WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 7, Issue 5, 863-873 Research Article ISSN 2278 – 4357

FORMULATION AND EVALUATION OF SODIUM CROMOGLYCATE OCUSERTS

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Article Received on
01 March 2018,

Revised on 22 March 2018,
Accepted on 11 April 2018

DOI: 10.20959/wjpps20185-11482

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ABSTRACT

Objective: The present work describes the formulation and evaluation of Sodium Cromoglycate ocuserts using different polymers to increase the residence time of the drug in the cul-de-sac of the eye. **Methods:** Aqueous solutions of varying concentrations of different polymers were prepared and evaluated in order to identify the compositions suitable for use as Ocuserts. Solvent casting technique was used to formulate Sodium Cromoglycate ocuserts using polymers carbopol 940, Sodium Alginate and Hydroxypropyl Methylcellulose (K_4M), at different concentrations. The promising formulations were evaluated for visual examination, thickness, drug content, folding endurance, percent moisture absorption, *in-vitro studies*, ocular irritation, and stability. **Results:** The *in vitro* diffusion studies gave the cumulative percent drug release which was found to be 80%. The uniformity of the weights of the films indicates good distribution of the drug, in polymer and plasticizer. The formulations did not produce any irritation when placed in the cul de sac since they were not thick enough to produce irritation**.** The results of drug content were found to be satisfactory. The percent moisture absorption study revealed that formulation F5 (4.20 ± 0.05) showed high moisture loss due to less hindrance offered by carbopol. **Conclusion:** The ocuserts resulted in increased drug residence time and the drug release was in controlled manner comparative to the marketed formulation.

KEYWORDS: Ocuserts, Sodium Cromoglycate, Sodium Alginate, Carbopol 940, HPMC K4M, folding endurance, in vitro diffusion.

INTRODUCTION

Topical application of drugs to the eye is well established route of administration for the treatment of various eye diseases like dryness, conjunctiva, eye flu etc. One of the main problems encountered in ophthalmic drug delivery is the rapid and extensive elimination of conventional eye drops from the eye.[1] An eye-drop, irrespective of the instilled volume, often eliminates rapidly within five to six minutes after administration, and only a small amount (1-3%) of an eye-drop actually reaches the intraocular tissue.[2] The reasons for this inefficient drug delivery include rapid tear turnover, lachrymal drainage, and drug dilution by tears. The higher drainage rate is due to tendency of the eye to maintain its residence volume at 7-10 µl permanently, whereas volumes of topically instilled range from 20 to 50µl. It has been demonstrated *in-vivo* that 90% of the dose was cleared within 2 min for an instilled volume of 50 µl. Consequently, the ocular residence time of conventional solution is limited to few minutes, and the overall absorption of a topically applied drug is limited to 1-10%. Thus, it is difficult to provide and maintain an adequate concentration of drug in the pre corneal area. More than 75% of applied ophthalmic solution is lost via naso-lachrymal drainage and absorbed systemically via conjunctiva; hence ocular drug availability is very low.[3]

To increase ocular bioavailability and duration of the drug action, various ophthalmic vehicles, such as viscous solutions, ointments, gels, or polymeric inserts, have been used. The corneal contact time has been increased to varying degrees by these vehicles, but because of blurred vision (i.e. ointments) or lack of patient compliance (i.e. inserts); they have not been widely accepted.

