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Physical properties and stability of grapeseed oil (*Vitis vinifera* L.) skincare formula with gelling agent combination of Na-CMC-carbopol and HPMC-carbopol

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ABSTRACT

Skincare products made from natural ingredients have become the choice of many people. Grapeseed oil contains ingredients that act as a moisturizer. Na-CMC-carbopol and HPMC-carbopol are gelling agents that are widely used in preparations due to their compatibility with various materials. All three are combined to cover their respective deficiencies. This study aimed to evaluate the effect of the combination of Na-CMC-carbopol and HPMC-carbopol on the physical properties and stability of grapeseed oil gel and to determine the optimum formula. The research method was carried out by optimizing the levels of Na-CMC (2-2.5%), HPMC (2-20%), and carbopol (0.5-1%) with the Simplex Lattice Design method. Eight runs of the resulting formula were gelled and tested for their physical properties to determine the optimum formula. The optimum formula obtained was verified with statistical analysis and tested for physical stability. The stability data were analyzed statistically, 95% confidence level. The optimum formula for NaCMC-carbopol was at a concentration of 2.220% Na-CMC and 0.780% carbopol, pH 6.246 ± 0.057, spreadability 12.96 ± 0.48 cm2, adhesion 6.33 ± 0.48 sec, viscosity 166.00 ± 4.88 dPas. HPMC-carbopol at both concentrations of 1% had a pH of 4.973 ± 0.172, a viscosity of 175.20 ± 5.44 dPas, a spreadability of 18.12 ± 1.61 cm2, and an adhesion of 6.94 ± 1.68 sec. All preparations were not significantly different between predictions and experiments. The optimum gel formula had good physical properties and was stable during 3 cycles of cycling stability test.

ABSTRAK

Skincare dari bahan alami menjadi pilihan masyarakat Minyak biji anggur mengandung bahan yang berperan sebagai pelembab. Na-CMC-karbopol dan HPMC- karbopol merupakan *gelling agent* yang banyak digunakan dalam sediaan karena kompatibilitasnya dengan berbagai bahan. Ketiganya dikombinasikan untuk menutup kekurangan masing-masing. Tujuan penelitian ini adalah untuk mengevaluasi pengaruh kombinasi Na-CMC-karbopol dan HPMC-karbopol terhadap sifat fisik dan stabilitas gel minyak biji anggur, serta menentukan formula optimumnya. Metode penelitian dilakukan dengan mengoptimasi kadar Na-CMC (2-2,5%), HPMC (2-20%) dan karbopol (0,5-1%) dengan metode *Simplex Lattice Design*. Delapan *run* formula masing-masing yang dihasilkan, dibuat gel dan diuji sifat fisiknya untuk menentukan formula optimum. Formula optimum yang didapat diverifikasi dengan analisis statistik dan diuji stabilitas fisiknya. Data stabilitas dianalisis dengan statistik, tingkat kepercayaan 95%. Formula optimum NaCMC-karbopol pada konsentrasi Na-CMC 2,220% dan karbopol 0,780%, pH 6,246 ± 0,057, daya sebar 12,96 ± 0,48 cm^2, daya lekat 6,33 ± 0,48 detik, viskositas 166,00 ± 4,88 dPas. HPMC-karbopol pada konsentrasi keduanya 1% memiliki pH 4,973 ± 0,172, viskositas 175,20 ± 5,44 dPas, daya sebar 18,12 ± 1,61 cm^2, dan daya lekat 6,94 ± 1,68 detik. Semua sediaan tidak berbeda signifikan antara prediksi dengan percobaan. Formula optimum gel memiliki sifat fisik yang baik dan stabil selama penyimpanan.

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INTRODUCTION

Grapes (*Vitis vinifera* L.) are fruits that people like because they taste sweet, sour, and fresh. Grapes are often produced as canned fruit, raisins, juice, and wine. Grapes contain polyphenolic compounds which have antioxidant activity and are beneficial to health.[1] Grape seeds have a high antioxidant content. Grapeseeds are generally discarded and become waste from direct consumption as well as from the processing of wine, jam, and raisins.

