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Design Formulation and Evaluation of Soluble Soft Gel Ocular Insert of Ketorolac Tromethamine using Modified Locust Bean Gum

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ABSTRACT

A major problem in ocular therapeutics is the attainment of optimal drug concentration at the site of action which is compromised mainly due to precorneal loss resulting in only a small fraction of the drug being ocularly absorbed. The effective dose administered may be altered by increasing the retention time of medication into the eye by using ocular inserts for treating various ocular diseases. The aim of the present study was to prepare and evaluate novel Ocular inserts of Ketorolac Tromethamine with polymers like HPMC K4M, PVA, Locust Bean Gum and Modified Locust Bean Gum with Glycerol as plasticizer by film casting method. Nine formulations of ocular inserts based on Comaprision Study On the basis of *In vitro* release studies & physicochemical parameters, the formulation MOG sustained with maximum cumulative of 97.244% for a period 12 hr and it was found to be better than other formulations; hence MOG 2% was selected as optimized formulation. *In vitro* drug release kinetic data revealed that all formulation followed near to zero order release kinetics, involving in the all formulation drug release by Super Case-II type of diffusion. Optimized formulation (MOG 12%) passed the test for sterility and in stability studies no change of physiological properties. On the basis of the present study, the ocular inserts of Ketorolac Tromethamine gives promising future for the ophthalmic drug delivery system.

Keywords: Ketorolac Tromethamine, Ocular inserts, HPMC K4M, PVA, LBG, MOG

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INTRODUCTION:

Ophthalmic drug delivery is one of the most interesting and challenging endeavors facing the pharmaceutical scienticts1. The eye as a portal for drug delivery is generally used for local therapy against systemic therapy in order to avoid risk of eye damage from high blood concentrations of the drug which is not intended. The unique anatomy, physiology and biochemistry of the eye render this organ impervious to foreign substances, thus presenting a constant challenge to the formulator to circumvent the protective barrier of the eye without causing permanent tissue damage. Drug absorption occurs through corneal and non-corneal pathways. Most non- corneal absorption occurs via the nasolacrimal duct and leads to non-productive systemic uptake, while most drugs transported through the cornea is taken up by the targeted intraocular tissue. Unfortunately, corneal absorption is limited by drainage of the instilled solutions, lacrimation, tear turnover, metabolism, tear evaporation, non- productive absorption, adsorption and limited corneal area, poor corneal permeability, binding by the lacrimal proteins, enzymatic degradation, and the corneal epithelium itself. These limitations confine the absorption window to a few minutes afte administration and reduce corneal absorption to less than 5%. Drugs administered into the eye are rapidly and totally absorbed. However, contrary to this belief, the moment drug is placed in the lower cul-de-sac of eye, several factors immediately begin to affect the bioavailability of drug absorption of drugs takes place either through corneal or non corneal routes. The non corneal route involves absorption across the sclera and conjunctiva into the intraocular tissues. This route is however not productive as it restrains the entry of drug into aqueous humor. Maximum absorption thus takes place through cornea which leads the drug into aqueous humor.

The mechanism of controlled drug release into the eye is as follows:

(A) Diffusion (B) Osmosis (C) Bio-erosion.

Advantages of Ocular Insert

Increased ocular residence, hence a prolonged drug activity and a higher bioavailability with respect to standard vehicles. Possibility of releasing drugs at a slow, constant rate.

MATERIALS AND METHOD:

Ketorolac tromethamine was received as a gift sample from Sun Pharma Baroda, LBG was received from chem. Dyes Rajkot, All the solvents used were of analytical grade.

INGREDIENTS	KT1	KT2	KT3
Ketorolac Tromethamine(mg)	495	495	495
Modified Locust Bean %	1.5	2	2.5
Glycerol %	30	30	30
Distilled Water (ml)	Upto 45ml	Upto 45ml	Upto 45ml

Ocular Inserts were preferably formulated using the solvent casting method, whereby the water soluble ingredients were dissolved to form a clear viscous solution and the drug along. with other excipients was dissolved in a suitable solvent then both the solutions were mixed and stirred and finally casted into the Petri plate and dried.

Modified Locust bean gum was prepared by Carboxymethylation process.

Table 1. Formulation of ocular insert by different polymers.

Interaction Studies: Interaction studies were conducted on the optimized formulations by comparing them with the pure drug and the placebo films. Drug-polymer compatibility was confirmed by ultraviolet, infrared and thin layer chromatography analysis.

