FORMULATION AND INVITRO EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF GLIMEPIRIDE BY USING NATURAL GUMS AS RELEASE MODIFIERS

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ABSTRACT

Glimepiride is a first third generation sulphonyl urea agent for the treatment type II diabetes mellitus. The main objective of present work was to develop sustained release matrix tablet system by using natural polymers carrgeenan and xanthan gum. Glimepiride is given once daily in doses from 1-8 mg. The sustained release matrix tablets of glimepiride was prepared from F1-F6 by wet granulation method varying the concentrations of polymers. The formulated granules were evaluated for angle of repose, bulk density, tapped density, carr's index and hausner's ratio. The formulated tablets were evaluated for uniformity weight, hardness, friability, drug content, invitro swelling studies, invitro dissolution study and kinetic data analysis. The obtained results were clearly indicating that the formulated tablets results are with in the range and when compared with all formulations F8 was sufficiently sustained for 24 hrs and release of drug was anomalous non-fickian transport of diffusion from zero order release from the formulation was observed.

Key words: sulphonyl urea, carrgeenan, xantaangum, wet granulation.

INTRODUCTION:

Diabetes mellitus is a condition in which a person has a high blood sugar level, either because the body doesn't produce enough insulin, or because body cells don't properly respond to the insulin that is produced. Insulin is a hormone produced in the pancreas which enables body cells to absorb glucose, to turn into energy. If the body cells do not absorb the glucose, the glucose accumulates in the blood, leading to vascular, nerve, and other complications[1, 2].

The recent estimation that there were 171 million people in the world was with diabetes in the year 2000 and this will be increase to 366 million by 2030[3]. Diabetes is a condition primarily defined by the level of hyperglycemia giving rise to risk of micro vascular damage (retinopathy, nephropathy and neuropathy). It is associated with reduced life expectancy, significant morbidity due to specific diabetes related micro vascular complications, increased risk of macro vascular complication (ischemic heart disease, stroke and peripheral vascular disease), and diminished quality of life. The American Diabetes Association (ADA) estimated the national costs of diabetes in the USA for 2002 to be $US 132 billion, increasing to $US 192 billion in 2020[4].

Diabetes mellitus is mainly classified as four types. They are, Type -I, Type –II, Gestational diabetes, other types of diabetes. Glimepiride is the first III generation sulphonyl urea it is a very potent sulphonyl urea with long duration of action. It is practically insoluble in water. Soluble in dimethyl formamide, slightly soluble in methanol, sparingly soluble in methylene chloride. It also dissolves in dilute alkali and in dilute acids. Half life is Approximately 5 hours following single dose. Completely (100%) absorbed following oral administration. Over 99.5% bound to plasma protein. Glimepiride is used with diet to lower blood glucose by increasing the secretion of insulin from pancreas and increasing the sensitivity of peripheral tissues to insulin. The mechanism of action of Glimepiride in lowering blood glucose appears to be dependent on stimulation the release of insulin from functioning pancreatic beta cells, and increasing sensitivity of peripheral tissues to insulin.

MATERIALS:

Glimepiride was obtained Dr.Reddy's laboratories limited, Hyderabad, Carrageenan was obtained from Hi-media laboratories, Xanthan gum obtained from S.D. Fine chemicals, Mumbai. Other ingredients are under laboratory grade.

COMPATIBILITY STUDY:

Identification of drug-excipients compatibility study by FT-IR

FORMULATION OF SUSTAINED RELEASE MATRIX TABLETS:

Dose calculation:

The dose of glimepiride for sustained release formulation was calculated by the following equation using available pharmacokinetic data

$$Dt = Dose (1+0.639 \times t/t1/2)$$

Where, Dt = total dose of drug, dose = immediate release part (1mg), t = time (hrs), t1/2 = 5hrs

$$Dt = 1(1+0.639 \times 24/5) = 4.0672mg$$

Hence, Glimepiride 4mg was taken as sustained release dose per tablet.

