

Comparative Study of the Antifungal Effectiveness of Massoia Essential Oil-Based SMMDF Formulations with HPMC and PVP Polymers against *Candida albicans*

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ABSTRACT

Oral diseases, like oral candidiasis caused by *Candida albicans*, remain a common and troubling health issue in Indonesia. Massoia essential oil (*Massoia aromatica* Becc.), which contains C-10 massoialactone, has proven antifungal properties. However, its limited solubility affects how well it is absorbed into the body. This study aimed to evaluate the antifungal effectiveness of Self-Micro-emulsifying Mouth Dissolving Film (SMMDF) formulations that incorporate massoia essential oil, using either HPMC or PVP polymers, against *C. albicans* in a laboratory setting. The test fungus was cultured on PDA and prepared into a suspension standardized to 0.5 McFarland, followed by antifungal testing using the well diffusion method on PDA medium. Nystatin served as the positive control, while formulations without massoia essential oil served as the negative control. The results showed that the average inhibition zones for SMMDF with HPMC and PVP polymers were 10.85 mm and 11.51 mm, respectively—both considered strong and larger than the positive control (6.68 mm). An independent sample *t*-test showed no significant difference between the two polymers ($p = 0.735$), suggesting that the antifungal activity mainly stemmed from the massoia essential oil itself. These results suggest that massoia essential oil-based SMMDF holds significant potential as an effective antifungal solution against *C. albicans*, with no major difference in effectiveness between HPMC and PVP as the polymers used to form the film.

Keywords: Massoia essential oil, Self-Microemulsifying Mouth Dissolving Film (SMMDF), *Candida albicans*, Antifungal activity, Polymers

INTRODUCTION

Oral and dental diseases remain common complaints for many people, particularly in Indonesia. Although most of these problems are relatively mild, they can still disrupt daily activities. Some of the most frequently occurring oral health issues include halitosis, oral infections, and canker sores (Putri *et al.*, 2018). Canker sores are infections that occur inside the mouth, usually appearing as round or oval white lesions that can be painful and uncomfortable. They are often caused by the fungal pathogen *Candida albicans*, also known as oral candidiasis (Septiyanti *et al.* 2023)(Rusmiati *et al.* 2023).

Masoyi essential oil contains C-10 massoialactone, a compound proven to exert antifungal effects against *Candida albicans* by damaging the cell membrane, disrupting biofilm formation, and impairing fungal cell integrity (Hamzah *et al.* 2023). However, masoyi oil is classified as Class II under the Biopharmaceutics Classification System (BCS), meaning it has low solubility despite its high permeability (Chen *et al.* 2021). Masoyi essential oil (*Massoia aromatica* Becc.) is lipophilic with a Log P value of 3.13, resulting in poor solubility in water (Yandriyani *et al.* 2019). This presents a major challenge in developing masoyi essential oil formulations, as low solubility limits dissolution and leads to suboptimal bioavailability (Dyah Ayu Nurismawati and Sani Ega Priani 2021).

To overcome these limitations, innovative drug delivery systems such as the Self-Microemulsifying Drug Delivery System (SMEDDS) combined with Oral Dispersible Films

(ODF) have been developed. SMEDDS enables the formation of oil-in-water microemulsions with extremely small droplet sizes, thereby enhancing solubility and bioavailability of poorly water-soluble active compounds (Praveena and Anne Vijetha 2021).

Polymers such as HPMC and PVP play a crucial role in developing high-quality Self-Microemulsifying Mouth Dissolving Films (SMMDF). HPMC serves as a rapidly dissolving film-forming agent in the oral cavity, providing sufficient structural strength to maintain formulation integrity during storage and handling. Additionally, HPMC improves the distribution of the active compound within the film and enables stable, controlled drug release. It has been shown to provide better palatability and reduce potential discomfort associated with certain drugs (Maheswari et al. 2014). PVP, on the other hand, is highly effective in enhancing the solubility of poorly water-soluble compounds. It forms complexes with active ingredients, thereby improving their bioavailability once the film dissolves in the mouth. Moreover, PVP has humectant properties that help retain moisture and maintain formulation stability, which is critical in preventing degradation or physical changes during storage (Habib et al. 2021).

This study aims to compare the antifungal effectiveness of SMMDF formulations containing masoyi essential oil against *Candida albicans* in vitro, in order to evaluate the most optimal drug delivery system to enhance the antifungal activity of masoyi essential oil.

MATERIAL AND METHODS

Equipment and Materials

The equipments used in this study included an Erlenmeyer flask, inoculating loop, hotplate, Laminar Air Flow (LAF), autoclave, Petri dishes, micropipette, test tubes, caliper, and UV-Vis spectrophotometer.

The materials used in this study were SMMDF formulations of masoyi essential oil with HPMC polymer, SMMDF formulations of masoyi essential oil with PVP polymer, nystatin, NaCl, *Candida albicans*, Potato Dextrose Agar (PDA), distilled water, and water for injection (WFI).

