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Influence of Various Dosage Forms on Stability and Corneal Bioavailability of Desloratadine Ophthalmic Preparations

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Abstract: Designing ophthalmic drug delivery system to a target tissue of the eye has become a major challenge for scientists. The aim of the present study was to formulate desloratadine (Des) in different ophthalmic preparations as eye gels and ocuserts using cellulose derivatives such as methylcellulose (MC), sodium carboxymethylcellulose (Sod. CMC) and hydroxypropyl methylcellulose (HPMC). These formulae were examined with respect to drug content, pH, viscosity, in-vitro release, and stability for 6 months. Kinetic analysis of release data was done. Ocular bioavailability of desloratadine from the selected formulations was of prime interest. Collectively, all formulations exhibited accepted drug content, pH, and viscosity. The drug release was varied with polymer type and dosage form in the order of ocuserts > eye gels, being the highest for HPMC preparations that also exhibited the greatest stability. These formulations exhibited the highest stability up to 6 months of storage at different temperatures, except the MC formulae, showed the least stable formulations. Also ocular bioavailability of drug from selected prepared formulations was more pronounced with ocusert compared to control formula.

***Keywords**: Desloratadine, ocular bioavailability, ophthalmic formulations, polymers, stability*

I. Introduction

Allergic conjunctivitis is inflammation of the conjunctiva due to allergy. The allergen initially forms peptides which cause cytokines to be formed. The allergy driven class of immunoglobulin antibodies (IgE), is formed in response to these cytokines by B cells. These antibodies bind to mast cells and basophiles causing a release of granules within the cell. The granules contain histamine and leukotrienes among many other allergic and inflammatory mediators. Histamine binds to certain receptors that have been identified throughout the body. These inflammatory mediators, in turn, cause a series of allergic reactions. Common allergic reactions can involve edema of the tissues, redness, tearing and swelling of the conjunctiva **[1]**.Treatment of allergic conjunctivitis is by antihistamines, either topical or systemic. Topical antihistaminic agents not only provide faster and superior relief than systemic ones, but they may also possess a longer duration of action than other classes including vasoconstrictors, mast cell stabilizers, NSAIDs and corticosteroids **[2]**.

Desloratadine is chemically named, 8-chloro-11-piperidin-4-ylidene-5, 6-dihydrobenzo [1, 2] cyclohepta [2, 4-b] pyridine, ($C_{19}H_{19}ClN_2$). It is a second generation, tricyclic antihistamine which has a selective and peripheral H_1-antagonist action. It is the active descarboethoxy metabolite of Loratadine (a second generation histamine). Topical drug delivery in ocular therapeutics is the best advantageous route for the treatment of eye diseases affecting the anterior segment because it avoids systemic absorption and serves to extend the drug effect in target tissues **[3]**. The main reason of continuingly researches in this field due to the poor ocular bioavailability of some drug. It is caused by, the complicated anatomical structure of the eye, small absorptive surface and low transparency of the cornea, lipophilicity of corneal epithelium, metabolism, enzymolysis, drug-protein bonding and defense mechanisms **[4, 5, 6]**. Low capacity of conjunctival sac, that is, approximately 30 μL without blinking **[7]**, and the defense mechanisms cause a decrease in drug concentration in the site of application and short contact time. The primary purpose for the development of ophthalmic dosage forms is to achieve the required drug concentration in the site of absorption and increasing contact time, which in turn contributes to reduce the application frequency **[8]**.

Because of these physiological and anatomical constraints, only a small fraction of the administered drug, effectively 1% or even less of the instilled dose is ocularly absorbed **[9, 10]**. Numerous routes were developed to increase the ocular bioavailability by prolonging the contact time between the formulation and the eye. Various approaches, like viscosity enhancement, use of mucoadhesive polymers, particulate drug delivery, vesicular drug delivery, prodrugs, and other controlled systems, like ocuserts, are being explored **[11, 12, 13, 14]**.The ocuserts are considered as one of the possibilities to achieve these goals **[15]**. It gives an extended-duration and so maintains an effective drug concentration in the target tissues and yet minimizes the required number of drug applications **[16]**. Ocuserts are solid or semi-solid devices, made of polymeric materials **[17]**. The potential advantages of ocuserts are the accurate dosing, increased ocular residence time, reduction in systemic side effects; better patient compliance due to reduced frequency of administration **[18]**.The aim of this

research was to formulate Des in two ophthalmic dosage forms; eye gels and ocuserts using different polymers. These formulations were subjected to various physical evaluation and *in-vitro* release study. Moreover the stability studies for the prepared formulations were investigated at different temperatures. In addition, the ocular bioavailability of drug from the selected formulations based on acceptable physical characteristics and *in-vitro* release study were studied.

