Formulation Development and Characterization of Sustained Release Matrix Tablet Containing Glipizide for the Management of Hyperglycemia

Ajay S. Pawar [1]*, Trusha P. Shangrapawar [2], Dr Ashok V. Bhosale [3],

Pratiksha B. Avhad [4], Kamlesh R. Deshmane [4], Tanvi V. Thorat [1], Damini S. Patil [1]

[1] Research Scholar, Department of Pharmaceutics, PDEA's Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Kharadi, Pune - 411014, Maharashtra, India.

[2] Assistant Professor, Department of Pharmaceutics, PDEA's Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Kharadi, Pune - 411014, Maharashtra, India.

[3] Principal, Department of Pharmaceutics, PDEA's Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Kharadi, Pune - 411014, Maharashtra, India.

[4] Research Scholar, Department of Pharmaceutical Quality Assurance, PDEA's Shankarrao Ursal College of Pharmaceutical Sciences and Research Centre, Kharadi, Pune - 411014, Maharashtra, India.

For Correspondence :Ajay Shivaji Pawar

ajaypawar5599@gmail.com

ABSTRACT

The purpose of present research work was to formulate the Glipizide (sulphonyl urea, antidiabetic agent) in sustained release tablet dosage form for the management of type II Diabetes Mellitus. Glipizide is having short biological half-life (2-4 h) & classified as class II in the biopharmaceutical classification system (BCS) thus, Sustained release delivery system is chosen to provide a uniform concentration of the Glipizide at the absorption site. The matrix tablets were prepared by direct compression method. The drug excipients compatibility was evaluated by Fourier transform infrared (FTIR) spectroscopy studies it confirms that there is no interaction between the drug and polymers used. The formulation batches of Glipizide matrix tablets were designed by employing three different hydrophilic polymers, HPMC K4M & HPMC K100M as synthetic polymer and Karaya Gum as natural polymer. All three polymers are used alone. The combination of Karaya Gum with synthetic polymers at various concentrations was taken to the see the combination effect. The effectiveness of the synthetic (HPMC K4M & HPMC K100M) and natural Polymer (Karaya Gum) was compared, also their combination effect on release profile of Glipizide was studied. The pre-compression study was performed and the results were reported. In pre-compression study the angle of repose, bulk density, tapped density, Hausner's ratio and Carr's index was calculated and results shown the good compliance as per IP standards. The tablets parameters were evaluated by testing weight variation thickness, hardness, friability test etc. From the dissolution Profile of formulation batches **F1 to F11** the effect of polymer concentration on dissolution profile of tablet can be seen clearly. As concentration of polymer increases the drug release decreases. The % drug content was found to be in the range of 97.12±0.51 to 99.83±0.42

for Glipizide. The Batch F11 is chosen as optimized formulation which showed best results. As high and optimum concertation of HPMC K100M (35 mg) & Karaya Gum (15 mg) used in the formulation **F11** showed **98.84 %** of drug release at the end of 12 hr. stability studies for on the optimized formulation F11 was carried out as per ICH guidelines & confirmed that the formulation is stable.

KEYWORDS:

Glipizide, Half-life, Sustained Release, Compatibility, HPMC, Karaya Gum, Diabetes, Dissolution, Hyperglycemia, Polymer

INTRODUCTION

Diabetes Mellitus type II [2-6]

Diabetes mellitus is characterized by abnormally high levels of sugar (glucose) in the blood. When the amount of glucose in the blood increases, e.g., after a meal, it triggers the release of the hormone insulin from the pancreas. Insulin stimulates muscle and fat cells to remove glucose from the blood and stimulates the liver to metabolize glucose, causing the blood sugar level to decrease to normal levels. In people with diabetes, blood sugar levels remain high. This may be because insulin is not being produced at all, is not made at sufficient levels, or is not as effective as it should be. The most common forms of diabetes are type I diabetes (5%), which is an autoimmune disorder, and type II diabetes (95%), which is associated with obesity. There is a decrease in the body's secretion and sensitivity to insulin, which usually caused by obesity. It is a disease of insulin resistance by cells. Type-II diabetes mellitus is the most common type of diabetes.

Treatments are

a. Agents that increase the amount of insulin secreted by the pancreas.
b. Agents that increase the sensitivity of target organs to insulin.
c. Agents that decrease the rate at which glucose is absorbed from the gastrointestinal tract.

Type II DM may cause by:

- Abnormality in gluco-receptor of β cells so that they respond at higher glucose concentration or relative β cell deficiency.
- Reduced sensitivity of peripheral tissue to insulin: reduction in number of insulin receptors 'down regulation' of insulin receptors.
- Excess of hyperglycaemic hormone causes relative insulin deficiency the β cells lag behind.

For a treatment to be effective, the medication concentration in the plasma must be kept within the therapeutic range. The idea of oral Sustained release drug delivery systems was developed in response to these factors, as well as factors including frequent dosing and unpredictable absorption.

The medication release rate is controlled by a variety of techniques used in sustained release drug delivery systems. For pharmaceutical technologists, creating oral sustained release matrix tablets for medications with steady release rates has always been a challenge. Water penetration, polymer swelling, drug dissolution, drug diffusion, and matrix erosion have all been used as formulation strategies to predict drug release through matrix systems.

Glipizide: [1, 2]

Glipizide is widely used sulphonyl urea antidiabetic agent, are frequently used to treat people with type II diabetes. Although it is a weak acid (pKa - 5.9) and essentially insoluble in water and acid solution, it is classified as a highly permeable substance (class II) in the biopharmaceutical classification system (BCS). With a 2-4hour elimination half-life, the oral absorption is uniform, quick, and complete. Due to glipizide's short biological half-life, 2-3 dosages of 5–10 mg must be taken each day. For glipizide once a day administration, SR formulations that would keep drugs plasma levels steady for 8–12 hours might be sufficient.

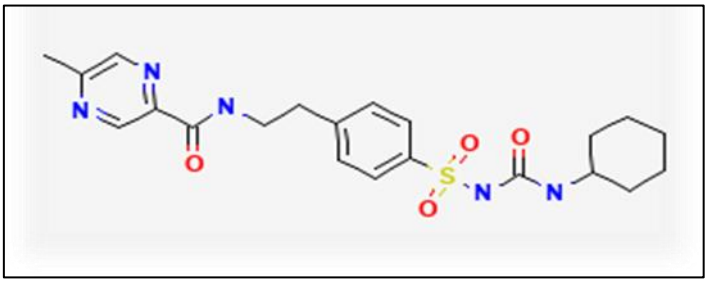

Figure 1: Chemical Structure of Glipizide

The molecular mechanisms of glipizide involve **a partial block of the potassium channels in the beta cells of the pancreatic islets**. This potassium channel blockade results in cell depolarization, which opens up the voltage-gated calcium channels, causing insulin secretion from the pancreatic beta cells It is used in patients with type II (non-insulin dependent) diabetes mellitus whose hyperglycaemia cannot be controlled by diet and exercise alone as an addition to diet. The pancreatic islets tissue cells are stimulated to secrete insulin, and the concentration of insulin in the pancreatic vein increases as a result of glipizide.[2]

SUSTAINED RELEASE TABLET [7, 8]

The medication release rate is controlled by a variety of techniques used in sustained release drug delivery systems. For pharmaceutical technologists, creating oral sustained release matrix tablets for medications with steady release rates has always been a challenge. Water penetration, polymer swelling, drug dissolution, drug diffusion, and matrix erosion have all been used as formulation strategies to predict drug release through matrix systems. sustained release tablets ensure better patient compliance

by reduction in total dose and dosage regimen, which can be of great help in the treatment of chronic diseases.

