IN VITRO STUDIES ON BUCCOADHESIVE TABLETS OF METOCLOPRAMIDE

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ABSTRACT

In this investigation an effort was made to develop buccoadhesive bilayered tablets comprising of drug containing bioadhesive layer and drug free backing layer to release the drug for extended period of time with reduction in dosing frequency. Buccoadhesive tablets of Metoclopramide (MCP) were prepared by direct compression method. The buccoadhesive tablets were evaluated for hardness, friability, drug content, surface pH, in-vitro mucoadhesion study and in-vitro drug release study. The physical characteristics, mucoadhesive strength and in-vitro drug release of formulated tablets were shown to be dependent on characteristics and composition of materials used. The surface pH of all tablets was found to be satisfactory, close to buccal pH. The mucoadhesive strength was increased by increasing polymer content. Formulations containing Carbopol 934P and HPMC K4M showed good bioadhesive strength. In order to ascertain the mode of release, the data was subjected to various release kinetic model. All the formulations followed Fickian release mechanism following Higuchi model.

KEYWORDS: Metoclopramide, HPMC-K4M, Xanthan Gum, Na CMC, Mucoadhesive Strength.
INTRODUCTION

Buccal layer is a mucosal layer, highly perfused with blood veins. Buccal delivery of drugs provides an attractive and alternative to the oral route of drug administration. Problems such as high first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via the buccal route.\textsuperscript{[1]} Moreover, buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity. It is also possible to administer drugs to patients who cannot be dosed orally to prevent accidental swallowing. It is an alternative route to administer drugs to patients who are unable to be dosed orally.\textsuperscript{[1,2]}

Metoclopramide (MCP) is a potent antiemetic and is effective in the treatment of nausea and vomiting associated with cancer therapy, pregnancy and migraine. To counter nausea or vomiting during cancer therapy MCP is usually administered to patients. During which need for water is essential, this might increase fluid level in stomach which would induce vomiting and thus anticancer drug may be spilled out. A conventional oral dose has good absorption, but extensively metabolized by the liver. It should be administered 30 min before chemotherapy. Intravenous administration of drug renders rapid effects to a patient, but the onset of effects is so rapid that it causes undesirable effects. In addition, it gives a local pain. The buccal region, within the oral cavity, offers an attractive route of administration for systemic drug delivery.\textsuperscript{[3,4]}

The objectives of the current investigation was to develop controlled release buccoadhesive tablets of MCP and evaluate the effects of different matrix forming polymers like Hydroxypropyl methylcellulose (HPMC K4M), Xanthan gum (XG), Sodium carboxymethylcellulose (NaCMC) and Carbopol 934P (CP) on mucoadhesion and drug release characteristics.

MATERIALS AND METHODS

Metoclopramide (MCP) was obtained as a gift sample by IPCA Laboratories Pvt. Ltd., Mumbai. Carbopol 934P (CP), Hydroxypropyl methylcellulose (HPMC K4M), Xanthan gum (XG), Sodium carboxymethylcellulose (NaCMC) Magnesium Stearate (MS) and directly compressible lactose (DCL) and Ethyl cellulose (EC) were purchased from Rajesh Chemicals, Mumbai. All other chemicals used in study were of analytical grade.
Analytical Method Development

Preparation of stock solution
Accurately weighed quantity of 10 mg MCP was transferred to a 100 ml volumetric flask. Then approximately 50 ml of phosphate buffer solution (PBS) of pH 6.8 was added and resulting solution was sonicated for 5 min. Further required quantity of PBS pH 6.8 was used to adjust volume of solution to 100 ml.

Preparation of serial dilution
From the stock solution, aliquots of 1 to 10 ml were transferred to the 10 ml volumetric flask and final volume was made to 10ml with PBS pH 6.8 to get 2-20 µg/ml concentration respectively. Finally the absorbances of prepared solutions were measured against blank (PBS pH 6.8) at 309 nm by using UV visible Spectrophotometer (Elico E20, India) and calibration curve was plotted.[5]

Compression of Bucoadhesive Tablets
The buccoadhesive tablets were prepared using different polymers in combinations with varying ratios as summarized in Table 1.

