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# Formulation development and evaluation of controlled release matrix tablets of glibenclamide

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## Abstract

The present study aimed to formulate and evaluate the controlled-release matrix tablets of Glibenclamide which is an antidiabetic drug that belongs to the second-generation oral hypoglycemics. Matrix tablets were prepared by three different polymers as sustained-release agents, using Glibenclamide as a model drug. Three polymers were selected for this study- HPMC K 15, HPMC K 100, and EC in different drug: polymer ratios. The drug was identified by FTIR spectroscopic method. The pre-compression and post-compression parameters of all formulations were found to be within acceptable limits. The release rate of Glibenclamide from matrix tablets was studied using the USP Dissolution Testing Apparatus type-I (Basket method). The formulation F6 which contained EC 50mg showed a maximum release of 99.28% in 24 hrs and revealed that EC was more effective in sustaining the drug release therefore formulation F6 was selected as the optimized formulation. The in-vitro release data of optimized formulation was fit into various kinetic models, among the different model's data of in-vitro release of best fit into Zero order kinetic model. The formulation best fit the Higuchi model and showed that drug release from the prepared matrix tablets occurs via a diffusion process.

**Keywords**

Glibenclamide, HPMC, EC, Controlled release, Matrix Tablet

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## INTRODUCTION

Controlled drug delivery systems have been introduced to overwhelm the drawback of fluctuating drug levels associated with conventional dosage forms. Numerous technologies have been used to control the systemic delivery of drugs. Controlled-release (CR) tablet formulations are much desirable and preferred for long-term therapy (Adepu and Ramakrishna, 2021).

The most commonly used method of modulating the drug release is to include it in a matrix system because they maintain uniform drug levels, better patient compliance, reduces the dose and side effects, increases safety margin for high-potency drugs, enhanced bioavailability, and reduce inter-patient variability. Matrix-type systems consist of drug crystals homogeneously dispersed in a matrix environment made up of cross-linked polymer (Nish *et al.,* 2012). Matrix systems can be divided into three types: Monolithic matrix, Gel forming the hydrophilic matrix, and Erodible (hydrophobic) matrix. On the basis of the retardant material used: Matrix tablets can be divided into 5 types; Hydrophobic matrices (Plastic matrices), Lipid matrices, Hydrophilic matrices, Biodegradable matrices, and Mineral matrices (Harnish *et al.,* 2011).

Glibenclamide is an anti-diabetic drug that belongs to the second-generation sulfonylurea oral hypoglycemic class. It is used to assist in the control of mild to moderately severe type 2 diabetes mellitus. Glibenclamide act by stimulating β cells of the pancreas to release insulin. Sulfonylurea increases both basal insulin secretion and meal-stimulated insulin release. Sulfonylurea also increases peripheral glucose utilization, decreases hepatic gluconeogenesis, and may increase the number and sensitivity of insulin receptors. Pharmacokinetic and Pharmacodynamic profile of Glibenclamide: duration of action; 18-24h, metabolism; hepatic, absorption (bioavailability); well absorbed, half-life; 4-6h, daily dose; 2.5 - 15mg (Brian, 2007). The main objective of the study is to formulate controlled-release matrix tablets of Glibenclamide.

The most prevalent and convenient to develop on a commercial basis are matrix-controlled release tablet formulations. As a crucial component of oral controlled-release dosage forms, matrix tablets are used. This led to the resolution of issues with traditional dose forms, such as patient non-compliance, local adverse effects, frequent administration, and variations in blood concentration levels. For

medications that are taken orally but have a short half-life and a high dose frequency, an oral controlled-release drug delivery device becomes a very viable strategy (Ajit Kulkarni *et al.,* 2017).

## MATERIALS AND METHOD

Glibenclamide was obtained as gift samples from Spectrum Pharma, Hyderabad. HPMC K 15 M, HPMC K 100 M, and EC were a sample from Chemdyes Corporation, Rajkot. Magnesium stearate was obtained from Research Lab, Poona. Lactose monohydrate was obtained from Merck Limited, Mumbai. All other chemicals such as talc, starch, potassium dihydrogen Oorthophosphate, and sodium hydroxide were obtained from Laboratory equipment stores, Edappally.

**Preformulation studies**

A preformulation study is defined as an investigation of the physical and chemical properties of a drug substance alone and when combined with the excipients (Trevor, 2018).

**Identification of drug**

Drug identification was done by performing IR spectra and compared with standards.The IR spectrum of the obtained drug sample was compared with the standard functional group frequencies of glibenclamide and the drug sample was identified as glibenclamide. (Equipment used - Model: IRAFINITY-I, Manufacturer: SHIMADZU, Japan).

**Pressed pellet Technique**

Sample and potassium bromide in the ratio of 1:100 were placed in a clean agate mortar and triturated well and the powder mixture is compressed under 15 tonnes of pressure in a hydraulic press to form a transparent pellet. The pellet was placed in the sampling area of the FTIR spectrophotometer and scanned from 4000 to 400cm-1 and peaks obtained were identified.

**Physicochemical properties of the drug**

The physicochemical properties of the drug were evaluated as per the procedure of Malan *et al.,* 2002.

**Physical appearance**

The physical appearance of the drug was observed and compared with pharmacopoeial specifications (Indian Pharmacopoeia. 2014, Vol. 2).

**Melting point**

The melting point of the drug was determined using melting point apparatus.

**Solubility**

The solubility of the drug in water, ether, ethanol, methanol, chloroform, and alkali hydroxide solutions was determined.

**Evaluation of pre-compression parameters of glibenclamide**

The pre-compression parameters of glibenclamide like the angle of repose, bulk density, tapped density, Carr's Index, and Hausner'sratiowere evaluated.

**Determination of drug-polymer compatibility**

By IR spectroscopy: IR spectroscopy was carried out to check the compatibility between the drug and polymers. IR spectrum of drug and polymers – glibenclamide and HPMC K 15M, HPMC K 100M, EC and mixtures of drug and polymers glibenclamide- HPMC K 15M, glibenclamide- HPMC K 100M, glibenclamide- EC were recorded and compared with individual reference spectra for any spectral interferences.

**Analytical methods**

Determination of λmax:λmax of glibenclamide was determined in phosphate buffer pH 7.4 by scanning 10 µg/ml solution of glibenclamide in respective vehicles in the range of 200-400 nm on a UV-visible spectrophotometer. The wavelength corresponding to the peak of the spectrum was noted.

**Development of standard curve of glibenclamide**

Preparation of calibration curve of glibenclamide in phosphate buffer pH 7.4, 10mg of glibenclamide was accurately weighed and dissolved in a required quantity of methanol and make up to 100ml with phosphate buffer pH 7.4 (100µg/ml). Aliquots equivalent to 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, 1.0 ml, and 1.2 ml were drawn from the stock solution and made up to 10 ml using phosphate buffer pH 7.4. All these solutions were analyzed spectrophotometrically at 226 nm and absorbance was noted. A plot of absorbance Vs concentration was drawn.

**Preparation of matrix tablets of glibenclamide**

Glibenclamide drugs with different concentrations of hydrophilic (HPMC K 15M, HPMC K 100M) and lipophilic (EC) polymer were prepared by wet granulation technique (Shantveer *et al.*, 2010). Required quantities of all ingredients were weighed individually on an electronic balance. All ingredients were first sieved and mixed for 5 min. Then the granulating fluid was added drop by drop till a suitable mass for granulation was obtained. The wet mass granulated through sieve 16#. The granules were dried at 60°C for 1 hour in an oven. The dried granules were passed through sieve 22# and fractions of granules retained on the sieve were

discarded and then blended with talc and magnesium stearate for lubrication of granules which were then compressed on Cadmach eight station rotary tablet press using a 4 mm cone cave punches the weight of tablet adjusted to 450 mg, each tablet containing 10 mg glibenclamide and other excipients listed in table 1.

