WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 6, 667-678. Research Article ISSN 2277– 7105

FORMULATION AND EVALUATION OF PHASE CHANGE SOLUTION BY USING DIFFERENT TRIGGERING MECAHNISM FOR OPHTHALMIC GEL

Deepak G. Wagh*, Dr. Sadhana R. Shahi, Mangesh Kahane, Priyanka D. Dabir, Sagar Patil

Department of pharmaceutics, Government College of Pharmacy, Opp. Govt. Polytechnic, Osmanpura, Aurangabad, Maharashtra, India.

Article Received on
23 March. 2017,

Revised on 13 April. 2017,
Accepted on 03 May. 2017

DOI:10.20959/wjpr20176-8418

***Corresponding Author**
Deepak Wagh
Department of pharmaceutics, Government College of Pharmacy, Opp. Govt. Polytechnic, Osmanpura, Aurangabad, Maharashtra, India.

ABSTRACT

The optimal drug concentration required at the site of action for the ocular treatment cannot be attained mainly due to precorneal drug loss; tear turn over, solution drainage by gravity and naso-lachrymal drainage. The purpose of present work was to overcome these problems by developing an in situ gel forming systems. Major progress has been made recently in ophthalmic drug delivery systems in the form of improved levels of patient acceptance and more specifically development of droppable gels (in situ forming gels).The droppable gels are liquid upon instillation and they undergo a phase transition in the ocular cul de sac to form a viscoelastic gel and this provides a response to environmental changes. Parameters that can change and trigger the phase transition of droppable gels include pH, temperature and ionic strength. In addition to this combination system also reported. Three methods have been employed to cause phase transition on the surface because of change in temperature, pH and ion composition.[1]

KEYWORDS: *In situ* ophthalmic gel, Nepafenac, Gelrite, Ion sensitive gelling system, HPMC E 50LV, Xanthan gum.

INTRODUCTION

Ocular drug delivery has remained as one of the most challenging task for pharmaceutical scientists. The unique structure of the eye restricts the entry of drug molecules at the required

site of action. Topical application of drugs to the eye is the most popular and well-accepted route of administration for the treatment of various eye disorders. The challenge to the formulator is to circumvent the protective barriers of the eye without causing permanent tissue damage.[2]

Conventional systems like eye drops, suspensions and ointments cannot be considered optimal in the treatment of vision threatening ocular diseases. However, more than 90% of the marketed ophthalmic formulations are in the form of eye drops. These formulations mainly target the anterior segment eye diseases. Most of the topically applied drugs are washed off from the eye by various mechanisms (lacrimation, tear dilution and tear turnover) resulting in low ocular bioavailability of drugs. Moreover, human cornea comprising of epithelium, substantia propria and endothelium also restricts the ocular entry of drug molecules. As a result of these factors less than 5% of administered drug enters the eye. The bioavailability of ophthalmic drugs is, however, very poor due to efficient protective mechanisms of the eye. Blinking, baseline and reflex lachrymation, and drainage remove rapidly foreign substances, including drugs, from the surface of the eye. Moreover, the anatomy, physiology and barrier function of the cornea compromise the rapid absorption of drugs[2]

A considerable amount of effort has been made in ophthalmic drug delivery since the 1970s.The various approaches attempted in the early stages can be divided into two main categories: bioavailability improvement and controlled release drug delivery.

