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# Formulation Development and Evaluation of Sustained Release Antidiabetic Tablet

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**Nitin N. Padole[1], Nilesh M. Mahajan[1], Fahim S. Kazi[1], Ujwala N. Mahajan[1], Ajay G.Pise[1]***

*[1]Department of Pharmaceutics, Dadasaheb Balpande College of Pharmacy, Besa, Nagpur-440037, India*

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**ABSTRACT**

Diabetes mellitus is chronic metabolic disorder caused by insufficient production of insulin. In type 1 diabetes mellitus there is failure in production of insulin as a result of destruction of the β cell of pancreas and in type 2 diabetes mellitus can be characterized by defect in both insulin action and insulin secretion and it is associated with elevated basal glucose production. Glipizide sustained release tablet were prepared using different hydrophilic polymer in different ratio that retard the release of drug from tablet and for improvement of patient compliance. The sustained release tablets were prepared by direct compression method. The formulated tablet was subjected to test like thickness, friability, weight variation, hardness, drug content , *in-vitro* release study, similarity factor and stability study. Drug and polymer compatibility study was performed by FTIR. From all formulated batches optimized batch is selected *in-vitro* dissolution of formulated batch showed that F1 batch released the drug in control manner for 12 h. FTIR study showed that there was no interaction between drug and excipients. Similarity factor was calculated for selection of optimized batch. Cumulative release of optimized batch compared with marketed product Glynase Xl. Stability study was performed on both control sample and optimized batch at temperature $30^{o}C \pm 2^{o}C$ up to month.

## INTRODUCTION

Glipizide is an oral hypoglycemic agent, which is a commonly prescribed for the treatment of patients which are affected with type II diabetes mellitus. Glipizide is a weak acid (pKa = 5.9) which is practically insoluble in water but as per the Biopharmaceutical Classification System (BCS), it is low solubility highly permeability. Glipizide has a short biological half-life (3.4 ± 0.7 hr) it is administered to be in 2 to 3 doses of 2.5 to 10 mg per day. Hence we have selected Glipizide for the development of once a day sustained release matrix tablets. [1]

Sustained release system is types of modified drug delivery system that can be used as a replacement to conventional dosage system. Sustained release system has various benefits like patient compliance, avoid multiple dosing, cost effectiveness, flexibility, increase the plasma drug concentration, avoid side effects and overcome the problems associated with conventional drug delivery system. Hydrophilic polymers are used in formulating oral sustained release matrix tablets. As the dissolution medium penetrates the tablets of matrix dosage form, the polymer material which is used in the tablet swells and it forms hydrogel by the time thus it is able to controlled drug release. However, the sustained release tablet formulated by direct compression method is a very simple approach in the pharmaceutical field for compliance, faster production, in comparison with other conventional dosage form and controlled release systems. Cellulose ethers of different viscosity such as hydroxypropyl methylcellulose (HPMC) are widely used hydrophilic polymers as release retardants for sustained activity.[2, 3]

## MATERIALS AND METHODS

### Material

Glipizide was procured as gift sample from Zydus Cadila Ponda Goa. HPMC K100M, HPMC K4M, Lactose were obtained as gift sample from Zim Laboratories Nagpur. All other ingredients are of analytical and Pharma grade.

### Method

### Tablet Preparation: [4, 5]

Sustained release tablet of Glipizide was prepared by direct compression technique. Glipizide and polymer of different viscosity was weighed accurately and geometrically shifted through

mesh 40. Then weighted accurately disintegrating agent lubricant and glidant geometrically serial dilution again done and passed through mesh 60 and added in first mixture blend for 3 minutes. Blend was compressed into tablet using 10 station rotary compression machine with punch size 8mm.

**Drug and Polymer Compatibility Study by FTIR: [5, 6]**

Fourier-transform infrared (FT-IR) spectrum of Glipizide was obtained on a model-2008 Shimadzu. The sample was prepared with KBr of IR grade in the ratio of 1:100 and compressed using motorized pellet press (Kimaya Engineers, India) at 10-12 tonnes pressure and the spectrum was scanned over the wave number range of 4000 to 400 $cm^{-1}$.

**Evaluation of Powder Mixture: [4, 5, 6]**

**Bulk Density**

To determine bulk and tapped density of powder mixture a quantity of powder mixture of each batch was previously lightly shaken for breaking any agglomerates formed and presented into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from a height of 2.5 cm at 2 second intervals. The tapping of cylinder was continued until no further change in volume was noted. Bulk density and tapped density of powder were calculated using the following formulae.

$$\text{Bulk Density} = \frac{\text{Weight of powder}}{\text{Bulk Volume of powder}}$$

$$\text{Tapped Density} = \frac{\text{Weight of powder}}{\text{Tapped volume of powder}}$$

**Compressibility Index**

The compressibility of the granules used for preparation of tablet was determined by Carr's Compressibility Index.

$$Carr's\ compressibility\ index = \frac{[(Tapped\ density - Bulk\ density) * 100]}{Tapped\ density}$$

**Hausner's Ratio**

A similar index like compressibility index has been defined by Hausner's. Hausner's ratio was calculated by formula:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Poured density}} X10$$

Values less than 1.25 indicate good flow (=20% Carr), whereas greater than 1.25 indicates poor flow (=33% Carr). Added glidant normally improve flow property of powder blend.

