AMERICAN JOURNAL OF PHARMTECH RESEARCH
Journal home page: http://www.ajptr.com/

Design and In-Vitro Evaluation of Sustained Release Matrix Tablets of Glimepiride

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ABSTRACT

The present investigation is to Design and *In-vitro* evaluation of the sustained release matrix tablets of Glimepiride used for the treatment of type 2 diabetes mellitus. The Glimepiride (6mg) sustained-release (SR) matrix tablets were prepared by wet granulation method using different concentrations of hydrophilic and hydrophobic polymers. Such as Xanthumgum, Microcrystalline Cellulose, Povidone, Guargum, Magnesium Stearate, Pectin. The mechanism of action of glimepiride in lowering blood glucose appears to be dependent on stimulating the release of insulin from functioning pancreatic beta cells. The mixture of Glimipride powder was subjected to pre compression evaluation such as angle of repose, loose bulk density, tapped bulk density, hausarner's ratio and compressibility index. The FTIR Spectrum is carried for the pure drug and for the optimized formula. This indicated that there was not any interaction between drug and polymer. All the formulations (F1-F12) were evaluated for weight variation, hardness, thickness, Friability, Content uniformity and invitro dissolution. The invitro dissolution studies were performed in pH 7.4 indicated that formulation F8 (Glimepiride and Guar gum in the ratio of 1:6) is the most success full formulation of this study and exhibited drug release 99.2% in 12 hr. To investigate the drug-release kinetics, data were fitted to various kinetic models such as zero-order, first-order, Higuchi equation, Korsmeyer-Pappas equation, and Hixson–Crowell equation.

Keywords: Glimepiride, sustained release, In-vitro evaluation, MCC, Avicel PH-102.

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Received 20 October 2017, Accepted02 November 2017

Please cite this article as: Sumalatha G *et al*., Design and In-Vitro Evaluation of Sustained Release Matrix Tablets of Glimepiride. American Journal of PharmTech Research 2017.

INTRODUCTION

Oral route is one of the most popular routes of drug delivery due to its ease of administration, patient compliance, least sterility constraints and flexible design of dosage form.

Tablets: [1, 2]

Over 90% of the formulations manufactured today are ingested orally. This shows that this class of formulation is the most popular worldwide and the major attention of the researcher is towards this direction. With advancement in technology and increase in awareness, towards modification in standard tablet is done to achieve better acceptability as well as bioavailability because of which newer and more efficient tablet dosage forms are being developed. The main reasons behind formulation of different types of tablets are to create a delivery system that is relatively simple and inexpensive to manufacture, provide the dosage form that is convenient from patient's perspective and utilize an approach that is unlikely to add complexity during regulatory approval process. To understand each dosage form, tablets here are classified by their route of administration and by the type of drug delivery system they represent within that route.

Conventional Drug Delivery System:

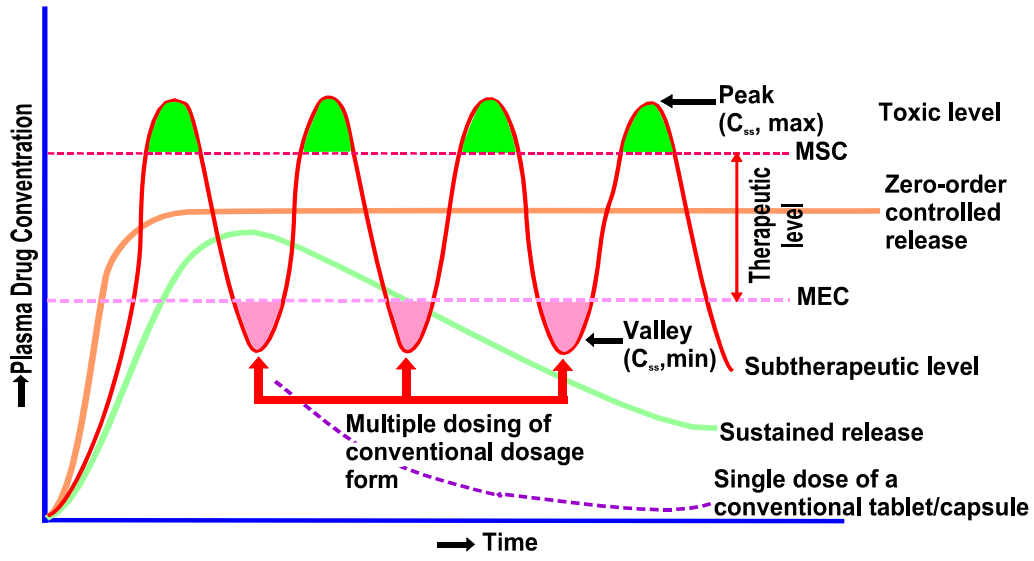

Figure 1: Hypothetical plasma concentration-time profile from conventional multiple dosing and single doses of sustained and controlled delivery formulations. (MSC = maximum safe concentration, MEC = minimum effective concentration).

Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid/immediate absorption[3]. As can be seen in the graph (Figure 1), administration of the conventional dosage form by extra vascular route

does not maintain the drug level in blood for an extended period of time. The short duration of action is due to the inability of conventional dosage form to control temporal delivery.