**Evaluation of matrix tablets of glibenclamide**

The pre-compression parameters were evaluated as per the procedure dictated by Tanbir *et al.,* 2011, Rajeshwar *et al.,* 2013 and Shantveer *et al.,* 2010. Evaluation of precompression parameters of tablet blends of controlled release matrix tablets of glibenclamide.

**Angle of repose**

The angle of repose was determined by the funnel method. The powders were allowed to flow through the funnel fixed to a stand at a definite height (h). The angle of repose (θ) was then calculated by measuring the height (h) and radius (r) of the heap of granules formed.

$\tan\theta = h/r$ or $\theta = \tan^{-1}(h/r)$ – Equation 1

**Bulk density**

A quantity of 10 g of granules from each formula, previously light Shaken for the break of any agglomerates formed, was introduced into the 100ml of measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall its weight from the hard surface from a height of 2.5cm at 2-sec intervals. The tapping was continued until no further change in the volume was noted.

**Poured density**

Apparent bulk density was determined by pouring a weighed quantity of powder into a graduated cylinder and measuring the volume of packing.

Poured (fluff) density = Weight of the powder / Volume of the packing

**Tapped density**

Tapped density was determined by the tapping method. Weighed quantity of powder was placed in a graduated cylinder and tapped until no further change in the volume of powder was noted and the volume of tapped packing was noted.

Tapped density = weight of the powder/volume of the tapped packing

**Compressibility index**

The compressibility of the powder was calculated by determining Carr's index and Hausner's ratio.

**Evaluation of post-compression parameters of the prepared tablets**.

The post-compression parameters of the prepared tablets were evaluated as per the guidelines of Sajid *et al.,* 2013, Hindustan *et al.*, 2011 and Sarika *et al.*, 2013.

**Thickness and diameter**

Physico-chemical properties of matrix tablets such as thickness and diameter (using a vernier caliper) were determined.

**Hardness**

The hardness of the tablets was tested using "Monsanto" hardness tester. In all the cases, means of six replicate determinations were taken.

**Friability**

Previously weighed 10 tablets were taken in Roche friabilator and the friability was checked at 25 rpm for 100 rotations. Then the tablets were dusted and reweighed and the percentage of powder eroded during 100 rotations was recorded. The resulting tablets were weighed and the percentage loss was calculated using the formula.

Initial weight – Final weight / Initial weight X 100

**Weight variation**

To study the weight variation, 10 tablets of each formulation were selected at random and determine their average weight. Not more than 2 of the individual weights may deviate from the average weight by more than the % deviation and none should deviate by more than twice the percentage.

**Drug content**

Five tablets were powdered in a mortar. From this, powder equivalent to 50 mg of the drug was taken in a 100 ml round bottom flask. It is extracted with 20 ml of phosphate buffer (pH 7.4) for ½ hour, filtered in a volumetric flask and the filtrate was made up to the mark with phosphate buffer. Further appropriate dilutions were made and the absorbance was measured at 226 nm against blank.

***In-vitro* dissolution study**

The release rate of glibenclamide from matrix tablets was studied using USP Dissolution Testing Apparatus type-I (Basket method), (Ashok Kumar Narayana *et al.,* 2001). The dissolution test was performed using 900 ml of pH 7.4 phosphate buffer, at 37 ± 0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at different time intervals and the samples were replaced with a fresh dissolution medium. The samples were filtered and diluted to a suitable concentration with the respective medium. The absorbance of these solutions was measured at 226 nm using a UV-Visible spectrophotometer.

**Kinetics of *in-vitro* drug release**

To study the release kinetics of in-vitro drug release (Bhavani *et al.,* 2012), data obtained from in-vitro release study were plotted in various kinetic models: Zero order as % drug released Vs time, First order as log % drug retained Vs time, Higuchi as % drug released Vs √time, Korsmeyer- Peppas as log % drug released Vs log time and Hixson-Crowell as (% drug retained) 1/3 Vs time.

**Zero-order**

$Q = K_0t$ - Equation 2

Where, Q is the amount of drug released at the time, t in hrs

$K_0$ is the zero-order release rate constant expressed in units of concentration/time

When the data were plotted as cumulative % drug release versus time, if the plot is linear then data obeys zero order kinetics with a slope equal to Ko. This model represents an ideal release profile to achieve prolonged pharmacological action.

**First order**

$\text{Log } Q = K_1 t$ - Equation 3

Where Q is the percent of drug released at a time, t

$K_1$ is the release rate constant.

When data were plotted as log cumulative % drug remaining versus time yielded a straight line indicating that the release follows first-order kinetics. The constant K can be obtained by multiplying slope values.

**Higuchi**

Drug release from the matrix device by diffusion has been described by Higuchi's Diffusion equation,

$Q = K_2 t^{1/2}$ - Equation 4

Where Q is the percentage of drug release at time t

$K_2$ is the diffusion rate constant.

When data were plotted according to this equation, i.e., the cumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism.

**Korsmeyer Peppas**

$Q = Kt^n$ - Equation 5

Where, Q is the percent of drug released at a time, t

K is the diffusion rate constant and n is a diffusional exponent.

This is a simple, semi-empiric model (Lisik and Musiał, 2019) when diffusion is the main drug release mechanism, relating exponentially the drug release to the elapsed time (t). This is used when the release mechanism is not well known or when more than one type of release phenomenon could be involved.

**Hixson-Crowell**

Drug release from the matrix device by diffusion has been described by the Hixon-Crowell diffusion equation;

$W_0^{1/3} - W_t^{1/3} = kt$ - Equation 6

where $W_0$ is the initial amount of drug in the pharmaceutical dosage form, Wt is the remaining amount of drug in the pharmaceutical dosage form at a time, and t and κ is a constant incorporating the surface-volume relation.

This expression applies to pharmaceutical dosage forms such as tablets where the dissolution occurs in planes that are parallel to the drug surface if tablet dimensions diminish proportionally in

such a manner that the initial geometrical form keeps constant all the time.

**Stability study protocol**

Batch selection and batch size: Stability studies were conducted for optimized formulation with a batch size of 50 tablets.

Containers and closure: The tablets were packed well in Aluminum foil and placed on an HDPE bottle.

Sampling test time point and storage conditions: The sampling plan and storage condition for the stability study were described in the following:

Storage conditions: 40° ± 2°C / 75 ± 5 % RH

Sampling point: 15, 30 days

Test parameters: The stability batch was subjected to evaluation studies like thickness, diameter, hardness, weight variation, friability, drug content, and in–vitro dissolution study.

## RESULTS AND DISCUSSION

**Preformulation study**

**Identification of drug**

Drug identification was done by performing IR spectra and compared with standards.

**Infra-red spectrum**

The IR spectrum is a powerful analytical tool for the identification and investigation of the drug in formulation (Ouhaddouch *et al.,* 2019) and was compared with the standard functional group frequencies of glibenclamide and the drug sample was identified as glibenclamide. The IR spectrum of glibenclamide is shown in Figure 2.

**Physicochemical properties of the drug**

**Physical appearance**

Glibenclamide was found to be a white, crystalline powder. The physical appearance of the drug complied fully with pharmacopoeial specifications.

