GASTRO-RETENTIVE FORMULATION OF METOCLOPRAMIDE: DESIGN AND OPTIMIZATION USING D-OPTIMAL DESIGN TECHNIQUE

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ABSTRACT:
The purpose of this research was to fabricate and optimize Gastro-retentive drug delivery system for Metoclopramide Hydrochloride. The effect of ethyl cellulose and sodium alginate on the drug release profile and floating properties was evaluated. Sodium carbonate was incorporated as gas generating agent. The addition of ethyl cellulose reduces the drug dissolution rate due to its hydrophobic nature. A D-Optimal Technique was applied systematically to optimize the drug release profile. The amounts of ethyl cellulose ($X_1$) and sodium alginate ($X_2$) were selected as independent variables. The cumulative percent of drug released at 8, 12 and 16 hours were selected as dependent variables. The study shows that, tablet composition and mechanical strength have great influence on floating properties and drug release. All formulations were evaluated for dimensional analysis, duration of buoyancy, floating lag time, drug content and in-vitro drug release. Optimized formulation’s data was subjected to various release kinetic models. The drug release was sufficiently sustained for 24 hours. Model equations of zero and first order, Higuchi, Hixson-Crowell and Peppas, intended to elucidate the drug release mechanism, were fitted to the release data. The zero order release was observed with $r^2$ values of 0.98. The difference in the release pattern and kinetics can be explained by the different swelling and erosion behaviors.

Keywords: Gastro-retentive, D-Optimal, Metoclopramide, Release Kinetics, zero order

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Running title: Gastro-retentive formulation optimization using D-optimal technique. Wamorkar et al

Abbreviations: MCP: Metoclopramide hydrochloride; RH: Relative humidity; rpm: rotations per minute; HPMC: Hydroxypropyl methyl cellulose;

INTRODUCTION
Effective oral drug delivery depends on several factors such as gastric emptying process, gastro-intestinal transit time of dosage form, drug release from the dosage form and site of

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absorption of drug. Most of the oral dosage forms possess physiological limitations such as, variable transit time, variable gastric emptying leading to non-uniform absorption profile, incomplete drug release and shorter residence time of dosage forms in stomach. Hence beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time can deliver the drugs in higher concentrations to the absorption site 1-3.

The Hydro-dynamically Balanced System (HBS) also known as Floating Drug Delivery Systems is an oral dosage form (capsule or tablet) designed to prolong the residence time of dosage form in gastro intestinal tract 3. Floating formulations are based on either low density or gas generation approach. In low density approach, the formulation floats on the surface of gastric fluid due to lesser density than that of gastric fluid (d<1). In gas generating approach, effervescent agents (NaHCO₃ alone) or combination of gas forming agents (NaHCO₃ and citric acid) can be used 4. The gas generated by these agents was trapped in polymeric matrix causing floatation of the formulations 5.

Metoclopramide hydrochloride (MCP) is one of the various drugs which are considered as first line treatment for emesis in various conditions like chemotherapy induced nausea and vomiting. MCP (4-amino-5-chloro-N-(2-diethylaminoethyl)-2-methoxy benzamide hydrochloride) is highly water soluble and is rapidly absorbed after oral administration. The maximum plasma concentration is reached in about 1-2 h. It has short biological half-life (5-6 h) and is usually administered in a dose of 10-20 mg four times daily in order to maintain effective concentration throughout the day 6-8. In long term therapy, drugs with rapid absorption elimination have higher tendency to result into fluctuation of drug concentration in plasma, resulting into adverse reactions in many subjects such as nervousness, confusion, dystonic reactions. Such characteristics which are also associated with MCP make it suitable candidate for controlled release delivery. Attempts have been made in past to formulate controlled release formulation of MCP by using various sustained or controlled strategies 9-10.

In present work, a controlled released formulation of MCP has been developed in the form of monolithic tablet using various hydrophilic and hydrophobic polymers. To formulate tablet formulations computer assisted optimization technique was used.

MATERIALS AND METHODS

MCP, hydroxypropyl methyl cellulose and carbopol were received as gift sample from Ajanta Pharmaceuticals Limited, Mumbai (India). Other ingredients used were ethyl cellulose (S.D. Fine-Chem Ltd. Mumbai), sodium bi-carbonate (Rankem Ltd. Mumbai), dibasic calcium phosphate (Nice Laboratory Ltd, Hyderabad), polyvinyl pyrrolidone K-30 (SISCO Research Laboratories Pvt. Ltd. Mumbai), sodium alginate (LOBA Chemie Pvt. Ltd. Mumbai), talc, methyl cellulose, carboxy methyl cellulose, and magnesium stearate (Qualikem Fine Chemicals Pvt. Ltd. New Delhi).

