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Research Article

Formulation And Evaluation Of Sustained Release Matrix Tablets Of Glimepiride

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ABSTRACT

The objective of the study was to formulate sustain release matrix tablets of Glimepiride by wet granulation technique based on the combination of two natural polymer Acacia and Guar gum respectively and one synthetic polymer Carbapol 934. Total nine formulations were formulated using variable concentration of polymer. Glimepiride is an oral hypo-glycaemic agent commonly used for the treatment of type II Diabetes Mellitus. Normal dose range of Glimepiride is 1 to 4 mg. In this study, Formulated Glimepiride sustained release matrix tablets were evaluated for Pre-formulation studies, Weight variation, Hardness, Friability, Swelling index, In-vitro dissolution study and In-vivo study (animal study). The obtained result from the study shown that Glimepiride sustained release matix tablets containing Carbapol 934 in F6 formulation fulfills all the requirements needed for the sustained release matrix tablet.

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INTRODUCTION

The oral route of administration of drug is considered to be most widely accepted route because of its easiness, compactness and convenience of self administration. Nearly 90% of all drugs were used for producing better systemic effect are administered orally (1).

For the sustained release system, from the oral route of drug administration attracts numerous attention for its convenient and safer route. Matrix tablets as sustained release gives advance step in novel drug delivery system (NDDS). Controlled drug release rate is obtained mainly due to the type and ratio of polymer used in the preparation. There are mainly two types polymers which are used in the formulation of sustained release hydrophilic polymer and hydrophobic polymer (2). Highly water soluble drugs can release rapidly and can cause toxicity. Matrix tablets are used for better approach and to sustain the drug release rate for longer period of time at expected rate after administration of its single dose (3).

Glimepiride is third generation sulfonylurea hypo-glycaemic agent generally used for the treatment of type II diabetes (1). According to BCS, Glimepiride is highly permeable class 2 drug. The oral absorption of glimepiride is uniform, rapid and shows nearly100% bioavailability (4).

Diabetes mellitus is a disease which is mainly caused by high blood sugar level either less production of insulin in the body or body does not response properly to insulin. Insulin is produced by pancreas which helps the body cells to absorb the glucose and turn into energy. Less or no absorption of glucose can accumulate in blood and can cause the complication to the vascular, nerve or many other damages to the body part (5). According to the WHO, nearly 422 million people of the world are suffering from the diabetes and it cause 1.6 million deaths every year. And there is a slight increase in the case of diabetes over the last few decades. According to survey done by the WHO in 2016 reveals that 7.8% of India's population is suffering from diabetes. And diabetes is one of the leading causes of the death. Diabetes also causes the dysfunction and failure of various organ or both.

Diabetes mellitus is classified into four parts: Type I, Type II, Gestational diabetes and other types of diabetes. Glimepiride is used with diet to treat type II diabetes lowers the blood glucose level by increasing the insulin secretion from the pancreas. Mechanism of action of Glimepiride depends on stimulation to release insulin functioning pancreatic β-cells and increase in the sensitivity of peripheral tissue to insulin and lowers the blood glucose level (6). The aim of this study is to develop Glimepiride sustained release matrix tablets using Acacia, Guar gum and Carbapol 934 as polymer at different concentration and to study the effect of *in-vitro* dissolution and *in-vivo* response.

Material and methods:

Materials:

Glimepiride was obtained as a gift sample from Globela Pharma Private Limited Surat, Acacia from High Purity Laboratory Chemicals Pvt. Ltd. Mumbai, Guar gum from Central Drug House Pvt. Ltd. New Delhi, Carbapol 934 from Pallav Chemicals & Solvent Pvt. Ltd., Mumbai, Calcium carbonate from Thomas Baker (Chemicals) Pvt. Ltd., Mumbai, Lactose from Merck Limited India, Mumbai, Magnesium stearate from Central Drug House Pvt. Ltd. New Delhi, Kaolin from Thomas Baker (Chemicals) Pvt. Ltd., Mumbai and Streptozotocin from Central Drug House, New Delhi.

