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Research Article

Formulation and Evaluation of Natural Gel Containing Ethanolic Extract of *Pandanus amaryllifolius* R. Using Various Gelling Agents

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Abstract

Ethanol extract of *Pandanus amaryllifolius* leaves contains quercetin has anti-inflammatory properties. The gel dosage form is very appropriate for wound healing therapy because it gives a cold sensation to the skin. This study aims to formulate a *P. amaryllifolius* gel by variation of a gelling agent to compare the effect of a natural gelling agent, semi-synthetic gelling agent, and synthetic gelling agent on the physical characteristics of the gel. The gel formulation was made in three formulas. Evaluations include organoleptic, homogeneity, spreadability, adhesion, pH, and viscosity. The optimum gel formula was tested for release study using a dissolution apparatus 5. Determination of release kinetics model using the kinetics approach of zero-order, first-order, Higuchi, and Korsmeyer-Peppas. The organoleptic shows the gel's dark green color, *P. amaryllifolius* aromas, and good homogeneity. The gel formulas had pH values that matched the physical quality criteria of the gel. Data obtained for the spreadability test for F1, F2, and F3 were 12.16, 14.66, and 10.75 g.cm/sec, respectively. The F1, F2, and F3 adhesion test results were 11.66, 10, and 47.33, respectively. The viscosity of F1 was 15750 cps, F2 was 4807 cps, and F3 was 19380 cps. This study concludes that the optimum formula is obtained from the gelling agent of Na-CMC as a gelling agent. The number of quercetins released from F2 was 42.76%, and the release kinetics model followed the kinetics of Higuchi.

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INTRODUCTION

Inflammation is the body's attempt to inactivate or destroy invading organisms, remove irritants or regulate levels of network repair. Inflammation is one of the main responses of the immune system body to infection and irritation and is a complex biological response of tissue in the presence of hazards such as cell damage[1]. The inflammatory process can occur when the skin has open sores. Wounds are damage or loss of body tissue due to a factor that disrupts the system's body protection. Such factors include trauma, temperature changes, chemicals, electric shock explosion, or biting animals[2]. An example of an open wound is an incision/cut with linear tears in the skin and tissues underneath. Scratches between the skin with sharp objects or blunt objects cause injuries. In addition to scratches, sores can occur due to heat or burns[3].

Treatment of patients with inflammation generally uses non-steroidal anti-inflammatory drugs (NSAIDs). NSAIDs cause severe various side effects that can harm the body[4]. Therefore, another alternative to overcoming inflammation with relatively smaller side effects from modern medicine is necessary, such as traditional medicine. The use of traditional medicine is generally considered safer than conventional medicine[5]. One of the plants that have anti-inflammatory activity is *Pandanus amaryllifolius* R. leaves[6]. *Pandanus amaryllifolius* (Indonesian: *pandan*) is one of the plants in Indonesia with many

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functions, especially fragrant and food coloring[7]. *Pandanus amaryllifolius* leaves contain polyphenols, flavonoids, saponins, essential oils, and alkaloids that have antibacterial, anti-inflammatory, and antifungal properties[8]. For inflammation treatment, flavonoids influence the inflammatory process by inhibiting the enzyme cyclooxygenase so that the formation of prostaglandins is inhibited[9]. However, giving the extract directly has several disadvantages, including making the extract and its application to the body both orally and topically. As a wound healing, it would be better to give it in a semisolid dosage form for topical preparations[10].

Topical preparations have several advantages, like easy to carry, easy to use, fast absorption, and provide protective treatment for the skin. Generally, wound healing preparations in a semisolid form, such as gels, ointments, and creams, allow a longer drug contact time and protect the wound from external contamination. This dosage form is more used and spreads on the skin faster, and the gel has good properties, cooling, moisturizing, and easily penetrates the skin to provide a healing effect[11]. Wijayantini *et al.*[12] has tested the effectiveness of fragrant pandan leaf ointment on healing burns in male white mice with concentrations of 5, 7.5, and 10%, and positive control using brand X gel containing neomycin sulfate 0.5%. At a concentration of 10%, it showed better burn healing results within 13 days, with a healing percentage of up to 100% compared to the positive control of Bioplacenton gel. However, using the ointment for wound healing gives an uncomfortable impression when applied to open skin because the ointment has a considerable consistency and does not contain much water, so it will provide an uncomfortable feeling when used[13]. Gel preparations can protect the skin from excessive dehydration. A gel contains much water and has better drug delivery than ointments. The gel has high water content to provide moisture and gives a sense of cold when applied to the skin[14,15].

