Available online on www.ijddt.com
International Journal of Drug Delivery Technology 2019; 9(2); 145-150
doi: 10.25258/ijddt.9.2.6

ISSN: 0975 4415

Research Article

Formulation and Evaluation of Chloramphenicole Opthalmic Hydrogel with Carbomer And Hidroxy Propyl Methyl Cellulose Combination Bases

Insan Sunan Kurniawansyah[1*], Marline Abdassah[1], Jalaludin[2]

[1]*Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Universitas Padjadjaran, Sumedang, Indonesia*
[2]*Faculty of Pharmacy, Universitas Padjadjaran, Sumedang, Indonesia*

Received: 3rd Jun, 19; Revised: and Accepted: 15th Jun, 19; Available Online: 25th Jun, 2019

ABSTRACT

The preparation of an eye medication is one of the most interesting and challenging for a pharmaceutical, because the typical and unique eye anatomy and physiology cause the difficulty of effective drug concentration to reach the target site. From some recent research has been developed an ophthalmic hydrogel dosage, which is an eye gel preparation that provides many advantages over the preparation of the eye ointment and may increase corneal permeability and can extend contact time with eyes, optimal drug concentration at the receptor so that it can be obtained good bioavailability. Ophthalmic hydrogel has been developed to discover the formula contained chloramphenicol 0.5% as active ingredients with the combination of gel hydroxy propyl methyl cellulose, and carbomer of (0:1, 1:0, 2:1, 4:1) as the base. Formula was made by several stages which were mixing with the active ingredient, and sterilization using autoclave at 121ºC for 15 minutes. Results which covered organoleptic evaluation, pH. viscosity, and the levels of the active substance showed that F4 was the best formula. F4 had a watery consistency, clear and odorless, pH of 7.49, viscosity of 55 cP, and the levels of the active substance at 100%. Test observations ophthalmic hydrogel for 28 days of storage showed no changes in the organoleptic. pH and viscosity changes occured, but still within the range of requirements, but levels of the active substance was decreased around 52.82% -53.66%. The antibacterial activity of preparations ophthalmic gel showed that it was effective against the bacteria *Staphylococcus aureus*. Ophthalmic hydrogel formulas on the basis of carbomer combinations and HPMC were successfully made and the best formula was F4, which was a formula with a ratio of 1: 4.

Keywords: Ophthalmic hydrogel, chloramphenicol, carbomer, HPMC.

INTRODUCTION

The conventional ocular drug delivery system like eye drops, ointments, suspensions, encounters the drawback like increased precorneal elimination of the drug, poor bioavailability and therapeutic response, nasolacrimal drainage, blurred vision and needs more number of applications for instillation of drug. The various approaches that are tried to extend the bioavailability and therefore the period of the therapeutic action of ocular medication will be divided into 2 classes. The first one is predicated on the employment of sustained drug delivery systems, which give the controlled and continuous delivery of ophthalmic medication[1,2]. The second involves increasing membrane drug absorption and minimizing pre membrane drug loss. Ideal ophthalmic drug delivery should be able to sustain the drug unleash and to stay within the neck of the woods of front of the attention for prolong amount of your time. Consequently it is imperative to optimize ophthalmic drug delivery; one of the way to do so is by addition of polymers of various grades, development of hydrogel[2].

The polymers employed in liquid kind to boost the ocular bio availability of drug, to increase the viscosity of the preparation, to reduce the drainage route. Polymer hydration results in the relaxation of stretched; twisted macro molecules with exposes the adhesive sites. The high molecular weight polymers capable of forming

hydrogen bonds and cannot crosses the biological membrane can ultimately increase the residence time. About 1,00, 000 Da of molecular weight of polymer require for successful mucoadhesion. The cellulose derivatives are employed in the liquid dosage forms as viscosity enhancing ophthalmic vehicle. The hydroxyl propyl methyl cellulose (HPMC) and hydroxyl propyl cellulose (HPC) are ph-sensitive polymers also exhibit surface–active properties influencing the blinking rate with ultimately alters the elimination of the drug instilled. The poly (acrylic acid) (PAA) and corbomers were the first muco adhesives polymers and the protonated form at an acidic pH responsible for the mucoadhesion. The polyacrylates or corbomers are used in dry eye syndrome as artificial tears[3,4].