**Melting point**

The melting point of the drug was found to be in the range of 169-175°C, which conforms with the reported value. It indicates the purity of the drug sample, (The International Pharmacopoeia - Sixth Edition, 2016).

**Solubility**

The solubility of the drug in water, ether, ethanol, and dilute solutions of alkali hydroxides was examined and found to conform with pharmacopoeial specifications. The solubility of glibenclamide in various solvents is shown in Table 2.

**Evaluation of precompression parameters of glibenclamide**

The angle of repose for the pure drug was very less and hence the poor flow of the pure drug was exhibited. The Hausner ratio and compressibility index of the pure drug was found to be high, confirming that the drug has poor flow properties and compressibility; hence blends should be done before compression. The physical characteristics of Glibenclamide are shown in Table 3.

A good flow of powders/ granules is essential in tableting because the compressibility and flow properties of the drugs are likely to influence the compression process in the preparation of sustained-release tablets (Morin and Briens, 2013). Hence to improve the flow property the formulations were prepared by wet granulation technique to improve the flow as well as compressibility.

**Drug polymer compatibility studies**

IR spectroscopy was carried out to check the compatibility between drug and polymers (Adriana 2019). IR spectrum of glibenclamide, HPMC K 15M, HPMC K 100M, EC and mixtures of drug and polymers glibenclamide- HPMC K 15M, glibenclamide- HPMC K 100M, glibenclamide- EC were taken and it was found that there were no signicant change in the major functional group frequencies of glibenclamide in these combinations and values were found to be within the range. The study confirmed the compatibility of the drug with polymers. The spectra were shown in Figure 2 - 8.

**Analytical methods**

The analytical method development recommends the quality, purity, and specificity of the drug during the manufacturing process and hence the standard of the drug may not vary, which produces the desired therapeutic effect (Grish KT *et al.,* 2013). Hence, the λmax of glibenclamide was evaluated in the present study.

**Determination of λmax of glibenclamide**

The spectrum of 10µg/mL solution of glibenclamide in phosphate buffer pH 7.4 showed the peak as given in Table 4. The results showed that glibenclamide shows maximum absorbance at 226 nm therefore 226 nm was taken as λmax.

**Preparation of calibration curve of glibenclamide in phosphate buffer pH 7.4.**

Table 5 shows the absorbances of glibenclamide standard solutions (2-12 µg/ml) and Figure 1 shows the calibration curve at 226 nm in phosphate buffer pH 7.4. The curve was found to be linear in the concentration range of 2-12 µg/ml at 226 nm.

**Evaluation of matrix tablets of glibenclamide**

**Evaluation of pre-compression parameters of tablet blends of**

**controlled release matrix tablets of glibenclamide.**

The drug was blended along with other excipients and evaluated for the pre-compression characteristics such as Angle of repose, Bulk density, Tapped density, Carr's Index, Hausner's ratio. The results are shown in Table 6 and 7. The results showed that the powder blends have required flow properties for compression into tablets.

**Evaluation of post-compression parameters of the prepared tablets**

Post compression parameters of matrix tablets such as thickness and diameter, hardness, friability, weight variation, and drug content were determined (Sirisolla J and Ramanamurthy KV; 2015), and the results tabulated are shown in Table 8.

Physico-chemical parameters of all matrix tablet formulations were found to be within acceptable limits. The tablets were uniform in size and shape, friable, and with acceptable hardness. In determinations of tablet weights, all formulations weights were found to be within pharmacopoeia limits (Indian Pharmacopoeia. 2014, Vol. 2). Friability of the tablet was well within the acceptable range of 1% and indicates that tablet surfaces are strong enough to withstand mechanical shock or attrition during storage and transportation and until they are consumed. The average percentage deviation of all tablet formulations was found to be within the limits, and hence all formulations passed the uniformity of weight as per official Pharmacopeia. The manufactured tablets showed low weight variations and a high degree of drug content uniformity among different batches of the tablets. The drug content of all batches was found to be within 90-110%.

***In-vitro* drug release study**

Drug release is dependent on polymer properties, thus the application of these properties can produce well-characterized and reproducible dosage forms (Nokhodchi A, 2012). The *in vitro* drug release study of all formulations of matrix tablets was carried out. The results of 6 formulations were shown in Table 9 and a comparison of the *In-vitro* dissolution graph of formulations F1-F6 is shown in Figure 9. An *In-vitro* drug release study indicated that EC was more effective in sustaining the drug release, followed by HPMC K 100 and HPMC K 15, release rate is decreased with increasing concentration of polymer. The formulation F6 which contained EC in 50mg and F5 with EC in 30mg sustained the drug release for 24 hours and 19 hours respectively. The formulation F4 and F3 which contained HPMC K 100 120mg and 60mg sustained the drug release for 12 hours. The formulation F2 which

contained HPMC K 15 in 120mg and F1 with HPMC K 15 in 60mg sustained the drug release for 8 hours and 6 hours respectively.

**Kinetics of *in-vitro* drug release**

The formulation F6 was selected as the best formulation based on the dissolution study. The in-vitro release data was fit into various kinetic models like Zero order, First order, Higuchi plot, Peppas model, and Hixson-Crowell model. The $R^2$ values obtained in various kinetic models are given in Table 10. The drug release kinetics and mechanism of drug release were studied for the optimized formulation, among the different models data of *in-vitro* release of best fit into Zero order kinetic model because $R^2$ values in this model were more close to unity. The release patterns of glibenclamide from controlled release matrix tablets in the Zero order kinetic model are shown in Figure 10. Among the different model's data of *in-vitro* release formulation best fit into the Higuchi kinetic model, because $R^2$ values in this model were closer to unity. It indicated that drug release from the prepared matrix tablets occurs via a diffusion process. To explore more about the kinetic behavior, in vitro release results were further fitted into the Peppasequation and the result indicates that the drug release is controlled by more than one process. The release patterns of glibenclamide from controlled release matrix tablets in the Higuchi model are shown in Figure 11 and Korsmeyer-Peppas in Figure 12.

**Stability study**

Stability studies of a pharmaceutical formulation were done to determine whether environmental factors such as temperature, and humidity light affect the physiochemical and therapeutic properties of the formulation. The stability study confirms that the formulation meets its specification during the shelf life. Test parameters for optimized formulation F6 and stability study data results are given in Table 11- 13 and Figure 13. As per the in – vitro dissolution study the optimized formulation F6 was found to be more desirable than other formulations and chosen for the stability study. The formulation F6 was subjected to accelerated stability conditions at 400 ± 20° C / 75 ± 5 % RH for 30 days in a humidity cabinet (environmental test chamber – Rotek). At the time intervals of 15 and 30 days tablets were withdrawn, and evaluated for various test parameters like thickness, diameter, hardness, weight variation, friability, drug content and in – vitro dissolution study. The tablets did not show any variation in the tested parameters and the results were within the limits but showed slight variation in the dissolution profile.

