

## IMPROVEMENT OF THE DISSOLUTION PROFILE OF SIMVASTATIN TABLETS WITH THE ADDITION OF CREMOPHOR-EL USING WET GRANULATION METHOD

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### ABSTRACT

**Objective:** Simvastatin is a drug used as a first-line anti-cholesterol in the treatment of dyslipidemia. Low solubility will affect its ability to penetrate the digestive tract membrane and will affect the amount of drug levels in the plasma. The use of Cremophor-EL as a surfactant has been shown to inhibit the action of P-glycoprotein so that it can increase the bioavailability of a drug and can increase the effect of a drug.

**Methods:** The preparation of simvastatin tablets was carried out using the wet granulation method. The dissolution test used the paddle method, a speed of 50 rpm at a temperature of  $37 \pm 0.5$  °C with a phosphate buffer pH 7.0 as the dissolution medium.

**Results:** The results showed that at 30 min the generic simvastatin tablets had 81.52% dissolution and the Simvastatin Tablets with Cremophor-EL were 85.520%.

**Conclusion:** Simvastatin cremophor-EL tablets are more dissolved than generic simvastatin at 30 min so that cremophor-EL simvastatin tablets have a better dissolution rate than generic simvastatin tablets.

**Keywords:** Simvastatin, Cremophor-EL, Dissolution

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### INTRODUCTION

One of the drugs used to lower blood cholesterol levels is simvastatin. Simvastatin is a statin group of drug that has a mechanism by inhibiting the HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase enzyme that will competitively inhibit the process of cholesterol biosynthesis in the body, so it will convert acetyl-CoA into mevalonic acid, which is a precursor to cholesterol [1]. In addition to lowering LDL cholesterol levels, inhibition of HMG-CoA reductase also causes anti-inflammatory effects and improved endothelial function [2].

In the Biopharmaceutics Classification System (BCS), simvastatin belongs to class II, which has low solubility and high permeability [3]. Low solubility will affect its ability to penetrate the membranes of the gastrointestinal and will affect the amount of drugs levels in plasma [4, 5]. Simvastatin administered by oral 95% will be bound to plasma proteins and have a bioavailability of less than 5%. Several studies on simvastatin have been conducted with the aim of increasing solubility with various methods, including solid dispersion [6] and cocrystal [7]. Characterization of simvastatin solid dispersion using aqueous solvents [8], improved solution of simvastatin with solid dispersion method consisting of carrier and wetting material [9]. Cremophor EL is a non-ionic surfactant that serves as a solubilizer and enhancer and also can increase the bioavailability of a drug. The use of Cremophor EL as a surfactant has been shown to inhibit the work of P-glycoprotein so it can increase the biological availability and effect of the drug [10]. In the present study, the researcher will conduct on the effect of adding Cremophor EL to the dissolution rate of simvastatin tablets and compared to commercial tablets.

### MATERIALS AND METHODS

#### Materials

Simvastatin was purchased from Gracia Pharmindo Inc. Cremophor EL (BASF®), Lactose (Bratachem®), Magnesium Stearate (Bratachem®), Amprotab (Bratachem®), Polyvinyl pyrrolidone-K30 (Bratachem®), Sodium Dihydrogen Phosphate (Merck®), Sodium Dodecyl Sulfate (Merck®).

### Simvastatin tablet formulations

Simvastatin tablets were made by wet granulation method. The binding substance was carried out by dissolving PVP K-30 in 96% of ethanol, then added to the mixture (simvastatin, cremophor EL, amprotab, lactose) until it can be clenched. The formed substance was filtered using mesh number 12. The resulting granules were dried in the oven at 40 °C for 18 h; the dried granules were re-filtered with mesh number 16. Qualified granules were added amprotab, magnesium stearate, and talk. Formula of the simvastatin-cremophor EL tablet is shown in table 1.

Table 1: Formula of simvastatin tablet (200 mg)

No	Ingredients	Quantity
1	Simvastatin	20 mg
2	Cremophor EL	0,6 %
3	Amprotab	5%
4	PVP-K 30	3%
5	Talk	1%
6	Mg. Stearate	2%
7	Amprotab	5%
8	Lactose	qs

### Dissolution test

Phosphate buffer as much as 900 ml was inserted into the dissolution tube. Each tablet was inserted into each tube, the sample was taken for 5, 10, 15, 20 and 30 min as much as 10 ml. After the sample was taken, the dissolution medium was inserted as much as 10 ml to keep the volume. It was measured with a UV-Vis Spectrophotometer at 238 nm [11].

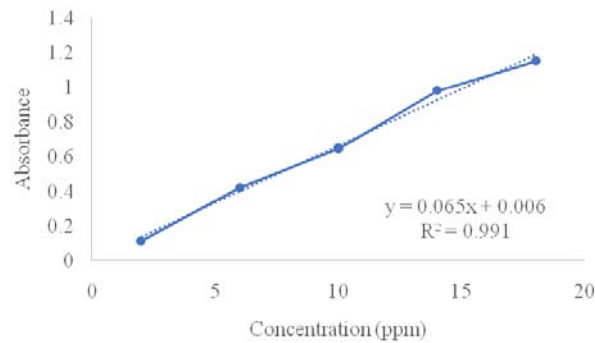
### RESULTS

Evaluation of the physical preparation of the tablet was carried out to determine the quality and to prove that the resulting tablet meets the requirements. In this study the evaluation of tablets conducted included weight uniformity test, tablet hardness test, tablet fragility test and tablet crush time test.

The evaluation of granules was carried out to determine the quality of granules. The examination includes moisture content, compressibility, flow rate, repose angle, and Hausner ratio (table 2). Determination of simvastatin wavelength was done by dissolving 50 mg of simvastatin in phosphate buffer (500 ppm). Then, it was diluted and examined using a UV-Vis spectrophotometer at 243 nm. Calibration curve of simvastatin was shown in fig. 1. The Result of Comparative Dissolution of Generic and Simvastatin-Cremophor EL Tablets was shown table 3.

