Preparation and Evaluation of novel ocular inserts of Diclofenac sodium amino acid conjugate for controlled Drug Delivery

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Abstract- The Aim and Objective of the present study was to formulate and evaluate the novel ocular Inserts of Diclofenac amino acid conjugate using different polymers such as HPMC, Eudragit L100 at various concentrations and combinations using dibutylphthalate as plasticizer. The ocuserts were prepared by using solvent casting technique. The main aim was to enhance the trancorneal permeation of diclofenac sodium using different amino acids.Ex vivo trancorneal permeation was studied across goat cornea. The study revealed that Diclofenac sodium and amino acid conjugate ocular inserts had greater permeation than Diclofenac sodium ocular inserts.Effect of concentration of Amino acids on the permeation of Diclofenac sodium was also studied and it was found that on increasing the concentration of amino Acid ,permeation of Diclofenac Sodium increases.Diclofenac sodium and Lysine conjugate produced maximum ocular bioavailability. Formulations(F1) of Diclofenac sodium was prepared and compared, with different formulations (F2,F3,F4) of Diclofenac sodium and Amino Acid Conjugates and it was found that F4 has maximum ocular availability.. The optimized formulation was subjected to stability studies as per ICH guidelines.

Index Terms- Diclofenac sodium,
Hydroxypropymethylcellulose, ocular inserts, Eudragit L100, solvent casting**,** Dibutylphthalate,amino acids,lysine, glysine, arginine.

I. INTRODUCTION

Drugs administered in traditional topical ophthalmic formulation such as aqueous eye drops have poor bioavailability due to rapid precoeneal elimination. To reach therapeutic levels frequent instillation of the drug are required ,leading to a low patient compliance.Furthermore,the drug level in the tear film is pulsed with an initial period of overdosing ,followed by a longer period of under dosing.[1,2] . Generally efforts have been directed along the following lines:

1. Prolongation of the ocular residence time of the medicine.
2. Enhancement of corneal permeability (enhancer approach).
3. Increasing drug penetration characteristic (chemical Approach).
4. Use of phase transition systems [3].
5. Use of Nanoparticle preparation.
6. Use of Liposomes preparation.
7. Use of cyclodextrins

The ocular inserts, which are solid devices placed in the cul-de-sac of the eye in comparison with liquid formulation might present valuable advantages, such as:

- Increased ocular permanence with respect to standard vehicles hence prolonged drug activity and a higher drug bioavailability.
- Increased ocular contact time.
- Accurate dosing (theoretically all of the drug is retained at the absorption site);
- Capacity to provide, in some cases, a constant rate of drug release;
- Possible reduction to systemic absorption, which occurs freely with standard eye –drops via the nasal mucosa;
- Better patient compliance, resulting from a reduced frequency of medication and a lower incidence of visual and systemic side effects;
- Possibility of targeting internal ocular tissues through non-corneal conjunctival-scleral penetration routes; and
- Increased shelf life with respect to eye –drops due to the absence of water. Another potential advantage of ocular insert therapy is the possibility of promoting non-corneal drug penetration, thus increasing the efficacy of some hydrophilic drugs that are poorly absorbed through the cornea

Conventional dosage forms for topical drug delivery are associated with their inherent limitations that make less drug availability and hence require frequent dosing to attain desired therapeutic concentration. Utilization of the principles of controlled release by means of ocusert formulation development seems attractive approach to enhance drug availability at the desired site.

Diclofenac sodium is an excellent non steroidal anti-inflammatory, analgesic and antipyretic drug. Eye solutions (0.1%w/v) of Diclofenac are available to treat ocular inflammatory conditions.Diclofenac sodium is a weakly acidic drug having low water solubility. It has also limited therapeutic availability across cornea because of lipophillic corneal epithelium. To overcome the less bioavailability, usually eye drops with higher concentrations are formulated or controlled release formulations have been formulated for many drugs.Diclofenac sodium is sparingly soluble in water hence high concentrated formulations are not suitable. Frequent dosing is required to attain desired therapeutic concentration of the available eye drops of Diclofenac (0.1%w/v).

Controlled release of drug from ocular inserts is an approach to increase drug availability.

.Diclofenac is applied topically in the eye for management of pain in corneal epithelial defects following surgery or accidental trauma,teartment of post operative ocular inflammations,chronic non-infectious inflammations and prevention of intra-operative miosis during cataract surgery and forsymptomatic relief of seasonal allergic conjunctivitis.Less ocular availability of topically applied eye drops is a matter of concern for longer time.various strategies have been investigated in an attempt to enhance the corneal permeability of topically adminis tered diclofenac sodium and it comprises formulation approaches such as liposomes,nanoparticles,ointments and collagen shields.other than this various penetration enhancers can be used to increase the transcorneal penetration.The use of absorption enhancers could be advantageous for most drugs and to be convient in the manufacturing of ophthalmic preparations.However ,possibility of corneal tissue damage is a major risk associated with the use of penetration enhancers.

Currently the most attractive approach to enhance the transcorneal permeability of hydrophilic moieties appears to be targeteddrug delivery via transporters.Drug amino acid conjugates are prepared and these transporters are targeted to increase the permeability of drug.Amino acid and peptide transporters are considered most effective for drug targeting as these transporters have huge range of substrates and direction of transport from epithelium to endothelium providing a potential role in the permeation of substrate molecule.There are evidences for the presence of amino acid transporters such as LAT1 ATB^{0+} and ASCT1 in the cornea.ASCT1 and ASCT2 are having different substrate specifities and sensitiveties to pH and also these transporters recognize small neutal amino acids like alanine,serine,threonine.ATB^{0+} is a Na^+ and Cl^- coupled amino acid transporter that belongs to the neurotransmitter transporter gene family SLC6 ,having affinity for neutral as well as cationic amino acids.ATB^{0+} does not recognize anionic amino acids as substrate because of the presence of negative charge in the side chain of amino acids.Amino acid derivatives of certain drugs (e.g. acyclovir) have been reported to have enhanced aqueous solubility along with improved ocular availability. Improved availability has been attributed to the interaction of amino acid derivative with amino acid transporters present on corneal epithelium.Keeping in view the above facts,efforts have been made to develop novel ophthalmic inserts of amino acid diclofenac sodium conjugate.