Instrumentation

Double beam UV-Visible Spectrophotometer (Elico, India) was used with two matched cuvetts for all spectral analysis. Tablets were compressed using eight-station semi-automated tablet punching machine (Camach, India). Six stations semi-automated USP Dissolution Test Apparatus (ELECTROLABS, India) was used for all dissolution studies.
Experimental design

For designing of formulation as per D-Optimal Design\textsuperscript{11-12}, two independent variables (concentrations of ethyl cellulose and sodium alginate) were selected at three different levels. The experimental design was generated using state-of-art computerized optimization software Design Expert Version 8.0\textsuperscript{13}. Total nine formulations were generated at three different levels of selected polymers (Table 1 and 2). These non-classical experimental designs are based on D-optimal criterion and on the principle of minimization of variance and co-variance of parameters. Initially, formulations were generated by trial and error method to obtain desired floating properties. During these studies amount of sodium bi-carbonate along with other matrix forming polymers were optimized.

Preparation of model formulation

Model formulation was prepared having fixed concentration of ethyl cellulose and sodium alginate and containing other excipients like fillers, matrix and gas forming agents, binders, lubricants and anti-adherents. The total weight of tablet was maintained at 265 mg. The range of each process variable was predetermined using preliminary experiments. The drug and excipients were weighed accurately and passed through sieve no #40, in order to break lumps if present. All ingredients except magnesium stearate and talc were mixed in double cone blender for 10-12 min. To this blend magnesium stearate and talc were added and further blended for 5 min in same blender. Tablets were compressed using Cadmach R&D Model compression machine in 10 mm flat beveled punch. Machine was operated at 10-15 RPM and forces were adjusted to target the hardness of 4-6 kg/cm\textsuperscript{2}.

<table>
<thead>
<tr>
<th>Table 1: Software generated composition of independent variable</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Block</strong></td>
</tr>
<tr>
<td>Ethyl Cellulose</td>
</tr>
<tr>
<td>Sodium Alginate</td>
</tr>
<tr>
<td><strong>Block</strong></td>
</tr>
<tr>
<td>Ethyl Cellulose</td>
</tr>
<tr>
<td>Sodium Alginate</td>
</tr>
<tr>
<td><strong>Block</strong></td>
</tr>
<tr>
<td>Ethyl Cellulose</td>
</tr>
</tbody>
</table>
### Table 2: Composition of floating tablet from FT-1 to FT-9

<table>
<thead>
<tr>
<th>Sl No</th>
<th>INGREDIENTS (in mg)</th>
<th>FT-1</th>
<th>FT-2</th>
<th>FT-3</th>
<th>FT-4</th>
<th>FT-5</th>
<th>FT-6</th>
<th>FT-7</th>
<th>FT-8</th>
<th>FT-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Metoclopramide hydrochloride</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>Di-calcium phosphate</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>Ethyl cellulose</td>
<td>31.5</td>
<td>34.5</td>
<td>31.5</td>
<td>34.5</td>
<td>33</td>
<td>34.5</td>
<td>33</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>Sodium alginate</td>
<td>63</td>
<td>69</td>
<td>69</td>
<td>63</td>
<td>69</td>
<td>66</td>
<td>66</td>
<td>63</td>
<td>66</td>
</tr>
<tr>
<td>5</td>
<td>HPMC K-4-M</td>
<td>55.5</td>
<td>46.5</td>
<td>49.5</td>
<td>52.5</td>
<td>48</td>
<td>52.5</td>
<td>49.5</td>
<td>54</td>
<td>51</td>
</tr>
<tr>
<td>6</td>
<td>Sodium bicarbonate</td>
<td>60</td>
<td>60</td>
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<td>60</td>
<td>60</td>
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<td>60</td>
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<tr>
<td>7</td>
<td>PVPK-30</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>Magnesium stearate</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>Talc</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td><strong>265</strong></td>
<td><strong>265</strong></td>
<td><strong>265</strong></td>
<td><strong>265</strong></td>
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<td><strong>265</strong></td>
<td><strong>265</strong></td>
<td><strong>265</strong></td>
<td><strong>265</strong></td>
</tr>
</tbody>
</table>

**Evaluation of tablets**

**Dimension studies**

20 tablets were selected randomly. Using calibrated vernier caliper these tablets were examined for thickness and diameter. Along with that tablets were also examined for presence of any flaws like sticking, picking, colored and rough surfaces in order to remove defective formulation, if any.

