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Research Article

Formulation and Evaluation of Celecoxib In-Situ Ophthalmic Gel

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ABSTRACT

Conventional ophthalmic solution has many disadvantages like rapid drainage, so repeated dosing is required. In order to have prolonged effect in-situ gel may be a better option, as it increases the contact time of drug with corneal tissue. The main objective of the present work is formulation and evaluation of in situ ophthalmic gel for sustained drug action, decrease precorneal drug loss, increase corneal contact time. Celecoxib is a lipophilic drug having very low water solubility, so modified physical form of celecoxib prepared by kneading with β-CD (1:1) can be used for formulation of ophthalmic in-situ gel with 6 %w/v NaCl to have prolonged drug release.

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INTRODUCTION

Many parts of the eye are relatively inaccessible to systemically administrated drugs and, as a result, topically drugs delivery remains the preferred root in most cases. Drugs may be delivered to treat the precorneal region of such infection as conjunctivitis and blepharitis, or to provide intraocular treatment via the cornea for disease such as glaucoma and uveitis.[1]

Corticosteroids used to be the mainstay of topical therapy in the management of ocular inflammations.[2] Their use is associated with an increase in intraocular pressure, cataract formation, and risk of infections.[3] Nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin,[4] flurbiprofen,[5] ketorolac, [6] and diclofenac [7] have been observed to be viable alternatives to corticosteroids in the management of ocular inflammation.

Celecoxib is a non-steroidal anti-inflammatory drugs (NSAIDs) used in the treatment of osteoarthritis, rheumatoid arthritis, acute pain, painful mensuration and menstrual symptoms, and to reduce numbers of colon and rectum polyps in patient with familial adenomatous polyposis. It is marketed by Pfizer under the brand name Celebrex. In some countries, it is branded celebra. Celecoxib is available by prescription in capsule from. Most NSAIDs inhibit the activity of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), and thereby, the synthesis of prostaglandins and thromboxanes. It is thought that inhibiting COX-2 leads to the anti-inflammatory, analgesic and antipyretic effects and that those NSAIDs also inhibiting COX-1, particularly aspirin, may cause gastrointestinal bleeding and ulcers.[8]

The main aim of pharmacotherapeutics is the attainment of an effective drug concentration at the intended site of action for a sufficient period of time to elicit the response. Poor bio-availability of drug from ocular dosage forms is mainly due to the tear production, non-productive absorption transient residence time, and impermeability of corneal epithelium.[9]

MATERIALS AND METHOD

Materials:

Celecoxib was procured as generous gift sample from Cadila Health Care, Ahmedabad, Gujarat. Hydroxy Propyl Methyl Cellulose (HPMC) was obtained from S&A chemicals, Mulund west, Mumbai. Beta-Cyclodextrin (β CD) was obtained from Dzone international, Mumbai. Sodium Chloride (NaCl) was purchased from E. Merck India Pvt. Ltd., Mumbai. All other chemicals were of analytical grade.

Standard curve of celecoxib in water at 248 nm

Standard stock solution

Celecoxib (100mg) was dissolved in 10 mi of methanol and volume was made to 100ml with distilled water to from a clear solution.

Working stock solution

A series of celecoxib solution ranging from 2 to 20 µg/ml were prepared from standard stock solution. The low concentration was scanned in the range of 200-400 nm to get the maximum absorbance of 248 nm and the absorbance of the solution was measured spectrophotometrically at 248 nm.

Table-1: Standard curve of celecoxib in distilled water

Celecoxib Concentration (µg/ml)	Absorbance at 248nm
2	0.098
4	0.194
6	0.291
8	0.378
10	0.479
12	0.577
14	0.671
16	0.766
18	0.862
20	0.959

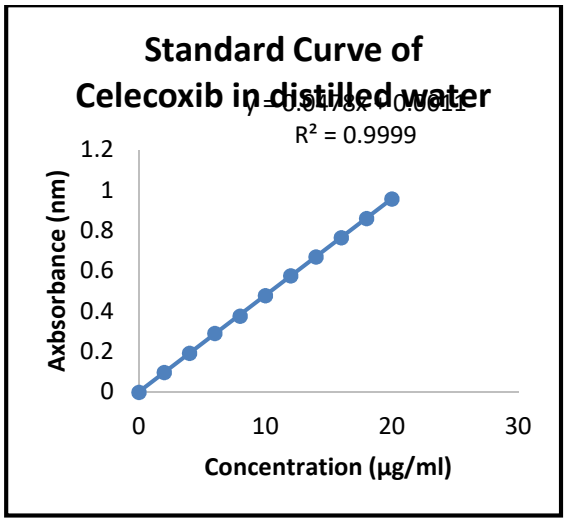

Figure-1 Standard curve of celecoxib in distilled water

Standard curve of celecoxib in bicarbonate ringer at 248 nm

Standard stock solution

Celecoxib (100 mg) was dissolved in 10 ml of methanol and then the volume was made to 100 ml with bicarbonate ringer to from a clear solution.