II. MATERIALS AND METHODS

Diclofenac sodium was procured as gift sample from Combitic Global Caplet Pvt.Ltd.Sonepat(Haryana).Polymers such HPMC and Eudragit L100 were obtained as gift samples from Combitic Global Caplet Pvt.Ltd.Sonepat(Haryana) and Excellent Pharmatech vikas puri, New delhi. Arginine,glysine and lysine were procured from Hi Media Laboratories Pvt.Ltd Mumbai.

The ocuserts were prepared by using solvent casting technique

Preparation of the drug reservoir

The reservoir containing 200mg of Diclofenac sodium with polymer at 3% concentration were dissolved in ethanol and casted on Petri dish having 16ml capacity and 8cm diameter (an area of 50.24 cm^2), circular films of 9mm (0.9cm)diameter (an area of 0.63 cm^2) each containing 2.006 mg (theoretical) drug were cut.

Preparation of the rate controlling membrane

The rate controlling membrane was casted on Petri dish using different polymers and dibutylphthalate (30%w/w of polymer) as plasticizer and circular membrane of 10mm (1cm) diameter were cut

Sealing The drug reservoir was sandwiched in between the two rate controlling membranes and sealing was done by applying chloroform on the edges of the rate controlling membrane so that both the sides of the drug reservoir were sealed to control the release from periphery.

drug-excipient interaction study using TLC [4]Drug-excipient interaction may be determined by simple Thin Layer Chromatography method. Mobile phase consists of 100 volumes of toluene, 10 volumes of n- hexane and 10 volumes of anhydrous formic acid. The TLC chamber was saturated with the solvent system for 20 minutes to ensure a concentrated zone of compound with better resolution. 2 µl of each of the following solutions was applied separately to the plate. The solutions were prepared separately as -

1. Prepared 250 mg of Diclofenac sodium pure drug solution in 5 ml of Methanol.
2. Prepared 5%w/v solution of physical mixture of EudragitL100 and Diclofenac sodium in Methanol.
3. Prepared 5%w/v solution of physical mixture of HPMC and Diclofenac sodium in Methanol.

After spotting; the TLC plates were developed in this chamber. After development the TLC plates were dried using hot air oven. It was sprayed with a 0.5% solution of potassium dichromate in sulphuric acid (20%). The R_f value of pure drug sample (R_f = 0.53) and physical mixtures (R_f = 0.53) obtained correspond to each other as shown in figure (Fig. 18).

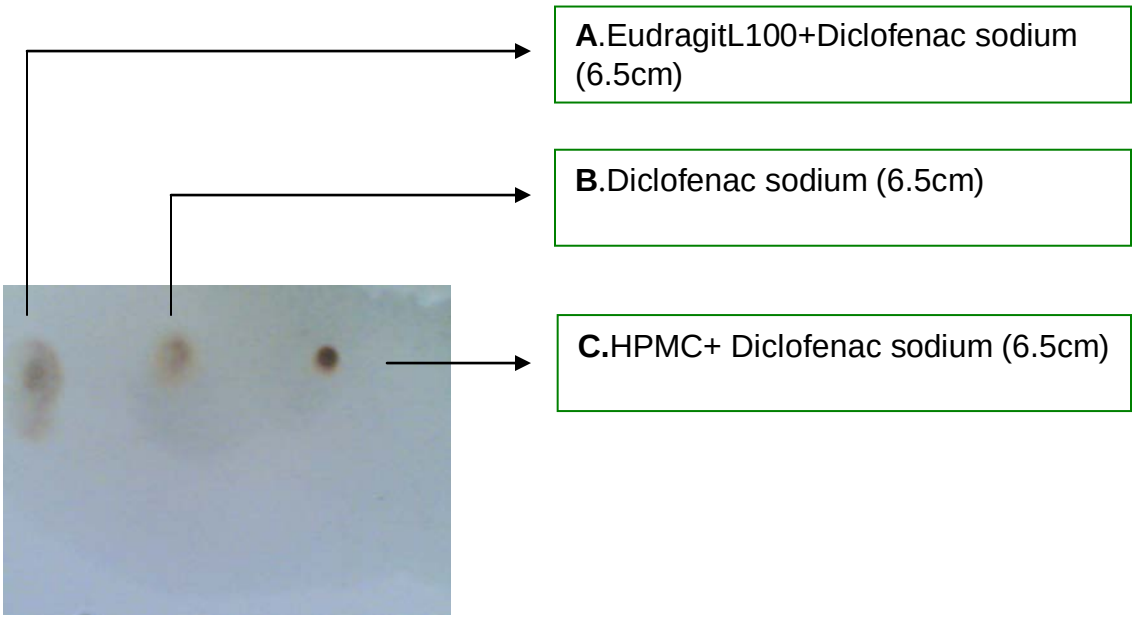


Figure 1. Photograph of TLC plate, A– spot of pure drug (Diclofenac sodium), B and C spot of physical mixtures

Looking upon similar R_f values, it seems there no interaction between Drug and excipients used to prepare ocuserts.

Characterization of prepared ocular inserts

Ocuserts prepared were evaluated for different parameters as follows:

1 Thickness

Thickness was measured using a screw gauge at different places of the ocusert and the average was calculated [5]

2 Weight

Weight was calculated on Digital balance. Three ocuserts were weighed individually and the average weight was calculated[6]

3 Drug content

Three ocuserts were taken and cut into small pieces, put into 100ml buffer (pH7.4) and shaken continuously until they dissolve. The solution was ultrasonicated for 15 minutes. After filtration, the drug was suitably diluted and analyzed at 276nm in UV visible spectrophotometer [7]

4 Folding Endurance

Folding Endurance was determined by repeatedly folding the film at the same place till breaking or appearance of breaking signs. The number of times the film could be folded at the same place without breaking gives the folding endurance value[7]

5 Moisture Uptake

The ocuserts were subjected to desiccation over calcium chloride at room temperature for 48h.These ocuserts were then weighed and the weight was recorded as initial weight .The ocuserts were then exposed to75% relative humidity(a saturated mple was taken solution of ammonium chloride) in a desicator until a constant weight of the ocuserts was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight[8]

6 Surface pH

The ocuserts were first allowed to swell by keeping them in contact with 5ml of distilled water for one hour in petridish. pH was noted by bringing the glass electrode near the surface of the formulation (ocusert) and allowing it to equilibrate for one minute[9]

