IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

FORMULATION AND EVALUATION OF OCULAR INSERTS OF DICLOFENAC SODIUM FOR CONTROLLED RELEASE DRUG DELIVERY

Devu.Satya Sireesha*[1], B.Lakshmi Prasanna[2], M.Harini[3], V.Shirisha[4], T.Rama Rao[5]

***Corresponding Author**: Devu.Satya Sireesha, Assistant Professor, CMR College Of Pharmacy, Kandlakoya, Hyderabad, 501401.

ABSTRACT

The main aim of the present study is to formulate an effective ocular inserts of Diclofenac sodium, which can produce a better ocular therapy against ocular infections by increased bioavailability through increased drug-eye contact time and controlling the trans-corneal permeation of drug. We intend to optimize the formulation to show constant release of drug for maintenance of dose over a prolonged period of time. For this purpose we prepared Diclofenac sodium ocular inserts formulations by use of different polymers, HPMC, Eudragit L100, Polyvinyl alcohol at various concentrations and dibutyl phthalate has plasticiser.The prepared formulations were evaluated for various physical and analytical parameter related to appearance, durability, uniformity of drug contents, in-vitro and in-vivo release of drug and for stability. ocular inserts of Diclofenac sodium were prepared by solvent casting method followed by preparing the drug reservoir film and rate controlling membrane separately. Evaluation of ocular inserts for weight and thickness variation were carried out.From current study we can conclude that by using different polymer in rate controlling membrane of an ocusert, release rate of drug from ocusert can be controlled or altered.

Keywords: Ocusert; Clotrimazole; HPMC, Eudragit L100 Polyvinyl alcohol dibutyl phthalate.

INTRODUCTION:

Ocular drug delivery is one of the most challenging tasks faced by Pharmaceutical researchers. Major barriers in ocular medication are the ability to maintain a therapeutic level of the drug at the site of action for a prolonged duration. The anatomy, physiology, and biochemistry of the eye is such that it is impervious to foreign substances, therefore, it is a challenge for the formulator to pass through the protective barriers of the eye without causing any permanent tissue damage. The introduction of new sensitive diagnostic techniques and therapeutic agents necessitates the development of a successful and advanced ocular drug delivery system[1].

Ocuserts are sterile, solid or semisolid dosage forms prepared to attain increased contact time between the drug and the conjunctival tissue to keep up a constant release of drug when placed in the lower cul-de-sac or conjunctival sac of the eye[4].

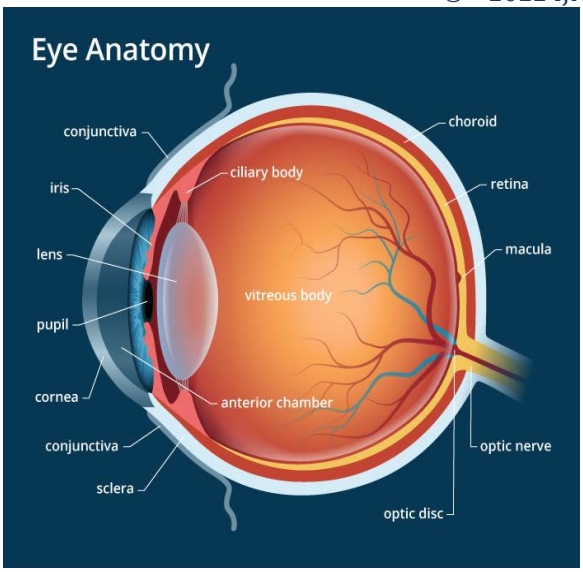


Fig-1

Mechanism of ocular drug delivery system:
The mechanism of controlled release of ocular drug delivery system as follows:

Osmosis:
In the osmosis mechanism the insert compromises a transverse impermeable elastic membrane dividing the interior of the insert into the first compartment and second compartment; the first compartment is bounded by a semipermeable membrane and the impermeable elastic membrane and the second compartment is bounded by and impermeable membrane and the elastic membrane. There is a drug release aperture in the impermeable wall of the insert. The first compartment contains a solute which cannot pass through the semi permeable membrane and the second compartment provides reservoir for the drug which again is in liquid or gel form. When the insert is placed in the aqueous environment of the eye, water diffuses into the first compartment and stretches the elastic membrane to expand the first compartment and contract the second compartment so that the drug is forced through the drug release aperture[14].