Methods

Preparation of Fungal Suspension

The test fungus *Candida albicans* was first grown on solid Potato Dextrose Agar (PDA) medium. To prepare the medium, 0.4 grams of PDA powder was dissolved in 10 mL of distilled water and sterilized in an autoclave. The sterilized liquid medium was then poured into sterile test tubes and placed in a slanted position until it solidified into slant agar. The fungus was inoculated onto the slant surface using the streak plate method, followed by incubation at 25–30°C for 24–48 hours, allowing visible fungal colonies to develop.

The fungal colonies that developed were then used to prepare a suspension. First, 10 mL of sterile NaCl solution was placed into a clean test tube. Using a sterile loop that was previously heated until red-hot and then cooled briefly to maintain sterility, a colony from slant agar was transferred into a tube containing NaCl solution. The mixture was homogenized using a vortex for about 15 seconds until the fungal cells were evenly dispersed. The test tube was sealed tightly to avoid contamination and incubated at 25–30 °C for 24–48 hours. After incubation, the resulting fungal suspension was transferred into a clean, dry cuvette for turbidity measurement. Measurements were performed with a UV-Vis spectrophotometer at a wavelength of 530 nm. Readings were taken gradually until the suspension reached a turbidity equivalent to McFarland standard 0.5, corresponding to an absorbance value of 0.08–0.1 (Lely and Rahmanisah 2017).

Antifungal Activity Test

The antifungal activity test against *Candida albicans* was carried out using the well diffusion method with PDA (Potato Dextrose Agar) as the growth medium. First, 10 grams of PDA powder was weighed and dissolved in 250 mL of distilled water, then heated on a hotplate until it reached boiling. Once boiling, the solution was cooled for a few minutes and covered with cotton wrapped in gauze to maintain sterility. The medium was then sterilized in an autoclave at 121 °C for 20 minutes. For fungal inoculation, the pour plate method was used. A 20 µL suspension of *Candida albicans* was placed in a sterile petri dish, followed by the addition of 10 mL of the PDA medium. The mixture was homogenized by gently swirling the plate in a figure-eight motion and then left to solidify. After the agar solidified, wells were carefully created in the medium to prepare for testing.

Each medium plate was divided into four sections: one for the SMMDF preparation without masoyi essential oil (negative control), one for nystatin (positive control), and two for the test samples. The samples consisted of SMMDF preparations containing masoyi essential oil formulated with HPMC and PVP polymers. Before testing, the SMMDF films (measuring 2 × 2 cm) were dissolved in 1 mL of sterile distilled water. From each preparation, 20 µL of negative control solution, positive control, and test sample were added to the wells designated on the medium. The plate was then incubated at 35 °C under aerobic conditions for 48 hours (Yandriyani et al. 2019). After incubation, clear inhibition zones were observed and their diameters were measured using a caliper.

RESULTS AND DISCUSSION

Self-Microemulsifying Mouth Dissolving Film (SMMDF) is an innovative dosage form that combines the Self-Microemulsifying Drug Delivery System (SMEDDS) technology with a thin film that rapidly dissolves in the oral cavity, thereby enhancing the bioavailability of lipophilic drugs through spontaneous microemulsion formation upon contact with saliva (Pattewar et al. 2016). In the development of SMMDF, film-forming polymers play a crucial role not only as the structural framework but also in determining the physicochemical characteristics of the formulation. Polymers serve to create a homogeneous matrix that incorporates oil, surfactants, and co-surfactants, resulting in a flexible and durable film. Furthermore, hydrophilic polymers influence the disintegration rate of the film in saliva and the release of the active compound. (Dyah Ayu Nurismawati and Sani Ega Priani 2021)

Hydroxypropyl Methylcellulose (HPMC) is a semi-synthetic polymer with the ability to form transparent, strong, flexible, and mechanically stable films. The hydration properties of HPMC allow the formation of a gel layer that controls the dissolution rate and drug release, thereby supporting consistent release of the active compound and prolonging the drug's supersaturation state (Pan et al. 2023). Polyvinylpyrrolidone (PVP) is a hydrophilic polymer that produces strong, transparent, and glossy films, and its hydrophilicity facilitates rapid water uptake and film dissolution in the oral cavity (Franco and De Marco 2020). This study aims to identify the polymer capable of providing films with the most effective antifungal activity.

The results of the antifungal test, as shown in Table 1, indicate that the average inhibition zone of SMMDF formulated with HPMC polymer was 10.85 mm, while that of SMMDF formulated with PVP polymer was 11.51 mm. These findings suggest that films containing PVP polymer exhibited a larger inhibition zone compared to those containing HPMC polymer.