7 In-vitro drug release[6] In vitro release of drug from ocusert was studied using Franz diffusion cell containing a donor and receptor cells.the donor cell was clamped over the receptor compartment,which was provided with a side arm for sampling and had an internal capacity of 50 ml.The receptor contained phosphate buffer of pH 7.4 as dissolution medium (50ml) The medium in the receptor compartment was agitated using a magnetic stirrer at 50rpm±4% maintaining a temperature at $37^0C \pm 1^0C$ through the water jacket surrounding the receptor cell.ocusert was placed on the epithelial surface of the cornea and placing a glass cover slip over the opening of the donor cell retarded the possible contamination in the donar compartment.The donor compartment represented the conjunctival sac of the eye where as the receptor compartment represented the anterior segment of the eye.After specified intervals of time; 3 ml of the sample was taken and replaced with fresh dissolution medium. Then after suitable dilution the absorbance of the sa

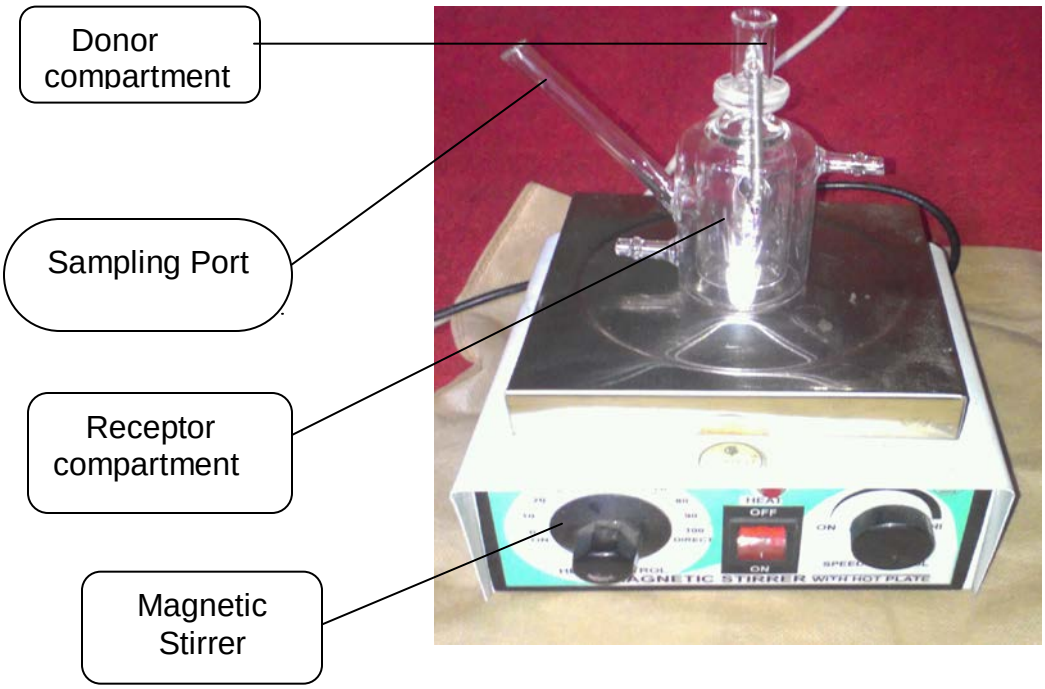
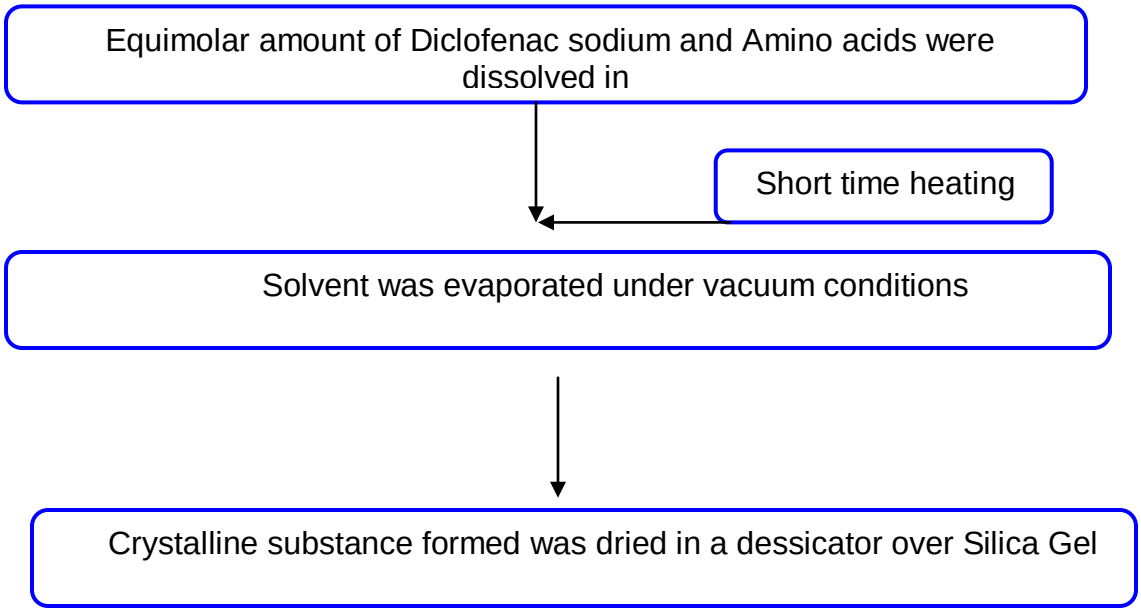


Figure 2 . Apparatus to study drug release from ocusert

III. SYNTHESIS OF DICLOFENAC AMINO ACID CONJUGATES

It was synthesized by the following scheme:

Synthesis of Diclofenac sodium and amino acid Conjugates [10]



Preparation of the drug reservoir for formulation F1

The reservoir film containing 200mg of Diclofenac Sodium with polymer at 3% concentration were dissolved in ethanol and casted on Petri dish having 16ml capacity and 8cm diameter (an area of 50.24 cm^2), circular films of 0.8cm diameter (an area of 0.5024 cm^2) each containing 2mg of Diclofenac sodium drug were cut.