Diffusion:
The diffusion mechanism, the drug is released continuously at the control rate through the membrane into the tear fluid. If the insert is formed of a solid non erodible body with pores and dispersed drug within matrix as a result of inward diffusion of aqueous solution. In a soluble device, true dissolution occurs mainly through polymer swelling., in swelling controlled devices the active agent is homogeneously dispersed in a glassy polymer. Since glassy polymers are essentially drug impermeable, no diffusion through the dry matrix occurs. when the insert is placed in the eye water from the tear fluid begins to penetrate the matrix, done swelling and consequently polymer chain relaxation and drug diffusion takes place. The dissolution of the matrix which follows the swelling process, depends on polymer structure linear amorphous polymers dissolve much faster than the crosslinked or partially crystalline polymers. Release from these devices follows in general fickian ‘square root of time’ kinetics in some instances, however, known as case 2 transport zero order kinetics has been observed[15].

Bio-erosion:
In the bio-erosion mechanism, the configuration of the body of the insert is constituted from an matrix of bioerodible material in which the drug is dispersed. Contact of the insert with tear fluid results in controlled sustained release of the drug by bio-erosion of the matrix. The dug may be dispersed uniformly throughout the matrix but it is believed a more controlled release is obtained if the drug is superficially concentrated in the matrix[16].

Advantages:

The advantages of ocular drug delivery systems have been summarized below:

- They impart accuracy and uniformity in dosing rate. Pulsed dosing of conventional systems can be avoided.
- Sustained and controlled release of drugs can be achieved.
- By increasing corneal contact time, they cause enhancement in the ocular bioavailability of drugs and it is achieved by effective adherence of the drug to the corneal surface.
- For the prevention of loss of ocular tissues, targeting within the ocular globe is to be done.
- They bypass the protective ophthalmic barriers, such as drainage, lacrimation and conjunctival absorption.
- They also improve patient's compliance, offer comfort and enhance therapeutic drug performance.
- They provide better housing of delivery systems.
- The make self-administration of drugs possible.
- Systemic and visual side effects are lower and absorption is faster[17].

DRUG PROFILE:

Diclofenac Sodium-

Generic name: Voltaren

Structure:

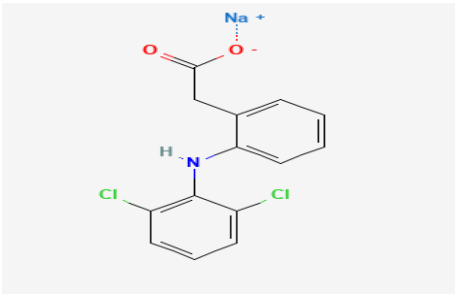


Fig-3

Chemical formula: $C_{14}H_{10}Cl_2NNaO_2$

IUPAC name: sodium;2-[2-(2,6-dichloroanilino) phenyl]acetate

Category: Non-steroidal anti-inflammatory drug (NSAID)

EXCIPIENTS PROFILE:

HPMC:

- HPMC (hydroxy propyl methyl cellulose) or Hypromellose.
- HPMC belongs to the group of medicines known as artificial tears.
- HPMC polymers for fabricating hydrophilic matrix systems are available in various viscosity grades ranging from 4000-1,00,000 mps

Chemical formula:$C_{56}H_{108}O_{30}$

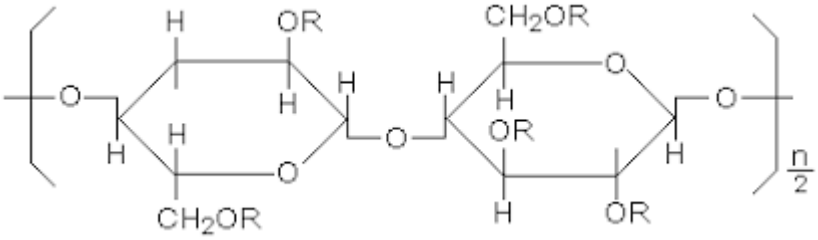


Fig-4

Uses:

- HPMC is used to relieve dryness and irritation caused by reduced tear flow.
- It helps prevent damage to the eye in certain eye diseases.

