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*Original Research Article*

# Formulation of Ketoconazole Niosomal Delivery System using Non-Ionic Surfactants

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ABSTRACT

Ketoconazole is a broad-spectrum Imidazole derivative antifungal that is effective for both superficial and systemic fungal infections that cannot be completely absorbed when administered orally because it has low solubility. This can be overcome by forming a ketoconazole niosome delivery system. Niosomes are vesicular systems formed using non-ionic surfactants that could increase the solubility and bioavailability of drugs. The purpose of this study was to form a ketoconazole niosome system to increase the bioavailability and therapeutic effectiveness of ketoconazole. Niosomes were made into nine formulas using 100 mg surfactant with variations in the combination of non-ionic surfactant concentrations Span 60 (70.80-98.29%):Sucrose Ester Palmitate (SEP) (1.71-29.20%), which produced Hydrophilic Liphophilic Balance (HLB) values between 4-8. The evaluations on niosomes were organoleptic tests, particle size tests, polydispersity indexes, zeta potentials, structural analysis using Forrier Transform Infra Red (FTIR), morphological analysis using Transmission Electron Microscope (TEM), entrapment efficiency tests and drug release tests. The results showed that the niosome system with an HLB value of 7.5 produced a vesicle size 336,13±3,14 nm, polydispersity index 0,000, zeta potensial -52,16±1,54 mV, spherical form of vesicle and no found chemistry interaction between the components (result of TEM and FTIR), an entrapment efficiency value of 87.86±0.18% and a drug release test value for 24 hours of 97.23±2.16%. This showed that the ketoconazole niosome system made using a combination of span 60 surfactants and SEP with an HLB value of 7.5 was able to produce an excellent niosome system.

*Keywords*: Ketoconazole, Span 60, Sucrose Ester Palmitat, Niosome

## Introduction

Fungal severe infections may increase due to the development of *Human Immunodeficiency Virus* (HIV), anticancer chemotherapy, and the increasing use of immunosuppressive drugs in organ transplants. Ketoconazole is an antifungal drug of the imidazole class that is widely used to treat fungal infections in various dosage forms such as tablet, cream, gel. Ketoconazole can cause side effects of nausea, vomiting, gastrointestinal disorders, and adrenal cortex suppression when given orally. In addition, oral absorption of ketoconazole is dependent on gastric pH and the possibility of interactions with other drugs. Ketoconazole is drug of Biopharmaceutical Classification System (BCS) class II, with very low solubility and high permeability, so the drug has limited bioavailability so that it can reduce the effectiveness of treatment.[1]

Various methods have been carried out to improve the bioavailability of drugs, one of which is by increasing the solubility of drugs, especially class II BCS compounds. The methods used are particle size reduction, water-soluble complex manufacturing, surfactant systems, liposomes, solid dispersion formulations, and other methods.[2]

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Niosomes are vesicular systems that are being developed for the delivery of transdermal and topical drugs. Niosomes have been shown to increase the bioavailability of preparations and can overcome various problems of active substances, such as those administered by the oral route. In addition, niosomes can also maintain therapeutic levels of the drug for a more extended period, thereby reducing the frequency of medication administration and improving patient compliance. The advantages of the niosome system include having better stability that avoids the possibility of aggregate formation, thereby reducing leakage that causes less active senate.[3]

The main components of the niosomes are surfactants, membrane stabilizers and hydration mediums. The selection of a suitable surfactant can affect the efficiency of drug adsorption and the size of the drug vesicle, which significantly affects the value of HLB and the chemical properties of the surfactant. The non-ionic surfactant group was chosen because it is safer, can flow freely, and has good solubility in water, making it easy to hydrate. Surfactants with HLB values between 14-17 are unsuitable for niosome preparation. The reported value of HLB surfactant can form niosomal vesicles, which ranges from 4 to 8.[4,5]

Some types of non-ionic surfactants that are widely used include alkyl ethers, alkyl esters, alkyl amides and fatty acid sucrose esters. tween 80 is able to increase drug release from mupirocin.[6] Span 60 is a surfactant widely used to manufacture niosomes, and based on previous research, it can increase the penetration of fluconazole niosomes. Span 60 also increases the insolvency of cyclosporin niosomes.[7,8,9]

Fatty acid sucrose esters (SE) include non-ionic surfactants that can also be used to manufacture niosomes. Fatty acids SE have sugar substituents, sucrose as the polar head group and fatty acids as the non-polar group. The type of fatty acid and the degree of esterification determine the HLB value of the fatty acid SE. One of these types of SE is sucrose ester palmitate (SEP), with an HLB value of 16.[4] The advantages of SEP are that it lowers the surface tension of oil and water and is non-toxic and *biodegradable*.[10]

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This study aims to improve the solubility of ketoconazole in the niosome system using a combination of Span 60 and SEP as surfactants, and it is expected to be able to increase the drug's penetration. This also impacts efforts to improve the effectiveness of fungal treatment using Ketoconazole.