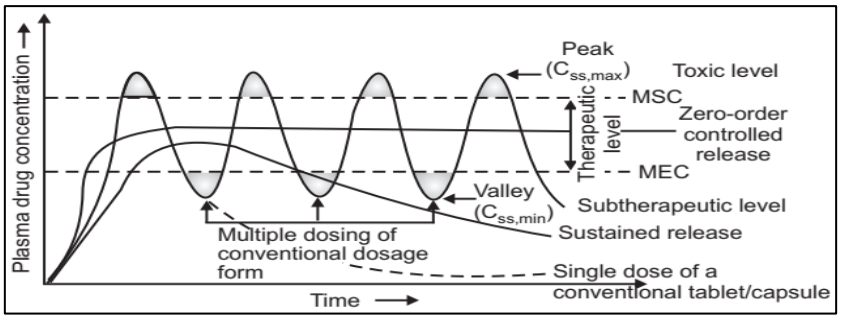

Figure 2: Plasma Drug Concentration Time Profile

EXPERIMENTAL (MATERIALS AND METHODS)

MATERIALS

Glipizide was a purchased from Yarrow chem, Mumbai. HPMC K4M & K100M were received as gift samples from Aster analytical, Pune, India. Karaya Gum & Microcrystalline Cellulose was purchased from Solanki Distributors, Pune. All other ingredients used were of analytical grade.

EXPERIMENTAL WORK

PRE-FORMULATION STUDY [8, 11]

Characterization of drug

Organoleptic Properties

The drug sample was evaluated visually for its appearance, colour, odour, and parameters. Results are shown in **Table: 3**

Melting point

Thiele tube set up method was used to identify the melting point of the Glipizide. Observed melting point was compared with standard value.

Spectrophotometric Analysis of Glipizide

Preparation of 0.1N HCL Solution:

1. Take a dried and cleaned 1000 ml volumetric flask and add 100 ml of water.
2. Add 8.3 ml of concentrated Hydrochloric acid.
3. Make up the volume up to the mark with water and mix the solution thoroughly.

Preparation of 6.8 pH Phosphate buffer Solution:

A) **Preparation of 0.2 M potassium dihydrogen phosphate -** 27.22gm of potassium dihydrogen phosphate was weighed and diluted up to 1000 ml with distilled water to get 0.2M potassium dihydrogen phosphate.
B) **Preparation of 0.2 M NaOH** - 8 gm Sodium hydroxide was weighed and diluted up to 1000 ml with distilled water to get 0.2M sodium hydroxide solution. After, 50 ml of the 0.2M potassium dihydrogen phosphate solution was taken from the stock solution in a 200 ml volumetric flask and 22.4 ml of sodium hydroxide solution from stock solution of 0.2M sodium hydroxide solution was added and then distilled water was used to make up the volume.

Determination of λ max in 0.1 N HCL - 1% w/v Glipizide was prepared 0.1 N HCL, scanned absorbance in UV double beam spectrophotometer (Shimandzu-1800) in 200 to 400 nm, using 0.1 N HCL. The λ max of the Glipizide was found to be 274 nm. The UV spectrum of Glipizide in 0.N HCL is shown in **Figure: 3.**

Determination of λ max in Phosphate Buffer PH 6.8 - 1% w/v Glipizide was prepared in phosphate buffer Ph 6.8, scanned absorbance in UV double beam spectrophotometer (Shimandzu-1800) in 200 to 400 nm, using phosphate buffer PH 6.8 as blank. The λ max of the Glipizide was found to be 274 nm. The UV spectrum of Glipizide in 6.8 Phosphate buffer in **Figure: 5.**

Preparation of Standard Curve for Glipizide

100 mg of Glipizide was accurately weighed and dissolved separately in 100 ml of phosphate buffer Ph 6.8 & 0.1N HCL to prepare first stock solution. 10ml of above solutions was taken and diluted to 100 ml with the same solvent to prepare II stock solutions. The aliquot amount of stock solutions II was diluted with same solvent to get 10 µg. 20 µg. 30 ug, 40 µg. 50 µg and 60 µg of drug per ml of the final solution. Then the absorbance was measured in a UV double beam spectrophotometer (Shimandzu-1800) at 274 nm against 0.1 N HCL & phosphate buffer Ph 6.8 as blank. The graph was plotted for absorbance vs concentration. The Standard Curve graph of Glipizide in 0.N HCL is shown in **Figure: 4** & in 6.8 Phosphate buffer in **Figure: 6**.

Drug-Excipient Compatibility Study [8, 19, 20]

Fourier Transform Infrared Spectroscopy (FTIR)

Infrared spectra matching approach was used for the detection of any possible chemical reaction between the drug and the excipients. FT-IR spectrum of Glipizide was recorded to confirm its purity on FTIR spectrophotometer (FTIR 84008, Shimadzu) by using KBr powder press technique. The base line correction was done using dried potassium bromide. The instrument was operated under dry air purge with resolution of cm-1 over the region 4000-400 cm The scans were evaluated for presence of principle peaks of drug. The identified peaks were compared with the principal peaks of reported IR spectrum.