Methods:

Pre-formulation studies:

Pre-formulation studies are one of the important aspects in the development of any drug delivery system. These were performed on the prepared granules of the drug, which include density, compatibility studies. Pre-formulation studies play an important aspect in investigation of various physio-chemical properties of drug molecule to develop safe, effective and stable dosage form (7).

Micromeritic study of pre-compressed powder:

The flow properties of the different batches of the pre-compressed powder were determined for their angle of repose using fixed-base cone method. A glass funnel was positioned at a fixed height (h) above a graph paper placed on the horizontal surface. Then sample was pored through funnel until the powder's conical pile touches to the tip funnel. The height and radius of the heap was measure and angle of repose was calculated by following formula:

Angle of Repose [θ] = tan-1 (h/r)

Where,

h = cone height,

r = radius of the circular base formed by the granules of the ground.

The bulk density and tapped density were measured. The known weighed of formulated granules were transferred to the graduated measuring cylinder, and obtain initial bulk volume was known as bulk density and after tapping the graduated measuring cylinder for 100 tapping. Then, the final value was noted as tapped density. The respective densities of the different batches of granules were calculated by using the following equations;

Carr's index:

Carr's index is widely used in pharmaceutics to determine the flow ability of the powder or granules. If the tapped density and bulk density are closer in value then the granules were free flowing and if the value between tapped density and bulk density over greater the Carr's index is larger. A Carr's index below 15 show good flowability but about 25 show poor flowability.

$$C = V_B - V_T \times 100$$

By using this following equation Carr's index calculated.

Where,

(V_B), is bulk density and

(V_T), is tapped density (8).

Hausner's ratio:

Hausner's ratio was calculated by different between tapped density and bulk density.

Hausner ratio = Tapped density / Bulk density

Carr's index having value greater than 25 is considered to be indication of poor flow ability, and below 15 is considered to be good flow ability (9).

FT- IR Spectrum:

The compatibility of drug and excipients are measured by using fourier transform infrared spectral analysis. Glimepiride and its binary mixture were recorded in the interval 4000-400 cm^{-1} optical resolution. The study was performed by taking 2 mg sample in 200 mg KBr pellet. The spectra were recorded with the use of software, and all spectral interpretations were done (10).

This spectral analysis was employed to observe the compatibility of drugs with excipients used. The FT-IR data showed that Glimepiride and Excipients did not react with each other and retained their action at room temperature (11).

Formulation of Sustained Release Glimepiride Matrix Tablets:

A total number of 9 formulations were formulated by wet granulation technique. Acacia, Guar gum and Carbapol 934 were used as polymer (matrix forming agent). Lactose were used as diluents, kaolin used as an anti adherent, calcium carbonate use as disintegrants and magnesium stearate used as lubricant.

All ingredients except magnesium stearate properly mixed in pistol mortar and then magnesium stearate were added and mixed. Then the granules were knitted with organic solvent and then pass through a 20 number of sieve. After passing with sieve, granules were compressed by using single tablet punching machine (12).

Table 1. Composition of sustained released matrix tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Glimepiride	6	6	6	6	6	6	6	6	6
Acacia	10	20	30	–	–	–	–	–	–
Carbapol 934	–	–	–	10	20	30	–	–	–
Guar gum	–	–	–	–	–	–	10	20	30
Calcium carbonate	55	45	35	55	45	35	55	45	35
Lactose	25	25	25	25	25	25	25	25	25
Magnesium stearate	2	2	2	2	2	2	2	2	2
Kaolin	2	2	2	2	2	2	2	2	2

Characterization of Glimepiride Sustained Release Matrix Tablets:

Visual Examination:-

Visual examination involves study of color appearance, size and shape of the tablet. The physical appearance is evaluated by visual assessment and vernier calipers were for the evaluation of uniformity of thickness (13).

Weight Variation:

All the prepared tablets were weighed and the weight of all the tablets had been added and then received numbers were divided by number of tablet which was weighed. Weight variation of the tablets were calculated for using following formula (14) -

% Weight Variation = Total Weight of all tablets / number of tablets

Hardness Test:

Randomly 5 tablets form each formulation were picked and evaluated by Pfizer hardness tester. It is expressed in Kg/cm^2 (15).

