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DESIGN AND OPTIMIZATION OF CONTROLLED RELEASE OCULAR INSERTS OF DORZOLAMIDE HYDROCHLORIDE AND TIMOLOL MALEATE FOR TREATMENT OF GLAUCOMA

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ABSTRACT

Goal of the present investigation was to formulate ocular inserts of dorzolamide hydrochloride and timolol maleate for the treatment of glaucoma. Ocular inserts of dorzolamide hydrochloride and timolol maleate were prepared using different polymers ethylcellulose, Eudragit RL 100, and Eudragit RS100 by solvent casting method with an objective to increasing the contact time, achieving controlled release, reducing in frequency of administration, and improving therapeutic efficacy. The drug-excipients interaction was studied by Fourier transform infrared spectroscopy (FTIR) studies. Prepared ocular inserts were evaluated for their physicochemical properties such as uniformity of thickness, weight uniformity, tensile strength, percentage elongation, drug content, moisture loss, moisture absorption. The *in vitro* diffusion of drug from the inserts was studied using the classical biochemical donor - receptor compartment model fabricated in the laboratory and the formulation that showed better release profile was subjected to *in vivo* studies on albino-rabbits. Ocular irritation study was performed using healthy albino rabbits and confirmed that there was no irritation in the rabbit eyes. All the inserts were found to be uniform thickness and uniform weight. The inserts possessed good tensile strength and percentage elongation. All the formulations followed a first order release pattern. Optimized formulation RSRL3 showed high correlation coefficient (R = 0.996 & 0.995 respectively for dorzolamide HCl & timolol maleate) between *in vitro* and *in vivo* release. Stability study was carried out on RSRL3 formulation and showed no significant changes in the drug content as well as physical characteristics of the film.

INTRODUCTION: Glaucoma is a disease in which the optic nerve is damaged, leading to progressive, irreversible loss of vision. It is often, but not always, associated with increased pressure (above 21 mm Hg or 2.8 kPa) of the fluid in the eye. Glaucoma can be categorized roughly into two main types, open angle and closed angle glaucoma.

Closed angle glaucoma can appear suddenly and is often painful; visual loss can progress quickly but the discomfort often leads patients to seek medical attention before permanent damage occurs. Open angle, chronic glaucoma tends to progress at a slower rate and the patient may not notice that they have lost vision until the disease has progressed significantly [1].

Topical beta blockers are often used as a front line drugs for the treatment of glaucoma. These drugs block β_2 receptors present on ciliary epithelium thereby reduces aqueous humor formation without affecting pupil size, tone of ciliary muscle, or outflow facility. This effect is probably because, down regulation of adenylcyclase due to β_2 receptor blockade and a secondary effect due to reduction in ocular blood flow.

Pharmaceutical technologists are advanced in developing drug delivery systems with very precise control over drug release for a prolonged period of time, dominating the need for a frequent dosing and minimizing side effects thereby increasing patient compliance and comfort. In conventional mode of therapy, many drugs do not reach the target site in the body in sufficient concentration because of prematurely inactivated and excreted. This problem can be overcome by administering the drugs directly into the intended site of action with lesser dose [2].

Therefore, designing formulations and delivery systems for topically applied ophthalmic chemotherapeutic agents is challenging. It requires a thorough understanding of the physiological basis of the protective mechanisms of the eye. Eye allows only 1-10% of the topically applied dose to be absorbed. These protective mechanisms include solution drainage, lacrimation, diversion of exogenous chemicals into the systemic circulation via the conjunctiva, and a highly selective corneal barrier to exclude exogenous compounds from the internal eye. Improvement of ocular drug delivery then amounts to determining the outer boundaries as well as the maximum duration over which these protective mechanisms can be compromised without causing harm to this vital organ [3].

A basic concept in ophthalmic research and development is that the therapeutic efficiency of an ophthalmic drug can be greatly improved by prolonging its contact with the corneal surface ophthalmic inserts offer many advantages over conventional dosages forms, like increased ocular residence, possibility of releasing drug at a slow and constant rate, accurate dosing, exclusion of preservatives and increased shelf life [4].

