Formulation And Evaluation of Glimepiride as Gastro-Retentive Dosage Form

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ABSTRACT

In order to increase Glimepiride's bioavailability, this research sought to extend the time it remained in the stomach by creating a floating tablet. Due to its limited window of absorption, glimepiride, which is a BCS class II medication, has an oral bioavailability of just 50–60%. Glimepiride floating tablet was created utilising the direct compression method with polymers such as HPMC K4M, HPMC K15M, HPMC K100M, Carbopol 937, and Xanthan gum. The evaluation of tablets included looking at their hardness, percent friability, in-vitro drug release profile, floating capacity, and drug content. The floating lag time and medication release are significantly impacted by the gas producing mechanism. Based on the findings, it was determined that the formulation F4 was found to be best among all the formulations batches as it showed floating lag time of (90 sec) and prolonged floating duration up to (12 hrs) which was controlled release characteristic and the maximum release observed at 8 hrs was (66.12%).

Keywords: Glimepiride, Floating tablet, Direct compression technique.

1. INTRODUCTION

For therapeutic medicines to have a systemic effect, oral medication delivery is the most desirable and recommended form of administration. The physiological issues with this route, however, include an unpredictable stomach emptying rate that varies from person to person, a gastro intestinal transit time (8–12 hr), and the existence of an upper small intestine absorption window for a number of medications [1-3]. There have been many different methods for creating gastro-retentive dosage forms, including as mucoadhesive, swellable, and floating systems.

Davis published the first description of floating medicine delivery devices in 1968. These technologies were employed to extend the stomach residence period of drug delivery systems [4,5,6]. They float around in the stomach for a long time without slowing down the rate at which other substances are emptied from the stomach. For medications that function locally in the proximal gastrointestinal tract (GIT), are unstable in the lower regions of the GIT, or are ineffectively absorbed in the gut, floating dosage forms can be helpful. The inherent density of floating dose forms is less than that of the gastric content, which is estimated to be 1.004–1.010 g/cm3, or they float as a result of the creation of a gaseous phase inside the system upon contact with the stomach fluid. This property enables them to float on the stomach content's surface for a longer amount of time without slowing down the rate of emptying [7,8,9].

Glimepiride is a first third generation sulphonyl urea agent for the treatment type II diabetes mellitus [10-15]. Due to the limited absorption window, oral bioavailability is 50–60%. Glimepiride's biological half-life is 5 hours. Dose of 1 mg to 8 mg of glimepiride is administered every day. The creation and assessment of floating Glimepiride tablets that are gastro-retentive were examined in the current experiment. The primary goal of the current work was to create floating tablets that were gastro-retentive by combining xanthan gum, a natural polymer, with synthetic polymers HPMC K4, HPMC K15, HPMC K100, and Carbopol 937. Glimepiride floating tablets were developed to maximise absorption and boost bioavailability by extending the stomach residence time. Glimepiride was selected as a model medication because of its inadequate absorption caused by its short gastric residence time.

2. MATERIALS AND METHODS

2.1 Materials

Glimepiride was used as the active ingredient and was purchased from (BDR Medi Labs. Baddi.), HPMC K100M, HPMC K15M HPMC K4M, Carbopol 934, PVP K30, Citric acid obtained from (Loba chemicals Pvt ltd.), Magnesium stearate and Talc obtained from (Central Drug House (Pvt. Ltd., Mumbai) and Lactose from (Signet Chemical Pvt. Ltd., Mumbai). All other chemicals and solvents were of analytical grade.

2.2Methods

2.2.1 Physical Appearance:

The several organoleptic qualities of Glimepiride, such as colour, odour, texture, and taste, were used to evaluate by its outward appearance.

2.2.2 Melting Point Determination

The capillary fusion method was used to measure the melting point of Glimepiride. A little amount of medication was placed inside a capillary that was sealed at one end, and the capillary was then positioned with the sealed end facing down into the melting point device. Using the

given thermometer, the temperature at which the solid medication becomes liquid was recorded. The melting point was recorded and compared with literature value.

2.2.3 Fourier Transform Infra-Red Spectral Analysis:

For the purpose of qualitative chemical identification, FTIR analysis of the material was performed. The infrared spectrum of Glimepiride was performed on the Fourier Transformed Infra-red Spectrophotometer. The sample was scanned at wavelength 4000-400 cm^{-1}.