Friability Test:

Friability test was done for the measurement of tablet strength. Roche type friabilator were used. Tablet was accurately weighed and then placed in tumbling apparatus for 4 minute at 25 rpm. It dropped tablet at six inches distance per round. After completion of 4 minutes tablet was weighed again and friability percentage were calculated by following formula-

% Friability = Initial Weight – Final Weight/Initial weight × 100

% Friability of tablets less than 1% is considered acceptable (16).

***In-vitro* Dissolution Study:**

Dissolution studies were performed for all the formulations using USP II paddle method. 900 ml of phosphate buffer at pH 7.8 were used as dissolution medium. Dissolution medium is allowed to be balanced at 37℃ ± 0.5℃.Tablet was placed in vessel and closed with apparatus operated for 24 hours at 50 rpm. At the decided time interval 5 ml of sample were withdrawn and the volume is replaced with fresh dissolution medium. The withdrawn sample were analyzed by UV spectrophotometer at 226 nm and obtain data was treated for the kinetic model (17).

Swelling Studies:

Swelling study is the study of swelling behavior of tablet. Tablets were placed in 900 ml of dissolution medium in dissolution apparatus at 37.5^0C. Tablet were removed at 2 hours of intervals and measured for weight gain and diameter. Swelling index was calculated by following equation (4)-

Swelling Index = Weight of the swollen tablet – Initial Weight of the tablet/Initial Weight ×100

Animal Study:

Experimental Animals:

Male wistar albino rat having weight around 150 to 210 grams received form Chakravarti Animals Pvt. Ltd., Kolkata, West Bengal. For the storage of animal polypropylene cages were used under standard condition. Animal were maintained at 25 ± 2^0C. Diet was maintained with standard pellet and water ad libitum was given to the animal during and before the experiments. Animals were quarantined for

straight 14 days before the experiments. IAEC has approved the protocol for the experiments.

Experimental induction of diabetes:

Streptpzotocin and 0.1M Citrate solution were mixed and a freshly formulated solution were prepared consist of 1 ml/Kg. Streptozotocin 60 mg/Kg of rat were used. Streptpzotocin induced animals were shows massive increase in blood glucose level within 2 days. Streptozotocin was given intraperitoneally. Blood glucose level was checked after 96 hours after injecting stz. The rat having >200 mg/dL blood glucose level were considered as positive diabetes.

Experimental Design and Procedure:

5 groups of the wistar albino rat were used and each group contains at least sic experimental animals.

Group 1: Positive control group which was not treated with any medication.

Group 2: Chemically induced diabetic rat which was treated with standard (marketed) glimepiride drug.

Group 3: Chemically induced diabetic rat which was treated with prepared formulation F3.

Group 4: Chemically induced diabetic rat which was treated with prepared formulation F6.

Group 5: Chemically induced diabetic rat which were treated with prepared formulation F9.

Anti-hyperglycaemic activity:

All wistar albino rats were adopted in cage for 2 days after it they were fasted overnight. Diabetes was induced using intra peritoneal injection having streptozotocin dissolved in normal saline. Rat having more than 200mg/dL fasting blood glucose level considered as diabetic and obly that were usd in the experimental study. Normoglycaemic animal were had 98 mg/Dl blood glucose level. Each group was separated and had six animals in each groups. Drugs were given orally with the help of oral gavage for twenty one days. Blood samples were collected from tail vein on zero, seven, fourteen, and twenty one days. The blood glucose were checked using glucometer (Accu Check). Sample value was compared with standard drug treated with glimepiride (10mg/kg).

RESULT AND DISCUSSION:

Micromeritic study of pre-compressed powder:

Granules of all prepared formulations were evaluated for various pre-formulation studies like angle of repose, bulk density, tapped density, compressibility study (Carr's Index), Hausner's Ratio. All the results were show in the table 2.