**Table 1.** Composition of different batches of matrix tablets.

| Sl.No | Ingredients (mg) | Formulation Code | | | | | |
|---|---|---|---|---|---|---|---|
| | | F1 | F2 | F3 | F4 | F5 | F6 |
| 1 | Glibenclamide | 10 | 10 | 10 | 10 | 10 | 10 |
| 2 | HPMC K 15 M | 60 | 120 | | | | |
| 3 | HPMC K 100 M | | | 60 | 120 | | |
| 4 | EC | | | | | 30 | 50 |
| 5 | Magnesiumstearate | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| 6 | Talc | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| 7 | Lactose | 377 | 317 | 377 | 317 | 407 | 387 |

**Table 2:** Solubility of glibenclamide in various solvents.

| Solvent | Solubility |
|---|---|
| Water | Practically insoluble |
| Ether | Practically insoluble |
| Ethanol | Slightly soluble |
| Methanol | Slightly soluble |
| Chloroform | Slightly soluble |
| Dilute solutions of alkali hydroxides | Soluble |

**Table 3**: Physical characteristics of Glibenclamide.

| Sl.No | TESTS* | RESULTS |
|---|---|---|
| 1. | Bulk Density | 0.4312g/$cm^3$ |
| 2. | Tapped Density | 0.5434 g/ $cm^3$ |
| 3. | Compressibility Index | 20.64% |
| 4. | Hausner Ratio | 1.26 |
| 5. | Angle of Repose | 30.24 |

*Average of three determinations ± Standard deviation

**Table 4:** Absorption maxima of glibenclamide.

| nm | Absorption maxima (pH 7.4 buffer) |
|---|---|
| 226 | 0.845 |

**Table 5:** Standard calibration table for glibenclamide in pH 7.4 phosphate buffer

| Concentration (µg/ml) | Absorbance (226 nm) |
|---|---|
| 0 | 0 |
| 2 | 0.142 |
| 4 | 0.286 |
| 6 | 0.423 |
| 8 | 0.569 |
| 10 | 0.705 |
| 12 | 0.845 |

**Table 6:** Bulk density and Tapped density.

| Sl No: | Formulations | Bulk density* (g/ cc) | Tapped density* (g/ cc) |
|---|---|---|---|
| 1 | F1 | 0.4166±0.20 | 0.4587±0.17 |
| 2 | F2 | 0.4000±0.10 | 0.4424±0.17 |
| 3 | F3 | 0.3802±0.01 | 0.4310±0.10 |
| 4 | F4 | 0.3602±0.45 | 0.4000±0.19 |
| 5 | F5 | 0.370±0.62 | 0.4201±0.18 |
| 6 | F6 | 0.390±0.48 | 0.4401±0.16 |

*Average of three determinations ± Standard deviation

**Table 7:** Carr's Index, Hausner's ratio and Angle of repose.

| Sl. No | Formulations | Carr's Index (%)* | Hausner's ratio* | Angle of repose($^0$)* |
|---|---|---|---|---|
| 1 | F1 | 09.17±0.72 | 1.10±0.01 | 23.12±0.48 |
| 2 | F2 | 09.09±0.90 | 1.10±0.01 | 23.26±0.42 |
| 3 | F3 | 11.62±0.42 | 1.13±0.06 | 22.29±0.19 |
| 4 | F4 | 10.00±0.53 | 1.11±0.05 | 24.22±0.24 |
| 5 | F5 | 11.90±0.64 | 1.13±0.04 | 24.70±0.43 |
| 6 | F6 | 11.36±0.53 | 1.12±0.06 | 24.89±0.18 |

*Average of three determinations ± Standard deviation

**Table 8:** Physico-chemical properties of matrix tablets.

| Formulation | Thickness* (mm) | Diameter* (mm) | Hardness* (kg/cm$^2$) | Friability* (%) | Drug Content*(%) | Weight variation |
|---|---|---|---|---|---|---|
| F1 | 4.1±0.15 | 11.5±0.05 | 8.2±0.24 | 0.20±0.02 | 99.98±0.05 | pass |
| F2 | 4.0±0.18 | 11.6±0.08 | 7.4±0.34 | 0.38±0.08 | 98.62±0.06 | pass |
| F3 | 4.2±0.19 | 11.3±0.02 | 7.9±0.35 | 0.28±0.03 | 100.08±0.08 | pass |
| F4 | 3.9±0.17 | 11.4±0.06 | 8.2±0.48 | 0.42±0.05 | 100.02±0.07 | pass |
| F5 | 4.2±0.15 | 11.5±0.08 | 7.8±0.48 | 0.36±0.06 | 98.71±0.08 | pass |
| F6 | 4.1±0.17 | 11.2±0.04 | 8.1±0.24 | 0.41±0.02 | 99.16±0.04 | pass |

*Average of three determinations ± Standard deviation

**Table 9:** *In-vitro* dissolution studies of formulation F1- F6.

| Time (hr) | % CDR*-F1 | % CDR-F2 | % CDR-F3 | % CDR-F4 | % CDR-F5 | % CDR-F6 |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 18.45 | 15.32 | 09.90 | 07.65 | 05.85 | 03.15 |
| 2 | 40.97 | 30.52 | 20.26 | 16.20 | 10.80 | 06.75 |
| 3 | 58.54 | 55.54 | 31.75 | 26.11 | 16.66 | 10.35 |
| 4 | 77.46 | 71.57 | 41.43 | 33.32 | 22.60 | 14.41 |
| 5 | 90.08 | 77.48 | 52.47 | 42.78 | 28.37 | 18.46 |
| 6 | 99.10 | 86.98 | 64.40 | 49.09 | 33.78 | 23.42 |
| 7 | | 90.99 | 72.16 | 59.00 | 39.98 | 28.37 |
| 8 | | 97.30 | 81.99 | 66.21 | 44.59 | 31.76 |
| 9 | | | 91.07 | 75.67 | 48.64 | 36.48 |
| 10 | | | 94.69 | 84.68 | 54.95 | 40.99 |
| 11 | | | 97.33 | 93.24 | 61.71 | 44.59 |
| 12 | | | 98.24 | 98.65 | 66.66 | 48.64 |
| 13 | | | | | 72.97 | 52.48 |
| 14 | | | | | 78.83 | 55.40 |
| 15 | | | | | 84.23 | 59.46 |
| 16 | | | | | 91.44 | 64.41 |
| 17 | | | | | 94.15 | 69.37 |
| 18 | | | | | 96.85 | 75.67 |
| 19 | | | | | 98.65 | 79.28 |
| 20 | | | | | | 84.23 |
| 21 | | | | | | 89.64 |
| 22 | | | | | | 93.24 |
| 23 | | | | | | 96.85 |
| 24 | | | | | | 99.28 |

**CDR*-** Controlled Drug Release

**Table 10:** Release kinetics of Formulation 6.

| Formulation | Zero Order | First order | Higuchi | Korsmeyer-Peppas | Hixson-Crowell |
|---|---|---|---|---|---|
| | $R^2$ | $R^2$ | $R^2$ | $R^2$ | $R^2$ |
| F6 | 0.997 | 0.739 | 0.925 | 0.805 | 0.899 |

**Table 11:** Test parameters for optimized formulation F6 and stability study data.

| Sl. No | Test Parameters | At the end of 15 days 40° ± 2° C / 75 ± 5 % RH | At the end of 30 days 40° ± 2°C / 75 ± 5 % RH |
|---|---|---|---|
| 1 | Thickness | 04.1±0.17 | 04.1±0.17 |
| 2 | Diameter | 11.2±0.04 | 11.2±0.04 |
| 3 | Hardness | 06.1±0.24 | 06.1±0.24 |
| 4 | Weight variation | pass | pass |
| 5 | Friability | 00.41±0.02 | 00.41±0.02 |
| 6 | Drug content | 99.16±0.04 | 99.16±0.04 |

**Table 12:** *In-vitro* dissolution studies of formulation F6 (After 15 days in 40° ± 2°C / 75 ± 5 % RH).

| Time (hrs) | Absorbance | Amount of drug release (mg) | % drug release | Cumulative % drug release |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 4 | 0.12 | 1.53 | 15.32 | 15.32 |
| 8 | 0.26 | 3.33 | 33.34 | 33.35 |
| 12 | 0.40 | 5.04 | 50.42 | 50.45 |
| 16 | 0.52 | 6.66 | 66.67 | 66.72 |
| 20 | 0.68 | 8.69 | 86.91 | 86.98 |
| 24 | 0.76 | 9.85 | 98.55 | 98.64 |

