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APPLICATION OF FACTORIAL DESIGN AND OPTIMIZATION OF GLIMEPIRIDE SUSTAINED RELEASE MATRIX TABLETS

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ABSTRACT

The objectives of the present investigation are to prepare and evaluate drug loaded sustained release matrix tablets for "diabetes", using hydrophilic and hydrophobic polymers, by applying 2^3 factorial designs. The sustained release tablets of Glimepiride were prepared employing different concentrations of Ethyl cellulose, HPMC K15M and Eudragit L100 in different combinations as a rate retarding polymer by wet granulation technique using 2^3 factorial designs. The quantity of polymers, Ethyl cellulose, HPMC K15M and Eudragit L100 required to achieve the desired drug release was selected as independent variables, X1, X2 and X3 respectively whereas, time required for 80% of drug dissolution (t_{80}%) was selected as dependent variables. Totally eight formulations were designed and are evaluated for hardness, friability, diameter, thickness, % drug content, *In-vitro* drug release and *In-vivo* studies. From the Results it was concluded that all the formulation were found to be within the Pharmacopoeia limits and the *In-vitro* dissolution profiles of all formulations were fitted in to different Kinetic models, the statistical parameters like intercept (a), slope (b) & regression coefficient (r) were calculated. Polynomial equations were developed for $t_{80\%}$. The formulation (F9) containing three polymers in optimized level using 2^3 factorial designs showed high $t_{80\%}$ value of 24 hours. The selected formulation (F9) follows Higuchi's kinetics, and the mechanism of drug release was found to be Anomalous type (Non-Fickian, n=0.5809).

KEYWORDS

Glimepiride, 2^3 factorial designs, Ethyl cellulose, HPMC K15M and Eudragit L100.

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INTRODUCTION

Drug delivery in conventional dosage forms often suffers from the drawbacks of repeated drug administration and large fluctuations in drug blood levels. The frequency with which a rapidly absorbed and distributed drug must be given in a conventional dosage form is dependent upon intrinsic properties of the drug, viz. elimination half-life ($t_{1/2}$)[1]. Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to

achieve better selectivity and longer duration of action including improved therapeutic effect, increased patient compliance by reducing dosing frequency and decrease in incidence and /or intensity of adverse effect by a constant blood concentration. Sustained release matrix tablet is relatively easy to fabricate by incorporating drug molecules into a matrix in slowly disintegrating or inert porous material containing a hydrophilic rate controlling polymer[1].

Glimepiride is an antidiabetic drug used in treatment of type-2 diabetic mellitus was used as a model drug to develop a sustain release formulation. Glimepiride has a short biological half-life of 5-hrs and rapid first pass metabolism which necessitates multiple daily dosing hence the present study was aimed to develop a sustain release matrix tablet of glimepiride[2]. Sustained release matrix tablet of Glimepiride is generally given in divided doses two times a day. The usual starting dose is 210 mg thrice daily. The aim of this present work is to formulate a sustained release[3] tablet of Glimepiride by wet granulation method using various polymers such as Ethyl cellulose, HPMC K15M and Eudragit L100 and applied the different kinetic models to study the drug release mechanisms. A 2^3 full factorial design was employed to investigate the effect of three independent variables (factors), i.e. the amounts of Ethyl cellulose, HPMC K15M and Eudragit L100.On the dependent variables, i.e. $t_{80\%}$ (Time taken to release 80% of drug, dosage form, and first order rate constant respectively)

MATERIAL AND METHODS

Materials

Glimepiride was received as gift sample from Aurobindo, Hyderabad, India. Ethyl cellulose, HPMC K15M and Eudragit L100.were procured from colorcon Asia Pvt Ltd, Goa. Other excipients such as Micro crystalline cellulose, Magnesium stearate, were procured from S.D. Fine Chem. Ltd., Mumbai.

Formulation Development of Glimepiride Sustained Release Tablets

The factorial design is a technique that allows identification of factors involved in a process and assesses their relative importance. In addition, any interaction between factors chosen can be identified. Construction of a factorial design involves the selection of parameters and the choice of responses[4,5].

A selected two level, three factor experimental designs (2^3 factorial designs) describe the proportion in which the independent variables Ethyl cellulose, HPMC K15M and Eudragit L100 were used in formulation of Glimepiride sustained release (SR) Tablets. The time required for 80% ($t_{80\%}$) drug dissolution was selected as dependent variables. Polynomial equations were developed for ($t_{80\%}$).

The two levels of factor X_1 (Ethyl cellulose) at a concentration of 100 mg and 150 mg. Two levels of factor X_2 (HPMC K15M) at a concentration of 50 mg and 150 mg. Two levels of factor X_3 (Eudragit L100) at a concentration of 75 mg and 125 mg was taken as the rationale for the design of the Glimepiride SR tablet formulation. Totally eight Glimepiride sustained release tablet formulations were prepared employing selected combinations of the three factors i.e. X_1, X_2 and X_3 as per 2^3 Factorial and evaluated to find out the significance of combined effects of X_1, X_2 and X_3 to select the best combination and the concentration required to achieve the desired prolonged/ sustained release of drug from the dosage form[6].

