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Research Article

# FORMULATION AND EVALUATION OF BILAYERED FLOATING TABLETS OF METFORMIN HYDROCHLORIDE

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**ABSTRACT**
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 bioavailbility 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 $NaHCO_3$ 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.

**Key Words :** Metformin Hcl, Bi-layer floating tablets.

## INTRODUCTION

Floating Drug Delivery Systems (FDDS) have a bulk density lower than gastric fluids and thus remain buoyant in the stomach for a prolonged period of time, without affecting the gastric emptying rate. While the system is floating on the gastric contents, the drug is released slowly at a desired rate from the system. After the release of the drug, the residual system is emptied from the stomach. This results in an increase in the GRT and a better control of fluctuations in the plasma drug concentrations. Floating systems can be classified into two distinct categories, non-effervescent and effervescent system.

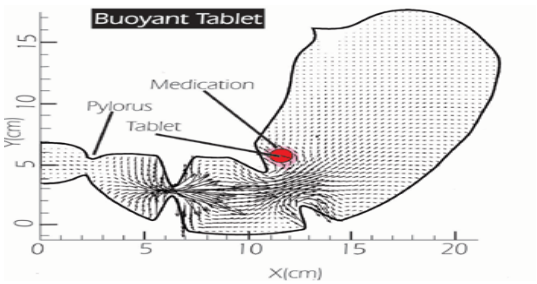


**Fig 1**: **Graphic Of Buoyant Tablet, Which Is Less Dense Than The Stomach Fluid Therefore It Remains In The Fundus.**

### Aim And Objective

The present study undertaken with the following objectives:
To design the controlled release oral bilayer floating tablet to increase the resident time of the drug in the stomach and release for extended period of time in order to:-

- Increase the bioavailability of drug
- Decrease the dosing frequency
- Improve patient compliance.

## MATERIALS AND METHODS

Metformin hydrochloride was procured by Micro Labs (Bangalore, India); HPMC K 100M, HPMC K 4M was gifted by Colorcon Asia pvt LTD(India); Sodium starch glycolate, PVP K 30, Micro-crystaline cellulose was gifted by Nice Chemicals Laboratory (India); Iron Oxide-Red, Sodium bicarbonate, Magnesium stearate was gifted by ABC Laboratory (Chennai, India).

## 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.
The composition is shown in Table 1

### 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 2. The well-mixed powder was compressed using a ELITE multi station punching machine. The hardness is adjusted for the required amount.

### 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.3

**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.

**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 7

**Hardness of Tablets**

Hardness was measured using monsanto hardness tester. For each batch three tablets were tested. The Results are shown in Table No.7

**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 7

**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.

The Results are shown in Table 4.

**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. The Results are shown in Table 10.

**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.

The Results are shown in Table 11.

**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.12.

***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.

**Details of dissolution test**

| | |
|---|---|
| Apparatus | : DA USP XXIII |
| Speed | : 50 rpm |
| Volume of medium | : 900 ml |
| Stirrer | : Paddle type |
| Aliquot taken at each time interval | : 10 ml |
| Medium used | : 0.1 N Hcl (pH 1.2) |
| Temperature | : 37±0.5 |

The Results are shown in Table 13-15.

**RESULTS AND DISCUSSION**

**Evaluation Of Bilayered Floating Tablet**

**Pre-Compression Parameters**

The excipients used in the formulation such as metformin HCl, HPMC, Sodium starch glycolate, Sodium bicarbonate, PVP-K-30,Micro crystalline cellulose were evaluated for Angle of repose, Bulk density, Tapped density, Compressibility index, Hausner ratio as per the procedure described under methodology section (6.5).

The data's are shown in Table 7.

**Post Compression Parameters**

**Thickness Of Tablets**

Thickness of tablets was measured by vernier calipers using the procedure described in methodology section(6.7.1). The diameter of all the formulations were found within the acceptable range i.e. ± 5% of the respective average weight. The results are shown in Table 8.