In its development, grapeseeds are processed and extracted to produce oil that is used in making cosmetics and skincare. Grapeseed oil has the highest antioxidant activity compared to other parts of the grape plant. Garavaglia *et a.l*[2] stated that the high antioxidant activity of grapeseed oil comes from the content of polyphenolic flavonoids such as oligomeric proanthocyanidins (OPC), catechins, epicatechins, and gallic acid content. Antioxidants can protect the skin from aging, UV rays, and acne, and can moisturize the skin.[3] Grapeseed oil also contains various kinds of fatty acids with the highest content of linoleic acid reaching 78%.[4] Linoleic acid is an essential unsaturated fatty acid that can prevent dry skin and soften the skin. Based on research conducted by Maamoun[5] grape seed oil can be used as an anti-aging, moisturizer, sunscreen, and anti-acne, can tighten and heal the skin, and reduce dark circles around the eyes. Thus, grapeseed oil has great potential to be developed in the world of cosmetics and skincare.

Skincare preparations can be in the form of creams, gels, or ointments. Gel preparations are generally preferred because they contain a lot of water so they provide moisture to the skin and have better penetration power than other topical preparations.[6] The percentage of humidity is obtained based on the following scale: dry (0-45%), normal or moist (46-55%), and very moist (56-100%).[7] Other advantages of gel preparations are that they are easy to spread when smeared, give a cold sensation, are easy to apply to the skin, do not leave marks on the skin, and are easy to wash.[8] Gel dosage forms have better potential to manage topical preparations because they are non-sticky, have an attractive appearance, and have good aesthetic value.[9]

The physical properties and stability of a gel are determined by the base or gelling agent used. One gelling agent is generally sufficient to form a gel, but a combination of two or more gelling agents is sometimes required to make a good gel. Na-CMC and carbopol are examples of gelling agents that are often used because they are compatible, non-toxic, and non-irritating.[10] Na-CMC is used because it can improve viscosity, stabilize preparations, and produce neutral preparations.[10,11] However, this gelling agent sometimes gives a small diameter of spread.[12] Carbopol or carbomer is a stable gelling agent, that can give a clear appearance and high viscosity, but still has good spreadability, homogeneity, and good adhesion to the skin.[10,13] The use of carbopol sometimes results in gels that are too thick because a low concentration is effective in forming a gel with high viscosity.[14]

Therefore, a combination of gelling agents is needed to cover the deficiencies of each material and produce a gel with optimum physical properties. The variation in the concentration of the gelling agent is optimized using the Simplex Lattice Design method. This method makes it possible to obtain gelling agent concentrations that have optimal physical properties.

MATERIALS AND METHODS

Tools

Analytical balance (Adventurer™ Ohaus), homogenizer (IKA T25 digital ultra turrax), semisolid pH meter (HANNA), ultra turrax (IKA T25 digital), refrigerator (LG), power spread test

kit (Faculty of Pharmacy UGM), tool adhesion test (Faculty of Pharmacy UGM), viscometer (Brookfield DV-1 Prime), stopwatch (Alba),

Materials

Grapeseed oil (Kowa oil), Na-CMC, carbopol, propylene glycol, DMDM hydantoin, triethanolamine (all pharmaceutical grades).

Preparation of gels

Distilleld water (aquadest) as much as 20x of the amount of gelling agent used were heated to 70°C. After reaching 70°C, the aquadest was poured little by little into the mortar containing the carbopol and stirred until mixed. Then, TEA was added to the carbopol to neutralize the pH and stirred until it swelled. On another mortar, Na-CMC was developed using aquadest which had been heated to 70°C. The swollen Na-CMC was then mixed into the carbopol, stirred until homogeneous, and a gel mass was formed. DMDM hydantoin and propylene glycol were added to the mixed gel mass and stirred until homogeneous. Grapeseed oil was added last and then homogenized using ultra turrax. The remaining aquadest were added little by little to the mixture until they reached 100 mL while being homogenized.[15,16]

Optimizing of gelling agents

Optimizing of gelling agents was carried out by optimizing the levels of Na-CMC (2-2.5%), HPMC (2-20%), and carbopol (0.5-1%) with the Simplex Lattice Design method (TABLE 1 and 2).

TABLE 1. Optimization of Na-CMC-carbopol gelling agent

Material	R1	R2	R3	R4	R5	R6	R7	R8
Grapeseed oil	10	10	10	10	10	10	10	10
Na-CMC	2	2.25	2	2.5	2.5	2.375	2.25	2.125
Carbopol	1	0.75	1	0.5	0.5	0.625	0.75	0.875
Propylene glycol	15	15	15	15	15	15	15	15
DMDM	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
TEA	1	1	1	1	1	1	1	1
Aquadest ad	100	100	100	100	100	100	100	100

