DESIGN AND DEVELOPMENT OF METFORMIN HYDROCHLORIDE BILAYERED SUSTAINED RELEASE TABLETS

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ABSTRACT
Diabetes is one of the major causes of death and disability in the world. Diabetes results from decreased secretion of insulin, decreased insulin action or both. The main aim of the investigation was to design and development of bilayer floating tablets of metformin hydrochloride and also study the influence of concentrations of HPMCK 100 on various properties of tablet. Bilayer tablets were formulated by wet granulation method. Drug - excipient compatibility studies were conducted by FTIR spectroscopy. The prepared granules and tablets were evaluated. In-vitro release data revealed that F5 formulation sustained the release for 12 hrs, the release data was fitted into zero order, first order, Higuchi and Peppas equations. The drug release from the formulation followed zero kinetics and exhibits Peppas mechanism. Release exponents ‘n’ was found less than 0.85 indicating the release governed by non-fickian anomalous transport mechanism.

Key words: Bilayer floating tablets, Hydroxy propyl methyl cellulose

INTRODUCTION
Diabetes [1] is one of the major causes of death and disability in the world. Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia (fasting plasma glucose \( \geq 7.0 \) mmol / 1 or 2 hours post 75 g oral glucose load plasma glucose \( \geq 11.1 \) mmol / on two or more occasions). Diabetes results from deficient insulin secretion, decreased insulin action, or both. The oral route of drug administration was most convenient method for controlled delivery of drug. It provides the continuous oral delivery of a drug also the system that target the delivery of a drug to a specific region within the GI tract for either local / systemic
action [2,3,4]. One of the most feasible approaches for affecting a prolonged and predictable drug delivery in the GI tract is to control the GRT.

Metformin hydrochloride is an anti-hyperglycemic agent, which improves the glucose tolerance in type 2 diabetes[5,6]. People with type 2 diabetes are not able to make enough insulin or respond normally to the insulin their bodies make. This lead to serious medical problems including kidney damage, amputations, and blindness.

The absolute bioavailability of metformin hydrochloride is 50-60% . biological half life is 1.5 - 3 hrs and the main site of absorption of metformin hydrochloride is proximal small intestine. The HBS system was planned for metformin as such a system when administered it remain buoyant on the gastric fluids for a prolonged period of time. And the drug n it remain buoyant on the gastric fluids for a prolonged period of time and the drug would be available in the dissolved format the main site of it’s absorption i.e proximal small intestine. This would leads to improvement in the bioavailability of the drug. To increase its bioavailability gastro retentive drug delivery systems are choosen[7,8,9]. In this way it stands as an advantage over conventional dosage form, which needs to be administered twice or thrice a day.

**MATERIALS AND METHODS**

Metformin hydrochloride was received from Alkem laboratories ltd, Mumbai as gift sample, HPMC, sodium bicarbonate, talc was procured from S.D fine chem. All other chemicals and solvents used in this study were LR grade

**Preparation of Bilayer Metformin Hydrochloride floating tablets.**

The preparation of Bilayer floating tablets of metformin hydrochloride involves two steps prepared by wet granulation method as shown in the table no1, in the first step floating layer granules were formulated and also sustained release layer granules were formulated in the second step. Required quantity of granules for the floating layer were compressed slightly by sixteen station rotary tablet machine with 16mm diameter flat faced punches and then required granules for sustained release layer was placed over the slightly compressed floating layer and then compressed into a bi layer tablet.
TABLE NO : 1 COMPOSITION OF METFORMIN HYDROCHLORIDE BILAYER FLOATING TABLETS WITH HPMC K100M.

<table>
<thead>
<tr>
<th>Ingredients (mg/ tablet)</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sustained layer</td>
<td>Floating layer</td>
<td>Sustained layer</td>
<td>Floating layer</td>
<td>Sustained layer</td>
</tr>
<tr>
<td>Metformin hydrochloride</td>
<td>500</td>
<td>-</td>
<td>500</td>
<td>-</td>
<td>500</td>
</tr>
<tr>
<td>HPMC K 100 M</td>
<td>60</td>
<td>80</td>
<td>80</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>-</td>
<td>90</td>
<td>-</td>
<td>90</td>
<td>-</td>
</tr>
<tr>
<td>Lactose</td>
<td>80</td>
<td>-</td>
<td>60</td>
<td>-</td>
<td>40</td>
</tr>
<tr>
<td>Talc</td>
<td>7.5</td>
<td>-</td>
<td>7.5</td>
<td>-</td>
<td>7.5</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>7.5</td>
<td>-</td>
<td>7.5</td>
<td>-</td>
<td>7.5</td>
</tr>
<tr>
<td>Total weight</td>
<td>825</td>
<td>825</td>
<td>825</td>
<td>825</td>
<td>825</td>
</tr>
</tbody>
</table>
CHARACTERIZATION OF GRANULES

