ISSN PRINT 2319 1775 Online 2320 7876

 Journal Volume 10,Iss 09, 2021

INVESTIGATION AND DEVELOPMENT OF CONTROLLED RELEASE MATRIX TYPE OCULAR INSERT OF PRESNISOLONE BY SOLVENT CASTING TECHNIQUE

[1]Mrs. D. Jyothi,[2]Dr. K. Rajitha,[3]Mrs. N. Anusha

[1,3]Assistant Professor,[2]Professor

[123]Department of Pharmaceutics

Vaagdevi Institute of Pharmaceutical Sciences, Bollikunta, Warangal. Telangana.

ABSTRACT The goal of the current experiment was to develop and assess a controlled-release matrix-type ocular insert that would maintain drug release in the eye's cul-de-sac by combining brimonidine tartrate with timolol maleate.

Methods: To find the drug-polymer interactions, infrared experiments were first conducted. Solvent casting was used to create ocuserts loaded with sodium alginate. Nine formulations were created by varying the concentrations of the polymer (sodium alginate), plasticizer (glycerine), and cross-linking agent (calcium chloride) while maintaining the same medication concentration. The look, drug content, weight homogeneity, thickness homogeneity, % moisture absorption, percentage moisture loss, and in vitro release profile of the occuserts were all assessed for these formulations. Finally, the improved formulation was subjected to accelerated stability investigations and release kinetics.

Findings: It was thought that the drug release was significantly influenced by the polymer, plasticizer, and calcium chloride. Based on the data gathered from the formulations, it was determined that formulation F9 was the optimal formulation with superior drug release. First-order release kinetics were demonstrated by the release data of the improved formulation when evaluated on the kinetic models.

In conclusion, water soluble and hydrophilic medicines like timolol maleate and brimonidine tartrate can be loaded onto a film former made of a naturally occurring bioadhesive hydrophilic polymer like sodium alginate. Regarding appearance, handling ease, thickness, in vitro drug release, and stability, F9, which contains 400 mg sodium alginate, 2% calcium chloride, and 60 mg glycerin, was determined to be the most appropriate insert out of all the formulations.

Design and assessment of controlled-release ocular inserts of brimonidine tartrate and timolol maleate in the original article

Rajajinagar Bangalore, 560010, Karnataka, India; PREETHI G. B., PRASHANTH KUNAL Department of Pharmaceutics, KLE University College of Pharmacy

Preethigb_100@yahoo.com is the email.

Keywords: Brimonidine maleate, timolol tartrate, ocular inserts, sodium alginate, glaucoma, in-vitro study

1. INTRODUCTION

The conventional medications such as eye ointments and drops administered into the eye have various constraints

ISSN PRINT 2319 1775 Online 2320 7876

 Journal Volume 10,Iss 09, 2021

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-desac 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.

2. 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

ISSN PRINT 2319 1775 Online 2320 7876

 Journal Volume 10,Iss 09, 2021

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].

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:

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

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:

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

In vitro drug release studies The in vitro release studies were determined by using the classical standard cylindrical tube of diameter 15 mm. Commercial semipermeable membrane tied at one end of the open cylinder acts as a donor compartment in which the ocuserts was

ISSN PRINT 2319 1775 Online 2320 7876

 Journal Volume 10,Iss 09, 2021

placed. The semipermeable 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 spectrophotometrically 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. $c = c_0 - K_0 t$(Eqn. 1)

Where, C = amount of drug dissolved or released C0 = initial concentration of the drug in solution K0 logc = logc0 + Kt 2.303(Eqn.2) C = 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.

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

C = 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. 0 C = Kt1/2(Eqn. 3) = 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.

$C = Kt^{1/2}$(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

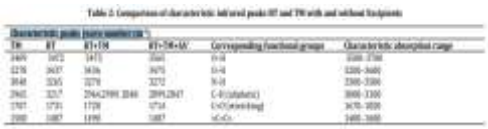
ISSN PRINT 2319 1775 Online 2320 7876

Research paper Journal Volume 10,Iss 09, 2021

3. RESULTS AND DISCUSSION

The current work is focused to design and evaluation of a controlledrelease 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 R2=0.9878 and R2 Characteristic peaks (wave number cm =0.9940 for BT and TM respectively (table 7).



