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DESIGN AND OPTIMIZATION OF GLIMEPIRIDE SUSTAINED RELEASE MATRIX TABLETS

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ABSTRACT

The present work made an attempt to formulate sustained release behavior of glimepiride tablet and also to optimize the polymer level, in order to reduce the dose frequency and to improve patient compliance. The tablets were prepared by Wet granulation using various grade of rate controlling polymers in combination with hydrophilic and hydrophobic polymers HPMC (K15M) and Eudragit (L100) and carbopol (974p). The drug polymer interaction was investigated by FTIR and DSC and their results directed further course of formulation. Prepared formulations were evaluated for various parameters like weight variation, hardness, friability, % drug content and swelling index. Tablets were subjected to *in vitro* drug release studies. The kinetics of the dissolution process was determined by analyzing the dissolution data using various kinetic equations, e.g. Zero-order, First-order, Higuchi and Korsmeyer equations**.** The prepared optimized formulations showed high regression value for Zero-order release kinetics. From these result F_5 has achieved the prolonged drug release, patient compliance, and cost effectiveness. Kinetic treatment to the in vitro release data revealed that the drug release followed Zero order non - fickian diffusion, It means the release of drug from tablet dissolution and diffusion both mechanisms are used.

Key Words:- Glimepiride, HPMC (K15M), Eudragit (L100), Carbopol (974p), *In vitro* release, Kinetic treatment.

INTRODUCTION

The oral route is considered as the most promising route of drug delivery. Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Most of the oral dosage forms possess several physiological limitations such as variable gastrointestinal transit, because of variable gastric emptying leading to non-uniform absorption profiles, incomplete drug release and shorter residence time of the dosage form in the stomach. This leads to incomplete absorption of drugs having absorption window especially in the upper part of the small intestine, as once the drug passes down the absorption site, the remaining quantity goes unabsorbed (Gilbert S Banker *et al*., 1987; Abraham M A *et al*., 1997). The gastric emptying of dosage forms in humans is affected by several factors because of which wide inter- and intra-subject variations are observed. Since many drugs are well absorbed in the upper part of the gastrointestinal tract, such high variability may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site (i.e. upper part of the small intestine).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

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metabolism which necessitates multiple daily dosing hence the present study was aimed to develop a sustain release matrix tablet of glimepiride. Sustain release matrix tablet of Glimepiride is generally given in divided doses two times a day. The usual starting dose is 210 mg trice daily.

MATERIALS AND METHODS

Materials

Glimepiride was obtained as a gift sample from Zydus pharmaceuticals, Gujarat. HPMC (K15M), carbopol 974, were obtained from Shasun ltd, Eudragit L 100 Were obtained from Zydus pharmaceuticals, Gujarat. All the ingredients used were of analytical grade.

Methods

Preparation of Sustained release tablets by wet granulation method

Nine different tablet formulations were prepared by dry granulation technique as reported. The composition of 2.5 mg Glimepiride of the drug, polymer(HPMC K15M) Carbopol 974 and Eudragit L100 and filler talc was dry mixed thoroughly and sufficient volume of granulating agent (5%w/v ethonolic solution of PVP-K90). Ethanolic solution of PVP was added slowly. After enough cohesiveness was obtained, the mass was sieved through 20 meshes. The granules were dried at 55ºc for 1 hour. These granule mixtures was blended with magnesium stearate (1.6%w/w) as lubricant, the appropriate and then compressed using a 27 station tablet compression machine round, flat-faced punches of 10-mm diameter and die set. All compressed tablets were stored in air tight container at room temperature for the study.

EVALUATION PARAMETERS

Pre-formulation Studies

Fourier Transform Infrared Spectroscopy (Snehal Khedkar *et al*., 2008; Arunachalam A *et al*., 2012)

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}.

Pre-compression studies of glimepiride sustained release matrix tablets

Bulk density

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weight powder (passed through standard sieve #20) into a measuring cylinder and initial weight was noted. This initial volume is called the bulk volume. It is expressed in g/ml and is given by

$$D_b = M / Vb$$

Where,
M is the mass of powder
Vb is the bulk volume of the powder.