Preparation of Glimepiride Sustained Release Tablets

Eight different tablet formulations were prepared by wet granulation technique as reported. The composition of 2.5 mg Glimepiride of the drug, polymer Ethyl cellulose, HPMC K15M and Eudragit L100 and filler talc was dry mixed thoroughly and sufficient volume of granulating agent (5%w/v ethanolic solution of PVP-K90). Ethanolic solution of PVP was added slowly. After enough cohesiveness was obtained, feeded in wet granulator and the mass was sieved. The granules were dried at 55º C for 1 hour. These granule mixtures was blended with magnesium stearate (1.6% w/w) as lubricant, the appropriate and then compressed using a 16 station tablet compression machine round, flat-faced punches of 12.5 mm diameter and die set. All compressed tablets were stored in air tight container at room temperature for the study. The detailed compositions of various formulations prepared employing 2^3 factorial designs.

Experimental Design

Experimental design utilized in present investigation for the optimization of polymer concentration such as, concentration of Ethyl cellulose was taken as X_1 concentration of HPMC K15M was taken as X_2 and concentration of Eudragit L100 was taken as X_3. Experimental design was given in the Table No.1 and 2.

EVALUATION PARAMETERS

Pre-formulation Studies

Fourier Transform Infrared Spectroscopy

The Fourier transform infra-red analysis was conducted for the structure characterization. FTIR spectra of the pure drug, polymers and formulations were recorded by using BOMENMB SERIES FTIR instrument. Approximately 5mg of samples were mixed with 50mg of spectroscopic grade KBr; samples were scanned in the IR range from 500 to 3500 cm^{-1}, with a resolution of 4 cm^{-1}.

Differential scanning colorimeter (DSC)

DSC thermo gram of Glimepiride and physical mixture of drug and polymers are shown in Figure No.4 and 5. DSC thermo gram of pure drug has shown a melting endotherm at 196.1 °C with normalized energy. The thermo gram of physical mixture showed that the Glimepiride melting onset temperature decreased to 201.40° C because of the presence of polymers in the physical mixture.

Pre-compression studies of Glimepiride sustained release matrix tablets

Angle of repose

Angle of repose ranged from19.29^O to 28.25^O. The results were found to be below 25^0 and hence the blend was found to have excellent flow property. Table No.4.

Bulk density and tapped density

Bulk and tapped densities are used for the measurement of compressibility index. The LBD and TBD ranged from 0.29 to 0.50 and 0.34 to 0.580 respectively. Table No.4.

Compressibility index :(Carr's index)

Compressibility index ranged from 12% to 16% the blend was found to have free flowing property as the result were found to be below16 %. Table No.4.

Hausner's ratio

The hausner ratio ranged from 1.13 to 1.2 the result indicate the free flowing properties of the granules. Table No.4.

Drug Content Uniformity

The drug content in a weighed amount of granules blend of all SR formulations ranged from 98.41% to 99.5%

Post-compression studies of Glimepiride sustained release matrix tablets

Hardness test

The hardness of all batches ranged from 4.68 to 5.13 kg/cm^2

Friability test:

The percentage friability of all batches ranged from 0.066 to 0.232 %.

Weight variation

The percentage weight variations for all formulations are present in (Table No.5). All the formulations passed weight variation test as per the pharmacopoeias limits of 5%.

Drug content uniformity

Drug content was found to be uniform among the all formulations and ranged from 98.21 to 99.08 %.

Swelling Index

Swelling study was performed for all batches Figure No.1 to Figure No.8) for 5 hours. The result is shown in the Table No.5 and swelling index against time (5 hours).

***In vitro* dissolution**[7]

The release of glimepiride from the sustained release tablet was studied up to 24 hours in phosphate buffer as dissolution medium using a USP dissolution paddle assembly at 50 rpm and 37˚± 0.5˚C. An aliquot (1ml) was withdrawn at specific time intervals, filtered and diluted to 10ml with the dissolution medium, and drug content was determined by UV- visible spectrophotometer at 226nm. An equal volume of fresh dissolution medium was replaced to maintain the dissolution volume.

Dissolution studies were performed for a period of 24 hrs and the value was taken. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

Kinetic modeling of drug release

The dissolution profile of all the formulations was fitted in to zero-order, first-order, and Higuchi and Korsmeyer-peppas models to ascertain the kinetic modeling of drug release[8, 9].

Experimental Hyperglycemia in rats

Hyperglycemia was induced by injecting alloxan at a dose of 150mg/kg S.C. The animals were kept under observation. After 48hrs, the animals were tested for blood glucose levels using glucose oxidase - peroxidase strips.7 days after the alloxan injection, rats with fasting blood glucose levels greater than 200mg/dL were considered diabetic.

RESULTS AND DISCUSSION

Sustained release tablets of glimepiride were prepared and optimized by 2^3 factorial designs in order to select the best combination of different rate retarding polymers, Ethyl cellulose, HPMC K15M and Eudragit L100 also to achieve the desired prolong/sustained release of drug from the dosage form. The three factorial parameters involved in the development of formulations are, quantity of Ethyl cellulose, HPMC K15M and Eudragit L100 polymers as independent variables (X_1,X_2 and X_3), and *In vitro* dissolution parameters such as $t_{80\%,}$ as dependent variables. Totally eight formulations were prepared using 2 levels of 3 factors and all the formulations containing 2.5 mg of glimepiride were prepared as a sustained release tablet dosage form by wet granulation technique as per the formulae given in Table No.3. The optimized formulation F9 formulated after applying 2^3 factorial designs were subjected for *in-vivo* studies.

