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# FORMULATION AND DEVELOPMENT OF SUSTAINED RELEASE MATRIX TABLETS OF METFORMIN HYDROCHLORIDE

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## ABSTRACT

Objective of the present study is to formulate and evaluate the matrix tablets of Metformin hydrochloride. Formulations were designed by using $3^2$ Factorial designs and a total of nine formulations were prepared (F1-F9). Preformulation tests were performed for identification of drug and characterization of polymers. Blend of powders of respective formulations were evaluated for Bulk density, tapped density, Hausner's ratio, Carr's Compressibility index, Angle of repose. Tablets were prepared by direct compression method and evaluated for thickness, hardness, friability, weight variations and drug content. Dissolution studies were performed and percent cumulative release was found to be satisfactory with 93.14% and formulation was found to be stable at $40^0C \pm 2^0C$ and 75% RH.

**KEY WORDS:** Metformin Hydrochloride, Matrix tablet, type 2 Diabetes mellitus, Factorial design.

## INTRODUCTION

### MATRIX TABLET[1]

Matrix tablets is a promising approach for the establishment of extended-release drug therapy as tablets offer the lowest cost approach to sustained and controlled release solid dosage forms. Matrix tablets may be defined as the "oral solid dosage forms in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serves as release rate retardants". These systems release drug in continuous manner by dissolution-controlled and diffusion-controlled mechanisms. Under gastric pH conditions, matrix tablet slowly erodes. However at a pH corresponding to the upper small

intestine, the tablet disintegrates rapidly to reduce coated particles, which in turn slowly releases drug. Two different release mechanisms are operative, either of which is zero-order erosion and decreasing surface area, and dissolution of coated particles, but the overall tablet release profile comprising the two mechanisms in sequence is nearly linear for most of the dose in the tablet. The result in the ability to control active pharmaceutical ingredient's blood level's in a narrow range, above the minimum effective level and below toxic level. This type of sustained-release tablet has clearly shown the potential of the tablet as a reliable sustained release dosage form with good release profile precision. Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of Pharmaceutical technology. It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations. One of the least complicated approaches to the manufacture of sustained release dosage forms involves the direct compression of blend of drug, retardant material and additives to formulate a tablet in which the drug is embedded in a matrix of the retardant. Alternatively drug and retardant blend may be granulated prior to compression.

**Advantages Offered By Matrix Tablets[1]**

1. Maintains therapeutic concentrations over prolonged periods.
2. Avoids the high blood concentration.
3. Reduction in toxicity by slowing drug absorption. Minimize the local and systemic side effects.
4. Improvement in treatment efficacy.
5. Better drug utilization. Minimize drug accumulation with chronic dosing.
6. Can be made to release high molecular weight compounds.
7. Increase the stability by protecting the drug from hydrolysis or other derivative changes in GIT.
8. Reduction in health care cost.
9. Usage of less total drug.
10. Improvement of the ability to provide special effects. Ex: Morning relief of arthritis through bed time dosing. Improved patient compliance.

**Disadvantages of Matrix Tablets[1]**

1. The remaining matrix must be removed after the drug has been released.

2. Greater dependence on GI residence time of dosage form.
3. Increased potential for first-pass metabolism.
4. Delay in onset of drug action.
5. Release rates are affected by food and the rate transit through the gut.

   Release rate continuously diminishes due to increased diffusional resistance.

## MATERIALS AND METHODS

### MATERIALS AND CHEMICALS

Following are the materials and chemicals were used for formulation development.

**Table 1: List of Materials and Chemicals**

| Sr. No. | Name of Drug / Excipients | Manufactured by |
|---|---|---|
| **Drugs** | | |
| 1. | Metformin Hydrochloride | Cipla Pharmaceuticals, Kurkumbh |
| **Excipients** | | |
| 1. | Hydroxy Propyl methyl cellulose | Ajanta Pharmaceuticals, Aurangabad |
| 2. | Ethyl cellulose | Ajanta Pharmaceuticals, Aurangabad |
| 3. | Microcrystalline cellulose PH-102 | Cipla Pharmaceuticals, Kurkumbh |
| 4. | Polyvinyl pyrrolidone K-30 | Ajanta Pharmaceuticals, Aurangabad |
| 5. | Magnesium Stearate | Ajanta Pharmaceuticals, Aurangabad |
| 6. | Talc | Ajanta Pharmaceuticals, Aurangabad |
| **Chemicals** | | |
| 1. | HCL | Merck Ltd., Mumbai |
| 2. | Potassium dihydrogen orthophosphate | Merck Ltd., Mumbai |
| 3. | NAOH | Merck Ltd., Mumbai |
| 4. | Water | _ |

