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Original Article

DESIGN AND EVALUATION OF CONTROLLED-RELEASE OCULAR INSERTS OF BRIMONIDINE-TARTRATE AND TIMOLOL MALEATE

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ABSTRACT

Objective: The current work was attempted to formulate and evaluate a controlled-release matrix-type ocular inserts containing a combination of brimonidine tartrate and timolol maleate, with a view to sustain the drug release in the cul-de-sac of the eye.

Methods: Initially, the infrared studies were done to determine the drug–polymer interactions. Sodium alginate-loaded ocuserts were prepared by solvent casting technique. Varying the concentrations of polymer—sodium alginate, plasticizer—glycerine, and cross-linking agent—calcium chloride by keeping the drug concentration constant, made a total of nine formulations. These formulations were evaluated for its appearance, drug content, weight uniformity, thickness uniformity, percentage moisture loss, percentage moisture absorption, and *in vitro* release profile of the ocuserts. Finally, accelerated stability studies and the release kinetics were performed on the optimised formulation.

Results: It was perceived that polymer, plasticizer, and calcium chloride had a significant influence on the drug release. The data obtained from the formulations showed that formulation—F9 was the optimised formulation, which exhibited better drug release. The release data of the optimised formulation tested on the kinetic models revealed that it exhibited first-order release kinetics.

Conclusion: It can be concluded that a natural bioadhesive hydrophilic polymer such as sodium alginate can be used as a film former to load water soluble and hydrophilic drugs like brimonidine tartrate and timolol maleate. Among all formulations, F9 with 400 mg sodium alginate, 2% calcium chloride and 60 mg glycerin were found to be the most suitable insert in terms of appearance, ease of handling, thickness, *in vitro* drug release and stability.

Keywords: Ocular inserts, Sodium alginate, Glaucoma, *in-vitro* study, Timolol tartrate, Brimonidine maleate

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INTRODUCTION

The conventional medications such as eye ointments and drops administered into the eye have various constraints such as poor bioavailability, reduced therapeutic efficiency due to the precorneal elimination of the drug, and frequent dosing of the medications may also lead to reduced patient compliance. All these limitations can be overcome by the continuous delivery of the medications into the eye, which could be accomplished by formulating an ocular insert [1, 2].

Ocular insert, a type of ocular drug delivery systems, is the interesting and challenging tasks facing by the pharmaceutical researchers till today [3, 4]. Ocular inserts are the sterile ocular films made of a polymeric vehicle comprising drug placed into the cul-de-sac of the eye [5]. It has numerous advantages such as accurate dosing, increased shelf-life, increased residence time, the possibility of slow, constant and pre-programmed drug release, reduced systemic absorption, and ensured patient compliance [6, 7].

Glaucoma, an eye disorder, is characterised by elevated intraocular pressure (IOP), damaged optic nerve, and the ganglion cells. If left untreated, it might lead to progressive and irreversible loss of eyesight. Brimonidine tartrate (BT) and timolol tartrate (TM) are the most widely used medications that lower the IOP [8, 9]. These are the non-selective beta-adrenergic blocker and the selective alpha 2-adrenergic receptor, respectively. These drugs act by lowering the IOP in the eye by impeding the production of aqueous humour [10, 11].

In the current work, an attempt has been made to design and evaluate ocular insert of BT and TM using sodium alginate as a polymer, glycerine as a plasticiser by solvent casting technique, with an objective of achieving controlled release, increasing residence time, decreased dosing frequency, and enhanced therapeutic efficiency.

MATERIALS AND METHODS

Chemicals

The chemicals BT and TM were procured from Micro labs, Bengaluru. The excipients sodium alginate, calcium chloride, and glycerine were procured from SD Fine Chemicals, Mumbai. All the other chemicals used in work were procured from the local market and used without any further purification.

Drug–excipient compatibility studies

Fourier transform infrared (FTIR) spectroscopic studies were conducted using FTIR spectrophotometer Jasco, 460 plus, Japan to determine any interaction between the drug and the excipients.

A small amount of the drug was taken and mixed uniformly with potassium bromide (KBr) of the spectrophotometric grade. The prepared mixture was taken in a palate and exposed to the Infrared (IR) beam and spectra were recorded in the range of 400–4000 cm^{-1} by using FTIR spectrophotometer. The IR spectra of the pure drug with excipient and without excipient were taken separately to point out any drug–excipient interactions.

Formulation of ocular films

Matrix films of sodium alginate containing a combination of BT and TM were prepared by solvent casting technique. The formulation of ocular inserts involves two steps:

Step-1: Preparation of precast Petri plates

A solution of (2% w/v) calcium chloride was prepared and transferred to the Petri plates measuring 2.38 cm in diameter and allowed to evaporate completely. These plates were used to cast the films of sodium alginate.

