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Design, Formulation, Evaluation of Levobunolol HCl Ocular Inserts.

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Abstract
Glaucoma is a group of diseases of the eye characterized by damage to the ganglion cells and the optic nerve. If left untreated, these effects may lead to various degrees of loss of vision and blindness. β-Blockers are the most widely prescribed drugs for the treatment of glaucoma and may be used alone or in combination with other drugs. A major problem in ocular therapeutics is the attainment of an optimal drug concentration at the site of action. The ocular inserts maintain an effective drug concentration in the target tissues. Ocuserts of Levobunolol HCl, antiglaucoma drug was designed by using different polymers such as Methyl cellulose (MC), Poly Vinyl Pyrrolidone (PVP) and Hydroxy Propyl Methyl Cellulose (HPMC) using Glycerin and Dibutyl Pthalate (DBP) as plasticizer. The prepared ocular inserts were characterized and evaluated for their physicochemical properties like thickness (0.191±0.0024 mm to 0.292±0.0040 mm), tensile strength (in terms of polymer used; HPMC & PVP > MC > HPMC), uniformity of the weight (24.91±0.0924 mg to 34.10±0.0834 mg), drug content analysis, folding endurance, content uniformity (93.1%±0.264 to 98.00%±0.321), percent moisture absorption and loss. The stability studies as per ICH guidelines were also carried out.
Key words: Glaucoma, β-Blockers, Levobunolol HCl, Ocuserts.

INTRODUCTION

Eye is the most marvelous creation of God among all the sense organs in the human body, as it makes us aware of various objects all around us, near and far away. Eye is nearly spherical in shape except the front portion i.e., transparent cornea bulges a bit forward. The eye is protected from the environmental and accidental injuries by the provisions such as eyelashes, eyelids, tears and blinking reflex. The eyelashes catch foreign materials while the blink reflex prevents injury by closing the lids. Blinking occurs frequently during waking hours to keep the corneal surface free of mucous and moistened by the tears secreted by the lachrymal glands. Tears wash away irritating agents and are bactericidal thus preventing infections. The protective operation of the eyelids and lachrymal system is a rapid removal of material instilled in to the eye, unless the material becomes suitably small in volume, chemically and physiologically compatible with surface tissues. The eye is one of the most delicate and yet most valuable of all the sense organs and is a challenging subject for topical administration of drugs to the eye.

Glaucoma is a group of diseases of the eye characterized by damage to the ganglion cells and the optic nerve (Eric T. Herfindal 2000). If left untreated, these effects may lead to various degrees of loss of vision and blindness. Increased intraocular pressure (IOP) remains the most important risk factor for the development of glaucoma. Glaucoma is typically classified as either open angle or angle closure (closed angle), based upon causes of increased intraocular pressure.

Glaucoma (Eugenia M Fulcher 2003) may be classified in a variety of ways, which describe causative factors, when known. Glaucoma is usually described as either angle closure or open angle glaucoma. These terms are based upon the mechanism of obstruction of outflow of aqueous humor and help clinicians develop treatment strategies. Open angle glaucoma occurs in 80 to 90% of cases. Angle closure glaucoma is usually a more acute form of disease and is seen in 5 to 10% of all patients. A third type is congenital glaucoma, which results from developmental ocular abnormalities and occurs in less than 2% of patients. Finally, glaucoma may be secondary to other ocular disorders, systemic disorders, or trauma, or may be seen with medication usage, or after intraocular surgery. Open angle glaucoma can be further described as either high tension or normal tension (also known as low tension) glaucoma.

Optic nerve damage caused by the different types of glaucoma is a result of a variety of initiating factors. Genetic predisposition, physical changes, systemic diseases, or medications may increase a person's risk of developing damage that may be broadly classified as intraocular pressure dependent (most commonly) or intraocular pressure independent. Increased intraocular pressure remains the major etiologic risk factor for the development of glaucoma. Myopia may be an additional risk factor, especially in younger patients. Glaucoma can occur as a secondary

manifestation of systemic disorders or trauma. There are five stages in the pathogenesis of glaucoma (Shields M 1996): (1) a variety of initial events, causing (2) Changes in aqueous outflow, resulting in (3) Increased IOP, which leads to (4) Optic nerve atrophy, and finally, (5) Progressive loss of vision.

