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Stability of High Concentration Capsaicin in Transfersome Carriers in Gel Dosage Form

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ABSTRACT

Topical capsaicin with high concentrations (8%) is effective in the treatment of pain in Post-Herpetic Neuralgia (PHN) and HIV-Associated Distal Sensory Polyneuropathy (HIV-DSP) patients. High concentrations of capsaicin encapsulated in transfersome nanovesicles aim to reduce the irritating ability of capsaicin when using as drugs. Gel preparations were chosen in the formulation because they are non-sticky, easy to wash, easy to apply, and more practical. The components contained in the gel affect the stability of the gel. Physical and chemical stability tests need to be carried out to ensure the quality, safety and efficacy of the gel so that it meets the expected specifications during its shelf life. This study aims to determine the stability of selected gel formulas containing high concentrations of transfersome capsaicin. The selected gel formula is a gel containing a mixture of phosphatidylcholine (Phospholiphon 90G®) and Tween 80 (80:20). Stability was carried out at high temperature (40±2oC), room temperature (30±2oC), low temperature (5±3oC), and cycling test. The stability parameters tested included organoleptic, pH, viscosity, and assay. The results of the transfersom capsaicin gel stability test showed no change in pH, viscosity, and assay in all storage conditions, but the gel showed a change in color, smell, and taste when stored at high temperatures (40 ± 2oC). It can be concluded that the resulting capsaicin transfersome gel formula with a phospholipid:tween ratio of 80 (80:20) was less stable during 12 weeks of storage at 40 oC

INTRODUCTION

Since 2009, capsaicin in high concentrations (8% w /w) has been approved in Europe and the United States for the treatment of Post-Herpetic Neuralgia (PHN) and HIV-Associated Distal Sensory Polyneuropathy (HIV-DSP) in adults1. But its use still causes some side effects such as erythema, pain, oedema and pruritus2. Topical delivery of high concentrations of capsaicin with minimal side effects at the site of use of the preparation is expected to be achieved by encapsulating it into a carrier-based nanoparticles, one of which is transfersom. Until now , there has not been a single study that has revealed the formulation of high concentrations of capsaicin into a nanoparticle-based carrier. Studies related to capsaicin-based nanoparticles such as liposomes 3, transfersomes4, transethosomal5, Solid Lipid Nanoparticles, and Nanosructured Lipid Carriers6.7 still use capsaicin low concentration (0.025 - 0.1% w/w).

Transfersom is a nanoparticle consisting of phospholipids and edge activators (such as Tween 80, Span 80, and sodium colate), measuring under 500 nm, and having a deformability of 8.9. Capsaicin which is hydrophobic and absorbed in a vesicle which is also hydrophobic is expected to provide a reduction in side effects when administering the preparation topically.

To facilitate the application, transfersom can be formulated in the dosage form of a gel. Gel is more comfortable to wear than other dosage forms such as creams and ointments due to its non-greasy nature. The gel also has several other beneficial properties in its use such as thixotropic, easy to spread, easy to clean, immaculate, transparent appearance, and a long shelf life of 10.

Physical and chemical stability tests need to be carried out to guarantee that the preparation has the same properties after the preparation is made and still meets the criteria parameters during its shelf life. To determine the stability of a drug, it is necessary to design special conditions that can accelerate the occurrence of changes that usually occur under normal conditions. The purpose of this study was to determine the stability of selected gel formulas containing high concentrations of capsaicin transfersomes under storage conditions at high temperature (40±2 o C), room temperature (30±2 o C), and low temperature (5±3oC) for 12 weeks, and cycling test.

Tools and Materials

Material

Capsaicin (Formosa, Taiwan, grant from PT. Pharos Indonesia), Phosphatidylcholine (Phospholiphon 90G®) (Lipoid, Germany), Propylene glycol (Caesar & Loretz, Germany), Potassium dihidrogen phosphate (Merck), Sodium hydroxide (Merck), Tween 80 (Kao Corporation, Japan), Sepigel 305 (Seppic, France), Methyl paraben (Brataco), Propyl paraben (Brataco), Sodium methabisulfite (Brataco), Dichloromethane (Merck), Methanol (Merck), and aquade mineralisata.

