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Original Article

Formulation and Evaluation of Chloramphenicol Hydrogel Ophthalmic Preparation

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ABSTRACT

Objective: To generate a hydrogel to increase the retention time of a drug in an ophthalmic drug delivery system. **Methods**: Research was conducted on the formulation and evaluation of a safe-to-use chloramphenicol ophthalmic hydrogel with various concentrations of hydroxypropyl methylcellulose (HPMC), F1 (0.2 % HPMC), F2 (0.3 % HPMC), F3 (0.4 % HPMC) and F4 (0.5 % HPMC). The organoleptic safety, pH, viscosity, sterility, potency, and *in vitro* drug release were evaluated. **Results:** The drug concentration had dissimilar effects on viscosity and release rate. F4 (0.5 % HPMC) had the least chloramphenicol diffused at 5 min (11.01 %) and after 8 h (71.13 %). The *in vitro* drug release from the hydrogel was significantly influenced by the HPMC concentration, which enhanced the bioavailability through longer pre-corneal residence time and the ability to sustain the release of the drug. **Conclusion:** The chloramphenicol hydrogel ophthalmic preparations formulated with HPMC have shown a good characteristic, and acceptable sustained released profile that may extend absorption of the drug for ensuring an optimum bioavailability at the site of action. The finding of this study indicated that chloramphenicol hydrogel ophthalmic preparations for the ophthalmic treatment was good is effective and safe.

Key words: Chloramphenicol, Hydrogel, Hydroxypropyl methylcellulose, Ophthalmic.

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INTRODUCTION

The eye is a specialized sensory organ that has a natural defense system towards bacterial invasion. The infection can occur if the defense system is damaged so that the bacteria penetrate the eye. Factors that can cause the infection is exposure to eye on the patient's environment eye infection. This condition causes the malfunctioning of the eye such as corneal discharge that shows the potential threat to vision. Eye infections must be dealt with immediately, before the infection becomes more severe and cause inflammation of the cornea and the possibility of vision loss. Eye infections were treated with a topical preparation that contains antibiotics. In severe infection, more intensive antibiotic treatment is needed.[1-2]

In dealing with an eye infection, there are various conventional ophthalmic formulations on the market such as eye drops, suspensions, and ointments containing antibiotics. However, conventional preparations have flaws that cause poor bioavailability of the drug in the ocular cavity. This is because a drug that delivered to the eye, experienced drying by nasolacrimal, and absorption of cornea productive decrease down the contact time with the eye.[3-5] Various approaches have made to increase bioavailability and time contact with drugs in the eye. One of the ways is with the design of ophthalmic preparation in the form of a hydrogel which can maximize absorption medicine in the eye and minimize deprived of the drug before penetration the cornea.[6-8]

The hydrogel is a preparation which added the polymers to extending drug retention of medicine in the eye, lowering the drying nasolacrimal and increase bioavailability.[8-10] Polymers capable of absorbing large amounts of water. Therefore, when dripped into the eyes, hydrogel has good mucoadhesive on mucous layer until the drug delivery to the eye can be optimized.[11-12] One of the antibiotics commonly used in the formulation of ophthalmic preparations is Chloramphenicol, because it has a very broad spectrum of Gram-positive bacteria, Gram-negative, and anaerobic bacteria. Chloramphenicol intraocular penetration is very good because of the high lipid solubility.[11,13]

From the above description, the researcher was interested in making hydrogel preparation formulation as an ophthalmic drug delivery system that has good therapeutics efficacy in treating eye infections. Therefore, the research conducted on the formulation and evaluation of hydrogel ophthalmic chloramphenicol dosage form using Hydroxypropyl Methylcellulose (HPMC) as the gel-forming base.