The goal of glaucoma therapy is the immediate and sustained reduction of intraocular pressure to prevent deterioration of the optic nerve and loss of vision. Medications used in the treatment of glaucoma may be classified as those that increase the elimination of aqueous humor and those that decrease its formation. The ocular hypotensive effect caused by β-blockers is probably due to suppression of aqueous humor formation by blockage of the β-adrenoreceptors in the ciliary body. β-Blockers decrease aqueous humor production by approximately one-third.

Levobunolol HCl (Tommy W Gage 2003) is a non-cardio selective β-blocker and is reported to lack intrinsic sympthomimetic activity and membrane stabilizing properties. It is used as hydrochloride salt to reduce raised IOP (raised intraocular pressure) in open angle glaucoma and ocular hypertension, which is non-selective between beta and beta-adrenergic receptors. It does not have significant intrinsic sympathomimetic activity direct myocardial depressant or local anesthetic (membrane-stabilizing) activity. Levobunolol HCl is effective in lowering intraocular pressure and is widely used in patients with open-angle glaucoma and aphakic glaucoma. Levobunolol HCl is also indicated for the treatment of hypertension (alone or in combination with other anti-hypertensive agents, especially thiazide-type diuretics) and to reduce cardiovascular mortality and the risk of reinfarction in patients who have survived the acute phase of myocardial infarction and who are clinically stable. It is usually used as 0.5% ophthalmic solution instilled once or twice daily: alternatively a 0.25% solution may be instilled twice daily. Levobunolol HCl available for oral dosing as tablets and for injection and ophthalmic dosing as distinct sterile aqueous solutions are usually well tolerated with most adverse effect being mild and transient.

To achieve effective ophthalmic therapy, an adequate amount of active ingredient must be delivered and maintained within the eye. For the therapeutic treatment of most ocular problems topical administration clearly seems the preferred route as for systemically administered drugs, only a very small fraction of their total dose will reach the eye from the general circulatory system. The poor accessibility of a number of ocular regions to systemic circulation makes local delivery via topical administration the preferred route for the treatment of ocular diseases. The biological barriers involved for ocular delivery are the permeability barrier posed by cornea and other regions, as well as the tear wash out and blinking reflexes designed to remove foreign substances from the eye. Furthermore the ocular region is very sensitive and cannot withstand high local concentration of the drug or vehicle without irritation. Because of these limitations, designing formulations and delivery systems for topically applied ophthalmic drugs is challenging. Recent advances have been made in topical drug delivery systems that improved ocular drug contact time and drug delivery.

Inserts are solid dosage forms and can overcome the disadvantage reported with traditional ophthalmic systems like aqueous solutions, suspensions and ointments. The ocular inserts maintain an effective drug concentration in the target tissues. A number of ocular inserts were prepared utilizing different techniques to make soluble, erodible, non-erodible and hydro-gel inserts.

In this present work Levobunolol HCl ophthalmic inserts were prepared and evaluated for their physicochemical properties like thickness, tensile strength, uniformity of the weight, drug content analysis, folding endurance, content uniformity, percent moisture absorption and loss and the stability studies as per ICH guidelines were carried out for the formulations.

METHODS

The formulation of the polymeric system is essential for providing suitable delivery rate; the components of the system have an impact on the rate of drug release to the conjunctival sac and hence affect the bioavailability of the drug to a large extent. The polymers were selected on the basis of their solubility and compatibility with each other as well as drug Levobunolol HCl. The blank polymeric patches were prepared using HPMC, MC and PVP alone and in combination by solvent casting technique.

