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Research Article

FORMULATION AND EVALUATION OF GLIMEPIRIDE SUSTAINED RELEASE MATRIX TABLETS

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ABSTRACT

The objective of this study was to develop sustained release matrix tablets of Glimepiride by wet granulation method based on combination of natural (acacia) and synthetic (Carbopol) polymers. Glimepiride is an oral hypoglycaemic agent, which is commonly prescribed for the treatment of patients with type II Diabetes Mellitus. Therapy with Glimepiride is usually initiated with 1 to 2 mg. The pharmacokinetics and dosage schedule supports once daily sustained release formulations for Glimepiride for better control of blood glucose level to prevent hypoglycaemia, enhance clinical efficacy and patient compliance. In this project Glimepiride sustained release matrix tablets are formulated with variable concentrations of natural and synthetic polymers and has been evaluated for its weight variation, Hardness, Friability, Disintegration, stability studies, order of kinetics and Dissolution studies. The results shown that Glimepiride containing Carbopol in F6 formulation fulfills all the requirements of a sustained release tablet.

Keywords :- Glimepiride, Acacia, Carbopol, Matrix tablets.

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INTRODUCTION

Introduction of matrix tablet as sustained release has given a new break through for novel drug delivery system (NDDS) in the field of Pharmaceutical technology [1]. It excludes complex production procedures such as coating during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. Hydrophilic polymer and hydrophilic polymer matrix is widely used for formulating an sustained release dosage form [2].

Matrix Tablets are one of the approaches to Sustained the drug release for longer period of time at expected rate after its single dose administration. When highly water soluble drugs are prepared as oral sustained release dosage form cause problems like they may be released more rapidly and result in toxicity if not prepared in appropriate fashion [3]. For sustained release systems, the oral route of drug administration received the most attention as it is natural, un complicated, convenient and safer route. Sustained release definition is more "controlled release" rather than "sustained" [4].

Glimepiride is an anti-diabetic drug. In the last few years, diabetes mellitus has reached epidemic proportion and is now becoming cause of premature mortality and morbidity. Novel drug delivery systems (NDDS) are techniques capable of controlling the rate of drug release, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to tissue. Glimepiride is an oral hypoglycaemic agent. It is third generation sulphonyl urea agent for the treatment of type II diabetes mellitus. Glimepiride is highly permeable class 2 according to biopharmaceutical classification

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system (BCS). The oral absorption is uniform, rapid and complete with nearly 100% bioavailability. The normal dose of Glimepiride is 1-2 mg [5].

MATERIALS AND METHODS

Materials

Glimepiride was procured as a gift sample from RA CHEM Private Limited, Hyderabad. All the other chemicals like poloxamer, carbopol, magnesium stearate, talc, starch, microcrystalline cellulose were obtained from SDFCL, S.D. fine-chemicals limited, Mumbai.

Apparatus

Digital vernier calliper (MITUTOYO), Hardness tester (ELECTROLAB), Disintegration tester (ELECTROLAB), Dissolution apparatus (LABINDIA), U. V. Visible Spectrophotometer (Analytical Technologies Ltd), Electronic balance (WENSAR), FTIR (JASCO).

Methods

Preformulation studies

Preformulation studies are one of the important prerequisite in development of any drug delivery system. These were performed on the drug, which included solubility and compatibility studies. It can also to investigate the various physic-chemical properties of a drug molecule in order to develop safe, effective and stable dosage form [6].

Micromeritic study of pre-compressed powder

The flow characteristics of the different batches pre-compressed powder were measured by determining their angle of repose using fixed-base cone method. A glass funnel was secured with its tip positioned at a fixed height (H) above graph paper placed on a horizontal surface. The sample was poured through the funnel until the apex of the conical pile touched to the tip of the funnel. The height and radius of the heap was measured. The experiment was repeated in triplicate, the angle of repose (tan θ) was calculated using the formula; **Angle of repose[θ] =tan -1(h/r)**

Where,

H = cone height,

r = radius of circular base formed by the granules on the ground [7].

The bulk and tapped densities of the pre-compressed powder were evaluated by using the bulk density apparatus. Known weights of formulated granules were transferred into a 50cc graduated measuring cylinder. The cylinder was fixed on bulk density apparatus and the timer knob was set for 500 tapings. Then, the initial bulk volume and final volume after 500 tapings were noted. The experiment was repeated in triplicate. The respective densities of different batches of granules were calculated by using the following formulas;

Carr's Index

$$C = \frac{V_B - V_T}{V_B} \times 100$$

V_B is the volume that a given mass of powder would occupy if let settled freely, and

V_T is the volume of the same mass of powder would occupy after tapping down [8].

