FORMULATION AND EVALUATION OF DORZOLAMIDE AND TIMOLOL OCUSERTS

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ABSTRACT: Objective: This study aims to formulate novel dorzolamide hydrochloride and timolol maleate ocuserts to enhance patient compliance through providing controlled drugs release from polymeric matrix. Methods: Ocuserts were prepared by solvent-casting method using different polymers Ethyl Cellulose, Eudragit S100 and Hydroxy propyl methyl cellulose in different ratios. The prepared ocuserts were physicochemically evaluated for their weight, thickness, drug content uniformity, surface pH, Swelling Index (SI) and folding endurance. In-vitro drug release was studied from the prepared formulas and the results were analyzed by drug release kinetic models. The ocuserts stability after three month’s storage at 40 ±0.5°C and 75 ±5% RH was estimated. In-vivo tests were done to study the release profile and estimate the safety of the incorporated drugs in rabbits’ eyes. Results: The prepared ocuserts show uniform weight, thickness and drug content. Their surface pH was in the physiological range and showed acceptable folding endurance. HPMC Formulas had higher SI values. Results of in-vivo testing for one of the prepared ocuserts shows slow release of both drugs up to 24 hours with no signs of eye sensitivity. Conclusion: One of the prepared ocuserts is promising for once-daily effective and safe drug delivery system of DHCL and TM for glaucoma treatment.

INTRODUCTION: Glaucoma is a group of eye diseases that damage the optic nerve usually as a result of elevated pressure of the fluid in the eye (aqueous humor). Glaucoma remains a worldwide leading cause of blindness in adults over 60 years old after cataract, according to the National Eye Institute (NEI), a division of the National Institutes of Health 1, 2. According to Quigley & Broman 3, the number of people with glaucoma will be nearly 79.6 million worldwide by 2020.

This alarming high number of anticipated patients requires urgent improvement in the current therapeutic approaches adopted for treatment of this disease.

Carbonic anhydrase inhibitor, including dorzolamide, is a promising group of drugs currently used to treat glaucoma 4, 5. Dorzolamide is a topical carbonic anhydrase inhibitor that reduces intraocular pressure (IOP) by 18-26% through decreasing the aqueous humor secretion in the ciliary processes of the eye. It is relatively specific against carbonic anhydrase types II and IV which are the key enzymes for the production of aqueous humor in the eye 6, 7.

However, when monotherapy doesn’t adequately lower the IOP; one or more agents are further added.
Clinical trials have demonstrated that the combination of dorzolamide hydrochloride (DHCL) and the beta-adrenergic antagonist, timolol maleate (TM) is safe, effective and generally well tolerated in lowering IOP in patients with open angle glaucoma or ocular hypertension, including individuals uncontrolled on beta-adrenoceptor antagonist or other monotherapy.

The long-term effectiveness and efficacy of the currently available eye drops for glaucoma treatment are being questioned due to poor patient compliance. Generally, the main prerequisites for ideal ophthalmic drug delivery system that ensures effective ocular therapy is its ability to: (a) be administered accurately without causing blurred vision or irritation, (b) have suitable mucoadhesive property to improve the drug retention in the precorneal area and thereby increase drug bioavailability, (c) have a limited systemic absorption through nasolacrimal drainage, and (d) reduce the need for frequent dosing regimen leading to improved patient compliance.

As a result of these factors, and the limited permeation of the corneal barrier, only a few percent of topically administered drug dose is actually delivered into the intraocular tissues.

Ocular inserts (ocuserts) are solid or semi-solid devices, usually made of polymeric materials, designed to be placed in the conjunctival sac to deliver drugs to the ocular surface. The potential advantages offered by the inserts are the accurate dosing, increased ocular residence time, reduction in systemic side effects, better patient compliance due to reduced frequency of administration, possibility of releasing drugs at a slow and constant rate as well as increase shelf life stability. These advantages overall lead to effective ocular therapy.

In spite of the numerous advantages demonstrated by ocluserts, its main disadvantage is the foreign body sensation accompanied with its initial administration. However, this disadvantage did not prevent the implementation of this technology in several successfully marketed ocuserts (Ocusert®, Ocufit® SR, and Minidisc®) as their numerous advantages extremely supersede their sole disadvantage.