PREPARATION OF OCUSERTS (Abhilash AS 2005)**:**

Accurately weighed quantity of HPMC was soaked in the $1/3^{rd}$ volume of the distilled water for 24 hours. Required quantity of plasticizer was then dissolved in the remaining amount of water. Both the solutions were slowly mixed together with the help of magnetic stirrer. 5ml. of the resultant mixture was poured into each fabricated

Table-1; Data of various formulations with different composition of DR & RCM

Formulation Code	*Drug Reservoir (DR)*				*Rate Controlling Membrane (RCM)*	
	Film Former (%w/v)			**Plasticizer (%w/w)**	**Film Former (%w/v)**	**Plasticizer (%w/w)**
	HPMC	**PVP**	**MC**	**Glycerin**	**EC**	**Dibutylphthalate**
OD_1	3	-	-	40	6	30
OD_2	4	-	-	40	6	30
OD_3	3	1	-	40	6	30
OD_4	4	1	-	40	6	30
OD_5	-	-	1	40	6	30
OD_6	-	-	2	40	6	30
OD_7	-	1	2	40	6	30
OD_8	-	1	3	40	6	30
OD_9	1	-	1	40	6	30
OD_{10}	1	-	2	40	6	30

glass ring placed on a mercury substrate. Drying was carried out at 40°C for 24 hours in hot air oven. After the drying, resultant polymeric patches are cut into a diameter of 6 mm for different evaluation studies. Similar procedure was carried out for the preparation of MC and PVP alone and in combination patches. The plasticizer was used in the percent of 30%, 40%, 50% w/w of the polymer weight.

From the preliminary physical observation of the patches prepared, the best polymeric patches were used for the incorporation of pure Levobunolol HCl as drug. Calculated amount of Levobunolol HCl was dispersed in the polymeric solution and after the complete dispersion of the drug; glycerin (plasticizer) was added and stirred to form a uniform dispersion. The air bubble produced during dispersion was removed by subjecting the solution for sonication. The dispersion was casted onto mercury substrate kept in the hot air oven at 40°C for 24 hours. The patches thus formed were cut into diameter of 6mm, each containing 0.64 mg of Levobunolol HCl.

The ethyl cellulose rate controlling membrane was prepared by casting technique. Ethyl cellulose was dissolved in $1/3^{rd}$ quantity of chloroform and the plasticizer dibutyl phthalate was dissolved in remaining chloroform, then both the solutions were mixed together thoroughly to get the uniform dispersion. The air bubble produced during dispersion was removed by subjecting the solution for sonication. This solution was poured on mercury substrate and dried at room temperature for 24 hours. After drying 7mm diameter were cut using stainless steel borer. Both the end of drug reservoir was sealed to control the release of drug from periphery. The composition of the ocusert containing Levobunolol HCl is given in Table No. 1.

The standard curve for Levobunolol HCl was constructed by reading the absorbance at 258 nm after preparing the absorption spectrum of the API using standard UV spectrophotometry and the constructed standard curve was used for the estimation of drug in this study. The standard curves were prepared with the solutions of Levobunolol HCl in distilled water and in simulated tear fluid with a pH of 7.4.

EVALUATION OF OCUSERTS:

Thickness (Pandit JK 2003)**:**

The thickness of the ocusert was measured using a screw gauge micrometer with a least count of 0.01mm at different spots of the patches. The thickness was measured at five different spots of the patch and average was taken.

Weight variation (Pandit JK 2003)**:**

Five films were taken from each batch and their individual weights were determined by using a digital electronic balance of Shimadzu Corporation Ltd, Japan.

Moisture Uptake (Pandit JK 2003)**:**

The percentage moisture uptake test was carried out to check physical stability or integrity of ocuserts. Ocuserts were weighed and placed in a dessicator containing 100ml of saturated solution of Aluminum chloride by which a humidity of 79.5% RH was maintained. After three days the ocuserts were taken out and reweighed, the percentage moisture uptake was calculated by using formula.

Percentage moisture uptake

$$= \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture Loss (Pandit JK 2003)**:**

The percentage moisture loss was carried out to check integrity of the film at dry condition. Ocuserts were weighed and kept in a desiccator

containing anhydrous Calcium chloride. After 3 days, the ocuserts were taken out and reweighed; the percentage moisture loss was calculated using the formula.