The angle of repose was found to be ranging from 21^0 to 25^0 of formulated granules. Compressibility index was ranging from 12 to 14% for the formulated granules. Hausner's ratio shows better flow property because of its value under the range of 1.25. The obtained result of the angle of repose (<25) shows good flow ability of the granules. Compressibility study value upto 15% results shows excellent flow property.

FT-IR Spectrum:

Spectra of the API Glimepiride and formulated granules were obtained between 400 - 4000 cm^{-1} wave number. The FT-IR analysis showed no appearance or disappearance of any characteristic peaks of the API which confirms that there is no presence of chemical interaction between drug and polymer. The contents of the drugs were observed for any changes by their physical characteristic and for their characteristic peaks by FT-IR spectrophotometer. The obtained results were shown in Fig.1, Fig.2, Fig.3, Fig.4.

Charactrization of Glimepiride Sustained Release Matrix Tablets:

Evaluation of Tablets:

The formulated tablets were evaluated for weight variation, hardness, thickness, friability within the range as specified in I.P. The results were shown in table 3.

***In-vitro* Dissolution study:**

The dissolution profile of Glimepiride from the different formulated batches was illustrated in table 4. *In-vitro* dissolution study was performed for all the various nine formulations. The formulation having greater percentage of

polymer shows greater sustained release. From the *in-vitro* dissolution study clears that F6 formulation showing better release than other formulation. The obtained graph was shown in Fig. 5, Fig. 6, Fig. 7, Fig. 8, Fig. 9, Fig. 10, Fig. 11, Fig. 12, Fig. 13, Fig. 14.

Swelling studies:

The swelling behaviors of the all formulated tablets were obtained. The % weight gain by the tablet was used for the estimation of swelling. The % weight gain of the tablets was show in Table 5.

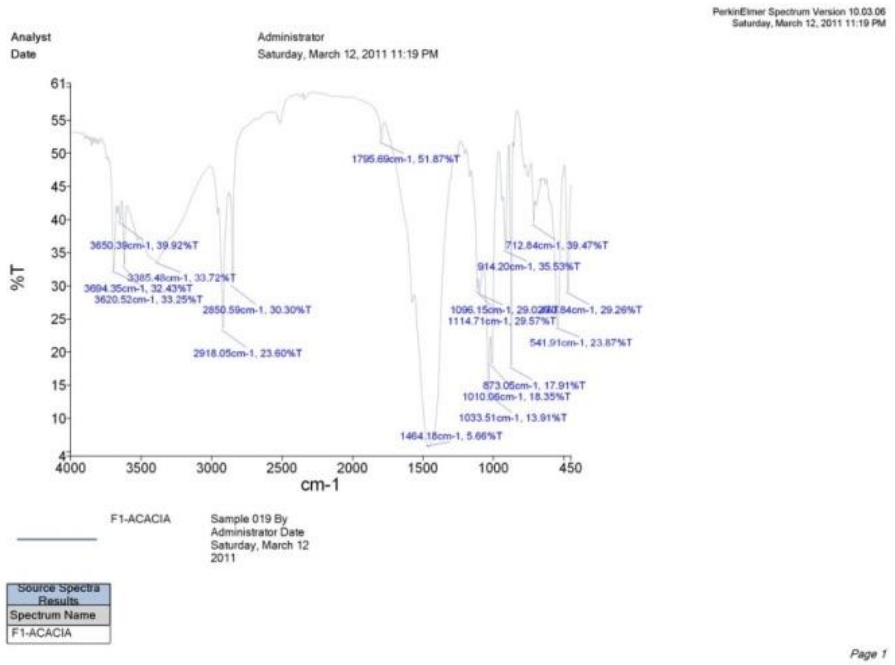
Animal study:

Anti-hyperglycaemic activity:

The formulated tablets having better *in-vitro* release was chosen to be orally administered F3, F6, F9 respectively. The effects of oral administration of the formulations were shown in table 6.