An ideal ophthalmic drug delivery system should possess following characteristics,

1. A good corneal penetration.
2. A prolonged contact time with corneal tissue.
3. Simplicity of instillation for the patient. [2-3]

This novel drug delivery system promotes the ease and convenience of administration, deliverance of accurate dose as well as to prolong residence time of drug in contact with mucosa, that problems generally encountered in semisolid dosage forms.[2-4] *In situ* gel formation occurs due to one or combination of different stimuli like pH change, temperature modulation and solvent exchange. Smart polymeric systems represent promising means of delivering the drugs; these polymers undergo sol-gel transition, once administered.[3,4] *In situ*

forming gels are liquid upon instillation and undergo phase transition in the ocular cul-de-sac to form viscoelastic gel and this provides a response to environmental changes.[4]

MATERIALS AND METHOD

Nepafenac was received as gift sample from Ajanta Pharma Ltd Mumbai, Gellan gum, Sodium alginate, Pluronic F-127, Hydroxyethylcellulose and Hypromellose METHOCEL E 50 LV, Carbopol-940, were procured as gift samples from Signet and Dow chemical, Mumbai. Benzalkonium Chloride, mannitol, gift sample from Merck

All other reagents and chemicals used of analytical grade.

EXPERIMENTAL

IA. Phase transition solution of nepafenac based on ion sensitive mechanism (Gellan gum)

Gellan gum which is known to undergo transition from sol to gel in the presence of captions present in tear fluid (Ca^{2+}, Na^{+}) was used in different concentration to form *in situ* gelling ophthalmic solutions of Nepafenac.[5]

Preparation of solution A

Accurately weighed quantity of SBE-β-cyclodextrin was dissolved in 30 ml deionized water followed by the addition of accurately weighed quantity of nepafenac. The mannitol, Boric acid and Benzalkonium chloride was added to above mixture with continuous stirring.

Preparation of solution B

The Gellan gum were sprinkled over 50 ml of boiling water and was allowed to hydrate for 15 min to produce a clear solution.

Compounding of ophthalmic solution

The solution B was mixed slowly to solution A with continuous mechanical stirring to produce clear and transparent solution. The pH of formulation was checked and adjusted with 0.1 N NaOH and volume was made up with deionized water to 100ml.

Sterilization /Filtration of ophthalmic formulation

The final formulation was sterilized by autoclaving at 121°C for 15 min or by filtration through 0.22µ PVDF filter 47mm (make: Millipore).

RESULTS AND DISCUSSION

1 *Characteristics of individual polymers for in situ gelling ophthalmic formulations*

Gelling ability of ophthalmic formulations prepared using individual polymers i.e., sodium alginate, gellan gum and poloxamer 407 is found to be dependent on both the type and the concentration of the gelling polymers. The range of individual polymer concentration was selected as per literature. It was observed that gellan gum showed gelling ability in very less concentration (> 0.5%) while sodium alginate required 1-2 % concentration. In case of poloxamer 407, unlike the gellan gum and sodium alginate, the concentration required to form satisfactory gels is much higher (more than 16%).

Table 1: *In situ* gelling ophthalmic formulations of Nepafenac using gellan gum

Code	Drug (% w/v)	Gellan gum (%w/v)	Mannitol (%w/v)	Boric acid (%w/v)	Benzalkonium chloride (%w/v)	Double Distilled water
G1	0.3	0.1	5	0.3	0.01	q. s. up to 100 ml
G2	0.3	0.2	5	0.3	0.01	
G3	0.3	0.3	5	0.3	0.01	
G4	0.3	0.4	5	0.3	0.01	
G5	0.3	0.5	5	0.3	0.01	

Table 2: *In situ* gelling ophthalmic formulations of Nepafenac using gellan gum and various viscosity modifiers

Code*	Drug (%w/v)	Gellan gum (%w/v)	HEC (%w/v)	Methocel E50 LV (%w/v)	Carbopol (%w/v)	Xanthan Gum (%w/v)	Double Distilled water
GE1	0.3	0.5	0.1	-	-	-	q.s up to 100 ml
GE2	0.3	0.5	0.2	-	-	-	
GE3	0.3	0.5	0.3	-	-	-	
GM1	0.3	0.5	-	0.2	-	-	
GM2	0.3	0.5	-	0.4	-	-	
GM3	0.3	0.5	-	0.6	-	-	
GC1	0.3	0.5	-	-	0.1	-	
GC2	0.3	0.5	-	-	0.2	-	
GC3	0.3	0.5	-	-	0.3	-	
GX1	0.3	0.5	-	-	-	0.1	
GX2	0.3	0.5	-	-	-	0.2	
GX3	0.3	0.5	-	-	-	0.3	

