SUSTAINED RELEASE FORMULATION OF METOCLOPRAMIDE HYDROCHLORIDE

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ABSTRACT

In this research, several formulations containing, an anti emetic agent (Metoclopramide hydrochloride), a hydrophilic polymer (hydroxypropylmethylcellulose) and a hydrophobic polymer (ethylcellulose 10 cp) were prepared by direct compression. Different factors such as: the effect of different ratios of the polymers, particle size, pressure force and differences of release in acidic and distilled water as media were investigated. After developing the ideal formulation, the effect of changing the ratio of drug in core: coating on the formulation was investigated. Coating of tablets with ethylcellulose, changed the release mechanism of drug and shifted it to near zero order release. The results showed that except when matrices were coated with ethylcellulose, drug release was proportional to the square root of time, which might be due to the change of release pattern from matrix to reservoir system.

Key words: Sustained release, Metoclopramide, Hydroxypropylmethylcellulose, Ethylcellulose, Matrix

INTRODUCTION

Metoclopramide hydrochloride is used as an antiemetic in the treatment of some forms of nausea and vomiting by increasing the gastro-intestinal motility (1). Sustained release (S.R.) form of Metoclopramide can improve patient compliance, especially in cancer therapy (2). Hydroxypropylmethylcellulose (HPMC) and ethylcellulose are widely used to control the dissolution rate of drugs from sustained-release products such as film-coated tablets, and matrix tablets (3). The aim of the present study was to investigate the preparation of sustained release formulation of metoclopramide hydrochloride in the form of matrix tablet with different polymers namely hydroxypropylmethylcellulose K15 M, ethylcellulose 10 cp and their mixtures, as well as the effect of ethylcellulose as coating on drug release.

MATERIALS AND METHODS

Methods

Calculation of doses for sustained release metoclopramide hydrochloride: The total amount of drug in a Sustained Release preparation comprises the normal dose (conventional dose), and the sustaining dose. For metoclopramide, the half-life is 4 hours, and conventional dose is 10 mg (4). Therefore, sustained release matrices of metoclopramide hydrochloride should contain 30 mg of drug.

Tablet Preparation: Flat-faced tablets of 10 mm were directly compressed by an Erweka single punch machine. Compaction was accomplished by direct compression of blends containing 30 mg metoclopramide hydrochloride, ethylcellulose 10 cp, HPMC or their mixtures in different ratios and 1% w/w magnesium stearate. The blends were made by a tumbler mixer at a mixing time of 15 minutes and tablets were prepared to quantify the following variables:

- The effects of metoclopramide hydrochloride and polymer ratios on the drug release. Tablets contained 100 or 200 mg of ethylcellulose 10 cp or HPMC K15M.
- The effects of HPMC and ethylcellulose ratios on drug release. Tablets contained 200 mg of HPMC ethylcellulose at the ratios 1:3, 1:1 or 3:1.

MATERIALS

Metoclopramide hydrochloride, Lot No. 950479, from Medichem, Australia; and ethylcellulose 10 cp, Lot No. 40792, from Hercules, France, were sieved through a # 125 mesh (125 μm) screen; Hydroxypropylmethylcellulose (HPMC K 15M), Lot No. MOSS3 was from Dow Chemicals USA; Magnesium stearate and dibasic calcium phosphate were of USP grade.

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- The effects of particle size and compaction forces on drug release. Tablets contained 200 mg ethylcellulose of 2 different particle size fractions: fine < 125 μm (between sieves 120 and 170 mesh) and coarse > 0.297 μm (between sieves 50 and 30 mesh). Both particle sizes were compressed at forces of 5, 10 and 15 tons.

- The effects of coating of tablets with ethylcellulose on drug release. Concave tablets containing 30, 25 or 20 mg of metoclopramide hydrochloride were coated with ethylcellulose solutions (ethylcellulose in chloroform) containing 0, 5 or 10 mg of drug respectively. At the end all matrices had 30 mg of drug in both core and coat.

**Dissolution Studies:** Dissolution was determined by dissolution tester (Erweka type DTA, Germany) and the USP XXII (Apparatus I). Dissolution method was used at a rotation speed of 100 rev min⁻¹, in 900 ml distilled water or phosphate buffer (pH 6.8) maintained at 37°C (5). The concentration of Metoclopramide hydrochloride was determined at 309 nm. Dissolution studies were performed in triplicate for each batch of tablets.