Compressibility index or Carr's index value of precompressed was computed according to the following equation;

Hausner's ratio = Tapped density / Bulk density

A Carr's index greater than 25 is considered to be an indication of poor flow ability, and below 15, of good flow ability [9].

FTIR Spectrum

Glimepiride and its binary mixtures were recorded in the interval 4000-400 cm^{-1} with an FT-IR instrument, at 4 cm^{-1} optical resolution. Standard KBR pellets were prepared from IR grade KBR 0.5 mg, 0.5 mg Glimepiride and 1.0 mg of binary mixture. The spectra were recorded with the use of software, and all spectral interpretations were done [10].

The contents of each Excipient were observed for any change by their physical characteristics and for their characteristics peaks by FTIR Spectrophotometer. The FTIR 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 six formulations were prepared by wet granulation method. Sustained release matrix tablets of Glimepiride were prepared by using Carbopol and acacia as matrix forming materials, while starch as a diluent, Magnesium stearate as a lubricant and talc as an anti-adherent.CMC act as disintegrating agent. All ingredients used were passed through a # 100 sieve, weighed and blended. The granules were prepared by wet granulation technique and evaluated for its flow properties. The granules were compressed by using 10 mm flat faced punches using in a rotary tablet press [12].

Characterization Of Sustained Release Glimepiride Standard Calibration graph

The calibration curve was obtained by preparing aliquots of working standard solution of Glimepiride in simulated gastric fluid (pH 1.2) and simulated intestinal fluid (pH 7.2) using methanol as a co solvent and the absorbance at 228 nm was measured after suitable

dilution using Perkin Elmer UV/ Visible Spectrophotometer [13].

Visual examination

Tablets were evaluated for physical appearance by visual assessment and uniformity of thickness using vernier callipers [14].

Weight variation

The weight variation test was conducted by weighing 20 randomly selected tablets individually, calculating the average weight and comparing the individual tablet weights to the average. The specification of weight variation is 10% [15].

Hardness test

Five tablets were randomly picked from each of the ten formulations and the hardness expressed as kg/cm2 was determined using Monsanto Hardness Tester [16].

Friability test

A friability test was conducted on the tablets using a Double drum friabilator. Twenty tablets were selected from each batch and any loose dust was removed with the help of a soft brush. The tablets were initially weighed (W initial) and transferred into friabilator. The drum was rotated at 25 rpm for 4 minutes after which the tablets were removed. Any loose dust was removed from the tablets as before and the tablets were weighed again (W final). The percentage friability was then calculated

$$\% \text{ Friability} = \frac{\text{Initial Weight} - \text{Final Weight}}{\text{Initial Weight}} \times 100$$

% Friability of tablets less than 1% is considered acceptable [17].

Drug Content uniformity

To find Drug content, spectrophotometric method was followed. Powdered tablets corresponding to weight of the tablet was extracted in minimum volume of methanol in 100 ml volumetric flask. Final volume was made up to 100 ml with phosphate buffer pH 7.2. The solution was then filtered and 0.5 ml of filtrate was pipetted into 25 ml volumetric flask and diluted upto the mark with phosphate buffer pH 7.2 and analysed at 228 nm using suitable blank. Concentration of Glimepiride in mg/ml was determined by using standard calibration curve of drug. Drug content studies were carried out in triplicate for each formulation [18].

The percentage of drug content of various formulations F1, F2, F3, F4, F5, F6 are tabulated in table

$$\text{Drug content} = \frac{\text{test absorbance}}{\text{Standard absorbance}} \times \frac{\text{standard dilution}}{\text{test dilution}} \times \text{average weight}$$

$$\% \text{ Drug content} = \frac{\text{Practical yield}}{\text{Label claim}} \times 100$$

Swelling Studies

Swelling behaviour of tablet was measured by placing the tablet matrices in dissolution test apparatus, in 900 ml of simulated intestinal fluid at 37±0.5oC. Tablets were removed periodically for every 2 hours from dissolution medium after draining free water. These were measured for weight gain and diameter. Swollen weights of tablets were determined at predefined time intervals. Swelling Index was calculated by:

$$\text{Swelling Index} = \frac{\text{Final weight at time t (Wt)} - \text{Initial weight (Wo)}}{\text{Initial weight (Wo)}}$$

