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# Formulation and Evaluation of Bilayered Floating Tablets of Metformin Hydrochloride

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Diabetes is a chronic metabolic disease characterized by high glucose levels in the blood. Sustained release gastro retentive dosage forms enable prolonged and continuous input of the drug to the upper parts of gastrointestinal tract and improve the bioavailability of medication that is characterized by narrow absorption window. Gastro retentive floating drug delivery systems (GFDDS) of Metformin HCl, an antidiabetic drug with an oral bioavailability of only 50% (because of its poor absorption from lower gastrointestinal tract) have been designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating bilayer matrix tablet by direct compression technique, by using HPMC as release retardant, and NaHCO3 as gas generating agent to reduce floating lag time. Bilayer Floating tablets were evaluated for Hardness, Friability, Weight Variation, Drug content, Floating properties and In-vitro release pattern. The In-vitro drug release followed Zero order Kinetics and drug release was found to be diffusion controlled.

*Keyword:* Metformin Hcl, Bi-layer floating tablets, HPMC, antidiabetic drug.

**INTRODUCTION:** Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that has been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage form[1]. Nowadays most of the pharmaceutical scientists are involved in developing an ideal DDS. This ideal system should have advantage of single dose for whole duration of the treatment and it should deliver the drug directly at specific site. Scientists have succeeded to develop a system that can be as near to an ideal system and it encourages the scientists to develop controlled release system.

The design of oral controlled drug delivery system (DDS) should be primarily aimed to achieve the more predictability and reproducibility to control the drug release, drug

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concentration in the target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose.Multilayered tablet concept has longer been utilized to develop controlled release formulations. Such tablets has fast release rate and may contain one (bilayered) or two (triple) layers to sustain drug release so as to maintain therapeutic concentration.

The gastro retentive dosage form will release the drug over an extened period in stomach and upper GI tract thus enhancing opportunity for absorption. The maintenance of a constant plasma level of a diabetes drug is important in ensuring the desired therapeutic response. Since the half life of metformin ~2 to 4 hours, multiple doses are needed to maintain a constant plasma concentration for a good therapeutic response and improved patient compliance.

## MATERIALS AND METHODS

Metformin Hydrochloride PROCURED BY Micro Labs,Banglore, HPMC K 100 M, HPMC K 4 M PROCURED BY Colorcon Asia pvt,Ltd,Goa, Sodium Starch Glycolate, PVP-K-30, Microcrystaline Cellulose procured by Nice Chemicals Laboratory, Magnesium Stearate, Sodium Bicarbonate, Iron Oxide-Red procured by Loba Chemie

## FORMULATION DESIGN:

### Preparation of bilayer floating release matrix tablets with immediate release layer:

### Preparation of immediate release layer:

Controlled release formulations take some time to achieve effective plasma levels. Therefore an immediate release layer is formulated along with controlled release layer to give an initial plasma level, which is then maintained by controlled release layer.Drug loading granules (as an immediate release dose) were prepared by mixing metformin hydrochloride with sodium starch glycolate and PVP-K-30 and micro crystalline cellulose granules and mixed with magnesium stearate and iron oxide red by direct compression technique.

**Table No.1**

**Formulation of Immediate Release**

| CONTENT | FORMULATIONS | | | |
|---|---|---|---|---|
| | FD/MTH/A | FD/MTH/B | FD/MTH/C | FD/MTH/D |
| Metformin HCL | 125 | 125 | 125 | 125 |
| Sodium Starch Glycolate | 4 | 8 | 12 | 16 |
| PVP-K-30 | 5 | 5 | 5 | 5 |
| Iron Oxide red | 2 | 2 | 2 | 2 |
| Micro crystalline cellulose | 35 | 31 | 27 | 23 |
| Magnesium stearate | 4 | 4 | 4 | 4 |

**All the Ingredients are taken in mg.**

**Total wt. of IR layer-175 mg**

### Preparation of matrix layer for controlled release:

The matrix layer contains uniform mixture of drug, polymer and excipients including gas-generating agent. The tablets were prepared by using direct compression technique. Weighed quantities of drug equivalent to 375 mg metformin hcl, was mixed properly in a mortar with weighed amount of polymer and excipients as shown in Table.No.11. The well-mixed

powder was compressed using a ELITE multi station punching machine. The hardness is adjusted for the required amount.