All the formulated tablets are prepared by wet granulation method by using PVP-K30 in isopropyl alcohol was used as granulating agent.

Quantity of raw materials per tablet (in mg):

S.NO	INGREDIENT	F1	F2	F3	F4	F5	F6	F7	F8
1	GLIMEPIRIDE	4	4	4	4	4	4	4	4
2	CARRAGEENAN	4	8	12	16	--	--	--	--
3	XANTHAN GUM	--	--	--	--	4	8	12	16
4	TALC	3	3	3	3	3	3	3	3
5	MAGNESIUM STEARATE	5	5	5	5	5	5	5	5
6	LACTOSE	184	180	176	172	184	180	176	172

EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF GLIMEPIRIDE:

Evaluation of formulated granules:

Lubricated blends of all formulations was evaluated for Angle of repose, Bulk density, tapped density, Carr's index and Hausner's ratio.

Evaluation of formulated tablets:

The formulated tablets are evaluated for uniformity of weight, hardness, friability, drug content, invitro swelling studies, invitro drug release studies, kinetic data analysis.

Uniformity of weight[5]:

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.

Hardness[6]:

Hardness of the tablet was determined using the Monsanto harness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by tuning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force.

Friability[7]:

The Roche friability test apparatus was used to determine the friability of the tablets. Twenty pre-weighed tablets were placed in the apparatus, which was given 100 revolutions. After which the tablets were reweighed. The percentage friability was calculated.

Drug Content[7]:

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 volumetric flask and by using pH 7.8 as the extracting solvent and samples were analyzed spectrophotometrically.

In vitro swelling studies of sustained release matrix tablets:

Matrix tablets were weighed individually (W1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at 37°C ±1°C. At regular 1-hour time intervals until 6 hours, the tablet was removed from the Petri dish, and excess surface water was removed carefully with filter paper. The swollen tablet was then reweighed (W2) and the swelling index (SI) was calculated using the formula.

$$\% \text{ Swelling index} = [(W_2 - W_1)/W_1] \times 100$$

INVITRO DISSOLUTION STUDIES OF TABLETS[7]:

Dissolution studies were carried out for all the formulations combinations in triplicate, employing USP - II paddle method and 900ml of pH 7.8 phosphate buffer 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 with drawn periodically and the volume replaced with equivalent amount of the fresh dissolution medium. The samples were analyzed spectrophotometrically at 226 nm using UV-spectrophotometer.

KINETIC DATA ANALYSIS [8, 9]:

The analysis of drug release mechanism from a pharmaceutical dosage from is an important but complicated process and is practically evident in the case of matrix systems. As a model-dependent approach, the dissolution data was fitted to five popular release models such as zero-order, first-order, diffusion and exponential equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero order kinetics or first orders kinetics. The mechanism of drug release from matrix systems was studied by using Higuchi equation and Peppas-Korsemeyer equation.

RESULTS AND DISCUSSION:

COMPATIBILITY STUDY: The FTIR 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 change in percent transmittance which may be due to change in crystalline and 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.

Peak in pure drug	Functional group	Type of vibration	Peak in Physical mixture
3372.27	Amine (-N-H)	Stretch (medium)	3376.71
2934.66	Aromatic (C-H)	Stretch (medium)	2933.16
1706.28	Amide (C=0)	Stretch (Strong)	1703.03
1080.92	Sulfoxides	Stretch (Strong)	1074.40
1543.09	Aromatic (C=C)	Stretch (Weak, multiple)	1547.86