All the prepared tablets were evaluated for different post compression parameters, drug content and in-vitro dissolution. Good uniformity in drug content was found among different batches of the tablet. All the tablets formulation showed acceptable pharmacopoeia limit specifications for weight variation drug content, hardness, and friability.

***In Vitro* Release Studies**

The *in-vitro* drug release characteristics were studied in 900 ml of 0.1N HCL for first 2 hours and 900 ml of P^H 7.8 for rest of hours, using USP XXIII dissolution apparatus type II (paddle) method. The difference in burst effect of the initial time is a result of the difference in the viscosity of the polymeric mixtures. Dortunc and Gunal have reported that increased viscosity resulted in a corresponding decrease in the drug release, which might be due to the result of thicker gel layer formulation[18]. The *In -vitro* dissolution data of Glimepiride formulations was subjected to goodness of fit test by linear regression analysis according to zero order and first order kinetic equations, Higuchi's and Korsmeyer-Peppas models to assess the mechanism of drug release.

The results of linear regression analysis including regression coefficients are summarized in Table No.7. It was observed from the above that dissolution of all the tablets followed zero order kinetics with co-efficient of determination (R^2) values above 0.9521. The values of r of factorial formulations for Higuchi's equation was found to be 0.9969 which shows that the data fitted well to Higuchi's square root of time equation confirming the release followed diffusion mechanism. Kinetic data also treated for Peppas equation, the slope (n) values ranges from 0.5972 - 0.6692 that shows Non-Fickian diffusion mechanism. Polynomial equations were derived for, $t_{80\%}$ values by backward stepwise linear regression analysis. The dissolution data of factorial formulations F1 to F8 are shown in Polynomial equation for 2^3 full factorial designs is given in Equation:-

$$Y = B_0 + B_1(x_1) + B_2(x_2) + B_3(x_3) + B_{12}(x_1x_2) + B_{13}(x_1x_3) + B_{23}(x_2x_3) + B_{123}(x_1x_2x_3)$$

Where, Y is dependent variable, B0 arithmetic mean response of nine batches, and B1 estimated co-efficient for factor X_1. The main effects (X_1, X_2 and X_3) represent the average result of changing one factor at a time from its low to high value. The interaction term (X_1, X2 and X_3) shows how the response changes when three factors are simultaneously changed. The polynomial terms (X_1^2, $X2^2$ and X_23) are included to investigate non-linearity.

The data demonstrate that both X_1 (amount of Ethyl cellulose) and X_2 (amount of HPMC K15M) and X_3 (amount of Eudragit L100) affect the time required for drug release ($t_{80\%}$). From the results it can be concluded that, and increase in the amount of the

polymer leads to decrease in release rate of the drug and drug release pattern may be changed by appropriate selection of the X_1, X_2 and X_3 levels. The final best (Optimized) formulation (F9) is compared with F1-F8.

***IN VIVO* STUDIES**

Histopathology report

The islets of alloxan induced diabetic rats showed extensive necrotic changes followed by fibrosis and atrophy (Group-1). The Alloxan diabetic rats treated with Glimepiride minimum degree of necrotic and fibrotic changes of islets of langerhans (Group-3). The necrotic and fibrotic changes were not detected in the rats were treated with F9 and Glimepiride SR (Group-2 and 4).

TECHNICAL PROGRESS AND RESULTS

Table No.1: Levels of Factors

S.No	Factor	Low level	High level
1	A	-	+
2	B	-	+
3	C	-	+

Table No.2: Two- level-3-factor- full-factorial Experiment design pattern

S.No	Combination	*Factors*		
		A	B	C
1	(1)	-	-	-
2	A	+	-	-
3	B	-	+	-
4	AB	+	+	-
5	C	-	-	+
6	AC	+	-	+
7	BC	-	+	+
8	ABC	+	+	+

Table No.3: Composition of Formulations of Glimepiride sustained release matrix tablet

S.No	Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8
1	Glimepiride	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
2	Ethyl cellulose	100	100	150	150	100	100	150	150
3	HPMC K15 M	50	150	50	150	50	150	50	150
4	Eudragit L100	75	75	75	75	125	125	125	125

Table No.4: Results of Pre-compression studies of Glimepiride sustained release matrix tablet

S.No	Parameter	F1	F2	F3	F4	F5	F6	F7	F8
1	Bulk density	3.87	3.27	3.00	4.012	4.329	3.996	4.32	4.329
2	Bulkiness	0.47	0.34	0.41	0.58	0.54	0.56	0.55	0.69
3	Angle of repose	23.80	23.55	19.29	21.54	28.25	21.32	19.31	20.30
4	Carr's index	12.0	14.7	12.1	13.7	14.17	14.2	15	13.9
5	Hausner's ratio	1.14	1.17	1.13	1.16	1.2	1.16	1.15	1.19
6	% Drug content (uniformity)	98.59	99.12	98.41	98.76	98.59	98.41	99.5	99.23

Table No.5: Results of Post-compression studies of Glimepiride sustained release matrix tablet