**Formulation of Floating layer(SR)**

**Table No.2**

| CONTENT | FORMULATIONS | | | | | |
|---|---|---|---|---|---|---|
| | FD/MTH/E | FD/MTH/F | FD/MTH/G | FD/MTH/H | FD/MTH/I | FD/MTH/J |
| Drug | 375 | 375 | 375 | 375 | 375 | 375 |
| HPMC K 4 M | --- | 57.5 | 32.5 | 27.5 | 23.75 | 21.5 |
| HPMC K 100 M | 57.5 | --- | 32.5 | 55.0 | 71.25 | 86.0 |
| $NaHCO_3$ | 46.0 | 46.0 | 46.0 | 46.0 | 46.0 | 46.0 |
| Citric acid | 11.5 | 11.5 | 11.5 | 11.5 | 11.5 | 11.5 |
| PVP-k-30 | 23.0 | 23.0 | 23.0 | 23.0 | 23.0 | 23.0 |
| MCC | 56.25 | 56.25 | 48.75 | 31.25 | 18.75 | 6.25 |
| Mag. Stearate | 5.75 | 5.75 | 5.75 | 5.75 | 5.75 | 5.75 |

**All the Ingredients are taken in mg. Total wt. of SR layer-575 mg**

## Preparation of Bi-layer Tablets:

Bi-layer tablets were prepared by combining batch FD/MTH/D of immediate release layer with various formulations of controlled release layer. Batch FD/MTH/D showed disintegration time of 1.45 min was selected for further studies.Matrix tablet is prepared as mentioned above in the procedure of preparation of matrix layer controlled release. After the compression upper punch was lifted and the blend of powder for immediate release layer was poured in the die, containing initially compressed matrix tablet and compression was controlled to produce a 4 to 6 kg crushing strength. These tablets are evaluated for Thickness, hardness, friability and Dissolution Profile. The composition is shown in Table No.12

## Compression of Bi-layer Tablets:

A tablet bi-layer press is simply a tablet press that has been modified so that it has 2 die filling and compression cycles for each revolution of the press.In short, each punch compress twice, once for the first layer of a two layer tablet and a second time for the second layer. If the first layer is compressed so hard that the second layer will not bond it, or will bond so poorly that upon ejection the layers are easily separated for weighing. Once the proper weight adjustment have been made by adjusting the die fill, the pressure is adjusted to the proper tablet hardness and bonding of the layers.

In this two layer tablet press, two hoppers above the rotary die table feed, granulated material to two separate feed frames without intermixing continuous, gentle circulation of the materials. Through the hoppers and feed frames assures uniform filling without segregation of particle sizes that would otherwise carry over to the second layer and affect layer weight, tablet hardness, so use colored granulation taken for one layer.

**Table No.3**

**Formulation of bilayered tablet**

| CONTENT | FORMULATIONS | | | |
|---|---|---|---|---|
| | FD/MTH/D+G | FD/MTH/D+H | FD/MTH/D+I | FD/MTH/D+J |
| Loading Drug | 175 | 175 | 175 | 175 |
| Metformin HCl | 375 | 375 | 375 | 375 |
| HPMC K4 M | 32.5 | 27.5 | 23.75 | 21.5 |
| HPMC K100 M | 32.5 | 55.0 | 71.25 | 86.0 |
| $NaHCO_3$ | 46.0 | 46.0 | 46.0 | 46.0 |
| Citric acid | 11.5 | 11.5 | 11.5 | 11.5 |
| PVP-K-30 | 23.0 | 23.0 | 23.0 | 23.0 |
| MCC | 48.75 | 31.25 | 18.75 | 6.25 |
| Mag.Stearate | 5.75 | 5.75 | 5.75 | 5.75 |

**All the Ingredients are taken in mg. Total wt. of Bi-layer-750 mg**

## II) Post-Compression Parameters:

## Evaluation of bilayer tablet:

## Thickness of Tablets :

Thickness and diameter were measured using a calibrated dial caliper. Three tablets of the formulation were picked randomly and thickness was measured individually. The Results are shown in Table No.19

## Hardness of Tablets:

Hardness was measured using monsanto hardness tester. For each batch three tablets were tested. The Results are shown in Table No.19

## Friability:

Twenty tablets were weighed and placed in the roche friabilator and apparatus was rotated at 25 rpm for 4 minutes. After revolutions the tablets were dedusted and weighed again. The percentage friability was measured using the formula,

$$\% F = \{1-(Wt/W)\} \times 100$$

Where, % F = Friability in percentage

W = Initial weight of tablet

Wt = Weight of tablets after revolution

The Results are shown in Table No.19

## Weight variation:

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more than two of the individual tablet weight deviate from the average weight by more than the percentage shown in and none deviate by more than twice the percentage shown.

