Research Article

Formulation and Evaluation of Ocular Monolithic Film of Selected Antibiotic

UD. Shivhare* and RS. Bobade

Sharad Pawar College of Pharmacy, Wanadongri, Hingna road, Nagpur-441110, Maharashtra, India.

ABSTRACT

A new formulation Ocular Monolithic film was designed particularly for conjuctivitis in the ocular region and for good retention property on the site. Ocular Monolithic films formulated to obtain treatment effectiveness, reduction of drug dose and increase residence time at the site. Ocular Monolithic films were prepared using solvent film casting method. The Ocular Monolithic of Ofloxacin were formulated using various polymers like tried, HPMC E-15 being selected as a base polymer while Eudragit RL 100 was used along with it. To improve the flexibility and to avoid brittleness of the Ocular Monolithic film PEG-400 was selected as plasticizer. Then films were characterized under following parameters physical appearance, mass uniformity, thickness, folding endurance, surface pH, drug content uniformity, swelling, percent moisture absorption and loss, *in vitro* drug release. On the basis of the results among the various polymeric combinations, the combination **F3** was found to be most suitable. The formulation **F3** comprising polymers HPMC and Eudragit RL 100 in 7:3 ratio fulfill the requirement of good ocusert, shows complete and controlled release with 93.20% at the end of the 18h, all the physical parameters were satisfactory.

Keywords: Ocular monolithic film, Ofloxacin, Eudragit RL-100.

INTRODUCTION

Ofloxacin is a synthetic fluroquinolone agent widely used in ocular conjunctivitis, ocular gingitis and other ocular disorders for symptomatic relief of pain and inflammation. Ofloxacin is reportedly used for topical applications. The drug undergoes substantial hepatic first-pass metabolism and only about 50% of administered dose reaches systemic circulation.This originates the need of an alternative choice of route of administration for such drugs. The ofloxacin also possesses the ideal characteristics such as poor bioavailability, short biological half life and smaller dose etc., to be formulated in to a ocular monolithic film[1].

Ocular monolithic films are sterile preparation, with a solid consistency, whose size and shape are especially designed for ophthalmic application. They are essentially composed of a polymeric support containing drug(s).

The permeability of drugs through the ocular films is dependent on characteristics of the polymer, the casting solvent, and the plasticizers used [2].

Ocular route of drug delivery is a good alternative, amongst the various routes of drug delivery. Oral route is perhaps the most preferred for the patients. Ocular region offers an attractive route of administration for systemic drug delivery. However, oral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Ocular routes of drug delivery offer distinct advantages over oral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of pre-systemic elimination within the GI tract, these factors make the ocular site of administration a very attractive and feasible site for systemic drug delivery[3].

MATERIALS AND METHODS

MATERIALS

Ofloxacin was Gift sample from Zim Laboratories, Kalmeshwar, Nagpur. Hydroxy propyl methyl cellulose was gift sample from Loba Pvt. Ltd. Mumbai. Eudragit RL-100 Gift sample from Rohm Pharma, Mumbai. All other ingredients used throughout the study were of analytical grade and were used as received.

METHOD OF PREPARATION OF OCULAR MONOLITHIC FILM

Solvent casting method

The Ocular Monolithic films of Ofloxacin were prepared by solvent casting method with HPMC E-15 in combination with copolymer namely Eudragit RL100 with PEG-400 as plasticizer. Ethanol, dichloromethane were used as casting solvent. The casting solutions

were prepared by dissolving the appropriate polymers (2% w/v) and plasticizer (30%w/w) in suitable solvents using a magnetic stirrer to get a uniform dispersion. Mercury was used as the substrate and is poured in to petri dish. The mould was kept on the smooth horizontal surface of the mercury and 10 ml of the solution was poured into mould. After 24 h the dried film obtained were taken out and stored over fused calcium chloride in a desiccators at room temperature for further use[4].

Table 1: Composition of Ocular Inserts In Different Formulations

Ingredients	Formulation code							
	F1	F2	F3	F4	F5	F6	F7	F8
Ofloxacin (mg)	3	3	3	3	3	3	3	3
HPMC E15 (mg)	200	160	120	80	40	500	525	550
Eudragit RL-100 (mg)	200	240	280	320	360	100	75	50
Ethanol (ml)	5	5	5	5	5	5	5	5
Dichloromethane (ml)	5	5	5	5	5	5	5	5
PEG-400 (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

EVALUATION OF PREPARED OCULAR MONOLITHIC FILM

Physical appearance

The films observed visually for their physical appearance such as color and transparency.