S.No	Parameter	F1	F2	F3	F4	F5	F6	F7	F8
1	Weight variation(mg)	505.5	502.5	508.0	507.0	502.0	508.0	506.0	508.2
2	% Friability	0.010	0.014	0.122	0.132	0.116	0.110	0.124	0.99
3	Hard ness test	5.05	4.81	4.80	4.85	4.68	5.13	5.01	5.07
4	Swelling study	77.89	78.47	78.11	76	81.3	80	79.7	84.04
5	% Drug content (uniformity)	98.54	99.08	98.21	98.72	98.56	98.38	98.57	98.78

Table No.6: *In vitro* drug release for oral sustained release Tablets of Glimepiride

S.No	Time in hrs	F1	F2	F3	F4	F5	F6	F7	F8
1	0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	1	9.73	8.01	9.44	8.87	9.44	9.44	10.59	9.73
3	2	16.62	14.61	16.62	11.75	12.61	12.33	14.62	14.62
4	3	30.35	26.66	30.35	26.33	28.87	26.62	31.43	26.67
5	4	38.51	38.07	39.77	31.04	35.59	29.39	37.50	31.71
6	5	44.44	41.87	41.36	34.81	38.20	30.33	39.65	33.46
7	6	51.23	46.98	44.50	39.90	43.02	35.70	43.63	35.46
8	7	55.79	50.69	47.92	43.89	47.29	43.03	49.30	39.71
9	8	59.96	52.74	52.76	48.73	51.01	46.19	51.33	44.25
10	9	61.02	55.34	55.92	53.01	54.18	51.02	53.38	47.96
11	10	62.52	59.36	58.53	56.47	55.67	53.07	54.86	50.84
12	11	64.58	60.85	60.86	57.97	57.73	54.84	56.91	53.16
13	12	66.93	63.08	63.20	59.19	60.07	56.90	58.97	55.20
14	13	68.44	63.86	66.95	60.13	61.58	58.40	60.47	56.97
15	14	70.51	65.37	68.74	61.64	63.65	59.62	62.81	61.55
16	15	71.19	67.44	70.54	63.43	64.32	60.84	66.28	63.34
17	16	72.60	70.20	72.05	65.79	65.27	62.63	67.23	64.84
18	17	73.67	71.32	73.58	67.59	66.79	64.70	69.03	66.07
19	18	75.20	73.41	74.82	69.95	71.11	68.15	71.67	67.87
20	19	77.29	75.22	76.63	72.04	73.20	69.70	73.19	69.67
21	20	80.78	77.03	78.16	73.85	75.01	72.07	75.28	72.03
22	21	81.76	78.29	79.14	75.10	77.67	73.32	76.26	73.83
23	22	82.74	79.83	80.11	76.08	79.49	75.13	77.79	76.20
24	23	85.41	83.61	81.93	77.06	80.48	78.91	80.45	78.58
25	24	87.80	85.72	83.47	82.81	82.58	80.74	82.83	80.40

Table No.7: Kinetic Analysis of *In – Vitro* Release Rates of Sustained Release Tablets of Glimepiride

S.No	Formula code	$t_{80\%}$	Zero order		First order		Higuchi's	Korsmeyer-Peppas	
			K_0	R	K_1	r	r	n	R
1	F_1	19.8	3.0111	0.92517	-0.0328	-0.9867	0.9833	0.6153	0.9627
2	F_2	22.05	3.0114	0.9413	-0.0307	-0.9899	0.9888	0.6593	0.9656
3	F_3	21.23	2.9960	0.9413	-0.3054	-0.9944	0.9910	0.6193	0.9726
4	F_4	23.27	2.9550	0.9521	-0.0275	-0.9909	0.9913	0.6692	0.9751
5	F_5	20.86	2.9422	0.9491	-0.0285	-0.9913	0.9910	0.6408	0.9698
6	F_6	22.82	2.9382	0.9520	-0.0267	-0.9927	0.9933	0.6576	0.9828
7	F_7	21.75	2.8704	0.9474	-0.0280	-0.9913	0.9919	0.5972	0.9714
8	F_8	23.88	2.9423	0.9503	-0.0270	-0.9967	0.9969	0.6333	0.9901

Table No.8: *In-vitro* Drug Release Profile of Extra Design Check Point

S.No	Time in hrs	Mean cumulative % drug release ±SD
1	0	0±0
2	1	9.73±0.57
3	2	14.61±0.575
4	3	26.66±1.135
5	4	31.16±1.228
6	5	33.45±1.135
7	6	35.46±1.14
8	7	39.71±1.14
9	8	44.25±1.14
10	9	47.96±1.14
11	10	50.83±1.145
12	11	53.15±1.145
13	12	55.20±1.145
14	13	56.97±1.145
15	14	61.55±1.15
16	15	63.33±1.145
17	16	64.84±1.15
18	17	66.07±1.155
19	18	67.86±1.155
20	19	69.66±1.155
21	20	72.02±1.155
22	21	73.83±1.155
23	22	76.20±1.155
24	23	78.58±1.16
25	24	80.4±1.16

Table No.9: *In- Vitro* Release Kinetic Data for Extra Design Check Point

S.No	Formula code	$t_{80\%}$	Zero order		First order		Higuchi's	Korsmeyer-Peppas	
			K_0	r	K_1	r	r	n	r
1	F_{9-1}	23.12	2.7948	0.94017	-0.02741	-0.9897	0.9833	0.5833	0.9741
2	F_{9-2}	22.98	2.8082	0.9393	-0.0271	-0.9900	0.9888	0.5839	0.9736
3	F_{9-3}	23.20	2.8120	0.9353	-0.274	-0.9888	0.9910	0.5756	0.9746

Pre-formulation studies

FT-IR Spectroscopy

The FT-IR spectrum of the pure drug was found to be similar to the standard spectrum of Glimepiride. The spectra of the drug and polymers were shown in the figures respectively.