**Evaluation of Tablet:** [21, 22]

**Thickness**

Ten randomly selected Glipizide matrix tablets from each formulation were used for determination of thickness. Thickness of each tablet was measured by using verniar caliper and the results were expressed in unit mm.

**Friability**

Previously weighed 10 tablets from each formulated batch were taken in Roche friabilator. After100 revolutions or 25 revolutions per minute of friabilator tablets were recovered. The tablets were then made free firstly from dust and the total remaining weight was measured. Friability was calculated using following formula.

$$\text{Percentage friability} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{Initial weight}} \times 100$$

**Uniformity of Weight**

Randomly selected 20 tablets were weighed and average weight was calculated. Results observed for not more than two of the individual tablet weights deviate from the average weight by more than the percentage.

**Uniformity of Content**

One formulated tablet was transferred to a 100ml volumetric flask containing 50 ml of phosphate buffer pH7.4. The solution was sonicated for about 15 min, cooled and diluted with phosphate buffer pH 7.4 to volume, mixed and filtered. The accurately measured portion

of the filtrate was diluted quantitatively with phosphate buffer pH 7.4 to obtain a final test preparation. Absorbance of solution was determined at 274 nm and content of Glipizide was calculated and expressed in percentage.

***In-vitro* Release Studies:** [1, 21]

The release rate of glipizide sustained release tablets was determined using USP Dissolution Testing Apparatus Type II (Paddle type). The dissolution test was performed using 900 ml 0.1 N HCL for first two hours followed by phosphate buffer pH 7.4 up to 12 hours, at 37 ± 0.5°C with 50 rpm. Aliquots were withdrawn from a zone midway between the surface of dissolution medium and the top of rotating paddle not less than 1 cm apart from the vessel wall after every hour for 12 hrs and were replaced with new fresh dissolution medium. Absorbance of withdrawn samples was measured at 274 nm. Percentage drug release was calculated using an equation obtained from a standard curve.

**Similarity Factor Study:** [7, 8]

Similarity factors ($f_2$) were calculated using following equation, for all formulations.

$$\text{Similarity factor}(f2) = 50\log\{[1 + 1/n\sum_{t=1}^{n}(Rt - Tt)^2]^{-0.5} \times 100\}$$

The dissolution profiles of tablet were considered to be similar when $f_2$ is between 50 and 100 given by Scale-Up and Post Approval Changes (SUPAC) guidelines for modified and sustained release dosage form.

**Stability Study:** [9, 24]

Stability studies were carried out according to ICH guidelines. The formulated optimized batch (F1) was selected for stability study on the basis of *in-vitro* drug dissolution studies. 20 tablets were wrapped in aluminum foil and stored at 30±2$^{o}$C temperature with relative humidity of 65±5%. The sampling was done after one month and evaluated for appearance, thickness, hardness, friability, drug content and percent drug release.

## RESULTS AND DISCUSSION

Sustained release tablets were prepared by direct compression technique as per formulae are given in Table1. Formulations F1 to F3 contained HPMC K100M, in formulation F4 to F6 contained HPMC K4M, and formulation F7 to F9 contained mixture of HPMC K100M and HPMC K4M in 1:1 ratio. The formulation F1 exhibited excellent release retarding which contain HPMC K100M in 1:1 ratio.

**Table1: Composition of Glipizide Sustained Release Tablet**

| Ingredient | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Glipizide | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| HPMC K100M | 10 | 20 | 30 | - | - | - | - | - | - |
| HPMC K4M10 | - | - | - | 10 | 20 | 30 | - | - | - |
| HPMC K100M+ | - | - | - | - | - | - | 10 | 20 | 30 |
| Lactose | 174 | 164 | 154 | 174 | 164 | 154 | 174 | 164 | 154 |
| Magnesium Stearate | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Talc | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| Total weight (mg) | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 | 200 |



**Compatibility Study by Infra-Red Spectrum Method:**

FTIR studies were carried out to identify the drug and polymer compatibility. Result showed that there was no interaction between drug and polymer. FTIR study of glipizide and polymer showed that one typical bands at 606.64 and 1527.69 $cm^{-1}$ due to C-S stretching vibration and a band at 1033.89 $cm^{-1}$ due to S=O stretching and characteristics bands at 3353.39 $cm^{-1}$ assigned to N-H stretching. No significant change in the appearance of characteristic peaks of pure drug spectra was observed as shown in Table 2 and Figure 1 to 7. Results indicated that drug is compatible with the polymers used in the investigation.

