CDD 2016

The 4th Current Drug Development International Conference 2016

June 1-3, 2016

Phuket Graceland Resort & Spa,
Patong Beach, Phuket, Thailand

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CDD2016

The 4th Current Drug Development International Conference 2016

June 1-3, 2016,
Phuket Graceland Resort & Spa, Patong Beach, Phuket, Thailand

Proceeding
The 4th Current Drug Development
International Conference 2016 (CDD 2016)

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First edition 200 copies

Price 500 Baht

National Library of Thailand Cataloging in Publication Data
Faculty of Pharmaceutical Sciences
Proceeding the 4th Current Drug Development International Conference (CDD 2016)
Songkhla • 2016 • 252 pages

ISBN 978-616-271-303-3

Design & Printing
Neo point
1/59 Ratuhit Road
Tambol hatyai Amphur hatyai
Songkhla 90110 Thailand

Published by Faculty of Pharmaceutical Sciences , Prince of Songkla University

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Effect of different types and amount of fatty acid content in corn oil and virgin coconut oil (VCO) on the characteristic, release rate, penetration and effectiveness of para methoxycinnamic acid (PMCA) in nanoemulsion

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Abstract- This study was aimed to determine the role of the type of vegetable oils. Corn oil and virgin coconut oil (VCO) were used as the oil phase in nanoemulsion drug delivery systems of p-methoxycinnamic acid (PMCA). The effect of differences of fatty acid contents in lipid of the oils on the characteristics of the nanoemulsion were observed in terms of, droplet morphology by TEM and droplet size by Delsa Nano. In addition, this research was also studied the effect on the release rate and penetration rate by Franz diffusion cell using cellophane membrane and full skin of male Wistar rats, and anti-inflammatory test of the PMCA in nanoemulsion was observed at mice's ear skin. Result of this research, showed the droplet morphology of the nanoemulsion that used VCO appeared more spherical than nanoemulsion using corn oil. Droplet size of nanoemulsion, the value of the release rate, and the rate of penetration of PMCA in nanoemulsion using corn oil and VCO were 157.4 ± 5.98, 62.63 ± 12.97 nm, 0.3925 ± 0.0100, 0.4024 ± 0.0339 g/cm^2, and 0.1398 ± 0.0384, 0.1513 ± 0.0314 g/cm^2/minute, respectively. The percentage decrease of edema thickness by PMCA in nanoemulsion using corn oil and VCO were 115.14 and 91.08 % respectively. Average number of inflammation cell (PMN) by PMCA in nanoemulsion using corn oil and VCO were 91.2 ± 47.36 and 27.36 ± 64.2 respectively. The result of statistical test using T-test resulted that there was significant differences between the droplets size of the nanoemulsion using corn oil larger than nanoemulsion using VCO. There were no significant differences between the value of the release rate and the rate of penetration of PMCA, percentage decrease of edema thickness and average number of inflammation cell by PMCA in nanoemulsion using corn oil and VCO. In conclusion, the differences in lipid fatty acid contents of corn oil and VCO influenced on the droplet morphology and droplet size of the nanoemulsion, but had no difference effect on the release rate, the rate of penetration and anti-inflammatory effects of PMCA.

Keywords: *p*-methoxycinnamic acid (PMCA), nanoemulsion, corn oil, virgin coconut oil (VCO), release rate, rate of penetration, anti-inflammatory effect.

