
The gel formulation of the aqueous phase of snakehead fish (*Channa striata*) extract with various combinations of HPMC K4M and Carbopol 934

Wintari Taurina, Mohamad Andrie, Lea Anjeli*

Faculty of Medicine, Study Program Pharmacy

Tanjungpura University Pontianak

Jl. Prof. Dr. H. Hadari Nawawi, Bansir Laut, Pontianak

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ABSTRACT

Gel is a clear, semi-solid, and translucent dosage form that contains an active substance. The aqueous phase of the extract of *Channa striata* (snakehead fish) contains reactive albumin that is effective in accelerating wound-healing process. Hydroxypropyl methylcellulose (HPMC) and carbopol are the commonly used gelling agents in gel formation. This research aimed to identify the effect of different base (gelling agent) combinations on the physical and chemical stability of the gel dosage form of the aqueous phase of *Channa striata* extract for 28-day storage. The variation of HPMC:Carbopol ratio was 25:75%, 50:50%, and 75:25%. The physical and chemical stability tests included organoleptic, spreadability, adhesive capacity, and pH tests. The results were analyzed with one-way ANOVA and followed by post hoc Least Significant Difference (LSD) test at 95% confidence level. The entire HPMC:Carbopol combinations showed that the aqueous phase of the gel dosage form was both physically and chemically stable during the 28-day observation. The higher the concentration of HPMC, the better the physical and chemical stability. The most optimum combination was F3 (75:25%), as evidenced by the following test results: stable organoleptic, homogeneous, preserved adhesion ($\pm 2,301.78$ second), and safe pH for skin (± 6.42). Furthermore, the gel dosage form was proven to have good spreadability under the weights of 50 g (± 14.517 cm²), 100 g (± 16.169 cm²), and 150 g (± 16.957 cm²), with an average of ± 15.881 cm².

Keywords: snakehead fish, gel, HPMC 4000, carbopol 934, gel stability.

Corresponding author:

Lea Anjeli

Faculty of Medicine, Study Program Pharmacy

Tanjungpura University Pontianak

Jl. Prof. Dr. H. Hadari Nawawi, Bansir Laut, Pontianak

Email: leaanjeli12@yahoo.co.id

INTRODUCTION

The Asian snakehead (*Channa striata*) is a natural medicine ingredient currently used to treat post-surgery wounds and burns (Saleh *et al.*, 1985). The basic principle of optimal wound healing is minimizing tissue damage by providing proper nutrition to create a moist environment for restoring the anatomical continuity and function of the damaged tissue in a short time (Gandhekar *et al.*, 2012). People have long consumed snakeheads as a treatment in wound healing by firstly processing them into a common side dish (Jangkaru, 1999). Nevertheless, until recently, there has been an absence of thorough studies about the aqueous phase of *Channa striata* extract that is made into topical dosage form with different combinations of HPMC K4M and Carbopol 934 as its base.

Gel is a clear and translucent semi-solid dosage form that contains active substances and is a type of colloidal dispersion characterized by strong adhesive due to interconnected network within the dispersed phase (Ansel, 1989). The most commonly applied bases are hydrophobic gel and hydrophilic gel. The widely used hydrophilic gel includes HPMC K4M and Carbopol 934. The 2:1 combination of Carbopol and HPMC is empirically proven to produce the highest viscosity and the highest percentage of diffusion of nystatin gel dosage form compared to the use of each base separately (Quinone and Ghaly, 2008). The combination of HPMC K4M and Carbopol 934 shows the best results because it promotes better drug release (Verma *et al.*, 2013). Carbopol and HPMC are combined for several purposes, i.e., to cover the shortcoming of Carbopol—when applied in high concentration, it forms new acidic gels—and to obtain a gel dosage form with better physical and chemical properties (Dewi and Saptarini, 2016). Therefore, to achieve optimal physical and chemical stability, the aqueous phase of the gel dosage form of *Channa striata* extract is better formulated with the combination of HPMC K4M and Carbopol 934.

