Available online at http://jddtonline.info

RESEARCH ARTICLE

# FORMULATION AND IN-VITRO EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF GLIPIZIDE

*** Timilsina Sourav,** Adhikari Angeela, Yadav Arun K, Gupta Nishant K, Shahi Pragya, Shakya Sabin R,

School of Health and Allied Sciences, Department of Pharmacy, Pokhara University, Kaski, Nepal

**Corresponding Author's Email: Saurav2043@hotmail.com*

Received 04 Aug 2012; Review Completed 26 Aug 2012; Accepted 26 Aug 2012, Available online 15 Sep 2012

**ABSTRACT**

Diabetes mellitus is a metabolic disorder caused by insufficient production of endogenous insulin, with or without resistance to insulin action, resulting in hyperglycemia. In type 1 diabetes mellitus, there is a failure in production of insulin as a result of destruction of the β cells of the pancreas, and patients require treatment with insulin whereas type 2 diabetes can be characterized by defects in both insulin action (i.e. insulin resistance) and insulin secretion, and is associated with elevated basal hepatic glucose production. Glipizide is a second-generation sulfonylurea that can acutely lower the blood glucose level in humans by stimulating the release of insulin from the pancreas and is typically prescribed to treat type II diabetes. Different formulations were prepared by varying the concentration of HPMC used as polymers. The effect of varying concentration of hydrophilic polymers (HPMC 5cps and 15 cps) was studied on the release pattern of glipizide. Sustained release glipizide matrix tablets were prepared by wet granulation and compression of hydroxypropylmethyl cellulose (5 cps and 15 cps), drug and other excipients mixture. The promising formulation was compared with the marketed sample of suatained release glynase in terms of release pattern. The release rate of a glipizide from matrix tablet was decreased with increasing the concentration as well as viscosity polymer. This might be probably due to increased swelling and reduced erosion rate of matrix tablet. The formulation 13 (F13) showed the similar result as marketed sample of sustained release glynase tablets in terms of release rate.
**Key Words:** Glipizide, Hydroxy propyl methyl cellulose (HPMC), Viscosity grades

## INTRODUCTION

Sulfonylurea represents a wide class of drugs used in the treatment of diabetes mellitus, compared to other drugs of sulfonylurea class; Glipizide has shown to have less chances of hypoglycemic shock as an adverse effect. The incidence of hypoglycemic symptoms with glipizide GITS is low (≤3%)[1].

Relatively high dose of Glipizide makes it a good candidate for formulating it as a Sustained release dosage form. Glipizide is a second generation sulphonylurea agent that is available in a Gastrointestinal Therapeutic System (GITS) extended-release formulation. Glipizide GITS provides more stable plasma drug concentrations than the immediate-release formulation and the once-daily regimen may optimize patient compliance. In patients with type 2 diabetes mellitus, glipizide GITS is at least as effective as the immediate-release formulation of glipizide in providing glycaemic control, and may have a greater effect on fasting plasma glucose levels. Any therapeutic advantage over other antidiabetic agent remains to be established, but in a preliminary report (n = 40) glipizide GITS provided better glycaemic control and produced less fasting insulinaemia than glibenclamide[1]. However from manufacturer point of view manufacturing gastrointestinal therapeutic system is comparatively more complicated process and requires more careful handling and control mechanism than formulating matrix tablets.

So manufacturing GITS is technically challenging for developing countries and it also results in increase cost of the tablets. Due to this reason matrix system tablet are required which require less technology and are cheaper compared to GITS[1]. Hydroxy propyl methyl cellulose is the methyl cellulose derivative used as binder in either wet or dry granulation. Depending upon the viscosity grades, concentration of 2-20% are used for film coating where as high viscosity grades may be used to retard the release of drugs from a matrix in tablets.