In Vitro-Release Testing

Dissolution studies were carried out for all the formulations combinations in triplicate, employing USP - II paddle method and 900ml of pH 7.8 phosphate buffers as the dissolution medium. The medium was allowed to equilibrate to temp of 37°C±0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 24 hrs in pH 7.8 phosphate buffer at 50 rpm. At definite time intervals of 5 ml of the aliquot of sample was withdrawn periodically and the volume replaced with equivalent amount of the fresh dissolution medium. The samples were analyzed spectrophotometrically at 226 nm using UV spectrophotometer. And this dissolution data was further treated for kinetic modelling [19].

Kinetics of in-vitro drug release

To study the release kinetics in-vitro release data was applied to kinetic models such as zero-order, first order, and Higuchi, Korsmeyer – peppas model.

Order of drug release

To determine the type order of drug release graphs were plotted between cumulative percent of release vs time, log cumulative % of drug remaining vs time. The plotted graphs are represented in figures.

Korsmeyer- Peppas model

Korsmeyer et al. (1983) derived a simple relationship which described drug release from a polymeric system.

$M_t / M_* = Kt^n$

Where,

M_t / M_* is a fraction of drug released at time t,

K is the release rate constant and

n is the release exponent.

In this model, the value of n characterizes the release mechanism of drug. $0.45 < n$ corresponds to a Fickian diffusion mechanism, $0.45 < n < 0.89$ to non – Fickian transport (the rates of solvent penetration and

drug release are in the same range). N = 0.89 to Case II (relaxational) transport, and n > 0.89 to super case II transport.

Accelerated Stability studies

Accelerated stability study was carried out to observe the effect of temperature and relative humidity on selected formulation (F6), by keeping at 40°± 2°C, in air tight high density polyethylene bottles for three months, at RH 75±5%. Physical evaluation was carried out in each month [20].

RESULTS AND DISCUSSION

Preparation of standard calibration for Glimepiride:

A calibration curve has been plotted by taking concentration on X- axis and absorbance on the Y-axis. From the calibration graph it is clear that the given depicted results given linear relationship.

Interaction studies:

Spectra of the pure drug, excipient and physical mixture of drug and excipient were recorded in between 400-4000 wave number (cm-1). The FTIR spectral analysis showed that there is no appearance or disappearance of any characteristic peaks of pure drug Glimepiride and in the physical mixture which confirms the absence of chemical interaction between drug and polymers.

The results are depicted below

The FTIR data showed that Glimepiride and excipients did not react with each other and retained their action at room temperature.

Micromeritic properties

Granules of all the formulations were subjected for various pre-compressional evaluations such as angle of repose, bulk and tapped density, compressibility index and Hausner's ratio. Results of all the pre-compressional parameters performed on granules for all formulations are shown in table.

The results of angle of repose (<30) indicates good flow properties of the powder. This was further supported by lower compressibility index values. Generally compressibility values up to 15% results in good to excellent flow properties.

Evaluation of Glimepiride tablets:

The tablets of different batches were found uniform with respect to hardness, weight variation, friability thickness and drug content within the range as specified in I.P. The results are depicted below.

Drug release study:

In vitro drug release studies are performed on all the six formulations. The formulation with greater percentage of polymer is showing greater sustained release. From the drug release studies it is clear that F6 formulation showing better release when compared to F1, F2, F3, F4, F5 formulations. The results are tabulated below.

Kinetics of drug analysis

Kinetic model fitting for the drug release data

To study the release kinetics in-vitro release data was applied to kinetic models such as zero-order, first order and Korsmeyer-Peppas graph. From the results it is clear that the given formulation is following first order of kinetics.

Zero order

Korsmeyer-Peppas graphs representing the drug release mechanism

As the *n* value is less than 0.45, it is clear that the drug release mechanism is following fickian transport. As it is showing Fickian transport it follows diffusion process.

Stability studies

After conducting stability studies it's clear that F6 formulation was found to be more stable when compared with other formulations because the % drug remaining for other formulations are lesser than the F6 formulation.

