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OPTIMIZATION AND *IN-VIVO* EVALUATION OF OCULAR FILMS OF AN ANTI-INFLAMMATORY AGENT

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Keywords:

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ABSTRACT: The present study focuses on the treatment of ocular inflammation with objectives of reducing the frequency of administration, obtaining controlled release and greater therapeutic efficacy of drug (Keterolac tromethamine) using ocular films. Various combinations were designed for different batches of ocular films as per factorial design study with 0.5 % w/v concentration by solvent evaporation method containing different combination of polymers such as HPMC K100M, ethyl cellulose, Carbopol 934 and PVP K30. The folding endurance and thickness of the films were in the range of 44±1.1to 92±1.8 and 4.5±0.6 to 6.8±0.3, respectively for different formulations. Surface pH was evaluated in the range of 6.6 to 7.2 for optimized formulations. % moisture absorption and % moisture loss were evaluated in the range of 1.17±1.1 to 6.72±1.5 and 0.58±0.9 to 1.23±0.9 respectively. No microbial growth was observed in any formulation during sterility testing by direct inoculation method. The drug release for prepared formulations of different batch codes PAH, PBE, PCP, PDC, PEEH & PFEC was found to be 93.3±1.1, 54.2±0.9, 92.3±1.2, 96.1±1.5, 97.7±0.9 & 93.5±1.1% respectively upto 12 hours. Ocular films of batch code PEEH was optimized for maximum drug release (97.7±0.9). The anti-inflammatory effect was noted periodically (0.5 hr to 06 hrs) after administration of sterile formulation in the treated eyes vs. control eyes of each rabbit. The optimized batch PEEH of ocular inserts reduced the inflammation completely upto 4 hrs in a single dose.

INTRODUCTION: In spite of being most challenging task to develop controlled release formulation for ocular route, it has been very interesting and inventive area of research for the pharmaceutical research scientists. The unique anatomy and physiology of the eye renders it a highly protected and sensitive organ, and the unique structure restricts drug entry at the target site of action.

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The unique anatomy and physiology of the eye renders it a highly protected and sensitive organ, and the unique structure restricts drug entry at the target site of action. Conventional drug delivery systems including eye drops, suspensions and ointments for the treatment of various infections in the cul-de-sac are frequently used but they cannot be considered optimal because most topically instilled drugs do not offer adequate bioavailability due to the wash off of the drugs from the eye through lacrimation and tear dilution [1, 2].

In addition, the human cornea composed of epithelium, substantia propria and endothelium hinders drug entry; consequently less than 5% of administered drug enters into the eye.

Alternative approaches (ocular inserts/ films, corneal shield, sol to gel system *etc*.) are continuously sought to facilitate significant drug absorption into the eye. In this research ocular films of a first generation non steroidal anti inflammatory drug (Keterolac tromethamine: a non selective COX inhibitor and able to prevent inflammation, pupil contraction, conjuctival hyperemia and changes in intraocular pressure by inhibiting the COX pathway and subsequent production of prostaglandins) was developed and evaluated for anti-inflammatory response with a programmed rate for a longer period by increasing precorneal residence time [3, 4, 36 - 38].

To achieve controlled and constant release of drug and to overcome the problems associated with conventional ophthalmic dosage forms, the ocular films were prepared with different concentrations of hydroxyl propyl methyl cellulose (HPMC K100M), polyvinyl pyrollidone (PVP K30), Carbopol 934 and Ethyl cellulose. The permeability of drugs through the polymeric films is dependent on characteristics of the polymer, the casting solvent, and the plasticizers used. Plasticizers (phthalate esters, phosphate esters, fatty acid esters, and glycol derivatives) are very useful in the preparation of polymeric ocular films to reduce the brittleness, to impart flexibility, to increase strength, and also to improve adhesiveness of the films with surfaces or membranes [5, 6, 28 - 30].

Numerous studies have been conducted on polymer viscolyzers, bioadhesive delivery system and colloidal systems, all in rabbits and in humans. Bioadhesive properties of polymers seemed to be related to precorneal retention of the drug more significantly in comparison with other isoviscous and non-bioadhesive polymers. Encapsulation of drugs in liposomes and nanoparticles was correlated to an increase of the drug concentration in the ocular tissues [31, 32, 33].