### EQUIPMENTS

**TABLE 2: LIST OF EQUIPMENTS**

| Sr.No | Name of Instrument | Make and Model |
|---|---|---|
| 1 | Analytical weighing balance | Shimadzu-AUX-220 |
| 2 | Pfizer hardness tester | Cadmach |
| 3 | Roche friabilator | Remi |
| 4 | Dissolution test apparatus | Disso 2000, LabIndia |
| 5 | Rotary press | Rimek |
| 6 | UV-visible Double beam Spectrophotometer | U- Shimadzu 2450 |

### Evaluation of powdered characteristics[4]

#### Density

The bulk density was determined by gently pouring the powders into a 50 ml volumetric cylinder to a total volume of 20 ml. After weighing the above volume of powder, the bulk density was determined using equation as presented below. Density = Weight (gm)/Volume

(ml) For the measurement of tap density, the cylinder was tapped over a 0.5 inch vertical drop, using a tap density tester, until a constant volume was observed.

**Hausner's ratio**

Hausner's ratio gives an idea regarding the flow of the blend. It is the ratio of tapped density to the apparent density.

**Compressibility index**

The compressibility index measures of the propensity of powder to be compressed. The packing ability of drug was evaluated from change in volume, which is due to rearrangement of packing occurring during tapping. It is indicated as Carr's compressibility index (CI).

**Angle of repose**

Angle of repose is defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle of repose was determined by the funnel method. A glass funnel was secured with its tip at a given height (H) above a piece of graph paper placed on a horizontal surface. Powder was poured through the funnel until the apex of the conical pile touched the tip of the funnel. The angle of repose was calculated with the formula

$\tan \theta = h/r$ OR

$$\theta = \tan^{-1} \frac{h}{r}$$

Where, θ = is the angle of repose,

h = height of the conical pile and

r = radius of the conical pile.

**Preparation of matrix tablet**

Matrix tablets containing 500mg of Metformin HCl along with various amount of polymers such as HPMC K100M, Ethyl cellulose and other inactive ingredients were mixed and tablet were prepared by direct compression technique. In the first step, active and inactive ingredients (except magnesium Stearate) weighed accurately and were screened through a 40-mesh sieve. Required materials except lubricant were then combined and passed through 40-mesh sieve. In, the screened powder following the addition of given amount of lubricant powder was again mixed. Before compression, the surfaces of the die and punch were lubricated with magnesium Stearate, and then desired amount of blend was compressed into

tablets using rotary tablet compression machine (Rimek tablet machine, Minipress) equipped with 13 mm flat circular punch. All the preparations were stored in airtight containers at room temperature for further study.

**Table.3. Composition of Metformin Hydrochloride Tablet**

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Metformin hydrochloride | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 | 500 |
| HPMC | 80 | 120 | 160 | 80 | 120 | 160 | 160 | 80 | 120 |
| Ethyl cellulose | 40 | 60 | 80 | 80 | 40 | 60 | 40 | 60 | 80 |
| Pvp k30 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| Avicel 102 | 160 | 100 | 50 | 120 | 120 | 60 | 80 | 40 | 80- |
| Talc | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Magnesium Stearate | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Total | 800 | 800 | 800 | 800 | 800 | 800 | 800 | 800 | 80 |

**EVALUATION OF TABLETS[4]**

The compressed matrix tablets were evaluated for thickness, weight variation, hardness and drug content.

**1. Thickness**

The thickness of tablet was determined using micrometer screw gauge. Six tablets from each batch of formulation were used and mean thickness value and SD was calculated for each formulation.

**2. Hardness**

For each formulation, the hardness of six tablets was measured using the Pfizer hardness tester and mean value and SD was calculated.

**3. Weight variation**

To study the weight variation, 20 tablets of each formulation were weighed using an electronic digital balance. The average weight of each tablet was calculated and from that the percentage deviation in weight was calculated.