The aim of the present work is to formulate and evaluate a novel polymeric ocular drug delivery system containing both DHCL and TM to be used once-daily to overcome the disadvantages of short duration and fast drainage associated with conventional ophthalmic dosage forms (eye drops and suspensions) and to achieve long duration of action and to improve ocular bioavailability.

2. Methodology:

2.1. Materials: DHCL and TM were kindly donated by Pharaonia Pharmaceuticals (New Borg El- Arab city, Alexandria, Egypt). Ethyl cellulose (EC) and Hydroxy propyl methyl cellulose (HPMC) were obtained from LOBA CHEMIE PVT. LTD. (India). Eudragit S100 (ES100) was purchased from Rohm GmbH & Co. KG, Pharma Polymers, Darmstadt, (Germany). Sodium chloride, sodium bicarbonate, calcium chloride dehydrate, dibutyl phthalate and glacial acetic acid were the products of Adwic-El NASAR Pharmaceutical chemicals (Cairo, Egypt). Methanol (HPLC reagent grade) was obtained from Romil (London, UK). All other chemicals were of reagent grade and used as received. All water used was distilled de-ionized water.

2.2. Preparation of the simulated tear fluid (STF): According to the USP, accurately weighed 6.7 g of sodium chloride, 2 g of sodium bicarbonate, and 0.08 g of calcium chloride dehydrate were placed in 1000 ml volumetric flask and 100 ml of distilled water was added to dissolve the components, then the volume was completed by distilled water to 1000 ml.

2.3 Estimation of DHCL and TM in STF: DHCL and TM were estimated in STF at room temperature using a high performance liquid chromatography (HPLC) method with UV-Visible detector wavelength (254 nm & 295 nm) for the two drugs, respectively according to Nagori et al. The mobile phase consisted of methanol: buffer (0.02 M Octane-1-sulfonic acid buffer) in a ratio of 3:2, the pH was adjusted to 3 with glacial acetic acid. The mobile phase was run through a C-18 column (EC 150/4.6 NUCLEOSIL 100-5).

2.4. Preparation of DHCL and TM ocuserts: Paolymeric ocuserts containing DHCL and TM were prepared using film-casting method. The used polymers were weighed and dissolved in 10 ml mixture of acetone and chloroform in a ratio of...
1:1 using magnetic stirrer (LabTech- LMS1003) until a homogenous solution was obtained. The drugs and the plasticizer were mixed and stirred to ensure complete distribution of drugs in the plasticizer. The prepared solutions were then poured in dry glass Petri dishes and dried at room temperature with an inverted funnel on each dish to prevent fast evaporation of the solvent. After ensuring the complete evaporation of the solvent, the produced films were cut into rectangular pieces (oculars) of dimensions 2×0.5 cm, then packed in aluminum foil and stored in desiccators for further studies. Three polymers were used in the preparation of the ocusert formulas namely, EC, ES100, and hydroxypropyl methyl cellulose (HPMC). The used plasticizer in all formulas was dibutyl phthalate (DBP). The detailed composition of the prepared ocular film formulas is given in Table 1.

| Table 1: Composition of the Prepared Ocusert Formulae |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Formula | DHCL (mg) | TM (mg) | EC (mg) | ES100 (mg) | HPMC (mg) | DBP (ml) |
| F1 | 80 | 20 | 100 | 300 | ---- | 0.5 |
| F2 | 80 | 20 | 200 | 200 | ---- | 0.5 |
| F3 | 80 | 20 | 300 | 100 | ---- | 0.5 |
| F4 | 80 | 20 | 200 | 100 | 100 | 0.5 |
| F5 | 80 | 20 | 100 | 200 | 100 | 0.5 |

1 Dorzolamide Hydrochloride  
2 Timolol maleate  
3 Ethyl cellulose  
4 Eudragit® S100  
5 Hydroxypropyl methyl cellulose  
6 Dibutyl phthalate

2.5. Physicochemical evaluation of the prepared ocuserts:

2.5.1. Visual examination: The prepared ocuserts were visually examined for their transparency, entrapped air bubbles, color homogeneity, and any other defects.

2.5.2. Weight uniformity: The prepared ocuserts were dried at 60°C for four hours and five different ocuserts from each prepared formula were weighed individually. The average weight of each formula and standard deviation (±SD) was calculated.

