ORIGINAL ARTICLE

Design and evaluation of guar gum-based ofloxacin sustained release ocular insert

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To prepare ocular inserts of ofloxacin using guar gum as a polymer for sustained delivery over a period of 24 h. Ofloxacin ocular inserts were prepared by the solvent casting method using guar gum in different proportions (0.5% w/v, 0.75% w/v and 1.0% w/v). The prepared formulations were evaluated for thickness, weight variation, percentage drug content, surface pH, folding endurance, percentage moisture absorption and loss, percentage swelling, mechanical strength and *in vitro* transcorneal permeation. *In vitro* transcorneal permeation study was performed on goat cornea using a modified Franz diffusion cell. The inserts were found to be of uniform thickness (ranging from 51.230 ± 0.385 μm to 109.275 ± 0.522 μm) and weight (1.720 ± 0.079 mg to 3.402 ± 0.105 mg). The % drug content in the inserts was found to vary between 95.450 ± 0.427% and 98.471 ± 0.225. The cumulative % drug releases from the formulation ranged from 38.19 to 75.21 over a period of 24 h. All the formulations followed a zero order release pattern. The *in vitro* transcorneal study revealed that an increase in concentration of the polymer slowed down the release of ofloxacin from the formulation. Ocular inserts using guar gum as a polymer were successfully prepared and can be effectively used for sustained ocular delivery over a period of 24 h.

Key words: *Guar gum, in vitro transcorneal permeation study, ofloxacin, ocular insert, sustained release*

INTRODUCTION

Delivery of medication to the human eye is an integral part of medical treatment. The delivery of drug to the site of action has been practiced since ancient times.[1] Many attempts have been made to deliver ophthalmic drugs to the eye by means of different drug delivery systems. Sustained and controlled delivery of drugs to the ocular tissue continue to remain the major objective for formulation scientists and engineers in light of the emergence of more potent drugs and biological response modification with limited biological half-lives.[2,3]

Ophthalmic inserts are probably a good choice for this purpose as they increase the contact time with the conjunctival tissues. They offer the following advantages: increased ocular residence time, drug release at a slow and constant rate, accurate dosing, reduction of systemic absorption, better patient compliance, possibility of targeting internal ocular tissues and increased shelf-life with respect to aqueous solutions.[4]

For ocular inserts, the following criteria are essential:

1. Elution kinetics of the effective drug from the insert should be of zero or nearly zero order for a long time.
2. The insert should be harmless when retained in the eye for a long time.
3. The insert must stay easily in the eye and not give any disagreeable feeling to the patients.[5]

Ofloxain is a broad-spectrum antibacterial agent with activities against gram negative bacteria (*E. coli, Klesbsiela pneumonia,* Serratia species, Proteus species, *Pseudomonas aerogenosa and H. influenzae*) and gram positive bacteria (Staphylococcus species, *Streptococcus enterococci*). It inhibits the enzyme bacterial DNA gyrase, which nicks double standard DNA, introduces negative supercoils

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and then reseals the nicked ends. This is necessary to prevent excessive positive supercoiling of the strands when they separate to permit replication or transcription. The bactericidal action probably results from digestion of DNA by exonucleases whose production is signaled by the damaged DNA.[6]

However, a great deal of attention and research effort has been concentrated on biodegradable polymers. These materials degrade within the body as a result of natural biological processes, eliminating the need of removal from the drug delivery system after release of the active agent. Most biodegradable polymers are designed to degrade as a result of hydrolysis of the polymer chain into biologically acceptable and progressively smaller compounds.[7]

Guar gum is a natural water-soluble nonionic galactomannan polysaccaride, obtained from the ground endosperm of Indian cluster bean, *Cyamposis tetragonolobus*(L.) Taub. (Family-Leguminosae). It has the ability to produce highly viscous, pseudoplastic aqueous solutions even at low concentrations due to the high molecular weight (up to 2 MDa) and due to the presence of extended repeating units formed by hydrogen bonding. This feature allows guar gum to be soluble and gelling even in cold conditions and in water. The therapeutic effect of guar gum is due to its ability to swell rapidly in aqueous media to form viscous dispersions or gel.

In pharmaceuticals, guar gum is used in solid-dosage forms as a binder and disintegrant to add cohesiveness to the drug powder, and in oral and topical products as a suspending, thickening and stabilizing agent. Today, guar gum is also used as a controlled-release agent for drug due to its high hydration rate (swelling in aqueous media).[8-13]

Although extensive research work has been reported on ocular inserts, it could be evidenced from the literature that guar gum is not reported as a polymer in ocular inserts. As guar gum is the main ingredient in SYSTANE eye drops, used in dry eye disease,[14] and guar gum with borax cross-linking is used in ophthalmic compositions, therefore, it can also be used as a polymer in ocular inserts.[15]

In the present study, it was aimed to prepare ocular inserts containing ofloxacin along with guar gum (biodegradable polymer) to overcome the disadvantages associated with conventional ophthalmic dosage forms (eye drops and suspensions), to achieve longer duration of action delivering the drug in zero order kinetics. The release of ofloxacin from inserts was examined by changing the guar gum (polymer matrix) concentration.