The FTIR spectra of Glipizide is depicted in **Figure: 7** and Glipizide + excipients in **Figure: 8 to Figure 18.**

FORMULATION OF SUSTAINED RELEASE MATRIX TABLET OF GLIPIZIDE [7, 8, 19]

Accurate quantity of Glipizide and all ingredients were weighed according to formula powders except talc and magnesium stearate was blended homogeneously in mortar and pestle for 15 minutes. Prepared powder blend was passed through sieve no. #60. Finally, Talc and Magnesium stearate passed from sieve no. #30 added and was further mixed for10 minutes. [8, 19]

Table 1: Selected excipients for prototype formulation

Sr. No.	EXCIPIENTS	ROLE OF EXCIPIENTS
01	HPMC K4M	Synthetic Polymer
02	HPMC K100M	Synthetic Polymer
03	Karaya Gum	Natural Polymer
04	Microcrystalline Cellulose	Diluent
05	Magnesium Stearate	Lubricant
06	Talc	Glidant

Table 2: Formulation of Sustain Release Matrix Tablet of Glipizide

Sr No	Ingredients	Formulation Batches (mg)										
		F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**
01	**Glipizide**	10	10	10	10	10	10	10	10	10	10	10
02	**HPMC K4M**	20	30	50	---	---	---	---	25	35	---	---
03	**HPMC K100M**	---	---	---	20	30	50	---	---	---	25	35
04	**Karaya Gum**	---	---	---	---	---	---	50	25	15	25	15
05	**Microcrystalline Cellulose**	166	156	136	166	156	136	136	136	136	136	136
06	**Magnesium Stearate**	2	2	2	2	2	2	2	2	2	2	2
07	**Talc**	2	2	2	2	2	2	2	2	2	2	2
Total		200	200	200	200	200	200	200	200	200	200	200

PRECOMPRESSION EVALUATION OF BLEND OF SUSTAINED RELEASE TABLET OF GLIPIZIDE [7, 8]

The prepared tablet blend of sustained release tablet of was subjected to precompression evaluation. Accurate quantity of drug and all ingredients were weighed according to formula all powders except talc and magnesium stearate was blended homogeneously in mortar and pestle for 15 minutes. Prepared powder blend was passed through sieve No.#60. Finally, magnesium stearate & Talc passed through sieve No. #30 was added and further mixed for10 minutes. The powder blend was evaluated for angle

of repose, bulk density, tapped density, compressibility index and Hausner's ratio & are reported in **Table: 6.**

Angle of Repose [7, 8]

This is the maximum angle possible between the height of pile of blend powder and horizontal plane. The frictional forces in the lose powder can be measured by angle of repose. The tangent of angle of repose is equal to the coefficient friction (θ) between the particles. Hence the rougher and more irregular the surface of particles the greater will be angle of repose.

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

Where, H = height of the pile

R = radius of the pile

Bulk density: [7, 8]

Apparent bulk density (BD) was determined by pouring blend into a graduated cylinder. Weighted quantity of the powder mass (M) was poured into measuring cylinder, then the powder was levelled carefully, and the unsettled apparent volume Vo was noted to the nearest graduated unit. The bulk density was calculated in gm/ml by the formula: The bulk density was calculated using the formula

$$\text{Bulk Density} = M/Vo$$

Tapped density: [8,11,25]

After determination of the bulk density, the cylinder was tapped mechanically by mounting on a holder in a mechanical tapped density tester that provided a fixed drop of 14 ± 2 mm at a nominal rate of 300 drops per minute. The cylinder was tapped for 500 times initially and the tapped volume Vt was measured to the nearest graduated unit. The tapping was repeated for an additional 750 times and the tapped volume was measured. Final tapped volume was measured and tapped density was calculated by the formula:

$$\text{Tapped Density} = M/Vt$$

Compressibility Index [7, 8]

The simplest way for measurement of free flow of powder is compressibility, a indication of the case with which a material can be induced to how is given by compressibility index (CI) which is calculated as follows

$$\text{Carr's Index} = [(\text{Tapped density} - \text{Bulk density})/ \text{Tapped density}] \times 100$$

Hausner's ratio [7, 8]

Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula;

Hausner's ratio (Hr) = [Tapped Density (ρtap)/Bulk Density (ρb)]

PREPARATION OF SUSTAINED RELEASE TABLET OF GLIPIZIDE BY DIRECT COMPRESSION METHOD

Different tablet batch formulation (**F1-F11**) was prepared by direct compression method by using the above prepared tablet blend shown in **Table: 2**. Accurate quantity of Glipizide and all ingredients were weighed according to formula powders except talc and magnesium stearate was blended homogeneously in mortar and pestle for 15 minutes. Prepared powder blend was passed through sieve no. #60. Finally, Talc and Magnesium stearate passed from sieve no. #30 added and was further mixed for10 minutes. Accurately weighed 200 mg homogeneously mixed powder blend was fed manually to the die of Rotary Tablet compression Machine (Karnavati Model RIMEK MINIPRESS-IIMT) and compressed with constant compression force and hardness. Total 11 formulations were prepared. Each tablet contains 10 mg of Glipizide.

POST COMPRESSION PEVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF GLIPIZIDE [7,8,25,64]

The prepared tablet batches (F1-F11) are subjected to post compression evaluation and evaluation parameters like appearance, weight variation, thickness, hardness, friability, content uniformity, disintegration time, dissolution time was performed and the results are shown in **Table: 7**

Weight Variation: [7, 8]

When a tablet is designed to contain a certain quantity of medication in a specific amount of tablet formula, the weight of the tablet is frequently tested to confirm that the correct amount of drug is included in the tablet. In actuality, ten tablets were consumed and weighed on a digital weighing balance individually. The average weight of the tablets was determined, and the weight of each tablet was compared to the average. If no more than two tablets are outside the % restriction and no tablet varies by more than twice the percentage limit, all formulation batches pass the weigh variation test.

Thickness: [7, 8]

The uniformity of tablet size is dependent on the thickness of the tablet. Vernier calliper was used to determine thickness. Randomly selected three pills from each formulation were tested to determine it.

Hardness: [7, 8]

The "force necessary to shatter a tablet in diametric compression test" is the definition of hardness. As a result, tablet crushing strength is also known as hardness. The resistance before use is determined by

the hardness of the material. For each formulation the hardness of 6 tablets was determined using a Pfizer hardness tester. In the hardness tester, tablet was held along its oblong axis in between the two jaws of the tester and the load necessary to crush it was measured. Then force was applied until the tablet fractured. The value at this point was noted in kg/cm2.

Friability: [7, 8]

This test is used to determine if tablets can survive abrasion while being packed, handled, or transported. Friability is a sign of inadequate tablet ingredient cohesiveness. Friability of the tablets was determined using Roche Friabilator. A total of ten pills are weighed and placed in the Friabilator, which is made up of a circular plastic chamber separated into two or three compartments. The chamber rotates at 25 revolutions per minute for 4 minutes, dropping the tablets 15 cm away and completing 100 rotations. The pills are then weighed for the second time. The weight difference is observed and given as a percentage difference. It's best if it's less than 1%.

$$\% \text{ Friability} = (W1-W2)/W1 \times 100$$

Where, W1 = Weight of tablet before test

W2 = Weight of tablet after test

Content uniformity [7, 8]

20 tablets were finely powdered and weight equivalent to 10 mg of Glipizide was dissolved in 100 ml of 0.1N HCL and assayed against 0.1 N HCL for drug content using UV-Visible spectrophotometer at 274 nm.

