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Gelatin Transformed from Catfish Skin (*Pangasius hypohthalmus*) as Gelling Agent in Piroxicam Gel Formulation

Gelatin Hasil Transformasi Kulit Ikan Patin (*Pangasius hypohthalmus*) sebagai *Gelling Agent* dalam Formulasi Gel Piroksikam

Muslim Suardi*[1], Azlaini Yus Nasution[1], Yosiana Putri[1]

[1]*Faculty of Pharmacy and Health Sciences, Universitas Abdurrab, Pekanbaru*
<muslim.suardi@univrab.ac.id>

ABSTRACT

Piroxicam is an effective non-steroidal anti-inflammatory drug, but it has serious side effects orally. The research was conducted to formulate piroxicam in gel dosage form using gelatin transformed from catfish skin (*Pangasius hypophthalmus)* as a gelling agent. Using this ingredient transformed from pig and cow is unacceptable for certain religious adherents. This study aims were to formulate piroxicam gel and determine the release of piroxicam from gel at various concentrations of 0.75, 0.875, and 1%, while innovator product (F4) was used as a positive control. The evaluations performed were organoleptic, homogeneity, pH, spreadability, and release profile. The release of piroxicam from the gel produced was conducted using a modified paddle-type dissolution device equipped with an eggshell membrane placed on a metal disk. The level of piroxicam dissolved was measured using a UV spectrophotometer at λ_{max} of 356.4 nm. The release kinetics of piroxicam gel formulas F1, F2, F3 and F4 followed zero-order kinetics model. The dissolution efficiency and T90 from formulas F1, F2, F3, and F4 value were highly significant differences ($p < 0.01$), while the dissolution rate were significant differences ($p < 0.05$). All of formula fulfill the requirements except spreadability characteristic.

Keywords: Gel, piroxicam, gelatin, *Pangasius hypophthalmus*

ABSTRAK

Piroksikam merupakan obat antiinflamasi nonsteroid yang efektif, tetapi memiliki efek samping yang serius jika diberikan secara oral. Penelitian ini dilakukan untuk memformulasi piroksikam dalam bentuk sediaan gel dengan menggunakan gelatin hasil transformasi kulit ikan patin (*Pangasius hypophthalmus*) sebagai bahan pembentuk gel. Penggunaan bahan hasil transformasi kulit babi dan sapi tidak dapat diterima oleh sebagian penganut agama. Penelitian ini bertujuan untuk memformulasi gel piroksikam dan mengetahui pelepasan piroksikam dari gel pada berbagai konsentrasi yaitu 0,75, 0,875, dan 1%, sedangkan produk inovator (F4) digunakan sebagai pembanding. Evaluasi yang dilakukan adalah organoleptik, homogenitas, pH, daya sebar, dan profil pelepasan. Uji pelepasan piroksikam dari formula gel dilakukan menggunakan alat disolusi tipe dayung yang dimodifikasi dan dilengkapi dengan membran kulit telur yang diletakkan pada piringan logam. Kadar piroksikam yang terlarut diukur dengan spektrofotometer UV pada λ_{max} 356,4 nm. Pelepasan piroksicam dari gel formula F1, F2, F3, dan F4 mengikuti model kinetika orde nol. Nilai efisiensi disolusi dan T90 dari formula F1, F2, F3, dan F4 menunjukkan perbedaan yang sangat signifikan ($p < 0,01$), sedangkan laju disolusi menunjukkan perbedaan yang signifikan ($p < 0,05$). Semua formula memenuhi persyaratan sediaan gel kecuali karakteristik daya sebar.

Keywords: Gel, piroksikam, gelatin, *Pangasius hypophthalmus*

INTRODUCTION

Piroxicam is a nonsteroidal anti-inflammatory drug (NSAID), an oxicam derivative. It is a non-selective cyclooxygenase (COX) inhibitor (Katzung et al., 2012). Piroxicam is very poorly soluble in water, in dilute acids and most organic solvents, poorly soluble in ethanol and in alkaline solutions (Ministry of Health of the Republic of Indonesia, 2020). In a study conducted by Beetge et al in 2000, the influence of the physicochemical characteristics and pharmacokinetic properties of several NSAIDs on their good absorption through the transdermal related with its smaller molecules. Its penetration into the skin is better than other NSAIDs. Oral administration of piroxicam is associated with gastrointestinal side effects, such as gastric irritation and also impaired kidney function (Khunt et al., 2012). To dissolve the problem, piroxicam is formulated in gel dosage form administered topically.

