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# Formulation And Evaluation Of Controlled Release Tablets Of Gliclazide

Madasu Swapna[1], Rajashekar Vadlakonda[2], Upender Rao Eslawath[3]
*(Department Of Pharmaceutics, Vikas College Of Pharmacy, Kakatiya University, India)*
*(Department Of Pharmaceutical Chemistry, Vikas College Of Pharmacy, Kakatiya University, India)*
*(Department Of Pharmaceutical Analysis, Vikas College Of Pharmacy, Kakatiya University, India)*

***Abstract:***
*Controlled release matrix tablets of Gliclazide were successfully prepared using some selected polymers as the release controlling matrices and by employing direct compression method. All the prepared formulations were evaluated for both pre-compressive and post-compressive parameters such as tablet thickness, hardness, friability, weight variation and drug content uniformity, the values obtained were found to be satisfactory and they complies with pharmacopoeial standards. The result generated in this study showed that the profile and kinetics of drug release were the functions of polymer type, polymer grade (viscosity) and polymer concentration. The present study showed that the release of Gliclazide depend on the ratio of polymers used. It was observed that there was a linear relationship between drug release and different viscosity grades of polymers. Thus, we can infer that drug release rate decreases with increase in polymer level in the formulations.*

***Keywords-*** *Gliclazide, controlled release matrix tablets, friability, content uniformity and viscosity.*

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## I. Introduction

The oral route for drug delivery is the most popular, desirable, and most preferred method for administrating therapeutically agents for systemic effects because it is a natural, convenient, and cost effective to manufacturing process. One of the most common approach used for prolonging and controlling the rate of drug release is incorporating the drug in a hydrophilic colloidal matrix such as hydroxypropyl methylcellulose, hydroxypropyl cellulose, carbopols, chitosan, alginates and gelatin. The mechanism and kinetics of release of drugs incorporated in these polymer matrices is depends the type and amount of polymer as well as on the physico-chemical properties of drug substance. Generally, the drug release from these matrices includes penetration of fluid, followed by dissolution of drug particles and diffusion through fluid filled pores. The diffusion of drug through a matrix is a rate-limiting step [1, 2].

The treatment of acute disease or chronic illness has been achieved by delivery of drugs to the patient for many years. These drug delivery systems include tablet, injectables, suspensions, creams, ointments, liquids, aerosols etc. Today these conventional drug delivery systems are widely used. The term drug delivery can be defined as techniques that are used to get the therapeutic agents inside the human body. Conventional drug therapy requires periodic doses of therapeutic agents. These agents are formulated to produce maximum stability, activity and bioavailability. For most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic ranges [3, 4].

Many strategies are available for the design and development of modified-release drug delivery formulations. The primary purpose of these drug delivery devices is to improve the state of disease management by modifying the pharmacokinetic profiles of therapeutic agents normally administered as conventional tablets or capsules. Conventional oral dosage forms often produce fluctuations of drug plasma level that either exceed safe therapeutic level or quickly fall below the minimum effective level; this effect is usually totally dependent on the particular agent's biologic half-life, frequency of administration, and release rate. It is recognized that many patients can benefit from drugs intended for chronic administration by maintaining plasma levels within a safe and effective range [5, 6].

## II. Experimental

List of Instruments:

| S. No. | INSTRUMENT | MODEL |
|---|---|---|
| 1 | Tablet compression machine | RIMEC, MINI PRESS |
| 2 | Tablet thickness and diameter tester | Vernier Calliper |
| 3 | Monsanto tablet hardness tester | ROLEX, India |
| 4 | Friabilator | Riche Rich, Bangalore , India |
| 5 | Single pan electronic balance | ORION digital precision balance |
| 6 | U.V Visible Spectrophotometer | Shimadzu UV-1700, Double beam |

List of Chemicals:

| S. No. | CHEMICAL | SUPPLIER |
|---|---|---|
| 1 | Gliclazide | Pharmatrain |
| 2 | Hydroxypropyl methyl Cellulose | FINAR chemical LTD |
| 3 | Ethyl Cellulose | Standard solutions Ltd |
| 4 | Magnesium stearate | Standard solutions Ltd |
| 5 | Methanol | MERCK |

Preformulation Studies:

Preparation of matrix tablets of Gliclazide:

Matrix tablets containing 500mg of Gliclazide along with various amounts of polymers such as HPMC (Various grades), Ethyl cellulose, and other excipients (such as, magnesium stearate and MCC) were used and tablets were prepared by direct compression technique. MCC and Aerosol were passed through mesh No. 40. In the first step, the drug and ingredients with the exception of magnesium stearate were blended in a turbula mixer for 5 minutes. Then magnesium stearate was added and formulation was mixed for an additional two minutes. Desired amount of blend was directly compressed into tablets using rotary tablet compression machine. Before compression, the surfaces of the die and punch were lubricated with magnesium stearate. All the preparations were stored in airtight containers at room temperature for further studies.