**Analyses of Drug Release:** In order to investigate the mode of drug release from matrices, the data corresponding to 5 up to 80% release were fitted to Equations 1 and 2 (6).

\[
Q = K_1 t^n \\
Q = K(t - t_0)^n
\]

Where Q is the percent of drug released at time t, K₁ and K are dissolution rate constants, n is lag time and n is the release exponent. The value of n indicates the release mechanism. For instance n=0.5 shows square root of time kinetics and n=1.0 shows zero-order release (6).

**RESULTS AND DISCUSSION**

**Effects of metoclopramide hydrochloride:**

**Polymer ratio on the drug release:** Results showed that by using polymers solely, with the increase of amount of polymer, release of drug decreased (Figs. 1 and 2). The release kinetics from matrices composed of various amounts of ethylcellulose or HPMC were analyzed by equations 1 and 2, and are shown in table 1. It can be observed that as the polymer content increased, the release rate of the drug decreased (values of K₁ and K). The highest T₅₀% (time for 50% of drug to be released) was obtained for matrices containing 200 mg HPMC K15M, which occurs following water absorption. Similar results have been reported by Dabbagh et al. (7) using ethylcellulose and propargyl alcohol hydrochloride.

Investigation of the effect of pH of the media on drug release showed that the release of drug from matrices containing ethylcellulose in HCl 0.1 N was rapid, but the pH of media (distilled water or buffer phosphate solution, pH 6.8) did not have a significant effect on the release of drug from ethylcellulose matrices which might be due to the solubility of metoclopramide hydrochloride in distilled water (8). Therefore, in other experiments the dissolution tests were carried out in distilled water.

**Effects of HPMC: ethylcellulose ratios on the drug release:** Drug release profiles of tablets prepared from different ratios of HPMC K15M: ethylcellulose are shown in Fig. 3 and the data obtained from equations 1 and 2 are presented in table 1. As the proportion of ethylcellulose in the matrix increased, the release rate increased from 1.29%min⁻¹/₂ (50 mg ethylcellulose) to 3.18%min⁻¹/₂ (150 mg ethylcellulose). The value of 'n' did not change significantly when matrices consisted of an admixture of two polymers. The results confirmed the finding of Ford et al. (9), who investigated the effect of replacement of HPMC by dibucaine (9). The value of 'n' between 0.581-0.643, indicates a coupling of diffusion (case I) and polymer relaxation phenomena (case II). This finding shows that the presence of HPMC resulted in erosion of the matrices (10). Because matrices containing 200 mg (3:1) of HPMC: ethylcellulose, gave the best release rate (table 1) and a high value of 'n' (0.643), it was chosen for further investigation (ideal formulation).

**Effect of particle size and compaction forces of ethylcellulose on drug release:** As mentioned previously, matrices were prepared from 2 different particle sizes of ethylcellulose: Fine (less than 0.125 μm) and coarse (more than 0.297 μm). Fig. 4 shows the effect of compaction force on drug release from matrices containing 200 mg ethylcellulose (coarser than 0.297 μm). Fig 5 shows drug release from fine particle size. The data obtained from both grades of particle size are presented in table 2. As the particle size of ethylcellulose increased, the release rate increased. This may be due to facilitation of penetration of
water into matrices when the coarser particle size fractions were used. In both grades of particle size of ethylcellulose, the effect of compaction force did not have significant effect (p<0.05) on drug release, except when the matrices compressed at low compaction force (3 tons and coarse particle size), a burst release of drug was observed, which is indicated by negative value of n in table 2).

Table 1. Effect of ethylcellulose, HPMC K15M polymers or their mixtures on the dissolution constants from matrices containing 30 mg metoclopramide hydrochloride in equations 1 and 2. Results are the mean ± SD of 3 determinations

<table>
<thead>
<tr>
<th>Polymer (mg)</th>
<th>T50% (min ± SD)</th>
<th>Equation 1</th>
<th>Equation 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC:EC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0:100</td>
<td>49.7 ± 1.2</td>
<td>7.34</td>
<td>0.492</td>
</tr>
<tr>
<td>0.200</td>
<td>184.1 ± 2.3</td>
<td>2.10</td>
<td>0.607</td>
</tr>
<tr>
<td>100:0</td>
<td>122.0 ± 2.0</td>
<td>3.24</td>
<td>0.559</td>
</tr>
<tr>
<td>200:0</td>
<td>400.0 ± 5.0</td>
<td>1.59</td>
<td>0.581</td>
</tr>
<tr>
<td>150:50</td>
<td>300.0 ± 3.0</td>
<td>1.29</td>
<td>0.643</td>
</tr>
<tr>
<td>100:100</td>
<td>197.0 ± 2.5</td>
<td>1.94</td>
<td>0.611</td>
</tr>
<tr>
<td>50:150</td>
<td>139.6 ± 1.8</td>
<td>3.18</td>
<td>0.546</td>
</tr>
</tbody>
</table>