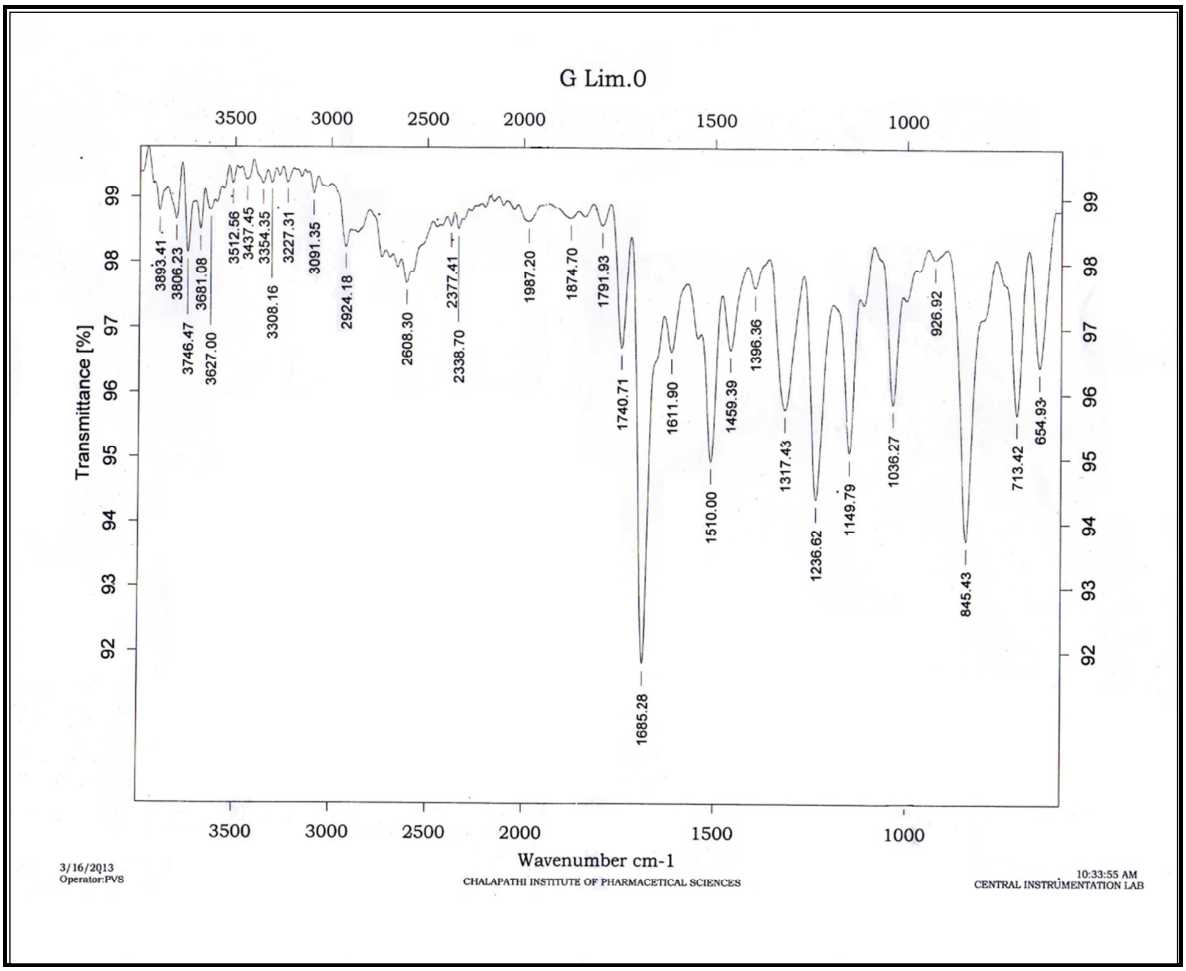

Figure No.1: FT-IR spectrum of pure Glimepiride

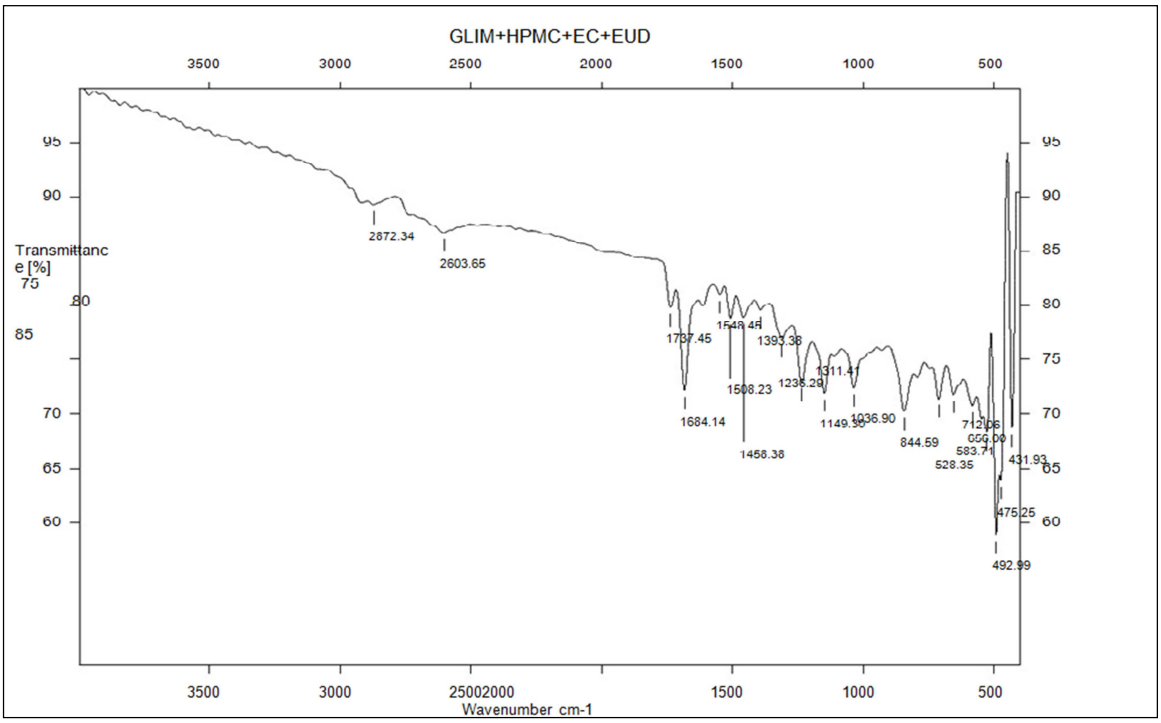

Figure No.2: FT-IR spectrum of Glimepiride+Ethyl Cellulose + HPMC K15M + Eudragit L100

Differential scanning colorimeter (DSC)

