Available online on 15.10.2019 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Research Article

Formulation and Evaluation of Tafluprost Ophthalmic Solution

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ABSTRACT

The aim of the present study was to formulate, develop and evaluate ophthalmic solution containing Tafluprost. The selected prostaglandin analogue belongs to BCS - II. So to increase the solubility of the Tafluprost in WFI Beta Cyclodextrin was used by performing various trials variables of the experiments procedure Stirring time and speed were optimized to enhance the solubility. From the experimental procedure with different trails 20mg/mL of Cyclodextrins was fixed for the optimized formula. The product were characterized for appearance, physical state, colour and odour of the drug characteristics. The prepared formulations were evaluated for pH, osmolality and assay and found to be in acceptable ranges. Stability study was carried out for optimized formulation at 40°C±2°C /NMT 25%RH and 30°C ±2°C/ 65%±5% RH for 3 months, were evaluated for pH ,osmolality ,assay found to be within acceptable limits. Finally it can be concluded that the in house product Tafluprost ophthalmic solution was met with in the specification.

Keywords: Tafluprost, prostaglandin analogue, BCS – II, Cyclodextrins.

Article Info: Received 04 July 2019; Review Completed 18 Aug 2019; Accepted 28 Aug 2019; Available online 15 Oct 2019

Cite this article as:

Tarun Kumar PV, Anil Kumar A, Srinivas Rao N, Formulation and Evaluation of Tafluprost Ophthalmic Solution, Journal of Drug Delivery and Therapeutics. 2019; 9(5-s):18-24 http://dx.doi.org/10.22270/jddt.v9i5-s.3612

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INTRODUCTION:

Ophthalmic preparations are specialized dosage forms designed to be instilled onto the external surface of eye (topical), administered inside (intraocular), adjacent to the eye (periocular) or used in conjunction with any special device[1].

Ocular drug delivery is one of the most appealing and arduous endeavours facing by the pharmaceutical scientist. The primitive ophthalmic solutions, suspensions and ointment dosage forms are unquestionably no longer satisfactory to combat some current virulent diseases[2, 3]. An analysis write-up proclaims that almost 90% of ready for use ophthalmic formulations in the US, and an equivalent percentage is still supposedly valid for the present international trade.

On the ground of anatomy and physiology eye is a complex and incomparable structure guarded by a number of defensive attitude machineries. The framework, biochemistry, and physiology of the eye set down this organ tremendously impervious to strange entities[4]. Assorted adaptations guarding the eye from noxious entities and agents such as lacrimation, reflex blinking, rapid tear turnover, drainage, and pre-corneal loss concludes in remarkably inadequate absorption of topically executed ophthalmic drugs.

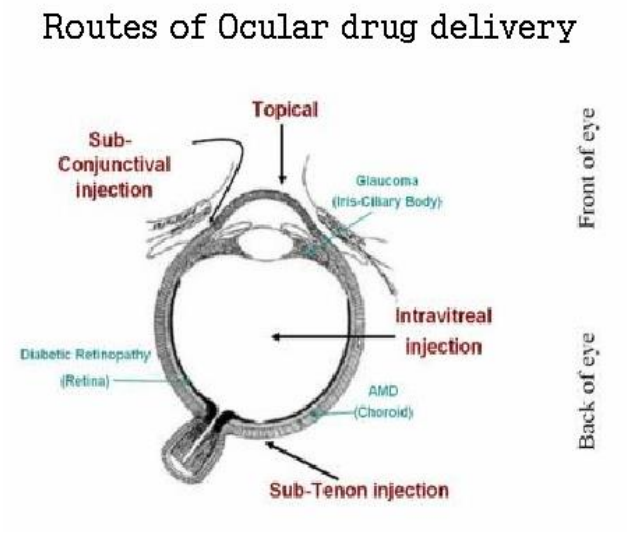
Development of newer, more sensitive diagnostic techniques and novel therapeutic agents continue to provide ocular delivery systems with high therapeutic efficacy. Conventional ophthalmic formulations like solution, suspension, and ointment have many disadvantages, which result into poor bioavailability of drug in the ocular cavity. The specific aim of designing a therapeutic system is to achieve an optimal concentration of a drug at the active site for the appropriate duration[1].

Prostaglandins analogues are main playing important role in ophthalmic eye formulations. It Tafluprost is used topically to control the progression of open angle glaucoma,

And in the management of ocular hypertension, alone or in the combination with other medications. It reduces intraocular pressure by increasing the outflow of aqeous fluid from the eyes.