2.2.4 Determination of Solubility

2.2.4.1 Qualitative Solubility of Glimepiride in Different Solvents

The solubility of Glimepiride was determined in different solvent systems. In screw-capped glass tubes, a little quantity of the drug was combined with 10 ml of each solvent and shaken on a continual water bath shaker for 24 hours at 25°C. Physical testing was done on the solutions to determine whether or not there were any drug particles.

2.2.4.2 Quantitative Solubility Glimepiride

10 mg of the drug was dissolved in 10 ml of distilled water and 10 ml of 0.1 N HCL buffer (pH 1.2) in 10 ml volumetric flasks to assess the solubility of Glimepiride in these solutions. The mouth of flask was properly covered with aluminium foil and placed in water bath shaker maintained at 37°C for 48 hrs, Samples were taken manually and filtered. Using a UV spectrophotometer (Shimadzu-1900 UV-Visible spectrophotometer), solutions UV absorbance was measured at 228 nm, and the quantity of medication dissolved was estimated using a calibration curve.

2.2.5 Partition Coefficient:

The lipophilicity and cell membrane-crossing potential of a drug are measured by the partition coefficient. In n-octanol: 0.1N HCL buffer (pH 1.2), the partition coefficient of Glimepiride was calculated. In a separating funnel, 10 mg of the drug was precisely weighed and added to 50 ml of n-octanol: 0.1N HCL buffer (1:1). Continuous shaking was applied to the mixture until equilibrium was reached. Distilled water was filtered using Whatman filter no. 41 after phases were separated using a separating funnel. Utilizing a UV spectrophotometer, the absorbance at 228 nm was measured to estimate how much Glimepiride was solubilized in 0.1N HCL buffer. Calculating the partition coefficient and comparing it to literature values.

$$P_{o/w} = C_{organic} / C_{aqueous} \ldots\ldots\ldots(1)$$

2.2.6 Determination of Absorption Maxima (λ_{max}) of Drug

By scanning a 10 µg/ml solution of the drug in methanol, 0.1 N HCL buffer (pH 1.2), and distilled water between 200 and 400 nm, the UV absorption maxima of the drug were identified.

The absorption maxima of pure drug in Methanol, Distilled water & 0.1 N HCL buffer (pH 1.2) was observed.

2.2.7 Preparation of calibration curve of Glimepiride:

Using a Shimadzu 1900I UV visible spectrophotometer, the calibration curves for Glimepiride were created in methanol, distilled water, and 0.1 N HCL buffer (pH 1.2). A 50 ml volumetric flask containing 50 mg of Glimepiride was accurately weighed, and the remaining volume was

filled with distilled water and co-solvent to create a 250 µg/ml stock solution of Glimepiride. From the stock solution, 1 ml was collected, placed into a 10 ml volumetric flask, and the remaining volume was filled with solvent to create a solution with a concentration of 250 µg/ml, from which further dilutions of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, and 0.8 mL were created. To construct a calibration curve, the same process was used for methanol and 0.1 N HCL buffer (pH 1.2).

2.2.8 Drug – Polymer Interaction Studies:

The compatibility of the medication and systemic polymers must be taken into account while creating gastro-retentive tablets. It is crucial to establish that under experimental and shelf conditions, the medicine does not interact with the polymer. The desired dosage of the medication was combined with the designated excipients, well mixed, and then put into dry vials. For four weeks, the vials were sealed and maintained at (45±2°C and 75±5% RH). The vials were regularly checked each day for liquefaction, clump formation, and discolouration. For drug excipient compatibility investigations, the infrared absorption spectra of a physical combination of polymers and drug were performed from 4000 cm^{-1} to 600 cm^{-1}.

2.3 Formulation of Floating tablet:

2.3.1 Direct compression method

The floating glimepiride tablets were created using the direct compression method. Before combining, each of the components was first individually processed through sieve #40. With the exception of talc and magnesium stearate, the needed amount of glimepiride and the other components were precisely weighed out, put to a mortar, and triturated to ensure a complete mixing. Talc and magnesium stearate were added to the aforementioned mixture and stirred for an additional two minutes. The combination was then crushed into 100mg tablet.

2.4 Evaluation Parameters

2.4.1 Hardness:

A tablet's hardness reveals its capacity to tolerate managing mechanical shocks. The hardness of the tablet was assessed using the Monsanto hardness tester. The unit of measurement is kg/cm^2. Five tablets were chosen at random, and their hardness was assessed.

2.4.2 Friability:

Roche Friabilator was used to gauge tablet strength. 20 tablets were weighed, put into the friabilator, turned 100 times, then were removed and dusted.