Percent moisture loss

$$= \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{x100}.$$

Folding Endurance (Pandit JK 2003)**:**

The flexibility of ocuserts can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the patches was determined by repeatedly folding a small strip of the patch (approximately 2.0 x 2.0 cm) at the same place till it break. The number of times patch could be folded at the same place without breaking gives the value of folding endurance.

MECHANICAL PROPERTIES

Tensile Strength and percent elongation at break:

The tensile strength of ocusert refers to tension or forced required to tear of the patch apart into two places. This was determined with an instrument assembled in the laboratory.

Instrument:

This instrument used to measure the tensile strength designed in our laboratory. For this both the ends of the patches were enclosed between two pairs of acrylic slides with the help of clamps. One pair of acrylic slides enclosed with the upper end of the patch is fixed to a metal stand elongation can be conveniently observed with the traveling microscope. To the other pair of acrylic slides a pan is suspended with the help of a wire loop.

Specimen:

Strips of 6cm. in length and 1cm in width were cut using a blade and stainless steel guide. This procedure was preferred to die cutting in order to avoid notching of the specimen. To small marking 4 cm. apart and 1cm of each end of specimen were made on sample with ink samples were than observed under microscope to detect flaws.

Procedure:

The specimen was held between two clamps in such a way that the marking towards the fixed clamp as joint inside it whereas marking towards the movable clamp was measured. The change in length of the specimen that occurred with increase in weight was measured. The rate of change of stress was kept constant by increasing the load on the pan at the rate of 10g/2min. because stress strain relationship changes with rate of changes in stress.

Drug Content Uniformity Studies (Babu GV 2001)**:**

All the ocuserts prepared were tested for drug content uniformity by direct ultraviolet spectrophotometry. Levobunolol HCl exhibits an ultraviolet absorption band near 258 nm. This absorption is the basis for the quantitative determination of the drug. Comparing the net absorbance at 258 nm performs assay of the compound of sample dissolved in distilled water with the net absorbance of standard in distilled water of known concentration. The net absorbance was calculated by subtracting the drug free matrix contribution to absorbance at the wavelength of determination from the absorbance of the drug solution at the same wavelength.

$$C_{sam} = \{[(A_{sam} - A_b)\, C_{std}] / (A_{std} - A_b)\}$$

Where,

C_{sam}=concentration of the sample solution.
C_{std} =concentration of the standard solution.
A_{sam}=Absorbance at 258 nm of sample solution.
A_{std} =Absorbance at 258 nm of standard solution.
A_b =Absorbance at 258 nm of drug free matrix solution.

The 3 discs of each selected formulations previously subjected to weight and thickness variation were calculated for their drug content estimation individually. The Levobunolol HCl content in each ocusert was estimated by dissolving in sufficient amount of distilled water and volume was adjusted to 30ml. The absorbance of this solution was measured in UV-spectrophotometer at 258nm against distilled water as blank.

IN-VITRO DRUG RELEASE (Sasaki H 1993)

The in-vitro drug release from different ophthalmic inserts were studied by making using the classical standard cylindrical tube which has the diameter 15mm by using commercial semi-permeable membrane which was tied to one end of open cylinder which acted as donor compartment. An ophthalmic insert was placed inside this compartment. The semi-permeable membrane acted as corneal epithelium. The entire surface of the membrane was in contact with the receptor compartment containing 50ml. 7.4 pH isotonic phosphate buffer (Simulated Tear Fluid). The content of the receptor compartment was stirred continuously using magnetic stirrer and temperature was maintained at 37±0.5°C. Samples of 1 ml. were withdrawn from the receptor compartment at periodic intervals and replaced by equal volume of fresh buffer solution. The samples were analyzed spectrophotometrically at 258nm

against reference standard using pH 7.4 isotonic phosphate buffer (Simulated Tear Fluid) as blank.
The release rate obtained is tabulated and graphed according to the following modes of data treatment (Rastogi SK 1996).
a) Cumulative percentage drug released Vs time (in-vitro diffusion plots)
b) Log percentage drug remained Vs time (First order rate plots)
c) Cumulative percentage drug released Vs Square root of time (Higuchi's plots)
d) Log percentage drug released Vs Log time (Peppa's exponential plots)