**Author for Correspondence: insan.sunan.kurniawansyah@unpad.ac.id*

Table 1: Formula of Hydrogel Ophthalmic Preparations.

Ingredients (%)	F1	F2	F3	F4
Chloramphenicol	0.5	0.5	0.5	0.5
Carbomer	0.1	-	0.05	0.025
HPMC	-	0.1	0.1	0.1
Propylene Glycol	15	15	15	15
Triethanolamin	1	1	1	1
aquadest	qs	qs	qs	qs
Phosphate buffer pH 7.4 add	100	100	100	100

Description:
F1 Hydrogel with 0.1% Carbomer
F2 Hydrogel with 0.1% HPMC
F3 Hydrogel with 0.05% Carbomer and 0.1% HPMC
F4 Hydrogel with 0.025% Carbomer and 0.1% HPMC

Table 2: Inspection result of melting point of Chloramphenicol.

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

Table 3: Chloramphenicol standard curve data by using ultraviolet spectrophotometry

Concentration (ppm)	Absorbance
2	0.2848
6	0.4022
10	0.5213
14	0.6304
18	0.7451

MATERIAL AND METHODS

Materials

Chloramphenicol (BioBasic©), hydroxypropyl methylcellulose (HPMC) (Colorcon®), carbopol, propylene glycol, propyl paraben (Merck®), triethanolamine (Merck®), potassium bromide (Merck®), Fluid Thioglycollate Media (Merck®), aqua bidestilata sterile (Ikapharmindo®), ethanol, potassium dihydrogen phosphate, *Staphylococcus aureus* (ATCC 29213), Mueller-Hinton Agar (Oxoid®), Tryptone Soya Broth (Oxiod®) and NaCl physiology.

Methods

Experimental laboratory was done with stages:

Preformulation Hydrogel

Examination of the active substances used (chloramphenicol) in accordance with the Indonesian Pharmacopoeia[5].

Melting Point Determination of Active Substance

The melting point of active substance were determined by the temperature at the time of chloramphenicol start to melt until become clear. Values obtained were compared with the Indonesian Pharmacopoeia[5].

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 done variety dilutions 2, 6, 10, 14, 18 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[6].

Compatibility Studies

The IR spectra of the pure drug (Chloramphenicol) was compared with IR spectrum of combination of Chloramphenicol and all the excipients to check the interaction using KBR pellets of 0.1 mm[7].

Formulations hidrogel ophthalmic preparations

Different formulations was prepared with a variety of HPMC according in Table 1.

Drug solution was added to the base while stirred. So that no foam was observed. Buffer solution was added to the formulation. Add 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 121^0C for 15 min[2,8].

Evaluation Chloramphenicol hydrogel ophthalmic preparations

Organoleptic examination

Organoleptic hydrogel checked by observing changes in color, odor and clarity visually and the observations made on the day-to-1, 3, 7, 14, 21 and 28.

pH measurement

pH measurement was performed on days 1, 3, 7, 14, 21 and 28.

Viscosity measurement

The viscosity measurements were done using Rion viscometer VT-04, using No.3 spindle. Measurements were taken during storage days 1, 3, 7, 14, 21 and 28.

Determination of chloramphenicol content in preparations

Chloramphenicol rate was determined by taking 0.1 ml formulation and diluted to 100 ml with phosphate buffer pH 7.4, then be measured at 280 nm using UV/Vis.

Sterility Test

Sterility test of preparation ophthalmic hydrogel was conducted using media FTM and media TSB. Aseptically, inoculated directly to each test preparation into a test tube FTM and TSB media and incubated at 30-35^0C and 20-25^0C for not less than 14 d. The occurrence of turbidity in a test tube was observed every day[5,8,9].

Antimicrobial Effectiveness Test

The test was performed by diffusion method in order for the storage days at 0, 1, 3, 5, 7, 14, 21, and 28 days. The chloramphenicol base was used as a comparison (standard)[10].