Reweighing the tablets allowed for the calculation of the weight reduction percentage.

The % friability was calculated by: $F= [(W_{initial}- W_{final}) \times 100]/ W_{initial}$

2.4.3 Weight variation:

From each batch, 20 tablets were chosen at random, and they were all weighed separately and collectively using an electronic balance. The typical weight was recorded.

$PD= [(WH-WL) \times 100]/ WH$

Where, PD= percentage deviation

WH= highest weight (mg)

WL= lowest weight (mg)

2.4.4 Uniformity of drug content

The 20 tablets of each formulation were weighed and pulverised. An amount of powder equivalent to 100 mg of glimepiride was added, and then a 100 ml volumetric flask's capacity was changed to 100 ml by adding 0.1 N HCL. Shimadzu 1900I UV visible spectrophotometer was used to measure the absorbance of the final solution at 228 nm after 1 ml of the aforementioned solution was further diluted to 100 ml with 0.1 N HCL.

2.4.5 In-vitro Buoyancy studies

The float delay time was used to determine the tablets in vitro floating behaviour. 0.1 N HCL was added to a 100 ml beaker that contained the tablets. The period of time it took for the tablet to surface—the float delay time—was calculated. the interval between the dosage form's administration and the onset of buoyancy in 0.1N HCl, as well as the duration of that interval. The term "total float time" refers to the whole amount of time that the dose form is buoyant. (TFT).

2.4.6 In-vitro drug release study

The USP basket technique was used for the release testing. 900ml of 0.1N HCL were added to the jar, and the medium was allowed to acclimate to a temperature of 370.5 °C while rotating at 50 rpm. The tablet was placed inside the container and basket, and the machine ran for eight hours at a speed of fifty rotations per minute. At regular intervals, five millilitres of the fluid were withdrawn, filtered, and then reintroduced. With the use of the dissolving solution, the samples were properly diluted before being spectrophotometrically tested at 228 nm.

2.4.7 Drug release kinetics

Data from in-vitro drug release experiments were treated to a variety of kinetic models to examine the drug release kinetics:

- **Zero order** as cumulative amount of drug release Vs time.

$F = Ko\ t$

Where, ‘F’ is the drug release at time ‘t’, and ‘Ko’ is the zero-order release rate constant. The plot of % drug release versus time is linear.

- **First order** as log % drug remaining Vs time.

$Log\ (100-F) = kt$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

- **Higuchi model** as % CDR Vs square root of time.

$F = k\ t1/2$

Where, ‘k’ is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

2.5 Stability Studies

Stability tests were performed on produced tablets to assess their stability with regard to their weight, hardness, friability, physical appearance, and drug content after storing them at $40^0C \pm 2^0C/75\%RH \pm 5\%RH$ for 28 days. Samples were removed after 0, 7, 14, 27, and 28 days.

2.6 Results and Discussion

2.6.1 Pre-formulation Studies of Glimepiride:

The sample of Glimepiride was received as a gift sample from BDR Medi Labs. Baddi. The sample of glimepiride was analyzed for the various organoleptic and physiochemical properties. The sample possessed similar colour, odour, taste and state as given in IP (Indian Pharmacopoeia). The melting point of glimepiride was found to be 208.67 ± 4.16 °C which is in close vicinity to the literature value. The FTIR spectrum (Figure 01) of the drug shows the peaks which is concurrent to the structure of glimepiride: 3368 (N-H stretching), 2931 (Aromatic C-H stretching), 1539 (CH_2 symmetric stretching), 1704 (C=O stretching), 1668 (Aromatic C=C stretching). From the qualitative solubility test of Glimepiride, it was found that the drug is very slightly soluble in methanol, practically insoluble in distilled water and sparingly soluble in 0.1 N HCl buffer. The qualitative solubility of glimepiride was found to be 0.004, 0.002 and 0.02 mg/mL in methanol, distilled water and 0.1 N HCl buffer respectively. The partition coefficient of glimepiride was found to be 3.0-3.2 in 0.1 N HCl (pH1.2) buffer.

The absorption maxima of glimepiride in methanol, distilled water and 0.1 N HCl Buffer [pH 1.2] was found to be (228 nm) respectively. The calibration curve was prepared in methanol, distilled water and 0.1 N HCl Buffer [pH 1.2] and obtained a straight line shown in Figure 02.

The drug and polymer mixture were analysed for 4 weeks and there is no change was obtained in physical appearance, FTIR peaks and absorption maxima of drug shows in figure 01 and table 02.