In-vitro Dissolution studies [7, 8]

Dissolution profiles of Glipizide tablets were determined using the USP Type II Dissolution test apparatus (paddle) (Electrolab, Mumbai, India). Set with a paddle speed of 50 rpm & at temperature 37° C ± 0.5°C. The dissolution media used were 900 mL of 0.1 N HCl for first 2 h followed by pH 6.8 phosphate buffer solutions for 12 h. 5 ml samples were removed at specified intervals up to 1h and filtered through Whatman filter paper. An equal volume of fresh medium, prewarmed at 37^0 C was replaced into the dissolution medium after each sampling to maintain the constant volume throughout the test. Samples were analysed by UV spectrophotometer at 274 nm. Drug dissolved at specified time periods was plotted as cumulative percent release versus time (h) curve.

Stability Study [64]

The prepared Sustained Release tablets of Glipizide were placed in plastic tubes containing desiccant and stored at ambient conditions, such as room temperature at 40^0C ± 2^0C /75 % RH ± 5% for period of 90 days. each tablet is weighed and wrapped in aluminium foil and packed in black PVC bottle and

put at above specified condition in a heating humidity chamber for 3 months and evaluated for their physical appearance, hardness, disintegrate time, dissolution testing and drug content at specified intervals of time.

RESULTS AND DISCUSSION

PRE-FORMULATION STUDY

Characterization of drug

Organoleptic Properties

The drug sample of Glipizide was evaluated for its Organoleptic Properties such as colour, odour, and appearance and it was found that, the drug sample of Glipizide complies with the standards of IP. The results are presented in **Table: 3.**

Table 3: Organoleptic Properties of Glipizide

Test	Specification/ Limit	Observation
Appearance	Fine Powder	Complies with IP
Color	White	Complies with IP
Odour	Odourless	Complies with IP

Melting Point

The Melting point of received drug sample of Glipizide was determined and it was found to be in range 200-203^{0C} which complies with standard, this study indicates purity of the sample and the sample provided in Glipizide and for further conformation more test is carried out.

Spectrophotometric Analysis of Glipizide

UV Spectrophotometric Analysis

Determination of λ max of Glipizide in 0.1 N HCL

In UV spectroscopy study, the maximum wavelength (λ max) of Glipizide in 0.1N HCL was found to be 274 nm. The reported λ max value of Glipizide in 0.1N HCL was also 274 nm, so the values similar with the reported value indicates that the given sample of Glipizide was in pure form.

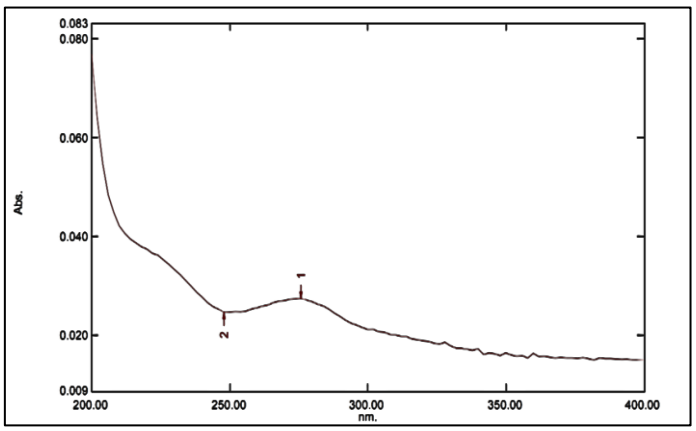

Figure 3: UV Spectrum of Glipizide in 0.1N HCl at 274 nn

Preparation of Standard Calibration Curve of Glipizide in 0.1N HCl

The Standard curve of Glipizide was determined by plotting absorbance Vs concentration at 274 nm. It was found that there was linear relationship between concentration and absorbance with R^2 value 0.9988. Which reveals that, the drug Glipizide obeys the Beers lamberts law.

Table 4: UV Absorbance of Glipizide in 0.1 N HCl at 274 nm

Sr.no.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.028
3	20	0.057
4	30	0.087
5	40	0.121
6	50	0.14

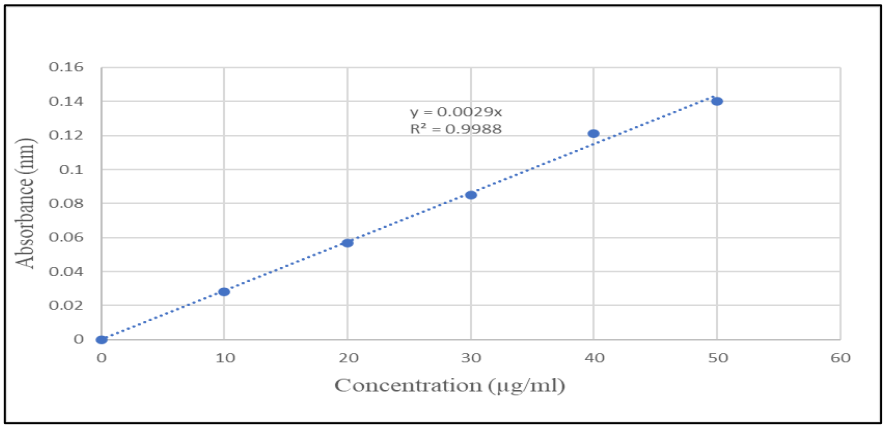

Figure 4: Standard Calibration Curve Graph of Glipizide in 0.1N HCL

Determination of λ max of Glipizide in 6.8 Phosphate Buffer

In UV spectroscopy study, the maximum wavelength (λ max) of Glipizide in 6.8 Phosphate Buffer was found to be 274 nm. The reported λ max value of Glipizide in 6.8 Phosphate Buffer was also 274 nm,

so the values similar with the reported value indicates that the given sample of Glipizide was in pure form.

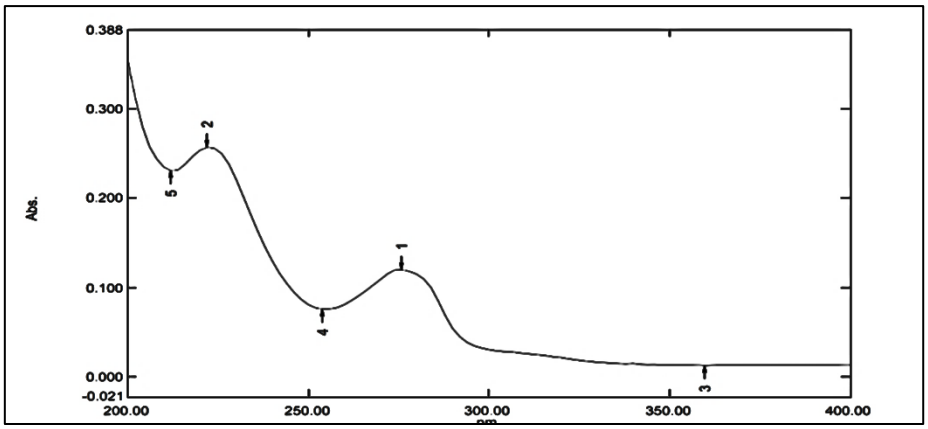

Figure 5: UV Spectrum of Glipizide in 6.8 Phosphate Buffer at 274 nm

Preparation of Standard Calibration Curve of Glipizide in 6.8 Phosphate Buffer:

The Standard curve of Glipizide was determined by plotting absorbance Vs concentration at 274 nm. It was found that there was linear relationship between concentration and absorbance with R^2 value 0.9988. Which reveals that, the drug Glipizide obeys the Beers lamberts law.

