Influence of cellulose polymers type on *in vitro* controlled release tablets containing theophylline

Evelyn Ojoe, Edna Mitie Miyauchi, Telma Mary Kaneko, Maria Valéria Rolbes Velasco, Vladi Olga Consiglieri*

Department de Farmácia, Faculdade de Ciências Farmacêuticas, Universidade de São Paulo

In this study, the effect of ethylcellulose (EC) and 6 types of hydroxypropylmethylcellulose (Methocel® K100M, K100MPRCR, K15MPRCR, K4MPRCR, K4MPR and E4MCR) on release profile of theophylline from matrix tablets was evaluated. Formulations tablets were prepared by either wet granulation or direct compression technique. The tablets were evaluated for physical characteristics and *in vitro* release of drug was performed as described in USP 30 ed. (Test 3). All formulations with cellulose polymer produced tablets easily and with physical characteristics in accordance with official limits. Drug dissolution tests showed that formulations with 15% of Methocel® K4MPR, 15% of Methocel® K4MPRCR and 30% of Ethocel® N10STD, obtained by direct compression method, complied with official specifications, in terms of release profile and diffusion was the main mechanism involved in theophylline delivery.

INTRODUCTION

Theophylline is a methylxantine derivative very effective in the chronic treatment of bronchial asthma and bronchospastic reactions. Its therapeutic concentration range is narrow (from 10 to 20 µg/mL) while toxicity usually appears at concentrations above 20 µg/mL and the fluctuations of its serum concentrations can result in variability in clinical response (Parvez et al., 2004; Boswell-Smith, Cazzola, Page, 2006). Theophylline is an example of drug with a narrow therapeutic range that may require drug monitoring both to achieve therapeutic levels and minimize toxicity. In order to overcome these problems, controlled release of theophylline seems to be the most appropriate preparation (Boswell-Smith, Cazzola, Page, 2006; Lordi, 1986; Siepmann, Peppas, 2001). Several reviews on the use of polymers for controlled release theophylline dosage forms had been reported (Raslan, Maswadeh, 2006; Ikegami, Tagawa, Osawa, 2006). Among the polymers available as possible for matrix-forming materials and multiparticulate systems, such as methacrylic resins, polysaccharidic gel, and hydrophilic polymers, cellulose derivatives appear particularly attractive (Jalal, Zmaily, Najib, 1989; Ford, Rubinstein, Hogan, 1985; Siepmann, Peppas, 2001; Sung et al., 1996; Lopes, Lobo, Costa, 2005).

Cellulose derivatives have been commonly used in the formulation of hydro gel matrices for controlled drug delivery. They are safe, nonionic and minimize interaction problems when used in acidic, basic, or other electrolytic system. They are suitable for preparing formulations with
soluble or insoluble drugs and at high or low dosage levels. Hydration of polymers results in the formation of a gel layer that controls the release rate of drug (Ojoe et al., 2003; Siepmann, Peppas, 2001; Costa, Souza Lobo, 1999).

The release of drug from controlled release tablets is influenced by factors relating to the physicochemical properties of the drug and to the dosage form. Factors associated with polymers, such as polymer content, molecular weight, concentration, degree of substitution, and particle size, have been shown to have a significant influence on drug release. However, the most important factor that affects the drug release rate from cellulose matrices are the polymer concentration and drug:polymer ratio (Ford, Rubinstein, Hogan, 1985; Mitchell et al., 1993; Xu, Sunada, 1995; Tahara, Yamamoto, Nishihata, 1995).

Despite the high number of papers on this subject, few of them discuss the efficiency of cellulose polymers available commercially. Therefore, the aim of the present work was to evaluate the suitability of different cellulose polymers to prepare theophylline matrix tablets able to assure controlled and well reproducible drug release profiles, also to verify release performances when soluble and insoluble fillers are used, as well as to study drug release profiles by fitting to kinetic models. The cellulose polymers hydroxypropylmethylcellulose (HPMC) and ethylcellulose (EC), the diluents lactose monohydrate and tribasic calcium phosphate, and the lubricant magnesium stearate were studied.