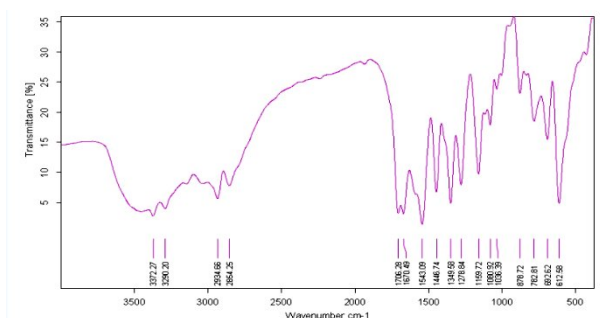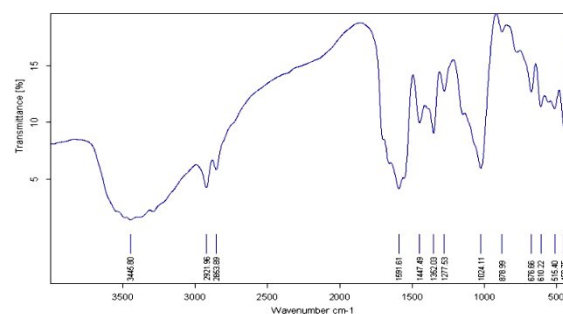Fig. No: 1: IR spectrum of Glimepiride

Fig. No: 2: IR Spectrum of physical mixture

EVALUATION OF FORMULATED GRANULES:

Evaluation of formulated granules:

Formulation code	Angle of repose (degree± SD)	BD (gm/ml± SD)	TD (gm/ml±SD)	Carr's index (%± SD)	Hausnerratio (%± SD)
F1	26.12±0.04	0.301±0.01	0.357±0.02	15.75±0.06	1.18±0.05
F2	27.07±0.01	0.317±0.03	0.379±0.04	16.41±0.07	1.19±0.04
F3	29.01±0.03	0.337±0.06	0.391±0.01	13.93±0.04	1.16±0.02
F4	26.77±0.07	0.307±0.04	0.347±0.07	12.66±0.01	1.13±0.06
F5	26.97±0.09	0.291±0.03	0.331±0.03	12.11±0.03	1.19±0.03
F6	25.71±0.06	0.286±0.01	0.342±0.01	16.47±0.01	1.15±0.01
F7	26.16±0.03	0.296±0.04	0.351±0.02	15.76±0.04	1.18±0.03
F8	27.11±0.09	0.307±0.05	0.359±0.03	14.51±0.07	1.17±0.05

The granules prepared by wet granulation method were evaluated for various flow properties. The granules of all batches showed good flow properties evident from the results shown in table-19. The angle of repose values were ranged from $25^o.71^{'}±0.06$ to $29^o.01^{'}±0.03$. The results were found to be below 30; hence they have good flow ability. The Carr's index value ranged from 12.11±0.03 to 16.47±0.01 and Hausner's ratio value ranged from 1.13±0.06 to 1.19±0.04; hence they have good flow and free flow ability.

EVALUATION OF FORMULATED TABLETS: Evaluation of formulated tablets

Formulation code	Weight variation (mg ± SD)	Hardness (kg/cm^2±SD)	Friability (%± SD)	Drug content (%± SD)	Thickness (%± SD)
F1	201±0.58	6.5±0.3	0.76	98.13±0.04	2.1±0.007
F2	202±0.61	6.3±0.1	0.74	99.19±0.01	2.0±0.006
F3	199±0.54	6.9±0.1	0.73	97.29±0.12	2.1±0.011
F4	199±0.91	6.6±0.3	0.75	98.19±0.09	2.1±0.008
F5	201±0.11	7.1±0.2	0.62	99.17±0.07	2.1±0.009
F6	202±0.23	7.3±0.2	0.67	98.11±0.03	2.1±0.010
F7	199±0.09	6.9±0.4	0.66	99.13±0.17	2.1±0.006
F8	198±0.91	7.0±0.1	0.68	99.91±0.14	2.0±0.011

The formulated sustained release matrix tablets were then evaluated for various physical characteristics like thickness, weight variation, hardness, friability, drug content. The weight variation of tablets was uniform in all formulations and ranged from 198±0.01to 202±0.061.