**Table 2: Drug- Excipients Compatibility Study**

| Material | Peak cm-1 | Functional group | Physical mixture |
|---|---|---|---|
| Glipizide | 606.64 | C-S Stretching vibration | 606.68 |
| | 1033.89 | S=O Stretching vibration | 1034.65 |
| | 1442.82 | C-H Stretching vibration | 1444.75 |
| | 1527.69 | C=S Stretching vibration | 1527.69 |
| | 3353.39 | N-H stretching vibration | 3353.39 |

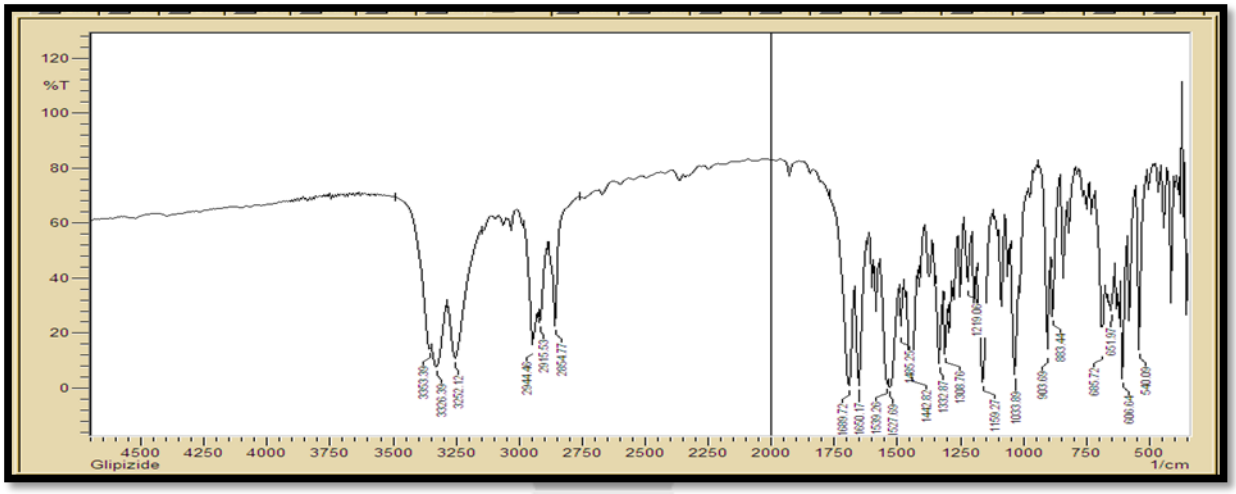


**Figure 1: Infrared spectrum of Glipizide**

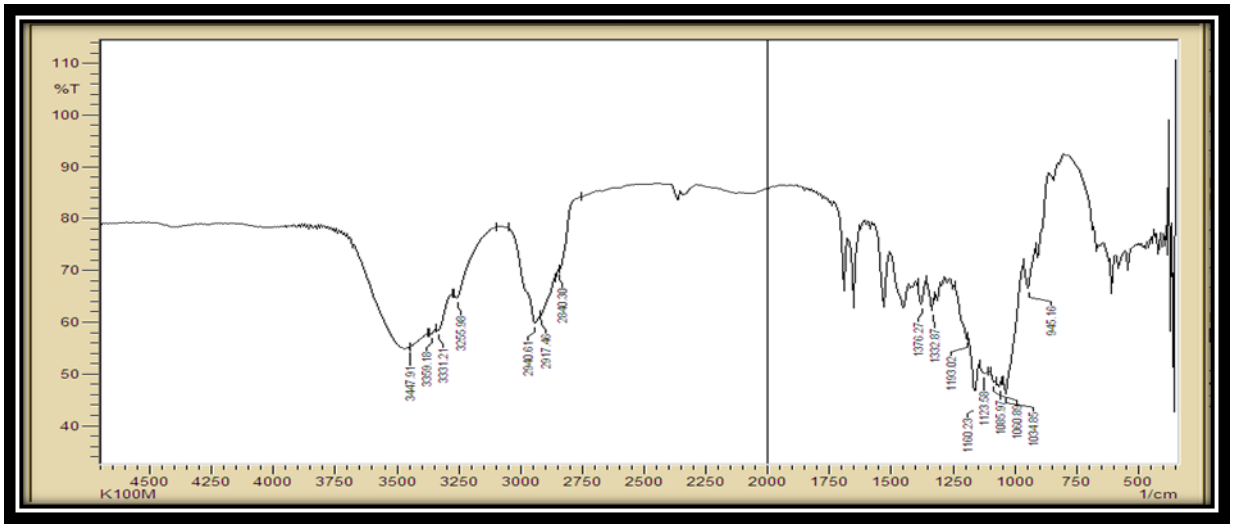


**Figure 2: Infrared spectrum of HPMC K100M**

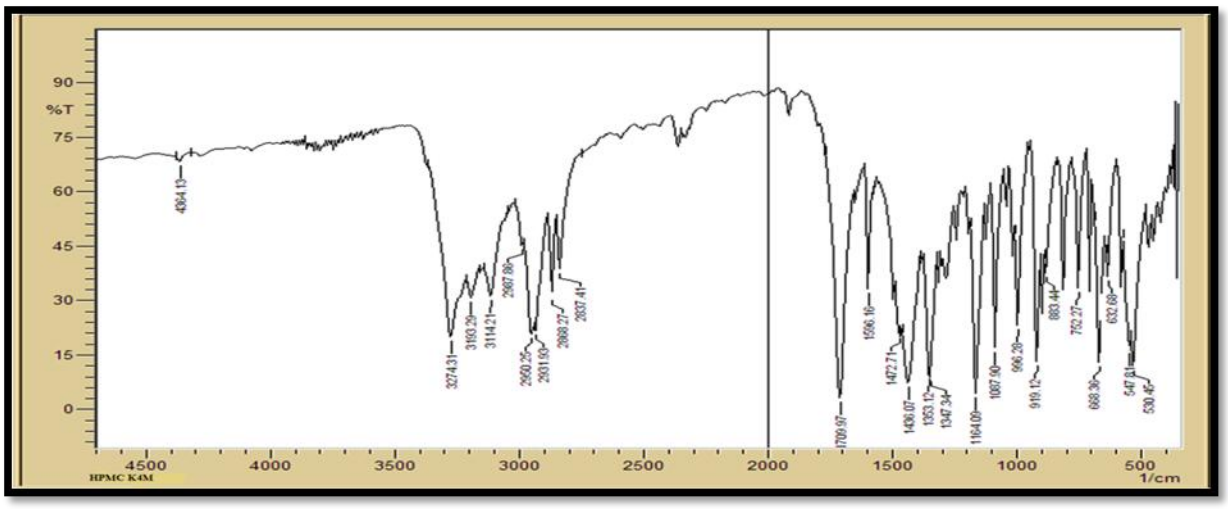


**Figure 3: Infrared spectrum of HPMC K4M**

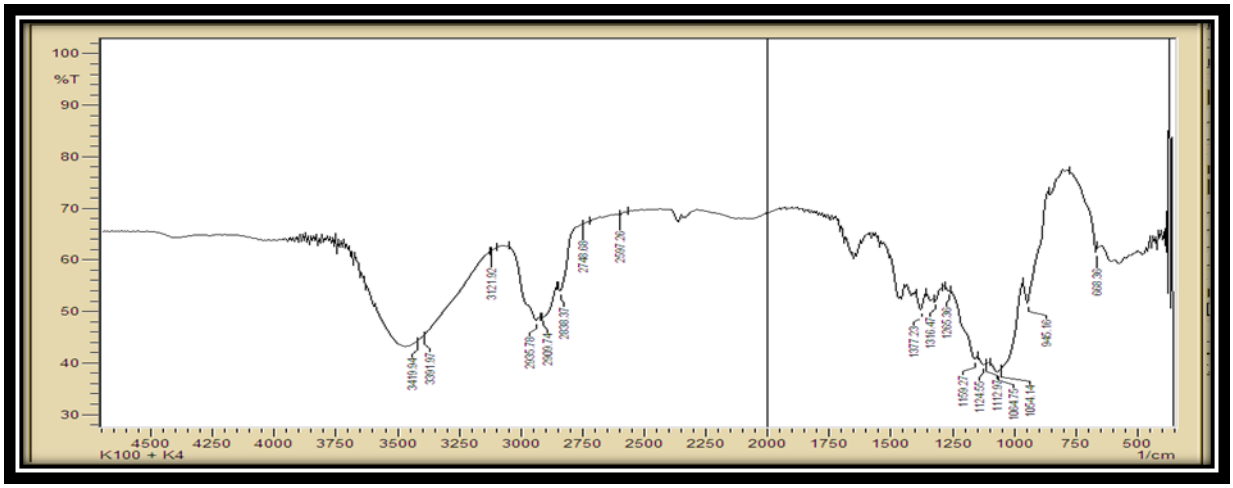


