



**DESIGN AND DEVELOPMENT OF DRUG-POLYMER MATRIX
FILMS USING POLY- -CAPROLACTONE-POLY ETHYLENE
GLYCOL 4000 BY FILM CASTING TECHNOLOGY**

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Abstract

The main purpose of the study was to deliver the drug in zero order kinetics by using Drug-polymer matrix films. Film casting technique was followed to prepare Drug-polymer matrix films. All formulations were subjected to various physiochemical evaluations like Thickness, Uniformity of weight, Swelling index, Surface pH, Folding endurance, Drug content, *in vitro* drug release studies, Release rate kinetics were investigated. The Drug-polymer matrix films were smooth and passed all the evaluation tests performed. The *in vitro* kinetic treatment (Zero order and Korsmeyer's regression value) and *n* values suggest that A6 was the best formulation with desired *in vitro* drug release for 48 hours which suffices the objective.

Keywords: Drug-polymer matrix films, Poly- -caprolactone, Poly Ethylene Glycol 4000, Release kinetics.

Introduction

Emergence of Control release technology has brought the revolution in the pharmaceutical dosage forms aided the researches to designing the dosage form with decreased administration frequency with better controlled release. Poly- -caprolactone has wide application in the biomedical field since last 3 decades. Polymer-dependent factors aids Drug-polymer matrix films towards intended delivery of drug predictable kinetics.¹⁻² Glaucoma is the second leading cause of blindness in the world, according to the World Health Organization. Glaucoma when untreated leads to increased Intra Ocular Pressure and possible loss of vision.³⁻⁴ Management of glaucoma involves chronic topical use of Anti-glaucomic agents with an aim to achieve long term control of Intra ocular pressure.⁵

Objective

The objective of work was to formulate and evaluate Acetazolamide Drug-polymer matrix films produced by solvent casting technique which are designed to achieve prolonged therapeutic effect by improving residence time at the site of the application. Local therapy against systemic therapy is suggested to avoid the risk of eye damage from high blood concentrations of the drug, which is not intended or acceptable.⁶

Materials and methods

Acetazolamide was obtained as Gift Sample by Bright Labs Hyderabad, Poly- -caprolactone three grades (CAPA 6250, 6400, 6500) were obtained as Gift sample by Non-invasive Research laboratory, Mississippi, USA. Dichloromethane, Poly Ethylene

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Glycol 4000, Potassium dihydrogen ortho phosphate AR, Sodium hydroxide LR were obtained from S.D Fine Chem Ltd., Mumbai. Dialysis Membrane was obtained from Hi Media Laboratories Ltd., Mumbai.

Drug-polymer matrix films were prepared by film casting technology

The matrix films containing Acetazolamide were prepared by solvent casting method by choosing Poly-ε-caprolactone as film former and dichloromethane as solvent.⁷ Accurately 44mg of Acetazolamide was weighed and dissolved in 10 ml of dichloromethane and kept aside for 5 minutes for swelling of the polymer. Specified quantity of Acetazolamide dissolved in 10 ml of Dichloromethane solvent. Required quantity of PEG 4000 mg was added to the prepared polymeric solution then stirred to form dispersion.⁸ Prepared Acetazolamide solution was added to polymeric solution and stirred with the magnetic stirrer 500 RPM for 10 minutes continuously. Prepared medicated gel was allowed to stand for 10 to 15

minutes to remove the air bubbles. The air bubble free solution was poured into the self-designed glass mould 35 cm² kept on flat surface. An inverted funnel was placed over the glass mould to prevent the sudden evaporation of the solvent.⁹ The mould was kept for 12 hours at room temperature for drying. After this period, the film was removed and cutted then preserved in the dessicator until further use.¹⁰

Size Calculation of Drug-polymer matrix film¹¹

Area of rectangle = breadth X height Film casted area in the glass plate = 7 X 5=35cm²

Area of one circular film cutted with diameter of 0.8cm = 0.502cm²

Quantity of Acetazolamide in one Drug-polymer matrix film = 1 mg

Therefore for 35cm² area of rectangle = 44 mg of acetazolamide was taken.

Number of ocuset in 35cm²area = 0.502/35=43.75 Drug-polymer matrix films¹²⁻¹⁶

Specially fabricated glass surface apparatus.

Table No. 01: Composition of Drug-polymer matrix film Formulations

S.No:	Formulation code	Acetazolamide (mg)	PEG [†] 4000 (mg)	PCL ^{††} 6250 (mg)	PCL ^{††} 6400 (mg)	PCL ^{††} 6500 (mg)	DCM ^{†††} (ml)
1	A1	44	264	396	-	-	10
2	A2	44	264	462	-	-	10
3	A3	44	264	528	-	-	10
4	A4	44	264	-	396	-	10
5	A5	44	264	-	462	-	10
6	A6	44	264	-	528	-	10
7	A7	44	264	-	-	396	10
8	A8	44	264	-	-	462	10
9	A9	44	264	-	-	528	10

[†]PEG = Poly Ethylene Glycol (mg), ^{††}PCL=Poly-ε-Caprolactone (mg),

^{†††}DCM=Dichloromethane (ml)

Formulations A1-A9 are evaluated for Physical Appearance and Surface Texture, Weight uniformity, Thickness, Surface pH, Folding Endurance, Drug content uniformity, Percentage Moisture Absorption, Moisture content, *In vitro* drug release studies and *In vivo* studies.