## MATERIALS AND METHODS

Sustained release glipizide matrix tablets were prepared by wet granulation and compression as reported in previous report with some modification2. For these matrix systems, glipizide, lactose, HPMC (5 cps and 15 cps), PVPK 30, magnesium stearate and aerosil were weighed individually. Lactose, HPMC and PVPK 30 were passed through sieve size 20 and magnesium stearate and aerosil were passed through sieve size 60. The drug was suspended in methylene chloride (100 ml) and then mixed with lactose slowly for uniform adsorption of drug on lactose particles. It was dried for 1 hour in open air. The dried granules were passed through mesh no 20. These granules were mixed with HPMC and PVP K30 in polythene bag for 15 minutes and then magnesium stearate and aerosil were finally added. Then it was compressed adjusting final weight of tablet equal to 600 mg.

© 2011, JDDT. All Rights Reserved ISSN: 2250-1177 CODEN (USA): JDDTAO

**Method of analysis**

**Standard preparation**

100 mg of reference standard were weighed and dissolved in 100 ml of 0.1 NaOH to make the concentration of 1 mg/ml. Serial dilution was done to make the final concentration of 0.01mg/ml.[2]

**Sample preparation**

10 ml of the samples were withdrawn at the time interval of 0.5 hr, 1 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 7 hr and 8 hr. The samples withdrawn were replaced by equal amount of dissolution medium.

**Dissolution**

The release of glipizide from sustained release formulation was studied using Elecrolab dissolution apparatus.[2] For each test, six formulation was placed in the flask containing 900 ml 0.1 M NaOH, dissolution medium[2], at 37±2°C at 50 rpm[2]. Ten ml aliquot of the medium was sampled at pre-determined time of 8 hours. The sample was filtered and the concentration of glipizide was determined by measuring ultraviolet absorption at 276 nm[3]. The mean of six determinants was used to calculate drug release from each formulation.

Table 1: Different formulations with varying HPMC 5cps and 15 cps grade.

| Formulation | Drug (mg) | HPMC 5cps (mg) | HPMC 15cps (mg) | Lactose (mg) |
|---|---|---|---|---|
| F1 | 10 | - | - | 575.6 |
| F2 | 10 | - | 120 | 455.6 |
| F3 | 10 | - | 180 | 395.6 |
| F4 | 10 | - | 240 | 335.6 |
| F5 | 10 | - | 360 | 215.6 |
| F6 | 10 | 420 | - | 155.6 |
| F7 | 10 | 480 | - | 95.6 |
| F8 | 10 | - | 480 | 95.6 |
| F9 | 10 | - | 420 | 155.6 |
| F10 | 10 | 140 | 280 | 155.6 |
| F11 | 10 | 160 | 320 | 95.6 |
| F12 with PVP | 10 | 240 | 240 | 95.6 |
| F13 with PVP | 10 | - | 480 | 71.6 |
| F14 with PVP | 10 | - | 300 | 251.6 |
| F15 with PVP | 10 | - | 360 | 191.6 |
| F16 with PVP | 10 | 140 | 280 | 131.6 |
| F17 with PVP | 10 | 160 | 320 | 71.6 |

***In the formulation F12-F17, PVP K30 was added and the amount used was 4% of total mass of each tablet. The amount of Magnesium Sterate and Colloidal Silicon dioxide (Aerosil) was fixed at 2% and 0.4% respectively for total weight of each tablet.***

**RESULTS AND DISCUSSIONS**

The release percentage of the glipizide drug from the formulation was studied by changing the viscosity grade as well as the mass of the polymer in the tablet matrix. Friability, hardness and weight variation results are also compared with variation in polymers used. The compression pressure was adjusted in such a way that it passes the physical parameters. As the physical parameter was passed, then dissolution test was carried out for each formulation. Firstly, the dissolution test of the formulations containing 20%, 30% and 40% HPMC were carried out. The dissolution of these concentrations did not give the desired result showing the release percentage of 83% to 94% within half hour as shown in table 4. So the mass of HPMC was increased according to Handbook of Excipients which states that concentration of HPMC can be increased within the range of 20%-80%. The data shown in Table 5 suggests that increasing the concentration of HPMC within the range 60%-80%, the release rate of the glipizide is decreased but it did not meet the desired objective of our research. Table 2 shows that increasing the HPMC up to maximum limit caused the failure in result of friability and hardness. To improve the hardness of a tablet in a formulation containing higher concentration of HPMC, PVP K30 (Polyvinyl Pyrrolodine K 30) as binder was added. The fixed quantity of binder used in these formulations had shown the desirable effect as shown in Table 7 and 8. Similarly, the dissolution test of the marketed sample (Glynase SR) was also carried out as illustrated in Table 9. The release percentage and pattern of the glipizide in marketed sample and F13 is nearly same.