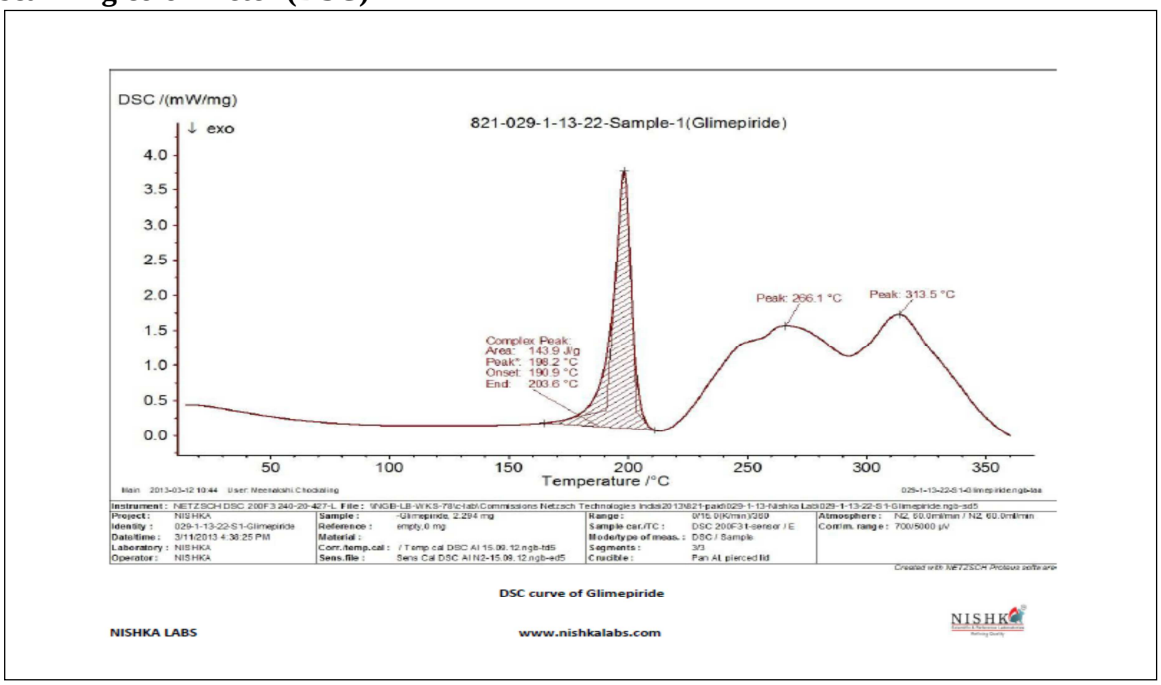

Figure No.3: DSC Spectra for pure drug of Glimepiride

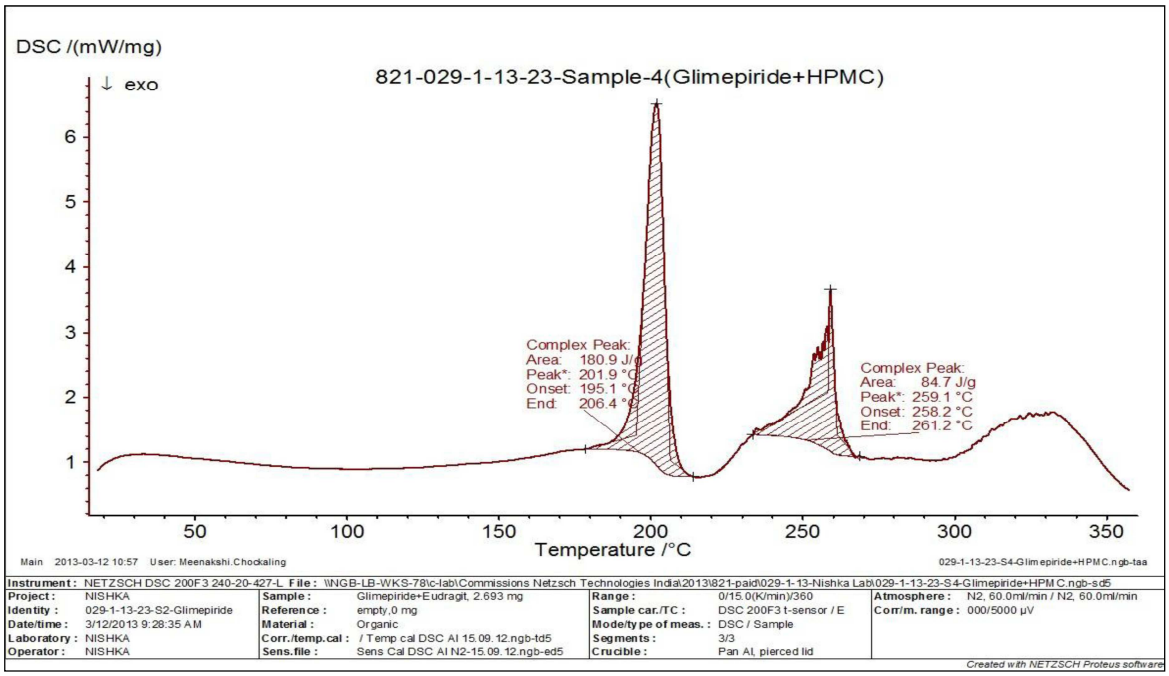

Figure No.4: DSC Spectra for pure drug of Glimepiride +HPMCK15M, + Ethyl cellulose +EUDR L 100