2.5.3. Thickness uniformity: The prepared ocuserts were evaluated for their thickness uniformity after being dried at 60°C for four hours. Ocuserts thickness was measured using micrometer (H-2781 Mitutoyo Micrometer). Film thickness was measured for three ocuserts from each batch and the mean values as well as the ±SD were calculated.

2.5.4 Drug content uniformity: Five ocusters from each formula were taken separately and dissolved by means of magnetic stirring in 10 ml STF pH 7.4, the solutions were filtered through filter papers and each solution was completed to 50 ml with STF. The amounts of both DHCL and TM were determined for each solution using the fore-mentioned HPLC method. Mean value and ±SD were calculated for each formula.

2.5.5 Surface pH: Agar (2% w/v) was dissolved in warm STF of pH 7.4, the solution was poured into Petri plates and left to cool at room temperature till gelling. Inserts were left to swell for 5 hours on the prepared agar plates. The surface pH was measured for different three ocuserts from each prepared formula by means of a pH paper placed on the surface of swollen film.

2.5.6 Swelling index (SI): Three ocuserts from each formula were weighed separately and each was placed in a beaker containing 4 ml STF. At predetermined time intervals, inserts were removed, the excess fluid on their surfaces was wiped using a blotting paper and they were separately weighed until there is no further increase in weight. SI was then calculated by the following equation:

\[ SI\% = \frac{W_2 - W_1}{W_1} \times 100 \]

Where, W1 is the weight of the film before soaking in STF; W2 is the final weight of the film at the end of the experiment.

The mean value of SI and its ±SD were calculated for each formula.

2.5.7 Folding endurance: The folding endurance of the prepared films is expressed as the number of times the insert can be folded at the same place without breaking or developing a visible crack. The ocusert was folded at the center, between the index
fingertip and the thumb and then opened 21. This was termed as one folding. This process was repeated until the ocusert show a breakage or cracks in the center; the number of folds was counted for each formula. This experiment was repeated three times for each formula and the mean values ±SD were calculated.

2.6. In-vitro Drug Release Studies: The in vitro release of both DHCL and TM from the prepared ocusert formulas was studied using the vial method. Each insert was placed into 10 ml capacity vial containing 5ml of STF that was previously warmed at 37±1°C. These vials were placed on an electromagnetic shaker (Electrolab-EMS-8) in a water bath so that the temperature was maintained at 37±1°C. The shaking speed was kept at minimum value (10 times / min) to simulate blinking of the eye. Aliquots of 0.5 ml samples were withdrawn at specific time intervals and equivalent amounts of fresh dissolution fluid were replaced 11, 22. The withdrawn aliquots were analyzed for DHCL and TM content using the forementioned HPLC method. Experiments were done in triplicates and the mean ±SD were calculated.

Data from in-vitro drug release were analyzed for its kinetics by zero and first order equations 23, 24 as well as Korsemeyers equation 25 to understand the release profile and release mechanism.

For zero order kinetics, when a graph of the cumulative percentage of the drug released from the dosage form versus time is plotted, a linear plot is obtained indicating that the release rate is independent of concentration. The release rate of the drug can be described by the following equation:

\[
\text{Rate of release} = \frac{(dC_s/t)}{t} = k
\]

Where \(C_s\) = concentration of the drug present in the matrix, \(k\) = rate constant and \(t\) = time.

For first order kinetics, plotting the log cumulative % drug remaining against time gives straight line from which the rate constant can be determined as follow:

\[
\log C = \log C_0 - kt/2.303
\]

Where \(C_0\) is the initial concentration of the drug, \(C\) is the final concentration of the drug, \(k\) is the constant and \(t\) is time.

For Korsemeyer equation, it is a simple empirical equation used to describe general solute release behavior from controlled release polymer matrices as follow:

\[
\frac{M_t}{M_\infty} = k \times t^n
\]

Where \(M_t/M_\infty\) = fraction of drug released, \(k\) = kinetic constant, \(t\) = release time and \(n\) = the diffusional exponent for drug release. The slope of the linear curve gives the \(n\) value which gives an indication of the release mechanism. When \(n = 1\), the release rate is independent of time (zero order); \(n = 0.5\) for Fickian diffusion; and when 0.5 < \(n < 1\), diffusion and non-Fickian transport are implicated. Lastly, when \(n >1\), super case II transport is apparent.