The gelling agent has functioned as a gel former. Formulation and gelling agents in the manufacture of gel preparations will affect the amount and rate of substance active to be absorbed ideally. In gel formulas, the critical factor that affects the physical properties of the gel is the use of gelling agents. Based on the source of gelling agents, there are three classes of gelling agents, natural gelling agents such as tragacanth, semi-synthetic gelling agents such as Na-CMC, and synthetic gelling agents such as Carbopol. Each of these gelling agents has different properties to the formation of a gel that will affect the physical characteristics of the gel. Using a gelling agent with a very high or large molecular weight can produce a gel that is difficult to remove from the packaging because very thick texture[16]. Some common gelling agents used in the gel formula are carbopol and carboxy methyl cellulose (CMC). Carbopol polymers are polymers hydrophilic with polyacrylic acid structure. A concentration of 0.5% Carbopol 941 or 981 at room temperature produces a viscosity of 4,000 to 11,000 cP[17]. At the same time, Na-CMC is included in the derived gelling agent cellulose. Cellulose derivatives are often used in gel formulas due to their neutral properties and increased viscosity, which is quite good[18]. This research aims to look at the effect of variations in types and concentrations of tragacanth, Na-CMC, and Carbopol as gelling agents on the physical properties of the *P. amaryllifolius* leaves gel, which gives the best gel.

MATERIALS AND METHODS

Materials

The research materials used include *P. amaryllifolius* leaves, ethanol 95% (technical grade), quercetin (analytical grade), tragacanth (technical grade), Na-CMC (technical grade), Carbopol (technical grade), and cellophane membrane. *Pandanus amaryllifolius* (**Figure 1**) were obtained from Martapura, South Kalimantan, Indonesia. The plant was determined at the Biology Laboratory of Math and Science Faculty of Universitas Lambung Mangkurat with certificate 148(a)/LB.LABDASAR/XI/2017. The instruments used were a rotary evaporator (IKA RV10, Germany), UV-Visible spectrophotometer (Genesys 10 UV Scanning, US), stormer viscometer (NDJ- 5S, China), and dissolution test apparatus.

Figure 1. *Pandanus amaryllifolius*.

Methods

Pandanus amaryllifolius extract preparation[19]

Older *P. amaryllifolius* leaves were selected as samples. Then the *P. amaryllifolius* leaves were cut into pieces and washed. Pandanus amaryllifolius leaves are dried in the open air and protected from sunlight directly. The simplicia was then made into powder using a blender and sieved. The extraction of *P. amaryllifolius* leaves was carried out by the maceration technique, using ethanol 95%. About 500 g of simplicia powder *P. amaryllifolius* leaves were put into a glass container, then added 1500 ml of ethanol 95%, stirred for 30 minutes, and allowed to stand 1 x 24 hours. After 24 hours, the mixture was filtered using a funnel. The macerate was then evaporated using a rotary evaporator and then concentrated using a water bath to obtain a concentrated ethanol extract of the fragrant *P. amaryllifolius* leaves.

Phytochemical screening of flavonoids with 10% NaOH[20]

About 200 mg ethanol extract of *P. amaryllifolius* leaves were added with 2 to 4 drops of 10% NaOH. The yellow color of the solution shows that *P. amaryllifolius* ethanol extracts contain flavonoids.

Phytochemical screening of flavonoids with Mg powder and HCl (Wilstatter test)[21]

About 200 mg ethanol extract of *P. amaryllifolius* leaves were added with small amount of Mg powder and concentrated HCl. The red, yellow, or orange color of the solution shows that *P. amaryllifolius* ethanol extracts contain flavonoids.

Preparation of quercetin standard curve[22]

About 5 mL of a 1000 ppm quercetin stock solution dissolved with 96% ethanol in a 50 mL flask, and several concentrations were made: 40, 50, 60, 70, 80, and 90 ppm. Each concentration was sufficient with 96% ethanol up to 10 mL volumetric flask.