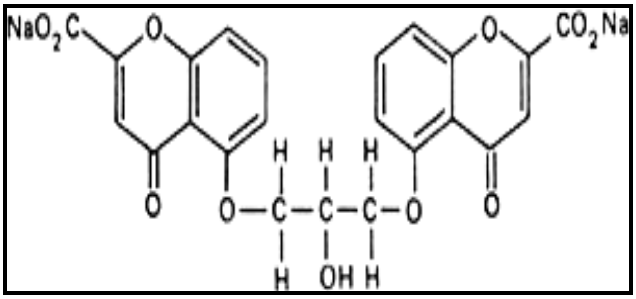
From the point of view of patient acceptability, a liquid dosage form that can sustain drug release and remain in contact with the cornea of the eye for extended periods of time is ideal. If the precorneal residence time of a drug could be improved from 5 min to say a few hours, then improved local bioavailability, reduced dose concentrations, dosing frequency, and improved patient acceptability may be achieved.[4]

Drug delivery systems based on the concept of *in-situ* gel formation should provide these properties. Such delivery systems consist of phase transition polymers that are instilled in a liquid form and shift to the gel phase once in the cul-de-sac of the eye. Several polymers, demonstrating phase transition due to changes in their microenvironment, were investigated. Among thempoloxamer407, whose solution viscosity increases upon increasing the

temperature to that of the eye, carbopol 940[5], cellulose acetophthalate (CAP) latex, that coagulates when its native pH 4.5 is raised by the tear fluid to pH 7.4 and sodium alginate, a polysaccharide which gels in the presence of mono or divalent cations.[6]

Sodium Cromoglycate is used for the prevention of allergic reactions. It acts by preventing the release of mediators of inflammation from, sensitized mast cells through stabilization of mast cell membranes. It has no intrinsic antihistaminic action and has generally been considered to possess no bronchodilator activity. Sodium Cromoglycate can prevent asthmatic response to a variety of allergic and non-allergic stimuli.[7].

Structure: Sodium Cromoglycate



Chemical name

Disodium 5, 5'-[(2-hydroxytrimethylene) dioxy] bis[4-oxo-4*H*-1-benzopyran-2-carboxylate]; disodium 5,5'-[(2-hydroxy-1,3-propanediyl) bis (oxy)]-bis[4-oxo-4*H*-1-benzopyran-2-carboxylate].

The present study is aimed to increase the drug residence time resulting in prolonged drug delivery in ocular site thereby decrease in dosage frequency of drug.

MATERIALS

Sodium Cromoglycate was gifted sample provided by Kopalle Pharma Chemicals Pvt. Ltd. Jeedimetla, Hyderabad, Sodium Alginate, Carbopol 940, and HPMC K4M was obtained from Hi-media Laboratories Pvt Ltd, Mumbai, India. Other ingredients used were of analytical grade which include Potassium Dihydrogen Phosphate, Sodium hydroxide, Ethanol and sterile distilled water.

METHOD OF PREPARATION

Total of eight formulations were prepared using different concentrations of different polymers and evaluated.

Preparation of Sodium Cromoglycate Ocuserts

Aqueous solutions of varying concentrations of different polymers were prepared and evaluated in order to identify the compositions suitable for use as Ocuserts. Ocular inserts containing different ratios of carbopol / sodium alginate / HPMC were prepared by solvent casting technique. Glycerin is added as a plasticizer. Ratio of plasticizer used in the preparation was 50% weight per gram of total polymer weight. Sodium Cromoglycate Ocuserts were prepared by using solvent casting method.

In solvent casting method glass molds were used. Polymers at definite concentration were dissolved and mixed well using magnetic stirrer to get different polymeric solutions using glycerin as a plasticizer. To the above solutions required quantity of drug is added. After complete mixing, the solution was poured into petri dishes in horizontal plane which were kept in hot air oven maintained at 35ºC. The solution gets evaporated slowly by inverting glass funnel (by plugging it with cotton in the stem at room temperature for 24 hrs). Solvents were evaporated to give ocular inserts. Then they were sterilized (UV radiation) by maintaining aseptic conditions and packed in aluminum foil and are placed in desiccators until use.

The films was then removed from a petri dish and cut to the required size. Films with air bubbles or other imperfections were discarded. 25 polymeric inserts for each formulation were fabricated then cut into circular or oval shaped inserts with the help of a borer. Ocular inserts with an appropriate area and dimensions were cut from the polymeric solution, producing approximately 25 inserts for each formulation. Theoretically the amount of drug contained in each ocular insert was calculated on the basis of standard paper weight surface area method.