Table 2: Drug release percentage from formulations containing 20%, 30% and 40% HPMC 15 cps (Without PVP), n=3 F2, F3 and F4 had shown the complete release within 0.5 hour.

| Formulation | Drug release % | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| F1 | 0.5 hr | 1 hr | 2 hr | 3 hr | 4 hr | 5 hr | 6 hr | 7 hr | 8 hr |
| F2 | 94% | - | - | - | - | - | - | - | - |
| F3 | 99.5% | - | - | - | - | - | - | - | - |
| F4 | 83% | - | - | - | - | - | - | - | - |

© 2011, JDDT. All Rights Reserved ISSN: 2250-1177 CODEN (USA): JDDTAO

Table 3: Drug release percentage from formulation containing 60%, 70% and 80% HPMC (Without PVP)

| Formulation | Drug release % | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0.5 hr | 1 hr | 2 hr | 3 hr | 4 hr | 5 hr | 6 hr | 7 hr | 8 hr |
| F5 | 35.8% | 56.14% | 102% | - | - | - | - | - | - |
| F6 | 42.01% | 91.27% | - | - | - | - | - | - | - |
| F7 | 33.01% | 67.32% | 101.26% | - | - | - | - | - | - |
| F8 | 25.13% | 43.23% | 68.11% | 77.06% | 89.32% | 98.26% | - | - | - |
| F9 | 29.13% | 42.62% | 64.12% | 76.29% | 92.11% | 104.11% | - | - | - |

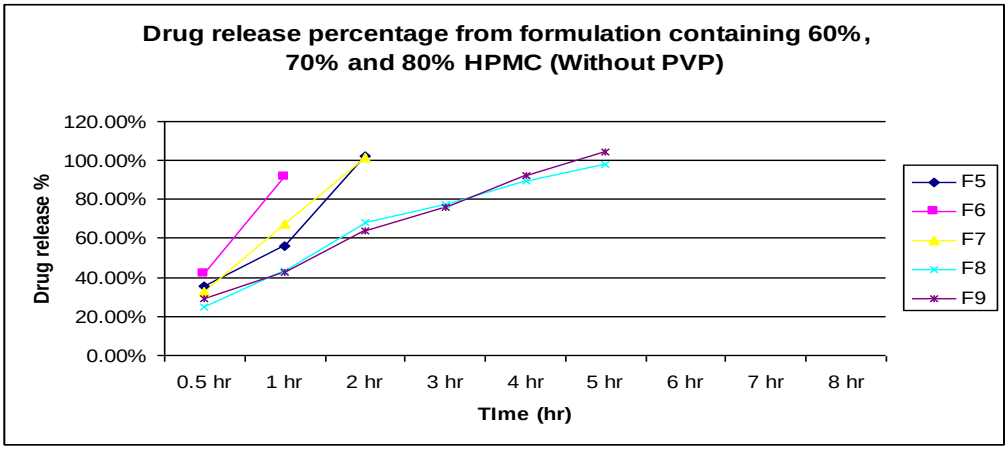


Figure 1: Drug release percentage from formulation containing 60%, 70% and 80% HPMC (Without PVP)

With the increase in mass of HPMC to 60%, 70% and 80% of total mass of formulation, the release percentage of glipizide is reduced. F8 and F9 had shown the release rate up to 5 hours.