MATERIALS AND METHODS

Materials

The main materials used in this research were the aqueous phase of *Channa striata* extract (in Padang Tikar Village, Batu Ampar District, Kuburaya Regency, West Kalimantan, Indonesia), hydroxypropyl methylcellulose (HPMC K4M) (Shanghai Honest Chem Co., Ltd, Room 204, No. 889, Yishan Road, Shanghai, China), and Carbopol 934 (D-616, Shiromani Complex, Nehrunagar-Satellite Road Ahmedabad-380015, Gujarat, India (Shree Chemicals, www.carbomers.com)).

Animal determination

The Asian snakeheads (*Channa striata*) used in this research were determined in the Laboratory of Biology, Department of Biology, Faculty of Mathematics and Natural Science, Tanjungpura University, Pontianak, West Kalimantan.

Sample collection

The Asian snakeheads were obtained from fish traders in Padang Tikar Village, Batu Ampar District, Kuburaya Regency, West Kalimantan. They were selected using purposive sampling technique (i.e., sampling under particular considerations) based on the following inclusion and exclusion criteria.

Inclusion criteria:

- a. Every fish weighed 500-1,000 g
- b. All fish were fresh (firmly adhering scales, bright and clear eyes, red to dark-red gills, and firm meat)

Exclusion criteria:

- a. Fish that were dead for more than 8 hours without low-temperature preservation
- b. Fish with dull and easily pulled scales
- c. Fish with spoiled and easily destroyed meat

Sample processing

A total of 1.505 kg of snakeheads was cleaned by scaling the head and removing the stomach contents, and then steamed in a pot for 30 minutes at 65-70°C. It was wrapped with cotton cloth and pressed with a high pressure using a hydraulic press for extraction. Afterward, the resultant extract was placed into test tubes and covered with a clean pack and aluminum foil, and then centrifuged for 60 minutes at 6,000 rpm. The top layer that contained oil was removed from the tubes. The aqueous phase of *Channa striata* extract was stored in a container and covered with aluminum foil and a clean pack (Astawan, 1998).

Albumin detection

A 5-ml sample of the aqueous phase of *Channa striata* extract was heated in a water bath for 30 minutes. The observation focused on any changes in this phase. Positive albumin content is indicated by white flocs floating on the top layer of the aqueous phase (Poedjiadi, 2006).

The formulation of gel dosage form

HPMC K4M was dispersed in distilled water that was 20 times the weight and then stirred slowly until a transparent color was reached. Meanwhile, in a different mortar, Carbopol 934 was dispersed in distilled water with a volume of 40-50% from the 60% total water used in the formula, crushed slowly until homogeneous. This mixture was added with triethanolamine (TEA) slowly and crushed at the same time until it was clear. The dispersed HPMC K4M was added to Carbopol 934 and crushed slowly until homogeneous. DMDM Hydantoin was added to the base, mixed, and crushed until homogeneous. Propylene glycol was also added to the base a little at a time, and then crushed and added with water simultaneously until a gel base was formed. The aqueous phase of *Channa striata* extract was added last to the gel base and then crushed until homogeneous. All of the three formulas (F1, F2, and F3) were replicated three times. In total, there were nine dosage forms analyzed in this research (Table I).

Table I. The formulas of the gel dosage form of the aqueous phase of *Channa striata* extract

Materials	Formula 1 (%)	Formula 2 (%)	Formula 3 (%)
The aqueous phase of <i>Channa striata</i> extract	20	20	20
HPMC K4M	0.25	0.5	0.75
Carbopol 934	0.75	0.5	0.25
TEA	0.75	0.5	0.25
DMDM Hydantoin	1	1	1
Propylene glycol	15	15	15
Distilled water	Ad 100	Ad 100	Ad 100

Notes: F1 = HPMC:Carbopol = 25:75%
 F2 = HPMC:Carbopol = 50:50%
 F3 = HPMC:Carbopol = 75:25%