There is a need for a polymer in which drug could be trapped physically to prolong drug residence time on the corneal surface and preserve visual acuity. Such system should be probably more hydrophobic than the materials currently employed, and would have to exhibit pseudoplastic behavior to minimize interference with blinking [7, 8]. To accomplish the aim of this research the predicted batches of ocular films of different concentration of polymer combinations were optimized through the factorial design study and the final batches were selected and developed containing HPMC K100M, PVP K30 and ethyl cellulose in the concentration of 0.5%, 0.5% and 1.0% respectively with PEG 400 10% w/w as plasticizer. Optimized ocular films were evaluated with various parameters such as folding endurance, thikness of films, surface pH, percent moisture absorption, percent moisture loss, percent drug release, stability study, sterility testing and *in-vivo* study.

MATERIAL AND METHODS: Jigs Chemicals, Ahmedabad, India provided a gift sample of Keterolac tromethamine while all the polymers of analytical grade were purchased from different suppliers of India like HPMC K100M from Loba Chemie Pvt. Ltd.-Mumbai, PVP K 30 and Ethyl cellulose from Qualikems fine chem. Pvt. Ltd.-Delhi. PEG 400 was purchased from Antares Chem. Pvt Ltd.-Mumbai and Arachidonic acid was purchased from Hi-Media Labs Pvt. Ltd., Mumbai. Microbial culture (Staphyloccocus aureus) was purchased from IMTECH, Chandigarh, 06 male Albino rabbits were provided by research place (animal house of R V Northland Institute) after IAEC protocol approval (Approval No.- 1149/PO/ ac/07/CPCSEA) through CPCSEA.

Preparation of Ocular Films*:* Various combinations were designed for different batches of ocular films as per factorial design study (six batch codes) such as PAH, PBE, PCP and PDP with 0.5 % w/v concentration, PEEH with 1.30 % w/v concentration and PFEC with 1.44 % w/v concentration by solvent evaporation method. The batch code PAH stands for HPMC K100M, PBE stands for ethyl cellulose, PCP stands for Carbopol 934, PDP stands for PVP K30, PEEH stands for HPMC K100M with ethyl cellulose & PVP K30 and PFEC stands for ethyl cellulose with Carbopol 934 & PVP K 30. Predetermined concentration of 0.5% w/v solution of polymers was prepared with suitable solvents using PEG-400 (10% w/w) as a plasticizer. The PVP K30 & ethyl cellulose solution was prepared with distilled water & ethanol, stirred at 80^{o}C. The calculated amount of solution of drug (Keterolac tromethamine) in their suitable solvents was added in the polymer mixer and homogenized.

The solution so obtained was poured onto the glass ring placed in petri dish. The glass ring has been mounted by the glycerin which works as a lubricant. An inverted funnel was placed over the ring and plugged with cotton wool to allow slow evaporation. The whole assembly was left undisturbed till the film dried. After this the ocular films were removed from the ring. Ocular films of calculated size were cut with the help of a die [9, 10, 35].

Physichochemical Characterization of Ocular Films: The ocular films of Keterolac tromethamine were evaluated for physicochemical characteristics such as folding endurance, thickness, surface pH, % moisture absorption, % moisture loss, stability study and % drug release. The folding endurance of ocular films was determined by the number of folds at a specific single place required to break the film into two parts. Thickness of the recovered films was measured using screw gauze. After performing the initial settings the film was placed on the anvil such that area where the thickness is to be measured lies.

The screw was gently tightened on to the specimen and reading of the gauze was noted to get the thickness of the film. The surface pH determination of the film was done by allowing them to swell by placing 2 drops of distilled water over it. After this the swollen film was taken and pH was determined using pH paper on the surface of the film [11].