2.7 Stability studies: Stability studies were carried out on all the prepared ocusert formulas by storing triplicates of each formula (packaged in aluminum foil) in a humidity chamber with a relative humidity of 75± 5% and a temperature of 40° ± 0.5°C 26.

Samples were withdrawn three times with one month time interval between each withdraw, and evaluated physicochemically for their appearance, weight and drug content as described for freshly-prepared ocuserts.

2.8. In-vivo drug release studies: The prepared ocuserts of formula F2 (0.3*0.6 cm) were sterilized separately by exposure to UV radiation for 90 minutes in a cabinet under aseptic conditions. The sterilized ocuserts packaged in a pre-sterilized aluminum foil and stored in a desiccators until use.

Eighteen New Zealand white albino rabbits (1.5 - 2 kg weight) were used in this study. The rabbits were divided into six groups (I-VI), each containing three animals. The sterilized ocusert formula F2 was carefully instilled into the lower conjunctival sac of the right eye of each rabbit and control ocusert having the same composition without drugs was instilled in its left eye. The ocuserts were removed from animals’ eyes after a pre-determined time interval. Six time intervals were set (1, 3, 6, 12, 18 and 24 hours) for the six groups of animals (I – VI), respectively. The removed ocuserts were dissolved in methanol for the assay of remaining DHCL and TM 27.

International Journal of Pharmaceutical Sciences and Research
The fore-mentioned HPLC method was used for analysis of both drugs. The in vivo release profiles of both DHCL and TM were constructed by plotting percentage drug release versus time, and they were compared with those of in-vitro release to estimate in-vitro / in-vitro correlation.

2.9. Ocular safety study: Draize Irritancy test was used to examine the ocular safety of the prepared ocusert formula of choice (F2). The test was applied to both medicated and non-medicated (control) ocuserts. Both eyes of each animal used in the in-vivo drug release study were examined after the removal of the ocusert at the same predetermined time intervals. Each examined eye was given a score according to an established scoring approach.

3. RESULTS AND DISCUSSION:
3.1. Physicochemical Evaluation of the Prepared Ocuserts: The prepared ocuserts were uniform in appearance with smooth texture and no visible cracks or imperfection. The values of mean weight of ocuserts ranged between 14.6±0.4 and 15.8±0.3 mg, while the mean thickness ranged between 0.38±0.06 and 0.44±0.05 mm. The narrow range of mean weight and thickness along with the small values of SD indicate that the ocuserts are homogenously mixed, well-poured and adequately dried, also low thickness of the ocuserts is good enough to prevent any irritation while placing and being in cul-de-sac. The mean values of film thickness for each of the prepared formulas are given in Table 2.

Mean drug content for the prepared formulas after being extracted in STF ranged from 96.5±1.2% to 98.7±0.8% and from 97.3±1.1% to 99.2±0.3% for DHCL and TM, respectively. These results revealed that none of the prepared formulas deviated from 100% drug content by more than 5%. This indicates that the used method of preparation resulted in reproducible uniform distribution of both drugs within the polymeric matrix of the film. Results of measuring surface pH revealed that all ocusert formulas lay in the physiological range of the eye (5.5-7.5). Therefore, the prepared ocuserts were having the essential requirement to prevent irritation potential as they did not alter the pH of tear fluid.

### TABLE 2: PHYSICOCHEMICAL EVALUATION OF THE PREPARED OCUSERT FORMULAS

<table>
<thead>
<tr>
<th>Formula</th>
<th>Thickness1 (mm ± SD)</th>
<th>Drug content2 (% ± SD)</th>
<th>SI% 3</th>
<th>Folding endurance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DHCL3</td>
<td>TM4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1</td>
<td>0.44±0.05</td>
<td>97.2±0.6</td>
<td>99.2±0.3</td>
<td>Negligible</td>
</tr>
<tr>
<td>F2</td>
<td>0.39±0.02</td>
<td>98.3±0.8</td>
<td>97.8±0.7</td>
<td>Negligible</td>
</tr>
<tr>
<td>F3</td>
<td>0.41±0.03</td>
<td>96.5±1.2</td>
<td>98.6±0.6</td>
<td>Negligible</td>
</tr>
<tr>
<td>F4</td>
<td>0.38±0.06</td>
<td>97.3±1.4</td>
<td>97.3±1.1</td>
<td>12±5</td>
</tr>
<tr>
<td>F5</td>
<td>0.42±0.02</td>
<td>98.7±0.5</td>
<td>98.7±0.8</td>
<td>18±3</td>
</tr>
</tbody>
</table>