Physical Appearance and Surface Texture

Includes visual inspection of patches and evaluation of texture by feel or touch.

Weight uniformity

For the evaluation of patch weight, ten patches of sizes 1.6 cm diameter from every formulation were taken and weighed individually on electronic

balance and the average weights were calculated. All measurements (Thickness and weight) were determined after residual solvent has been removed from samples by storing the films in dessicator with anhydrous Calcium chloride at an appropriate temperature 27±2°C for a week prior to evaluation and testing.

Thickness

The thickness of the film was measured at six different points on one film using screw gauge. For each formulation three selected films were used and average thickness was recorded.

Surface pH

Each patch was placed in petri plate and allowed to swell in contact with 2 ml of phosphate buffer, pH 7.4 for 2 hours at room temperature, and the pH was recorded with the aid of a digital pH meter. These measurements were conducted by bringing a glass microelectrode near the surface of the tablets and allowing it to equilibrate for 1 min prior to recording the readings. Experiments were performed in triplicate and average values were reported.

Folding Endurance

The flexibility of patches can be measured quantitatively in terms of as folding endurance. Folding endurance of the patches was determined by repeatedly folding a small strip of the patch (approximately 2x2 cm) at the same place till it broke. The number of times patch could be folded at the same place, without breaking gives the value of folding endurance.

Drug content uniformity

The formulated polymeric films were assayed for drug content in each case. Drug content was determined the homogenization of the wafer in 100 ml of pH 7.4 phosphate buffer for 4-6 h until the patch was completely dissolved in the solvent and the resulting solution was filtered through Whatmann filter paper No.1. The solution was diluted suitably and the absorbance of the solution was measured using UV-Vis spectrophotometer at a wavelength of 266 nm against phosphate buffer as blank. The experiment was performed in triplicate and average values were reported.

Percentage Moisture Absorption

The moisture uptake studies give an indication about the relative moisture absorption capacities of polymers and an idea whether the formulations maintain their integrity after absorption of moisture. 5% w/v agar was dissolved in hot water. It was transferred into petri plates and allowed to solidify. Six patches from each formulation were selected, laminated on one side with water impermeable backing membrane. They were placed on the agar plates, incubated at 37±1°C, and examined for any physical changes. At regular 1-hour intervals until 6 hours, patches were removed from the plates, excess surface water was removed carefully using a filter paper and were reweighed.

$$(\%) \text{Moisture absorption} = \frac{\text{final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

Moisture content

The ocular patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After 3 days, the patches were taken out and weighed. The moisture content (%) was determined by calculating the moisture loss using the formula:

$$\text{Moisture Content (\%)} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

In vitro drug release studies

A diffusion system was employed to *In vitro* release studies. The *In vitro* drug release study was performed on Franz diffusion cell using cellulose acetate membrane (0.45µm pore size, cut off 1000Da).¹⁷⁻²⁰ The insert was placed on the donor chamber. The receptor compartment (30 mL) was filled with phosphate buffer, pH 7.4. The experiment was performed at 37±0.5°C, at a stirring speed of 50 rpm using a magnetic stirrer. 3 ml of sample was collected from the receptor compartment at appropriate time intervals up to 60 h and replaced with phosphate buffer pH 7.4. Analysis was carried out using UV-Visible Spectrophotometer at 266 nm against phosphate buffer pH 7.4 as reference. The % cumulative drug release was calculated and reported. Mathematical expressions like Zero order, First order and Higuchi model Korsmeyer –Peppas model were applied to analyze the release mechanism from the patches.²¹⁻²⁴

Sterilization Studies

Sterilization of optimized film was done placing films under UV light in UV germicidal chamber, exposing both sides for 15 min at a 10 cm height from UV lamp.²⁴⁻³¹

Stability studies

The selected formulations were subjected to short term stability testing. Films wrapped in aluminium foil and kept in a humidity chamber maintained at 40 ± 2°C and 75 ± 5 %RH for 3 months as per ICH guidelines.

Results and discussion

The Acetazolamide ocular films were prepared by the method of Film casting technique employing glass surface well as substrate by using different of polymers such as Poly-ε-caprolactone 25,000,

Poly-ε-caprolactone 37,000, Poly-ε-caprolactone 50,000 grades, as film formers and release rate retardants and Poly Ethylene Glycol 40000 as pore forming, solubility enhancing carrier also serves as plasticizer and permeation enhancer. Dichloromethane is used as solvent. Drug polymer compatibility studies were performed by FTIR (Fourier transform infrared spectroscopy). The prepared Acetazolamide ocular films were characterized based upon their physico chemical characteristics like Physical Appearance and Surface Texture, Thickness, Surface pH measurement, Folding Endurance, Drug content uniformity, Percentage Moisture Absorption, Moisture content, *In vitro* drug release studies, Sterilization Studies, Stability study results found satisfactory.

