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Formulation and Stability Test of HPMC and Carbomer 940 based-Gel Formulation Containing Plantago major L. hydroalcoholic extract

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ABSTRACT
The *P. major* plant has long been utilized in traditional herbal medicine and is widely accessible in Indonesia and globally. Extensive research has demonstrated its efficacy in wound healing through both clinical and preclinical studies. Gel formulations are recognized for establishing a conducive moist environment essential for wound healing, thus rendering them suitable for topical wound treatment. This study assesses the stability of HPMC gel base, carbomer 940, and their combination as carriers for the ethanol extract of *P. major* leaves. Stability testing involved a freeze-thaw cycle test at temperatures of 4°C and 40°C for three cycles. The findings indicate no significant alteration in the organoleptic properties and pH of the gel formulations before and after stability testing. However, t-test analysis reveals a noteworthy decrease in viscosity for carbomer and its combination, albeit not for HPMC alone. In conclusion, HPMC exhibits superior stability as a gel base compared to Carbomer 940 and their combination.
Keywords: Carbomer 940; Gel; HPMC; *P. major*; Stability test

INTRODUCTION
Sendok (*P. major*) is an Indonesian herbal plant characterized by short stems and elongated leaves measuring 15–30 cm in diameter. It bears small brownish-green flowers with purple stamens. Widely distributed across the globe, especially in Europe, Northern and Central Asia (Adom et al., 2017). This plant has been traditionally used for treating skin inflammation or wounds, digestive issues, and cardiovascular ailments (Jarić dkk., 2018). In Indonesia, it's employed as a remedy for wounds, swelling, postpartum pain, and as an aphrodisiac (Susiarti et al., 2018). Aucubin compound found in *P. major* leaves exhibits wound healing activity in diabetic-induced rats, indicating its potential in accelerating chronic wound recovery (Kartini K et al., 2018). Therefore, Sendok holds promise to be formulated for topical application in treating chronic wounds

Gels are semi-solid formulations containing a pair of components, with the liquid phase being predominant. Upon application, the liquid phase evaporates, leaving behind a thin film of gel containing the drug, which adheres to the skin (Fateh & Sharma, 2023). The predominant water content in the liquid phase of gels allows them to maintain a moist environment near the wound's surface, aiding in tissue repair. This characteristic enables hydrogels to effectively support the healing process (Gounden & Singh, 2024). Compared to creams and other ointments, gels offer superior drug release characteristics. They are highly biocompatible, resulting in minimal risk of adverse reactions and inflammation. In dermatology, gels possess several advantageous properties, including thixotropy, easy removal, non-greasiness, desirable spreadability, non-staining effects, emollient qualities, and compatibility with various excipients (Fateh & Sharma, 2023).

Research by Kartini et al. (2021) formulated 5% Sendok extract in Carbomer base for treating wounds in diabetic-induced rats. The results showed that the Sendok gel could expedite wound

Table I. Formula of the Sendok gels

No	Ingredient	Formula 1 (%)	Formula 2 (%)	Formula 3 (%)
1	HPMC	1	0	0,5
2	Carbomer 940	0	1	0,5
3	Propylene glycol	15	7	15
4	Triethanolamine	0	0,8	0,8
5	Propyl paraben	0,02	0,02	0,02
6	Methyl paraben	0,18	0,18	0,18
7	SLE	1	1	1
8	Water	Add to 100	Add to 100	Add to 100

closure and reduce re-epithelialization time. Similarly, in the study by Ghanadian et al. (2022), 10% Sendok extract in HPMC gel base was formulated for treating wounds in diabetic patients or pressure ulcers. The results indicated a reduction in wound erythema and size. Both studies demonstrate the wound healing ability of Sendok gel in two different bases, Carbomer and HPMC, with favorable outcomes.

Sendok extract exhibited good stability in Carbomer 940 gel base. Research by Yusuf & Nugraha (2021) showed no physical changes in the gel after stability testing, with pH measurements remaining unchanged. However, viscosity measurement, an important parameter in gel stability and effectiveness, was not conducted in this study (Sudjono et al., 2012). On the other hand, Kartini et al., (2017) indicated instability of the Sendok gel with carbomer base after accelerated stability testing, as evidenced by viscosity measurements. Additionally, it's crucial to compare the stability of the two gel bases that have shown effectiveness in in vivo wound healing trials. Hence, this study aims to assess the stability of Sendok gel formulations in Carbomer, HPMC, and their combination, focusing on physical appearance and viscosity parameters.

METHODOLOGY

This experimental research investigates the stability of gel bases incorporating carbomer 940, HPMC (Hydroxypropyl Methylcellulose), and their combination as carriers for Sendok leaves extract (SLE). The study aims to compare the stability parameters, including organoleptic properties, pH, and viscosity, of each gel base. The research was conducted at the Semisolid Preparations Laboratory, Faculty of Pharmacy, Universitas Gadjah Mada, from August to December 2023.