PHYSIOCHEMICAL EVALUATION OF OCULAR INSERTS

1. **Thickness Determination:** Thickness of the insert was measured at different points using digital micrometer screw gauge (Mitutoyo, Japan) and mean film thickness was noted[6] .
2. **Weight Uniformity:** Ocular inserts were taken from different areas of the film and weighed individually. The mean weight of insert was noted[7].
3. **Folding Endurance:** The folding endurance is expressed as the number of folds (number of times the insert is folded at the same place, either to break the specimen or to develop visible cracks)[8]. The insert was folded in the centre, between the fingers and the thumb and then opened. This was termed as one folding. The total folding operations was named as folding endurance value.

4. **Drug Content:** The ocular inserts from different areas of the film were taken. Drug content was estimated by triturating the ocular insert in 50ml of methanol with the help of a mortar and pestle. The solution was filtered through whatman no.42 filter paper and drug content determined by UV- Visible spectrophotometer method.

5. ***In vitro* Drug Diffusion Studies:** *In vitro* drug release studies were carried out using a Franz diffusion cell. Ocular inserts were placed in the donor compartment over the dialysis membrane. [11] 0.7 ml of isotonic phosphate buffer of pH 7.4 was placed in the donor chamber, which acted as the tear fluid. 20ml of isotonic phosphate buffer was taken as the receptor medium and the apparatus was maintained at 37± 2^{O}C being continuously stirred using a magnetic stirrer. The samples were withdrawn at regular intervals and analyzed at 313nm.

6. **Stability Studies:** The stability studies of ocular inserts were conducted according ICH guidelines[15]. The ocular inserts were packed in blister (PVC-Aluminium) and stored at 40±0.5°C / 75±5% RH, 25°/60% RH, 40°C for 3 months. Samples were withdrawn on days 0, 30, 60 and 90 and analyzed for physico chemical properties, assay and drug release.

7. Surface pH Determination:-

Inserts were left to swell for 5 hours on agar plate prepared by dissolving 2% (m/v) agar in warm simulated tear fluid (STF) sodium chloride: 0.670 g, sodium bicarbonate 0.200 g, calcium chloride 0.008 g, and purified water q.s. 100 g of pH 7.4 under stirring and then pouring the solution into Petri dish till gelling at room temperature. The surface pH was measured by means of a pH paper placedon the surface of swollen patch.

8. Percentage Moisture Loss:-

The percentage moisture loss was carried out to check the integrity of the film at dry condition. The ocular inserts were pre weighed accurately and kept in desiccators containing 100ml of saturated solution of aluminum chloride. After 3 days, the films were taken out and weighed.

$$\% \text{ Moisture Loss} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

9. Kinetic modelling:

Zero order: Mt = M0 + k0t

First order: $\ln M_t = \ln M_0 + k_1 t$

Matrix (Higuchi Matrix) model:- Mt = M0 + k1t1/2

Peppas-Korsmeyer Equation:-

Log (Mt /M∞) = log k + n log t

Hixson-Croswell Equation:- (%Unreleased)1/3 = kt

10. Sterility Test:-

Ultra-Violet radiation was used to sterilize the ocular inserts and sterility testing was carried out under aseptic conditions. Alternate thioglycolate and Soyabean casein digest media was used to check sterility of formulation.

11. **Comparison of dissolution profile**

A model-independent method for comparison of two dissolution profiles is based on determination of difference factor f1 and similarity factor f2 which are calculated using following formulae:

$$f1 = \left\{\frac{[\Sigma \mid Rt - Tt \mid]}{[\Sigma\, [Rt]}\right\} \times 100, \text{ where t = 1 to n}$$

$$f_2 = 50 \times \log \left\{\left[1 + (1/n)\sum_{t=1}^{n}(R_t - T_t)^2\right]^{-0.5} \times 100\right\}$$

Where,

n = number of dissolution time points

Rt = dissolution value of the reference drug product at time t

Tt = dissolution value of the test drug product at time t

The guidelines adopted for interpreting f1 and f2 values are given in table

Table 2. Comparison of f1 and f2 value

Difference factor f1	Similarity factor f2	inference
0	100	Dissolution profiles are identical
≤ 15	≥ 50	Similarity or equivalence of two profiles

RESULT AND DISCUSSION:

Table 3. Thickness, Folding endurance and Drug content of MOG

Formulation			
MOG 1.5	0.11 ± 0.012	125 ± 3	91.33 ± 1.527
MOG 2	0.22 ± 0.031	282 ± 8	97.33 ± 2.516
MOG 2.5	0.34± 0.032	212 ± 6	95.05 ± 1.527

Table 4. Thickness, Folding endurance and Drug content of hpmc k4m

Formulation			
HPMC K4M 1.5	0.8 ± 0.08	126 ± 1	91.33 ± 1.19
HPMC K4M 2	0.9 ± 0.065	198± 1	95.33 ± 2.63
HPMC 2.5	0.11 ± 0.045	210 ± 1.5	97.05 ± 0.79

Table 4. Percentage moisture loss and Percentage moisture absorption

Formulations	% Moisture loss*	%Moisture Absorbption*
HKT1	1.29±0.54	2.38±0.57
HKT2	1.76±0.52	2.51 ±1.04
HKT3	2.39±0.94	2.58±1.18
MKT1	2.54±1.16	2.73±0.52
MKT2	2. 61±0.40	2.79±0.92
MKT3	2.91±0.94	3.14±0.76

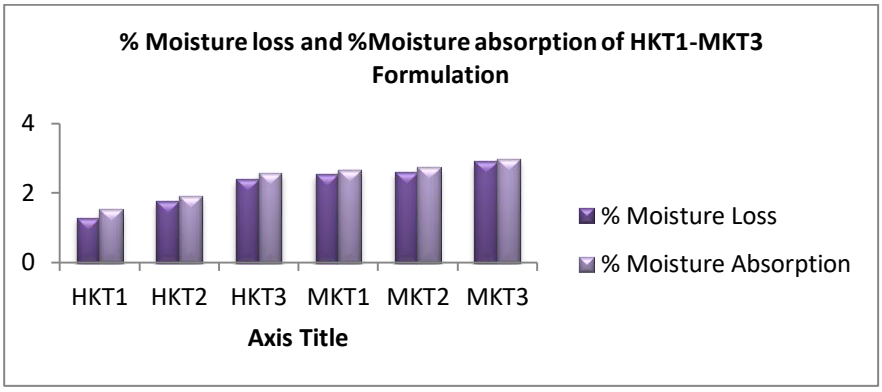

Figure 1.- Graph of % moisture loss and % moisture absorption

The values of percentage moisture loss are shown in table 5.11. Percentage moisture loss of all formulations is in range of 1.29±0.54 to 2.91±0.94. It was found that with the increase in the concentration of MOG there was increase in the percentage moisture loss. This was due to the hydrophilicity of the polymer.

The values of percentage moisture absorption are shown in table 5.11. Percentage moisture absorption of all formulations is in range of 2.38±0.57 to 3.14±0.76. It was found that with the increase in the concentration of MOG there was increase in the percentage moisture absorption. This was due to the hydrophilicity of the polymer.

In vitro diffusion study:

Table 5.- Comparison studies between MOG and HPMC K4M

TIME	MOG 2	HPMC K4M 2.5
0	0.00	0.00
1	12.303±0.278	12.819±0.310
2	22.013±0.223	18.909±2.01
3	32.499±0.13	32.909±0.455
4	41.401±0.080	39.536±1.340
5	49.332±0.554	46.02±0.436
6	57.839±0.536	52.375±0.1
7	67.431±0.486	62.672±1.035
8	75.217±0.557	71.486±0.432
9	85.223±0.994	82.612±0.530
10	92.25±0.607	87.622±0.999
11	95.181±0.390	96.957±0.969
12	97.458±1.452	98.987±0.49

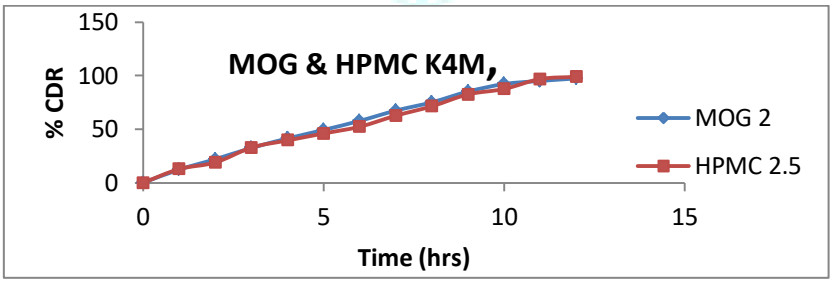

Fig 2. Comparison study of MOG and HPMC

CONCLUSION:

From this comparison data of HPMC K4M and MOG we can assume that both gives drug release at 12 hrs but MOG graph is more linear as compared to HPMC K4M graph.