RESULTS AND DISCUSSIONS

Inspection result of melting point of Chloramphenicol

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

Standard curve of chloramphenicol

Chloramphenicol standard curve data by using ultraviolet spectrophotometry seen in Table 3. Using the Least Square equation and was obtained straight line equation as follows: $y = 0.0287x + 0.2296$

Compatibility Studies

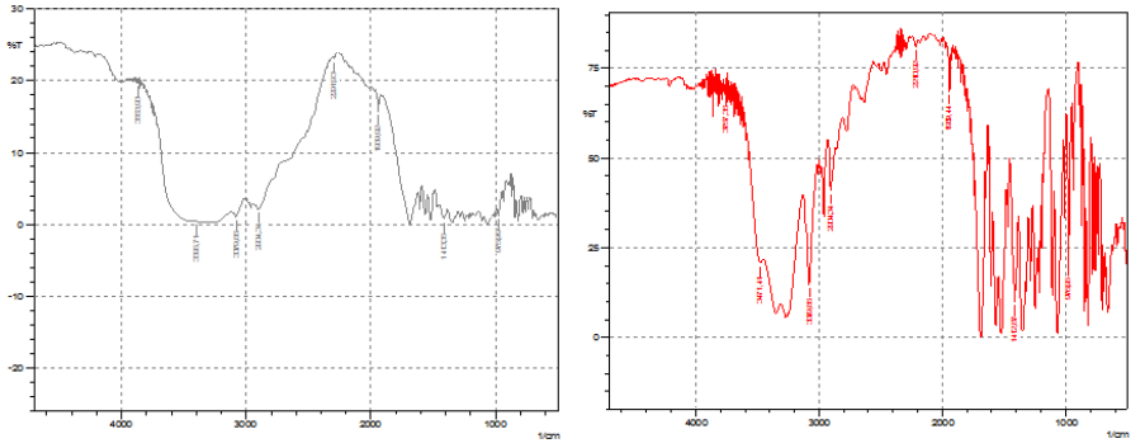

Figure 1: The infrared spectrum of chloramphenicol and the combination of chloramphenicol with HPMC and Carbomer (red colour).

Table 4: Absorption area of chloramphenicol functional group.

Functional group	Absorption area (cm^{-1})	Chloramphenicol	Chloramphenicol+HPMC+Carbomer
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 5: Evaluation of Chloramphenicol Hydrogel Ophthalmic.

Formula	Physical properties			Active Substance
	Organoleptic	pH	Viscosity (cps)	
1	Liquid, colorless, odorless	7.48	25	100 %
2	Liquid, colorless, odorless	7.58	98,5	100.07 %
3	Liquid, colorless, odorless	7.51	77	100.07 %
4	Liquid, colorless, odorless	7.49	55	100 %
Requirements				
Organoleptic	colorless, clear, odorless.[5]			
pH	Range 3.5 – 8.5.[5]			
Viscosity	Between 5 - 100 cps.[10,11]			
Active substance	Contains no less than 90% and no more than 130% of chloramphenicol.[5]			

Description:
F1 Hydrogel with 0.1% Carbomer
F2 Hydrogel with 0.1% HPMC
F3 Hydrogel with 0.05% Carbomer and 0.1% HPMC
F4 Hydrogel with 0.025% Carbomer and 0.1% HPMC

Table 6: Results of Measurement of Chloramphenicol Levels for 28 days of storage.

Time storage (day)	Actiive substance level (ppm)			
	F1	F2	F3	F4
1	5000	5003,48	5003,48	5000
3	4857,14	4874,56	4881,53	4860,63
7	4540,07	4533,10	4508,71	4515,68
14	3926,83	3811,85	3808,36	3818,82
21	2794,43	2770,03	2832,75	2801,39
28	2390,24	2358,89	2317,07	2386,76

The infrared spectrum of chloramphenicol, HPMC, and the combination of chloramphenicol with HPMC obtained can be seen in Figure 1 and Table 4.
The infrared spectrum of chloramphenicol, and the combination of chloramphenicol with HPMC and Carbomer obtained were shown in the Fig. 1 and Table 4. All of the characteristic peaks of Chloramphenicol were seen in the formulation graph so as to showed the suitability between the drug and the polymer. The

The results of the four pH measurements of the sterilized ophthalmic hydrogel dosage are shown in the chart below.