MATERIALS AND METHODS

Materials

Chloramphenicol (BioBasic©), hydroxypropyl methylcellulose (HPMC) (Colorcon®), tween 80 (Brataco®), propylene glycol (Brataco®), methyl paraben (Merck®), glycerin (Brataco®), potassium dihydrogen phosphate (Merck®), sodium hydroxide (Merck®), Fluid Thioglycollate Media (Merck®), Soybean Casein Digest (TSB) (Merck®), Nutrient Agar (Merck®), cellophane membrane (Sigma©), Escherichia coli (E.coli) (29998ATCC), ethanol (Brataco®), and aqua bidestilata sterile (Ikapharmindo®).

Methods

The experimental laboratory was conducted in stages.

Preformulation

Examination of the active substances used (chloramphenicol) by the monograph of the Indonesian Pharmacopoeia were:[14]

Melting point determination of active substance

Determined by the temperature at the time of chloramphenicol start to melt until becoming a liquid form. The result was compared with chloramphenicol monograph in the Indonesian Pharmacopoeia.[14]

Standard curve of chloramphenicol

Chloramphenicol weighed 500 mg and dissolved in 100 ml of phosphate buffer pH 7.4 to obtain a stock solution of 5000 ppm. From a stock solution did variety dilutions 6, 8, 10, 12, 14 ppm. The absorbance was measured at a wavelength of 280 nm with a spectrophotometer UV/Vis. Absorbance obtained, was used to form a standard curve chloramphenicol.[14-15]

Potential testing of chloramphenicol

Sample solution and standard solutions, that has been diluted were filled into each reservoir about 50µl using a micropipette. The Petri dishes were incubated at 37°C for 18-24 h. Measured and recorded diameter clear zone (zone lysis). Calculated the potential of *chloramphenicol*.[14,16]

Hydrogel formulations

Different formulations were prepared with a various concentration of HPMC as described in Table 1. The drug solution was added to the hydrogel base while stirred. So that no foam was observed. The buffer solution was added to the formulation, and the following by addition of distilled water up to 100 ml. Formulations that have been made were stored in 10 ml closed vials. This formulation was terminally sterilized by autoclaving at 121°C for 15 min.[11,17]

Evaluation

Organoleptic examination

Checked by observing changes in color, odor, and clarity visually and the observations made on the day of production, 1st, 3rd, 7th, 14th, 21st and 28th day of storage.

pH measurement

Performed on the day of production and after 3rd, 7th, 14th, 21st and 28th days of storage at room temperature.

Viscosity measurement

Measurements were taken on the day of production and after 3rd, 7th, 14th, 21st and 28th days of storage at room temperature.

Determination of chloramphenicol

Chloramphenicol rate was determined by taking 0.1 ml formulation and diluted to 100 ml with phosphate buffer pH 7.4, then analyzed the absorbance at wavelength 280 nm using a UV/Visible Spectrophotometer.

Compatibility Study

The IR spectra of the pure (Chloramphenicol) was compared with IR spectrum of combination a mixture of Chloramphenicol and all the excipients using KBR pellets of 0.1 mm to check examined the incompatibility interaction.[18]

Sterility test

Conducted using Fluid Thioglycollate Media (FTM) media and Soybean Casein Digest (SCD) media. Aseptically, inoculated directly to each test preparation into a test tube FTM and SCD media and then incubated at 30-35°C and 20-25°C for not less than 14 days. The occurrence of turbidity in t-test tube was observed every day.[14,17,19]

Potential test

Created inoculum by entering the suspension of bacteria into Nutrient Agar (NA) in the petri dish. The Petri dish was shaken a little bit so that the bacteria solution covered up the surface of NA and allowed to clot.

Table 1: Formula of hydrogel ophthalmic preparations.