II. Materials and Methods

Desloratadine (Des) was provided by Delta pharm. Chem. Co. Cairo, ARE. Hydroxypropyl methylcellulose and methylcellulose were purchased from Dow Chemical Company, USA. Potassium dihydrogen orthophosphate, propylene glycol and sodium carboxymethylcellulose were provided from Adwic, El Nasr, Pharmaceutical Chemicals Co., Egypt. Disodium hydrogen phosphate and n-octanol were supplied by Prolabo, Chemicals, Paris, France. The HPLC grade solvents acetonitrile and methanol were purchased from Fisher scientific, UK. All other chemicals and solvents were of fine analytical grade.

Methodology

2. Preparation of desloratadine ophthalmic formulations

2.1. Preparation of desloratadine eye gels

Desloratadine (0.05%w/v) was dissolved in 20 ml propylene glycol and added to aqueous solutions of different polymers; Sod. CMC, MC and HPMC **(Table 1)** containing 0.01% benzalkonium chloride (BKC) as a preservative and stirred till complete dissolution **[19]**. The weight of eye gel adjusted to 100 gm and then filled in clean, dry and sterile glass containers.

2.2. Preparation of desloratadine ocuserts

Ocuserts containing desloratadine were formed according to the film-casting method **[20]**. Desloratadine (0.05% w/v) was dissolved in 20 ml of propylene glycol which employed as a plasticizer to aid the formation of flexible films as well as to protect the polymeric inserts from being brittle upon storage **[17]**. Then, this solution was added to the different polymeric solutions as shown in **Table 1** containing 0.01% benzalkonium chloride (BKC) as a preservative and stirred till complete dissolution **[19]**. All of the prepared polymeric solutions were then sonicated for 2 hrs in an ultrasonic water bath (Sonix IV, Saris Ultrasonic Bath, USA) to exclude entrapped air and then stored for 24 hrs at ambient temperature to ensure total hydration of the polymers. Then, equal volumes of the prepared solutions were transferred into the teflon plate. The solvent was permitted to evaporate for 72 hrs at ambient temperature. The formed films were accurately weighed and stored in desiccators having silica gel for another 24 hrs **[21]**. The prepared ocuserts (0.4-0.5 mm thickness) were cut in the form of circular discs, 5 mm in diameter, and individually sealed in foil sachets until use.

Table1: Composition of desloratadine ophthalmic formulations

Formula code / Ingredients	Eye gels			Ocuserts		
	F1	F2	F3	F4	F5	F6
Des	0.05	0.05	0.05	0.05	0.05	0.05
HPMC	-	-	4.5	-	-	1
Sod. CMC	4	-	-	1	-	-
MC	-	3	-	-	1	-
Sod. ALG	-	-	-	1	1	1
Propylene glycol	20	20	20	20	20	20

Where; all formula completed to 100 ml with distilled water. Des, desloratadine; HPMC, hydroxypropyl methylcellulose; MC, methylcellulose; Sod. CMC, sodium carboxymethylcellulose; Sod. ALG, sodium alginate.

2.3. Physicochemical properties of different formulations

2.3.1.Determination of the drug content

One gram of each formula was accurately weighed and dissolved in 100 ml phosphate buffer (pH 7.4) and heated to 37±0.5^{o}C on thermostatically controlled water bath for 15 min, and then 10 ml was centrifuged. The supernatant was filtered and measured spectrophotometrically (UV/VIS spectrophotometer V-530, Jasco, Japan) at 247 nm against a blank of corresponding plain formula.

2.3.2. Determination of the formulations pH

One gram of each formula was dissolved in 25 ml of double distilled water to measure pH using pH-meter (Beckman Instruments fullerton, CA 92634, Germany) **[22]**.

2.3.3. Determination of the formulations viscosity

The viscosity of eye gels was determined using a cone and plate rotary viscometer (Haake Inc., Germany) which has been calibrated before use. One gram of each formula was placed on the stationary plate of viscometer and allowed to equilibrate for 5 min. to attain the running temperature. The rotary viscometer was thermostatically controlled at 37 ± 0.5°C. Then, the viscosity values were calculated according to the following equation:

$$\eta = \frac{G.S}{N}$$

Where;

η = Viscosity in mPa.s (mPa. S = 1 contipoise).