Drug content estimation:

Standard solution: 100 mg of pure Gliclazide drug was dissolved in water in a volumetric flask and the volume was makeup to 100ml mark with the same solvent and sonicated for 5 minutes.

Sample solution: 20 tablets from each batch were randomly selected and were weighed accurately and then finely powdered. To a powder equivalent to 100mg of Gliclazide, about 70ml of water was added and dissolved with the aid of shaker for 15 minutes; sufficient quantity of water was added to produce 100 ml in a volumetric flask, mixed well and filtered.

*In-vitro* Dissolution studies:

In vitro drug release studies of the prepared matrix tablets were conducted for a period of 10 hours using an eight station USP XXII type 2 apparatus (ELECTROLAB, India) at $37\pm0.5^0$C the paddle speed was 100 ± 1 rpm. The dissolution medium used in each flask was 900 ml of buffer media pH – 6.8. At every 1 hour interval samples of 5 ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant and maintain sink conditions. After filtration and appropriate dilution, the sample solutions were analyzed at 233nm by using double beam U.V/vis spectrophotometer (SHIMADZU- 1700) and dissolution medium as blank. Experiments were performed in triplicates. The amount of drug present in the samples was calculated with the help of calibration curve constructed from reference standard.

Preparation of Dissolution Medium:

Preparation of simulated gastric fluid pH -1.2: Place 250 ml of 0.2M potassium chloride solution(14.911g/litre of distilled water) in a 1 Litre volumetric flask add 425.0ml of *0.2M* hydrochloric acid, and add sufficient quantity of distilled water to produce 1000ml, mix it well.

Preparation of simulated intestinal fluid pH -6.8: Place 250ml of disodium hydrogen phosphate (22.218g/1 litre) in a 1liter volumetric flask add 112.0ml of *0.2M* sodium hydroxide solution and add sufficient quantity of distilled water to produce 1000ml, mix it well.

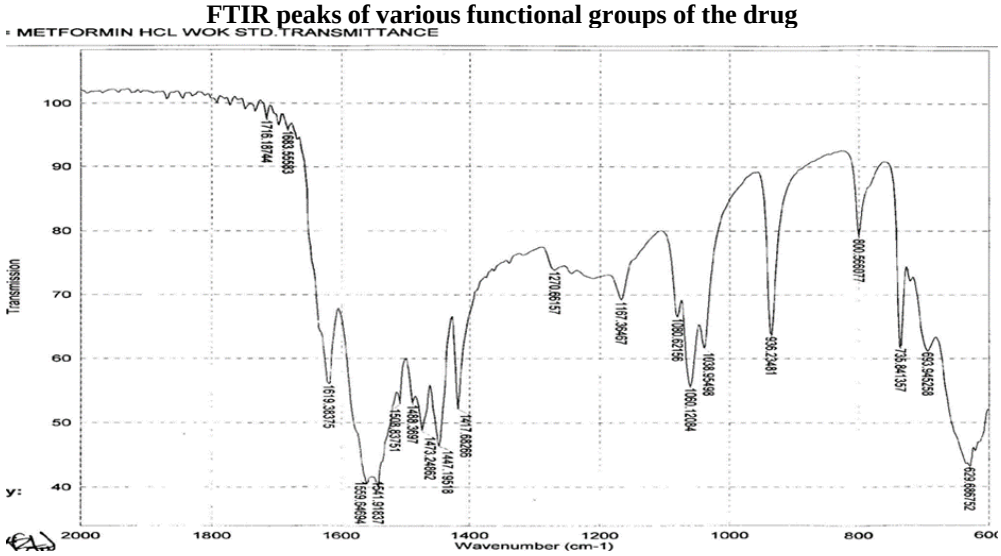
Preparation of simulated intestinal fluid pH -7.4: Place 250ml of disodium hydrogen phosphate (22.218g/1 litre) in a 1liter volumetric flask add 195.5ml of 0.2M sodium hydroxide solution and add sufficient quantity of distilled water to produce 1000ml, mix it well.