Table 1. Antifungal Activity Test Results Against *Candida albicans*

Replication	SMMDF Polymer (mm)
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	HPMC	PVP	Positive Control (mm)	Negative Control (mm)
1	6,43	4,18	5,15	0,00
2	5,86	6,32	7,10	0,00
3	7,77	6,14	6,69	0,00
4	12,19	12,64	6,60	0,00
5	10,09	14,13	6,71	0,00
6	14,65	14,23	6,80	0,00
7	14,11	14,40	5,08	0,00
8	14,40	14,27	7,49	0,00
9	12,15	17,34	6,24	0,00
Average	10,85	11,51	6,68	0,00

The effectiveness results showed that both formulations produced inhibition zones categorized as strong, according to the classification of antifungal activity, which is divided into very strong (>20 mm), strong (10–20 mm), moderate (5–10 mm), and weak (<5 mm) (Arista et al. 2013). This result was further supported when compared with the positive control, which exhibited an average inhibition zone of only 6.31 mm, whereas the SMMDF formulations demonstrated larger inhibition zones. The positive control used was nystatin, an antifungal agent that works by binding to ergosterol in the fungal cell membrane, causing leakage of intracellular contents and ultimately leading to fungal cell death (Novi Yanti, Samingan 2016). The larger inhibition zones observed in the test formulations compared to the positive control indicate that masoyi essential oil possesses strong antifungal activity against *Candida albicans*. This activity is attributed to the main constituent of masoyi oil, massoia lactone, which has been shown to exert antifungal effects by disrupting fungal cell membrane integrity and inhibiting ergosterol biosynthesis (Hamzah et al. 2023). Massoia lactone acts by damaging fungal cell membrane integrity, interfering with lipid membrane synthesis, and increasing membrane permeability, which leads to leakage of essential ions and intracellular compounds (Burhan et al. 2017).

On the other hand, no inhibition zone was observed in the negative control, which was the SMMDF formulation without masoyi essential oil. This further confirms that the antifungal activity observed originated from the active ingredient, not from the film base or other excipients. It also demonstrates that film-forming polymers such as HPMC and PVP do not possess intrinsic antifungal activity and therefore did not influence the interpretation of the results.

Table 2. Results of Independent Sample T-Test

Mean ± SD		Levene's Test (Sig.)	Uji t (Sig. 2-tailed)	Conclusion
HPMC	PVP			
10,85 ± 3,4	11,51 ± 4,6	0,233 (Homogeneous)	0,735	Not significantly different

To determine whether there was a difference in antifungal effectiveness between SMMDF formulations containing the polymer combination of amylum manihot–HPMC and those containing amylum manihot–PVP, an independent sample t-test was performed. This test

aimed to assess whether there was a statistically significant difference in the mean values between the two tested samples (Razak and Hidayati 2019).

The analysis began with assessing data homogeneity using Levene's test. If the result showed $\text{sig} > 0.05$, it indicated that the variances of the two samples were equal, and the t-test result was interpreted under the assumption of equal variances. Conversely, if $\text{sig} < 0.05$, it suggested unequal variances, and the t-test result was interpreted under the assumption of unequal variances (Priyatno, 2010).

The results of the t-test showed no significant difference in the antifungal activity between the two formulations. This finding indicates that the difference in polymers, whether HPMC or PVP, did not affect the antifungal effectiveness. This is because the antifungal activity originated from the active ingredient, masoyi essential oil, which was present in the same concentration in both formulations, thus producing a comparable level of effectiveness.

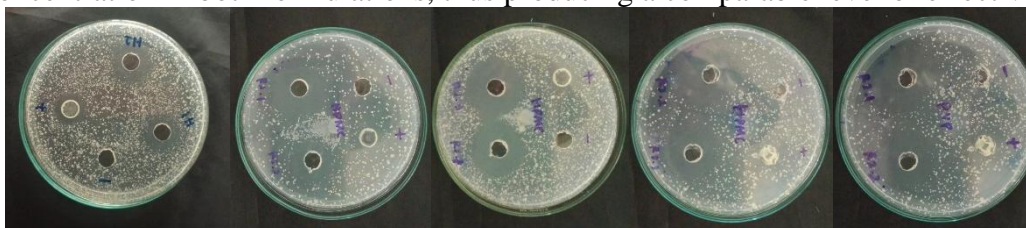


Figure 1. Antifungal Test Results of SMMDF Formulation with HPMC Polymer



Figure 2. Antifungal Test Results of SMMDF Formulation with PVP Polymer

CONCLUSION

The formulation of Self-Microemulsifying Mouth Dissolving Film (SMMDF) containing masoyi essential oil demonstrated strong antifungal activity against *Candida albicans*, with inhibition zones larger than those of the positive control (nystatin). No significant difference was observed between the use of HPMC and PVP polymers in terms of antifungal effectiveness, indicating that the choice of polymer may be adjusted based on other formulation considerations such as physical properties, user convenience, and dosage form stability. These findings confirm that masoyi essential oil has great potential as an active ingredient in antifungal SMMDF formulations for the treatment of *Candida albicans* infections.

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