Table 5: UV Absorbance of Glipizide in 6.8 Phosphate Buffer at 274 nm

Sr.no.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.12
3	20	0.215
4	30	0.315
5	40	0.4
6	50	0.48
7	60	0.6

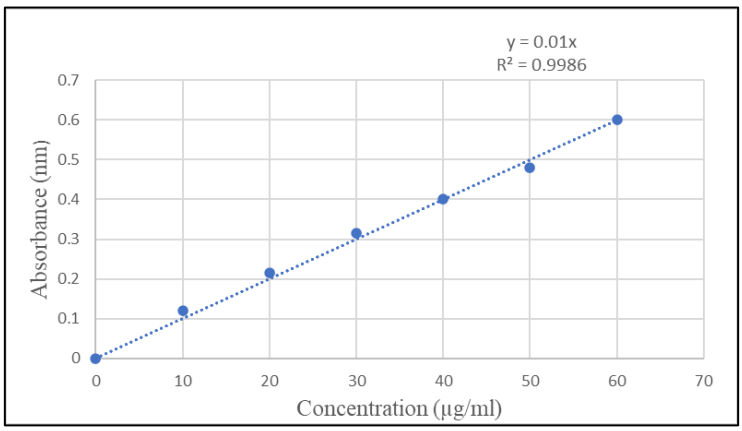

Figure 6: Standard Calibration Curve Graph of Glipizide in 6.8 Phosphate Buffer

Drug-Excipient Compatibility Study

Fourier Transform Infra-red Spectroscopy (FTIR) Interpretation of Glipizide

Major functional groups present in Glipizide show characteristic peaks in IR spectrum (Fig.7). It shows peaks observed at different wave numbers and the functional group associated with these peaks. The major peaks are identical to functional group of Glipizide. Hence, the sample was confirmed as Glipizide.

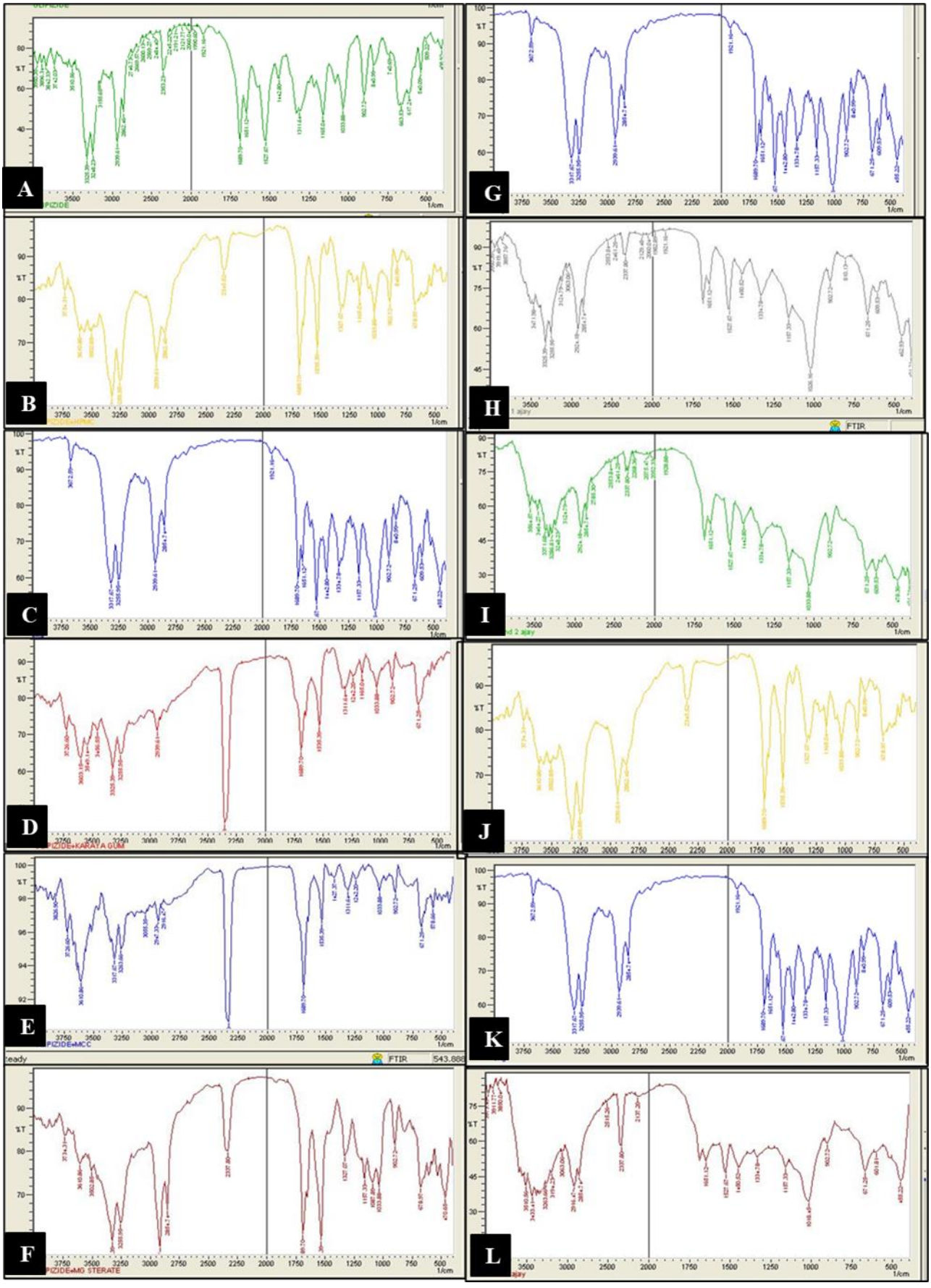

Figure 7: FTIR Spectroscopy

Table 6: List of FT-IR Spectra

Graph	FT-IT Spectra
A	FTIR Spectrum of Glipizide
B	FTIR Spectrum of Glipizide + HPMC K4M
C	FTIR Spectrum of Glipizide + HPMC K100M
D	FTIR Spectrum of Glipizide + Karaya Gum
E	FTIR Spectrum of Glipizide + Microcrystalline Celllulose
F	FTIR Spectrum of Glipizide + Magnesium Stearate
G	FTIR Spectrum of Glipizide + Talc
H	FTIR Spectrum of Glipizide + HPMC K4M + MCC + Mg. Stearate + Talc
I	FTIR Spectrum of Glipizide +HPMC K100M + MCC + Mg. Stearate + Talc
J	FTIR Spectrum of glipizide + Karaya Gum + MCC + Mg. Stearate + Talc
K	FTIR Spectrum of Glipizide + HPMC K4M + Karaya Gum + MCC + Mg. Stearate + Talc
L	FTIR Spectrum of Glipizide + HPMC K100M + Karaya Gum + MCC + Mg. Stearate + Talc