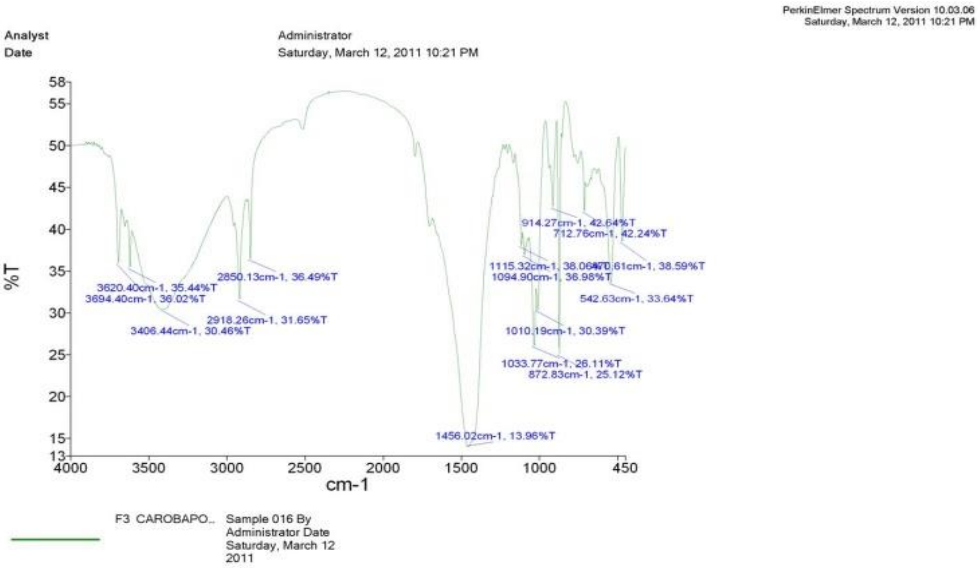
Table 2: Micromeritic study of pre-compressed powder

Formulations	Angle of Repose	Bulk Density	Tapped Density	Carr's Index	Hausner'S Ratio
F1	$22^0 \pm 2$	0.234 ± 0.024	0.278± 0.011	14.36± 0.015	1.14± 0.014
F2	$21^0 \pm 2$	0.028 ± 0.016	0.268± 0.014	14.57± 0.022	1.14± 0.016
F3	$26^0 \pm 3$	0.214 ± 0.016	0.298± 0.018	14.98± 0.021	1.14± 0.014
F4	$24^0 \pm 2$	0.226 ± 0.019	0.255± 0.019	13.44± 0.019	1.15± 0.018
F5	$23^0 \pm 3$	0.211 ± 0.022	0.241± 0.022	13.92± 0.014	1.18± 0.019
F6	$25^0 \pm 2$	0.291 ± 0.017	0.263± 0.021	13.87± 0.016	1.16± 0.021
F7	$23^0 \pm 3$	0.243 ± 0.018	0.287± 0.017	12.65± 0.024	1.13± 0.022
F8	$25^0 \pm 2$	0.283 ± 0.014	0.286± 0.024	12.59± 0.021	1.15± 0.017
F9	$22^0 \pm 2$	0.292 ± 0.019	0.289± 0.016	12.48± 0.017	1.14± 0.015



(Fig. 1: FT-IR of Glimepiride)

(Fig. 2: FT-IR of F3 Formulation)



(Fig. 3: FT-IR of F6 Formulation)