2.6.2 Evaluation of Floating Tablets:

Among all the nine formulations F4 formulation was selected for the further evaluation studies. The evaluation parameters results are listed in table no.2.

2.6.3 Release / Kinetics pattern of F4 formulation

The acquired data were fitted into several kinetics equations of Zero order, first order, Higuchi order in order to analyse the mechanism of drug release kinetics of the floating tablets but F4 formulation follow 1^{st} order release among the Zero and Higuchi release order. Calculation of the regression coefficient was done and kinetic model graphs were created using the appropriate data are shown in figure 03.

2.6.4 Stability studies

The stability study's findings showed that the drug closely conforms to the suggested stability standard. The statistics reveal that neither a substantial physical change nor a significant chemical change has occurred, indicating that the formulation will retain its potency and quality for the duration of its shelf life. The stability data is showed in table no.3. The drug release study was done after the storage period and the difference was showed in figure 04 and table 04.

2.6.5 Determination of Similarity Factor

Floating Tablets of formulation F4 was selected for the stability studies. For the determination of the similarity factor between before and after storage drug release data of the F4 formulation. The US-FDA placed emphasis on determining the degree of similarity between in-vitro drug release tests of various formulations. As implied by the name, it places a focus on the similarity of two comparative formulations. According to US-FDA, a similarity factor of 50 to 100 is generally considered appropriate. It can be determined by using the formula:

$$\mathbf{f2= 50. Log \{[1+1/n \sum_{t=1}^{n}. (R_t - T_t)^2]^{-0.5}.100\}}$$

where,

n is the number of dissolution sample time

R_1 and T_1 are the individual or mean reference and test diffuse values at each time point.

F2 = 100 when two profiles are identical. And f2 value of 50 is produced by an average difference of 10% across all recorded time points.

The f2 value was determined to be 89.52, which is greater than 50 and indicates that both diffusion profiles are quite similar to one another.

CONCLUSION

From the above evaluation test formulation F4 is selected as best formulation because it showed floating lag time of (90 sec) and prolonged floating duration up to (12 hrs.) which was controlled release characteristic and the maximum release observed at 8 hrs. was (66.12%). The results shows that drug release rate was increased as viscosity of the polymer was increased. It was confirmed that effervescent floating tablet of Glimepiride containing (HPMC K100M + Carbopol 934) provide better option for controlled release and improve bioavailability whereas decrease amount of citric acid increase the floating lag time therefore tablet float for longer duration.

No significant changes were observed on physical characteristics, drug content and on drug release of floating tablets after keeping the tablets for one-month at $40^0C \pm 2^0C$/75% ±5% RH. So, it was concluded that the prepared tablets were stable under these stress condition.

It was concluded from the current experiment that creating floating tablets might be an inventive and promising method of delivering glimepiride with better bioavailability.

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Table no.1: Composition of floating tablets of Glimepiride

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Glimepiride	2	2	2	2	2	2	2	2	2
HPMC K100M	15	----	15	10	----	19	19	10	10
HPMC K15M	15	15	----	----	19	----	19	15	5
HPMC K4M	----	15	15	15	19	19	----	10	15
Sodium bicarbonate	20	20	20	20	7	12	7	15	10
Magnesium stearate	5	5	5	5	5	5	5	5	5
Citric Acid	5	----	----	5	10	----	10	5	10
Lactose	10	15	15	15	10	15	10	10	15
Carbopol 934	15	15	15	15	15	15	15	15	15
PVP K30	3	3	3	3	3	3	3	3	3
Talc	10	10	10	10	10	10	10	10	10

Table 2: Precompression/ Post-compression Evaluation data of formulation F4

Parameters	Bulk Density (g/cm^3)	Tapped Density (g/cm^3)	Compressibility Index (%)	Hausner's Ratio	Angle of Repose (°)
F4	0.59	0.55	12.45	0.932	24.31

Para-meters	Average Weight (mg)	Hardness(kg/cm^2)	Friability (%)	%Drug content (mg)	Floating Lag Time(sec)	Buoyancy (hr)
F4	100.16± 0.017	4.97	0.29	100.17± 0.72	90	12