## Drug content:

The assay of the drug content was carried by weighing ten tablets and calculated the average weight. Then the tablets were triturated to get a fine powder. From the resulting weighed accurately about 155 mg of the powder (equivalent to 100 mg) of metformin hcl was taken, shake with 70 ml of water for 15 minutes, dilute to 100 ml with water and filter. Dilute 10 ml of the filterate to 100 ml with water. Further dilute 10 ml to 100 ml with water and measure the absorbance at the maximum at about 233 nm.

**Table No.4**
**Pre-compression parameters of Drug and Excipients**

| Parameters | Angle of repose (°) | Bulk density (gm/cc) | Tapped density (gm/cc) | Compressibility index (%) | Hausner's ratio |
|---|---|---|---|---|---|
| Metformin Hcl | 38.24 | 0.524 | 0.614 | 14.68 | 1.17 |
| HPMC K100 M | 26.72 | 0.298 | 0.477 | 37.17 | 1.58 |
| HPMC K 4 M | 25.25 | 0.304 | 0.481 | 36.45 | 1.57 |
| S S G | 26.42 | 0.468 | 0.670 | 29.88 | 1.42 |
| PVP-K-30 | 23.32 | 0.590 | 0.702 | 15.69 | 1.17 |
| $NaHCO_3$ | 25.17 | 0.334 | 0.423 | 20.80 | 1.25 |
| M C C | 22.14 | 0.512 | 0.691 | 25.41 | 1.33 |

## Buoyancy Determination:

The time taken for dosage form to emerge on surface of madium is called floating lag time, duration of time by which the dosage form constantly emerges on surface of medium is called Total floating time (TFT).One tablet from each formulation batch was placed in USP type II dissolution apparatus containing 900 ml 0.1 N HCl dissolution medium using paddle at a rotational speed of 75 rpm.The temperature of medium was maintained at 37° ± 2°c. The time taken for tablet to emerge on surface of medium and the duration of time by which the tablet constanly remain on surface of medium was noted.

**Table No.5**
**Results of Evaluation of Thickness, Hardness and Friability of Bilayered Floating Formulations.**

| Formulation Code | Thickness in mm ± S.D. | Hardness $Kg/cm^2$ ± S.D. | Friability % ± S.D |
|---|---|---|---|
| **FD/MTH/D+G** | 5.13±0.11 | 6.23±0.05 | 0.322±0.1 |
| **FD/MTH/D+H** | 5.06±0.11 | 6.33±0.15 | 0.771±0.13 |
| **FD/MTH/D+I** | 5.40±0.2 | 6.16±0.05 | 0.833±0.11 |
| **FD/MTH/D+J** | 5.33±0.23 | 6.63±0.05 | 0.642±0.14 |

## Swelling Study:

The individual tablets were weighed accurately and kept in 50ml of water. Tablets were taken out carefully after 60min, blotted with filter paper to remove the water present on the surface and

weighed accurately. Percentage swelling was calculated by using formula;

Swelling study = wet weight – dry weight/ dry weight × 100

The Results are shown in Table No.24

## In-Vitro drug release study:

Dissolution of the tablet of each batch was carried out using USP type II apparatus using paddle. 900 ml of dissolution media was filled in a dissolution vessel and the temperature of the medium were set at 37° ± 2°c. one tablet was placed in each dissolution vessel and the rotational speed of paddle was set at 50 rpm.The 10 ml of sample was withdrawn at predetermined time interval for 12 hours and same volume of fresh medium was replaced. The samples were analyzed for drug content against dissolution media as a blank at 233 nm using double beam UV visible spectrophotometer.

**Table No.6**
**Disintegration time of different immediate release formulations**

| Formulation Code | Disintegration Time (min) |
|---|---|
| **FD/MTH/A** | 3.23 |
| **FD/MTH/B** | 2.53 |
| **FD/MTH/C** | 2.16 |
| **FD/MTH/D** | 1.45 |

**Table No.7**
**Results of Evaluation for Weight Variation of Bilayered floating formulations**

| Formulation Code | % Weight Variation Range |
|---|---|
| **FD/MTH/D+G** | **0.762±0.019** |
| **FD/MTH/D+H** | **0.769±0.019** |
| **FD/MTH/D+I** | **0.770±0.015** |
| **FD/MTH/D+J** | **0.769±0.017** |