Working stock solution

A series of the stock solution ranging from 2 to 16 µg/ml were prepared from standard stock solution. The concentration was scanned in the range of 200-400 nm to get the maximum absorbance of 248 nm and the absorbance of the solution was measured spectrophotometrically at 248 nm.

Table-2: Standard curve of celecoxib in bicarbonate ringer

Concentration (µg/ml)	Absorbance (248 nm)
2	0.128
4	0.224
6	0.335
8	0.458
10	0.549
12	0.669
14	0.783
16	0.911

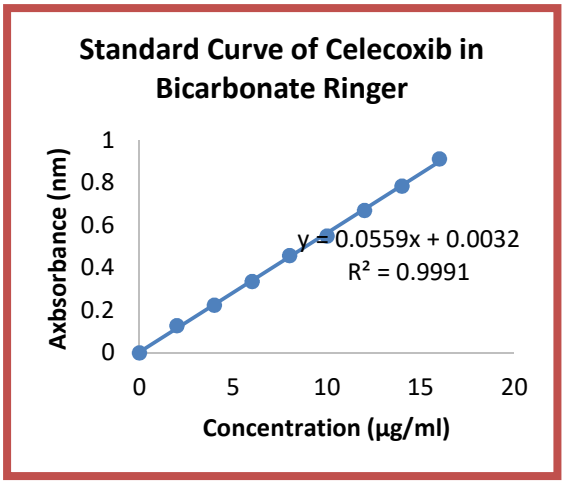

Figure-2 Standard curve of celecoxib in bicarbonate ringer

Preparation of Formulation:

***Modification by kneading method [10]*:**

Celecoxib & β-CD (1:0.5, 1:1 and 1:1.5 molar ratios) was triturated in a mortar and pestle with hot water to get a pasty mass. The wet mass was dried in hot air oven at 45 °C, passed through sieve #80 and designated as KNB_1, KNB_2 and KNB_3 respectively was kept in desiccators.

***Saturated solubility studies*:**

Excess amount of Celecoxib (pure drug) and the prepared physical forms were added to the glass vials containing 10mL of distilled water. The sealed vials were shaken for 24 hour at 25 °C followed by equilibrium for three days. The aliquots were withdrawn through whatman filter paper. The concentration of celecoxib was determined by UV spectrophotometer at 248 nm.

***Test sample*:**

The prepared physical form showed highest solubility (i.e, KNB_2, 0.0048 gm, equivalent to 0.003% w/v of pure drug) was used for preperations of formulations. 1% w/v HPMC solution was prepared in distilled water with stirring and kept in refrigerator overnight in order to obtain a clear solution. Complex KNB_2 was added with further stirring. 5mL of each of the solution 4% & 6% w/v NaCl was added to the above solution and designated as F_1 & F_2. The pH was adjusted to 7.4 by NaOH & HCl.

Table-3 Formulation of Gel

F.C.	Amount prepared physical form of Celecoxib (gm)	Amt of HPMC (% w/v)	Amt of NaCl (%w/v)
F_1	0.0048	1	4
F_1	0.0048	1	6

EVALUATION OF FORMULATIONS:

***Appearance*:**

Formulations were examined visually for texture and clarity against white background and for the presence of particulate matter any if present.

***In-vitro gelation studies*:**

The reversible sol-gel transition temperature was measured by test tube tilting method (TTM). To measure the gelation temperature, the solution (20ml) was sealed in a 20ml glass tube and placed in controlled temperature bath. The temperature of bath was increased at a very slow rate. At a certain temperature the solution was completely converted into gel. The gel became viscid and did not flow with the tilting of the test tube. This characteristic temperature is called gelation time. Same process has been repeated 2-3 times to get the accurate value.

***Gel strength*:**

Gel strength is important in finding the condition, which can delay the anterior leakage. Optimal in-situ gel must have suitable gel strength so as to be administered easily and can be retained at ophthalmic mucosa without leakage after administration. The gel strength of the in situ gels were performed by using the ball (10mg) placed in a 100ml beaker containing in-situ gel and measured by time taken by time taken for ball to penetrate 5cm.

***Drug content*:**

Drug content was determined by dissolving an accurately weighed quantity of formulation (100mg) in 50ml of methanol. The solution were then further diluted with methanol and filtered through 0.45m membrane filter and analyzed for celecoxib content by UV spectrophotometer at 248nm.