**MATERIAL AND METHODS**

**Reagents and Materials**

Anhydrous theophylline (Ariston -98060278); hydroxypropylmethylcellulose - Methocel® K100M, Methocel® K100MPRCR, Methocel® K15MPRCR, Methocel® K4MPRCR, Methocel® K4M PR and Methocel® E4MCR (Dow Chemical, obtained from Colorcon Brazil), ethylcellulose - Ethocel® N10STD (Dow Chemical), lactose M200 (Henrifarma), tribasic calcium phosphate (Merck), magnesium stearate (Quimibrás Brazil), siliceous dioxide (Henrifarma) and polyvinyl pyrrolidone (PVP) - Kollidon® 30 (Basf). Anhydrous theophylline, 99.80% donated by Ariston, was used as standard in quantitative determinations. Monobasic potassium phosphate (Merck) and hydrochloric acid 37% (Merck) were of analytic reagent grade. All other reagents were special grade commercial preparations.

**Preparation of Theophylline HPMC and EC Matrix Tablets**

Tablet formulations were prepared by direct-compression or wet granulation methods.

Batches from HPMC 1 to 5 were prepared by wet granulation and batches from HPMC 6 to 11 and EC were directly compressed. A schematic illustration of the preparation method of the sustained-release theophylline tablets is shown in Figure 1. For the direct compression method, the steps 3, 4, 5, and 6 were not included. The composition of the prepared tablets is listed in Tables I, II and III. Then, tablets (diameter, 10 mm) containing 200 mg of theophylline were obtained by the Fabbe single punch machine. The compression forces were adjusted for the different formulations to obtain similar tablet hardness.

![FIGURE 1 – Schematic illustration of theophylline tablets preparation.](image-url)
Determination of theophylline from HPMC matrix tablets

Theophylline content in tablets was determined by spectrophotometric analysis at 270 nm using a Shimadzu UV 1601 analyzer. The tablets were powdered and aliquots theoretically corresponding to 200 mg of theophylline were transferred to 200 mL volumetric flasks and mixed with 200 mL of distilled water, in an ultrasound apparatus, for 5 minutes. After centrifugation, samples of 1 mL were taken, diluted to 100 mL with simulated gastric fluid (pH 1.2). Simultaneously, a 10 µg/mL theophylline standard solution was recorded. The assay of theophylline in formulations was carried out in triplicate.

Physical tests

The compressed tablets were characterized by their physical properties. The average tablet weight was determined from 20 tablets (USP, 2007).

Hardness of the tablets was tested using a Pharma Test PTB 311 hardness tester. Friability of the tablets was
determined in an Etica friabilator. Tablet friability was calculated as the percentages of weight loss of 20 tablets after 100 rotations (USP, 2007).

**In vitro dissolution tests**

Dissolution measurements were carried out in a USP 30 ed. method described for theophylline extended-release capsules (test 3) at 37 ± 0.5 °C, with paddle at 50 rpm and 900 mL of dissolution medium using pH 1.2 simulated gastric fluid for the first 1 h and pH 7.5 of simulated intestinal fluid for the following 6 h. Samples of 10 mL were taken from the dissolution medium at appropriate intervals and the absorbancies were measured by UV spectrophotometer at 270 and 271 nm. These values of the drug released from tablets were plotted in graphs of drug released versus time. For elucidation of the drug release mechanism, dissolution data were analyzed using zero order, first order and Higuchi equations, with linear regression (Chambin *et al.*, 2004; Manadas, Pina, Veiga, 2002).

**RESULTS AND DISCUSSION**

Theophylline tablets provided good weight uniformity, according to 7.5% of variation, referring to tablets with weight between 200 mg and 300 mg (United States Pharmacopoeia, 2007). All the formulations were within the USP limits for friability (< 1% weight loss), hardness, diameter and height (Table IV). The tablets showed no physical defects such as capping or lamination (USP, 2007).

Cellulose polymers showed to be efficient to control the theophylline release from the tablets. As polymer percentages increased in tablet formulations, the amounts of drug delivered decreased in dissolution tests (Figure 2). The effect of fillers on drug release was observed in formulations using 10% and 20% of Methocel® K100M with lactose (HPMC 1 and HPMC 2) or trisbasic calcium phosphate (HPMC 3 and HPMC 4). Higher quantities of drug dissolved were obtained from formulations with soluble fillers (Figure 2).

Tablets with 10% of Methocel® K100M released about 92% of the drug after 420 min when 0.5% of magnesium stearate and lactose were used (HPMC 5); therefore the addition of 3.0% of magnesium stearate to the similar formulation (HPMC 1) resulted in 74% of dissolved drug (Figure 2). According to Hussain, York, Timmins (1992) dissolution rate retardation in the presence of magnesium stearate has been attributed to the formation of a hydrophobic film on the surface of the particles. This hydrophobic barrier might effectively result in reduced wettability and reduced particle surface area available for dissolution.