Total flavonoid content[22]

About 10 mg of extract dissolved with 96% ethanol in a 10 mL volumetric flask (1000 ppm). As much as 1 mL of the available solution (1000 ppm) was pipette into a 10 mL volumetric flask and then fixed to 10 mL with 96% ethanol. About 1 mL of solution was pipette and reacted with 4 mL of aquadest, and 0.3 mL of 5% $NaNO_2$, allowed to stand for six minutes, added 10% $AlCl_3$ into the solution, and let stand again for six minutes. The solution reacted again with 4 mL of 4% NaOH, then fixed to 10 mL with aquadest, and let stand for 15 minutes.

Formulation of Pandanus amaryllifolius leaves ethanol extract gel (tragacanth and Na-CMC based gel)

The gel formulation was prepared by dispersing a gelling agent tragacanth and Na-CMC in hot water by continuous stirring until homogenous (solution one). Methylparaben dissolved in water, then added with glycerin and propylene glycol (solution two). Solution two was added gently to solution one under continuous stirring. The mixture was stirred gently until the homogenous gel formed, then added with ethanol extract of *P. amaryllifolius* leaves. The remaining aquadest was added and stirred until homogenous. The gel formula of *P. amaryllifolius* leaves ethanol extract gel can be seen in **Table I**.

Formulation of Pandanus amaryllifolius leaves ethanol extract gel (Carbopol based gel)[15,23]

All the ingredients were weighed, then Carbopol dissolved in distilled water and stirred until homogeneous and formed a gel base (solution one). Methylparaben was dissolved in water and added glycerin, propylene glycol, and TEA (solution two). Solution two was added gently to solution one under continuous stirring. The mixture was stirred gently until the homogenous gel formed. Then, an ethanol extract of *P. amaryllifolius* leaves was put in. The remaining aquadest was added and then stirred until homogenous. The gel formula of *P. amaryllifolius* leaves ethanol extract gel can be seen in **Table I**.

Table I. Formulation of *P. amaryllifolius* leaves ethanol extract gel.

Component	Concentration (%)		
	F1	F2	F3
Pandanus amaryllifolius leaves ethanol extract	1.8	1.8	1.8
Tragacanth	4	-	-
Na-CMC	-	6	-
Carbopol	-	-	2
Glyserin	10	10	10
Propylen glycol	5	5	5
Methylparaben	0.15	0.15	0.15
TEA	-	-	2
Aquadest ad	100	100	100

Note: F1: Tragacanth 4%; F2: Na-CMC 6%; F3: Carbopol 2%

Evaluation characteristics of Pandanus amaryllifolius leaves ethanol extract gel (Organoleptic characteristic)

These characteristics were evaluated by visual observation of the gel's shape, color, and odor.

Evaluation characteristics of Pandanus amaryllifolius leaves ethanol extract gel (Homogenity test)[23]

A total of 0.5 g of gel was applied to the object glass, and the homogeneity of the gel was visually observed. The presence of coarse particles was used to evaluate the homogeneity of the gel. All measurements were made in triplicate.

Evaluation characteristics of Pandanus amaryllifolius leaves ethanol extract gel (pH values)[24]

pH measurement of the gel was carried out using a digital pH meter by dipping the glass electrode completely into the gel system to cover the electrode. The measurement was carried out in triplicate, and the average of the three readings was recorded.

Evaluation characteristics of Pandanus amaryllifolius leaves ethanol extract gel (Spreadability test)[25]

The spreadability of the gel was measured by spreading 0.5 g of the gel on a circle of 2 cm diameter premarked on a glass plate, and then a second glass plate was employed. A half kilogram of weight was permitted to rest on the upper glass plate for five minutes. The diameter of the circle after spreading the gel was determined.

Evaluation characteristics of Pandanus amaryllifolius leaves ethanol extract gel (Adhesion test)[15]

About 0.5 g of the preparation was placed on a glass object. Another glass object was put on the preparation, then given a weight of 0.5 Kg for five minutes. Remove the weight of 80 g so that it pulls the bottom glass object. All measurements were made in triplicate. The time needed for the two glass objects to be released was recorded.