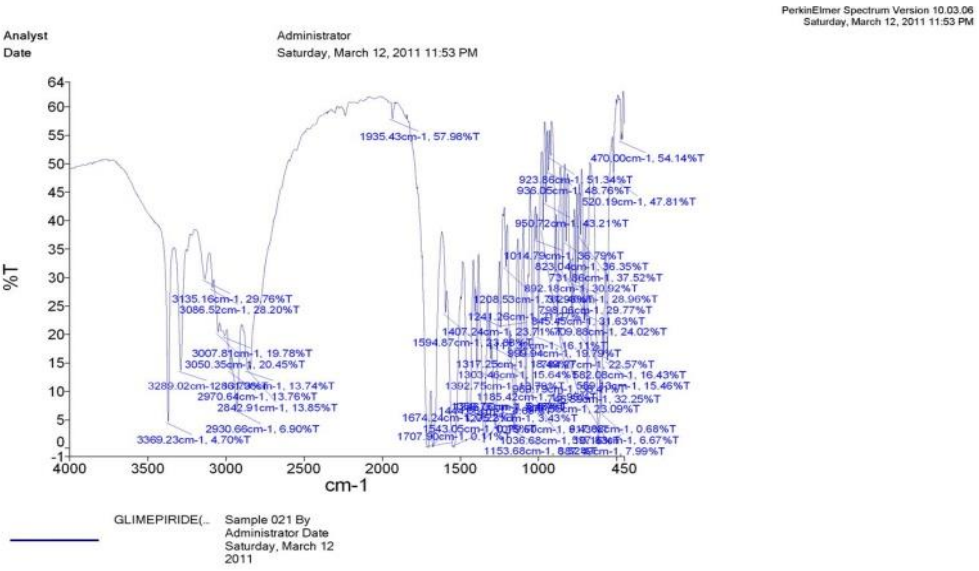


Fig. 4: FT-IR of F9 Formulation

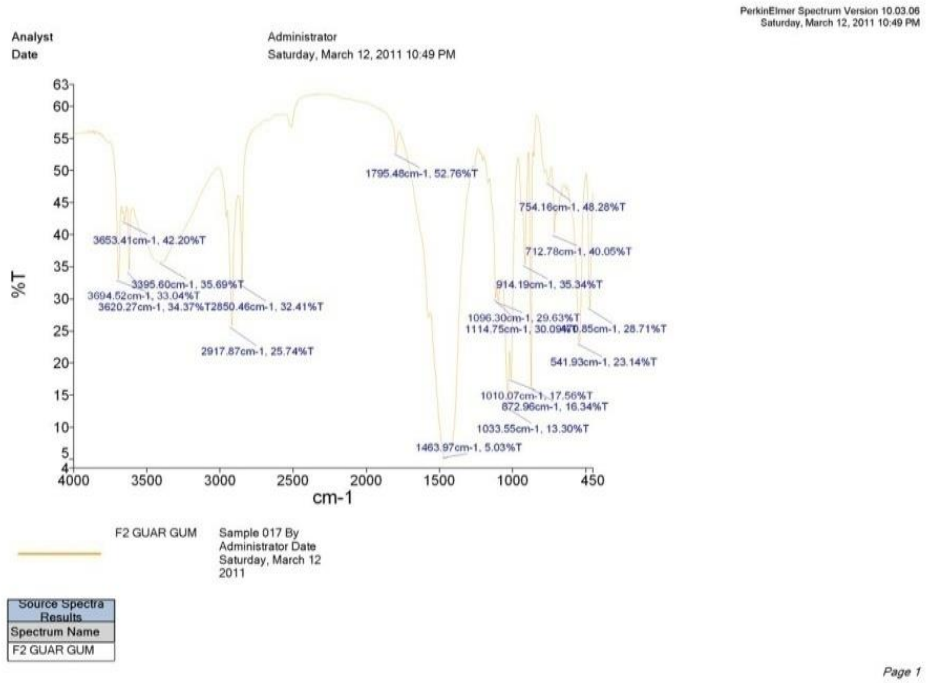


Table 3: Evaluation of Tablets

Formulations	Weight Variation	Hardness	Thickness	Friability
F1	148 ± 3	3	4.66 ± 0.02	0.35 ± 0.02
F2	145 ± 3	4	4.36 ± 0.3	0.38 ± 0.03
F3	147 ± 3	4	4.73 ± 0.2	0.28 ± 0.02
F4	148 ± 3	5	4.27 ± 0.2	0.22 ± 0.03
F5	149 ± 3	6	4.96 ± 0.2	0.28 ± 0.02
F6	150 ± 3	5	4.66 ± 0.0	0.15 ± 0.02
F7	146 ± 3	4	4.06 ± 0.2	0.33 ± 0.02
F8	147 ± 3	3	4.96 ± 0.3	0.35 ± 0.02
F9	149 ± 3	4	4.66 ± 0.3	0.30 ± 0.02