**Table No.8**
**Results of Evaluation of Drug content of Bilayered floating formulations**

| Formulation Code | Amount of Metformin HCl (mg) | Drug Content (%) |
|---|---|---|
| **FD/MTH/D+G** | 494.50 | 98.90 |
| **FD/MTH/D+H** | 497.28 | 99.45 |
| **FD/MTH/D+I** | 495.72 | 99.14 |
| **FD/MTH/D+J** | 498.85 | 99.80 |

**Table No.9**
**Evaluation of Floating Lag Time and Total Floating Time**

| Formulation Code | Floating Lag Time (min) | Total Floating Time (hrs) |
|---|---|---|
| FD/MTH/D+G | 4.15 | 7.35 |
| FD/MTH/D+H | 3.40 | 8.10 |
| FD/MTH/D+I | 2.45 | 10.30 |
| FD/MTH/D+J | 1.45 | 12.17 |

**Plot's of Swelling Index:**

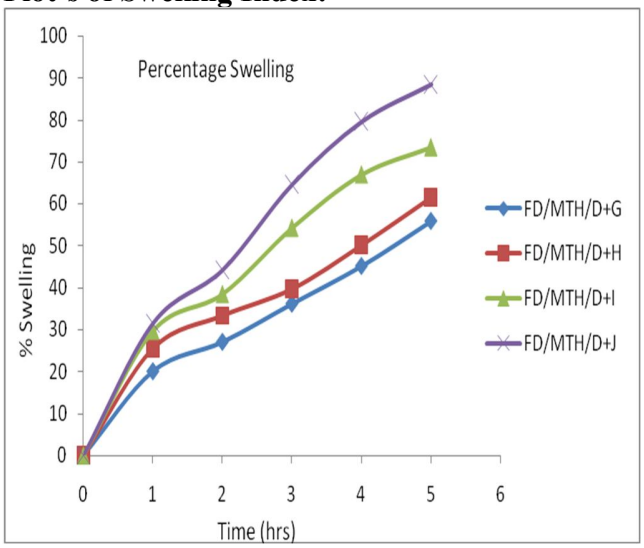


**Fig No.1**

**Table No.10**
**PERCENTAGE SWELLING OF BILAYERED FLOATING FORMULATIONS**

| Time (hrs) | PERCENTAGE SWELLING | | | |
|---|---|---|---|---|
| | FD/MTH/D+G | FD/MTH/D+H | FD/MTH/D+I | FD/MTH/D+J |
| 1 | 20.13 | 25.52 | 29.72 | 31.52 |
| 2 | 27.11 | 33.33 | 38.51 | 44.23 |
| 3 | 36.24 | 39.68 | 54.32 | 64.63 |
| 4 | 45.23 | 50.13 | 67.02 | 79.60 |
| 5 | 55.97 | 61.50 | 73.51 | 88.47 |

## INVITRO DRUG RELEASE PROFILE OF IMMEDIATE RELEASE LAYER

**Table No.11**

| TIME (min) | Cumulative Drug Release (%) | | | |
|---|---|---|---|---|
| | FD/MTH/A | FD/MTH/B | FD/MTH/C | FD/MTH/D |
| 5 | 23.60 | 38.55 | 44.06 | 59.80 |
| 10 | 37.00 | 52.76 | 62.21 | 76.39 |
| 20 | 50.42 | 69.34 | 75.65 | 85.91 |
| 30 | 68.57 | 82.79 | 85.18 | 100.17 |
| 40 | 78.10 | 93.12 | 99.44 | 97.92 |
| 50 | 90.76 | 100.30 | 97.19 | 96.44 |
| 60 | 99.53 | 97.19 | 95.72 | 94.09 |