Table 2. Effect of particle size of ethylcellulose and compaction force on the dissolution constants from matrices containing 30 mg metoclopramide hydrochloride in equations 1 and 2. Results are the mean ± SD of 3 determinations

<table>
<thead>
<tr>
<th>Force Ton</th>
<th>Mesh</th>
<th>T50% (min ± SD)</th>
<th>Equation 1</th>
<th>Equation 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>&gt;0.297</td>
<td>38.9 ± 3.0</td>
<td>9.33</td>
<td>0.475</td>
</tr>
<tr>
<td>10</td>
<td>&gt;0.297</td>
<td>38.5 ± 2.8</td>
<td>4.57</td>
<td>0.519</td>
</tr>
<tr>
<td>15</td>
<td>&gt;0.297</td>
<td>39.6 ± 0.8</td>
<td>7.39</td>
<td>0.518</td>
</tr>
<tr>
<td>5</td>
<td>&lt;0.125</td>
<td>75.4 ± 1.2</td>
<td>3.65</td>
<td>0.605</td>
</tr>
<tr>
<td>10</td>
<td>&lt;0.125</td>
<td>85.6 ± 1.3</td>
<td>3.72</td>
<td>0.584</td>
</tr>
<tr>
<td>15</td>
<td>&lt;0.125</td>
<td>87.5 ± 0.6</td>
<td>3.24</td>
<td>0.611</td>
</tr>
</tbody>
</table>

Table 3. Effect of metoclopramide hydrochloride content on the surface of tablets on the dissolution constants from matrices containing 30 mg metoclopramide hydrochloride in equations 1 and 2. Results are the mean ± SD of 3 determinations

<table>
<thead>
<tr>
<th>Core Mg</th>
<th>Coat Mg</th>
<th>T50% (min ± SD)</th>
<th>Equation 1</th>
<th>Equation 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>10</td>
<td>91.2 ± 0.8</td>
<td>12.90</td>
<td>0.303</td>
</tr>
<tr>
<td>25</td>
<td>5</td>
<td>161.0 ± 1.1</td>
<td>6.32</td>
<td>0.406</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>610.2 ± 6.8</td>
<td>0.02</td>
<td>1.270</td>
</tr>
</tbody>
</table>

Effects of ethylcellulose coating on the drug release: Since the formulation of HPMC : ethylcellulose (3:1) was chosen as the ideal formulation, matrices containing 30, 25 or 20 mg of metoclopramide in a core were made and then covered by 0, 5 or 10 mg of ethylcellulose solution containing metoclopramide hydrochloride. The results for the effect of the amount of the drug on the surface of tablets are presented in table 3 and fig.6. Formulations coated with 5 mg of drug (25 mg in the core and 5 mg in the coat), showed better release pattern of the drug in comparison to the formulation with no drug in the coating. This property was not observed with tablets coated with 10 mg of drug which showed very fast release. Coating of tablets with ethylcellulose film (without drug), changed the mechanism of the drug liberation.
Figure 1. Effect of different formulation parameters on metoclopramide release.

- **Figure 1**: Particle size > 0.25 μm (10 μm, 15 μm, 20 μm).
- **Figure 2**: Particle size < 0.25 μm (5 μm, 10 μm, 15 μm).
- **Figure 3**: Drug loading (0.5% w/w, 1% w/w, 1.5% w/w).
- **Figure 4**: HPMC content (100%, 200%, 300%).

% Metoclopramide released
and shifted it to near zero order release. The resulting n values (0.889) indicate near zero order release (11). However it did not have proper release rate, since T_{95%}, of release was about 610 min (table 3) which might be due to change in the release pattern from matrix to reservoir system elute.

CONCLUSION

The use of HPMC or ethylcellulose alone did not provide a proper release of metoclopramide hydrochloride. Dissolution rates decreased as the polymer content of the matrices increased. Coating of tablets with ethylcellulose alone, changed the liberation mechanism of drug and shifted it to near zero order release which might be due to change in the release pattern from matrix to reservoir system. Matrices containing 25 mg metoclopramide hydrochloride in a core coated with 5 mg of drug in ethylcellulose as a film, showed better release pattern of the drug. The results showed that in all cases, drug release was proportioned to square root of time, except when matrices were coated with ethylcellulose.

REFERENCES