Gel, sometimes called jelly, is a semi-solid system consisting of a suspension made of small inorganic particles or large organic molecules, penetrated by a liquid (Ministry of Health of the Republic of Indonesia, 2020). Gel preparations are prepare using high water content that can provide moisture to the skin and penetration of drugs will be better than other topical preparations (Rehman & Zulfakar, 2014).

Gelatin is one of gel-forming materials. It is a protein derivative product obtained by partial hydrolysis of collagen from bones, white connective tissue, or animal skin. It is used as a gel former, whipping agent, protective colloid, binding agent, clarifying agent, film former, thickener, process aid, emulsifier, stabilizer, and adhesive agent (GMIA, 2012).

In previous research conducted by Soetji Woelandari in 2005, the effect of manufacturing techniques on the effectiveness of piroxicam penetration power from gelatin base. However, the type of gelatin used was not explained. Generally, gelatin is obtained from mammals, especially the skin and bones of pigs and cows (Sae-leaw et al., 2016). The source of gelatin from pigs is unacceptable for Muslims and Jews, while gelatin from cows is acceptable if it has been processed according to religious requirements (Choi & Regenstein, 2000). In other hand, cow is prohibited for Hindu adherents. Therefore, alternative raw materials are needed that are acceptable to all groups, namely by utilizing aquatic sources, one of its is catfish.

Data from the Ministry of Marine Affairs and Fisheries in Indonesia (Ministry of Marine Affairs and Fisheries, 2022) states that the total production of catfish cultivation in 2022 reached 154,400 tons and is projected to increase continuously. Catfish are generally marketed in whole and fillet form. The fillet industry will produce skin and bones as a by-products or waste. This waste has not been utilized optimally, so it can be used as raw material in production of gelatin.

In previous research conducted by Nasution et al in 2018, the characterization of gelatin extracted from catfish skin (*Pangasius hypopthalmus*) using acid and base processes, resulted in catfish gelatin. A base process showing better properties compared to the acid method.

In this study, the author wants to make sure the potential of catfish skin as a source of gelatin in the formulation of piroxicam gel produced at various concentrations of 0.75, 0.875, and 1%, so that catfish skin waste can be utilized as an alternative source of gelatin and contribute to the development of sustainable and environmentally friendly natural resources. So far, no gel formulation was found using gelatin transformed from catfish skin.

METHODE

Materials and Equipments

Equipments used were spectrophotometer UV-Vis (PG Instruments Model T60) dissolution tester with diffusion cell, moisture balance analyzer, Viscometer Brookfield (First Touch Lamy Rheology), analytical balance, pH meter, oven, blender, thermometer, water bath, furnace, desiccator and glassware usual used in laboratory.

Materials used were catfish skin gelatin, acetic acid, NaCl, NaOH, piroxicam, propylene glycol, methylparaben, propyl paraben, distilled water, KH2PO4. All chemical used is pro analysis grade. Catfisf (*Pangasius hypophthalmus),* eggshell of *Gallus domesticus* (Determination Letter of Chief of Biology Laboratory Universitas Muhammadiyah Riau).

Method

1. **Transformation of Catfish Skin**

Catfish skin was separated from the meat, cleaned from the remaining meat, weighed, and washed with 6 L 0.8 N NaCl solution for 1 kg cleaned catfish at a temperature of 5 °C for 10 minutes, then rinsed with running water. Furthermore, it was mixed with a 6 L 0.2 N NaOH solution for 1 kg of cleaned skin at room temperature. Then, it was rinsed with water until reached a neutral pH. The fish skin was soaked again with 6 L 0.05 N acetic acid for 1 kg catfish skin at room temperature for 3 hours, then rinsed with water (n = 3). Furthermore, the extraction process was carried out using distilled water at a temperature of 60 °C for 10 hours. The extract obtained were filtered with gauze three times and dried in an oven at a temperature of 55 °C. The solid gelatin was then crushed in a mortar to find gelatin powder (Nasution et al., 2018).