Surface texture

The surface texture of the film was evaluated by simply touching the surface of the film.

Mass uniformity

For the mass uniformity three films from every formulation were taken and weighed individually on electronic balance. The average weights were calculated in table[5].

Thickness

Three films of each formulation of different batches were selected randomly and the thickness of the film was measured at different places using screw guage. The average film thickness and standard deviation was computed in table[6].

Folding endurance test

The folding endurance of the film was determined by repeatedly folding one film at same place till it broke[7].

Surface pH

Ocular inserts were left to swell for 5 h on agar plate which was prepared by dissolving 2 % (w/v) agar in warm STF (pH 7.4) under stirring and then pouring the solution into petri plate allow it till gelling at room temperature. The surface pH was measured by means of a pH paper placed on the surface of swollen film.

Drug Content Uniformity

Three film units of each formulation were taken in separate 100 ml volumetric flasks, 100 ml of pH 7.4 simulated tear fluid was added and continuously stirred for 24 h. The solutions were filtered, diluted suitably and analyzed on a UV spectrophotometer. The average of drug contents of three films was taken as final reading[8,9].

Estimation of percentage moisture absorbed

Ocular inserts were weighed and kept in a desiccators containing aluminium chloride. After three days ocular inserts were taken out and reweighed. Percentage moisture absorbed was calculated using the equation[10].

% Moisture Absorbed = $M_f - M_i / M_i \times 100$.

Estimation of percentage moisture loss

Ocular inserts were weighed and kept in a desiccator containing 22g of anhydrous calcium chloride. After three days insets were taken out and reweighed. Percentage moisture loss was calculated using the equation[10]

% Moisture Absorbed = $M_i - M_f / M_i \times 100$

Swelling

The three films were tested for each formulation. After determination of the original film diameter, the sample was allowed to swell on the water, were observed in 4 ml water. Measurement of the diameter of the swollen film was done a for one-hour in 10min,20min interval[11].

In Vitro Drug Release

In vitro diffusion studies of Ofloxacin ocular inserts were carried out using dialysis membrane in STF pH 7.4 solution. The *in vitro* release studies were carried out using a bichambered donor–receiver compartment model designed using commercial semi permeable membrane of transparent and regenerated cellulose type (Sigma Dialysis Membrane).

The formulation prepared was subjected to diffusion tests for 18 h. At every 1 h interval, sample was withdrawn, and replaced by an equal volume of diffusion medium. Drug

content in the diffusion sample was determined at 293.5 nm by UV spectrophotometer**.** Cumulative percent drug released was found out at each time interval and graph was plotted between cumulative % drug released and time in h. The release data were given in the table no. 3, respectively for the formulation F1 to F8. The comparative plots of the formulation F1 to F8 were plotted and shown in figures 1 to 4 respectively[12].

RESULTS

Table 2: Physical Evaluation of Formulation F1-F8

Formulation	Appearance	Surface texture	Mass uniformity (mg±SD)	Thickness (mm±SD)	Folding endurance
F1	Transparent	Smooth	33.0 ± 1.000	0.251 ± 0.0010	173
F2	Transparent	Smooth	34.2 ± 0.836	0.311 ± 0.0013	215
F3	Transparent	Smooth	36.2 ± 0.836	0.351 ± 0.0008	240
F4	Transparent	Smooth	38.4 ± 1.140	0.326 ± 0.0013	251
F5	Transparent	Smooth	36.2 ± 0.836	0.377 ± 0.0012	277
F6	Opaque	Smooth	40.0 ± 1.000	0.342 ± 0.0013	243
F7	Opaque	Smooth	35.3 ± 1.000	0.380 ± 0.0011	247
F8	Transparent	Smooth	37.0 ± 1.000	0.299 ± 0.0011	239

All values are expressed as mean ± SD (n=3).

Table 3: Estimation of Drug Content of Formulations

Formulation code	Amount of drug present (mg) *	Percent drug present (%)
F1	2.920 ± 0.071	89.698
F2	2.803 ± 0.993	92.788
F3	2.434 ± 0.013	93.430
F4	2.693 ± 0.023	93.594
F5	2.812 ± 0.190	92.036
F6	2.540 ± 0.009	93.168
F7	2.338 ± 0.035	92.386
F8	2.732 ± 0.012	91.478

All values are expressed as mean ± SD (n=3).