An attempt was made to prepare ocular inserts with the target of increasing the contact time, reducing the frequency of administration, improving patient complacent and obtain greater therapeutic efficacy.

MATERIALS AND METHODS: Dorzolamide Hydrochloride and Timolol maleate were obtained as gift samples from Wockhard Pvt. Ltd., Aurangabad. Eudragit RL100 and Eudragit RS100 were provided as gift samples from Aurobindo Pharma Ltd., Hyderabad. Ethylcellulose was obtained from SD Fine Chem Ltd. All other chemicals and solvents used were of analytical grade. Concentrations of dorzolamide HCl and timolol maleate were measured with a UV-Vis spectro-photometer (UV 1700, Shimadzu, Kyoto, Japan) at 254 nm and 294.8 nm respectively. Interaction between dorzolamide HCl, timolol maleate and polymers was ruled out using FTIR (Jasco Corporation, Japan) and UV-Visible spectrophotometric methods.

TABLE 1: FORMULATION DESIGN OF OCULAR INSERTS USING EUDRAGIT RS 100 AND EUDRAGIT RL 100

INGREDIENTS	FORMULATIONS					
	RSRL1	RSRL2	RSRL3	RSRL4	RSRL5	RSRL6
Dorzolamide HCl	120 mg	120 mg	120 mg	120 mg	120 mg	120 mg
Timolol maleate	30 mg	30 mg	30 mg	30 mg	30 mg	30 mg
Eudragit RS 100	300 mg	150 mg	300 mg	150 mg	200 mg	200 mg
Eudragit RL 100	500 mg	500 mg	300 mg	300 mg	500 mg	300 mg
Dibutyl phthalate	120 mg	120 mg	120 mg	120 mg	120 mg	120 mg
Tween 20	40 mg	40 mg	40 mg	40 mg	40 mg	40 mg
Ethanol	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml
Methanol	5 ml	5 ml	5 ml	5 ml	5 ml	5 ml

Preparation of ocular inserts: Ocular films containing dorzolamide hydrochloride and timolol maleate were prepared by mercury substrate method using varying ratios of different grades of polymers as shown in the table 1. The polymers Eudragit RS 100 and Eudragit RL 100 were accurately weighed in requisite ratios and dissolved in equal volume of ethanol (5 ml) and methanol (5 ml) to form a 4.5% to 8% w/v solution. 120 mg of dorzolamide hydrochloride and 30 mg of timolol maleate were then added in to the polymeric solution under mild agitation until it was dissolved. Plasticizer Dibutyl phthalate (DBP) and ocular penetrating enhancer tween-20 was added to the above solution under mild agitation for complete mixing of the solution.

The mixture was set for mixing on magnetic stirrer for 4 h to ensure uniform distribution of ingredients. Afterwards the mixture was kept in vacuum desicator and was subjected to vacuum to remove the entrapped air bubbles. The solution was poured on the mercury placed in a glass mould (5 x 3 cm^2) and dried at room temperature for 24 hours. During drying the glass mould was covered with inverted funnel plugged with cotton in the stem to ensure slow evaporation of the organic solvent. The organic solvent evaporates to leave stable Eudragit RS /Eudragit RL (RS/RL) films.

After drying, the films were taken out and were cut into round shaped inserts using tablet punch of 9 mm diameter. All the inserts were wrapped in wax paper and were kept in desciator till further use [5]. Here the words films and ocular inserts were carefully used. Former represents 5 x 3 cm^2 and later represents 9 mm diameter in size. Similarly dummy films were prepared without adding drug. Films with any imperfections such as entrapped air, differing in thickness, weight or content uniformity were excluded from further studies.

Simultaneous Estimation of dorzolamide hydrochloride and timolol maleate in STF 7.4 pH: A simple, accurate, economical, and reproducible procedure for the simultaneous estimation of dorzolamide hydrochloride and timolol maleate in ocular films has been developed. The absorbance was measured using UV-Visible spectrophotometer at 254.0 nm and 294.8 nm corresponding to absorption maxima of dorzolamide hydrochloride and timolol maleate respectively.