MATERIALS AND METHODS

Materials

Ofloxacin was obtained as a gift sample from Cadila Pharmaceuticals Ltd., Ahmedabad, India. Guar gum was procured from Ases Chemicals, Jodhpur, India. Sodium chloride, sodium bicarbonate and calcium chloride dihydrate were purchased from S.D. Fine Chemicals, Mumbai, India. Glycerin was purchased from Siphon Laboratories, Jodhpur, India. All the chemicals used were of analytical grade.

Preparation of ocular insert

The ocular inserts were prepared by the solvent casting method.[16] Four batches (Batch A–Batch D) of ofloxacin ocular inserts were prepared using different concentrations of guar gum [Table 1]. Required amounts of guar gum were weighed and dissolved in distilled water by pouring guar gum gradually with vigorous stirring. The mixture was stirred for 2–4 h for complete hydration of guar gum. Required amount of plasticizer (glycerin - 10% w/w of the polymer) was added followed by the drug (previously dissolved in a minimum quantity of 2% v/v glacial acetic acid) and stirring was continued to form a homogenous solution. After complete mixing, the solution was kept overnight to remove any entrapped air bubbles. The solution (10 mL) was poured into glass moulds, which were then placed on a flat surface and were covered by an inverted funnel with cotton plug to prevent aerial contamination and to allow slow and uniform evaporation at room temperature for 48 h. The dried films so obtained were peeled from the casting surface and cut into an appropriate size using a sterile stainless steel borer. An area of 0.50 cm^2 containing 1.5 mL of ofloxacin was used in all studies.

These formulations were sterilized separately by exposing to UV radiation for 90 min in a cabinet under aseptic conditions and were finally packaged in presterilized aluminum foil. The ocular inserts were placed in a desiccator until use.[17]

Evaluation of the ofloxacin ocular inserts

Thickness of film

The thickness of 10 randomly selected ocular inserts was measured using a trianocular microscope. The mean thickness and standard deviation were calculated.

Weight variation

Weight variation between the formulated films can lead to difference in drug content and *in vitro* behavior.

The weight variation test was carried out using an electronic balance. Ten inserts from each batch were randomly selected

Table 1: Composition of polymeric matrices for the different batches

Ingredients	Batch A	Batch B	Batch C	Batch D
Ofloxacin (mg)	425	425	425	425
Guar gum (% w/v)	0.5%	0.75%	1.0%	1.25%
Glycerin (w/w of polymer)	10%	10%	10%	10%
Purified water (mL)	100	100	100	100

and weighted individually. The average weight and standard deviations of weight variation were calculated.[18,19]

CPercentage drug content

Percentage drug content was determined by assaying the inserts. The optimized ocular insert was placed into a 10-mL volumetric flask containing simulated tear fluid of pH 7.2 and sonicated for 20 min to extract the drug from the insert. The resultant solution was filtered through a G-2 glass filter.[20] From this, the sample was taken, diluted suitably and analyzed spectrophotometrically by measuring the absorbance at 287.60 nm.

Surface pH determination

The surface pH of the inserts was determined by placing two drops of double distilled water over it, allowing it to swell. After this, the swollen devices were placed on the pH paper to determine the surface pH. After 1 min the color that developed was compared with the standard color scale.[21]

Folding endurance value

The folding endurance is expressed as the number of folds or number of times the inserts are folded at the same place, either to break the specimen or to develop visible cracks. This test is important to check the ability of the sample to withstand folding. This also gives an indication of brittleness. The specimen was folded in the center, between the fingers and the thumb, and then opened. This was termed as one folding. The process was repeated till the insert showed breakage or cracks in the center of the inserts. The total folding operations were named as folding endurance value.[19-22]

Percentage moisture absorption

Ocular inserts were weighed and hung in a desiccator containing 100 mL of saturated solution of ammonium chloride (79.5% humidity at 20°C). After 3 days, the ocular inserts were taken out and re-weighed.[23,24] The percentage moisture absorption was calculated using the following formula:

$$\% \text{ moisture absorption} = \frac{W_F - W_I}{W_I} \times 100 \quad (1)$$

Where W_I and W_F are the initial and final weights of the ocular inserts, respectively.