**Weight variation test**
20 tablets were selected randomly. From these tablets, each tablet was weighed individually. After completion of this, all tablets were weighed collectively to obtain average weight.

**Hardness test**

Hardness is the crushing strength, which determines the ease and ability of handling and rigors of formulation. For each formulation, a set of six tablets were selected randomly. *Monsanto* hardness tester was used for determining hardness of tablets and is determined in terms of kg/cm².

**Friability test**

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap, crack or break. *Roche* friability tester (Digital, Double Drum, and Automated) was used for this purpose. The instrument subjects tablets to the combined effect of abrasion and shock by utilizing plastic chambers that revolves at 25 rotations per minutes (rpm), dropping the tablets at distance of 6 inches in each revolution, for 100 revolutions. For each set of tablet formulation, pre-weighed sample of 20 tablets were placed in friability test apparatus and 100 revolutions were set in machine with speed of 25 rpm. After completion of experiment, tablets were removed from plastic chambers, de-dusted and re-weighed.

**Floating lag-time**

This test was performed in order to accesses time required for formulation to become buoyant after administration. *In-vitro*, this test was performed by using dissolution medium. Selected tablets were added in medium and time required to reach formulation to dissolution medium surface was noted using calibrated stop-clock.

**Floating behavior/ time studies**

To study the nature and behavior of formulation, floating behavior/ time studies were performed. During this test, formulations were selected randomly and placed in dissolution medium. Formulations were observed for changes in nature and time it stay buoyant.

**In-vitro dissolution studies**

*In-vitro* dissolution studies were carried out in United State Pharmacopoeia dissolution Type II test apparatus (Paddle). 900 ml of dissolution was placed in each six bowls and temperature was set at 37 ± 0.5°C. After desired temperature was achieved, paddles were lowered, tablet was dropped in individual bowl and experiment was started at 100 rpm. At predetermined sampling interval of 30 min, 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, and 20 hrs, 2 ml of aliquot was withdrawn. Same amount of fresh dissolution medium was replaced which is pre-heated at 37 ± 0.5°C.

**Swelling index studies**

The swelling index of all formulated tablets was determined in 0.1 N HCl at room temperature. The swollen weight of the tablet was determined at the end of specified (Dissolution test) time interval. The swelling index was calculated by following equation as:

\[ \text{Swelling Index (SI)} = \frac{W_1 - W_0}{W_0} \times 100 \quad \text{Eq. No: 1} \]
Where, \( W_1 \) = Weight of tablet at specified time \( t \)
\( W_0 \) = Initial weight of tablet.

**Release Kinetics (Model Fitting) Studies**

In order to study release mechanisms of MCP from designed formulations of floating tablets different model fitting studies were carried out. The results of dissolution studies were examined in accordance to different kinetic models like zero-order and first-order release kinetics, Higuchi Release mechanism, Korsmeyer-Pappas Release mechanism. The regression coefficient \( R^2 \) value near to 1 indicates the model fitting of the release mechanism\(^{18}\).

**Assay**

20 tablets were selected randomly and powdered using mortar and pestle. The powder collected so was mixed thoroughly and powder equivalent to label claim was weighed accurately. This weighed mass was dissolved in 0.1 N HCl with continuous shaking on mechanical shaker, followed by sonication for 30 min. From this sample, contents were filtered and further dilutions were made followed by in UV-Visible Spectrophotometer (ELICO, Hyderabad) scanning individually at 272 nm against reagent blank. (The drug content should be within 95 to 105% of labeled claim of formulation.)

**Accelerated Stability Studies**

Developed formulations were wrapped in aluminum foils individually and placed in stability chamber. Conditions were set at 40°C and 75% relative humidity (RH) as per ICH guidelines. Stability studies were carried out for 6 months. Samples were withdrawn at intervals of 1, 2, 3, 6 months and analyzed for *in-vitro* dissolution and floating behavior studies\(^{19}\).

**RESULTS AND DISCUSSION**

**Pre-compression parameters**

a. Angle of repose: The angle of repose for all formulation blends (FT-1 to FT-9) was carried out. It concludes that all formulation blends were found to be in the range of 23° to 25°.

b. Compressibility index: The compressibility index studies was carried out and found to be 11 to 17% indicating powder blend has good flow properties for compression.