Both the drugs obey Beer-Lambert's law in the concentration range employed in the method. The result of analysis has been validated by recovery studies [5, 6].

Evaluation of prepared ocular inserts:

Physical appearance: All the prepared ocular films and inserts were evaluated for their physical appearance. The parameters such as transparency, color, texture, and other defects were studied.

1. **Weight variation test** [7, 8]: Inserts from each batch were randomly selected and weighed individually on electronic balance (Shimadzu Corporation, Japan). Mean weight of inserts (n = 10) of each formulation was recorded.

2. **Folding endurance:** The film was folded at center, between the fingers and the thumb and then opened. This was termed as one folding. The process was repeated till the film showed breakage or cracks in center. The total folding operations were named as folding endurance value. This test was done on five films of each formulation.

3. **Surface pH:** Agar (2% m/v) was dissolved in warm simulated tear fluid (STF), pH 7.4 under stirring and then poured the solution into petri plates, allowed till gelling at room temperature. Inserts were left to swell for 5 h on agar plate. The surface pH was measured by means of a pH paper placed on the surface of swollen film.

4. **Swelling index determination** [9, 10]**:** Three inserts were weighed and placed separately in beakers containing 4 ml of distilled water. At regular time intervals, inserts were removed and the excess water on their surface was wiped using a blotting paper and again weighed. The procedure was continued till there was no increase in the weight of inserts. Swelling index was then calculated by dividing the increase in weight by the original weight and was expressed as percentage.

5. **Percentage moisture absorption** [11, 12, 13]**:** Three inserts were kept in a desiccator at room temperature for 24 hrs containing calcium chloride. They were then taken out; initial weight

was taken and exposed to 75% relative humidity using a saturated solution of sodium chloride in desiccator. These inserts were weighed repeatedly until they showed a constant weight. Percent moisture uptake was calculated using the following formula:

Percentage moisture absorption = [(Final weight - Initial weight) / Initial weight] × 100.

6. **Percentage moisture loss** [11,14]**:** Three inserts were weighed individually and kept in a desiccator at room temperature containing anhydrous calcium chloride. The inserts were weighed repeatedly until they showed a constant weight. The percentage moisture loss was calculated using the following formula:

Percentage moisture loss = [(Initial weight - Final weight) / Initial weight.] × 100.

7. **Tensile strength of the films** [7, 8]**:** Tensile strength of the films was determined using Hounsfield universal testing machine. The sensitivity of the machine is 1 mg to 500 kg. It consists of two load cell jaws; the upper one is movable and lower one is fixed. The test film of specific size (4 × 1 cm^2) was fixed between these cell grips and the upper jaw was moved at a speed of 100 mm/min (ISI Standard speed) applying force gradually till the film breaks. The tensile strength of the films was taken directly from the dial reading in kilograms. The tensile strength per cm^2 was calculated using the formula; Tensile strength (kg/cm^2) = break force (kg)/cross-sectional area of the sample (cm^2).

8. **Drug content uniformity** [7, 15]**:** Ocular inserts (n = 6) of 9 mm diameter were dissolved individually in methanol/ethanol in a 100 ml volumetric flask. Then required volume of solution was taken out and further dilutions were made with STF pH 7.4. Similarly, a blank was carried out using a drug free insert. Then absorbance was taken at 254.0 nm and 294.8 nm by UV spectroscopy respectively.

9. **Ocular irritation study** [16]**:** Ocular irritation study was conducted in albino rabbits after getting prior approval from institutional animal ethics committee. Six albino rabbits were used in the study and were examined thoroughly for any pre-existing ocular damage. The sterile optimized formulation RSRL3 was then placed in one eye of each animal by gently pulling the lower eyelid away from the eye ball (conjunctival cul-de-sac). The eye lids were then being gently held together for few seconds and the animal was released. The other eye, remaining untreated was served as the control. The eyes of each rabbits were examined at 1, 4, 12, 24, 48, and 72 hrs after treatment for irritation, inflammation etc., by naked eye or by means of a pen torch. At the time of examination period each rabbit was scored for ocular reaction given in **Table 2**. The test may be considered positive if three or more animal exhibit positive reactions at any observation period.