Ingredients (%)	F1	F2	F3	F4
Chloramphenicol	0.5	0.5	0.5	0.5
HPMC	0.2	0.3	0.4	0.5
Propylene Glycol	5.0	5.0	5.0	5.0
Glycerin	2.0	2.0	2.0	2.0
Tween 80	0.5	0.5	0.5	0.5
Methyl paraben	0.02	0.02	0.02	0.02
Phosphate buffer pH 6.8	5	5	5	5
add water	100	100	100	100

Description:
F1 Hydrogel with 0.2% HPMC
F2 Hydrogel with 0.3% HPMC
F3 Hydrogel with 0.4% HPMC
F4 Hydrogel with 0.5% HPMC

The bottom surface of the petri dish was divided into four areas of equal size. Labeled each of these areas follow hydrogel ophthalmic dosage formulations chloramphenicol (F1, F2, F3, F4). Aseptically, made four prints reservoir in a petri dish using the perforator. Loaded as many as 50 ml sample into each reservoir using a micropipette. Petri dishes were incubated at 37°C for 18-24 h. Measured and recorded diameter clear zone (zone of inhibition lysis) that occur around the reservoir that had been containing antibiotics. Calculated the potency of antibiotics.[14]

In vitro dissolution studies

Performed using Franz diffusion apparatus and phosphate buffer (pH=7.4) as the receptor medium. Phosphate buffer with pH 7.4 will simulate the lachrymal fluid. The temperature was maintained at 37+0.5°C with the speed of rotation maintained at 100 rpm. The samples were withdrawn at various time intervals and analyzed the drug concentration using a UV/Visible Spectrophotometry.[17,20-21]

RESULTS

Preformulation Hydrogel

Inspection result of melting point of chloramphenicol

Determining the melting point of active substance chloramphenicol present in Table 2.

Standard curve of chloramphenicol

Chloramphenicol standard curve data by using ultraviolet spectrophotometry presented in Table 3. Using the Least Square equation and was obtained straight line equation as follows: $y = 0.0533x - 0.0285$

Potential testing of chloramphenicol

The data of inhibitory diameter of chloramphenicol have been compared to the standard reference (work reference). Potential that obtained seen in Table 4.

Evaluation

Observation result of organoleptic

Based on the observation result for 28 d, the four hydrogel formulation of chloramphenicol had not changed in organoleptic where the preparation remains colorless, clear and odorless as shown in Table 5.

pH measurement

The observation result of the pH of hydrogel ophthalmic chloramphenicol present in Figure 2.

Viscosity measurement

Observation result of the average viscosity can be seen in Figure 3.

Table 2: Inspection result of melting point of chloramphenicol.

Observation result	Refer (Ministry of Health RI, 1995)
142°C – 152.4°C	142°C – 153°C

Table 3: Chloramphenicol standard curve data by using ultraviolet spectrophotometry.

Concentration (ppm)	Absorbance
6	0.2916
8	0.3860
10	0.5168
12	0.6170
14	0.7086

Table 4: Potential of chloramphenicol.

Observation result	Refer (Ministry of Health RI, 1995)
101.8 %	97% - 103 %

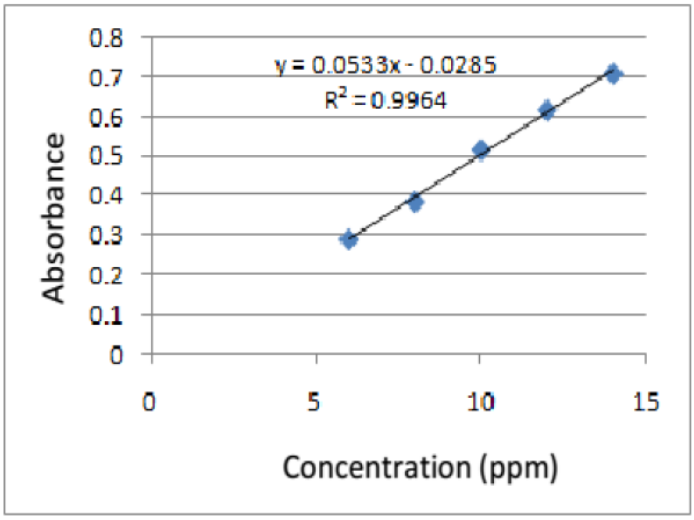


Figure 1: Standard curve of chloramphenicol.

Determination of levels of ophthalmic hydrogel chloramphenicol preparations

Determination of levels of Chloramphenicol results in the preparation of the hydrogel during the 28th days of storage can be seen in Figure 4.

