ORIGINAL ARTICLE

Factors affecting on *in vitro* release of miconazole from *in situ* ocular gel

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ABSTRACT

The reason for conducting this study is to prolong release of miconazole in the ocular site of action by ocular-based gels (OBGs) formulations. The formulation factors affecting on the release from OBG should be studied using various gelling agents in various concentrations to achieve the improvement in retention and residence time in response to prolonged release. In this study, the formulations were prepared using carbopol 940, pectin, sodium alginate, poloxamer 407, and poly(methacrylic acid) at 0.5%, 1%, and 1.5% w/v, respectively. Hydroxypropyl methylcellulose E5 (HPMC E5) 1% was added as thickening agent/viscosity builder. The formulation containing carbopol 940, pectin and sodium alginate at 1.5% w/v, displayed a noticable improvement in viscosity, gelling capacity, and extended release for 7 h in comparison with the reference drug. Overall, the release showed that the sodium alginate with HPMC E5 form *in situ* gel which had longer time of release reach to 12 h compared with other polymers. the release of miconazole from the OBGs affected significantly by two factors includes gelling capacity and viscosity builder. The novelty of this study is supporting the delivery of ocular drugs through a cornea as an important key of the eye instead of dependence on an internal blood supply using an oral or a parental administration.

Key words: Gelling capacity, *in situ* gels and sodium alginate, miconazole, ocular, poloxamer 407

INTRODUCTION

It is an important to mention that the entry of drugs from internal blood supply to the eye is limited by the blood–retinal barrier. Therefore, cornea can be considered as the main route of entry of ocular drugs to the site of action unless blinking and drainage conflict with entry of administered drugs. Many ocular products such as liquids (solutions and suspensions) or ointment and conventional gelled products have been used in cases such as conjunctivitis, allergy, glaucoma, and corneal ulceration.[1] Moreover, viscous *in situ* formulations can be used in ocular delivery instead of conventional forms to reduce the loss of the drugs and enhance precorneal retention which obtained by prolong drug release due to the formation of gel after administration. They undergo sol-to-gel phase transition as contact with the site of administration depending on their sensitivity to change in the temperature and pH and increase their viscosity. In addition to that, the viscosity of the *in situ* sol increases with contact to the ions available naturally in the lacrimal fluids. In detail, the polymeric solutions can crosslink with the monovalent and divalent cations of the tear fluid.[2] Miconazole is water insoluble drug for this reason, β-cyclodextrin (β-CD) was used in

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this study as carrier. β-CD can be considered as water soluble complex because of its semi-cyclic hydrophilic outer margins with an interior lipophilic center. They can carry poorly water soluble drugs in the interior center, thus it can also deliver irritant drugs more safely as they are not presence in free form but caught in the center of carrier/complex.[1] In this study, different ocular *in situ* gels were formulated containing cyclodextrin-miconazole (1%w/w) complex with different type of polymers or gelling agents include carbopol 940, pectin, sodium alginate, poloxamer 407 and poly(methacrylic acid) (PMA) in three percentages (0.5, 1, and 1.5%) w/v. The aim of this study is to investigate the effects of types of polymers and their percentages on gelling of miconazole and release ocular-based gels (OBGs).

MATERIALS

Miconazole, β-CD and sodium alginate were obtained from Sigma-Aldrich Pvt. Hydroxypropyl methylcellulose (HPMC K15), sodium alginate, pectin, and benzalkonium chloride (Himedia, India). Sodium chloride acid was from Kelong (China).

METHODS

Preparation of ocular-based gels

Polymers solutions (carbopol 940, pectin, sodium alginate, poloxamer 407 and PMA) were prepared as *in situ* gels in three percentages 0.5%, 1%, and 1.5% (w/v), as shown in Table 1. Alginates gels were prepared by gently adding alginates to 75 ml cold distilled water. Then, the mixture was agitated by stirrer for 10 min. The resultant mixture was kept at 4°C overnight to ensure complete dissolution.[3,4] Pectins gels were prepared by dissolving pectins in 75 ml of pH 7.4 buffer and agitated by stirring unceasingly until a clear solution were obtained and allowed to hydrate overnight.[5] The formulations of carbopols and poloxamers were equipped by adding them into 75 ml preheated 70°C distilled water with slow agitation by stirrer to inhibit the appearance of foam in case of poloxamers. HPMCE5 was added in combined with polymers for formulation containing viscosity builders see composition in Table 1.