## INVITRO DRUG RELEASE PLOT'S OF IMMEDIATE RELEASE LAYER

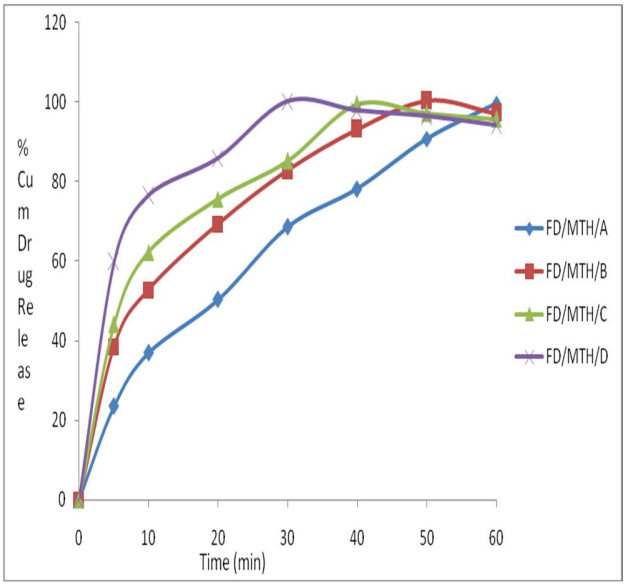


**Figure No.2**

| | | | | | | |
|---|---|---|---|---|---|---|
| 6 | 48.15 | 64.43 | 61.02 | 64.71 | 69.72 | 72.10 |
| 7 | 54.76 | 76.05 | 72.10 | 76.59 | 82.39 | 84.51 |
| 8 | 65.05 | 81.64 | 82.94 | 86.38 | 89.24 | 90.90 |
| 9 | 74.82 | 85.66 | 87.22 | 90.67 | 91.50 | 94.41 |
| 10 | 85.92 | 88.12 | 93.36 | 95.23 | 97.11 | 98.97 |

**Table No.12**
**INVITRO DRUG RELEASE PROFILE OF FLOATING LAYER (SUSTAINED RELEASE LAYER) FORMULATIONS**

| Time (hrs) | Cumulative Drug Release (%) | | | | | |
|---|---|---|---|---|---|---|
| | FD/MTH/E | FD/MTH/F | FD/MTH/G | FD/MTH/H | FD/MTH/I | FD/MTH/J |
| 1 | 12.85 | 16.0 | 7.34 | 8.91 | 9.70 | 10.22 |
| 2 | 20.21 | 21.52 | 23.36 | 25.72 | 30.18 | 35.17 |
| 3 | 27.57 | 29.94 | 28.37 | 33.36 | 37.30 | 41.50 |
| 4 | 36.52 | 40.20 | 36.79 | 44.41 | 48.88 | 52.04 |
| 5 | 40.49 | 52.05 | 49.69 | 52.33 | 57.85 | 62.07 |

## VITRO DRUG RELEASE PLOT'S OF FLOATING LAYER (SUSTAINED RELEASE LAYER) FORMULATIONS

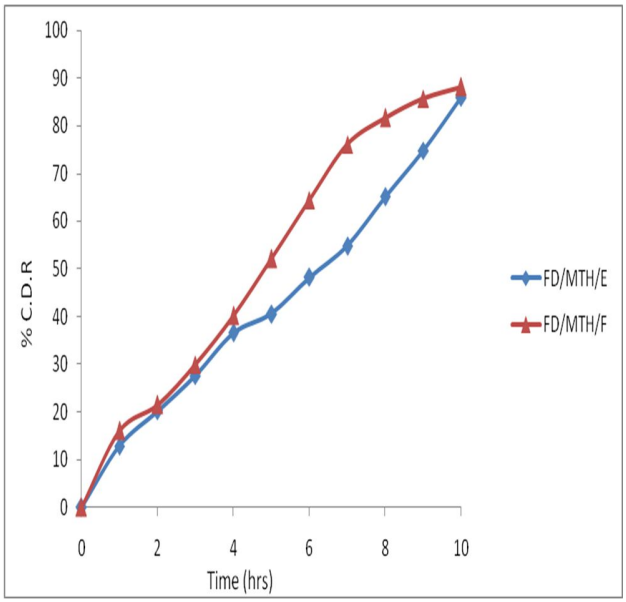


**Fig No.3**

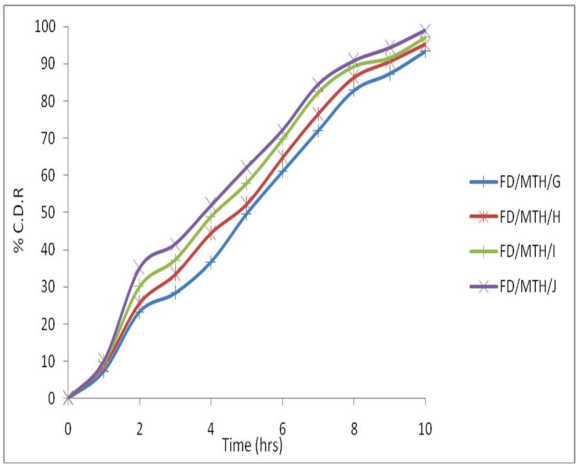


**Fig.No.4**

**Table No.13**
**INVITRO DRUG RELEASE PROFILE OF BILAYERED FLOATING FORMULATIONS**

| Time( hrs) | Cumulative Drug Release (%) | | | |
|---|---|---|---|---|
| | FD/MTH/ D+G | FD/MTH/ D+H | FD/MTH /D+I | FD/MTH /D+J |
| 1 | 31.27 | 32.85 | 34.42 | 36.0 |
| 2 | 36.8 | 39.16 | 41.15 | 42.12 |
| 3 | 45.11 | 46.89 | 48.66 | 49.46 |
| 4 | 49.49 | 53.03 | 54.82 | 55.79 |
| 5 | 58.01 | 59.59 | 60.98 | 62.15 |
| 6 | 67.31 | 69.88 | 71.07 | 72.27 |
| 7 | 74.87 | 76.25 | 78.03 | 79.42 |
| 8 | 83.02 | 84.6 | 85.4 | 86.78 |
| 9 | 88.42 | 90.4 | 92.18 | 94.56 |
| 10 | 94.62 | 95.16 | 97.41 | 98.59 |

**Table No.27**

## INVITRO DRUG RELEASE PROFILE OF BILAYERED FLOATING FORMULATIONS

The immediate release layer was formed by using SSG as a Disintegrant that was widely used due to its effectives in standard concentration range of 2-8%. SSG gives the maximum disintegration at the 8%. In the prepared formulations FD/MTH/D had given less disintegration time as compared to the remaining formulation. In these formulations FD/MTH/D gives the best result as compared to FD/MTH/A, FD/MTH/B, and FD/MTH/C.

Bilayered tablets were formulated as per formulation design, in that sustained layer was considered to have an important effect on the release from the HPMC matrices. Different grades of HPMC (K 100 M and K 4 M) were used as a polymer.

HPMC K 100 M was chosen because it is widely used as low density hydrocolloid system, upon contact with water a hydrogel layer would be formed, it act as a gel boundary for the delivery system. But it would fail to retard the release of drug through the matrix and the tablet integrity problems also. HPMC K 100 M were reported to have a duration of buoyancy of more than 8hrs. in the simulated meal media as well as in the distilled water.

HPMC K 4 M was used in the combination with HPMC K 100 M to slow the drug release at the initial type of drug release (sustained part) and K 4 M rectified integrity problems and retard the release.

To overcome an initial burst effect, the high viscosity HPMC polymer used. HPMC K 4 M gives prolonged floating and drug release as compare to the low viscosity polymers.

Our main focus was on the floatability of the dosage form in the stomach, so the HPMC concentration was increased toward the experimental design.