The conventional dosage forms like solution; suspension, capsule, tablets and suppository etc. have some limitations such as

1. Drugs with short half-life require frequent administration, which increases chances of missing the dose of drug leading to poor patient compliance.
2. A typical peak-valley plasma concentration-time profile is obtained which makes attainment of steady state condition difficult. The unavoidable fluctuations in the drug concentration may lead to under medication or overmedication as the steady state concentration values fall or rise beyond the therapeutic range.
3. The fluctuating drug levels may lead to precipitation of adverse effects especially of a drug with small therapeutic index, whenever overdosing occurs (Figure 1).

In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits[4].

Controlled / Sustained release drug delivery system:

For many disease states the ideal dosage regimen is that by which an acceptable therapeutic concentration of drug at the site (s) of action is attainted immediately and is then maintained constant for the desired duration of the treatment. Over the past 30 years as the expense and complication involved in marketing new drug entities have increased, with concomitant recognition of the therapeutic advantage of modified release per oral dosage forms, greater attention has been focused on development of sustained, controlled release and delayed release system.

Sustained release drug delivery system has been constantly used to retard the release of therapeutic agents such that it‘s appearances in the circulation is delayed or prolonged and its plasma profile is sustained in duration. The onset of its pharmacological action is often delayed and duration of therapeutic action is sustained.

Advantages:

1. Overcome patient compliance problems.
2. Employ less total drug

a) Minimize or eliminate systemic side effects

b) Minimize drug accumulation with chronic dosing.

3. Improve efficiency in treatment

a) Improves control of condition i.e., reduced fluctuation in drug level.

b) Improves bioavailability of some drugs.

c) Make use of special effects, e.g. Sustained-release aspirin for morning relief of arthritis by dosing before bed time.

Disadvantages:

1. Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.
2. Poor *in- vitro – in-vivo* correlation.
3. Reduced potential for dose adjustment of drugs normally administered in varying strengths.

Mechanism of Drug Release from Matrix Tablets:

As shown in (Figure 2), in erodible matrices, polymer erosion from the surface of the matrix determines the drug release, on exposure to aqueous fluid, hydrophilic matrices take up water, and polymer starts hydrating to form a gel layer[6]. Drug release is controlled by diffusions barriers / or by surface erosion. An initial burst of soluble drug may occur due to surface leaching when a matrix containing a swellable glassy polymer comes in contact with an aqueous medium, there is an abrupt change from a glassy to a rubbery state which is associated with swelling process with time, water infiltrates deep into the case increasing the thickness by the gel layer[5]. Concomitantly the second layer becomes fully hydrated and starts dissolving or eroding. When water reaches the center of the system and the concentration of drug falls below the solubility value, the release rate of drug begins to reduce. At the same time, an increase in thickness of the barrier layer with time increases the diffusion path length, reducing the rate of drug release. Drug release kinetic associated with these gel – layer dynamic, range initially from Fickian to anomalous (Non – Fickian) and subsequently from quasi – Constant (near Zero order) to constant[9]. In general, two major factors control the drug release from swelling controlled matrix system[7]. They include

1. The rate of aqueous medium infiltration into the matrix, followed by a relaxation process (hydration, gelation or swelling).

2. The rate of matrix erosion.

Swelling of HPMC matrix tablet was higher for higher molecular weight. They attributed this to the large hydrodynamic volume occupied by higher molecular weight chain when hydrated. As the polymer chain becomes more hydrated and the gel becomes more dilute, the disentanglement

concentration may be reached, i.e., the critical polymer concentration below which the polymer chain disentangles and get detached from gelled matrix (Figure 2).

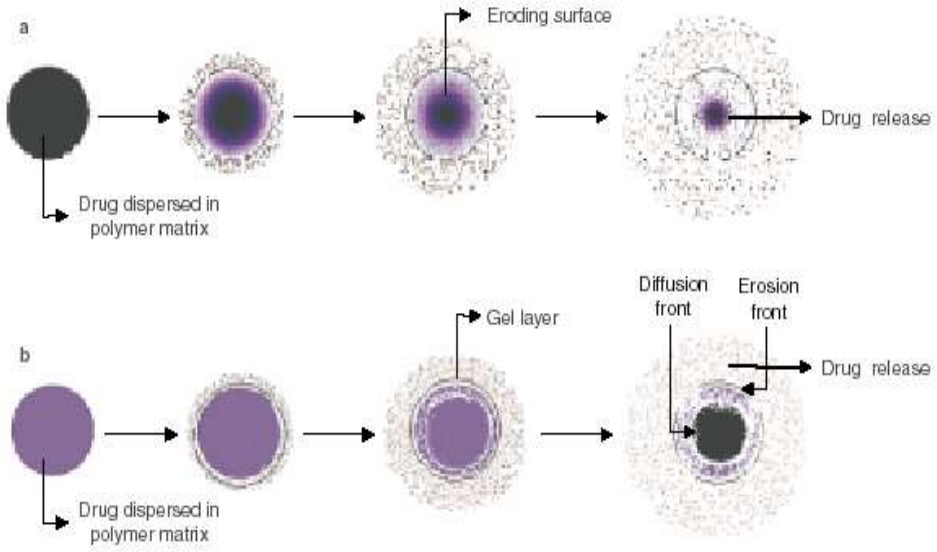

Figure 2: Schematic drug release from matrix diffusion controlled-release drug delivery systems with the drug homogenously dispersed in: (a) an erodible polymer matrix; and (b) a hydrophilic, swellable polymer matrix.