Table 1. Composition of sustained released Matrix tablets

Ingredients	F1	F2	F3	F4	F5	F6
Glimepiride	6	6	6	6	6	6
Acacia	10	20	30	-	-	-
Carbopol	-	-	-	10	20	30
Microcrystalline cellulose	55	45	35	55	45	35
Starch	25	25	25	25	25	25
Talc	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2
Total	100	100	100	100	100	100

Table 2. Calibration curve data

S. no	Concentration (µg/ml)	Absorbance
1	0	0
2	5	0.102
3	10	0.242
4	15	0.298
5	20	0.325
6	25	0.426

Table 3. Angle of Repose

Formulations	Angle of Repose
F1	21^0. 34’
F2	22^0.30’
F3	26^0.16’
F4	25^0.26’
F5	24^0.25’
F6	23^0.24’

Table 4. Density

Formulation	Bulk density g/ml	Tapped density g/ml
F1	0.224	0.264
F2	0.238	0.278
F3	0.241	0.289
F4	0.216	0.245
F5	0.221	0.256
F6	0.229	0.263

Table 5. Carr’s Index and Hausner’s ratio

Formulation	Carr’s Index (%)	Hausner’s ratio (%)
F1	14.57	1.16
F2	14.36	1.18
F3	14.44	1.15
F4	13.98	1.12
F5	13.87	1.14
F6	13.92	1.14

Table 6. Evaluation of sustained release matrix tablets of Glimepiride

Formulations	Weight variation(mg)	Hardness (kg/ cm^2)	Thickness (mm)	Friability %	Drug content (%)
F1	149	3.24	3.42	0.38	97.81
F2	148	4.00	3.48	0.35	98.32
F3	150	3.10	3.53	0.28	98.73
F4	148	3.70	3.46	0.20	97.92
F5	149	4.00	3.49	0.16	98.69
F6	150	4.82	3.52	0.13	99.12

Table 7. Data of in-vitro Drug release studies

Time	F1	F2	F3	F4	F5	F6
0:30	38.78	32.61	27.45	37.18	30.85	26.98
1	55.11	47.88	39.26	49.93	42.12	35.66
2	78.29	63.24	47.03	70.22	61.64	47.13
3	86.37	74.16	65.98	85.67	79.96	66.54
4	98.06	82.32	78.77	97.49	85.32	73.09
5		97.84	89.14		98.71	86.72
6			98.36			99.27

Table 8. Kinetic models

S. no	Formulations	Kinetic models			
		Zero order R^2	First order R^2	Korsmeyer-Peppas	
				R^2	n
1	F1	0.9162	0.9946	0.9966	0.366
2	F2	0.9086	0.9925	0.9521	0.374
3	F3	0.9505	0.9735	0.9500	0.446
4	F4	0.9155	0.9874	0.9384	0.322
5	F5	0.9162	0.991	0.963	0.414
6	F6	0.9252	0.989	0.976	0.397

Table 9. Stability studies data

Time in days	Log % of drug remaining in F6 formulation		
	At 30^0 C	At 40^0 C	At 50^0 C
0	2	2	2
30	1.998346	1.998012	1.998608
60	1.997037	1.996599	1.997523

Fig 1. Preparation of KBR pellets

Fig 2. Sample with KBR pellet

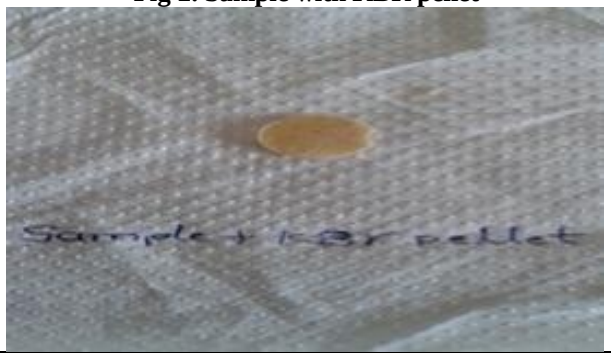


Fig 3. Hydraulic press

Fig 4. FTIR (JASCO)