Step-2: Preparation of the drug loaded film of Sodium alginate

An accurately weighed 7.5 mg of BT and 7.5 mg of TM were dissolved in 10 ml of distilled water. Then, an accurately weighed sodium alginate was dissolved in the aqueous solution of the drug. The resultant solution obtained was cast in a Petri plate. Nine formulations containing different amount of polymer—sodium alginate, glycerine, and concentration of calcium chloride were obtained as per table 1. The different concentrations of glycerine were chosen based on the dry weight polymer. The preparation was left undisturbed for 48 h at room temperature for drying. After drying, they were cut into 9-mm circular films each containing 1 mg of the drug [1-3].

Table 1: Formulation of various batches of ocular inserts

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
BT (mg)	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
TM(mg)	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Water (ml)	10	10	10	10	10	10	10	10	10
Sodium alginate (mg)	200	200	200	300	300	300	400	400	400
Glycerine (mg)	40	50	60	40	50	60	40	50	60
Calcium chloride (%)	2.0	1.0	1.5	1.5	2.0	1.0	1.0	1.5	2.0

Evaluation of ocular films

All the prepared ocular films were evaluated by following parameters:

Drug content uniformity

Drugs-loaded ocular films of diameter 9 mm were placed in 10-mL volumetric flask and equilibrated with 10 ml of sodium phosphate buffer for 24 h. The flasks were shaken intermittently during this period and filtered. From the filtrate, 1 ml of sample was withdrawn, diluted accordingly, and assayed spectrophotometrically at 250 nm for BT and 295 nm for TM.

Uniformity of thickness

The thickness of each ocular insert was measured at three different points by using Baker digital caliper. The average of three readings was taken to determine the thickness of the film.

Uniformity of weight

From each batch, three ocular films were taken randomly and weighed individually using a digital balance.

Percentage moisture loss

The percentage moisture loss was performed to determine the integrity of the ocular film at dry conditions. Three concerts from each batch were chosen randomly, weighed, and kept in the desiccator containing anhydrous calcium chloride. After 3 d, the ocuserts were withdrawn and weighed again. The percentage moisture loss was determined by the formula:

$$\%\text{Moisture Loss} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \text{x } 100$$

Percentage moisture absorption

Percentage moisture absorption test was performed to determine the integrity of the ocular insert at moisture conditions. Three inserts were taken randomly and weighed individually. The inserts were placed in the desiccator and exposed to high relative humidity (RH) using a saturated solution of potassium chloride. The percentage moisture absorption was calculated by the formula:

$$\%\text{Moisture Absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \text{x } 100$$

***In vitro* drug release studies**

The *in vitro* release studies were determined by using the classical standard cylindrical tube of diameter 15 mm. Commercial semi-permeable membrane tied at one end of the open cylinder acts as a donor compartment in which the ocuserts was placed. The semi-permeable membrane that acts similar to the corneal epithelium was in contact with the receptor compartment containing 50 ml of 7.4 pH phosphate buffer. The content in the receptor compartment was stirred continuously by using a magnetic stirrer and the temperature was maintained at 37±0.5 °C.

For each predetermined interval, 1 ml of the aliquot was withdrawn and exchanged with the same volume of freshly prepared buffer solution. The collected aliquots were determined spectro-photometrically at 250 and 295 nm for BT and TM, respectively against pH 7.4 phosphate buffer as a reference standard. The percentage drug release of each formulation for each hour for 24 h was calculated from the slope of the calibration standard curve [4-6].

Accelerated stability study

Accelerated stability studies for the optimised F9 formulation of the ophthalmic insert was determined by exposing them to three storage conditions of temperatures (25±2 °C, 37±2 °C, and 42±2 °C) for 3 mo. After the specific period, the ocuserts were detected for any physical changes such as appearance, colour, thickness, texture, flexibility, and drug content [12].

The data obtained from the *in vitro* release make use of various kinetic models to describe the release kinetics. The drug release data obtained from the dissolution test were plotted in various models [13, 14].

Zero order rate kinetics

It describes that the release rate of the formulation is independent of the drug concentration. The formulation which follows zero order rate kinetics is expressed by the Eqn. 1.

$$c = c_0 - K_0 t \text{(Eqn. 1)}$$

Where,

C = amount of drug dissolved or released

C_0 = initial concentration of the drug in solution

K_0 = zero order rate constant, expressed in units of concentration/time.

t = time in hours.