*each formulation contains 5 %w/v mannitol ,boric acid 0.3% and 0.01 %w/v Benzalkonium chloride

IB. Phase transition solution of nepafenac based on ion sensitive mechanism (sodium alginate)

Preparation of solution A

Accurately weighed quantity of SBE-β-cyclodextrin was dissolved in 30 ml deionized water followed by the addition of accurately weighed quantity of nepafenac. The mannitol, Boric acid and Benzalkonium chloride was added to above mixture with continuous stirring.

Preparation of solution B

The sodium alginate were sprinkled over 50 ml of boiling water and was allowed to hydrate for 15 min to produce a clear solution.

Compounding of ophthalmic solution

The solution B was mixed slowly to solution A with continuous mechanical stirring to produce clear and transparent solution. The pH of formulation was checked and adjusted with 0.1 N NaOH and volume was made up with deionized water to 100ml.

Sterilization /Filtration of ophthalmic formulation

The final formulation was sterilized by autoclaving at 121°C for 15 min or by filtration through 0.22µ PVDF filter 47mm (make: Millipore)

Table 3: *In situ* gelling ophthalmic formulations of Nepafenac using sodium alginate

Code	Drug (% w/v)	Sodium alginate (%w/v)	Mannitol (%w/v)	Boric acid (%w/v)	Benzalkonium chloride(%w/v)	Double Distilled water
S1	0.3	0.5%	5	0.3	0.01	q.s. to 100ml
S2	0.3	1%	5	0.3	0.01	
S3	0.3	1.5%	5	0.3	0.01	
S4	0.3	2%	5	0.3	0.01	
S5	0.3	2.5%	5	0.3	0.01	

Table 4: *In situ* gelling ophthalmic formulations of Nepafenac using sodium alginate and various viscosity modifiers

Code	Drug (%w/v)	Sodium alginate (%w/v)	HEC (%w/v)	Methocel E50 LV (%w/v)	Carbopol 940 (%w/v)	Xanthan Gum (%w/v)	Double Distilled water
SE1	0.3	2	0.1	-	-	-	q.s to 100ml
SE2	0.3	2	0.2	-	-	-	
SE3	0.3	2	0.3	-	-	-	
SM1	0.3	2	-	0.2	-	-	
SM2	0.3	2	-	0.4	-	-	
SM3	0.3	2	-	0.6	-	-	
SC1	0.3	2	-	-	0.1	-	

SC2	0.3	2	-	-	0.2	-	
SC3	0.3	2	-	-	0.3	-	
SX1	0.3	2	-	-	-	0.1	
SX2	0.3	2	-	-	-	0.2	
SX3	0.3	2	-	-	-	0.3	

*each formulation contains 5 %w/v mannitol ,Boric acid 0.3% and 0.01 %w/v Benzalkonium chloride

II. *Phase transition solution of nepafenac based on Temperature sensitive mechanism(poloxamer 407)*

Poloxamer which is known to undergo transition from sol to gel at the physiological temperature (35-37°C) was used in different concentration to form *in situ* gelling ophthalmic solutions of brimonidine tartrate.[6]

Table 5: *In situ* gelling ophthalmic formulations of Nepafenac using poloxamer 407

Code	Drug (% w/v)	Poloxamer (%w/v)	Mannitol (%w/v)	Boric acid (%w/v)	Benzalkonium chloride(%w/v)	Double Distilled water
P1	0.3	14	5	0.3	0.01	q.s. to 100 ml
P2	0.3	16	5	0.3	0.01	
P3	0.3	18	5	0.3	0.01	
P4	0.3	20	5	0.3	0.01	
P5	0.3	22	5	0.3	0.01	

