. Results of the analysis of the entrapment efficiency with software *design expert* 12

Knowing the effect of each factor, the equation obtained is as follows:

Y= +91,1978 – 0,0982 (A) –0,4563 (B) + 0,6778 (C) + 0,0034 (AB) + 0,0102 (AC) – 0,0006 (BC) .....(3)

Where y is the sorption efficiency, A is 90G phosphatidycholine, B is tween 80, and C is sonication.

Based on the regression coefficients, it shows that the interaction between 90G phosphatidycholine and tween 80 is positive, meaning that with the addition of 90G phosphatidycholine and tween 80 with sonication is predicted to increase the adsorption efficiency, for the addition of tween 80 and sonication has a negative value, which means it will decrease the adsorption efficiency.

In Figure 3(A) it can be seen that the intersection of the separate interaction lines on the graph means that the combined use of phosphatidicin 90G and tween 80 will decrease the response of the entrapment efficiency. Figure 3(B) the results of the countor plot examination in yellow color show that the higher the concentration of phosphatidicin 90G and tween 80, the lower the absorbed drug, on the other hand, the lower the concentration of phosphatidylcholine 90G and tween 80, the higher the adsorbed drug, which is marked in green blue

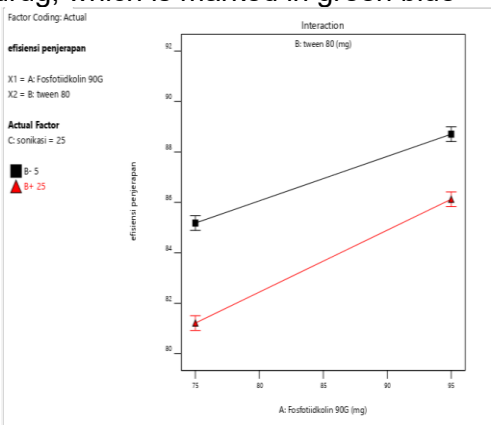
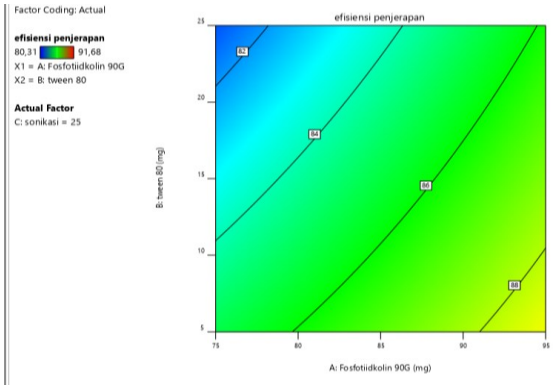



**Figure 3(A). Transfersome entrapment efficiency interaction diagram of fenofibrate**




**(B). *Contour plot* of entrapment efficien**

## CONCLUSION

First, combining phosphatidicholine 90G, tween 80, and sonication as a transfersome-forming agent can alter phenofibrate transfersome features such as particle size, zeta potential, and adsorption effectiveness.

Second, using the factorial design approach, the results of assessing the crucial parameters on the optimum formula yielded phosphatidycholine 90G of 95 percent, tween 80 of 5%, and sonication of 33.39 minutes.

Third, the results of a good phenofibrate transfersome ability test based on the optimum formula, namely particle size and sorption efficiency, with results of 23.675 nm particle size, 52.231 mv zeta potential, and 96.915 percent entrapment efficiency.

## ACKNOWLEDGMENTS

The authors would like to thank the Faculty of Pharmacy Masters at Setia Budi University who has facilitated research during the laboratory until this research was completed.

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