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Studies on Gel Tears

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ABSTRACT

Artificial tear substitutes, namely gel tears, were formulated and evaluated in the treatment of keratoconjunctivitis sicca. A preservative efficacy test was performed to evaluate the most suitable preservative for the gel tears. The gel tears were subjected to varying stability conditions and assessed for various parameters, viz pH, viscosity, clarity, extrudability, and sterility. Eye irritation studies were performed on albino rabbits using the Draize technique. Clinical trials were conducted on normal volunteers and volunteers with mild to moderate conditions of keratoconjunctivitis sicca.

INTRODUCTION

Dry eye syndrome, referred to as keratoconjunctivitis sicca (KCS) is a serious problem encountered in recent times. It involves the deficiency of lacrimal secretions giving rise to:(i) conjunctival irritation, (ii) erosion of cornea, and (iii) corneal scarring. Therefore a logical (1) approach to the treatment of lacrimal deficiency, whether it represents an insufficiency in tear production or abnormality in the distribution of tears on the ocular surface, calls for replacement of the deficient secretions by topical application of artificial tear preparations. Patients with dry eyes with or without associated systemic abnormalities remain one of the most common and most difficult management problems in ophthalmology (2). The research work was undertaken to develop tear substitutes in the form of a gel which mimics the lacrimal secretions; hence the name.

EXPERIMENTAL

Materials

The materials used were: carbopol®-940, xanthan gum, hydroxypropylmethyl cellulose K-15M (HPMC K-15M), propylene glycol, disodium edetate, sodium sulfite, sodium chloride, potassium chloride, triethanol amine, benzalkonium chloride, phenyl mercuric nitrate, parabens, sodium phosphate dibasic anhydrous, sodium dihydrogen orthophosphate.

The formulations are given in Table 1.

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Table 1

Formulations

Ingredients	G1	G2	G3	G4	G5	G6	G7	G8	G9
Carbopol-940	2.5 g	2.5 g	2.5 g	—	—	—	—	—	—
HPMC K-15M	—	—	—	3.0 g	3.0 g	3.0 g	—	—	—
Xanthan gum	—	—	—	—	—	—	4.0 g	4.0 g	4.0 g
Propylene glycol	20.0 g	20.0 g	20.0 g	10.0 g	10.0 g	10.0 g	10.0 g	10.0 g	10.0 g
Disodium edetate	0.1 g	0.1 g	0.1 g	—	—	—	—	—	—
Sodium sulfite	0.3 g	0.3 g	0.3 g	—	—	—	—	—	—
Sodium chloride	0.45 g	0.45 g	0.45 g	0.45 g	0.45 g	0.45 g	0.45 g	0.45 g	0.45 g
Potassium chloride	0.37 g	0.37 g	0.37 g	0.37 g	0.37 g	0.37 g	0.37 g	0.37 g	0.37 g
Triethanol amine	q.s.	q.s.	q.s.	—	—	—	—	—	—
Benzalkonium chloride	0.01%	—	—	0.01%	—	—	0.01%	—	—
Phenyl mercuric Nitrate	—	0.003%	—	—	0.003%	—	—	0.003%	—
Methyl paraben	—	—	0.18%	—	—	0.18%	—	—	0.18%
Propyl paraben	—	—	0.02%	—	—	0.02%	—	—	0.02%
Sodium phosphate dibasic anhydrous	0.5052 g	0.5053 g	0.504 g	0.570 g	0.570 g	0.569 g	0.564 g	0.564 g	0.562 g
Sodium dihydrogenorthophosphate (dihydrate)	0.269 g	0.269 g	0.268 g	0.269 g	0.269 g	0.268 g	0.265 g	0.265 g	0.265 g
Purified water	100 g	100 g	100 g	100 g	100 g	100 g	100 g	100 g	100 g

Method of Preparation

Carbopol-940 Gel Tears

To half the quantity of purified water were added all the ingredients, along with the respective preservatives. The solution was stirred with an impellar under moderate agitation. The entire amount of Carbopol-940 polymer was directed toward the vortex of the solution. Triethanolamine diluted with the remaining purified water was added and pH adjusted to neutral.

HPMC K-15M Gels

The water-soluble ingredients along with the respective preservatives were added to the entire amount of purified water; solution was maintained at 45°C and stirred with the help of an impellar. HPMC K-15M was sprinkled slowly into the solution. The resulting dispersion was kept overnight to account for the complete hydration of HPMC-K15M.

Xanthan Gum Gels

The water-soluble ingredients along with the respective preservatives were added to the entire amount of purified water. Xanthan gum was sprinkled on the surface of the solution being stirred. The gel tears were buffered at a pH of 7.2. USP XXI (3) recognizes five methods of sterilization:

1. Steam sterilization at 121°C
2. Dry heat sterilization
3. Sterilization by filteration
4. Gas sterilization (ethylene oxide, propylene oxide)
5. Sterilization by ionizing radiation (electron accelerators, radiosotopes)

The formulated gel tears were sterilized by autoclaving at 15 lb (121°C) for 20 min and aseptically filled in previously sterilized collapsible aluminum tubes.

Preservative Efficacy Test

The evaluation was done as per the BP—1988 specification with slight modifications.The microorganisms chosen for the test were *Staphylococcus aureus* (S.a) and *Pseudomonas aeruginosa* (P.A.).

One gram of each of the respective formulations was allowed to come into contact with 10^6 organisms/ml in

the nutrient broth, for periods of 0, 6, 24, 48 hrs; 7, 14, 28 days. After the respective time period appropriate dilutions were made using nutrient broth and tested by the pour plate technique. The preservative was found to be effective if no growth of microorganisms was observed after a period of 24 hr and thereafter.