The percentage moisture absorption test was carried out to check physical stability or integrity of the ocular films. Ocular films were weighed and placed in a desiccator containing 100 ml of saturated solution of ammonium chloride. After 3 days the ocular films were taken out and reweighed. The percentage moisture absorption was calculated using the formula:

% moisture absorption = final weight - initial weight/ initial weight x 100

Percentage moisture loss was carried out to check integrity of the film at dry condition. Ocular films were weighed and kept in the desiccators containing anhydrous calcium chloride. After 3 days the ocular films were taken out and reweighed, the percentage moisture loss was calculated using the formula [12]:

% moisture loss = initial weight - final weight/ initial weight x 100

Stability studies were carried out on batch code PEEH, according to ICH guidelines by storing replicates of ocular films (packaged in aluminium foil) for a period of 0, 30, 90 and 180 days with a relative humidity 75% ± 5% at a temperature 40 ± 2 ºC and 180 days at room temperature using the stability chamber. The sample was collected after 30, 90, 180 days under accelerated conditions and 180 days at RT, respectively and evaluated [13].

Stability Study of Optimized Batch of Ocular Film*:* Stability studies were carried out on batch code PEEH, according to ICH guidelines by storing replicates of ocular films (packaged in aluminium foil) for a period of 0, 30, 90 and 180 days with a relative humidity 75% ± 5% at a temperature 40^{0} ± 2 ºC and 180 days at room temperature using the stability chamber. The sample was collected after 30, 90, 180 days under accelerated conditions and 180 days at RT, respectively and evaluated [13].

In-vitro **Drug Release Study:** The inserts were placed on modified version of Franz diffusion cell using cellophane membrane in contact with isotonic phosphate buffer pH 7.4 kept at 37 ± 1°C with constant stirring of 50rpm. 1 ml Sample was withdrawn at different time intervals analyzed for drug content spectrophotometrically (Shimadzu UV 1700) at 322 nm[14, 20 - 25, 39 - 41].

Sterility Testing of Optimized Batch of Ocular Film: Optimized batch of ocular films were taken in two different sterile nutrient agar petri dishes. One uninoculated nutrient agar petri dish was taken as negative control (to test sterility of the medium). A lab isolated culture of Staphylococcus aureus was inoculated in one nutrient agar petri dish served as positive control. Both the petri dishes were incubated at 37 °C for 24 hrs.

Results were interpreted with positive and negative control petri dishes. The growth of microorganism was observed in positive control and no growth of micro organisms was observed in negative control test, which confirmed that all the apparatus used for the test were sterile and aseptic conditions were maintained.

Now the sample formulation were placed in the negative control test and incubated at same conditions. There was no growth of microorganism in the samples under test, confirming the sterility of ocular films. These sterile ocular films were considered suitable for *in-vivo* studies [15].

Sterilization of Optimized Batch of Ocular Film: These formulations were sterilized separately by exposing both sides to UV radiation for 90 minutes in a cabinet under aseptic conditions and were finally packaged in pre-sterilized aluminium foil [16].

***In-vivo* Study:** The protocol for *in-vivo* studies in rabbit was designed and approved by institutional animal ethics committee of research place. The rabbits were fed balanced diet pellets and maintained in a temperature-controlled room, at 20°C to 24 °C before the experiment. Arachidonic acid (05%) subconjunctivally instilled with a 100 microlitre syringe into left and right eyes of each rabbit (06 male Albino rabbit, 2.5 kg), produced a dose-related rise of inflammation.

The inflammation was observed with lid closure in both eyes immediately prior to applying the drug (zero-time), and at predetermined intervals after inserting an ocular film containing Keterolac tromethamine into the conjunctival sac of right eyes (treated) of each rabbits. Dose-response relationships were demonstrated and suggested its use in the topical treatment of ocular inflammation. Lid closure was scored according to peyman scale as follows: 0= fully open; 1= two-third open; 2= one-third open; and 3= fully closed [17, 19, 26 - 27].

RESULTS AND DISCUSSION: The ocular films of Keterolac tromethamine were prepared by solvent evaporation method using glycerin as lubricant and characterized on the bases of physicochemical parameters, sterility testing, *in-vitro* and *in-vivo* release studies. All the formulations with each polymer were evaluated for various parameters such as folding endurance, thickness, surface pH, % moisture absorption, % moisture loss, drug release of Ketorolac tromethamine (**Table 1**).