G = Instrumental factor = 14200 (mPa.s/scalagrad. min).

S = Torque (scale grad.).

N = Speed (rpm).

2.3.4. *In-vitro* drug release

The drug release from ophthalmic formulations in phosphate buffer pH 7.4was performed according to the method adopted by Levy and Benita **[23]** using the dialysis method. Cellophane membrane (molecular weight cut-off of 14,000 Da.) was previously soaked in the buffer, stretched over the open end of a glass tube with a diameter of 3 cm and made water tight by rubber band. Two grams of each formula were accurately weighed and thoroughly spreaded on the membrane. To each tube, 1.5 ml of buffer solution was added. The tubes were then immersed upside-down in a beaker containing 50 ml buffer which is maintained at 37±0.5°C using thermostatically controlled water bath(Grant Instrument Cambridge Ltd., Barrington Cambridge, B2, 5002, England). The tube height was adjusted, so that the membrane was just below the surface of the release medium. The whole assembly was shaked at 25 strokes per min. At predetermined time intervals of 5, 15, 30, 60, 120, 180, 240, 300, 360, 420, 480, 540, 600, 660 and 720 min., aliquots of 1 ml were withdrawn and replaced by fresh dissolution medium. Each sample was diluted and the released amounts were analyzed spectrophotometrically at 247 nm against a blank of the corresponding plain formula. The experiments were done in triplicate and the mean value was recorded.

2.3.5. Kinetics of release data

In order to determine the release mechanism of drug, the *in-vitro* release data were analyzed according to zero-order, first order **[24]**, and diffusion controlled release mechanism according to the simplified Higuchi model **[25].** Korsmeyer-peppas model was also used to elucidate the release mechanism of Des from ophthalmic formulations **[26]**. The model with the highest correlation coefficient of determination (r^2) was considered as the best fitting one.

2.4. Stability study

The stability of formulations containing drug was investigated by storage in air tight amber glass jars and stored in thermostatically controlled hot air ovens (Gering model SPA-GELMAN Instrument No. 16414, Germany) at different temperatures of 30 ± 1, 35 ± 1 and 40 ± 1°C for 6 months. The relative humidity was maintained at 75 ± 5% using saturated solution of sodium chloride **[27]**. Monthly measurements of drug content, pH and viscosity were done according to the previously illustrated procedures. As well, any changes in color and odor were recorded. Accelerated stability testing was demonstrated in different literature **[28]**. Some functions of drug concentration in each formula monthly determined at each temperature were plotted against time and analyzed according to zero-order and first-order kinetics. The rate constant (K)values at each temperature were calculated using the slope of the linear plot of the fitting kinetic model with the highest correlation coefficient (r^2).The slope of Arrhenius plot of log k against the reciprocals of the absolute temperature was used to estimate the activation energy (Ea) employing the relation slope = −Ea/2.303R. The values of K_{25} were calculated using the relation Log (k_2/k_1) = Ea ($T_2 - T_1$)/2.303RT_2T_1 provided that$K_1 = K_{25}$ and $K_2 = K_{30}$, K_{35}, or K_{40}. The value of K_{25} was then used to obtain a measure of the stability of the drug under ordinary shelf storage conditions (shelf life, $t_{90\%}$) and (half-life , $t_{50\%}$) through the relations ($t_{90\%} = 0.105/K_{25}$) and ($t_{50\%} = 0.693/k_{25}$) **[29]**.

Arrhenius equation:

Log k = Log A- Ea / 2.303 RT

Where;

K = The specific reaction rate constant at temperature (t).
A = The frequency factor
Ea = Activation energy (Cal/mole).
R = The gas constant (1.987 Cal/de.mole).
T = The absolute temperature ($^oC + 273$).

2.5. Ocular bioavailability of desloratadine from selected formulations

According to the *in-vitro* release and stability studies, the optimized formulations were F3 and F6 **(Table 1)**. The ocular bioavailability of the optimized formulations was examined in comparison to drug suspension in water as a control (Ct).