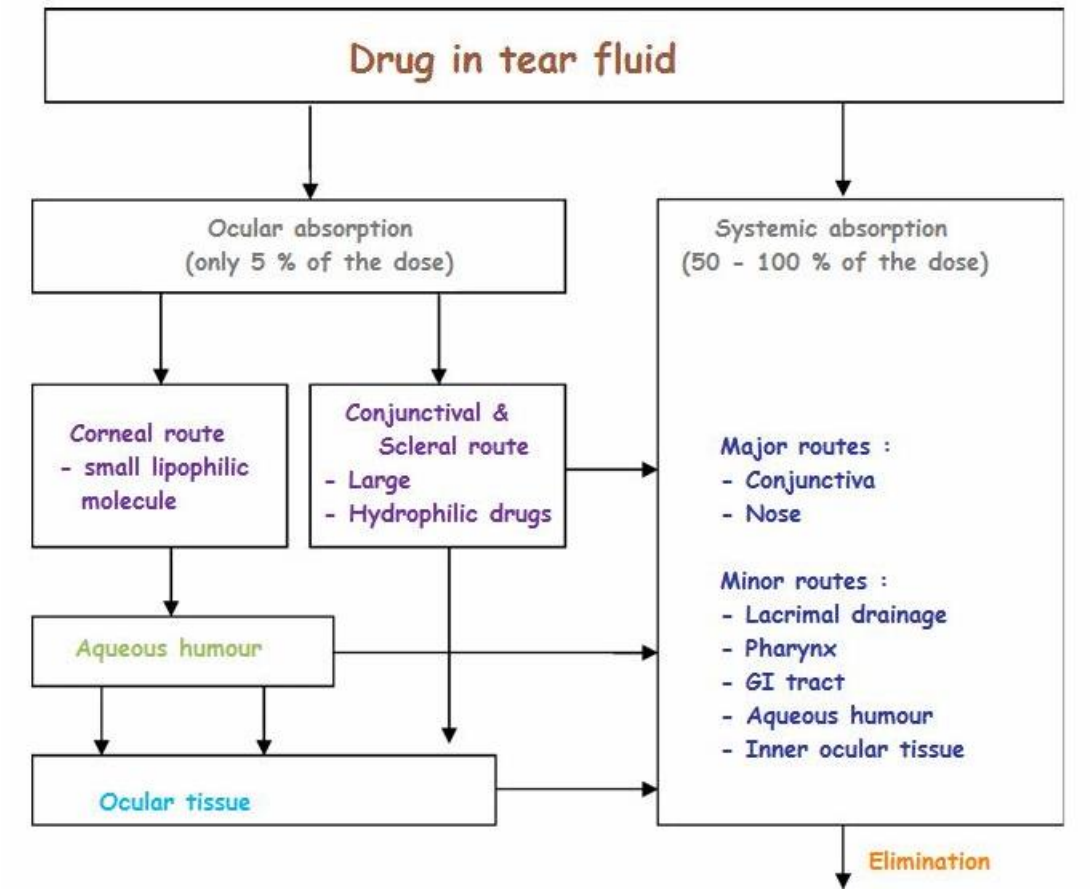
Routes of Ocular Drug Delivery

There are several possible routes of drug delivery into the ocular tissues. The selection of the route of administration depends primarily on the target tissue[1].



Mechanism of Ocular Drug Absorption

Corneal permeation[8, 9]



The Tafluprost acid is a Prostanoid selective FP receptor agonist so that it is believed to reduce the intraocular pressure and also increasing the outflow of aqueous humor in the eye[5, 6, 7]. So that the Studies in animals and humans recommend mechanism of action is increased uveoscleral outflow[10].

MATERIALS AND METHODS:

Tafluprost (Symbiotic), Sodium dihydrogen phosphate monohydrate (Merck), anhydrous disodium phosphate (Merck), Beta cyclodextrins (Casymchem), Benzalkonium chloride (Merck), Sodium Chloride (Merck) and water for injection (WFI) are used in the preparation of Tafluprost Ophthalmic Solution. All chemicals used in this study are analytical grade.

Method:

The experimental work are conducted in stages as follow_

Preformulation Studies:

Physical Characterization of Active Pharmaceutical Ingredient (Tafluprost) was observed regarding Appearance, Physical state, Colour & Odour.

Procedure for Physical Characterization of Tafluprost:

2g of sample was taken into clean and dry petridish, spread uniformly with spatula and above parameters were observed.