RESULTS AND DISCUSSIONS

In the present research work Levobunolol HCl ocuserts were prepared by using HPMC, MC and HPMC-PVP combination with EC as rate controlling membrane. The prepared ocuserts were evaluated for number of parameters like thickness, weight variation, moisture uptake and loss, drug content uniformity, tensile strength, *in-vitro* drug release studies etc. The details of these results are given in Table No.2 and discussed below.
Thicknesses of the ocuserts were found to be directly related to the concentration of the polymers. Thickness of the ocuserts varied between 0.191±0.0024 mm to 0.292±0.0040 mm. The result showed that thickness was uniform and ocuserts were not thick enough to produce any irritation while placing and being in *cul-de-sac.*
The weight of formulations was determined by digital electronic balance. The result showed that weights of formulations were ranging from 24.91±0.0924 mg. to 34.10±0.0834 mg. This indicates that there was no significant weight variation in all formulations.
Among the formulations tested OD_4 and OD_{10} shows the maximum and minimum moisture uptake i.e., 14.922±0.791 and 6.927±0.071 respectively. The maximum moisture uptake from ocusert may be due to the high concentration of HPMC, which readily absorbs moisture when exposed to atmosphere. And the minimum moisture uptake was due to more hydrophobic nature of $OD_{10.}$
Among the formulations tested OD_7 and OD_9 shows maximum and minimum moisture loss i.e. 9.825±0.254 and 6.235±0.574 respectively. The minimum moisture loss shown by the formulation F10 was mainly due to the EC as rate controlling membrane, which retain the moisture within the matrix.
The folding endurance for all formulations was good. The maximum folding endurance for OD_4 ophthalmic insert was 148±22 folding which may be due to presence of PVP and formulation OD_8 showed minimum folding endurance 82±15 folding. This shows that as the concentration of MC is less tensile.
Ocuserts containing HPMC and PVP showed more tensile strength than the ocuserts containing MC alone and HPMC alone. The order of tensile strength is HPMC & PVP > MC > HPMC.
The drug content uniformity of all formulations was in the range of 93.1%±0.264 to 98.00%±0.321. This indicates the method used for preparing ocusert was reliable.

Table-2; Physical parameters of ocusert formulations prepared

Formulation code	*Thickness**	*Weight Variation**	*Moisture Uptake***	*Moisture Loss***	*Folding Endurance***	*Tensile Strength***	*% Elongation at Break***	*Drug Content*	
								In mg	*In %*
OD_1	0.272 ± 0.0037	29.20 ± 0.0853	11.531 ± 0.932	7.201 ± 0.281	94 ± 15	0.091 ± 0.031	21.54 ± 0.23	95.30 ± 0.529	0.609 ± 0.003
OD_2	0.292 ± 0.0040	32.15 ± 0.0631	12.102 ± 0.685	7.124 ± 0.203	87 ± 17	0.087 ± 0.063	23.12 ± 0.53	97.20 ± 0.264	0.621 ± 0.001
OD_3	0.284 ± 0.0037	32.12 ± 0.0573	13.754 ± 0.623	6.715 ± 0.251	132 ± 25	0.129 ± 0.042	26.21 ± 0.25	93.10 ± 0.264	0.592 ± 0.001
OD_4	0.321 ± 0.0024	34.10 ± 0.0834	14.922 ± 0.791	9.921 ± 0.451	148 ± 22	0.130 ± 0.033	28.05 ± 0.26	93.70 ± 0.321	0.599 ± 0.002
OD_5	0.214 ± 0.0024	24.91 ± 0.0924	9.153 ± 0.651	8.712 ± 0.452	112 ± 12	0.043 ± 0.042	30.28 ± 0.52	95.60 ± 0.251	0.611 ± 0.001
OD_6	0.232 ± 0.0024	26.21 ± 0.0732	8.231 ± 0.895	9.207 ± 0.564	92 ± 15	0.053 ± 0.034	32.30 ± 0.35	95.60 ± 0.251	0.611 ± 0.001
OD_7	0.243 ± 0.0024	27.53 ± 0.0541	8.005 ± 0.562	9.825 ± 0.254	114 ± 13	0.178 ± 0.075	35.30 ± 0.51	98.00 ± 0.321	0.626 ± 0.002
OD_8	0.272 ± 0.0037	32.20 ± 0.0752	8.312 ± 0.527	4.203 ± 0.652	82 ± 14	0.127 ± 0.037	27.25 ± 0.42	95.00 ± 0.620	0.607 ± 0.010
OD_9	0.191 ± 0.0024	25.17 ± 0.0811	7.214 ± 0.361	6.235 ± 0.574	124 ± 16	0.148 ± 0.055	26.92 ± 0.34	94.30 ± 0.360	0.603 ± 0.002
OD_{10}	0.281 ± 0.0024	26.53 ± 0.0203	6.927 ± 0.071	8.921 ± 0.555	118 ± 13	0.139 ± 0.044	26.11 ± 0.21	96.40 ± 0.251	0.616 ± 0.001