2.5.1. Ocular bioavailability studies

Ocular bioavailability of the selected formulations was performed on male New Zealand albino rabbits, each weighing 2-2.5 kg. All rabbits were healthy and free of clinically observable abnormalities. Rabbits were housed singly in standard cages, in a light controlled room (12-hrslight and 12-hrs dark cycles) at 20–24°C, with no restriction to food or water. The animal experimental procedures conform to the ethical principles of the scientific committee of the Faculty of Pharmacy, Mansoura University, Egypt. The rabbits were divided into three groups; each group consists of 18 rabbits. Each animal was received 30 µg of eye gels or one ocusert which instilled into the center of the lower lid (cul-de-sac) of the right eyes of the rabbits, while the left eyes were served as control by application of the plain formulation. All rabbits were kept in up-right position in restraining boxes. Three rabbits were sacrificed for each formulation at each time intervals of 1, 2, 3, 4,6 and 7 hrs. Both eyes were enucleated and dissected while fresh to separate different eye tissues (cornea, conjunctiva, iris-ciliary body and aqueous humor) which were kept frozen at -80^{o}C until subjected for further analysis. The amount of the drug disposed in different eye tissues and aqueous humor at each time interval was determined using HPLC.

2.5.2. HPLC assay

At every time interval, each eye tissue and aqueous humor were separated immediately, then each eye tissue rinsed with normal saline solution, weighed and grinded with powdered glass, the grinded tissues were extracted with 6 ml acetonitrile for 24 hrs at 25^{o}C to extract the drug from different eye tissues and aqueous humor. These solutions were filtered using 0.45 µm nylon membrane filter. The tissue extracts were spiked with 200µl of Loratadine as an internal standard (200 ng/ml). Each mixture was mixed using vortex mixer (Snijders Scientific Tilburg-Holland) for 1 min, then filtered through 0.45 µm nylon membrane filter and 20 µl of the solution was injected into HPLC system. The concentration of drug in each tissue was determined by HPLC assay. The quantitative analysis of drug was performed by a reverse phase HPLC system consisting of a pump (LC -20 AD), degasser (DGU-20A5), CBM-20A interface, UV-Vis spectrophotometric detector (SPD-20A UV-Vis detector) and a reverse phase column C-18 column, 5 µm, 4.6 x 250 mm, USA. The mobile phase was prepared by mixing 30 volumes of, 35 methanol volumes of a 6.8 g L-1 solution of potassium dihydrogen phosphate in water which previously adjusted to pH 2.80±0.05 with phosphoric acid and 40 volumes of acetonitrile. The mobile phase was filtered under vacuum through a 0.45 µm nylon membrane filter and pumped at a flow rate at 1.5 ml / min **[30]**.Detection of the drug and internal standard peaks were done using UV/VIS detector at 210 nm. The retention time of the Loratadine and desloratadine was 5 and 9.5 min, respectively. The concentration of drug was expressed as ng of drug / mg of tissue.

2.5.3. Pharmacokinetic parameters

The pharmacokinetic parameters were calculated for each rabbit **[31]**. The maximum drug concentration in eye tissues (C_{max}) and the time required to reach the maximum eye tissue concentration (T_{max}) were directly estimated from the eye tissue concentration-time curves. Also, the elimination rate constant (K_e) was calculated from the terminal linear portion of the plot by linear regression analysis. The biological half-life ($T_{1/2}$) was calculated as $0.693/K_e$. In addition, the area under eye tissue concentration-time curve from 0-7 hrs (AUC_{0-7hr}) was calculated using the linear trapezoidal methods. AUC was extrapolated to infinity ($AUC_{0-\infty}$) by adding AUC_{0-7} to C_{last}/K_e**,** where C_{last} is the last measurable concentration of the drug after 7 hrs. The relative bioavailability of drug was determined as the ratio between $AUC_{0-\infty}$ of the tested formulation to that of control.

2.6. Statistical Analysis

The data are expressed as mean ± SD. Statistical analysis was carried out using one way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparisons test. Statistical calculations were carried out using Instate Graphpad prism software (version 5.00 Graph pad software, San Diego, CA, USA) **[32]**.

III. Results and Discussion

3.1. Physicochemical characterization of different formulations

3.1.1. Drug content

The actual drug content was determined for each formulation **(Table 2)**. It was found that, the percentage of drug content ranged from 99.26±0.58% to 100.33±1.28% which complies with the official requirements of pharmacopeal limits ranging from 90 to 110% **[33]**.

3.1.2. pH measurements

The pH of eye tears is 7.4 and because of their natural buffering capacity, the eye can tolerate a pH range of 3.5 –10.5 without patient discomfort **[29]**. Because the ideal ophthalmic dose is only one drop, the tear film can be rapidly restored neutral pH **[22]**.The obtained results showed that the pH values were within the acceptable range 6.5±0.65 to 7.6±0.08 which can be tolerated by the eye without any irritation or discomfort **(Table 2)**.