Table 3: Evaluation data of F4 formulation during storage period

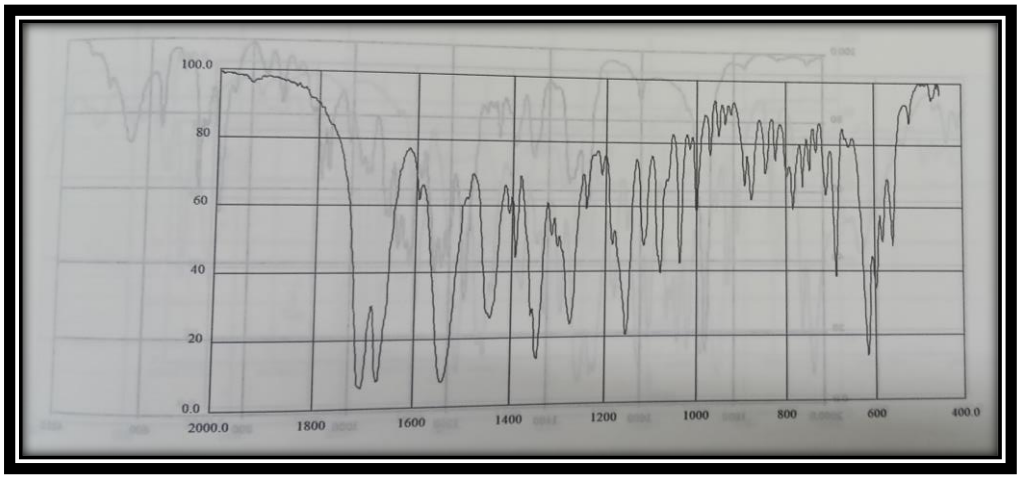
Time (days)	Real Time(30^0C/65%RH)				Accelerated(45^0C/75%RH)			
	Weight (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Weight (mg)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
0	100.16	4.97	0.29	100.17	100.16	4.97	0.29	100.17
7	100.16	4.97	0.29	100.15	100.16	4.96	0.28	100.07
14	100.16	4.97	0.27	99.97	99.89	4.93	0.25	99.65
21	99.65	4.93	0.24	98.94	99.64	4.89	0.21	98.12
28	99.60	4.90	0.21	98.41	98.76	4.84	0.18	97.34

Table 4: Comparison of drug release data of formulation F4 before and after storage

Time	% Cumulative Drug Release	
	Before Stability Studies	After Stability Studies
0	0	0
1	6.42	6.37
2	23.45	22.98
3	33.14	32.87
4	42.36	40.99
5	49.14	48.34
6	57.98	56.16

7	63.14	61.12
8	66.12	64.10

A



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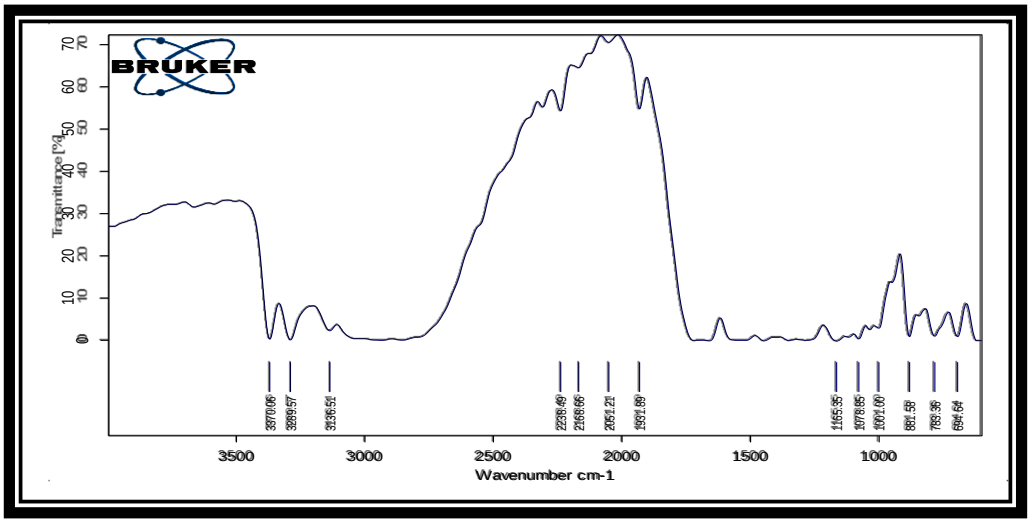