TABLE 2. Optimization of HPMC-carbopol gelling agent

Material	R1	R2	R3	R4	R5	R6	R7	R8
Grapeseed oil	10	10	10	10	10	10	10	10
HPMC	1.375	1.25	1.125	1.5	1	1.5	1	1.25
Carbopol	0.625	0.75	0.875	0.5	1	0.5	1	0.75
DMDM hydantoin	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Propylene glycol	10	10	10	10	10	10	10	10
TEA	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Aquadest ad	qs	qs	qs	qs	qs	qs	qs	qs

Physical properties test

pH test

The pH test was carried out by dipping the electrode from a semisolid pH meter into the preparation. The pH value obtained was recorded and adjusted to the pH range of the skin.[17] Topical preparations that are safe for the skin are in the pH range of 4.5 – 7.[18]

Spreadability test

The spreadability test was carried out by placing 0.5 g of gel on a round glass scale. The gel mass was covered with another round glass and allowed to stand for 1 min then the diameter of the spread was measured. Then the measurement of the diameter of the gel distribution was continued by adding a weight of 50, 100, 150, 200, and 250 g, and was allowed to stand every 1 min. The spreadability of good topical preparation is 3-5 cm (semi-fluid) or 5-7 cm (semi-fluid).[17,19]

Adhesion test

The adhesion test was carried out by placing 0.25 g of the gel preparation on a glass object, covered with another glass, and giving 1 kg of load for 5 min. The object glass was then mounted on the test equipment and an 80 g of weight was released. The time until the two glass objects are separated is called adhesion. Good adhesion requires more than 4 sec.[17,20]

Viscosity test

Tests were carried out using a Brookfield viscometer. The gel preparation was put into the tube container on the viscometer and then the spindle was installed. The spindle must be immersed in the gel to a certain extent and make sure the spindle can rotate when the tool is turned on. The viscometer was set at 100 rpm for 15 sec. The gel viscosity value was obtained when the numbers on the screen were stable. The requirement for a good gel has a viscosity in the range of 30 – 500 dPas.[17,21]

Cycling test grapeseed oil gel

Grapeseed oil gel preparations were tested for stability using the Cycling Test method. The gel preparations were put in glass pots which were tightly closed and then placed in the refrigerator for 24 h at 4^{o}C then the gel preparations were transferred to the oven for 24 h at 4^{o}C (1 cycle). This process was repeated for 6 d or 3 cycles. It was then observed whether there was a phase separation that occurs at the end of each cycle.[22]

Gel syneresis power test

The gel preparation was taken in 10 mL and placed in a conical centrifuge tube. It was stored for 72 h at ±10^{o} C and the reduction in gel weight was observed at the 24th, 48th, and 72nd h. The % syneresis was calculated with Equation 1.[23]

$$\text{Syneresis}(\%) = \frac{\text{Initial weight(g)} - \text{final weight(g)}}{\text{initial weight(g)}} \text{x}100\% \quad (1)$$

Data analysis

Data on the physical properties of the gel were analyzed by SPSS using the Shapiro-Wilk test with a 95% confidence level to determine whether the data were normally distributed or not. Data that were normally distributed were analyzed by one sample t-test, and data that were not normally distributed were analyzed with Mann-Whitney. This analysis was to determine whether there was a significant difference between software predictions and experimental results.

Optimum formula stability data were analyzed using the Shapiro-Wilk test and the Homogeneity of Variance test

with a 95% confidence level. Normal and homogeneous data were analyzed with one-way Anova and Tukey (post hoc). The one-way Anova was aimed to determine whether there were significantly different data from each cycle, and the post hoc test was aimed to determine the position where these differences occurred. Data that were not normally distributed and not homogeneous were analyzed with the Friedman test.

RESULT

Determination of optimum formula

The pH response, spreadability, and viscosity obtained previously were used to determine the optimum formula using the Design Expert software version 10. The physical properties of Na-CMC-carbopol and HPMC-carbopol formula are showed in TABLE 1.

TABLE 3. The results of the physical properties test of 8 runs of the Na-CMC-carbopol and HPMC-carbopol gel formulas