Table 4: Drug release percentage from formulation containing HPMC 5 cps and 15 cps in 1:2 ratio (Without PVP)

| Formulation | Drug release % | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0.5 hr | 1 hr | 2 hr | 3 hr | 4 hr | 5 hr | 6 hr | 7 hr | 8 hr |
| F10 | 24.26% | 32.14% | 44.18% | 68.18% | 82.13% | 102.13% | - | - | - |
| F11 | 20.11% | 28.25% | 37.12% | 59.25% | 79.22% | 98.56% | - | - | - |

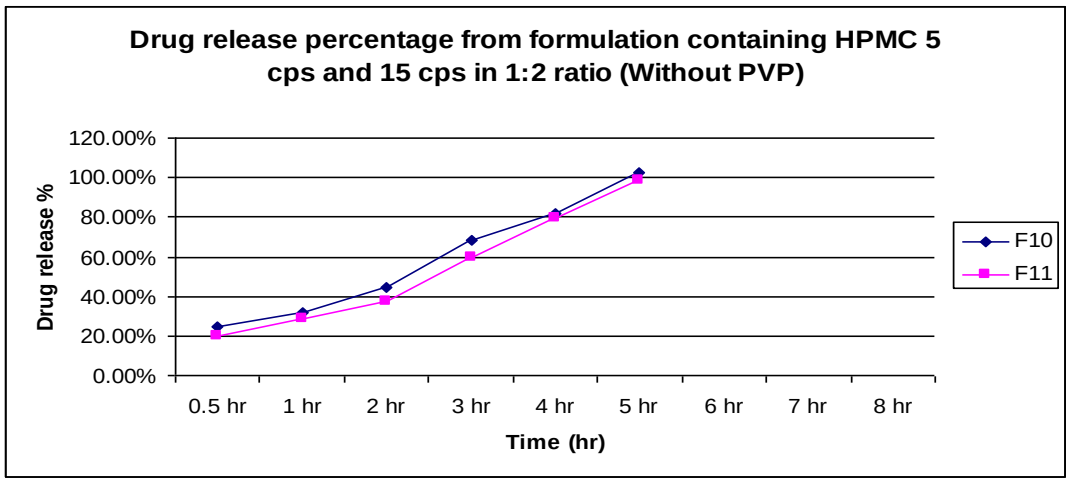


Figure 2: Drug release percentage from formulation containing HPMC 5 cps and 15 cps in 1:2 ratio (Without PVP)

F10 and F11 contain the formulations of HPMC 5 cps and 15 cps in the ratio 1:2. These formulations had shown the complete release within 5 hours.

© 2011, JDDT. All Rights Reserved ISSN: 2250-1177 CODEN (USA): JDDTAO

Table 5: Drug release percentage from formulations containing 70% and 80% HPMC i.e. 5 cps and 15 cps in the ratio 1:2 (with PVP K30) in the formulation F16 and F17 whereas 1:1 in that of F12

| Formulation | Drug release % | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0.5 hr | 1 hr | 2 hr | 3 hr | 4 hr | 5 hr | 6 hr | 7 hr | 8 hr |
| F12 | 19.94% | 29.71% | 39.18% | 47.07% | 55.74% | 66.79% | 75.07% | 98.35% | - |
| F 16 | 22.7% | 27.62% | 41.08% | 50.29% | 66.83% | 72.99% | 87.57% | 96.25% | - |
| F 17 | 16.9% | 27.55% | 36.08% | 45.35% | 53.43% | 68.61% | 74.33% | 90.88% | - |