Table 1: Composition of Sodium Cromoglycate Ocuserts.

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Sodium Cromoglycate (% w/v)	2	2	2	2	2	2	2	2
HPMC K4M (% w/v)	-	0.6	1	1.4	-	0.6	1	1.4
Sodium alginate	2	1.4	1	0.6	-	-	-	-
Carbopol 940 (% w/v)	-	-	-	-	2	1.4	1	0.6
Glycerin	1	1	1	1	1	1	1	1
Distilled water (% w/v)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

*all the above ingredients are calculated on percentage basis

Dose calculations

The amount of drug for one day treatment with eye drops containing 2% w/v sodium Cromoglycate is given below:

One drop of sodium Cromoglycate = 0.04 ml

One drop - 0.8 mg of Sodium Cromoglycate

Quantity of drug instilled at one time (2drops) =0.16mg

Quantity of Drug instilled in one day (8 drops X 0.8 mg=6.4mg)

Internal diameter of the ring = 5cm

Area of the ring = 3.14 X 2.5 X 2.5 = 19.6 cm^2

Diameter of the single Ocusert = 1 cm

Area on single ring = 3.14 X 0.5 X 0.5 = 0.785cm^2

No. of films casted in the ring = 19.6/0.785=25

Amount of drug loaded on single Ocusert = No. of single film × dose

=25 X 6.4=160mg

Evaluation parameters

Visual examination: The prepared Ocuserts were visually examined for their transparency, entrapped air bubbles, color homogeneity, and any other defects**.**

Weight uniformity: Weight was calculated on Digital balance. Ocuserts were weighed individually and the average weight was calculated.

Thickness uniformity: Thickness was measured using a screw gauge at different places of the ocuserts and the average was calculated.

Drug Content uniformity

Ocular inserts of Sodium Cromoglycate was assayed by Spectrophotometric analysis. The formulation was taken in a 100 ml volumetric flask diluted with phosphate buffer saline (PBS) pH 7.4 and was shaken to dissolve the drug in PBS pH 7.4.The solution was filtered through Whatmann filter paper; this filtrate was further diluted if necessary with PBS pH 7.4. Drug content was determined using a Shimadzu UV 1800 double beam spectrophotometer at 327 nm.

Folding endurance: Folding Endurance was determined by repeatedly folding the film at the same place till breaking or appearance of breaking signs. The number of times the film could be folded at the same place without breaking gives the folding endurance.

Percent moisture absorption

Simulated tear fluid was prepared with sodium chloride, sodium bicarbonate, calcium chloride, purified water. 3-4 ocuserts were taken and initial weight was weighed and placed in the simulated tear fluid and at regular intervals of time, the ocuserts were weighed again. The percentage moisture absorption was calculated using the following equation

Percentage moisture absorption = Final weight−Initial weight/Initial weight×100

Composition of Simulated Tear Fluid (STF).

Ingredients	Quantity(gm)
Sodium chloride	0.670
Sodium bicarbonate	0.200
Calcium chloride, $2H_2O$	0.008
Purified water Q.S	100

Sterility studies

The test for sterility is intended for detecting the presence of viable forms of bacteria, fungi and yeast in or on sterilized preparations. The sterility test was performed according to Indian Pharmacopoeia. It was carried out by incubating for not less than 14 days at 30 to 35^{o}C in the fluid thioglycolate medium to find the growth of bacteria and at 20 to 25^{o}C in the Soybean-Casein digest medium to find the growth of fungi in the formulations.

Stability studies

Stability is defined as the extent to which a product retains, within specified limits and throughout its period of storage and use (shelf life), the same properties and characteristics that it possessed at the time of its manufacture.

The principle of accelerated stability studies were adopted to avoid the undesirable delay with the long term stability studies, in which the product degrades under refrigerator temperature.