Tapped Density (Alfred Martin *et al*., 1996)

It is the ratio of the total mass powder to the tapped volume of the powder. It was determined by placing a graduated cylinder, containing a known mass of drug-excipients blend. The cylinder was allowed to fall under its own weight onto a hard surface from the height of 10cm at 2 second intervals. The tapping was continued until no further change in volume was noted.

$$D_t = M / Vt$$

Where,
M is the mass of powder
Vt is the tapped volume of the powder.

Angle of Repose

It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. The angle of repose was determined by the funnel method suggested by Newman. Angle of repose is determined by the following formula

$$\text{Tan } \theta = h/r$$

Therefore $\theta = \text{Tan}^{-1} h/r$

Where,
θ = Angle of repose
h = height of the cone
r = Radius of the cone base.

Compressibility Index

The compressibility index has been proposed as an indirect measure of bulk density, size, shape, surface area, moisture content and cohesiveness of materials because all of these can influence the observed compressibility index.

$$\text{Carr's compressibility index (\%)} = [(D_t - D_b) \times 100] / D_t$$

Where,
D_t is the tapped density
D_b is the bulk density

Hauser's ratio

Hausner's ratio is an indirect index of the ease of powder flow. It is calculated by the following formula.

$$\text{Hausners ratio} = D_t / D_b$$

Where, Dt is the tapped density,
Db is the bulk density.

Post compression studies of glimepiride sustained release matrix tablets

Weight variation test

The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets from each formulation was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

Measurement of tablet hardness

The hardness of tablet is an indication of its strength. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation was determined by Monsanto hardness tester.

Friability test

It is measured of mechanical strength of tablets. Roche Friabilator is used to determine the friability by following procedure. Twenty tablets were weighed and placed in Roche Friabilator where the tablets were exposed to rolling and repeated shocks resulting from free falls within the apparatus. After 100 revolutions, tablets are removed, dedusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

% Friability = (loss in weight / Initial weight) X 100

Content uniformity

From each batch of prepared tablets, ten tablets were collected randomly and powdered. A quantity of powder equivalent to weight of one tablet was transferred in to a 100 ml volumetric flask, to this 50 ml pH 7.8 buffer was added and then the solution was subjected to sonication for about 2 hrs. The solution was made up to the mark with pH 7.8 buffer. The solution was filtered and suitable dilutions were prepared with pH 7.8 buffer. Same concentration of the standard solution was also prepared. The drug content was estimated by recording the absorbance at 226 nm by using UV-Visible spectrophotometer.

***In vitro* dissolution** (Bhalala chirag *et al*., 2012)

The release of Glimepiride from the SR tablet was studied up to 2 hours in 900ml of 0.1N HCl and 900ml phosphate buffer up to 24 hours 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 24hrs and the value was taken. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

Data Analysis (Curve Fitting Analysis)

To analyze the mechanism of the drug release rate kinetics of the dosage form, the

Data obtained were plotted as:

1) Cumulative percentage drug released Vs time (Zero order plots)
2) Cumulative percentage drug released Vs Square root of time (Higuchi‘s plots)
3) Log cumulative percentage drug remaining Vs time (First order plots)
4) Log percentage drug released Vs log time (Peppas plots)

RESULTS AND DISCUSSION

Glimepiride is an anti-diabetic drug and is presently considered as an important drug for the treatment of type-2 diabetic mellitus. However, the main limitation to therapeutic effectiveness of Glimepiride is its dose dependent biological half-life. Conventional formulation of Glimepiride is administered multiple times a day 210mg trice a day because of its moderate half- life (t½=2.5hrs). After oral administration, Glimepiride is rapidly absorbed, maximum plasma concentrations are attained within an hour of administration.