Table 4: In-vitro Dissolution Study

TIME /FORMULATIONS	F1	F2	F3	F4	F5	F6	F7	F8	F9
0:30	37.58	34.61	29.45	39.18	29.85	26.98	39.45	36.45	27.18
1	59.02	49.11	41.36	47.92	44.12	37.66	61.36	51.92	29.93
2	80.39	65.36	49.30	72.24	62.63	45.12	83.41	63.30	51.30
3	86.37	72.01	67.93	87.69	81.54	68.67	91.93	70.93	65.69
4	97.09	84.22	80.99	99.51	89.09	75.67	99.22	86.99	82.51
5		96.91	88.26		98.27	88.32		98.04	90.32
6			99.33			99.36			98.06

(Fig. 5: In-vitro Dissolution of Glimepiride sustained release matrix tablet)

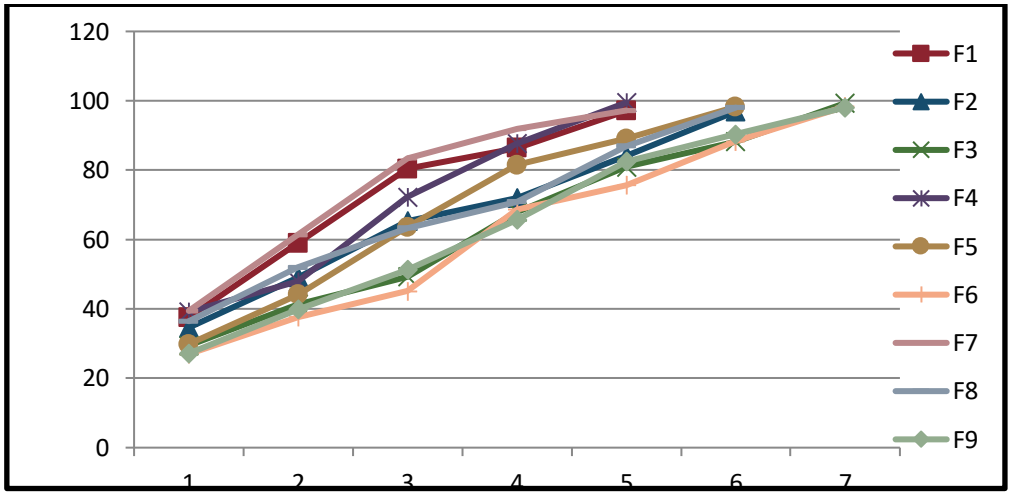


Table 5: Swelling Behavior of Tablets

Times (hours)	Swelling Index								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	30	25	15	40	35	25	50	45	35
4	35	30	20	45	40	30	55	50	40
6	40	35	25	55	45	35	60	55	45
8	45	40	30	60	50	40	65	60	50
10	50	45	35	60	55	45	70	65	50
12	55	45	35	60	60	50	75	70	50

Table 6: Anti-hyperglycemic activity

Treatment (dose)	0 Day (mg/dL)	7 Days (mg/dL)	14 Days (mg/dL)	21 Days (mg/dL)
Diabetic Control	300.66 ± 5	279.33 ± 3	246.33 ± 2	227.83 ± 2
Glimepiride (10mg/kg)	329.50 ± 10	302.66 ± 22	203.66 ± 20	107.66 ± 15
F3 Formulation (10mg/kg)	331.50 ± 25	270.16 ± 22	196.83 ± 24	112.83 ± 30
F6 Formulation (10mg/kg)	328.16 ± 40	293.33 ± 27	198.38 ± 15	114.16 ± 14
F9 Formulation (10mg/kg)	334.16 ± 30	273.50 ± 19	199.83 ± 15	117.88 ± 10

CONCLUSION:

The objective of the study was formulation and evaluation of sustained release matrix tablets using various concentrations of polymer and to perform *in-vitro* dissolution study and anti-hyperglycemic activity on animal. From the above result, it concluded that formulation F6 containing Carbapol 934 fulfills all the requirements of sustained release tablet.

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