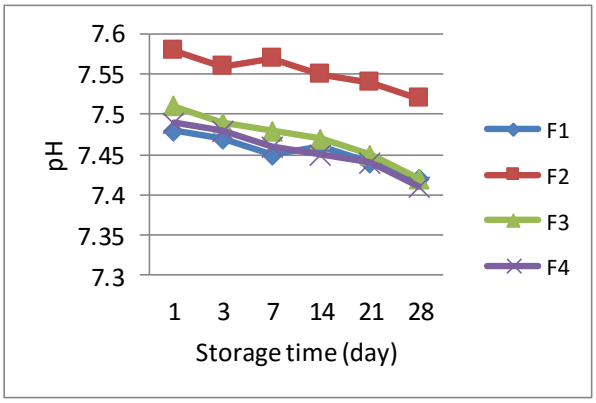

Figure 2. pH measurement results for 28 days of storage.

The results of the four viscosity measurements of the sterilized ophthalmic gel dosage are shown in the chart below.

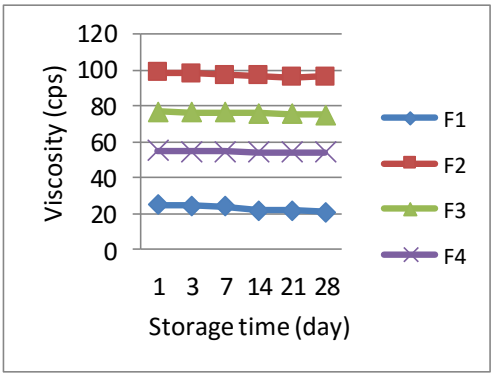

Figure 3. Viscosity measurement results for 28 days of storage.

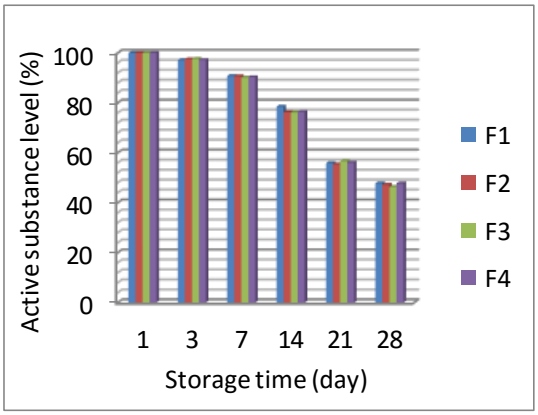

Figure 4. Decreasing Chloramphenicol Levels for 28 days of storage.

resulting spectrum confirms that there was no significant change in chemical integrity of the drug[7].

Ophthalmic hydrogel formulation

The ophthalmic hydrogel of Chloramphenicol were prepared by autoclaving technique and under aseptic condition, characterized on organoleptic and physicochemical characteristics, sterility testing, and antibacterial effectiveness studies. The physicochemical characteristics of different formulations are shown in Table Fig. 2 showed that the ophthalmic gel dosage underwent a pH change, either increase or decrease over 28 days of storage. Changes in pH occur in each formula was not too significant, which is only about 0.01-0.03 every week. The pH changes that occur still met the requirement of eye preparation, and it is safe to use.

From Table 5 and Fig. 3 of measurement of gel viscosity during the storage period, it is known that all formulas tend to decrease viscosity for 28 days of storage. Decreasing viscosity can be caused by storage environment conditions such as air humidity, packaging that is less impermeable can cause water vapor to increase the volume of water in the gel.

The evaluation of chloramphenicol opthalmic hydrogel was conducted to knew the changing of physical or chemical in the preparations may occur during storage, which would affect the stability and activity of the opthalmic hydrogel preparations. Physical observation preparations was done on day 1, 3, 5, 7, 14, 21 and 28. The results of evaluation can be seen in Table 5. Its showed that the preparation was clear, colorless, odorless. Accordingly, pH test results evaluation of preparation demonstrated during 28 days of storage at room temperature were meets the requirements of the pH material of opthalmic hydrogel i.e. 3.5-8.5[5]. Nevertheless the viscosity showed that the preparation was meeting the requirements i.e. 5-100 cps[10,11].