Introduction

Nanoemulsion is one of drug delivery systems that may improve solubility of active ingredients which is expected to increase the release rate, rate of penetration and effectiveness [1,2]. Nanoemulsion component consists of a water phase, surfactant-co surfactant and oil phases. The type of oil used as oil phase was one factor that can play role in the formation of nanoemulsion system. Many types of vegetable oils that can be used as oil phase of the nanoemulsion system. Each type of vegetable oils has different types and amount of fatty acid content in its lipids. The differences between the types of fatty acids are in the C atom chain length and the existence of a double bond (unsaturated) hydrocarbon chain. This research was conducted to determine the role of the type of vegetable oils on nanoemulsion drug delivery systems. Corn oil and virgin coconut oil (VCO) were used as oil phase in drug delivery systems nanoemulsion type O/W for topical application. The content of fatty acids in the lipid of corn oil has chain of carbon atoms, namely C18 atom chain of 67.5% and the C16 atom chain was 26.86%. VCO contains fatty acids with C18 atom chain was only about 18.57%, where as total C12 and C14 atom chain were nearly 60%. Corn oil fatty acids namely C18 atom chain consist much straight configuration (saturated) than the fatty acid with a bending configuration (unsaturated) [3]. Effect of differences in lipid fatty acid content of the two types of oil have been investigated on nanoemulsion characteristics (morphology and droplet size), the increase of the release rate, and the increase of the penetration rate and effectiveness of poorly soluble drugs. Para methoxycinamic acid (PMCA) was used as a model of poorly soluble drug which has anti-inflammatory effects [4].

Materials and Methods

1) Materials Para methoxy cinnamic Acid (Sigma Aldrich), corn oil and VCO (PT Kurniajaya), Tween 80 (Sigma Aldrich), Span 80 (Sigma Aldrich), ethanol 96 % (Merck), acetic acid (Merck), sodium acetate (Merck), NaCl (Merck), NaH2PO4 (Merck), Na2HPO4 (Merck), croton oil (Sigma) and aquademineralisata (PT Brataco)

2) Animals Male Wistar rats (150 - 230 gm) and mince (20 - 30 gm) were taken from PUSVETMA Surabaya. The animals were housed under standard conditions of temperature (25±2)°C, 12/12 hours light/dark cycles and fed with standard pellets. All animal experiments were conducted with the permission from Animal Care and Use Committee (ACUC) of Veterinary Faculty, Airlangga University, Indonesia. (Reference number; 378-KE).

3) Nanoemulsion formula used in this study is the result of a previous study by Erawati et.al, using a combination of surfactant Tween 80 and Span 80 with a ratio of 9:1 (having HLB 14), the ratio of surfactant and co surfactant 6:1, the ratio of oil phase and water phase (acetate buffer solution pH 4.2 ± 0.2) is 27.5:1.[3]

4) Release and penetration test: using Franz diffusion cell with cellophane membrane for release test and rat skin for penetration test during 24 hours. **Measurement the amount of the PMCA release from the nanoemulsion**; receptor compartment of Franz diffusion cell filled with phosphate buffer pH 6.0 ± 0.2 up to full (temperature of 32 ± 2°C, stirrer at 100 rpm). Then, 2 ml of nanoemulsion PMCA inserted into the donor compartment. And than 1 ml sample were taken within certain interval of time (0, 5, 10, 15, 30, 45 minutes, and then 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24 hours), and it was replaced with phosphate buffer pH 6.0 ± 0.2 at equal volume. Subsequently, samples were measured by spectrophotometer. PMCA concentration in the sample was calculated using the regression equation of standard curve. Determination of PMCA cumulative amount released per unit membrane area (mg /cm^2) was calculated from the concentration obtained at any time (µg /ml) , which has been corrected by the Wurster's equation. Furthermore, multiplied by the volume of media and divided by the surface area of the membrane. PMCA release profile is obtained by making the curve of the relationship between the cumulative number of PMCA released (mg/cm^2) versus time (minute). The rate of release (release Flux) PMCA obtained from the slope of the regression equation in steady state. **Measurement the amount of PMCA penetrate through rat skin;** receptor compartment of Franz diffusion cell filled with phosphate buffer pH 7.0 ± 0.2 up to full (temperature of 37 ± 2°C, stirrer at 100 rpm). Then, 2 ml of nanoemulsion PMCA inserted into the donor compartment. Samples of 1 ml were taken within a certain time interval as in release test.

5) Anti-inflammatory activity of PMCA in nanoemulsion was measured by histological test on mice's ear skin with the observation of percentage decrease of edema thickness and average number of inflammation cell.

