FORMULATION AND EVALUATION OF TEAR SUBSTITUTES

Somnath Vibhute, Pravin Kawtikwar*, Sunil Kshirsagar, Dinesh Sakarkar.
S.N. Institute of Pharmacy, Pusad, Maharashtra (India) – 445 204
***Email:** pskawtikwar@rediffmail.com

ABSTRACT

Dry eye syndrome or dry eye (also known as *keratoconjuctivitis sicca*) occurs when there is a problem with the tear film that normally keeps the eye moist and lubricated. Among the management modes used for dry eye; tear substitutes or artificial tears are most popular due to their certain benefits. In the present study different viscosity enhancers (e.g. Sod. CMC, HPMC, PEG-400, propylene glycol, etc) were used alone and/or in combination along with other useful ingredients in different concentrations. Various physicochemical parameters were evaluated. Among all the prepared formulations batch A-7 has shown optimum results for management of dry eye. Optimized batch has passed the sterility test as per USP. The results of accelerated stability testing were also satisfactory showing no significant changes in parameters of preparation. This ensures the compatibility of formulation ingredients and thus can offer satisfactory shelf life of preparation. The quantitative estimation of elements in same batch was found to be quite similar to that of labeled amount of elements.

Key words: Dry eye syndrome, artificial tears, viscosity enhancers and sterility test.

INTRODUCTION

Dry eye syndrome or dry eye (also known as Keratoconjuctivitis sicca) occurs when there is a problem with the tear film that normally keeps the eye moist and lubricated[1]. It is evident from its name that *Keratoconjuctivitis sicca* is a drying inflammation: kerato (corneal) conjunctivitis (conjunctival inflammation) *sicca* (from the Latin *sicco*, meaning "to dry") [2, 3]. Dry eyes can affect anyone, but it becomes more common with increasing age[4]**.** A dry eye affects about 7% people in their 50s, and about 15 % people in their 70s[5, 6]**.** Women are affected more often than men. An estimated 12 million Americans have dry eyes[7].

The goals of treating dry eyes are to control the dryness of the eye, relieve symptoms, improve quality of life, minimize risk factors and prevent ocular damage. Though dry eyes cannot be cured, there are a number of steps that can be taken to treat them. The use of artificial tear drops is the primary treatment for dry eye. Artificial tears are similar to the natural tears, lubricate the eyes and help replace the natural moisture layer of the tear film[8]. General composition of artificial tears includes ophthalmic lubricants or demulcents/ viscosity imparting agents, surfactants, preservatives, and tonicity adjusters. Artificial tears play vital role to provide comfort by giving relief from symptoms of dry eyes. Artificial tears are supplemented with other treatments in moderate to severe forms of dry eye. Application of artificial tears every few hours can provide temporary relief from the symptoms of dry eyes. Presently various brands of artificial tears or tear-substitutes are containing viscosity imparting agents like sodium CMC, HPMC, PVP-K30, PVA, PEG-400, propylene glycol, HP-guar, sodium hyoluronate. The ideal tear substitute for dry eye syndrome should have following features[9]: 1. pH: 6.5-7.6, 2. Refractive index: 1.336, 3. Surface tension: 40.1±1.5 dyne/cm,. 4. Osmolarity: 302±6.3 mOsm/l 5.Viscosity: 6-12 cps,

MATERIALS AND METHODS

Sodium CMC, HPMC, PVP-K30 and PVA were received as gift samples from Ajanta Pharma, Mumbai. PEG-400 and propylene glycol were obtained as gift samples from Alkem Lab. Mumbai.

In present study, for the formulation development different viscosity enhancing agents were used in different concentrations. Other useful ingredients like sodium chloride (tonicity agent), glycine (surfactant), glycerine (humectant) sodium perborate (preservative) and necessary electrolytes are employed in appropriate concentrations. The formulations were developed in such a way that it will mimic the natural tear composition with respect to the physicochemical properties.

Preformulation studies

Preformulation testing is the first step in the rational development of dosage forms. The preformulation study was carried out to find suitability of ingredients for developing the stable and effective formulation[10, 11].