The prepared granules were evaluated for the following parameters[10,11].

1. Bulk density
The bulk density was determined by measuring the volume occupied by the pre weighed granules. It was calculated by the following equation.

\[ \text{Bulk density} = \frac{\text{Mass of Granules}}{\text{Volume of packing}} \]

2. Tapped bulk density
The granules whose weight was determined earlier were transferred to 100ml graduated cylinder, and subjected to 100 taps. Then the volume occupied by the granules (Tapped volume) was determined. Tapped density was calculated by the following formula

\[ \text{Tapped density} = \frac{\text{Mass of granules}}{\text{tapped volume}} \]

3. Carr's index
The percentage of compressibility of granules was determined by Carr's/Compressibility index.

\[ \text{Carr's index} (%) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{tapped density}} \times 100 \]

4. Hausner’s ratio
Hausner's ratio of granules determined by comparing the tapped density to the bulk density by using the formulae

\[ \text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{bulk density}} \]

5. Angle of repose:
The prepared granules were assessed for its flow property by determining the angle of repose by open tube method. The angle of repose was d by formulae.

\[ \theta = \tan^{-1}\left(\frac{h}{r}\right) \]

\[ h = \text{height of heap} \]
\[ r = \text{radius of the base} \]

6. Loss on drying
Granules (1 gm) were kept in an oven at 105°C and dried up to constant weight. Loss on drying was calculated using the following formulae.

\[ \text{Loss on drying} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{initial weight}} \times 100 \]
7. **Moisture content**

Granules (1gm) were kept in an oven at 105° c and dried up to constant weight. Moisture content was calculated using the following formulae.

\[
\text{Moisture content} = \frac{(\text{Initial weight} - \text{Final weight})}{\text{final weight}} \times 100
\]

**EVALUATION OF PHYSICAL PROPERITIES OF TABLETS**

The formulated tablets were evaluated for the following parameters.

1. **THICKNESS**

The thickness and diameter of the formulated tablets were measured by using Vernier calipers.

2. **WEIGHT VARIATION**

The formulated tablets were tested for weight uniformity. 20 tablets were collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it is within permissible limits or not.

\[
\% \text{ Weight Variation} = \frac{(\text{Average weight}-\text{Individual weight})}{\text{average weight}} \times 100
\]

3. **HARDNESS**

The tablet crushing strength, which is the force required to break the tablet by compression in the diametric direction was measured in triplicate using Pfizer tablet hardness tester.

4. **FRIABILITY**

The Roche friability test apparatus was used to determine the friability of the tablets. 20 pre weighed tablets were placed in the apparatus, which was subjected to 100 revolutions. Then the tablets were reweighed. The percentage friability calculated was using the formula.

\[
\% \text{ Friability} = \frac{\text{Initial weight} - \text{Final weight}}{\text{initial weight}} \times 100
\]

5. **FLOATING CHARACTERISTICS** [12,13]

Floating characteristics were determined using USP dissolution XI apparatus at 100 rpm using 900 ml of 0.1 N HCl and temperature was maintained at 37°C.

**Floating lag time**

The tablet was placed in dissolution apparatus and the time taken to float on the dissolution medium was noted.
Floating time
The total duration of the time that the tablets float on dissolution medium was noted.

6. SWELLING INDEX [14]
Tablet was weighed (W_0) and placed in dissolution medium containing 0.1N HCl maintained at 37°C. At predetermined time intervals the tablet was and blotted to remove excess water and weighed (W_t). The percentage of swelling index calculated.
Swelling index = (W_t - W_0)/W_t x 100
W_t = final weight of the tablet
W_0 = initial weight of the tablet

7. DRUG CONTENT
Twenty tablets were weighed and powdered. The quantity of powder equivalent to 100 mg of Metformin hydrochloride was dissolved in 0.1 N HCl diluted to 100ml with 0.1N HCl then the solution was filtered and suitably diluted. The drug content was estimated spectrometrically at 233 nm.