Eudragit L100:

- It is an anionic copolymerization product of methacrylic acid and methyl methacrylate.
- The molecular formula is $C_8H_{12}O_4$.
- The molecular weight is 172.18

Mechanism of action: EudragitL100 is a commonly used polymer in a coating layer of modified-release drug formulation to prevent drug release in the stomach.

Chemical structure:

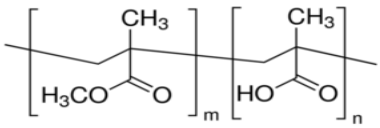


Fig-5

Dibutyl phthalate:

Dibutyl phthalate is an organic compound which is commonly used as plasticizer because of its low toxicity and wide liquid range.

Chemical formula: $C_{16}H_{22}O_4$

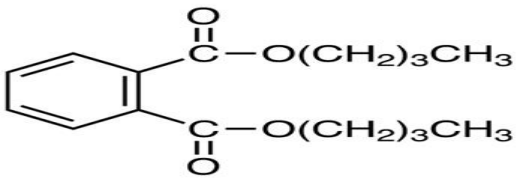


Fig-6

Molecular weight: 278.3441

IUPAC Name: dibutyl benzene-1,2-dicarboxylate

Uses:

- DBP is used as a plasticizer in resins and polymers.
- DBP is also used as a softener in adhesives, lacquers, and printing inks.

List of Materials:

Table 6.1 Material used in formulation

S. No	Materials Used
1	Diclofenac sodium
2	HPMC (hydroxy propyl methyl cellulose)
3	Dibutyl phthalate
4	Eudragit L100
5	Glycerine
6	Ethanol

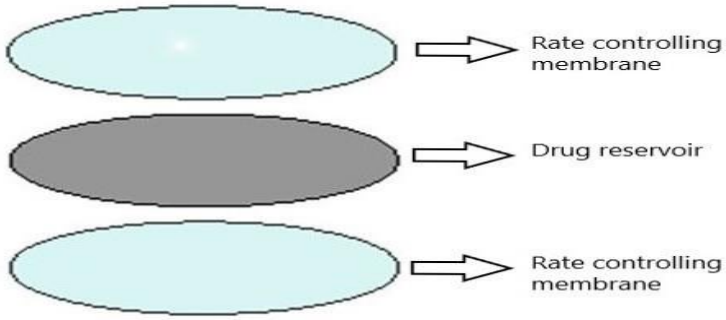
List of instruments: Table 6.2 Instruments used during formulation development

S. No	Instrument	
1	Digital balance(ELB-300)	Shimandzu, Japan
2	UV- Visspectrophotometer (3000+)	Lab India
3	Digital p^H meter	INCO, instruments and chemicals pvt, ltd, India

Pre formulation studies are the first step in the rationale development of dosage form of a drug substance. It can be defined as investigation of physical and chemical properties of the drug substance alone and when combined with excipients. The overall objectives of the pre-formulation testing is to generate useful to the formulator in developing stable and bioavailable dosage form, which can be mass produced.A thorough investigation of physicochemical properties may ultimately provide a rationale for formulation design or support the need for molecular modification or merely confirm that they are no significant barriers to compound development the goals of the program therefore are to establish the necessary physicochemical characteristic of a new drug substance.Hence every formulation study on the obtained sample of drug includes physical test determination and evaluation.

Methodology: Preparation of the drug reservoir: The reservoir containing 200mg of Diclofenac sodium with polymer at 3% concentration were dissolved in ethanol and casted on Petri dish having 16ml capacity and 8cm diameter (an area of 50.24 cm2), circular films of 9mm (0.9cm) diameter (an area of 0.63 cm2) each containing 2.006 mg (theoretical) drug were cut. Preparation of the rate controlling membrane: The rate controlling membrane was casted on Petri dish using different polymers and dibutyl phthalate (30%w/w of polymer) as plasticizer and circular membrane of 10mm (1cm) diameter were cut.

Sealing: The drug reservoir was sandwiched in between the two rate controlling membranes and sealing was done by applying chloroform on the edges of the rate controlling membrane so that both the sides of the drug reservoir were sealed to control the release from periphery.



Evaluation tests:

Uniformity of weight:

- The weight variation test was carried out using electronic balance by weighing three patches from each formulation. The mean value was calculated, and the standard deviations of weight variation were computed from the mean value.