Formulation development

Different viscosity imparting agents were used alone and/or in combination of another in different concentrations as shown in Table 1-3. In addition to the viscosity enhancers, all the formulation batches contain ingredients in %: Polysorbate-80 (0.05), Sod. Chloride (0.5), Cal. Chloride (0.3), Mag. Chloride (0.05), Zinc chloride (0.002), Boric acid (0.4), Glycerin (0.3), Glycine (0.1), Sod. Perborate (0.01) and S.WFI - q. s.

Procedure for preparation of artificial tear formulation: Aseptic conditions were maintained during entire process of formulation development. Solution A containing viscosity enhancing agent/s and solution B containing various electrolytes as well as additives were prepared by using previously sterilised glass wares. Both solutions were sterilised by moist heat sterilisation. Then solution B is added to solution A using membrane filter.

Finally required pH was adjusted by using NaOH and stored in sterile containers[12, 13, 14.] No buffering system was used as sodium perborate provides stability by itself[14.]

Table 1: Formulation development using HMPC and sod. CMC

Sr. No.	Batch No.	A1	A2	A 3	A 4	A 5	A 6	A 7	A 8	A 9
1	HPMC	0.1	0.4	0.7	-	-	-	-	-	-
2	CMC	-	-	-	0.1	0.4	0.7	-	-	-
3	HPMC+ CMC	-	-	-	-	-	-	0.1 + 0.1	0.2 + 0.2	0.3 + 0.3

Table 2: Formulation development using PEG -400 and propylene glycol (PG)

Sr. No.	Batch No	B1	B 2	B 3	B 4	B 5	B 6	B 7	B 8	B 9
1	PEG -400	0.5	0.7	0.9	-	-	-	-	-	-
2	PG	-	-	-	0.5	0.7	0.9	-	-	-
3	PEG-400+ PG	-	-	-	-	-	-	0.3 + 0.4	0.4 + 0.3	0.3 + 0.3

Table 3: Formulation development using PVP K-30 and polyvinyl alcohol (PVA)

Sr. No.	Batch No	C1	C 2	C 3	C 4	C 5	C 6	C 7	C 8	C 9
1	PVP K-30	1.5	1.7	1.9	-	-	-	-	-	-
2	PVA	-	-	-	0.3	0.5	0.7	-	-	-
3	PVPK-30+ PVA	-	-	-	-	-	-	1.5 + 0.5	0.5 + 1.5	01 + 01