## Materials and Methods

*Materials*

Ketoconazole (Aarti Drugs Limited), Span 60 (Nitro Chemical), SEP (Compass Food), Cholesterol (Nippon Fine Chemical), Chloroform (Merck), Methanol (Merck), Phosphate Buffer Saline (Solarbio), Aqua pi (Ikapharmindo Putramas), Dialysis Bag.

*Equipment*

Spectrophotometer UV-Vis (Shimadzu), Rotary Evaporator (Eyela), Forrier Transform Infra Red (FTIR) (Agilent), Transmission Electron Microscope (TEM) (JEOL JEM-1400), Particle Size Analyzer (Beckman Coulter), magnetic stirrer (MSH Pro) and glassware.

*Method*

*Determination of Composition of Niosome*

The composition of the niosome is a surfactant, a membrane stabilizer and a carrier. Previous research has determined the ratio between membrane stabilizers and surfactants, which is 0.2:1.[11] In this study, a ratio of surfactant and membrane stabilizer of 0.2:1 was used with various variations of the combination of Span 60 and SEP. The formula is seen in Table 1.

**Table 1:** Design of ketoconazole niosomal formula

| Formula | Ketoconazole (mg) | Cholesterol (mg) | Total Surfactant (mg) | HLB Needs | Span 60 (mg) | SEP (mg) | Chloroform (mL) | PBS pH 7.4 (mL) |
|---|---|---|---|---|---|---|---|---|
| F1 | 100 | 20 | 100 | 4.0 | 94.49 | 5.51 | 10 | 20 |
| F2 | 100 | 20 | 100 | 4.5 | 98.29 | 1.71 | 10 | 20 |
| F3 | 100 | 20 | 100 | 5.0 | 97.35 | 2.65 | 10 | 20 |
| F4 | 100 | 20 | 100 | 5.5 | 92.92 | 7.08 | 10 | 20 |
| F5 | 100 | 20 | 100 | 6.0 | 88.50 | 11.50 | 10 | 20 |
| F6 | 100 | 20 | 100 | 6.5 | 84.07 | 15.93 | 10 | 20 |
| F7 | 100 | 20 | 100 | 7.0 | 79.65 | 20.35 | 10 | 20 |
| F8 | 100 | 20 | 100 | 7.5 | 75.22 | 24.78 | 10 | 20 |
| F9 | 100 | 20 | 100 | 8.0 | 70.80 | 29.20 | 10 | 20 |

*Niosomes Preparation Method*

Ktoconazole, Span 60, SEP, and cholesterol added to 10 mL of chloroform: methanol 1:1. Afterwards, the mixture is transferred into a round flask and dried with a rotary evaporator at a temperature of 45ºC until the mixture is dehydrated and forms a layer.[12] The film layer is hydrated using 20 mL of phosphate pH 7.4 for 1 hour in a rotary evaporator at 55-65ºC until niosomes are formed, then sonicated for 20 minutes.[11]

*Evaluation*

Niosomal Organoleptic Test

The organoleptic tests carried out include shape, colour, and adhesion. The tests were carried out using the five senses.

*Vesicle Size, Polydispersity Index and Potential Zeta Testing*

Vesicle size, polydispersity index, and zeta potential were observed by diluting the sample with aquarium distillate in a ratio of 1:10. Then, the sample was put into the cell for reading, and the results obtained were analyzed.[13]

*FTIR Analysis*

All components contained in the niosome, and their functional groups are evaluated using FTIR. The sample is placed on the sample place, the FTIR machine is turned on, and the results are analyzed.[11]

*Morphological*

Sample 0.5 µL niosome was added with a 1% uranyl acetate solution and then analyzed using a Transmission Electron Microscope (TEM). The test was carried out using a TEM tool at Gadjah Mada University.[14]