Table 6: *In situ* gelling ophthalmic formulations of Nepafenac using poloxamer and various viscosity modifiers

Code	Drug (%w/v)	Poloxamer (%w/v)	HEC (%w/v)	Methocel E50 LV (%w/v)	Carbo pol 940 (%w/v)	Xanthan Gum (%w/v)	Double Distilled water
PE1	0.3	18	0.1	-	-	-	q.s. to 100 ml
PE2	0.3	18	0.2	-	-	-	
PE3	0.3	18	0.3	-	-	-	
PM1	0.3	18	-	0.2	-	-	
PM2	0.3	18	-	0.4	-	-	
PM3	0.3	18	-	0.6	-	-	
PC1	0.3	18	-	-	0.1	-	
PC2	0.3	18	-	-	0.2	-	
PC3	0.15	18	-	-	0.3	-	
PX1	0.15	18	-	-	-	0.1	
PX2	0.15	18	-	-	-	0.2	
PX3	0.15	18	-	-	-	0.3	

*each formulation contains 5 %w/v mannitol, Boric acid 3% and 0.01 %w/v Benzalkonium chloride

1.1 ***Physical characteristics of ophthalmic formulations prepared with the individual polymer***

Table 7: Physical characteristics of ophthalmic formulations prepared with gellan gum

Code	Drug (% w/v)	Gellan gum	Appearance and clarity	Ph	Osmolality	Gelling ability
G1	0.15	0.1	+++	6.42	271	-
G2	0.15	0.2	+++	6.62	276	++
G3	0.15	0.3	+++	6.65	288	+++
G4	0.15	0.4	+++	6.75	292	+++
G5	0.15	0.5	+++	6.83	311	+++

Table 8: Physical characteristics of ophthalmic formulations prepared with gellan gum and with viscosity modifier

Code	Appearance & clarity	pH	Gelling ability
G3	+++	6.65	+++
GE1	+++	6.72	+++
GE2	+++	6.75	+++
GE3	+++	6.79	+++
GM1	+++	6.74	+++
GM2	+++	6.80	+++
GM3	+++	6.85	+++
GC1	+	4.28	+++
GC2	+	4.23	+++
GC3	+	4.19	+++
GX1	++	6.66	+++
GX2	++	6.73	+++
GX3	++	6.79	+++

Clarity

(-) Turbid

(+) Slightly turbid

(++) Clear solution

(+++) Clear and transparent

Formulations with gellan gum in polymer concentration 0.3% w/v and viscosity modifiers i.e. Hydroxyethylcellulose, xanthan gum in concentration 0.1% to 0.3% and Methocel E50 LV in concentration 0.2%,0.4%,0.6% were found to be clear. The carbopol formulations GC1, GC2, GC3 were found to be slightly turbid, this is because carbopol at lower pH shows hazy appearance. The gelling ability of the selected formulations was also having phase transition

behavior within 60 seconds and had stable gel structure. pH of all the formulations were in the range of 4.19-6.85.

The plain gellan gum formulation (G3) gels showed moderate mucoadhesive property because of anionic nature. By addition of HPMC polymers (HEC, Methocel E50 LV) in gellan gum, there was marginal increase in mucoadhesive property. While addition of carbopol and xanthan gum showed increase in mucoadhesive property because of anionic nature of both polymers, free COOH group in these polymers forms hydrogen bonds with mucin. As concentration of mucoadhesive polymer increased there was increase in mucoadhesive property.

Gelling ability

(-) No phase transition

(+) Phase transition after 60 sec, collapse of gel structure within 1-2 hrs

(++) Phase transition after 60 sec, collapse of gel structure within 3-4 hrs

(+++) Phase transition within 60 sec and gel structure stable for more than 6 hrs

1.2 Appearance*/ clarity*

The formulations were found to be clear. All the formulations were free from any suspended particulate matter when observed carefully against a dark and white background.