**Figure 4: Infrared spectrum of HPMC K100M+HPMC K4M**

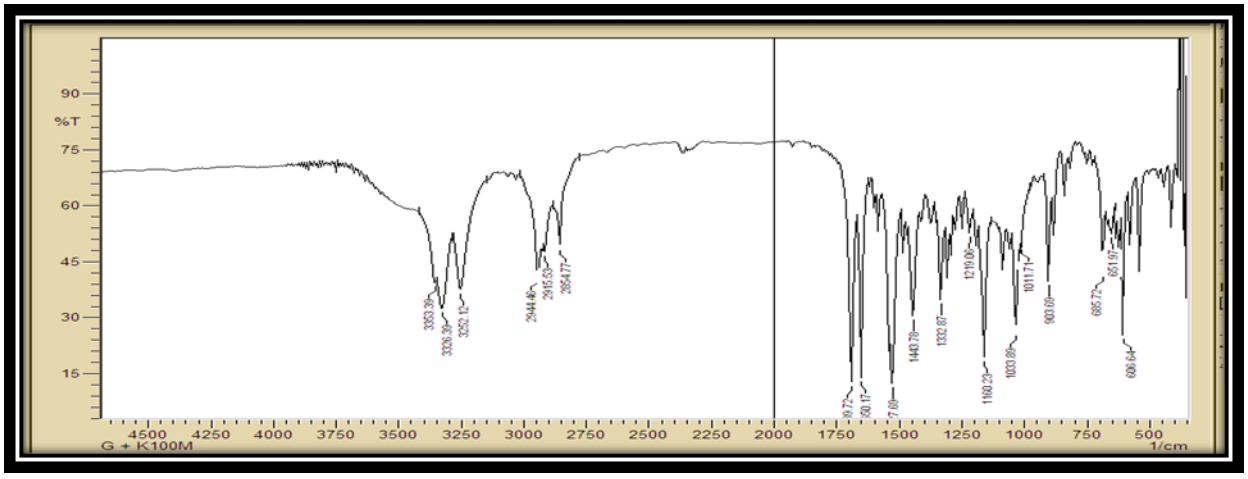


**Figure 5: Infrared spectrum of Glipizide+ HPMC K100M**

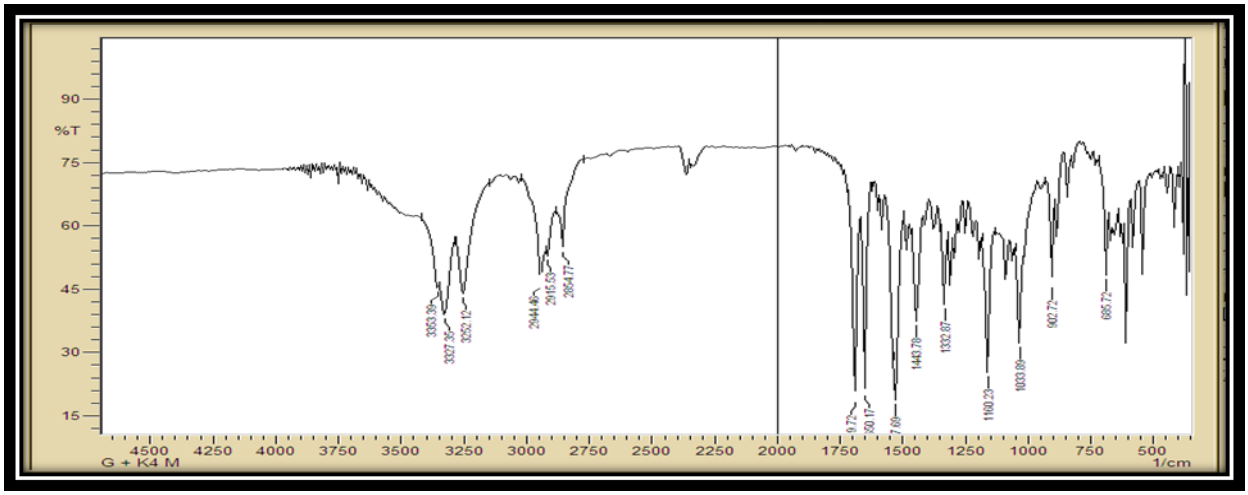


**Figure 6: Infrared spectrum of Glipizide + HPMC K4M**

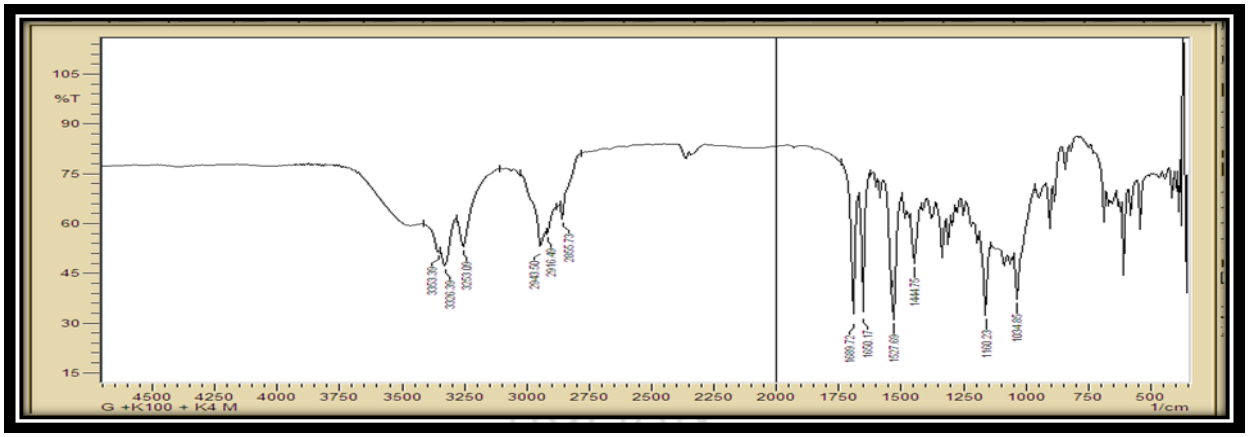


**Figure 7: Infrared spectrum of Glipizide+ HPMC K100M + HPMC K4M**

All formulations showed acceptable results in precompression and post compression parameters study. In pre-compression parameter like tapped density (g/ml), bulk density (g/ml), Carr's index (%), Hausner's ratio and in post compression parameters such as weight variation, drug content uniformity and friability were within a prescribed limit.

All formulations showed less than 1% (w/w) friability, which was within the prescribed limits. According to the Pharmacopoeia recommendation for tablets weighing more than 120 mg, ±10 % deviation from the mean weight is acceptable for the tablet. From the results show, the average weight deviation percentage of 20 tablets taken from each formulation was less than ±0.5%, and all the formulations met the requirement. The manufactured tablets showed low weight variations and a high degree of drug content uniformity as drug content was more than 95% among different batches of the tablets. Results are shown in Table 3 and Table 4.