Evaluation characteristics of Pandanus amaryllifolius leaves ethanol extract gel (Viscosity measurement)[23]

The viscosity of the gel was measured with a stormer viscometer. The gel is put into a container glass. Then the spindle was installed and lowered, so the spindle limit dipped in the gel. The stirring rod rotates to a stable speed at 30 rpm. All measurements were made in triplicate.

Determining of formula optimum

The optimum formula was determined based on the results of the physical characteristics of the gel, which include spreadability, adhesion, pH, and viscosity. Evaluation results that indicate the criteria according to the requirements were then determined as the optimum formula.

Preparation of phosphate buffer saline pH 7.4

Phosphate buffer saline (PBS) of 7.4 was made by dissolving 8 g of NaCl, 2.86 g of Na_2HPO_4, 0.2 g of KH_2PO_4, and 0.19 g of KCl in an 800 mL aquadest, then the solution was stirred until dissolved. The homogenous solution was sufficient with aquadest up to 1000 mL. The degree of acidity was determined using a pH meter.

In vitro release test[26]

The *in vitro* release tests were performed using dissolution apparatus 5 with the paddle-over disk method. Before starting the experiment, the cellophane membranes were cut to a diameter of 3 cm (7.065 cm^2) and saturated for an hour in a receptor medium (phosphate buffer pH 7.4). The apparatus was filled with a 500 mL receptor medium then one g of gel was applied to the disk apparatus. The receptor medium was maintained at 37±1°C under constant stirring. As much as 5 mL of samples were collected at intervals of 5, 10, 15, 30, 60, and 120 minutes. The volume collected was replaced with a fresh receptor medium. A total flavonoid release was determined by the UV-VIS spectrophotometer at 420 nm.

Kinetics of drug release[27]

The release mechanism of a drug describes the pattern of drug release from the bases. The *in vitro* release data was analyzed according to Zero-order kinetics, First-order kinetics, Higuchi, and Korsemeyer-Peppas. Kinetics model drug release was determined with linearity regression ($r > 0.999$) between the percent amount of drug release and time.

Data analysis

Data analysis was carried out with SPPS 18.0. The normality of the data was analyzed using Kolmogorov-Smirnov. If the data is normally distributed, then data analysis is continued with a one-way analysis of variance (ANOVA) with a 95% confidence level to see significant differences between gel formulas.

RESULTS AND DISCUSSION

The results of the phytochemical screening of P. *amaryllifolius* leaves can be seen in **Table II**, with a comparison of the content of compounds from the results of other studies using 70% and 96% ethanol extract of *P. amaryllifolius* leaves. The results are similar to the results obtained in this study. There is no difference between the flavonoid content of 70% and 95% ethanol extract. This is because the polarity of the solvent used can attract these polar compounds. Flavonoid compounds have a role in wound healing by influencing the inflammatory process by inhibiting the enzyme cyclooxygenase so that the formation of prostaglandins is inhibited[28].

Table II. Phytochemical screening of *P. amaryllifolius* extract.

Compounds	70% ethanol extract of *P. amaryllifolius* leaves[7]	95% ethanol extract of *P. amaryllifolius* leaves[29]	Recent studies with 95% ethanol extract of *P. amaryllifolius* leaves
Tannin	√	-	-
Alkaloid	√	√	-
Flavonoid	√	√	√
Saponin	√	√	-
Polyphenol	√	√	-

The fragrant *P. amaryllifolius* extract obtained was 28.84 g, with a yield of 11.53%. Based on phytochemical screening, the ethanol extract of *P. amaryllifolius* leaves contains flavonoids. The flavonoid content of the ethanolic extract of *P. amaryllifolius* leaves was 65.88 mg/g of extract, equal to mg/g of quercetin. Flavonoid contents are used as a reference to get the percentage of flavonoids released. The total flavonoid content extract of *P. amaryllifolius* leaves can be seen in **Table III**.

Table III. Total flavonoid content of ethanol extract of *P. amaryllifolius* extract.

