e-ISSN : 2686-2506

Majalah Farmasetika, 4 (Suppl 1) 2019, 50 – 59
https://doi.org/10.24198/mfarmasetika.v4i0.25858

IMPROVEMENT DISSOLUTION RATE AND BIOAVAILABILITY OF SIMVASTATIN TABLET

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(Submit 15/03/2019, Revisi 05/09/2019, Diterima 20/12/2019)

Abstract

Simvastatin is used to reduce cholesterol levels via inhibition of the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. The low bioavailability in simvastatin is due to the influence of P-glycoprotein, the transporter efflux that plays a role in drug absorption. To increase the bioavailability of simvastatin, it is necessary to add a surfactant which serves as a solubilizer and enhancer. The purpose of the study is to determine the effect of Cremophor RH 40 to the dissolution rate and bioavailability improvement of simvastatin tablet. The experiment was consist of four formula with different concentration of Cremophor RH 40 that were 0% (F1), 0,5% (F2), 1%(F3), and 1,5% (F4). Preparation of simvastatin tablets was done by wet granulation method. The tablets obtained were done dissolution test and in vivo test. The formulas with the best value were tested in vivo to the animals. For in vivo study, on the 7th day, the rats blood were taken as $Cmax_{\infty}$ and then the plasma was analyzed with HPLC. Based on the dissolution test results,F2 and F3 gave significant differences ($p < 0.05$) compared to F1. Addition of Cremophor RH 40 of 1% in F3 has the largest simvastatin dissolution rate. The analyze of HPLC on F3 which is the best dissolution result and significant differences was Cmax of F3 (0.3968 ppm). It can be concluded that the addition of Cremophor RH 40 as a surfactant can increase dissolution rate and bioavailability of simvastatin tablet.

Keywords: Simvastatin, Cremophor RH 40, Dissolution, HPLC

Outline

Introduction

P-glycoprotein (P-gp) is a transporter that is included in the ATP Binding Cassette (ABC) superfamily which contributes to the therapeutic effect and detrimental effects of the drug and has a role as an efflux pump in the body (Brunton, et al., 2011). The ability of p-gp as an efflux pump has benefits in inhibiting toxins and xenobiotics that enter the body. In addition, p-gp can reduce the bioavailability of drugs in the body by binding to drug compounds (Lin, J.H; Yamazaki 2003). Simvastatin is a statin drug that functions as a decrease in blood cholesterol levels in patients with hypercholesterolemia. The mechanism of action of this drug is by inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase which competitively inhibits the process of cholesterol biosynthesis in the body. Simvastatin given orally has less than 5% bioavailability while 95% is bound to plasma proteins (Alakhali, et al., 2013).

The low solubility will affect its ability to penetrate the digestive tract membrane and will affect the amount of drug levels in the plasma (Amidon, et al., 1995). To increase the bioavailability of simvastatin, it is necessary to add a surfactant, surfactant added to the manufacture of simvastatin tablets, namely Cremophor RH 40.

Cremophor RH 40 is a non-ionic surfactant that can be used as a solubilizer and enhancer and can improve the bioavailability of drugs (Rowe, et al., 2009). RH 40 as a non-ionic surfactant has been shown to inhibit p-gp work and can improve the bioavailability of a drug.Based on the description above, the researcher will conduct research on the effect of adding Cremophor RH 40 to dissolution rate and bioavailability of simvastatin tablets by in vitro and in vivo testing on male white *Rattusnorvegicus* strain Wistar strain. Examination of simvastatin levels in rat plasma will be analyzed by High Performance Liquid Chromatography (HPLC).

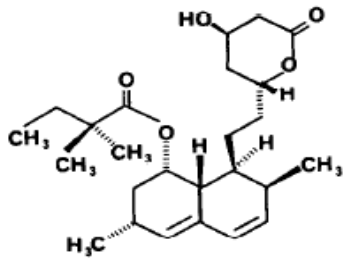

Figure 1. Simvastatin chemical structure (Sweetman, 2009)

Its use of the dose of simvastatin tablets given orally is between 5-80 mg / day. The administration of simvastatin via oral drugs which reaches the blood circulation as active metabolites is less than 5% and as much as 95% is bound to plasma proteins. Simvastatin found in urine in the form of inactivity is 10-15% (Sweetman, 2009).

Methods

Research design

This research was carried out experimentally, simvastatin tablets were printed as many as 300 tablets made in 4 formulas by varying the concentration of cremophor RH 40 with the weight of each tablet which was 300 mg / tablet. Preparation of simvastatin tablets was carried out by wet granulation method, after dissolution test was carried out and bioavailability test was carried out.