MATERIALS AND METHOD

Materials used:

Glimepiride purchased (Dr.Reddy's laboratories Pvt. ltd, Hyderabad) Xanthangum, Gaur gum (Cadila Pharma, Ahmedabad).Pectin (S.D. Fine chemical Pvt. Ltd), Microcrystalline cellulose (Loba Chemie Pvt. Ltd, Mumbai), Polyvinyl pyrrolidone (Vilin Biomed, New Delhi). Talc, Magnesium Stearate (Qualikems Fine Chemicals Pvt. Ltd), Sodium Hydroxide Pellets (Finar Chemicals Limited), Hydrochloric acid (Merck specialties Pvt. Ltd) , Isopropyl alcohol (RFCL Ltd).

Method :

Preformulation Studies:

Preformulation may be described as a phase of the research and development process where the formulation scientist characterizes the physical, chemical and mechanical properties of new drug substances, in order to develop stable, safe and effective dosage forms. Ideally the preformulation phase begins early in the discovery process such that the appropriate physical and chemical data is available to aid the selection of new chemical entities that enter the development process. During this evaluation, possible interaction with various inert ingredients

intended for use in final dosage form is also considered in the present study. The following data must be considered.

Table 2: Formulation of Glimepride Sustained release Tablets Prepared by Wet Granulation Technique.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Glimepiride	6	6	6	6	6	6	6	6	6	6	6	6
Pectin	18	24	30	36	-	-	-	-	-	-	-	-
Gaur gum	-	-	-	-	18	24	30	36	-	-	-	-
Xanthan gum	-	-	-	-	-	-	-	-	18	24	30	36
MCC(Avicel P^{H}101)	107	101	95	89	107	101	95	89	107	101	95	89
PVPK90	10	10	10	10	10	10	10	10	10	10	10	10
Isopropyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Mg, Stearate	6	6	6	6	6	6	6	6	6	6	6	6
Talc	3	3	3	3	3	3	3	3	3	3	3	3
Total weight (mg)	150	150	150	150	150	150	150	150	150	150	150	150

Drug-Excipient Compatibility Studies by FTIR Spectroscopy:

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients, which are added to facilitate administration, to promote the consistent release and bioavailability of the drug and protect it from degradation. Infra red spectroscopy is one of the most powerful analytical techniques to identify functional groups of a drug.

Method:

Compatibility study was performed by preparing compatibility blends at different ratios of different excipients with the drug, based on tentative average weight. These blends were stored at accelerated condition of 40^{0}C/75% RH. Control samples were stored at 40^{0}C. The ratio of drug to excipient varies from 1:1 to 1:10 depending on the purpose of use, and the samples were kept in double lined poly-bags. The samples were evaluated for any change in the physical characteristics with reference to its controlled sample stored at 40^{0}C for a period of 15 days. In the present study, the potassium bromide disc (pellet) method was employed. Fourier-transform infrared (FT-IR) spectra of the Drug and polymer were obtained on Alpha Brooker FT-IR (Tokyo, Japan). The spectra were scanned over the wave number range of 4000 to 400 cm-1

Analytical method:

Construction of Calibration curve of Glimepiride by UV-Visible spectroscopy:

Preparation of Standard stock solutions:

Glimepiride equivalent to 10 mg was weighed and transferred to 10 ml volumetric flask, dissolved in methanol and the final volume was made up to 10ml with methanol. The resulted solution had the concentration of 1mg/ml (1000µg/ml) which was labeled as "stock solution A" From the stock solution A, 1 ml was pipette out in 10ml volumetric flask and the final volume was made up to 10ml with phosphate buffer (pH 7.4).The resulted solution had the concentration of 0.1mg/ml (100µg/ml) which was labeled as "stock solution B". This stock solution B is used as working stock solution for further study. Further dilutions were prepared from the same solution.

Preparation of Standard solutions:

From the stock solution B, further dilution was made with phosphate buffer (pH 7.4) in 10 ml volumetric flasks to get the solutions in the range of 2-16 µg/ml concentration and absorbance was recorded at 228 nm against suitable blank using UV-Spectrophotometer (UV-1601, Shimadzu, Japan).A calibration curve of absorbance against concentration was plotted and the drug follows the Beer's & Lambert's law in the concentration range of 2-16µg/ml. The regression equation and correlation coefficient was determined.

Preparation of matrix tablets:

All the tablets, each containing 6mg of glimepiride were prepared by wet granulation method. The manufacturing process involves following steps they were

1) Sifting: Drug (Glimepiride), polymers (Xanthangum, Guargum & pectin) and diluents were sifted through 40 mesh sieve (stage 1).

2) Binder preparation: Povidone (K- 90) was dissolved in isopropyl alcohol.

3) Granulation

a) Dry mixing: The drug and diluent after stage 1 were mixed well to ensure the uniformity of premix blend. Several drug –diluent premixes were then mixed with the selected ratio of polymer (s) previously shifted through sieve no 40 for 5 min.

b) Granulation: Granules were prepared by adding step 2 in step 3a and the wet mass pass through sieve no.18.

c) Drying: The produced glimepiride granules were dried at 55°C ± 5°C for 1 hour in a hot-air oven.