Procedure for Preparation of Tafluprost Ophthalmic Solution:

Different trials were taken to optimize the method of preparation of Tafluprost Ophthalmic Solution which are mentioned in step wise as below_

Optimization of Osmolality:

As per pack insert from the quantities of Tafluprost, Benzalkonium chloride and are listed as follows;

Tafluprost : 50Mcg/mL

Benzalkonium chloride : 0.1%

The basis of osmolality of eye fluid (i.e; 280-320mosm/kg) the remaining excipients were optimized. The quantities of API and preservative are kept as same that of reference product. Different solutions with varying concentrations of Sodium Chloride, Sodium dihydrogen phosphate monohydrate, Disodium phosphate prepared and measured for osmolality. Experiment shows, increase or decrease of osmolality upon increase or decrease of quantity in solutions. So that the below illustrate the osmolality value for different trials.

Method of Preparation for Optimization of concentration of osmolality agent:

Collect approximately required quantity of Water for injection for batch size from that Collect 70% batch size of WFI in Duran bottle. To it add Sodium dihydrogen phosphate followed by disodium hydrogen phosphate anhydrous, sodium chloride & benzalkonium chloride and dissolve under stirring until to get clear solution. Finally add the batch quantity of API and stir until it get dissolve and make up the volume to 100% batch size.

NAME OF THE INGREDIENT	CONCENTRATION mg/mL			
	Trail-1	Trail-2	Trail-3	Trail-4
Tafluprost	0.05	0.05	0.05	0.05
Sodium Dihydrogen phosphate monohydrate	13	8	4.6	4.6
Disodium phosphate	12	7	4.7	4.7
Sodium chloride(Concentration)	7	6	5.4	4.1
BKC	0.1	0.2	0.2	0.2
Water for Injections	q.s	q.s	q.s	q.s
Osmolality	597.83	454.93	325.5	289.91
pH	7.8	7.3	7	6.7

Conclusion: Based on above trails, it was found that trail -4 was meeting the requirement.so that further studies were carried out with the trail 4. **(**i.e.; 280-320mosm/kg). So quantification of Excipients was fixed as per trail-4.

Optimization of API Solubility:

Tafluprost generally belongs to BCS class 2 which is less soluble and high permeability drug. The proposed formulation in aqueous eye drop preparation. Hence water for injection is selected as a vehicle as already known that Tafluprost is practically insoluble in water (It indicates less than 0.1 mg/mL).

So Hydroxy propyl Beta cyclodextrins used to improve the solubility of the Tafluprost in aqueous phase without degradation of product. The concentration of hydroxyl propyl beta cyclodextrins was fixed based on trial basis.

Method of Preparation for Optimization of API Solubility:

Collect Approximately 110% batch size of Water for injection and purge nitrogen for 30 minutes to remove dissolved oxygen content levels. (Limit of D.O level-Less than 2 mg/L. Collect 70% batch size of WFI in duran bottle and add Hydroxypropyl betadextrins under stirring followed by Sodium dihydrogen phosphate, disodium hydrogen phosphate anhydrous and sodium chloride& benzalkonium chloride and dissolve under stirring until to get clear solution. Finally add the batch quantity of API and stir until it get dissolve and make up the volume to 100% batch size.

NAME OF THE INGREDIENT	CONCENTRATION mg/mL			
	Trail-5	Trail-6	Trail-7	Trail-8
Tafluprost	0.05	0.05	0.05	0.05
Beta cyclo dextrins	3	7	15	20
Sodium Dihydrogen phosphate monohydrate	4.6	4.6	4.6	4.6
Disodium phosphate	4.7	4.7	4.7	4.7
Sodium chloride	4.1	4.1	4.1	4.1
Benzalkonium chloride	0.1	0.1	0.1	0.1
Water for Injections	q.s	q.s	q.s	q.s
Assay (percentage)	**40**	**68**	**94**	**100.2**

From the above data it was found that Trial 8was found to be better compared to other trials. Further manufacturing process was optimized (i.e., stirring speed and stirring time)

Optimisation of Manufacturing Process:

Stirring time and speed:

Generally stirring time and speed alter the solubility. Various trails were taken to optimize the solubility of the drug. Different batches were prepared and stirred at different speed on a magnetic stirrer. Time taken for solubilisation of Tafluprost was noted with assay. Results are as follows.

RPM/Time taken for solubilisation	Trail-9	Trail-10	Trail-11	Trail-12
RPM	100	150	200	250
Time (hr)	4	4	4	6
Assay	88.5	92.3	97.6	101.9

Based on the above analytical results, as the stirring time and RPM increases the solubility also increased. It was found that the 250 RPM for minimum 6 hours stirring shown better assay value.