Inactivating agents for the preservatives were:
Benzalkonium chloride: 0.5% lecithin and 3% polysorbate 80
Phenyl mercuric nitrate: 0.025% L-cysteine
Methyl and propyl paraben: 10% polysorbate 80

Rabbit Eye Irritation Studies

McDonald, Carpenter (4), and several other researchers have elaborated the various advantages the use of albino rabbits offer for carrying out ocular irritation studies. In the present study the gel tear formulations were evaluated for their ocular irritation potential according to the Draize technique (5). Six rabbits were used for the test; of these 5 rabbits were used for the test and 1 rabbit was used exclusively for control. Test formulations, 0.1 g, were instilled into the eye of the respective rabbits. Comparison was made with a standard market formulation.

Positive control → dioctyl sodium sulfosuccinate
Negative control → 0.9% NaCl

The gel tears were instilled twice a day for 21 days and rabbits were observed periodically for redness, swelling, watering, etc. Evaluation was done as per the scale given by Draize.

Clinical Study of Gel Tear Formulations

The first formulation was HPMC K15M gel tears. Subjects were volunteers of either sex in the age group 23–50 years:

1. 2 volunteers with mild conditions of KCS
2. 1 volunteer with severe conditions of KCS
3. 5 normal volunteers

The second formulation was Carbopol 940 gel tears. Subjects were volunteers of either sex in the age group 23–25 years:

1. 2 volunteers with mild condition of KCS
2. 5 normal volunteers

The gel tears were instilled thrice a day for a period of 1 week.

RESULTS AND DISCUSSION

As indicated in Table 2 and Table 3, benzalkonium chloride and phenyl mercuric nitrate were evaluated as the most suitable preservatives. The use of parabens in ophthalmics is doubtful. Owing to the side effects of the mercurial preservatives, further work was carried out with benzalkonium chloride. No further work was carried out with xanthan gum formulations as these formulations highly supported the growth of *P. aeruginosa* irrespective of the preservative added.

Ocular irritation results in rabbits are summarized in Table 4.

Table 2

Effectiveness of the Preservatives Against S. aureus

	Time				
Formulation	24 hr	48 hr	7 days	14 days	28 days
G1	–	–	–	–	–
G2	–	–	–	–	–
G3	+	+	+	+	+
G4	–	–	–	–	–
G5	–	–	–	–	–
G6	+	+	+	+	+
G7	–	–	–	–	–
G8	–	–	–	–	–
G9	+	+	+	+	+

Note. –, absence of growth; +, presence of growth.

Table 3

Effectiveness of the Preservatives Against P. aeruginosa

	Time				
Formulation	24 hr	48 hr	7 days	14 days	28 days
G1	–	–	–	–	–
G2	–	–	–	–	–
G3	+	+	+	+	+
G4	–	–	–	–	–
G5	–	–	–	–	–
G6	+	+	+	+	+
G7	+	+	+	+	+
G8	+	+	+	+	+
G9	+	+	+	+	+

Table 4

Ocular Irritation Studies in Rabbits

Preparation	Average Score
1. HPMC K-15M Gel tears	0
2. Carbopol-940 gel tears	0
3. Moisol[a]	0
4. Dioctyl sodium sulfosuccinate	9
5. 0.9% NaCl	0

[a]Artificial tears, FDC Ltd.

According to the results indicated in Table 5 and Table 6, it can be concluded that in the clinical studies:

1. No irritation was observed with HPMC K-15M gel tears; 1 volunteer (normal) experienced irritation with Carbopol-940 gel tears.
2. Blurring of vision to a tolerable extent was observed with both HPMC K-15M and Carbopol-940 gel tears.
3. No inflammation or discomfort was observed with either of the formulations.

Table 5

Clinical Evaluation of HPMC K-15M Gel Tears

Parameters	Normal Volunteers	Volunteers With KCS
Irritation	-5 (-5)	-3 (-3)
Blurring of vision	-4, +1 (-5)	+3 (-3)
Lacrimal secretions	-5 (+5)	-2, +1 (+2, -1)
Inflammation	-5 (-5)	-3 (-3)
Discomfort	-5 (-5)	-3 (-3)

Note. +, present but tolerable; ++, severe; -, absent. Figures in parentheses indicate scores for marketed formulation; other figures are scores for test formulations.
Interpretation of Clinical Data. Irritation -5 (-5) → absent in 5 volunteers; blurring of vision -4, +1 (-5) → with test formulation absent in 4 and present in 1, with marketed formulation absent in all 5 volunteers.

Table 6

Clinical Evaluation of Carbopol-940 Gel Tears

Parameters	Normal Volunteers	Volunteers with KCS
Irritation	+1, -4 (-5)	-2 (-2)
Blurring of vision	-5 (-5)	+2 (-2)
Lacrimal secretions	-5 (+5)	-2 (+2)
Inflammation	-5 (-5)	-2 (-2)
Discomfort	-5 (-5)	-2 (-2)

Note. +, present but tolerable; ++, severe; -, absent. Figures in parentheses indicate scores for marketed formulation; other figures are scores for test formulations.

CONCLUSIONS

The rabbit eye irritation studies showed that the Carbopol-940 gel tears and HPMC gel tears exhibited no ocular irritation potential. In the clinical evaluation, slight irritation was observed with Carbopol-940 gel tears while a comfortable response was observed with HPMC K-15M gel tears. Benzalkonium chloride was evaluated as the most suitable preservative. Thus gel tears seem to be a viable alternative for the treatment of deficient lacrimal secretions.

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