Table 4: Data of % Moisture Absorbed and % Moisture Loss of the Ocular Inserts

S. No.	Formulation code	Percent moisture absorbed*	Percent moisture loss*
1.	F1	11.069 ±2.119	3.230 ± 1.138
2.	F2	10.684 ±2.471	5.244 ± 1.240
3.	F3	6.317 ±2.433	3.215 ± 1.146
4.	F4	5.642 ±2.069	3.631 ± 1.430
5.	F5	3.828 ±1.509	4.822 ± 2.185
6.	F6	3.856 ±1.347	6.680 ± 1.143
7.	F7	2.794 ±0.065	6.257 ± 3.072
8.	F8	2.702 ±0.051	5.423 ± 2.729

All values are expressed as mean ± SD (n=3)

Table 5: *In Vitro* Diffusion Study of Ofloxacin Ocusert From Formulation F1-F8

Time in hour (h)	Cumulative % drug release							
	Formulation							
	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	8.23±0.12	8.29±0.15	9.55±0.19	7.89±0.13	8.78±0.16	7.34±0.19	7.11±0.15	7.5±0.14
2	12.45±0.13	12.01±0.13	13.33±0.13	11.74±0.16	11.12±0.12	10.23±0.15	10.79±0.12	11.12±0.17
3	16.89±0.54	15.76±0.19	16.46±0.15	14.99±0.14	15.44±0.15	14.44±0.13	13.39±0.16	14.42±0.13
4	20.79±0.25	19.93±0.12	20.11±0.17	19.45±0.12	20.29±0.13	19.29±0.18	18.13±0.18	19.91±0.13
5	26.23±0.15	25.28±0.18	25.13±0.12	25.21±0.19	26.22±0.12	24.65±0.14	22.21±0.12	25.61±0.11
6	30.46±0.13	31.45±0.17	32.39±0.15	31.39±0.19	30.44±0.15	30.12±0.12	26.61±0.12	29.57±0.28
7	35.78±0.12	34.47±0.19	35.99±0.16	33.81±0.18	36.79±0.01	34.16±0.14	29.44±0.18	35.79±0.23
8	41.77±0.14	41.69±0.12	42.9±0.19	40.65±0.12	40.78±0.18	39.13±0.19	35.51±0.21	42.78±0.12
9	48.93±0.15	47.81±0.15	48.89±0.12	46.82±0.13	47.90±0.16	44.69±0.21	42.41±0.32	47.98±0.11
10	55.68±0.24	54.67±0.14	56.55±0.17	54.69±0.15	54.51±0.09	52.51±0.45	50.22±0.51	56.11±0.22
11	60.64±0.19	61.66±0.14	62.68±0.15	60.65±0.12	59.65±0.08	57.75±0.65	54.46±0.19	59.17±0.32
12	64.55±0.17	65.54±0.12	69.93±0.13	64.55±0.11	62.20±0.25	61.19±0.15	58.81±0.02	61.44±0.21
13	69.87±0.15	68.73±0.13	71.7±0.13	67.77±0.15	67.70±0.23	66.45±0.03	64.44±0.01	65.00±0.14
14	75.73±0.13	74.44±0.18	77.7±0.18	74.43±0.13	73.74±0.08	72.19±0.08	69.90±0.33	68.77±0.05
15	81.21±0.12	80.22±0.19	82.91±0.19	79.22±0.16	79.75±0.03	78.91±0.15	73.71±0.21	74.41±0.09
16	86.84±0.14	84.44±0.20	85.94±0.20	83.41±0.20	84.43±0.13	83.44±0.18	79.17±0.23	79.90±0.28
17	88.81±0.21	87.73±0.22	89.11±0.21	86.74±0.22	86.59±0.12	88.58±0.19	83.33±0.25	84.40±0.44
18	90.9±0.22	89.9±0.21	93.2±0.21	89.98±0.21	88.82±0.13	91.00±0.09	87.95±0.02	89.11±0.18

All values are expressed as mean ± SD (n=3).