Run	pH Na-K	pH H-K	Spreadability (cm^2) Na-K	Spreadability (cm^2) H-K	Viscosity (dPas) Na-K	Viscosity (dPas) H-K
1	5.70 ± 0.001	5.9 ± 0.0	11,94 ± 0.310	18.11 ± 1.507	185.6 ± 2.466	152.8 ± 3.8
2	6.40 ± 0.01	5.9 ± 0.2	13,85 ± 0.385	17.35 ± 0.738	161.6 ± 3.394	152.4 ± 1.5
3	5.62 ± 0.01	5.0 ± 0.3	12.56 ± 0.358	15.22 ± 1.382	184.4 ± 1.131	168.4 ± 3.0
4	7.24 ± 0.01	6.0 ± 0.2	13.85 ± 0.110	18.89 ± 2.308	158.4 ± 1.980	147.6 ± 2.4
5	7.22 ± 0.04	5.6 ± 0.3	14.52 ± 0.659	18.11 ± 1.507	157.6 ± 4.530	168.4 ± 5.3
6	6.70 ± 0.01	6.0 ± 0.1	13.20 ± 0.367	20.42 ± 0.801	170.8 ± 3.672	134.4 ± 0.9
7	6.35 ± 0.00	4.9 ± 0.1	13.20 ± 0.921	16.66 ± 2.167	171.6 ± 1.672	188.4 ± 1.8
8	6.02 ± 0.03	5.5 ± 0.2	12.25 ± 0.178	15.92 ± 1.413	182.4 ± 2.263	174.2 ± 3.3

Notes: Na-K = NaCMC-carbopol mixture and H-K = HPMC-carbopol mixture

The three responses had a significant model and the lack of fit value was not significant so it can be used to determine the optimum formula.

Optimum formula verification

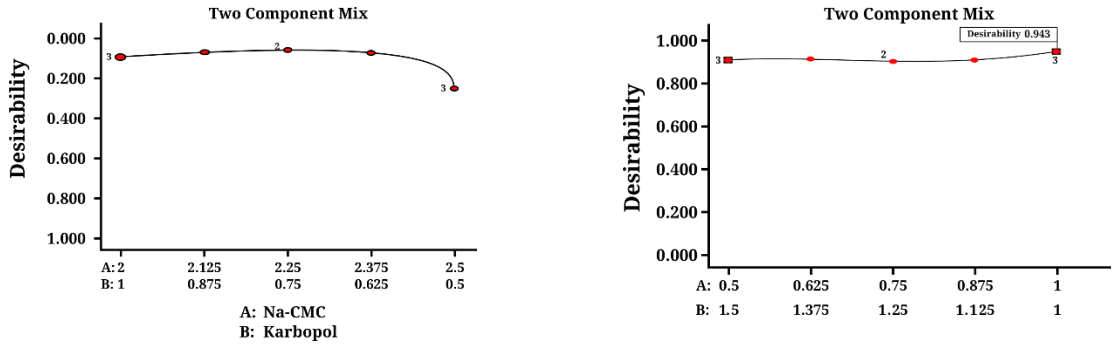
The data from the physical properties test was verified to find out whether there was a significant difference in the predictions of the software or not. Verification was done by comparing the experimental results with software predictions and was analyzed using the One sample t-test. The results of the analysis show that there is no significant difference because the significance value is <0.05.

TABLE 4. Response prediction and gel test of Na-CMC-carbopol and HPMC-carbopol gel formulas

Response	Prediction		Test		Sig. (2-tailed)		Conclusion
	Na-K	H-K	Na-K	H-K	Na-K	H-K	
pH	6.265	5.147	6.246 ± 0.057	4.925±0.86	0.560	0.135	NS
Spreadability (cm^2)	13.054	17.12	12.959 ± 0.479	18.325 ±0.252	0.719	0.239	NS
Viscosity (dPas)	173.136	179.18	166 ± 4.877	176±2.471	0.061	0.303	NS

*Notes: Na-K = NaCMC-carbopol mixture; H-K = HPMC-carbopol mixture; NS= not significant

The target pH response chosen was minimize, the spreadability target chosen was *maximize*, and the target viscosity selected was in range.