**Table 2: The evaluation of granules simvastatin-cremophor EL**

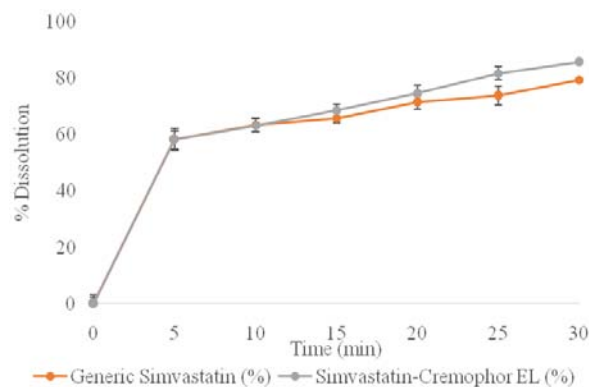
Evaluation	Results
Moisture Content (%)	1.5
Flow Rate (g/s)	0.6
Angle of Repose ( $\alpha$ )	26.1
Compressibility (%)	14.5
Hausner ratio	1.17



**Fig. 1: Calibration curve of simvastatin**

**Table 3: The result of comparative dissolution of generic and simvastatin-cremophor EL tablets**

Times	Generic simvastatin (%)	Simvastatin-cremophor EL (%)
5	57.46±2.3	58.096±3.2
10	64.38±3.8	63.200±3.1
15	66.78±2.3	68.630±2.2
20	72.06±2.3	74.612±2.2
25	75.06±1.8	81.686±2.6
30	81.19±3.2	85.520±2.3



**Fig. 2: The result of comparative dissolution of generic and simvastatin-cremophor EL tablets**

Based on the results of the dissolution test, more simvastatin-cremophor EL tablets dissolved compared to generic simvastatin in 30 min so that simvastatin-cremophor EL tablets have a better dissolution rate than generic simvastatin tablets (fig. 2).

## DISCUSSION

Granule moisture examination aimed to find out the water content contained in the granules after drying. The moisture content of granules will affect the nature of the granule flow. The tool used for testing granule moisture content is Moisture analyzer (Ohaus®). Granule content of Simvastatin-Cremophor EL tablets was 1.5%. The compressibility check aims to determine the flow properties from granules. Compressibility testing was measured using the Tap Density Meter Tool. Granule compressibility was 14.5% [12].

Flow rate check was carried out with the aim of knowing the nature of the granule flow to be made into a tablet. The tool used to

determine the flow rate is flow tester. The test result of granule flow rate was 0.6 grams/second. The results of the examination of granule flow rate against simvastatin-Cremophor EL tablets meet the established requirements, a good flow rate is 10 g/s [13].

The flow rate is influenced by the angle of rest; the smaller repose angle, the better flow rate [3]. The result of the resting angel test was 26.10  $\alpha$  ( $^{\circ}$ ). This result showed that simvastatin-cremophor EL tablets meet the requirements because it has an angle of repose between 25-30 $^{\circ}$  [14] Comparison of Hausner's ratio is derived from mammoth weight and real weight. The higher the Hausner's ratio, the poorer the granule flow properties. The result of Hausner's ratio testing was 1.17. Based on the result, simvastatin-Cremophor EL is eligible because it has a Hausner's ratio  $\approx$  1 [13].

Evaluation of the physical tablets was done to determine the quality and prove that the resulting tablet meets the requirements. In this

study the evaluation of tablets conducted included weight uniformity test, tablet hardness test, friability test and hardness tester. Weight uniformity test was performed as one of the homogeneity indicators in mixing tablets. Tablets that weigh uniformly are expected to have the same ingredients, so that the resulting therapeutic effect is also the same. Testing was conducted on 20 tablets from each generic and simvastatin cremophor EL tablet which was taken randomly, then it was weighed using analytical balance.

The results of uniformity of tablet weight was 205.11 mg [13]. Tablet hardness testing was performed with the aim of knowing the strength of the tablet against mechanical pressure during the manufacturing, packaging, distribution and storage process. Hardness testing of tablets was conducted on 20 tablets from each generic simvastatin and simvastatin with cremophor EL tablets using Hardness tester tool of 5.292 kg/cm<sup>2</sup>. The results obtained from hardness testing of each formula have met the established requirements, good hardness requirements that are 4-7 kg/cm<sup>2</sup> [13].

Friability testing was performed to determine the fragility of the tablet when dropped from a certain height. The tool used to measure the fragility of tablets is friabilator. The test result of fragility of Simvastatin tablets with Cremophor EL was 0.87% and for generic simvastatin was 0.86%. The fragility of a good tablet is no more than 1%, so it can be concluded that fragility of generic and simvastatin with Cremophor EL tablets meets the requirements [13].

Disintegration test was performed to estimate the release time of active substance from the preparation when it comes into contact with bodily fluids. This crushed time test is very important for tablet because it will affect the onset of drug. Disintegration tester used for this study. Simvastatin-Cremophor EL has a crushed time of 4.5 min while generic simvastatin was 1.1 min [15].

#### CONCLUSION

The results showed that at 30 min generic simvastatin tablets were dissolved by 81.19% and simvastatin. Cremophor EL tablets were 85.52%. More simvastatin-cremophor EL tablets dissolved compared to generic simvastatin in 30 min so that simvastatin-cremophor EL tablets have better dissolution rate than generic simvastatin tablets.

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Nil

#### AUTHORS CONTRIBUTIONS

All the authors contributed equally.

#### CONFLICT OF INTERESTS

Declared none

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