INTRODUCTION

Miconazole nitrate is one of the broad spectrum antifungal compounds of the imidazole group [1]. This antifungal agent is a fungicide used in the treatment of fungal infections in topical and transdermal [2]. This drug works by inhibiting ergosterol biosynthesis on the fungal cell membranes that cause damage to the cell wall of the fungus, resulting in increased membrane permeability, and ultimately, causing the fungal cell to lose its cellular nutrients. The drug is mainly used for the treatment of mycosis skin diseases [3]. The bioavailability of miconazole nitrate is very low when taken orally because it is very difficult to dissolve and has a small absorption, and therefore, the use of miconazole nitrate as an antifungal agent is given topically, but the main problem of this drug in topical treatment is poor skin penetration [4].

To design effective formulations of miconazole nitrate has long been a major challenge due to the very limited efficacy due to the unstable or poor drug solubility in the carrier. One of the pharmaceutical preparations that can be used in a drug delivery system to overcome the above problem is a nanoemulsion drug delivery system, which is applied to improve solubility and bioavailability of a lipophilic drug [5].

Nanoemulsions do not creaming, sedimentation, and flocculation or coalescence compared to macroemulsions [14]. Nanoemulsions also have the potential as a carrier in topical treatment because it is able to optimize the dispersion of active substances in the skin layer [2]. Based on the above background, the researchers conducted research on the development of formulations of miconazole nitrate in the form of nanoemulsion with better hope and effective as an antifungal.

METHODS

Preparation of miconazole nitrate nanoemulsion
The ingredients of the oil phase, namely, oleic acid are added with miconazole nitrate stirred with magnetic stirrers to homogeneous. Meanwhile, the aqueous phase including sodium metabisulfite and aqua bidestilat was mixed and stirred with a stirring bar until homogeneous. In a separate container, an emulsifier comprising Tween 80 and PEG 400 is mixed and stirred with a magnetic stirrer up to homogeneous. Next, the oil phase is added to the water phase while the addition of the emulsifier mixture is piecemeal and stirred using a magnetic stirrer. After all the ingredients are mixed, then the mixture of the material homogenized using a homogenizer which is set at 1000 rpm for 30 min until it was formed the clear nanoemulsion [6].

Measurement of nanoemulsion particle size distribution
The particle size was measured using a particle size analyzer (PSA). Drops of 4 drops of the formulation miconazole nitrate nanoemulsion at the site of the sample in the PSA. Then, the instrument closes and reads the measurement results on a computer monitor directly connected to the PSA.

Organoleptic test of miconazole nitrate nanoemulsion
The organoleptic test of the nanoemulsion preparation was performed visually including color, odor, phase separation or nanoemulsion rupture, and clarity [7].

pH measurement
Measurement of pH of the formula was done using pH-meter. First, the electrode is calibrated in advance with a neutral buffer standard.
(pH 7.01) and a buffer solution of acidic pH (pH 4.01). Then, the electrode is immersed in a nanoemulsion preparation. The pH value listed on the tool is recorded. Measurements were made at room temperature [8].

**Measurement of viscosity**
The viscosity of the formula was measured using a Brookfield viscometer at room temperature (28°C±20°C). The formula was inserted into a beaker glass until it becomes a 100ml formula, then the spindle is lowered until the spindle boundary was immersed in the preparation. Spindle used is spindle number 3. Then, the viscometer was turned on by pressing the on button. Then, the spindle speed is set at the used rpm (30 rpm). Then, read the scale (dial reading) where the moving red needle has stabilized. The viscosity value in centipoise (cps) is obtained from the multiplication of dial reading with correction factor.

**Test of the nanoemulsion type**
The test of nanoemulsion type was performed by sprinkling a water soluble, namely, methylene blue, on the surface of the nanoemulsion on top of the cleaned object glass. If nanoemulsion is a type of oil in water, then the methylene blue will dissolve in it and diffuse evenly throughout the water. If nanoemulsion is a type of water in oil, the methylene blue particles will cluster on its surface [9].

**Cycling test**
The nanoemulsion preparation is stored at 4°C±2°C for 24 h, then into the oven at 40°C±2°C for the next 24 h. This treatment is one cycle. The experiment was repeated for 6 cycles. After a cycling test, see the physical condition of nanoemulsion before and after the test [7].

**Centrifugation test**
The sample is inserted into a centrifugation tube then inserted into a centrifuge with a spin speed 3800 rpm for 5 h. Treatment results are equivalent to a gravity effect for 1 year. After centrifugation was observed, the physical condition of the preparation compared before and after the test [8].

**Formulation miconazole nitrate cream**

**Preparation of miconazole nitrate cream**
All necessary materials are weighed. The materials are separated into two groups: The oil phase and the water phase. The oil phase consists of vaseline, stearic acid, and cetyl alcohol melted over a water bath with a temperature of 70–75°C. After a perfect melt was added, miconazole nitrate into it. In a separate container, aqueous phases comprising aquadest, propylene glycol, and TEA are dissolved in hot water. On a continuous phase, the water in a hot melt is then slowly added to the oil phase with a constant stirring at a temperature more or less 70°C, until a cream mass was obtained [10].

**Homogeneity test of the miconazole nitrate cream**
As many as 50 mg of cream preparations smeared on a clean object glass, the preparation should show a homogeneous arrangement and no visible grain [10].

**Physical evaluation of miconazole nitrate**
Physical evaluation of the cream preparations of miconazole nitrate includes organoleptic testing, pH, and type of emulsion.

**RESULTS AND DISCUSSION**

**Homogenitas sediaan krim**
The aim of homogeneity test was to show the materials distribution in the formula. Based on the homogeneity, observation of cream formula had been shown not any coarse grains found on object glass so that should be concluded that this formula was homogeneous as presented in Fig. 1.

**Organoleptic observation**
All nanoemulsion formulations were made clear, odorless, and weak yellow color, while the cream preparation is white, odorless, and no phase separation occurs. All formulas have no significant difference during storage.

**pH measurement**
The pH of a topical preparation should be within the pH range corresponding to the pH of the skin, namely, 4.5–6.5. The pH should not be too acidic as it may cause skin irritation and should not be too alkaline.
Nanoemulsion particle size measurements
Based on particle size measurements using PSA, nanoemulsion preparations containing 1% miconazole nitrate had the smallest particle size before and after storage, namely, 102.36 nm and 177.88 nm. The higher concentration of miconazole nitrate in the preparation results in greater nanoemulsion. From the results, it appears that particles more than 100 nm in size before and after storage, but the particle size is still in the provisions of the specified nanoemulsion dosage size in the range of 2–500 nm [12]. This theory is also supported by research by Shahid and Chowdeswari which states that nanoemulsion can be defined as an oil in water emulsion having a droplet diameter of 50–1000 nm. Usually, the average droplet size is between 100 and 500 nm [13]. The particle size measurement results can be seen in Table 5.

CONCLUSION
The results of evaluation nanoemulsion were better than cream preparations.

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AUTHOR CONTRIBUTION
Hetty Lendora Maha was contributed.

CONFLICT OF INTEREST
Conflict of interest declared none.

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