Dürig, Venkatesh, and Fassihi (1999) related that magnesium stearate is a critical erosion-controlling excipient, particularly if it is used over 1.0%. In an investigation of controlled release tablets using HPMC, they observed that high levels of magnesium stearate (> 2.5%), influenced the balance between radial and axial.

**TABLE IV -** Tablets data from physicochemical analyses and drug content. Relative standard deviations (%) are in parenthesis

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Weight (mg)</th>
<th>Drug content % w/w</th>
<th>Friability %</th>
<th>Hardness (kgf)</th>
<th>Diameter (mm)</th>
<th>Height (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC 1</td>
<td>303.16 (5.87)</td>
<td>103.44</td>
<td>0.61</td>
<td>4.59 (0.06)</td>
<td>10.07 (0.03)</td>
<td>4.34 (0.27)</td>
</tr>
<tr>
<td>HPMC 2</td>
<td>300.60 (5.99)</td>
<td>99.07</td>
<td>0.82</td>
<td>4.64 (0.11)</td>
<td>10.06 (0.01)</td>
<td>4.09 (0.09)</td>
</tr>
<tr>
<td>HPMC 3</td>
<td>298.90 (1.50)</td>
<td>103.39</td>
<td>0.22</td>
<td>4.59 (0.11)</td>
<td>9.92 (0.41)</td>
<td>4.12 (1.33)</td>
</tr>
<tr>
<td>HPMC 4</td>
<td>302.73 (4.02)</td>
<td>101.01</td>
<td>0.31</td>
<td>6.78 (0.07)</td>
<td>10.04 (0.02)</td>
<td>4.12 (0.02)</td>
</tr>
<tr>
<td>HPMC 5</td>
<td>310.40 (6.19)</td>
<td>93.38</td>
<td>0.42</td>
<td>5.20 (0.81)</td>
<td>10.03 (0.02)</td>
<td>3.96 (0.11)</td>
</tr>
<tr>
<td>HPMC 6</td>
<td>303.79 (8.88)</td>
<td>97.60</td>
<td>0.75</td>
<td>9.44 (0.20)</td>
<td>10.03 (0.03)</td>
<td>3.86 (0.15)</td>
</tr>
<tr>
<td>HPMC 7</td>
<td>296.48 (9.45)</td>
<td>96.78</td>
<td>0.81</td>
<td>9.03 (0.33)</td>
<td>10.03 (0.05)</td>
<td>3.68 (0.17)</td>
</tr>
<tr>
<td>HPMC 8</td>
<td>300.42 (8.75)</td>
<td>98.42</td>
<td>0.56</td>
<td>7.29 (0.12)</td>
<td>10.02 (0.03)</td>
<td>3.96 (0.33)</td>
</tr>
<tr>
<td>HPMC 9</td>
<td>303.58 (9.54)</td>
<td>96.41</td>
<td>0.86</td>
<td>9.95 (0.39)</td>
<td>10.03 (0.05)</td>
<td>3.60 (0.16)</td>
</tr>
<tr>
<td>HPMC 10</td>
<td>292.35 (13.41)</td>
<td>95.01</td>
<td>0.64</td>
<td>7.35 (0.29)</td>
<td>10.05 (0.02)</td>
<td>4.33 (0.29)</td>
</tr>
<tr>
<td>HPMC 11</td>
<td>296.55 (8.90)</td>
<td>90.66</td>
<td>0.44</td>
<td>8.72 (0.43)</td>
<td>10.02 (0.01)</td>
<td>4.38 (0.28)</td>
</tr>
<tr>
<td>EC</td>
<td>295.56 (10.46)</td>
<td>94.74</td>
<td>0.72</td>
<td>5.56 (0.29)</td>
<td>10.07 (0.03)</td>
<td>4.49 (0.32)</td>
</tr>
</tbody>
</table>

HPMC – Formulations with hydroxypropylmethylcellulose; EC – formulation with ethylcellulose
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erosion rates, leading to lower percentages of drug dissolved. This fact is of particular importance when drugs with poor solubility, like theophylline, are formulated with high amounts of this lubricant, because, as stated by Sung et al. (1996), they are released preferentially by erosion while soluble drugs can dissolve and diffuse through the hydrated gel layer (Reza, Quadir, Haider, 2003; Ibrhim, Daes, Bangudu, 2000).