Fig 5. Glimepiride with Excipients

Fig 6. Dump mass of Glimepiride

Fig 7. Dried granules of Glimepiride

Fig 8. Glimepiride matrix tablet

Fig 9. Calibration graph

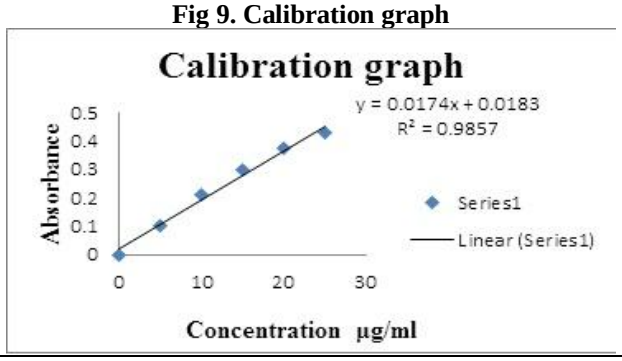


Fig10. FTIR F3 formulation

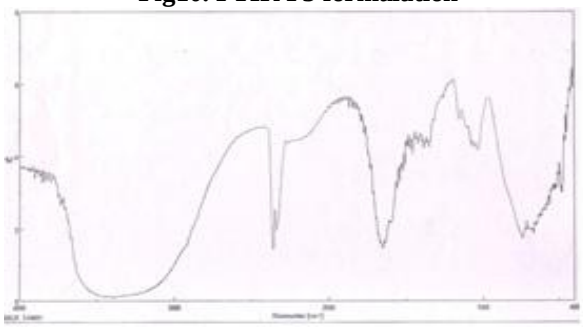


Fig 11. FTIR of Carbopol

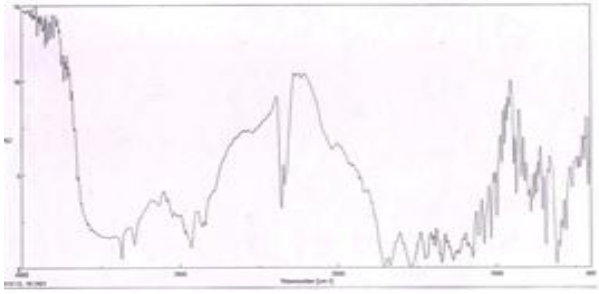


Fig 12. FTIR of Acacia

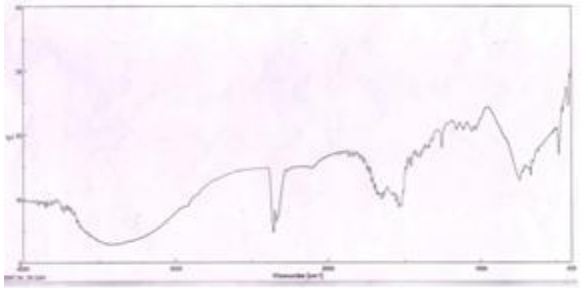


Fig 13. FTIR of F6 formulation

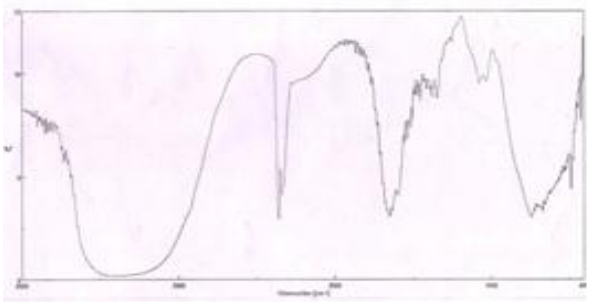


Fig 14. FTIR of Glimepiride

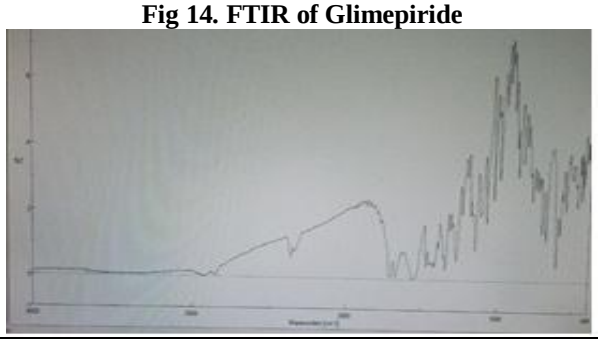


Fig 15. FTIR of Magnesium stearate

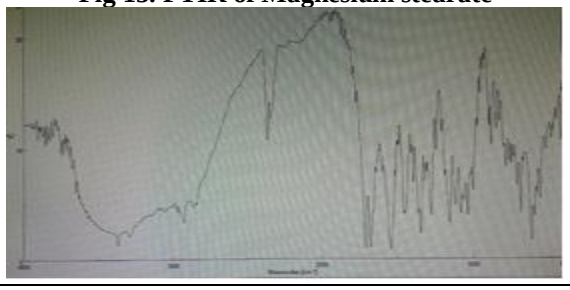


Fig 16. FTIR of MCC

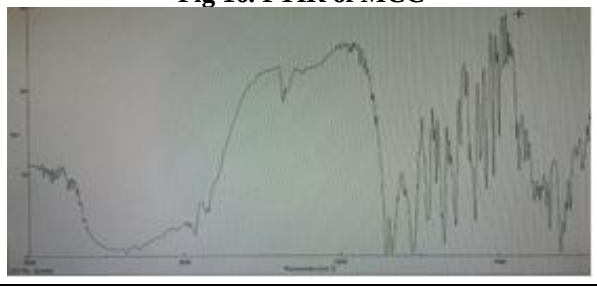


Fig 17. FTIR of Starch

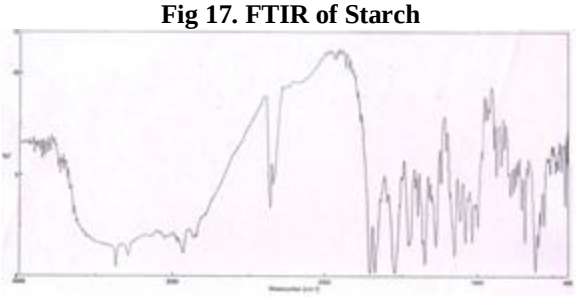


Fig 18. In-Vitro drug release study of Glimepiride

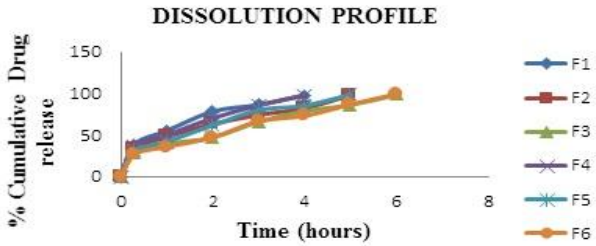


Fig 19. F1 formulation

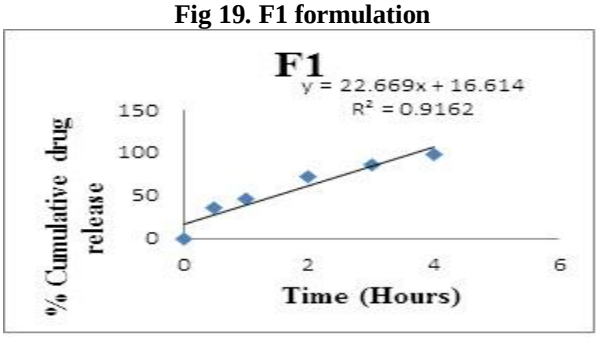


Fig 20. F2 formulation

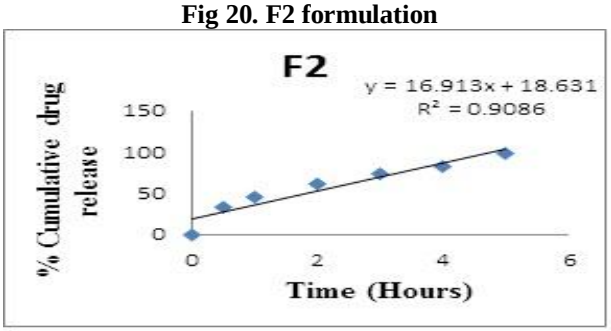


Fig 21. F3 formulation

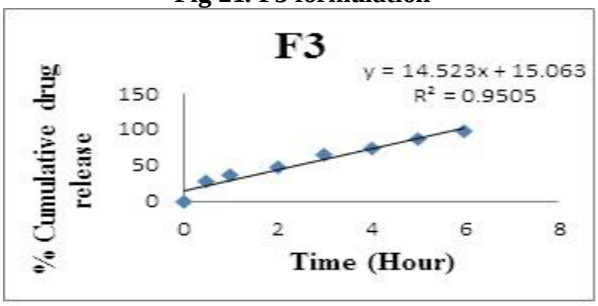


Fig 22. F4 formulation

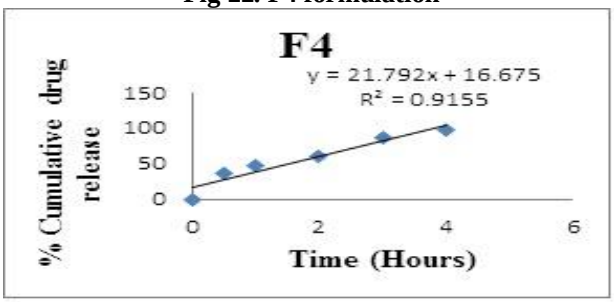


Fig 23. F5 formulation