1 Results are mean values (n=3) ±SD  
2 Results are mean values (n=5) ±SD  
3 Dorzolamide Hydrochloride  
4 Timolol maleate  
5 Swelling index, mean values (n=3) ± SD

SI of different prepared ocuserts was investigated to measure the bulk hydrophilicity and hydration of polymers which affects the drug release from polymeric matrix. The results of swelling studies, Table 2, revealed that formulas F1-F3 did not swell and have negligible values of SI in STF even after 90 minutes. This can be explained by the hydrophobic nature of EC and poor swelling ability of ES100. On the other hand, formulas F4 and F5 have SI values of 12±5 and 18±3, respectively. According to Stephen & Larry who stated that the water absorption rate of hydrophilic polymers increases as the viscosity of the polymer increases, presence of the hydrophilic polymer HPMC K100M with nominal viscosity of 1,00,100 cps in formulas F4 and F5 enhanced their absorption capacity which reflected on their SI. Ocusert swelling is a disadvantage as it may result in discomfort of the patient. Accordingly, formulas F1- F3 are more preferred than formulas F4 and F5. Folding endurance of the prepared formulas was found to be in the range of 58±6 to 72±8 as shown in Table 2. This indicates that the prepared ocuserts have sufficient elasticity and adequate brittleness to withstand handling during preparation, application and removal from the eye.

3.2. In-vitro drug release study: Since there is no specific official method prescribed for in vitro studies of drug release from ocuserts, the vial
method described by Dandagi et al., and Ashture et al., 11, 22 was used to simulate the drug release into the aqueous humor of the eye. Release profiles of DHCL and TM from the prepared oculers are represented in Fig. 1 and 2 and their data kinetic analysis is collected in Tables 3 and 4. From these figures and tables, it could be concluded that more than one generalized character of DHCL and TM release profiles from the prepared oculers were noticed. First of these characters is that for both drugs, the composition of the polymer matrix in the oculer formula greatly affects the drug release, as a result, the release profiles of both drugs are highly comparable. Second is that the release profile of both drugs from F1: F3 (which contain only EC and ES100 and don’t contain HPMC) follows near zero or zero order kinetics which is emphasized and explained by Korsemeyer kinetics, while DHCL and TM releases from F4 and F5 (which contain EC, ES100, and HPMC) follow the first order kinetics. The third observation is that the reaction rate constant (Ko) significantly decreases by increasing the amount of EC used in the formulation relative to ES100 and HPMC polymers.

### TABLE 3: KINETIC ANALYSIS OF IN-VITRO RELEASE DATA OF DHCL FROM DIFFERENT PREPARED OCUSERTS

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Zero Order</th>
<th>First Order</th>
<th>Korsemeyer-Peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K_0</td>
<td>R^2</td>
<td>K_1</td>
</tr>
<tr>
<td>F1</td>
<td>7.95</td>
<td>0.981</td>
<td>0.097</td>
</tr>
<tr>
<td>F2</td>
<td>4.113</td>
<td>0.996</td>
<td>0.070</td>
</tr>
<tr>
<td>F3</td>
<td>2.657</td>
<td>0.979</td>
<td>0.018</td>
</tr>
<tr>
<td>F4</td>
<td>5.93</td>
<td>0.908</td>
<td>0.111</td>
</tr>
<tr>
<td>F5</td>
<td>7.816</td>
<td>0.930</td>
<td>0.335</td>
</tr>
</tbody>
</table>

### TABLE 4: KINETIC ANALYSIS OF IN-VITRO RELEASE DATA OF TM FROM DIFFERENT PREPARED OCUSERTS

<table>
<thead>
<tr>
<th>Formula code</th>
<th>Zero Order</th>
<th>First Order</th>
<th>Korsemeyer-Peppas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>K_0</td>
<td>R^2</td>
<td>K_1</td>
</tr>
<tr>
<td>F1</td>
<td>7.95</td>
<td>0.981</td>
<td>0.097</td>
</tr>
<tr>
<td>F2</td>
<td>4.113</td>
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</tr>
<tr>
<td>F5</td>
<td>7.816</td>
<td>0.930</td>
<td>0.335</td>
</tr>
</tbody>
</table>