Organoleptic assessment

The organoleptic assessment of the dosage form relied on the use of human's basic sense to describe the shape or consistency (e.g., solid, viscous, or water), color (e.g., yellow or brown), and odor (e.g., natural smell, aromatic, or odorless). It observed sensible texture, color, and scent (Andrie, 2015). In this research, the organoleptic observation was performed on day 0, 1, 3, 7, 14, 21, and 28 (Hapsari *et al.*, 2014). It also included examining the homogeneity of the gel dosage

form by spreading it on a glass or other transparent materials. In this case, the dosage form had to show homogeneous structure without any visible coarse grains (Department of Health, 2014).

Spreadability test

Spreadability is defined as the ability of a gel to spread when applied to the skin. The procedure of the spreadability test was as follows. A 1-gram sample of the gel produced from the formulation in point 5 was placed carefully on a graph paper that was covered with transparent plastic. The spread diameter was calculated after 15 seconds. Afterward, the gel was covered with plastic again, pressed with standardized masses of up to 150 g, and left for 60 seconds (Ameliana and Lina, 2011). The spreadability was observed on day 1, 7, 14, 21, and 28 (Hapsari *et al.*, 2014).

Adhesive strength test

The adhesive strength test was performed to determine the capability of gel to adhere to the skin. A sample of 0.1 g of the gel was applied between two object glasses and compressed by placing a weight of 1,000 g for 5 minutes. It was set in the test tool, and extra weight of 80 gram was added. The time required to separate the two glasses was recorded (Miranti, 2009). The adhesive strength of the gel was observed on day 0, 1, 3, 7, 14, 21, and 28 (Hapsari *et al.*, 2014).

pH determination

The acidity was measured by placing a pH meter in the sample. The pH meter used in this research had been previously calibrated with a standard solution. pH analysis aimed to determine the suitability of the pH of the dosage form with the pH of the skin's physiology, i.e., 4.5-6.5 (Tranggono and Latifah, 2007). The acidity of the sample was measured three times on day 1, 7, 14, 21, and 28 (Hapsari *et al.*, 2014).

Data Analysis

The test results of the physical and chemical properties of the gel dosage form (organoleptic, adhesive strength, spreadability, and pH) were statistically analyzed with homogeneity and Kolmogorov-Smirnov tests. If the data are homogeneous ($\alpha \geq 0.05$) and normally distributed ($\alpha \geq 0.05$), then parametric statistical test, namely one-way ANOVA and post hoc analysis, is performed. Otherwise, the non-parametric Kruskal-Wallis and Mann Whitney tests are performed. The data have statistically different meaning when the parametric or non-parametric test yields $\alpha \geq 0.05$.

Results and Discussion

The albumin detection in *Channa striata* extract

Heating can cause protein denaturation. The first step of this process is flocculation, which is the aggregation of unstable particles into irregular clusters or flocs. It reduces protein levels (Yuniarti *et al.*, 2013). The *Channa striata* extract was heated at 90°C for 30 minutes. This heating produced white flocs floating on the surface (Figure 1), indicating positive albumin content.