*Entrapment Efficiency*

A total of 1 mL of niosomal suspension is inserted into an eppendorf tube and then centrifuged for 1 hour at 4ºC and 10000 rpm. The precipitate formed is then added to a PBS solution pH 7.4 (containing 10% v/v methanol) up to 10 mL and then sonicated. The amount of substances adsorbed was determined indirectly using a UV spectrophotometer at a wavelength of 295.4 nm. The percentage of adsorption efficiency is calculated using the formula:[9,11]

$$\%EE = \frac{amount\ of\ drug\ in\ niosome}{amount\ of\ drug\ use\ in\ preparation} \times 100$$

*In Vitro Drug Release Test*

Testing the release of ketoconazole from the system was carried out using a dialysis bag set at 100 rpm at 37±0.2°C in 200 mL of PBS pH 7.4 (containing 10% v/v methanol) as the solution. Samples of as much as 10 mL are taken at a certain time interval, which is 0.25, 0.5, 1, 4, 8, 12, or 24 hours. The sampled samples were filtered using a 0.45 µm membrane and analyzed with a UV Spectrophotometer at a wavelength of 295.4 nm.[11,15]

## Results and Discussion

*Organoleptic Test*

Visual observation results, shown in Figure 1, show that the niosomes of F1-F9 are liquid homogeneous and milky white in colour. This indicates that niosome dispersion has been formed due to the presence of cholesterol and surfactants (Span 60:SEP).[16]

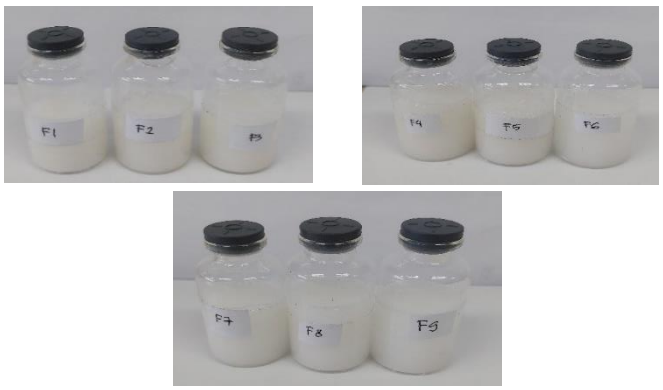


**Figure 1:** Ketoconazole niosomes

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*Vesicle Size, Polydispersity Index and Zeta Potential Test*

The results of vesicle measurements of all niosome formulas in Table 2 were in the range of 283.33-535.83 nm. The size of the resulting vesicles is highly dependent on the niosome-making technique. In this study, the manufacturing method used is a thin-layer hydration method to produce a large vesicle size.[17] The polydispersity index produced in F1-F9 was 0.000. The polydispersity index shows the homogeneity of the vesicle size. A value of 0.000 indicates that the size of the resulting vesicles is very uniform, while a value of 1,000 indicates that the size of the resulting vesicles is very non-uniform.[18] The potential value of zeta indicates the electrical charge in the vesicles, which affects the movement of particles to form aggregates. In this study, the zeta potential produced by all formulas (F1-F9) was -56.61 to -30.21 mV. All formulas had good zeta potential values so that the formed niosomal system would be more stable and had a slight possibility of aggregate formation.[19]

**Table 2:** Test results of vesicle size, polydispersity index and zeta potential

| Formula | Results | |
|---|---|---|
| | **Particle Size (nm)** | **Zeta Potensial (mV)** |
| F1 | 343.07±13.37 | -30.21±0.71 |
| F2 | 387.67±13.32 | -35.00±1.98 |
| F3 | 423.30±8.65 | -46.49±1.11 |
| F4 | 535.83±10.19 | -39.23±0.24 |
| F5 | 300.97±3.49 | -42.06±1.45 |
| F6 | 283.33±4.55 | -50.21±0.80 |
| F7 | 481.17±9.90 | -52.66±1.63 |
| F8 | 336.13±3.14 | -52.16±1.54 |
| F9 | 411.50±3.70 | -56.61±1.89 |

*Results are expressed as of mean ±SD (n=3)