Fourier Transform Infrared Spectroscopy (FTIR)

The pure drug (Acetazolamide) and polymers were subjected to IR studies alone and in combination. Pure drug, combination of drug-PEG4000, Pure drug-Poly-ε-caprolactone, and pure drug-PEG4000-Poly-ε-caprolactone were mixed with 100mg of potassium bromide. Through grinding in smooth agate mortar effected mixing. The mixtures were then pressed in to a discs using pellet maker) and placed in the sample holder of the instrument. These were analysed by FTIR to study the interference of poly-ε-caprolactone and PEG 4000 with the drug. The FTIR diagrams are shown in figure below.

Table No. 02: Interpretation of FTIR Spectra.

Interpretation	IR Absorbance band (cm ⁻¹)			
	Pure drug Acetazolamide	PEG 4000	Poly-ε-caprolactone	Pure drug + PEG4000 Poly-ε-caprolactone
O-H Stretching	-	3437	-	-
N-H Stretching	3329	-	-	3329
CH ₂ Stretching	-	2957	2997	2297
CH ₃ Stretching	2999	-	-	2999
C=O Stretching	1625	-	1707	1625
C=N Stretching	1590	-	-	1634
C-O Stretching	-	-	-	1495
S=O Stretching	1350	-	-	1340
C-O Stretching	-	-	1495	-
C-N Stretching	1290	-	-	1305
C-S Stretching	1250	-	-	1243

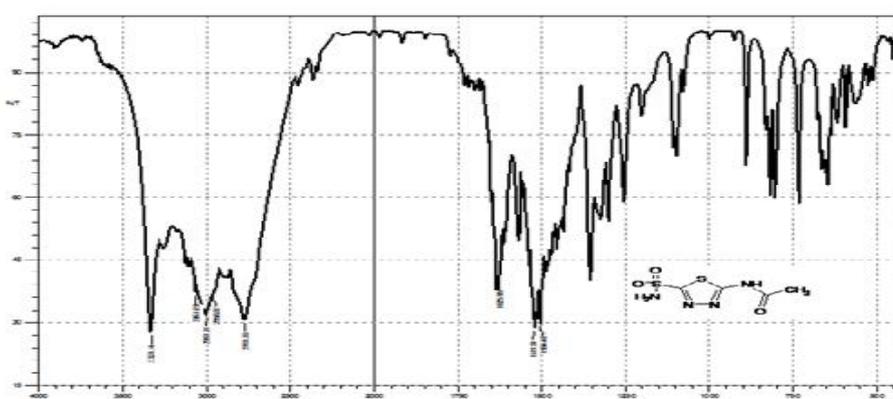
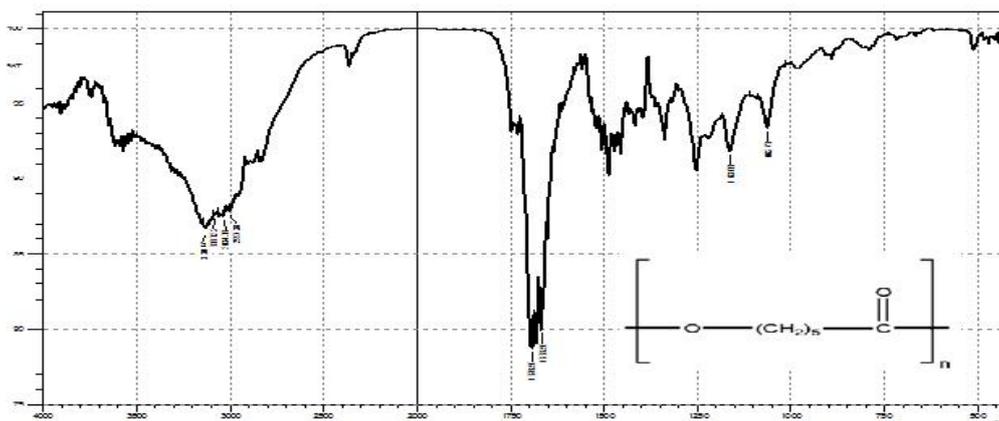
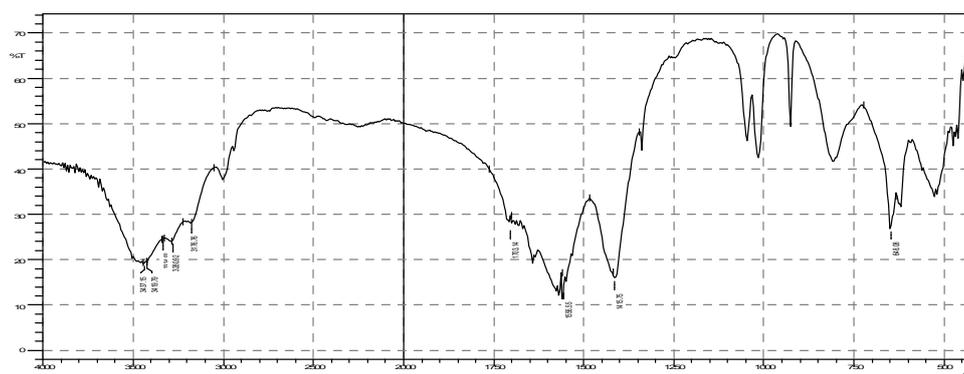
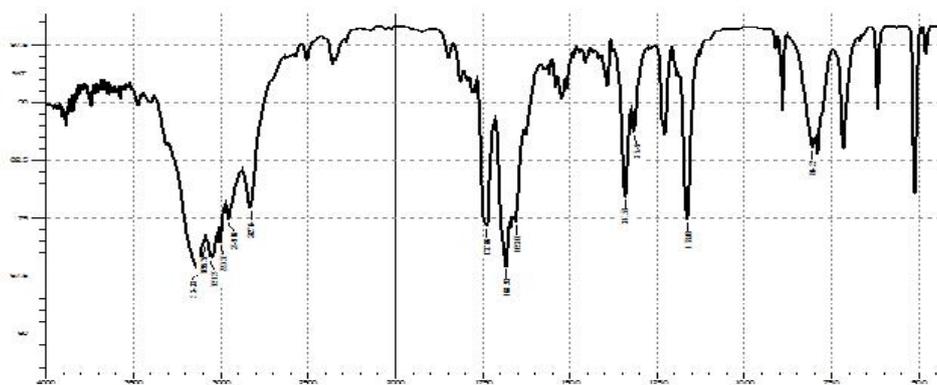
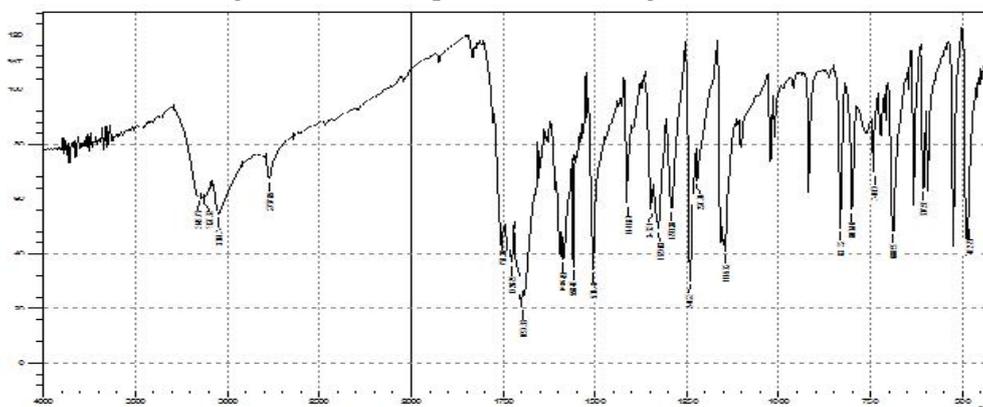