2. **Organoleptic Evaluation of Gelatin**

Organoleptic observation of gelatin was carried out based on the Indonesian National Standard (SNI) 01-33735-1995. Gelatin was extracted from catfish skin, observed for its solidity and solution color. A total of 5 g of gelatin was dissolved in 100 mL of distilled water at a temperature of 60 ºC. The solution was kept until the temperature reached 32 °C and in this state the solution gave a normal taste (almost tasteless). Then, it was left for 48 hours in a cup. No unpleasant odor occurred (Nasution et al., 2018).

3. **Determination of the Acidity Gelatin**

One gram of gelatin was diluted with 100 mL of distilled water. The acidity of the solution was measured using a calibrated pH meter. The pH requirement for gelatin is between 5 and 7.5 (GMIA, 2012).

4. **Determination of Lost on Drying of Gelatin**

One gram of gelatin was weighed in an aluminum cup on a moisture analyzer by spreading it all over the sides of the aluminum cup. Furthermore, the temperature of the device was set to 105°C for 15 minutes. The water content will be obtained after the test was completed (Manno & Setianto, 2022). The requirement for gelatin water content according to the Indonesian Industrial Standard is below 16% (Hastuti & Sumpe, 2007).

5. **Ash Content Analysis**

One gram of gelatin is weighed in a porcelain cup. The cup containing the sample was heated over a small flame of a Bunsen burner until it became charcoal, then ashed in a furnace at a temperature of 550 ± 10 °C until white or grayish for 5 hours. After the ashing stage, the cup was cooled in a desiccator for 30 minutes and then weighed. The ash content requirement is 0.5 to 2% (GMIA, 2012).

6. Gelatin Viscosity Analysis

A total of 6.67 grams of gelatin was dissolved in water at 60 ºC to 100 mL. The viscosity of the solution was measured using a Brookfield viscometer. The standard viscosity of gelatin is 20 - 75 mps (GMIA, 2012).

7. Preparation of Piroxicam Gel

The pioxicam gel was prepared following the formulation as in Table I

Table I. Formulation of Piroxicam Gel

Materials	Function	Concentration (%)				
		F0	**F1**	**F2**	**F3**	**Positive Control**
Piroxicam	Active ingredient	-	0.5	0.5	0.5	Inovator
Catfish skin gelatin	Gelling agent	0.75	0.75	0.875	1	No Batch: FY2502
Na CMC	Gelling agent	3	3	3	3	
Propylene glycol	Co-solvent	6	6	6	6	Expire Date: May 2027
Methyl paraben	Preservative	0.06	0.06	0.06	0.06	
Propyl paraben	Preservative	0.01	0.01	0.01	0.01	
Distilled water (mL)	Solvent	ad 100	ad 100	ad 100	ad 100	

F0 : Formula gel without piroxicam
F1 : Formula gel (0.75% gelatin)
F2 : Formula gel (0.875% gelatin)
F3 : Formula gel (1% gelatin)

8. Preparation of Piroxicam Gel

Weighted gelatin was dissolved in hot distilled water at a temperature of 45° C in a beaker glass and stirred until a gel formed. The gel was mixed with prepared NaCMC gel and added with solution of piroxicam, methyl paraben, and propylene glycol, and then, stirred until homogeneous. The remaining distilled water was added step by step.

8. Evaluation of Piroxicam Gel

The acidity of piroxicam gel was evaluated following the procedure. One gram of prepared gel was weighed and diluted with 100 mL of distilled water, the pH of the solution was measured using a calibrated pH meter.

The spreadability was evaluated as follows: One gram of prepared gel was weighed and placed in the middle of the glass and covered with another glass which was then given a weight of 100 grams. Let stand for 1 minute, then the spreadability of the gel was measured.