Uniformity of thickness:

- Films were evaluated for the thickness using a vernier calliper/Screw gauze. The average of 5 readings was taken at different points of film, and the mean thickness was calculated. The standard deviations (SDs) in thickness were computed from the mean value.

Folding Endurance:

- A small strip of ocusert was cut evenly and separately folded at the same place till it breaks. The number of times the ocusert could be folded at the same place without breaking gave the folding endurance.

Surface p^H:

- The inserts were allowed to swell in closed petri dish at room temperature for 30 minutes in 0.1 ml of bi distilled water. The swollen device was removed and placed under digital p^H meter to determine the surface p^H.

Drug content

- Drug content is determined to measure the amount of active ingredients present in each formulation. Ocusert was dissolved in 10 mL of simulated tear fluid (STF) in a beaker. The sample was withdrawn from the above solution and the absorbance was measured by UV-Visible spectrophotometer at 276 nm.

Percent moisture absorption

- This is done to check the physical stability or integrity of the ocuserts in humid conditions. The ocuserts from each batch were weighed and placed in desiccators containing aluminum chloride. The ocuserts were taken out and re- weighed, after a successive period of 3 days . The % moisture absorption was calculated using the following formula,

% Moisture absorption = Final weight – Initial weight / Initial weight x 100

Percent moisture Loss

- This is carried out to check the integrity of the ocuserts in dry condition. The ocuserts were weighed and kept in desiccators containing anhydrous calcium chloride. After three days, the ocuserts were taken out and weighed again . The % moisture loss was calculated using the following formula
- % Moisture loss = Initial weight – Final weight / Initial weight x 100

Swelling index

- Ocusert was weighed and placed 4 mL of simulated tear fluid in a beaker. After 5 minutes, the ocusert was re- moved and the excess simulated tear fluid on the ocuserts was wiped and the ocusert was weighed again. The % swelling index was calculated by the following formula
- %Swelling index = (Weight of swollen ocusert after time t – original weight of ocusert) / original weight of ocusert x 100

Sterility test

- Sterility test is performed according to Indian Pharmacopoeia. 2 mL of prepared ocusert solution is removed and is aseptically transferred to fluid thioglycollate medium and soybean-casein digest medium separately. The media are then incubated for not less than 14 days at 30°C to 35°C in case of fluid thioglycolate and 20°C to 25°C in the case of soybean-casein digest medium.

In vitro drug release study

- In vitro release of drug from ocusert was studied using an Franz diffusion cell. The drug preparation was kept in a glass tube having a diameter of 3cms and both sides open. Translucent egg membrane

was used as semipermeable membrane and then preparation was inserted into it. The tube was tied to a stand and fixed to such a level so that the surface of membrane touches the brim of dissolution medium in receptor compartment. 10ml of 7.4 pH phosphate buffer was taken as dissolution medium. The medium in the receptor compartment was agitated using a magnetic stirrer at 50rpm±4% maintaining a temperature at 37^0C±10. After specified intervals of time, 1 ml of the sample was taken and replaced with fresh dissolution medium. Then after suitable dilution the absorbance of the sample was taken against blank at 276 nm in UV visible spectrophotometer.