*Results of structural analysis using FTIR*

The span spectrum 60 shows a sharp and broad peak at wavelength 3390, indicating the presence of hydroxyl groups, 2916/cm, indicating the presence of aromatic groups, and C=O ester bonds at wavelength 1731/cm. The cholesterol spectrum showed a broad and sharp peak at a wavelength of 2931/cm, indicating the presence of an acetyl group, 2901/cm, indicating the presence of a CH=CH group, 3401/cm, indicating the presence of a hydroxyl group and 2866/cm indicating the presence of a symmetrical -CH3 group. The spectrum of SEP shows a sharp peak at wavelength 1720/cm, showing that there is an ester group (C=O bond), 2916/cm, indicating the presence of a -CH3 group. The ketoconazole spectrum showed a sharp peak at the wavelength of 1645/cm, indicating the presence of C=O bonds; 1584/cm, indicating the presence of symmetrical aromatic C=C bonds; and 1509, showing that there is asymmetrical aromatic C=C bonds. FTIR testing (Figure 2 and 3) proves that the niosome system does not form new compounds but only physical interactions.[16,20,21,22]

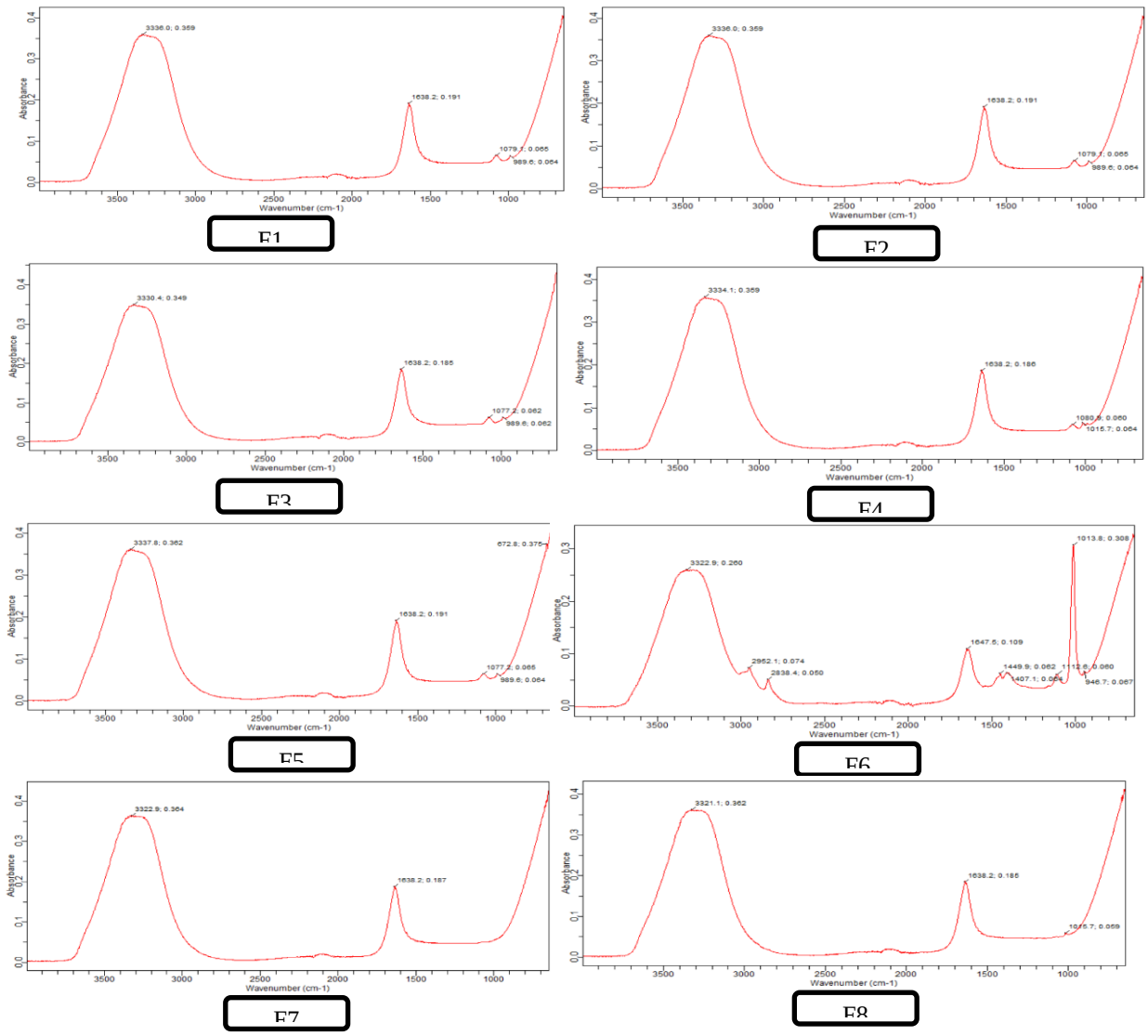


**Figure 2:** FTIR formula 1-8 results

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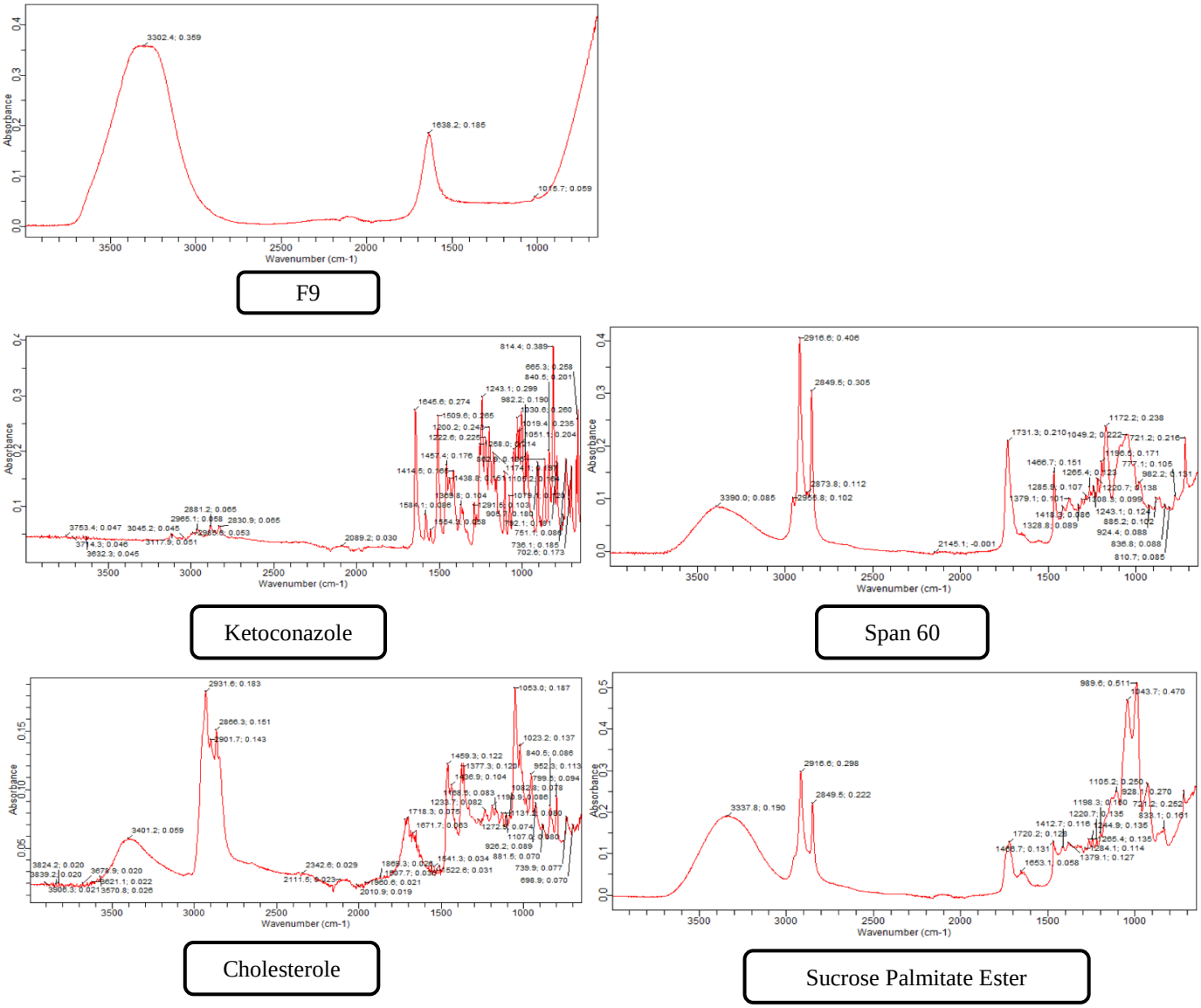