Results and discussion

Determination of characteristics nanoemulsion included morphology droplet, the droplet size, polydispersity index (PI), conductivity, zeta potential, pH and viscosity. Observation result of the droplet morphology was obtained nanoemulsion using VCO appear more spherical than the nanoemulsion using corn oil. This can caused by VCO that had a number of fatty acids with short chains C atoms (C12 and C14) much more than fatty acids with long chain C atoms (C18), so it was easier formed globule. Corn oil has fatty acids with the highest number of a long chain hydrocarbon (C18). These results were in accordance with the results of statistical analysis using Frequency Distribution and Scoring, which obtained a total score of lipid fatty acids in corn oil, amounted to 391.24, larger than the total score of fatty acids in the lipid VCO amounted to 223.53. It is proved that the longer hydrocarbon chains in the lipid of corn oil produced droplet sizes 157.4 ± 5.98 nm larger than fatty acids which have a shorter hydrocarbon chains in the lipid VCO was 62.63 ± 12.97 nm. The polydispersity index (PI) value of the system nanoemulsion containing PMCA were between 0.253 - 0.587. It indicated that the droplet size distribution of nanoemulsion was included moderate dispersion.[5] Nanoemulsion PI value showed an increasing trend in the smaller droplet size. Nanoemulsion conductivity values ranged from 3.35 to 5.65 mS, where the addition of PMCA into nanoemulsion system did not affect the conductivity values. Nanoemulsion zeta potential values were between - 0.125 to - 0,497mV. Statistical test results using T-test showed the value of the zeta potential of PMCA nanoemulsion systems that use each type of oil was no significantly different and did not change after storage for 21 days. But after three moth's nanoemulsion using corn oil appeared cloudier than nanoemulsion using VCO, it indicated tend to

be unstable. Nanoemulsion pH value that contained PMCA (200 mg/100g nanoemulsion) was ranged from 4.47 to 4.48. Nanoemulsion pH value was in the pH range of skin, which is expected will not cause irritation when used. Then the pH value of nanoemulsion was smaller than the PMCA pKa of 4.9 which are expected much more PMCA molecules were not ionized and made it easier penetrates through the skin.

The viscosity of nanoemulsion containing PMCA using corn oil amounted to 5.93 ± 0.07 cP larger than the viscosity of nanoemulsion using VCO is 5.58 ± 0.05 cP. The release rate (flux release) of PMCA in nanoemulsion system with corn oil and VCO were respectively 0.3925 ± 0.0100 and 0.4024 ± 0.0339 g/cm^2. Statistical test result with T-test method on the release rate of PMCA in nanoemulsion using the two oils showed no significant differences. Penetration test results of PMCA in nanoemulsion system using corn oil and VCO obtained penetration rate (flux penetration) APMS respectively was 0.1398 ± 0.038 and 0.1513 ± 0.0314 g/cm^2/minute. The PMCA penetration rate statistical test results used T-test shown no significant differences in the rate of penetration (flux penetration) PMCA in that two nanoemulsion system. Penetration rate (flux penetration) PMCA in the nanoemulsion was greater than its in the acetate buffer at pH 4.2 ± 0.2 of 0.0341 ± 0.0003 g/cm^2/minute. Increased penetration rate of APMS in the nanoemulsion system using corn oil and VCO were respectively 4.10 and 4.44 times. Membrane permeability value of PMCA in the nanoemulsion system with corn oil and VCO were respectively 6.99 x 10^{-5} ± 1.92 x 10^{-5} and 7.57 x 10^{-5} ± 1.57 x 10^{-5} cm/minute. Statistical test result used T-test method there was no significant difference in membrane permeability value to the PMCA in the nanoemulsion system with corn oil and VCO.