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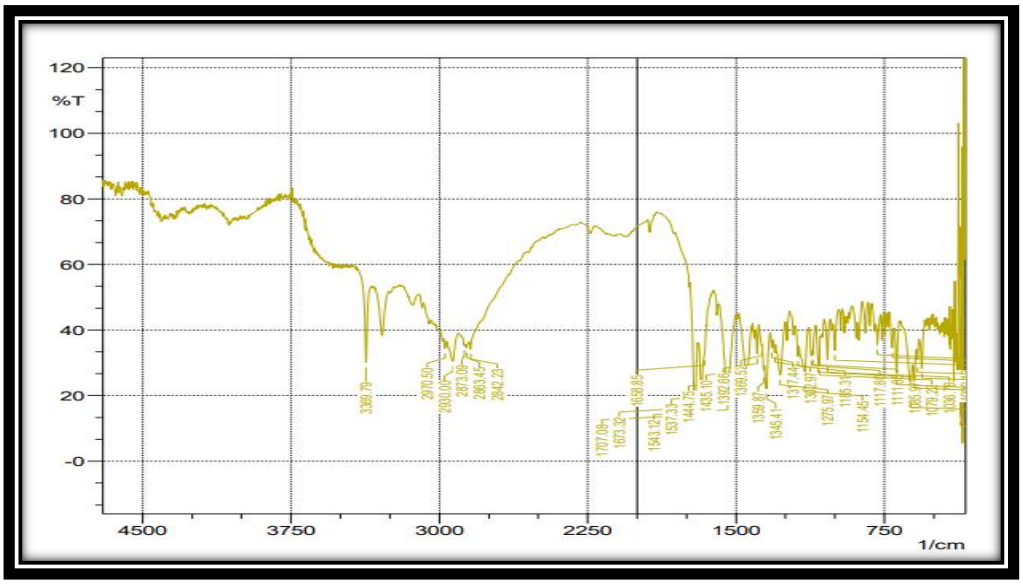

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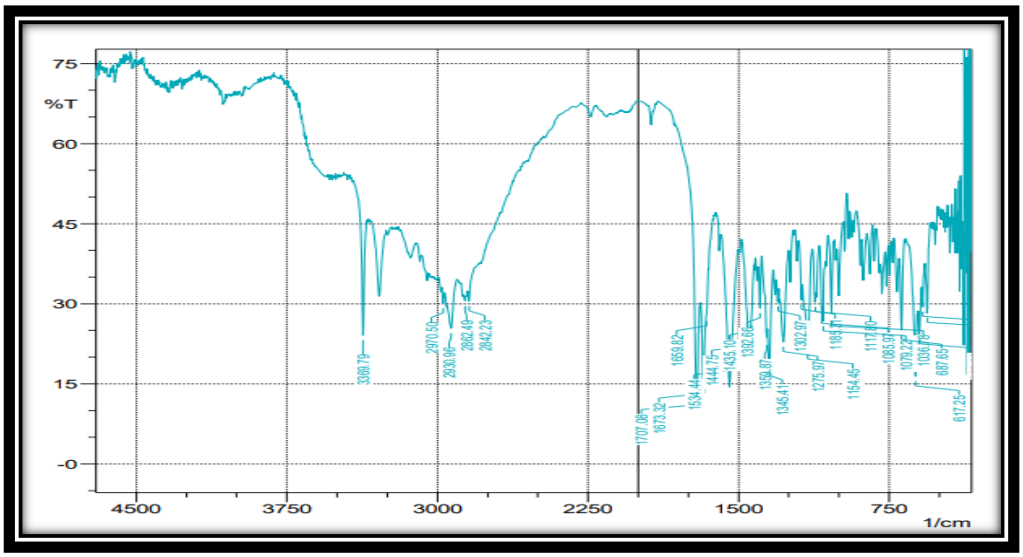