*-Average of Five Readings; **-Average of Three Readings with SD.

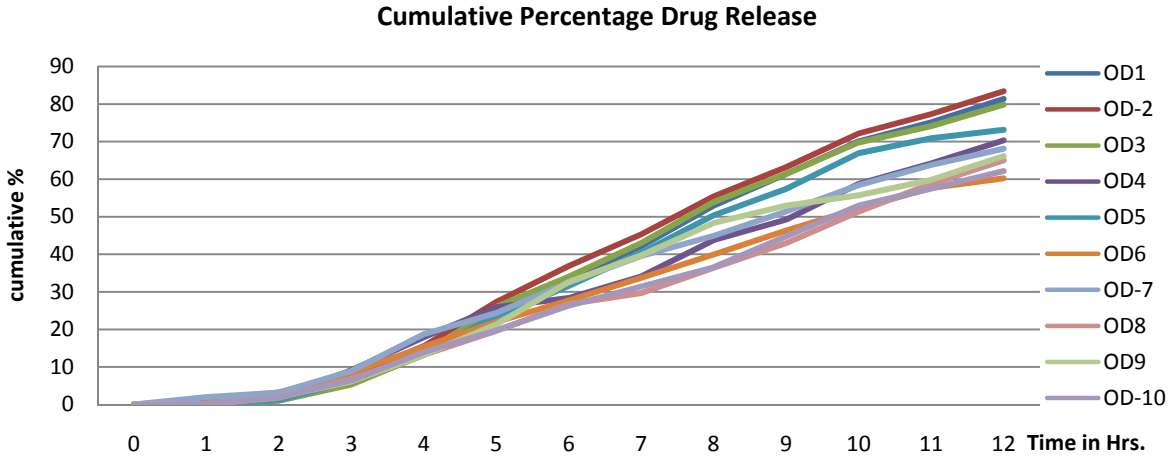
Table-3; Cumulative percentage *in-vitro* drug release from Levobunolol HCl ocuserts

Time In Hrs.	*Cumulative Percentage Drug Release (in %)*									
	OD_1	OD_2	OD_3	OD_4	OD_5	OD_6	OD_7	OD_8	OD_9	OD_{10}
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
1	0.082	0.050	0.041	0.058	0.028	1.138	1.981	0.023	0.098	0.131
2	2.010	2.036	1.019	1.562	1.119	3.231	3.153	1.781	2.013	1.991
3	6.232	7.501	5.316	9.129	6.421	8.432	8.921	6.913	6.121	6.423
4	13.162	15.527	13.297	17.914	13.731	15.398	18.724	13.215	13.214	13.921
5	24.981	27.321	25.978	25.921	23.478	21.981	24.398	19.623	21.321	19.731
6	33.190	36.871	34.002	28.321	31.598	27.712	32.471	26.721	32.615	26.313
7	42.121	45.312	42.991	34.080	40.412	33.691	39.563	29.691	39.724	31.423
8	52.989	55.428	53.901	43.782	50.398	39.913	44.923	36.423	48.321	36.521
9	61.381	63.211	61.423	49.231	57.401	46.312	51.414	42.981	52.943	44.731
10	70.086	72.182	69.791	58.711	66.928	52.192	58.398	51.319	55.691	52.938
11	75.126	77.312	74.111	64.191	70.886	57.631	63.782	58.791	59.798	57.431
12	81.360	83.423	79.830	70.316	73.138	60.213	68.132	65.024	66.139	62.140