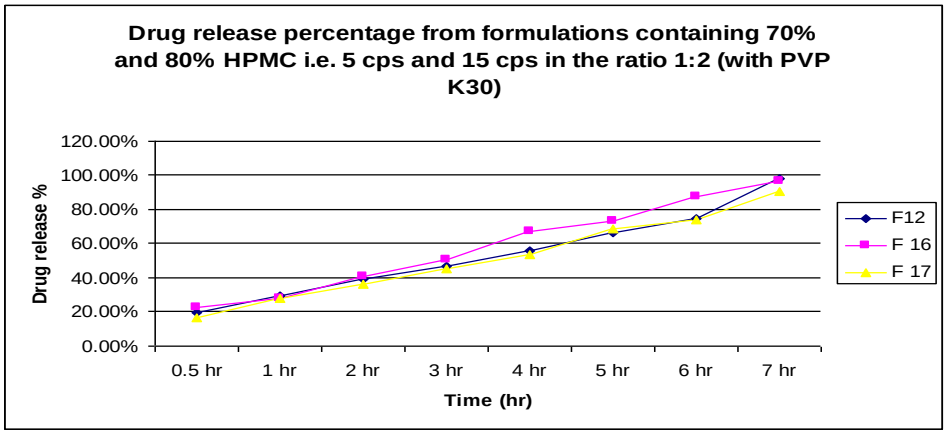


Figure 3: Drug release percentage from formulations containing 70% and 80% HPMC i.e. 5 cps and 15 cps in the ratio 1:2 in F16 and F17 and 1:1 in F12 (with PVP K30) which increased the binding property. These formulations showed the release rate upto 7 hours.

Table 6: Drug release percentage from formulation containing 80%, 50% and 60% HPMC 15 cps (With PVP), n=3

| Formulation | Drug release % | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0.5 hr | 1 hr | 2 hr | 3 hr | 4 hr | 5 hr | 6 hr | 7 hr | 8 hr |
| F13 | 13.62% | 23.47% | 34.46% | 37.64% | 57.09% | 64.19% | 71.84% | 80.22% | 87.47% |
| F 14 | 31.42% | 63.08% | 98% | - | - | - | - | - | - |
| F 15 | 24.10% | 33.42% | 42.62% | 54.63% | 93.25% | - | - | - | - |

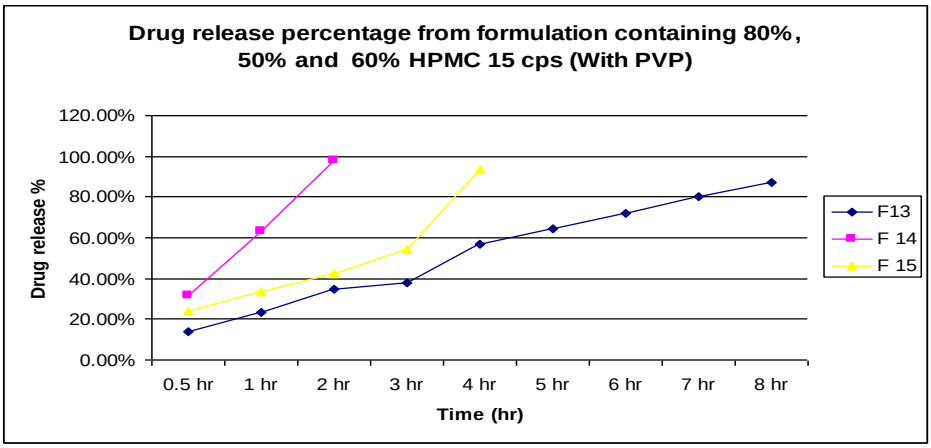


Figure 4: Drug release percentage from formulation containing 80%, 50% and 60% HPMC 15 cps (With PVP)

*F13, F14 and F15 are the formulations containing 80%, 50% and 60% HPMC respectively. Out of these formulations, F13 showed the release rate up to 8 hours.*

© 2011, JDDT. All Rights Reserved ISSN: 2250-1177 CODEN (USA): JDDTAO

Table 7: Drug release percentage of glipizide shown by dissolution of marketed sample (Glynase SR)

| Formulation | Drug release % | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 0.5 hr | 1 hr` | 2 hr | 3 hr | 4 hr | 5 hr | 6 hr | 7 hr | 8 hr |
| Glynase SR | 21.60% | 30.89% | 34.88% | 38.85% | 56.03% | 62.75% | 71.86% | 78.91% | 90.42% |