4) Sizing: Dried granules were passed through 20 mesh sieve[10].

5) Lubrication: These granules were blended with lubrication mixture (magnesium stearate and talc) for 5min in polythene bag.

6) Compression: after the lubrication granules were compressed using 16 station rotary tableting machine, equipped with flat-faced, round punches of 10-mm diameter.

The drug polymer ratio was developed to adjust drug release as per theoretical release profile and to keep total weight of tablet constant for all the fabricated batches under experimental conditions of preparations. The total weight of the matrix tablets was 200 mg with different drug, polymer ratios like 1:3, 1:4, 1:5, and 1:6. The various polymers used were Xanthangum, Guargum & pectin. Diluents like MCC (water-insoluble) were used for the preparation of matrix tablets[8].

Evaluation of granules:

Evaluation was performed to assess the physicochemical properties and release characteristics of the developed formulations[9].

a) Bulk density (B.D):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and the initial volume was noted. This initial volume is called the bulk volume. From this, the bulk density is calculated according to the formula mentioned below. It is expressed in g/cc and is given by

$$B.D = m/V_O$$

Where, m=mass of the powder

V_O= bulk volume of the powder

b) Tapped density (T.D):

It is the ratio of total mass of powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted (the difference between these two volumes should be less than 2%). If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. It is expressed in g/cc and is given by:

$$T.D = m/V_i$$

Where, m= mass of the powder.

V_i = tapped Volume of the powder.

c) Hausner's Ratio (H.R) :

It is measurement of frictional resistance of the drug. The Ideal range should be 1.2 –1.5

it was determined by the ratio of tapped density and bulk density.

$$H.R = T.D / B.D$$

d) Compressibility Index (C.I):

The flowability of powder can be evaluated by comparing the Bulk density (BD) and Tapped

bulk density (TD) of powder and the rate at which it packed down. Compressibility index was calculated using the following formula;

$$C.I = 100 \text{ X } (1 - 1/H.R.)$$

e) Flow properties (**Angle of Repose (θ) :**

This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane.

The angle of repose of granules was determined by funnel method. The funnel was fixed at a particular height (2.5 cm) on a burette stand. The powder sample was passed through the funnel until it forms a heap. Further adding of granules was stopped as soon as the heap touches the tip of the funnel. A circle was drawn across it without disturbing the pile. The radius and height of the heap was noted down. The same procedure was repeated for three times and the average value was taken. The angle of repose was calculated by using equation.

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

$$\theta = \tan^{1}(h/r)$$

Where, θ = Angle of repose

h = Height of the heap

r = Radius of the heap

Evaluation of matrix tablets:

The prepared tablets were evaluated for General appearance, thickness, hardness, weight variation, friability and uniformity of weight[8].

General appearance:

The prepared tablets were evaluated visually for their appearance, texture and tablets defects.

Uniformity of weight (Weight variation test):

20 tablets were weighed individually and collectively. Average weight was calculated from the total weight of all tablets. The individual weights were compared with the average weight. The percent deviation was calculated using the following formula**.**

$$\% \text{ Deviation} = \text{Individual weight–Average weight/ Average weight x } 100$$

The percentage difference in the weight variation should be within the permissible limits of 10% as per the limits mentioned as per Indian pharmacopoeia.

Hardness test:

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical

stress during handling and transportation. The hardness was tested using Monsanto hardness tester. The average of the five determinations was determined and reported.

Friability test (F):

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. This In-process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment. Roche friabilator was used to measure the friability of the tablets. It was rotated at a rate of 25 rpm. Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting from free fall of tablets within the chamber of the friabilator. After 100 rotations (i.e. in 4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively. Permitted friability limit is 1.0%. The percent friability was determined using the following formula.

$$(W_1 - W_2)/W_1 \times 100$$

Where,

W_1 = weight of the tablets before test

W_2 = weight of the tablets after test

Thickness: Thickness of the tablets was calculated by the use of Vernier callipers.

Content Uniformity Test:

Drug content:

For determination of drug content three tablets from each formulation were weighed individually and powdered. The quantity of powder was equivalent to 10 mg. The equivalent weight glimepiride was transferred into 100 ml volumetric flask diluted to 100ml with sufficient amount of phosphate buffer (pH 7.4). Then aliquot of the filtrate was diluted suitably and analyzed spectrophotometrically at 228nm against blank.

RESULTS AND DISCUSSION:

Melting point determination of Glimepiride

The melting point of Glimepiride was found to be 205-207^{o}C, which complied With USP standard, thus indicating purity of obtained drug sample.

Determination of solubility:

The solubility of the Glimepiride was determined and found to be soluble in Dimethyl formamide, slightly soluble in methanol, sparingly soluble in methylene chloride and insoluble in water.