**Post-compression parameters**

On compression, all batches of tablet were found to be having thickness in the range of 2.5 to 2.67 mm (SD ± 0.18) indicating smooth compression. Weight variation test was performed on all the batches and average weight of tablets found to be in acceptable range (265 ± 1.47 mg). Hardness and friability of all batches were found to be 5.5 ± 0.1 and 0.46 ± 0.21 respectively. The drug content of MCP was obtained in the range of 98 to 100 (SD ± 1.21). All relevant data are presented in Table 3.
Table 3: Post-Compression Parameters of Formulated Tablets.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>FORMULATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FT-1</td>
</tr>
<tr>
<td>Thickness</td>
<td>2.5 ± 0.1</td>
</tr>
<tr>
<td>Hardness</td>
<td>5.2 ± 0.2</td>
</tr>
<tr>
<td>Weight variation</td>
<td>265 ± 1.26</td>
</tr>
<tr>
<td>Friability</td>
<td>0.57</td>
</tr>
<tr>
<td>Assay</td>
<td>100 ± 0.75</td>
</tr>
</tbody>
</table>

In-vitro buoyancy studies

All batches showed good in-vitro buoyancy. For all tablets floating lag time (25 sec.) and floating tendency of tablet was studied in 0.1 N HCl. The figure also indicates that tablet remained buoyant for 24 hours. The in-vitro buoyancy studies were also conducted at an elevated pH conditions (pH ~4.5). The floating remained unaltered at higher pH. Fig 1

The tablet swelled radically and axially. Swelling polymers used in these formulations were hydroxypropyl methylcellulose and sodium alginate. Swelling of tablets were showed predicted dependence these polymer’s contribution. Formulation FT-5 showed swelling index of 94% while FT-3 showed 78%, which supports the hypothesis that swelling depends on nature and amount of swellable polymer. All relevant data is presented in Table 4.

In-vitro dissolution studies and kinetic modeling of drug release

From in-vitro dissolution data it was found that formulation FT-1 to FT-7 released more than 90% of its content within 20 hours and formulation FT-8 and FT-9 released its contents in shorter time than that of other formulations. This indicates that although rate of release is controlled by ethyl cellulose and sodium alginate, it also depends on concentration of HPMC in the formulation.
Fig 1: *In-vitro* buoyancy study of formulation FT-4 (Time 0 sec to 24 hours)

**Swelling index**

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Table 4: Swelling indices for formulation FT-1 to FT-9

<table>
<thead>
<tr>
<th>Parameters</th>
<th>FT-1</th>
<th>FT-2</th>
<th>FT-3</th>
<th>FT-4</th>
<th>FT-5</th>
<th>FT-6</th>
<th>FT-7</th>
<th>FT-8</th>
<th>FT-9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swelling Index</td>
<td>92.0 ± 0.34</td>
<td>92.0 ± 0.33</td>
<td>78.0 ± 0.07</td>
<td>94.0 ± 0.34</td>
<td>92.0 ± 0.23</td>
<td>80.0 ± 0.42</td>
<td>90.0 ± 0.57</td>
<td>83.0 ± 0.02</td>
<td>86.0 ± 0.79</td>
</tr>
</tbody>
</table>

**IN-VITRO DISSOLUTION OF FT1 TO FT-9**

![Graph showing in-vitro dissolution profile of formulations FT-1 to FT-9](image)

Fig 2: Combined in-vitro Dissolution profile of Formulation FT-1 to FT-9

Table 5: Release kinetics values of FT-5 in-vitro dissolution

<table>
<thead>
<tr>
<th>Kinetic Model</th>
<th>Intercept</th>
<th>Slope</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero Order</td>
<td>12.72</td>
<td>5.11</td>
<td>0.955</td>
</tr>
<tr>
<td>First order</td>
<td>1.211</td>
<td>0.057</td>
<td>0.847</td>
</tr>
<tr>
<td>Higuchi Plot</td>
<td>-9.056</td>
<td>3.196</td>
<td>0.997</td>
</tr>
<tr>
<td>Korsmeyer-Pappas</td>
<td>0.00</td>
<td>0.666</td>
<td>0.983</td>
</tr>
<tr>
<td>Hixson-Crowell</td>
<td>4.577</td>
<td>0.4785</td>
<td>0.9213</td>
</tr>
</tbody>
</table>

The release data obtained for formulations FT-1 to FT-9 were shown in Fig 2 shows the graph of cumulative percentage release as a function of time for different formulations. The results obtained in in-vitro studies were subjected to various models of release kinetic, like zero and first order release kinetics, Higuchi Classical diffusion equation, Peppas exponential equation, Hixson-Crowell erosion equation. The kinetic values obtained for formulation FT-5 was shown in Table 5.
Fig 3: Response surface plots for T₈
Fig 4: Response surface plots for $T_{12}$
Design-Expert® Software