Preparation of the drug reservoir for formulation F2(Diclofenac sodium arginine conjugate)

The reservoir film containing 309.48 mg of Diclofenac Amino acid conjugate equivalent to 200mg of Diclofenac Sodium with polymer at 3% concentration were dissolved in ethanol and casted on Petri dish having 20ml capacity and 8cm diameter (an area of 50.24 cm^2), circular films of 0.8cm diameter (an area of 0.5024 cm^2) each containing 3.0948mg of Diclofenac amino acid conjugate equivalent to 2.0 mg (theoretical) drug were cut.

Preparation of the drug reservoir for formulation F3(Diclofenac sodium Glycine conjugate)

The reservoir film containing 247.16mg of Diclofenac Amino acid conjugate equivalent to 200mg of Diclofenac Sodium with polymer at 3% concentration were dissolved in ethanol and casted on Petri dish having 20ml capacity and 8cm diameter (an area of 50.24 cm^2), circular films of 0.8cm diameter (an area of 0.5024 cm^2) each containing 2.4716 mg of Diclofenac amino acid conjugate equivalent to 2.002 mg (theoretical) drug were cut.

Preparation of the drug reservoir for formulation F4(Diclofenac sodium Lysine conjugate)

The reservoir film containing 314.8mg of Diclofenac Amino acid conjugate equivalent to 200mg of Diclofenac Sodium with polymer at 3% concentration were dissolved in ethanol and casted on Petri dish having 20ml capacity and 8cm diameter (an area of 50.24 cm^2), circular films of 0.8cm diameter (an area of 0.5024 cm^2) each containing 3.148 mg of Diclofenac amino acid conjugate equivalent to 2.002 mg (theoretical) drug were cut

IV. RESULTS AND DISCUSSION

EVALUATION OF THE OCUSERTS

Table 1. Comparative evaluation of formulated ocuserts with different proportions of polymers (Values are mean ±SEM of three experiments in each group)

Formulation code	Thickness (mm)	Weight (mg)	Drug content (mg)	Folding endurance	Moisture uptake	Surface pH
F1	0.48 ± 0.014	50.66 ± 3.480	1.64 ± 0.020	45 ± 2.906	4.47 ± 0.396	6.68 ± 0.225
F2	0.51 ± 0.020	60.33 ± 1.453	2.19 ± 0.024	65 ± 2.887	7.42 ± 0.389	7.17 0.055
F3	0.53 ± 0.037	76.66 ± 0.881	1.77 ± 0.010	54.33 ± 1.764	8.69 ± 0.465	7.18 ± 0.040
F4	0.44 ± 0.017	57.66 ± 1.202	1.89 ± 0.048	48.33 ± 1.667	5.72 ± 0.469	7.02 ± 0.020

The thickness measured for different formulations (F1, F2, F3, F4,) was in the range of 0.44 to 0.55mm.Formultion F4 was thinnest (0.44mm) while F3 was thickest (0.55mm. Weight of ophthalmic inserts was in the range of 50.66 to 76.66mg.The drug content was found from 1.64mg to 2.19mg as compared to theoretical 2mg of drug to be incorporated in each ocusert.The weight and drug content results showed less extent of patch variability.

Folding endurance of a film is a measure of breaking strength and endurance. This is the number of times the film may be folded at one place until it breaks or sign of breakage appears. This was in the range of 45 to 65 times .The folding endurance results shows enough strength of ocuserts to withstand handling shocks. Sometimes ocuserts comprises of hydrophilic polymers and likely to gain moisture from environment. Hence, it becomes imperative to measure moisture uptake extent for such formulation. Moisture uptake value for prepared formulations was from 4.47 to 8.69% of total ocusert weight after exposing this to predetermined environment having 75% RH.

Eye can tolerate fairly a wide range of pH from 4 to 11.However from comfort point of view the favorable pH should be around physiologic pH of tears i.e. pH 7.4.The surface pH of ocuserts was found 6.68 to 7.18 that indicates these should not cause any discomfort (tear flow stimulation) and damage to eye.

IN-VITRO RELEASE STUDIES OF DICLOFENAC SODIUM FROM OCUSERTS:

Whole eye ball of goat was transported from the butcher shop to the laboratory in cold (4^0C) normal saline (0.9%NaCl) within 1hour of slaughtering of the animal. The cornea was immediately excised along with 2 to 4 mm Scleral portion remaining adhered to the cornea for ease of mounting. Cornea was d washed with normal Saline till the washing was free from proteins. Excised cornea was mounted between donar and

receptor compartment. The receptor compartment was filled with phosphate buffer pH 7.4 and ensured that no air bubble was present in the compartment.To study the drug release characteristics from ocuserts, a two chambered diffusion cell was used. Ocuserts was placed in the donor compartment with 0.7 ml of pH 7.4 phosphate[12].At specified time interval the drug released from ocuserts was measured.

Table 2. Comparative in-vitro drug release from ocuserts F1, F2, F3, F4 (Values are mean ± SEM of three experiments in each group)

Time (hrs)	Cumulative % Drug Release			
	F1	F2	F3	F4
0	0	0	0	0
0.25	2.22±0.156	0.98±0.230	2.24±0.480	5.64±0.049
0.50	3.29±0.417	1.98±0.057	3.54±0.479	6.82±0.354
1	5.81±0.190	5.11±0.300	10.82±0.383	8.80±.073
2	7.42±0.296	6.78±0.204	12.76±0.118	10.49±0.406
3	10.81±0.180	9.79±0.108	17.63±0.148	16.88±0.167
4	15.49±0.328	10.75±0.16	20.57±0.554	20.45±1.080
5	18.05±0.376	13.11±0.208	23.05±0.205	25.12±0.324
6	19.87±0.349	16.31±0.086	24.82±0.132	29.31±0.111
7	21.47±.448	20.23±0.846	26.66±0.249	32.48±0.160
8	24.26±0.398	23.84±0.074	29.07±0.439	37.5±0.242
9	27.08±0.133	28.81±0.326	33.86±1.915	41.07±0.399

[94] 10	[95] 28.76 ±0.226	[97] 31.39± 0.539	[98] 39.11± 0.552	[99] 44.91 ±0.307
[100]11	[101]31.08 ±0.244	[103]38.99± 0.459	[104]43.11± 0.389	[105]48.52 ±0.238