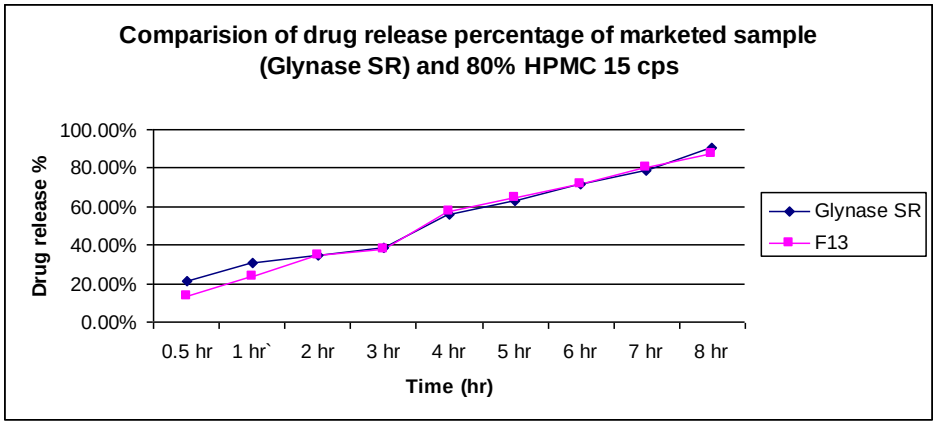


Figure 5: Comparison of drug release percentage of marketed sample (Glynase SR) and 80% HPMC 15 cps

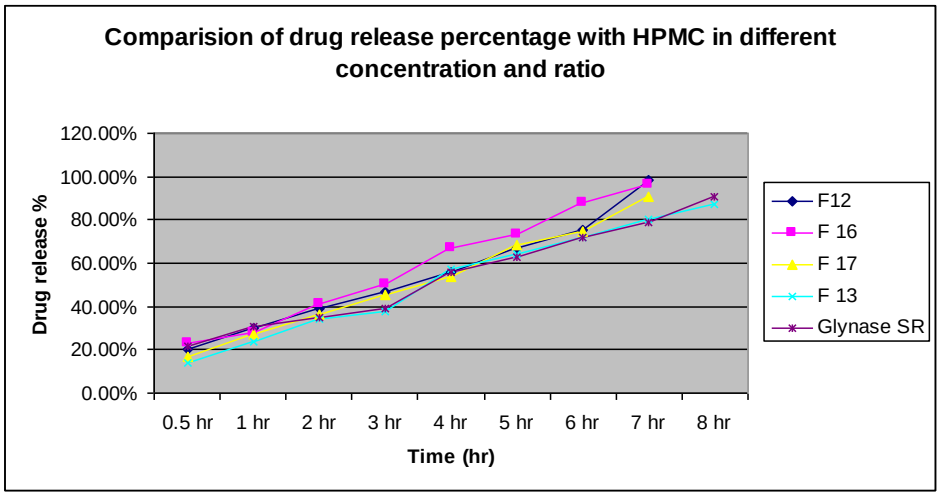


Figure 6: Comparison of drug release percentage with HPMC in different concentration and ratio. Comparing F12, F13, F16, F17 and Glynase SR, the F13 showed the similar release pattern and percentage of drug as marketed sample.

## CONCLUSION

Different formulations of sustained release tablets of glipizide were prepared by wet granulation method using different grade of HPMC. Increasing the amount of HPMC resulted in decreasing the release rate of glipizide drug. The mass of HPMC as well as viscosity grade plays the crucial role in the release of glipizide from the formulation. The *in vitro* analysis of the different formulation performed shows that the F13 achieved the objective of developing sustained release formulation. Hence, future studies of this formulation are recommended to prove its efficacy in *in vitro* and *in vivo*.

The advantage of such formulation is that it is cheaper and do not require expensive equipments for manufacture than other sustain release formulation of glipizide like osmotic pump dosage form.

## REFERENCES

1. Foster HR and Plosker LG, A Review of pharmacoeconomic implications of extended-release formulation in type 2 diabetes mellitus, Pharmacoeconomics 2000, 18, 289-306.
2. Nazir I, Rehman N, Madni A, Preparation and in-vitro dissolution of glipizide sustained release tablets, Turkish journal of Pharmaceutical science 2009, 6, 43-50.
3. Sankalia MJ, Sankalia GM, Mashru CR, Drug release and swelling kinetics of directly compressed glipizide sustained release matrices, Journal of Control Release 2008, 129, 49-58.

© 2011, JDDT. All Rights Reserved ISSN: 2250-1177 CODEN (USA): JDDTAO