Fig. No. 01: FTIR Spectra of Pure drug Acetazolamide

**Fig. No. 02: FTIR Spectra of Poly-ε-caprolactone****Fig. No. 03: FTIR Spectra of PEG 4000****Fig. No. 04: FTIR Spectra of Pure drug+PEG4000****Fig. No. 05: FTIR Spectra of Pure drug+PEG4000+ Poly-ε-caprolactone**

The FTIR spectrum of pure drug Acetazolamide matches with that of Acetazolamide with excipients. Hence it can be concluded that there is no interaction of the excipients with the pure drug used in formulations. The FTIR spectrum of pure

drug Acetazolamide matches with that of Acetazolamide with excipients. Hence it can be concluded that there is no interaction of the excipients with the pure drug used in formulations.

Table No. 03: Physicochemical Evaluation of Acetazolamide Drug-polymer matrix films A1-A9

S.No	Formulation code	Weight uniformity* (mg)	Average Thickness* (mm)	Surface pH*	Folding Endurance*	Drug content uniformity* (%)	Percentage Moisture absorbed*	Percentage Moisture content*	Swelling Index
1	A1	14.39±0.61	0.053±0.003	7.22±0.005	44±2	99.1 ± 0.23	1.174±0.629	3.42±0.37	113.84
2	A2	15.81±0.52	0.056±0.002	7.29±0.005	46±2	98.4 ± 0.12	1.026±0.412	3.34±0.81	118.96
3	A3	17.32±0.37	0.063±0.003	7.31±0.015	49±1	99.8 ± 0.12	1.075±0.512	3.22±0.26	123.67
4	A4	14.31±0.21	0.073±0.003	7.34±0.050	53±2	99.6 ± 0.06	1.875±0.930	3.09±0.56	113.96
5	A5	15.97±0.29	0.08±0.001	7.32±0.015	56±3	98.7 ± 0.31	1.761±0.433	3.22±0.26	118.74
6	A6	17.48±0.74	0.083±0.001	7.24±0.03	58±2	98.4 ± 0.29	1.653±0.191	2.83±0.26	122.82
7	A7	14.81±0.81	0.093±0.001	7.36±0.03	56±1	98.6 ± 1.12	1.574±0.379	2.49±0.27	113.51
8	A8	15.93±0.66	0.103±0.003	7.30±0.015	61±2	99.1 ± 0.23	1.645±0.563	2.52±0.45	118.86
9	A9	17.89±0.64	0.11±0.002	7.26±0.005	63±3	98.6 ± 1.09	1.278±0.634	2.32±0.65	122.34

* Mean±S.D, n=3

Physical appearance and surface texture of ocular patches

These parameters were checked simply with visual inspection of patches and by feel or touch. The observation suggests that the patches are having smooth surface and they are elegant enough to see.