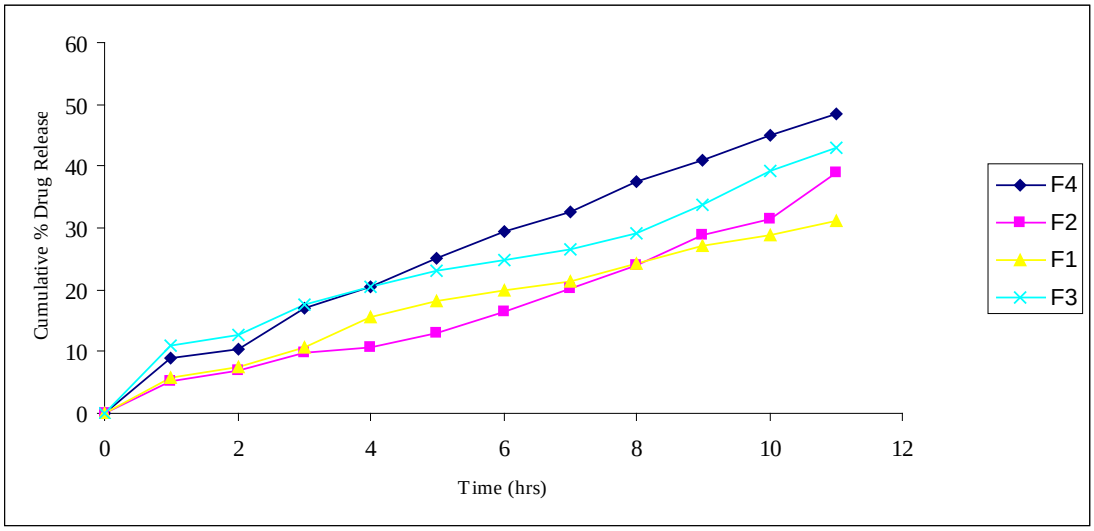


Figure 3. In-vitro Release of ophthalmic inserts from F1,F2,F3,F4.

Table3. In-vitro Release of ophthalmic inserts from F4 after increasing the amino acid content

Time(hrs)	1	2	3	Mean±SEM
0	0	0	0	0
1	14.61	14.66	14.38	14.57±0.085
2	19.38	20.61	19.77	19.92±0.362
3	27.77	28.5	27.11	27.79±0.401
4	33.33	34.05	33.72	33.7±0.208
5	39.66	41	40.11	40.25±0.393
6	49.11	50.5	49.55	49.72±0.410
7	57.88	59.38	58.38	58.54±0.441
8	64.88	68.61	72	68.49±2.056
9	79.33	80	79	79.44±0.294

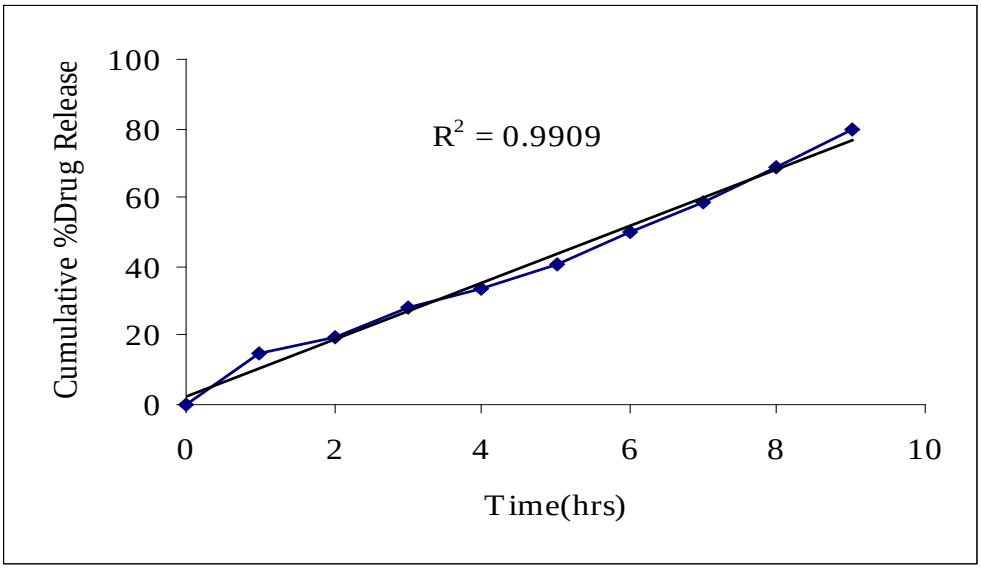


Figure 4. In-vitro Release of ophthalmic inserts from F4 after increasing the amino acid content

Table 4. In vitro drug release from formulation F4 containing Diclofenac sodium lysine conjugate in drug reservoir for 24 hours

Time(hrs)	1	2	3	Mean±SEM
0	0	0	0	0
0.25	6.23	5.90	5.90	6.01±0.110
0.50	8.31	6.45	7.44	7.40±0.537
2	17.18	14.28	14.41	15.29±0.945
4	18.92	18.84	21.56	19.77±0.893
6	32.73	27.74	29.71	30.06±1.451
8	36.17	35.89	38.97	37.01±0.983
10	48.58	46.73	47.66	47.65±0.534
12	57.82	56.89	55.42	56.71±0.698
14	64.32	63.55	63.44	63.77±0.276
16	73.72	72.77	70.70	72.39±0.891
18	83.34	82.21	80.34	81.98±0.859
20	88.35	87.69	86.06	87.36±0.680
22	93.40	92.25	91.76	92.47±0.486
24	97.68	96.75	96.15	96.86±0.445