TABLE 1: *IN VITRO* EVALUATION OF OPTIMIZED BATCHES

Batch Code	Folding endurance (no. of folds)	Thickness (µm)	Surface pH	% moisture Absorption (w/w)	% moisture loss (w/w)	% Drug Release
PAH	73 ± 1.2	5.6 ± 0.2	6.9	6.72 ± 1.5	1.02 ± 0.8	93.3 ± 1.1
PBE	92 ± 1.8	4.6 ± 0.1	7.1	1.17 ± 1.1	0.58 ± 1.7	54.2 ± 0.9
PCP	47 ± 0.9	6.8 ± 0.3	6.6	4.88 ± 1.2	0.98 ± 1.0	92.3 ± 1.2
PDC	44 ± 1.1	6.3 ± 0.2	7.1	6.15 ± 1.6	1.23 ± 0.9	96.1 ± 1.5
PEEH	82 ± 1.1	4.9 ± 0.2	7.2	2.97 ± 1.1	0.58 ± 0.9	97.7 ± 0.9
PFEC	48 ± 0.7	4.5 ± 0.6	7.1	3.04 ± 1.2	0.69 ± 1.8	93.5 ± 1.1

Values are expressed as mean ± SD (n=5)

The nature of rate-controlling membrane had influences on the physico-chemical characteristics of the ocular films. The plasticizer is the most important component which may affects mechanical properties of the films by lowering the glass-transition temperature of the polymer. In this study, PEG-400 at concentration of 10% w/w of total polymer was selected since it gave sufficiently pliable films to allow for uniform subdivision into films without breaking the film.

Ocular films of HPMC K100M with rate-controlling membranes of EC and PVP K30 were flexible and elastic. Thickness and folding endurance were optimum in all batches and the % cumulative drug release (**Table 2** and **Fig. 1**) was evaluated with all six batches, the batch code PEEH was optimized with a maximum drug release (97.7 ± 0.9) having surface pH (7.2), % moisture absorption (2.97 ± 1.1w/w) and % moisture loss (0.58 ± 0.9 w/w).

TABLE 2: % CUMULATIVE RELEASE OF OPTIMIZED BATCHES OF OCULAR FILMS OF KETEROLAC TROMETHAMINE

Time (hrs)	PAH	PBE	PCP	PDC	PEEH	PFEC
0.5	9.32	7.45	5.65	6.28	6.11	8.13
1	14.57	11.78	15.36	12.41	17.09	14.89
1.5	22.92	19.62	20.45	25.95	21.14	21.36
2	30.86	23.10	37.20	36.02	38.77	31.22
3	40.45	29.17	44.55	42.83	42.44	40.35

4	49.45	30.93	52.27	55.14	53.50	52.97
5	61.91	38.05	58.29	58.56	63.15	64.91
6	69.44	40.53	74.13	70.97	72.32	70.34
7	79.22	45.83	80.69	77.51	80.94	77.27
8	84.58	49.31	82.83	84.80	86.61	82.01
10	89.98	52.25	90.18	90.30	92.30	90.84
12	93.30	54.20	92.30	96.10	97.70	93.50

Formulation code PEEH shows maximum drug releases upto 12 hrs comparatively with six batches.

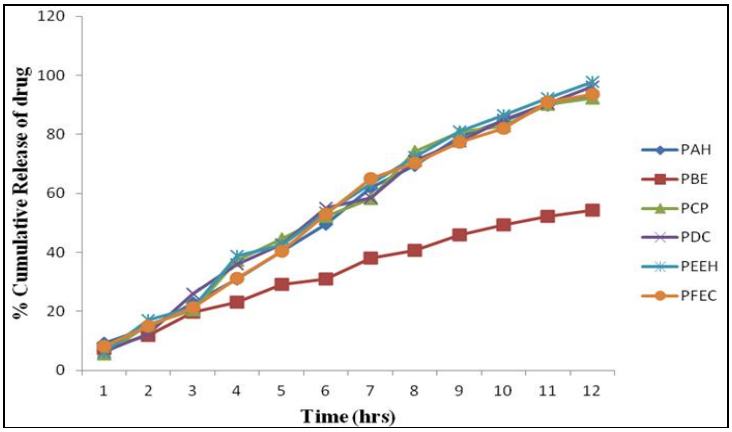

FIG. 1: *IN-VITRO* COMPARATIVE RELEASE OF OCULAR FILMS OF OPTIMIZED BATCHES

All the batches of formulations except batch code PBE shows approximate linearity but batch code PEEH shows desirable cumulative release of drug within 12 hrs.