Tool

Timbangan analitik (Sartorius, Jerman), rotary vacuum evaporator (Buchi R-100, Switzerland), vortex mixer (VM – 300 Germany Industrial Corporation, USA), sonikator (QSonica, USA), pH meter (Jenway 550 pH meter, UK), viscometer Cole-palmer (Cole-palmer, USA), Spektrofotometer UV-Vis (Shimadzu UV-1800, Jepang), magnetic stirrer (Boeco MSH-300, Jerman), oven (Menmert, Jerman), micropipette (Socorex), lemari pendingin (LG, Korea), homogenizer IKA-Ultra-Turax T25 (Staufen, Germany).

METHODS

Creation of Transfersom

Transfersom is made by the method of thin-layer hydration. Weigh capsaicin, phospholipon 90G®, and tween 80, then dissolve them into dichloromethane, stirring until homogeneous. Transfer the solution into a round base flask and evaporate it with a rotary vacuum evaporator at a temperature of 40±2 °C and a pressure of 850±5 mbar at an initial speed of 50 rpm and then gradually increase until it reaches 150 rpm. After evaporation is complete, flow the tube with nitrogen gas for 2 minutes then let it sit for 24 hours in a closed state in the refrigerator.

The thin layer formed is then slowly hydrated using a phosphate buffer solution pH 7.4 until a homogeneous transfersom dispersion is formed. The hydration process is carried out at a speed of 50 rpm and then increased by 25 rpm every 5 minutes to reach 250 rpm at a temperature of 40 °C. The resulting transfersomes were reduced in size using a sonicator for 10 min at an amplitude of 60 KHz.

Tabel 1. Formula Capsaicin Transfersom

Material	Percentage (%)	Function
Capsaicin	20	Active Substances
Phospholipon 90G®	40	Phospholipids
Tween 80	10	Edge Activator
Phosphate buffer solution pH 7.4	Ad 100	Sat Penghidrasi

Manufacture of Capsaicin Transfersom Gel

First of all, propylparaben and methylparaben are dissolved in propylene glycol, then sodium metabisulfite is dissolved in purified water. Sepigel 305® was then developed in purified water containing sodium metabisulfite, while stirring until homogeneous. After that, a solution of methyl paraben and propyl paraben is added to it, and then stirred until homogeneous. This mixture is referred to as a gel base. To the gel base, transfersom capsaicin is added and then stirred until homogeneous.

Tabel 2. Formula Gel Capsaicin Transfersom

Material	Percentage (%)	Function
Transfersom Capsaicin	8% Capsaicin equivalent	Active Substances
Sepigel 305®	3	Gelling agent
Propilene glycol	7	Emollient
Metil paraben	0,1	Preservatives
Propil paraben	0,05	Preservatives
Sodium metabisulfite	0,01	Antioxidant
Purified water	Ad 100	Solvent

Stability Test

The stability test of the finished product was carried out at a low temperature of 5±3 o C, a room temperature of 30±2 o C, and a high temperature of 40±2 o C. Testing was carried out for 12 weeks with a test interval every 4 weeks (weeks 0th, 4th, 8th, and 12th). The measured parameters are organoleptic (color, smell, taste, shape, separation fase), pH, homogeneity, viscosity and grade. The cycling test is also carried out on the preparation by means of the preparation stored in a refrigerator with a temperature of 5 o C for 24 hours and then removed and placed in an oven with a temperature of 40 o C for 24 hours. This treatment is one cycle. The experiment was carried out in 6 cycles. The physical condition of the preparation is compared during the experiment with the previous preparation, whether syneresis or crystallization occurs.