Fourier transform infrared spectroscopy (FTIR) spectrum of glipizide showed characteristic bands at 1689 cm^{1} which is due to C = O stretch of amides, a band at 1165 cm^{1} is present because of C-N stretching vibrations of amines, bands at 1651 cm^{1}, and 1442 cm^{1} were assigned to C = C stretching of aromatic ring, a peak observed at 1663 cm1 attributed to C = N stretching, strong band at 1527 cm^{1} was assigned to N-H bending vibrations. A band at 3325 cm^{1} could probably be assigned to N-H stretching vibrations. A band present at 1033 cm1 is due to S = O.

Major functional groups present in Glipizide show characteristic peaks in IR spectrum, The major peaks are identical to functional group of Glipizide. Hence, the sample was confirmed as Glipizide.

The IR spectra obtained for their respective physical combination of Glipizide & excipients showed no significant differences. There was no indication of an interaction between Glipizide and ingredients, according to the findings. These findings show that the excipients listed above may be utilized to make Glipizide SR tablet without causing any interactions.

PREPARATION OF SUSTAINED RELEASE MATRIX TABLET OF GLIPIZIDE BY DIRECT COMPRESSION METHOD

After confirming that the drug & excipients are compatible & There was no indication of an interaction between Glipizide and ingredients, Blend of sustained release tablets of Glipizide was prepared as per the Formulation table (**Table 2**).

PRECOMPRESSION EVALUATION OF BLEND OF SUSTAINED RELEASE TABLET OF GLIPIZIDE:

The characterization of mixed blend was done for determination of mass-volume relationship parameter. The evaluated parameters are angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index was reported in table below **Table: 7.**

Table 7: Precompression Evaluation of tablet blend for Sustained Release tablet

Bactches	Angle of repose (Θ^o)	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Hausner's Ratio (H_R)	Carr's Compressibility index (%)
F1	21.41±1.88	0.42±0.8	0.49±0.03	1.16±0.10	14.28±0.20
F2	19.33±0.95	0.44±0.06	0.51±0.09	1.15±0.21	13.72±0.33
F3	21.80±1.78	0.45±0.07	0.50±0.06	1.11±0.11	10.00±0.52
F4	21.88±1.27	0.41±0.10	0.47±0.07	1.14±0.42	12.76±0.53
F5	23.26±1.45	0.43±0.08	0.51±0.08	1.18±0.36	15.68±0.39
F6	23.26±1.14	0.45±0.02	0.52±0.10	1.15±0.51	13.46±0.91
F7	22.35±1.66	0.47±0.09	0.56±0.08	1.19±0.44	16.07±0.88
F8	24.22±0.54	0.46±0.05	0.52±0.11	1.13±0.40	11.53±0.12
F9	21.80±1.67	0.44±0.09	0.53±0.04	1.20±0.10	16.98±0.10
F10	21.29±0.47	0.42±0.4	0.51±0.02	1.21±0.21	17.64±0.21
F11	22.29±0.47	0.48±0.07	0.56±0.06	1.21±0.20	14.28±0.10

Results are mean of three determinations.

Angle of Repose:

Angle of repose of various powder blends (F1-F11), prepared with different ingredients, was measured by funnel method. **Table: 7** indicates the results obtained for angle of repose of all the formulations. The values were found to be in the range of **19.33 0˚ to 24.22 0˚** all formulations showed the angle of repose within 30˚. It indicates that all formulations showed excellent flow properties.

Bulk density

Bulk density of formulation batches F1 to F11 is reported in **Table: 7** The bulk density of mixed blend varies between **0.41 to 0.48 gm/ml,** indicating good packaging capacity of tablets

Tapped Density:

The tapped density results of formulation batches F1 to F11 are reported in **Table: 7** The tapped density of mixed blend was found in the range of **0.47 to 0.56 gm/ml**, indicating good packing capacity of tablet

Hausner's Ratio:

Hauser's ratio of formulation batches F1 to F11 is shown in table. Hauser's ratio of all the formulation lies within the acceptable range. The Hauser's ratio of all the formulations in the range **of 1.11 to 1.21.**

Compressibility Index:

The percent compressibility of formulation batches F1 to F11 powder mixture was determined by Carr's compressibility index. **Table: 7** indicates result obtained for percentage compressibility. The percent compressibility for all the four formulations lies within the range of **10.00 % to 15.68 %** all the formulations showing good compressibility. From the results of pre- compression studies of the batch F1-F11, it is concluded that powder mixture has good flow property and compressibility property.

POST COMPRESSION EVALUATION OF SUSTAINED RELEASE MATRIX TABLET OF GLIPIZIDE:

The SR tablets of Glipizide were prepared & subjected to post compression parameters like weight variation, thickness, hardness, friability, drug content, in vitro disintegration time, wetting time, water absorption ratio, in vitro dissolution studies were carried out. All the formulations were passed the parameter which was reported in below **Table: 8.**

Table 8: Evaluation of Sustained Release Tablet of Glipizide

Batches	Weight variation (mg)	Thickness (mm)	Hardness (Kg/cm^2)	Friability (%)	Drug Content (%)
F1	198±0.50	3.50±0.10	5.9± 0.5	0.57±0.05	99.22±0.55
F2	199±0.58	3.40±0.18	6.0± 0.2	0.55±0.06	98.72±0.45
F3	201±0.20	3.45±0.25	5.9± 0.3	0.51±0.04	97.45±0.39
F4	197±0.85	3.55±0.10	5.7± 0.4	0.62±0.03	99.35±0.62
F5	199±0.65	3.48±0.17	5.9± 0.3	0.55±0.07	98.51±0.08
F6	200±0.40	3.51±0.10	5.8± 0.5	0.63±0.04	99.75±0.52
F7	198±0.52	3.50±0.15	5.9±0.4	0.62±0.05	98.52±0.21
F8	199±0.58	3.49±0.11	6.1± 0.3	0.48±0.06	98.82±0.18
F9	198±0.72	3.52±0.05	5.7± 0.5	0.67±0.08	98.92±0.51
F10	199±0.22	3.48±0.09	6.0± 0.2	0.55±0.06	99.05±0.30
F11	200±0.12	3.50±0.10	6.0± 0.4	0.50±0.08	99.83±0.12

Weight variation

Tablets were prepared using direct compression technique. Since the material was free flowing, tablets were obtained of uniform weight due to uniform die fill. Tablets of batch F1 to F11 were obtained in the range with acceptable weight variations as per Pharmacopoeia specifications, limit of ±5%. It was found to be from 197.85±0.85 - 201±0.20mg.