The homogeneity test of piroxicam gel was performed as follows: The visual homogeneity test was carried out by applying one gram of gel to a clear glass, then covering it with another clear glass, and observed whether the gel preparation is homogeneous and the surface is smooth and even (Setyawan et al., 2023).

10. Analysis of Piroxicam in Gel Formulation

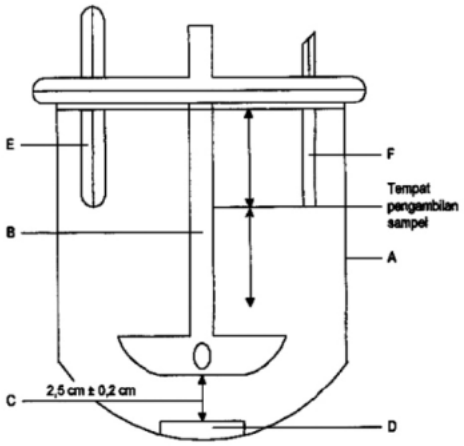
Determination of Maximum Absorption Wavelength. One mL of 100 µg/mL was diluted to obtain a concentration of 10 µg/mL using phosphate buffer solution of pH 7.4. The absorbance of the final solution was measured using a UV-Vis spectrophotometer at a range of wavelengths of 190-380 nm (Ministry of Health of the Republic of Indonesia, 1979).

Preparation of Calibration Curve. The stock solution of piroxicam 1000 µg/mL was diluted until a series of standard solutions of 4, 6, 8, 10, and 12 µg/mL. The calibration curve was created by plotting the absorbance value versus concentration. The linear equation obtained from the curve was used to determine the concentration of piroxicam to be analyzed (Vani et al., 2018).

Determination of Piroxicam Levels in Prepared Gel. The gel was weighed, dissolved in a phosphate buffer solution of pH 7.4 to obtain concentration of piroxicam approximately equal to 10 ppm. Absorbance of solution was measured using a UV spectrophotometer at the maximum wavelength (Umesh et al., 2021). The concentration of piroxicam was calculated using the calibration curve obtained.

9. **Evaluation of Piroxicam Release from Gel**

Preparation of chicken eggshell membrane (Vani et al., 2018). The eggshell membrane was washed using distilled water, then the membrane was dried at room temperature by placing it on a filter paper to accelerate the drying process. The membrane was cut at a diameter of approximately 2-3 cm according to the diameter of the membrane disk.

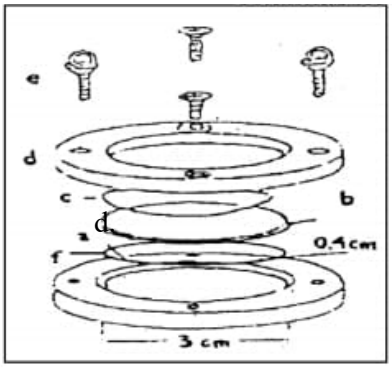


A. Vessel contains dissolution medium.
B. Paddle
C. The distance between the tip of paddle and the disc surface
D. Disc contains gel
E. Thermometer
F. Pipette to take out sample solution

Figure 1. Dissolution apparatus and equipped with a disc.

Set-up of Release Test Equipment. The release test of piroxicam gel was carried out *in vitro* using a 5-paddle over disk apparatus equipped with a membrane disk (Anggraeni et al., 2012). A flat cylinder disc was create using stainless steel. Outer and inner diameter were 55 and 28 mm, respectively, top cover 5mm, bottom 10mm. As a safety measure to prevent leakage, the disc was equipped with a rubber ring-shaped seal as a connector between the gel container and its cover.