Compatibility Study

The infrared spectrum of chloramphenicol, HPMC, and the mixture of chloramphenicol with HPMC obtained can be seen in Figure 5 and Table 6.

Sterility testing

The sterility data of from the chloramphenicol hydrogel ophthalmic preparations are present in Table 7.

Potency testing

The chloramphenicol potency value that has been obtained can be seen in Table 8.

In vitro dissolution studies

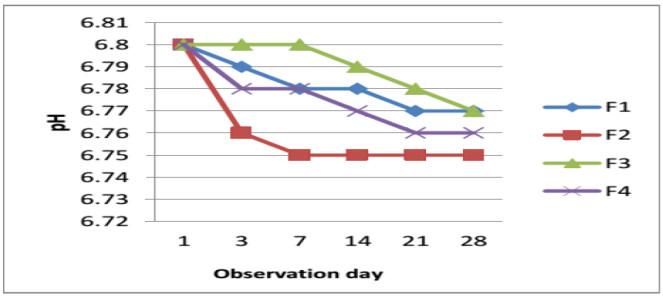
The chloramphenicol released profile test of the preparation can be seen in Figure 6.

Table 5: Observations of hydrogel organoleptic during storage over time.

Formula	Observation	Observation of organoleptic day to-					
		1	3	7	14	21	28
F1	Clarity	clear	clear	clear	clear	clear	clear
	Color	c	c	c	c	c	c
	Odor	o	o	o	o	o	o
F2	Clarity	clear	clear	clear	clear	clear	clear
	Color	c	c	c	c	c	c
	Odor	o	o	o	o	o	o
F3	Clarity	clear	clear	clear	clear	clear	clear
	Color	c	c	c	c	c	c
	Odor	o	o	o	o	o	o
F4	Clarity	clear	clear	clear	clear	clear	clear
	Color	c	c	c	c	c	c
	Odor	o	o	o	o	o	o

Description:

F1 : Hydrogel with HPMC 0.2 %
F2 : Hydrogel with HPMC 0.3 %
F3 : Hydrogel with HPMC 0.4 %
F4 : Hydrogel with HPMC 0.5 %
c : colorless
o : odorless

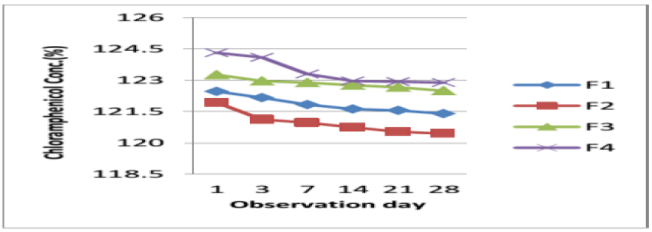


F1 : Hydrogel with HPMC 0.2 %

F2 : Hydrogel with HPMC 0.3 %

F3 : Hydrogel with HPMC 0.4 %

F4 : Hydrogel with HPMC 0.5 %



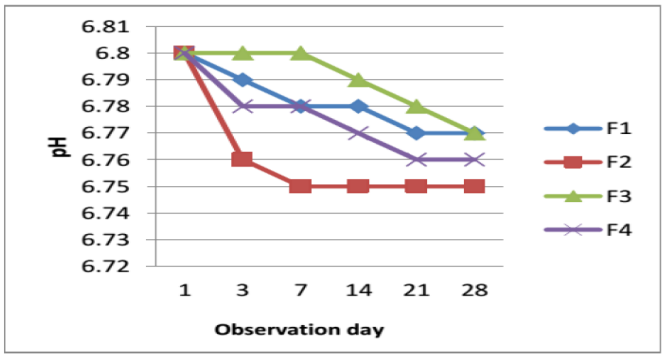
F1 : Hydrogel with HPMC 0.2 %

F2 : Hydrogel with HPMC 0.3 %

F3 : Hydrogel with HPMC 0.4 %

F4 : Hydrogel with HPMC 0.5 %

Figure 4: Graphic levels of chloramphenicol in hydrogel preparation during 28 days of storage time.