Final Optimized formula:

S.No.	Formula	Quantity(mg/ml)
1.	Tafluprost	0.05
2.	Hydroxy propyl beta cyclodextrins	20
3.	Sodium Dihydrogen phosphate monohydrate	4.6
4.	Disodium phosphate	4.7
5.	Benzalkonium chloride	0.1
6.	Sodium chloride	4.1
7.	Water for injection	Q.S.

Final Optimized Method:

Collect Approximately 110% batch size of Water for injection and purge nitrogen for 30 minutes to remove dissolved oxygen content levels. (Limit of D.O level-Less than 2 mg/L). Collect 70% batch size of WFI in duran bottle to it add Hydroxypropyl beta dextrins in above step 2 and set magnetic stirrer speed 100 RPM followed by addition of Sodium dihydrogen phosphate, disodium hydrogen phosphate anhydrous & Sodium chloride and stir until it get dissolve. From the above solution 30 % of total batch size of above solution in a beaker and add batch quantity of API and stir to get dissolve. To the remaining solution add benzalkonium chloride which have been dissolved in water and stir to get dissolve. API containing solution was added to benzalkonium chloride solution and stirred for 4 hrs and makeup the solution 100% batch size. Same process and same formula was repeated in trail-14 to trail-16 to check the reproducibility.

Sr.No.	Formula	Quantity(mg/ml)			
		Trail-13	Trail-14	Trail-15	Trail-16
	Tafluprost	0.05	0.05	0.05	0.05
	Hydroxy propyl beta cyclodextrins	20	20	20	20
	Sodium Dihydrogen phosphate monohydrate	4.6	4.6	4.6	4.6
	Disodium phosphate	4.7	4.7	4.7	4.7
	Benzalkonium chloride	0.1	0.1	0.1	0.1
	Sodium chloride	4.1	4.1	4.1	4.1
	Water for injection	q.s	q.s	q.s	q.s

RESULTS AND DISCUSSION

Appearance:

All the formulation batches of tafluprost ophthalmic solution were found to be Clear Colourless solution.

Drug Content:

The drug content was found to be in acceptable range for all the formulations in the initial.

The in process specification 95%-105% and tafluprost ophthalmic solution was found with in the limit and the results are tabulated below.

Osmolality:

The Osmolality of all formulation was found to be satisfactory and was in the range and the data was found mentioned in the below table..

pH:

The pH of all formulations was found to be satisfactory and was in the range of 6.7 and the data was mentioned in below the table.

Batch No	Test Parameter		
	Drug Content	Osmolality (m Osm/kg)	pH
F1 (Initial)	105.4	289	6.72
F2 (Initial)	103.6	290	6.73
F3 (Initial)	104.1	289	6.72

Viscosity Study: The tafluprost ophthalmic solution shown data tabulated in the below from the initial to 40°C±2°C /NMT25%RH up to 3 months in the accelerated condition. There is no significant changes observed from the initial to 3 months. So that the product is stable up to 3 months.

Viscosity		
Batch No	Condition	Results
F1(715/051A)	Initial	2 cps
F1(715/051B)	Initial	3 cps
F2(715/039)	Initial	2 cps
F1(715/051A)	40/25 3M	2 cps
F1(715/051B)	40/25 3M	3 cps
F2(715/039)	40/25 3M	2 cps

Drop Size:

The Drop size of the Tafluprost ophthalmic solution was performed formed the results in the below table:

Calculation of the drop size

Drop size in µL = Average Wt .of drops(mg)/Density of the solution

S.No	TEST PARAMETER	Weight of the Drop (mg)	
		Orientation	
		Inverted 90°	Inclined 45°
1	DROP SIZE STUDY	48.63	35.95
2		49.05	37.21
3		48.54	37.36
4		49.18	37.31
5		48.25	34.45
6		49.01	38.68
7		49.79	38.57
8		47.65	38.49
9		47.98	37.71
10		48.65	37.24
11		48.43	37.36
12		47.99	39.58
13		48.12	37.95
14		47.65	38.66
15		49.42	38.36
16		48.15	38.2
17		47.77	38.34
18		47.65	37.82
19		49.02	38.42
20		47.75	37.89
21		48.24	37.89
22		48.01	37.36
23		48.91	37.18
24		48.06	38.84
25		47.78	38.8
26		48.11	38.31
27		47.8	38.01
28		47.95	39.49
29		47.94	37.72
30		47.95	38.28
Total weight(mg)		1449.43	1137.43
Average weight of 30 Drops(mg)		48.31	37.91
Density of the solution		1.0058	1.0059
Drop Size (µL)		48.04	37.69

Stability Study:

Prepared formulations Anti-Glaucomal ophthalmic solution was subjected to pH stability and containers compatibility studies at 40˚C ± 2 ˚C /NMT 25% , for a period of 1 month,2 and 3 months. From the above data 3-piece LDPE container was better compatible with formulation. Also the pH remained within desired range for 3-piece LDPE containers.