First order rate kinetics

In first order kinetics, the release rate of the formulation is dependent on the drug concentration. As the concentration of drug increases the release rate also increases linearly. It is expressed in an equation.

$$\log c = \log c_0 + \frac{Kt}{2.303} \text{(Eqn.2)}$$

C_0 = initial drug concentration

C = drug concentration at time t

K = the first order rate constant

t = time in hours

Higuchi square root kinetics

It is the most famous mathematical equation to define the drug release from the micro particles, which is expressed in the Eqn.3.

$$C = Kt^{1/2} \text{(Eqn. 3)}$$

Where,

C = drug concentration at time t

Q = percentage of drug release at time t.

K = Higuchi release rate constant that depends on drug concentration, solubility, and drug release from the matrix system

RESULTS AND DISCUSSION

The current work is focused to design and evaluation of a controlled-release ocuserts containing a combination of BT and TM to treat glaucoma. Studies had revealed that fixed dose combinations of both the drugs are well tolerated in patients with glaucoma with least side effects [15-17]. Hence, an attempt was done to design ocular inserts that could remain in the cul-de-sac of the eye for a sustained period of time with a vision to maximise the ocular bioavailability.

The FTIR spectral studies were accomplished to determine the drug–excipient interaction. Data from the studies revealed no any significant interaction between the drugs (BT and TM) and sodium alginate (table 2).

The data on drug content, uniformity of thickness and weight, percentage moisture loss, percentage moisture absorption, *in vitro* drug release, and accelerated stability studies obtained for the ocuserts were confirmed to the IP (Indian Pharmacopoeia) specifications (table 3-6). The thickness of all the formulated ocular inserts was in comparison with that of marketed product—Pilo-20 (0.30 mm), manufactured by Alza Corporation. Which indicated the homogeneous distribution of polymer in the ocular insert. The weights of ocular inserts were varied within the range of 0.17–0.35 gm. This specifies that the technique was reproducible to prepare inserts with uniform weight [1]. The concentration of Calcium chloride and Concentration of plasticizer was found to play a major role in influencing the amount of drug release from the inserts [18]. The results obtained from the percentage moisture show that at lower polymer concentrations the percentage moisture absorption was 6.38–8.65 %. But as the polymer concentration increases the moisture absorption was found to decrease from 8.84–3.04%. The difference in the percentage moisture could be attributed to the difference in film porosity, which was shown to vary depending on the type and concentration of plasticiser [19].

Ocular inserts of formulations F1–F3 having low polymer concentration resulted in the poor drug release; F4–F6 with medium concentration resulted in moderate release, whereas F7–F9 with higher concentration resulted in the better drug release on completion of 24 h.

Of all formulations tested, the optimised F9 was found stable at different temperatures as per ICH guidelines and showed better drug release of 78% for BT and 77% for TM. In order to understand the release mechanism, the release data were tested on the kinetic models. From the results obtained, it was finally concluded that ocular inserts had followed first-order kinetics that is R^2=0.9878 and R^2=0.9940 for BT and TM respectively (table 7).

Table 2: Comparison of characteristic infrared peaks BT and TM with and without Excipients

Characteristic peaks (wave number cm^{-1})					
TM	**BT**	**BT+TM**	**BT+TM+SA***	**Corresponding functional groups**	**Characteristic absorption range**
3409	3472	3473	3565	O–H	3500–3700
3278	3437	3436	3475	O–H	3200–3600
3040	3265	3270	3272	N–H	3300–3500
2965	3217	2964,2909, 2848	2899,2847	C–H (aliphatic)	3000–3100
1707	1731	1728	1714	C=O (stretching)	1670–1820
1500	1487	1490	1487	>C=C<	1400–1600

*Sodium alginate

Table 3: Drug content of different ocular inserts

Formulation	Drug content (mg/cm^2)	
	Brimonidine tartrate	**Timolol maleate**
	mg±SD (mg)	**mg±SD (mg)**
F1	0.48±0.003	0.48±0.003
F2	0.49±0.005	0.49±0.004
F3	0.49±0.003	0.47±0.007
F4	0.48±0.006	0.50±0.008
F5	0.48±0.008	0.49±0.005
F6	0.48±0.006	0.48±0.006
F7	0.47±0.004	0.49±0.002
F8	0.47±0.003	0.47±0.001
F9	0.49±0.002	0.50±0.006

Values were expressed as mean±Standard Deviation (SD) of sample replicate, n=3

Table 4: Data showing physical characteristics of BT and TM of ocular inserts prepared