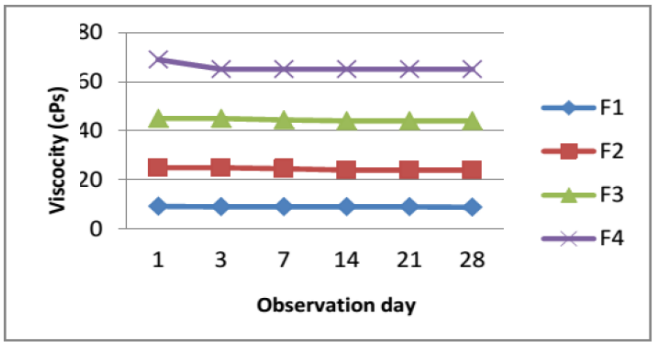
F1 : Hydrogel with HPMC 0.2 %

F2 : Hydrogel with HPMC 0.3 %

F3 : Hydrogel with HPMC 0.4 %

F4 : Hydrogel with HPMC 0.5 %

Figure 2: Graph of pH changes of hydrogel over the storage time.



F1 : Hydrogel with HPMC 0,2 %

F2 : Hydrogel with HPMC 0,3 %

F3 : Hydrogel with HPMC 0,4 %

F4 : Hydrogel with HPMC 0,5 %

Figure 3: Viscosity changes of hydrogel over storage time.

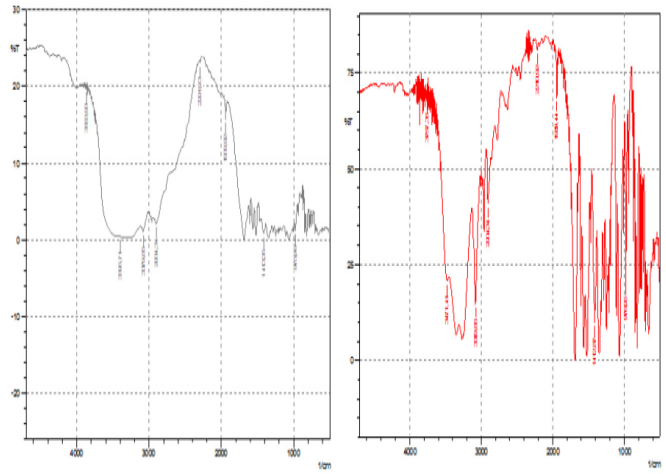


Figure 5: The infrared spectrum of chloramphenicol, HPMC, and the combination of chloramphenicol with HPMC (red colour).

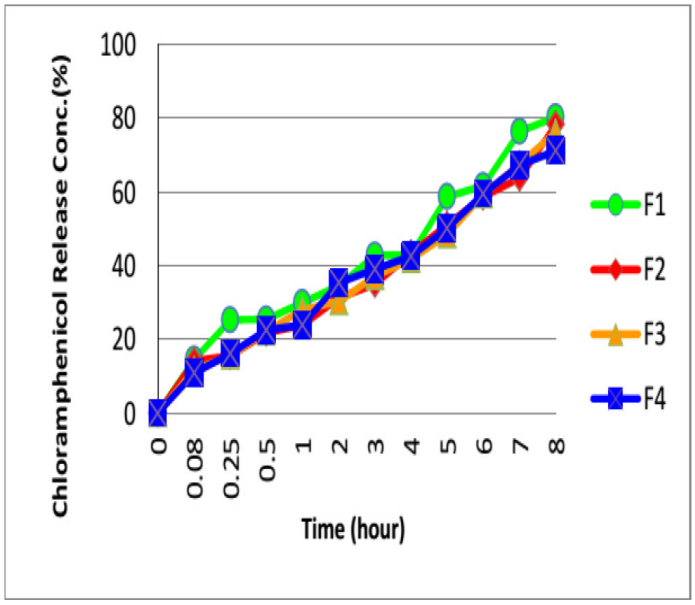


Figure 6: Graphic of release of chloramphenicol from hydrogels ophthalmic preparations.