Replication	Absorbance	Content (mg QE/g extract)	Total flavonoids content (mg QE/g extract)
1	0.365	65.3	
2	0.366	65.5	65.8
3	0.371	66.8	

To increase the effectiveness of *P. amaryllifolius* leaves extract on the skin, a topical formulation was made in the form of a gel. Gel with high water content has a cooling and moisturizing effect, thereby reducing the inflammatory reaction. In addition to this dosage form, it is easily used and spread on the skin more quickly and penetrates it to provide an excellent healing effect[14]. A gelling agent is an essential factor that influences the characteristics of a gel. The gelling agent is a polymer that has different molecular weights. The higher the molecular weight of a gelling agent, the thicker the gel formed. The concentration of each gelling agent must always be considered to produce a good gel[16]. The gelling agents used for gel formulation are tragacanth, Na-CMC, and Carbopol.

The physical evaluation includes organoleptic, homogeneity, adhesion, spreadability, pH value, and viscosity. This evaluation aims to determine the quality of the gel formula based on the required standard parameters. The organoleptic visualization of the gel appearance (**Table IV**) shows that the gel formulas have a semisolid form, a dark green color obtained from *P. amaryllifolius* leaves, and a strong aroma like *P. amaryllifolius*. Homogeneity testing aims to see the distribution of particles in the gel. The results showed that F1 with tragacanth as a gelling agent has less homogeneity due to particles not being well dispersed in the gel. F2 and F3 showed good homogeneity because the particles were wholly dispersed in the gel. The homogeneity of the gel is an indicator of the quality of the gel that will affect the efficacy of the formulas. Na-CMC and Carbopol are hydrophilic polymers, so when dispersed in water, they will be easily dispersed compared to tragacanth, which has a strong polymer structure and will be difficult to disperse to break the polymer chains[30].

The pH testing shows that all three formulas have a pH that meets the requirements. Consequently, the pH obtained for F1, F2, and F3 was 6.0; 6.5, and 6.1. The pH required for topical preparations is 4.5 - 6.5[31]. A topical preparation with a too acidic pH can irritate the skin, whereas if the pH is too alkaline, it can cause dry skin. In addition to affecting the safety of the application, the pH also affects the release of the drug. If a topical preparation has a different pH from the skin, then the active substance from the formulas will ionize, and the active substance will be difficult to penetrate. Gel formulas are expected to have the same pH as the skin, so it is not ionized and easy to penetrate the skin[32].

Spreadability testing aims to know the ability of a gel to spread on the skin. The greater the spreadability, the easier the gel is applied on the skin surface[15]. The spreadability test shows that F1 has a spreadability of 12.16 g.cm/sec, F2 of 14.66 g.cm/sec, and F3 of 10.75 g.cm/sec (**Table IV**). The spreadability is related to viscosity; the lower the viscosity, the greater its spreadability. At F3, the spreadability is very low, and this is because Carbopol is a polymer with a large molecular weight, so the viscosity of Carbopol can reduce the spreadability of the gel[33]. The greater spreadability can enhance drug release because of the larger the membrane. The statistical analysis shows that the data in the spreadability test were normally distributed after being analyzed with the Kolmogorov-Smirnov with a significance value of 0.385 (p-value >0.05). Based on ANOVA analysis, a significance value of 0.00 (p-value <0.05) indicates a significant difference in the spreadability generated due to the influence of the gelling agent used. The higher the molecular weight of the gelling agent used, the thicker the resulting gel will have; it affects the area of gel spread when applied[34].

Adhesivity testing aims to determine the ability of the gel to attach to the skin. The results of the adhesivity test showed that F1 had an adhesivity of 11.6 seconds, F2 of 10 seconds, and F3 of 47.3 seconds (**Table IV**). Mukhlishah *et al*.[35] states that the best adhesion for topical preparations is more than 4 seconds. Adhesivity is related to the viscosity of the gel. The higher viscosity, the longest gel can attach to the skin surface, which will affect the diffusion of the drug from the base to the skin's surface. ANOVA analysis shows significant differences in the characteristic of three gel formulas influenced by the gelling agent used.

Viscosity is related to the spreadability of a gel. The higher viscosity of the gel caused the ability of the gel to spread on the skin surface. Based on the test shows that F1 and F3 have a higher viscosity than F2 (**Table IV**). F2 has better viscosity in

2000-4000 cps. Viscosity also affects drug release because of the higher viscosity of gel, an active substance difficult to diffuse from the base, which causes the number of drugs to penetrate to be small. Carbopol with a concentration of 0.1-0.5% will form a gel at pH 7.4, but the viscosity is low. If the concentration of Carbopol increases, the resulting viscosity increases, but an increasingly acidic pH is required to form a gel[36].