**Table 3: Pre-compression Parameters of Designed Formulation**

| Formulations code | Bulk density (g/ml) | Tapped density (g/ml) | Carr's index (%) | Hausner's ratio |
|---|---|---|---|---|
| F1 | 0.4291±0.02 | 0.4715±0.02 | 08.91±1.62 | 1.09±0.01 |
| F2 | 0.4264±0.02 | 0.4734±0.04 | 09.93±0.98 | 1.11±0.01 |
| F3 | 0.4054±0.02 | 0.4555±0.01 | 10.98±1.56 | 1.12±0.01 |
| F4 | 0.4505±0.02 | 0.4995±0.02 | 09.81±0.95 | 1.10±0.01 |
| F5 | 0.4242±0.02 | 0.4786±0.04 | 11.29±1.72 | 1.12±0.01 |
| F6 | 0.4074±0.02 | 0.4521±0.02 | 09.95±1.82 | 1.11±0.01 |
| F7 | 0.4439±0.04 | 0.5058±0.01 | 12.27±1.32 | 1.13±0.01 |
| F8 | 0.4226±0.03 | 0.4736±0.04 | 10.78±1.16 | 1.12±0.01 |
| F9 | 0.4019±0.02 | 0.4596±0.03 | 12.63±1.13 | 1.14±0.01 |

**Table 4: Post Compression Parameter for Designed Formulation**

| Formulation Code | Weight variation | Thickness (mm) | Friability (%) | Diameter (mm) | Hardness ($Kg/cm^2$) | *In-vitro* Release | Content (%) |
|---|---|---|---|---|---|---|---|
| F1 | 202 | 3.3 | 0.697 | 8.04 | 7.23 | 92.64 | 99.73 |
| F2 | 200 | 3.1 | 0.697 | 8.01 | 7.47 | 73.50 | 99.87 |
| F3 | 201 | 3.3 | 0.782 | 8.01 | 7.36 | 70.78 | 98.95 |
| F4 | 204 | 3.4 | 0.583 | 8.01 | 6.84 | 91.36 | 97.52 |
| F5 | 200 | 3.2 | 0.595 | 8.01 | 7.57 | 90.90 | 97.24 |
| F6 | 201 | 3.1 | 0.757 | 8.02 | 7.67 | 81.41 | 97.08 |
| F7 | 202 | 3.2 | 0.813 | 8.03 | 7.28 | 89.20 | 99.96 |
| F8 | 206 | 3.3 | 0.622 | 8.04 | 7.15 | 84.89 | 99.47 |
| F9 | 202 | 3.1 | 0.630 | 8.02 | 7.21 | 75.38 | 98.44 |

The results of dissolution studies of formulations F-1, F-2, and F-3, composed of HPMC K100M shown in Figure 8 and Table 4. Formulation F-1, F-2, and F-3 showed 92.73, 73.50 and 70.78% of Glipizide release at the end of 12 h respectively. The results of dissolution studies of formulations F-4, F-5, and F-6, composed of HPMC K4M showed 91.36, 90.90 and 81.41 % of Glipizide released at the end of 12 h respectively and results are shown in

Figure 9. Formulations F-7, F-8, and F-9, composed of HPMC K100M and HPMC K4M in 1:1 Ratio showed 89.20, 84.89 and 75.38 % of Glipizide released at the end of 12 h respectively. Results are shown in Figure 10. % drug release of all formulations were compared with marketed product Glynase XL.