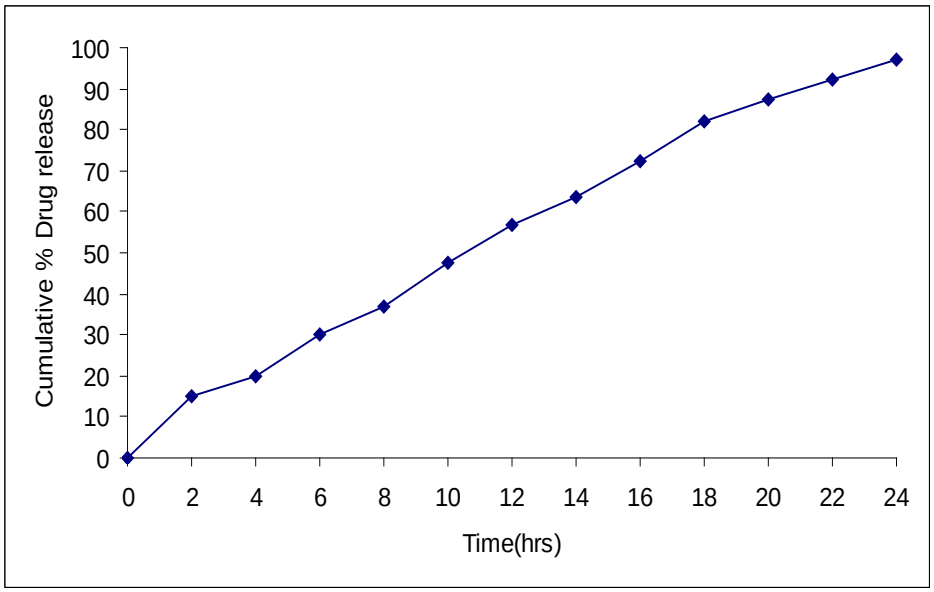


Figure 5. In vitro drug release from formulation F4 containing Diclofenac sodium lysine conjugate in drug reservoir for 24 hours