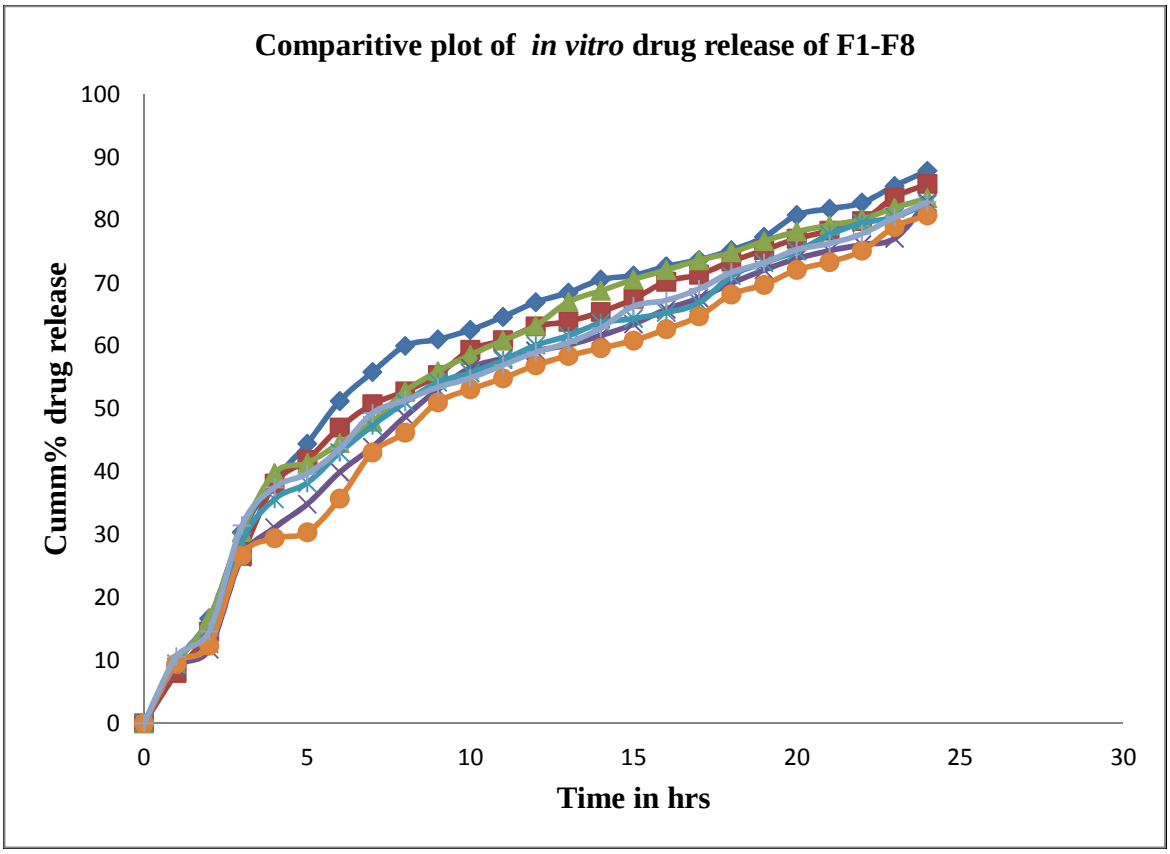

Figure No.6: *In-Vitro* Drug Release Profile of F1-F8

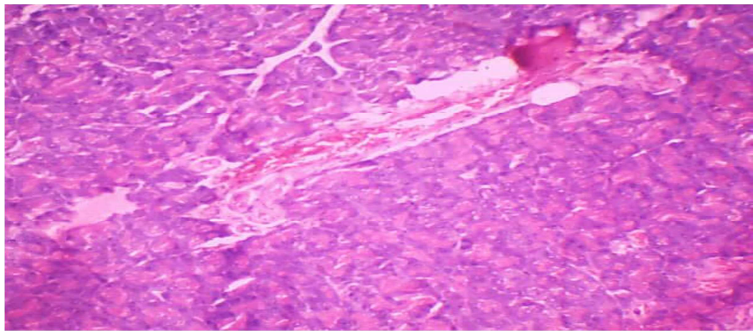

Figure No.7: Group-1

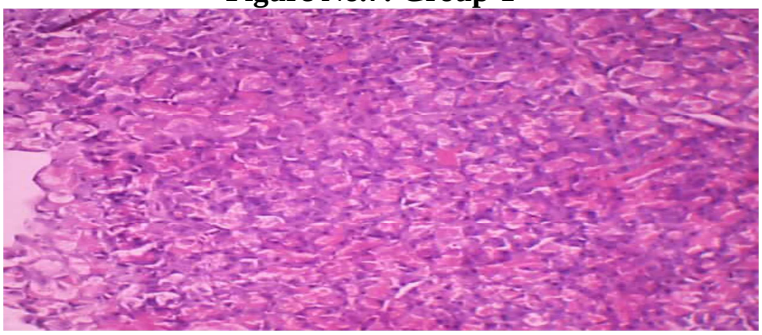

Figure No.8: Group 2

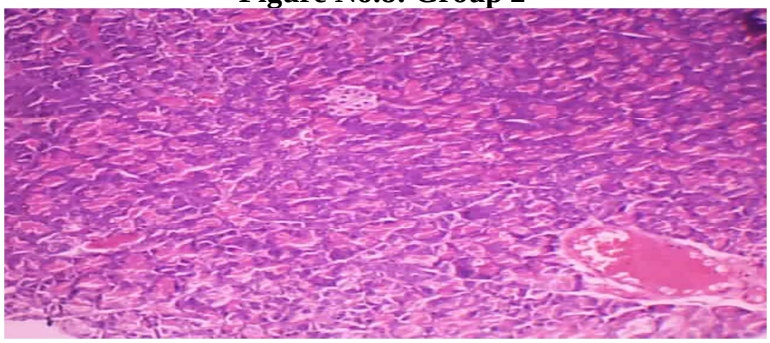

Figure No.9: Group 3

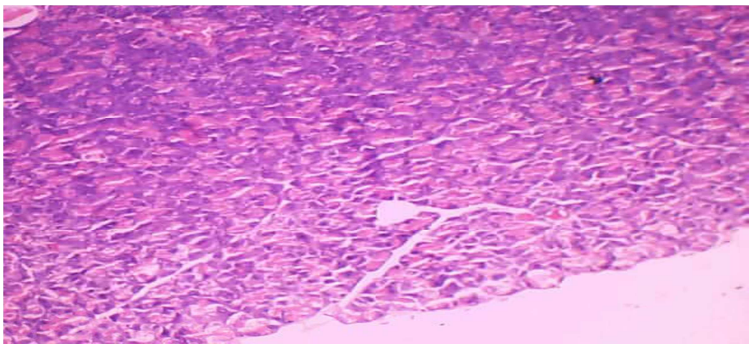

Figure No.10: Group 4

F9 was subjected for in vivo studies (anti-diabetic activity) using alloxan induced diabetic in Rats model. From the above results, The F9 (EC-137.5mg, EudragitL100-112.5mg, HPMCK15M-125mg) shown very significant reduction of blood glucose level (at 168hrs, 99±2.79), when compared to control (at 168hrs, 373.83±4.20) and Marketed product Glimepiride SR (at 168hrs, 105.5±1.77).

CONCLUSION

The present research work shows the applicability of hydrophilic polymers such as HPMC K15M, Ethyl cellulose and Eudragit L100 in the design and development of sustained release tablet formulations of Glimepiride utilizing the 2^3 factorial designs. From the results it was clearly understand that as the polymer concentration increases the release rate of drug was retarded and both of these polymers can be used in combination since do not interact with the drug which may be more helpful in achieving the desired sustained release of the drug for longer periods. The optimized formulations followed Higuchi's kinetics while the drug release mechanism was found to be Non Fickian, anomalous type, controlled by diffusion through the swollen matrix. On the basis of evaluation parameters, the optimized formulation F9 may be used once a day administration in the management of diabetic.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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