Glimepiride, with all evident advantages proved to be suitable candidates for development of a sustained release dosage form. In the present study, developing an oral sustained –release dosage form of Glimepiride as an anti-diabetic drug with using HPMCk15M, which are commonly used in hydrophilic matrix drug delivery systems. However, the use of hydrophilic matrix alone for extending drug release for highly water soluble drug is restricted due to rapid diffusion of the dissolved drug through the hydrophilic gel network. For such drug it becomes additional to include hydrophobic polymers in the matrix system. Hence in the present work, an attempt has been made to formulate the sustained release matrix tablets of Glimepiride using different polymers such as HPMC K15M, Carbapol 974, Eudragit L100.

Characterization of bulk drug and effect of various formulation excipients:

FT-IR spectra of pure Glimepiride and its physical mixtures (1:1 ratio w/w) with polymers used in

this study. The characteristic peak are present in entire spectrum indicates the stable structure of Glimepiride in solid admixture.

Differential scanning colorimeter (DSC)

Differential scanning calorimeter is used to measure the specific heat and enthalpies of transition. When a sample undergoes a thermal transition, the power to the heater is adjusted to maintain the temperature, and a signed proportional to the power difference is plotted on the second axis of the recorder is known as thermogram. The area under the resulting curve is direct measure of the heat of transition. Thermograms were obtained by using a differential scanning colorimeter at a heating rate 10ºC /min over a temperature range of 30to 300°C. The sample was hermetically sealed in an aluminium crucible. Nitrogen gas was purged at the rate of 40 ml/min. For maintaining inert atmospheres.

Physical properties of granules

The granules for the tablet preparation were prepared according to formula given in (Table No-1). The granules of different formulations were evaluated for angle of repose, LBD, TBD, compressibility index, Hauser's factor and drug content (Table No-2). The results of angle of repose from19.29^{o} to 28.25^{o} indicating good flow properties of granules.

This was further supported by lower compressibility index values (TableNo-2).Generally, compressibility index values from 12 to16 result in fair flow properties. The Hauser's ratio of granules of all formulations was<1.2 indicating free flowing. The drug content in the weighed amount of granules of all formulations was found to be uniform. Other parameter, such as bulk density, tapped density was found to be within acceptable limits (Table No-2). All these results indicate that the granules possessed satisfactory flow properties, compressibility and drug content. Finally both polymer level and polymer type did not affect the physical properties of the prepared granules.

Physical properties of tablets

The tablets of different formulations were subjected to various evaluations tests such as hardness, friability and uniformity of weight, 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 results of dissolution studies indicates that F_1, F_2, F_3 released 94%, 94.98%, 96.42% of Glimepiride at the end of 8, 22, 24 hours. HPMC K15M of F_1 formulation extended up to 8 hours, with maximum release of 94%. By increasing the viscosity of HPMC K15M of F_2 formulation goes on increases the duration up to 24hours with maximum release of 94.9%. However By increasing the further amount of HPMC (K15M) release the drug up to 24 hours with maximum of 96.42%, due to high proportion of high viscosity of Hydrophilic polymers, the time duration sustained up to 24 hours but drug release from polymer decline due to high diffusion path length compared to F_2.

In formulation F_4, F_5, F_6 formulated with CARBOPOL 974 Shows following drug release 91.75%,98.91%,88.8% of Glimepiride at end of 10,24,24 hours. This results several that , formulation F_4 Could not able to sustained up to 24hours, desiarably by due to less consistence of gelatinous layer, also the gel formed presents very low level, so the drug dissolve rapidly, so they cannot prolong the drug release. By further increase of polymer level in F_5, F6, able to sustained for 24hours.but compared to HPMC K15M (F_1, F2, F3) the polymer concentration is low in (F_4, F5, F6) and the drug release also achieved prolong this is due to greater elasticity of CARBOPOL- 974 that depend on presence of a greater number of cross-links This make interesting system, to prolong the drug residence time.