Stability study: On the bases of physicochemical characteristics and *in-vitro* comparative release study of all six batches, the stability study was performed for batch code PEEH with accelerated study from 0 day to 6 months & upto 6 months with room temperature and the folding endurance, thickness, surface pH, % moisture absorption (**Table 3**) and % drug release **(Table 4** and **Fig. 2**) were further evaluated.

TABLE 3: STABILITY STUDY OF FINAL SELECTED BATCH PEEH

Parameters evaluated	Accelerated Study				Room Temp.
	0 day	30 days	90 days	180 days	180 days
Folding endurance	82	81	78	75	81
Thickness (µm)	4.9	4.9	4.9	4.8	4.9
Surface pH	7.2	7.2	7.2	7.3	7.2
% moisture Absorption (w/w)	2.97	3.09	3.18	3.33	2.99
% Drug Release	96.70	96.10	95.30	94.50	95.99

Stability data (batch code PEEH) shows comparative range for evaluated parameters

TABLE 4: RELEASE STUDY OF FINAL SELECTED BATCH PEEH

Time(Hrs)	Drug release				
	Accelerated Study				Room Temp.
	0 day	30 days	90 days	180 days	180 days
0.5	5.65	9.10	9.70	5.99	5.78
1	15.36	16.10	11.09	15.76	14.96
1.5	20.45	23.10	28.83	22.20	21.12
2	37.20	33.11	34.78	32.65	31.23
3	44.55	40.26	47.86	45.66	47.31
4	52.27	55.88	55.22	48.96	53.46
5	58.29	64.60	59.86	58.72	60.59
6	74.13	72.63	67.83	73.62	71.61
7	80.69	77.13	81.27	76.85	80.75
8	82.83	85.59	86.08	85.25	84.82
10	90.18	91.64	90.46	89.87	89.81
12	96.70	96.10	95.30	94.50	95.99

Drug release for batch code PEEH during accelerated stability study found to be optimum at different time intervals

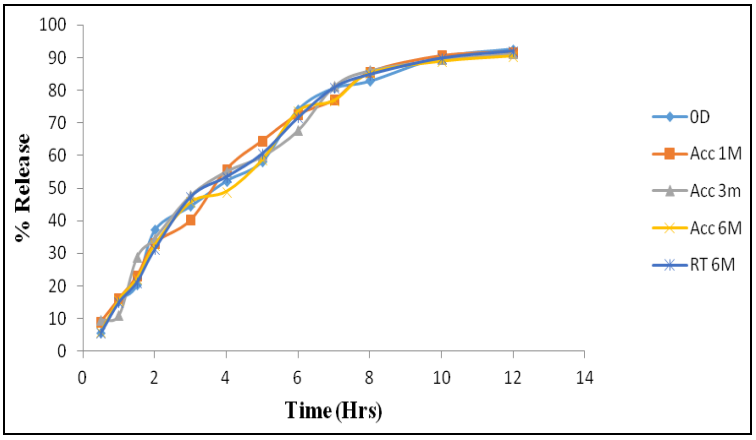

FIG. 2: % DRUG RELEASE FROM BATCH PEEH DURING STABILITY STUDY

***In-vivo* Study:** Inflammation was noted periodically (0.5 hr to 06 hrs) in both eyes of each animal after administration of final optimized sterile formulation in the treated eyes vs. control eyes. One-way ANOVA, followed by Tukey-Kramer multiple comparison test were used for comparison of the means of different groups. There is significant decrease ($P < 0.05$ & $P < 0.01$) in scores of inflammation as compared with control group. As per the data presented in the **Table 5** and **Fig. 3**, the optimized batch PEEH of ocular inserts reduced the inflammation completely upto 4 hrs in a single dose.