## INVITRO DRUG RELEASE PLOT'S OF BILAYERED FLOATING FORMULATIONS

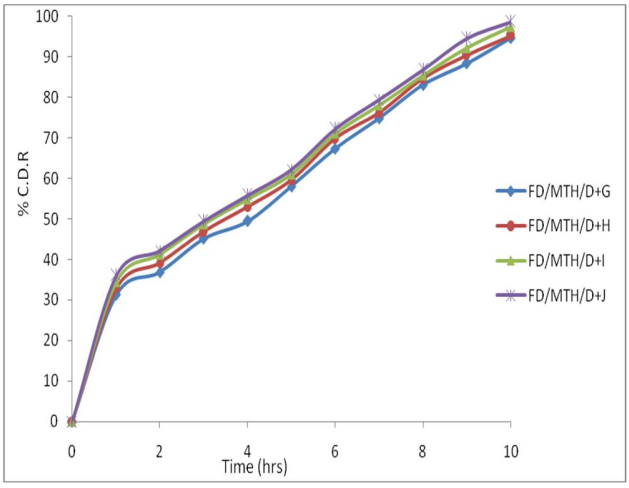


**Fig.No.5**

**7 Comparative Kinetic plots of Bilayer floating formulations:**

**Zero order plot for bi-layer floating formulations**

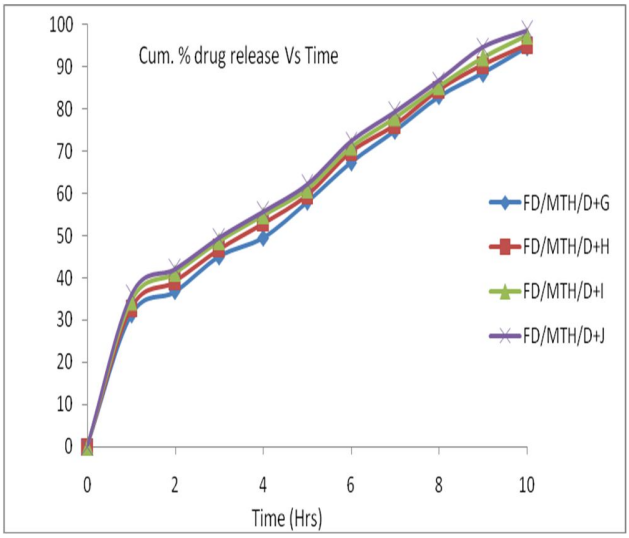


**Fig No.6**

**First order plot for bi-layer floating formulations**

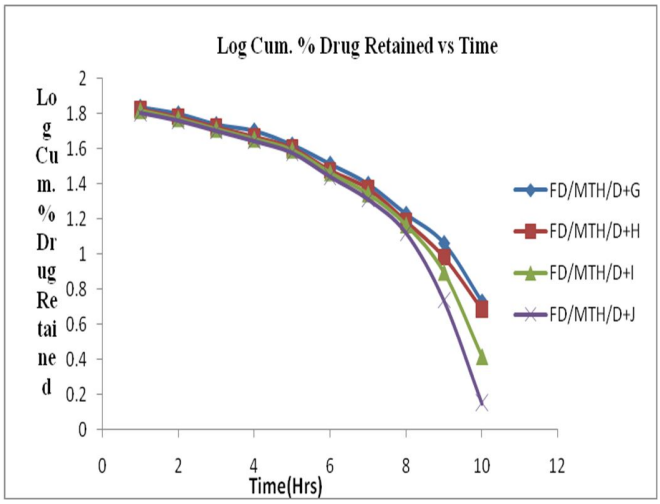


**Fig No.7**

**Higuchi plot for bi-layer floating formulations**

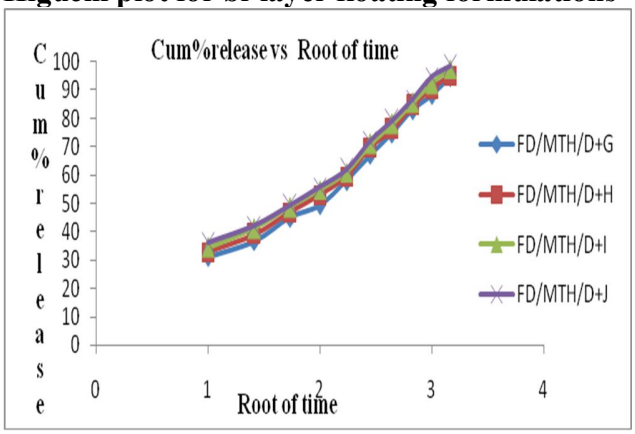


**Fig No.8**

**Peppas plot for bi-layer floating formulations**

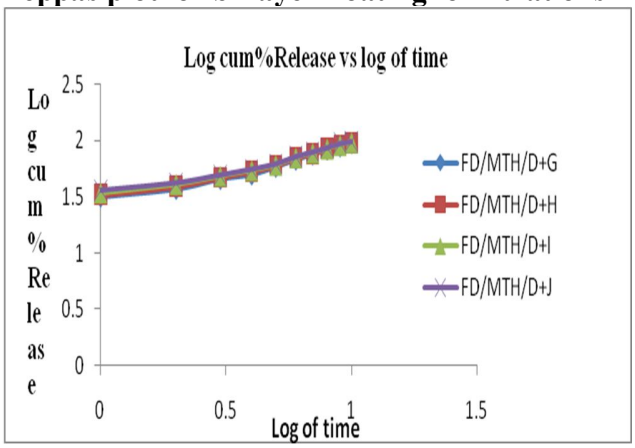


**Fig No.9**

**Hixon-crowell plot for bi-layer floating formulations**

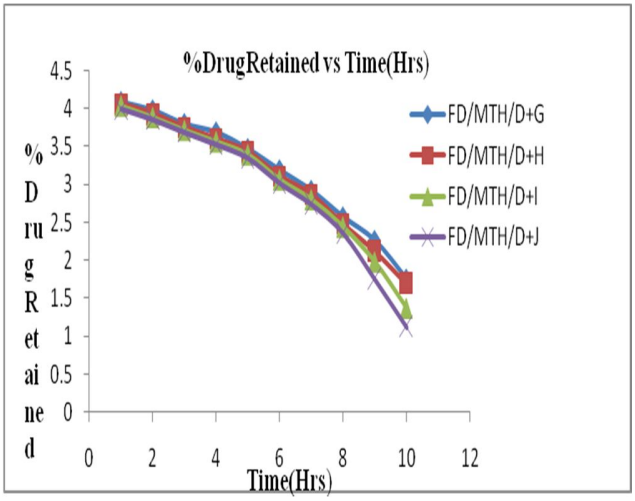


**Fig No.10**

## Stability Studies:

Stability study is mainly carried out for the selected formulation for observe the effect of temperature on the hardness, drug content and drug release of the tablets, the results are shown in Table No.33-34.