Percentage moisture loss

Ocular inserts were weighed and kept in the dessicator containing anhydrous $CaCl_2$. After 3 days, the inserts were taken out and re-weighed.[19,20,23] The % moisture loss was calculated using the following formula:

$$\% \text{ moisture loss} = \frac{W_1 - W_f}{W_1} \times 100 \quad (2)$$

Where W_I and W_F are the initial and final weights of the ocular inserts, respectively.

Swelling study

Swelling of the polymer depends on the concentration of the polymer, ionic strength and the presence of water. Water uptake was determined gravimetrically. The inserts were placed on a filter paper, which was presoaked overnight in an agar gel plate (2% m/v agar in STF, pH 7.2) and weighed (presoaked filter paper + insert). The inserts were incubated at 32°C (the eye surface temperature). Inserts with filter paper were removed at predetermined time periods and the surface water was removed with the help of a filter paper and reweighed using an analytical balance.[22,25] The % of swelling was calculated using the following formula:

$$\% \text{ Swelling} = \frac{W_t - W_0}{W_0} \times 100 \quad (3)$$

Where W_t is the weight of the swollen insert after time t and W_0 is the initial weight of the insert.

Mechanical strength

Ocular inserts with good tensile strength and percent elongation would resist tearing due to stress generated by the blinking action of the eye. Percentage of elongation at the break and tensile strength of the film were measured using a pully-based tensile strength apparatus. The total weight necessary to break the film (weight of pan + weight on pan) was noted as the break force, and the simultaneous distance travelled by the pointer on the graph paper indicated the elongation at the break.[17,22,26]

$$\text{Tensile Strength (g/mm}^2\text{)} = \text{Break Force} \times \frac{1 + \Delta L/L}{a.b} \quad (4)$$

$$\% \text{ elongation at break} = \frac{(l_b - l_0)}{l_0} \times 100 \quad (5)$$

Where ΔL = elongation at break
L = length of the film
a = width of film
b = thickness of film
Break force = weight required to break the film
$l_{0 =}$ original length of film
l_b = length of film at break when stress is applied

In vitro transcorneal permeation study

Corneal preparation

The whole eye ball of the sheep was obtained from a local butcher's shop within half an hour of slaughtering of the animal, and was transported to the laboratory in cold (4°C) normal saline (0.9% w/v NaCl) immediately. The cornea was carefully excised along with 2–4 mm of the surrounding

scleral tissues and was washed with cold normal saline till it was free from proteins.

Permeation experiment

Fresh cornea was mounted by sandwiching the surrounding scleral tissue between the clamped donor and the receptor cells of the modified version of a Franz diffusion cell in such a way that its epithelial surface (apical) faced the donor compartment and the endothelial surface faced the receptor compartment. The cell was placed on a magnetic stirrer in a holding position. The receptor compartment was filled with 11 mL of freshly prepared simulated tear fluid (pH 7.2) and stirred using a Teflon-coated magnetic stir bar. The ocular insert was placed to the epithelial side of the cornea in the donor cell and stirring of the receptor fluid (jacketed with water at 32 ± 1°C) was started. At appropriate intervals, 1 mL samples were withdrawn from the receptor compartment and the withdrawn sample volume was replaced with an equal volume of fresh simulated tear fluid to ensure sink conditions.[27,28] The withdrawn samples were filtered and diluted suitably with STF and analyzed spectrophotometrically (Simantzu 1800) by measuring the absorbance at the $\lambda_{max.}$ of 287.6 nm. Each experiment was continued for about 24 h, and was performed in triplicate.

RESULTS AND DISCUSSIONS

Thickness

The thickness of the ocular inserts varied between 51.230 ± 0.385 µm and 109.275 ± 0.522 µm [Table 2]. This indicated that as the concentration of the polymer (guar gum) increased, there was an increase in the thickness of the ocular inserts. The inserts were found to possess uniform thickness within the batch.

Weight

The weights of the ocular inserts were found to be in the range of 1.720 ± 0.079 mg to 3.402 ± 0.105 mg [Table 2]. The uniformity of the weights indicated good distribution of the drug, polymer and plasticizer. These values revealed that the process was reproducible in its capability to give films of a uniform magnitude.

Percentage drug content

The drug content was consistent in all batches, and varied from 95.450 ± 0.427% to 98.471 ± 0.225% [Table 2]. The drug content uniformity values owed the fact that the process used was capable of giving films with uniform drug content, with unsubstantial differences in the targeted drug loading.

Surface pH

The surface pH of the prepared inserts was within the range of 6.5–7.0 [Table 2]. This indicates that the prepared inserts would not alter the pH of the tear fluid in the eye and they are not expected to cause irritation to the eye.

Folding endurance value

The films were folded manually and the value recorded was more than 200 for all batches, which was considered good, and revealed good film properties. Batch B showed the maximum folding endurance.