The homogeneity test is carried out by applying the top, middle, and bottom 3 parts of the gel on transparent glass. Homogeneity is indicated by the absence of coarse grains in the preparation. The pH test is carried out by looking at the acidity level of the gel preparation to ensure that the gel preparation does not irritate the skin. The pH test is carried out with a pH meter device. The viscosity test is performed by placing the sample in a Cole-Palmer viscometer until the spindle is submerged. The spindle is set at a speed of 12 rpm. The active substance level test was carried out using a UV-Vis spectrophotometer device at a wavelength of 281 nm with methanol solvent.

RESULTS AND DISCUSSION

The capsaicin transfersom gel tested for stability has a mixed ratio of phospholipids and tween 80 of 80:20, this formula results from the optimization of the formula that has been carried out by researchers. The formula is a formula that produces the best nanoparticle characteristics in terms of particle size distribution parameters that are below 500 nm, polydispersity index below 0.5, zeta potential > - 30 mV, deformable and has a absorption efficiency above 50%. The formula was then tested for stability for 12 weeks under storage conditions of high temperature (40±2 oC), room temperature (30±2 oC), and low temperature (5±3 oC) and carried out a stability test of the cycling test method

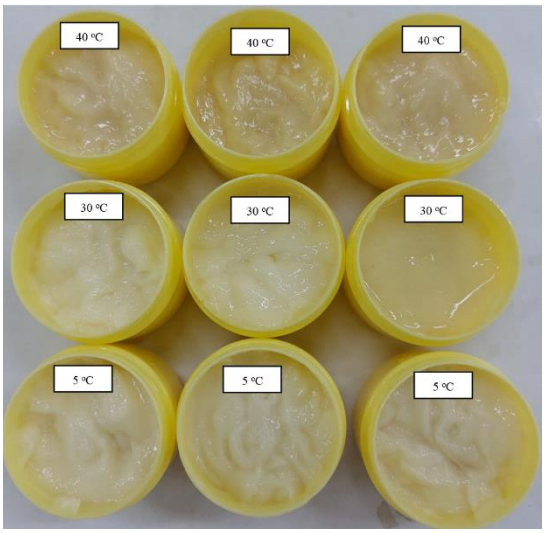

Figure 1. Gel Capsaicin Transfersom After 12 Weeks of Storage

Gel transfersomes stored at low temperatures and room temperatures do not undergo discoloration, odor, and homogeneity for up to 12 weeks. Meanwhile, transfersom gel stored at high temperatures has changed color to browner and smells a bit rancid (Figure 1). This may be because the lipids contained in the transferom are not resistant to hot temperatures so that they undergo chemical reactions such as oxidation so that they turn browner and smell rancid. In general, nanovesicles are not resistant to high temperatures due to the presence of lipids as the main component forming vesicles. It may be of concern that a preparation containing transfersomes cannot be stored at high temperatures.

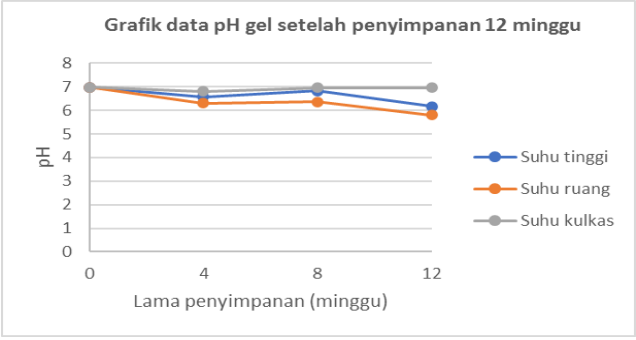

Figure 2. Graph of PH Data of Gel Transfersom Stored for 12 Weeks

Based on the graph in Figure 2, during 12 weeks of storage there is a decrease in pH mainly for room temperature and high temperature. However, the decrease in pH is still in the ideal semi-solid preparation pH range of 4.5-7.