Preparation of Disc. The disc was filled with gel until full, the eggshell membrane was placed on the top of the gel preparation and then black rubber was installed on top of the membrane so that it adheres to the lower disc that already contains piroxicam gel. The upper and lower discs are connected with bolts. Make sure the disc was properly installed and there were no leaking.



a. Gel holder
b. Rubber seal
c. Cover
d. Screw
e. Membrane

Figure 2. Membrane disc

In Vitro Release Test of Piroxicam Gel. The prepared disc was inserted into the chamber of the paddle-type dissolution tester containing 300 mL of saline phosphate buffer solution pH 7.4 ± 0.05. The temperature was set at 37 ± 0.5 °C, and the paddle rotated at a speed of 50 rpm. Five mL of sample solution were taken at 5, 10, 15, 30, 60, 120, and 240 minutes and filtered with filter paper. After taking the sample, 5 mL of a new saline phosphate buffer solution pH 7.4 ± 0.05 at the same temperature was added. The concentration of diffused piroxicam was measured using a UV spectrophotometer at the maximum absorption wavelength.

RESULTS AND DISCUSSION

rendement of gelatin found from catfish gelatin was 15.14%. It was pale yellow in color, granulated in shape, and odorless. pH, lost on drying, ash content and viscosity were 5.36 ± 0.05, 10.4%, 1.3 % ± 1.47, 47.71 mps ± 3.39, respectively. The maximum absorbance wave length was 356.4 nm, while the calibration curve equation obtained was y = 0.0471x + 0.0562 (r = 0.9941).

Table II. Organoleptics of piroxicam gel

Formula	Color	Odor	Texture	Homogeneity
F0	Transparent	Odorless	Sedikit Kental	Homogeneous
F1	Yellowish Transparent	Odorless	Sedikit Kental	Homogeneous
F2	Yellowish Transparent	Odorless	Sedikit Lebih Kental	Homogeneous
F3	Yellowish Transparent	Odorless	Kental	Homogeneous
F4	Yellowish Transparent	Odorless	Sedikit Kental	Homogeneous

Table III. Characteristics of piroxicam gel

Formula	pH	Drug content	Dissolution rate (min^{-1})	T90 (h)	Dissolution Efficiency (%)	Spread-ability
F0	6.16 ± 0.05	-	-	-	-	4.43 ± 0.05
F1	6.13 ± 0.05	98.26 ± 1.59	0.32 ± 0.002	4.55 ± 0.995	41.90 ± 0.125	4.36 ± 0.05
F2	6.16 ± 0.05	99.7 ± 2.25	0.17 ± 0.003	8.68 ± 7.754	22.55 ± 0.254	4.1 ± 0.05
F3	6.16 ± 0.05	97.26 ± 0.47	0.12 ± 0.000	12.48 ± 2.650	15.78 ± 0.061	4.0 ± 0.05
F4	6.0 ± 0.1	102.73 ± 8.49	0.22 ± 0.002	5.83 ± 3.323	39.94 ± 0.105	4.93 ± 0.11

Tabel IV. Determination of release kinetics of piroxicam from gel

Formula	Parameter	Kinetic Models			
		Zero Order	**First Order**	**Higuchi**	**Korsmeyer -Peppas**
1	r^2	0.99 ± 0.002	0.81 ± 0.006	0.68 ± 0.005	0.81 ± 0.006
	K	0.32 ± 0.002	0.01 ± 0.050	0.02 ± 0.003	0.01 ± 0.00
	N	-	-	-	0.68 ± 0.001
2	r^2	0.996 ± 0.0004	0.822 ± 0.004	0.720 ± 0.015	0.822 ± 0.003
	K	0.169 ± 0.003	0.012± 0.050	0.03 ± 0.0003	0.005 ± 0.00
	N	-	-	-	0.56 ± 0.001
3	r^2	0.99 ± 0.0001	0.76 ± 0.002	0.57 ± 0.006	0.76 ± 0.001
	K	0.1184 ± 0.0004	0.0124 ± 0.00	0.056 ± 0.0005	0.005 ± 0.00
	N	-	-	-	0.355 ± 0.001
4	r^2	0.9947 ± 0.0005	0.9251 ± 0.0046	0.9029 ± 0.002	0.9251 ± 0.004
	K	0.2175 ± 0.0023	0.0064 ± 0.00	0.0043 ± 0.00	0.0028 ± 0.00
	N	-	-	-	1.2022 ± 0.001