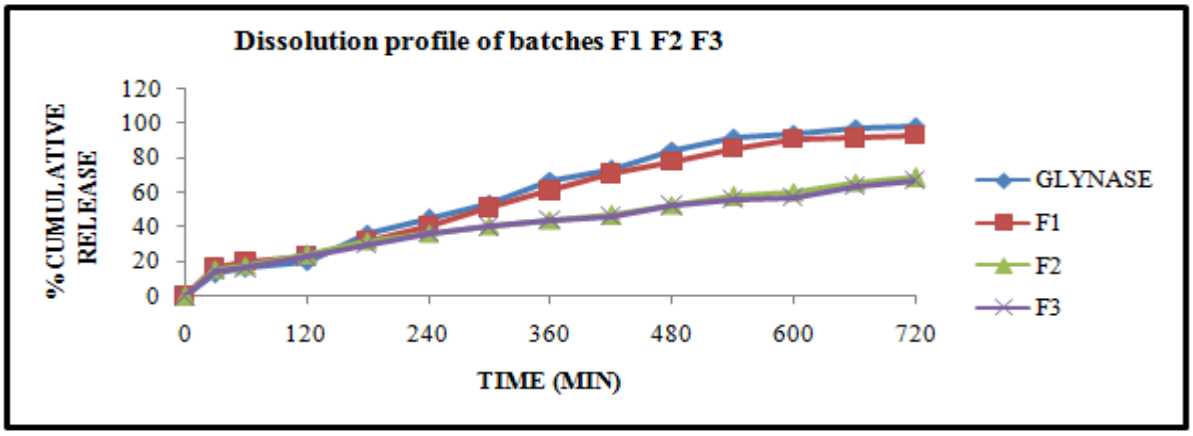


**Figure 8: Comparative release profile of formulation F1 to F3**

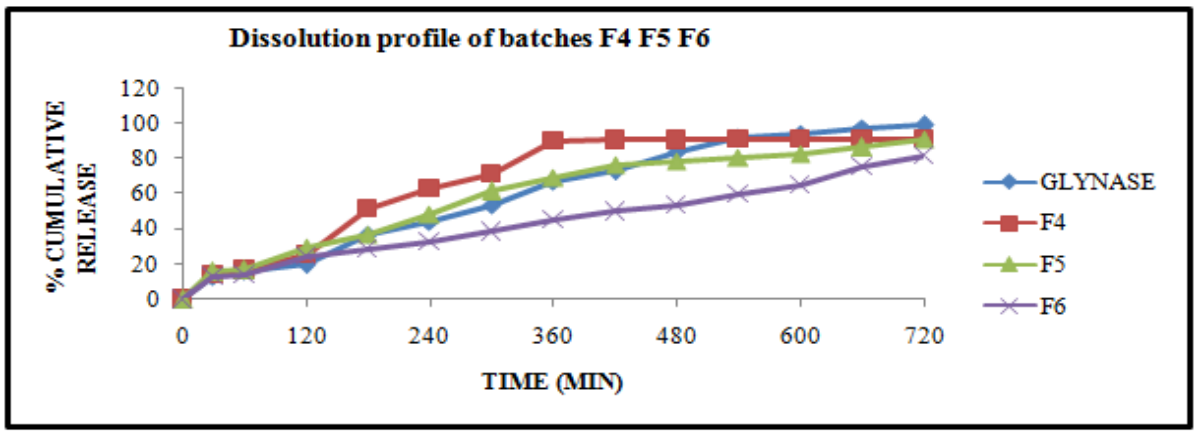


**Figure 9: Comparative release profile of formulation F4 to F6**

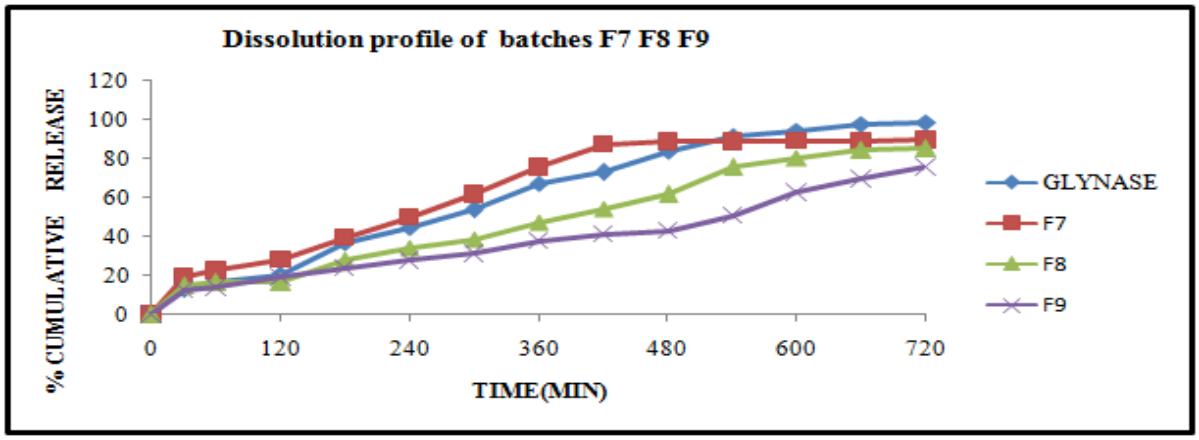


**Figure 10: Comparative release profile of formulation F7 to F9**

To describe the kinetics of drug release from sustained release tablets, release data was analyzed according to different kinetic equations. The data were analyzed by the method of regression coefficient and regression coefficient values ($r^2$) of all batches were shown in Table 5. On analyzing regression coefficient values of all batches, it was found that Batch F-1, 2, 3, 4, 5 and 7 tablet exhibited almost Higuchi model. Batch F-6, 8, and 9 tablets followed first order kinetics. Results are shown in Table 5.

**Table 5: Kinetic Treatment of Dissolution Profiles of Formulations F1 – F9**

| Batch | Zero order | First order | Higuchi | Korseme-yer Peppas | Best fitted |
|---|---|---|---|---|---|
| F1 | 0.957 | 0.564 | 0.993 | 0.019 | Higuchi |
| F2 | 0.971 | 0.614 | 0.960 | 0.094 | Higuchi |
| F3 | 0.956 | 0.556 | 0.992 | 0.018 | Higuchi |
| F4 | 0.828 | 0.558 | 0.926 | 0.140 | Higuchi |
| F5 | 0.930 | 0.586 | 0.969 | 0.103 | Higuchi |
| F6 | 0.985 | 0.627 | 0.957 | 0.040 | 1st order |
| F7 | 0.890 | 0.595 | 0.951 | 0.115 | Higuchi |
| F8 | 0.983 | 0.662 | 0.933 | 0.055 | 1 st order |
| F9 | 0.974 | 0.654 | 0.914 | 0.017 | 1st Order |

Similarity factor (*f2*) was calculated for all nine batches represented in Table 6. It was suggested that among 9 batches F1 batch having similarity factor more than 50 values. For the formulations, F1 similarity factor was 65, whereas other formulations showed less than 50value concluding that they do not have similar release as that of theoretical profile as given in Table 6.