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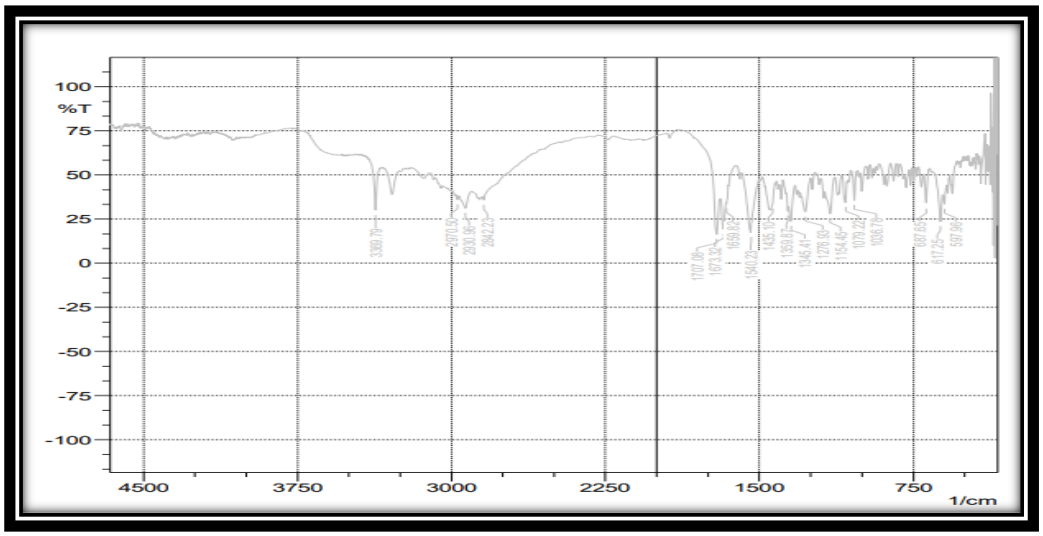
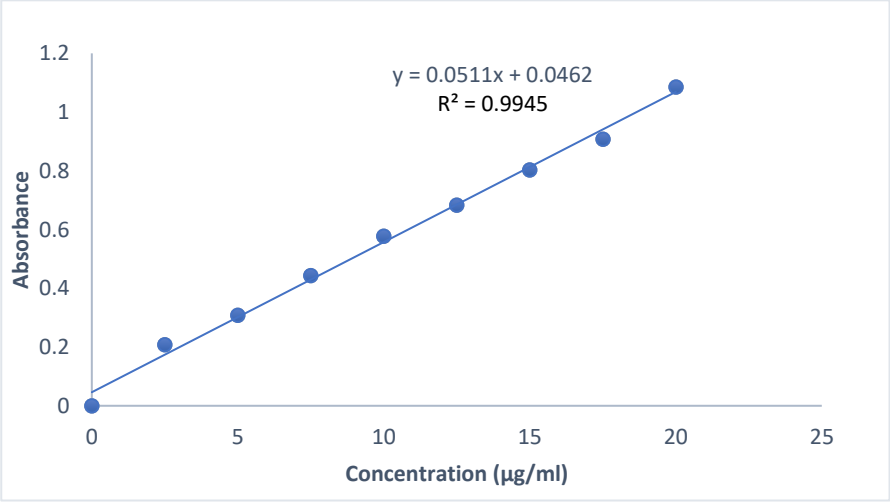


Fig 1: FTIR spectrum (A) FTIR acc to I.P (B) FTIR of Pure drug Glimepiride (C) Drug+ HPMC K15 M (D) Drug + HPMC K100 M (E) Drug + HPMC K4M

A



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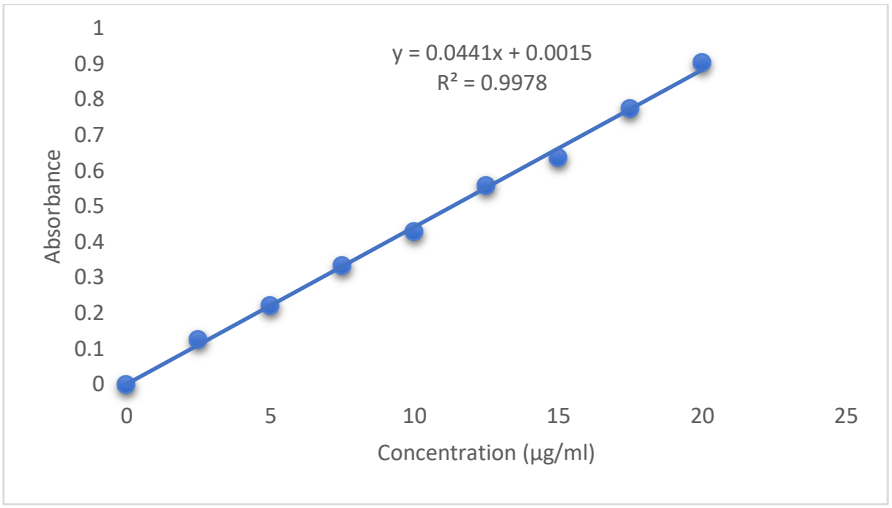