Weight uniformity of patches

The weight was determined using digital balance. The patches prepared with Poly-e-caprolactone and PEG 4000 polymers with formulations codes A1-A9 were weighed about 14.39±0.61 to 17.89±0.64 mg respectively. In all the cases the calculated standard deviation values are very low suggesting that the prepared patches were uniform in weight.

Thickness of patches

The thickness of the patch was measured using screw gauge. The thicknesses of patches prepared were about 0.053±0.003 to 0.110±0.002 mm respectively. As the molecular weight of Poly-e-caprolactone increases the increased thickness was observed. Formulation A9 had a thickness of 0.11±0.002 mm, which was highest amongst all the formulations.

Surface pH

Considering the fact that acidic or alkaline pH may cause irritation to the cornea and influence the rate of hydration of the polymers, the surface pH of the films was determined. The observed surface pH of the formulations was found to be in the range of 7.22±0.05 to 7.36±0.03. The results are found that

there is no significant difference of surface pH in all the formulations and the pH range lies within the range of lacrimal fluid pH i.e.7.2 to 7.4, hence do not cause irritation and achieve patient compliance.

Folding endurance

The folding endurance was found to be greater than 44±2 times in case of all the formulations. This makes the system acceptable as Drug-polymer matrix films, indicating good mechanical strength and elasticity. Folding endurance test results indicated that the films would maintain the integrity within the *cul-de-sac* when applied.

Drug content uniformity

The observed results of content uniformity indicated that the drug was uniformly dispersed and with minimum intra batch variability.

Percentage Moisture Absorption

Checking the physical stability of the film at high humid conditions and integrity of the film at dry conditions, the films were evaluated for the moisture absorption, moisture uptake studies give an indication about the relative moisture absorption capacities of polymers. The formulations maintained their integrity after absorption of moisture. The formulation A4 has shown the highest value of moisture absorption of 1.875±0.930.

Percentage Moisture content

Percentage moisture content was found to be between 2.52 ± 0.45 to 3.42 ± 0.37 for formulations A1-A9, All the formulations maintained their integrity. The literature survey discussed reveals the research work done to develop ophthalmic inserts with the hydrophilic polymers which have the tendency of moisture absorption which can be overcome with the usage of Poly- ϵ -caprolactone.

Swelling percentage

The swelling behaviour of the polymer was reported. The formulation A9 (264 mg of PEG 4000, 528 mg of Poly- ϵ -Caprolactone 6500) shows higher value of Swelling percentage 122.3 which is due to presence of higher concentration of Poly- ϵ -Caprolactone 6500.

Sterilization Studies

The Drug-polymer matrix films were sterilized by UV radiation.

In vitro Diffusion Studies

The *in vitro* diffusion studies were performed in triplicate using Franz diffusion cell and Inserts of known dimensions and weights were placed in a donor compartment and the flow rate of was maintained at 0.50 ± 0.10 ml/hr over the insert with phosphate buffer pH 7.4. The amount of drug released was determined by collecting aliquots from the receiving chamber at fixed time intervals.

The temperature was maintained at $35 \pm 2^\circ\text{C}$ throughout the study. Absorbance was measured by UV spectrophotometer at 266 nm using a Double beam UV- spectrophotometer T60 (Analytical Technologies Ltd). Finally, the concentration corresponding to a specific absorbance was determined from a calibration curve. The drug release profile of Acetazolamide from inserts after predetermined time intervals is expressed as a percentage. The results of cumulative percentage drug release from the formulations A1, A2, A3 were $99.11 \pm 0.96\%$, $89.50 \pm 2.46\%$ and $99.25 \pm 3.48\%$ respectively and the results, these formulations were able to release the drug for only 44 hrs the desired objective of two days delivery was not achieved.

The results of cumulative percentage drug release from the formulations A4, A5, A6 were $99.25 \pm 3.48\%$, $98.50 \pm 3.19\%$ and $99.89 \pm 2.34\%$ respectively and the results are represented in Figure. Formulation A4 was able to release the drug for only 46 hrs the desired objective of two days delivery was not achieved. A5 and A6 formulations showed a 48 hrs drug release profile i.e for a period of two days for this reason it was considered as the best formulations. From the above evaluation parameters it was concluded that the formulation A6 having the higher percentage of drug release in a sustained manner, so the formulation was selected as the best formulation.

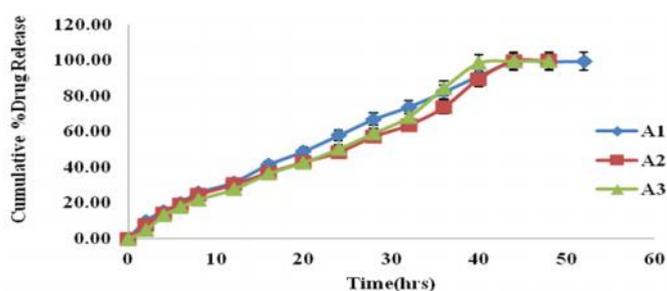


Fig. No. 06: *In vitro* Diffusion of Drug-polymer matrix film formulations A1, A2, A3.