According to the ICH guidelines the storage conditions were as follows:

Long term testing: 5ºC ± 3ºC for 12 months

Accelerated testing: 25ºC ± 2ºC; 60% RH ± 5% RH for 6 months

Since the formulations performed better product performance, they were subjected to stability studies at 25^{o}C ± 2°C and 60% RH ± 5% RH for a period of three months. The samples were withdrawn after 15, 30, 60 and 120 days and were evaluated for the parameters of percentage drug content and *In vitro* drug release.

In vitro drug release studies

The bi chambered donor–receiver compartment model, designed using commercial semi-permeable membrane of transparent and regenerated cellulose type (Sigma dialysis membrane), was used to carry out the in vitro drug release studies. Semi-permeable membrane was used to mimic in vivo conditions, such as corneal epithelial barrier. The insert (n = 3) was placed in the donor compartment, and 7 µL of STF with pH 7.4 was maintained at the same level throughout the study in the donor compartment to simulate tear volume. The entire surface of the membrane was in contact with the reservoir compartment that contained 25 mL of STF with pH 7.4, which was stirred continuously using a magnetic stirrer at 20 rpm to simulate blinking action. Drug release was determined by withdrawing a defined quantity of sample from the sampling port at periodic intervals, which was replaced with equal volume of phosphate buffer pH 7.4. The aliquots were diluted with the receptor medium and analysed by UV-Vis spectrophotometer at 327 nm using STF pH 7.4 as blank.

RESULTS AND DISCUSSION

Visual examination: All the formulations were examined for transparency, entrapped air bubbles, color homogeneity, and any other defects. Ocuserts were transparent, clear without any air bubbles.

Weight uniformity

The weights of the Sodium Cromoglycate ocular inserts were found to be in the range of 4.97 ± 0.43mg to 5.40 ± 0.45 mg. The uniformity of the weights of the films indicates good distribution of the drug, in polymer and plasticizer.

Thickness uniformity

The thickness of the Sodium Cromoglycate ocular insert varied between 0.045 ± 0.007 mm to 0.055 ± 0.003 mm. The formulations did not produce any irritation when placed in the cul-de-sac since they were not thick enough to produce irritation**.**

Drug Content uniformity

Various formulations (F1 to F8) of Sodium Cromoglycate ocular insert drug content was found to vary between 97.9±0.1 to 99.8±0.4mg. The drug content was found to be almost same with their low standard deviation values.

Folding endurance

Folding endurance of Sodium Cromoglycate ocular insert was a measure of breaking strength and endurance. The various formulations (F1 to F8) of Sodium Cromoglycate ocular insert folding endurance were found to be 2. This result shows enough strength of ocular insert to withstand handling shock.

Percent moisture absorption

The % moisture absorption study revealed that formulation F5 (4.20 ± 0.05) showed high moisture loss may be due to less hindrance offered by carbopol (5%). Formulation F2 (2.52 ± 0.05) showed less moisture loss might due to presence of more hydrophilic polymer (HPMC), sodium alginate.

Formulation	Thickness	Weight variation	%drug content	%moisture absorbance
F1	0.045 ± 0.007	5.50 ±0.20	98.5 ± 0.7	3.20 ± 0.2
F2	0.049 ± 0.008	5.10 ± 0.60	99.7 ±0.8	2.52 ±0.05
F3	0.050 ±0.005	5.00 ± 0.42	99.5 ± 0.3	3.30 ± 0.06
F4	0.051 ± 0.007	5.40 ±0.45	99.6 ±0.4	3.37 ± 0.05
F5	0.055 ±0.003	4.97± 0.43	97.9± 0.1	4.20 ±0.05
F6	0.051 ±0.008	5.10± 0.31	99.8 ±0.4	4.11 ±0.03
F7	0.050 ± 0.007	5.00 ± 0.70	98.4 ± 0.2	4.08 ±0.06
F8	0.050 ± 0.003	5.30 ± 0.20	98.5 ±0.8	3.48 ± 0.06

Sterility testing

The sterility test was performed according to Indian Pharmacopoeia 1996. It was carried out by incubating for not less than 14 days at 30 to 35^{o}C in the fluid thioglycolate medium to find the growth of bacteria at 20 to 25^{o}C in the Soyabean-Casein digest medium to find the growth of fungi in the formulations.