The dissolution assay results demonstrated that the amount of polymer used was very important to control the drug release. According to Figure 3, the theophylline release profiles from formulations with 15% of Methocel® K4MPR (HPMC 6) and Methocel® K4MPR® (HPMC 7) was similar. Both of them showed a slight difference in their dissolution profiles and higher percentage of drug dissolved than the other formulations containing 15% of Methocel® K100MPR® (HPMC 8) and K15MPR® (HPMC 9) polymers. The letters CR of the Methocel® refers to controlled-release grade, represented by ultra-fine particle size materials, that is able to hydrate fast, leading to effective formation of protective gel barrier. In this research, however, no difference regarding theophylline release was found when CR polymers were used (Figure 3).

However, in our work, no significant differences were observed between the release profiles from HPMC 8 and HPMC 9 formulations, with 15% of Methocel® K100MPR® and 15% of Methocel® K15MPR®, respectively. Similar reports were found in literature by Sung et al. (1996) that reported no differences on the adinazolam mesilate release between formulations produced with Methocel® K15M and Methocel® K100M. They concluded that there were limitations in the polymer viscosity when small amounts are used.

Methocel® K and E possess different ratios of hydroxypropyl and methyl substitution, which influences properties such as organic solubility and thermal gelation temperature of aqueous solutions. The texture and the strength of gel produced by these polymers vary with the type, viscosity grade, and concentration of polymer used. The size, shape and ionization of the drug affect its diffusion through the gel layer. The drug diffusion through most types of polymeric systems is often best described by Fickian diffusion (Patel, Patel, 2007).

The viscosity of the polymers had a dominant role as controlling factors on kinetics of drug release. In general, the strength of the gel increases with increasing molecular weight (Patel, Patel, 2007). K100M is the higher molecular weight polymer, consequently, in the systems with different viscosity grades of K-Methocel® products, the release rates

![FIGURE 2 - Effect of polymer type, excipient type and lubricant concentration on release of theophylline from tablet formulations.](image-url)
decreased with increasing polymer molecular weights, according to the Figure 4.

The substitution’s groups are essential for the polymer hydration of controlled release systems and the choice of polymer is very important because the fast polymer hydration is needed to form the gel barrier, and this gel layer should be sufficiently strong to control the drug and water diffusion. For this reason, the K-polymers

**FIGURE 3** - Effect of polymer type, excipient type and lubricant concentration on release of theophylline from tablet formulations.

**FIGURE 4** - Effect of polymer type, lactose excipient and lubricant concentration on release of theophylline from tablet formulations.
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Hydrated result on stronger barrier than those formed by E-polymers. Methocel® K has the highest ratio of hydroxypropoxyl to methoxyl substitution.

Comparing HPMC 10, HPMC 11 and EC formulations, when 30% of polymer was used (Methocel® E4MCR, K100M and Ethocel® N10STD), higher quantities of drug dissolved were obtained from tablets formulated with Ethocel® N10STD (Figure 4).

Formulations HPMC 6, HPMC7 and EC corresponding respectively to Methocel® K4MPR (15%), Methocel® K4MPRCR (15%) and Ethocel® N10STD (30%) showed amount of theophylline release (%) according to specifications in Test 3, USP 30. The release data of matrix tablets were fitted into various mathematical models (zero, first, Higuchi’s square root equation) to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation coefficient (r) value in various models. The model that gives high ‘r’ value is considered as the best fit of the release data. The ‘r’ values in zero, first order and Higuchi models are given in Table V. It was found Higuchi as a kinetic model that best fitted in the majority of the formulations tested and for the others, first-order (Chowdary, Mohapatra, Murali Krishna, 2006).

Drug release from matrix tablets, in general, becomes progressively slower with time, like Higuchi’s model, in which the amount of drug released is proportional to the square root of time. Kinetic models which fit zero order and Higuchi are more suitable for controlled release formulations, while first order model is more appropriate for conventional tablets (Chowdary, Mohapatra, Murali Krishna, 2006).

The analysis of the $T_d_{50%}$ and $K_d$ values (Table V) revealed that the release kinetics is mainly affected by cellulose polymer and excipient type (lactose and calcium phosphate) content.

**CONCLUSION**

The mixing formulation of granules formed with theophylline and cellulose polymers like Methocel® and Ethocel® to prepare oral controlled release tablets showed appropriate compression.

Theophylline tablets prepared with Methocel® K100M polymer, showed influence on percentage of drug release when amounts of 10% and 20% of polymer was used, also the type of diluents (soluble and insoluble) and amount of lubricant showed significant differences. Higher quantities of drug dissolved were obtained from formulations using 10% of Methocel® K100M with lactose and 0.5% of magnesium stearate.