**Hardness Of Tablets**

The hardness of all the formulations were checked by using Monsanto Hardness tester, by the method described in methodology section(6.7.2). The average hardness of

bilayered tablet formulations in the range of 5-7kg/cm$^2$. The results are shown in Table 8.

**Fraibility Of Tablets**

The friability of all the formulations was checked using roche friabilator according to the method in methodology section(6.7.3). The average friability for all the formulations comes in the range of 0.320-0.650% . The results are shown in the Table 8.

**Weight Variation Test**

Uniformity of weight test for all the formulations were carried out using the procedure described in the methodology section (6.7.4). Results of uniformity of weight are shown in the Table No.10. All the formulations were came under the acceptable limit of ±5%.

**Disintegration Time Test**

In the formulation of bilayered floating tablets, the purpose of immediate release layer is to quick release of drug. Therefore this layer should disintegrate immediately for drug to be readily available for dissolution and absorption. Disintegration time mainly depends upon the concentration of disintegrant, SSG is used as a disintegrant. The disintegration time was found to be 3.23-1.45 min. The disintegration times are shown in the Table No.9. and the rate of disintegration was found to be in the following order.

FD/MTH/D > FD/MTH/C > FD/MTH/B > FD/MTH/A

**Drug Content Uniformity**

The content uniformity of tablets was determined as per the procedure described under methodology section. (6.7.5).All the formulations passes the content uniformity tests as per the BP specifications.

The results are shown in the Table 11.

**Buoyancy Determination**

In this evaluation study, Floating lag time (FLT) and the Total floating time (TFT) of the tablet was determined. The floating time of the tablet was determined as per the procedure mentioned in the methodology section.(6.7.6). The results are shown in the Table 9.

Results of floating properties study reveals that all tablets had good floating properties. This might be due to the presence of gas generating agent i.e., $NaHCO_3$, content. These finding were supported by study of Baumgartner et al. Who reported that incorporation of sodium bicarbonate helps to improve floating properties by reacting with gastric fluid when dosage form comes in contact and produce carbon dioxide gas which entrapped inside the hydrophilic matrices leads to increase in volume of dosage form resulting in lowering of density and dosage form starts to float. From the results of floating lag time it was concluded that as the concentration of gas generating agent increases the floating lag time get shortens. These findings were supported by study of park et al. who reported that as the concentration of gas generating agent ($NaHCO_3$) was increased the floating lag time get shortened and at the same time floating ability get increased. Another aspect of result of these studies clears that the level as well as viscosity of the polymer had a great impact over the floating lag time and total floating time, as the level and viscosity of the polymer was reduced greater when the viscosity of the polymer used was greater, which was supported by Li and Co-workers et al. who reported that higher viscosity grade generally exhibited greater floating capability.

**Swelling Study**

Swelling study was performed on all batches (FD/MTH/D+G to FD/MTH/D+J) for 5 hrs. The results of swelling index were shown in Table No.10 and swelling index against time (hrs) was plotted in Fig.3. From the results it was concluded that swelling increases as the time passes because the polymer gradually absorb water due to hydrophilicity of polymer. The outermost hydrophilic polymer hydrates and swells and a gel barrier are formed at the outer surface. As the gelatinous layer progressively dissolves and/or is dispersed, the hydration swelling release process is continuous towards new exposed surfaces, thus maintaining the integrity of the dosage form. The viscosity of the polymer had major influence on swelling process, matrix integrity, as well as floating capability, hence from the results it can be studied that linear relationship exists between swelling process and viscosity of polymer.