***In- vitro* diffusion studies**

The in vitro drug release data ensured that the formulation F8 showed drug release for longer period of time of 6 hr. figure 2 shows the in vitro release of sodium Cromoglycate ocuserts. It is concluded from the results that the ocusert containing only one polymer sodium alginate (F1) showed faster release of the drug. It showed sustained release of the drug for only 3 hours. In the next formulations F2, F3, F4 the concentration of HPMC polymer was added to the sodium alginate which increases the ability of the ocusert to sustain the drug. This is because HPMC is a water retaining polymer unlike sodium alginate. Formulation F4 containing higher concentration of HPMC sustained the drug for 5 hours. This indicates that addition of HPMC to the alginate inserts enhances the sustained release nature of the drug. Carbopol films (F5) had shown slower drug release than alginate films. But on addition of HPMC to carbopol had prolonged the drug release up to 6 h. Formulation F8 having a higher content of HPMC sustained the drug for the longest period of 6 h.

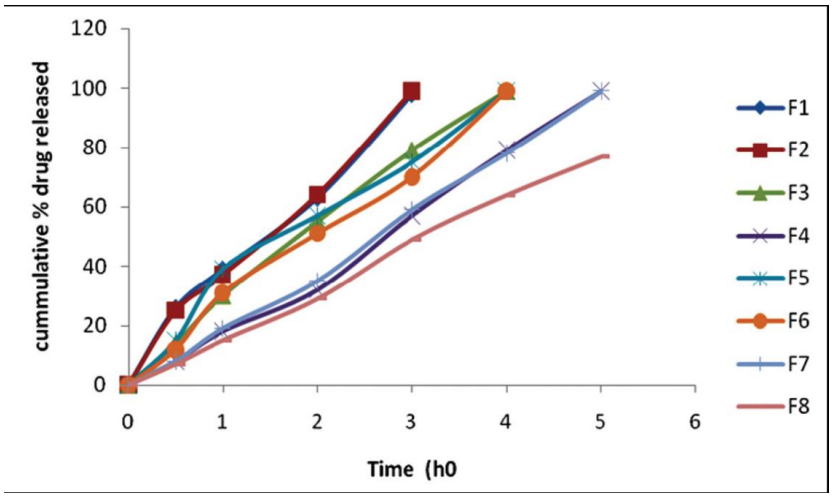


Figure 2: in vitro drug release profile of prepared Sodium Cromoglycate ocuserts.

CONCLUSION

Sodium cromoglycate has been formulated as ocular insert delivery system for the treatment of ocular infections. The Sodium Cromoglycate ocuserts based on carbopol and HPMC has shown a sustained drug release as well as good ocular tolerability. All the ocuserts were prepared by taking appropriate concentrations of the hydrophilic and hydrophobic polymers. These inserts were evaluated for thickness, weight variation, drug content, folding endurance, percent moisture absorption, and in vitro diffusion studies. The physicochemical characteristics of all inserts were satisfactory. Drug content was determined by spectrophotometric analysis.

The drug release of all the inserts with varying polymer concentration was determined by in vitro diffusion studies. The in vitro drug release data of the inserts showed sustained action for about 6 hours with the formulation containing carbopol and HPMC polymers (F8). The drug release in this particular formulation is less when compared to the inserts prepared with sodium alginate. As the main aim of the ocular drug delivery system is to increase the drug residence time in the cul-de-sac of the eye, the formulation which releases moderate amount of drug in a controlled manner is considered as the best formulation. Further the best formulation was taken for in vivo studies to know the therapeutic efficacy of the drug.

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