Drug- Excipients Compatibility Studies: Drug Interaction Study:

The IR spectrum of pure drug was found to be similar to the standard spectrum of Glimepiride. The results were shown in the figure 3 & 4. The FTIR Spectrum is carried for the pure drug and for the optimized formula (F8). The IR spectra for the pure drug was done and the result showed the amine group ranges at 3265^{cm-1}, carbonyl group at 1723 $^{cm-1}$ and benzene ring at 2936^{cm-1}. All the characteristic peaks of pure drug were observed in the spectrum of mixture. This indicated that there was not any interaction between drug and polymer.

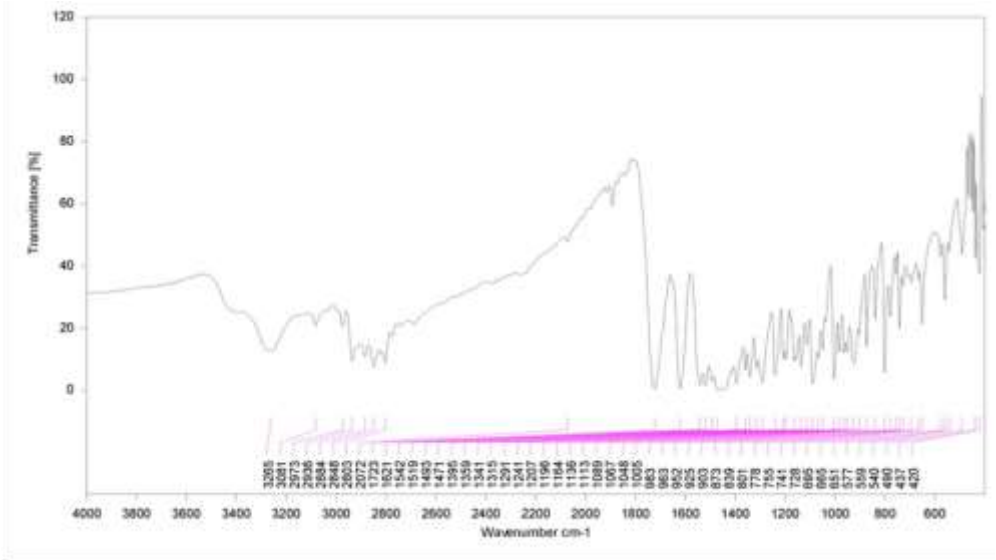

Figure 3: FT-IR Spectra of Glimepride Pure Drug

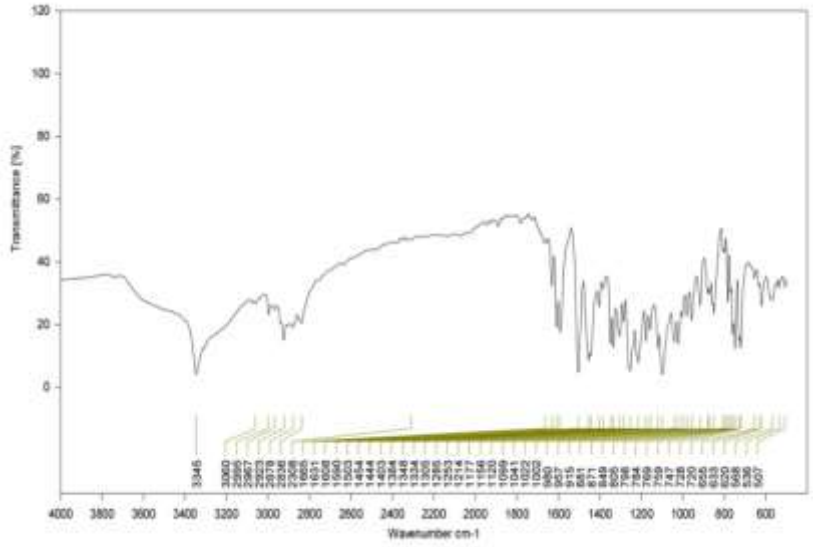

Figure 4: FT-IR spectra of optimized formulation (F8)

UV-Spectroscopy - Analysis of drug

Calibration curve of Glimepiride in phosphate buffer pH 7.4:

Wavelength of maximum absorption: 228 nm. (Figure 5)

Table 1: Concentration and absorbance of Glimepiride in phosphate buffer pH 7.4.

S.No	Concentrations(µg/ml)	Absorbance at 228nm
1	2	0.086
2	4	0.154
3	6	0.245
4	8	0.326
5	10	0.410
6	12	0.492
7	14	0.574
8	16	0.650