TABLE 2: OCULAR IRRITATION SCORING SYSTEM

Ocular reaction	Score
Cornea	
No ulceration or opacity	0
Scattered or diffuse areas of opacity (other than slight dulling of normal luster, details of iris are clearly visible)	1
Easily discernible translucent areas, details of iris slightly obscured	2
Nacreous areas, no details of iris, size of pupil barely discernible	3
Opaque cornea, iris is not discernible through the opacity	4
Iris	
Normal	0
Markedly deepened rugae, congestion, swelling, moderate circumcorneal hyperemia, or injection, any of these or combination thereof, iris is still reacting to light (sluggish reaction is positive)	1
No reaction to light, hemorrhage, gross destruction (any or all of these)	2
Conjunctivae	
Blood vessels are normal	0
Some blood vessels are definitely hyperemic (injected)	1
Diffuse crimson color, individual vessels not easily discernible	2
Diffuse beefy red	3
No swelling	0
Any swelling above normal	1
Obvious swelling with partial eversion of lids	2
Swelling with lids about half closed	3
Swelling with lids more than half closed	4

10. *In Vitro* Drug Diffusion Study [8, 17, 18] : The *in vitro* diffusion of drug from the inserts was studied using the classical biochemical donor - receptor compartment model comprising a cylindrical tube (15 mm internal diameter and 80 mm height) and a glass beaker fabricated in the laboratory. The dialysis membrane No.50 (HiMedia Laboratories, Mumbai) was tied to one end of open cylinder. This acted as a donor compartment. The insert was placed inside this compartment. The dialysis membrane acted as conjunctival epithelium. The entire surface was in contact with the receptor compartment containing 25 ml of STF pH 7.4 in 100 ml beaker. The content of receptor compartment was stirred continuously at low speed maintaining a temperature of 37 ^{0}C ± 1 ^{0}C. At specific time intervals samples were withdrawn from the receptor compartment and replaced with fresh STF pH 7.4. The samples were analyzed using UV spectrophotometer at 254.0 nm and 294.8 nm.

11. *In Vivo* Drug Release Study [11, 19, 20]**:** *In vivo* study was carried out using healthy albino rabbits weighing 2 to 3 kg with prior approval of institutional animal ethics committee. Among ten formulations, RSRL3 which showed a better *in vitro* release was taken for *in vivo* study. The inserts were placed into the conjunctival cul-de-sac of six healthy rabbits and at the same time the other eye was served as the control. At specific time intervals inserts were carefully removed and analyzed for the residual drug content. The drug remained in the insert was subtracted from initial drug content of the insert to give the amount of drug released into the rabbit's eye. After a wash out period of one week the experiment was repeated for two times as before.

RESULTS AND DISCUSSION: In this present study, effort has been put to prepare controlled release combined drug dorzolamide HCl and timolol maleate ocular inserts Eudragit RL 100, Eudragit RS 100 and Ethyl cellulose to control the drug release for prolonged period of time. A suitable analytical method for dorzolamide hydrochloride and timolol maleate was developed by UV Spectroscopy. Dorzolamide hydrochloride and timolol maleate showed maximum absorption at wavelength 254.0 nm & 294.8 nm respectively in STF pH 7.4. Drug-polymer compatibility study by UV method, and FTIR method, ruled out that no interaction between the drug and selected polymers used in the formulations and confirmed their purity. The IR spectra of pure drugs and its combination with polymers are shown in **figure 1**.