3.1.3. Viscosity of the eye gels

Viscosity values of the prepared eye gels were measured and the values were ranged from 1100 ± 89 to 1200 ± 102 cP. From the obtained results, it was found that the higher viscosity of eye gels led to an increase in their contact time with the eye surface and prevented the rapid drainage of the formulations from the eye which in turn improved their bioavailability **[34]**.

Table 2: Physicochemical characterization of different formulations

Formulae	Formula code	Drug content (% w/v)	pH	Viscosity (cP)
Eye gels	F1	100.33±1.28	7±0.90	1150±96
	F2	99.26±0.58	6.5±0.65	1200±102
	F3	99.67±0.58	7.2±0.52	1100±89
Ocuserts	F4	99.73±0.85	7.5±0.74	-
	F5	99.39±0.27	7.1±0.07	-
	F6	99.93±0.35	7.6±0.08	-

3.1.4. *In-vitro* drug release

Figure 1 illustrates the *in-vitro* release behavior of Des from different eye gels and ocuserts. From the obtained results, it was found that no complete dissolution was obtained for Des alone, only 13.23 % even after 12hrs was released. This may be referred to the hydrophobic nature of Des which prohibited its contact with the release medium and consequently hindering its dissolution. It can be observed that, dissolution rate was significantly improved by the addition of propylene glycol which solubilizes the drug **[17]**. The nature of hydrophilic polymers affected the release of Des from the prepared formulations. The release of Des from eye gels was in the following order; HPMC > Sod. CMC > MC. While, the release of Des from ocuserts was in the following order; HPMC & Sod. ALG > Sod. CMC & Sod. ALG >MC & Sod. ALG. After 12 hrs., it was found that, the release of the drug from different formulations was significantly ($p<0.05$) compared to its release from control. Additionally, the obtained results revealed that, the dosage form vehicles played an important role in controlling the drug release rate, as we found that the release rates from ocuserts were higher than that from eye gels. This may be due to the difference in their viscosities upon exposure to the release conditions, as the higher the viscosity the slower drug release rate **[35]**. Generally, desloratadine formulations can be arranged in the following order according to the percent drug released; **F4 > F6 > F3 > F1 > F5 > F2.**

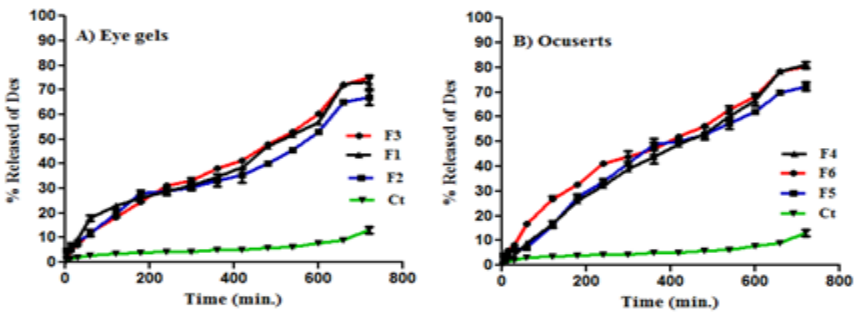

Figure 1: *In-vitro* dissolution profiles of desloratadine from different ophthalmic formulations.

3.1.5. Kinetics of drug release

Table 3 illustrates the release kinetic parameters and correlation coefficients (r^2) calculated for the investigated formulations. The *in-vitro* release results showed that the release of desloratadine from different formulations is most fitted to diffusion- controlled mechanism (Higuchi model) except F4 and F5 followed first order kinetic. This suggests that, the drug release is governed by a diffusion release mechanism and first order kinetic. However, the control followed zero-order kinetics. Further analysis of the release data by the Korsmeyer–Peppas equation showed that the release exponents (n) for formulations were located between 0.4944 and 0.79, which indicates that they exhibited a non-Fickian (anomalous diffusion) while (n) values for Ct were below 0.45, which suggests Fickian mechanism. These results indicate that no one model was able adequately to describe the release situation of these formulae. At least two mechanisms are present, in which one is more predominant than the other.

Table 3: Kinetic analysis of the release data of desloratadine.