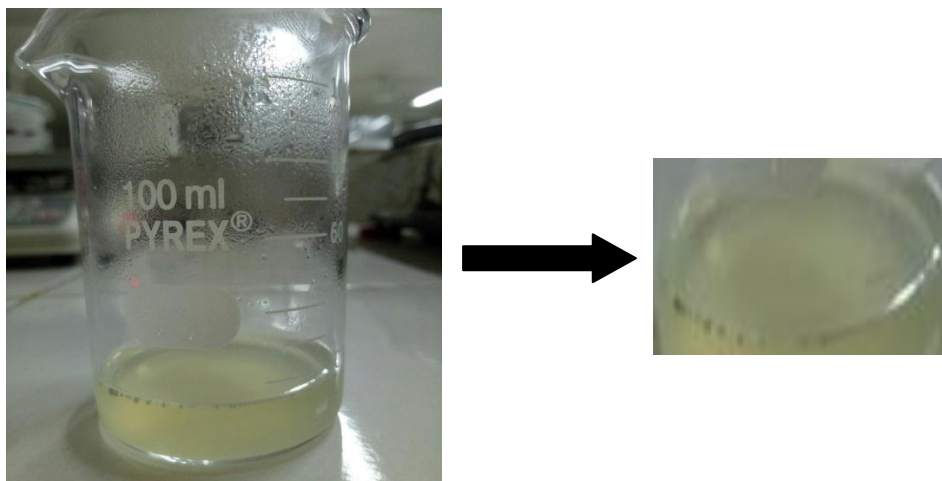


Figure 1. The Results of Albumin Detection in *Channa striata* Extract

Organoleptic assessment

Organoleptic assessment plays a significant role in determining the nature of a dosage form. In this research, it presented any indications of damage and deterioration in the quality of the formulated gel. The assessment results showed that the three formulas were stable during the 28-day observation (Table II).

Table II. The organoleptic assessment results of the gel dosage form of the aqueous phase of *Channa striata* extract

No	Descriptions	F1	F2	F3
1	shape/consistency	viscous	fairly viscous	moderately viscous
2	color	colorless	colorless	colorless
3	odor	natural	natural	natural
4	homogeneity	homogeneous	homogeneous	homogeneous

Spreadability

The spreadability test aimed to identify the ability of a gel dosage form to spread easily on skin without significant pressure during its application. It used three standardized masses, namely 50 g, 100 g, and 150 g. The factors that contribute to the spreadability of gels are, for instance, the number and strength of the gel matrix. The greater the number and the strength, the lower the spreadability. In a gel system, the determinant of the formation of a gel matrix is a gelling agent. A higher concentration of gelling agent increases and strengthens the gel matrix (Zats and Gregory, 1996).

A semi-solid topical dosage form is considered to have a good spreadability when its spreading diameter is between 3 cm and 5 cm (Garg *et al.*, 2002). Compared to the other formulas, F3 had the best spreadability. When compressed with a standardized mass of 50 g during the 28-day observation, the average spreadability of F3 (75:25%) was $\pm 14.517 \text{ cm}^2$ (Table III). Meanwhile, the average spreadabilities under the masses of 100 g and 150 g were $\pm 16.169 \text{ cm}^2$ (Table IV) and $\pm 16.957 \text{ cm}^2$ (Table V), respectively.

The spreadability of F1 and F2 showed a decreasing trend from day 3 to day 7, but the spreadability of F3 experienced a significant decrease from day 7 to day 14. Such decline was caused by the use of Carbopol, which is an acrylic polymer. Spreadability is attributed to viscosity, which strongly depends on pH. Carbopol forms a solution at pH 3 but turns into a gel (increased viscosity) at pH 6-8 (Quinones and Ghaly, 2008). Therefore, the decreasing pH on some

observation days reduced the viscosity but increased the spreadability of the gel. On the contrary, when the pH increased, the viscosity also increased and resulted in low spreadability.

Table III. The spreadability test results of the gel dosage form of the aqueous phase of *Channa striata* extract under a mass of 50 g

Day	Spreading Extents (cm ²), Compressed with a Mass of 50 g (n=3, mean ± SD)		
	F1	F2	F3
1	12.700 ± 0.599	14.017 ± 0.337	10.734 ± 0.030
3	14.878 ± 0.344	12.946 ± 0.050	17.301 ± 0.283
7	9.702 ± 0.270	10.806 ± 0.050	18.276 ± 0.259
14	11.515 ± 0.181	12.906 ± 0.825	12.091 ± 0.080
21	10.490 ± 0.909	12.756 ± 0.749	13.524 ± 0.663
28	13.810 ± 0.377	14.562 ± 0.550	15.178 ± 0.630

Table IV. The spreadability test results of the gel dosage form of the aqueous phase of *Channa striata* Extract under a Mass of 100 g