Table 6. Kinetic model of all formulation

Formulation	Zero order R^2	First order R^2	Higuchi model R^2	Korsemeyer-peppas R^2	N value	Hixon-Crowell R^2
HKT1	0.894	0.491	0.99	0.593	0.5	0.988
HKT2	0.960	0.611	0.978	0.705	0.70	0.93
HKT3	0.993	0.675	0.941	0.78	0.784	0.924
MKT1	0.979	0.597	0.96	0.679	0.67	0.955
MKT2	0.986	0.660	0.954	0.780	0.780	0.964
MKT3	0.989	0.817	0.88	0.874	0.874	0.94

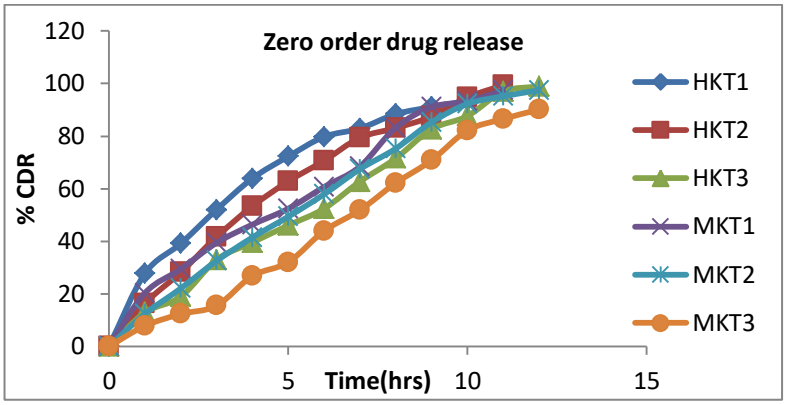

Figure 3.:-Kinetic model of Zero order

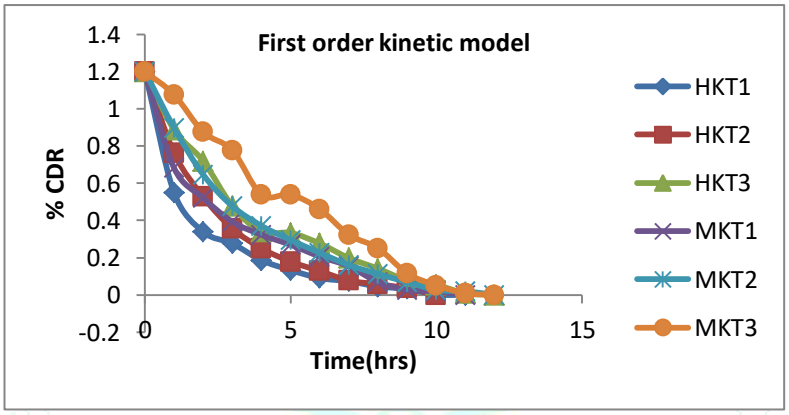

Figure 5.24:-Kinetic model of F irst order

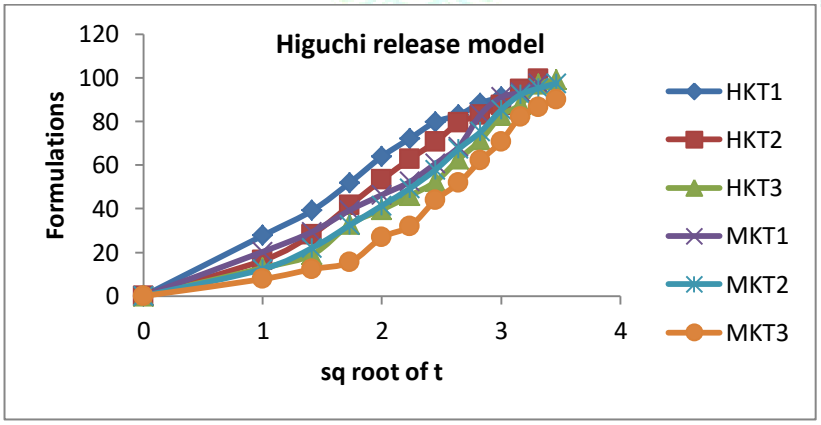

Figure 4.:-Kinetic model of Higuchi release model

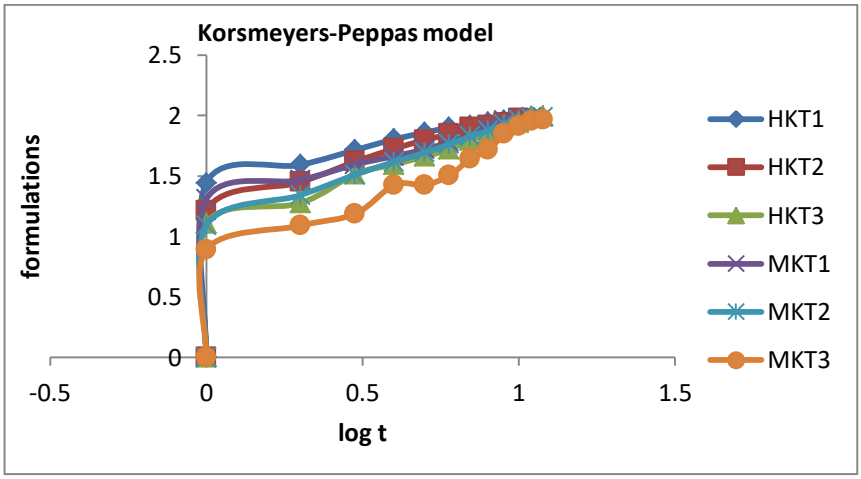

Figure 5.:-Kinetic model of Korsmeyers-Peppas model

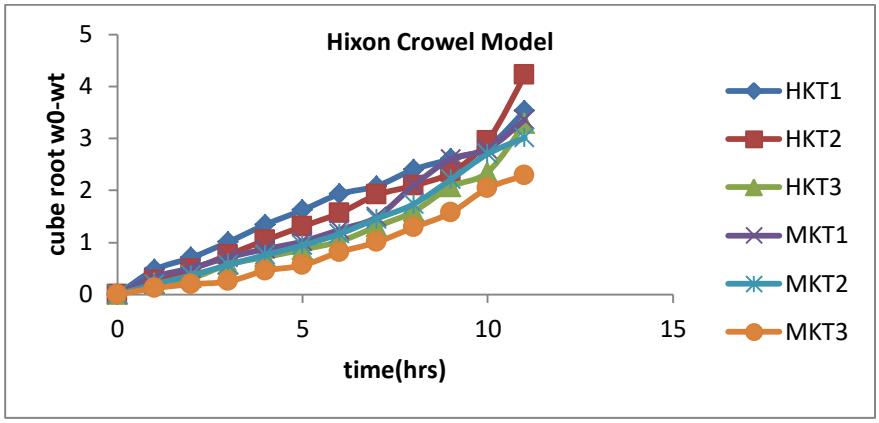