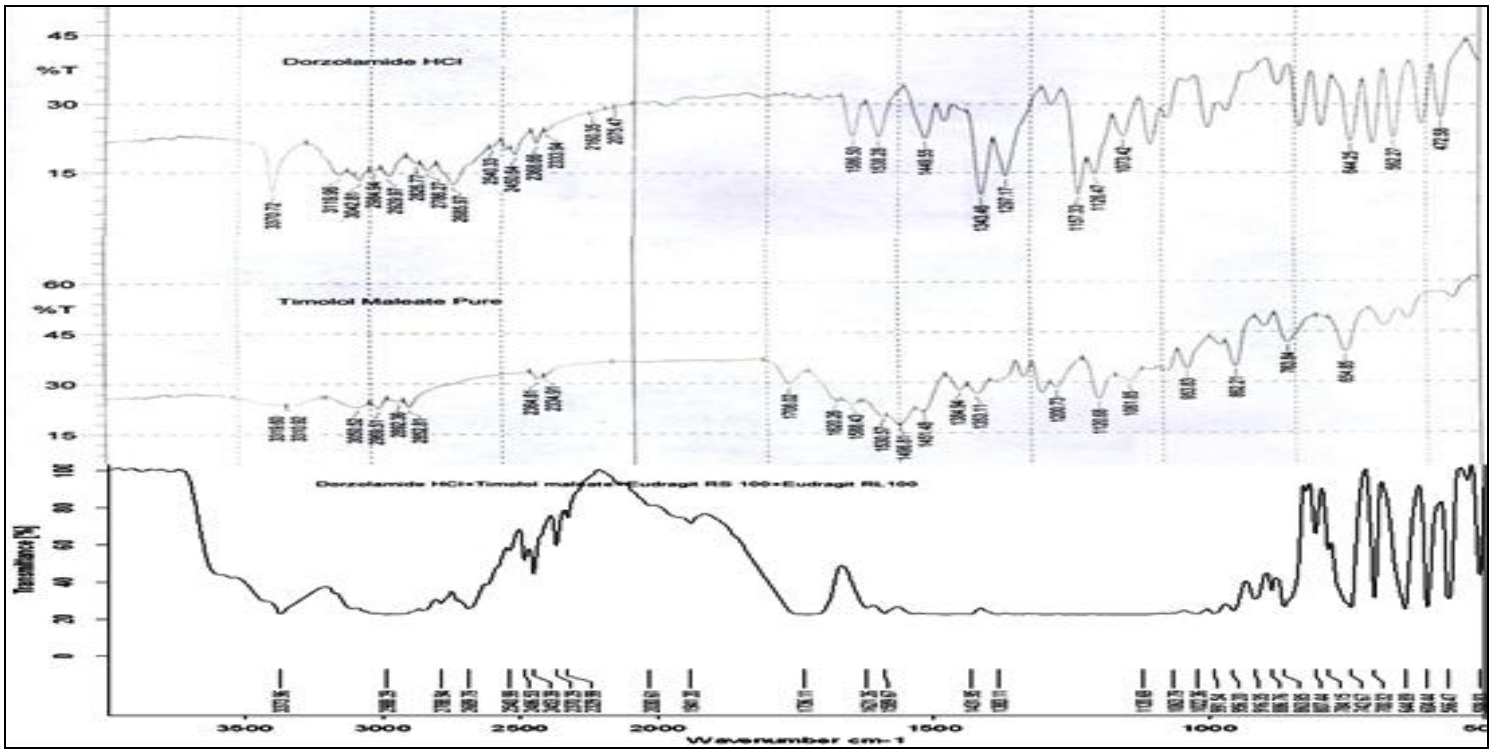

FIGURE 1: IR SPECTRUM OF DORZOLAMIDE HYDROCHLORIDE, TIMOLOL MALEATE ALONE AND MIXTURE OF DRUGS AND EUDRAGIT RL100

Various formulations were developed by using release rate controlling and bioadhesive polymers like Eudragit RS 100, Eudragit RL 100, and Ethyl cellulose in combinations by solvent casting method with incorporation of tween-20 as a penetration enhancer and dibutyl phthalate (DBP) as a plasticizer.

Developed ocular films possessed the required physicochemical properties such as translucent, smooth in texture, uniform in appearance and showed no visible crack or imperfection. A few defective films formed were eliminated from the study. Drug loaded ocular inserts were tested for weight uniformity. The data of weight uniformity, moisture absorption, moisture loss, thickness, weight uniformity and tensile strength studies are shown in **Table 3**. Perusal to the table indicates that the ocular inserts were found uniform in thickness with standard deviation ranging from 0.0015 to 0.0681 mm.