***In-vitro* Drug Release Studies**

*In-vitro* drug release studies were performed as per the procedure described in methodology section. (6.7.8). The percentage cumulative drug release was plotted against time to obtain drug release profiles. The results are shown in respective Table 14-16 and Figure 4. It is clear from the Tables 14-16 and Fig 3-6. That the formulations show biphasic release of metformin HCl. In the first phase the loading dose (immediate release) was released in less than 30 min, because of prompt disintegration of the fast releasing layer and the enhanced rate of dissolution of metformin HCl from the system. This behavior was identified for all formulations (sustained part) after the release of first part (loading drug).Two different batches were formulated individually with HPMC K 4 M and HPMC K 100 M. when these polymers are formulated alone, the release rate was not that much retarded with in the fisrt hour. The release rate was found to be 12.85 and 16.0 % respectively. As we discussed earlier the other batches were formulated with mixture of two polymers. Four different batches were formulated for bilayered tablets of Metformin HCl, the first batches formulated with the polymer to polymer ratio of 1:1(FD/MTH/G). It showed the cumulative % release of 93.36% at 10 hrs. The remaining three batches were formulated with the polymer to polymer ratio's of 1:2 (FD/MTH/H), and 1:3 (FD/MTH/I), and 1:4 (FD/MTH/J) respectively, which showed a cumulative % release of 95.23, 97.11, 98.97 % of Metformin HCl. The release rate was not that much affected in all the formulations i.e., (FD/MTH/D+G, H, J and I). But the increasing concentration of polymer to polymer ratio will increase the drug release to a maximum level. As our main aim was on the floatability the dosage form in stomach, the batch FD/MTH/D+J showed a minimum lag time and maximum floating time with maximum % release, it was considered as a successful batch from our formulations .

**Table 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

**Table 2: Formulation of Floating layer (SR)**

| 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

**Table 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

**Table 4: Weight Variation Tolerances for Uncoated Tablets**

| S. No. | Average weight of Tablets (mg) | Maximum percentage difference allowed |
|---|---|---|
| 1. | 130 or Less | 10 |
| 2. | 130 to 324 | 7.5 |
| 3. | More than 324 | 5.0 |

**Table 5**

| Time (Hours) | Percentage of drug release |
|---|---|
| 1-3 | 10-25 |
| 9 | 45-85 |
| 12 | Not Less Than 75 |

**Table 6 : 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 |

**Table 7 : 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 |

**Table 8 : 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 9 : 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 10 : 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 11: 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 |

**Table 12: 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 |

**Table 13: Invitro Drug Release Profile Of Immediate Release Layer**

| 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 |

**Table 14: 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 |
| 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 15 : 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 16: Regression coefficient values obtained from the plots of bilayer floating formulations (FD/MTH/D+G, H, I and J)**

| Formulation Code | Zero order eqn. | First order eqn. | Higuchi eqn. | Peppas eqn. | Hixon-crowel eqn. | Possible release kinetic models |
|---|---|---|---|---|---|---|
| | Regression Coefficient (r) | Regression Coefficient (r) | Regression Coefficient (r) | Regression Coefficient (r) | Regression Coefficient (r) | |
| **FD/MTH/D+G** | 0.954 | 0.903 | 0.970 | 0.959 | 0.959 | Zero order |
| **FD/MTH/D+H** | 0.944 | 0.909 | 0.976 | 0.966 | 0.963 | Zero order |
| **FD/MTH/D+I** | 0.939 | 0.858 | 0.975 | 0.965 | 0.943 | Zero order |
| **FD/MTH/D+J** | 0.936 | 0.822 | 0.972 | 0.958 | 0.929 | Zero order |