Thickness

The thickness of the tablets (Batch F1 to F11) was measured by using Vernier calliper by picking the tablets randomly. The values are almost uniform in all formulations. Thickness was found in the range

from 3.40 ± 0.18 mm – 3.52 ± 0.05 mm. Uniform in the values indicates that formulations were compressed without sticking to the dies and punches.

Hardness

The result of the hardness of batch F1 to F11 is given in **Table:8** Hardness test was performed by Monsanto hardness tester. Hardness was maintained to be within 5.7±0.5 kg/cm2 to 6.1± 0.3 kg/cm^2. The lower standard deviation values indicated that the hardness of the all the formulations were almost uniform and possess good mechanical strength with sufficient hardness.

Friability Test

Friability of tablet was determined by using Roche Friabilator. The results of batch F1 to F11 are tabulated in **Table: 8** was found well within the approved range of 0.48±0.06 to 0.67±0.08 % i.e., less than 1%. Results revealed that the prepared tablets; resistance to loss of weight indicates the tablet's ability to withstand abrasion in handling, packaging, and shipment and good mechanical strength.

Drug content of Glipizide

Tablets of batch F1 to F11 were evaluated by using assay method. The drug content was obtained in the acceptable limit. The drug content was found in the range 97.45±0.39 to 99.83±0.12 %w/w. The found range was within the specified limit as per Pharmacopoeia.

***In-vitro* % Drug Release of Drug from Tablet**

All the 11 tablet batches (batch F1 to F11) of Sustained release tablet of Glipizide were subjected for the in vitro dissolution studies using tablet dissolution test apparatus (USP type II). The dissolution media used were 900 mL of 0.1 N HCl for first 2 h followed by pH 6.8 phosphate buffer solutions for 12 h. Dissolution profile of Batch F1 to F11 is demonstrated in in **Table: 9. Figure: 8** shows graph of Cumulative % drug release of F1-F11 formulations.

From the dissolution Profile of formulation batches **F1 to F11** the effect of polymer concentration on dissolution profile of tablet can be seen clearly. As concentration of polymer increases the drug release decreases. In all three polymers used alone, HPMC K100M found to be most effective polymer. The **F6** batch containing 50 mg of HPMC K100M has given 11 hr sustained effect.

As high and optimum concertation of HPMC K100M & Karaya Gum used in the formulation **F11** showed **98.84 %** of drug release at the end of 12 hours. hence **F11** is selected as **optimized batch**. In the combination of natural & synthetic polymers Formulation batch F11 containing 35 mg of HPMC K100M & 15 mg of Karaya Gum showed better results in comparison of other formulation batches. It can be seen that when polymers are used in combination, they showed additive effect & retard the drug release effectively.

Table 9: *In-vitro* Cumulative % Drug Release from Tablet

Time (Hours)	*In-vitro* Cumulative % Drug Release										
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**
0	0.00	0.00	0.000	0.00	0.00	0.00	0.00	0.000	0.000	0.000	0.00
1	18.92± 0.52	15.80± 0.44	7.07± 0.48	9.57± 0.45	9.57 ±0.32	7.07± 0.50	10.21± 0.25	9.57± 0.51	7.70± 0.64	12.68± 0.25	9.57±0. 55
2	35.15± 0.51	30.16± 0.54	18.30 ±0.52	22.05± 0.52	20.18± 0.25	16.43± 0.42	22.11± 0.58	20.18 ±0.48	17.06± 0.63	23.92± 0.84	15.81±0 .35
3	53.26± 0.38	42.66± 0.56	26.43 ±0.85	36.41± 0.38	30.17± 0.42	23.93± 0.26	25.20± 0.84	31.42 ±0.25	25.80± 0.85	34.54± 0.51	22.69±0 .65
4	72.02± 0.56	58.91± 0.25	38.92 ±0.55	53.90± 0.51	40.80± 0.53	32.68± 0.52	38.45± 0.25	42.67 ±0.68	34.56± 0.35	45.80± 00.55	31.44±0 .26
5	87.69± 0.45	72.07± 0.64	51.43 ±0.84	68.92± 0.28	51.44± 0.28	41.45± 0.55	51.14± 0.35	55.19 ±0.56	45.82± 0.78	57.70± 0.52	40.20±0 .45
6	97.52± 0.58	82.74± 0.45	63.33 ±0.52	82.71± 0.36	62.72± 0.88	50.84± 0.48	65.12± 0.45	67.72 ±0.78	56.47± 0.65	65.86± 0.	48.35±0 .58
7	98.89± 0.21	96.55± 0.48	75.25 ±0.15	95.27± 0.42	72.77± 0.46	59.63± 0.62	79.21± 0.46	82.75 ±065	65.88± 0.45	75.91± 0.15	57.13±0 .69
8		98.17± 0.028	85.93 ±0.45	98.18± 0.51	85.31± 0.27	69.67± 0.45	91.65± 0.25	95.94 ±0.75	76.55± 0.22	82.85± 0.51	65.30±0 .22
9			96.62 ±0.48		96.71± 0.35	78.47± 0.37	96.21± 0.54	98.23 ±0.72	86.61± 0.89	91.6±0. 45	72.85±0 .62
10			97.01 ±0.85		98.01± 0.56	87.91± 0.64	98.58± 0.45		97.92± 0.51	96.61± 0.59	81.66±0 .44
11						96.11± 0.72			98.46± 0.52	97.98± 0.12	89.23±0 .64
12						97.07± 0.45					98.84±0 .25

Release kinetics studies:

The *in-vitro* drug release data of all formulations were analysed for determining kinetics of drug release. The obtained data were fitted to zero order kinetics, first order kinetics, Higuchi model. The highest correlation coefficient (R^2) obtained from these methods gives an idea about model best fitted to these release data. From the results of kinetic studies, the examination of correlation coefficient (R^2) indicated that the drug followed Korsmeyer-Peppas model for release kinetics. It was found that the value of R^2 for Korsmeyer-Peppas model ranged from0.9984 to 0.9999, which is near to 1. The n value showed that drug followed Super case II Drug Release Mechanism. Data of Drug Release Kinetics was shown in **Table: 10.**