The hardness of the prepared tablets was ranged from 6.3±0.1 to 7.3±0.2, friability values were ranged from 0.96±0.07 to 1.03±0.13. Drug content of tablets was ranged from 97.29±0.12 to 99.17±0.07, thickness of tablets was uniform and values are ranged from 2.0±0.006 to 2.1±0.011.

Swelling index of formulated matrix tablets:

Fig.No-3 (a): **% Swelling index plot**
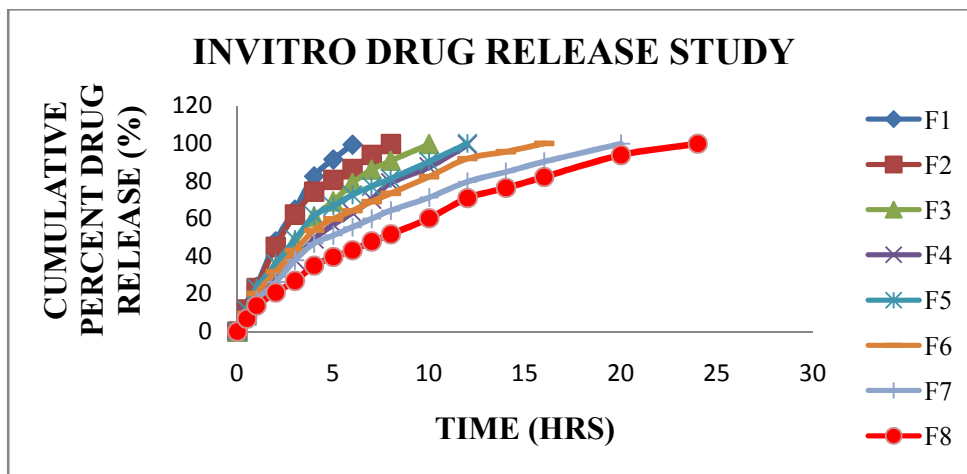
Fig.No-3 (b): **% Swelling index plot**

The swelling behaviors all formulated tablets were calculated and results were ranging from 19.27 to 83.33. The results are clearly indicating that swelling capacity increases by increasing polymer concentration

Invitro drug release study of formulated sustained release matrix formulations

Fig: 4- Invitro drug release study

The formulated sustained release matrix tablets were then subjected to Invitro dissolution test for evaluating drug release from the formulation. The Invitro dissolution test was carried out in 900 ml of phosphate buffer pH-7.8 in USP-II paddle type apparatus at 50 rpm and 37±0.5°C. The results of dissolution study was depends on polymer concentration. Formulation containing Xanthan gum 16 mg had given drug release 99.39% in 24 hrs. Then the formulations containing Xanthan gum were given better release profiles when compared with carrageenan formulations.

KINETIC STUDIES OF GLIMEPIRIDE SUSTAINED RELEASE MATRIX TABLETS:
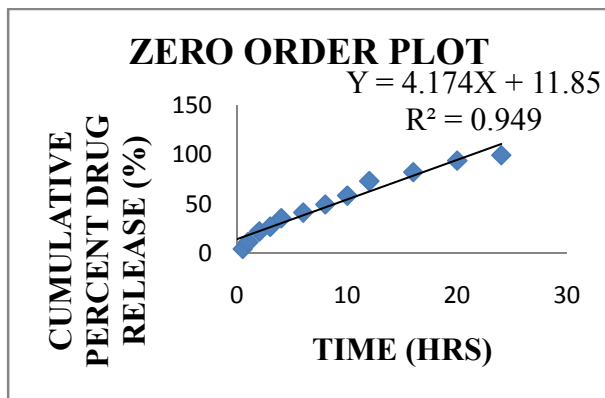
Fig.No-5**: zero order plot**
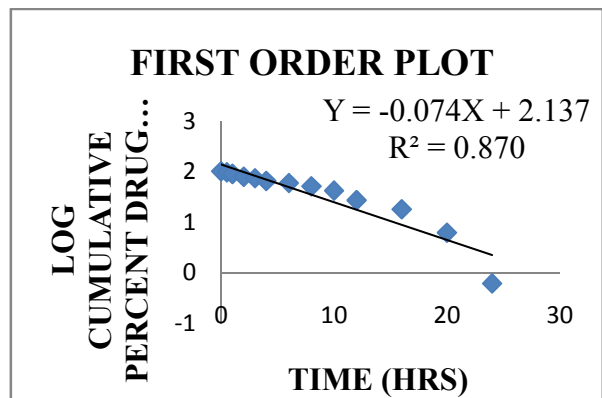