**Table 13**: *In- vitro* dissolution studies of formulation F6 (After 30 days in 40° ± 2° C / 75 ± 5 % RH).

| Time (hrs) | Absorbance | Amount of drug release (mg) | % drug release | Cumulative % drug release |
|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 |
| 4 | 0.13 | 1.66 | 16.65 | 16.65 |
| 8 | 0.26 | 3.37 | 33.75 | 33.76 |
| 12 | 0.38 | 4.90 | 49.05 | 49.08 |
| 16 | 0.53 | 6.61 | 66.15 | 66.20 |
| 20 | 0.69 | 8.82 | 88.25 | 88.32 |
| 24 | 0.76 | 9.85 | 98.55 | 98.64 |

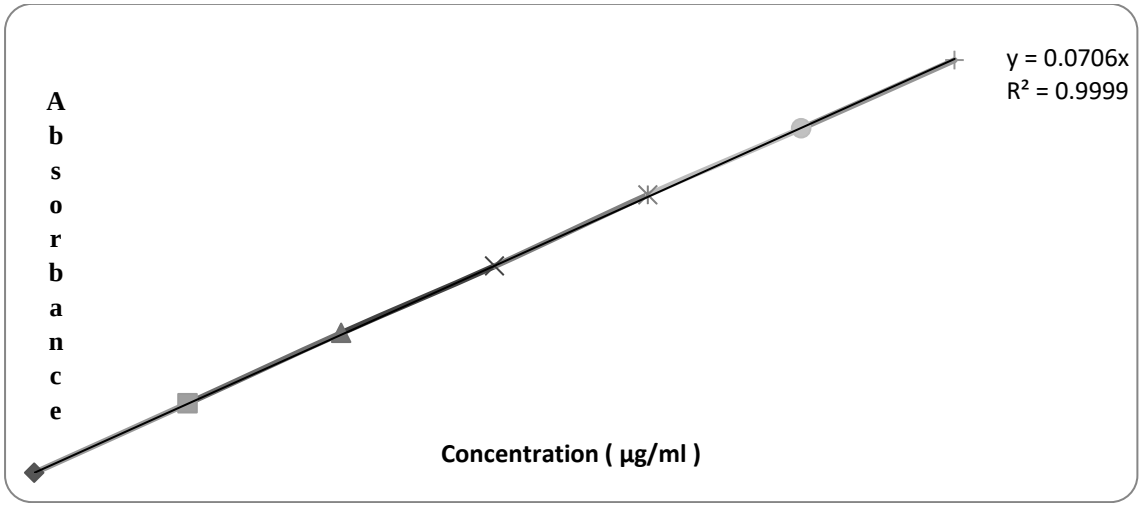


**Figure 1:** Calibration curve of glibenclamide in pH 7.4 phosphate buffer.

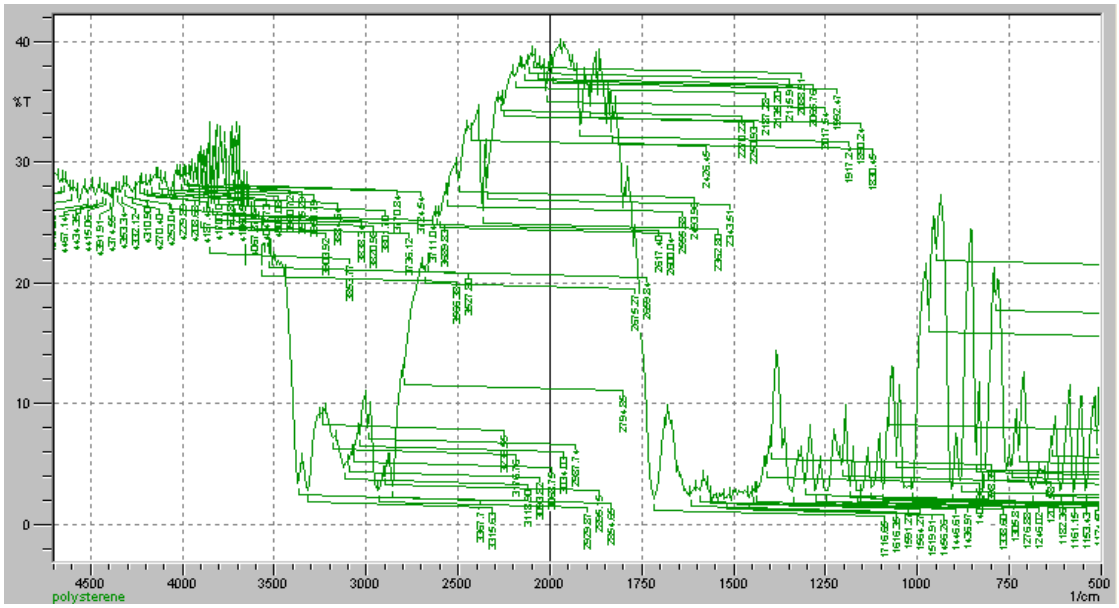


**Figure 2:** IR spectrum of Glibenclamide.

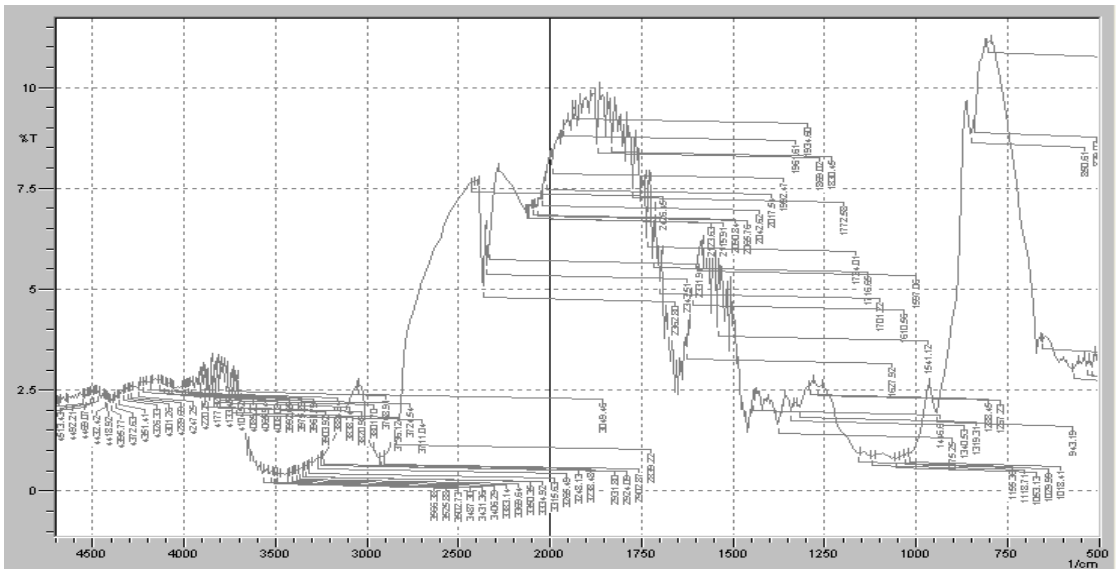


**Figure 3:** IR spectrum of HPMC K 15M.

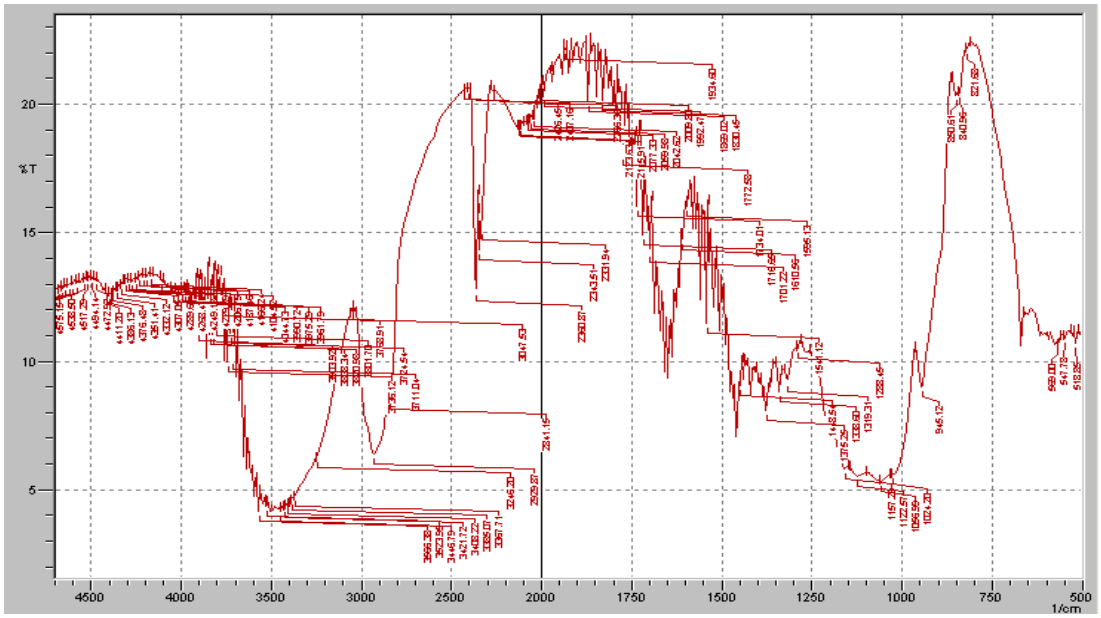


**Figure 4:** IR spectrum of HPMC K 100M.

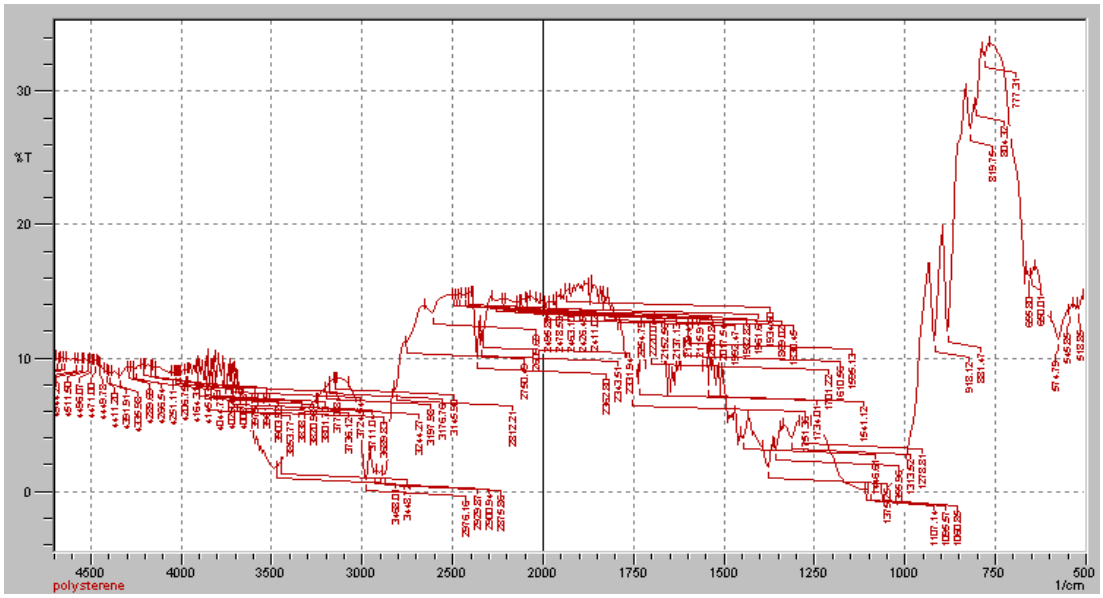