Figure 6.:-Kinetic model of Hixon Crowel model

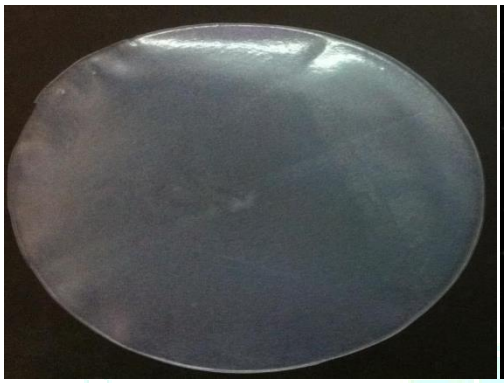

Fig 7. Photograph of MOG ocular insert **Fig 8. Photograph of HPMCocular insert**

COMPARISION STUDY OF THEORETICAL AND TWO OPTIMIZED DRUG RELEASE PROFILE

Table 7. Comparison of theoretical value with HPMC and MOG

Time	Theoretical Value	HPMC 2.5	MOG2
1	8.33	12.819	12.30
2	16.66	18.909	22.013
3	24.99	32.909	32.499
4	33.32	39.536	41.401
5	41.65	46.02	49.332
6	49.98	52.375	57.839
7	58.31	62.672	67.431
8	66.64	71.486	75.217
9	74.97	82.612	85.223
10	83.30	87.622	92.25
11	91.63	96.957	95.181
12	99.96	98.987	97.458
Average	Avg- 54.145	Avg-58.57	Avg-62.97

*f1 value between 0-15 shows less difference in dissolution profile of reference (Rt) and test product (Tt).