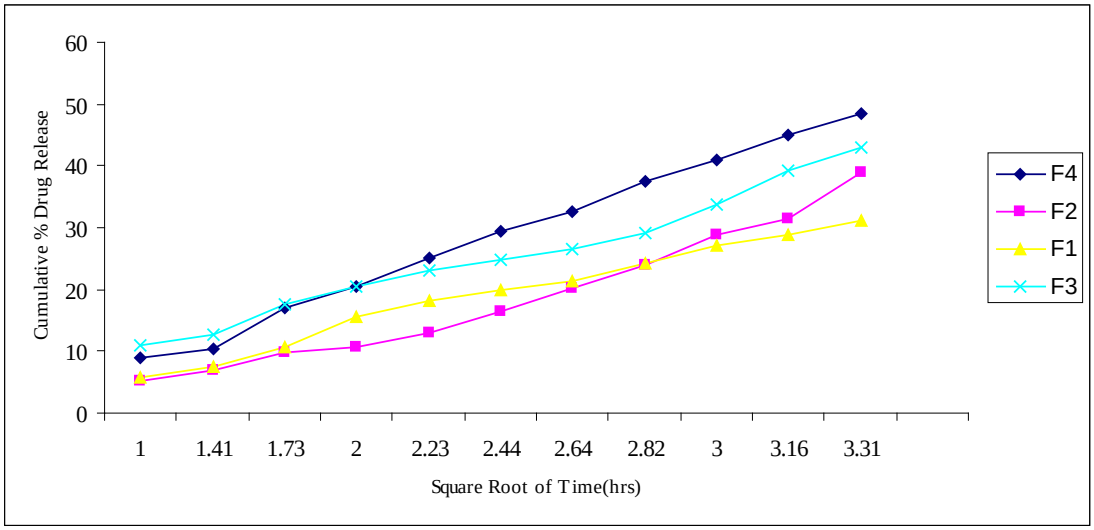


Figure 6.Highuchi plot of ophthalmic inserts from F1 ,F2,F3,F4

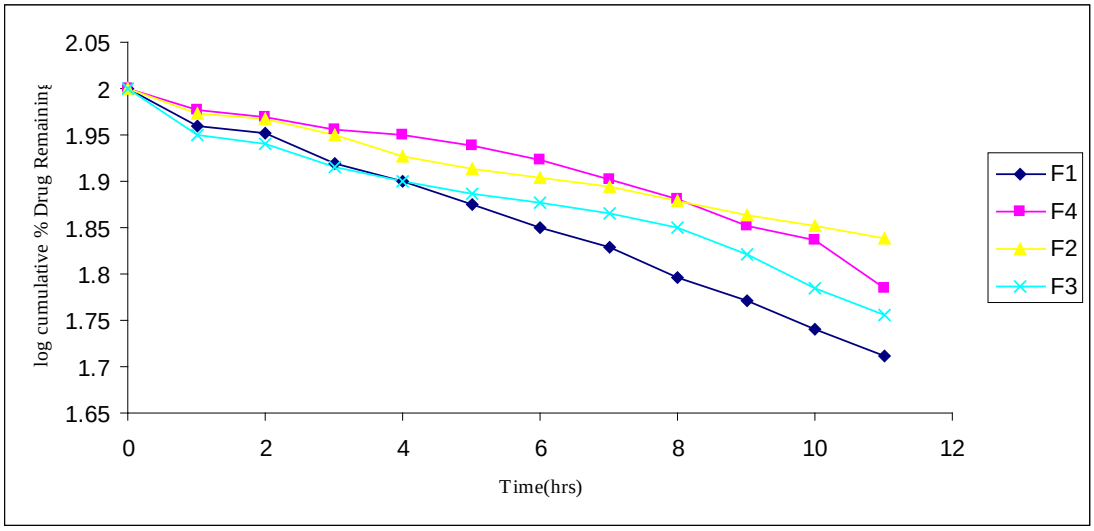


Figure 7.First order plot of ophthalmic inserts from F1 ,F2,F3,F4

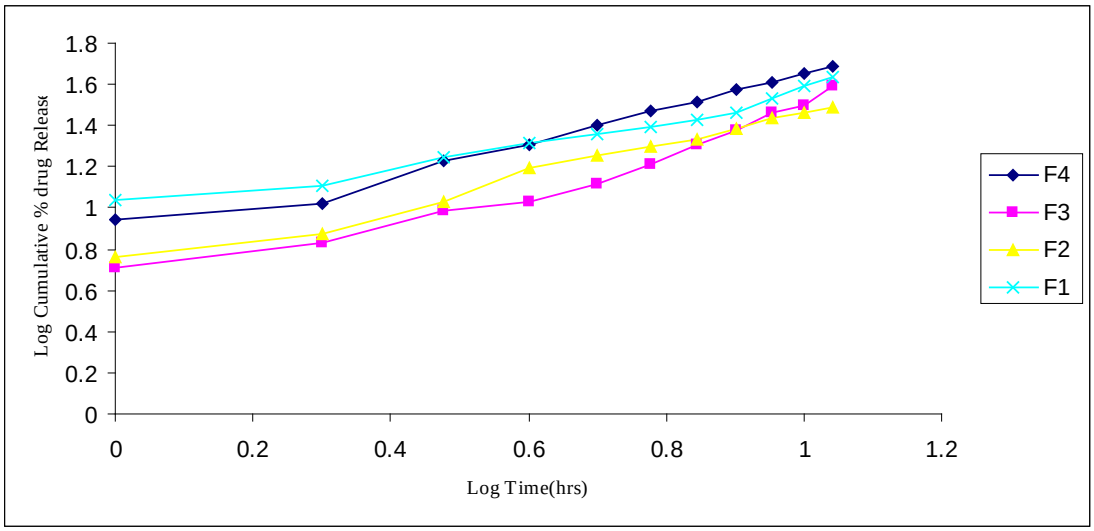


Figure 8.Korsmeyer plot of ophthalmic inserts from F1 ,F2,F3,F4

Table 5. Comparative Release kinetics of ocular inserts of Diclofenac sodium from formulations F1, F2, F3 and F4

[106]**Formulation** [107]**code**	[108]**Zero order model** [112]R^2	[109]**Highuchi model** [113]R^2	[110]**First order model** [114]R^2	[111]**Korsmeyer et al,s model**	
				[115]R^2	[116]**n**
[117] F4	[118]0.9896	[119]0.9651	[120]0.9799	[121]0.9787	[122]0.76
[123] F2	[124]0.9711	[125]0.9640	[126]0.9468	[127]0.9469	[128]0.85
[129] F1	[130]0.9823	[131]0.9922	[132]0.9916	[133]0.9833	[134]0.74
[135] F3	[136]0.9639	[137]0.9786	[138]0.9661	[139]0.9609	[140]0.57

Release studies were carried out for 11 hours for all formulations (Table 2).To know the mechanism of drug release from these formulations, the data were treated according to zero order (cumulative % of the drug released vs. time), First order (log cumulative % of drug remaining vs. time), Highuchi,s model (cumulative % of the drug released vs. Square root of time) and Korsmeyer,s model(log cumulative % of drug released vs log time)[11]

After 11 hours the cumulative drug release from formulation F4, F2 ,F1 ,F3, was found to be 48.52%, 38.99%,31.08% and 43.11%, respectively. Drug release from F 4, F3 was faster compared to formulation F1, F2 during 11 hr.Further it was seen on increasing the amino acid(Lysine) content in the formulation F4 increases the release of drug from 48.52% to 79.44%.

It is evident from the correlation coefficients for zero order model (Table 5) that neither of the above four formulations shows a perfect or complete zero order pattern. The values of R^2 for Highuchi's model (0.9640 to 0.9922) also suggest the same result .When the data was plotted according to first order equation, the formulations showed a fair linearity, with R^2 values between 0.9468 to 0.9916.In order to confirm the release kinetics of the formulations the data was fit into Korsmeyer's equation. As is evident from Korsmeyer's equation that for all the formulations the value of n (slope value of log mt/m∞) is less than 1(0.57 to 0.85), which further confirms that release rate is not independent of time. In other words none of formulation obeys zero order equation (case II transport).In all the four formulations the value of n obtained was between 0.57 to 0.85,which indicates that there is a coupling diffusion and erosion mechanism (anomalous diffusion/non-Fickian transport) in these formulations. Presence of swellable polymer (HPMC) within such formulations might be responsible for the drug release controlled by more than one process.The presence of plastic polymer Eudragit L100 might be responsible for diffusion type of drug release mechanism from such formulations.

Figure 9. Formulation F1 before 24 hours

Figure 10. Formulation F1 after 24 hours

On the basis of above drug release studies it may be stated that drug release from the all the four formulation anomalous diffusion controlled with predominately first order kinetics. On the basis of the drug release study it was seen that maximum amount of drug is release within 24hrs (96.86%) from formulation F4 as compared to rest of the formulations. Further it has got minimum thickness (0.44mm) and other parameters are also within the limit i.e. it will not produce any discomfort upon insertion. So formulation F4 containing 3% Eudragit L100 in Rate controlling membrane and 3% HPMC in Drug Reservoir seems best optimized formulation among the four formulated Formulations.

Figure 11.Photograph of optimized formulation (F4)

STABILITY STUDIES FOR OPTIMIZED FORMULATION[13]

In view of the potential utility of F-4 formulation for targeting of Diclofenac sodium to eye, stability studies were carried out 40°C/75% RH. The protocol of the stability studies was in conformation with the recommendation in the ICH document for stability testing of products intended for global market. After storage the formulation was subjected to evaluation of physical parameters, drug content and in-vitro drug release studies.

Table 6. Characteristics of ocuserts containing Diclofenac sodium lysine conjugate in the Drug reservoir (optimized Formulation F4) at accelerated conditions: (Values are mean ±SEM of three experiments in each group) before and after stability studies

Days	Thickness (mm)	Weight (mg)	Drug Content (mg)	Folding endurance	Surface pH
0	0.44± 0.017	57.66± 1.202	1.89±0.048	48.33±1.667	7.02± 0.020
30	0.44±0.005	57±2.517	1.88±0.008	47.66±1.453	6.98±0.044