A **B**

FIGUE 1. (A) desirability of NaCMC-carbopol and (B) HPMC-carbopol

Gel syneresis test of NaCMC-carbopol and HPMC-carbopol formulas

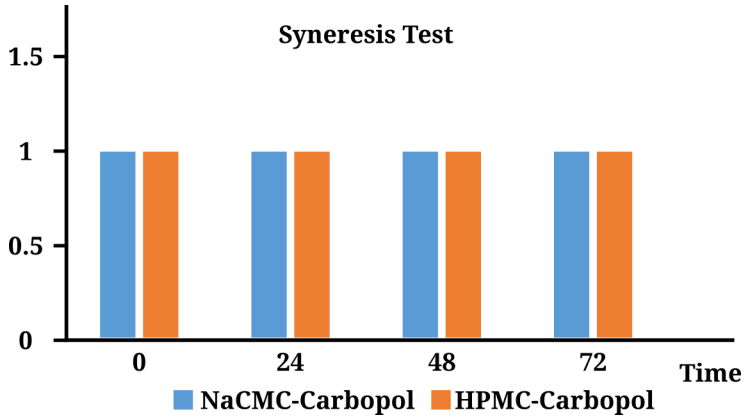


FIGURE 2. Gel syneresis test of NaCMC-carbopol and HPMC-carbopol

DISCUSSION

Optimization produces a solution with a certain desirability value, which is closer to one, meaning that the optimum formula obtained is closer to the desired target. The selected solution has a desirability value of 0.937 with a concentration of 2.220% Na-CMC and 0.780 % of carbopol. The predicted response to the resulting physical properties consisted of a pH of 6.265, a spreadability of 13.054 cm2, and a viscosity of 173.136 dPas.

Optimum formula physical stability test

Na-CMC had a greater positive effect on increasing the pH of the preparation. The higher the concentration of Na-CMC, the higher the pH produced. This is due to carbopol which has an acidic carboxylic group, hence the lower the concentration in the preparation, the more alkaline the pH of the preparation is. Na-CMC has a pH of 6.5 – 8.5 so increasing levels of Na-CMC in the preparation will increase the pH of the preparation.[10] The optimum

formula for HPMC-carbopol Grapeseed Oil gel did not change the pH value during storage. This means the gel has good stability against temperature changes in the pH test.

The tests (TABLE 4) showed that the pH decreased but remained within the required range (pH 4.5-7). The Anova test yielded a significance value of 0.123 (>0.05), which means that there was no significant difference in the pH of the gel during storage. It can be said that the optimum formula had a stable pH during 3 cycles of storage.

Carbopol has a greater positive effect on increasing viscosity. The higher the level of carbopol added, the higher the resulting viscosity. This is because carbopol can expand 1000 times when it meets water and is neutralized to form a rigid network structure.[24] Carbopol can be easily developed in small concentrations (0.5-2%) in polar conditions. Neutralizing bases such as triethanolamine or sodium hydroxide are needed to increase the viscosity of the carbopol gel.[25] HPMC requires a concentration of around 2-10% to form the desired gel structure.[26]

The tests (TABLE 4) showed that the viscosity increased until the 2nd cycle, but the viscosity was still good within the 20-200 dPas requirement range.[27] The Anova test yielded a significance value of 0.191 which means that the viscosity of the gel during storage did not differ significantly and was stable during 3 cycles of storage.

Na-CMC has a positive effect on spreadability. The higher the Na-CMC content in the carbopol mixture, the higher the result on spreadability. This gel contains carbopol which has a more rigid structure than Na-CMC.[10] Spreadability test to test the ease with which the preparation spreads when applied to the skin. A good spreadability will increase the patients' comfort with its use. A good gel preparation has a diameter of 5-7 cm.[28] Both gelling agents gave a positive response to the increase in spreadability. CMC-Na had a greater positive response than HPMC so the addition of CMC-Na had a greater effect on the increase in spreadability. The results of this analysis are inversely proportional to the viscosity response, HPMC has more influence on the increase in viscosity than CMC-Na.

The test of spreadability (TABLE 4) show that the spreading power had decreased but remained within the requirements range (3-5 cm). The spreadability was inversely proportional to viscosity; the higher the viscosity, the smaller the spreadability. The nova test yielded a significance value of >0.05, which means that there was no significant difference in the spreadability of the gel during storage so the optimum formula had stable spreadability during 3 cycles of storage.

Gel adhesion test of NaCMC-carbopol and HPMC-carbopol

The optimum adhesion of the formula meets the requirements for topical preparations with adhesion of >4 sec. The stability test shows that the adhesion had increased until the 2nd cycle. The adhesion was directly proportional to the viscosity; the higher the viscosity, the longer the adhesion. The Anova test yielded a significance value of >0.05 which means that the adhesion of the gel during storage was not significantly different and stable.

The syneresis test for the two gels which were stored at ±10^{o} C and observed a reduction in gel weight at the 24th, 48th, and 72nd h, showed that both did not experience a weight change, meaning that the gels from NaCMC-Carbopol and HPMC-Carbopol had a syneresis value of one. Both gels were able to completely retain water during storage, therefore this preparation is suitable for use as a moisturizer.

CONCLUSION

The optimum formula for the NaCMC-carbopol gel of grapeseed oil obtained

has a Na-CMC concentration of 2.220% and a carbopol of 0.780%, while the same concentration of HPMC-carbopol gel was 1 %. The resulting optimum formula has physical properties that meet the requirements of a good topical preparation. The optimum formula of grapeseed oil gel is also stable during storage.

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