***In vitro drug release*:**

The in vitro releases of the prepared formulations were studies through dialysis membrane using a Franz diffusion cell [11, 12]. The dialysis membrane was previously soaked overnight in a dissolution medium (bicarbonate ringer, P^H 7.4) the dialysis membrane was placed between the donor and receptor compartment. The receptor compartment was filled with 50ml of freshly prepared bicarbonate ringer (P^H 7.4). One milliliter of test formulation was placed on the donor compartment. Evaporation of the test formulation was prevented by sealing

the opening of the donor compartment with a glass cover sip, while the receptor fluid was maintained at 37^0C with constant stirring at a 50 rpm, using a Teflon-coated magnetic stir bead. 3 ml sample was withdrawn from the receptor compartment at various time interval up to 240 minutes and withdrawn sample were replaced with equal volume of the bicarbonate ringer. The sample were analyzed for the celecoxib by the measuring absorbance at 248 nm in a UV-spectrophotometer.

RESULTS & DISCUSSION

Table-4: Solubility study

S.N.	Name	Amount (mg/ml)	%w/v
1	Celecoxib (pure drug)	0.013± 0.012	0.001±0.11
2	KNB_1	0.024± 0.018	0.002±0.23
3	KNB_2	0.073± 0.035	0.007±0.021
4	KNB_3	0.052± 0.041	0.004±0.014

Values are mean ±SD (n=3)

Table-5: Drug content in Methanol

Name	Amount (mg/ml)	% Drug content
KNB_2	1.863± 0.034	93.19149± 0.045

Values are mean ±SD (n=3)

Table-6: in-vitro evaluation of in-situ gel

Formulation	pH	Texture	Clarity	Gelation temperature (^{o}C)	Gel strength (Sec)	Drug content (%)
F1	7.4±0.054	Sticky, non-greasy	Clear	37±0.046	42±0.01	84.7±0.08
F2	7.4±0.031	Sticky, non-greasy	Clear	37±0.18	58±0.17	89.12±0.13

Values are mean ±SD (n=3)

Table-7: in-vitro drug release in bicarbonate ringer (pH 7.4)

Time (min)	Cumulative % drug release (F_1)	Cumulative % drug release (F_2)
0	0	0
15	8.74	5.21
30	11.4	8.77
60	24.56	16.99
90	32.48	25.67
120	42.78	30.31
150	50.734	37.67
180	59.644	43.09
210	68.554	49.87
240	79.358	52.35

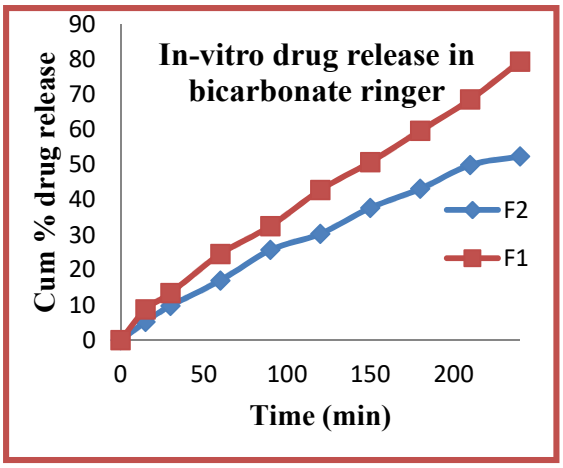

Fig-3 In-vitro drug release in bicarbonate ringer

Solubility of pure drug in distilled water (Table-4) was 0.013 mg/ml; whereas solubility of prepared physical forms were 0.024 to 0.073 mg/ml with KNB_2 showed the highest solubility (0.073 mg/ml), which may be due to formation of stoichiometric complex. Drug content of the complex KNB2 was found to be 93.19% (Table-5). HPMC has gelation temperature around 500C but addition of NaCl might reduce the gelation temperature. The results (Table-6) showed the gelation temperature was 37±0.5 0C. All the formulations were clear, sticky and non-greasy with pH of 7.4. Gel strength was 42 & 58 second respectively for F1 & F2. Which indicates is high viscous product, indicating slow drug release from gel matrix. Drug content of the formulations were 84.7% and 89.12 % respectively.

In-vitro drug release study (Table-7, figure-3) shows, in 15minutes 8.74 % & 5.21% from the formulation F1 & F2 respectively. While at 240 minutes it was 79.35% & 52.35%. Which indicates F2 formulation could sustain drug release better than F1 formulation as its gel strength was more.

CONCLUSION

Conventional ophthalmic solution has many disadvantages like rapid drainage, so repeated dosing is required. In order to have prolonged effect in-situ gel may be a better option, as it increases the contact time of drug with corneal tissue. Celecoxib is a lipophilic drug having very low water solubility, so modified physical form of celecoxib prepared by kneading with β-CD can be used for formulation of ophthalmic in-situ gel with 6 %w/v NaCl to have prolonged drug release.

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CONFLICT OF INTEREST

There is no conflict of interest.

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