1.3 *pH of ophthalmic formulations*

pH of the ophthalmic formulations prepared using gellan gum as gelling agent ranged between 6.42-6.83. These pH values are considered to be acceptable since the ophthalmic pH ranges between 4.4 –7.4. Hence, no discomfort excessive tear flux may occur on installation.

The appearances of formulations containing gellan gum in varying concentrations, 0.1% to 0.5% w/v were found to be clear. The formulation G1 was not forming gel at 37^{o}C in STF. The formulation G2 required more time to form gel in STF. Also formulations G4, G5 were very thick solution and forms gel immediately in STF. The formulation G3 has good clarity and gelling property. So among all the formulations, G3 was selected for further studies.

1.4 Osmolality of Ophthalmic *formulations*

Osmolality of ophthalmic formulation prepared by using all triggering mechanism ranged between 260-320 mOsm/Kg. it should be matching with tear lacrimal fluid to avoid the irritation

Table 9: Physical characteristics of ophthalmic formulations prepared with sodium alginate

Code	Drug (% w/v)	Sodium alginate (%w/v)	Appearance and clarity	pH	Osmolality	Gelling ability
S1	0.15	0.5	++	6.18	270	-
S2	0.15	1	++	6.57	275	++
S3	0.15	1.5	++	6.86	280	++
S4	0.15	2	++	6.80	290	+++
S5	0.15	2.5	-	6.94	310	+++

Table 10: Physical characteristics of ophthalmic formulations prepared with sodium alginate and viscosity modifier

Code	Appearance & clarity	pH	Gelling ability
S4	++	6.80	+++
SE1	++	6.87	+++
SE2	++	6.83	+++
SE3	++	6.62	+++
SM1	++	6.29	+++
SM2	++	6.48	+++
SM3	++	6.69	+++
SC1	+	4.61	+++
SC2	+	4.54	+++
SC3	+	4.45	+++
SX1	++	5.61	+++
SX2	++	5.52	+++
SX3	++	5.34	+++

Formulations with sodium alginate in polymer concentration 2% w/v and viscosity modifiers i.e. hydroxyethylcellulose, xanthan gum in concentration 0.1% to 0.3% and Methocel E50 LV in concentration 0.2%,0.4%,0.6% were found to be clear. While formulation SC1, SC2 and SC3 contains carbopol 940 as viscosity modifier was found to be slightly turbid, this is because carbopol at lower pH shows hazy appearance. The gelling ability of the selected formulations was also having phase transition behavior within 60 seconds and had stable gel structure. pH of all the formulations were in the range of 4.45-6.87.

The plain sodium alginate (S4) formulations gels are inhomogeneous appearance. They showed moderate mucoadhesive property because of anionic nature. By addition of HPMC polymers (HEC, Methocel E 50 LV) only marginal increase in mucoadhesive strength, this is because HPMC was poor mucoadhesive polymer due to its neutral nature. With carbopol and xanthan gum there was increase in mucoadhesion strength because of anionic nature of both

polymers. Free COOH group present in all these polymers forms hydrogen bonds with mucin. As concentration of mucoadhesive polymer increased there was increase in mucoadhesive property.

Table 11: Physical characteristics of ophthalmic formulations prepared with poloxamer 407

Code	Drug (% w/v)	Poloxamer (%w/v)	Appearance and clarity	pH	Osmolality	Gelling ability
P1	0.15	14	+++	6.15	272	-
P2	0.15	16	+++	5.82	274	-
P3	0.15	18	+++	5.90	285	+++
P4	0.15	20	+++	5.65	297	+++
P5	0.15	22	+++	6.3	302	+++

Table 12: Physical characteristics of ophthalmic formulations prepared with poloxamer 407 with viscosity modifier

Code	Appearance & clarity	pH	Gelling ability
P3	**+++**	5.90	**+++**
PE1	+++	5.94	+++
PE2	+++	5.98	+++
PE3	+++	6.04	+++
PM1	+++	5.97	+++
PM2	+++	6.02	+++
PM3	+++	6.10	+++
PC1	+	4.54	+++
PC2	+	4.50	+++
PC3	+	4.46	+++
PX1	++	5.71	+++
PX2	++	5.78	+++
PX3	++	5.81	+++

The formulations were found to be clear. All the formulations were free from any suspended particulate matter when observed carefully against a dark and white background. pH of the ophthalmic formulations prepared using poloxamer 407 as gelling agent ranged between 5.65-6.3. These pH values are considered to be acceptable since the ophthalmic pH ranges between 4.4 –7.4. Hence, no discomfort excessive tear flux may occur on installation.