Table 1: Composition of buccal adhesive tablets of Metoclopramide hydrochloride.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Ingredients (mg)</th>
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<tbody>
<tr>
<td></td>
<td>MCP</td>
</tr>
<tr>
<td>F1</td>
<td>15</td>
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<tr>
<td>F2</td>
<td>15</td>
</tr>
<tr>
<td>F3</td>
<td>15</td>
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<td>F4</td>
<td>15</td>
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<tr>
<td>F5</td>
<td>15</td>
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<td>F6</td>
<td>15</td>
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<tr>
<td>F7</td>
<td>15</td>
</tr>
<tr>
<td>F8</td>
<td>15</td>
</tr>
<tr>
<td>F9</td>
<td>15</td>
</tr>
</tbody>
</table>

All the ingredients in Table 1, were powdered, passed through sieve # 60. This buccoadhesive bilayer tablets were prepared by a direct compression method involving two steps. In first step drug, polymers (CP and HPMC or XG or NaCMC) and diluent were mixed homogeneously in a double cone blender for 15 minutes in ascending order. Finally lubricant was added and mixed for 5 minutes. The blended powder was then lightly compressed on 8 mm flat faced punch using single punch tablet compression machine (Cadmach, Ahmedabad), at 4 Kg/cm² force. Later, upper punch was raised and the ethyl cellulose was
placed inside the die cavity and subsequently two layers were then compressed at 5-6 Kg/cm² force.

**Evaluation of Bucoadhesive Tablets**

**Determination of Drug Content**

Five tablets from each formulation were powdered individually and a quantity equivalent to 15 mg of MCP was weighed accurately and dissolved into 100 ml phosphate buffer solution (PBS) having pH 6.8. This stock solution was sonicated for 20 min. This resulting solution was further diluted to 10 ml with PBS pH 6.8 for achieve concentration upto 15 µg/ml and analyzed on spectrophotometer (Shimadzu UV, 1700, Japan) at 309 nm.

All formulations were evaluated for uniformity in tablet weight and thickness. Diameter and thickness of tablets were determined by using vernier caliper (Mitutoyo, Japan). Each formulation was also examined for friability using a Roche-type friability apparatus and hardness using a Monsanto-type hardness tester.[6]

**Surface pH Study**

The surface pH of the buccal tablets was determined in order to understand compatibility of pH in buccal pouch. Buccoadhesive tablets were left to swell in 2 ml distilled water for 2 h. The surface pH of the tablets was determined by placing the electrodes just above the wet surface of the slightly swollen tablet.[7] A mean of three readings was recorded.

**Determination of Mucoadhesive Strength**

The mucoadhesive strength of each formulation (n = 3) was determined by using modification of a mucoadhesion test assembly described by Gupta A et al.[8] A balance was modified; both the pans of the balance were detached and in their place polypropylene cylinders were hung. One polypropylene cylinder was to hold the membrane with the tablets and onto the other cylinder, gradually standard weights were added. In brief, buccal mucosa was carefully removed from the buccal cavity of sheep obtained from the local slaughterhouse. At the time of testing, a section of buccal mucosal membrane was placed on the lower polypropylene cylinder and tablet was then stuck to the upper polypropylene cylinder using a cyanoacrilate adhesive. The exposed part of the tablet was wetted with a drop of buffer and then lowered onto the wet mucosa under a constant weight of 5 g for a total contact period of 2 min. This step ensured intimate contact between tissues and tablet. Then remove that weight and gradually standard weights were added on other cylinder.
Mucoadhesive strength was assessed in terms of weight (g) required to detach the tablet from the membrane.

**In vitro drug release studies**

Drug release studies (n=3) were conducted for all the formulations using Keshery-Chien diffusion cell in pH 6.8 buffer medium. The sheep buccal mucosa was carefully mounted in between the two compartments of a Keshary-Chien diffusion cell with internal diameter of 2.1 cm (3.46 cm² area) with a receptor compartment volume of 12 ml of solution containing phosphate buffer pH (6.8) were placed in the receptor compartment. Temperature was maintained at 37 ± 2°C. Aliquots of small samples were periodically withdrawn and the sample volume replaced with an equal volume of fresh medium. The samples were suitably diluted and analyzed spectrophotometrically (Shimadzu UV, 1700, Japan) at 309 nm.

The drug release profile of all the batches were fitted to ascertain the kinetic modeling of drug release and the results were analyzed according to the following equation $Q = K \cdot t^{1/2}$.  

**Stability Studies**

The stability experiments were conducted to investigate the influence of temperature and relative humidity on the drug release profile of formulated buccoadhesive tablets. Stability studies were carried out according ICH protocol, at 40°C±2°C/75% ± 5% RH. Formulations F2, F5, F8 were selected for this study. At regular intervals, 0, 30, 60, 90, 120, 150 and 180 days, the dosage forms were sampled from stability chamber (Bio-Technics India) and *in vitro* release profile was carried out. The drug release profiles were compared with drug release profile performed on tablets kept at ambient conditions. Average of triplicate readings was taken.

**Statistics**

The raw data of *in vitro* studies was subjected to linear regression by least squares method. The data was also analysed using ANOVA and a value of $p<0.05$ was considered to be statistically significant.

**RESULTS AND DISCUSSION**

The aim of this investigation was to formulate buccal adhesive tablets to release the drug at mucosal site in unidirectional way for extended period of time without wash out of drug by saliva., CP as mucoadhesive polymer with constant amount, HPMC K4M, XG and NaCMC
were selected as polymers on the basis of their matrix forming properties with different concentration, while ethyl cellulose being hydrophobic, as backing material.

Analytical method was developed for the drug and validated. Absorbance maxima were found to be 309 nm, which corresponds to the literature. The results of the study are given in the following table 2.

Table 2: Observations of Analytical method development in a UV spectrophotometer

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Parameters</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Absorbance Maximum</td>
<td>309 nm</td>
</tr>
<tr>
<td>2</td>
<td>Slope</td>
<td>0.0357</td>
</tr>
<tr>
<td>3</td>
<td>Intercept</td>
<td>-0.0037</td>
</tr>
<tr>
<td>4</td>
<td>Correlation Coefficient (R²)</td>
<td>0.9985</td>
</tr>
</tbody>
</table>

The drug content of the tablet varied between 14.459 and 14.995 mg. Thickness of tablets was found in the range of 2.32 to 2.36 mm and diameter of the tablets was found in the range of 8.03 to 8.06 mm. The hardness of the tablets was found to be varying between 3.1 to 5.3 kg/cm² and higher with increasing amounts of HPMC or XG. Weight variation, content uniformity and friability of all the formulations showed acceptable results, (149.70±1.57), (96.23± 0.47% to 99.97% ± 0.21) and (0.52% to 0.78%) respectively. Thus, all the physical parameters of the compressed matrices were practically within permissible limits. The difference in the tablet strengths are reported not to affect the release of the drug from hydrophilic matrices. Drug is released by diffusion through the gel layer and/or erosion of this layer and is therefore independent of the dry state of the tablet.\(^{12}\)

Surface pH was found to be in the range of 5 to 7 (n = 3). Thus surface pH test indicated no risk of mucosal damage or irritation to buccal mucosa.

The mucoadhesive property of buccal adhesive tablets of MCP containing varying proportions of polymers was determined with an insight to develop the tablets with adequate bio adhesiveness without any irritation and other problems. The mucoadhesion characteristics were found to be affected by the nature and proportions of the polymers used as seen from figure 1. The highest adhesion force i.e. highest strength of the mucoadhesive bond was observed with the formulations containing CP: HPMC K4M, followed by formulations containing CP: XG and CP: NaCMC respectively. The reason for such findings might be ionization of CP at salivary pH which leads to improved attachment of the device to mucosal surface. Also study indicate that, swelling ability of CP: HPMC is highest than
CP: XG or CP: Na CMC. Tablets of formulation containing Na CMC showed least adhesion force than tablet of all other formulations, which might be due to low viscosity of the Na CMC.[13]

![Figure 1](image1.png)

**Figure 1:** Mucoadhesive strength in grams of various formulations.

*In vitro* drug release studies revealed that the release of MCP from different formulations varies with characteristics and composition of matrix forming polymers as shown in figures 2 to 4. Linear regression by least squares on the observations The raw data was analysed by ANOVA and a value of p<0.05 was considered statistically significant.

![Figure 2](image2.png)

**Figure 2:** *In Vitro* Drug Release of MCP from Formulations F1-F3 across Sheep Buccal Mucosa

![Figure 3](image3.png)

**Figure 3:** *In Vitro* Drug Release of MCP from Formulations F4-F6 across Sheep Buccal Mucosa.
The drug release from the HPMC K4 M formulations showed a release of nearly 20% of the total drug within 1 hour and almost 50% of the drug was found to be released within 5 h. Such a release would be effective in treating patients being treated for nausea in cancer, minimum loading dose would be available within 60 min. Further the curve tends to be linear indicating the release is controlled up to 12 h, indicating that, 2 tablets in a day would be sufficient for a day.

Similarly from formulations F4, F5 and F6, the data showed a release of nearly 20% of the total drug within 1 hour and almost 40% of the drug was found to be released within 5 h. Linear regression by least squares on the observations The raw data was analysed by ANOVA and a value of p<0.05 was considered statistically significant.

The release rate of MCP decreased with increasing amounts of HPMC K4M and XG.[14] respectively. HPMC and XG swell in *in-vitro* fluid, as a result the path of drug to travels usually tortuous, will increase further. Hence decline in release rate is observed with increase in polymer content. These findings are in compliance with the ability of HPMC and XG to form complex matrix network which leads to delay in release of drug from the device CP is more hydrophilic than both HPMC and XG.[12,16]

Further the drug release from the Na CMC formulations, F7, F8 and F9 showed a release of nearly 30% of the total drug within 1 hour and almost 80% of the drug was found to be released within 5 h indicating the dosage would be suitable when immediate action is required and this could be attributed to the least bonding strength and muco-adhesiveness. The tablets of Na CMC even at 30% level might break into lumps. Linear regression by least

![Graph of In Vitro Drug Release](image_url)
squares on the observations. The raw data was analysed by ANOVA and a value of \( p<0.05 \) was considered statistically significant.

Formulations F7 and F8 showed relatively high rate of release of MCP which is due to rapid swelling and erosion of NaCMC. Formulation F9 with NaCMC gets eroded during release study before stipulated study period. Also, the increase in rate of drug release could be explained by the ability of the hydrophilic polymers to absorb water, thereby promoting the diffusion and hence the release, of the highly water soluble drug. Moreover, the hydrophilic polymers would leach out and hence, create more pores and channels for the drug to diffuse out of the device.\(^{12,17}\)

The drug release profile of all the batches were fitted to ascertain the kinetic modeling of drug release and the model with the higher correlation coefficient was considered to be the best fit model and Higuchi’s model was the best fitted with the higher correlation coefficient. Figure 5-7 and Table 3 gave detail idea about that buccoadhesive formulation follows Higuchi’s diffusion kinetics.

![Figure 5: Drug release from F1-F3 following Higuchi’s diffusion kinetics.](image1)

![Figure 6: Drug release from F4-F6 following Higuchi’s diffusion kinetics.](image2)
Figure 7: Drug release from F7-F9 following Higuchi’s diffusion kinetics.

Table 3: Correlation Coefficient of Higuchi’s diffusion kinetics.

<table>
<thead>
<tr>
<th>Formulation</th>
<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
<th>F5</th>
<th>F6</th>
<th>F7</th>
<th>F8</th>
<th>F9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correlation Coefficient ($R^2$)</td>
<td>0.998</td>
<td>0.997</td>
<td>0.997</td>
<td>0.992</td>
<td>0.992</td>
<td>0.994</td>
<td>0.997</td>
<td>0.994</td>
<td>0.996</td>
</tr>
</tbody>
</table>

Stability studies of formulations F2, F5 and F8 were conducted according to ICH protocol at 40°C±2°C/75%±5% RH for a period of 180 days. The selected formulations F2, F5 and F8 were sampled from stability chamber (Remi, India) and were studied for their in vitro release profiles periodically, 30th day, 60th day, 90th day, 150th day and 180th day. The results of these studies were compared to initial in vitro data studied under ambient conditions. The data was analysed by ANOVA and a value of $p<0.05$ was considered statistically significant. The data so obtained is given in table 4 and it was found that, there was no significant difference between the means at $p<0.05$.

Table 4: Stability study of buccoadhesive tablets at 40°C/75% RH.

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Drug release At Initial Day (%)</th>
<th>Drug release At 180th day (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F2</td>
<td>F5</td>
</tr>
<tr>
<td>0</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>1</td>
<td>20.40</td>
<td>14.91</td>
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<tr>
<td>2</td>
<td>32.77</td>
<td>21.77</td>
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<tr>
<td>3</td>
<td>40.11</td>
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<tr>
<td>4</td>
<td>48.35</td>
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<td>55.42</td>
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</tr>
<tr>
<td>6</td>
<td>59.64</td>
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<td>10</td>
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</tr>
<tr>
<td>12</td>
<td>83.27</td>
<td>61.92</td>
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</table>
CONCLUSIONS
The study suggests that the prepared hydrophilic compressed matrices of HPMC K4M, XG and NaCMC with CP provide regulated release till 12 h. The matrices demonstrated sufficient mucoadhesive strength with sheep buccal mucosa. It was concluded that buccal adhesive MCP formulation with satisfactory release characteristics was successfully prepared with selected mucoadhesive polymers. In light of aforesaid discussion it can be concluded that the MCP could be delivered in buccal cavity for extended period of time without the risk of mucosal irritation. Also HPMC K4M and Xanthan gum could be used as potential polymers for mucoadhesive dosages.

ACKNOWLEDGEMENTS
The authors are thankful to The Management of HSBPVT’s, GOI, College of Pharmacy, Kashti for permitting to carry out the research work in the laboratories. The authors are also thankful to IPCA Lab. Pvt. Ltd. (Mumbai) for providing the gift sample.

REFERENCES