Fig 5: Response surface plots for $T_{16}$
A D-optimal design was constructed to study the effect of amount of ethyl cellulose and sodium alginate on drug release from tablets. The dependent variables chosen were release at 8, 12 and 16 hrs. A statistical model incorporating interactive and polynomial terms was utilized to evaluate the response.

\[ Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad \text{Eq. No: 2} \]

Where \( Y \) is dependent variable, \( b_0 \) is arithmetic mean response of 9 runs, and \( b_1 \) is estimated coefficient for factor \( X_1 \). The main effect represents \((X_1 \text{ and } X_2)\) average result of changing one factor at a time from its low to high value. The interaction \((X_1X_2)\) term shows how the response changes when two factors changed simultaneously. The polynomial terms \((X_1^2X_2^2)\) are included to investigate nonlinearity. The data clearly indicate that the values of release at 8, 12 and 16 hour strongly depends on independent. The fitted equations relating the response \( T_8, T_{12}, \) and \( T_{15} \) to the transformed factors are shown in equation 3, 4 and 5 respectively.

\[ T_8 = 63.65-13.595X_1 + 11.845X_2 - 7.395X_1X_2 + 16.675X_1^2 + 5.615X_2^2 \quad \text{Eq. No: 3} \]

\[ T_{12} = 81.437 - 1.395X_1 + 6.12X_2 - 7.097X_1X_2 + 8.23X_1^2 + 3.72X_2^2 \quad \text{Eq. No: 4} \]

\[ T_{16} = 94.77 - 0.911X_1 + 1.24X_2 - 4.052X_1X_2 + 1.066X_1^2 + 0.677X_2^2 \quad \text{Eq. No: 5} \]

The values of correlation coefficient indicate good fit. The polynomial equation can be used to draw conclusion after considering the magnitude of coefficient and mathematical sign it carries (i.e. positive or negative). The \textbf{Fig 3, 4, and 5} shows the plot of concentrations of ethyl cellulose and sodium alginate verses release at 8, 12 and 16 hrs respectively. The data demonstrate that amount of both \( X_1 \) and \( X_2 \) affects the drug release. It may also be concluded that higher level of \( X_2 \) (sodium alginate) and moderate levels of \( X_1 \) (ethyl cellulose) favor the preparation of floating tablets. The higher level of \( X_1X_2 \) coefficient also suggests that the interaction between \( X_1 \) and \( X_2 \) has a significant effect on \( T_8 \). It can be concluded that the drug release pattern may be changed by appropriate selection of \( X_1 \) and \( X_2 \) levels.

\textbf{Stability studies}

The stability studies results were as shown in \textbf{Table 6}. The results revealed that no significant changes in appearance, floating lag time, hardness, friability and \textit{in-vitro} release for \textit{FT-5} formulation when it was stored in different stability conditions.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
Sl. No. & Time (in months) & \textit{In-vitro} dissolution \hspace{0.5cm} (% CDR) & Floating lag time (in sec) & Hardness (kg/cm\textsuperscript{2}) \\
\hline
1. & 0 & 101.42 & 30 & 4.43 ± 0.10 \\
2. & 1 & 101.40 & 30 & 4.43 ± 0.12 \\
3. & 2 & 101.40 & 30 & 4.43 ± 0.12 \\
4. & 3 & 101.38 & 30 & 4.43 ± 0.12 \\
5. & 6 & 101.38 & 30 & 4.43 ± 0.13 \\
\hline
\end{tabular}
\caption{Accelerated stability studies analysis.}
\end{table}
CONCLUSION

The present study was carried out to develop the gastro-retentive drug delivery system with controlled release of metoclopramide hydrochloride using HPMC, K-4M as a carrier, and ethyl cellulose (hydrophobic) and sodium alginate (hydrophilic) as rate controlling polymers. A systematic study using D-Optimal Design revealed that the amount of sodium alginate and ethyl cellulose had a significant effect on T₈, T₁₂ and T₁₆. In vitro dissolution studies showed controlled release for 20 hrs, followed by the Higuchi diffusion mechanism. Thus, results of the current study clearly indicate, a promising potential of the Metoclopramide Hydrochloride floating system as an alternative to the conventional dosage form. However, further clinical studies are needed to assess the utility of this system for patients.

REFERENCES


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