Table-4; Data of drug release kinetics Vs formulations of Levobunolol HCl

Formulation Code	*Zero Order Release Plot*			*First Order Release Plot*			*Higuchi's Diffusion Plot*			*Peppa's Log-Log Plot*		
	A	*B*	*r*	*A*	*B*	*r*	*A*	*B*	*r*	*A*	*B*	*r*
OD_1	-21.38	35.980	-21.38	71.986	0.9190	1.834	1.311	0.9970	0.919	2.198	-0.281	-0.852
OD_2	-21.14	37.020	-21.14	74.059	0.9291	1.858	1.290	0.9988	0.929	2.208	-0.299	-0.856
OD_3	-21.47	35.992	-21.47	71.991	0.9240	1.858	1.694	0.9580	0.923	2.91	-0.273	-0.864
OD_4	-15.93	29.712	-15.74	59.259	0.9320	1.778	1.228	0.9914	0.932	2.128	-0.202	-0.874
OD_5	-19.68	33.611	-19.68	67.228	0.9251	1.829	1.427	0.9970	0.925	2.165	-0.242	-0.874
OD_6	-12.68	26.010	-12.68	52.041	0.9376	1.705	1.015	0.9994	0.937	2.096	-0.165	-0.900
OD_7	-14.27	29.224	-14.26	58.453	0.9354	1.761	1.065	0.9990	0.935	2.119	-0.199	-0.891
OD_8	-15.19	26.757	-15.19	53.520	0.9176	1.708	1.199	0.9990	0.917	2.111	-0.171	-0.862
OD_9	-16.22	29.656	-16.22	59.316	0.9365	1.765	1.235	0.9988	0.936	2.122	-0.195	-0.903
OD_{10}	-14.76	26.561	-14.76	53.127	0.9251	1.695	1.161	0.9984	0.925	2.107	-0.168	-0.880

A = Constant, B = Slope, r = Regression co-efficient



Graph-1; Cumulative percentage *in-vitro* drug release from Levobunolol HCl ocuserts

The data has been plotted for Cumulative Percent Drug Released Vs time. To know precisely the rate of drug release, the basic in-vitro data was plotted according to the Zero order release kinetics as Cumulative Percent Drug Released Vs time. The results showed that the plots are fairly linear; the degree of linearity was ascertained by carrying out regression analysis and the regression co-efficient values. Taking cumulative percent drug remaining Vs time also plots first order plots.

To ascertain the drug release mechanism, the formulations are plotted for Higuchi diffusion plots by taking Cumulative Percent Drug Released Vs Square root of time. The plots are fairly linear and the regression co-efficient values are calculated and the drug release mechanism was diffusion controlled. The formulations are also treated to Peppa's log-log plots by taking log percent cumulative release Vs log time.

The plots are found to be fairly linear and the regression values are calculated. The slope values of Peppa's exponential equation for the formulations were more than 1 and hence the drug release was found to be case II transport mechanism. This indicates the drug release follows zero order kinetics. The in-vitro studies, cumulative percentage release of drug from the formulations were given for all the ten formulations in Table No.3. The kinetic studies in zero order and first order were calculated and Higuchi's diffusion plot and Peppa's Log-Log plot values for drug release kinetic data were given in Table No.4.

CONCLUSION

The Levobunolol HCl, a β-blocker used widely in the treatment of glaucoma, was used for designing ocusert formulation and physical parameters were evaluated for optimizing the polymer, plasticizer composition. The formulations were studied for in-vitro drug release and kinetics of drug release from formulations was studied for zero-order, first-order, Higuchi's diffusion and peppa's log-log plot kinetics models.

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