DISCUSSION

Based on the examination obtained that the melting point and potency and used in the formulation of Chloramphenicol have been met the requirements according to the Chloramphenicol monograph in Indonesian Pharmacopoeia.[14] The testing results of evaluation as follows the four ophthalmic chloramphenicol hydrogel formulations (F1, F2, F3, and F4) can be considered to be physically stable throughout 28 days of storage. Base on the visual observation, there was no separation between the hydrogel-forming materials with the carrier (water) for all chloramphenicol hydrogel preparations.

As preparation given topically to the eye; the chloramphenicol ophthalmic hydrogel should have pH range adjusted to a pH range of ophthalmic preparations in general, so it will not irritate the eye. It showed that the hydrogel ophthalmic chloramphenicol preparations had a pH value which was appropriated for topical preparations during the 28 days of storage. Moreover, it can be seen that the pH value of each of the preparation declined during the storage time. The decrease in pH was probably caused the chloramphenicol having a pH range of 4.5 to 7.5 which indicated an interaction with other excipients in the hydrogel formulation. The ophthalmic preparations should have a pH range of 5.0 to 7.4, so that the formulation will be stable and does not cause irritation to the patient at the time of drug administration. The pH of hydrogel during 28 days of storage has not declined decreased drastically due to the addition of phosphate buffer 6.8 in formulations which act as a pH stabilizer.[22]

Table 6: Absorption area of chloramphenicol functional group.

Functional group	Absorption area (cm^{-1})	Chloramphenicol	Chloramphenicol+ HPMC
O-H	3700 - 3500	3863.93	3757.36
N-H	3400 - 3300	3386.71	3471.41
C-H	3100 - 3010	3079.86	3079.86
C-H	2950 - 2850	2901.34	2901.34
C=N	2260 - 2220	2291.93	2210.92

Table 7: Sterilization test.

Day	Test Sample								Control			
	F1		F2		F3		F4		FTM		TSB	
	FTM	TSB	FTM	TSB	FTM	TSB	FTM	TSB	+ve	-ve	+ve	-ve
1	-	-	-	-	-	-	-	-	+	-	+	-
2	-	-	-	-	-	-	-	-	+	-	+	-
3	-	-	-	-	-	-	-	-	+	-	+	-
4	-	-	-	-	-	-	-	-	+	-	+	-
5	-	-	-	-	-	-	-	-	+	-	+	-
6	-	-	-	-	-	-	-	-	+	-	+	-
7	-	-	-	-	-	-	-	-	+	-	+	-
8	-	-	-	-	-	-	-	-	+	-	+	-
9	-	-	-	-	-	-	-	-	+	-	+	-
10	-	-	-	-	-	-	-	-	+	-	+	-
11	-	-	-	-	-	-	-	-	+	-	+	-
12	-	-	-	-	-	-	-	-	+	-	+	-
13	-	-	-	-	-	-	-	-	+	-	+	-
14	-	-	-	-	-	-	-	-	+	-	+	-

Description:

F1 : Hydrogel with HPMC 0.2 %
F2 : Hydrogel with HPMC 0.3 %
F3 : Hydrogel with HPMC 0.4 %
F4 : Hydrogel with HPMC 0.5 %
FTM : Fluid thioglycollate medium for bacterial growth
TSB : Trypticase soybean broth for fungus growth
+ve : Found growth of microorganisms
-ve : Not found growth of microorganisms

Table 8: Results of potential testing on chloramphenicol hydrogel ophthalmic preparations.