## III. Results And Discussions

FTIR Spectroscopy:

FTIR spectra were recorded on samples in potassium bromide disks using Shimadzu FTIR 8400S spectrophotometer. Sample was prepared in potassium bromide disks by means of a hydrostatic pallet press. The scanning range was 250-4500 $Cm^{-1}$ and the resolutions was 4 $cm^{-1}$.

**Figure 1**
**FTIR peaks of various functional groups of the drug**




Evaluation of Tablets:

The tablet formulations were subject to various post-compressive evaluation tests, such as thickness, diameter, and uniformity of weight, drug content, and hardness, friability, swelling characteristics, and in vitro dissolution studies. The results for all the formulations were shown in *the table*.

**Table 1**
Physical characteristics of prepared matrix tablets (n=3**)**

| Formulation Code | Thickness (mm) | Hardness 2 | Weight Variation (mg) (%devn.) | Friability (%) | Drug Content (%) |
|---|---|---|---|---|---|
| **F 1** | 4.11±0.18 | 6.33±0.25 | 2.655±0.124 | 0.513±0.090 | 97.1±1.04 |
| **F 2** | 4.70±0.22 | 6.22±0.22 | 4.516±0.214 | 0.380±0.044 | 96.66±0.70 |
| **F 3** | 4.54±0.18 | 6.22±0.23 | 3.311±0.154 | 0.485±0.086 | 98.94±0.88 |
| **F 4** | 4.78±0.20 | 6.36±0.21 | 2.963±0.413 | 0.266±0.027 | 99.00±0.66 |
| **F 5** | 4.56±0.18 | 6.66±0.06 | 1.051±0.622 | 0.385±0.020 | 98.01±1.04 |
| **F 6** | 4.11±0.11 | 6.06±0.11 | 2.922±0.266 | 0.578±0.04 | 96.33±1.18 |
| **F 7** | 4.54±0.21 | 6.63±0.20 | 3.288±0.544 | 0.444±0.04 | 97.24±0.66 |
| **F 8** | 4.70±0.16 | 6.70±0.10 | 2.444±0.222 | 0.300±0.038 | 99.04±0.66 |
| **F 9** | 4.16±0.20 | 6.44±0.20 | 4.450±0.234 | 0.204±0.06 | 96.99±0.88 |
| **F10** | 4.52±0.22 | 6.36±0.18 | 3.348±0.333 | 0.544±0.080 | 99.44±0.66 |
| **F11** | 4.72±0.10 | 6.44±0.24 | 1.464±0.176 | 0.30±0.068 | 98.28±0.68 |
| **F12** | 4.28±0.18 | 6.65±0.11 | 2.569±0.188 | 0.233±0.066 | 97.42±0.88 |

Table 2
Swelling indices of matrix tablets of Gliclazide (n=3)

| Formula Code | Initial Weight (mg) | Final Weight (mg) | Swelling Index (%) |
|---|---|---|---|
| F 1 | 852.23 | 1398.87 | 64.14 |
| F 2 | 850.77 | 1425.44 | 67.55 |
| F 3 | 853.69 | 1534.43 | 79.74 |
| F 4 | 848.11 | 1413.22 | 66.63 |
| F 5 | 851.34 | 1457.13 | 71.16 |
| F 6 | 853.56 | 1569.61 | 83.89 |
| F 7 | 850.47 | 1576.76 | 85.40 |
| F 8 | 850.21 | 1402.23 | 64.93 |
| F 9 | 848.82 | 1564.76 | 84.35 |
| F10 | 851.45 | 1377.40 | 61.77 |

| | | | |
|---|---|---|---|
| F11 | 848.87 | 1456.62 | 71.6 |
| F12 | 849.38 | 1594.29 | 87.7 |

*In-vitro* drug release study:

In vitro drug release studies of the prepared matrix tablets were conducted for a period of 10 hours using an eight station USP XXII type 2 apparatus (ELECTROLAB, India) at 37±0.5 $^{o}$C the paddle speed was 100 ± 1 rpm. The dissolution medium used in each flask was 900 ml of buffer media pH 6.8. At every 1 hour, interval samples of 5 ml were withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant and maintain sink conditions. After filtration and appropriate dilution, the sample solutions were analyzed at 233nm by using double beam U.V/vis spectrophotometer (SHIMADZU-1700) and dissolution medium as blank. Experiments were performed in triplicates. The amount of drug present in the samples was calculated with the help of calibration curve constructed from reference standard. Dissolution data of matrix tablets are reported in the following table.