Evaluation of the ophthalmic gel preparation was also carried out on the levels of the active substances in the gel preparation using UV spectrophotometry. Analysis of the levels of this active substance was carried out for 28 days of storage. The results of measuring the fourth level of the ophthalmic gel preparation formula can be seen in Table 6

Decreasing levels in the form of percentages can be seen in the following figure 4:

From Table 6 and Fig 4 it can be seen that there was a decrease in chloramphenicol levels in ophthalmic gel preparations for 28 days of storage. The level dropped dramatically after the 7th day's storage. At the 7th day storage, chloramphenicol levels decreased by 9.2% - 9.83%, on the 14th day the levels decreased almost reaching 21.46% - 23.83%, on the 21st day the grade decreased gel almost reached 44.35% - 44.6%, and on the 28th day the preparations had decreased chloramphenicol levels by 52.82% - 53.66%. Decreased levels may be caused by the use of phosphate buffers, in the use of phosphate buffers, where the rate of reaction does not depend on the concentration of reactants but is influenced by the presence of other factors such as catalysts. the decomposition is affected by the catalyst. In addition, decreasing levels may be caused by the use of preservatives that are not suitable.

Sterility Testing

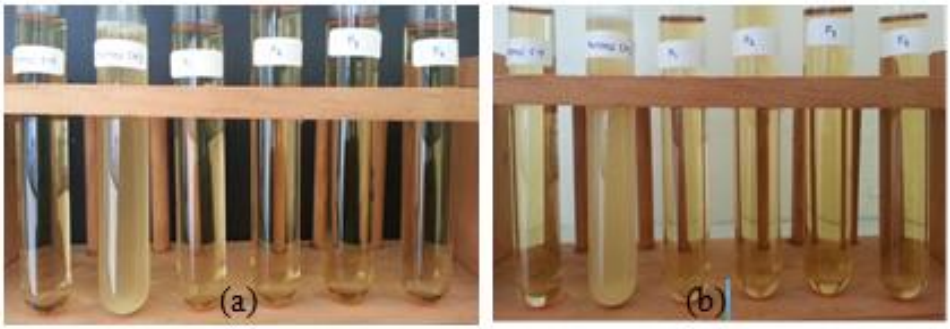

Figure 5: Sterility Test Results (a: FTM Media) (b: TSB Media)

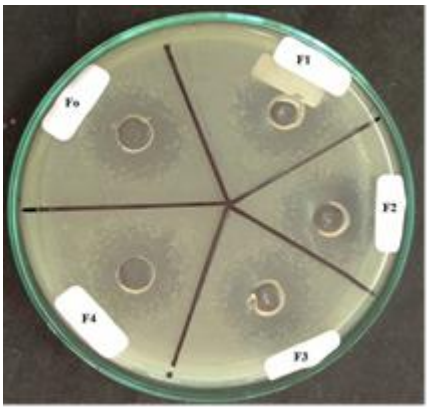

Figure 6: Test result antibacterial activity of ophthalmic hydrogel dosage.

The results of sterility examination of hydrogel preparations carried out for fourteen days can be seen in Figure 5. From Fig. 5 it can be seen that in the whole ophthalmic gel formula there is no growth of bacteria or fungi. This means that the whole formula meets the requirements of sterility, which is free from microbes that have life force. So aseptic formulations and autoclave sterilization methods can be used to make ophthalmic gel formulas that are in accordance with sterility requirements.

Antibacterial activity

Activity testing carried out against the *Staphylococcus aureus* bacteria aims to determine the effectiveness of the ophthalmic gel dosage that has been made. The results can be seen in Figure 6.

The results obtained were only a qualitative limit to prove that the preparations that have been made still provide inhibitory activity to the growth of bacteria. From these results it is possible that the ophthalmic hydrogel preparations that have been made and stored within the 28-day retention period still provide antibacterial activity[12].

CONCLUSION

Ophthalmic hydrogel formulas on the basis of carbomer combinations and HPMC are successfully made and the best formula is F4, which is a formula with a ratio of 1: 4. Based on the evaluation carried out during 28 days of storage, there was a decrease in pH and viscosity but still within the range of requirements. Hydrogel meets the requirements of sterility, and provides good antibacterial activity, but the levels of active substances are unstable, decreased by 52.82% -53.66%.

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