On other hand, miconazole (1% w/v) was solubilized in the distilled water containing 1% w/v of β-CD after that added into previously prepared polymeric solutions. In addition to solution of miconazole, benzalkonium chloride and sodium chloride were added to polymeric solutions. Finally, the volumes were completed to 100 mL, and then, the resultant solution was filtered.[6-9] The viscosity of the formulations was evaluated after gelling at 25°C using a Brookfield Viscometer at 60 rpm rotational speed.[10]

Evaluation of ocular based gel formulations

Visual clearness and appearance

All prepared formulations were assessed for clearness by visual appearance against a black and white background.[11]

Gelling capacity

Gelling capacity was assessed by adding a drop of a formula into a flask containing 2 ml of the simulated tear fluid (STF) at 35 ± 1°C. The optical observations of gelation were determined with time.(+) Gelation continue for short time

Table 1: Compositions of ocular-based gel formulations

Formula codes	Cyclodextrin miconazle (1:1) w/v %	Carbopol 940 (w/v %)	Pectin (w/v %)	Sodium alginate (w/v %)	Poloxamer 407 (w/v %)	PMA (w/v %)	HPMC E50 (w/v %)
F1	1	0.5					
F2	1		0.5				
F3	1			0.5			
F4	1				0.5		
F5	1					0.5	
F6	1	1					
F7	1		1				
F8	1			1			
F9	1				1		
F10	1					1	
F11	1	1.5					
F12	1		1.5				
F13	1			1.5			
F14	1				1.5		
F15	1					1.5	
F16	1	1					1
F17	1		1				1
F18	1			1			
F19	1				1		1

HPMC: Hydroxypropyl methylcellulose, PMA: Poly(methacrylic acid)

and re-disperse quickly.(++) Gelation continue for <8 h then re-disperse.(+++) Gelation continue for 8 h.[12]

The pH measurement

The pH was detected for all formulations using an instrument of pH measurement.[13]

Content of drug

Using 1 ml of each formulation which was dissolved in pH 7.4 phosphate buffer to analyze the content of miconazole.[14]

Dissolution study

The release was studied using a dialysis membrane. First, the membrane (molecular weight cut-off 12000–14000 Da) was set aside overnight in the buffer. After that, the membrane was fitted as a bag and filled with 1 mL of formula and 0.5 mL of STF. The fitted bag was dipped in a media of 100 mL of phosphate buffer pH 7.4 placed in a beaker. Then, the media was shacked in water bath at 37°C. Finally, the samples of 2 ml were measured at 1, 2, 3, 4, 5, 6,7,9,10,11 and 12 h and substituted the media to maintain the sink conditions.[6] The samples were investigated using ultraviolet-visible spectrophotometer at 284 nm.[15]

Statistical analysis

The results viscosity and drug contents are obtained as mean ± SD. The percentage of drug release was analyzed statistically by (ANOVA) to investigate the significance of the results ($P < 0.05$).

RESULTS AND DISCUSSION

The polymers which sensitive to temperature characterized with a gel-sol transition temperature higher than the room temperature such as poloxamer 407. The polymers have acidic or basic groups that receive or donate protons undergo the transition with change of pH such as carbopol and carbomer.[16,17] If pH value is beyond 4–8, the patient has irritation associated with tearing, subsequently the administered drug was lost as a result of increased tearing in response to the irritation.[18] The pH measurements were in range of 5–7. Therefore, all formulations were safe as well as had no irritation Table 2. The ideal viscosity was required to reach rapid sol to gel transition.[19,20] Table 3 summarizes the gelling of all formulations which improved by increasing the percentages of the polymers.