Semisolid dosage forms with lower viscosity produce a spreading diameter that is larger because it flows more easily. Gel formulas that provide the best characteristic are gel formulas with Na-CMC as a gelling agent. ANOVA analyzes show significant differences in gel characteristics because of the influence of the gelling agent used[37]. The selection of the best formula is based on the physical evaluation results of gel formulas that meet the requirements of good gels. Physical evaluations that affect the quality of gel preparations include adhesivity, spreadability, and viscosity. Based on the evaluation results, the best formula is F2 with Na-CMC as a gelling agent.

Table IV. Evaluation of the characteristics of ethanol extract of *P. amaryllifolius* extract.

Evaluation characteristic	F1	F2	F3
Form	Semi-solid gel	Semi-solid gel	Semi-solid gel
Odor	Typical *P. amaryllifolius*	Typical *P. amaryllifolius*	Typical *P. amaryllifolius*
Color	Dark green	Dark green	Dark green
Homogenity	Non-homogenous	Homogenous	Homogenous
pH value	6.0 ± 0.06 (%CV:0,94)	6.05± 0.00 (%CV:0,00)	6.1 ± 0.06 (%CV:0.81)
Spreadability (g.cm/sec)	12.16 ± 0.14 (%CV:1.18)	14.66 ± 0.57 (%CV:3.93)	10.75 ± 0.43 (%CV:4.02)
Adhesivity (seconds)	11.66 ± 0.57 (%CV: 4.94)	10.00 ± 0 (%CV: 0)	47.33 ± 0.57 (%CV: 1.21)
Viscocity (cPs)	15753 (%CV: 0.14)	4807 (%CV: 0.24)	19380 (%CV: 0.00)

Note: F1: Tragacanth; F2: Na-CMC; F3: Carbopol; CV (Coeffisient of Varians) ≤5%

Na-CMC is a gelling agent from cellulose derivatives. Na-CMC produces a gel with neutral and stable viscosity. Na-CMC showed better vehicle properties for drugs, such as high solubility and biocompatibility[18]. In other research[38], the characteristics of *P. amaryllifolius* leaves gel using HPMC showed good physical characteristics, including organoleptic tests, pH, and dispersibility. HPMC belongs to the same group as Na-CMC, a semi-synthetic gelling agent. In comparison, the research using Carbopol obtained gel characteristics that meet the requirements. Carbopol is a synthetic gelling agent with good gel properties, but Carbopol has a very high price compared to Na-CMC. In addition, Carbopol is acidic so it can irritate the skin, so it needs to be neutralized to reach the targeted pH of a formulation[39].

Several factors that influence the release of drugs to penetrate the skin include viscosity. The higher the concentration of the gelling agent, the higher its viscosity. But with increasing gel viscosity, the drug absorption will decrease, so in gel, formulation needs to consider the gelling concentration agents used[40]. Na-CMC as a gelling agent produces lower viscosity than other gelling agents, this is one of the factors that cause *P. amaryllifolius* leaves extract to be released from the gel relatively faster, and there is no lag time in **Figure 2**.

The addition of propylene glycol significantly affects the penetration and flux of the drug; therefore, propylene glycol is called an enhancer. An addition enhancer can increase penetration in the topical dosage form. Enhanced penetration occurs because the keratin layer is dissolved on the stratum corneum by reduced drug binding to skin tissue so that the number of drugs can be increased to enter through the skin[41].

A release test was carried out to see the amount of drug released at intervals of time. Based on the release test on F2, the percentage of flavonoids released from the gel was 42.76%. The cumulative amount released within two hours of 398.263 µg/cm^2 and flux of 36.458 µg/cm^2.minute. The percent amount of flavonoid release can be seen in **Figure 2** and **Table V**. The initial fast release of extract from the gel could be explained by the fact that these systems were formulated in the aqueous vehicle (Na-CMC). The matrix formed was already hydrated; therefore, hydration and water permeation would no longer limit the drug release. As the polymer concentration increases, it leads to a decrease in drug release.