Formula code	The correlation coefficient(r^2)			Release order	Korsmeyer-Peppas		Main transport Mechanism
	Zero-order	First-order	Higuchi-order		r^2	n	
Ct	0.8656	0.8527	0.7840	Zero	0.9014	0.442	Fickian
F1	0.898	0.9226	0.9728	Diffusion	0.9727	0.4944	Non-Fickian
F2	0.9223	0.9357	0.9691	Diffusion	0.9691	0.5009	Non-Fickian
F3	0.9746	0.9878	0.9934	Diffusion	0.9972	0.6436	Non- Fickian
F4	0.9900	0.9939	0.9686	First	0.9677	0.7937	Non- Fickian
F5	0.9398	0.9904	0.9837	First	0.9085	0.6375	Non- Fickian
F6	0.9515	0.9746	0.9908	Diffusion	0.9888	0.6508	Non- Fickian

Where; (n) is release exponent.

3.2. Stability study

At 30^{o}C and 35^{o}C, physical stability was indicated by the absence of color or odor changes. At 40^{o}C, turbidity has been noticed with MC formulations (F2 and F5) after two months. The turbidity was also found in blank formulations (formula without drug) stored at the same conditions.

Table 4 showed slightly lowered drug content, pH and viscosity than those initially determined. However, percentage drug content values were still complying with pharmacopeal limits **[33]**, and pH range still could be tolerated by the natural buffering system of the eye **[29]** and maintain the drug stability. Storage temperature might affect the integrity of the polymer and lowering the viscosity to the same extent. The kinetic analysis data used to determine the mechanism of degradation, $t_{50\%}$ and $t_{90\%}$ was represented in **Table 4**. After the analysis of the data, the degradation rate of desloratadine followed the first-order model.

These results indicate that, the MC formulae whether ocuserts or eye gel showed the highest degradation rate constant and the shortest half-life. In addition, the change in the viscosity of F2 may be attributed to the intermolecular hydrogen bonding or reaction that leads to the formation of benzilic acid **[36]**. While, the observed turbidity in this case may due to the formation of insoluble complex of banzalkonium chloride when mixed with MC solution at high temperature. It was reported that benzalkonium chloride may cause a change in the viscosity or form a precipitate when added to hydrophilic polymer solutions **[37]**. HPMC formulations exhibited the highest $t_{90\%}$, thus were selected for further investigation of Des ocular bioavailability in rabbit's eyes.

Table 4: **Stability study at different temperatures after storage for six months.**

Storage Temp. (ºC)	Parameters	F1	F2	F3	F4	F5	F6
30	Drug content	96.77±0.39	96.18±0.17	97.10±0.19	97.23±0.19	95.54±0.39	97.27±0.26
	pH	7.00±0.37	6.50±0.41	7.20±0.32	7.50±0.72	7.10±0.05	7.60±0.11
	Viscosity	1141±30	1192±37	1097±20	---	---	---
35	Drug content	95.99±0.00	94.20±0.19	96.32±0.33	96.66±0.33	94.54±0.19	96.21±0.19
	pH	6.85±0.50	6.40±1.04	7.10±0.74	7.40±0.98	6.93±0.21	7.48±0.38
	Viscosity	1132±42	1182±36	1091±27	---	---	---
40	Drug content	95.10±0.19	93.09±0.19	95.43±0.19	94.87±0.19	93.59±0.51	94.76±0.19
	pH	6.79±0.82	6.31±0.85	7.00±0.39	7.36±0.78	6.88±0.27	7.40±0.09
	Viscosity	1125±35	1177±44	1088±24	---	---	---
K_{25} x10^{-3} month^{-1}		5.07	6.19	4.32	4.12	5.27	4.07
Half-life, $t_{50\%}$ (month)		136.67	112.00	160.42	168.20	131.50	170.27
Shelf life, $t_{90\%}$ (month)		20.71	16.95	24.33	25.48	19.92	25.77

3.3. Ocular bioavailability of desloratadine from selected formulations

The eye tissues and aqueous humor concentrations of desloratadine after single application of selected formulations or control to rabbits were studied. The pharmacokinetic parameters of desloratadine are illustrated in **Table 5** and **Figure 2**. From the obtained results, it is obvious that, the selected formulations improved the bioavailability of the drug in all eye tissues compared to that of control. This improvement was indicated by the higher C_{max}, AUC_{0-7} and $AUC_{0-\infty}$ of the tested formulations than the control. Also, the tested formulations extended the duration of desloratadine which indicated by the higher T_{max}, $T_{1/2}$ and the lower K_e than that of the control. Desloratadine bioavailability can be arranged in the order of; cornea > conjunctiva > iris-ciliary body > aqueous humor as indicated by the values of C_{max}, AUC_{0-7}, $AUC_{0-\infty}$ and the relative bioavailability. The higher desloratadine bioavailability in cornea and conjunctiva may be attributed to the direct contact of these tissues with the tear pool which housing the drug. These results are in agreement with the results obtained by **Abd El-Gawad *et al* [21]** who reported that, the higher econazole-nitrate-cyclodextrin complexes concentration in cornea than in aqueous humor.