### FIG. 1: IN VITRO RELEASE PROFILE OF DORZOLAMIDE HYDROCHLORIDE FROM THE PREPARED OCUSERTS
It was also noted that formula F2 having a complete prolonged drug release up to 24 hours. Also it was the most fitted one to the zero order kinetics ($R^2 = 0.998$ and 0.996 for DHCL and TM respectively) which further explained by korsemeyer equation to given values of 1.001 and 0.996 for DHCL and TM respectively to ensure zero order release profile of both drugs from this formula. Zero order release profile is usually used to describe the release profile from several controlled dosage forms such as films.

The controlled release of both drugs from F1: F3 compared to F4 and F5 is due to the hydrophobicity of EC along with the poor solubility of ES100 at physiological pH of the eye. The combination of EC and ES100 polymers in the formula resulted in the formation of a tight and non-porous matrix which resists water penetration resulting in slow drug release. While addition of the hydrophilic polymer (HPMC) in the ocusert matrix of formulas F4 and F5 resulted in faster release of both drugs. This is due to the formation of more porous matrix that enhances water penetration and drug release.

That is why these two formulas followed the first order kinetics which is used to describe the drug release of water soluble drugs from porous matrix.

3.3. Stability studies: The prepared ocusert formulas were found to maintain their homogenous appearance with complete absence of cracks or imperfection after three month storage at the forementioned conditions. The weight and the drug content of the stored ocuserts were determined and statistically compared with those of the fresh prepared ocuserts. The results of stability studies showed that there are no significant differences ($p<0.05$) between stored and freshly-prepared formulas F1, F2, and F3. On the contrary, formulas F4, and F5 showed significant increase in the weight and decrease in the drug content ($p<0.05$) which contribute to water absorption due to the presence of the hydrophilic polymer, HPMC.

3.4. In-vivo drug release study: As formula F2 provides satisfactory in-vitro drug release patterns as well as superior physicochemical properties: SI and stability during three-month storage, it was selected for further in-vivo studies. The in-vivo release profiles of both DHCL and TM from formula F2 are shown in Fig. 3. This figure reveals the slow release of both drugs from the prepared ocusert formula. At the end of the release experiment, 88.8±8.1% and 98.9±1.3% of the incorporated DHCL and TM was released, respectively. This indicates a promising enhancement of patient compliance. According to Bansal et al, 2013, the in-vivo / in-vitro correlation was estimated by plotting a scatter diagram between the cumulative percentage of the drugs released from the chosen formula in both studies. Release of both drugs from formula F2 showed good in-vitro /in-vivo correlation as revealed from Fig. (4 and 5) where the calculated $R^2$ values were 0.973 and 0.997 for DHCL and TM, respectively.
FIG. 3: IN-VIVO RELEASE PROFILES OF DHCL AND TM FROM THE PREPARED OCUSERT FORMULA F2 IN RABBITS’ EYES.

FIG. 4: IN-VIVO / IN-VITRO CORRELATION OF DORZOLAMIDE HYDROCHLORIDE RELEASE FROM THE PREPARED OCUSERT FORMULA F2

FIG. 5: IN-VIVO / IN-VITRO CORRELATION OF TIMOLOL MALEATE RELEASE FROM THE PREPARED OCUSERT FORMULA F2
3.5 Ocular safety study: None of the examined rabbits’ eyes showed any irritation, inflammation or abnormal discharges. The collected scores were zero which is interpreted in Draize test as non-irritant application. This indicates that both medicated and control ocuserts of formula F2 are safe. In other words, the used polymers as well as the incorporated drugs are suitable to be applied as ocuserts in the eye.

CONCLUSION: From the results of this study it is concluded that controlling the hydrophobicity of the polymer matrix greatly affects the physicochemical properties of the prepared ocuserts as well as the release profiles of the incorporated drugs. For DHCL and TM, the optimum composition of the polymer matrix is 1:1 ratio of EC and ES100. This produces ocuserts with adequate physicochemical properties, drug release patterns, stability and safety. The prepared novel ocuserts provide a promising approach for once-daily effective and safe drug delivery system of DHCL and TM, which enhance the patient compliance, and decrease the used drug doses and the major side effects for glaucoma treatment.

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How to cite this article: