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FORMULATION AND EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF AN ANTIDIABETIC DRUG USING NATURAL AND SYNTHETIC POLYMERS

Mahesh V. Dhumal*, Dr. A.M.Godbole, Lokesh Sajjanshette, Ketan B. Deore

Department of Pharmaceutics, SET's College Of Pharmacy, Dharwad, Karnataka-580002, India

Keywords:

Sustained release, matrix tablets, Glimepiride, xanthan gum, povidone, wet granulation Method

For Correspondence:

Mahesh V. Dhumal

SET's College Of Pharmacy, Dharwad, Karnataka-580002, India

E-mail:

mvdhumal@gmail.com

ABSTRACT

The objective of this study was to design and evaluate oral sustained drug delivery system for Glimepiride using natural and synthetic polymers as a release modifier such as xanthan gum and povidone respectively. Matrix tablets were prepared by wet granulation method. The formulation blend was evaluated for pre compression parameters. Formulated tablets were evaluated for post compression parameters. Among the formulations studied, formulation F8 containing combination of XG and povidone (1:1) having concentration of 6% showed sustained release of drug for 12 hrs with cumulative percent release of 98.97%. Formulation F8 follow Higuchi release pattern. No chemical interaction between drug and polymer was seen as confirmed by FTIR studies.

INTRODUCTION

Sustained release, sustained action, prolonged action, controlled release, extended release dosage forms are terms used to identify drug delivery systems that are designed to achieve prolonged therapeutic effects by continuously releasing medication over an extended period of time after administration of single dose. The goal of a sustained release dosage form is to maintain therapeutic blood level of drug.[1] For sustained release systems, the oral route of administration has received the most attention with respect to research on physiological and drug constraints as well as designing and testing of products. It is assumed that increasing concentration at the absorption site will increase the rate of absorption and, therefore, increase circulating blood levels, which in turn promotes greater concentrations of the drug at the site of action.[2] Glimepiride has a short half life 3-5 hrs. after single dose and usual oral dosage regimen 1mg to 8mg daily. To reduce the frequency of administration and to improve patient compliance, a once daily sustained release formulation of Glimepiride is desirable.[3]

Advantages: Reduce dosing frequency, decrease incidence and intensity of adverse effect and toxicity, better drug utilization, improved patient compliance, more uniform blood circulation, more consistent therapeutic effect.[4,5]

MATERIAL AND METHODS:

Glimepiride was obtained from FDC LTD Mumbai as gift sample. Xanthan gum, povidone, microcrystalline cellulose, magnesium stearate were purchased from HiMedia Mumbai. A Sustained release matrix tablets of an antidiabetic drug was prepared by wet granulation method. Glimepiride and all ingredients are passed through sieve no. 85, then weighed appropriate quantity then add a granulating agent isopropyl alcohol 0.1%w/v. and compressed by using 9 mm size punch using cadmach tablet punching machine (10 station).

Angle of repose: The internal angle between the surface of the pile and the horizontal surface is known as the angle of repose and is related to the density, surface area, and coefficient of friction of the material.

$$\text{Angle of repose } \Theta = \tan^{-1} h/r$$

Where h is height of pile and r is radius of pile.[6]

Bulk density[7]: "It is the ratio between a given mass of a powder and its bulk volume". Bulk density is calculated by using the formula-

Bulk Density = Mass of powder / Bulk Volume of the powder

Tapped density: This volume is the bulk volume and it includes true volume of the powder and the void space among the powder particles. Tapped density is calculated by using the formula-

Tapped density = Weight of powder / Tapped volume of the powder

Carr's Index[8]:

The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated according to equation given below:

% Compressibility = tapped density-bulk density/tapped density X 100

Hausner's Ratio:

Hausner's Ratio indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density.

Hausner's Ratio = Tapped density/Bulk Density

Formulations of sustained release tablets of Glimepiride

INGREDIENS (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Glimepiride	2	2	2	2	2	2	2	2
Xanthan gum	1.5	3	4.5	6	7.5	9	10.5	12
Povidone	1.5	3	4.5	6	7.5	9	10.5	12
Micro crystalline cellulose	190	187	184	181	178	175	172	169
Isopropyl alcohol(0.1%w/v)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	5	5	5	5	5	5	5	5
Total weight (mg)	200	200	200	200	200	200	200	200

Thickness:

Twenty tablets were randomly selected from formulations and thickness was measured individually by using vernier caliper. It was expressed in millimeter and average was calculated.

c) Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined by using Monsanto hardness tester. It was expressed in Kilogram per centimeter square (kg/cm^2). Ten tablets were randomly selected from each formulation and hardness of the same were determined. The average value was calculated.

d) Friability:

Twenty tablets were weighed and placed in the Roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions, the tablets were dedusted and weighed again. The percentage friability was measured using formula-

$$\% F = \{1-(Wt/W)\} \times 100$$

Weight variation:

The USP weight variation test was carried out by weighing 20 tablets individually, calculating the average weight, comparing the individual tablet weight to average weight. The tablet meet USP test if no tablet differs by more than two times of percentage deviation.

Drug content uniformity: [9]

Five tablets of each formulation were weighed and powdered. The quantity of powder was equivalent to 10 mg. The equivalent weight Glimepiride was transferred into 100 ml standard volumetric flask and by using pH 7.4 buffer solution as the extracting solvent and samples was analyzed at 231nm UV spectrophotometrically.

Swelling behavior of matrix tablets: [10]

The extent of swelling was measured in terms of % weight gain by the tablet. One tablet from each formulation was kept in a petridish containing pH 7.4 phosphate buffer. At the end of 1h, the tablet was withdrawn, soaked with tissue paper, and weighed. Then for every 2 h, weights of the tablet were noted, and the process was continued till the end of 12 h. percentage weight gain by the tablet was calculated by formula;

$$\% \text{ Swelling index} = \{(Mt-Mo) / Mo\} X 100$$

Stability studies:[11]

Stability studies for sustained release matrix tablets were carried out by keeping them in high density polyethylene sealed cover at refrigeration, 40ºC and 75% RH. Samples were withdrawn for every month of storage and evaluated for appearance, weight variation, friability, thickness, hardness and drug content.

***In vitro* Dissolution Studies:**

The *In vitro* release of dissolution studies from the formulated tablets was carried out in tablet dissolution tester USP- type II (paddle) apparatus using 900 ml of dissolution medium maintained at 37.0 ±0.5°C at a stirring rate of 50 rpm. One tablet from each formulation were tested individually in 0.1 N HCl for the first 2 hr and in phosphate buffer (pH 7.4) for the following 10 hr. Samples measuring 10 ml were withdrawn at different time intervals such as 1 hr, 2 hr.

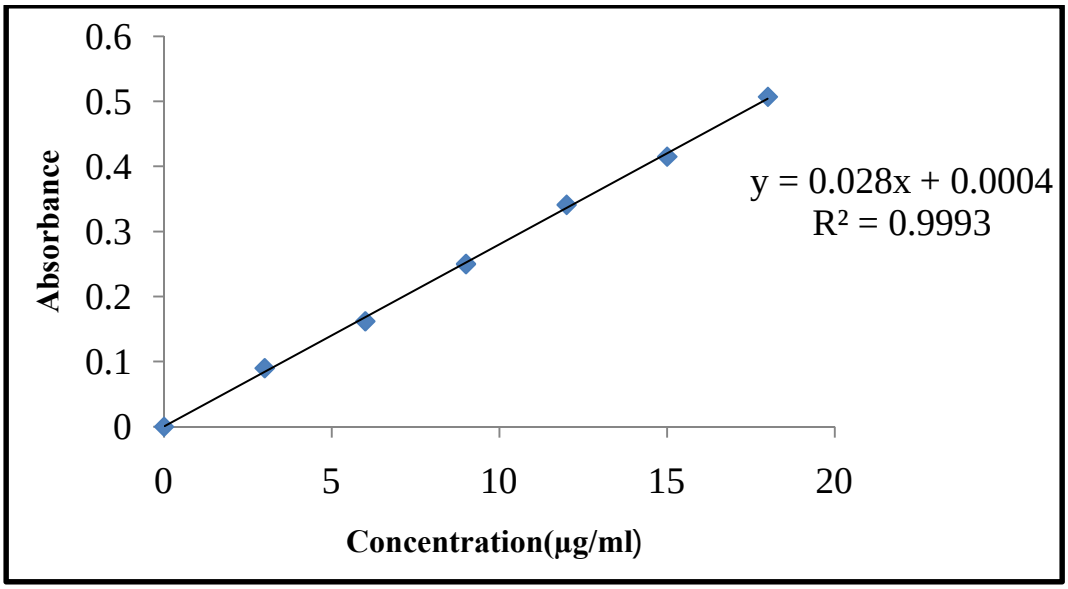
RESULTS AND DISCUSSION:

PREFORMULATION STUDIES:

Melting Point: 207°C

Color: A white to almost white powder.

Standard calibration curve of Glimepiride in 0.1N HCl pH 1.2



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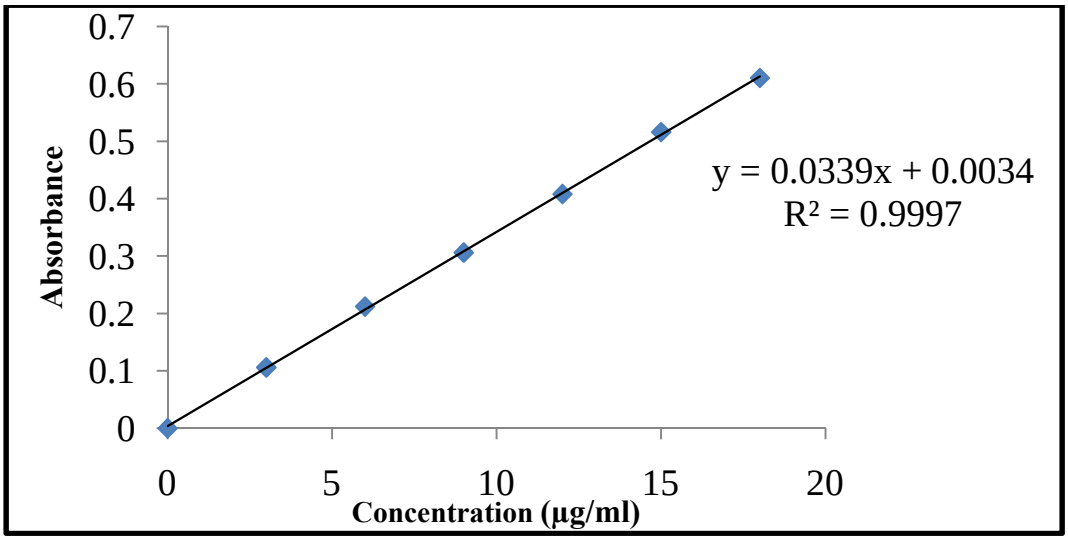
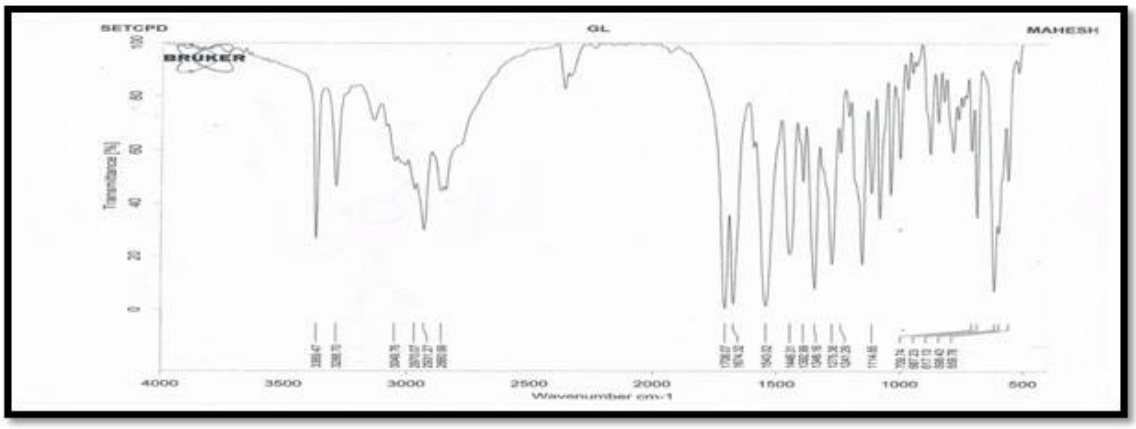
Standard curve of Glimepiride in phosphate buffer of pH 7.4

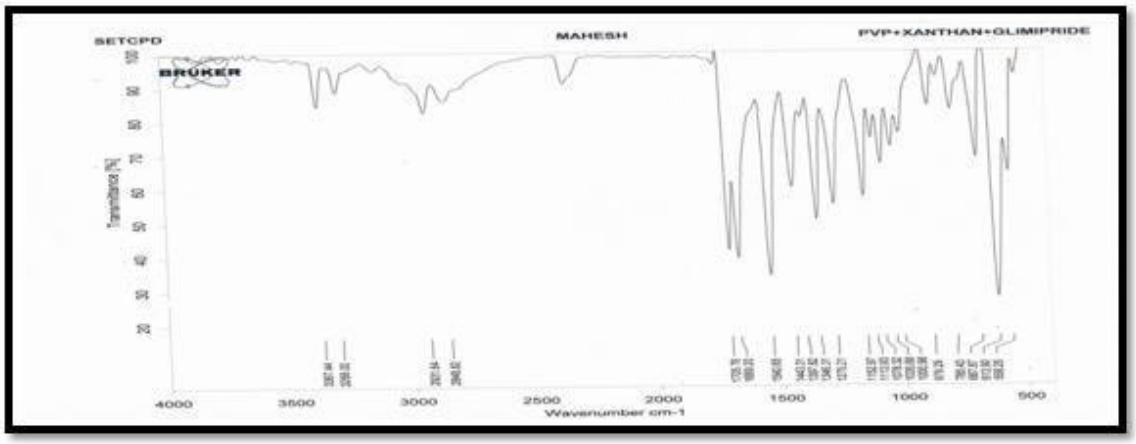


DRUG POLYMER COMPATIBILITY STUDIES:

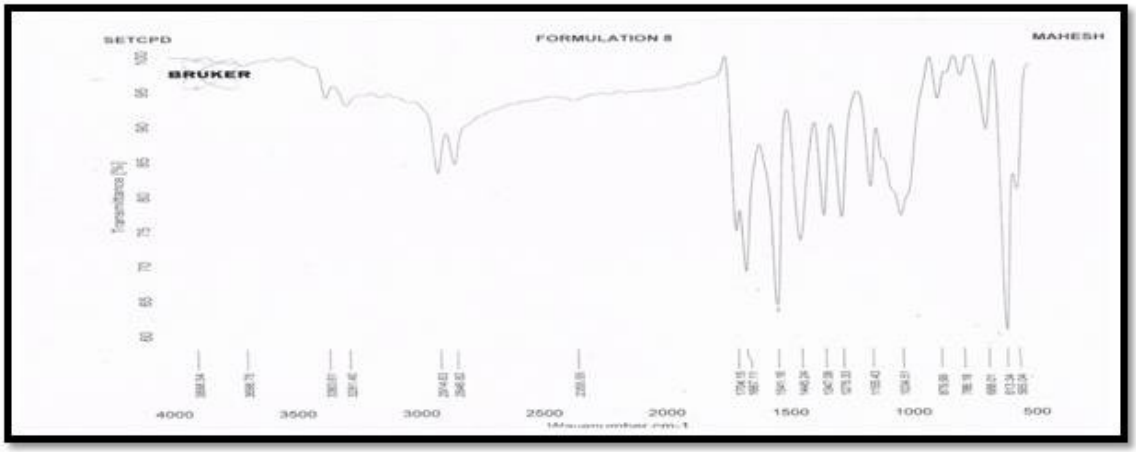
IR spectra of pure drug:



IR Spectrum of Glimepiride +Povidone +xanthan gum



IR Spectrum of Formulation



FT-IR Spectra of Glimepiride, polymer, & physical mixture of drug: polymer and formulation containing different excipients were recorded. The Glimepiride present in the formulation was confirmed by FT-IR spectra. The characteristic peaks due to pure Glimepiride shows IR absorption at 3369.47cm^{-1} (CO-NH, stretching), 3288.70 cm^{-1} (SO_2NH, stretching), 1708.07cm^{-1} C=O stretching (Aromatic Ketone), 1674.32cm^{-1} C=O stretching (Amide), 1346.16 cm^{-1} (Asymmetric SO_2, stretching,) 1114.85 (Symmetric SO_2, stretching) which are shown in Tableno.5.3. All these peaks have appeared in pure Glimepiride, physical mixture and formulation 8 indicating that no chemical interaction has taken place between Glimepiride and polymers. It also confirmed that the stability of drug during formulation.

EVALUATION PARAMETERS OF POWDER BLEND:

F	ANGLE OF REPOSE*(°)±S.D.	BULK DENSITY* (gm/ml) ±S.D	TAPPED DENSITY* (gm/ml) ±S.D	COMPRSSBILITY* (%) ±S.D	HAUSNER'S RATIO* ±S.D
F1	30°.32'±0.64	0.212±0.006	0.252±0.009	15.15±0.4911	1.18±0.007
F2	27°.93'±0.31	0.208±0.007	0.252±0.010	16.52±0.638	1.2±0.008
F3	27°.72'±1.00	0.205±0.006	0.241±0.008	16.02±1.80	1.17±0.006
F4	29°.79'±0.33	0.211±0.004	0.253±0.005	16.33±0.307	1.19±0.004

F5	30°.96'±0.21	0.209±0.006	0.245±0.007	14.80±0.255	1.17±0.003
F6	31°.03'±0.25	0.217±0.021	0.257±0.031	15.33±2.797	1.18±0.038
F7	30°.55'±0.73	0.208±0.006	0.243±0.008	14.29±0.404	1.16±0.005
F8	31°.04'±0.41	0.207±0.004	0.241±0.008	14.21±1.268	1.16±0.017

*Average of three values, F- Formulation code

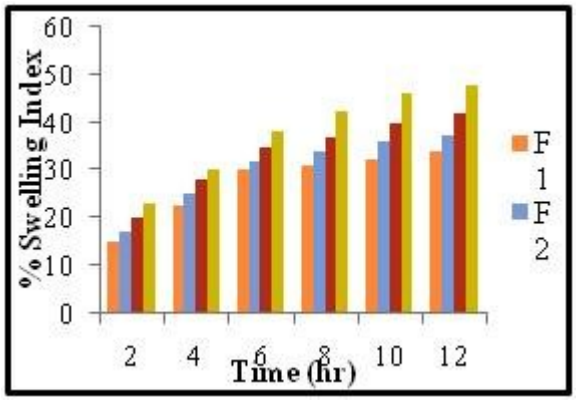
EVALUATION PARAMETERS OF FORMULATIONS:

F	Thickness* (mm) ± S.D.	Hardness* (kg/cm^2) ± S.D.	Friability (%)	Average weight variation*(mg) ± S.D.	Drug content*(%) ± S.D.
F1	5±0.01	7.33±0.57	0.279	197.1±6.21	95.59±0.79
F2	5.03±0.305	6.33±1.52	0.558	198.3±7.03	93.66±0.71
F3	5.06±0.115	7.00±1	0.50	198.1±7.33	97.67±0.96
F4	5.03±0.208	6.33±0.57	0.532	198.1±6.73	96.43±0.69
F5	5.1±0.1	7.66±0.57	0.305	196.5±7.52	100.39±0.73
F6	5.06±0.047	7.00±1	0.457	197.5±6.95	93.42±0.70
F7	5.03±0.152	6.66±0.57	0.536	197.1±7.08	98.10±0.75
F8	5.06±0.115	7.66±0.57	0.403	196.9±6.60	91.40±0.87

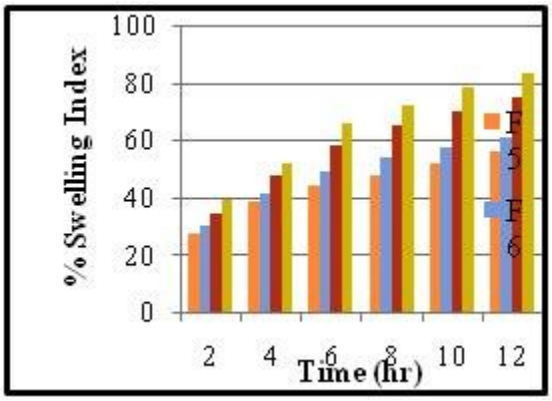
*Average of three values, F- Formulation code

SWELLING INDEX STUDIES:

% Swelling Index of formulation F1-F4

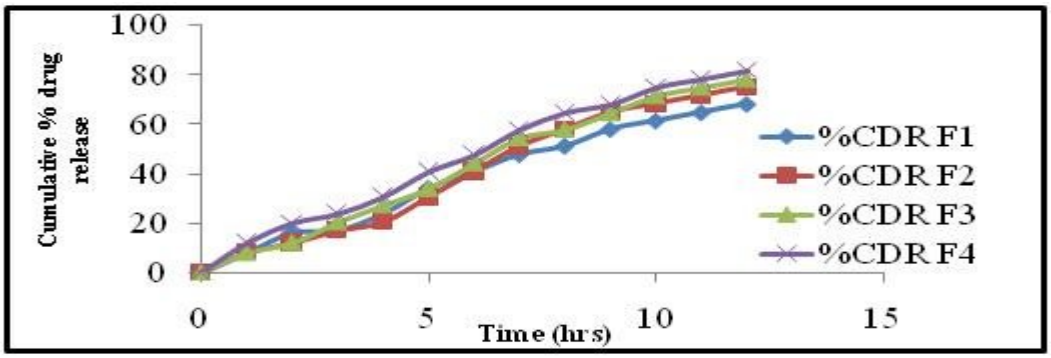


% Swelling Index of formulation F5-F8

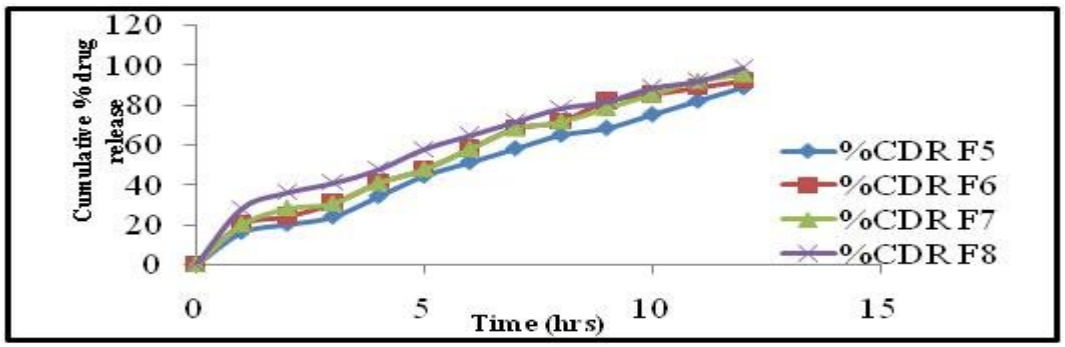


***IN-VITRO* RELEASE PROFILE:**

Zero order release plots F1-F4

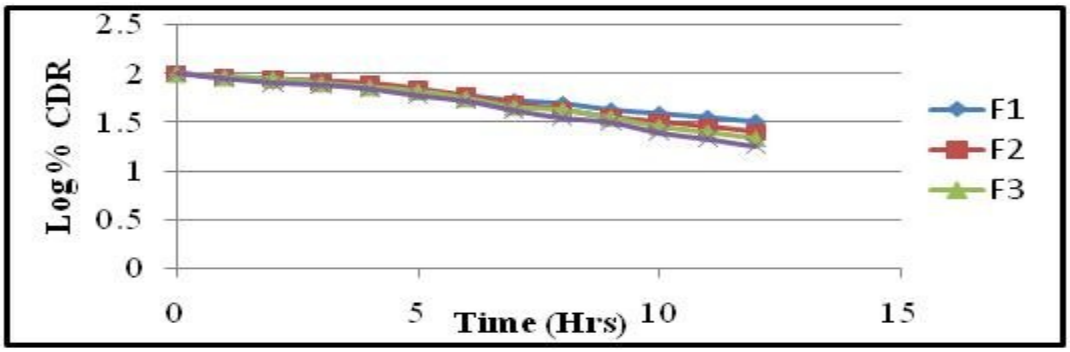


Zero order release plots F5-F8

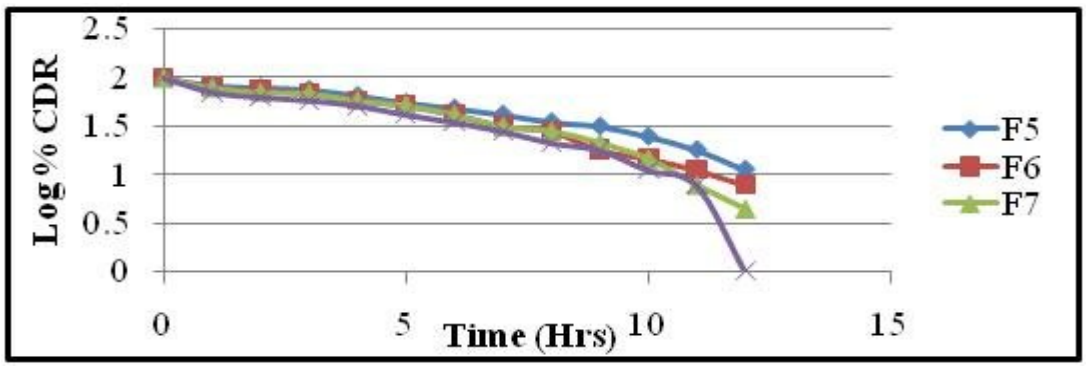


DRUG RELEASE KINETIC:

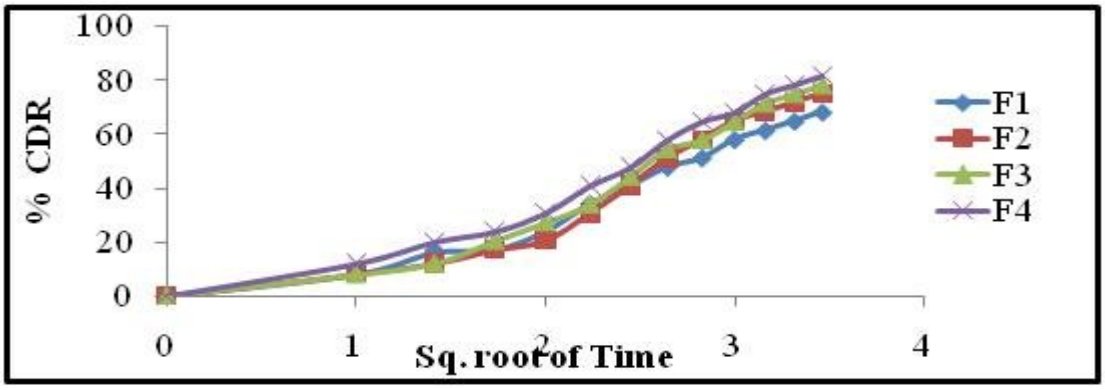
First order release plots F1-F4



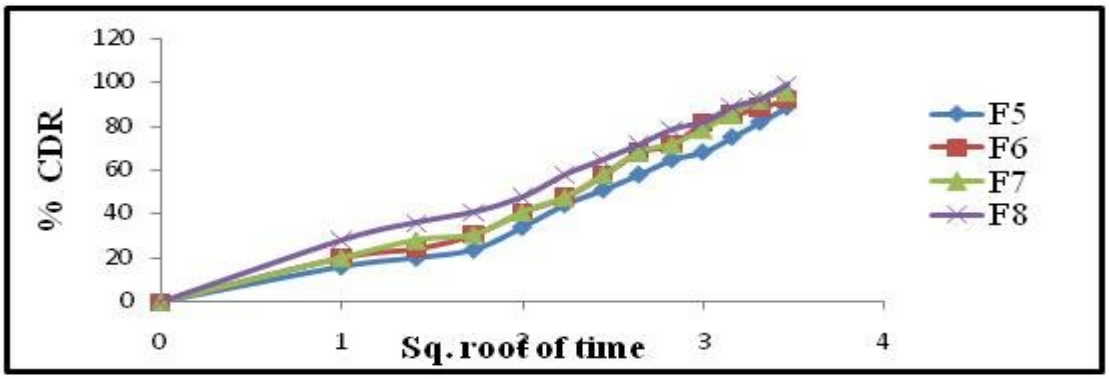
First order release plots F5-F8



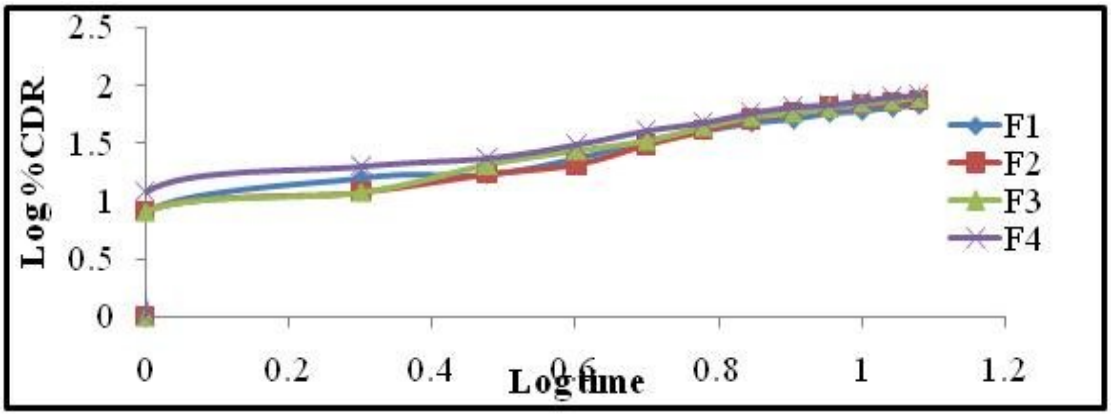
Higuchi plots F1-F4



Higuchi plots F5-F8



Korsmeyer peppas plots F1-F4



Formulation F2, F3, F4, F5, F6 and F7 with r^2 values of 0.982, 0.990, 0.986, 0.989, 0.976 and 0.982 respectively show zero order release kinetics. But however formulation F1 with r^2 value of 0.991 shows first order release kinetics, formulation F8 with r^2 value 0.989 shows Higuchi release pattern. Hence it was concluded mean release mechanism followed zero order release kinetics.

STABILITY STUDIES:

Summary of formulation F8 before and after accelerated stability studies

Parameter	Initial	1 Month (40ºC/75% RH) Accelerated Condition	2 Month (40ºC/75% RH) Accelerated Condition	3 Month (40ºC/75% RH) Accelerated Condition
Description	White to off white colored, round shape uncoated tablet	White to off white colored, round shape uncoated tablet	White to off white colored, round shape uncoated tablet	White to off white colored, round shape uncoated tablet
Thickness (mm)	5.06±0.115	5.06±0.112	5.06±0.110	5.06±0.108
Friability (%)	0.403	0.402	0.401	0.400
Weight variation (mg)	196.9±6.60	196.9±6.60	196.9±6.60	196.9±6.34
Hardness (kg/cm^2)	7.66±0.57	7.66±0.55	7.66±0.53	7.66±0.51
Drug content (%)	99.66	99.64	99.61	99.60
Dissolution (% Release of Glimepiride)	98.97%	98.90%	98.89%	98.23%

SUMMARY AND CONCLUSION: For the formulation of sustained release matrix tablet xanthan gum, povidone were used as matrix forming agents. Other excipients used are microcrystalline cellulose (diluent) and Magnesium stearate (lubricating agent). Fourier transform Infrared spectral studies confirmed the absence of drug/polymers/ excipients interactions. The tablets were compressed using 9 mm circular flat-headed punch and die

on cadmach 10 station rotary punching machine. The prepared granules of sustained release tablets were evaluated for pre- compression parameters like angle of repose, bulk density, tapped density, compressibility index, hausner's ratio and prepared tablets were evaluated post compression parameter like hardness, weight variation, thickness, friability, drug content uniformity, *in-vitro* dissolution studies. Stability studies were carried out for F8 formulation showed good stability when stored at accelerated stability state as per the ICH guideline and the values are within acceptable limits. It was observed that Formulations F8 gave the drug release up to 12 hrs. All formulations were subjected for four different kinetic models viz. Zero order, First order, Higuchi matrix and Peppas model. Formulations F2, F3, F4, F5, F6,and F7 best fitted in to the zero order release kinetics with r^2 regression values 0.982, 0.990, 0.986,0.989, 0.976, 0.982 respectively. But however formulation F1 with r^2 regression value 0.991 shows first order release kinetics and formulation F8 with r^2 regression value 0.989 shows Higuchi release pattern. The natural polymers xanthan gum synthetic polymer povidone were selected to retard the drug release over a period of time. The preformulation studies like melting point, solubility of Glimepiride comply with IP standards. The FTIR Spectra revealed that, there was no interaction between polymers and drug. Hence it is concluded that these polymers were compatible with Glimepiride. Formulated tablets were found to comply with various physical parameter like tablet thickness, hardness, weight variation, friability, content uniformity and *in vitro* drug release. *In vitro* drug release of Glimepiride tablets showed sustained release pattern, which may be attributed to the use of various concentration of xanthan gum and povidone. After treatment with various mathematical models, it was concluded that out of the eight formulations, six formulations i.e. F2 to F7 were best fitted with zero order release kinetics where as formulation F1 was best fitted with first order release kinetics and formulation F8 was best fitted with Higuchi pattern.

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