Preparation of simvastatin tablet formula

Simvastatin tablets are made in 4 different formulas by varying the concentration of cremophor RH 40. The ingredients used are weighed according to calculations. The first step is to make a binding solution by dissolving PVP K-30 with 96% ethanol, then adding it to the mixture (simvastatin, cremophor RH 40, amprotab, lactose) to form a head mass. Then sieved using a No. 12 sieve. Then dried in an oven at a temperature of 40^{o}C + 30 minutes and sieved again using sieve number 16. The phase is inserted into the outer phase mixture consisting of amprotab, talc, magnesium stearate.

Table 1. Simvastatin tablet formulation

No	Component	Mass (mg)			
		Formula 1 (0 %)	Formula 2 (0,5%)	Formula 3 (1%)	Formula 4 (1,5%)
1	Simvastatin	20	20	20	20
2	Cremophor RH 40	-	1,5	3,0	4,5
3	Amprotab	15	15	15	15
4	PVP K-30	9	9	9	9
5	Lactose	232	230,5	229	227,5
6	Amprotab	15	15	15	15
7	Mg stearate	6	6	6	6
8	Talcum	3	3	3	3

Evaluation of Physical Preparation of Tablets

1. Uniformity test of tablet weight
   Weighed as many as 20 tablets in each formula, calculated the average weight of each tablet and the deviation of tablets to the average weight. There should not be 2 tablets, each of which deviates from the average weight greater than the price specified in column A, and there should not be any tablet that deviates from the average weight more than the price in column B (MOH, 2014).
2. Hardness tester
   A total of 20 tablets measured their hardness using the Hardness Tester. When the tablet breaks, the tool will read the maximum load or force that can be received by the tablet (MOH, 2014).
3. Friability test
   Twenty tablets are debited with an Aspirator. Carefully weigh on the analytic balance and then put it into a friabilator. This test is carried out for four minutes or 100 rounds. Remove the tablet from the device, free from debris and weigh (Lachman, 1989).

4. Disintegration time
   Six tablets were inserted into the disintegration tester. Every the tube is filled with one tablet, then put into a water bath containing one liter of water with a temperature of 370C. The water surface is set 2.5 cm from the sieve with a frequency of 28-32 times per minute. Turn on the device and record the time needed as the tablet breaks down (Lachman, 1989). The tube is filled with one tablet, then put into a water bath containing one liter of water with a temperature of 370C. The water surface is set 2.5 cm from the sieve with a frequency of 28-32 times per minute. Turn on the device and record the time needed as the tablet breaks down (Lachman, 1989).

Simvastatin Tablet Dissolution Test

Dissolve 30 g of sodium dodecyl sulfate and 8.28 g of sodium dihydrogen phosphate in 6000 ml of water. Set the pH to 7.0 with the addition of 50% (b / v) sodium hydroxide solution (MOH, 2014). Add 10 g of manganese dioxide to the container, add 50 ml of dissolved medium, centrifuged for 5 minutes, the clear part is discarded (repeated twice) the first by using the second dissolution medium using water, dried in an oven at 1000C for 1 hour before use (MOH RI, 2014).

Treatment of Test Animals

1. Initial treatment of test animals
   A total of 16 male white rats, RattusNorvegicus, Wistar strain weighing 200-300 g, were acclimatized first with the environment for 2 weeks, of course with the applicable protocol (Wei Chen, et al, 2011)
2. Provision of drug suspension to test animals
   Before being given medicine, each mouse was divided into 2 groups and fasted first for 12 hours while still being given a drink. Giving is done for 7 days with the same time and place. On the 7th day, right at the point where the blood was taken, the levels were read on the HPLC as Cmak∞, and the statistics were validated using the ANOVA test.

Results and Discussion

Results of Optimization of Determination of Cremophor Concentration RH 40

The results of the measurement of the standard curve of simvastatin standard solubility test with UV-Vis spectrophotometer at a wavelength of 238 nm resulted in a linear regression equation that is y = 0.0496x + 0.134.

Solubility test was carried out for the determination of the concentration of cremophor RH 40 which was added to the simvastatin tablet formula. The results of the optimization of simvastatin solubility test with the addition of cremophor RH 40 with various variations of concentration the higher the concentration added the solubility is increased but it has decreased again at high concentrations.

Preparation of Simvastatin Tablet

The manufacture of simvastatin tablets in this study was carried out by wet granulation method. The choice of method in making this tablet is based on its advantages that can improve granular flow properties and can increase dissolution rates of active substances which are insoluble with the right selection of binders (Siregar, 2010).

Simvastatin tablets were printed with a weight of 300 mg per tablet and made in four different formulas by varying the concentration of Cremophor RH 40. Addition of Cremophor RH 40 concentration in simvastatin tablet formula based on the results of the optimization of solubility test. Cremophor RH 40 concentration added to each formula is F1 (0%), F2 (0.5%), F3 (1%) and F4 (1.5%). The tablet manufacturing process is done by first dissolving PVP K-30 with 96% ethanol, the addition of PVP K-30 is used as a binder, in addition to having a good flow rate is expected to produce good compactibility. The dissolved PVP K-30 was added to the mixture (simvastatin, cremophor RH 40, amprotab, lactose) until it formed a mass that could be clenched. Then sieved using No. 12 sieve and then dried in an oven at a temperature of 40^{o}C + 30 minutes and sifted again using sieve No. 16. The phase is inserted into the outer phase mixture consisting of amprotab, talc and magnesium stearate.

Simvastatin Tablet Dissolution Test Results

This test was conducted to determine the dissolution rate ratio from the effect of adding Cremophor RH 40 in various concentrations. Addition of cremophor RH 40 concentration in simvastatin tablet formulas are F1 (0%), F2 (0.5%), F3 (1%) and F4 (1.5%). Dissolution test was carried out based on the method that has been set out in the 2014 edition of Indonesian Pharmacopoeia V using type 2 dissolution, phosphate buffer pH 7.0 as much as 900 mL which was put into a dissolved tube and regulated at a speed of 50 rpm at 37 ± 0,5^{o}C. In vitro dissolution test is a test that can be used to determine the rate of drug release which can describe the pharmacokinetic profile of the drug in the body (Lachman, 1994).

Dissolution testing is carried out using six tablets of each formula. The time taken for the dissolution test is 30 minutes with 10 ml sampling taken at the 5, 10, 15, 20, and 30 minutes, the sample taken is replaced with the same volume of dissolution medium, it is done to maintain the volume from the dissolution medium remains the same. The results of dissolution testing are then shaken with a centrifuge which has been added to the heated manganese dioxide. Then measurements were taken by UV-Vis spectrophotometer at 238 nm. The dissolution test results are presented in Table 2.

Table 2. Simvastatin tablet dissolution test results

Time (minutes)	Drug dissolved (%)			
	F1 (0%)	F2 (0,5%)	F3 (1%)	F4 (1,5%)
5	31,81±0,28	44,51±4,93	45,72±5,05	36,18±6,29
10	42,52±0,27	64,76±0,22	67,41±0,88	56,15±0,26
15	48,24±0,46	72,10±0,33	76,65±2,52	66,55±1,98
20	58,12±0,30	79,05±2,07	81,20±3,34	74,50±2,35
30	75,16±0,14	83,13±2,13*	89,08±2,96*	80,08±3,77*

*There is a significant difference ($p < 0.05$) compared to F1. Testing is done with 6 tablets of each formula.

Based on the dissolution test results on the simvastatin tablet formula with different RH 40 cremophor concentrations namely F1 (0%), F2 (0.5%), F3 (1%) and F4 (1.5%) showed that formula 2 and formula 3 gave a significant difference ($p < 0.05$) compared

to formula 1. In addition, formula 4 did not give a significant difference ($p < 0.05$) compared to formula 1. Therefore, it can be ascertained that the addition of 1% cremophor RH 40 has the biggest dissolution rate of simvastatin with an average value of 89.08%.

Table 3. Physical evaluation of simvastatin tablet

Formulation	Weight variation (N=20)	Hardness (N) (N=20)	Friability (%)	Disintegration time (N=6) (min)
F1	305,7±4,05	47,00±4,91	0,06	5,55±1,06
F2	282,3±6,45	47,98±5,73	0,31	6,53±1,71
F3	290,2±4,40	46,73±3,33	0,24	6,41±1,19
F4	280,5±8,15	46,50±5,64	0,38	9,08±1,05