Table 3
In-vitro cumulative % release of drug from matrix tablets of Gliclazide - HPMC K4-M (n=3)

| Time (Hrs) | Cumulative % release (±SD) DRUG: HPMC K-4M | | |
|---|---|---|---|
| | **F 1(5:1)** | **F 2 (5:1.5)** | **F 3 (5:2)** |
| 0 | 0.0 | 0.0 | 0.0 |
| 1 | 22.544(±1.23) | 15.123(±0.55) | 13.222(±0.72) |
| 2 | 43.660(±1.37) | 38.660(±1.22) | 36.662(±0.224) |
| 3 | 56.177(±1.44) | 46.440(±1.44) | 45.222(±1.12) |
| 4 | 68.402(±1.16) | 55.660(±1.25) | 56.442(±0.98) |
| 5 | 74.225(1.33) | 63.662(±1.67) | 61.780(±1.12) |
| 6 | 82.343(±2.2) | 69.128(±0.54) | 67.542(±1.66) |
| 7 | 84.566(±1.37) | 73.015(±1.24) | 71.442(±0.88) |
| 8 | 89.290(±1.31) | 79.773(±1.21) | 79.224(±0.122) |
| 9 | 93.666(±1.1) | 82.212(±0.78) | 80.462(±1.88) |
| 10 | 98.284(±0.87) | 87.192(±0.55) | 86.220(±0.12) |

Table 4
Dissolution parameters of Gliclazide matrix tablets

| Formulation Code | Correlation coefficient | Release exponent (n) | Kinetic constant (k) (mg/hr) | $T_{50\%}$ (hr) | $T_{70\%}$ (hr) |
|---|---|---|---|---|---|
| **F 1** | 0.9855 | 0.653 | 8.941 | 2.5 | 4.75 |
| **F 2** | 0.9832 | 0.689 | 8.130 | 3.55 | 6.72 |
| **F 3** | 0.9789 | 0.698 | 8.102 | 3.68 | 6.84 |
| **F 4** | 0.9785 | 0.630 | 7.64 | 2.62 | 5.78 |
| **F 5** | 0.9773 | 0.712 | 8.677 | 3.62 | 6.0 |
| **F 6** | 0.9915 | 0.663 | 7.217 | 4.43 | 7.84 |
| **F 7** | 0.9684 | 0.648 | 7.470 | 2.81 | 6.7 |
| **F 8** | 0.9799 | 0.671 | 7.785 | 3.58 | 6.68 |
| **F 9** | 0.9804 | 0.728 | 7.619 | 5.0 | 8.32 |
| **F10** | 0.9748 | 0.651 | 11.62 | 2.43 | 4.5 |
| **F11** | 0.9756 | 0.668 | 9.893 | 2.35 | 5.5 |
| **F12** | 0.9674 | 0.685 | 8.893 | 3.68 | 5.41 |

Figure 1
First order kinetic treatment for drug-HPMC K-4M matrices

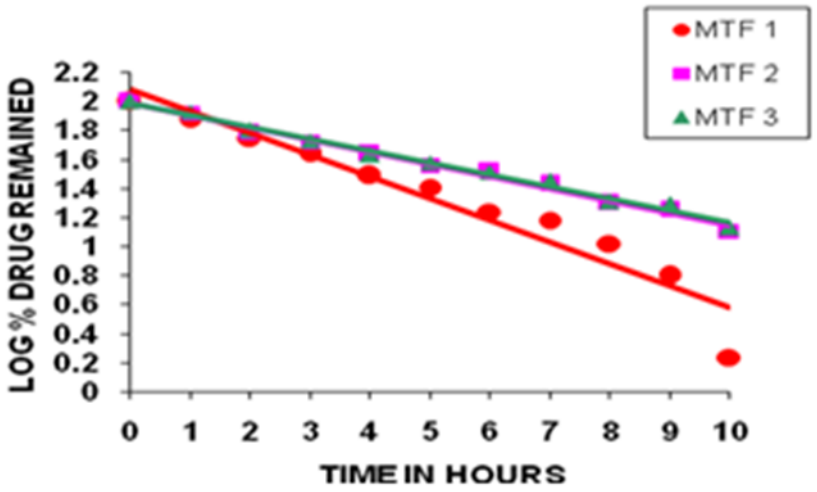



Table 5
Results of stability studies of matrix tablets containing different grades of HPMC