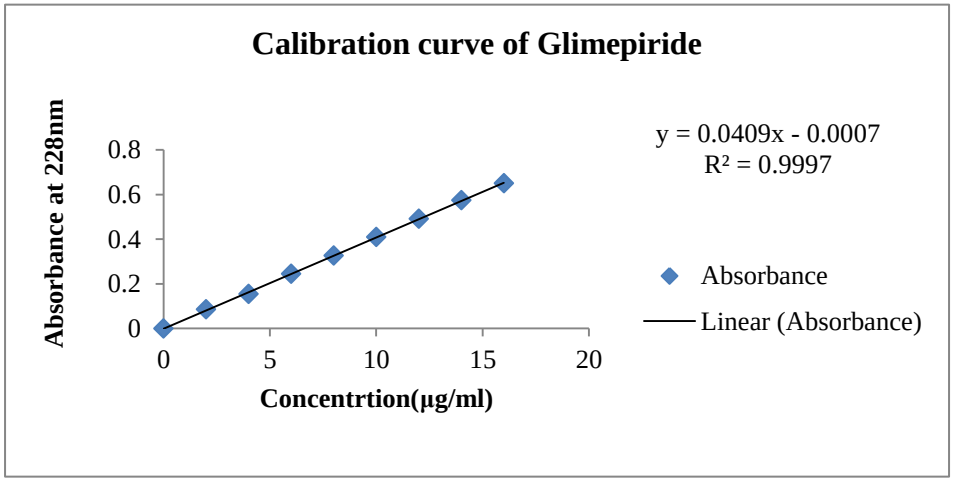

Figure 5: Standard Calibration Curve of Glimepiride in P^H7.4 phosphate buffer

Evaluation of Blend:

The enteric coated tablets of Glimepiride were prepared using wet granulation method. Before granulation, the powder blends were subjected to pre-granulation evaluation to determine the flow properties and the compressibility. The results of the pre-compression evaluation are as given below (Table 3).

Table 3: Pre-Compression Parameters for Prepared Tablet by Wet Granulation Technique

Micromeritic Evaluation:

Formulation code	Bulk density (gm /ml)	Tapped density	Hausner's ratio	Carr's index (%)	Angle of repose (θ)
F1	0.317	0.376	1.18	15.69	26.38
F2	0.291	0.331	1.19	12.11	27.14
F3	0.307	0.347	1.13	12.26	26.85
F4	0.326	0.384	1.17	15.10	29.12
F5	0.286	0.342	1.19	16.37	28.47
F6	0.301	0.350	1.16	14.00	26.96
F7	0.298	0.344	1.15	13.33	25.72
F8	0.307	0.356	1.15	13.76	26.38
F9	0.314	0.361	1.14	13.00	26.54

F10	0.324	0.375	1.15	13.6	25.64
F11	0.316	0.365	1.15	13.42	26.4
F12	0.318	0.371	1.16	14.28	36.59

Bulk Density and Tapped Density:

The power of different formulations was evaluated for Loose Bulk Density (LBD) and Tapped Bulk Density (TBD). Both the bulk density and tapped density results are shown in (Table 2). The bulk density and the tapped density for all the formulations varied from 0.286 to 0.326.

The values obtained lies within the acceptable range and not a large difference exists between the bulk density and tapped density. This result helps in calculating the % compressibility of the powder.

Hausner's Ratio:

The flowability of powder blend was determined using Hauser's Ratio. Hauser's Ratio lies within the range of 01.13 to 01.19. All the formulations show good flow ability. The results are shown in (Table 2).

Compressibility index:

The percentage compressibility of powder was determined using Carr's compressibility index. Compressibility index lies within the range of 12.11 to 15.69. All formulations show good compressibility. The results are shown in (Table 3).

Angle of Repose:

The values were found to be in the range of 25.64 to 36.59. All the formulation showed angle of repose below 30^{o} which indicates an excellent flow property of the granules. The results obtained for all the formulations shown in (Table 2).

Formulation of sustained release matrix tablets: In the present study an attempt has been to formulate and evaluate sustained release matrix tablets of Glimepiride by wet granulation (Non aqueous granulation) technique, employing swellable polymers like Xanthan gum, Pectin & Guargum taken along with pharmaceutically acceptable, easily available inert excipients like, isopropyl alcohol, talc, magnesium stearate, povidone, microcrystalline cellulose (MCC, Avicel PH-102). The drug and polymers (guar gum, xanthan gum, pectin) were sifted through sieve no 40 and the preparation of binder solution of povidone followed by dry mixing of drug and diluents to form pre-mixes of drug and polymer which are passed through sieve no 40 to obtain granules. The produced Glimepiride granules were dried at 55°C ± 5°C for 1 hour in a hot-air oven. Twelve formulations were prepared. The formulations were subjected to both pre and post formulation studies.

Physical characterization of SR Tablets of Glimepiride:

Uniformity of weight:

All the prepared tablets of Glimepiride were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits of ±7.5%.

Hardness and friability:

The hardness of the tablet formulations was found to be in the range of 6.3 to 7.2 kg/cm^2. The friability values were found to be in the range of 0.65to 0.72 %.

Uniformity of drug content:

The low values of standard deviation indicates uniform drug content within the tablets The percent drug content of all the tablets was found to be in the range of 97.16 to 102.6 percent (which was within the acceptable limits of ±5%.)

In -vitro drug release study:

In vitro dissolution studies were performed in pH 7.4 phosphate buffers on the above promising formulation, namely, formulation 8 for 12 hours. The *in-vitro* release profiles of formulation F1 to F12 containing different composition of polymers. In the dissolution studies the Guargum polymers were showing better drug release up to 12hrs.