Also prepared formulations of Anti-Glaucomal ophthalmic solution was subjected to stability studies at 30˚C ± 2 ˚C /65% ± 5 % RH for a period of 1 month, 2 month and 3 month as per ICH guidelines. The samples were withdrawn after period of 1 month, 2 month and 3 month and were evaluated for following parameters such as Description, Drug content, pH, and Osmolality as given in table.

STABILITY RESULT OF BATCH NO F1 (715/051A)							
Stability Condition	**Initial**	**40°C±2°C /NMT25%RH**			**30°C ±2°C/ 65%±5%RH**		
Test parameters		**1M**	**2M**	**3M**	**1M**	**2M**	**3M**
Description	#	#	#	#	#	#	#
Assay of API (%)	105.4	103.6	104.1	103.7	103.2	105.4	107.3
pH	6.72	6.73	6.74	6.71	6.72	6.74	6.72
Osmolality (mOsm/kg)	272	273	267	291	262	277	289

STABILITY STUDY STABILITY RESULT OF BATCH NO-F1 (715/051B)							
Stability Condition	**Initial**	**40°C±2°C /NMT25%RH**			**30°C ±2°C/ 65%±5%RH**		
Test parameters		**1M**	**2M**	**3M**	**1M**	**2M**	**3M**
Description	#	#	#	#	#	#	#
Assay of API (%)	105.4	98.5	96.6	95.7	102.2	98.4	107.6
pH	6.71	6.72	6.74	6.73	6.72	6.74	6.73
Osmolality (mOsm/kg)	272	267	274	306	261	277	315

STABILITY STUDY: STABILITY RESULT OF BATCH NO- F2 (715/039)							
Stability Condition	**Initial**	**40°C±2°C /NMT25%RH**			**30°C ±2°C/ 65%±5%RH**		
Test parameters		**1M**	**2M**	**3M**	**1M**	**2M**	**3M**
Description	#	#	#	#	#	#	#
Assay of API(%)	100.2	96.7	97.3	101.2	97.8	99.3	98.6
pH	6.71	6.73	6.72	6.75	6.71	6.72	6.73
Osmolality (mOsm/kg)	272	267	274	306	261	277	315

The Physical parameters like Description and pH Osmolality was found to be satisfactory and the assay of tafluprost was found to be with in the Specification Limit. The above data represents that the Tafluprost ophthalmic solution was found to be stable with in respective from the initial to the 3 months of the accelerated and long term condition.

SUMMARY AND CONCLUSION

Ophthalmic solutions mainly used in the Topical administration for the treatment of Glaucoma. So that Tafluprost ophthalmic solutions are mainly used for the treatment of the open angle Glaucoma. Tafluprost is belongs to BCS class II, which is having high permeability and low solubility. Hydroxy propyl beta cyclodextrins was used to enhance the solubility of Tafluprost API in the Tafluprost ophthalmic solution. Various trails of beta cyclodextrins were taken with different concentrations as the concentration of beta cyclodextrins increases solubility of the Tafluprost also increased. The concentration hydroxy propyl beta cyclodextrins i.e. (20mg/ml) shown 100% solubility in the experimental procedure. Optimization of Osmolality studies were done by taking various trails of sodium chloride with 7mg, 6mg and 4.1mg of different concentration used to bring the Osmolality value of lacrimal fluids. Finally Sodium chloride (4.1mg/mL) was concentration was fixed for the Tafluprost ophthalmic solution. Optimization of stirring speed and time studies were done with the various trails were taken with different RPM and time. As the time increases the solubility of the drug also increased in the Tafluprost ophthalmic solution stirring at 250rpm for 6 hours shown better assay value. Prepared formulations Tafluprost ophthalmic solution was subjected to pH stability and containers compatibility studies at40˚C C ± 2 ˚C /NMT 25%, for a period of 1 month, 2 and 3 months. Also prepared formulations of Tafluprost ophthalmic solution was subjected to stability studies at 30˚C ± 2 ˚C /65% ± 5 % RH for a period of 1 month, 2 month and 3 month as per ICH guidelines. The product was found to be stable and no significant chang e was observed during the Accelerated and intermediate term stability conditions. There is no change in the Viscosity in the Tafluprost ophthalmic solution through the Stability period up to 3months in both the accelerated and intermediate term condition. Finally it is concluded that the product Tafluprost ophthalmic solution was met the specifications.

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