Table 1. Composition of 210mg Glimepiride tablets

S.No	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Glimepiride	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
2.	HPMC k15M	50	150	200	-	-	-	-	-	-
3.	Carbopol 974	-	-	-	10.5	14.7	18.9	-	-	-
4.	Eudragit L100	-	-	-	-	-	-	75	100	125
5.	Talc	152.5	52.5	2.5	192	187.8	183.6	127.5	102.5	77.5
6.	Magnesium Sterate	5	5	5	5	5	5	5	5	5

Table 2. Results of flow properties of Glimepiride sustained tablets (F1 to F9)

S.No	Formulation code	Angle of repose(θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Compressibility index (I)	Hausner's ratio
1	F1	23.80	0.41	0.47	12.0	1.14
2	F2	23.55	0.29	0.34	14.7	1.17
3	F3	19.29	0.36	0.41	12.1	1.13
4	F4	21.54	0.50	0.58	13.7	1.16
5	F5	28.25	0.45	0.54	16	1.2
6	F6	21.32	0.48	0.56	14.2	1.16
7	F7	19.31	0.47	0.55	15	1.15
8	F8	20.30	0.60	0.69	13.9	1.19
9	F9	21.23	0.55	0.51	13.4	1.20

Table 3. Hardness, Friability, and Weight variation of Glimepiride sustained tablets (F1 to F9)

S.No	Formulation code	Weight Variation (mg)	Hardness (kg/cm^3)	Friability %	Drug content uniformity %
1	F1	209.5	5.05	0.010	98.54
2	F2	210	4.81	0.014	99.08
3	F3	208.0	4.80	0.122	98.21
4	F4	209.0	4.85	0.132	98.72
5	F5	209.0	4.68	0.116	98.56
6	F6	210.0	5.13	0.110	98.38
7	F7	210.0	5.06	0.124	98.57
8	F8	209.2	5.02	0.99	98.78
9	F9	208.6	5.04	0.13	98.0

Table 4. *In vitro* release study of Glimepiride sustained tablets (F1 to F9)

Time (HRS)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	29.67	15.87	11.42	26.17	16.48	14.47	12.48	10.48	8.48
2	34.90	23.90	15.69	34.87	27.37	25.69	18.67	16.67	13.67
4	52.68	27.2	19.36	78.36	40.25	38.62	26.04	23.04	20.04
6	78.45	34.19	27.35	84.40	49.5	44.80	32.0	29.0	27.0
8	94	39.34	30.39	88.53	53.69	49.94	35.76	34.76	31.76
10	-	48.80	37.4	91.75	60.16	53.90	39.5	39.5	35.5
14	-	59.28	42.82	-	65.96	60.47	46.3	46.3	40.3
16	-	67.15	54.29	-	75.96	69.57	53.46	53.46	44.46
18	-	79.99	62.39	-	86.49	71.30	68.0	68.0	53.0
20	-	85.74	72.59	-	91.91	77.93	79.15	79.15	66.15
22	-	94.98	89.99	-	94.9	82.16	87.55	87.55	78.55
24	-	-	96.42	-	98.91	88.88	95.21	93.21	87.21

Table 5. Kinetic models of optimized batch (F5)

Release Kinetics	Correlation Coefficient(R^2)
Zero order equation	0.9765
First order equation	0.875
Higuchi(diffusion)co-efficient	0.9405
Korsmeyer Peppas equation	0.990