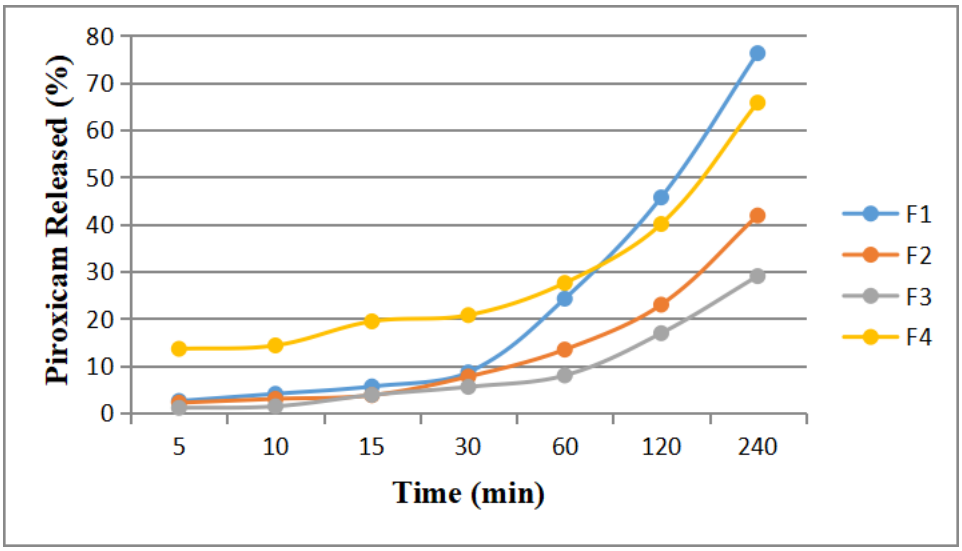


Figure 3. Profile of piroxicam released from gel.

The Characteristics of Gelatin Transformed from Catfish Skin

The rendement of gelatin was 15.14%. This obtaining seem to be higher than the results of the study done by Nasution et al. (2018). Their obtaining was 14.30%. The difference in yield values produced can be influenced by the type of raw material and the gelatin extraction process, including the pretreatment process (Ratnasari et al., 2014). The characteristics of gelatin were slightly yellowish in color, granulated powder, and odorless. In additon, the pH of gelatin obtained was 5.36. The pH requirement for gelatin is 5–7.5 (GMIA, 2012). It could be stated that, the acidity of the gelatin produced meets the standards.

The lost on drying (LOD) of gelatin produced was 10.4 %. The water content of gelatin is an important parameter and must be considered, because the water content is closely related to the shelf life of gelatin (Ulfah, 2011). The requirement for water content of gelatin according to the Indonesian Industrial Standard is below 16% (Hastuti & Sumpe, 2007). So, the water content of the gelatin obtained has met the standard.

The ash content test of gelatin obtained was 1.3%, it met the gelatin quality requirements according to the Gelatin Manufactures Institute of America (2012) standards, i.e. 0.5 - 2%. The ash content reflects the mineral content including heavy metals in the product. Low ash content indicates that the lower heavy metal residue and washing process was carried out properly, so that the minerals contained in the material dissolve during the washing process (Sari et al., 2020).

The gelatin viscosity was 47.71 mps. The viscosity value obtained from this study is in the range of the Gelatin Manufactures Institute of America (GMIA) (2019) standard (20 - 75 mps). It can be concluded that gelatin produced from catfish skin has fulfilled GMIA and National Indonesian Industry Standard.

The Characteristics of Piroxicam Gel Using Gelatin Transformed from Catfish Skin

Piroxicam gel produced has a clear color or transparent in F0. While, in F1, F2, F3, and F4 was pale yellow color. There were no odor in all formula and inovator product. The piroxicam gel was slightly thick in F0, F1 and F4, slightly thicker in F2 and thick in F3. The difference in gel

consistency is influenced by the different concentrations of gelatin. It was seem the higher the concentration of gelatin, the thicker the gel produced.