Ocular films did not show any cracks even after folding for more than 200 times which reflects the flexibility of the films. Folding endurance did not vary when the comparison was made between plain films and drug loaded films. Surface pH was within the range of 6.2 – 7.5 which confirms that prepared inserts would not alter the pH of tear fluid and cause no irritation of eye so obviously achieve patient compliance.

TABLE 3. PHYSICOCHEMICAL PARAMETERS OF OCULAR INSERTS

Formulations	*Average thickness (mm) (AM ± SD)	*Average weight (mg) (AM ± SD)	Tensile strength (kg) (AM ± SD)	*Percentage moisture loss (AM ± SD)	*Percentage moisture uptake (AM ± SD)
RSRL1	0.281 ± 0.0294	8.94 ± 0.7600	0.29 ± 0.0555	4.27 ± 0.6444	1.57 ± 0.7584
RSRL2	0.244 ± 0.0100	7.23 ± 0.8078	0.532 ± 0.0101	4.18 ± 0.6611	1.54 ± 1.4227
RSRL3	0.268 ± 0.0015	6.35 ± 0.8492	0.683 ± 0.129	2.09 ± 0.1238	1.14 ± 0.2791
RSRL4	0.257 ± 0.0681	5.56 ± 0.3910	0.276 ± 0.0387	2.11 ± 0.4127	1.08 ± 0.4805
RSRL5	0.275 ± 0.0080	8.05 ± 0.4613	0.375 ± 0.0396	3.97 ± 0.4731	1.66 ± 0.9942
RSRL6	0.259 ± 0.0092	6.53 ± 0.2829	0.342 ± 0.018	2.32 ± 0.4251	1.12 ± 0.5891

Swelling of the films observed in STF (pH 7.4) is as shown in **Figure 2**. The results of swelling studies revealed that in all formulations the swelling index was not high as the polymers used in the preparation of inserts were hydrophobic. However, swelling index was observed to be a function of concentration of Eudragit RL 100. With decrease in concentration of Eudragit RL100 there was decrease in the swelling index of inserts which could be attributed to the high permeability of the polymer owing to the presence of more number of quaternary ammonium groups in the structure.

The order of inserts for their increase in weight due to swelling is RSRL2 < RSRL4 < RSRL1 < RSRL3 < RSRL5 < RSRL6. The results reveals that swelling was insignificant in all the formulations indicating that the prepared ocular inserts could not cause, as extraneous body in the eye, less discomfort.

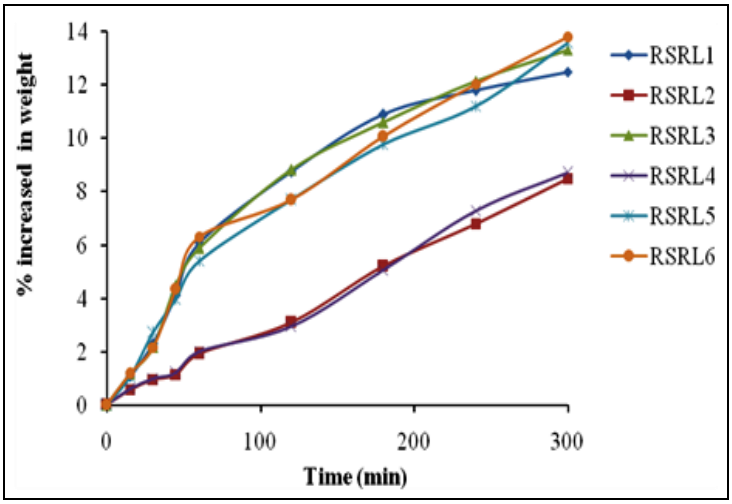

FIGURE 2: SWELLING STUDIES OF EUDRAGIT PATCHES - CHANGE IN WEIGHT IN DISTILLED WATER

The order of tensile strength for Eudragit ocular films is RSRL3 > RSRL2 > RSRL5 > RSRL6 > RSRL1 > RSRL4 as shown in the **figure 3**. Eudragit films exhibited less percentage elongation as the concentration of Eudragit RS 100 was increased