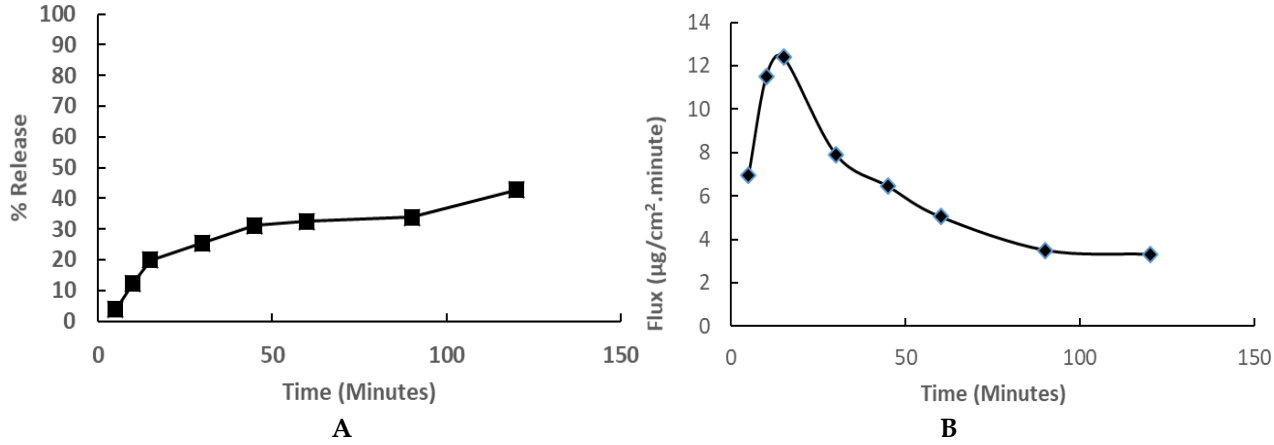

Figure 2. Percent release of optimum formula (F2) [**A**] and penetration flux of flavonoid from gel [**B**].

Table V. The cumulative amount of flavonoid release

Time (minutes)	Cummulative amount of flavanoid release (µg/cm²)	% release	Flux (µg/cm²/minutes)
5	34.887	3.746	6.977
10	114.979	12.345	11.498
15	185.900	19.960	12.393
30	237.583	25.509	7.919
45	289.764	31.112	6.439
60	302.573	32.487	5.043
90	315.481	33.873	3.505
120	398.264	42.762	3.319

Different kinetic models (zero-order release, first-order release, Higuchi equation, and Korsmeyer-Peppas) were used to fit the data relating to the kinetics of the release of flavonoids from the gel. The kinetic release of the gel formula with Na-CMC as a gelling agent follows the Higuchi equation because it has a linearity value of 0.9141. Drug release by following the kinetics of the Higuchi equation has a release diffusion mechanism where the drug released follows Ficks Law. The drug dissolved in a saturated solution diffuses into the solvent from an area of high concentration to a low drug concentration[42]. According to Korsmeyer-Peppas, the release of F2 has a value at <0.45 n <0.89, so the mechanism that occurs is non-fickian diffusion. This indicated that the drug release mechanism might involve a combination of both diffusion and chain relaxation mechanism. Therefore, the release of drugs from the formulated gels is controlled by swelling of the polymer, followed by drug diffusion through the polymer and slow erosion of the polymer[27]. The release kinetics model can be seen in **Table VI** and **Figure 3**.

Table VI. Kinetics release model of *P. amaryllifolius* leaves ethanol extract gel

Parameter	Kinetics release model			
	Zero-order	First-Order	Higuchi	Korsmeyer-Peppas
R^2	0.8093	0.8585	0.9141	0.8511
k	0.2778	0.0016	3.919	4.478
n	-	-	-	0.6551