Day	Spreading Extents (cm ²), Compressed with a Mass of 100 g (n=3, mean ± SD)		
	F1	F2	F3
1	12.516 ± 0.448	14.127 ± 0.123	14.391 ± 0.290
3	15.813 ± 0.261	15.183 ± 0.205	18.285 ± 0.272
7	10.109 ± 0.301	11.704 ± 1.073	19.237 ± 0.210
14	12.898 ± 0.319	13.396 ± 0.768	12.850 ± 0.133
21	13.586 ± 0.509	13.396 ± 0.768	15.270 ± 0.314
28	15.201 ± 0.203	15.550 ± 0.711	16.980 ± 0.841

Table V. The spreadability test results of the gel dosage form of the aqueous phase of *Channa striata* extract under a mass of 150 g

Day	Spreading Extents (cm ²) under a Mass of 150 g (n=3, mean ± SD)		
	F3	F4	F5
1	11.996 ± 0.945	12.996 ± 0.056	15.428 ± 0.499
3	16.457 ± 0.489	15.929 ± 0.286	19.078 ± 0.001
7	10.563 ± 0.416	14.432 ± 0.810	19.559 ± 0.283
14	14.476 ± 0.772	13.767 ± 0.791	13.260 ± 0.183
21	13.655 ± 0.970	14.339 ± 0.654	17.571 ± 0.844
28	15.645 ± 0.831	16.588 ± 0.496	16.844 ± 1.290

The results of One-Way ANOVA, followed by post hoc LSD test (95% confidence level), showed that there was no statistically significant difference between the spreadabilities of F1, F2, and F3 compressed with a mass of 50 g ($P > 0.05$). However, when compressed with 100 g and 150 g, the spreadability of F3 was significantly different from F1 but not substantially different from F2 ($P > 0.05$). F3 had the highest spreadability among the other formulas because it had the lowest

concentration of Carbopol. Lower levels of HPMC and Carbopol, as polymers or gelling agents, are followed with higher spreadability. On the contrary, higher concentrations likely increase and strengthen the gel matrix; hence, lower spreadability. Compared to F1 and F2, F3 had a lower share of Carbopol but a higher percentage of HPMC. For a 30-gram dosage form, the concentration of HPMC was only 0.75% of the weight of the dosage form, which is practically smaller than the commonly used concentration in the manufacture of gel dosage form.

In comparison to Carbopol, HPMC is a gelling agent that has the most optimal physical stability in gel dosage form. Also, as a hydrophilic polymer, its advantage includes producing better spreadability on the skin (Nursiah and Faradiba, 2011).

Adhesive strength

Greater adhesive strength is followed by a higher drug diffusion because it allows a more extended bond or contact between the gel and the skin. A dosage form that can adhere well to the skin can optimize its use efficiency because it does not require repeated application. Meanwhile, low adhesive strength indicates that a dosage form can easily separate from the skin; therefore, the supposed effect is not optimally achieved. Despite the absence of specific requisites concerning the adhesive strength of a semi-solid dosage form, adherence of more than 1 second is preferable (Zats and Gregory, 1996).

The test results showed that a higher adhesive strength was attributed to a higher concentration of HPMC. The 28-day test showed that the adhesive strength became greater as the observation day increased. HPMC forms colloids when added with water (Rowe *et al.*, 2009). Colloids are formed because the dispersed substance absorbs the dispersed medium and creates a viscous and sticky material. Therefore, the higher the concentration of HPMC, the more the number of colloids and the greater the adhesive strength. In this research, a good adherence was presented by F3. From day 21 to 28, the adhesive strength of F3 was nearly constant and stable (Table VI). The results of One-way ANOVA and post hoc test showed that the adhesive strength of F3 was significantly different from F1 and F2 ($P < 0.05$).