Preparation Formula	Potential (%)
F1	101.89
F2	101.27
F3	98.04
F4	100

The viscosity of the four hydrogel formula has been experienced very little declined during the 28 days of storage. Preparation F3 and F4 have shown the viscosity values were relatively larger than the preparation F1 and F2. It could be influenced by the difference number of HPMC amount used in formulations affect the viscosity of the preparation of hydrogels. Thus, it can be seen that the greater the amount of HPMC was used, the greater the viscosity of the resulted value. The viscosity was directly dependent on the concentration of polymer in the formulation. Also, the viscosity value in the range of 5 cPs -100 cPs was significantly increased the contact time of the formulation on the surface of the cornea, and the higher viscosity grades do not provide any significant benefits, but tends to leave a residue on the eyelids.[11,23]

The level of chloramphenicol in the formula that has been made can be determined by using UV/Visible spectrophotometer. The measurements of absorbance were carried out towards the wavelength that can be shown the maximum absorption was 280 nm. The determination of each formula was done calculated by entering the absorbance values into the equation of the standard curve was created on preformulation. Based on the quantitative analysis by ultraviolet spectrophotometry method, in Figure 4 can be seen that that the levels of chloramphenicol in the four formula above has shown the results of a relatively large level, which was between 120.45% to 124.32%. The range of levels at the four formula indicated that a uniform distribution of the drug. Throughout the 28 days of storage time, the levels of four preparation of hydrogel formula have been decreased slightly. However, the four formula still have been qualified because the measure shown by the requirements of the Indonesian Pharmacopoeia, which were not less than 90% and not more than 130% of the amount listed on the label.[14]

The infrared spectrum of chloramphenicol, HPMC, and the combination of chloramphenicol with HPMC obtained were shown in the Figure 5. All of the characteristic peaks of Chloramphenicol can be seen in the infrared spectrum graph, indicated the compatibility of drug and the polymer. The resulting spectrum confirms that there was no significant change in the chemical integrity of the drug.[18]

From the results of sterility tests were conducted, it was found that there was no growth of microorganisms, from that it can be concluded that the Chloramphenicol hydrogel ophthalmic preparations have been met the requirements of sterility. Because the results showed no growth of bacteria and fungi in preparation during the 14 d of test time.[14]

The potency of chloramphenicol hydrogel ophthalmic preparations has been determined by calculating the dosage potency against bacteria Escherichia coli which was proportionated the potential value of chloramphenicol before it was used in the formulation. Based on data we can conclude that the chloramphenicol hydrogel ophthalmic preparation has the potency potential to kill or inhibit the growth of microbes according to the requirements in the Indonesian Pharmacopoeia.[14]

Chloramphenicol release testing was performed by using *in vitro* Franz diffusion cells. From the test results, obtained that F4 was the preparation by which the amount of chloramphenicol that has been diffused at least in 5 min, where the levels of chloramphenicol were separated was 11.01%, and at 8 h of time, the levels of chloramphenicol were separated was 71.13%. In F1, the greatest number of chloramphenicol release than F2, F3, and F4 where the number of chloramphenicol were released after 5 min was 14.73% and after 8 h about 80.30%. That was due to the addition of different polymer concentrations of HPMC in each formula.

From the data can be calculated the chloramphenicol released rate from the hydrogel preparations. The formula has a release rate of highest for F1 = 0.828 (mg/l), followed by F2 = 0.811 (mg/l), F3 = 0.812 (mg/l) and F4 0.759 (mg/l). Based on the data, the released rate of chloramphenicol hydrogel ophthalmic preparations, it can be concluded that the F4 has a longer retention time versus F1, F2, and F3. The adding of HPMC to the hydrogel ophthalmic preparations can extend the drug retention in the eyes and reduce the passage of drug in the eyes before penetration into the cornea. The extension of the retention of a drug in the eyes will increase the ocular bioavailability, the frequency of dosing can be reduced, and patient compliance may be will level.[11,17] Four formulas can be shown sustained release over a period of 8 h. Chloramphenicol release levels can be optimized for a high viscosity. It can be concluded that the F4 has the most excellent bioavailability, followed by F3, F2, and F1.[17]

CONCLUSION

The chloramphenicol hydrogel ophthalmic preparations formulated with HPMC have shown a good characteristics, and acceptable sustained released profile that may extend absorption of the drug for ensuring an optimum bioavailability at the site of action. The finding of this study indicated that chloramphenicol hydrogel ophthalmic preparations for the ophthalmic treatment are effective and safe.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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