Sendok leaves samples were collected from Balai Penelitian Teknologi Perbenihan (BPTP) Bogor and extracted using the optimized UAE method (unpublished data). The resulting liquid hydroalcoholic extract underwent evaporation via a rotary evaporator. Formulation was performed with the ingredient composition detailed in Table I.

Preparation of Gel in various gelling agent

Formula 1 is prepared by gradually dissolving HPMC (MakingCosmetics, USA) using a sieve into distilled water at 70°C, stirred using a magnetic stirrer to form Solution A1. Solution A1 is stirred for 30 minutes at 70°C until a homogeneous gel base is formed. Nipagin (MedChemExpress, USA) and nipasol (Alpha Chemika, India) are dissolved in propylene glycol (PG) (Brataco, Indonesia) (Solution B). PG is subsequently added to SLE (Solution C). Solutions B and C are slowly added to Solution A and stirred for 30 minutes until a homogeneous gel is formed. The mixture is cooled overnight and then transferred into aluminum tubes.

Formula 2 is prepared by slowly dissolving carbomer 940 (Lubrizol, USA) into distilled water using a sieve and a magnetic stirrer for approximately 30 minutes until fully dispersed. Triethanolamine (TEA) (Merck, Germany) is subsequently added and stirred to form a gel base (Solution A2) (Yusuf & Nugraha, 2021). Solutions B and C are prepared as before. The subsequent steps are carried out similarly to the preparation of Formula 1. Formula 3 is created by mixing Solutions A1 and A2. The subsequent steps are performed as in the previous stages in Formula 1.

Figure 1. Physical appearance of the Sendok gel formulations (F1) HPMC 1% (F2) Carbomer 940 1% (F3) HPMC 0,5 %: Carbomer 940 0,5%

Stability test

The gel underwent assessment utilizing a freeze-thaw cycle test (FTCT) protocol, which involved 24-hour storage at 4ºC followed by 24 hours in a 40ºC oven, with each repetition constituting one cycle (Yusuf & Nugraha, 2021). After completing three cycles, the gel was evaluated for viscosity, organoleptic properties, and pH (Sudjono et al., 2012).

RESULT AND DISCUSSION

Stability test results: organoleptic and pH

The results pertaining to the organoleptic properties and pH assessment of SLE in different bases, both before and after undergoing the FTCT, are presented in Figure 1 and Table II.

Following the FTCT, minimal changes were observed in the organoleptic characteristics and pH values of the Sendok gels, as evidenced by parameters such as uniformity, odor, consistency, color, and pH. These findings are consistent with those reported by Yusuf & Nugraha (2021), who found similar results with Sendok gel utilizing carbomer 940 as the base. Each gel exhibited distinct characteristics in terms of organoleptic properties and pH. Notably, the fragrance of the Sendok gel with Carbomer 940 base was relatively subdued compared to that of the HPMC gel and their combination. These variations in scent are often influenced by the types of gel bases and aromatic compounds (Pangborn & Szczesniak, 1974). Additionally, while viscosity had minimal impact on scent, other parameters such as consistency, color, and pH of each gel base demonstrated unique features, as detailed in Table II and Figure 1. Overall, based on organoleptic and pH testing, all three gel bases exhibited satisfactory stability following the FTCT for 3 cycles.

Stability test results: Viscosity measurement

The viscosity test results for Sendok gels with Carbomer 940 and their combination bases revealed significant discrepancies before and after FTCT, in contrast to the relatively stable organoleptic and pH test outcomes (Figure 2 and Table III). This observation aligns with the findings of Kartini et al. (2017), indicating instability of Sendok gel formulations employing carbomer as the base under accelerated conditions. Conversely, Sendok gels formulated with an HPMC base exhibited no substantial changes in viscosity. This disparity underscores the importance of viscosity assessment, as it directly impacts the gel's efficacy in wound healing. The differences in viscosity may influence the release rate of active compounds from the formulation bases (Sudjono et al., 2012).

Carbomer 940 polymers, initially dry and tightly coiled acidic molecules, necessitate neutralization for maximum viscosity. When dispersed in water, these molecules hydrate and partially uncoil. Optimal thickening is achieved by neutralizing the acidic carbomer 940 polymer with bases like sodium hydroxide (NaOH) or triethanolamine (TEA), converting them into salts (Lubrizol, 2009). In non-aqueous formulations, carbomer 940 polymer augments viscosity through hydrogen bonding between acrylic acid and the hydroxyl groups of alcohols/polyols (Lubrizol, 2022). However, this mechanism may compromise the stability of carbomer 940, especially in the presence of ethanol-extracted SLE, which can extract compounds with a wide polarity range, potentially