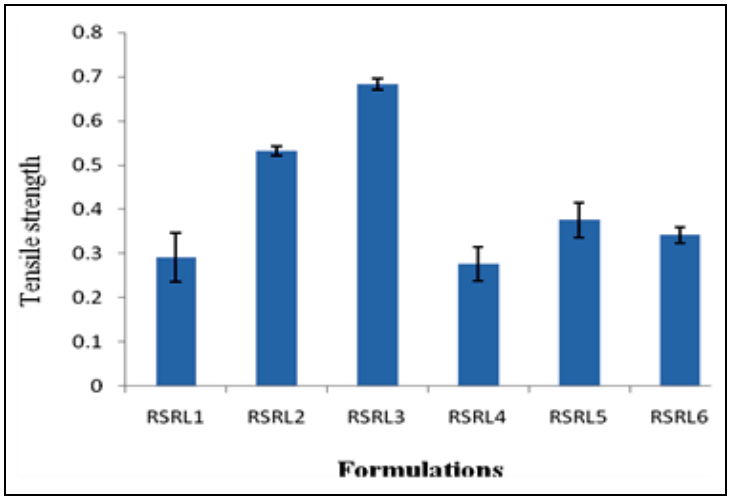

FIGURE 3: TENSILE STRENGTH OF THE LOADED EUDRAGIT OCULAR INSERTS

From the results of drug content determination, it was inferred that there were proper distribution of both drugs in the films and the deviations were within the acceptable limits. The result of the ocular irritation study proved that the optimized formulation RSRL3 is non irritant to the rabbit eye.

***In Vitro* Drug Diffusion Study:** The formulations RSRL1 showed 89.44% and 82.15% release for dorzolamide HCl and timolol maleate respectively whereas RSRL2 and RSRL4 showed 79.08% - 92.76% and 92.99% - 95.90% release at the end of 24 hours respectively. The formulations RSRL3 showed 95.36% and 95.41% release at the end of 72 hours respectively whereas RSRL5, RSRL6 showed release of 88.14% - 90.10% and 96.38% - 94.28% release in 48 hours respectively for dorzolamide HCl and timolol maleate. Both Eudragit inserts (RS & RL series) showed prolonged release of the drug. The formulation RSRL3 showed the potential of sustaining the drug release for the longest period of time and hence, it was selected as optimized formulation for further sterility test, ocular irritation test, and *in vivo* study. The comparative data of percentage drug release from *in vitro* studies of all the formulation RSRL1 to RSRL6 are shown in **Table 4**. The comparative plots of *in vitro* drug release from formulations RSRL1 to RSRL6 were as shown in **figure 4.**

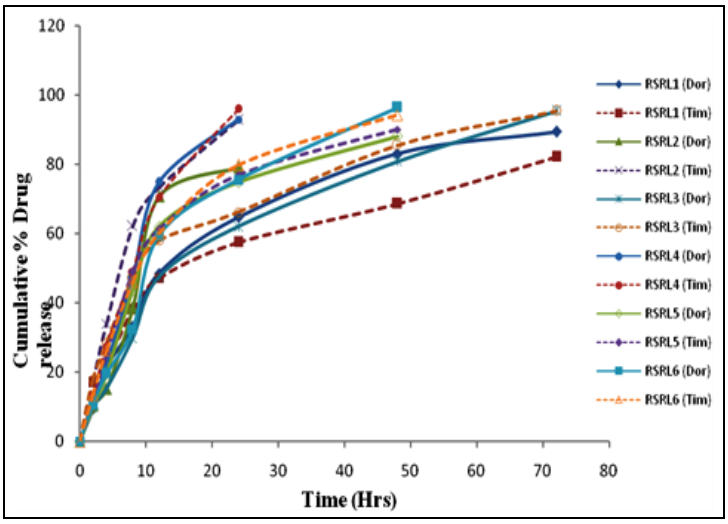

FIGURE 4: COMPARATIVE I*N VITRO* CUMULATIVE % DRUG RELEASE PLOTS OF RSRL1-RSRL6

***In vivo* Drug Release Study:** *In vivo* drug release study was carried out on the optimized formulation (RSRL3). The study was conducted in albino rabbits by measurement of the residual drug content in the ocular inserts at periodic time intervals. Rabbits which were subjected for *in vivo* study didn't show any irritation, inflammation and abnormal discharge which confirmed the safety of the polymers used in the formulation. The drug release from the formulation (RSRL3) after 72 hours was found to be 98.22% & 98.82% respectively for dorzolamide HCl and timolol maleate. The *in vivo* drug release from the optimized formulation is plotted in **figure 5**.