ISSN PRINT 2319 1775 Online 2320 7876

Research paper **Journal Volume 10,Iss 09, 2021**

Table 3: Drug content of different ocular inserts

Formulation	Drug content (mg/cm²)	
	Brimonidine tartrate	Timolol maleate
	mg±SD (mg)	mg±SD (mg)
F1	0.48±0.003	0.49±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	0.52±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	0.52±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	0.252±0.003	0.17±0.0010	0.66±0.0264
F2	0.200±0.004	0.20±0.0005	7.36±0.0708
F3	0.274±0.003	0.18±0.0026	4.92±0.0264
F4	0.280±0.011	0.21±0.0026	4.04±0.0264
F5	0.217±0.005	0.21±0.0026	0.81±0.0264
F6	0.227±0.003	0.22±0.0029	3.35±0.0264
F7	0.247±0.001	0.23±0.0026	3.04±0.0556
F8	0.252±0.003	0.35±0.0020	3.25±0.0264
F9	0.250±0.000	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±0.066	6.66±0.505	9.84±0.262	10.75±0.013	12.79±0.618	32.57±1.818
F2	2.47±0.194	6.33±0.198	8.71±0.705	11.51±0.076	13.98±0.448	14.46±0.536	33.76±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±0.457	16.95±1.131	23.79±0.830	28.59±1.007	32.53±2.748	51.98±3.259
F5	5.51±0.136	12.06±0.308	19.73±0.315	26.77±0.532	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±0.762	43.86±1.085	61.29±0.648
F7	7.28±0.080	18.55±0.309	20.14±0.207	38.32±0.485	44.55±0.445	48.69±0.162	68.55±1.305
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±1.076	20.71±2.923	31.08±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	15.09±1.235	23.02±0.251	38.21±0.197	44.23±0.712
F2	4.12±0.401	8.91±0.568	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±0.186	15.92±0.441	22.85±0.628	27.28±0.532	33.21±0.716	54.89±0.284
F4	4.31±0.521	8.75±0.201	13.21±0.254	19.61±0.652	24.32±1.012	29.69±0.562	55.81±0.714
F5	3.26±0.214	8.24±0.421	13.29±0.701	22.67±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	25.19±2.01	32.48±0.317	43.21±0.198	66.71±0.223
F7	5.29±0.8.533	12.09±0.485	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	31.38±0.287	39.11±0.451	47.69±0.417	74.29±0.421
F9	7.97±0.601	15.08±0.412	23.85±0.251	32.87±0.352	40.23±0.633	50.12±0.426	76.77±0.771

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

4. 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.

REFERENCES

1. Mundada AS, Shrikhande BK. Design and evaluation of soluble ocular drug insert for controlled release of ciprofloxacin hydrochloride. Drug Dev Ind Pharm

2. Khurana G, Arora S, Pawar PK. Ocular insert for sustained delivery of gatifloxacin sesquihydrate: preparation and evaluations. Int J Pharm Invest 2012;2:70-7. 2006;32:443-8.

3. Shafie MAA, Rady MAH. In vitro and in vivo evaluation of timolol maleate ocular inserts using different polymers. J Clin Exp Ophthalmol 2012;3:246.

4. Kaul S, Kumar G, Kothiyal P. Design and evaluation of soluble ocular drug insert for controlled release of Acyclovir. Int J Drug Res Technol 2012;2:393-8.

5. Nair RV, Nair SC. KRA current trends in ocular drug delivery systems and its applications. Res J Pharm Technol 2015;8. Doi:10.5958/0974-360X.2015.00101.8

6. Parmar RB, Tank DHM. Design formulation and evaluation of reservoir type controlled released moxifloxacin hydrochloride ocular insert. Asian J Res Pharm Sci 2013;3:19-24

7. Himmelstein KJ, Guvenir I, Patton TF. Preliminary pharmacokinetic model of pilocarpine uptake and distribution in the eye. J Pharm Sci 1978;67:603-6.

8. Sachdeva D, Bhandari A. Design, formulation, evaluation of levobunolol HCl ocular inserts. J Pharm Sci Res 2011;3:1625-31.

9. Gupta SK, Niranjan DG, Agrawal SS, Srivastava S, Saxena R. Recent advances in the pharmacotherapy of

ISSN PRINT 2319 1775 Online 2320 7876

 Journal Volume 10,Iss 09, 2021

glaucoma. Indian J Pharmacol 2008;40:197-208.
10. Rathore KS, Nema DRK, Sisodia DSS. Preparation and characterization of timolol maleate ocular films. Int J PharmTech Res 2010;2:995-2000.
11. Gupta S, gilhotra RM. Enhancement of antiglaucoma potential by novel ocular drug delivery system. Int J Pharm Pharm Sci 2011;3:55-8.
12. Amar A, Ashish K, Ajaykumar P, Anand J. Formulation and evaluation of controlled release ocular inserts of betaxolol hydrochloride. IOSR J Pharm 2012;2:34-8.
13. Shaikh HK, Kshirsagar RV, Patil SG. Mathematical models for drug release characterization: a review. World J Pharm Res 2015;4:324-38.
14. Carstensen T. Drug stability, Principles and practices. New York: Markel Dekker; 1989.
15. Chrai SS, Makoid MC, Eriksen SP, Robinson JR. Drop size and initial dosing frequency problems of topically applied ophthalmic drugs. J Pharm Sci 1974;63:333-8.
16. Chrai SS, Robinson JR. Ocular evaluation of methylcellulose vehicle in albino rabbits. J Pharm Sci 1974;63:1218-23.
17. Keister JC, Cooper ER, Missel PJ, Lang JC, Hager DF. Limits on optimizing ocular drug delivery. J Pharm Sci 1991;80:50-3.
18. Gurtler F, Gurny R. Patent literature review of ophthalmic inserts. Drug Dev Ind Pharm 1995;21:1-18.
19. Yuan J, Shang PP, Wu S. Effects of polyethene glycol on morphology, thermomechanical properties and water vapour permeability of cellulose acetate free films. Pharm Technol North Am 2001;25:62.