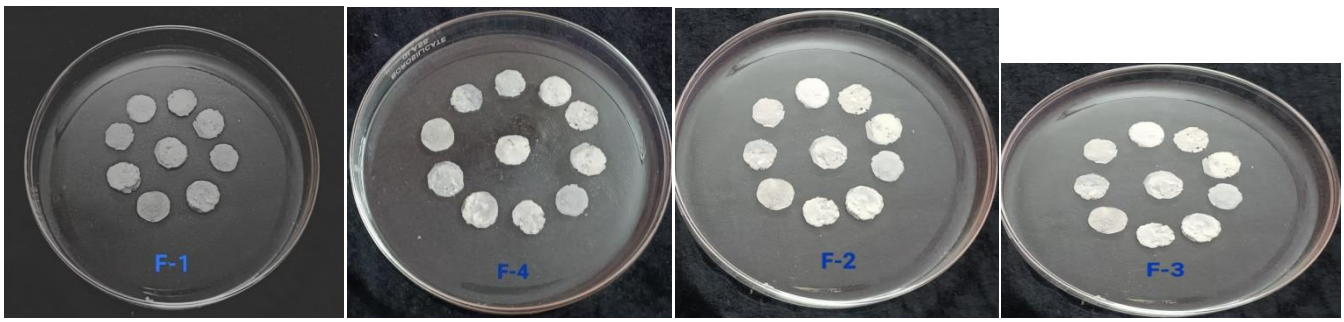
RESULTS AND DISCUSSION

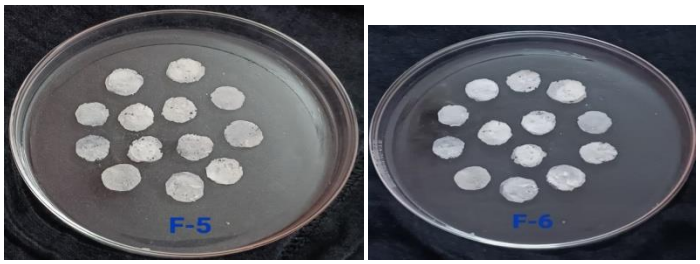
Formulation code	Weight (mg)	Thickness (mm)	Surface pH	Folding endurance	%Moisture absorption	%Moisture loss	Swelling Index	Drug content(%)
F1	24.20±0.1	0.112±0.07	7.23±0.04	78.33±0.404	2.89±0.16	4.9±0.13	2.13±0.15	8
F2	26.94±0.4	0.127±0.02	6.91±0.09	72±14.0	3.47±0.07	6.34±0.19	3.04±0.11	.23
F3	28.32±0.15	0.135±0.08	7.54±0.17	64.33±4.16	5.12±0.13	7.69±0.17	3.45±0.25	±0.14
F4	32.21±0.09	0.143±0.006	7.12±0.39	51±2.0	8.52±0.29	8.57±0.8	3.60±0.10	4.89±0.12
F5	35.37±0.13	0.115±0.010	7.63±0.24	45.66±2.51	2.44±0.08	4.09±0.0	2.37±0.31	7.44±0.9
F6	27.13±0.17	0.129±0.015	7.68±0.10	44.66±4.16	3.59±0.21	5.75±0.29	2.55±0.50	7

Results of various evaluation parameters of prepared ocuserts

Organoleptic characteristics of prepared ocuserts Prepared ocuserts (all batches) were analyzed for color, odor, appearance, and texture. The uniformity of weight suggested good distribution of the drug, polymer, and plasticizer.A sterility study was done for the prepared ocuserts. Results showed no turbidity and no microbial growth during and after the completion of the sterility test. As there was no appearance of microorganism, the prepared ocuserts can be used for the ophthalmic purpose.

The efforts in ocular drug delivery during the past two decades has been on the design of systems, to prolong the residence time of topically applied drugs in the conjunctival sac. Prepared ocuserts were smooth, flexible, and were uniform in weight and thickness. All the formulations were to be followed by zero order kinetics. The physicochemical evaluation of ophthalmic inserts indicates that thickness values were in a range of 0.0034mm to 0.005mm. The formulations were not very thick and hence did not cause irritation. The best formulation batch F4 was the best amongst the 6 formulations in term of evaluation in parameters. Use of less amount of plasticizer (0.03g) was observed to cause brittleness in the medicated discs, the weight of the ophthalmic inserts varied between 0.04 to 0.01g. The results of short term stability studies indicated that the formulated ocuserts of batch F4 were showed negligible or no changes in evaluation parameters as per ICH guidelines. Results suggested that prepared optimised ocusert formulation would be a suitable alternative to eye drops to treat conjunctivitis and other bacterial infections with better bioavailability and less frequent dosing.