Fig 1. FT-IR spectrum of pure Glimepiride

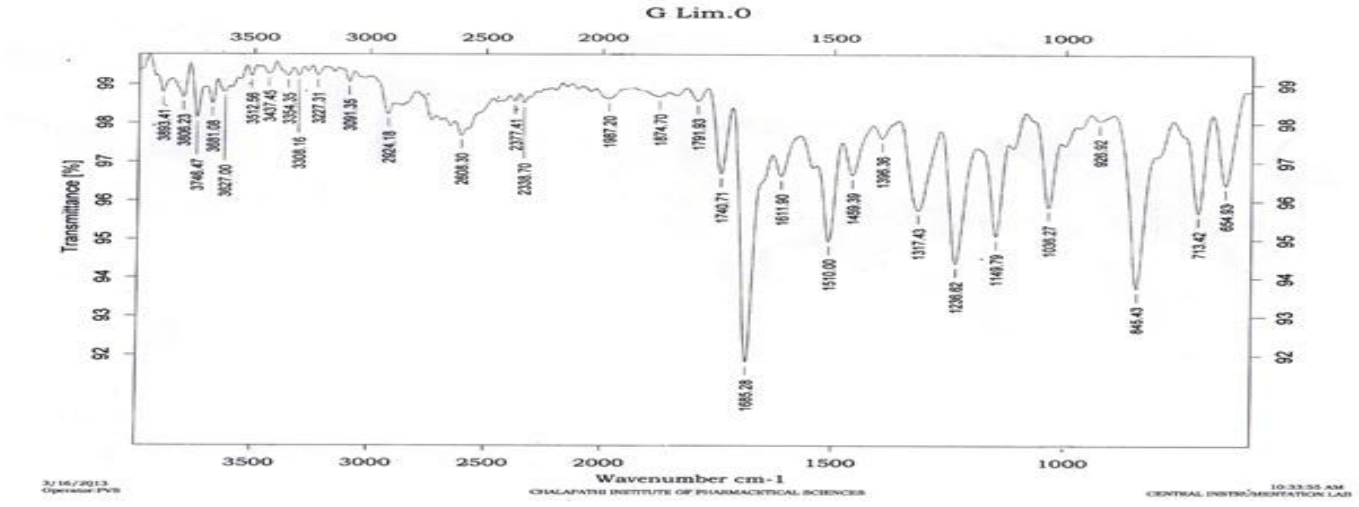


Fig 2. FT-IR spectrum of pure Glimepiride+HPMCK15M+EUDRAGIT L 100

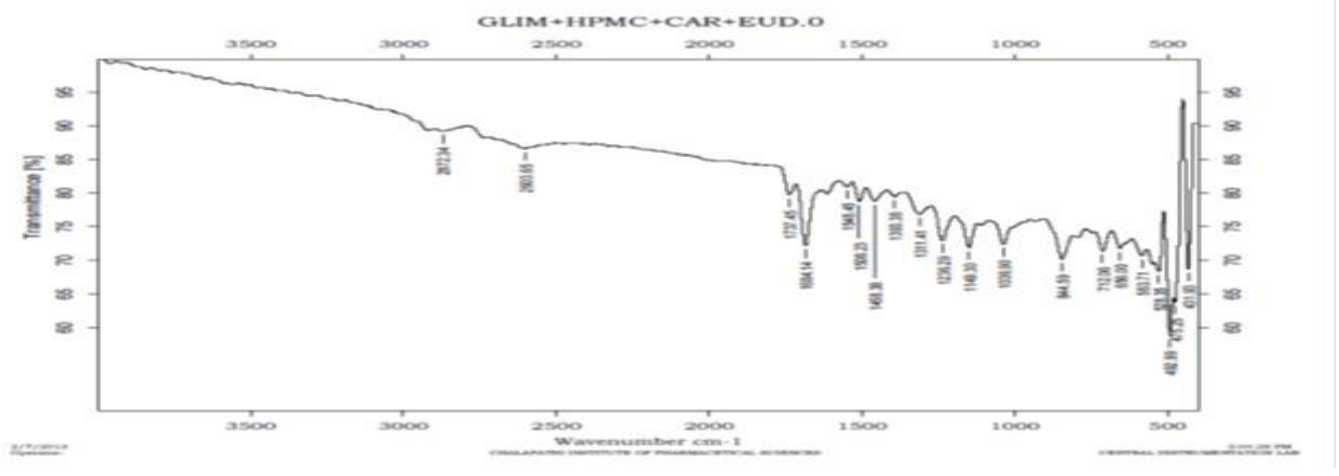


Fig 3. DSC curve of pure Glimepiride

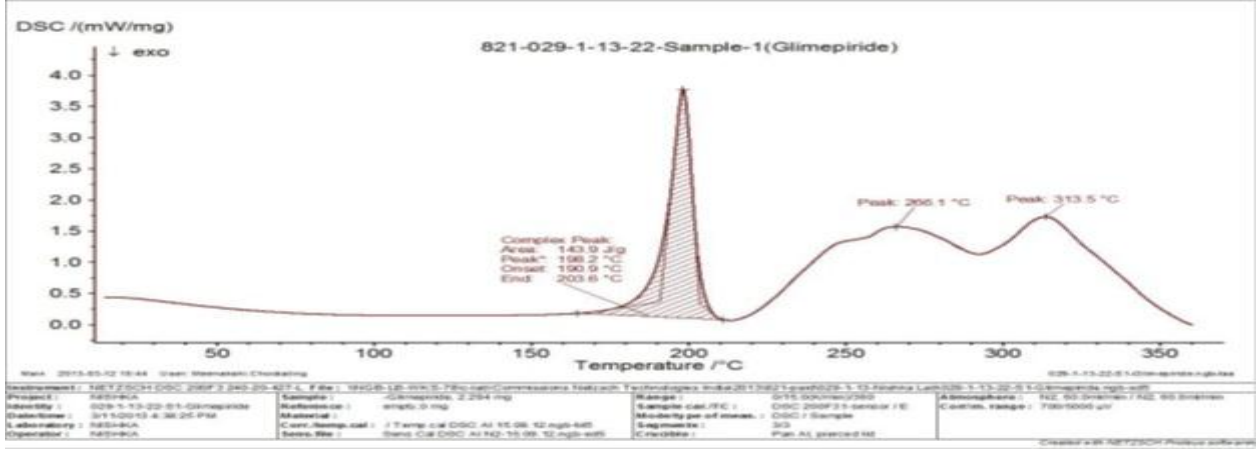


Fig 4. DSC curve of pure Glimepiride+Carbopol

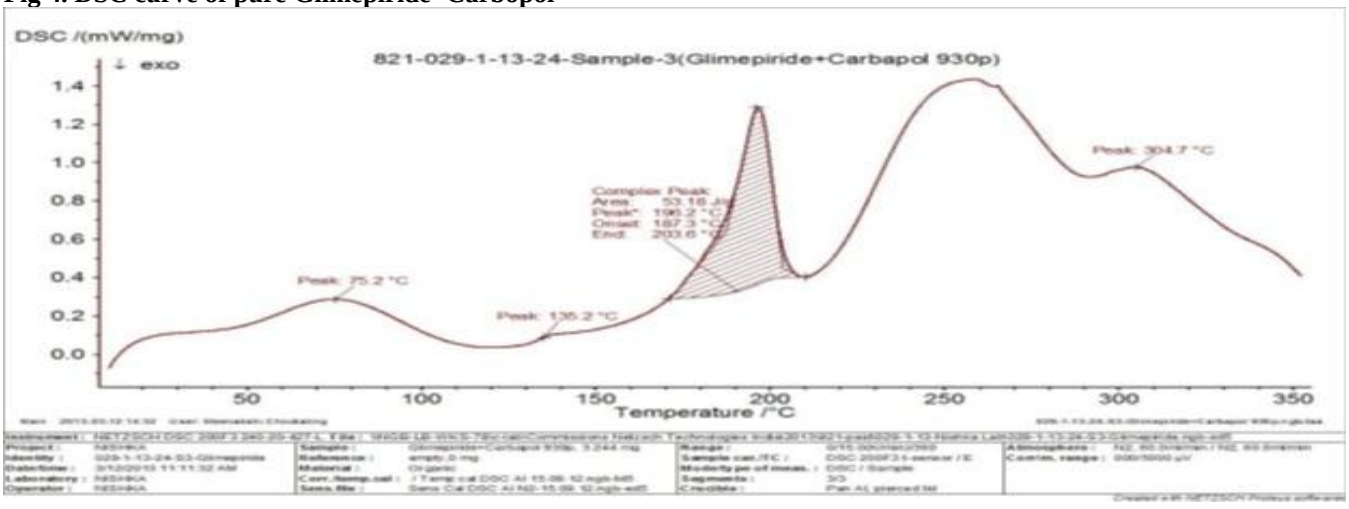