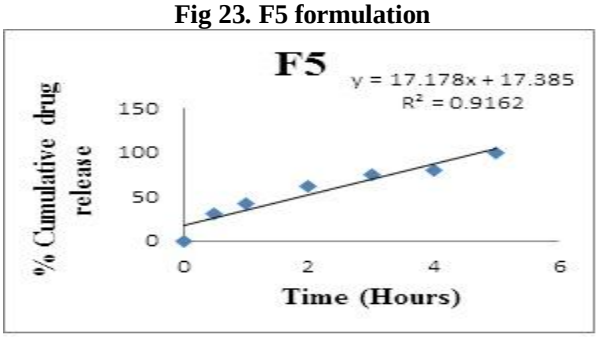


Fig 24. F6 formulation

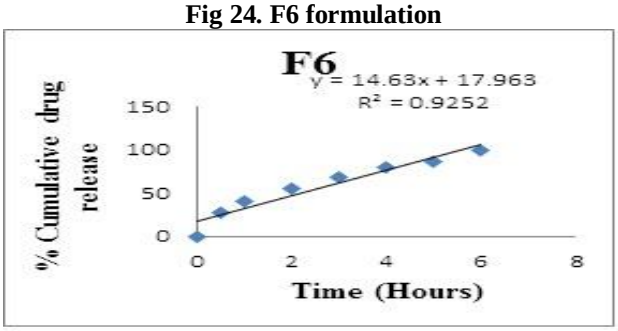


Fig 25. F1 formulation

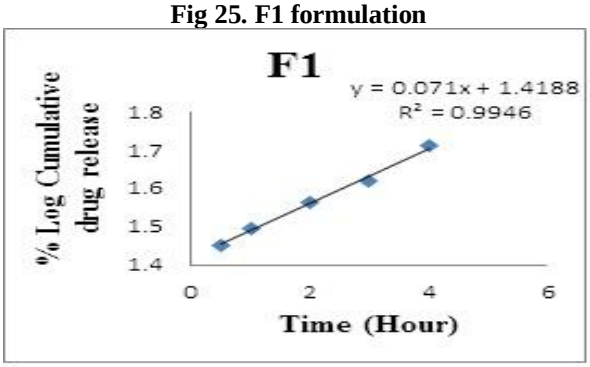


Fig 26. F2 formulation

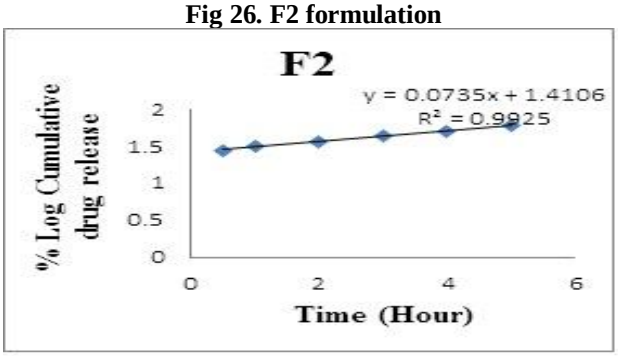


Fig 27. F3 formulation

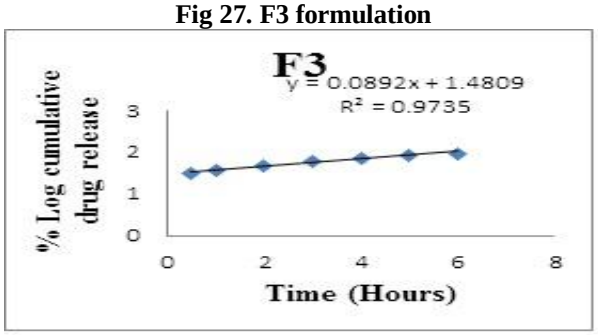


Fig 28. F4 formulation

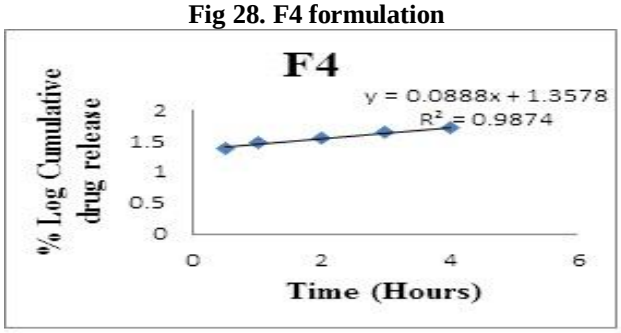


Fig 29. F5 formulation

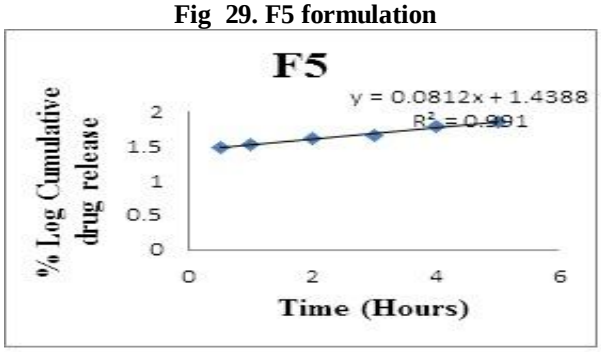


Fig 30. F6 formulation

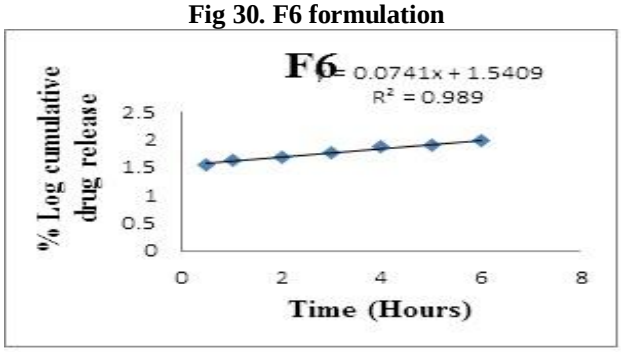


Fig 31. F6 formulation

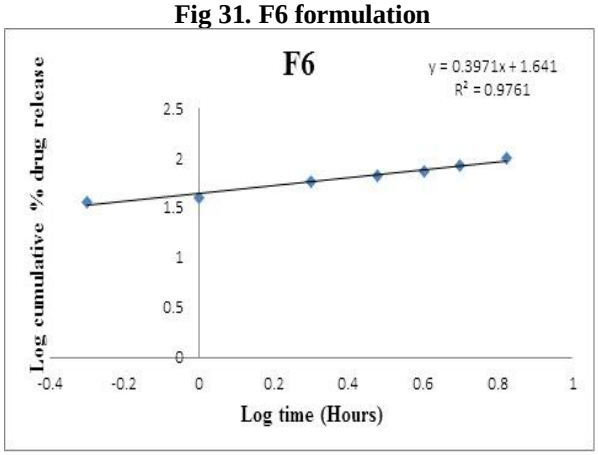
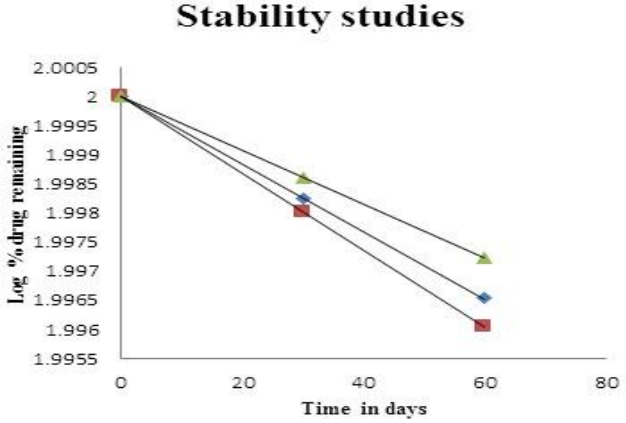


Fig 32. F6 formulation Stability studies



CONCLUSION

The study was undertaken with the aim to Formulation and evaluation of Glimepiride sustained-release matrix tablets using various concentrations of polymers. From the above results and discussion, it is concluded that the formulation of sustained release tablet of Glimepiride containing Carbopol in F6 formulation fulfills all the requirement of sustained release tablet.

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Nil

CONFLICT OF INTEREST

No interest

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