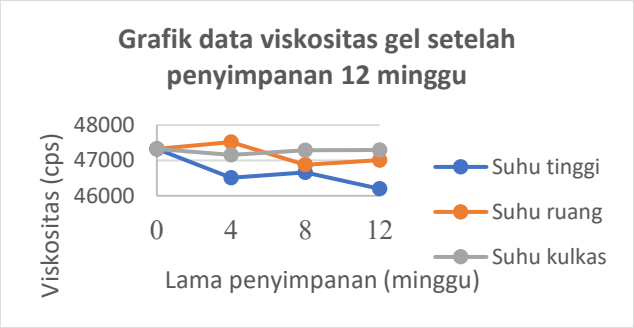

Figure 3. Graph of Viscosity Data of Transfersom Gel Stored for 12 Weeks

Based on the graph in Figure 3, during 12 weeks of storage there was a decrease in viscosity especially for high temperatures. This may be because the heat obtained will increase the distance between the particles so that the distance becomes tenuous and the viscosity of the gel decreases

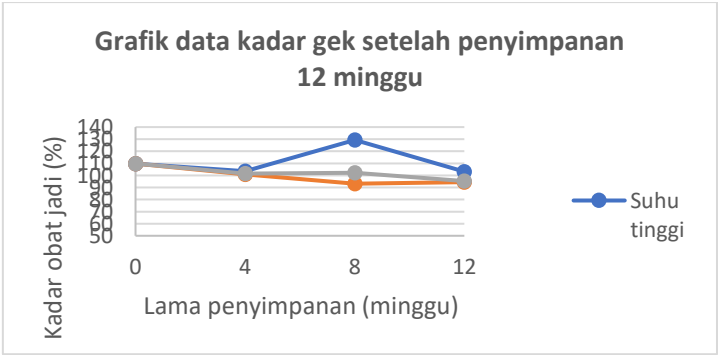

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Figure 4. Graph of Transfersom Gel Content Data Stored for 12 Weeks

Based on the graph in Figure 4, during 12 weeks of storage there was a decrease in levels for all three temperatures. Although there was an increase in levels at high temperatures in week 8, it is still unknown whether it caused this level increase, there may be an error at the time of preparations or other things that Peneliti does not yet know. A decrease in the level of the active substance in the preparation can be caused by the influence of temperature, humidity, light, solvent, ionic strength, catalysis, dielectric constant , collision theory and transition theory 12. However, the decrease in capsaicin levels is still within the accuracy range for pharmaceutical preparations of 90-110%.

Cycling test is carried out for 6 cycles, 1 cycle is carried out by storing the gel at a low temperature (5±3 o C) for 24 hours then stored at a high temperature (40±2 o C) for 24 hours. Then organoleptic observations are carried out. The results of the cycling test are shown in Figure 5.

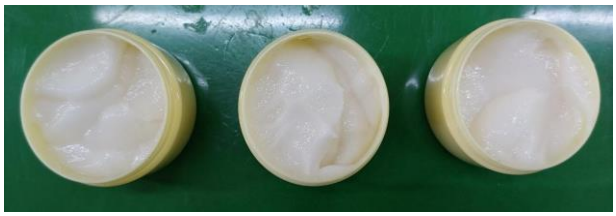

Figure 5. Results of Cycling Test Gel Capsaicin Transfersom for 6 Cycles (Triplo)

Based on organoleptic observations, there was no discoloration, crystallization, or syneresis in the gel after a cycling test of 6 cycles. Sepigel 305® as a gelling agent is able to maintain water to remain in its matrix so that it can be concluded that the emulgel preparation is physically stable in the cycling test.

CONCLUSIONS

It can be concluded that the formula of capsaicin transfersom gel with a phospholipid:tween ratio of 80 (80:20) produced is unstable in storage at a temperature of 40 oC for 12 weeks.

SUGGESTIONS

It is necessary to conduct stability tests from the microbiological side to see if the gel formula can keep the preparation stable against bacteria and fungi.

Thank You Speech

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