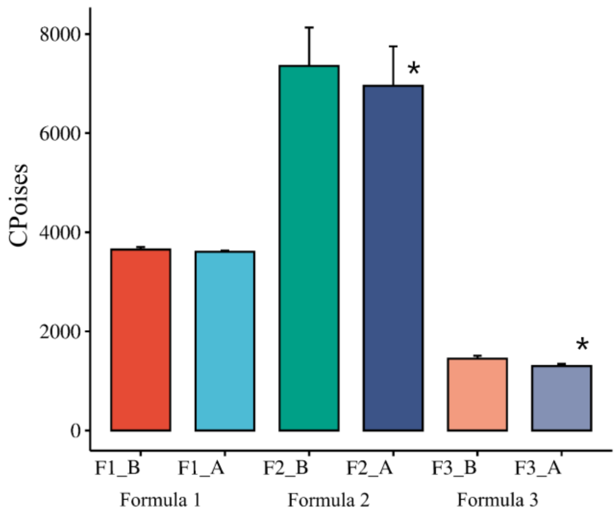

Figure 2. Viscosity measurement results of the Sendok gels before (B) and after (A) FTCT. Formula 1, HPMC (1%); Formula 2, Carbomer 940 (1%); Formula 3, HPMC (0,5%): Carbomer 940 (0,5%)

Table II. Organoleptic and pH test results of the Sendok gels

Parameters	Repli-cation	Before FTCT			After FTCT		
		F1	F2	F3	F1	F2	F3
Homogeneity	1	Homo-geneous	Homo-geneous	Homo-geneous	Homo-geneous	Homo-geneous	Homo-geneous
	2	Homo-geneous	Homo-geneous	Homo-geneous	Homo-geneous	Homo-geneous	Homo-geneous
	3	Homo-geneous	Homo-geneous	Homo-geneous	Homo-geneous	Homo-geneous	Homo-geneous
Scent	1	Strong	Moderate	Strong	Strong	Moderate	Strong
	2	Strong	Moderate	Strong	Strong	Moderate	Strong
	3	Strong	Moderate	Strong	Strong	Moderate	Strong
Texture	1	Thick	Very thick	Slightly thick	Thick	Very thick	Slightly thick
	2	Thick	Very thick	Slightly thick	Thick	Very thick	Slightly thick
	3	Thick	Very thick	Slightly thick	Thick	Very thick	Slightly thick
Color	1	Transparent deep brown	Wavy dark brown	Deep brown	Transparent deep brown	Wavy dark brown	Deep brown
	2	Transparent deep brown	Wavy dark brown	Deep brown	Transparent deep brown	Wavy dark brown	Deep brown
	3	Transparent deep brown	Wavy dark brown	Deep brown	Transparent deep brown	Wavy dark brown	Deep brown
pH	1	5	5	7	5	5	7
	2	5	5	7	5	5	7
	3	5	5	7	6	5	7

affecting stability. Additional factors like electrolytes and pH can further decrease carbomer 940 stability (Lubrizol, 2010). Further investigation is warranted.

HPMC, derived from cellulose through partial substitution with methyl groups as the main substituents and a small proportion of hydrophilic hydroxypropyl groups, exhibits amphiphilic

Table III. Viscosity measurement results of the Sendok gels

No	Formula	Viscosity before FTCT	Normality Test (Shapiro-Wilk)	Viscosity after FTCT	Normality Test (Shapiro-Wilk)	Paired t-test
1	F1 HPMC	3652±83,20	0.867	36056 ± 45	0.938	0.175128
2	F2 Carbomer	7355 ± 1341	0.352	6952 ± 1384	0.565	0.04749
3	F3 HPMC: Carbomer	1452 ± 101	0.679	1302 ± 76	0.201	0.044652

properties, striking a balance between its hydrophilic and hydrophobic groups. Upon heating above its gelation temperature (70°C–90°C), HPMC forms a gel in water, with gelation contingent upon the degree of methylation and hydroxypropylation (Lim et al., 2021). These properties and interaction mechanisms may render it more compatible with various polar and non-polar compounds in SLE.

This study is limited by its utilization of only one concentration of each gel base. Future research involving diverse types and concentrations of gel bases is imperative. Direct application of Sendok gels on test animals is also warranted to validate formulation efficacy post-storage. Additionally, employing nanoencapsulation technology may enhance the stability of the carbomer 940 base. Exploring nanohydrogel formulation with SLE as active ingredients presents a promising avenue for further exploration.

CONCLUSION

The findings of this study suggest that there were no significant alterations observed in the organoleptic properties and pH values among HPMC, carbomer 940, and their combination bases following freeze-thaw cycle tests. However, the viscosity test results indicate that HPMC base demonstrates superior stability as a carrier for SLE compared to carbomer 940 and their combination bases. This outcome can be attributed to the amphiphilic nature of HPMC, which allows for compatibility with SLE containing a diverse range of compounds, both polar and non-polar. It is worth noting that this study is limited by its use of only one concentration of gel base and the absence of testing on animal models. Further research is warranted to validate these findings and explore potential applications.

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