**4. Friability**

For each formulation the friability of 6 tablets was determined using Roche Friabilator. (Remi Equipments).

**5. Drug content**

Five tablets were weighed and powdered. Weigh accurately a quantity of the powder equivalent to 0.1 g of Metformin HCl shake with 50 ml of 6.8 pH phosphate buffer for 10 minutes, and add sufficient buffer to produce 100.0 ml and filter. After suitable dilution with solvent measure the absorbance of the resulting solution at the maximum at about 233 nm. Calculate the content of $C_4H_{11}N_5$, HCl, at the maximum at about 233 nm.

**6. In-vitro drug release study**

In vitro drug release studies of the prepared matrix tablets were conducted for a period of 12 hours by using an USP 24 Dissolution Apparatus type II(2000) (Labindia) at 37± 0.5° C. The agitation speed was 100 rpm. The Dissolution study was carried out in 900 ml 0.1N HCl at 37±0.5 ºC for first 2 hours and then in 900 ml of phosphate buffer (pH 6.8).5ml of the sample was withdrawn at regular intervals and the same volume of fresh dissolution medium was replaced to maintain the volume constant. The samples withdrawn were filtered and the drug content in each sample was analyzed after suitable dilution with a Shimadzu 2501PC UV/VIS spectrophotometer at 233 nm. The amount of drug present in the samples was calculated with the help of calibration curve constructed.

**7. Stability Study**

Optimized Metformin HCl matrix tablets were packed in thick aluminum foil strips laminated with The packed tablets were placed in stability chamber maintained at 40±2°C and 75±5% RH for 1 month. The samples were withdrawn after one month and were observed for changes on the physical parameter (i.e. change in color, appearance of spot, any bad odor, smoothness). Samples were evaluated for drug content and *in*-vitro drug release.

**RESULTS AND DISCUSSIONS**

**COPMATIBILITY STUDY BY IR**

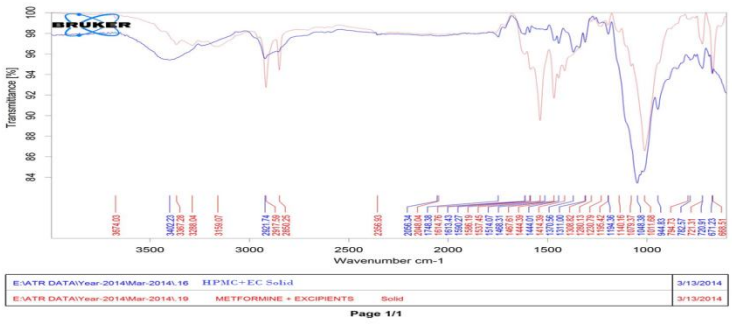


**Fig.1.IR mixture of HPMC+EC+MET+Excipients**

**Table no.4. Interpretation of IR Spectra of Mixture**

| Band assignment | Wave no observed($CM^{-1}$) | Wave no reported($CM^{-1}$) |
|---|---|---|
| **N-H** | 3367.28 | 3300-3500 |
| **C-N** | 1079.37 | 1030-1230 |
| **C-H** | 2917.59 | 3000-3300 |
| **C-O** | 1048.38 | 1000-1300 |
| **O-H** | 3402.23 | 3200-3400 |
| **C-H str** | 2921.74 | 3000-3300 |
| **C-H bend** | 1468.31 | 1300-1500 |

**Table.5.Powder flow characteristics**

| Formulation no | Bulk Density $gm/cm^3$ | Tapped Density $gm/cm^3$ | Hausner's Ratio | Carr's Index % | Angle of Repose(Ɵ) |
|---|---|---|---|---|---|
| F1 | 0.34 | 0.38 | 1.11 | 10.52 | 22.46 |
| F2 | 0.3 | 0.33 | 1.10 | 9.09 | 20.12 |
| F3 | 0.32 | 0.36 | 1.125 | 11.11 | 23.41 |
| F4 | 0.34 | 0.39 | 1.14 | 12.82 | 26.82 |
| F5 | 0.35 | 0.40 | 1.14 | 12.50 | 25.36 |
| F6 | 0.34 | 0.39 | 1.14 | 12.82 | 27.82 |
| F7 | 0.36 | 0.40 | 1.11 | 10.00 | 22.58 |
| F8 | 0.3 | 0.32 | 1.06 | 6.25 | 17.34 |
| F9 | 0.3 | 0.34 | 1.13 | 11.76 | 24.21 |