**Table No.33**

**Selected formulation stored at 25°C/60% RH**

| Formulation Code | Tested after time (in Days) | Hardness Kg/cm$^2$ | Drug content (%) | % CDR |
|---|---|---|---|---|
| FD/MTH/D+J | 10 | 6.60±0.20 | 100.10 | 97.41 |
| | 20 | 6.53±0.05 | 100.07 | 97.39 |
| | 30 | 6.56±0.05 | 100.02 | 97.0 |

**Table No.14**

**Selected formulation stored at 40°C/75% RH**

| Formulation Code | Tested after time (in Days) | Hardness Kg/cm$^2$ | Drug content (%) | % CDR |
|---|---|---|---|---|
| FD/MTH/D+J | 10 | 6.60±0.1 | 99.97 | 97.47 |
| | 20 | 6.53±0.05 | 99.89 | 97.39 |
| | 30 | 6.46±0.1 | 99.84 | 97.36 |

## SUMMARY AND CONCLUSION

Metformin Hcl is a biguanide antihyperglycemic agent that improves glucose tolerance in patients with type II diabetes. Metformin Hcl is incompletely absorbed from gastrointestinal tract, it has absorption window confined to upper part of gastrointestinal tract. It has half life of 1.7 hours and its absolute bioavailability is reported to be about 45-50% of the administered dose, hence it is a suitable candidate for gastroretentive floating drug delivery system. Therefore an attempt is made to retain the dosage form in stomach for longer period of time. This is achieved by developing gastro retentive drug delivery system i.e., bilayered floating drug delivery system. These bilayered tablets mainly prepared for reduction of lag time and may also increase the bioavailability of the drugs by utilizing the drug to full extent avoiding unnecessary high plasma level. For the formulation of floating tablets HPMC (K 100 M and K 4 M) used as a matrix forming agent. Other excipients used are sodium starch glycolate (disintegrate), sodium bicarbonate (as a gas generating agent), PVP-K-30 (Binder), microcrystalline cellulose (Diluent) and Magnesium stearate as a lubricant. The drug and polymers are subjected to various preformulation studies such as Angle of repose, Bulk density,

Tapped density, Compressibility Index, Hausner ratio.characterization using FTIR spectral analysis, Drug and excipients compatibility studies. The tablets were compressed using multi station rotary bilayer punching machine.

From the above experimental results it can be concluded that,

- Sodium bicarbonate has predominant effect on the buoyancy lag time, while HPMC K 100 M and HPMC K4 M has predominant effect on total floating time and drug release.
- Bilayered floating matrix tablet with immediate release layer give good floating and a controlled release pattern after initial immediate release.
- In-vitro release rate studies showed that the maximum drug release was carried out in the FD/MTH/D+G, FD/MTH/D+H, FD/MTH/D+I, and FD/MTH/D+J in the required period of time. But FD/MTH/D+J showed a minimum lag time and maximum floating time with maximum % drug release (98.59%) and considered as a successful batch.
- When the release data was analyzed as per Zero and First order kinetic models, indicating that the drug release from all the batches followed Zero order kinetics, and the prepared formulations followed Higuchi profile.When the release data was analyzed as per peppas equation, the release exponent n was found in the range of 0.46 to 0.50 indicating non-fickian (anomalous) diffusion controlled as the release mechanism from all the prepared tablets.
- The stability study revealed that there was no significant change in dissolution profile for a period of 1 month of the selected formulation (FD/MTH/D+J) found to be stable over the storage period and conditions tested as per ICH Guidelines.
- From the study it is evident that a promising controlled release by bilayered floating tablets of metformin Hcl can be developed. Further detailed investigations are required to establish efficacy of these formulations.
- Further In-vivo investigations are required to correlate In-vitro release studies.

Further preclinical and clinical study is necessary for use of Metformin Hcl bilayered floating tablets as oral controlled drug delivery system.

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