The results of the anti-inflammatory effects of PMCA in the nanoemulsion system using corn oil (FI*) and the VCO (FII*) was obtained the percentage decreased in thickness edema (% PTE) respectively amounted to 115.14 ± 13.74 and 91.08 ± 9.94%; and the average number of inflammatory cells (PMN) in Figure 1, amounted to 91.2 ± 47.36 and 27.36 ± 64.2 respectively. There was no significant difference between the average number of inflammatory cells in the ear skin of mice after induced with croton oil and then treatment with PMCA in the acetate buffer at pH 4.2 ± 0.2 9 (control) compared to the ear skin of mice induced by croton oil only (K +). There was a significant difference between the average number of inflammatory cells in the ear skin of mice after induced with croton oil and then treatment with PMCA in each nanoemulsion with the average number of inflammatory cells in the ear skin of mice that is treatment with APMS in acetate buffer at pH 4.2 ± 0.2 and that was only induced by croton oil (K +). This phenomenon showed that PMCA in acetate buffer at pH 4.2 ± 0.2 did not provide anti-inflammatory effect, while PMCA in nanoemulsion system using corn oil and VCO has similar anti-inflammatory effect. It can be concluded nanoemulsion system with corn oil and VCO can increased the effectiveness of PMCA. The cumulative amount PMCA that was penetrated at 24th hour compared to the number of PMCA in the initial sample was obtained percentage of PMCA that is penetrated from nanoemulsion. There was no difference between anti-inflammatory effect of PMCA in nanoemulsion using corn oil and VCO. Percentages of PMCA that is penetrated at 24th hour from nanoemulsion system using corn oil was only reached 11.21% and VCO was 12.11%, however it produced anti-inflammatory effects. This showed that the nanoemulsion can function as controlled release system.[1, 2]

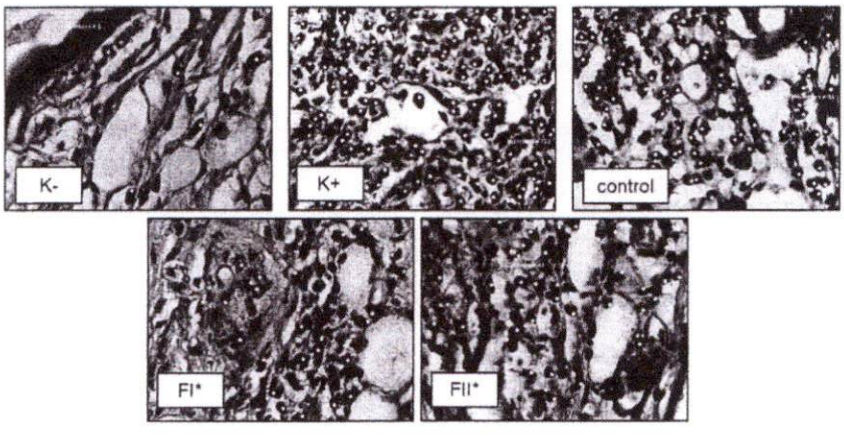

Figure 1 The histology profile of ears mice skin with inflammatory cells in health skin (K-), inflammation skin (K+), after treated with PMCA in acetic buffer pH 4.2 ± 0.2 (control), after treated with PMCA in nanoemulsion using corn oil (FI*) and after treated with PMCA in nanoemulsion using VCO (FII*)

Based on this research it can be concluded that the composition of fatty acid content in lipid of corn oil and VCO influenced the morphology and size of the nanoemulsion droplet, but has no effect to the the solubility, release rate, rate of penetration and effectiveness PMCA (as a poorly soluble drug model with a log P around 2.5).
Suggestions of these research results for using vegetable oil as the oil phase in nanoemulsion preferably use oils with fatty acid content of lipid of oil that has short chain of C atoms, or vegetable oils that have smaller amounts of fatty acids with long-chain unsaturated hydrocarbons.

Acknowledgement
The authors want to thank Indonesia Government who give research fund through Rector of Airlangga University (through LPPM-UA), also to my students; Ayu Wijayanti and Anneke Indraswari Prasyuliningrum.

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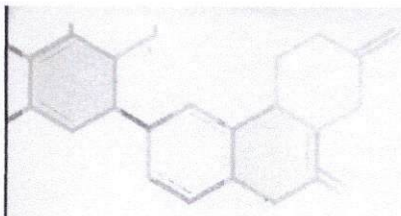

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