Formulations	Thickness (mm) of different ocular inserts	Weight (gm) of different ocular inserts	Percentage moisture absorption of different ocular inserts
F1	0.212±0.003	0.17±0.0000	8.66±0.0264
F2	0.200±0.004	0.20±0.0005	7.36±0.0700
F3	0.219±0.003	0.18±0.0026	6.92±0.0264
F4	0.208±0.011	0.21±0.0026	4.04±0.0264
F5	0.217±0.005	0.21±0.0026	8.81±0.0360
F6	0.227±0.003	0.22±0.0020	3.25±0.0360
F7	0.247±0.001	0.33±0.0026	3.04±0.0556
F8	0.251±0.003	0.35.±0.0020	3.22±0.0360
F9	0.251±0.003	0.33±0.0026	4.27±0.0701

Values were expressed as mean±Standard Deviation (SD) of sample replicate, n=3

Table 5: Percentage cumulative drug release (% CR) of BT in ocular inserts containing sodium alginate polymer of batch F1–F9

Formulations	Time (h)						
	2	4	6	8	10	12	24
F1	2.88±0.570	5.63±0.866	6.66±0.505	9.84±0.262	10.75±0.813	12.79±0.610	32.57±1.818
F2	2.47±0.194	6.33±0.198	8.71±0.705	11.51±0.378	13.98±0.448	14.40±0.536	33.70±0.898
F3	2.67±0.045	7.43±0.429	10.73±0.098	13.20±0.525	17.20±0.645	19.41±0.672	39.15±0.584
F4	5.15±0.058	10.13±0.427	16.95±1.131	23.70±0.830	28.59±1.807	32.53±2.740	51.90±3.259
F5	5.51±0.136	12.06±0.308	19.73±0.315	26.77±0.512	33.17±1.673	38.55±0.886	57.39±1.220
F6	8.99±0.190	16.74±0.740	21.88±0.574	29.91±0.244	38.51±0.742	43.00±1.085	61.29±0.648
F7	7.28±0.080	18.55±0.309	28.14±0.207	38.32±0.405	44.55±0.445	48.69±0.162	68.55±1.105
F8	7.62±0.290	18.48±0.790	28.79±0.725	38.85±1.037	45.10±1.441	50.44±0.395	72.96±1.537
F9	7.49±2.076	20.71±2.923	31.88±2.591	42.73±3.091	51.54±3.154	57.19±3.518	78.18±0.987

Values were expressed as mean±Standard Deviation (SD) of sample replicate, n=3

Table 6: Percentage cumulative drug release (% CR) of TM in ocular inserts containing sodium alginate polymer of batch F1–F9

Formulations	Time (h)						
	2	4	6	8	10	12	24
F1	3.56±0.387	7.36±0.515	10.92±0.613	15.89±1.235	23.02±0.251	28.21±0.197	44.23±0.712
F2	4.12±0.401	8.91±0.560	13.79±0.610	18.57±1.541	24.13±0.623	30.42±0.365	51.29±.502
F3	4.79±0.093	9.98±0.106	15.92±0.441	22.05±0.620	27.28±0.532	33.21±0.726	54.89±0.284
F4	4.31±0.521	8.75±0.201	13.21±0.254	19.01±0.652	24.32±1.012	29.69±0.562	55.81±0.714
F5	3.36±0.214	8.24±0.421	13.29±0.701	22.07±0.523	29.55±0.254	39.27±0.652	62.13±1.101
F6	5.43±1.202	11.73±0.854	18.94±0.321	25.13±2.01	32.48±0.317	43.21±0.198	66.71±0.223
F7	5.29±0.0.533	12.89±0.405	18.98±0.412	26.75±0.203	33.44±0.238	42.33±0.289	71.29±0.605
F8	6.12±0.721	14.56±0.881	22.47±0.254	31.18±0.287	39.11±0.451	47.69±0.417	74.29±0.421
F9	7.97±0.601	15.88±0.412	23.85±0.251	32.87±0.352	40.23±0.613	50.12±0.426	76.77±0.771

Values were expressed as mean±Standard Deviation (SD) of sample replicate, n=3

Table 7: Regression coefficient (R^2) of the drugs brimonidine tartrate and timolol maleate

Optimized formulation	BT			TM		
	Zero-order kinetics	First-order kinetics	Higuchi kinetics	Zero-order kinetics	First order kinetics	Higuchi kinetics
F9	0.9021	0.9878	0.9758	0.9764	0.9940	0.9917

CONCLUSION

The bioavailability of topically applied drug as eye drop is extremely poor and can be enhanced by ocular inserts formulated with natural bioadhesive polymers. In the present study ocular inserts of brimonidine tartrate and timolol maleate prepared from natural bioadhesive polymer, sodium alginate exhibited good control in the release of the drug for a period of 24 h. Further studies need to be carried out to check the feasibility of the inserts as an alternative choice for the treatment of glaucoma.

CONFLICT OF INTERESTS

Declared none

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