Table 6: Kinetic Treatment of Drug Release Data from Various Batches

Formulation code	Zero order	First order	Higuchi's matrix	Peppas model	Diffusion coefficient (n)
	R^2				
F1	0.9958	0.9166	0.6998	0.9887	0.63
F2	0.9948	0.9160	0.6947	0.9854	0.58
F3	0.9928	0.9258	0.7035	0.9763	0.56
F4	0.9953	0.9141	0.6856	0.9861	0.62
F5	0.9959	0.9151	0.7022	0.9828	0.61
F6	0.9978	0.9162	0.6589	0.9883	0.64
F7	0.9952	0.9314	0.6454	0.9818	0.59
F8	0.9946	0.8967	0.7028	0.9892	0.63

DISCUSSION

The fabricated ocular insert were thin, transparent and visually smooth surfaced. The thickness (table 2) of the films varied from 0.251 ± 0.001 to 0.380 ± 0.0012. Formulation F1 having the least thickness i.e. 0.251 ± 0.001 while F7 having the highest 0.380 ± 0.0012. The average weight of ocular insert from each group of formulation was reported in (table 1) by using six ocular insert for standard deviation. The weight of ocular insert ranges from 33.0 ± 1.000 to 40.0 ± 1.000. Results indicated that formulation F6 having highest mass while formulation F1 having the least among the different formulations.

The recorded folding endurance of the formulation shows 173-277 times (table 2), which reflects the flexibility of the films. This test ensures that the ocular inserts were prepared without breaking or tearing. Result indicated that all the formulation of ocular insert shows good folding endurance, among all ocular insert F1 shows least folding endurance which having equal concentration of HPMC E15 and Eudragit RL-100(1:1). As the concentration of HPMC E15 decreases and concentration of Eudragit RL-100 increases the folding endurance was increases.

The surface pH of all the films exhibited almost uniformity in their values and they were found in between 6.00 to 7.00 indicating its compatibility with eye pH.

Swelling study was performed on all the batches of ocular insert F1 to F8 for 1 h. From the results it was concluded that swelling increases as the time passes because the polymer gradually absorb water due to hydrophilicity of polymer. As the concentration of Eudragit RL-100 increases, swelling index of the film also increases.

In the present study, the higher swelling index was found for ocular insert of batch F5 containing Eudragit RL-100 and HPMC E15. Thus, the viscosity of the polymer had major influence on swelling process, matrix integrity.

The percentage of drug content for F1 to F8 was found to be between 89.69 - 93.59 % of Ofloxacin given in table 3, the results indicated that the drug was uniformly dispersed and it complies with official specifications.

The percentage moisture absorption of the ocular inserts was determined. It was reported in table 4. It was observed that as the concentration of Eudragit RL-100 increases percentage moisture absorption decreases. The percentage moisture loss of the ocular inserts was determined. It was reported in table 4. It was observed that as the concentration of Eudragit RL-100 increases percentage moisture loss.

It was observed that the 'r' values of zero order were in the range of 0.992 to 0.997 whereas the 'r' values of first order plots were found to be in the range of 0.89 to 0.93 indicating drug release from all the formulations were found to follow zero order kinetics.

The good fit of the Higuchi model to the diffusion profiles of all the formulations suggested that is the predominant mechanism limiting drug release since the 'r' values of Higuchis plots were nearer to unity.

The *in vitro* diffusion data as log cumulative percent drug release versus log time were fitted to Korsmeyer equation, values of the exponent 'n' was found to be in the range of 0.56 to 0.64 indicating that the drug release is by Non-Fickian diffusion mechanism, given in table no.6.

Among the various formulations studied, formulation F3 was considered as an ideal formulation which exhibited 93.20 % of drug release in 18 h.

In vitro diffusion studies

The *in vitro* release study was carried out on all the batches using diffusion cell apparatus at 80 rpm, STF pH 7.4 used as diffusion media and temperature was maintained 37^0C ± 0.5^0C. The *in vitro* drug diffusion data was given in table 4.

From the result it was observed that, formulations F1 to F5 containing polymer concentration(HPMC E15, Eudragit RL-100) ratio 1:1, 2:3, 3:7, 1:4 and 1:9 exhibited 90.90%, 89.90%, 93.20%, 89.98% and 88.82% of drug diffusion in 18 h. Formulations F6 to F8 containing polymer ratio 5:1, 7:1, and 11:1 prepared with Eudragit RL-100:HPMC E15 exhibited 91.00%, 87.95%, and 89.11% of drug diffusion in 18 h.

From the above results, it was observed that formulation F3 shows highest drug diffusion, while F7 shows the lowest drug diffusion. Much difference was not observed in the drug diffusion rates of formulations. Only highest concentration of HPMC E15 in F7 shows low drug diffusion.

CONCLUSION

Thus from the present study it can be concluded that, ocular monolithic film for ofloxacin with HPMC E-15 and Eudragit RL 100 meet the ideal requirement for ocular inserts(films)devices which can be good way to bypass other traditional drug delivery systems and increases bioavailability.

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