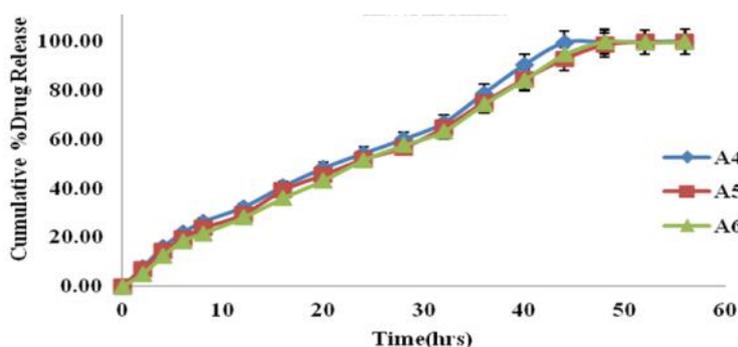


Fig. No. 07: *In vitro* Diffusion of Drug-polymer matrix film formulations A4, A5, A6

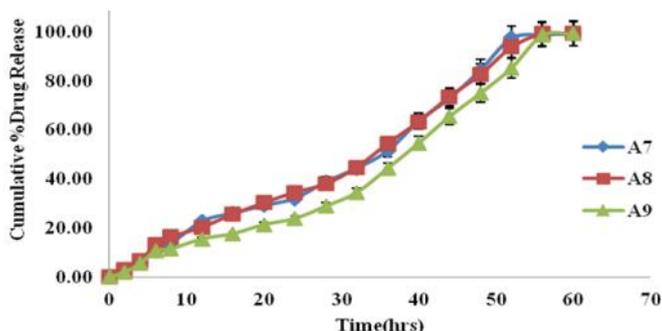


Fig. No. 08: *In vitro* Diffusion of Drug-polymer matrix film formulations A7, A8, A9.

The results of cumulative percentage drug release from the formulations A7, A8, A9 were 97.46±2.91%, 99.25±2.66% and 99.25±3.16% respectively and the results are represented in

above figures these formulations were able to release the drug for 52 hrs, 56hrs and 56 hrs respectively so desired objective of two days delivery was not achieved.

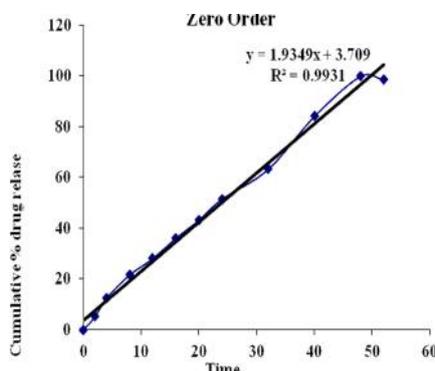


Fig. No. 09: Zero order graph of Best Drug-polymer matrix film formulation A6.

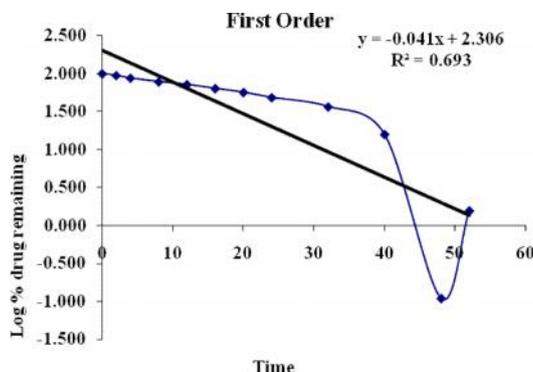


Fig. No. 10: First order graph of Best Drug-polymer matrix film formulation A6.

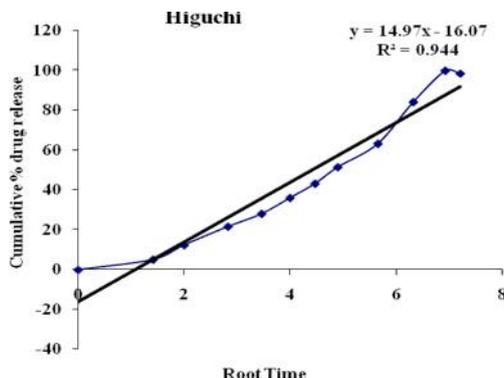


Fig. No. 11: Higuchi graph of Best Drug-polymer matrix film formulation A6.

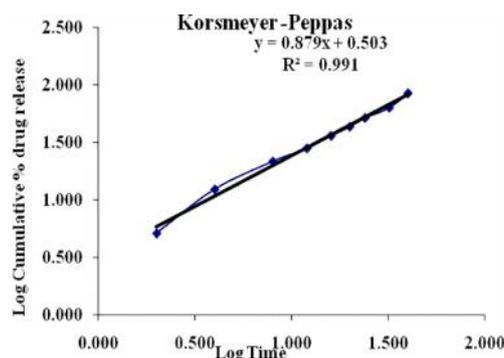


Fig. No. 12:Korsmeyer-Peppasgraph of Best Drug-polymer matrix film formulation A6.