TABLE 5: EFFECT OF ANTI-INFLAMMATORY RESPONSE OF FINAL SLECTED BATCH PEEH (AVG. MEAN OF SCORE WITH TIME)

Group (Avg. ± SD)	Time (hrs)						
	0.5	1	2	3	4	5	6
Control (Left eye)	2.6666 ± 0.5163	2.6666 ± 0.5163	2.3333 ± 0.5163	1.5 ± 0.5477	0.6666 ± 0.5163	0.5 ± 0.5477	0 ± 0
Treated (Right eye)	2.5 ± 0.5477	1.8333 ± 0.4082	1.1666 ± 0.7527	0.3333 ± 0.5163	0 ± 0	0 ± 0	0 ± 0

(* P< 0.05, **P<0.01 vs. control group)

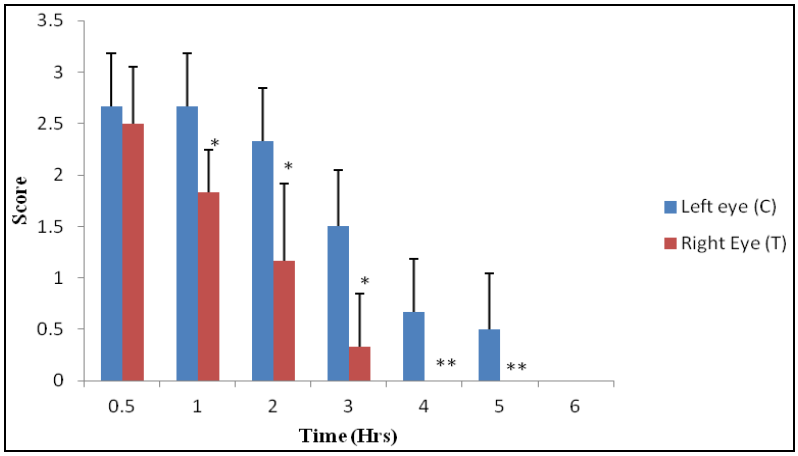

FIG. 3: EFFECT OF ANTI-INFLAMMATORY AGENT (± SD) BETWEEN CONTROL AND TREATED GROUP
(*P < 0.05 & **P < 0.01 vs. control group)

CONCLUSION: Ocular films of Keterolac tromethamine prepared by solvent evaporation method using a good film forming hydrophilic polymer (HPMC K100M) with satisfactory rate controlling membranes of ethyl cellulose and PVP K30 included PEG 400 as a plasticizer. Various concentrations were designed with different combinations but the concentration of batch code PEEH was smooth, flexible and transparent. Physicochemical parameters *viz* folding endurance, thickness, surface pH, percentage moisture absorption/ loss, stability study, sterility testing

were in optimum range for optimized batch of ocular film. *In-vitro* and *in-vivo* study revealed that the optimized formulation would be able to offer benefits such as increased residence time, prolonged drug release, reduced frequency of administration and improved patient compliance with complete removal of inflammation and redness from the cul-de-sac.

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REFERENCES:

1. Chien YW: Novel Drug Delivery Systems (Drugs and the Pharmaceutical Sciences). New York: Marcel Dekker Inc., Second Edition 1996.
2. Gaudana R, Jwala J, Boddu SHS and Mitra AK: Recent perspectives in ocular drug delivery. Pharmaceutical Research 2009; 26:1197-1216.
3. Peneva PT: Non-steroidal anti-inflammatory drugs for topical ophthalmic administration: Contemporary Trends. International Journal of Pharmacy and Pharmaceutical Sciences 2015; 7 (9):13-19.
4. Smith SE: Ocular NSAIDs. Therapeutics 2005; 124-127.
5. Kothawade SN, Deshpande ST, Lunkad AS and Dighe PA: Formulation and *in-vitro* characterization of Ketorolac Tromethamine ophthalmic inserts. Research Journal of Pharmaceutical Dosage Forms and Technology 2014; 5 (6):311-314.
6. Sankar V, Chandrasekaran AK, Durga S, Geetha G, Ravichandra V, Vijayakumar A and Raguraman S: Design and evaluation of diclofenac sodium ophthalmic inserts. Acta Pharmaceutica Sciencea 2006; 48:5-10.
7. Tanwar YS, Patel D and Sisodia SS: *In-vitro* and *in-vivo* evaluation of ocular inserts of ofloxacin. DARU 2007; 15 (3):139-145.
8. Perry HD and Donnenfeld ED: An update on the use of ophthalmic Ketorolac tromethamine 0.4%. Expert Opinion on Pharmacotherapy 2006; 7(1):99–107.
9. Patel DH, Patel MP and Patel MM: Formulation and evaluation of drug-free ophthalmic films prepared by using various synthetic polymers. Pharmaceutics 2009; 1(2):116-120.
10. Kumar S, Issarani R, Nagori BP and Ahuja M: Design and evaluation of guar gum based ofloxacin sustained release ocular inserts. Asian Journal of Pharmaceutics 2012; 6 (3):198-203.
11. Mundada AS and Shrikhande BK: Formulation and evaluation of Ciprofloxacin Hydrochloride soluble ocular drug insert. Current Eye Research 2008; 33(5-6):469-475.
12. Jethava JK and Jethava GK: Design, formulation and evaluation of novel sustain release bioadhesive *in-situ* gelling ocular inserts of Ketorolac tromethamine. International Journal of Pharma Investigation 2014; 4(4): 226-232.
13. Kerur S, Dandgi P and Deshpande P: Controlled release polymeric ocular inserts for delivery of acyclovir. Turkish Journal of Pharmaceutical Sciences. 2010; 7:75-90.
14. Jayaprakash S, James CC, Maria NS, Saisivam S and Nagarajan M: Design and evaluation of Keterolac Tromethamine ocuserts. Indian Journal of Pharmaceutical Sciences 2000; 62 (5):334-338.
15. Shivhare UD, Chavan MA, Bhusari KP, Mathur VB and Kakade VN: Formulation development and evaluation of controlled release ocular insert. International Journal of Biological and Pharmaceutical Research 2012; 3(1):66-74.
16. Sreenivas SA, Hiremath SP and Godbole AM: Ofloxacin ocular inserts: Design, formulation and evaluation. Iranian Journal of Pharmacology and Therapeutics 2006; 5(2): 159-162.
17. Mohamed AA and Mohamed al-A: Design and evaluation of ciprofloxacin hydrochloride ocular inserts. International Journal of Pharm Tech Research 2011; 3 (3):1750-1763.
18. Rao V and Shyale S: Preparation and evaluation of ocular inserts containing norfloxacin. Turkish Journal of Medical Sciences 2004; 34(4):239-46.
19. Pawar PK, Katara R and Majumdar DK: Design and evaluation of moxifloxacin hydrochloride ocular inserts. Acta Pharmaceutica 2012; 62:93-104.
20. Nageshwara RG and Ramakrishna A: Formulation design and *in-vitro* evaluation of natamycin ocular insert. International Journal of Pharmaceutical Research and Bioscience 2014; 3(2):687-695.
21. Jervis LP: A summary of recent advances in ocular inserts and implants. Journal of Bioequivalnce and Bioavailability 2017; 9(1); 320-323.
22. Balguri SP, Adelli GR and Majumdar S: Topical ophthalmic lipid nanoparticle formulations (SLN, NLC) of indomethacin for delivery to the posterior segment ocular tissues. European Journal of Pharmaceutics and Biopharmaceutics 2016; 109: 224-235.
23. Franca JR, Foureaux G, Fuscaldi LL, Ribeiro TG, Rodrigues LB, Bravo R, Castilho RO, Yoshida MI, Cardoso VN, Fernandes SO, Cronemberger S, Ferreira AJ and Faraco AAG: Bimatoprost loaded ocular inserts as sustained release drug delivery systems for glaucoma treatment: *In-vitro in-vivo* evaluation. Plos One 2014; 9(4):1-11.
24. Kumar KPS, Bhowmik D, Harish G, Duraivel S and Kumar BP: Ocular inserts: a novel drug delivery system. The Pharma Innovation-Journal 2013; 1(12):1-16.
25. Kumar A, Mittal A, Kumar S, Singh A and Gupta A: Effect of Gelrite concentration on the release through ocular inserts of ciprofloxacin hydrochloride. Journal of Pharmacy Research 2009; 2 (3):487-490.
26. Pandey P, Panwar AK, Dwivedi P, Jain P, Agarwal A and Jain D: Design and evaluation of ocular inserts for controlled drug delivery of Acyclovir. International Journal of Pharmaceutical and Biological Archives 2011; 2 (4):1106-1110.
27. Abraham S, Furtado S, Bharath S, Basavaraj BV, Deveshwaran R and Madhavan V: Sustained ophthalmic delivery of Ofloxacin from an ion-activated in situ gelling system. Pakistan Journal of Pharmceutical Sciences 2009; 22 (2):175-179.
28. Sasaki H, Nagano T, Sakanaka K, Kawakami S, Nishida K, Nakamura J, Ichikawa N, Iwashita J, Nakamura T and Nakashima M: One-side-coated insert as a unique ophthalmic drug delivery system. Journal of Control Release 2003; 92 (3):241-247.