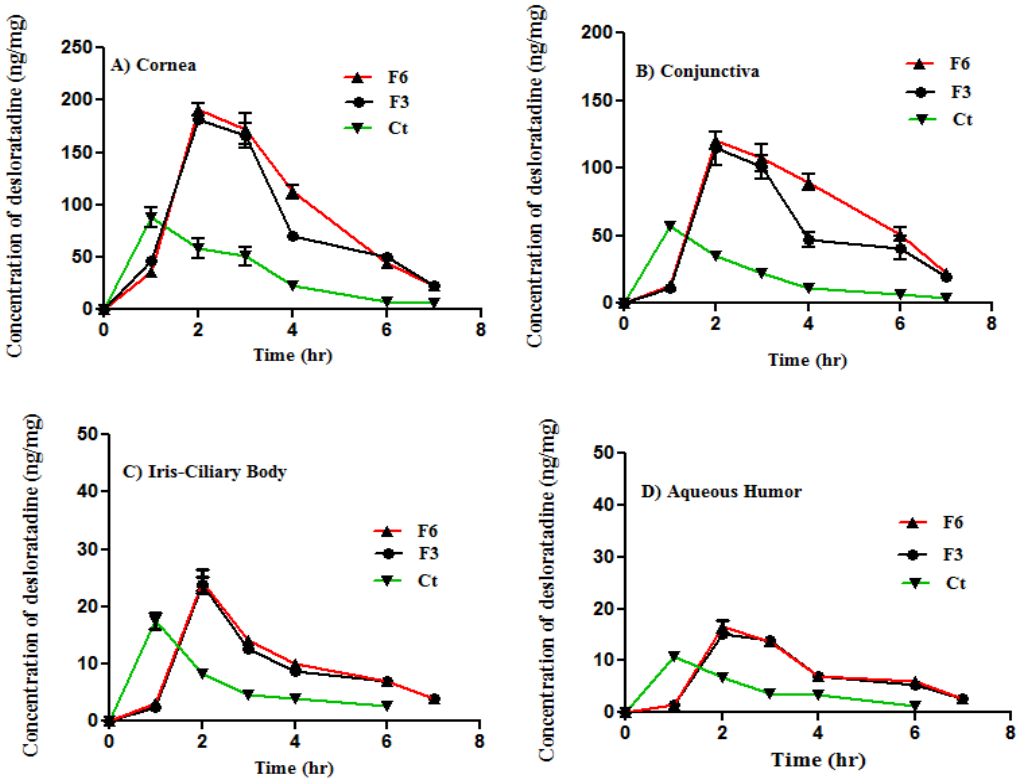

Figure 2: The eye tissue concentration-time profiles of desloratadine following topical application of the optimized formulations.

Regarding T_{max} values, the tested formulations gave extended T_{max} values which reached up to 2 hrs for selected formulations in different eye tissues. Thus, the results revealed that there was about 2 fold higher in the time required to reach the maximum eye tissue concentration (T_{max}) with tested formulations than control. This can be explained by the mucoadhesive properties of the polymer used, and hence, retain it in the eye for longer period, so, the sustained effect of selected formulations was expected to be stronger than that control. It is worth noting that, the C_{max}, T_{max}, AUC_{0-7} and $AUC_{0-\infty}$ of tested formulations were significantly ($p< 0.05$) superior to that of control in all eye tissues and aqueous humor. The elimination half-life ($T_{1/2}$) of desloratadine from tested formulations was more than control indicating that the drug was eliminated from the eye slowly, which in turn was supported by low K_e values of desloratadine in tested formulations in comparison with control. Ocusert formula showed a high AUC value indicating the greater extent of drug absorption. Thus, the higher T_{max}, $T_{1/2}$ and AUC values together indicated enhancement bioavailability of desloratadine from the tested formulations in comparison with control. The tested formulations showed prolonged $T_{1/2}$ that ranged from 1.587±0.07 to 2.228±0.072 hrs compared to the control with a range of 1.46±0.106 to 1.919±0.289 hr. The enhanced bioavailability of ocusert (F6) than eye gel (F3) could be due to the bioadhesiveness of Sod. ALG that lead to increase their contact time with the ocular surface and hence improve their bioavailability **[38]**.