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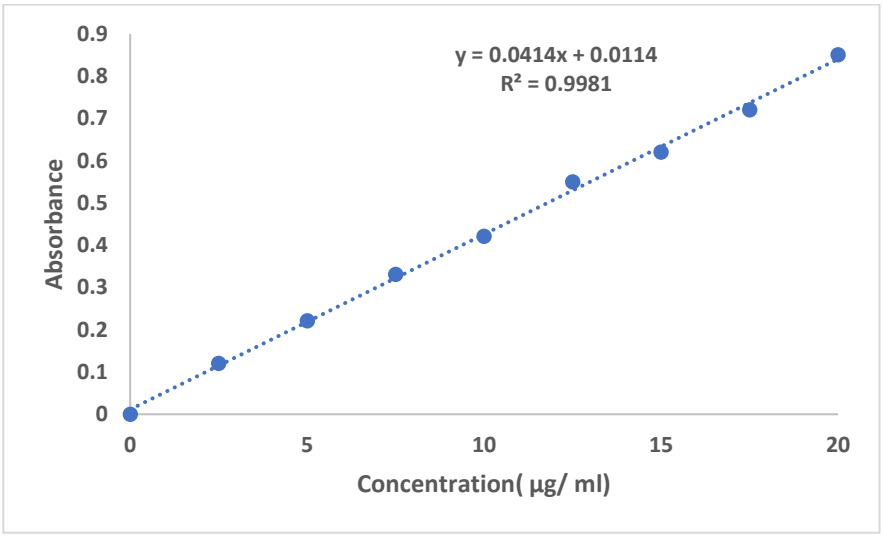

Fig 2: Standard plot of Glimepiride (A) in Methanol (B) in Distilled water (C) in 0.1N HCl (pH 1.2) Buffer

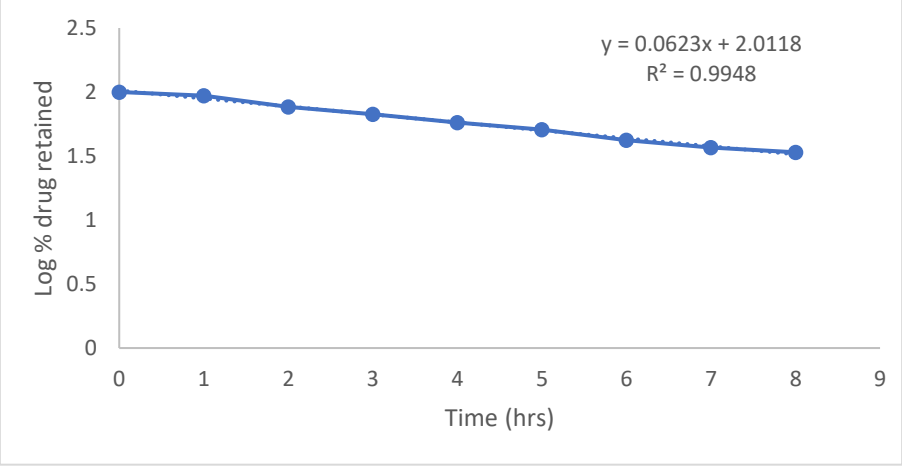

Fig 3: First Order Release of Formulation F4

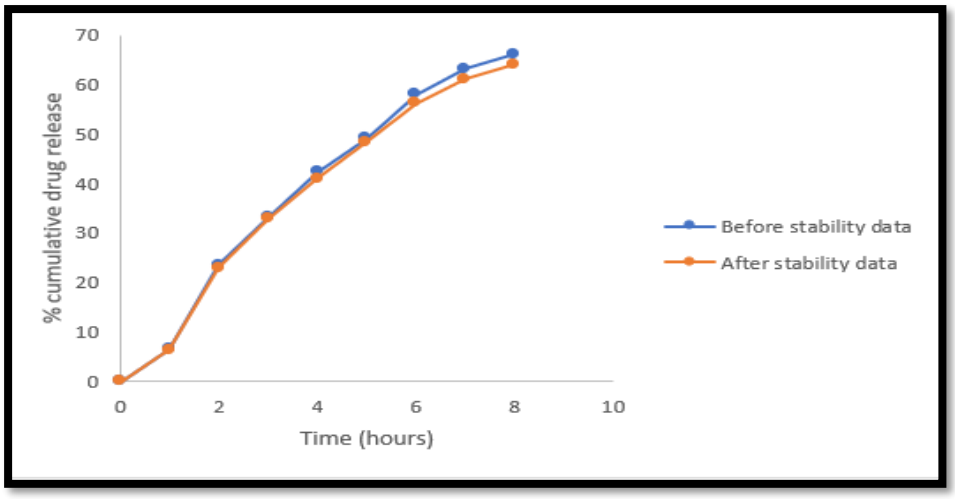

Fig 4: Drug release data of formulation F4 before and after storage