Note: R^2= Linearity regression; k=constanta release; n= exponent

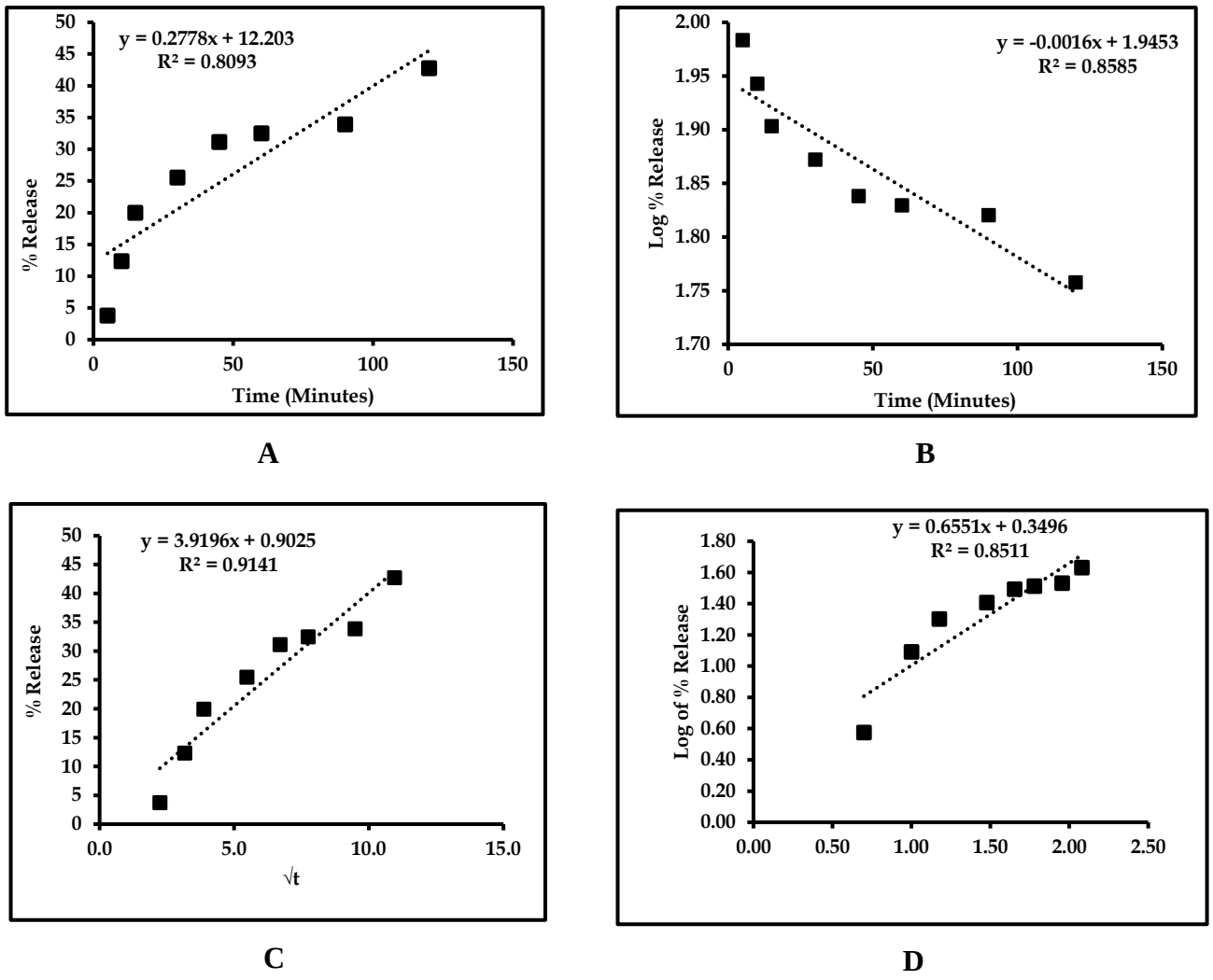

Figure 3. Release kinetics model [**A**] Zero-order; [**B**] First-order; [**C**] Higuchi; [**D**] Korsmeyer-Peppas of *P. amaryllifolius* leaves ethanol extracts gel.

CONCLUSION

The optimum formula is F2 with Na-CMC as a gelling agent because it has physical quality characteristics to the requirements. Flavanoids released at F2 were 42.76%, with a cumulative release of 398.264 µg/cm^2. In the future, the optimum formula (F2) can be tested for its efficacy in wound healing.

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AUTHORS' CONTRIBUTION

DF: Guidance, monitoring formulation design and development, analytical method development; **AH**: Pre-formulation studies and optimization of formulation parameters for the development of of gel and *in vitro* characterization studies; **ANP**: Pre-formulation and formulation development of gel containing ethanolic extract of *P. amaryllifolius*. All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY

Not applicable.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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