The studies showed that the theophylline release profiles from formulations with 15% of Methocel® K4MPR and Methocel® K4MPRCR was similar and no difference regarding theophylline release was found when CR polymers were used. Formulations with 15% of Methocel® K4MPR or 15% of Methocel® K 4MPRCR showed higher amount percentage of drug dissolved if comparing with formulations containing 15% of K100MPRCR or 15% of K15MPRCR polymers.

The hydrated K-polymers result on stronger barrier than those formed by E-polymers, for this reason Methocel® K showed lower amount percentage of drug dissolved if comparing with Methocel E.

**TABLE V** - Kinetic assessment: correlation coefficient (r) of kinetics model, dissolution rate ($K_d$) half-life of release ($T_d_{50%}$)

<table>
<thead>
<tr>
<th>Formulations</th>
<th>Zero-order</th>
<th>First-order</th>
<th>Higuchi</th>
<th>$K_d$ (min⁻¹)</th>
<th>$T_d_{50%}$ (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPMC 1</td>
<td>0.8404</td>
<td>0.9664</td>
<td>0.9709</td>
<td>0.0408</td>
<td>93.49</td>
</tr>
<tr>
<td>HPMC 2</td>
<td>0.8519</td>
<td>0.9216</td>
<td>0.9655</td>
<td>0.0330</td>
<td>194.31</td>
</tr>
<tr>
<td>HPMC 3</td>
<td>0.8705</td>
<td>0.9603</td>
<td>0.9753</td>
<td>0.0305</td>
<td>193.62</td>
</tr>
<tr>
<td>HPMC 4</td>
<td>0.9317</td>
<td>0.9679</td>
<td>0.9890</td>
<td>0.0220</td>
<td>490.02</td>
</tr>
<tr>
<td>HPMC 5</td>
<td>0.8705</td>
<td>0.9767</td>
<td>0.9930</td>
<td>0.0358</td>
<td>176.49</td>
</tr>
<tr>
<td>HPMC 6</td>
<td>0.8687</td>
<td>0.9890</td>
<td>0.9877</td>
<td>0.0032</td>
<td>79.91</td>
</tr>
<tr>
<td>HPMC 7</td>
<td>0.8763</td>
<td>0.9890</td>
<td>0.9868</td>
<td>0.0035</td>
<td>80.34</td>
</tr>
<tr>
<td>HPMC 8</td>
<td>0.9324</td>
<td>0.9839</td>
<td>0.9946</td>
<td>0.0285</td>
<td>314.96</td>
</tr>
<tr>
<td>HPMC 9</td>
<td>0.9330</td>
<td>0.9878</td>
<td>0.9983</td>
<td>0.0247</td>
<td>417.51</td>
</tr>
<tr>
<td>HPMC 10</td>
<td>0.9365</td>
<td>0.9695</td>
<td>0.9973</td>
<td>0.0211</td>
<td>551.91</td>
</tr>
<tr>
<td>HPMC 11</td>
<td>0.9528</td>
<td>0.9726</td>
<td>0.9959</td>
<td>0.0161</td>
<td>995.56</td>
</tr>
<tr>
<td>EC</td>
<td>0.9852</td>
<td>0.6021</td>
<td>0.9562</td>
<td>0.0023</td>
<td>184.10</td>
</tr>
</tbody>
</table>
The fit to the Higuchi model indicated that the drug release mechanism from these polymers matrices was controlled by the diffusion.

Dissolution rate was higher for EC than for HPMC excipients, but both formulations showed adequate chemical analyses data and these results demonstrated that Methocel® and Ethocel® were a useful material for a controlled release tablet.

RESUMO

Desenvolvimento e avaliação de comprimidos matriciais de teofilina baseados em ésteres da celulose

Os efeitos das variáveis das formulações na liberação da teofilina a partir da hidroxipropilmetilcelulose (HPMC) e etilcelulose (EC) em comprimidos matriciais foram estudados. Formulações de comprimidos foram preparadas pelos métodos da granulação úmida ou compressão direta usando diferentes viscosidades de HPMC. Propriedades físico-químicas dos comprimidos e liberação do fármaco foram estudadas conforme resolução descrita no Teste 3 da Farmacopéia Americana 30ed. Ensaios “in vitro” mostraram que as formulações com 15% de Methocel® K4MPR, 15% de Methocel® K4MPRCR e 30% de Ethocel® N10STD obtidas por compressão direta apresentaram bom perfil de liberação de teofilina e a difusão foi o principal mecanismo envolvido na liberação.


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