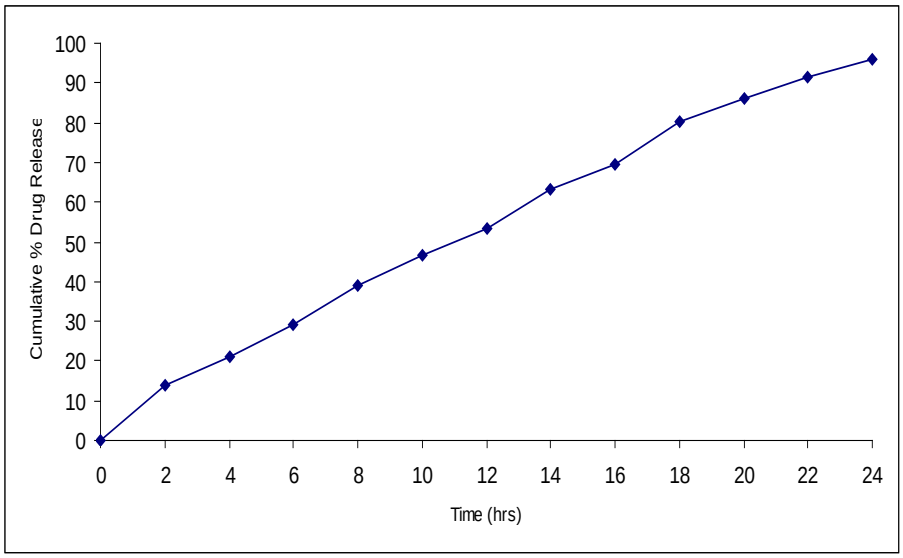


Figure 12. In vitro drug release from formulation F4 containing Diclofenac sodium lysine conjugate in the Drug reservoir at accelerated conditions

Table 7. In vitro drug release from formulation F4 containing Diclofenac sodium lysine conjugate in the Drug reservoir

Time(hrs)	Before	After
0	0	0
0.25	6.01±0.110	5.45±0.147
0.50	7.40±0.537	6.48±0.192
2	15.29±0.945	13.99±0.410
4	19.77±0.893	21.01±0.605
6	30.06±1.451	29.20±0.203
8	37.01±0.983	38.99±0.251

10	47.65±0.534	46.46±0.043
12	56.71±0.698	53.26±0.859
14	63.77±0.276	63.17±0.472
16	72.39±0.891	69.57±0.275
18	81.98±0.859	80.39±0.330
20	87.36±0.680	86.13±0.345
22	92.47±0.486	91.30±0.438
24	96.86±0.445	96.13±0.224

When the ocuserts were stored at accelerated conditions (400C/75% RH), there appeared no significant change in their physiochemical properties viz. thickness, weight, folding endurance, drug content, surface pH & in vitro drug release when compared to physiochemical properties and in vitro drug release from the same formulation before storage.

V. CONCLUSION

The conclusions drawn from the present study are

Drug –polymer compatibility studies were carried out using FT-IR and TLC styudy.It shows there is no significant interaction between polymers and Drug.Ocular inserts of Diclofenac sodium and Diclofenac sodium Amino acid Conjugates were Prepared suceesfully by solvent cating method using different polymers(HPMC,Eudragit L100) in different combinations and proportions.Dibutylphthalate was used as plasticizer.

Conventional ocular drug delivery such as eye drops, ointments, gels etc; have got various disadvantages like Precorneal loss, Evaporation by tears, Drug-protein interaction, Drug metabolism, Drainage, Induced lacrimation, Sticking of eye lids, Poor patient compliance, blurred vision; systemic side effects etc; Utilization of the principles of controlled release by means of ocular inserts offers an attractive approach to the problem of prolonging precorneal drug residence time. Thus reducing frequency of administration & hence increasing patient compliance. Besides the systemic side effects of the drug taken (Diclofenac sodium) could be overcome by utilizing the ophthalmic insert approach.

The prepared ocusert were evaluated for different parameters & in vitro drug release. On the basis of the Drug release studies it was concluded that drug release from all of the four formulations anomalous diffusion controlled with predominately first order kinetics. On the basis of the drug release study it was seen that maximum amount of drug is release within 24hrs (96.86%) from formulation F4 as compared to rest of the formulations. Further it has got minimum thickness (0.44mm) and other parameters are also within the limit i.e. it will not produce any discomfort upon insertion. So formulation F4 containing 3% Eudragit L100 in Rate controlling membrane and 3% HPMC in Drug Reservoir seems best optimized formulation among the six formulated Formulations.

The study revealed that Diclofenac sodium and amino acid conjugate ocular inserts had greater permeation than Diclofenac sodium ocular inserts.Effect of concentration of Amino acids on the permeation of Diclofenac sodium was also studied and it was found that on increasing the concentration of amino Acid ,permeation of Diclofenac Sodium increases.Diclofenac sodium and Lysine conjugate produced maximum ocular bioavailability. Formulations(F1) of Diclofenac sodium was prepared and compared, with different formulations(F2,F3,F4) of Diclofenac sodium and Amino Acid Conjugates and it was found that F4 has maximum ocular availability. Method of preparation of Novel amino Acid conjugates was found to be simple and reproducible .The polymers used were non-toxic, relatively less expensive and easily available. Polymers were found to be effective at different concentrations in providing constant release of the drug from the formulations for a long period of time. The optimized formulation was subjected to stability studies as per ICH guidelines.

So by formulation of Novel ocuserts the undesirable side effects of conventional dosage forms like frequent administration, poor availability, massive and unpredictable doses, drainage of medication by tear and nasolacrimal fluid, visual and systemic side effects can be overcomed.Thus the formulated ocuserts will eliminate such undesirable effects and will provide the therapeutic effect over a prolonged period of time. Thus will increase the patient compliance and therapeutic efficacy with minimal or no side effects.

The present study showed that Novel amino acid conjugate ophthalmic inserts can be a choice of drug delivery for the treatment of inflammatory conditions of eye as a controlled ocular drug delivery system and conjugation technique was effective to enhance the drug release and it can be concluded that Amino Acids can be used as a better tool for targeted drug Delivery to the eye.

Conventional ocular drug delivery such as eye drops, ointments, gels etc; have got various disadvantages like Precorneal loss, Evaporation by tears, Drug-protein interaction, Drug metabolism, Drainage, Induced lacrimation, Sticking of eye lids, Poor patient compliance, blurred vision; systemic side effects etc; Utilization of the principles of controlled release by means of ocular inserts offers an attractive approach to the problem of prolonging precorneal drug residence time. Thus reducing frequency of administration & hence increasing patient

compliance. Besides the systemic side effects of the drug taken (Diclofenac sodium) could be overcome by utilizing the ophthalmic insert approach.Various formulations of Diclofenac sodium ocular inserts were prepared using solvent casting method and were evaluated for various physicochemical parameters and Drug release. Method of preparation of Novel amino Acid conjugates was found to be simple and reproducible .The polymers used were non-toxic, relatively less expensive and easily available. Polymers were found to be effective at different concentrations in providing constant release of the drug from the formulations for a long period of time.

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