Table 5: Pharmacokinetic parameters of desloratadine after topical application of the optimized formulations compared to the control solution.

Tissues	Pharmacokinetic Parameters	F3	F6	Ct
Cornea	C_{max} (ng/mg)	181.67±3.46*	191.48±5.86*	87.667±9.762
	T_{max} (hr)	2*	2*	1
	K_e (hr-1)	0.411±0.012*	0.437±0.020	0.477±0.033
	$T_{1/2}$ (hr)	1.685±0.05*	1.587±0.070	1.46±0.106
	AUC_{0-7} (ng. hr/mg)	525.67±14.97*	566.83±10.47*	229.73±29.90
	$AUC_{0-\alpha}$ (ng. hr /mg)	581.06±14.72*	619.45±6.36*	242.523±30.67
	Relative bioavailability	2.417±0.257	2.580±0.325	-----
Conjunctiva	C_{max} (ng/mg)	114.40±12.68*	120.457±6.757*	56.683±2.026
	T_{max} (hr)	2*	2*	1
	K_e (hr^{-1})	0.336±0.023*	0.321±0.011*	0.426±0.022
	$T_{1/2}$ (hr)	2.067±0.136	2.162±0.074*	1.631±0.083
	AUC_{0-7} (ng. hr /mg)	323.67±20.812*	392.07±23.247*,a	134.50±2.007
	$AUC_{0-\alpha}$(ng. hr/mg)	442.07±34.262*	531.237±32.21*,a	269.637±9.07
	Relative bioavailability	2.64±0.2	3.20±0.28a	-----
Iris-cillary body	C_{max} (ng/mg)	23.92±2.074	24.35±3.674	17.490±2.533
	T_{max} (hr)	2*	2*	1
	K_e (hr^{-1})	0.311±0.01	0.321±0.028	0.367±0.060
	$T_{1/2}$ (hr)	2.228±0.072	2.167±0.187	1.919±0.289
	AUC_{0-7} (ng. hr/mg)	56.517±2.311*	60.633±2.79*	35.647±2.271
	$AUC_{0-\alpha}$(ng. hr/mg)	69.220±3.085*	73.240±1.472*	43.234±4.664
	Relative bioavailability	1.60±0.10	1.710±0.211	-----
Aqueous humor	C_{max} (ng/mg)	15.169±0.952*	16.48±2.085*	10.817±0.605
	T_{max} (hr)	2*	2*	1
	K_e (hr^{-1})	0.333±0.007*	0.327±0.036*	0.419±0.013
	$T_{1/2}$ (hr)	2.082±0.044	2.136±0.251*	1.656±0.049
	AUC_{0-7} (ng. hr /mg)	44.247±0.685*	45.960±3.538*	25.223±0.884
	$AUC_{0-\alpha}$(ng. hr /mg)	52.450±0.78*	54.640±2.468*	28.182±1.254
	Relative bioavailability	1.86±0.058	1.947±0.139	-----

All values are expressed as means ± SD (n=3), C_{max} (the maximum concentration of drug in eye tissue); T_{max} (time required to reach the maximum eye tissue concentration); K_e (the elimination rate constant); $T_{1/2}$ (the biological half life); AUC_{0-7} (the area under eye tissue concentration time curve from 0-7 h) and $AUC_{0-\infty}$ (the area under eye tissue concentration time curve from 0-∞). (*) considered significant compared to control ($P< 0.05$); (a) considered significant compared to eye gel ($P< 0.05$).

IV. Conclusion

Desloratadine release was affected by formulation nature and polymer used. The nature of polymer utilized affected the drug release with highest for HPMC formulations. Ocuserts exhibited a significant higher release ($p<0.05$) of desloratadine compared to eye gels. These preparations possessed pH and viscosity values that are compatible with the eye and have uniform drug contents that comply with the USP official requirement. These formulations exhibited the highest physical and chemical stability up to 6 months of storage at different temperature except formulae containing MC polymer showed the least stable formulations. Eye gels and ocuserts containing drug significally ($p<0.05$) improved its bioavailability in rabbits eyes compared to control. On the basis of these results, ocuserts of Des containing HPMC and Sod. ALG may be represented as a potential ophthalmic formulation for enhanced ocular delivery of desloratadine.

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