**Table 6: Similarity Factors of Prepared Batches**

| Formulation code | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Similarity Factor | 65 | 46 | 46 | 32 | 57 | 43 | 31 | 35 | 30 |
| Difference Factor | 8 | 16 | 12 | 31 | 10 | 20 | 32 | 28 | 36 |

Stability study was conducted on optimized batch and controlled batch as per ICH guidelines. The parameters evaluated were physical appearance, diameter, thickness, hardness, friability,

drug content and % cumulative release. Cumulative release of controlled sample and stability sample was shown in Figure 11. The optimized formulation was found to be stable after evaluation of these parameters and the results are given in Table 7 and Table 8.

**Table 7: Evaluation of Stability and Controlled Sample**

| Parameter | Controlled sample | Stability sample |
|---|---|---|
| Physical appearance. | White color, Circular, Biconvex. | White color, Circular, Biconvex. |
| Diameter (mm) | 8.04 | 8.04 |
| Thickness (mm) | 3.3 | 3.3 |
| Hardness (kg/cm3) | 7.23 | 7.23 |
| Friability (%) | 0.697 | 0.697 |
| Drug content (%) | 99.73 | 99.58 |

**Table 8: *In-vitro* Drug Release of Marketed Tablet Glynase Xl, F1 Controlled Sample, & One Month Stability Sample**

| Time (Min) | Marketed Tablet Glynase XL | Controlled sample F1 batch | Stability sample F1 batch |
|---|---|---|---|
| 30 | 12.85 | 16.28 | 18.59 |
| 60 | 16.35 | 20.23 | 21.15 |
| 120 | 19.80 | 23.25 | 24.18 |
| 180 | 36.53 | 31.84 | 34.13 |
| 240 | 44.34 | 40.46 | 42.56 |
| 300 | 53.81 | 51.22 | 51.78 |
| 360 | 67.15 | 60.71 | 62.19 |
| 420 | 72.80 | 70.62 | 72.64 |
| 480 | 83.97 | 77.53 | 77.68 |
| 540 | 91.75 | 85.71 | 87.91 |
| 600 | 94.36 | 90.47 | 91.04 |
| 660 | 97.37 | 91.35 | 91.98 |
| 720 | 98.68 | 92.64 | 93.91 |

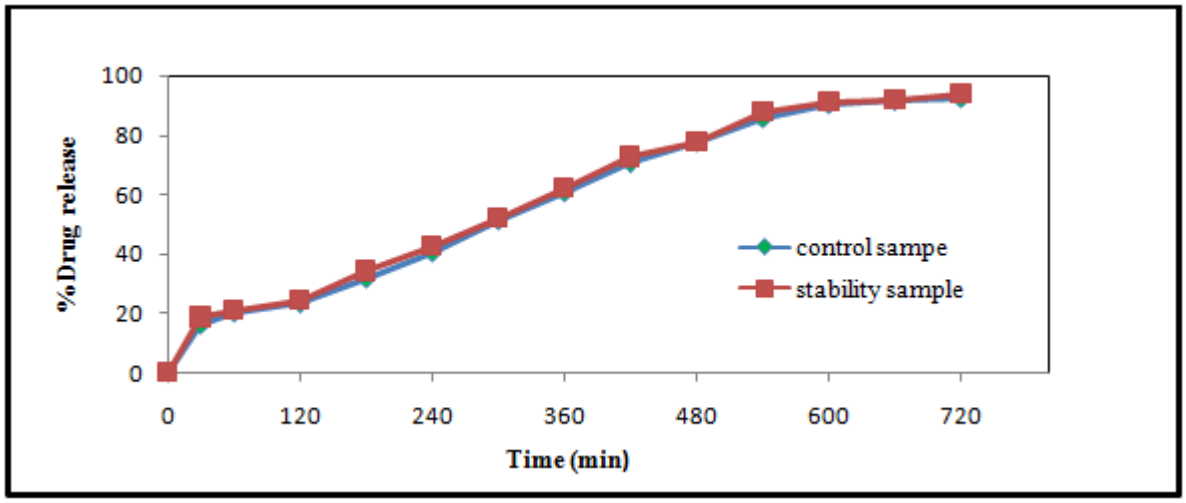


**Figure 11: Comparative release of controlled sample & one month stability samples of F1**

## CONCLUSION

In this research work, Preformulation studies of the drug were carried out which includes powder properties and compatibility studies using FTIR. Sustained release tablets were prepared using mixture of hydrophilic polymers such as of HPMC K4M and HPMC K100M in various ratios. The increasing proportion of polymer in tablet retards the release of drug from tablet. Formulated tablets were evaluated for hardness, friability, thickness, drug content and *in-vitro* study. F1 batch was selected as optimize batch from the similarity factor, cumulative drug release and drug content study. Then stability study and cumulative release study carried out on optimized batch and compared with marketed product Glynase Xl. Results of present study demonstrated that methodology successfully employed for formulating sustained release matrix tablets of Glipizide. The *in-vitro* dissolution result of batch F1 was fitted best to the kinetic properties as well as showed better similarity to innovator brand Glynase XL (10 mg).

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