| TIME IN DAYS | HPMC K 4M MATRICES | | | | | | | | | HPMC K15M MATRICES | | | | | | | | | HPMC K100M MATRICES | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F1 | | | F 2 | | | F 3 | | | F 4 | | | F 5 | | | F 6 | | | F 7 | | | F 8 | | | F 9 | | |
| | P | H | % | P | H | % | P | H | % | P | H | % | P | H | % | P | H | % | P | H | % | P | H | % | P | H | % |
| 0 | + + + + | 6.24 | 99.1 | + + + + | 6.22 | 96.66 | + + + | 6.21 | 98.94 | + + + + | 6.58 | 99.00 | + + + | 6.08 | 98.01 | + + + | 6.80 | 96.33 | + + + + | 6.28 | 97.24 | + + + + | 6.40 | 99.02 | + + + | 6.40 | 96.99 |
| 30 | + + + | 6.24 | 99.10 | + + + | 6.50 | 96.60 | + + + | 6.20 | 98.32 | + + + | 6.56 | 98.90 | + + + | 6.08 | 97.66 | + + + | 6.75 | 96.0 | + + + | 6.26 | 96.97 | + + + | 6.38 | 98.65 | + + + | 6.38 | 96.90 |
| 60 | + + + | 6.23 | 99.0 | + + + | 6.58 | 95.98 | + + + | 6.18 | 98.11 | + + + | 6.56 | 98.75 | + + + | 6.0 | 96.77 | + + + | 6.74 | 95.80 | + + + | 6.25 | 96.13 | + + + | 6.36 | 97.77 | + + + | 6.36 | 96.89 |

Physical characteristics of prepared Gliclazide (G) matrix tablets:

Prepared matrix tablets of Gliclazide of all the formulations (F1 to F12) were about white in color, circular in shape with convex surfaces. All the formulations were evaluated for thickness, hardness, friability, weight variation and drug content. As summarized in Table14 and 15, the drug content for all formulations ranged from 97.94 to 99.87% that is within the IP limit. For all formulations, % friability was less than 1% and sufficient hardness ranging from 6.0 to 7.0 Kg/cm$^2$. The values of Compressibility indices were between 17.352 to 20.897% indicate excellent flow property. Tablets were evaluated for weight variation, thickness and diameter and the values were found to be within BP limits.

## IV. Conclusion

Gliclazide (is an antihyperglycemic agent available as 1.5 and 2.0g/day tablet to be taken. Its biological half-life is about 1.5-3.5 hours .so, the most prominent being the high dose (1.5-2.0 g/day), low bioavailability (60%) and high incidence of GI side effects (30%cases) becomes necessary to maintain a steady- state drug concentration of this drug in plasma (minimum inhibitory concentration) throughout the therapy. Therefore, it was clear that, there was a need of fabricating a controlled release dosage form of Gliclazide, which can produces a desired concentration of drug throughout the entire period of therapy. Gliclazide was used as a model drug and released was controlled by inclusion of some selected polymers of various grades. The prepared tablets were evaluated for both for pre-compressive and post-compressive parameters. All the parameters were under acceptable ranges. The polymer with high ratios greatly

retarded the release of drug from the polymeric matrix. The retardation of drug release was greatly influenced when the concentration of polymer was increased. The formulations containing combined (ethyl cellulose – HPMC K100M) and HPMC K4M in ratios of 5:1:1 and 5:1 with respect to drug showed drug release 99.443%, 98.284% respectively after a study of 10 hours. The drug release followed zero order and Higuchi kinetic and mechanism of release was by swelling and erosion (Non-Fickian diffusion). Thus, this polymer can be successfully employable to formulate controlled release tablets for existing drug. Formulation of controlled release matrix tablets of Gliclazide thus helped to decrease dosing frequency, reduces local adverse effects, and extends release of drug from the matrix to a prolong period of time, thus improves patient compliance. This may also extends biological half-life of existing drug.

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