**Figure 5:** IR spectrum of Ethyl Cellulose.

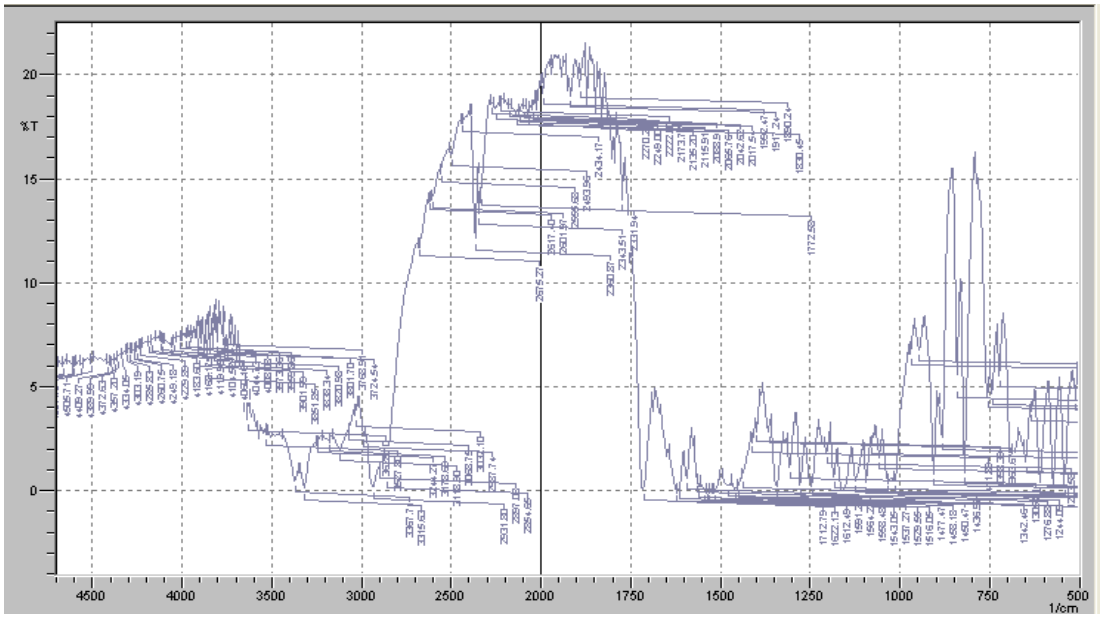


**Figure6:** IR spectrum of Glibenclamide - HPMC K 15M.

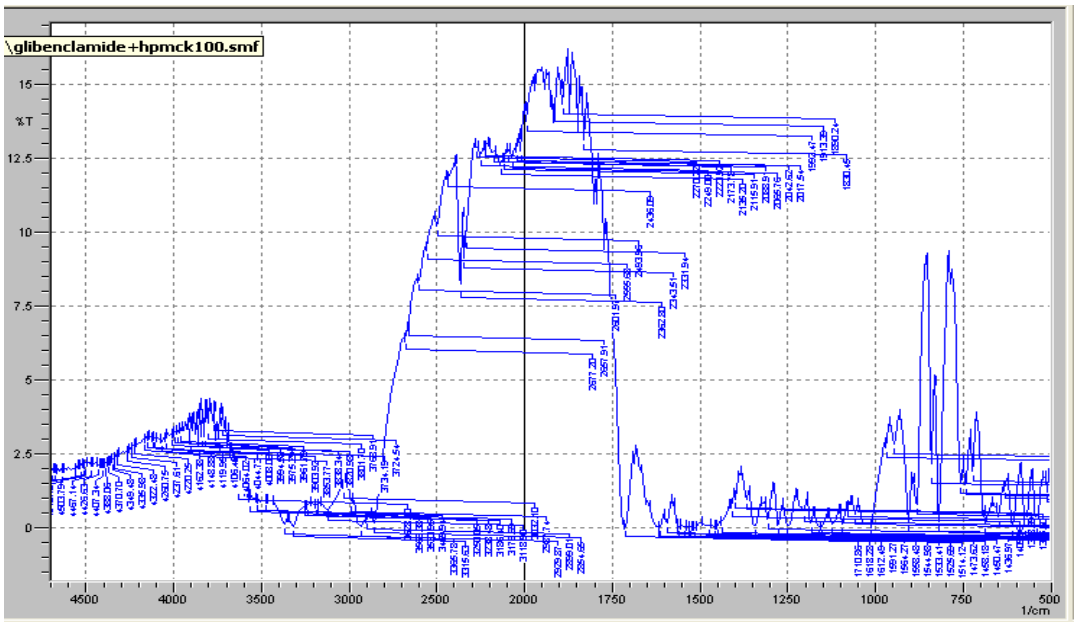


**Figure 7:** IR spectrum of Glibenclamide - HPMC K 100M.

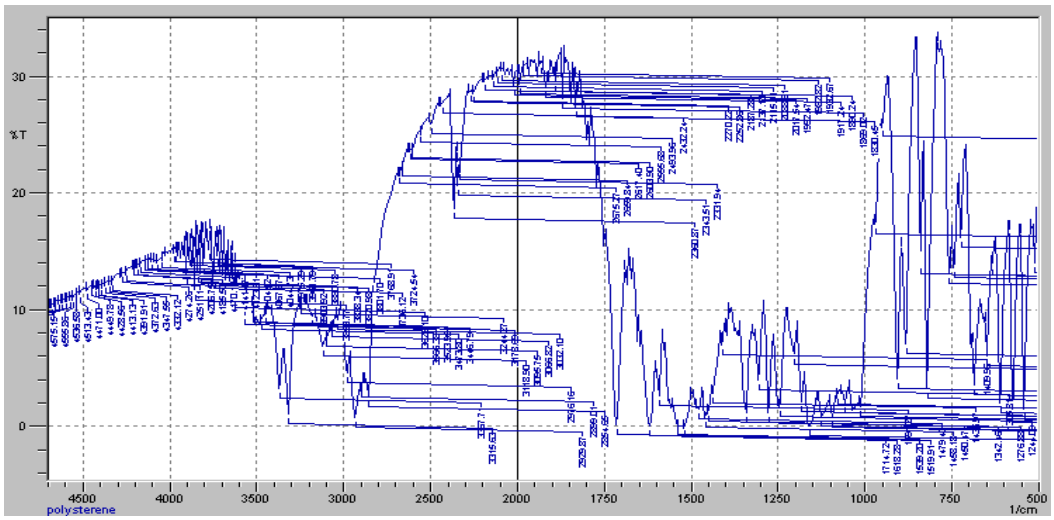

**Figure 8:** IR spectrum of Glibenclamide - Ethyl Cellulose.

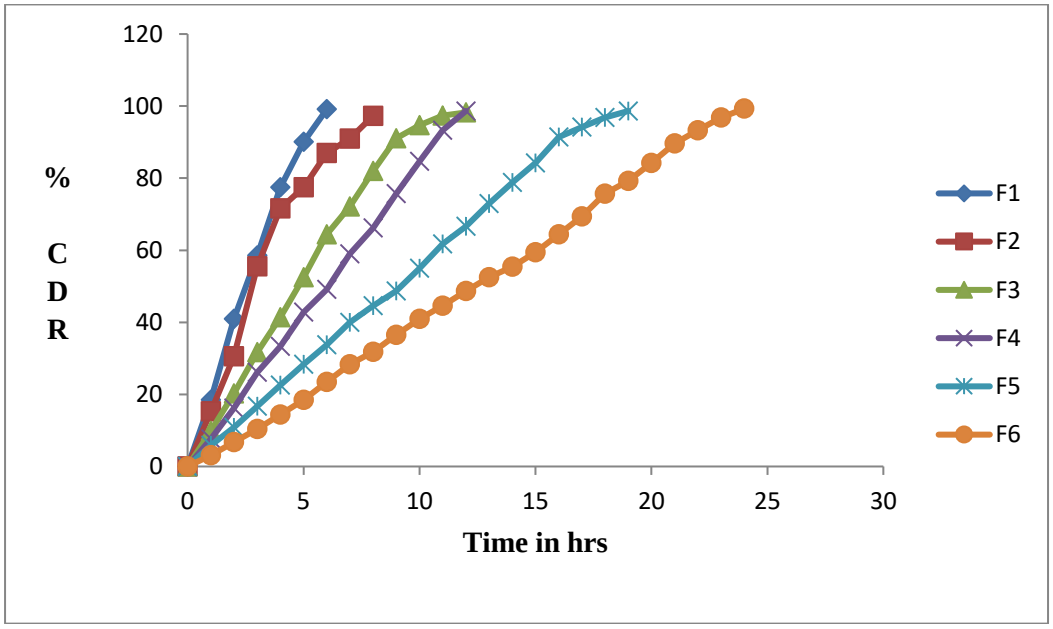


**Figure 9:** Comparison of In-vitro dissolution graph of formulation F1-F6.

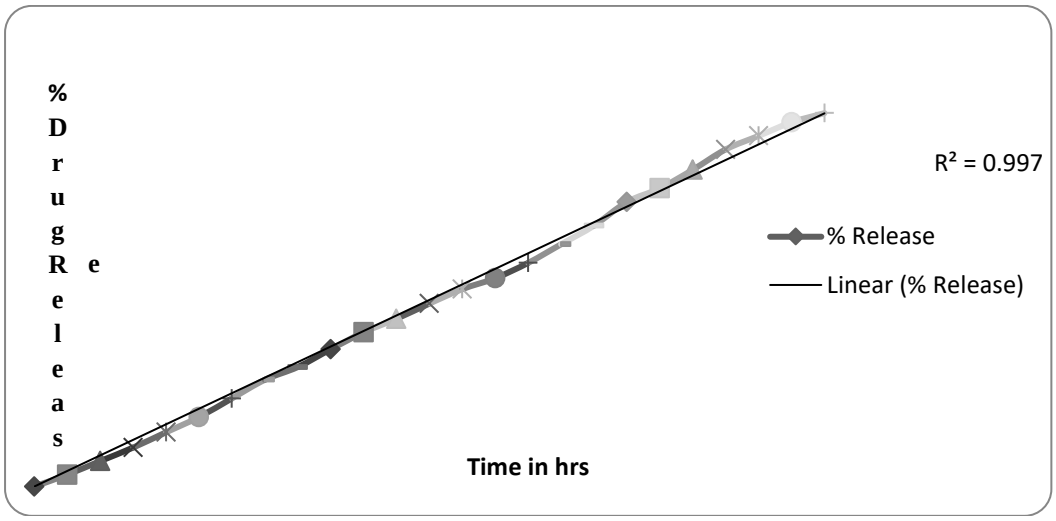


**Figure 10**: Zero-order plot of – Formulation 6.

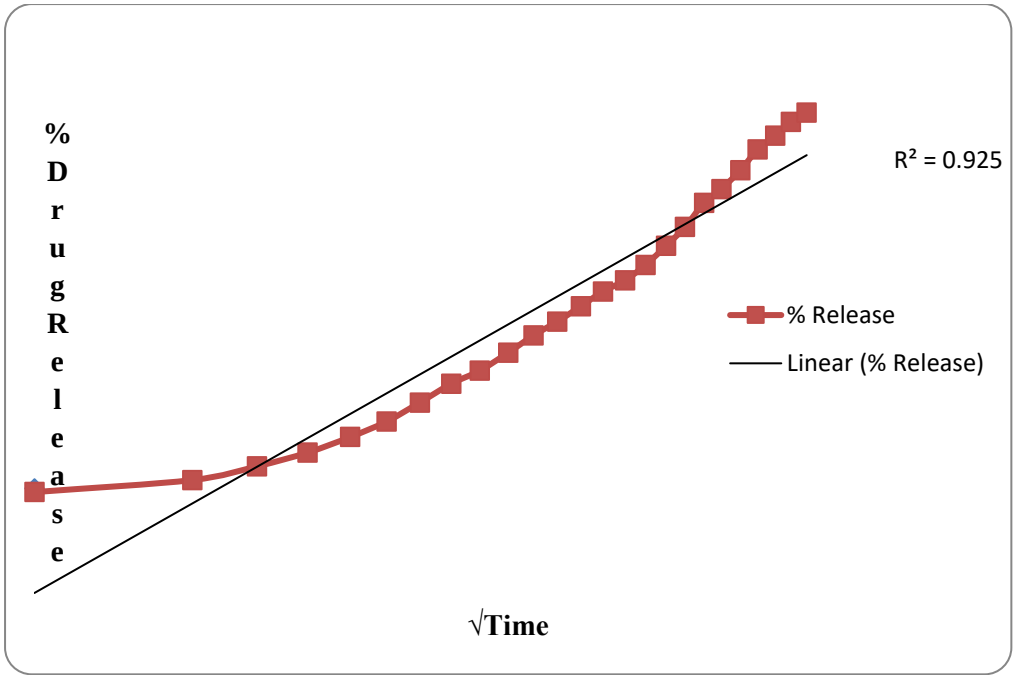


**Figure 11:** Higuchi plot – Formulation 6.

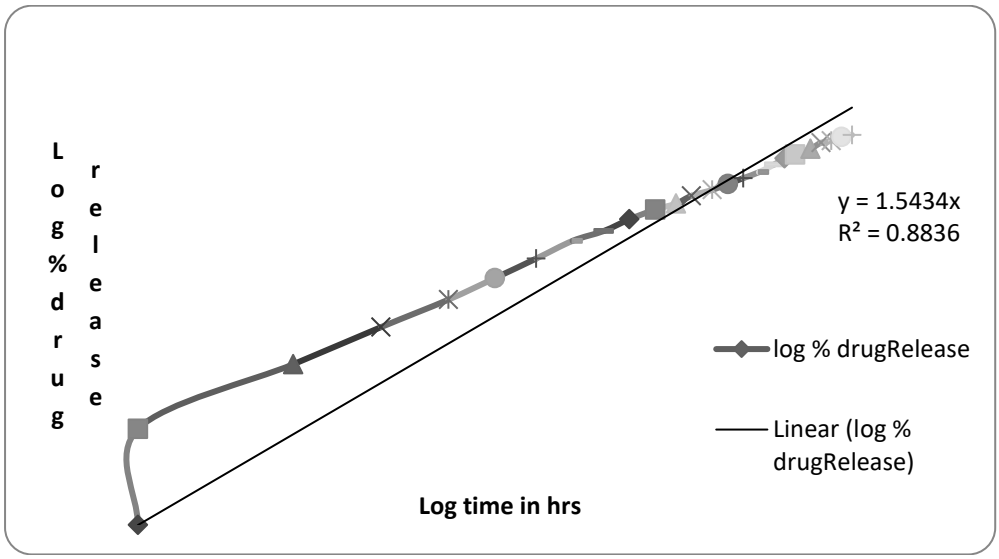


**Figure 12:** Korsmeyer-Peppas plot – Formulation 6.

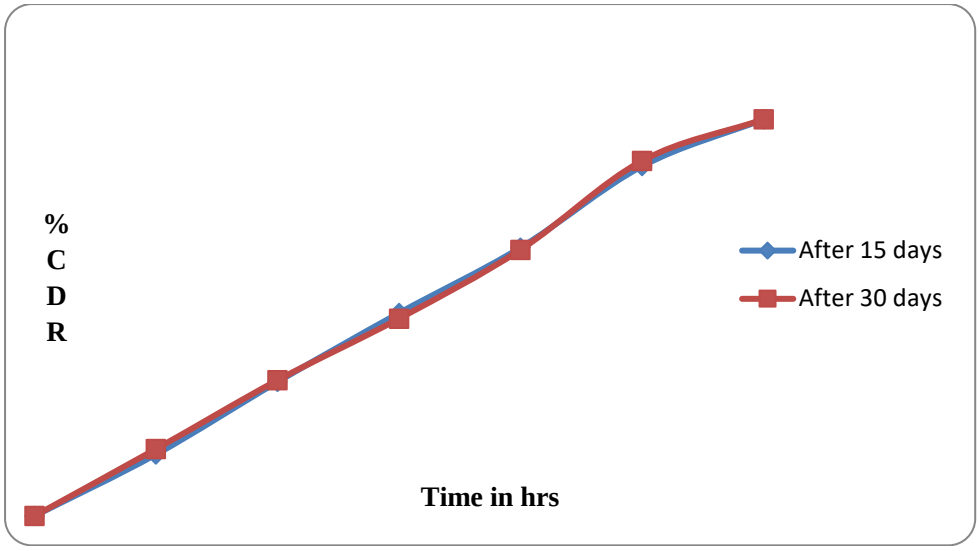