Table VI. The adhesive strength test results of the gel dosage form of the aqueous phase of *Channa striata* extract

Day	Adhesive Strength (Seconds) (n=3, mean \pm SD)		
	F1	F2	F3
1	30.00 \pm 0.00	80.33 \pm 0.58	1400.33 \pm 0.58
3	46.00 \pm 1.00	150.33 \pm 0.58	1480.33 \pm 0.58
7	147.33 \pm 0.58	540.33 \pm 0.58	1859.33 \pm 0.58
14	620.33 \pm 0.58	1230.33 \pm 0.58	2400.00 \pm 0.00
21	920.67 \pm 0.58	1930.00 \pm 0.00	3330.33 \pm 0.58
28	1840.33 \pm 0.58	2535.33 \pm 0.58	3340.33 \pm 0.58

pH Determination Results

The average pH of the gel dosage form was F3 (± 6.42) > F2 (± 6.23) > F1 (± 6.12). The higher the concentration of Carbopol, the more acidic the gel (Table VII). The three formulas produced a variety of pH following the different concentration ratios of the gel bases. The variation of the pH on every observation day was due to the influence of Carbopol—the pH is highly unstable—and the different pH levels at which HPMC and Carbopol exhibited good stability (HPMC forms a stable gel at pH 3-11, while Carbopol at pH 6-8) (Quinones and Ghaly, 2008).

Unstable storage temperature also affects the resultant pH. The use of 0.1-0.5% Carbopol forms a gel with a pH of 7.4 and low viscosity (Dewi and Saptarini, 2016). F2 and F3, composed of 0.5% and 0.25% Carbopol, respectively, from the 100% total production of 30 g in weight, produced a pH of < 7.4. The addition of triethanolamine (pH 10.5) as an alkali agent helps Carbopol to achieve the pH of a stable gel; therefore, the concentration of triethanolamine has to be considered in gel formulation. Overall, the three formulas produced pH levels (4.5-6.5) within the standard range of safe or tolerable pH for the skin (5-10) (Christopher *et al.*, 1993; Tranggono and Latifah, 2007).

Table VII. The pH determination results of the gel dosage form of the aqueous phase of *Channa striata* extract

Day	pH (n=3, mean ± SD)		
	F1	F2	F3
1	6.15 ± 0.12	6.30 ± 0.21	6.53 ± 0.08
3	6.02 ± 0.11	6.17 ± 0.18	6.42 ± 0.09
7	6.22 ± 0.12	6.34 ± 0.14	6.51 ± 0.08
14	6.08 ± 0.16	6.21 ± 0.21	6.42 ± 0.07
21	6.44 ± 0.05	6.56 ± 0.01	6.66 ± 0.10
28	5.80 ± 0.14	5.79 ± 0.18	6.00 ± 0.06

The physical and chemical stability test results of the gel dosage form of the aqueous phase of *Channa striata* extract showed excellent stability during the 28-day observation. These results also showed that all of the formulas, which were replicated three times, created a reproducible dosage form. Since the test results were close (insignificant difference), repeated production will produce similar quality. This research was performed to provide an overview of the physical and chemical stability of the gel dosage form, as well as its safe application to the skin. Therefore, future studies are recommended to perform a thorough irritation test, focusing on whether the gel dosage form formulated in this research causes irritation when applied to human skin. During the development of topical dosage form, which involves the identification and selection of the best formulation, in vitro studies of skin penetration and the release of active substances through the skin are necessary. A proper formulation will provide optimal release and deposition of active substance to the desired skin layers (corneum, epidermis, or dermis) (Witt and Bucks, 2003).

One of the widely applied techniques in measuring in vitro skin permeation is the Franz diffusion cell. Therefore, the in vitro penetration test of the gel dosage form using the Franz diffusion cell is necessary. Also, the future research can focus on various concentrations of the aqueous phase of *Channa striata* extract for the formulation of gel dosage form and recommend the addition of aromatic scent in the formulation form to reduce the natural odor of *C. striata*.

CONCLUSION

Each formula of the gel dosage form showed a good physical and chemical stability during the 28-day observation. However, the HPMC-Carbopol concentration ration in F3 (75:25%) showed the best physical and chemical properties.

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