Percentage moisture absorption

The percentage moisture absorption study revealed that the increase in hydrophilic polymer (guar gum) concentration increased the percent moisture absorption [Table 3]. However, there was less or no change in the integrity of the film at that condition, which was observed by its physical appearance.

Percentage moisture loss

The % moisture loss of the prepared formulations was found to be in the range of 3.636 ± 0.070 to 4.234 ± 0.197 [Table 3]. The results revealed that as the concentration of the hydrophilic polymer increases, the tendency of the inserts to lose moisture also increases.

Swelling study

The swelling index was found to be minimum in Batch A (33.303 ± 0.329) and found to be maximum in Batch D

Table 2: Evaluation of ocular inserts

Code	Thickness (µm)	Weight (mg)	Surface pH	% drug content
Batch A	51.230±0.385	1.720±0.079	6.5–7.0	95.450±0.427
Batch B	63.920±0.540	2.420±0.063	6.5–7.0	96.711±0.314
Batch C	95.645±0.531	2.890±0.089	6.5–7.0	97.394±0.261
Batch D	109.275±0.52	3.400±0.105	6.5–7.0	98.471±0.225

Table 3: Evaluation of ocular inserts

Code	% moisture absorption	% moisture loss	Folding endurance value	% swelling	Elongation at break	Tensile strength
Batch A	10.833±0.380	3.636±0.070	212±4	33.303±0.329	3.333±0.144	0.325±0.010
Batch B	12.287±0.491	3.836±0.176	221±3	37.608±0.594	10.833±0.176	0.428±0.045
Batch C	12.957±0.281	3.910±0.098	215±4	40.361±0.347	11.667±0.144	0.534±0.034
Batch D	13.830±0.295	4.234±0.197	215±5	45.634±0.216	14.167±0.164	0.538±0.013

(45.634 ± 0.216) [Table 3]. The results revealed that as the concentration of the hydrophilic polymer increased, the swelling index also increased.

Mechanical strength

Tensile strength

Tensile strength measures the ability of the film to withstand rupture. The tensile strength of the ofloxacin ocular inserts increased as the total amount of polymer was increased [Table 3].

Percentage elongation at break

Batch A showed the minimum % elongation at break while Batch D showed the maximum % elongation at break [Table 3].

In vitro transcorneal permeation study

The cumulative percent of ofloxacin released from the ocular inserts as a function of time is shown in Figure 1. The overall cumulative percentage drug release for Batch A–Batch D was found to be 75.21, 71.65, 61.85 and 38.19, respectively, at the end of 24 h, as shown in Table 4.

The data obtained from the *in vitro* transcorneal permeation studies of all four batches were subjected to kinetic treatment in order to determine the order of release. The regression coefficient calculated was found to be 0.998, 0.996, 0.981 and 0.977 for the batches A, B, C and D, respectively. Therefore, it was ascertained that Batch A could release the drug in 24 h following zero order kinetics.

Table 4: *In vitro* transcorneal permeation study

Time (h)	Cumulative % drug release			
	Batch A	Batch B	Batch C	Batch D
1	0.36	0.07	0.02	0.01
2	2.70	1.31	0.79	0.52
3	4.88	2.92	2.06	1.76
4	8.39	5.40	4.13	3.68
5	11.05	8.29	6.29	5.75
6	14.66	12.48	8.54	7.47
12	34.17	31.71	21.01	12.92
24	75.21	71.65	61.85	38.19

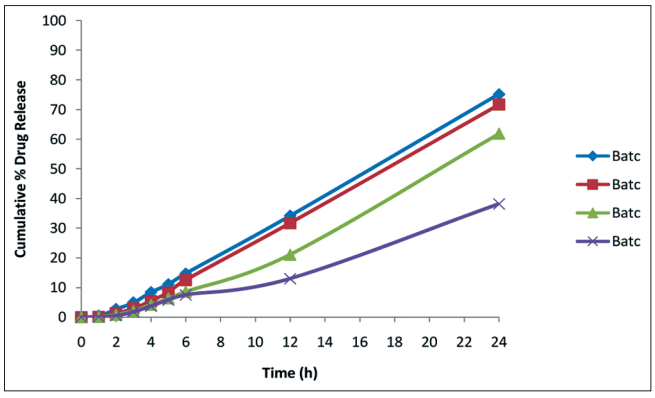

Figure 1: Cumulative % drug release versus time

CONCLUSION

The present investigation was undertaken with the objective of preparing a sustained release ocular delivery system of ofloxacin using guar gum as the polymer. The guar gum ocular inserts of ofloxacin showed appreciable film-forming properties. The study indicates potential usefulness of the guar gum-based ocular insert to provide an effective and time constant controlled delivery of ofloxacin. *In vitro* release studies revealed that the ocular inserts followed zero order release kinetics.

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