**Table.6. Various evaluation parameters of Metformin HCl tablet formulations containing HPMC K100 M and ethylcellulose**

| Formulation Code | Thickness(mm) (Mean± S.D) | Hardness($kg/cm^2$) (Mean± S.D) | Weight Variation (%) | Friability(%) (Mean± S.D) | Drug Content |
|---|---|---|---|---|---|
| F1 | 4.41±0.02 | 7.4±0.35 | 2.695 | 0.58±0.019 | 100.12 |
| F2 | 4.56±0.033 | 7.9±0.11 | 1.765 | 0.48±0.069 | 101.1 |
| F3 | 4.66±0.02 | 7.5±0.25 | 2.722 | 0.35±0.007 | 100.08 |
| F4 | 4.53±0.04 | 7.8±0.32 | 2.570 | 0.20±0.007 | 99.12 |
| F5 | 4.50±0.03 | 7.3±0.10 | 2.286 | 0.29±0.056 | 99.67 |
| F6 | 4.43±0.03 | 7.8±0.27 | 3.046 | 0.45±0.021 | 99.02 |
| F7 | 4.53±0.02 | 7.2±0.11 | 2.634 | 0.30±0.028 | 99.80 |
| F8 | 4.58±0.06 | 7.5±0.05 | 2.440 | 0.61±0.06 | 99.93 |
| F9 | 4.46±0.03 | 7.8±0.14 | 1.937 | 0.47±0.035 | 100.15 |

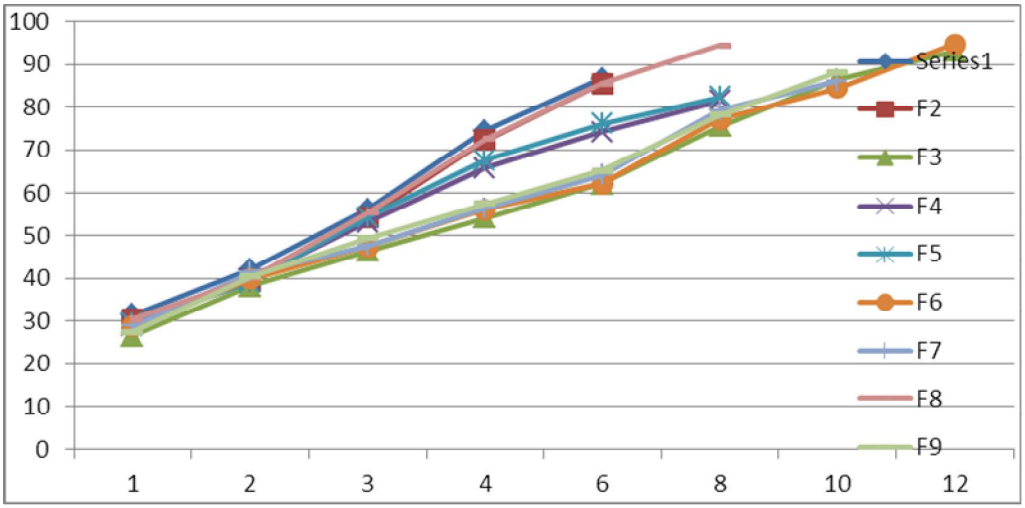


**Fig.2.Effect of polymer HPMC K 100 M and ethyl cellulose on release pattern of Metformin hydrochloride**

**Table.7. Release Models**

| BATCH NO | ZERO ORDER | FIRST ORDER | HIGGUCHI |
|---|---|---|---|
| F1 | 0.940 | 0.876 | 0.991 |
| F2 | 0.939 | 0.878 | 0.988 |
| F3 | 0.971 | 0.895 | 0.991 |
| F4 | 0.921 | 0.882 | 0.988 |
| F5 | 0.910 | 0.886 | 0.982 |
| F6 | 0.969 | 0.896 | 0.985 |
| F7 | 0.975 | 0.897 | 0.984 |
| F8 | 0.944 | 0.873 | 0.991 |
| F9 | 0.959 | 0.898 | 0.991 |