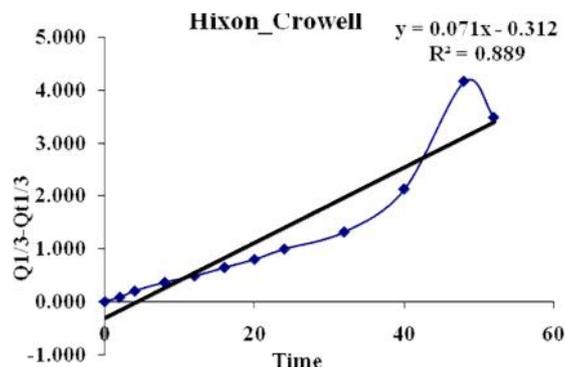


Fig. No. 13:Hixon-Crowellgraph of Best Drug-polymer matrix film formulation A6.

Table No. 04: Release Kinetic Summary A1-A9

Formulation Code	Zero order	First order	Higuchi	Hixon-Crowell	Korsmeyer-Peppas	
	r^2	r^2	r^2	r^2	r^2	n value
A1	0.9809	0.8524	0.9647	0.9531	0.980	0.6896
A2	0.9893	0.716	0.9268	0.070	0.990	0.7683
A3	0.9848	0.7849	0.9133	0.8874	0.916	0.9167
A4	0.9889	0.7463	0.9515	0.9056	0.991	0.766
A5	0.9923	0.7950	0.9538	0.9227	0.994	0.7862
A6	0.9931	0.6939	0.9442	0.8897	0.991	0.8792
A7	0.9741	0.7217	0.9741	0.8453	0.983	1.031
A8	0.9825	0.8116	0.8820	0.8932	0.988	0.952
A9	0.9541	0.8339	0.8185	0.8830	0.978	0.9866

The *in vitro* drug release data of Acetazolamide Drug-polymer matrix films were processed for regression analysis and the correlation coefficient (R^2) values obtained from the kinetic equations indicated that the release of the drug from the all formulations majority of formulations followed Zero order kinetics, Higuchi release pattern with non-erodable swelling release was followed and obeys release rate mechanism was Korsmeyer-

Peppas with Non -Fickian transport obeys Super case II transport.

Stability studies

The selected formulations were subjected to short term stability testing. Films wrapped in aluminum foil and kept in a humidity chamber maintained at $40 \pm 2^\circ\text{C}$ and $75 \pm 5\% \text{RH}$ for 1 month as per ICH guidelines.

Table No. 05: Data of stability studies of the formulation A6

Time(days)	Physical appearance	Surface pH*	Folding Endurance*	Drug content uniformity*	Percentage drug released at 48 hrs*
30	No changes	7.2-7.4	48±2	96.83±0.043	96.93±0.132
60	No changes	7.2-7.4	46±2	95.35±0.071	96.12±0.098
90	No changes	7.2-7.4	44±1	95.08±0.044	95.87±0.146

* Each reading was an average of three determinations

Conclusion

On the basis of results of evaluation A6 formulation was found to be the best formulation. A6 formulation has met the objective of 48 hour release with zero order, following Higuchi with supercase II transport. It was concluded that Acetazolamide: PEG 4000: PCL 6400 in the ratio of 1:4:12 (Drug: Polymer) would act as a suitable ocular drug delivery system for effective treatment of Glaucoma.