Paddle method Dissolution data of Matrix tablets formulations of Glimepiride by Paddle method (USP II) are reported in (Table 4)

Table 4: Evaluation of Glimepiride Formulations

Formulation code	Weight variation	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	Content uniformity
F1	150±0.61	6.4±0.30	0.72±0.12	3.8±0.02	99.28±0.21
F2	149±0.54	6.3±0.20	0.68±0.08	3.6±0.08	97.16±0.17
F3	149±0.91	6.7±0.25	0.69±0.09	3.7±0.06	101.18±0.14
F4	152±0.58	6.6±0.10	0.66±0.15	3.8±0.04	97.68±0.23
F5	151±0.46	6.7±0.40	0.68±0.14	3.8±0.01	99.41±0.10
F6	148±0.23	6.9±0.25	0.65±0.06	3.6±0.02	98.19±0.17
F7	151±0.53	7.2±0.30	0.67±0.08	3.8±0.04	102.6±0.12
F8	149±0.42	7.1±0.10	0.68±0.16	3.8±0.06	99.31±0.21
F9	148±0.45	7.0±0.11	0.66±0.15	3.78±0.08	98.25±0.64
F10	151±0.14	6.9±0.15	0.68±0.14	3.79±0.10	99.68±0.98
F11	148±0.19	6.9±0.25	0.71±0.17	3.8±0.02	101.10±0.05
F12	151±0.36	7.01±0.54	0.72±0.07	3.8±0.08	99.25±0.41

According to above R^2 value, best formulation, i.e., F-8 formulation follows korsmeyar-peppa's plot which shows that drug is released from matrix**.**

Stability Studies:

There was no significant change in physical and chemical properties of the tablets of formulation F-8 after 3 Months. Parameters quantified at various time intervals were shown in (Table 6).

Table 5: **Release profile of Glimepiride sustained release tablets by Wet Granulation Technique**

T	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
1	31.86	27.06	26.73	26.52	21.38	18.74	14.46	10.77	25.64	23.14	19.45	15.64
2	44.35	40.68	42.24	40.35	35.09	30.92	29.54	24.53	44.6	38.79	29.47	24.69
4	70.82	66.82	66.38	55.46	62.15	59.66	41.75	36.99	61.87	52.64	43.67	39.87
6	87.43	80.72	83.35	78.65	73.85	70.39	64.28	58.25	72.64	68.02	61.58	56.9
8	95.64	88.25	90.1	85.52	82.39	81.31	76.36	72.65	82.36	80.12	76.9	69.45
10	-	95.12	96.32	89.47	91.04	93.15	89.94	91.24	95.61	91.64	80.64	86.9
12	-	-	-	93.21	96.21	98.32	98.59	99.28	-	96.54	93.51	93.64

Table 6: Results of stability study of optimized formulation (F8)

S.NO	Parameters	Initial	1 month	2 month	3 month	Limits as per specification
1	400C/75% RH% Release	99.28	99.22	99.11	99.02	Not less than85 %
2	400C/75% RH Assay Value	99.31	99.28	99.22	99.17	Not less than90 % Not more than110 %

Effect of Polymers (Xanthangum, Guargum & Pectin) on In-vitro release Glimepiride:

In present study, the high viscosity grade Guar gum as specified by USP was used as hydrophilic matrix forming agent. It forms a strong gel in aqueous media which may be useful to control the drug release of both, water soluble as well as water insoluble drugs from formulations.

The half life of Glimepiride is 5 hrs. So the drug release up to 10 hrs will be able to show the pharmacological action up to 24 hrs. In attempt to prolong the drug release of drug up to 10 hrs, the release retarding agent Xanthan gum, Guar gum & Pectin were used.

Guar gum is high viscosity grade polymer and results in increased hydration rate. Consequently distance required for drug to travel from tablet to dissolution medium increases. Furthermore, cross linking in the inter polymer chain increases with increasing viscosity of polymer grade.

Formulation F-8 containing Guar gum in different concentration shows the sustained release the drug for up to12 hrs. So, among all the formulations F8 is considered as optimized formulation.

Drug Release Kinetics -Model Fitting of the Dissolution Data

Whenever a new solid dosage form is developed or produced, it is necessary to ensure that drug

dissolution occurs in an appropriate manner. The pharmaceutical industry and the registration authorities do focus, nowadays, on drug dissolution studies. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q=f(t). Some analytical definitions of the Q(t) function are commonly used, such as zero order, first order, Hixson–Crowell, Higuchi, Korsmeyer–Peppas models. Different models expressing drug release kinetics were given in (Table 3).

Mechanism of Drug Release:

To find out the drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix, first 60% drug release data can be fitted in Korsmeyer–Peppas model which is often used to describe the drug release behavior from polymeric systems when the mechanism is not well-known or when more than one type of release phenomena is involved.

$$\mathbf{Log\ (M_t / M_\infty) = Log\ K_{KP} + n\ Log\ t}$$

Where, M_t is the amount of drug release at time t,, M_∞ is the amount of drug release after infinite time, K_{KP} is a release rate constant,n is the release exponent indicative of the mechanism of drug release.