**Table.8.Evaluation parameters of Formulation F3 stored at $40^0$C for 1month**

| Parameter | After 1 month |
|---|---|
| Appearance | White color |
| Thickness(mm) | 4.5 |
| Hardness(kg/cm$^2$) | 7.8 |
| Friability (%) | 0.20 |
| Drug content (%) | 99.12 |

**Table.9. % Cumulative release of formulation F3**

| Time(hr) | % cumulative release after 1 month |
|---|---|
| 1 | 25.82 |
| 2 | 39.14 |
| 3 | 47.47 |
| 4 | 53.45 |
| 6 | 63.78 |
| 8 | 76.16 |
| 10 | 85.42 |
| 12 | 92.86 |

## DISCUSSION

### Compatibility studies

Mixture of Metformin HCL and different excipients were compared with HPMC and Ethyl cellulose and it was found from the spectra that principle peaks of drug Metformin HCL was retained and there was no interaction between drug and polymers.

### Powder flow characteristics

Formulation (F1-F9) were evaluated for angle of repose, tapped density, bulk density, compressibility index, Hausner's ratio and angle of repose. The results of Hausner's ratio was found to be in the range of 1.06-1.14 which shows excellent to good flow. The results of compressibility index were found to be in the range of 6.25-12.82% which according to standard values shows excellent flow. Results of angle of repose were found to be in the range of 17.34-27.82 which according to standard values shows excellent to good flow.

### Evaluation of Tablets

The tablet formulations were subjected to various evaluation tests such as thickness, diameter, hardness, and friability, uniformity of weight, drug content, and in vitro dissolution. The results for all the formulations are shown in Table. The **thickness** of all the formulations were varies within ranges from 4.1-4.58 all the formulation showed uniform thickness. The **weight variation** test was carried out as per official method and it was found that all formulation to be within the limit (as per pharmacopoeial standard) The **content uniformity** test was also carried out as per official method and it was found that different batches shown good content uniformity. It was found that all batches shown percent drug content more than 98 %. The tablet **hardness** of all the formulations was determined and it was found sufficient in the range 7.1-7.9 kg/cm$^2$. Another measure of tablet hardness was the **friability**. A compressed tablet that loses less than 1 % of their weight is generally considered acceptable. For all formulation tried here the weight loss was less than 1 % hence acceptable.

### In-vitro release study

The in vitro drug release characteristics were studied in 900 ml 0.1N HCl for a period of 2 hours and 6.8 pH phosphate buffer for Remaining 10 hrs using USP XXIII dissolution apparatus 2. According to the USP release pattern, the conventional formulation release not less than 70% in 45 minute. Various formulations were tried here and out of that F3 was the best formulation of the study.

**Influence of quantity of HPMC K100M and addition of Ethylcellulose on in vitro release rate of Metformin HCl from Matrix Tablets.**

To study the effect of HPMCK 100M and ethyl cellulose on release of Metformin Hydrochloride, optimization was applied and $3^2$ factorial design was selected and accordingly 9 batches (F1-F9) were prepared with different varying concentrations of HPMC K 100 M and ethyl cellulose batches Fig reveal the effect of quantity of HPMC K 100M and ethyl cellulose on release of Metformin Hydrochloride from the tablet matrix. As expected the release rate was slower with higher quantities and higher viscosities of HPMC and ethyl cellulose. Formulation F1, F2 and F8 shows drug release 95.45%, 93.13% and 94.44% within 8 hrs respectively. Formulation F4 and F5 shows complete release of drug within 10hrs only with 94.22 and 95.55 respectively. Formulation F3, F6, F7 and F9 shows complete release of drug within 12hrs but formulation F3 shows comparatively slower release of drug than other formulation and hence formulation F3 has been selected as optimized formulation. Different kinetic treatments (zero order, first order, and Higuchi's square root equation were applied to interpret the release of Metformin HCl from different matrices. The data was given in Table. The Higuchi's square root equation gave consistently higher values (0.982 to 0.991) for all formulations. First order kinetic treatment gave lower values (0.882 to 0.898). Zero order kinetic treatment gives higher values (0.910 to 0.975).

**Stability studies**

Form stability studies it was established that the formulation F3 stable at $40^0$c and 75% RH and does not show significant variation in appearance, thickness, friability, hardness and drug content and percent cumulative release.

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