Table 4: Formulation evaluation

Parameter→ Batch↓	pH	Refractive index	Surface tension (dyne/cm)	Viscosity (cps)	Osmolarity (mOsm/l)
A1	6.8 ±0.3	1.33 ±0.01	38.4 ±1.0	3.50 ±0.2	290 ±3.5
A2	6.9 ±0.2	1.33 ±0.01	37.5 ±1.2	8.75 ±0.3	302 ±2.5
A3	6.8 ±0.3	1.32 ±0.01	40.2 ±1.2	26.25 ±0.5	288 ±3.2
A4	7.4 ±0.3	1.33 ±0.02	36.9 ±1.2	3.25 ±0.2	295 ±1.9
A5	7.5 ±0.2	1.33 ±0.01	37.5 ±1.1	6.50 ±0.2	298 ±1.3
A6	7.3 ±0.4	1.34 ±0.03	38.4 ±1.2	18.50 ±0.3	290 ±3.2
A7	**7.3 ±0.4**	**1.33 ±0.02**	**39.8 ±1.1**	**9.50 ±0.2**	**305 ±1.2**
A8	7.2 ±0.3	1.32 ±0.01	37.9 ±1.3	13.25 ±0.2	290 ±3.7
A9	7.3 ±0.2	1.33 ±0.01	38.5 ±1.2	15.50±0.2	288 ±3.5
B1	6.7 ±0.2	1.33 ±0.01	38.7 ±1.2	4.75 ±0.2	280 ±3.5
B2	6.8 ±0.2	1.34 ±0.01	38.4 ±1.2	6.50 ±0.3	287 ±2.7
B3	6.5 ±0.2	1.33 ±0.02	37.5 ±1.2	9.25 ±0.2	285 ±3.2
B4	6.8 ±0.3	1.33 ±0.01	40.2 ±0.9	4.75 ±0.2	290 ±4.3
B5	6.6 ±0.3	1.33 ±0.01	36.9 ±1.3	6.25 ±0.2	284 ±3.0
B6	6.9 ±0.4	1.33 ±0.02	37.5 ±1.3	8.50 ±0.3	286 ±3.7
B7	7.3 ±0.1	1.32 ±0.01	38.4 ±1.1	8.50 ±0.2	286 ±1.6
B8	6.9 ±0.1	1.34 ±0.03	38.7 ±1.2	11.25±0.2	278 ±2.5
B9	7.1 ±0.2	1.31 ±0.01	37.9 ±1.2	10.50 ±0.4	284 ±3.5
C1	6.7 ±0.2	1.33 ±0.01	38.7 ±1.4	5.75 ±0.2	283 ±3.5
C2	6.4 ±0.4	1.34 ±0.01	38.4 ±1.2	6.50 ±0.3	289 ±1.7
C3	6.9 ±0.3	1.33 ±0.02	37.5 ±1.4	8.25 ±0.4	278 ±2.5
C4	7.1 ±0.1	1.33 ±0.01	40.2 ±1.2	4.75 ±0.2	275 ±3.5
C5	6.9 ±0.3	1.31 ±0.01	36.9 ±1.3	6.25 ±0.2	287 ±3.3
C6	7.1 ±0.2	1.33 ±0.02	37.5 ±1.3	7.50 ±0.3	289 ±4.1
C7	6.9 ±0.1	1.32 ±0.01	38.4 ±1.2	8.50 ±0.2	293 ±2.5
C8	6.7 ±0.2	1.34 ±0.03	38.7 ±1.2	10.25 ±0.2	285 ±3.3
C9	6.8 ±0.4	1.32 ±0.01	37.9 ±1.2	11.50 ±0.4	288 ±2.4

±: Standard deviation, n = 3

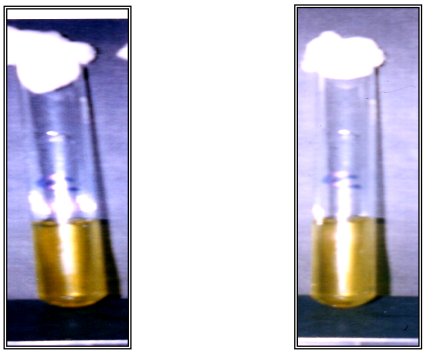
Table 5: Results of accelerated stability study

Sr. No.	Parameter	Storage period (days) at 40°C and75% RH			
		0	30	60	90
1	Appearance	Clear	Clear	Clear	Clear
2	pH	7.1± 0.3	7.1± 0.4	7.2± 0.3	7.3± 0.3
3	Viscosity (cps)	9.50± 0.3	9.50± 0.3	9.25± 0.3	9.25± 0.3
4	Surface tension (dynes/cm)	39.7± 0.5	39.7± 0.5	39.6± 0.3	39.5± 0.4
5	Refractive index	1.34± 0.03	1.34± 0.2	1.34± 0.2	1.33± 0.3
6	Osmolarity (mOsmo/L)	305± 3.2	305± 4.1	303± 3.6	303± 3.3

±: Standard deviation, n = 3

Table 6: Elemental estimation

Labeled quantity (gm/100ml)					Actual quantity (gm/100ml)				
Na	**Ca**	**K**	**Mg**	**Zn**	**Na**	**Ca**	**K**	**Mg**	**Zn**
0.5	0.0053	0.035	0.006	0.0002	0.5	0.0051	0.030	0.0058	0.00017



I. II.

Figure 1: Sterility test: I. Before and II. After stability test

Evaluation

Formulations were evaluated for appearance, pH, refractive index, viscosity, surface tension, osmolarity, sterility, elemental content. All the prepared formulations were examined for appearance using standard black and white back ground and no visible particulate matter was observed. Digital pH meter (Model no. 614, Toshniwal) was used to determine the pH of formulations. Abbe's refractometer (RSR 1, Rajdhani) was used to find out the refractive index. Viscosity was determined by using Brookfield viscometer (LV model Brookfield engg.); capillary rise method was used for surface tension study. Vapor Pressure Osmometer (model 5500, Wescor Logan, USA) was used for osmolarity study. Accelerated stability testing was conducted as per ICH guidelines using stability chamber (Labtop). Sterility test was carried out by direct inoculation method[15]. Quantitative estimation of elements within optimized batch was carried out by atomic absorption spectroscopy (Model 220, Perkin Elmer) [16].