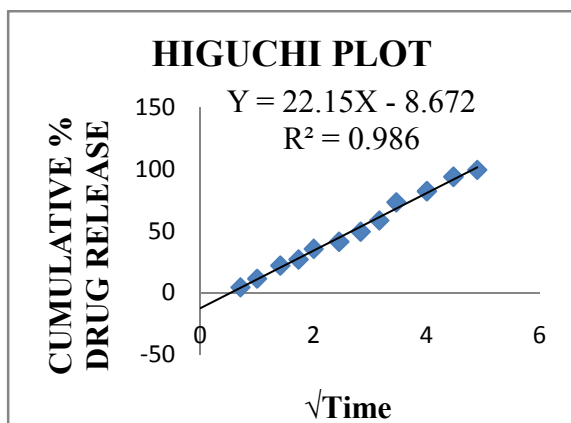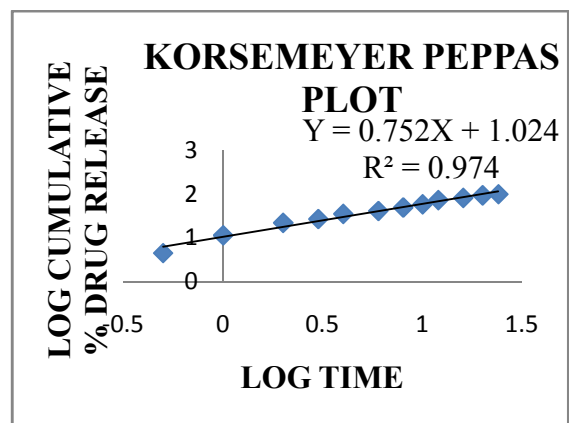Fig.No-6: **First Order Plot**

Fig.No-7: **Higuchi Plot**

Fig.No-8: **Korsemeyer Peppas Plot**

In order to determine the mechanism of drug release form the formulations , the Invitro dissolution data was fitted to Zero order, First order, Higuchi plot and Korsemeyer - peppa's plot was drawn for optimized formula and interpretation of release exponent value (n) was calculated. The results of R^2 for zero and first order were obtained as 0.949, 0.870. Based on that we will confirm the optimized formulation followed Zero order release.

The half life time T_{50} and T_{90} was founded as 8.06 and 19.07, the rate constant values for zero and first order was founded as 4.174 and -0.074. The drug release was diffusion controlled as the plot of optimized formulation F8 was found 0.986 as regression co-efficient in higuchi plot. From Korsemeyer peppa's plot the release exponent value n was found as 0.752 and it was confirmed as the release of drug from the formulation was founded as anomalous non-fickian transport of diffusion.

CONCLUSION:

The main objective of the present study was to develop sustained release matrix tablet formulation containing 4mg of Glimepiride for once daily therapy. In the present work it has been observed that using of Xanthan gum retarded the drug release up to 24 hrs satisfactorily when compared with same concentrations of Carrageenan. When compared with all the formulations F8 was sufficiently sustained the release of the drug and anomalous non-fickian transport of diffusion from zero order release from the formulation was observed.

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