The poloxamer containing formulations at varying concentrations, 14% to 22% w/v were found to be very clear. But formulations P1, P2 were not forming gel at 37^{o}C in STF. formulation P4,P5 was formed gel immediately at room temperature. Hence, the formulation P3 was selected for further studies.

The increase in concentration of individual polymers increased gellability of the ophthalmic formulations and imparted greater shear thinning property. However, the gels were less viscous and could not remain stable. Hence, different polymers were added to modify the viscosity and to prolong the release of drug.

Viscosity modifying polymers like hydroxyethylcellulose, carbopol 940 and xanthan gum in concentration 0.1% to 0.3% and Methocel E50 LV in concentration 0.2%, 0.4% and 0.6% were added in formulations containing selected concentration of *in situ* gelling polymer.

Formulations with poloxamer 407 in polymer concentration 18% w/v and viscosity modifiers i.e. hydroxyethylcellulose, xanthan gum in concentration 0.1% to 0.3% and methocel E50 LV in concentration 0.2%,0.4%,0.6% were found to be glassy clear. While formulation PC1, PC2 and PC3 contains carbopol 940 as viscosity modifier was found to be slightly turbid, this is because carbopol at lower pH shows hazy appearance. The gelling ability of the selected formulations was also having phase transition behavior within 60 seconds and had stable gel structure. pH of all the formulations were in the range of 4.46-6.10.

CONCLUSION

It can be concluded that different triggering mechanism successfully implemented to see the effect of formulation parameters on in situ gel formulation with pH and gelling capacity. Amount of Gelrite, sodium alginate and poloxomer identified and with different viscosity agent. Based on that we employed to conduct design of experimentation. From the experiments, it can be concluded that if formulation parameters were operated within the proposed pH and gelling agent ,From this study it can be concluded that formulation prepared within specified limit to produce optimised gelling capacity and it can produce formulation with acceptable

REFERENCES

1. Rajpal RK, Ross B. (Bromfenac ophthalmic solution for the treatment of postoperative ocular pain and inflammation : safety, efficacy, and patient adherence). Patient Preference and Adherence, 2014; 925-931.
2. Carreno E, Portero A, Galarreta DJ, Herreras JM. (Update on twice-daily bromfenac to treat postoperative ocular inflammation following cataract extraction). Sci. Med. Research, 2012; 637-44.

3. Gill HK, Bhagat S. (A novel *in situ* gel for sustained ophthalmic delivery of Ciprofloxacin hydrochloride and diclofenac sodium : design and characterization). World Journal of Pharmacy and Pharmaceutical Sciences, 2015; 4(10): 1347-56.
4. Shaikh A, Farheen T, Shahi S, Zaheer Z. (Formulation development and evaluation of ion sensitive in situ ophthalmic gel of Olapatadine hydrochloride). World Journal of Pharmacy and Pharmaceutical Sciences, 2015; 4(10): 2059–71.
5. Rao M, Shelar SU. (Controlled release ion sensitive floating oral *in situ* gel of a prokinetic drug using gellan gum). Indian Journal of Pharmaceutical Education and Research, 2015; 49(2): 158-67.
6. Vengurlekar P, Singh A, Rathod S. (Microspheric *in situ* gel for ocular drug delivery system of bromfenac sodium). International Journal of Pharma Sciences and Research, 2014; 5(04): 179-85.