29. Charoo NA, Kohli K, Ali A and Anwer A: Ophthalmic delivery of ciprofloxacin hydrochloride from different polymer formulations: *In-vitro* and *in-vivo* studies. Drug Development and Industrial Pharmacy 2003; 29 (2):215-221.
30. Gupta A, Sharma SK and Ahuja M: *In-vitro* and *in - vivo* evaluation of gellan based ocular inserts of Phenylephrine. Acta Pharmaceutica Sciencia 2007; 49:55-63.
31. Sultana Y, Aquil M and Ali A: Ocular insert for controlled delivery of pefloxacin mesylate: Preparation and evaluation. Acta Pharmaceutica 2005; 55:305-314.
32. Venkateshwar R and Somashekar S: Preparation and evaluation of ocular inserts containing norfloxacin. Turkey Journal of Medical Sciences 2004; 34:239-246.
33. Kaur IP and Kanwar M: Ocular preparations: The formulation approach. Drug Development and Industrial Pharmacy 2002; 28 (5): 473 – 493.
34. Upadhyay N, Patidar A and Agrawal S: Development and evaluation of polymeric sustained release levofloxacin ocuserts. Research Journal of Pharmaceutical Biological and Chemical Sciences 2011; 2:411–421.
35. Mortazavi SA, Jaffariazar Z and Damercheli E: Formulation and *in-vitro* evaluation of ocular ciprofloxacin containing minitablets prepared with different combinations of carbopol 974P and various cellulose derivatives. Iran Journal of Pharmaceutical Research 2010; 9:107–114.
36. Lee VH, Li SY, Sasaki H, Saettone MF and Chetoni P: Influence of drug release rate on systemic Timolol absorption from polymeric ocular inserts in the pigmented rabbit. Journal of Ocular Pharmacology 1994; 10:421–429.
37. Friedrich SW, Saville BA, Cheng YL and Rootman DS: Pharmacokinetic differences between ocular inserts and eyedrops. Journal of Ocular Pharmacology and Therapeutics. Spring 2006; 12(1):5-18.
38. Lee YC, Millard J, Negvesky GJ, Butrus SI and Yalkowsky SH: Formulation and *in vivo* evaluation of ocular insert containing Phenylephrine and Tropicamide. International Journal of Pharmacy 1999; 182(1):121-126.
39. Devarajan PV, Bhogte CP, Majali AB and Sabharwal S: Feasibility of an *in-vitro* microbiological model as an alternative to the rabbit eye model. Drug Development and Industrial Pharmacy 1999: 25 (6):781 – 788.
40. Fuchs-Koelwel B, Koelwel C, Gopferich A, Gabler B, Wiegrebe E, Lohmann C.P: Tolerence of a new calcium-alginate-insert for controlled medication therapy of the eye. Ophthalmologe 2004; 101(5):496-499.
41. Calvo P, Vila-Jato JL and Alonso MJ: Comparative *in-vitro* evaluation of several colloidal systems, nanoparticles, nanocapsules and nanoemulsions as ocular drug carriers. Journal of Pharmaceutical Sciences. 1996; 85(5):530-536.

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