**Figure 3:** FTIR Formula 9, Ketoconazole, Span 60, Cholesterol and Sucrose Ester Palmitate results

*Results of Entrapment Efficiency*

Lipophilic drugs will be adsorbed to the bilayer of the niosome. Cholesterol in niosomes is able to regulate the flexibility and strength of the vesicles.[23] The entrapment efficiency is affected by the surfactant's transition temperature, C chain, and HLB value. Surfactants with high transition temperatures and long alkyl chains can improve adsorption efficiency. In addition, the value of HLB surfactant also affects the adsorption efficiency of the niosome. The lower the HLB value, the lower the value of niosomal adsorption efficiency. The results of the adsorption efficiency test show that F8 (HLB value 7.5) has the highest adsorption efficiency when compared to other formulas. The length of the alkyl chain of the material used greatly influences the adsorption efficiency. Span 60 shows lower HLB value with longer C17 chain thus has more hydrophobic nature and results in better drug adhesion in its core than SEP because SEP have longer alkyl chain, so it can cause a decrease in entrapment efficiency in F9 because concentration of Span 60 on F9 is smaller than the number of Span 60 on F8. The entrapment results can be seen in Table 3.[7,24,25]

*Morphological Imaging Results*

Morphological testing of niosomes using TEM aims to see the shape of the niosomal vesicles formed. The test results shown in Figure 4 show that the resulting vesicle shape is a sphere.[14]

**Table 3:** Results of entrapment efficiency

| Formula | Entrapment Efficiency (%) |
|---|---|
| F1 | 31.05±0.04 |
| F2 | 23.36±0.05 |
| F3 | 35.68±0.19 |
| F4 | 41.59±1.71 |
| F5 | 37.32±0.04 |
| F6 | 37.86±0.13 |
| F7 | 61.59±0.16 |
| F8 | 87.68±0.18 |
| F9 | 38.00±0.06 |

*Results are expressed as of mean ±SD (n=3)

*In Vitro Drug Release Test Results*

The drug release test in this study (Table 4) was selected only for two formulas, namely F7 and F8 because it has a higher drug adsorption efficiency value than other formulas. The results of the drug release test in vitro showed that F8 was higher than F7, presumably because F8 has a higher adsorption efficiency value than F7. In this formula using Span 60 and sucrose ester palmitate as surfactans where Span 60 has a long alkyl chain which can increase drug absorption in niosomes and SEP is a surfactant with a hydrophilic group at the head and a lipophilic fatty

acid at the tail so that it can help increase the solubility of hydrophilic drugs. The more drugs are adsorbed in the niosome, the more drugs are also able to be released because the niosomes contain non-ionic surfactants that contain hydrophilic and lipophilic groups, which can help the adsorbed drug ability to penetrate the membrane and can increase the solubility of the drug.[26]

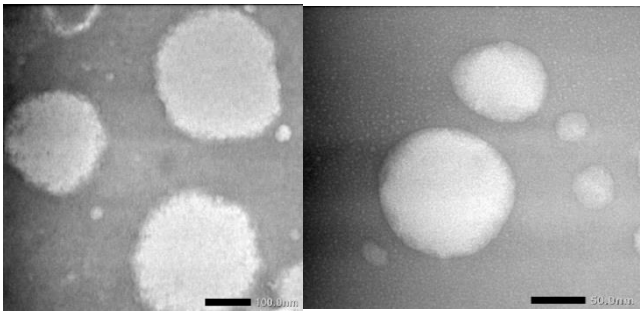


**Figure 4:** Results of niosomal morphological analysis using TEM

**Table 4:** *In vitro* drug release test results

| Time (Hours) | Drug Released (%) | |
|---|---|---|
| | F7 | F8 |
| 0.25 | 8.18±0.00 | 8.12±0.14 |
| 0.5 | 9.59±0.09 | 11.53±0.10 |
| 1 | 18.87±0.00 | 21.51±2.05 |
| 4 | 40.25±0.06 | 42.11±0.16 |
| 8 | 52.00±0.06 | 52.75±0.00 |
| 12 | 60.71±0.06 | 66.71±0.10 |
| 24 | 91.11±0.10 | 97.23±2.16 |

*Results are expressed as of mean ±SD (n=3)

## Conclusion

Forming ketoconazole niosomes with the combination of Span 60 and SEP as surfactants provided physical evaluation results that met the requirements, with a practical HLB value of 7.5. The HLB value of surfactants significantly affects the formed niosome system. In this study, a combination of non-ionic surfactant Span 60 with SEP resulted in HLB values of 4 to 8. The results of the evaluation of adsorption efficiency and drug release test showed that the HLB value of 7.5 was able to produce a better ketoconazole niosomal system when compared to other HLB values.

## Conflict of Interest

The authors declare no conflict of interest.

## Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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