The concentration of carpobol 940 alone 1% and 1.5 (w/v) showed moderate/or adequate gelling (++) in F6 and F11, respectively. Furthermore, that for combination formula F16 containing viscosity builder HPMC 1% with carbopol 1% showed significant gelling (+++). Whereas, the concentration of carbopol 0.5% had low gelling capacity for formula F1 in which gels rapidly formed and continued for few minutes (+). Therefore, the gelling ability improves by increasing percentages of polymers. The OBG formed

Table 2: Physicochemical properties of ocular-based gel formulations

Formulation	Clarity	pH	Drug content
F1	Transparence and clear	6	99%±0.7
F2	Transparence and clear	5.5	98%±0.9
F3	Transparence and clear	6.5	97%±0.1
F4	Transparence and clear	7.1	99%±0.10
F5	Transparence and clear	6.4	99%±0.2
F6	Transparence and clear	6.02	98%±0.2
F7	Transparence and clear	5.7	99%±0.3
F8	Transparence and clear	6.5	98%±0.2
F9	Transparence and clear	6.8	97%±0.15
F10	Transparence and clear	6.7	97%±0.76
F11	Transparence and clear	6	98%±0.2
F12	Transparence and clear	5.8	98%±0.3
F13	Transparence and clear	6.5	99%±0.1
F14	Transparence and clear	6.9	97%±0.20
F15	Transparence and clear	6.7	98%±0.3
F16	Transparence and clear	6.03	99%±0.4
F17	Transparence and clear	6.3	98%±0.5
F18	Transparence and clear	6.5	99%±0.6

with pectin alone (F2, F7 and F12) at concentrations 0.5%. 1% and 1.5%, respectively, continued for 10 min but the addition of HPMC (1%) as viscosity builder to 1% pectin enhanced the gelling time F17 (+++) for more than 8 h. The concentrations of sodium alginate alone 0.5% and 1% (w/v) showed low gelling (+) for F3 and F8, respectively. The gels formed with poloxamer alone (F4, F9 and F14) at concentrations 0.5%, 1% and 1.5%, respectively showed no gelation (-). Itis a distinguished that the main shortcoming of poloxamer 407 alone had low mucoadhesive and gelling tendency. In addition, using poloxamer 407 may cause hypertriglyceridemia in the eye. So that, the addition of HPMC can minimize the amount of poloxamer 407 required to form OBG.[21] Thereby, HPMC (1%) as viscosity builder in was added in combination with 1% poloxamer 407 in this study and showed gelling for few minutes F19 (+), whereas in combination with sodium alginate in same concentration showed significant enhancement in gelling ability F18 (+++). The gelation was not obtained by PMA at different concentration (0.5%, 1% and 1.5%) used for formulation of F5, F10 and F15 because this type of polymer may be used as blends with polyethylene glycol to get gelling.[2] Over all, the formulation containing poloxamer 407 and PMA had no gelling capacity F4, F5, F9, F10, F14 and F15 (-) were excluded from the release study. The polymers and concentrations which showed gelling for more than 8 h were selected to investigate the formulations factors affecting on miconazole from OBG. Therefore, the formulations (F1, F2, and F3), respectively, containing carbopol 940, pectin and sodium alginate in 1.5% concentration were used for *in vitro* release study. In addition to the extended gelling time, the concentration of 1.5% of these polymers showed enhanced viscosity in comparison with the other

Table 3: Evaluations of ocular-based gel formulations

Formula codes	Carbopol 940 (w/v %)	Pectin (w/v %)	Sodium alginate (w/v %)	Poloxamer 407 (w/v %)	PMA (w/v %)	HPMC E50 (w/v %)	Gelation capacity	Viscosity (cP)
F1	0.5						+	77±0.5
F2		0.5					+	102±0.8
F3			0.5				+	51±0.2
F4				0.5			−	
F5					0.5		−	
F6	1						++	146±0.6
F7		1					+	211±3
F8			1				+	108±0.7
F9				1			−	
F10					1		−	
F11	1.5						++	278±2
F12		1.5					++	298±3
F13			1.5				++	263±1
F14				1.5			−	
F15					1.5		−	
F16	1					1	+++	341±6
F17		1				1	+++	370±2
F18			1			1	+++	320±0.7

+: Rapidly gelling and continue for few minutes, ++: Gelling and continue for few hours, +++: Gelling and continue for >8 h, −: No gelation. HPMC: Hydroxypropyl methylcellulose, PMA: Poly(methacrylic acid)

concentrations [Table 3]. Consequently, the two main factors affecting on formulation of ocular gelling systems and its release are viscosity and gelling capacity. The gelling time can be enhanced significantly as consequences of increase in viscosity by combining two polymers (F16–F18) Table 3.