TABLE 4: COMPARATIVE I*N VITRO* CUMULATIVE % DRUG RELEASE DATA OF RSRL1-RSRL6

Time in Hours	Cumulative % drug release											
	RSRL1		RSRL2		RSRL3		RSRL4		RSRL5		RSRL6	
	DOR HCl	TM	DOR HCl	TM	DOR HCL	TM	DOR HCl	TM	DOR HCl	TM	DOR HCl	TM
0	0	0	0	0	0	0	0	0	0	0	0	0
2	9.43	17.01	10.49	17.08	9.87	17.82	10.24	13.31	9.62	10.67	10.64	13.31
4	21.44	22.33	15.19	33.93	15.26	28.50	22.02	27.45	19.64	25.18	19.59	26.33
8	33.15	37.97	38.49	62.14	29.79	47.09	47.47	49.00	43.55	48.88	32.47	46.08
12	48.54	47.17	70.75	73.35	47.52	58.07	74.89	70.56	62.09	61.45	59.50	60.13
24	64.77	57.45	79.08	92.76	62.00	66.20	92.99	95.90	74.92	77.01	75.59	79.79
48	83.01	68.67	--	--	80.83	85.58	--	--	88.14	90.11	96.38	94.28
72	89.44	82.15	--	--	95.36	95.41	--	--	--	--	--	--

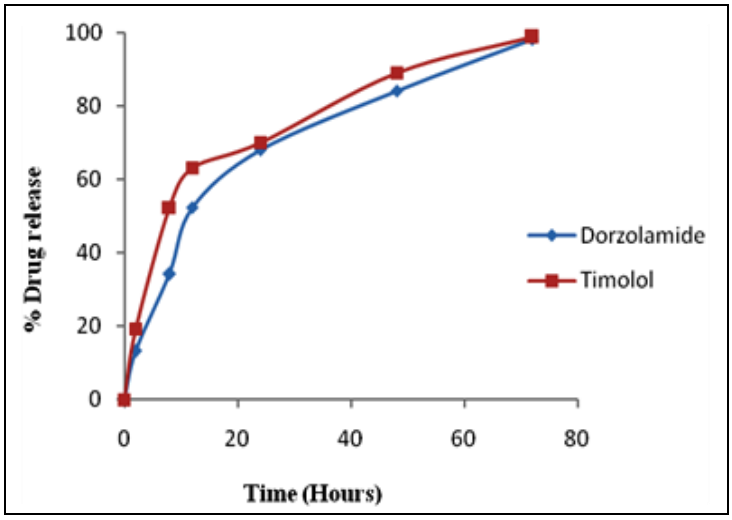

FIGURE 5: *IN VIVO* DRUG RELEASE PROFILE OF RSRL3

The controlled release of dorzolamide hydrochloride and timolol maleate was observed under *in vivo* condition and complete drug release was taken place in about 60 hours however the *in vitro* studies showed that the drug release lasted for 72 hours. It may be due to factors like tear flow rate, tear volume secretion, etc. The correlation coefficient (R^2) value for the percentage drug released *in vivo* was found to be very high, and a positive correlation of both drugs was found to be significant (R^2 = 0.995 & R^2 = 0.996).

The concept of *in vitro* and *in vivo* correlation studies was used in pharmaceutical research work because a simple *in vitro* release study on a drug product will be insufficient to predict its therapeutic efficiency. Correlation between *in vitro* release behavior of a drug and its *in vivo* absorption in rabbits must be established experimentally to reproduce therapeutic response.

The formulation RSRL3 was selected as the best formulation based on the prolonged *in vitro* release of the drug and the same was used for *in vivo* studies conducted in rabbits.

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