

Increasing dissolution rate of telmisartan tablet by dispersion method

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Abstract. Telmisartan is an antihypertensive drug which has a low bioavailability value around 42% after a dose of 40 mg and 58% after a dose of 160 mg, this is influenced by the poor level of Telmisartan solubility and directly affects the Telmisartan therapeutic activity. So that Telmisartan research with Gelucire 44/14 was conducted by a solid dispersion method to determine the effect of Gelucire 44/14 usage on increasing dissolution rate of Telmisartan tablets. The study was conducted with 4 Telmisartan tablet formulas by varying the number of Gelucire 44/14 in each formula in the recommended range of use of 15-50%. Formula 1 is a formula with 0% Gelucire 44/14, formula 2 is a formula with 15% Gelucire 44/14, formula 3 is a formula with 30% Gelucire 44/14, formula 4 is a formula with 45% use of Gelucire 44/14. After the mass was printed then dissolution tests were carried out on each formula. From the results of the study, formula 1 produces the average value of dissolution 3,760%, formula 2 produces the average value of dissolution of 22,675%, formula 3 results in an average dissolution value of 34,131%, formula 4 produces an average dissolution value of 45,691%. So it can be concluded that the use of Gelucire 44/14 by the solid dispersion method on the Telmisartan tablet formula has an influence in increasing the dissolution rate of Telmisartan Tablets and formulas that provide the best dissolution rate obtained from formula 4.

1. Introduction

Telmisartan is an antihypertensive drug of the angiotensin II receptor antagonist class that is commonly used in the treatment of hypertension. Telmisartan is rapidly absorbed after oral administration with bioavailability depending on the dose, which is about 42% bioavailability after a dose of 40 mg and 58% after a dose of 160 mg [1]. There is a classification known as the Biopharmaceutical Classification System which divides drugs into four classes based on solubility and permeability.

Based on the Biopharmaceutical Classification System, Telmisartan belongs to the class II category. Drugs in this category show high levels of absorption with low levels of dissolution. The bioavailability of drugs belonging to this category usually has a limited dissolution rate [2]. The level of bioavailability for this class II category can be increased by improving the solubility and rate of drug dissolution [2].

The bioavailability of the drug orally depends on its solubility and / or the level of dissolution. Therefore, there are various methods that can be used to increase the dissolution of drugs including salt formation, micronization, addition of solvents or surfactants and solid dispersion. In some studies solid dispersion is often used as the main choice to improve dissolution [3]. Solid dispersion is a technique to increase absorption, dissolution and therapeutic effect of a drug. This method is best suited to pharmaceutical techniques. The term solid dispersion can be defined as a mixture of one or more active



substances (hydrophobic) in an inactive carrier or carrier (hydrophilic) in a solid preparation [4].

The disperser that has been used in several studies is Telmisartan with Poloxamer 407 [3], Telmisartan with PVP K-30, HPMC E4 and PEG 6000 [3], Telmisartan with PVP K-30, PEG 4000 and -cyclodextrin [4], and Telmisartan with Gelucire 43/01 [3]. Gelucire 43/01 was used as a disperser in increasing the rate of Telmisartan dissolution. However, no Gelucire 44/14 has used it as a disperser at Telmisartan. In the Sixth Edition Handbook of Pharmaceuticals, Gelucire 44/14 or Lauroyl polyoxyglycerides are categorized into excipients that function as enhancers of dissolution [5]. Based on this, Telmisartan Tablet with Gelucire 44/14 dispersion will be made in this study with a solid dispersion method so that it can be seen the effect of Gelucire 44/14 on increasing the Telmisartan dissolution rate.

2. Methods

In this study, the arrangement of Telmisartan tablet preparation by solid dispersion method using Gelucire 44/14 was done at Bandung Research and Development Unit owned by PT. Kimia Farma. In this study the steps taken were the making of Telmisartan print mass, print mass testing, tablet printing, tablet testing and data analysis.

The tools that were used in this research are tools owned by PT Kimia Farma Bandung Research and Development Unit. The tools that were used include Sartorius analytical scales, 18 size sieves, 30 size sieves, mortar, stempers, visual lights, fiber, Restch size sieves, density tester, Pharma Test flow tester, High Performance Liquid Chromatography, single punch printing machines Corsch, calipers, Pharma Test hardness tester, Erweka disintegration tester, Erweka tester friability, Erweka dissolution tester.

The raw materials that were used in this research are raw materials obtained from PT Kimia Farma Bandung Research and Development Unit. The raw materials were used are Telmisartan, Gelucire 44/14 (Lauroyl polyoxyglycerides), Avicel PH 102 (Microcrystalline), PVP (Povidone), Magnesium Stearate, KH₂PO₄, NaOH, Acetonitrile, Aquadest. The formula design that will be used can be seen in table 1.

Table 1. *Designing Formula*

Material	Usage/ Tablet	Percentage/Tablet (%)			
		F1	F2	F3	F4
Telmisartan	40 mg	11,43	11,43	11,43	11,43
Gelucire 44/14	15 - 50%	0	15	30	45
Avicel	20 - 90%	84,07	69,07	54,07	39,07
PVP	0,5 - 5,0%	2,5	2,5	2,5	2,5
Magnesium Stearate	0,25 - 5,0%	2	2	2	2
TOTAL		100	100	100	100

The making of Telmisartan Print Mass was carried out by entering Telmisartan and Gelucire 44/14 into a 250 mL beaker glass container, then dispersing it above the Magnetic Stirrer. Magnetic Stirrer temperature was set at 60 - 70 °C, speed of 100 - 200 rpm for 1 hour. After Telmisartan with Gelucire 44/14 was melted and then removed from the Magnetic Stirrer then stored in a Freezer at -20°C. The mixture of condensed Telmisartan and Gelucire 44/14 was mashed using a mortar. The mashed mixture was mixed with Avicel then sieved using a size 18 sieve. Then PVP (Povidone) was added and mixed for 15 minutes. The next process is added Magnesium Stearate which has been sieved using a size 30 sieve, then mixed for 5 minutes.

Print Mass Evaluation is carried out with several tests, namely: Description Test, Print Mass Particle Size Distribution Test, Compressibility Test, Flow Rate and Angle of Rest, Determination of Print Mass Content to make a standard solution. After the print mass has been analyzed, a single punch printing machine is prepared by installing punch and dies that have a diameter of 9 mm and biconvex then the printing process is carried out by adjusting the hardness at (30 - 50) N and weight (0.340 - 0.360) g. The next process is Evaluation of the Telmisartan Tablet, which is carried out with Organoleptic Test, Size Uniformity Test, Weight Uniformity Test, Tablet Hardness Test, Tablet Crush Time Test, Tablet

Toughness Test, and Dissolution Test.

3. Results and discussion

3.1 Material Retrieval

This research begins with the collection of raw materials. The materials used in this study include Telmisartan, Gelucire 44/14, PVP, Avicel PH 102 and Magnesium Stearate.

3.2 Determination of Bets Size

The bets size determination is carried out by considering the needs of the print mass and tablet as the test sample. The bets size used in the study was 70 grams = 200 tablets @ 350 mg.

3.3 Formula for Telmisartan Tablet

The usage percentage per tablet of Telmisartan is 40 mg adjusting to a dose of 1 Telmisartan Tablet. The number of Telmisartan per tablet is equated to each formula to provide the same comparison. The percentage of Gelucire 44/14 usage is varied for each formula referring to the recommended usage range which is 15-50% [5]. Gelucire 44/14 was not used in formula 1 to determine the dissolution value of Telmisartan tablets without the addition of Gelucire 44/14 so that it could be used as a reference for the addition of Gelucire 44/14 in the next formula. In formula 2, Gelucire 44/14 is used about 15%; in formula 3, Gelucire 44/14 is used about 30% and in formula 4, Gelucire 44/14 is used about 45%. This value is determined based on the determination of the percentage of recommendations low, middle, and high. This was done to determine the concentration of Gelucire 44/14 which gave the best effect on increasing the dissolution rate of Telmisartan Tablet. Tablet formula is shown in table 2.

Table 2. *Formula of Telmisartan Tablet*

Material	Total/Tablet (mg)			
	F1	F2	F3	F4
Telmisartan	40,01	40,01	40,01	40,01
Gelucire 44/14	0,00	52,50	105,00	157,50
Avicel	294,25	241,75	189,25	136,75
PVP	8,75	8,75	8,75	8,75
Magnesium Stearate	7,00	7,00	7,00	7,00
TOTAL	350,00	350,00	350,00	350,00

The usage percentage per tablet of Telmisartan is 40 mg adjusting to a dose of 1 Telmisartan Tablet. The number of Telmisartan per tablet is equated to each formula to provide the same comparison. The percentage of Gelucire 44/14 usage is varied for each formula referring to the recommended usage range of 15-50% [5]. The percentage of Avicel usage varies in each formula. Because the use of Avicel in the design of this research formula which is focused on the fill function of Avicel is in the range of 20-90% [5]. Therefore the amount of Avicel in each formula is justified on the desired tablet weight (up to 350 mg per tablet). In addition to being used as filler, Avicel is also used as an absorbent to absorb the remaining wetting factors from the results of the solid dispersion of Telmisartan and Gelucire 44/14. The percentage of PVP (Povidone) usage is 2.5% in each formula to provide the same comparison and refers to recommended range of use for tablet formulas is 0.5% - 5.0% [5].

3.4 Making Print Mass

In the making of Telmisartan print mass by dispersion method (Hot Melt Fusion) melting is done between Telmisartan and Gelucire 44/14 using Magnetic Stirrer at 65°C at a speed of 100 rpm for 1 hour. The refined Telmisartan and Gelucire 44/14 mixture has a texture that is still slightly wet, so to improve the texture of the mass, Avicel PH 102 is added as an absorbent (also has a function as a filler) [5].

3.5 Print Mass Evaluation

3.5.1. Description Test. Description Test was performed using Visual Lights and Fiber by means of print mass taken about 30 grams and then placed on fiber, illuminated by a visual lamp at a minimum light intensity of 1,000 lux. All formulas show the same description, namely the print mass with the form of a fine white granule.

3.5.2. Particle Size Distribution Test. The particle size was tested using the Laboratory Sieving Machine Restch [6] in a way that the print mass was taken about 30 grams. Then it was put on top of the sieve that has been arranged from 30 mesh, 45 mesh, 60 mesh, 80 mesh, 100 mesh, 120 mesh, 170 mesh, then the base on the sieve shaker tool. The tool is turned on for 25 minutes then count the number of granules left on each sieve. The particle size distribution value is shown in Table 3.

Table 3. Result of Particle Size Distribution Test

Mesh Size	Particle Size Distribution (%)			
	F1	F2	F3	F4
30	7.70	7.82	13.72	44.30
45	15.31	20.67	10.69	20.26
60	10.76	4.53	15.19	21.86
80	15.01	14.94	17.06	7.19
100	20.32	12.81	7.86	2.83
120	10.79	9.85	16.16	2.03
170	15.57	15.24	11.66	0.66
Alas	4.48	14.01	7.60	0.13

3.5.3. Compressibility Test. Compressibility of the print mass was tested using the Density tester [7], by the way the print mass to be tested was inserted into the density tester pipe to 50 mL, then it was weighed. It was compressed 500 times, then the last volume was recorded. The congestion value of the printed mass is shown in Table 4.

Table 4. Result of Compressibility Test

Test Result	Formula 1	Formula 2	Formula 3	Formula 4
<i>Bulk Density(g/mL)</i>	0.48	0.57	0.60	0.63
<i>Tapped Density(g/mL)</i>	0.62	0.66	0.70	0.71
% Compressibility	14	9	10	9
Category	Good	Excellent	Excellent	Excellent

The compressibility test results above show that the presence of Gelucire 44/14 in the Telmisartan Tablet formula can increase the percentage and compressibility category [8].

3.5.4. Flow Rate and Rest Angle Test

Flow Rate and Rest Angle are tested using the Pharma Test flow tester by taking 50 grams of print mass. It was put in a funnel flow tester. The results of the print mass flow rate above show that the mass flow rate increases with the addition of Gelucire 44/14. Changes in the flow rate category are also shown in formula 4, where categories increase from "bad" to "good" [9]. The results of the rest angle test are shown in Table 5.

Table 5. Result of Rest Angle Test

Formula	Rest Angle (°)	Category
Formula 1	32.3	Easy to Flow
Formula 2	29.1	Very Easy to Flow
Formula 3	26.8	Very Easy to Flow
Formula 4	26.1	Very Easy to Flow

The test results of the rest angle above show that with the addition of Gelucire 44/14 it is able to increase the category of rest angle from "easy to flow" to "very easy to flow".

3.5.5. Print Mass Level Test. Print mass level was tested using High Performance Liquid Chromatography by means of (to make standard solutions) 40 mg of Telmisartan that was weighed then dissolved in a 20 mL volumetric flask. It was dropped about 1 mL into a 20 mL volumetric flask and solvent. The solution was filtered by using a 0.45µm millex and is inserted into the High Performance Liquid Chromatography vial. The solution was analyzed by High Performance Liquid Chromatography. The test results showed that the presence of Gelucire 44/14 has an effect on the achievement of the Telecommunication Range levels at ideal values in tablets according to the specifications listed at 90.0 - 110.0% [10]

3.6 Printing of Mass Telmisartan Tablet by Machines

Print the single punch Corsch by installing punch and dies that have a diameter of 9 mm and biconvex. Then the printing process is done by adjusting the hardness at (30 - 50)N and weight (0.340 - 0.360)g.

3.7 Telmisartan Tablet Evaluation

3.7.1. Organoleptic Test. Organoleptic tests were carried out using Visual and Fiber Lamps by taking 20 Telmisartan tablets and then placing them on the fiber which was irradiated by the light and then carefully observed. The results of organoleptic test showed that the tablets produced are in the form of tablet, biconvex, white plain and not indicated by contamination, sticking, capping or spotting.

3.7.2. Size Uniformity Test. The size uniformity test was carried out using calipers to measure the thickness and diameter of the tablet by means of 20 Telmisartan tablets were measured in thickness and diameter. The results of the test above show that the presence of Gelucire 44/14 has an effect on the size of the Telmisartan Tablet, where tablets using Gelucire 44/14 have a lower tablet size (thickness and diameter), this is due to the increasing compressibility of the Telmisartan print mass. High standard deviation from the uniformity test results in values at 0.01 - 0.02. This shows that all formulas are able to produce uniform (not having significant differences) tablet sizes (thickness and diameter) and fulfilling the requirements.

3.7.3. Weight Uniformity Test. Uniformity of weights was carried out using the Sartorius Analytical Scales by means of 20 Telmisartan tablets that were weighed then the results were recorded. The average tablet value and the resulting deviation value were calculated. The test results showed that all formulas were able to produce tablets with eligible weights and there were no significant changes with the addition of Gelucire 44/14 to the weight of the tablet. The standard deviation of the weight uniformity test of formula 1 was 0.0019; the formula2 is 0.0017; formula 3 is 0.0013; formula 4 is 0.0018. This shows that the entire formula is able to produce a uniform tablet weight (does not have a significant difference in deviation) and the result is qualified.

3.7.4. Tablet Hardness Test. The tablet hardness test was carried out using the Hardness Tester Pharma Test [11]. The test results showed that the addition of Gelucire 44/14 was able to produce tablet hardness with a lower standard deviation. This shows that the addition of Gelucire 44/14 can reduce the deviation value from the hardness of the tablet produced.

3.7.5. Tablet Disintegration Time Test. The disintegration time of the tablet was tested using Erweka's Disintegration Tester [12]. Shatter time test results showed that the presence of Gelucire 44/14 was able to increase the disintegration time of tablets. The standard deviation produced in formula 1 is 0.001; in formula 2 is 0.003; formula 3 is 0.004; and formula 4 is 0.004. This shows that the entire formula is able to produce tablets with uniform disintegration time (not having significant deviations) and the results

meet the requirements.

3.7.6. Tablet Firmness Test. Tablet Firmness was tested using the Erweka Friability Tester. The results of the tablet firmness test showed that the entire formula was able to produce a tablet firmness value that met the eligible condition (a good tablet firmness requirement is <1%) [8]. In addition, the presence of Gelucire 44/14 can reduce the friability of the tablet surface against the treatment that causes abrasion on the tablet surface.

3.7.7. Dissolution Test. Dissolution Test was carried out using the Rowing Type Erweka Dissolution Tester [13]. Dissolution test results showed that Gelucire 44/14 was able to increase the dissolution rate of the Telmisartan Tablet. Where in formula 1 as a comparison formula (without the addition of Gelucire 44/14), the average value of dissolution is 3.760; formula 2 as a formula with the addition of Gelucire 44/14 at a low recommendation percentage is 22,675; formula 3 as a formula with the addition of Gelucire 44/14 with the middle recommendation percentage is 34,131; formula 4 as a formula with the addition of Gelucire 44/14 with the highest percentage is 45,691. This shows the rate of dissolution which increases with the addition of Gelucire 44/14. And Gelucire 44/14 concentration which gave the best effect on increasing dissolution rate of Telmisartan Tablet was Formula 4 with the use of Gelucire 44/14 about 45% in the formula.

4. Conclusion

Based on the results of the study, Gelucire 44/14 has an effect on increasing the dissolution rate of Telisartan Tablet. The Gelucire 44/14 concentration which gives the best effect on increasing dissolution rate of Telmisartan Tablet is Formula 4 with the use of Gelucire 44/14 about 45% in the formula. In addition, the results of Gelucire 44/14 research also have a good influence on test parameters of other Telmisartan Tablets. Gelucire 44/14 on the Telmisartan Tablet formula shows that it can increase the compressibility of the print mass which directly affects the print mass flow rate, the rest angle of the print mass and the firmness of the tablet.

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