**Figure 13:** *In-vitro* dissolution graph of formulation F6 (After 15 & 30 days in 40° ± 2° C / 75 ± 5 % RH).

## CONCLUSION

The objective of the present study was to formulate and evaluate the controlled release matrix tablets of glibenclamide. The results generated in this study lead to the following conclusions: - *In- vitro* drug release study indicated that, from the selected three polymers for this study, ie; HPMC K 15, HPMC K 100, and EC- the formulation F6 which contained EC in 50mg showed a maximum release of 99.28% in 24 hrs and revealed that EC was more effective in sustaining the drug release. The formulation F6 showed better results when compared to all other formulations and was therefore selected as the optimized formulation. The pre-compression and post-compression parameters of all formulations were found to be within acceptable limits. FTIR studies showed that there was no significant interaction between drugs and excipients. The drug release kinetics and mechanism of drug release were studied for the optimized formulation, among the different model's data of *in-vitro* release of best fit into Zero-order kinetic model because $R^2$ values in this model was more close to unity. The release kinetics of the formulation best fit to Higuchi model, because $R^2$ values in this model were more close to unity. It indicated that drug release from the prepared matrix tablets occurs via a diffusion process. To explore more about the kinetic behavior, *in-vitro* release results were further fitted into the Peppasequation and the result indicates that the drug release is controlled by more than one process. Stability studies of optimized formulation had not shown any variation in the tested parameters and the results were within the limits.

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