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References

1. Woodruff, Hutmacher *et al*, "The return of a forgotten polymer—Polycaprolactone in the 21st century", *Progress in Polymer Science* 35 (2010) 1217–1256.
2. Narsimha Murthy, S., *et al.*, "Biodegradable polymer matrix based Drug-polymer matrix films of Diclofenac sodium". *Indian Drugs*, 1997; 34(6): 336-8
3. Ritu M Gilhotra *et al*, "Enhancement of anti- glaucoma potential by novel ocular drug delivery system", *International Journal of Pharmacy and Pharmaceutical Sciences*, Vol 3, Issue 2, 2011.
4. Thirukkavaluri S Ashwin kumar, AnanyaParikibandla*, "Optimization of Anti-glaucoma Drug-polymer matrix films Using 3² Factorial Design with Response Surface Methodology", *Inventi Impact: Pharm Tech* Vol 1. Issue 1 2014
5. Sarim Imam *et al*, "Novel ocular dosage form in the treatment of glaucoma", *The Pharma Research* Vol:01, Year: 2009.
6. Kamal Singh Rathore *et al*, "Timolol maleate a gold standard drug in glaucoma used as ocular films and inserts: an overview", Volume 3; Article 005 Issue 1, July – August 2010.
7. Banerjee *et al*, "Biodegradable hybrid polymeric membranes for ocular drug delivery", *Acta Biomaterialia* 6 (2010) 1370–1379.
8. Berson *et al.*, Acetazolamide Dosage Forms in the Treatment of Glaucoma, *Arch Ophthalmol* 98:1051-1054, 1980.
9. U. L. Patel *et al*, "Design and evaluation of polymeric ocular drug delivery system for controlled delivery of moxifloxacin hydrochloride: *in vitro* and *in vivo* evaluation", *Acta Pharmaceutica Scientia*, 2010, 52:523-35.
10. K.S.Rathore, R.K.Nema, S.S.Sisodia, "Formulation and Evaluation of Brimonidine Tartrate Ocular Films". *The Pharma Review* (Mar 2010), p.133-138.
11. Macoul Pavan Langston, "Pilocarpine Drug-polymer matrix film Control of Ocular System for Sustained Hypertension", *Arch Ophthalmol.*, vol 93 Aug 1975.
12. Yogyata N. Tandale *et al*, "Formulation and Evaluation of Dorzolamide Hydrochloride Polymeric Film", *International Journal of PharmTech Research*, Vol. 3, No.2, pp 1211-1218, April-June 2011.
13. Biswajit Mukherjee *et al*, "A comparison between povidone-ethylcellulose and povidone-eudragit transdermal dexamethasone matrix patches based on *in vitro* skin permeation", *European Journal of Pharmaceutics and Biopharmaceutics* 59 (2005) 475–483.
14. Hitesh B. Gevariya *et al* "Sustained ophthalmic delivery of levofloxacin from once a day Drug-polymer matrix films", *International Journal of Pharmacy and Pharmaceutical Sciences*, Vol. 1, Suppl 1, Nov.-Dec. 2009.
15. Joseph R. Robinson *et al*, "Ocular pharmacokinetics/pharmacodynamics", *European Journal of Pharmaceutics and Biopharmaceutics* 44 (1997) 71-83.
16. Kumaresan C *et al*. "Development of novel Drug-polymer matrix film contains norfloxacin and *in-vitro* evaluation", *Journal of Pharmacy Research* 2011,4(2),393-395.
17. Purna Chandra Rao.M *et al*, "Fluconazole Ocular Inserts: Formulation and *In -Vitro* Evaluation", *J. Pharm. Sci. & Res.* Vol.2 (6), 2010, 344-35.
18. Banker GS, Christopher T. Rhodes, "Drugs and Pharmaceutical Science *Modern Pharmaceutics*", 2nd Edition, 1990, Marcel Dekker INC, New York, pp 406, 410,412 and 413.
19. Saettone MF, Burglousi S and Chetoni P, Bioadhesive Drug Delivery Systems, Fundamental novel approaches and development. Edited by Mathiowitz W, Chickering III DE, Lehr CM, New York, Marcel Dekker Inc., 1999; 621-625.

20. Maria Ann Woodruff, Dietmar Werner Hutmacher“ The return of a forgotten polymer—Polycaprolactone in the 21st century”*Progressin Polymer Science* 35 (2010) 1217–1256.
21. P Rohini *et al*, “Studies on Dissolution Enhancement of Itraconazole Using Water-Soluble Carriers”, *Inventi Rapid: Pharm Tech* Vol. 1, Issue 1, 2010
22. Sreenivas SA *et al*, “Ofloxacin ocular inserts: Design, Formulation and Evaluation” *Iranian journal of pharmacology & therapeutics*, 5:159-162, 2006.
23. Swati C. Jagdale *et al*, “Solid State Characterization of Clonazepam in Solid Dispersion and Formulation of Fast Dissolving Tablet”, *Journal of Pharmacy Research* 2011,4(2),480-487
24. Tamara Elzein *et al*, “FTIR study of polycaprolactone chain organization at interfaces”, *Journal of Colloid and Interface Science* 273 (2004) 381–387.
25. Tanwar *et al*, “*In vitro* and *in vivo* evaluation of ocular inserts of ofloxacin”, *DARU* 2007 15(3) 139-145.
26. Wen-Jen Lin, Chia-Hui Lu.,“Characterization and permeation of microporous poly(-caprolactone) films”, *Journal of Membrane Science* 198 (2002) 109–118.
27. Ashwin Kumar T. S.*, Kameswara Rao C. H. , Gurudeep N., Rama KrishnaRaparla., (2010), “Design and Evaluation of Binding, Compression, and Release Properties of PVP-K30 in the Formulation of Paracetamol Tablets”,*Inventi Impact: Pharm Tech* Vol. 1, Issue 3.
28. Thirukkoyaluri S Ashwin kumar, Ananya Parikibandla, “Optimization of Anti-diabetic Microspheres Prepared with Emulsification (o/w) Solvent Evaporation Technique”, *Journal of Medical and Pharmaceutical Innovation*; 1 (2) 2014; 38-44.
29. Ashwin Kumar T. S.Santhosh Duddelli*, “Formulation and *In vitro* Evaluation of Zolmitriptan Sublingual Tablets” *International Journal of Pharmacy and Biological Sciences*. Volume 3. Issue 2. Pg 235-246, Apr-Jun.2013.
30. Ashwin kumar T.S., et al Formulation and Evaluation of Bio-adhesive Buccal Drug Delivery of Esomeprazole Magnesium Tablets. *Research Journal of Pharmacy and Technology* 2013; 6 (2);220-224.
31. Aulton ME, *Pharmaceutics. The Design and Manufacture of Medicines*, 3rd edition, London, Churchill Living stone, Elsevier, 2007.p. 443-445.