Fig 5. DSC curve of pure Glimepiride+Eudragit L100

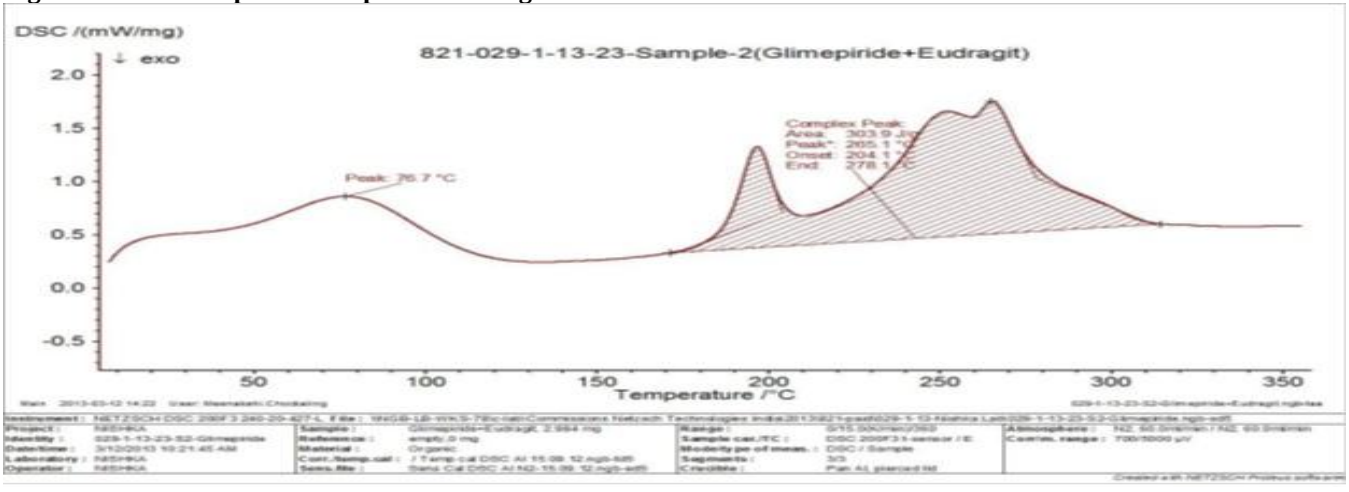


Fig 6. DSC curve of pure Glimepiride+HPMC K15M

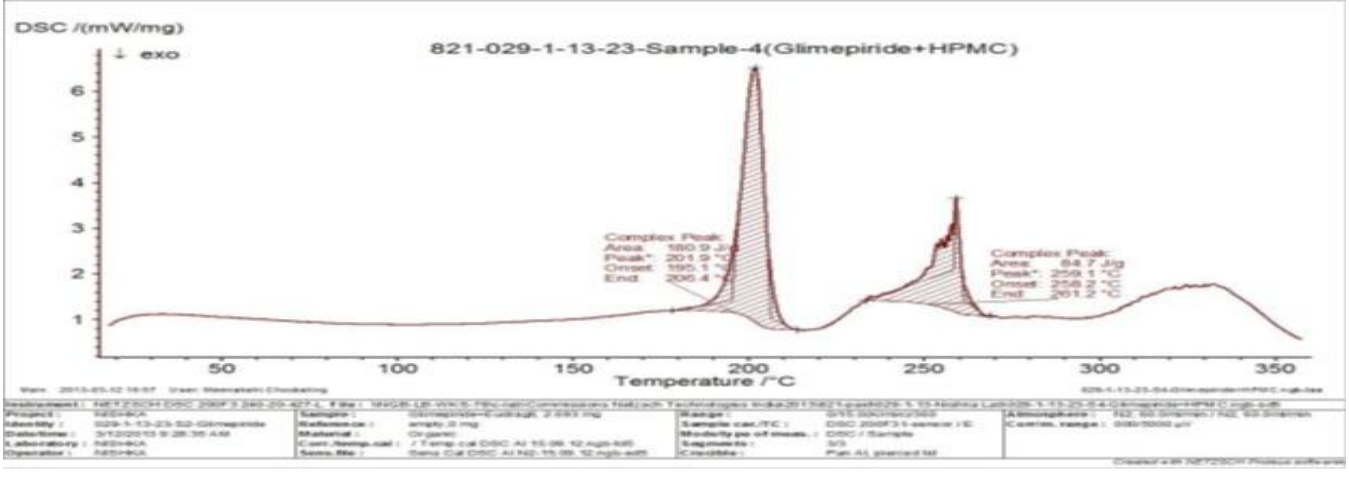


Fig 7. *In-Vitro* Drug Release Profile of F1-F5

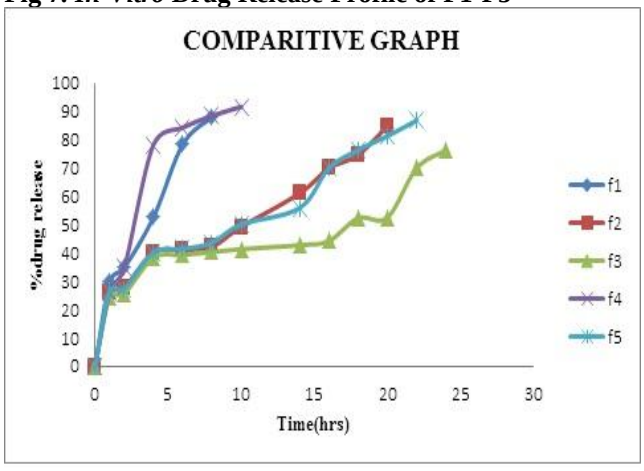
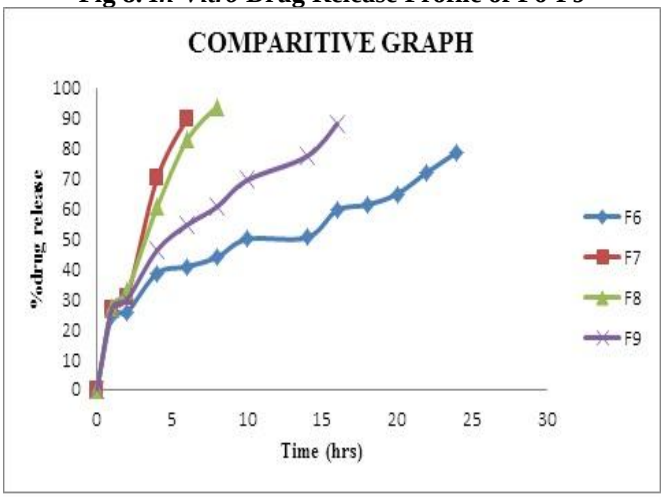


Fig 8. *In-Vitro* Drug Release Profile of F6-F9



CONCLUSION

Success of the *In vitro* drug release studies recommends the product for further *In vivo* studies, this may improve patient compliance**.** Therefore, from above cited results the formulation F_5 formulated with (7% of carbopol 974) shows better drug release with extending for 24hours. The data obtained from in vitro release study were fitted to various mathematical model like zero order, First order, Higuchi model and Peppas model. The results of mathematical model fitting of data obtained indicated that, the best fit model in all the cases the release was found to be by diffusion for optimized formulation (F5). Thus the release of the drug from the dosage form was found to be diffusion and non fickian release.

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