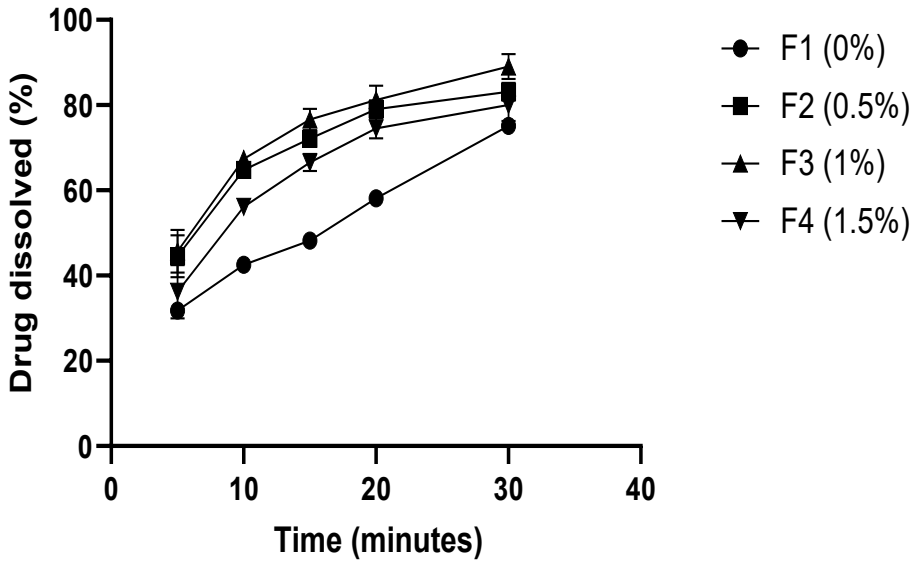

Figure 1. Dissolution profile of simvastatin tablet

Results of Simvastatin Tablet Bioavailability

The bioavailability test was carried out on the formula with the best results of dissolution, the best dissolution result was formula 3 with the addition of cremophor RH 40 1%. Bioavailability testing was carried out on 2 formulas namely formula 1 (0%) and formula 3 (1%). The measurement results of the control sample (F1) and test (F3) using HPLC are presented in Table 4.

Based on the results of the bioavailability comparison between F1 and F3 presented in Fig. 2, it was found that there was a difference between the average maximum concentration of Formula 1 (0.1211 ppm) compared to the maximum concentration of Formula 3 (0.3968 ppm), so that it could mean that addition of cremophor RH 40 as a surfactant can increase the bioavailability of simvastatin tablets. This is based on Cremophor RH 40 inhibiting the P-gp substrate which binds to simvastatin, so that the accumulation of imvastatin levels in the blood has increased.In research conducted by

Table 4. Bioavailability of selected simvastatin tablet

Subject number	Cmax∞(N=8)	
	Control (F1) (ppm)	Sample (F3) (ppm)
1	0,1323	0,4968
2	0,1126	0,3677
3	0,1621	0,3970
4	0,0705	0,3132
5	0,1785	0,2578
6	0,1022	0,4500
7	0,1147	0,4728
8	0,0962	0,4196
average	0,1211±0,03	0,3968±0,08

Hanke, *et al* (2010) states that the use of cremophor RH 40 as a surfactant has been shown to inhibit the action of P-glycoprotein, so that the bioavailability of a drug can increase. Research conducted by Tayrouz, et al., (2003) states that the addition of cremophor RH 40 in digoxin can increase bioavailability.

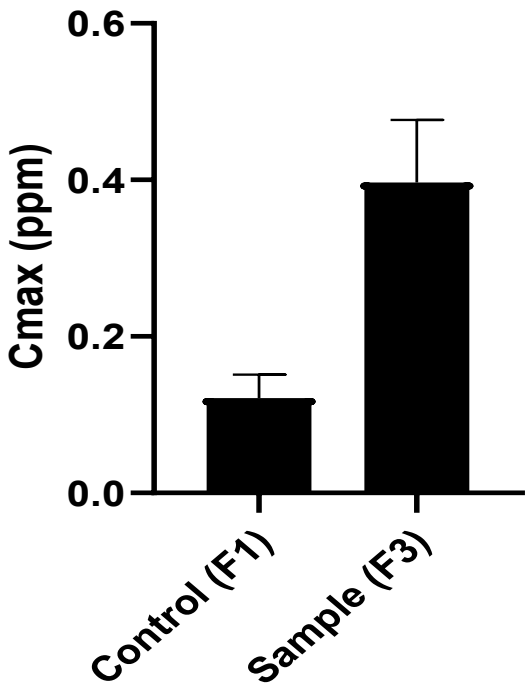

Figure 2. Average of maximum concentration of selected simvastatin tablet

Conclusion

The selected simvastatin tablets were F3 tablet formulation with 1% addition of cremophor RH 40.

The addition of cremophor RH 40 on simvastatin tablets can significantly increase dissolved percent (Q).namely in Formula 2 (cremophor RH 40 0.5%) and Formula 3 (cremophor RH 40 1%). Addition of cremophor RH 40 on simvastatin tablets can increase bioavailability seen from the parameters of maximum concentration (Cmak∞) between the control group (0.1211 ppm) and the test group (0.3968 ppm).

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