8. IN VITRO DISSOLUTION STUDIES
Dissolution rate was studied using USP II paddle dissolution apparatus, in 900ml of 0.1N Hydrochloric acid at 37±0.5°C at 100 rpm. Aliquot of dissolution medium was withdrawn at regular time intervals and the same volume of pre-warmed (37±0.5°C) fresh dissolution medium was replaced. The samples were filtered and drug content of Metformin hydrochloride in each sample was analyzed after suitable Dilution by Shimadzu UV-spectrophotometer at 233 nm.

RESULTS AND DISCUSSION
Drug- excipient compatibility studies were conducted by FTIR spectroscopy, results revealed that no chemical interaction was observed from the FTIR as shown in fig 2, 3 and 4.

The prepared granules for floating layer and sustained release layer were evaluated found to have free flow properties, resuls given in table 2 and also the tablets were subjected to thickness, weight variation, hardness, floating time, floating log time, swelling index, drug content and in-vitro dissolution studies. The thickness of the tablets was found in the range of 3.2± 0.01mm to 3.9±0.05mm. The weight variation ranged between 4.27± 0.02 to 4.62±0.02, the hardness of the floating tablets were ranged between 6.1kg/cm² to 7.3kgcm². The percent
The friability of prepared tablets was as within the acceptable limit. The range between the formulations had desired floating log time $3.0 \pm 0.01$ to $4.0 \pm 0.04$mg and total floating time found between 7-9hrs regardless of concentrations of polymers incorporated, results given in the table 3.

The swelling index result was observed in a range between $29.27 \pm 0.02$ to $47.62 \pm 0.03$, that increase in percent swelling was increasing with increasing concentration of polymers. The drug content in all formulations was within the range of $499.2$mg $\pm 0.01$ to $499.5$mg $\pm 0.03$, ensuring the uniformity of the drug content in the formulation. The percentage of drug release for F1, F2, F3, F4, F5 were found to be $90.54 \pm 0.83$, $42 \pm 0.83$, $96.42 \pm 0.83$, $98.04 \pm 0.5$, $96.23 \pm 0.85$, $92.87 \pm 0.64$ and $90.61 \pm 0.32$ at the end of 7, 8, 8.5 and 9hrs respectively, in vitro release profiles as shown in fig 1. In vitro release data fitted into the zero order, first order, matrix and peppas equations. The formulations followed zero order kinetics and exhibited peppas transport mechanism, release exponent found less than 1, indicates non fickian diffusion mechanism. Results revealed that as concentration of polymer increases, the floating time was found to be increased and prolonged the release of the drug due to the swelling of HPMC and high uptake of medium and floating time influenced by the gas generating agent, it influences the drug release. Among all prepared formulation F5 sustained the release for prolonged time, hence it was suitable for the sustained release for the patient in the treatment of diabetis and enhance the bioavilabilty of the drug in the form of floating delivery system.