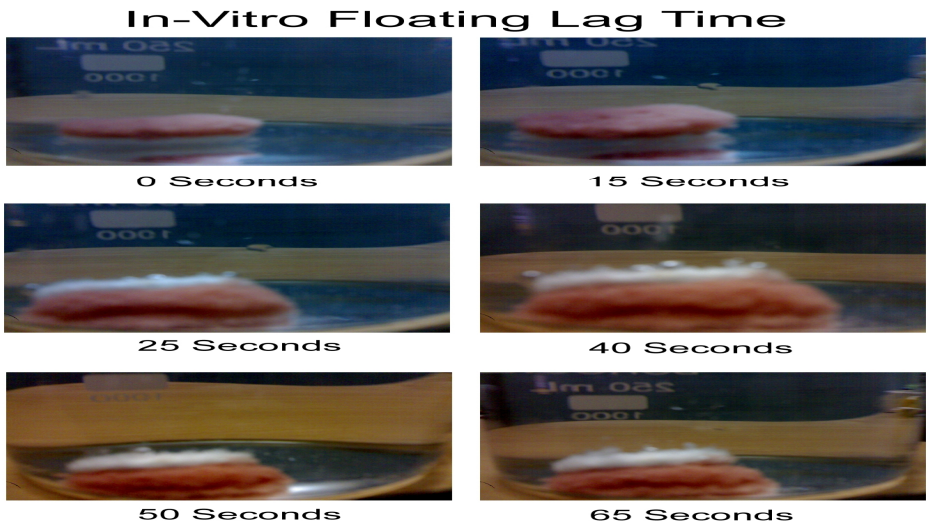


**Fig 2**

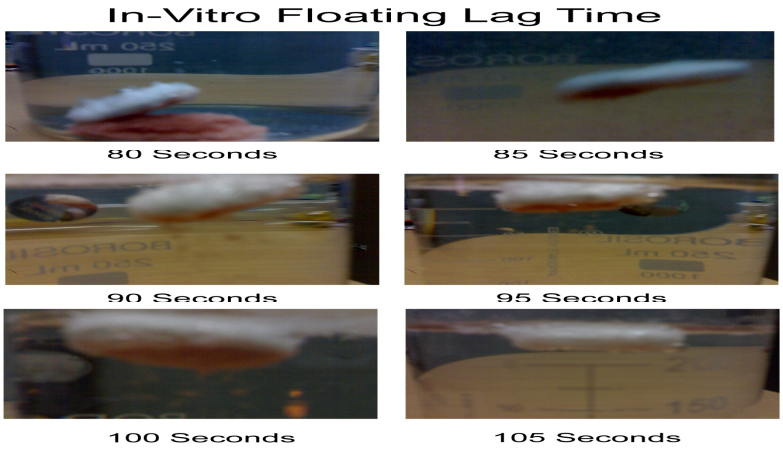


**Fig 3**

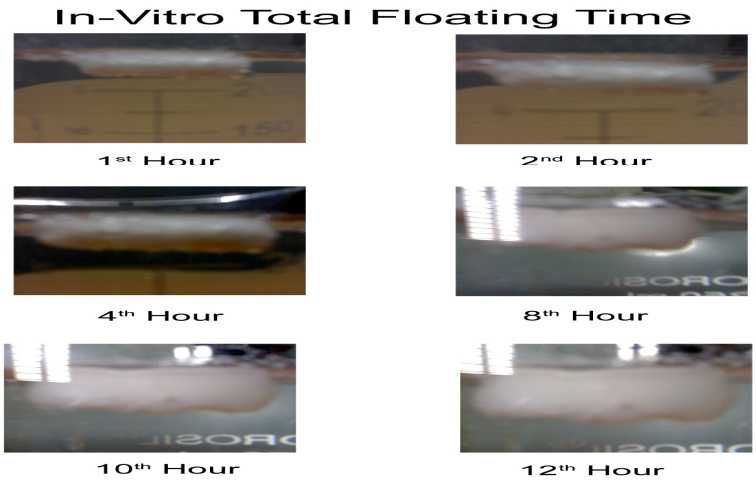


**Fig 4**

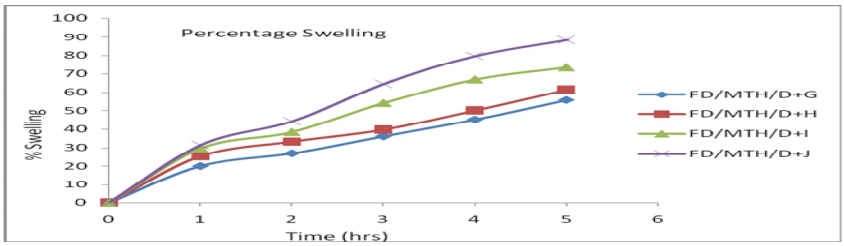


**Fig 5: Plot's of Swelling Index**

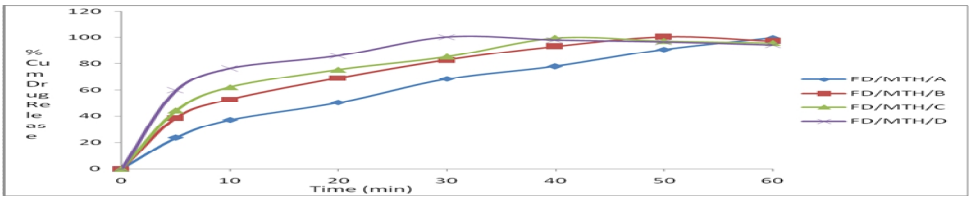


**Figure 6: Invitro Drug Release Plot's Of Immediate Release Layer**

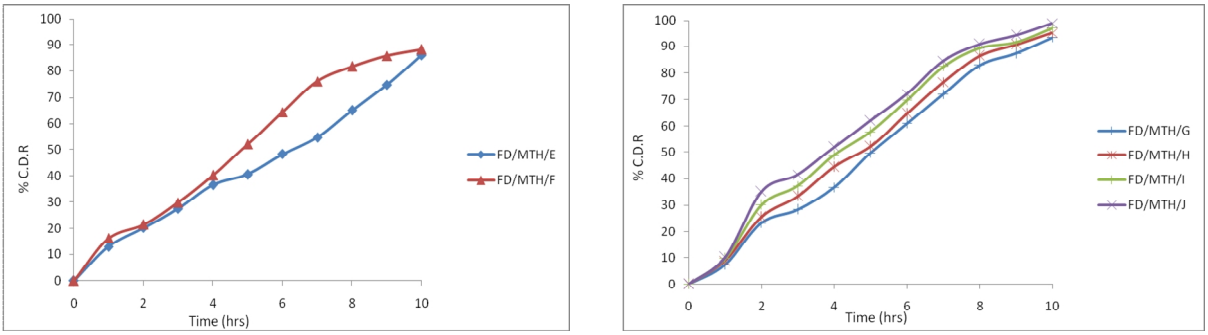


**Fig 7 & 8: Invitro Drug Release Plot's Of Floating Layer (Sustained Release Layer) Formulations**

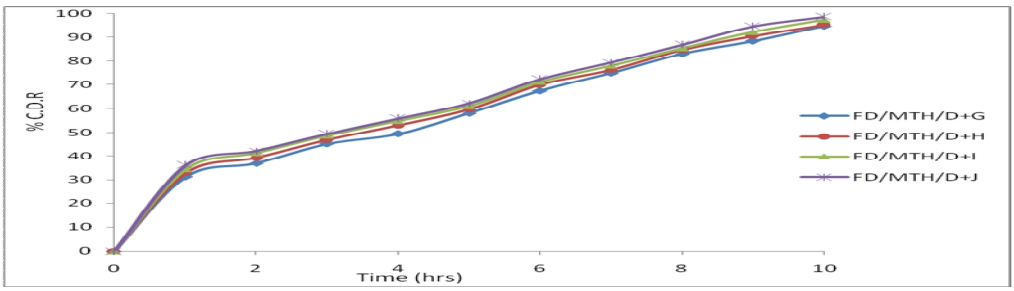


**Fig 9: Invitro Drug Release Plot's Of Bilayered Floating Formulations**

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.

When the release data was analyzed as per Zero and First order kinetic models, the best fit with high correlation ($r>0.936$) was observed with Zero order model 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.

**SUMMARY**

Hence in present investigation, 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. Prepared tablets were subject to various evaluation parameters such as Thickness, Hardness, Weight variation, Friability, Disintegration, Buoyancy study and In-vitro drug release study, Kinetic Parameters, and Accelerated stability studies as per ICH guidelines. From FTIR Spectral analysis, it was concluded that there was no interference in the functional group as the principle peaks of the drug were found to be unaltered in the drug polymer physical mixture. Thus, conclusion can be made that stable floating dosage form can be developed for metformin Hcl for the controlled release by bilayered floating tablets. It was observed that tablet of batch FD/MTH/D+J given maximum drug release and good floatability.

**CONCLUSION**

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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