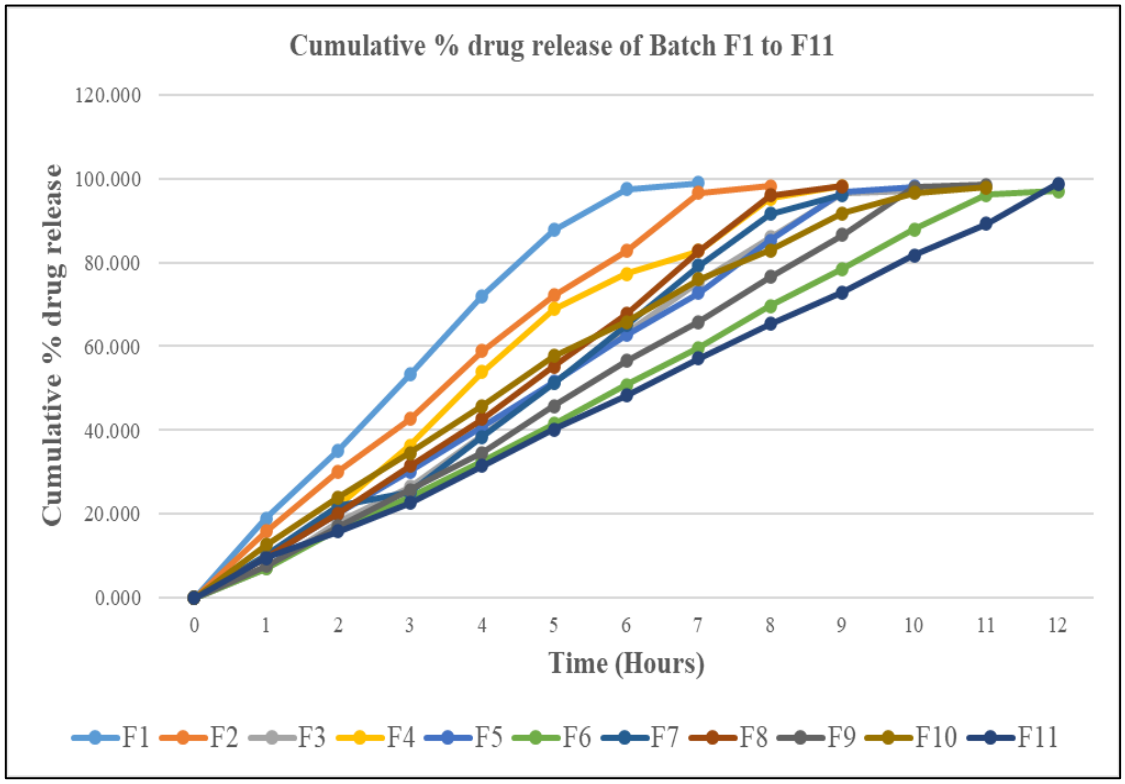

Figure 8: Cumulative % drug release of F1-F11 formulations

Table 10: Kinetics of drug Release

Batches	Zero Order	First Order	Higuchi Model	Korsmeyer-Peppas Plots		Hix. Crow.	Best Fit Model	Drug Release Mechanism
	R^2	R^2	R^2	R^2	n	R^2		
F1	0.9954	0.9299	0.9524	0.9984	0.9357	0.9759	Peppas	Super case II
F2	0.9985	0.8886	0.9472	0.9996	0.9332	0.9584	Peppas	Super case II
F3	0.9967	0.8669	0.9072	0.9989	1.1844	0.9388	Peppas	Super case II
F4	0.9963	0.8902	0.9111	0.9992	1.2003	0.9485	Peppas	Super case II
F5	0.9994	0.8750	0.9221	0.9999	1.0453	0.9445	Peppas	Super case II
F6	0.9991	0.8794	0.9167	0.9996	1.0782	0.9465	Peppas	Super case II
F7	0.9990	0.8295	0.9254	0.9998	1.2012	0.9465	Peppas	Super case II
F8	0.9966	0.8587	0.9084	0.9998	1.1071	0.9307	Peppas	Super case II
F9	0.9982	0.8319	0.9117	0.9998	1.7559	0.9261	Peppas	Super case II
F10	0.9917	0.9383	0.9562	0.9988	0.8947	0.9823	Peppas	Super case II
F11	0.9980	0.8410	0.9182	0.9996	1.0088	0.9307	Peppas	Super case II

STABILITY STUDY

The formulation **F11** was selected for stability studies on the basis of their high cumulative % drug release and also hardness thickness etc. The stability study showed that the formulation **F11** was physically stable when stored at 40±20°C and 75±5% RH for three months and there was no significant difference in dissolution parameters of optimized formulation. The results are shown in **Table: 11.**

Table: 11: Comparative stability study of Sustained Release Tablet of Glipizide

Sr. No.	Parameters	Initial	After 2 Months	After 3 months
1	**Weight variation (mg)**	200±0.12	199±0.51	198±0.21
2	**Thickness (mm)**	3.50±0.10	3.51±0.18	3.53±0.16
3	**Hardness (Kg/cm^2)**	6.0± 0.2	5.9± 0.2	5.7± 0.5
4	**Friability (%)**	0.50±0.06	0.61±0.05	0.76±0.08
5	**Drug Content (%)**	99.83±0.42	99.75±0.10	99.68±0.12
6	**Cumulative % Drug Release**	98.84±0.65	98.35±0.50	98.10±0.60

CONCLUSION

The purpose of present research work was achieved successfully as formulation of the Glipizide (sulphonyl urea, antidiabetic agent) in sustained release tablet dosage form for the management of type II Diabetes Mellitus was done. Glipizide is having short biological half-life (2 - 4 h) & classified as class II in the biopharmaceutical classification system (BCS) thus, Sustained release delivery system is provided a uniform concentration of the Glipizide at the absorption site & also reduced dosing frequency. All raw materials were subjected to pre-compression studies such as bulk density, tapped density, compressibility index and Hausner's ratio showed good flow properties. In FTIR spectra it is found that there is no physical interaction between drug and all excipients.

From the dissolution Profile of formulation batches **F1 to F11** the effect of polymer concentration on dissolution profile of tablet can be seen clearly. As concentration of polymer increases the drug release decreases. In Formulation batches of single polymers, HPMC K100M was found to be the best polymer among other polymers used. The hydrophilic matrix of HPMC K4M, HPMC K100M & Karaya Gum alone cannot control the release of glipizide for 12 H. therefore When 35 mg of HPMC K100M was combined with 15 mg of Karaya Gum (**Batch F11**), may slow down the release of the drug for 12 hours and therefore, Karaya Gum can be successfully employed for the formulation of sustained release matrix tablets. The Batch F11 is chosen as optimized formulation which showed best results. As high and optimum concertation of HPMC K100M used in the formulation **F11** showed **98.84 %** of drug release

at the end of 12 hr. It concludes that when natural and synthetic polymers are used in combination, they showed additive effect & retarded the drug release for 12 hours. The release data of In vitro kinetic study indicates that formulations follow Koresmeyer-Peppas model & drug release takes place via supper case II transport. The stability study of optimized batch **F11** was performed which showed stable formulation after three months.

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CONFLICT OF INTEREST:

All authors declared no conflict of interest for the work.

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