Gel strengths can be increased using moderate concentration of polymers 1% with the addition of HPMC E5 in same concentration 1%. It is an important to mention that viscous sols would lessen the outflow of formulations from the eye, thus reduce loss of administered drug. This enhancement in viscosity would be obtained by previous studies which give the reasons of this to cross-links between the polymers and HPMC E5.[22-25]

The formation of viscous gel with high gelling capacity might be due to hydrophobic constituent of polymers pectins, carbopols, and alginates which exhibit moderate gelling (++) when used alone. Furthermore, they formed firm backbone recording high gelling capacity (+++) in combination formulations F16, F17, and F18 with HPMC. Furthermore, the ionization of functional groups might cause a strong repulsion along the functional group of these polymers and the subsequent extension of polymeric backbone.

The gels with favorite concentration (1.5%), viscosity, and adequate gelling capacity (++) were selected to *in vitro* release study as shown in Figure 1. The miconazole alone released about 100% within 2 h.

The selected viscous gels F11, F12 and F13 released 88%, 70% and 100% of drug within 7 h, respectively Figure 1. These

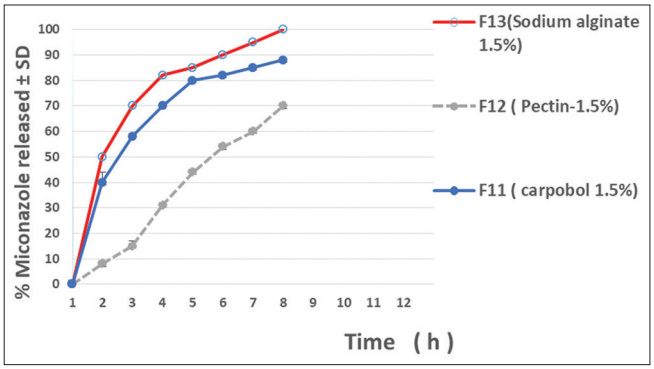

Figure 1: The effect of types of gelling agent on Miconazole release from ocular-based gel formulations

formulations had same concentration of polymers (1.5%) but the types were varied using carbopol, pectin, and sodium alginate, respectively. The release with prolonged period of time, obtained with F18 may be to the absence of erosion which usually has a role in rapid release from formulations, as shown in Figure 2. The formulation F18 and F13 contained same amount of sodium alginate (1.5%w/v) but in F18, HPMC E5 was added to increase gelling capacity from (++) to (+++). Sodium alginate contains carboxyl and hydroxyl groups that form cross linking with increasing in the polymer concentration and presence of HPMC, resulting in strength the backbone of *in situ* gel.[26,27]

CONCLUSION

In the current study, the optimum polymer was sodium alginate at concentration of 1.5% (w/v) with gelling

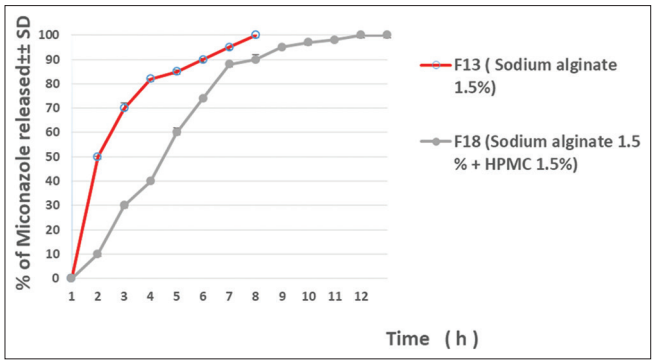

Figure 2: The effect of adding viscosity builder hydroxypropyl methylcellulose E5 on *in vitro* miconazole release

capacity (++) and prolonged release for 7 h. When 1% w/v of HPMCE5 was added as viscosity builder, the prolonged in release was significantly reaching 12 h with gelling capacity (+++).

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Conflicts of interest

There are no conflicts of interest.

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