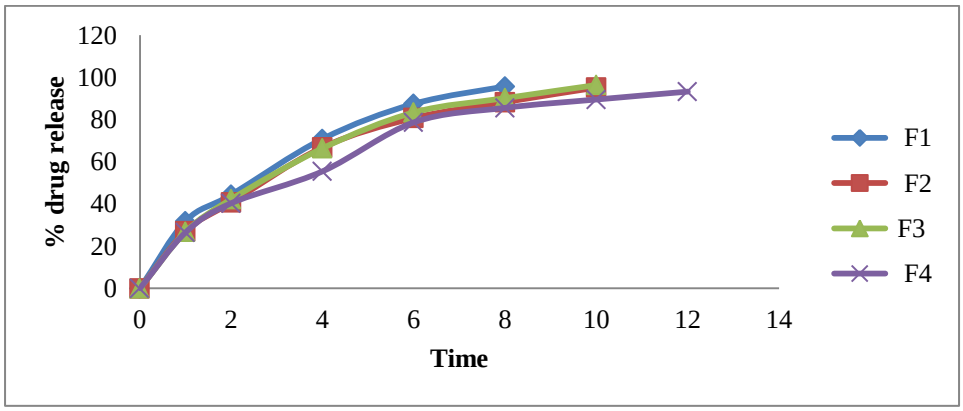

Figure 6: Percentage drug release of Glimepiride (F1-F4)

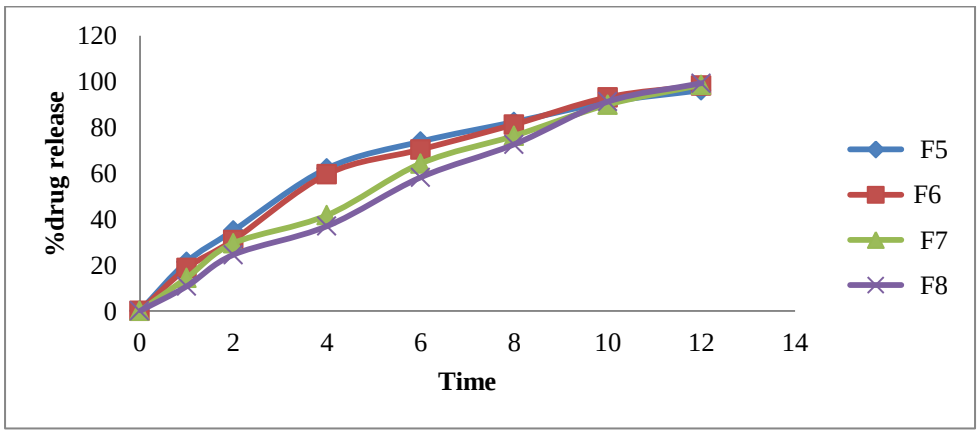

Figure 7: Percentage drug release of Glimepiride (F5-F8)

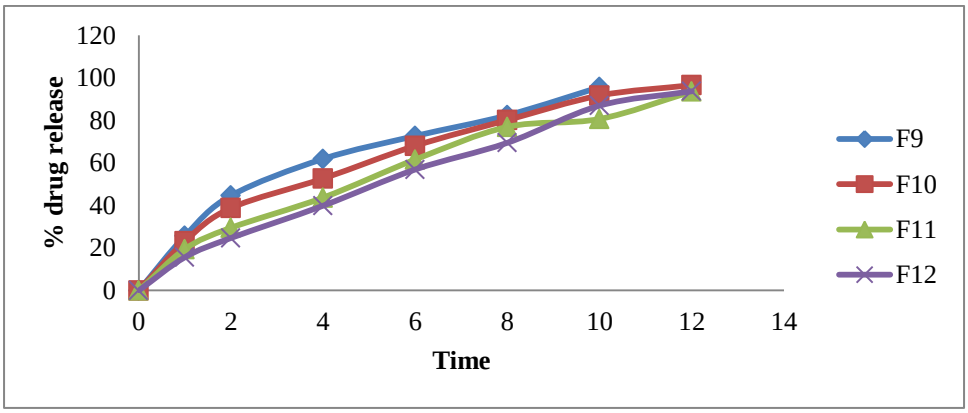

Figure 8: Percentage drug release of Glimepiride (F9-F12)

Table 7: Cumulative %release of optimized formulation (F8)

S.No	Time(Hrs)	Cumulative %Drug Release
1	0	0
2	1	10.77
3	2	24.53
4	4	36.99
5	6	58.25
6	8	72.65
8	10	91.14
9	12	99.28

Table 8: Dissolution Kinetic Parameters

S.No	kinematic model	r^2	n(slope)
1	Zero Order Plot	0.9906	8.4078
2	First Order Plot	0.8538	-0.1462
3	Higuchi Plot	0.9493	30.584
4	Korsmeyar-Peppa's Plot	0.9951	0.8254
5	Hixon Crowell Plot	0.8398	-0.0742

CONCLUSION:

The objective of the present work was design and characterization of Glimepiride in sustained release dosage form by incorporating natural polymers (Xanthan gum, Guar gum and Pectin) which will prolong the drug release leading to minimize the peak and valley effect in the plasma and provides patient convenience. It was concluded after the in-vitro dissolution study that formulation F8 (Glimepiride and Guar gum in the ratio of 1:6) shows the best release profile. It shows good release profile in the group of such polymer combinations. All the formulations were subjected to model fitting analysis by treating the data according to zero-order and korsmeyar-peppa's equations. F8 followed zero-order kinetics. Stability studies were conducted for F8 at 25ºc/60 ºc RH and 40 ºc/75%RH for 30 days. The results of stability studies released no change in physical appearance, hardness, drug content and in-vitro dissolution profiles, thus indicating that

formulations are stable.

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