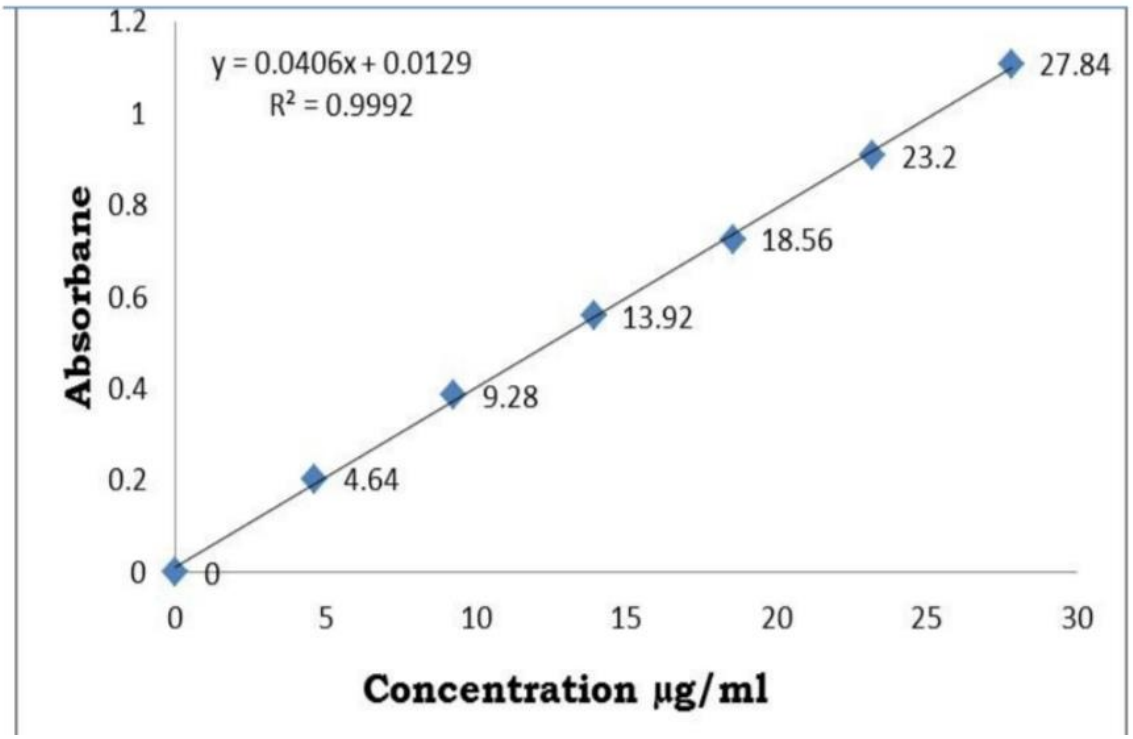
Formulation code	Rate controlling membrane		Drug	Drug reservoir	Plasticizer	solvent
	HPMC	EudragitL100	Diclofenac sodium	HPMC	Dibutyl phthalate	Ethanol ml
F1	-	0.2g	200 mg	200 mg	30%w/w	5
F2	-	0.4g	200 mg	200 mg	30%w/w	5
F3	-	0.6g	200 mg	200 mg	30%w/w	5
F4	0.2g	-	200 mg	200 mg	30%w/w	5
F5	0.4g	-	200 mg	200 mg	30%w/w	5
F6	0.6g	-	200 mg	200 mg	30%w/w	5

Organoleptic properties of prepared ocuserts

S.no.	Parameters	Observation
1.	Color	White
2.	Appearance	Uniform
3.	Texture	Smooth
4.	Odor	Odorless

Calibration curve of Diclofenac sodium:

S.No.	Concentration (mcg/ml)	Absorbance at 276 nm
1	4.64	0.20465
2	9.28	0.38656
3	13.92	0.56009
4	18.56	0.72635
5	23.2	0.90894
6	27.84	1.10823



CONCLUSION:

The ocular insert represents a significant advancement in the therapy of eye disease. Ocular inserts are characterized as clean, thin, multi-layered, medicate impregnated, strong or semisolid consistency gadgets set into the cul-de-sac or conjunctival sac, whose size and shape are particularly intended for ophthalmic application. They are made out of a polymeric bolster that might possibly contain a medication. Expanding contact time and along these lines enhancing bioavailability. Conceivable diminishment of systemic absorption and in this manner lessened systemic antagonistic impacts. Lessened recurrence of organizations and therefore better patient consistence with lower occurrence of visual side effects. In this survey, we have focused on the advanced approaches in ocular drug delivery system. Advantages with ocuserts such as,accurate dosing capacity to provide at constant rate and prolong drug release thus a better efficacy. Increasing contact time and thus improving bioavailability. Possible reduction of systemic absorption and

thus reduced systemic adverse effects. Reduced frequency of administrations and thus better patient compliance with lower incidence of visual side effects.

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