RESULTS AND DISCUSSION

The results of evaluation of different parameters are shown in Table 4. All the batches have shown satisfactory results for parameters. Batch-7 has shown optimum results for dry eye as values obtained are quite similar to required ones.

The results of accelerated stability in Table 5 suggest the compatibility of formulation ingredients and thus can offer satisfactory shelf life of preparation.

Sterility test

The most important feature of these tear substitutes was sterility. The sterility test was performed before and after accelerated stability test as shown in Fig. 1. No turbidity observed after incubation period; indicating the sterility of formulation.

Quantitative estimation of elements

Table 6 shows the results of quantitative estimation of elements within batch-7; that the actual quantity of elements found in preparation is quite similar to that of labeled quantity of same.

CONCLUSION

The evaluation of all the 27 batches shown that most of them have found to be satisfactory values of required parameters. The batch 7 had shown optimal values of parameters. It was also found that HPMC and sodium CMC shows synergistic effect in viscosity enhancing

action. Hence fewer amounts of these polymers will suffice the need. The preparation has passed the sterility test before as well as accelerated stability study. This suggests that the aseptic techniques followed during manufacture were effective and also the preservative was suitable for the concentration employed. The actual quantities of elements in formulation were found to be quite similar to that of labeled amounts. Thus it can be concluded that the prepared formulation of tear-substitute possess physicochemical properties similar to the natural tears

REFERENCES

1. Clinical Knowledge Summaries, Dry eye syndrome, (March 2008), www.patient-pharmacy.co.uk.
2. Dry Eye, Eye Facts, The Eye Digest, www.uic.edu.
3. Dry Eyes, dry eye information centre, www.agingeye.net.
4. Brewitt H, Sistani F, Dry eye disease: The scale of problem, Surv. Ophthalmol. 2001; 45(2), S199-202.
5. Dalzell M., Dry Eye: Prevalence, Utilization and Economic Implications – a peer reviewed compendium of formulary consideration, P&T Digest, vol.28 (12), 2003, 9-13.
6. Lee AJ., et al, Prevalence and risk factors associated with dry eye symptoms: A population based study in Indonesia, Br. J. Ophthalmol, Dec 2002; 86: 1347-1351**.**
7. Dry eyes, MedlinePlus Medical Encyclopedia. U.S. National Library of Medicine (04/10/2006). Retrieved on 16/11/2006.
8. Tear substitute benefits, Highlights Ophthalmol, Int Ophthalmol Clin 1991, 31: 83-90
9. Lambert DW, Physiology of tear film. In: Smolin G, Thoft RA, eds, The Cornea, 3rd ed. Boston: Little, Brown, 1994, 439-455.
10. James W., Preformulation, in Phaermaceutics: The science of dosage form design, edited by Aulton ME., 2nd edition, Churchill Livingsttone, London, 2002; 113-137.
11. Cartensen JT., Preformulation, in Modern pharmaceutics, edited by Bankar GS., and Rhodes CT., vol.121, 4th edition Marcel Dekker, New York; 2002, 167-186.
12. Reynolds LA, Closson RG, Extemporaneous Ophthalmic Preparations, Vancouver WA, Applied Therapeutics, Inc., 1993.
13. Anon. Ophthalmic Drug Facts 1998. St Louis MO, Facts and Comparisons-A Wolters Kluwer Commpany, 1998.
14. WO/2005/089715): Ophthalmic solution comprising sodium carboxymethylcellulose and hydroxypropylmethylcellulose, 2005.
15. The United State Pharmacopoeia United State Pharmacopoeial Covenction, Rockville, MD. Asian Edn. 2000; 1352.
16. Indian Pharmacopoeia, vol. I & II, Govt. of India, Ministry of health and family welfare,The Indian Pharmacopia commision, Controller of publication, New Delhi, 2007, 812.

****