*f2 value should be between 0 and 100. It is 100 when two comparative groups of reference and test are identical and approaches to 0 as the dissimilarity increases.

f1& f2 values were found to be 8.18 & 66.5, for HKT3 and 12.06, 58 for MKT2Which showed more optimized than HKT3

MKT2) had similarity with theoretical dissolution profile. So, it was identical

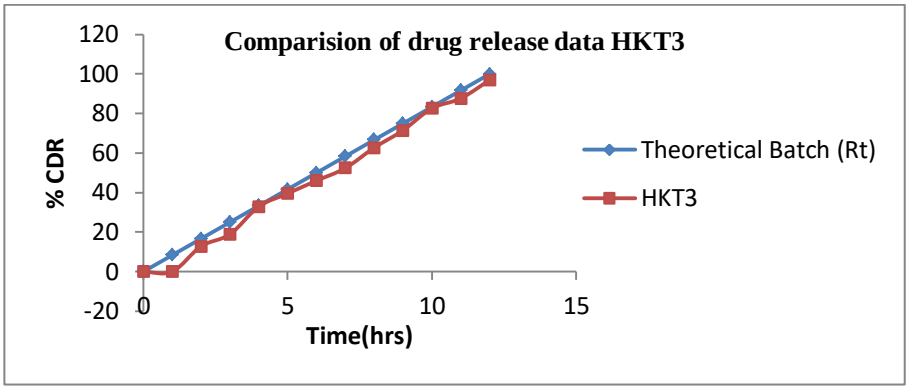

Figure 8.- Comparison graph between Theoretical batch and HKT3

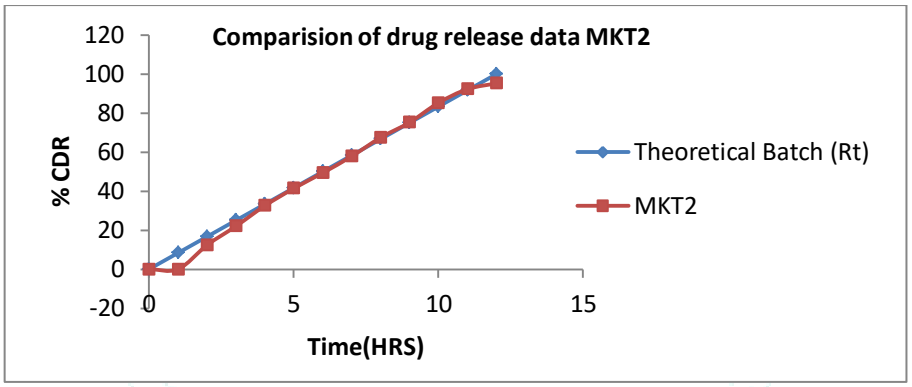

Figure 5.29:- Comparison graph between theoretical batch and MKT2

Table 8. Simmilarity and dissimilarity factor of HKT3 and MKT2

Formulation	Drug Release Study	F1	F2
HKT3	In Vitro Diffusion Study	8.18	66.5
MKT2	In Vitro Diffusion Study	12.06	58

Stability test:

A short term stability study was carried out. A sufficient number of optimized ocular inserts (packed in aluminum foil) were stored in the stability chamber at temperature 40ºC and 75% RH for 1 month. After a month the ocular inserts were taken out and were evaluated for thickness, folding endurance and % in vitro drug release at 12^{th} hour.

Table no 9.:- Evaluation parameters for stability study

Formulation	Days	Parameters evaluated for the stability study			
		Physical appearance	Thickness	Folding endurance	%CDR
HKT3	0	Smooth, opaque	0.11 ± 0.032	210 ±1.52	98.987±0.49
	15	Smooth, opaque	0.13 ± 0.045	221 ±1.49	96.611 ±0.39
	30	Smooth, opaque	0.12 ± 0.037	222 ±0.96	97.6 23±1.28
Formulation	**Days**	**Parameters evaluated for the stability study**			
		Physical appearance	**Thickness**	**Folding endurance**	**%CDR**
MKT2	0	Smooth, transparent	0.22 ± 0.068	452 ± 2.365	97.458±0.658
	15	Smooth, transparent	0.21 ± 0.015	449 ± 1.658	96.325 ± 0.105
	30	Smooth, transparent	0.20 ± 0.010	454 ± 2.365	97.698 ± 0.014

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