The normal pH of human skin ranges from 4.5-6.5. If the pH of the gel is outside the skin pH interval, it will cause dry skin or even irritation (Wardani & Septiarini, 2021). The gel F0, F1. F2 and F3 showed a pH of 6.1, while for F4, the pH was 6.0. It means the piroxicam gel prepared from catfish skin gelatin still meets the requirements for a gel dosage form in terms of acidity.

A good and preferred preparation can be easily spread on the skin and is comfortable to use (Wyatt et al., 2008). The spreadability of semi-solid preparations that meets the requirements is 3-5 cm (Wardani & Septiarini, 2021). The spreadability of formula F0, F1, F2, F3, and F4 were 4.43, 4.36, 4.1, 4, and 4.93 cm, respectively. These results indicated that F0 and F1 with low gelatin concentrations produced gels that were less viscous than formulas F2 and F3, so that they have a wider spread range than F0 and F1. This decrease in spreadability is due to differences in gelatin concentration in each formula. The higher the concentration of the gelling agent used, the lower the spreadability. These results indicate that, all formulas still met the requirements for gel.

Homogeneity testing can be done by applying the gel to a piece of glass, then smoothing it out. If there are no grains on the piece of glass, then the preparation can be stated to be homogeneous. In the observation, there were no grains on the glass. It could be stated that, the gel produced were homogeneous.

In determining the level of piroxicam in gel preparations, the concentration of piroxicam in F1, F2, F3, and F4 were 98.26 ± 1.59, 99.7 ± 2,25, 97.26 ± 0,47, and 102.73 ± 8,49 %, respectively. The results obtained met the requirements according to the Indonesian Pharmacopoeia Edition VI (not less than 97.0% and not more than 103.0%). These results indicated, that all formulas meet the requirements.

Figure 3 showed the relationship between the percentage of released levels and sampling time at certains time intervals. F1 seems to have the highest level at 240 minutes compared to other formulas. F4 has the highest level at 5 minutes compared to other formulas. While F2 and F3 show the lowest increasing concentration compared to F1 and F4. The consistency of the preparation can affect the release rate of piroxicam from gel related to the mobility of the active ingredient from the base (Carter, 1975). It was known that the consistency of Formulas F1, F2 and F3 was thicker than the innovator product (F4). So that, it could reduced the mobility of piroxicam molecules, resulting in obstacles to its release.

The drug release profile of each formula was analyzed based on the zero-order, first-order, Higuchi and Korsmeyer-Peppas equations. The release profile of piroxicam from F1, F2, F3 and F4 followed zero-order release kinetics, with the regression coefficient were 0.9877, 0.9963, 0.9911, and 0.9947, respectively, as seen in Table IV. These findings were in accordance with the results of Vani et al (2018) in a research related to the release of piroxicam from emulgel. Zero-order kinetics reflects where the rate of drug release does not depend on its concentration (Shaikh et al., 2015). Meanwhile, in another study conducted by (Nining et al., 2023), they found that, the release kinetics of piroxicam through iontophoresis at various pH of polyelectrolyte hydrogel with sodium alginate-tragacanth polymer from formula F1 followed the Korsmeyer-Peppas kinetics, F2 followed first-order kinetics, while F3 and F4 followed zero-order kinetics. The difference in kinetics in previous researchers was thought to be associated with the different ionized piroxicam conditions due to different pH values (Nining et al., 2023).

The data were normally distributed in the dissolution efficiency test ($p>0.05$). So, the data was analyzed using ANOVA statistical analysis. There were a highly significant difference in all formulations in terms of dissolution efficiency ($p <0.01$). The T90 data were distributed normally ($p>0.05$). So that, the data was analyzed using ANOVA. There was a very significant difference between F1, F2, F3 and F4 in terms of T90 ($p<0.01$). Dissolution rate obtained data were not normally distributed ($p < 0.01$). So, it was further tested using Kruskal Wallis analysis. The dissolution rate from F1, F2, F3, and F4 was significant difference ($p < 0.05$).

CONCLUSSIONS

The release of piroxicam from formula F1, F2, F3 and F4 followed the zero-order release kinetic model. All of these formulations fulfill the requirement as a gel formulation except spreadability.

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