**TABLE NO 2: CHARACTERIZATION OF METFORMIN HYDROCHLORIDE BILAYER FLOATING GRANULES FORMULATED WITH HPMC K100 M**

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Bulk density(g/ml)</th>
<th>Tapped density(g/ml)</th>
<th>Carr’s index(%)</th>
<th>Hausner’s ratio</th>
<th>Angle of repose(°)</th>
<th>Loss on drying(%)</th>
<th>Moisture content(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>$0.337\pm0.05$</td>
<td>$0.362\pm0.01$</td>
<td>$6.90\pm0.02$</td>
<td>$1.074\pm0.04$</td>
<td>$22.61\pm0.05$</td>
<td>$7.9\pm0.01$</td>
<td>$8.5\pm0.01$</td>
</tr>
<tr>
<td>F2</td>
<td>$0.342\pm0.02$</td>
<td>$0.368\pm0.03$</td>
<td>$7.01\pm0.04$</td>
<td>$1.076\pm0.03$</td>
<td>$23.82\pm0.04$</td>
<td>$7.8\pm0.02$</td>
<td>$7.4\pm0.03$</td>
</tr>
<tr>
<td>F3</td>
<td>$0.349\pm0.02$</td>
<td>$0.377\pm0.03$</td>
<td>$7.4\pm0.03$</td>
<td>$1.080\pm0.01$</td>
<td>$23.91\pm0.03$</td>
<td>$7.4\pm0.03$</td>
<td>$6.7\pm0.02$</td>
</tr>
<tr>
<td>F4</td>
<td>$0.354\pm0.03$</td>
<td>$0.389\pm0.04$</td>
<td>$8.93\pm0.04$</td>
<td>$1.098\pm0.02$</td>
<td>$24.03\pm0.02$</td>
<td>$6.3\pm0.05$</td>
<td>$6.0\pm0.04$</td>
</tr>
<tr>
<td>F5</td>
<td>$0.361\pm0.04$</td>
<td>$0.397\pm0.02$</td>
<td>$9.21\pm0.03$</td>
<td>$1.099\pm0.02$</td>
<td>$24.17\pm0.03$</td>
<td>$5.9\pm0.01$</td>
<td>$5.8\pm0.01$</td>
</tr>
</tbody>
</table>
TABLE NO : 3 CHARACTERIZATION OF METFORMIN HYDROCHLORIDE
BILAYER FLOATING TABLETS FORMULATED WITH HPMC K 100 M

<table>
<thead>
<tr>
<th>Formulaition</th>
<th>Thickness (mm)</th>
<th>Weight variation (%)</th>
<th>Hardness (kg/cm²)</th>
<th>Friability (%)</th>
<th>Floating lag time (min)</th>
<th>Floting time (hr)</th>
<th>Swelling index (% I)</th>
<th>Drug content (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F1</td>
<td>3.2±0.01</td>
<td>4.62±0.01</td>
<td>6.1±0.04</td>
<td>0.98±0.01</td>
<td>4±0.04</td>
<td>7</td>
<td>29.27±0.02</td>
<td>499.2±0.01</td>
</tr>
<tr>
<td>F2</td>
<td>3±0.02</td>
<td>4.53±0.04</td>
<td>6.4±0.03</td>
<td>0.97±0.02</td>
<td>4±0.02</td>
<td>8</td>
<td>31.01±0.03</td>
<td>499.3±0.03</td>
</tr>
<tr>
<td>F3</td>
<td>3.6±0.04</td>
<td>4.47±0.03</td>
<td>6.8±0.01</td>
<td>0.97±0.03</td>
<td>4±0.03</td>
<td>9</td>
<td>37.92±0.01</td>
<td>499.4±0.04</td>
</tr>
<tr>
<td>F4</td>
<td>3.8±0.03</td>
<td>4.31±0.02</td>
<td>7.1±0.02</td>
<td>0.96±0.02</td>
<td>3±0.02</td>
<td>9</td>
<td>42.01±0.02</td>
<td>499.4±0.05</td>
</tr>
<tr>
<td>F5</td>
<td>3.9±0.05</td>
<td>4.27±0.02</td>
<td>7.3±0.03</td>
<td>0.94±0.04</td>
<td>3±0.03</td>
<td>9</td>
<td>47.62±0.03</td>
<td>499.5±0.03</td>
</tr>
</tbody>
</table>

FIGURE: 1 DISSOLUTION DATA OF METFORMIN HYDROCHLORIDE
BILAYER FLOATING TABLETS FORMULATED WITH VARIOUS
CONCENTRATIONS OF HPMC K100M

FIGURE: 2 IR spectrum of Metformin hydrochloride
CONCLUSION

The objective of present study was design and development of bilayered floating tablet of metformin hydrochloride for sustained release. The HPMCK 100M as a polymer more reliable and sustained the drug for a prolonged period of time by increasing the concentration of it. Moreover the high swelling property of the polymer helped in maintaining the buoyancy with the minimal utilization of gas evolving excipients such as sodium bicarbonate which if increased a marked impact on the gastro intestinal fluids by its alkaline nature. The formulation followed zero order kinetics and exhibits peppas transport mechanism.
REFERENCES


2. Drs jse gutierrez-Rocca, Hoscinomidium, khalidshah., progresses in gastro retentive drug delivery systems


